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Contre-mesures médicales contre les risques NRBC : quelles solutions pour un développement facilité dans une économie de marché ?

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Résumé

Contre-mesures médicales contre les risques NRBC : quelles solutions pour un développement facilité dans une économie de marché ?

Pour certaines maladies causées par des agents chimiques, biologiques, radiologiques et nucléaires (CBRN), il n'existe pas de contre-mesures médicales (MedCM) et bon nombre de celles qui existent pourraient ne pas être disponibles en cas de besoin. En cas d'accident CBRN, des efforts inadéquats de financement de la R&D et de mise à disposition par les gouvernements peuvent avoir de graves conséquences économiques nettement supérieures aux coûts d'initiatives préventives. Compte-tenu des contraintes budgétaires auxquelles de nombreux gouvernements sont confrontés, il est nécessaire de définir des priorités. Parallèlement à la mise en place d'indicateurs de décision de santé efficaces qui identifient et mesurent les effets de causalité de l'impact négatif sur la santé, le processus de décision doit également prendre en considération le rapport coût-efficacité pour rendre le financement durable.

Cette thèse a pour objectif de définir une voie vers une politique économique de santé publique visant à renforcer la disponibilité des MedCM pour les agents CBRN. Dans la première partie, les causes des défaillances du marché sont identifiées (lorsque les opportunités de profit ne compensent pas l'effort de R&D nécessaire). Dans la deuxième partie, des études de cas illustrent les caractéristiques et les conséquences économiques d'exemples d'accidents CBRN et des scénarios sont analysés afin de mettre en évidence comment la disponibilité de MedCM pourrait potentiellement devenir rentable. Enfin, la troisième partie propose des approches plus complètes pour mesurer et compenser les facteurs contribuant à la défaillance du marché en appliquant des modèles économiques spécifiques.

Mots clés : Economie comportementale ; Agents chimiques, biologiques, radiologiques et nucléaires ; Faisabilité économique ; Défaillances du marché ; Contre-mesures médicales ; Economie politique ; Politique économique de santé publique ; Offre et Demande

Abstract

International Availability of Medical Countermeasures against Chemical, Biological, Radiological, and Nuclear Agents

For some diseases caused by chemical, biological, radiological, and nuclear (CBRN) agents, innovative medical countermeasures (MedCMs) do not exist while many of those that do might not be readily available. In case of a CBRN event, inappropriate medical research and development (R&D) funding and government procurement efforts can result in adverse economic consequences (e.g. lost income) far exceeding the costs of strong and comprehensive preparedness initiatives. Given the budgetary constraints many governments face, priorities must be defined. Parallel to determining effective health decision metrics that identify and weigh the causal effects of negative health impact, decision making must also consider cost-effectiveness to make funding sustainable. Moreover, international cooperation is necessary since the risks increasingly transcend borders due to global travel and the global threat of terrorism.

This dissertation ultimately seeks to define a path to public health economic policy to enhance the international availability of CBRN MedCMs. In Part I, the root causes of market failure are identified and depicted (i.e., where rewards for supply do not adequately compensate for the R&D effort). In Part II, case study examples illustrate the characteristics and economic consequences of CBRN incidents. Scenarios for each case are outlined to show where the availability of MedCMs in these situations could potentially be cost-effective. Finally, Part III construes more comprehensive approaches for gauging and offsetting the deterrence factors of market supply and demand by compiling and applying additional economic models and frameworks.

Keywords: Behavioural Economics ; Chemical, Biological, Radiological, and Nuclear agents ; Economic Feasibility ; Market Failure ; Medical Countermeasures ; Political Economics ; Public Health Economic Policy ; Supply and Demand

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Text Abbreviations

AAPCC	American Association of Poison Control Centres
ACh	Acetylcholine
AChE	Acetylcholinesterase
AMC	Advanced Market Commitment
AMR	Antimicrobial Resistance
ARS	Acute Radiation Syndrome
ASPR	Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
BSL	Biological Safety Level
CBRN	Chemical, Biological, Radiological, and Nuclear
ChE	Cholinesterase
CDC	Centers for Disease Control and Prevention
CGE	Computable General Equilibrium
COC	Cost of Capital
CWA	Chemical Warfare Agent
CWC	Chemical Weapons Convention
DALY	Disability-Adjusted Life Year
DoD	Department of Defense
EC	European Commission
EMA	European Medicines Agency
EPPM	Extended Parallel Process Model
ESA	European Space Agency
EU	European Union
EVD	Ebola Virus Disease
FDA	Food and Drug Administration
FIF	Financial Intermediary Fund
GDP	Gross Domestic Product
GHSA	Global Health Security Agenda

GHSI	Global Health Security Initiative
GSK	GlaxoSmithKline
HHS	Department of Health and Human Services
HSC	Health Security Committee
IAEA	International Atomic Energy Agency
IFFIm	International Finance Facility for Immunization
IHR	International Health Regulations
IP	Intellectual Property
IPO	Initial Public Offering
IS	Islamic State
JPA	Joint Procurement Agreement
M&A	Mergers and Acquisitions
MEDC	More Economically Developed Countries
MedCM	Medical Countermeasure
MP³	Multi-Public-Private Partnerships
MPP	Multi-Public-Partnership
NIH	National Institutes of Health
NME	New Molecular Entity
NPV	Net Present Value
OP	Organophosphorus Compound
OPCW	Organization for the Prohibition of Chemical Weapons
PDP	Product Development Partnership
PEF	Pandemic Emergency Financing Facility
PhRMA	Pharmaceutical Research and Manufacturers of America
PPP	Public Private Partnership
PRV	Priority Review Voucher
R&D	Research and Development
RDD	Radiological Dispersal Device
ROE	Return on Equity
ROI	Return on Investment
SME	Small and Medium-Sized Enterprise

TATFAR	Trans-Atlantic Task Force on Antimicrobial Resistance
Tufts CSDD	Tufts Center for the Study of Drug Development
UK	United Kingdom
UN	United Nations
US	United States
VSL	Value of Statistical Life
WBG	World Bank Group
WHO	World Health Organization
WMD	Weapons of Mass Destruction
WTP	Willingness to Pay
YLD	Years Lived with a Disability
YLL	Years of Life Lost
SEYLL	Standard Expected Years of Life Lost
TMP³	Transatlantic Multi-Public-Private Partnerships
UACT	Union for Affordable Cancer Treatment

Introduction

Events such as the September 11, 2001 ("9/11") attacks on the World Trade Center, Pentagon and other targets in the United States (US) – marked the necessity for countries to prepare for attacks aimed at killing as many people as possible without warning. The 9/11 events, which killed some 3,000 people, gave cause for the US, NATO and other allies to initiate a "Global War on Terrorism". Given terrorism's deadly new objective of mass killing, the use of chemical, biological, radiological, and nuclear (CBRN) materials was perceived as a great threat for future attacks. Given as well the global nature of international terror, appropriate measures today include a coordinated worldwide approach which aims to prevent, detect and mitigate the consequences of CBRN attacks (Sabol, Šesták, Polívka, & Mroz, 2015). By November 2001 health ministers from several nations – Canada, France, Germany, Italy, Japan, Mexico, the United Kingdom (UK) and the US – called for concerted global action to strengthen the public health response to the threat of international CBRN terrorism. They decided to create the Global Health Security Initiative (GHSI). The GHSI continues to reiterate the increasing importance of their purpose, as observed in 2016: "The rise in terrorist related events over the past year has reinforced that our collaborative efforts in response to CBRN threats remain a high priority" (Global Health Security Initiative, 2016).

At the same time the GHSI was established, the European Union's (EU) Health Security Committee (HSC) was set up at the request of Europe's national health ministers and used by the European Commission (EC) to coordinate health-security measures across the union. This enables EU governments to exchange information, evaluate health events, advise their health ministers, and carry out coordinated crisis response. In the US, the Biomedical Advanced Research and Development Authority (BARDA) launched its Project BioShield in 2004 to strengthen its availability of innovative

medical countermeasures (MedCMs) against the threat of international CBRN terrorism. The EC began preparing against the same when it launched its CBRN action plan in 2009. The EC plan included a request for each EU member state to assess the amounts and types of CBRN MedCMs required for its national readiness plan and aimed to address associated regulatory issues. Despite the EC's encouraging CBRN action plan, the MedCM preparedness situation for the 28 EU Member States remains unclear. Nonetheless, it did at least raise the possibility of sharing MedCMs across borders in case of an incident. Further stimulated by the experience of the 2009 H1N1 influenza pandemic, the role of the HSC was formalised in late 2013 to coordinate public health measures dealing with serious cross-border threats to health in the EU. As of November 2015, all EU member states with populations under five million signed the EU Joint Procurement Agreement (JPA). This allows for multi-country procurement of MedCMs against cross-border health threats. Although its element of central funding was not achieved, the mechanism could still be advantageous for smaller member states because it would increase their ability to secure supply, increase price savings and reduce operational costs and administrative burden (Azzopardi-Muscat, Schroder-Beck, & Brand, 2017). The EU's larger countries, however, might perceive disadvantages associated with forfeiting their sovereign rights to negotiate directly with suppliers.

MedCMs are defined as either a drug, biological product or device that prevents, identifies or treats the consequences of exposure to CBRN agents (Stroud, Nadig, & Altevogt, 2010). To achieve an effective MedCM, medical research and development (R&D) for the discovery, testing and assessment of a compound against a well-defined therapeutic target is a prerequisite (Pammolli, Magazzini, & Riccaboni, 2011). Assuming efficacious research is carried out, populations could be protected via new prophylactic drugs and vaccines or post-exposure treatments such as antidotes and antimicrobials. The US Centers for Disease Control and Prevention (CDC) have classified biological agents of great concern as "Category A Biological Threats". Examples of these agents include anthrax, plague, smallpox, tularaemia and viral haemorrhagic fevers such as Ebola (U.S. Centers for Disease Control and Prevention,

2000), though smallpox was declared eradicated in 1980 by the World Health Organization (WHO) (Henderson, 1998). In addition to potential exposure via natural release, the pathogens responsible for many such diseases have been militarized in the past (e.g., in the US, UK, and former Soviet Union). While rarely seen in nature within developed countries, they pose high risk to national security even if they cannot be easily weaponized. Whether naturally, accidentally or intentionally released, the reasons, according to the CDC, are that they:

- can be easily disseminated or transmitted person-to-person
- cause high mortality, with potential for major public health impact
- might cause public panic and social disruption (especially if the "human hand" is proved to be behind an event)
- require special action for public health preparedness (U.S. Centers for Disease Control and Prevention, 2000).

Similarly, some chemical and radiological agents are high on the threat list of possible agents to be used by terrorist organizations, non-state actors or state-sponsored groups (e.g., Tokyo subway attack in 1995 by the cult Aum Shinrikyo with the highly toxic nerve agent sarin). Their release could also easily occur by accident (e.g. radionuclides released during the nuclear disasters in Chernobyl in 1986 or the Fukushima Daiichi plant in 2011) or even via industrial pollution. For example, studies suggest that the number of people per year who suffer from pesticide-related health effects, which often include organophosphorus compounds (OPs), could be quite significant. The annual incidence rates of acute pesticide poisoning in agricultural workers may be as high as 18.2 per 100,000 full time workers in developed countries and up to 180 per 100,000 workers in less developed countries such as Sri Lanka (Thundiyil, Stober, Besbelli, & Pronczuk, 2008).

Subsequent to the terrorist events of September 2001, the US government realised that sufficient technology and availability of MedCMs against the newly perceived health threats would not be provided by industry (U.S. Centers for Disease Control and Prevention, 2000). In the absence of an acute threat of a natural, intentional, or

accidental release, the cause was the severely low-to-nil market demand for CBRN MedCMs that are rarely needed in a free market environment – a marketplace of few customers with low and volatile sales potential. Indeed, the R&D process to develop MedCMs is extremely lengthy, risky and expensive, meaning that developers and manufacturers of MedCMs are not economically motivated to address all these threats. That is, free market rewards and incentives are uncertain and usually insufficient to entice the resources of those developers and manufacturers with proven capabilities. Within normal conditions of a market economy, adequate assurances such as market rewards and incentives must be identifiable before developers and manufacturers are willing to strive for solutions to meet market demand. To entice industry to engage, not only is the prospect of profitable business needed but opportunities must be weighed against alternative prospects that might offer better business growth models.

Further complicating the availability of MedCMs is that there are numerous CBRN agents proficient enough to cause harm to individuals. Also, there is the unpredictable nature of when the health risks of specific CBRNs might arise. Although some CBRN agents pose a low prevalence (proportion of individuals in a population at risk that are adversely affected) and incidence (number of new cases of a disease caused by CBRN agents over a given period divided by the population at risk), or even unlikely to emerge at all, some of them have the potential to cause catastrophic impact on society. Yet it is important to note that all MedCMs do not suffer the same problem. Unless otherwise specified, the focus of this dissertation is on the case of medicinal drugs that require licensure for their delivery and use since investment for drugs tend to be the most resource intensive in terms of time, risks, and costs.

Consequently, the US Project BioShield aimed to provide funding for R&D. A “Special Reserve Fund” was appropriated for the Department of Homeland Security, including 5.6 billion USD over 10 years (2004-2013) for the development and procurement of so-called qualified countermeasures to protect against CBRN agents. The countermeasures could be a drug, biological product or device that the US Department of Health and Human Services (HHS) secretary determines as a priority. Besides

enabling the acquisition of late-stage MedCMs to be stockpiled, Project BioShield included other essential components such as increasing the authority of the National Institutes of Health (NIH) to accelerate advanced R&D. Also, the US Food and Drug Administration (FDA) was empowered to authorize use of unlicensed CBRN MedCMs in the event of an emergency (Russell, 2007; Gronvall, 2008). BioShield's Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 authorized up to 2.8 billion USD for 2014-2018 (U.S. Department of Health and Human Services, 2014a) for the continuation of these objectives.

Yet, for some diseases caused by CBRN agents, innovative MedCMs do not exist and many of those that do might not be readily available internationally. In the event of a release, inappropriate R&D funding and government procurement efforts can have adverse economic consequences (e.g. lost income for society) far exceeding the costs of strong and comprehensive preparedness initiatives. That is because the availability of relevant CBRN MedCMs can be cost-effective in helping minimise the loss of human life and impact on social and economic structures. Given the budgetary constraints many governments face, however, priorities must be defined. Moreover, international cooperation is necessary since risks increasingly transcend borders due to global travel and the global threat of terrorism. While conventional health decision metrics strive to identify and weigh the causal effects of negative health impact relative to each metric, decision making must also consider cost-effectiveness so that funding is sustainable. Yet there are indications that the potential impact certain CBRN agents pose to social and economic structures is not adequately reflected in current health decision metrics.

The rationale to support both market supply and demand can be reinforced by augmenting current economic models and frameworks. This dissertation aims to synthesize and discuss the existing evidence, and then define a path to public health economic policy for enhancing the international availability of CBRN MedCMs. In Part I, the root causes of market failure are identified and depicted. These include the lengthy, risky, and expensive R&D process required to produce CBRN MedCMs (Chapter 1) versus the associated market rewards which are low and uncertain (Chapter

2). Chapter 2 shows that the associated market is not compatible with conventional industrial business models intended to combat company growth challenges. In Part II, case study examples (Chapters 3, 4 and 5) illustrate the characteristics and economic consequences of different types of CBRN incidents. Scenarios for each case, whether involving naturally, accidentally or intentionally released agents, are outlined to indicate where the availability of MedCMs in these situations could potentially be most cost-effective. Finally, Part III construes more comprehensive approaches to gauge and offset the deterrence factors of market supply and demand by compiling and applying supplementary economic models and frameworks. To achieve this, Chapter 6 introduces components of a risk-informed framework, emphasising the components' utility for shaping the political motivation, funding and global collaboration needed to drive market demand. In Chapter 7, the counteraction of supply-side deterrents is examined by presenting incentive examples and showing how these tools can systematically exceed the impact of more traditional approaches.

Part I – Components of Market Failure

The core concept of a "market failure" corresponds to situations where the pursuit of individuals' pure self-interest leads to an inefficient allocation of goods and resources, often resulting in a net social welfare loss. These situations can be improved from a societal point of view and are often related to time-inconsistent preferences, information asymmetries, externalities or public goods. The concept is applicable here since the risk and cost of the MedCM R&D process is not adequately balanced by market rewards that would normally incentivize product supply. This section describes the features of the medical R&D process and market mechanisms that fail to incentivize, and hence deter industry from developing MedCMs against many CBRN agents. Chapter 1 sets out to increase the lengthy, risky, and expensive drug R&D process's transparency and to demarcate the lines of associated controversy. Chapter 2 portrays the root causes of market failure by contrasting the market rewards and characteristics offered for drugs that target conventional diseases with those that protect against CBRN agents.

> *"[The individual] neither intends to promote the public interest, nor knows how much he is promoting it… [H]e intends only his own security; and by directing that industry in such a manner as its produce may be of the greatest value, he intends only his own gain, and he is in this, as in many other cases, led by an invisible hand to promote an end which was no part of his intention"* (Smith, 1776) .

Chapter 1 CLARIFYING DRUG R&D EFFORT AND COST

Medical R&D is the study directed towards discovering, testing and assessing a compound against a well-defined therapeutic target (Pammolli et al., 2011). The estimation and reporting of drug R&D costs has significant influence on major issues for the pharmaceutical and biopharmaceutical industry. These include drug prices, regulatory policy, barriers to generic entry as well as laws involving drug importation from countries where drugs cost less (Adams & Brantner, 2006). For this reason, most estimates are subject to controversy depending on the particular interest involved (e.g. industry, healthcare payers, customers/patients). While verification of high R&D costs would lend industry the justification for pricing policy and laws that protect the market sales potential of its products, healthcare payers (and often consumers) are at the opposite end. That is, they might reap lower prices for medicine if R&D costs could be revealed as "overstated" and then demythologized. Even so, any generic prediction or assessment of costs for a particular pharmaceutical product (also referred to as "small" molecules) and biopharmaceutical ("large" molecules) probably lacks accuracy. This is due to many unique and unforeseen events as well as varying degrees of complexity and mechanistic knowledge available concerning a given disease. The significant sales potential and market stability of drugs that target conventional diseases create an attractive environment for substantial private R&D funding from the investor community. For example, it is expected that by 2020, global annual sales for medicines will reach 1.4 trillion USD (Aitken, 2015). This represents an increase of roughly 30 percent compared to 2015. As for the annual worldwide R&D investment in life science technologies, this currently equals nearly 170 billion USD (Industrial Research Institute, 2016). While this figure for life science technologies includes medical instruments and devices, and animal and agricultural bioscience, R&D in the biotechnology sector alone accounts for some 85 percent of the industries' total R&D expenditure.

Given controversies surrounding R&D cost estimates, their implications for drug development and the need for government to fund many non-commercial CBRN

MedCMs, a clear understanding of cost definition can enhance cooperation potential between industry and government. Hence, this chapter sets out to demarcate the lines of argument associated with this lengthy, risky, expensive and necessary R&D process. This is achieved by clarifying how cost and effort are defined and accumulated. Section 1.1 outlines a standard R&D paradigm derived from drug development studies that target conventional diseases, including depiction of its various controversies and how they stand up to periodic debate. Section 1.2 describes R&D characteristics that are more unique to CBRN MedCMs in order to assess whether significant variance to the standard paradigm occurs.

1.1 Standard R&D Process and Cost Paradigm

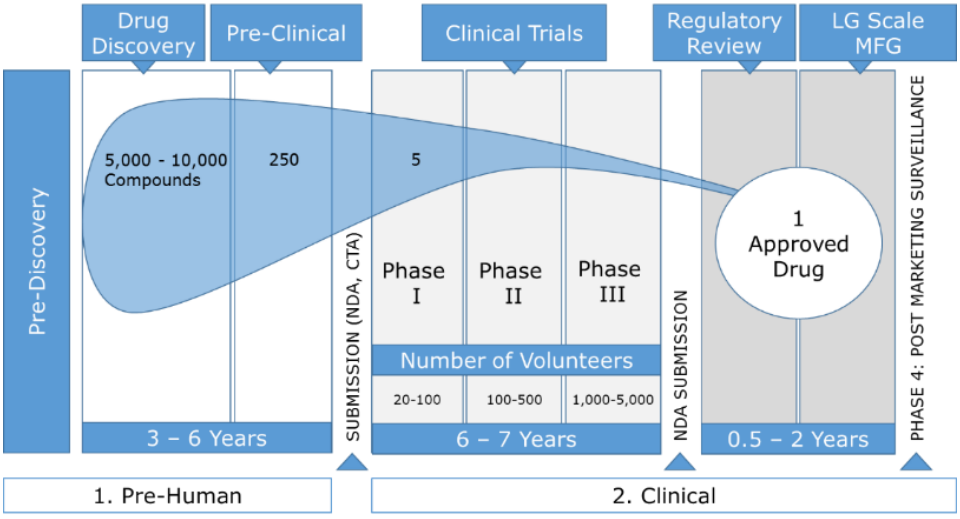
Although a number of factors make it difficult to accurately predict the related costs needed to successfully achieve a particular pharmaceutical or biopharmaceutical product, it is possible to frame a standard R&D process and cost paradigm based upon the available study of drug development. After illustrating the common trends when targeting conventional diseases in this section, the arguments concerning such cost estimations are then highlighted.

1.1.1 Process

Based on an earlier comprehensive R&D study (DiMasi, Hansen, & Grabowski, 2003) hosted by the Tufts Center for the Study of Drug Development (Tufts CSDD), it was estimated to take about 10-15 years to develop one new drug. This is measured from the time of the drug's discovery to its availability for patients. Figure 1 illustrates the various phases and statistical failure rates incurred before one drug can be successfully approved. The probability of success is very low while the probability of success increases only as each R&D trial phase is completed. For example, for every 5,000-10,000 compounds – also known as new molecular entity (NME) – that enter the R&D pipeline, it was estimated that 250 reach a preclinical phase, five reach Phase I and ultimately only one from these NME receives market approval (Pharmaceutical Research and Manufacturers of America, 2007). While a new drug development

process cannot be completely pre-determined, a standard R&D paradigm has evolved to frame the general process (DiMasi, Grabowski, & Hansen, 2016).

Figure 1 – Phases of R&D (Pharmaceutical Research and Manufacturers of America, 2007)



All phases of R&D – labelled pre-human and clinical in Figure 1 – must be successfully completed before marketing approval can be attained. Each individual phase represents a different probability that its relevant criteria can be successfully met; leading to confirmation that the NME is efficacious against the disease it targets and safe for humans. As previously indicated, the probability that a NME passing through phase I could also successfully reach market approval has been assessed at about one-in-five (or 21.5 percent, to be exact). But according to more recent evaluations, this overall success rate has fallen from 21.5 to 11.8 percent (Tufts Center for the Study of Drug Development, 2014a; DiMasi et al., 2016). This lower overall success probability means that to achieve one successful candidate, nearly 8.5 compounds must be launched into phase I development. Assuming successful completion of the pre-human phase, the probabilities of entering each individual clinical trial phase are listed in Table 1. The reduction of overall success probability to 11.8 percent is likely attributable to factors that include increased clinical trial complexity and a greater focus on targeting chronic and degenerative diseases (Policy and Medicine, 2014). A

description of Tufts CSDD's database cost parameters that served as a basis for the earlier and more recent DiMasi et al. studies is offered in Table 2.

Table 1- Probability of Entering Clinical Trial Phases after Successful Pre-Human Phase Completion (DiMasi et al., 2016)

TESTING PHASE	PERCENT
PHASE I	100
PHASE II	59.5
PHASE III	21.1
PROBABILITY OF RECEIVING MARKET APPROVAL:	**11.8**

Table 2 – Description of Tufts CSDD Database (DiMasi et al., 2003*;* Tufts CSDD, 2014a)

PERIOD	GEOGRAPHY	DATABASE DESCRIPTION
1980 – 1999	Both foreign and US-owned firms	68 randomly selected new drugs were obtained from a survey of 10 multinational pharmaceutical firms (DiMasi et al., 2003)
1995 – 2007	First tested in human subjects anywhere in the World	106 investigational compounds from ten randomly selected drug firms of varying size, which together accounted for 35 percent of top 50 firm pharmaceutical sales and pharmaceutical R&D expenditures, Data were also collected from the cost survey participants on their aggregate annual pharmaceutical R&D expenditures from 1990 to 2010 (Tufts Center for the Study of Drug Development, 2014a)

Throughout pre-human trial phases, researchers are typically dedicated to discovering and developing new drugs and assuring that promising drug candidates can be tested safely in humans before clinical trial phases can begin – see Table 3 for further detail. Three subsequent phases of clinical trials are structured to establish high confidence in the direct relationship between the NME and its effect on disease. Studies are then designed to compare the NME to placebo and/or alternative treatments. Treatment options for individual study subjects can be achieved either by a randomised or double-blinded selection process – where neither the researcher nor the subject is informed of the applied treatment option until after the study's completion. Further clinical phases include the approval process, transformation from small-scale to large-scale manufacturing, and a continued monitoring of patients to ensure the reporting of any

adverse reactions to the new drug. Additional details of the clinical phases are depicted in Table 4 (Pharmaceutical Research and Manufacturers of America, 2007).

Table 3 – Description of the Pre-Human R&D Phases

TESTING PHASE	DESCRIPTION
PRE-DISCOVERY	Researchers from government, academia and industry contribute to creating an understanding of the disease in order to reveal the cause of the condition. Objectives to achieve a basis for treating the problem are identifying and validating the target molecule (e.g. a single gene or protein) that is involved in the disease and one which will interact with a drug molecule (Pharmaceutical Research and Manufacturers of America, 2007).
DRUG DISCOVERY	Early research aimed to identify the most efficacious new drug molecule (or "lead compound") that can interact with the chosen target to alter the course of a disease. There are various ways to discover lead compounds. For example, compounds can be found in nature (e.g. bacteria in soils and mouldy plants), De novo (e.g. creating molecules from scratch, computer modelling, high-throughput screening, robotics) as well as biotechnology (e.g. genetically engineering living systems to produce disease-fighting biological molecules). Despite initial potential of drug compounds, early prioritization is required to determine key safety and efficacy compatibilities. By conducting tests in living cells, animals, and via computer models, compatibilities of drug's pharmacokinetics can be determined. Pharmacokinetics include its absorbability in blood stream, distribution to proper site of action in the body, safely and effectively metabolized, excreted from the body, and nontoxic properties. Based on results of such initial tests, it is possible to optimize lead candidates by altering its structure. For example, a drug molecule can be altered to be less likely to react with other non-related chemical pathways; thus, reducing side-effects. Even at these early stages, alternatives concerning suitable large-scale manufacturing, delivery mechanisms (e.g. how drug is taken), and formulations (e.g. drug recipe) are considered (Pharmaceutical Research and Manufacturers of America, 2007).
PRECLINICAL	This development phase can be highlighted as trying to understand via lab and animal testing how the lead compound works and if the drug is safe enough for human testing. During this phase, researchers are also challenged with how to create large enough drug quantities to conduct clinical trials. Although this is the first scale up as related to manufacturing, this small scale is far different than the scale up which would be needed if the drug is approved for market (Pharmaceutical Research and Manufacturers of America, 2007).

Table 4 – Description of Clinical R&D Phases

TESTING PHASE		DESCRIPTION
SUBMISSION (IND, CTA)		Before clinical testing in humans can begin, researchers must submit an investigational new drug (IND) application to the FDA (in the US) or clinical trial application (CTA) to EMA (European Medicines Agency) in Europe. The submission data includes results from the preclinical phase, description of the drug candidate's chemical structure and how it works, potential side-effects, manufacturing information, as well as a detailed description of the trial plan – e.g. where and by whom the tests will be performed (Pharmaceutical Research and Manufacturers of America, 2007).
CLINICAL TRIALS	Phase I	A phase I clinical trial is typically defined with a group of healthy volunteers (about 20 to 100) who are administered the drug to confirm the drug is safe in humans. In addition to again testing the drug's pharmacokinetics (as explained in the drug discovery phase), the drug's pharmacodynamics (e.g. side effects vs. desired effects) can be monitored. Hence, safe dosing ranges and feasibility for further development can be determined (Pharmaceutical Research and Manufacturers of America, 2007).
	Phase II	Traditionally, phase II clinical trial requirements include testing the drug candidate's effectiveness in about 100 to 500 patients with the disease or condition under study. Evaluation focuses on possible short-term side effects (adverse events) and risks associated with the drug as well as if it is working by the expected mechanism; thus, improving the condition in question. Lastly, dose strengths and schedules are optimized in this phase (Pharmaceutical Research and Manufacturers of America, 2007).
	Phase III	This key phase clinical trial studies the drug candidate in a large number of patients (about 1,000 – 5,000) to generate statistically significant data about safety, efficacy, and the overall benefit-risk relationship of the drug. Especially since this phase can involve hundreds of testing sites around the world, it is most expensive and time intensive. In addition to studying main benefits of the drug, other requirements are finalized during this phase – e.g. plans for full scale manufacturing, approval application and labelling requirements (Pharmaceutical Research and Manufacturers of America, 2007).
REGULATORY REVIEW: NEW DRUG APPLICATION (NDA) AND APPROVAL		Upon completion of all three clinical trials, the sponsoring company analyses the full data sets. If all findings can demonstrate both safety and efficacy, the company requests market marketing approval. Following rigorous review, authorities can either 1) approve the medicine, 2) send the company an "approvable" letter requesting more information or studies before approval can be given, or 3) deny approval (Pharmaceutical Research and Manufacturers of America, 2007).
LARGE SCALE MANUFACTURING		The transformation from small-scale to large-scale manufacturing is a major project. Because production processes for each drug are sensitive, complex, and unique, often a new facility must be built (or an old one reconstructed). Each facility must meet strict guidelines for Good Manufacturing Practices (GMP) (Pharmaceutical Research and Manufacturers of America, 2007).
ONGOING STUDIES AND PHASE IV TRIALS		Upon launch of a drug on the market, companies are required to monitor patients and report any adverse events to authorities. In fact, sometimes phase IV studies can be required to evaluate long-term safety or how the drug affects specific patient subgroups (Pharmaceutical Research and Manufacturers of America, 2007).

1.1.2 Costs

In the absence of defining R&D costs more precisely, there is high potential that growing controversy concerning costs could derive from misunderstanding. For example, it may be intuitive to focus solely on the actual direct expenses invested to complete the pre-human and clinical R&D phases for one successfully approved product candidate. However, to depict a cost evaluation that is economically viable and comparable, it is often necessary to amortise the expenses of previous but failed NMEs and to differentiate between forms of expenditures that typically compile total costs. As summarized in Table 5, key cost areas which require differentiation are actual cash outlays (or out-of-pocket costs) and the cost of capital (COC), also referred to as opportunity costs. Both combined out-of-pocket and COC expenses represent capitalised costs.

Table 5 – Components Applied to Defining Costs

COSTS	DESCRIPTION
ACTUAL CASH OUTLAYS (OR OUT-OF-POCKET COSTS)	1. Costs incurred during the R&D process for the one specific NME which could be successfully approved.
	2. Costs of developing NMEs which failed before a successful candidate could be determined.
COST OF CAPITAL (COC) – OR OPPORTUNITY COSTS	3. When R&D funding is provided by private investors – which is most frequently the case for NMEs that target conventional/commercial diseases), a discount rate is applied which best matches the expected return investors must forego during development when they invest in pharmaceutical R&D instead of an equally risky portfolio of financial securities. Over the full lengthy R&D timeline, these capitalized costs can reach roughly the same level as the out-of-pocket expenses itself (Adams & Brantner, 2006; DiMasi et al., 2016).

So how much does it cost to develop a new drug? In 2003, a cost analysis study represented by the Tufts CSDD came up with an estimate of pharmaceutical R&D capitalised costs for conventional diseases at 802 million dollars (DiMasi et al., 2003). Hence, a rounded ballpark figure of 1 billion USD became one of the most widely referenced figures when citing the development costs for one new pharmaceutical drug. From this total capitalized cost estimate of 802 million, one half represented actual out-of-pocket expenses, with the other half being COC with a discount rate of 11 percent.

As explained in Table 5, when R&D funding is provided by private investors, a discount rate is applied. Obtaining real COC for study purpose can be viewed in Table 6. The nominal values were first computed, then the expected rate of inflation was subtracted. The nominal COC in 1994 is from a capital asset pricing model study (Myers & Howe, 1997). The estimates for 2000, 2005, and 2010 are based on the DiMasi et al. (2003) methodology derived from the Tufts CSDD large pharmaceutical company sample data. The estimated nominal COC for pharmaceuticals was fairly stable during 1994-2000 (i.e., 14.2 percent to 14.9 percent, respectively). However, a substantial decrease after 2000 can be observed particularly after the global recession (DiMasi et al., 2016). The key driver related to lower COC is that reduced interest rates diminish alternative foregone investor opportunity costs.

Table 6 – Nominal and Real COC for the Pharmaceutical Industry, 1994 – 2010 (DiMasi et al., 2016)

	1994	2000	2005	2010
NOMINAL COC (%)	14.2	14.9	13.3	11.4
INFLATION RATE (%)	3.1	3.1	2.5	2.0
REAL COC (%)	11.1	11.8	10.8	9.4

Responding to criticisms about the Tufts CSDD publication's total capitalised cost estimate of 802 million, a market watch evaluation (Adams & Brantner, 2006) independently validated these cost estimates. While applying modification to methodology as well as scrutinising various inputs (e.g. accessing an alternative international database called "Pharmaprojects" to obtain pharmaceutical cost calculations), it was possible to increase the evaluation process's transparency. A description of database parameters collected from Adams & Brantner (2006) is listed in Table 7. Although maintenance was initially provided by PJB Publications, the database was acquired by Informa in 2003 where it is maintained and accessed via its business intelligence division called Pharma Intelligence. In contrast to the Tufts CSDD database, which maintained confidential information about companies and products, estimates from the Pharmaprojects database were collected via global public

information sources (e.g. press releases, academic presentations); thus, it allowed others to verify the results. Despite scrutiny of each step of the Tufts CSDD analysis, Adams & Brantner (2006) concluded total capitalized drug development costs (in year 2000 dollars) to be slightly higher than the Tufts CSDD study (~868 million vs. 802 million USD). In fact, their assessment went further to suggest that, depending on the therapy under development, the figure ranged between 500 million USD and more than 2 billion USD. While their study strongly supported the high pharmaceutical R&D estimations provided by the Tufts CSDD, the authors also urged caution when using one generalized figure to represent the cost of drug development.

Table 7 – Summary of Pharmaprojects Database (Adams & Brantner, 2006)

DATABASE	PERIOD	GEOGRAPHY	MAINTENANCE	CONTENT	USD YEAR
PHARMAPROJECTS DATABASE	1989 and 2002	Both foreign and US-owned firms	PJB Publications	Public information (e.g. press releases, academic presentations) – Includes information on 3,181 compounds	2000

Consequently, the highly referenced but ballpark figure of 1 billion USD continued to represent the total costs of developing a new drug. However, in 2014 the Tufts CSDD announced their most recently updated cost estimates (DiMasi, 2014b; Tufts Center for the Study of Drug Development, 2014b; DiMasi et al., 2016). With a sustained focus on conventional diseases, this latest cost estimate reaches a total of nearly 2.6 billion USD in capitalized costs (2.558). Of the 2.6 billion USD, 1.395 billion USD are actual out-of-pocket costs (see Figure 2). The proportion of COC accounted for 45 percent of total costs, whereas, in the Tufts CSDD study from 2003, it was 50 percent. The reduced portion of capitalization is attributed to a shorter pre-human trial period and a lower discount rate (10.5 percent, instead of 11 percent). While the prevailing low interest rates likely contributed to a lower discount rate, the reasons for a shorter pre-human trial remain speculative. One possible influence may be attributed to pharmacogenomics, the study of the influence that genetic factors play in drug response. Some suggest pharmacogenomics may accelerate drug development pipelines

as it identifies new targets for treatment and boosts the success of drug development. From only a few pharmacogenomic products in the US in 2001, an increasing trend led to several dozen by 2011 (Gibson, Raziee, & Lemmens, 2015). By adjusting the USD value of the Tufts CSDD 2003 study estimate of 802 million USD to the same dollar year (2013) so it can be compared with the most recent study, this would equal 1.044 billion USD. Thus, the new figure of roughly 2.6 billion USD represents an increase of 145 percent between the two study periods – or compounded annual growth rate of 8.5 percent (Tufts Center for the Study of Drug Development, 2014b). For this latest study, it notes that the estimated average costs of post-approval R&D studies (e.g. testing new indications, new formulations, new dosage strengths, and monitoring safety and long-term side effects) equals an additional 312 million USD, thus, potentially lifting costs to 2.87 billion USD.

To illustrate the methodology for calculating average out-of-pocket clinical period costs for investigational compounds in the most recent estimate, key factors for each phase (phase I to phase III) are listed in Table 8. First, to calculate expected costs per approved new compound, the mean cost of each individual phase is multiplied by the probability that the NME will be worthy enough to enter the phase, that is: able to successfully complete the previous phase. In this particular example, entering phase I is certain because the base reflects the assumption that all previous pre-human trials have already been successfully completed. The resulting total expected cost of these three phases is 114.2 million USD. Secondly, to portray the costs incurred of including failed NMEs, this total is then divided by the previously indicated overall success rate of 11.83 percent that a NME will be approved; thus, the total for the clinical trial phases equals 965 million USD. By adding 430 million USD for the previously incurred cost of pre-human trials, the aforementioned total of 1.395 billion USD for actual out-of-pocket cost becomes apparent. It should be mentioned that almost 31 percent of the out-of-pocket costs represent those incurred in the preclinical phase (430/1.395). Even though the probability is that NMEs will likely fail to enter later phases, this demonstrates that significant costs arise at the early development stages. In order to derive COC, the mean COC costs of each individual phase are subjected to the same

methodology as demonstrated in Table 8, with their identical probabilities of success serving as the basis for calculation.

Figure 2 – Out-of-Pocket and Capitalized Cost per Approved New Compound (DiMasi, 2014a)

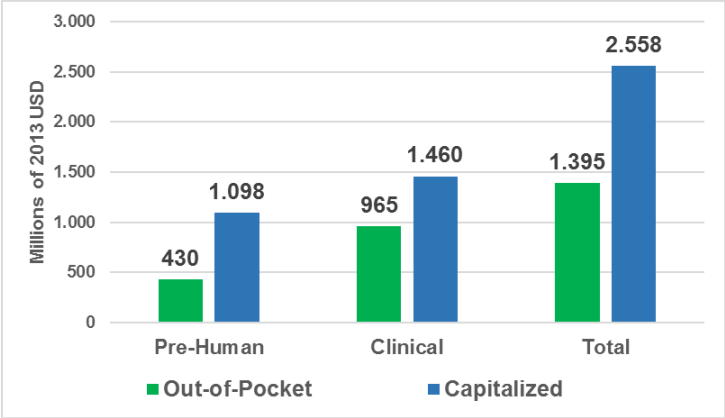


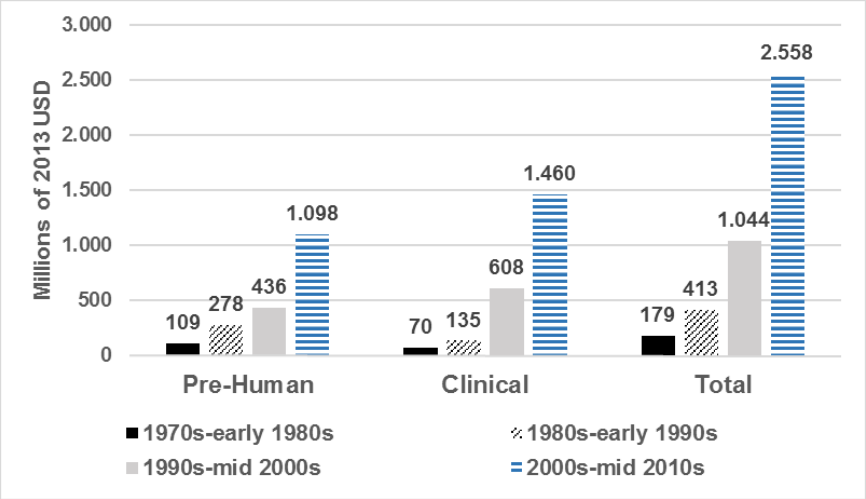
Table 8 – Average Out-of-Pocket Clinical Period Costs for Investigational Compounds – in millions of 2013 dollars (DiMasi, 2014a*;* DiMasi et al., 2016)

TESTING PHASE	MEAN COST	PROBABILITY OF ENTERING PHASE (%)	EXPECTED COSTS
PHASE I	25.3	100	25.3
PHASE II	58.6	59.5	34.9
PHASE III	255.4	21.1	54.0
CLINICAL PHASE TOTAL			114.2
OVERALL SUCCESS RATE:	**11.83%**	*114.2 / 0.1183 =*	**965**

To gain a perspective on the trend of total capitalized cost development over the last decades, Figure 3 depicts the results of diverse past studies. To enable comparison, each original study figure has been adjusted to year 2013 dollars. The particular cost drivers identified for the most recent cost assessment study include costs for increased NME failures, increased clinical trial complexity, larger clinical trial sizes, higher cost

of inputs from the medical sector used for development, greater focus on targeting chronic and degenerative diseases, changes in protocol design to include efforts to gather health technology assessment information, and testing on comparators (i.e., alternative treatments or placebos used as a reference in clinical trials) to accommodate payer demands for comparative effectiveness data (Policy and Medicine, 2014).

Figure 3 – Trends in Capitalized Pre-Human, Clinical and Total Costs per Approved Drug (DiMasi et al., 2016)



1.1.3 Controversy and Debates

Tufts CSDD estimates have generated controversy. Some critics argue that Big Pharma lies about R&D costs to increase profits (Huff, 2011) or they posit there is some sort of conspiracy theory generated by pharmaceutical lobbyists. Others more objectively request specific information and/or criticize the inputs and methodology applied by Big Pharma to portray their R&D costs. For example, Light and Warburton (2011) set out to discredit DiMasi et al. (2003) by inferring that all the co-authors are industry-supported economists; thus, their estimates are intentionally overstated. Although Light and Warburton acknowledged the estimate of 802 million USD to be the most widely cited figure (by government officials and industry trade associations), they argued that

Tufts CSDD has received substantial industry funding. Moreover, they point to the fact that for years the Tufts CSDD has functioned as a repository for pharmaceutical companies to submit selected and closely guarded figures on R&D costs. Consequently, these critics say its sample basis is probably skewed with higher R&D costs, with any related decisions for calculation methods reflecting an inherent bias. In fact, there are those who argue that while industry leaders and lobbyists warn that lower prices would inhibit innovation by reducing R&D spending potential, the opposite is the case. They posit that the current situation rewards companies to develop new medicinal products with little added advantage (the so-called "me too" products). This happens, they claim, because companies are vested to compete for market share by simply raising prices on their "me too" products rather than develop clinically superior medicines with public funding to lower company costs and risks.

A more specific criticism concerns the sampling and data used in the Tufts CSDD hosted study (DiMasi et al., 2003) and the accusation that many key data facts are not indicated in it. For instance, Light and Warburton (2011) state there is lack of transparency on how time was estimated for the COC. Furthermore, they argue that the authors of the Tufts study did not mention any sort of data cleaning to reflect a fair representation of costs. Data cleaning refers to efforts to ensure that costs are correctly allocated and accurately calculated. Hence, it is unknown how companies exactly calculated their R&D costs. Given that situation, one could surmise that R&D costs might include items such as general administrative (G&A) overhead and major equipment, large fees paid to doctors to promote clinical trials as key opinion leaders during premarketing activities, cost of land and buildings not used exclusively for R&D and, finally, large legal expenses – e.g. developing patents and intellectual property (IP) protection. Indeed, because the time and cost of drug discovery is unknown and extremely variable (e.g. three months to 30 years) – with some discoveries (e.g. penicillin) happening by accident – no R&D estimate can rightfully include this in an analysis. More specifically, these authors maintain that drug discovery is often achieved by academic institutes and government laboratories, and not industry. Nonetheless, Tufts CSDD includes 121 million USD at the start of their analysis which

adds 52 months to the average time from a compound's synthesis to initial human testing. When compounded by the COC, this accounts for more than one-third of the 802 million USD estimate. They also criticize several other points of the Tufts CSDD 2003 study such as the omission of taxpayer subsidies or tax reductions/credits specifically tied to R&D expenditures, the addition of capitalization costs and the exaggeration of trial costs, R&D time and risks. Likewise, the use of mean costs (and not average) drive up R&D cost estimates. Finally, they conclude that, based on independent sources and reasonable argumentation, one could have calculated a median R&D cost of 43 million USD per new drug instead of the 802 million USD estimate of 2003.

In direct response to Light and Warburton (2011), Tufts CSDD defended the institute's position in an official statement (Kaitin, 2011) by declaring:

> *"…DiMasi's peer-reviewed article has received worldwide recognition for its scholarship and scope, and its methodology has been critically examined and validated by the U.S. Office of Technology Assessment and others… Light and Warburton restate arguments about the methods and data used for our R&D cost study that they have had published elsewhere…* (DiMasi, Hansen, & Grabowski, 2005a*;* DiMasi, Hansen, & Grabowski, 2005b)...
>
> *…In short, every one of Light and Warbuton's adjustments are invalid. Furthermore, two peer-reviewed papers by current and former FTC [US Federal Trade Commission] economists… validate our work using other methods and public data* (Adams & Brantner, 2006*;* Adams & Brantner, 2010)*…"*

In support of their claim that Light and Warburton (2011) merely make use of erroneous adjustments to simulate lower R&D cost estimates, the Tufts CSDD argued:

> *"They inappropriately mix median values reported for individual drugs with what are mean values for the costs of clinical failures and preclinical fixed costs, and for which the concept of a median has no meaning; they misconstrue the nature of the corporate income tax and incorrectly consider manufacturing tax credits; they use discount rates that are meant for other contexts but that are inappropriate here; they treat line extension approvals as separate and independent units of observation alongside their original approvals; and they grossly misstate the meaning of and misuse figures in our paper on industry-reported data on expenditures on self-originated drugs, licensed-in drugs, and already-approved drugs".*

However, the Tufts CSDD itself was again the target of more criticism after it updated its study estimates of capitalised costs to nearly 2.6 billion USD (DiMasi, 2014b; Tufts Center for the Study of Drug Development, 2014b). In this case, the Union for Affordable Cancer Treatment (UACT) raised several probing questions in a public letter (Gray et al., 2015). For example, UACT questioned whether drug companies provided funding for Tufts CSDD research, whether orphan drug tax credits (up to 50 percent of the clinical trials) are ignored, and whether acquired public funding of research lowers private cost estimates. The Tufts CSDD responded in a statement (DiMasi, 2015) where DiMasi denied that neither he, Tufts CSDD nor co-authors who are at different universities receive any outside funding earmarked for study or related publication activities. DiMasi also asserted that Tufts CSDD publicly discloses its finances, which clearly state that, as a non-profit, they receive unrestricted grants from pharmaceutical, biotechnology and other companies, which represent approximately 40 percent of their operating expenses (Tufts Center for the Study of Drug Development, 2016). Concerning questions related to the inclusion of orphan drug tax credits, DiMasi said the Tufts CSDD study openly states that R&D estimates are pre-tax. This is because their objective is to measure investment by private developers, regardless of who ultimately pays. DiMasi adds that the inclusion of tax credits would distort the picture when comparing cost estimates over time because tax structures change. Furthermore, while orphan drug tax credits may be important for particular drugs, they

represent only a small share of U.S. aggregate R&D spending by its domestic biopharmaceutical industry: thus, it not empirically relevant. Measuring total payments (not broken down by the actual payer) can provide a more stable comparison in an environment where structures vary across time and geography. This comparison basis can allow better interpretation of unresolved debates, especially given the estimation and reporting of drug R&D costs can have significant influence on major issues across industry such as drug prices, regulatory policy and barriers to generics (Adams & Brantner, 2006). Inevitably, when one single estimate of total capitalised cost is widely applied internationally as a benchmark (e.g. ~2.6 billion USD in 2014, 802 million USD in 2003), this could be perceived as an attempt to leverage industry interests. Given that notion, it is plausible that distinctions between countries and their R&D funding initiatives such as reduction of direct public (ex-ante) and increase of (ex-post) financial support via tax credits are difficult to accurately reflect and counterbalance.

On the issue of whether acquired public funding of research lowers private cost estimates, DiMasi argues that their estimates measure only what private developers actually spend on development. In this vein, if private developers absorb useful public-funded research, then the resulting lower cost would be reflected in their estimates. Along the same lines, Avorn (2015) raises many of the same issues addressed in previous criticisms. Simultaneously, within the same issue of the review, DiMasi, Grabowski, & Hansen (2015) took the opportunity to make the additional point concerning the offering of lower cost corporate bonds as an alternative to raising R&D funding. Directed toward the use of high capitalisation costs that make up roughly 50 percent of the total estimated R&D costs, they avowed that pharmaceutical companies are heavily reliant on equity-finance. Asserting that investors would not fund R&D activities at lower rates, they posit that the discount rate used in their study reflects the rate actually incurred on average during the relevant time periods.

1.2 CBRN MedCMs – R&D Comparisons

Even though a vast study of the R&D process and associated costs has evolved to signify a standard paradigm for conventional diseases, it should be noted that only a handful of scholars from Tufts CSDD have contributed to this. Whether developing drugs that target widespread conventional diseases or rare but dangerous ones such as those caused by CBRN agents, the R&D process and cost effort linked to the achievement of a medicinal product bear some similarities (e.g. lengthy and risky process), but many differences are also posed. For example, conventional diseases are often targeted by both biopharmaceutical and pharmaceuticals products whereas diseases caused by rare biological agents are more often targeted by biopharmaceutical medicinal products. Other R&D differences with CBRN MedCMs include factors such as frequent dependence on animal data, government funding and a high level of laboratory safety requirements. Since this could potentially impact the nature of the R&D process and its corresponding costs, the following section explores the R&D process and cost characteristics which are more specific and unique to CBRN MedCMs.

1.2.1 R&D Costs of Small vs. Large Molecules

To begin drawing parallels for R&D effort and cost analysis between conventional drugs and CBRN MedCMs (particularly for those against biological agents), one should first determine if there are significant cost differences between small and large molecules (pharmaceutical vs. biopharmaceutical). This can be approached by depicting results from yet another Tufts CSDD study (DiMasi & Grabowski, 2007). To conduct this study, US company data was pooled from two sources: one was a group of 17 main biotechnology compounds – recombinant proteins and monoclonal antibodies (mAbs) – and the other was a Tufts CSDD commercial database of biopharmaceutical compounds during 1990-2003. By using growth rates to reflect inflation over a five-year period, database figures from the DiMasi et al. (2003) pharmaceutical study (in year 2000 dollars) could be adjusted to match the biopharmaceutical study (in year 2005 dollars). Hence, a comparison between pharmaceutical and biotechnology drugs could be achieved. Although there are

potentially mitigating factors when interpreting the results (e.g. limited number of biopharmaceutical molecules available with out-of-pocket expenses, varying therapeutic classes compared and uncertainty concerning real growth rates), DiMasi & Grabowski (2007) concluded that out-of-pocket expenses for biopharmaceuticals was somewhat lower than for pharmaceuticals (559 million USD vs 672 million USD). The difference is likely attributable to the higher probability that a biotechnology candidate will successfully reach marketing approval (30.2 percent as opposed to 21.5 percent for pharmaceutical candidates at the time of study). Nonetheless, the total estimated capitalised costs for either was nearly the same: 1,241 million USD for biopharmaceuticals vs. 1,318 million USD for pharmaceuticals. The proportionately higher capitalised cost in this study for the former is due to longer development times required for approval (DiMasi & Grabowski, 2007). One potential reason that development could take longer for the biotechnological sector is that its products often include vaccines. And since these are usually administered to healthy individuals, they face higher regulatory scrutiny and litigation risks (Matheny, Mair, Mulcahy, & Smith, 2007). Although DiMasi & Grabowski (2007) suggest that the approval rates for biotechnological products were higher than pharmaceuticals, it is noteworthy that Matheny et al. (2007) cite vaccine studies which indicate that the probabilities of success at each stage are lower than for many other pharmaceuticals (Struck, 1996; Kaitin, 2006). A possible explanation for this discrepancy may be found in a Dutch study that refers to various sources regarding each phase of vaccine development during 1998-2009 (Pronker, Weenen, Commandeur, Claassen, & Osterhaus, 2013). These sources embraced the Medtrack commercial database (comparable to the earlier-mentioned Pharmaprojects), including 902 vaccine candidates in any stage of development. When separating the candidates into acute or chronic indications and therapeutic or prophylactic applications, significant variations were observed for transition time and success probability from one phase to another. While supporting the notion that vaccine development time is significantly shorter than for small molecules, the study confirms that one vaccine profile cannot generally represent productivity across the board. The factors influencing vaccine development include incremental innovation vs. known correlates of protection. Subject to further research,

the question arises whether manufacturer size and experience impact the vaccine risk profile (Pronker et al., 2013).

1.2.2 Specific R&D Features for CBRN MedCMs

Because R&D initiatives to achieve new CBRN MedCMs are the most extensive and, at the same time, the most transparent in the US, this section considers further distinctions between CBRN and standard medical R&D from a US perspective. Given the lack of relevant studies, observations have been provided by US CBRN regulatory experts.[1] Following independent interviews, R&D characteristics that deviate from the standard paradigm were identified. Regarding R&D for MedCMs against rare but highly dangerous CBRN agents, at least four main factors contribute to making the R&D process more difficult. These are highlighted in Table 9.

First, there is a significant lack of test persons with the relevant disease, even more so than in the case of many orphan diseases. For instance, per definition of the EMA (European Medicines Agency), criteria that determine orphan disease status include a life-threatening or chronic debilitating condition for which prevalence of the condition in the EU is five or fewer persons per 10,000 (European Medicines Agency, 2016). However, for diseases caused by some CBRN agents, there are currently no patients (e.g. smallpox since it was declared eradicated). Because patients exposed to rare and highly dangerous CBRN agents are often not available to test a MedCM's efficacy, animal studies designed and proven relevant to humans must be established. Such studies are highly complex, time consuming and costly.

A second hindrance to R&D comes from the disadvantages associated with financial dependency on government funding, especially in terms of delays, flexibility and easiness in the use of funds. Such funding is often not available when needed (e.g. difficulty to estimate when the next study phase will begin). In addition, transitions from one government agency to another are not always smooth. Lack of budget can

[1] Acknowledgement to Johnson, V. G. (2015, Oct 21). President at Regulatory Science, LLC and Tong, X. (2015, Oct 22). Sr. Regulatory & Quality Affairs Consultant at Smart Consulting Group, LLC for providing their comments

disrupt studies, causing delays that can derail the stability of small companies and even lead to layoffs.

A third hindrance of R&D for MedCMs against CBRN agents is found in the required laboratory conditions that are often difficult to meet. For biological agents, biological safety level (BSL) rules for biocontainment precautions must be taken to isolate dangerous agents in an enclosed laboratory facility. The levels of containment range from the lowest biosafety level 1 (BSL-1) to the highest at level 4 (BSL-4). Given that many MedCMs target highly dangerous biological agents, access to BSL-3 & 4 labs is essential. However, gaining access to these laboratories can be difficult, resulting in long waiting times and significant costs. Moreover, defence laboratories and their workforces are limited in number. In the study of MedCMs against chemical warfare agents (CWAs), access to dangerous chemicals is limited by the Chemical Weapons Convention (CWC), meaning that academic laboratories must work most of the time just on simulants (surrogate agents). The evaluation of MedCMs against radionuclide contamination or irradiation also requires specific equipment and laboratories.

Finally, the fourth hindrance is the exigencies of unique product characteristics. That is, given the required availability of CBRN MedCMs (e.g. stockpiling in the absence of an emergency vs. high demand in a catastrophic emergency situation), extra robustness is often required (e.g. use without a cold chain, extended shelf-life, reduced dosages, self-application ability such as a patch).

Table 9 – R&D Hindrances for CBRN MedCMs

R&D HINDRANCE	DESCRIPTION
SIGNIFICANT LACK OF TEST PERSONS	Even more so than in the case of many orphan diseases
DISADVANTAGES WITH FINANCIAL DEPENDENCY ON GOVERNMENT FUNDING	In terms of delays, flexibility and easiness in the use of funds
DIFFICULT LABORATORY REQUIREMENTS	i.e. for biological agents, rules for biocontainment precautions must be taken to isolate dangerous agents in an enclosed laboratory facility
UNIQUE PRODUCT CHARACTERISTICS	Extra robustness is often required (e.g. use without a cold chain, extended shelf-life, self-application ability such as a patch).

In contrast to the distinctions that hinder R&D efforts for CBRN MedCMs, there are also those aspects that favour it. This may potentially work to counterbalance at least

partly any extra costs which may result due to hindrances. For instance, according to regulatory experts as previously acknowledged at the beginning of this section, at least three factors help lower barriers to R&D for CBRN MedCMs.

First, while CBRN MedCMs must endure the challenges of designing and proving that their animal models are relevant to humans, companies may not be required to size up to the large (and often global) patient study demands as required for conventional drugs. In contrast, phase III studies for conventional diseases can be very large and extensive, requiring anywhere from 1,000 to 5,000 patients to generate statistically significant data on safety and efficacy (Pharmaceutical Research and Manufacturers of America, 2007).

Second, because R&D for CBRN MedCMs tends to be mainly funded by government and not by private investors, the high costs of capitalisation are averted for the company. This reduces the overall R&D costs by roughly half (DiMasi et al., 2003; Adams & Brantner, 2006) when compared to costs for conventional drugs which require investor lending.

Finally, when developing drugs that protect against conventional diseases, there is often high market competition due to multiple drug choices. Additional studies must often be conducted to target product diversification/advantages and unique selling points. Furthermore, commercial drug candidates can be dropped (and considered a "failure") not for reasons of efficacy and safety but because they lack competitiveness or the ability to secure a premium market price. This is less the case with CBRN MedCM candidates because there are generally few MedCMs for a particular disease (or even none at all).

With the exception of COC, the potential quantitative downside and upside cost impact of these factors is not explored within the scope of this section. Taking into account both the negative and positive features of R&D; however, an equilibrium towards the standard paradigm for conventional drug costs is indicated by comparing out-of-pocket expense estimates. For example, based on many years of experience at the US Department of Defense (DoD), the estimated costs to achieve one successful CBRN

MedCM candidate are roughly 850 million USD[2], depending on the type of drug. Congruent with the standard paradigm for conventional drugs, this estimate represents not only total out-of-pocket costs to achieve NME approval but also expenses incurred for other drug candidates that were weaker or failed to reach approval. However, it should be noted that the US DoD figure may be lower than other estimates due to the fact that, for most MedCMs which protect against CBRN agents, US DoD studies target only a healthy population (18-60 years of age) and thus exclude paediatrics and geriatrics. Indeed, once gaining evaluation from the US HHS which is responsible for protecting the civilian population against CBRN agents (including healthy populations, geriatrics and paediatrics), representatives of the US HHS state that out-of-pocket expenses range from 1.2 to 1.5 billion USD (Robinson, 2015). This would appear to validate the lower US DoD cost estimates. However, another factor contributing to higher US HHS cost estimates could be its own R&D cooperation with industry. By contrast, the US DoD tends to have much of its own governmental R&D infrastructure and scientific capacity, which probably influence the related costs.

The US HHS depiction of this expensive, lengthy and risky R&D process is presented in Figure 4. Phase descriptions for vaccines which are often the type of MedCM required against biological agents is very briefly summarised in Table 10. It should be noted that, particularly in the US, early stage development is often funded via the NIH while advanced research development is funded via the BARDA program. For this reason, COC does not need to be considered for government funded R&D. While US DoD and US HHS out-of-pocket cost estimates ranging from 850 million to 1.5 billion USD already emphasis the intense investment required to establish new and innovative CBRN MedCMs, another analysis goes even further. Namely, the US HHS considered it a top priority to successfully develop eight different biodefense MedCMs by 2015. Yet, there remained a high probability that any one of these individual NMEs could fail. To increase the chances of success to 90 percent for each targeted MedCM, its analysis proposed that additional MedCM candidates were needed to enhance the

[2] Acknowledgment to Reeves, S. V. (2015, Oct 20). Major General, US (Ret) for providing estimate and comment

development pipeline. Hence, an average of 1.75 million USD per approved drug would have been required (Matheny, Mair, & Smith, 2008). This suggests that dependence on a high probability of success of at least one candidate can have a direct and significant impact on the overall cost of obtaining a new CBRN MedCM. So, an additional parameter demanding consideration when communicating the cost of developing CBRN MedCMs is how important the success might be. For example, if a rare CBRN agent for which there were no MedCM unexpectedly became widespread and highly deadly, one might expect R&D costs to be significantly higher because at least a 90 percent probability of success would likely be the policy choice.

Figure 4 – R&D Process and Costs for CBRN MedCMs (Robinson, 2015)

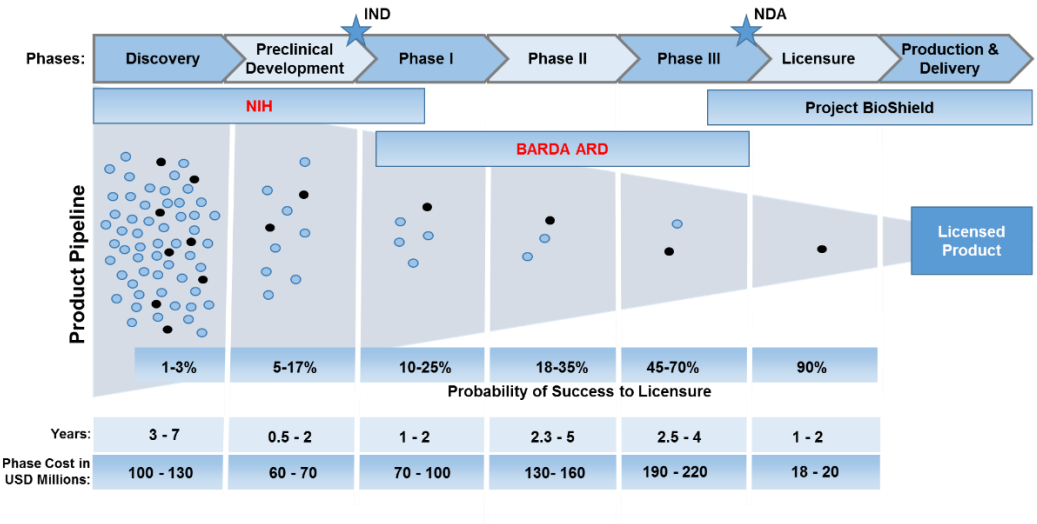


Table 10 – Trial Phases for Vaccines (World Health Organization, 2015a)

TRIAL PHASE	DESCRIPTION
PRE-CLINICAL TRIALS	Carried out in laboratories and animals and aim to: 1) determine whether a vaccine works as intended and 2) to identify any harmful effects.
PHASE I TRIALS	Involve 20 to a few hundred healthy individuals and examine safety and immune response. They also identify commonly-occurring adverse reactions.
PHASE II TRIALS	Involve several hundred to a few thousand people and determine the optimum vaccine composition for achieving protection while ensuring safety.
PHASE III TRIALS	Involve thousands to tens of thousands of people and examine the vaccine's ability to prevent a disease as intended. They also provide further safety information.
POST-LICENSURE MONITORING	Also known as formal Phase IV trials involve the target population. These surveillance activities identify, through spontaneous reporting systems to health authorities, less common adverse events, events which could occur after a long time, or events that may occur in specific subgroups of the target population.

When comparing the Tufts CSDD's latest average out-of-pocket estimates of 1.395 billion USD (DiMasi et al., 2016) for conventional pharmaceutical/biotechnology drugs against the estimates provided by the US DoD and US HHS for CBRN MedCMs, one sees significant similarity: US DoD 850 million USD vs. US HHS 1.2 to 1.5 billion USD. Moreover, upon calculating the US HHS' range of years to complete the R&D process (10.3 to 22 years), the time range of 10 to 15 years (DiMasi et al., 2003) as projected by the standard paradigm for drugs that target conventional diseases is well framed. Hence, the overall R&D out-of-pocket cost estimates for CBRN MedCMs vs. drugs against conventional diseases are considered highly similar for the purposes of this section. However, it is important to note that the real cost of financing includes an external finance premium related to: the financial condition of firms, the financial risk associated with the project and the problems of related information, particularly information asymmetries due to moral hazard and adverse selection effects. It is well established (Hall, 2002) that this premium is important for R&D projects and leads to significant financial constraints and their negative impact on R&D investment. In the case of CBRN MedCMs, this premium is certainly amplified because of the uncertainty of return and the importance of information asymmetries. Financial constraints are especially severe in this case where firms are consequently dependent on internal finance and public support to finance this kind of project. This is often the case when

there is a small number of buyers associated with high risk and technological content, particularly for defence R&D (Belin & Guille, 2008).

1.3 Conclusion

Due to an array of factors linked to a drug's approval, the R&D process can be lengthy, risky and expensive. Whether promoting drugs that target conventional diseases or MedCMs against rare CBRN agents, out-of-pocket expenses can reach 1.5 billion USD. While some differences in the R&D process for CBRN MedCMs could be identified, it appears that overall costs associated with the R&D process for both conventional diseases and CBRN MedCMs are similar. Consequently, a range for out-of-pocket costs of both disease groups could possibly be generalised as being at equilibrium. Yet, given that the sample size and integrity of the study basis for each group is dissimilar (i.e. estimates for CBRN MedCMs could be provided by representatives from 2 US government departments – BARDA, the military – and not via formal study which is lacking and is required in the future), this equilibrium can only be concluded with caution. One factor in support of their likeness may stem from the simple fact that to derive costs for conventional drugs, a mean cost value is being applied from a more representative data population. This mean cost value is calculated from a broad and diverse range of drug types (i.e. small and large molecule), and each one of the individual drugs represents varying clinical trial complexities. As this condition is most likely also presented for ballpark estimates associated with CBRN MedCMs, cost values of both groups would reflect an analogous mean trend. If so, significant variance is unlikely, unless more specific subgroups (e.g. drug types vs. trial complexities) within each group can be defined and studied separately.

If R&D funding is to be provided by private investors, COC must be added to out-of-pocket expenses; thus, total overall capitalised costs for drugs that target commercial diseases can reach nearly 3 billion USD. Nonetheless, should R&D funding for rare CBRN MedCMs be provided by investors, one may expect higher COC due to the additional risk posed by low market opportunity. It is possible that the controversy

associated with R&D cost estimates could be reduced if a clear and unified understanding of cost definition was agreed upon. For example, to ensure a congruent debate, figures should refer to commonly defined and distinct terms – e.g. out-of-pocket expenses, including failed candidates and COC. Indeed, a plausible basis for misinterpretation is that while some cost sceptics may have knowledge of the cost expenditures of trials for an approved product, the business feasibility of the approved product can only be obtained if the sunken costs of previously failed candidates are recouped. Likewise, a more comprehensive awareness of cost-intensive R&D prerequisites such as manufacturing capability for upscaling production and COC may help avert controversy.

Because developers and manufacturers can be ambiguous when communicating their specific costs and definitions, this can lead to distrust and conspiracy theories. At the same time, however, full disclosure of internal proprietary information could potentially compromise the security of a company's IP in the marketplace. Moreover, increased transparency could subject them to further scrutiny concerning their profitability expectations. Although the Tufts CSDD study basis has been subjected to various criticisms and debate, its integrity has prevailed and remains the most prominent gold standard reference for industry and politicians alike. In fact, it cannot be ruled out that it has had some influence on the cost estimate expectations of the US DoD and the US HHS regarding their cost planning for CBRN MedCM programs. Nonetheless, given the US's vast R&D learning curve, which accelerated in 2004 when the increased threat of CBRN agents was perceived and legislation for BARDA was signed, it is assumed that a reality check for the accuracy of these figures has taken place. Hence, a high correlation between estimated out-of-pocket expenditure between Tufts CSDD vs. US government CBRN MedCM programme remains. Given the need for governments to cooperate with industry to create funding mechanisms that encourage the discovery and successful approval of CBRN MedCMs that lack free market feasibility, a mutual understanding of cost and effort associated with drug development could be highly conducive to building more trustful partnerships.

Chapter 2 SUPPLY-SIDE DETERRENTS RELATED TO MEDCMS

The aim of this chapter is to describe the market failure surrounding CBRN MedCMs and to recognize the key economic levers that motivate mainstream industry and influence its business models. To portray the root causes of market failure, Section 2.1 strives to contrast the market rewards and characteristics offered for those drugs that target conventional diseases versus those that protect against CBRN agents. Despite industry's clustering around the higher market rewards associated with mainstream conventional diseases, Section 2.2 describes the emerging market challenges that threaten the sustainability of even classical business models. Hence, an evolving "financialised" business model aimed at securing company revenue growth threatens to widen the gap for achieving the international availability of CBRN MedCMs.

2.1 Market Rewards and Characteristics

It is paramount to consider the objectives which may financially justify the development and marketing of CBRN MedCMs. In a free market environment, the entrepreneurial rationale for private investment would certainly include the concept of "sensible" risk-taking regarding the goal of reaping market rewards that are compatible with a company's objectives. Hence, a prerequisite for increasing the chances of meeting company/investor expectations would be to consider a marketing plan. This is traditionally based on a "marketing mix" consisting of answers to a series of product- and customer-related questions (Stanford University, 2010). A basic example would include assuring that the targeted market and its characteristics can support at least a minimum threshold of market rewards. Despite high similarity between the R&D costs and efforts of developing drugs targeted to conventional diseases and those which target rare CBRN agents, the market opportunities presented for each vary considerably. To put the opportunities of both disease categories into proper perspective, this section first briefly describes the market rewards and characteristics

surrounding conventional diseases and then compares those with the prospects associated with diseases caused by rare CBRN agents.

2.1.1 Conventional Diseases

Global annual spending on conventional medicines is expected to reach 1.4 trillion USD by 2020, an increase from 1,069 trillion USD in 2015 of approximately 32 percent. Predicted spending by geography and disease area are illustrated in Figure 5 and Figure 6 (Aitken, 2015). Roughly 40 percent of sales forecasted for 2016 were expected to be achieved by the top 10 companies, ranging from Pfizer/Allergan at 70.4 billion USD to AstraZeneca at 22.7 billion USD (Urquhart, Gardner, & December, 2016). Focusing only on large molecule biopharmaceuticals (i.e., excluding small molecule pharmaceuticals), global sales were estimated to be 289 billion USD in 2014 and are projected to grow to 445 billion USD by 2019 (Deloitte, 2016). Nearly 70 billion USD of the 2014 net biotechnology sales were achieved by the top 10 biotechnology companies (BioSpace, 2015). This ranking is headed by Gilead Sciences at 20.7 billion USD, with Agilent coming in at the bottom of the list with 7 billion USD. Looking specifically at the biotechnology sectors of Europe and the US, 670 public companies generated sales of 132.7 billion USD in 2015 (Ernst & Young, 2016), or an average of almost 200 million USD in annual sales per company.

Figure 5 – Medicine Spending in 2020 by Geography in percent (Aitken, 2015)

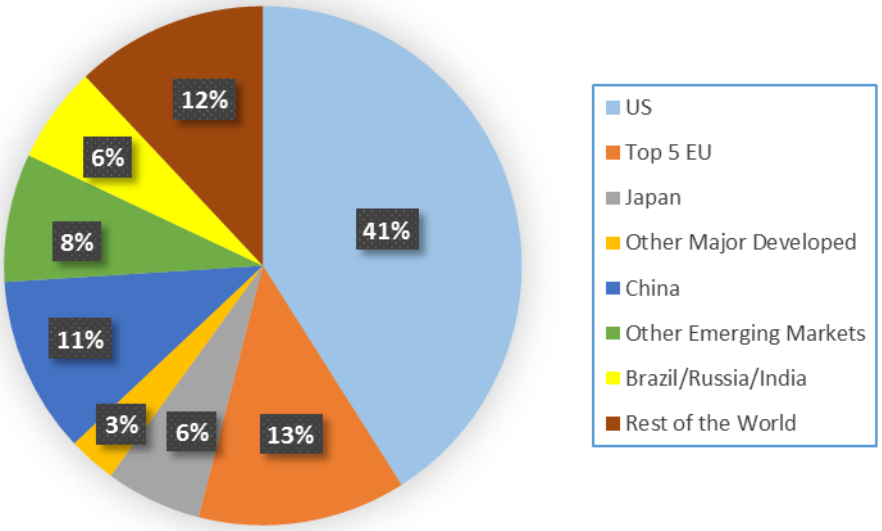
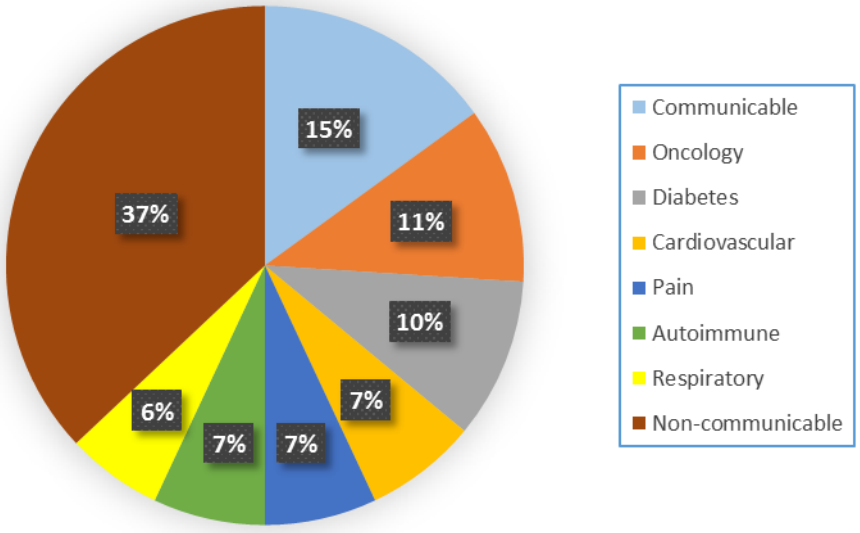


Figure 6 – Medicine Spending in 2020 by Disease Area in percent (Aitken, 2015)



The biggest selling biotechnology product, Humira®, is indicated for rheumatoid arthritis which reached global revenues of nearly 16 billion USD in the year of 2016 alone (Urquhart et al., 2016). Overall, the high market value of conventional diseases is predominantly driven by substantial and widespread prevalence rates (e.g. number

of sufferers) of conventional diseases. For example, the prevalence rate for chronic rheumatic conditions varies between 0.3 and 1 percent of the population (World Health Organization, 2016a). Since the global population is estimated at over 7 billion people, this would represent a total of roughly 21 to 70 million potential sufferers of the disease. Global demand is influenced by factors that include increases of population over the age of 65 and emerging market growth (e.g. improved access to healthcare). Future growth rates are affected by influences such as sustained global economic recovery or political stability – e.g. events surrounding the Russian/Ukrainian crisis, Africa, and Middle East (IMS Institute for Healthcare Informatics, 2014). While actual predicted growth rates are subject to variation, the shear mass of sales potential is well-anchored. Consequently, prior to launching any R&D investment efforts to address these diseases, analysis of historic market characteristics can support developer and manufacturer confidence in business feasibility. Examples of basic market characteristics are briefly described in Table 11.

Table 11 – Basic Market Characteristics for Conventional Drugs

BASIC MARKET ATTRIBUTE	EXAMPLE
NUMBER OF SUFFERERS	Given that prevalence data for most key therapy areas are well studied (e.g. percent of population affected is often known), a dependable and stable number of sufferers can be reliably estimated. Thus, potential customers via their relevant physicians can be targeted.
MARKET SALES POTENTIAL	There are abundant sources (e.g. IMS Health) which monitor and document global market sales as well as historic market research information. Such sources on a regional geographic basis are available to manufacturers and allow them to understand sales potential volumes for individual disease areas. Given sales data in both value and quantity (as well as access to various price listing databases), price structures are also apparent. In accordance, once a manufacturer evaluates its realistic quantity market share at its desired price for its drug, sales revenue can be forecasted.
PRODUCT DEFINITION	While disease prevalence is likely to directly correlate with market demand for drugs that target the corresponding therapy area, a large customer base (e.g. sufferers, physicians, sick fund payers) can provide information on its preferred product features. In addition, analysis of competitor products can indicate to developers and manufacturers which product features could be diversified for achieving the most advantageous price and market share.
PAYER AND PAYMENT STRUCTURES	Global manufacturers often build internal knowledge surrounding payers of medicine (e.g. sick funds). For innovative medicine, the aim is to justify payment/reimbursement of their product's prices by also presenting its economic value added (e.g. reduction of hospital costs).
RISK MITIGATION	Globally, each individual country often presents its own unique market challenges. Nonetheless, the fact that numerous countries can be simultaneously targeted offers a diverse and widespread customer base. Namely, while some countries may perform lower than expected, some may perform higher.

2.1.2 Rare CBRN Agents

The CBRN MedCM initiatives of the US are the most extensive (Matheny et al., 2007) and the most transparent. Hence, it is also appropriate for the scope of this section to refer to US market data exclusively to evaluate sales potential. Procurement opportunities are presented by a handful of other countries, but their market demand remains ambiguous, spontaneous and far less substantial. Indeed, prompted by the "Amerithrax" anthrax letter attacks, the US government soon recognized that government itself would be required to initiate funding mechanisms capable of encouraging biotechnology developers and manufacturers to develop new MedCMs which protect against CBRN agents. Consequently, President George W. Bush proposed Project BioShield in his 2003 State of the Union address and signed the Act

into law in 2004. While this initiative underscored the US government's recognition of industry's role in developing and manufacturing CBRN MedCMs, it went further by attempting to target the components required to incentivize that industrial engagement. For instance, one advantage of making advanced purchase commitment – by specifying price and number of doses to be purchased contingent upon successful medicinal development – is that it reduces risk for developers which prefer more favourable market conditions (Mossialos et al., 2010). Nonetheless, due to the availability of only a few MedCMs for procurement, it quickly became apparent that Project BioShield was failing to sufficiently entice industry.

Three key reasons contributed to the lack of industry engagement at the time (Gronvall, 2008). First, the scope of BioShield left a gap in the area of advanced stage development. While there were alternative opportunities for early development funding (e.g. grants from NIH or Small Business Innovation Research), developers remained highly exposed to financial and developmental risk until a new MedCM could qualify for stockpile procurement under the BioShield programme. To qualify, the MedCM had to be either licensed or likely to be licensed within eight years. The gap between early development and late stage is referred to as the "Valley of Death" and represents a significant disincentive for industry to develop MedCMs. This leads to the BioShield programme's second shortcoming: it was not able to attract significant attention from large and more experienced pharmaceutical and biopharmaceutical companies. The Pharmaceutical Research and Manufacturers of America (PhRMA) represents leading US biopharmaceutical researchers and biotechnology companies and advocates public policies to encourage the discovery of new medicines for patients (Pharmaceutical Research and Manufacturers of America, 2016). Although PhRMA expressed their hopes that BioShield's budgets would be able to create a market sales volume comparable to that for drugs targeting conventional diseases, its total spending of 5.6 billion USD over a 10-year period fell far short of this.

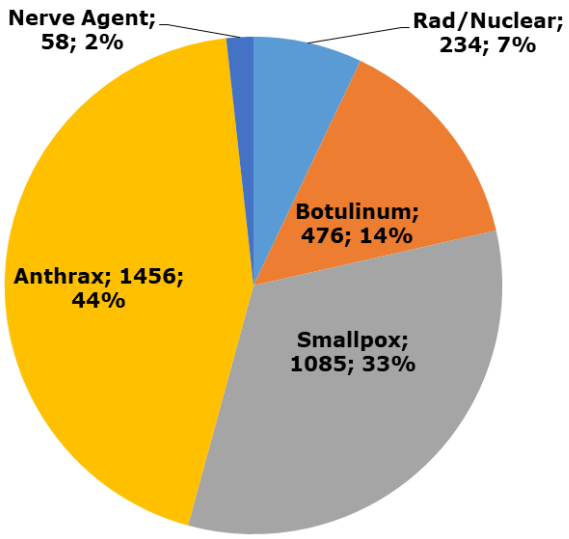
The programme's third weakness was the uncertainty and exposed risk surrounding the achievement of its contracts. Not only were developers subjected to the usual high

probability that MedCM candidates might technically fail during the R&D process, but there were also no guarantees their candidates would be purchased by BioShield, even if they succeeded. This procurement uncertainty derived from unclear product definitions and delayed contracts (Gronvall, 2008). To eliminate some of these inadequacies (e.g. by increasing support for late-stage R&D), the US Pandemic and All-Hazards Preparedness Act was signed in 2006. This initiative was intended to reduce risk for developers by narrowing the gap created by the "Valley of Death". New departments within the US HHS such as BARDA and the National Biodefence Science Board – since renamed as the National Preparedness and Response Science Board – were established. Aiming to spur development of MedCMs that protects against rare CBRN threats, BARDA's role was to boost cooperation between the US government, biotechnology developers and academic researchers. This could be achieved, for example, by awarding contracts, prizes and other early stage activities (Gronvall, 2008).

Despite these early stage initiatives and adjustments to improve BioShield's effectiveness, market sales potential for CBRN MedCMs could not be increased. In fact, of the 5.6 billion USD appropriated for BioShield for fiscal years 2004 to 2013, only 3.3 billion USD (roughly an average of 330 million USD annually) were dedicated specifically for the purchase of CBRN MedCMs (Gottron, 2014). Figure 7 summarises the total acquisition by threat area (in USD and percentage) during the whole fiscal year period 2004 to 2014 while in Table 12 the overall procurement activity by product that was enabled by these funds is listed. Although these funds – averaging 275 million USD for each of but 12 manufacturers over a decade – appear noteworthy, this represents only an average of 27.5 million per year per company. When contrasting this to the average annual sales of nearly 200 million USD for biotechnology companies in Europe and the US for conventional drugs (illustrated in the previous section), one immediately sees that a mere 14 percent of this average can be achieved. In addition to drastically lower sales potential, these market niche players are exposed to high market volatility. Only one customer – the US government – remains the foremost provider of spending budgets, while there can be no certainty how CBRN threat will be perceived

by future political leaders. Thus, the reliability associated with long-term financial planning is feeble. Moreover, this current spending basis can only provide some incentive so long as the number of suppliers remains low. Should too many manufacturers compete for market share with their comparable and efficacious CBRN MedCMs within the same therapy area, there would be an imminent erosion of financial incentive. Whilst the US plans to continue its stimulation package and to strengthen its approach (e.g. product portfolio, regulatory science, flexible manufacturing, new technologies), most other countries are maintaining their passive stance. Despite high-level political claims from GHSI for concerted global action to strengthen the public health response to the threat of international CBRN terrorism, comparable little market demand for CBRN MedCMs outside the US can be perceived.

Figure 7 – BioShield MedCM Acquisitions by Threat Fiscal Year 2004 – 2014 (Gottron, 2014)



(USD millions and percent of spending)

Table 12 – Project BioShield Procurement Activity (Gottron, 2014)

THREAT	PRODUCT	DOSES (thousands)	COST (USD millions)	COMPANY	AWARD DATE
ANTHRAX	rPA vaccine	0	2	VaxGen	11/2004
	AVA vaccine	28,750	700	Emergent BioSolutions	5/2005, 5/2006, 9/2007, 4/2012
	Raxibacumab®	125	530	GSK	6/2006, 7/2009, 9/2013
	Anthrax Immunoglobulin	20	224	Cangene Corp.	7/2006, 4/2012, 9/2013
SMALLPOX	MVA vaccine	24,000	652	Bavarian Nordic	6/2007, 4/2012, 9/2012, 4/2013
	Arestvyr®	1,700	433	SIGA Technologies	5/2011
BOTULINUM TOXIN	Botulinum Antitoxin	200	476	Cangene Corp.	6/2006, 6/2011
RADIOLOGICAL/ NUCLEAR	Potassium Iodine	4,800	18	Fleming Pharmaceuticals	3/2005, 2/2006
	Calcium/Zinc DTPA	474	22	Akorn	2/2006
	Neupogen®	541	157	Amgen US	9/2013
	Leukine®	67	37	Sanofi US	9/2013
NERVE AGENT	Midazolam	776	58	Pfizer	9/2013
TOTAL			**3,309**		

The reasons for non-US complacency could include satisfaction with existing products, differing threat and risk perceptions, and prioritisation of other more acute health needs. However, it is also plausible that most countries are merely depending on the efforts of the few that are actively developing MedCMs. Even if other countries perceive the threat of intentional or unintentional exposure to CBRN agents, they can choose a wait-and-see or free-rider behaviour, meaning they expect to use a MedCM developed by others. If free rider behaviour is the case, tapping the resources of other countries may not prove to be a very viable strategy. For example, during the "Amerithrax" letter attacks, many countries attempted to purchase the US-manufactured anthrax vaccine in response to a perceived threat in their own countries. However, foreign access to the FDA-approved anthrax vaccine was not possible for at least two reasons: the US government required full manufacturing capacity for its own stockpile and export was restricted in the name of US strategic national interest.

The low-probability, high-risk characteristics of CBRN threats make structuring any viable development and manufacturing base – for a sufficient availability of MedCMs during emergency demand – very difficult. The level of complexity increases especially for MedCMs that are rarely needed in a natural environment without the threat of intentional release. For example, WHO's success in its global smallpox eradication campaign pushed the disease back to the Horn of Africa and then to a single, natural case that occurred in Somalia in 1977 (World Health Organization, 2010). Likewise, when considering other top bioterrorism threats such as anthrax, botulism and plague, the prevalence of natural disease hardly justifies significant government investment to develop modern MedCMs. Correspondingly, many such MedCMs will only be developed, licensed, manufactured and made readily available when governments define a policy that reflects a threat perception level worthy of justifying the costs associated with such defence preparedness measures. To stimulate industry activity toward their development and manufacturing, there must be clarity about which threats governments perceive, which relevant MedCMs they want to include in their stockpiles, and clarity about the associated market characteristics (e.g. predictability, size). Furthermore, it should be decided in the early stages of product development process which products will be stockpiled (e.g. prophylactic vs. post-exposure, mode of administration, shelf-life, conservation, packaging aspects, multilingual labelling and formulation requirements). Similarly, it is essential that agencies responsible for preparedness have an adequate understanding of the difficulties, timelines, and expenses associated with developing products for which they may someday have the ability and willingness to pay (WTP).

Although BioShield's Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 authorised up to 2.8 billion USD for fiscal years 2014-2018 (U.S. Department of Health and Human Services, 2014a) – an average of 560 million per year – the overall global market for CBRN MedCMs continues to represent inferior market potential, with few customers compared to pharmaceutical/biotechnology markets for conventional diseases. The key points concerning the basic market attributes for CBRN MedCMs are summarised in Table 13. A business environment that offers a limited

customer base, along with low and unpredictable sales potential, signifies a market that is volatile and unprofitable. Exacerbating the lack of profitable appeal is the fact that while there is frequent need to develop vaccines that offer long-term immunity against rare CBRN agents, the use of some vaccines – unless mutation does not make it necessary to constantly adapt the vaccine in the future –, can dramatically reduce the market sales potential even further (Hoyt, 2012). The best example of this is found in the smallpox vaccination campaign, which allowed the WHO to declare the eradication of the disease in 1980. With that eradication, the market potential for smallpox vaccines dissipated.

Table 13 – Basic Market Characteristics for CBRN MedCMs

BASIC MARKET ATTRIBUTE	EXAMPLE
NUMBER OF SUFFERERS	In many cases, there may be nil or few patients suffering from diseases caused by rare CBRN agents. Many CBRN agents pose low historical prevalence and incidence or even lack probability of emerging at all (Matheny et al., 2007).
MARKET SALES POTENTIAL	Global market sales remain ambiguous, spontaneous, and unsubstantial. Even the total US 10-year contribution of 3.3 billion USD (Gottron, 2014) represents roughly 1 percent of a single year of sales for conventional biotechnology drugs – e.g. 289 billion USD in 2014 (Matheny et al., 2007; Deloitte, 2016).
PRODUCT DEFINITION	While threat of exposure to particular CBRN agents presumably will vary country by country, few are willing to reveal its perceived threat or clarify its requirements for CBRN MedCMs.
PAYER AND PAYMENT STRUCTURES	Although ministries of defence generally aim to protect the health of its troops and ministries of health protect its civilians, their WTP for CBRN MedCMs remains ambiguous – with the exception of the US (Matheny et al., 2007).
RISK MITIGATION	Few customers with low and unpredictable sales potential signifies a market that is volatile and unprofitable. In addition, when MedCMs are vaccines and cause long-term immunity against rare CBRN agents, their use can dramatically reduce the market sales potential even further (Matheny et al., 2007; Hoyt, 2012).

Given the market environment for CBRN MedCMs, most well-established companies with proven ability to successfully push a candidate through the R&D process are reluctant to commit their resources to this market. This leaves eager, but often less experienced and smaller biotechnology companies (usually start-ups) that depend on government funding to finance the development of CBRN MedCMs (Maher, Hu-Primmer, Macgill, Courtney, & Borio, 2012). In addition, large- and medium-sized

commercial product developers with proven capabilities could potentially miss out on more lucrative commercial market opportunities if they were to invest time and capital in this small and volatile niche market. Thus, the opportunity costs alone significantly narrow the range of industry partners interested to mostly small biotechnology companies who have fewer alternatives for development programs (Wizemann, Stroud, & Altevogt, 2010).

2.2 Escalation of Supply-Side Deterrence

Funding initiatives to counterbalance market failure such as the US BioShield programme, particularly for CBRN MedCMs, have undoubtedly borne their notable fruits and learning curves. But in the absence of global concerted action, it remains questionable if such solo measures can augment market rewards enough to entice companies with proven R&D capabilities to compromise their focus on the vast market sales potential offered by alternative conventional diseases. Concurrent to market rewards and characteristics that function to deter the international availability of CBRN MedCMs, other factors also threaten to increase the gap. The next section aims to summarise the emerging challenges of mainstream industry and its influence on business models. Understanding this will be key to determining why major industry is increasingly deterred from engaging with CBRN MedCMs.

2.2.1 Modern Business Challenges

Given the historical prosperous business climate for the global industry base that targets drugs against conventional diseases, a rise of blockbusters (drugs with annual sales of at least 1 billion USD) was supported during the 1985-2000 period. PhRMA members were able to deliver an annual Return on Equity (ROE) of more than 20 percent to shareholders (Gleadle, Parris, Shipman, & Simonetti, 2014). Even until quite recently this profitability was secured by just a small number of blockbuster drugs. However, this traditionally high return on investment (ROI) have been presented with multiple challenges (see Table 14). As a result, industry's ROI rates have not only fallen but the business climate has become more uncertain. Compounding the problem

is that the therapeutic advantage of new product developments has generally decreased, offering only minor advantages compared to existing treatments.

Table 14 – Challenges Facing the Pharmaceutical Industry

CHALLENGE	DESCRIPTION
LOW R&D PRODUCTIVITY	Despite consistently increasing R&D investment as a percentage of sales (from roughly 8 percent in 1975 to 17 percent in 2010), the discovery of NMEs has slowed. Consequently, it has become more difficult for a company to replenish its diverse portfolio with value-added products from its own pipeline (Gleadle et al., 2014).
PATENT CLIFF	As patents of safe and efficacious blockbuster drugs expire, revenue and growth are threatened by the gap created in the product portfolio. In fact, key patent expirations from 2010 to 2014 were estimated to threaten more than 209 billion USD in annual sales (Gleadle et al., 2014). Given industry's ability to produce only few new innovative and value-added products to replace many nearing patent life, portfolio erosion is the trend.
GENERIC ENTRY	Upon patent expiration of drugs, they are deemed generic drugs. As a generic, the drug can freely be manufactured by competing companies. Already in 2010, it could be reported that almost 70 percent of all prescriptions written in the US were generic drugs. While customers benefit with lower prices by the entry of generic drugs – prices can quickly decrease by 80 percent (Gleadle et al., 2014) –, this means that overall lower sales are suddenly transferred from innovation seeking original manufacturers to generic manufacturers.
REGULATORY SCRUTINY	Raised concerns about the industry's integrity and transparency as related to drug safety and efficacy has increased regulatory scrutiny. Not only does this negatively impact confidence of customers (e.g. patients, healthcare professionals), but also shareholders. Thus, it threatens the industry's share price/earnings ratio of its stocks (Paul et al., 2010).
HEALTHCARE BUDGETS	As healthcare budgets become more and more strained, prices are challenged. Hence, this potentially restricts industry's profitability and growth prospects (Paul et al., 2010).

Contrary to previous profitability, industry productivity has continuously declined. It has become increasingly expensive to achieve one new approved drug (or NME). This trend was reflected in Chapter 1. What is more, Figure 8 shows that from 1950 to 2010, the estimated NME per 1 billion USD of R&D spending plummeted in the US from more than 30 to well less than one. Although PhRMA members report a consistent increase of R&D spending as a percentage of sales from roughly 9 percent in 1975 to 17 percent in 2010, the relatively unchanging number of NME approved by the FDA of around 20 per year for the 1990-2010 period can only lead to a decline in R&D productivity (Gleadle et al., 2014). As a glance at more recent worldwide developments during 2004-2014 reveals, the analysis of data (EvaluatePharma, 2015b) in Figure 9

illustrates that, although the trend indicates an increasing number of NME per year, the number of NME per billion USD spent on R&D continues to fall drastically.

Figure 8 – Decline in US R&D Productivity (Scannell, Blanckley, Boldon, & Warrington, 2012)

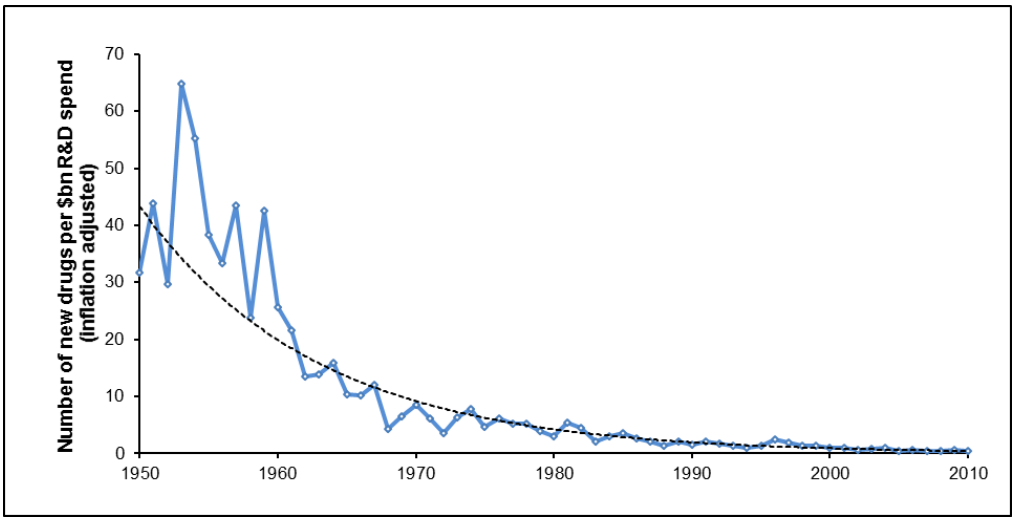
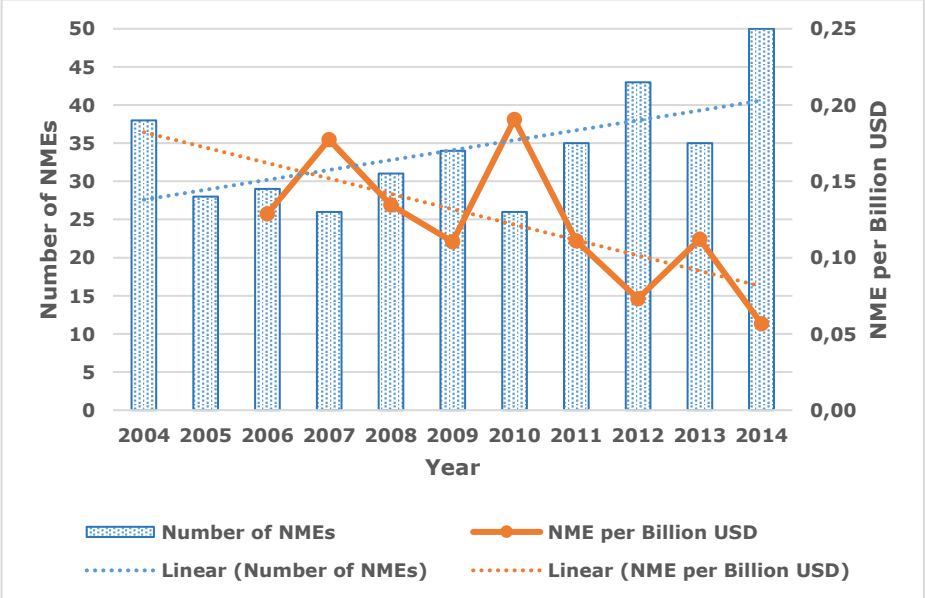


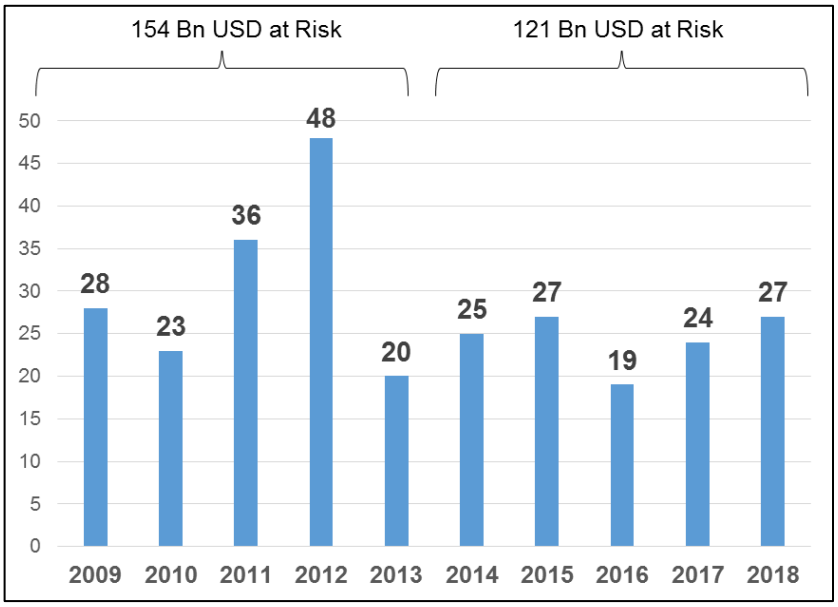
Figure 9 – Worldwide Number of NMEs vs. NME per Billion USD Spent on R&D



EvaluatePharma (2015b) Data Source

Aggravating the central problem of R&D productivity is the fact that patent cliffs have accumulated for major manufacturers. As patents of large blockbuster pharmaceutical and biopharmaceutical products expire, generic pharmaceutical and biosimilar products can flood the market. This severely decreases price levels. To highlight patent cliffs, Figure 10 shows that in the period 2009-2013 (with a peak in 2012), sales volumes of 154 billion USD were at risk due to the expiration of patents. This burden is repeated as it only slightly falls to 121 billion USD for 2014-2018.

Figure 10 – Sales Exposed to Risk Due to Patent Expiration (IMS Institute for Healthcare Informatics, 2014)



2.2.2 The Evolving Business Model

Historically, pharmaceutical and biopharmaceutical companies are typically thought to be vertically integrated firms, meaning they are capable of carrying out all or most functional aspects of their value chain – from the discovery of a drug to its commercialisation (see Figure 11). With some exceptions, segments of the chain of lesser value could be contracted to other companies. In this integrated "productionist" scenario, a basic business model is almost intuitively distinguishable. Namely, a manufacturer invests its capital to maintain all segments of its value chain in order to

first develop a diverse pipeline of medicinal products and then to manufacture and sell its' product portfolio on the market.

> *"The productionist bio-pharma business model describes a long-term financial commitment by equity investors because the R&D spending process is driven by scientific discovery and clinical testing and development takes place over decades"* (Andersson, Gleadle, Haslam, & Tsitsianis, 2010).

Hence, a rudimentary profitable business model would entail the targeting of various lucrative disease areas for which to develop a product portfolio that balances associated market opportunities and threats.

Figure 11 – Main Value Chain Segments for the Pharmaceutical & Biotechnology (IBM Business Consulting Services, 2004)

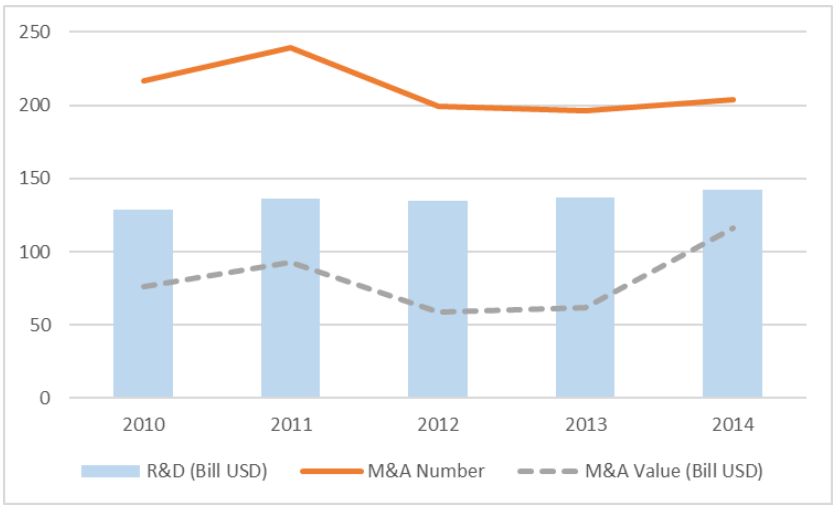
Despite the decline of the traditional environment of price-insensitive buyers, friendly regulatory guidelines and strong patent rights that protect development cost recovery, a high ROI is likely achievable via approved products that target conventional diseases. However, modern challenges such as low R&D productivity and patent cliffs increase the probability of significant deterioration in sales and growth. Consequently, the pharmaceutical industry has vertically disintegrated and adapted structural changes in order to maintain its market position and growth requirements. Indeed, a big pharma trend has been to engage in mergers and acquisitions (M&A) (Gleadle et al., 2014). In fact, 79 M&A transactions took place worldwide in the sector between 2008 and 2012 worth an aggregate value of 388 billion USD (Shimura, Masuda, & Kimura, 2014), with the top 10 of these transactions representing roughly half the total (see Table 15).

Of the latter, only two do not involve the acquirement of research-oriented pharmaceutical companies: Synthes, which focuses on medical equipment, and Barr Pharmaceuticals, a generic manufacturer (Shimura et al., 2014). The trend during 2000-2009 indicates that PhRMA members paid more for M&A than for R&D spending (Gleadle et al., 2014). However, more recent worldwide analysis from 2010 to 2014 (see Figure 12) suggests that strong spending for both M&A and R&D occurred (EvaluatePharma, 2015b). This suggests there is a determined move by companies to swiftly improve their own "pipeline" position and/or future sales expectations via M&A. Such decision often includes the enhancement of their international distribution options (Gleadle et al., 2014).

Table 15 – Global Top 10 M&A by Value (Shimura et al., 2014)

DATE	COMPANIES		VALUE (USD millions)
2009/1	Pfizer	Wyeth	68,000
2008/07	Roche	Genentech	46,800
2009/03	Merck & Co	Schering-Plough	41,000
2011/04	Johnson & Johnson	Synthes	21,300
2010/08	Sanofi-Aventis	Genzyme	20,100
2011/05	Takeda Pharmaceuticals	Nycomed	13,684
2010/01	Novartis	Alcon Laboratories	12,900
2011/11	Gilead Sciences	Pharmasset	11,000
2008/04	Takeda Pharmaceuticals	Millennium	8,800
2008/07	Teva	Barr Pharmaceuticals	7,460

Figure 12 – Worldwide R&D Spending vs. M&A Activity



Data Source: EvaluatePharma (2015b)

Beyond M&A activity, an interdependence between pharmaceutical and biotechnology companies has emerged to compensate the decline in overall R&D productivity. Here large pharmaceutical firms increasingly rely on small biotechnology companies to discover new drugs. Given that small biotechnology firms usually entail a less bureaucratic environment that is more conducive to supporting scientific creativity, large pharma is keen to evaluate the innovative and marketing qualities of biopharmaceutical pipeline products. Concerned about the high costs associated with each stage of a new product's development and the uncertainty that it will succeed, it behoves large pharma to take note of later-stage pipeline biotechnologies whose success is more predictable. Simultaneously, biotechnology firms are increasingly dependent on large pharma's financial resources for late-stage testing and commercialisation due to the enormous investment scope these stages can incur, especially for large scale phase III clinical trials (Gleadle et al., 2014). Consequently, the pharma strategy to secure future products from new biotechnology opportunities stems from a biotechnology company's ability to raise funds for its early and highly risky cost of innovation via various sources such as initial public offerings (IPO), debt and venture capital (addressed specifically in Chapter 7, Section 7.1.2). This interdependency between the pharma and biopharmaceutical industry has led to a structural change, namely a "financialised" market (Gleadle et al., 2014).

Despite the very high risks that a new product will not make it to market, investors are nonetheless willing to purchase stock in IPO-listed biotechnology companies, thus enabling the biotechnology business model's wheels to turn. The stock market creates an opportunity for venture capitalists and other parties to easily enter and exit from their investments with substantial returns in the short-term and even in the absence of a successfully developed new product (Lazonick & Tulum, 2011). As opposed to an integrated "productionist" bio-pharma business model that often requires long-term financial commitment over decades by equity investors, speculative funding can be short-term. Figure 13 symbolises this situation where investors are often "not in a development marathon but a relay race" (Andersson et al., 2010). In that environment, investors want to swiftly transfer ownership in order to extract high returns on invested capital through perceived market value. To facilitate and stimulate a frenzied trading environment, the reporting of product development milestones can identify recognisable points in time for investors to buy or sell a company's stock. In addition, a company can repurchase its own stock at the expense of its investors – a decision that not only boosts the stock prices for shareholders but benefits the company's executives who often receive stock and/or stock options as compensation or perks (Lazonick & Tulum, 2011). Summarising this notion's consequences, Table 16 portrays the shift that has occurred between the business model approaches of "Integrated" vs. "Financialized" regarding priority stakeholders, main product focus, and main performance indicators. Based on such financing models, the sustainability of growth shifts away from product revenues to the value and earnings of their stocks; thus, stock price management is key.

Figure 13 – The Financialized Bio-pharma Product Development Chain (Andersson et al., 2010)

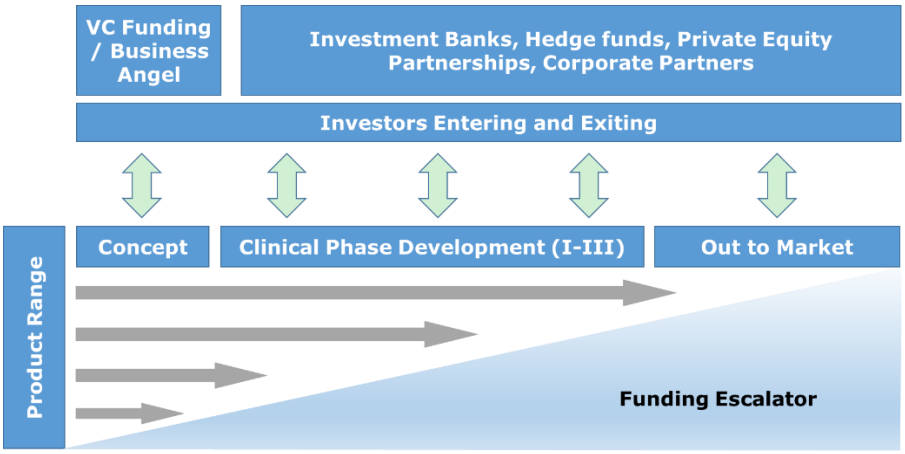


Table 16 – Strategic Priorities under idealist "integrated" and "Financialized" Business Models (Gleadle et al., 2014)

	INTEGRATED APPROACH		FINANCIALIZATION APPROACH	
	Pharma	Biotech	Pharma	Biotech
PRIORITY STAKEHOLDER	Customers (doctors, patients, state agencies)	Customers (Pharma companies, independent distributors)	Shareholders, bondholders, banks	Pharma partners, other equity and bond holders
MAIN PRODUCT FOCUS	Marketable drugs	Marketable or development-stage drugs	Retrade-able bonds, shares, strategic share-holdings	Retrade-able shareholdings, development-stage drugs
MAIN PERFORMANCE INDICATOR	Market share, growth rate, patents, new product pipeline	Patents, new products	ROE, distributable profit, share price	ROE, IPO, valuation, share price

2.3 Conclusion

Along with being exposed to high market volatility, manufacturers of CBRN MedCMs can only hope – in the best of cases – to reap a potential sales volume merely a fraction of that achievable for drugs against conventional diseases. Without further intervention, trends indicate that established companies with proven R&D capability will deploy their resources for mainstream drugs. To capture and retain company

growth rates, corporate business models have transformed themselves to better leverage stock market principles and to respect corporate pledges to maximise shareholder value. The market rewards associated with CBRN MedCMs are clearly incapable of supporting these models. If one assumes that current global demand levels for CBRN MedCMs do reflect a well contemplated CBRN agent threat level perception (i.e. deemed as trivial by the international community), then the associated low market potential is perhaps justification for allowing the CBRN MedCM market to die a natural death. However, if global demand levels are inappropriately low because governments are postponing associated policy measures and/or free-riding the efforts of others, then global public health economic policy for demand must be reviewed and adjusted to overcome market failure.

To increase R&D investment and market sales, a better understanding of the characteristics of CBRN threats and their potential economic consequences – especially for unprepared governments – may boost investments to more appropriately levels. If market failure is to be overcome, it will need to attract the entrepreneurial spirit of those mainstream industrialists with proven abilities. Dominance of financialised business models obliges mainstream corporations to promote their financial growth by targeting market prospects that not only offer sufficient ROI but also stand to influence stock prices and maximise ROE. To create recognisable time points for investors to buy or sell a company's stock, a timely release of financial news to the investor community about potential blockbuster opportunities is strategic. Yet, rare or even hypothetical diseases such as those caused by some CBRN agents currently remain contrary to those financial standards of mainstream industry. Hence, market rewards and its characteristics must be significantly enhanced, and targeted in manner that can be perceived as being compatible with "financialised" approaches.

Part II – CBRN Case Studies

To understand the characteristics and economic consequences of various CBRN incidents, case studies are proffered and discussed in Part II. The scenarios for each case, whether the incident occurs naturally, accidentally or intentionally, are outlined to show where availability of MedCMs in these situations could potentially be cost-effective. In Chapter 3, a natural event of the rare but dangerous biological agent, Ebola, is studied. Chapter 4 examines cost-effective scenarios for MedCMs against a negligent use of chemical nerve agents, given its widespread applications in both the civil and military sectors. And in Chapter 5, the effects of radiological and nuclear agent exposure, whether intentionally or accidentally released, are evaluated.

Chapter 3 STRENGTHENING COST-EFFECTIVENESS OF MEDICAL COUNTERMEASURE DEVELOPMENT AGAINST RARE BIOLOGICAL THREATS – THE EBOLA OUTBREAK[3]

The consequences of low investment in R&D for MedCMs can be very detrimental, as illustrated by the latest natural outbreak of Ebola Virus Disease (EVD) that began in March 2014. This latest natural outbreak in Africa is used as a case study to illustrate an example of risks that such biological agents can pose to social and economic structures. Rather than addressing risks associated with exposure from terrorist events, this case study highlights the potential to strengthen the case to fund relevant MedCMs for naturally occurring diseases with epidemic potential that could also impact Western countries due to consequences on their armed forces operating in the area of the outbreak, on trade or even travellers who may disseminate the disease. To that end, causal factors which led to a lack of a MedCM prior to the 2014 outbreak are identified, then opportunities that may have triggered a re-evaluation as a threat worthy of high actionable concern are probed.

3.1 The Ebola Outbreak

Since the first known outbreak of EVD in 1976, there have been multiple natural outbreaks in Africa throughout the years. In fact, countries experiencing reoccurrence include Sudan, Uganda, Republic of Congo and Gabon. Prior to the 2014 outbreak, a total of only some 2,000 cases and 1,200 deaths were reported. To illustrate the random nature and low incidence of the EVD, a summary of cases and deaths in chronological order is depicted in Figure 14 – with the highest number of cases caused by a single outbreak being 425 in Uganda in 2001 (U.S. Centers for Disease Control and Prevention, 2016b). Even though these natural outbreaks were relatively low in number, a strategic planning workgroup of the US CDC identified EVD as a top "Category A" biological threat in 2000 (U.S. Centers for Disease Control and Prevention, 2000). Fourteen years later in March 2014, however, the outbreak of EVD in Guinea showed that a MedCM (e.g. vaccine, antiviral) had not been sufficiently

[3] This chapter refers to parts of a published article by Johnson, Belin, Dorandeu, & Guille, 2017

fostered. Although the US BioShield programme was launched as early as 2004, its initial efforts focused on securing next-generation vaccines for anthrax and smallpox. While the US and a handful of other countries included the availability of MedCMs for these two agents in their national stockpiles, EVD's deadly march across Western Africa emerged as the headline news, thereby underscoring the difficulty of the health establishment's prioritization versus threat assessment. With unprecedented magnitude, that 2014 EVD outbreak claimed over 11,000 deaths in the three most-affected countries of Guinea, Liberia and Sierra Leone, as of February 28, 2016 (World Health Organization, 2016c) – see Figure 15. Compared to the 28,000 cases recorded during that outbreak, the average rate of mortality was about 40 percent but varied according to the country (30 percent in Sierra Leone, 43 percent in Liberia and 64 percent in Guinea).

Figure 14 – Impact of Natural EVD Outbreaks before March 2014 (U.S. Centers for Disease Control and Prevention, 2016b)

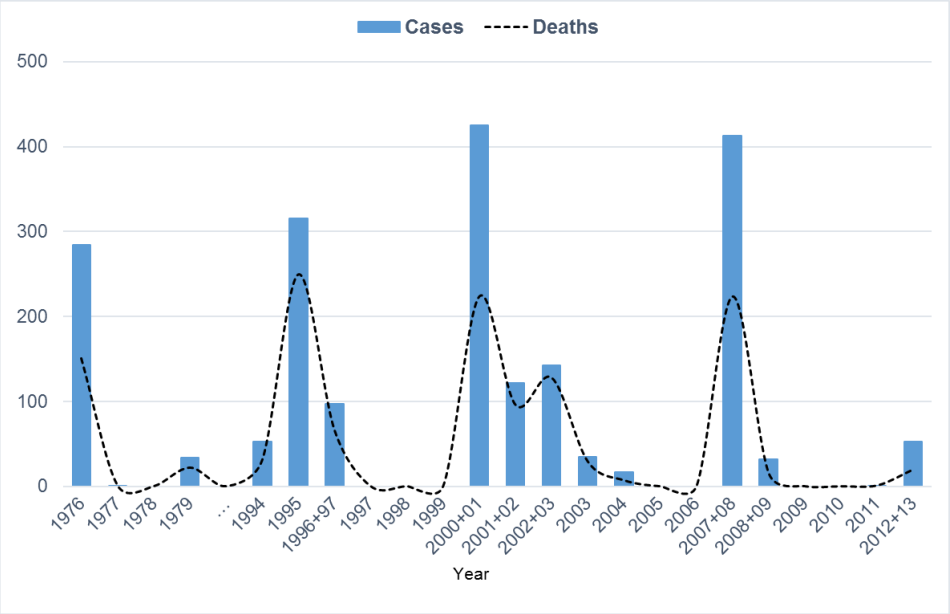
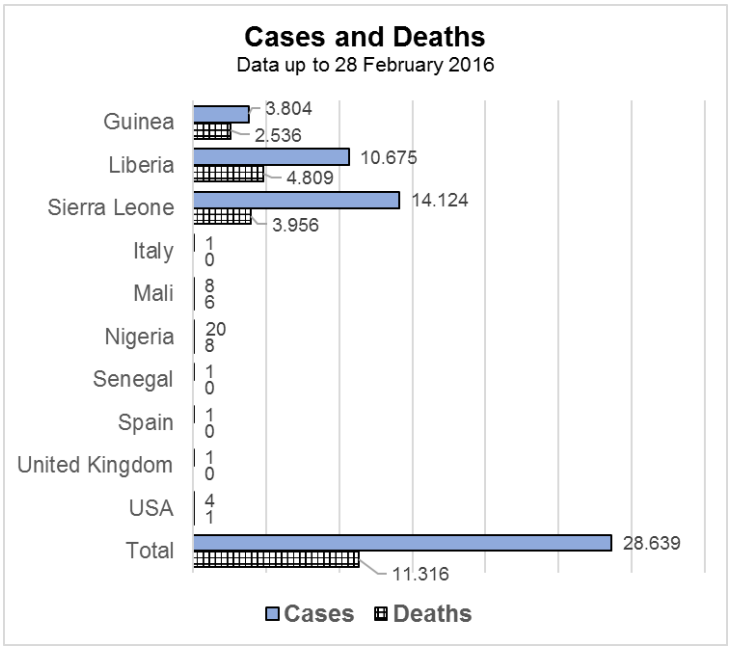


Figure 15 – Impact of EVD following the March 2014 Outbreak (World Health Organization, 2016c)



Although these official numbers of EVD cases and deaths are substantial compared to past EVD outbreaks, the real number is likely to remain hypothetical since it is highly probable that many cases were not recorded due to the remote areas where they occurred and because victims died before treatment could be administered and logged. Nonetheless, that outbreak's dimension triggered the medical world to begin prioritizing the availability of innovative MedCMs which protect against EVD (Helleringer & Noymer, 2015).

3.2 Response for Medical Intervention

The strong response to the EVD threat included the formation of the world's first international consortia to accelerate the development of two EVD vaccines. The first was co-developed by GlaxoSmithKline (GSK) and the US NIH, and the second by NewLink Genetics, developed by researchers at the Public Health Agency of Canada. During the 2014 EVD outbreak, the experimental drug from Mapp Biopharmaceuticals known as ZMapp received much press coverage, but the ability to scale up supply in

the short-term was extremely limited and ZMapp's efficacy was unproven (Tully, Lambe, Gilbert, & Hill, 2015). In response, the US HHS of the Assistant Secretary for Preparedness and Response (ASPR) announced in September 2014 that its BARDA division would provide funding (and other technical support) through a 24.9 million USD, 18-month contract with Mapp – a contract extendable up to a total of 42.3 million USD (U.S. Department of Health and Human Services, 2014b).

This project with Mapp was only the first BARDA programme supporting the development of a MedCM against viruses that cause viral haemorrhagic fever (such as EVD). It would be announced roughly a year later that BARDA's total accumulated investments for various EVD vaccines and therapeutics, manufacturing, diagnostics, and studies reached almost 215 million USD (Disbrow, 2015). Of this 215 million USD, Table 17 lists funding by company projects specifically for vaccines and therapeutics which totals roughly 176 million USD.

It is especially interesting to note that, rising to address international crises and a newly perceived state-of-emergency, some of the companies listed in Table 17 are large global pharmaceutical players with proven abilities (e.g. Merck, GSK, Janssen). They participated despite the fact that profitable scenarios similar to those offered for widespread conventional diseases remain highly unlikely. One could assume that such action by large companies is motivated by their desire to positively position their public image and reputation, or perhaps by a sense of patriotic duty during a time of emergency. Supporting the latter notion, high dedication to vaccine development was also seen during World War II. For example, many institutions (including Merck & Co) offered free of charge the services of their highly experienced staffs and the availability of their laboratories (Hoyt, 2012). However, with the receding public attention to EVD and the continuing insufficient market demand, the sustainability of mainstream company R&D initiatives remains to be seen.

Empirical analysis (Travisi, Nijkamp, & Vindigni, 2006) and CBRN events (e.g. the 2001 US anthrax letter attacks, the 2014 EVD outbreak) suggest that a high WTP for

MedCMs materialises when risk perception is imminent and objective, and/or that WTP can increase due to emotional factors (press coverage, social media output, etc.). But to generate the availability of CBRN MedCMs before a threat is imminent, WTP must precede the lengthy, risky, and expensive R&D process several years prior. As underscored by Flessa & Marx (2015), there is need for rational allocation of resources beyond political preferences.

Table 17 – BARDA's investments in EVD for vaccines & therapeutics (Disbrow, 2015)

	Company	Country of HQ registration	Funding (USD millions)
Vaccines	Merck & NewLink Genetics	Both US	49.8
	GSK	UK	12.98
	Janssen & Bavarian Nordic	Belgium / Denmark	28.6
	Profectus BioSciences	US	5.9
		Total:	**97.28**
Therapeutics	Mapp Biopharmaceutical	US	19.9
	BioCryst Pharmaceuticals	US	17.8
	Regeneron	US	17.1
	CIADM (a BARDA center) & Genentech	Both US	19.8
	CIADM & DuPont	Both US	0.4
	Medicago	Canada	2
	Fraunhofer	Germany	1.8
		Total:	**78.8**

During the peak of the 2014 EVD outbreak, there was international support to accelerate R&D initiatives to achieve new vaccines and therapeutics. Despite the requisite lengthy and risky R&D process required, it would indeed appear at first glance that significant R&D advances could be made within months. Yet these semi-advanced MedCM candidates were already in the development pipeline at various stages. For example, one of the most advanced and promising vaccines, VSV-ZEBOV, was licensed to Merck and NewLink Genetics – a vaccine previously developed by the Public Health Agency of Canada which had already undergone animal trials in the early 2000s. Following the 2014 EVD outbreak, it was decided to fast-track VSV-ZEBOV's development (Stoye, 2015). BARDA's funding and technical support is monumental

for enabling regulators, clinicians, and manufacturers to improve the efficiency of available clinical trial data. However, a license has not yet been achieved for any of these vaccines and therapeutics (U.S. Department of Health and Human Services, 2015). To step up funding for vaccine and diagnostic development, the EC announced in January 2015 that 215 million Euros (~250 million USD) would be provided for research projects under the new "Ebola+" programme of the Innovative Medicines Initiative (IMI), which is jointly sponsored by the Commission's Horizon 2020 research programme and the pharmaceutical industry (European Commission, 2015).

Direct public funding and technical support have been complemented by incentive measures. In an attempt to further incentivize industry to develop MedCMs against EVD, the US FDA granted ZMapp "orphan drug" status in August 2014. Two month later, the EMA also offered developers of EVD treatments and vaccines the benefits of "orphan" drug status. Receiving orphan drug status (discussed more thoroughly in Chapter 7) increases the value proposition to industry because they include additional rewards such as free scientific advice, fee waivers, fast-track approval evaluation, extended market exclusivity and even tax benefits (Wellman-Labadie & Zhou, 2010).

The EVD outbreak also contributed to inspiring other outcomes such as the Coalition for Epidemic Preparedness Innovations (CEPI) and the Pandemic Emergency Financing Facility (PEF). CEPI is an international non-profit association hosted by the Norwegian Institute of Public Health, and its start-up phase was planned to run until the end of 2017. CEPI aims to achieve global consensus on new and sustainable partnership models required to achieve MedCMs that can contain various emerging infectious diseases. To that end, founding members plan to fill financing gaps created by market failure by pooling and coordinating funds for associated R&D, manufacturing capabilities, as well as the harmonization of effective regulatory requirements (Coalition for Epidemic Preparedness Innovations, 2017b). Initial investments of 540 million USD for this cause have been received internationally from governments and foundations (Coalition for Epidemic Preparedness Innovations, 2017a). The PEF initiative (further discussed in Chapter 6) involves collaboration with

the World Bank Group (WBG), the insurance industry, and capital markets. Its objective is to bridge the critical financing gap that begins in the early stages of an outbreak up to the point where the crisis level rallies further monetary support (World Bank Group, 2016b). PEF pay-outs are triggered when an outbreak meets pre-defined threshold values such as number of deaths or infections within a given timeframe (Estrada, Griffith, Prim, & Sinn, 2016). Although the monetary basis for these pay-outs is provided via both insurance and cash, it also requires long-term pledges from development partners to pay insurance premiums and interest on catastrophe bonds. The purchase of this coverage in both the insurance and capital markets helps to lower the cost and increase the amount of coverage the PEF can obtain. To stimulate this mechanism, the private risk-takers, bond investors or insurance companies, are paid a premium proportionate to the risk they are taking (World Bank Group, 2016c).

Similar to the PEF's partial use to support monetary pay-outs, it is conceivable that associations working to achieve global consensus for prioritized MedCMs (i.e. CEPI) may also find it beneficial to adapt contemporary principles from traditional insurance models. Namely, while insurance protection potentially benefits everyone because its funding comes from shared and reasonable contributions to mitigate the financial risk of specified threats, core competencies of insurance companies include the coordination of sufficient membership to secure substantial "pay out" capability. Hence, to fill financing gaps created by market failure, an international non-profit association able to achieve global consensus for prioritized MedCMs could propose an alternative form of insurance to multiple governments worldwide. Instead of making monetary pay-outs available upon specified disease outbreak as with the insurance component of the PEF initiative, R&D progress and eventually the availability of MedCMs against prioritized naturally occurring diseases that can also be weaponized (or intentionally released) could be offered. Upon considering the US CDC's "Category A Biological Threats", this could include examples such as anthrax, plague, smallpox, tularaemia, and viral haemorrhagic fevers such as EVD. Targeting such diseases would render the larger international community as a potential policyholder because all or most are susceptible to bioterrorism. This is likely not the case when only rare or

potentially emerging diseases are considered. If a high number of insurance policyholders could be achieved, insurance premium rates would most certainly be far lower and much more sustainable than when emergency measures for MedCMs are dependent only on a handful of voluntary donors. Moreover, establishment of such an insurance mechanism may potentially even align the missions of different government agencies and philanthropic organizations focused on CBRN MedCMs and global health concerns, thus, possibly even setting the stage to enable a more global and mandatory insurance coverage requirement.

However, given that EVD was discovered in 1976 and re-emerged multiple times after that, the international effort to achieve a vaccine could have been considered as a global public good since its potential benefits would have extended across borders. Yet, a global government or organisation does not exist to assure that action is launched for such health-related global public goods (Smith, 2003). So, what exactly drove diverse members of the international community to attempt to achieve a MedCM during the 2014 outbreak? To address this question, one must investigate the root causes of the barriers that can lead to inaction or insufficient achievements toward the development of a MedCM before framing the reasons behind a re-evaluation of EVD's prioritization as a threat worthy of high actionable concern.

3.3 Contributor to Lack of Preparedness

To understand the situation that led to the quasi-laissez-faire attitude towards EVD, it is important to put the threat into perspective. First, on a global scale (or even just for the African region), there are a number of widespread diseases that cause far greater fatality rates, according to the WHO. These include pneumonia, HIV, malaria, diarrhoea, tuberculosis, measles, whooping cough, tetanus, meningitis and syphilis. In fact, for many of these diseases, developed countries are already trying to transform African's current medical management programs to more state-of-the-art capabilities.

For example, roughly 3.2 billion people remain at risk of malaria. For 2015 alone, an estimated 214 million new cases were reported to have caused 438,000 deaths. Approximately 80 percent of malarial deaths are concentrated in just 15 countries, mainly in Africa. Millions of people are still not able to access health services to prevent or treat the disease. As for EVD, even if international responsibility and partnership could have supported early EVD MedCM programs, establishing the latters' financial priority against other international programs aimed at meeting basic medical needs would have remained a challenge. Thus, a paramount reason why a MedCM for EVD could not be adequately prepared was that the disease is still a fairly rare one, even if it reached an unprecedented peak of almost 30,000 cases and more than 11,000 deaths. Although the treatment of patients does present great medical challenges, the epidemic is not primarily a medical problem. That is, the improvement of healthcare systems alone could significantly contribute to the disease's containment via increased technical and allocative efficiencies (Flessa & Marx, 2015). Correspondingly, one could argue that, assuming appropriate conditions and effective isolation of those afflicted, the next EVD outbreak could be effectively managed (Khan, Naveed, Dur-E-Ahmad, & Imran, 2015).

In view of these aspects, the current economic tools and metrics applied to allocating funding resources did not produce monetary levels sufficient enough to effectively develop MedCMs against EVD. To quantify the burden of disease from mortality and morbidity, the WHO applies a metric known as Disability-Adjusted Life Year (DALY). One DALY can be thought of as one lost year of healthy life (World Health Organization, 2016d) and is calculated by adding the adjusted number of years lived with a disability (YLD = Number of cases × duration till remission or death × disability weight) to the number of years of life lost due to premature mortality (YLL = Number of deaths × life expectancy at the age of death) (Devleesschauwer et al., 2014).

Based on total DALY calculations, the top four leading causes of disease burden in Africa are ranked in Table 18. When comparing these leading diseases to their ranking in other regions (e.g. Americas, Europe), it is apparent that these diseases are far less

prevalent. To see this contrast in terms of its relative percentage share in DALYs and deaths, refer to Table 19. The total DALY share of these diseases reaches ~27 percent for developing nations but represents less than 13 percent for developed nations. Likewise, regarding the share of deaths, roughly 20 percent occurred in the developing countries versus less than 8 percent in developed ones.

Table 18 – Top Ranking Causes of Disease Burden by Region, based on DALYs (World Health Organization, 2014)

LOWER RESPIRATORY INFECTIONS	**1**	**9**	**1**	**14**	**1**	**10**	**1**
HIV/AIDS	2	19	15	16			6
DIARRHOEAL DISEASES	3		3		3		4
MALARIA	4						13
	Africa	**Americas**	**South-east Asia**	**European**	**E. Mediterranean**	**Western pacific**	**Global**

Table 19 – Relative Comparison of Disease Burden (Bloom, 2014)

	Share of DALYs			**Share of deaths**		
	Global	*Developing*	*Developed*	*Global*	*Developing*	*Developed*
Infectious diseases						
Diarrhoea, lower respiratory infections & other common infectious	11.4	13	2.5	10	12	4
HIV/AIDS and tuberculosis	5.3	6	1.7	5	6.3	1.1
Neglected tropical & malaria	4.4	5.2	0.1	2.5	3.3	0.03
Other	24.9	27.2	12.6	17.1	19.9	7.37
Source: Institute for Health Metrics and Evaluation, Global Burden of Disease (2010)						

DALYs may be used to evaluate health policies, compare intervention alternatives, and assess risk factors. When evaluating cost-effectiveness, the WHO's threshold values

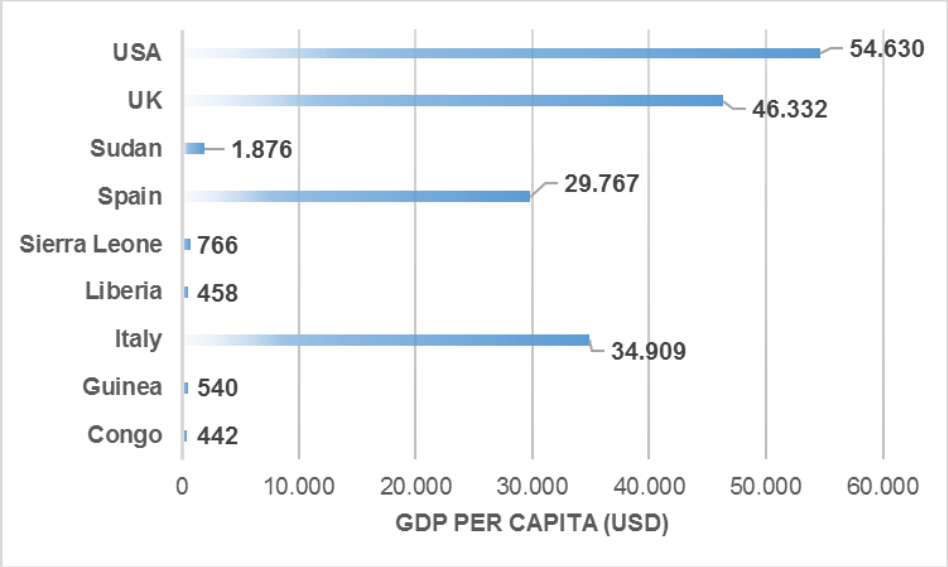
for intervention are defined as very cost-effective if the cost per DALY averted is less than the gross domestic product (GDP) per capita. It then becomes less and less cost-effective the more that investment exceeds per capita GDP – meaning it is no longer cost-effective once GDP per capita is exceeded by a factor of three (World Health Organization, 2016b).

Although use of the DALY concept is widespread and applied in many countries for policy-making since it was presented in the World Bank's "World Development Report 1993", it remains subject to criticism. For example, it has been argued that due to flaws in the DALY metric, it should not be applied in its current form to measure the burden of disease or to prioritize medical intervention. These putative flaws include the use of a theoretical maximum age, inaccurate disability weights, and ethically questionable principles (Lyttkens, 2003). Others have noted that "*results are not presented in a way that allow researchers or policymakers to re-calculate and re-interpret findings for use in an alternative context*" (Fox-Rushby & Hanson, 2001). It is further argued that, in some cases, improvement could be gained by using relevant cohort life expectancies, local life tables or a population model instead of the standard expected years of life lost (SEYLL) method. Nonetheless, DALYs in its current state heavily influences the amount of money donors are willing to invest in medical intervention.

Considering its application for determining investment for EVD, one must bear in mind that even 11,000 deaths are low as compared to other major diseases and, thus, the number of DALYs is low. In sharp contrast, the WHO reports that worldwide annual epidemics of influenza are estimated to result in 3-to-5 million cases of severe illness, with about 250,000 to 500,000 deaths. Besides the influence of low EVD incidence (thus, DALYs) to restrict funding capacities for EVD medical intervention, the cost-effectiveness calculation benchmarks GDP per capita in the African nations affected and this, too, is particularly low. For example, Figure 16 shows that GDP per capita in those African countries hit by EVD (Congo, Guinea, Liberia, Sierra Leone, Sudan) ranged between roughly 440 and 1,900 USD in 2014. This compares to a GDP per capita in developed countries recently experiencing a few EVD cases (e.g. US, UK,

Spain, Italy) that ranges from 30,000 to 55,000 USD. To avoid placing a substantially lower value on human life in developing countries by using the DALY approach, it is argued that if a cost-effectiveness threshold of 10,000 USD per DALY averted were applied, at least 1.25 billion USD for the development of a vaccine against the EVD could have been determined to be cost-effective (Barder, 2014). Indeed, contrary to such cost effectiveness thresholds – which are directly dependent on relative national GDP per capita – setting a global baseline cost effectiveness monetary value could enhance transparency and fairness because it would enable cross-country comparisons and represent a universal minimum value on human health (Drake, 2014).

Figure 16 – GDP per Capita in 2014 for Countries often hit by EVD (World Bank Group, 2014b)



To illustrate the potential impact of the DALY tool applied to EVD, a sensitivity analysis for medical management funding is shown in Table 20. To reduce complexity and thus focus exclusively on the impact of mortality, it is assumed in this model that survivors of EVD fully recover and experience zero YDL. Likewise, it is presumed the average YLL per fatality was 35. This model indicates that in the event there is the will, time, and ability to pay, a country or region with GDP per capita of 600 USD (Scenario a) could, at most, consider 75 million USD for medical intervention against

EVD as cost-effective. The previously mentioned threshold of 10,000 USD per DALY averted is presented as Scenario b. While countries such as Spain (Scenario c) could create a very cost-effective investment if they successfully implemented 1 billion USD, the US (Scenario d) could remain very cost-effective with 2 billion USD and even extend to a maximum threshold of almost 7 billion USD.

Table 20 – Sensitivity Analysis for Medical Management Funding for EVD

Cases:	2.000			
Deaths:	1.200			
Years Lived with Disability (YLD)@ *(assumed null)* :	0			
Years of Life Lost (YLLs) @ *(assumed average of 35)* :	42.000			
DALY (YLD + YLL)	**42.000**			
SCENARIO	**(a)**	**(b)**	**(c)**	**(d)**
GPD per Capita (in USD)	**600**	**10.000**	**30.000**	**55.000**
Very Cost-Effective Budget @ *(20% less GDP per capita)*	480	8.000	24.000	44.000
Maximum Threshold @ 3 x GDP:	1.800	30.000	90.000	165.000
Very Cost-Effective Budget (USD):	**20.160.000**	**336.000.000**	**1.008.000.000**	**1.848.000.000**
Maximum Threshold Budget (USD):	**75.600.000**	**1.260.000.000**	**3.780.000.000**	**6.930.000.000**

Very Cost-Effective = Cost per DALY averted is less than the gross domestic product (GDP) per capita
No Longer Cost-Effective = Once 3 times the GDP per capita is exceeded

3.4 Reasons to Act

Given that the lack of a vaccine certainly contributed to EVD's spread, one can assess the various costs that arose due to its absence. Although routine cost-effectiveness modelling may have contributed to the lack of MedCM availability for EVD, new awareness appeared to have sparked the initiation of new and urgent EVD MedCM projects as previously outlined. With both the GDP per capita in the affected African countries and the level of disease incidence still comparatively low, what has changed to thrust EVD before the international community's radar and to attract significant investment? The main economic driver of change seems to be the realization that failing to respond in time could have severe financial consequences for all concerned. For instance, if 100 million USD in response funding had been made available in early summer of 2014 instead of the autumn when the crisis had already skyrocketed, the

tenfold increase in EVD cases would have been avoided, according to the World Bank (World Bank Group, 2016b). Early surge funding would not only have prevented deaths but would have saved billions of USD. In other words, there is a cost of inaction and growing awareness about it. Thus, accepting the high costs of medical intervention and MedCM's development became more attractive than ignoring the EVD threat. Correspondingly, as the spread of EVD outpaced the response, more forceful international support was summoned by the United Nations (UN) Security Council in September 2014 when it adopted Resolution 2177 (2014). This called on UN countries to urgently respond to the crisis and refrain from isolating the affected countries (United Nations, 2014c). In fact, only shortly after this resolution, EVD cases began to surface even in developed countries – e.g. Spain and the US – by the end of September 2014. While the "unprecedented extent" of the outbreak was perceived to constitute a threat to international peace and security, it is plausible that several countries also viewed the unique adverse impact the EVD threat could pose within its own borders. At least four key drivers emerged which possibly led to a robust initiation of MedCM development. These drivers were: indirect impact of public panic, the disease's political and geostrategic implications, its social disruption and emotional factors affecting GDP, and the international community's ROI.

3.4.1 Indirect Impact of Public Panic

Although comparatively low disease incidence methodically leads to low priority DALY rankings, it may be necessary to include an additional factor for some diseases to capture their potential to cause public panic. For example, public panic and/or the overburdening of local healthcare systems can create additional indirect impact on mortality and cost-effectiveness measures which are not reflected in the current DALY approach. Despite comparatively low historical mortality rates directly associated with EVD – even when including the unprecedented EVD Outbreak 2014/15 – the medical management for other major diseases endemic to the region such as malaria, HIV/AIDS, and tuberculosis were impaired (Ansumana et al., 2016). Presumably stemming from high mortality rates associated with EVD, panic triggered the public to

avoid healthcare facilities that were concurrently distracted with the outbreak. For instance, Guinea saw a 50 percent drop in outpatient visits and a 54 percent decrease in hospital admissions between August 2013 and August 2014. In Liberia, 62 percent of the health facilities were closed, hospital deliveries were reduced by half, and children received 26 percent less immunisations. Although roughly 96 percent of the health facilities in Sierra Leone remained open, child treatment for malaria decreased by 39 percent (Ansumana et al., 2016). To evaluate the corresponding consequences that reduced access to health services for diagnosis and treatment of malaria, HIV/AIDS, and tuberculosis can impose, computational models for disease transmission and infection progression were developed. The model estimated that a 50 percent reduction in access to healthcare services during the EVD outbreak raised additional mortality counts for malaria, HIV/AIDS, and tuberculosis by a total of 10,623 (6,269 in Guinea, 1,535 in Liberia, and 2,819 in Sierra Leone) (Parpia, Ndeffo-Mbah, Wenzel, & Galvani, 2016). Although a comprehensive understanding of the disabilities and mortalities caused indirectly via public panic over the EVD outbreak is subject to further study, a reason for its contribution to adverse economic impact is provided.

3.4.2 Political and Geostrategic Implications

Whilst the DALY approach may hold its ground for putting diseases into a cost-effective perspective, it does not consider political and geostrategic implications. One theme raised by the international community during its deliberations over whether to engage its member states' resources to help control the spread of EVD was its political and geostrategic aspects. It was argued that if EVD were to continue its uncontrollable spread across Guinea, Liberia and Sierra Leone and perhaps neighbouring regions, the social and economic structures of these countries could weaken further, with the resulting havoc and instability threatening their governments.[4] To illustrate EVD's impact in the countries most afflicted, an analysis of EVD deaths showed that at the

[4] Acknowledgement to Claus Haugaard Sorensen from the European Commission for providing this comment

peak of the EVD outbreak, EVD was actually the leading cause of death in Liberia and possibly even in Sierra Leone, while in Guinea it was the third leading cause of death (Helleringer & Noymer, 2015).

Given the valuable natural resources in some of these countries, there was a fear of rising terrorism and that these resources would fall under the control of radical groups. For example, Guinea is one of West Africa's most mineral-rich countries. Although its economy is in ruins, the country has the world's largest reserves of bauxite and some of the highest grade iron ore deposits (Condé, 2013). Another example is presented by Nigeria, which suffered at least 20 cases of EVD during the 2014 outbreak. With crude oil production of ~1,000 barrels per day, Nigeria's oil and gas sector accounts for almost 35 percent of its GDP, while revenues from petroleum exports represent more than 90 percent of total export-related revenue (Organization of the Petroleum Exporting Countries, 2015). Because the EVD outbreak could be deemed a likely destabilizing factor for the economies of the countries it hits, only a strong response against the virus could mitigate severe economic turmoil associated with disruption of the supply and procurement of natural resources.

3.4.3 Impact of Social Disruption and Public Panic on GPD

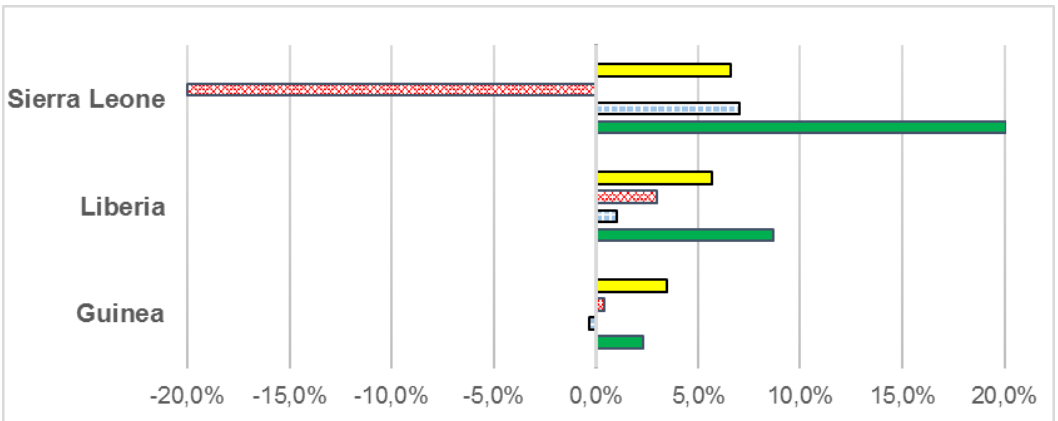
A paramount trigger behind the united effort against the spread of EVD was the growing awareness that the virus could be exported to More Economically Developed Countries (MEDC), resulting in adverse economic and social consequences. This spread would not only have led to higher outbreak incidence (thus, increased DALYs) but would have also significantly raised funding levels for medical intervention since the DALY metric benchmarks GDP per capita of countries that would have been hit. With this being significantly higher in MEDC, higher investments can be determined as cost-effective. Of course, it can be argued that the robustness of healthcare infrastructure in MEDC would be capable of quickly containing any imported EVD case. However, the effectiveness of non-medical containment measures is dependent on the establishment of trust in government if associated government-mandated social

distancing mechanisms are to be abided by the potentially exposed population (Blair, Morse, & Tsai, 2017). Assuming so, the cost-effectiveness model's ability to increase investment would not be realistic because there would not be a significant change to incidence. Nonetheless, the fear alone of being exposed to EVD might have a negative impact on GDP in MEDC and others.

In October 2014, it was estimated that EVD could potentially cause up to 33 billion USD in losses for West Africa's economy (World Bank Group, 2014d). Such economic damage would have been induced by the lower output due to changed behaviour in various economic sectors (e.g. workers/farmers failing to show up for work, shop owners closing their stores, an exodus of foreign professionals in key positions in the economy, reduced tourism, etc.). However, thanks to international efforts to improve the treatment capabilities of the three affected West African countries, the economic damage was subsequently estimated at 1.6 billion USD. This still represented over 12 percent of their combined GDP, a significant number. Besides the economic damage caused in countries hit by EVD, it is estimated that an additional financial loss of 0.5 billion USD was incurred for a swath of countries stretching from Gambia through Kenya to South Africa due to the impact on their tourism. Taking the two losses together makes a total of 2.1 billion USD in economic damage (Thomas, 2015) for the African region. In terms of real GDP growth for the three hardest-hit countries, refer to Figure 17. As the EVD crisis receded, GDP growth rebounded somewhat in Liberia, but remained weak in the other two countries (Guinea, Sierra Leone). In Sierra Leone, for example, its fall in absolute GDP by 20 percent in 2015 was not exclusively due to the EVD outbreak. The discovery of a major iron ore deposit in 2009 led to high growth projections, but delays in starting up a mining project plus a concomitant drop in global iron ore prices by 50 percent saw a severe reduction in growth (World Bank Group, 2016a). Ultimately, a loss of 5 percent growth was attributed to the EVD outbreak for each of the three countries in 2014, according to the WBG, which puts the total loss for the three countries at previously mentioned 2.2 billion USD – or more than 12 percent of their combined GDP (U.S. Department of Health and Human Services, 2016a; World Bank Group, 2016d).

EVD threatened not only West Africa's macroeconomic stability via lower investment and a substantial loss in private sector growth, but also a decline in its agricultural production. The latter triggered concerns about food security and a decrease in cross-border trade as restrictions on the movement of people, goods, and services increased. The contrast with the possible economic impact on developed countries is striking. The combined total GDP in 2014 of the Western countries that experienced an EVD case – the US, UK, Italy, and Spain – equals almost 24 trillion USD. Even if only a fraction of the EVD fear due to further incidence and delayed containment were to have reached these four developed economies, a negative impact of just 1 percent to their combined GDP would have incurred an overall economic loss of over 200 billion USD.

Figure 17 – Real GDP Growth Rates (World Bank Group, 2016a)



	Guinea	Liberia	Sierra Leone
2016	3,5%	5,7%	6,6%
2015	0,4%	3,0%	-20,0%
2014	-0,3%	1,0%	7,0%
2013	2,3%	8,7%	20,1%

REAL GDP GROWTH AT MARKET PRICES

3.4.4 Impact on ROI

Another reason the international community may have opted to establish a MedCM programme for EVD could be based purely on economic defence mechanisms to reduce

direct costs. Aside from the role and interests of governments to protect the health of their populations and their economies' growth rates and stability, there are other financially sound reasons why the international community paid so much attention to the EVD threat. When considering ROI calculations for previous vaccination projects, the supportive guidance for EVD may be presented. For example, as a result of the WHO's enormous smallpox eradication programme during 1967-1979 the costs totalled ~300 million USD, but these costs have been "repaid" many times in the human lives saved and the averted costs for vaccines, treatment, and international surveillance. Those savings are estimated at more than 2 billion USD each year (Ehreth, 2003). Since smallpox's eradication in 1980, the US has recouped nearly 500-fold the value of its contribution to that historical effort (Kenny, 2014). While the immensity of ROI achieved by eradicating smallpox does not necessarily apply directly to EVD, which has a higher mortality rate but is less contagious, it does demonstrate that its substantial savings potential may have been underestimated. Although not known at the time of this writing exactly how the cost figures were defined and whether comprehensive reporting could be executed, the cost of fighting the EVD epidemic was estimated at more than 3.6 billion USD by the end of 2015 (U.S. Centers for Disease Control and Prevention, 2016a). The top donators to the international EVD response are listed in Table 21. In addition to providing personnel, technical expertise, and resources to the response, these funds have been used to establish three new emergency operation centres in Guinea, Liberia, and Sierra Leone (U.S. Centers for Disease Control and Prevention, 2016a).

Table 21 – Top Donators to the International EVD Response, in USD (U.S. Centers for Disease Control and Prevention, 2016a)

COUNTRY	DONATION
US GOVERNMENT	2,369 billion (including 798 million to the CDC, 632 million to the DoD, and 939 million to the US Agency for International Development)
UK	364 million
GERMANY	165 million
WORLD BANK	140 million

As early as September 2014, the UN predicted it would need nearly 1 billion USD for the international response to EVD's outbreak in West Africa. The money was required not only for MedCMs, but for a range of auxiliary initiatives, ranging from compensation for health workers and the purchase of supplies to the tracing of people exposed to the virus. At the time roughly 23.8 million USD was needed just to pay burial teams and buy body bags since the corpses of EVD victims are highly infectious, requiring protective gear for workers (United Nations, 2014a). In its attempt to end the EVD epidemic in West Africa and to strengthen its own domestic preparedness against EVD, the US announced on February 11, 2015 the passage of legislation that included 5.4 billion USD in emergency funding (U.S. White House, 2015). Later estimates suggest the international community ended up committing more than 7 billion USD for response and recovery initiatives (World Bank Group, 2016b). Hence, as asserted by enabling launch of the PEF initiative, it is logical to assume that EVD's impact could have been far easier, quicker and less costly to contain if a MedCM against the virus had been available. Thus, a clear argumentation surfaces that would justify investment for innovative MedCMs against it.

At the other end of the spectrum, it is clear that the cost of doing nothing – restraining the response and medical intervention efforts – would have been far greater. For instance, despite the intensity of response, the three hardest-hit countries were required to put EVD recovery plans in place. These map out strategies for responding to the epidemic's human and economic devastation. The projected price tags are substantial: 812 million USD for Liberia, 844 million USD for Sierra Leone, and 2.89 billion USD for Guinea (Mullan, 2015). As discussed in the previous section on development costs, out-of-pocket costs to develop a MedCM of this nature can reach roughly 1.5 billion USD. Thus, when considering ROI, it is plausible that at least a breakeven point would have been achievable based solely on this single outbreak event. And since the availability of a MedCM should substantially decrease the impact of EVD outbreaks in the future (or even prevent them), it would appear that a strong business case with an attractive ROI could be prepared for relevant financial donors.

3.5 Conclusion

Given limitations on the sources of funding, and so the need to set priorities, it quickly becomes clear that a holistic blanket of protection with MedCMs against all potential CBRN agents cannot be considered as a viable option. A warranted array of current and future medical intervention programs will inevitably continue to compete for finite time, financial resources and diverse interests. For diseases currently causing high prevalence and incidence, mainstream industry will continue to identify sufficient market rewards. Hence, industry will independently intercept accountability to develop and provide innovative medical solutions within the context of free market forces. This is because the high market sales potential associated with such medical solutions are best compatible with the growth objectives of their financialised business models. This is not the case for several highly dangerous but rare biological agents. Even taking the latest unprecedented EVD outbreak into account, that virus' historical and unpredictable impact on disability and life stands little chance of leading to a blockbuster vaccine. Hence, while mainstream industry may view its own associated potential profitability as an opportunity cost, it would appear governments view their own associated prospects as a mandatory measure to protect their populations and in some cases, their own economic stability. Due to the long, risky and expensive R&D process necessary to acquire new MedCMs, governments are challenged to set timely and appropriate priorities. Despite current decision metrics which guide disease categories and the funding levels that governments and donors are willing to commit towards these types of medical interventions, the lack of MedCM preparedness for the EVD outbreak in 2014 suggests there is room for improvement.

As illustrated, the EVD threat may have been easy to ignore because of its perceived lack of magnitude and geographical reach but it ultimately imposed a sharing of the costs of response of many countries. Given that an EVD outbreak can occur naturally and impact Western armed forces operating in the area of the outbreak or travellers who may transfer the disease back to their home countries, it serves to demonstrate benefits of aligning the missions of different government agencies and international non-profit associations focused on CBRN MedCMs and global health concerns. If cost-

benefit analysis may help to allocate resources in a timely manner to achieve sustainable MedCMs against rare CBRN agents, the international community – at least those countries sharing a vested interest to mitigate their risks – should agree on priority metrics capable of capturing their unique threat characteristics. Indeed, the EVD case demonstrates that direct costs of emergency response and interconnection between political, economic, and emotional factors that may affect GDP should not be ignored. Whilst tremendous foresight will be required of the international community to prioritize and incentivize the availability of MedCMs against rare threats, their investments must aim to strike a better balance between market reward levels for MedCMs against CBRN agents and conventional diseases. Namely, it is most likely not profitable for businesses to develop a MedCM and wait for events of low prevalence and/or probability to occur. That means there is need for sustainable public intervention to cope with market failure by providing new sources of timely financing and/or incentives. Alternative approaches to evaluating the "real" threat of specific CBRN agents to the security and peace of the international community need to be developed and utilized. National leaders must recognize that everyone is worse off if there are no cooperative and aggregate efforts to create well-funded and effective MedCM capability against CBRN agents. It may appear paradoxical that, although substantial benefit can be achieved from appropriate MedCMs, free market characteristics most often do not provide sufficient incentives for MedCM developers and manufacturers. Whilst individual governments can in theory more easily finance national public goods in the form of taxes or licensing, many countries typically lack the financial resources to deal with the more acute but basic public health needs. Even if the international community acknowledges that rare agents can easily spread by travel, it can always recede into wait-and-see or free-rider behaviour where a MedCM is paid by others.

To minimize disaster, several lessons can be drawn from the 2014 EVD outbreak. These include the need for public intervention to cope with market failure that comprises financial aid and incentives to create more favourable market conditions, as in the case of orphan drugs. Additionally, due to substantial costs and financial constraints, appropriate research is needed, along with medical and industrial infrastructure. Given

that CBRN exposure is likely to extend across borders, there is also need for international cooperation at state level (or even via management of global public goods), especially when less developed countries are hit by CBRN events. Given the high sensitivity of using DALYs to GDP inequalities between countries, this would imply creation of a platform for determining appropriate metrics to assess cost-effectiveness.

A more careful prioritisation of MedCM development and availability can be viewed as a sort of international health insurance policy: protection for human and economic health irrespective of whether the event occurs in a particular country or not. Should global consensus for prioritized MedCMs be achieved by a separate entity (e.g. an international non-profit association), it is plausible that the adoption of an insurance model concept similar to the PEF could also contribute to filling R&D financing gaps for CBRN MedCMs created by market failure. For example, insurance pay-outs to global policyholders upon outbreak of specified naturally occurring diseases that can also be weaponized (or intentionally released) could be fulfilled by the provision of associated R&D progress and eventually the availability of MedCMs (Johnson, Belin, Dorandeu, & Guille, 2017).

The PEF initiative involves collaboration with profit-driven sectors (the insurance industry, and capital market proceeds from catastrophe bonds). Hence, at least two influences could be supported to join the interests of different government agencies and international non-profit associations with different missions to establish R&D progress and availability of MedCMs against mutually targeted diseases. Firstly, it is likely that medical response readiness could reduce pay-outs required under the PEF's mission to bridge the critical financing gap that begins in the early stages of an outbreak. Secondly, the profit-driven sector may even choose to proactively drive risk mitigation initiatives to retain and maximize its own financial platform (e.g., by supporting preparedness of MedCMs). Thus, the creation of an alternative managing mechanism for developing and procuring global public goods such as MedCMs against particular CBRN agents could emerge. Although this concept may not apply to all biological

agents (such as those causing more limited damage), further economic and governance analysis should be performed to determine various cost-effective and feasible case scenarios.

Chapter 4 EVOLUTION OF CHEMICAL WEAPONS TO MODERN DAY EXPOSURE AND FUNDING OF MEDCMS

Although toxic substances have been used as weapons for hunting purposes for several thousand years (e.g. poisoned arrows, spears, poisoning of water holes, fishing), the significant iterations of chemical warfare agents (CWAs) evolved in modern times, spanning the period from World War I to the 1990s. Given repeated use of sarin and sulfur mustard in Iraq and Syria even today, this evolution continues. With intention to kill, injure or incapacitate an enemy for military purposes, these CWAs include highly lethal choking agents, blood agents, blister agents and various types of nerve agents, the organophosphorus compounds (OPs). More precisely, OPs are a class of phosphorus-containing organic chemicals that disrupt the mechanism by which nerves transfer messages to organs. OPs are considered to be among the most lethal weapons of chemical warfare which are unusually stable and suitable for filling different types of chemical ammunitions (Pitschmann, 2014). As the name "nerve agent" implies, OPs attack the human nervous system. Although the use of such chemical weapons had been banned in much earlier treaties, they were first classified as weapons of mass destruction (WMD) by UN Resolution 687 of April 1991. The Chemical Weapons Convention (CWC) on the prohibition of the development, production, stockpiling and use of chemical weapons was submitted for ratification in 1993 and entered force in 1997. While the convention had 192 signatory countries as of 19 October 2015, Israel remains the single signatory state that has not ratified it (Organisation for the Prohibition of Chemical Weapons, 2015).

This CWC participation status represents about 98 percent of the global population and landmass and also 98 percent of the worldwide chemical industry. Rising to this vastly united cause, the mandate of Organization for the Prohibition of Chemical Weapons (OPCW) strives to ensure the destruction of existing CWA stocks and to effectively implement the UN's global ban on chemical weapons. Marking its significant contributions toward that ban, the OPCW received the Nobel Peace Prize in 2013 (Nobelprize.org, 2013). Also in that year, the OPCW's director general announced that

nearly 80 percent of all declared stockpiles of Category 1 chemical weapons – i.e., CWAs with no or limited application for peaceful purposes – had been destroyed (Patrick, Stanbrook, & Flegel, 2013). In March 2016, roughly 91 percent of the declared stockpile has been destroyed. To put these percentages and progress into numerical perspective, a total of roughly 71,000 tons (65 810 metric t) of chemical toxic substances (and their precursors) have been declared. With the bulk of these stocks acknowledged by Russia (40,000 tons) and by the US (30,000 tons), remaining quantities have been declared by Albania, India, Iraq, South Korea, Libya and, more recently, Syria. Originally, the CWC targeted the destruction of such chemical weapons by the end of April 2007; however, by 2012, only about 51,000 tons (72 percent) could be destroyed. Nonetheless, this included the total declared stocks in Albania, India, and South Korea (Pitschmann, 2014). Additionally, the Special Coordinator for the Joint Mission of the OPCW and the UN (OPCW-UN) informed the Security Council in September 2014 that 96 percent of Syria's declared stockpile had been destroyed and that actions were still underway for remaining facilities (United Nations, 2014b).

Progress on the CWC suggests that signatory nations are unwilling to use chemical agents, thus leading to the perceived low demand for currently available or new innovative MedCMs such as diagnostic devices and antidotes to OPs. If so, the related consequences would be two-fold. First, initiatives from private investors to kindle R&D for new and innovative MedCMs would diminish. Second, even the availability of existing MedCM technologies could be undermined as relevant manufacturing facilities stand idle before being converted for more commercial purposes offering financial sustainability and profit maximization. However, the repeated use of sarin (one example of OP) and sulfur mustard in Iraq and Syria since 2013 and the two recent assassination attempts using nerve agent (in February 2017 and March 2018), showed that the threat has not disappeared.

Although official government use of OPs for warfare purposes remains improbable, similar compounds (although less toxic) dually serve long-standing and widespread commercial purposes within the civilian sector (e.g. as pesticides and industrial

additives). Consequently, there is a double imperative to maintain funding sources for MedCMs that protect against these OPs. One stems from the probability, however low, of military or terrorist use of OPs. The other is linked to the benefits MedCMs offer against the health risks of OP's prevalent use and availability within the civilian sector.

The purpose of this chapter is to describe the evolution of chemical weapons and disclose how exposure to OPs, the most potent of all chemical agents, can happen intentionally and accidentally along multiple routes. While exposure to some chemical threats remain rare and/or hypothesized, OP exposure has already often materialized given its applications in both the military and civil sectors. For this reason, these sectors will be focused, with less emphasis on the potential threat as posed by terrorist groups. Following a brief review in Section 4.1 of chemical agents' evolution for military purposes, Section 4.2 emphasizes the health risks associated with OP poisoning and the relevant MedCMs that could be applied in OP exposure routes. To help validate the economic feasibility of medical intervention, Section 4.3 illustrates models to depict stakeholder incentive to provide funding as well as determine which stakeholders may have a vested interest to do so. The case is strengthened by outlining examples of cost-effective opportunities that were missed.

4.1 CWA Evolution for Military Purpose

The history of chemical weapons for military purpose ranges from the first primitive Chinese chemical grenades of the pre-industrial era to the more advanced developments that accompanied the onset of industrialisation. For example, during the Crimean war (1853 – 1856) toxic sulfur dioxide and artillery shells filled with cacodyl cyanide were considered. In the subsequent U.S. civil war (1861 – 1865), there were proposals to fill artillery shells with chorine, hydrogen cyanide, arsenic compounds, or poisonous plant material (Pitschmann, 2014). However, driven by its vast scale and the era's rapidly advancing science and technology, it was the First World War (1914 – 1918) that saw CWAs become an important operational-tactical factor. Although the use of dangerous gases in warfare was forbidden by previous treaties such as The Hague Conventions of

1899 and 1907, the Germans launched their first devastating CWA attack with chlorine against the French army on April 22, 1915 in Ypres, Belgium. The horror of such weapons led later to their interdiction under the Geneva Protocol of 1925.

The Germans' use of CWAs initially produced a significant tactical advantage, but this quickly shrank as other large nations involved in the conflict (France, UK, Russia, and the US) understood its military effectiveness. Correspondingly, more than 200,000 tons of CWAs were produced by the belligerents. These could be typically distributed via gas cylinders, artillery shells, mortars, gas projectors, hand grenades, and even rifle cartridges. The use of first-generation CWAs effectively halted the active duty of roughly 1 million soldiers, killing about 100,000 of them (Pitschmann, 2014). Summarized in Table 22 are the various agents, their relevant duration of effectiveness (persistency), and rate of action which represent the evolution of chemical weapons. During the period between the World Wars, society already viewed the use of chemical weapons as inhumane. Nonetheless, by this time the first generation of CWAs had been born and was further developed and adapted for military practices. They were newly deployed, as the record shows, by both sides during the Russian civil war, by the Spanish army in Morocco, Italy's troops in Abyssinia and by the Japanese Army in Manchuria. The peak of such "progress" for first-generation CWAs in the late 1930s came with German chemists' production of a series of OPs, ostensibly for pesticides. Hence, nerve agents such as tabun and sarin became the basis for the second generation of CWAs which increased toxicity by a factor of 100 compared to, for example, sulfur mustard – the so-called "mustard gas" from the first generation (Pitschmann, 2014). During World War II the big powers were technically and logistically prepared to use first-generation CWAs on a mass scale. In fact, they stored over 400,000 tons of the materials. However, probably unknown to the other intelligence services as the discovery of the stockpiles in 1945 came as a surprise, only Germany was able produce and store more than 12,000 tons of second-generation CWAs (tabun and smaller amounts of sarin). Given the vast stocks of highly lethal first-generation as well as the far deadlier second-generation CWAs, it is of particular interest that total chemical warfare did not occur in the European theatre, its use having been limited to Japan in

China. It is very likely this restraint over CWA engagement flowed from fear of retaliation and mutual destruction. From the end of World War II to the 1960s key advancements in the maturation of second-generation CWAs were: mass manufacturing of G nerve agents (sarin, soman), the development of even more lethally potent V nerve agents (VX, R-33), and creation addition of modern delivery devices to facilitate chemical attacks – e.g. tube and rocket artillery, air force and ballistic missiles. To illustrate just how much CWA's potency has grown over the years, the inhalation toxicity of sulfur mustard increased by a factor of 10 compared to chlorine in just a few years during World War I. During the next 20 to 40 years the toxicity of G and V nerve agents increased by a factor of 100 compared to mustard. Finally, the V nerve agent has reached the peak of toxicity, representing an enhanced toxicity factor of 1000 when compared to chlorine, which was developed in 1915 (Pitschmann, 2014).

Table 22 – CWA Group, Persistency Rate of Action (Pitschmann, 2014; Organisation for the Prohibition of Chemical Weapons, 2016)

GENERATION	CWA GROUP	PERSISTENCY	RATE OF ACTION	PERIOD
1	**Choking Agents:**	Attacking lung tissue, primarily causing pulmonary edema		
	Chlorine (Cl)	Low	Variable	World War I
	Phosgene (CG)	Low	Delayed	
	Diphosgene (DP)	Low	Delayed	
	Chloropicrin (PS)	Low	Delayed	
	Blood Agents:	Affect bodily functions by inactivating the cytochrome oxidase system		
	Hydrogen cyanide (AC)	Low	Rapid	World War I
	Cyanogen chloride (CK)	Low	Rapid	
	Arsine (SA)	Low	Delayed	
	Blister Agents:	Causing inflammation, blisters, and total destruction of tissue		
	Sulfur mustard (H, HD)	Very high	Delayed	World War I/1930s
	Nitrogen mustard (HN)	High	Delayed	
	Phosgene oxime (CX)	Low	Immediate	
	Lewisite (L)	High	Rapid	
2	**Nerve Agents G:**	Disrupt the functions of the nervous system by interfering with the enzyme, Cholinesterase (ChE)		
	Tabun (GA)	High	Very rapid	World War II
	Sarin (GB)	Low	Very rapid	
	Soman (GD)	Moderate	Very rapid	
	Cyclosarin (GF)	Moderate	Very rapid	
	Nerve Agents V:	Disrupt the functions of the nervous system by interfering with the enzyme, ChE		
	V (VX, R-33)	Very high	Rapid	1950s-1960s
3	**Nerve Agents Binary:**	Disrupt the functions of the nervous system by interfering with the enzyme, ChE		
	GB-2, VX-2, Intermediate Volatility Agent-2		Very rapid	1970s-1980s

During the height of the Cold War during the 1970s and 1980s, the US introduced third-generation nerve agents (sarin, VX, IVA) based on the principles of binary ammunition.

A key attribute of such ammunition is that two individual somewhat non-toxic and separate components must be combined to produce their toxic characteristics. The toxicity is induced via a chemical reaction as a result of mixing the two substances shortly before reaching a target. The advantages of this approach include safe manufacturing, storage, transfer, use, and destruction of such chemical weapons. However, because the toxic yield of the chemical reaction is responsive to temperature and time, various climates and target distances can directly enhance or degrade the potency of binary chemical weapons. Moreover, there are issues of efficacy associated with binary chemical ammunition impact, meaning they tend to be at least 1.5 to 2 times less potent when compared to single-component ammunition (Pitschmann, 2014).

To facilitate the destruction and verification process of chemical weapons in modern day, the OPCW formally separates toxic chemicals and precursors that could be used as (or used in the manufacturing of) chemical weapons into three schedules as depicted in Table 23. In turn, these schedules are grouped within three categories. “Category 1” are “Schedule 1” chemical agents (and munitions filled with such agents). “Category 2” chemical agents are weaponised chemical agents (and filled munitions) other than those listed on “Schedule 1”. Finally, falling into “Category 3” are any unfilled device or equipment specifically designed to aid in the deployment of chemical weapons. Accordingly, the CWC sets prioritized timelines for the destruction of all three Categories of chemical weapons (Organisation for the Prohibition of Chemical Weapons, 2016).

Table 23 – Three Schedules defined for CWAs (Organisation for the Prohibition of Chemical Weapons, 2016)

SCHEDULE	DESCRIPTION
1	Chemicals known to have been used as chemical weapons in the past and/or have very few or no peaceful application
2	Chemicals are primarily precursors to schedule 1, but most also have some application for commercial purposes
3	Chemicals defined as those which were used in some cases as CWAs, but can also serve as precursors to schedule 1 or 2 chemicals

4.2 Nerve Agents – Organophosphorus Compounds (OPs)

This section aims to highlight health risks associated with OP exposure, introduce MedCMs which defend against such health hazards, and briefly depict OP's modern-day exposure routes given its multipurpose applications in the warfare and civilian sectors.

4.2.1 Health Risks and Medical Countermeasures

OPs are neurotoxins that, upon entering the body via ingestion, inhalation, or skin contact, inhibit an enzyme in the human nervous system referred to as cholinesterase (ChE). This enzyme breaks down acetylcholine (ACh), a neurotransmitter that carries signals between nerves and muscles. When ChE is inhibited (or inactivated), ACh builds up in the nerves; thus, the nerves become overactive (Roberts & Reigart, 2013). Victims of OP poisoning often have difficulty to breathe; however, there are several other signs and symptoms which can affect areas of the central nervous system, respiratory, cardiovascular, gastrointestinal, musculoskeletal as well as skin and mucous membrane as depicted in Table 24 (U.S. Centers for Disease Control and Prevention, 2013). The rapidity and severity of such signs and symptoms are dependent on the level of OP exposure, so reactions can vary from sudden death induced by high OP doses to possible long-term effects caused by extended (or chronic) low exposures (Than, 2013; Rao Vemula, Naveen Kumar, & Polasa, 2012). For example, long-term effects include neuropsychological or psychiatric impairment expressed as clinically significant levels of anxiety and depression, memory loss, response speed, and loss of fine motor control, mental flexibility or ability to strategize (Mackenzie Ross et al., 2010). Levels of toxicity can even have adverse effects on the reproductive and immune systems, and can express carcinogenicity (Than, 2013). It should be noted however that, given the time lag between exposure to the agents and manifestation of the disease, it can often be difficult to establish an evidential connection between the route of exposure and the disease (United Nations Environment Programme, 2004).

The standard and effective therapy for treating OP poisoning – atropine and an acetylcholinesterase (AChE) reactivator (oxime) – has remained unchanged for almost five decades (Worek, Thiermann, & Wille, 2015). Atropine blocks the ACh receptors in order to prevent the undesired action, thus alleviating symptoms, while oxime works to reactivate the ChE enzyme and replenish the body's natural level (Jaga & Dharmani, 2003). Another example of treatment that functions as an anticonvulsant against seizures is benzodiazepine (Shih, Duniho, & McDonough, 2003). With current drug treatment models having essentially remain static for half a century, recent advances made with catalytic bioscavengers may indeed present a new alternative against both OP insecticides and nerve agents (Iyer, Iken, & Leon, 2015). Catalytic bioscavengers could act as a prophylactic. That is, by having bioscavengers in the body's systemic circulation prior to nerve agent exposure, toxic compounds could be detoxified in the blood stream before reaching target tissues such as the brain or respiratory muscles. R&D progress regarding this prophylactic appears promising and, once available, such a product would not only ensure survival but prevent incapacitation in the first place (Worek et al., 2015). These bioscavengers can also be used as treatments following percutaneous exposure (Masson & Nachon, 2017).

OP poisoning can be diagnosed by clinical examination or by trying different drugs (Aas, 2014); however, since ChE depression is a diagnostic indication of OP toxicity, exposure can also be assessed by determining ChE activity in red blood cells or serum. To perform these measurements, several optional methods such as electrometric (of Michel), pH stat (titrimetric), colorimetric (of Ellman), and gas chromatographic method (of Cranmer) are available. However, the most widely used method for relevant ChE activity measurement in blood is based on a point of care diagnostic device using the Ellman method. This method is easy to use, can be deployed in the field with relatively inexpensive equipment, and the results are accurate and quantitative. In suspected cases, blood samples should be drawn to measure AChE and Pseudocholinesterase levels – also known as Butyrylcholinesterase (BChE) (Lionetto et al. 2013; Worek et al., 2013; Jaga & Dharmani, 2003). Such medical devices and/or even newly initiated innovations could be made available to diagnose OP exposure for

cases where symptoms are nonspecific at early stages. After all, R&D efforts and procurement costs of such devices tend to be significantly far less than drugs. In addition, the use of diagnostic devices could more easily establish an evidential connection between the route of low dose exposure and the disease. Nonetheless, even in areas where exposure to OPs is highly probable, there is evidence that such MedCMs are not being sufficiently deployed. These cases and their associated economic consequences are examined later in Section 4.3.2.

Table 24 – Signs and Symptoms that may be Encountered upon Exposure to a Nerve Agent or OP Pesticide (U.S. Centers for Disease Control and Prevention, 2013)

SIGNS AND SYMPTOMS	
CENTRAL NERVOUS SYSTEM	Miosis
	Headache
	Restlessness
	Convulsions
	Loss of consciousness
	Coma
RESPIRATORY	Rhinorrhea (perfuse watery runny nose)
	Bronchorrhea (excessive bronchial secretions)
	Wheezing
	Dyspnea (shortness of breath)
	Chest tightness
	Hyperpnea (increased respiratory rate/depth) - early (increased respiratory rate/depth)
	Bradypnea (decreased respiratory rate) - late (decreased respiratory rate)
CARDIOVASCULAR	Tachycardia (increased heart rate) - early (increased heart rate)
	Hypertension (high blood pressure) - early (high blood pressure)
	Bradycardia (decreased heart rate) - late (decreased heart rate)
	Hypotension (low blood pressure) - late (low blood pressure)
	Arrhythmias Dysrhythmias (prolonged QT on EKG, ventricular tachycardia)
GASTROINTESTINAL	Abdominal pain
	Nausea & and vomiting
	Diarrhea
	Urinary incontinence, frequency
MUSCULOSKELETAL	Weakness (may progress to paralysis)
	Fasciculations (local or generalized)
SKIN AND MUCOUS MEMBRANE	Profuse sweating (local or generalized)
	Lacrimation (tear formation)
	Conjunctival injection

4.2.2 OP Exposure Routes

Although Germany did not use its manufactured and stockpiled nerve agents for military purposes against rival troops during World War II, various paths to human exposure multiplied and remain prevalent. This is due to the many broad applications

for OPs across the world. Hence, the likelihood of human exposure to various OP forms and strengths ranges from the highly improbable to the chronic. Such situations can be categorized as occupational and environmental. Examples of occupational exposure include soldiers, agriculture workers, manufacturing industry workers, pesticide exterminators, greenhouse workers and florists. Non-occupational examples include residential exposure (e.g. exterminator use, dietary, accidental), close proximity to farms, aerial spraying and chemical warfare/terrorism (Jaga & Dharmani, 2003). The next sections briefly summarize OP sources of exposure in three main areas (warfare, use of pesticides and industrial additives) and provide examples of incidence.

4.2.2.1 Warfare

Human exposure to OPs for warfare purposes was first experienced in 1984 when Iraq used tabun on the battlefield during the Iraq-Iran war (Dizaye, 2012). Other recorded military uses of nerve agents include Iraq's attack launches during 1987 and 1988 in approximately 40 Kurdish villages against thousands of civilians. In fact, the attack on March 16, 1988 with various chemical agents, including sulfur mustard and nerve agents (sarin, tabun, and VX), in the town of Halabja may be the largest chemical attack ever against civilians: more than 5000 people were killed and more than 20,000 people were injured (Dizaye, 2012). A more recent reminder of the reality of this threat arose on August 21, 2013 when the nerve agent sarin was released on the outskirts of Damascus, killing 1400 civilians and severely affecting thousands (Rosman et al., 2014). An example of occupational exposure during military duty likely occurred during the Persian Gulf War (1990-1991) when allied troops destroyed Iraqi munitions (e.g. sarin, cyclosarin) in Khamisiyah, Iraq. Nine years after that event roughly 2,900 US veterans reported relevant symptoms and there are estimates that as many as 100,000 US troops may have been exposed to low OP levels. Moreover, 76 US special forces may have also been exposed to low levels during the bombing of a munitions storage in Muhammadiyat (Jaga & Dharmani, 2003).

Although the CWC may reduce the probability that its signatory states will inflict OP exposure via warfare paths, OP chemical agents remain high on the threat list of possible agents to be used by terrorist organizations, non-state actors or even state-sponsored ones. This was demonstrated by the Japanese cult, Aum Shinrikyo, when its members disbursed the highly toxic nerve agent sarin during the Tokyo subway attack in 1995 – killing 19 people, but injuring about 6,000 (Chauhan et al., 2008; Mangerich & Esser, 2014). Even as recently as November 2015 French Prime Minister Manuel Valls warned that attacks by the self-proclaimed Islamic State (IS) terrorist group could include chemical weapons (The Telegraph, 2015), though no particular chemical was cited. Another newspaper had previously reported in 2014 that the jihadist army had gained access to some 2,500 rockets containing sarin which were housed at the Muthanna State Establishment in Iraq (Thornhill, 2014) but this was not confirmed. Consequently, despite the official adherence of countries to CWC and related OPCW initiatives, the intentional use of OPs to cause widespread exposure to civilians would appear to remain highly possible. Noteworthy is that two of the latest most prominent uses appear to have been carried out by medical physicians. The respected Tokyo physician, Ikuo Hayashi, was among those who pleaded guilty to releasing sarin gas on the Tokyo subway in 1995, while Syrian President (and UK-trained medical doctor) Basshar-al-Assad remains suspect as responsible for the Syrian attack in 2013 involving sarin (Patrick et al., 2013). More recently the assassination of the North Korean leader's half-brother with VX (February 2017) and the assassination attempt on a Russian former intelligence officer and his daughter with a new type of OP (March 2018) keeps attention high on these agents. Because other types of OPs have important industrial uses, their manufacture cannot easily be banned.

4.2.2.2 Pesticides

Since pesticides containing OPs present a health risk, an alternative approach to providing MedCMs against these agents could be to promulgate regulation that decreases or even prohibits their use. However, OP pesticides are also the world's most widely used insecticides, guarding millions of people against starvation and disease

(Ross, McManus, Harrison, & Mason, 2013). Indeed, it is predicted that the global insecticides market could reach 16.7 billion USD by 2020 – a compound annual growth rate of 5 percent from 2014 to 2020 (Allied Market Research, 2014). Other types of widely applied insecticides include pyrethroids, methyl carbamates, neonicotinoids, and bio-insecticides. In terms of value, the Asia-Pacific regional market accounted for 44 percent of the total global market in 2013. Within the Asia-Pacific regional market, India alone is expected to account for 50 percent of this total market share due to its high agricultural production of sugarcane, paddy, and cotton. By contrast, North America and Europe are on the gradually declining side of these chemicals' use due to their increased production of insect/pest-resistant genetically modified crops. Together, these two regions represent about 40 percent of the global pesticides market in terms of volume (Allied Market Research, 2014). There are roughly 890 active OP ingredients registered as pesticides in the US where more than 20,000 pesticide products are marketed. Globally, OPs are most often associated with serious cases of human toxicity and account for more than 80 percent of pesticide-related hospitalizations. While non-occupational exposure to populations occurs via air, water, and food, there are multiple opportunities for occupational exposure of OP involving their formulation, manufacture, and application (Vijaya, Sudhakar, & Venkateswarlu, 2010).

OPs probably account for the largest number of acute poisonings (Richter, 2002). The first global attempt to estimate the worldwide incidence of overall acute pesticide poisonings projected that 3 million cases annually lead to 220,000 deaths, with the majority being suicidal (Vijaya et al., 2010). Nonetheless, there remain no reliable estimates as to how many people per year actually suffer from pesticide-related health effects, so various studies have revealed its interpretations. For example, the annual incidence rates of acute pesticide poisoning in agricultural workers may be as high as 18.2 per 100,000 full time workers in developed countries up to 180 per 100,000 in more underdeveloped countries such as Sri Lanka (Thundiyil et al., 2008). How many of these deaths occur with suicidal intention is not clear. The UN reports that an estimated 1 million to 5 million cases of pesticide poisonings occur annually, resulting

in 20,000 fatalities among agricultural workers. Due to inadequate precautions in developing countries, it is suspected that these regions suffer 99 percent of the deaths, even though they use but only a quarter of the world's production of pesticides. The true impact of pesticide exposure probably remains highly underestimated since common symptoms may go undetected for several reasons such as lack of medical access and reporting to medical authorities or administrative inability to monitor conditions (United Nations Environment Programme, 2004).

Given the multi-purpose usage of OP agents (e.g. fumigant, systemic or contact insecticide) and its cost-effectiveness, these compounds have continued to be widely used for decades and have a nearly 30 percent share in the global market in terms of value by type of insecticide. The OP insecticide segment of this market is expected to continue dominating the global insecticides market in volume during the forecast period of 2020, with a compound annual growth rate of 5.3 percent. Driven by strong worldwide demand, readily available OP insecticide stocks are manufactured by many large-sized companies (e.g. DOW, Syngenta, BASF) via trade names such as Lorsban, Dursban, Curacron and many others (Allied Market Research, 2014). Over and above the health risks posed by OPs in their application as pesticide, there is the potential for industrial accidents during the manufacturing process.

4.2.2.3 Industrial Additives

In 2001, the global consumption of OPs was estimated at 186,000 tons. OPs are frequently used as an additive agent for multiple industrial applications. For example, OPs (e.g. TBP, TPP) are added to hydraulic fluids, lubricants, and oils to prevent surface damage during extreme pressure. Other OP agents (e.g. TBEP, TEHP, TPhP) function as softeners in synthetic rubber and polyvinyl chloride (known as PVC) to create flexibility and flame resistance. For a listing which depicts the abbreviated parent OP esters and their metabolites, refer to Table 25. Further applications include flame retardants and plasticizers. Plasticizers are agents that enhance fluidity in products such as paints, glues, and varnishes as well as antifoaming for lubricants and

hydraulic fluids. OPs also increase flexibility to textile coatings such as flexible foams (e.g. used in upholstered furniture and mattresses) and thermal insulation (Marklund, Andersson, & Haglund, 2005). Because of OP's frequent use over decades for multiple and diversified purposes within indoor and outdoor environments, various studies indicate that many environments can contribute to OP exposure (Marklund et al., 2005; Fromme et al., 2014). For example, studies have shown it has even been possible to detect OP agents in sewage treatment plants which are fed from households, industrial sites and the drainage of storm water (Marklund et al., 2005). In another study, indoor samples taken from 63 day-care centres in Germany revealed concentrations of commonly used OP flame retardants and plasticizers – TBEP, TCPP, and DPEHP in dust samples, and TBEP, TCPP, and TnBP in air samples. The OP agents (e.g. DBEP, DPhP) could even be traced in the urine of the children attending these facilities (Fromme et al., 2014). Other industrial areas of concern include the aviation industry since the OP agent known as TCP is used in jet engine oil as a high-pressure lubricant. Hence, activists argue that the health of crew members is adversely affected by long-term exposure to low amounts of OP contaminants which may be present in bleed air due to leaking engine oil seals (Bagshaw, 2013). The reality of the so-called "aerotoxic syndrome" is nonetheless a matter of debate among toxicologists. Via the same oil source, activists also suggest that workers stationed at oil platforms are exposed to TCP via the exhaust from on-site jet pumps.

Table 25 – Organophosphate Esters and their Metabolites

ABBR.	PARENT SUBSTANCE	METABOLITE	ABBR.
DPEHP	Diphenyl(2-ethylhexyl) phosphate		
TBEP	tris(2-butoxyethyl) phosphate	Di-(2-butoxyethyl) phosphate	DBEP
TBP	tributyl phosphate		
TCP	tri-cresyl-phosphate-Isomers	Di-o-cresyl phosphate Di-m-cresyl phosphate Di-p-cresyl phosphate	DoCP DmCP DpCP
TCPP	tris(chloropropyl) phosphate	Di-(2-chloroisopropyl) phosphate	DCPP
TEHP	tris(2-ethylhexyl) phosphate		
TnBP	tri-n-butyl phosphate	Di-n-butyl phosphate	DnBP
TPhP	triphenyl phosphate	Diphenyl phosphate	DPhP

4.3 Deduction of Stakeholders and their Incentives to Fund Medical Intervention

This section depicts models to illustrate stakeholder incentive as well as validate which stakeholders may stand to gain from the availability of MedCMs against OP agents in given situations. In addition, case examples of cost-effective opportunities that were missed are outlined to further emphasis cost-benefits associated with preparedness measures.

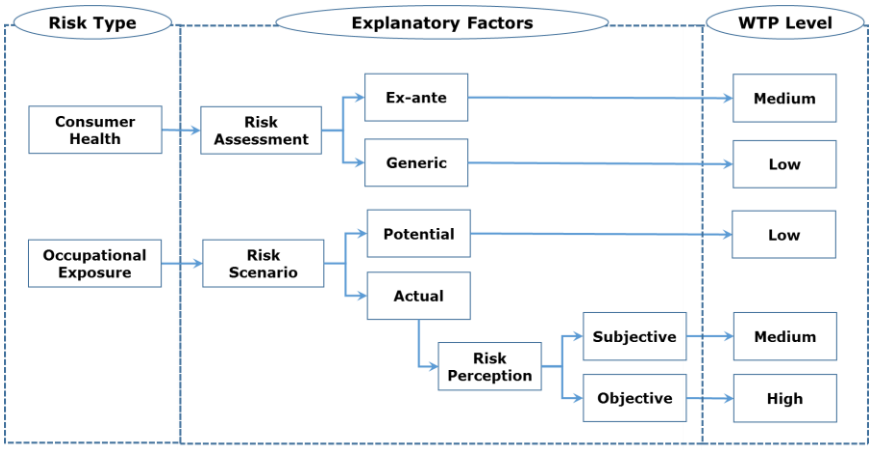
4.3.1 Stakeholder and Incentive Modelling

Despite the CWC and standard industrial practice at present, it has been emphasized previously that multiple and widespread exposure routes to OP agents have emerged and remain active sources. While exposure via some of these routes comes with a low level of probability (e.g. warfare, terrorist attack, industrial accident), many other routes continuously cause human illness and even death (e.g. exposure via acute and/or chronic OP pesticides or industrial additives). Hence, one area of key interest would be to assess how to establish more motivation to achieve an optimized provision of

MedCMs against OP agents. Yet, since doing so could consume significant financial resources, analysis of this goal's economic feasibility and sustainability is paramount. Attention in this section is first directed to a WTP model, then an ROI analysis which was commissioned by the American Association of Poison Control Centres (AAPCC). The objective of reviewing these models will be to recognize the incentives of relevant stakeholders – those who may stand to directly benefit financially by establishing medical intervention – and to determine the methods used for calculating a stakeholder's level of sustainable contribution.

Based on the prevalent health risks posed by pesticide use, a comparative empirical study (Travisi et al., 2006), presented as a tree analysis in Figure 18, outlines the interconnection between various scenarios of WTP in order to decrease risk. For instance, one would expect that when faced with an economic and/or scientific evaluation of a "real" versus hypothesized occupational risk, WTP for its reduction will be high. By contrast, a consumer health risk that is well-forecasted in advance (Ex-ante) is likely to summon a medium level of WTP, while only low WTP levels arise for generic and unsubstantiated claims (Travisi et al., 2006). Consequently, once the related economic justification for MedCMs begins, key WTP questions must be addressed. For example: which stakeholders stand to benefit from risk reduction, how "real" is the threat, and can the threat be well-forecasted? Other questions point to which stakeholders are willing and able to pay, and how much? For answers, an analysis was commissioned by the AAPCC (The Lewin Group Inc, 2012). Here, the AAPCC executes a number of diverse toxicological services extending beyond pesticide poisoning. Nonetheless, this analytical method for quantifying the value of using US poison centres could, potentially, offer support for recognising stakeholders and their sustainable contribution levels which are relevant for MedCMs against OPs.

Figure 18 – WTP Decision Tree (Travisi et al., 2006)



Given the preventive nature of the AAPCC, its value was not self-evident; as a result, contributions from their annual funding sources of 136 million USD faced the threat of severe reductions. However, an analysis from the Lewin Group concluded that via AAPCC's direct consultation to its stakeholders (e.g. general public, healthcare providers, law enforcement authorities, product manufacturers, insurers, and local, state and federal governments) the AAPCC saves a total of more than 1.8 billion USD per year in avoided medical costs and lost productivity. This represents a total ROI of 13.39 USD for every dollar invested. Areas of savings can be seen in Table 26. Upon comparing the total funding contributions of each stakeholder with their directly related total estimated medical care savings and lower productivity losses, an ROI per stakeholder was calculated (see Table 27). While the application of this model could economically justify total budget expenditure, it also demonstrates how the value for stakeholders with a vested interest in relevant preparedness measures could be substantiated and quantified. Moreover, this model could serve as a guide for determining a stakeholder's "fair" cost-effective contribution share. For example, given the extremely high ROI for the federal government of 38.74 USD for every 1 USD invested, an increase in their funding contribution could be debated. Likewise, as this analysis makes clear, one may argue that state and local government are comparably financially overburdened in view of their significantly lower ROI of 3.39 USD for every 1 USD invested.

Table 26 – Areas of Annual Savings in USD Millions (The Lewin Group Inc, 2012)

ANNUAL SAVINGS	AREA OF SAVINGS
753	Avoided Medical Utilization (e.g. enabling people to treat poisonings at home instead of medical facilities)
441	Reduced Hospital Length of Stay (e.g. treatment requires extensive specialized knowledge that not all physicians can be expected to possess and maintain)
24	In-Person Outreach (e.g. provision of educational programs for both lay persons and medical professionals)
603	Reduced Work-Loss Days (e.g. Productivity losses related to the value of goods and services never produced)
~1,820	**TOTAL**

Table 27 – Total Estimated Direct Medical Care Savings Attributed (The Lewin Group Inc, 2012)

FUNDING SOURCE	TOTAL FUNDING IN 2011 (USD MILLIONS)	ESTIMATED MEDICAL CARE SAVINGS AND REDUCED PRODUCTIVITY LOSS	
		TOTAL PER YEAR (USD MILLIONS)	ROI PER YEAR PER DOLLAR OF FUNDING
FEDERAL GOVERNMENT (e.g. FEDERAL CIVILIAN AND MILITARY HEALTH PROGRAMS)	17.1	663	38.74
STATE AND LOCAL GOVERNMENT (e.g. GOVERNMENT HEALTH INSURANCES, WORKERS' COMP.)	83.8	284	3.39
PRIVATE (INCL. HOSPITAL, INSTITUTIONS, DONATIONS, HEALTH INSURERS)	35.1	873	24.86
TOTAL	**136**	**~1,820**	**13.39**

When taking the OP exposure routes as described in Section 4.2.2 and the AAPCC analysis regarding the ROI for stakeholders' contributions for the poison centres into account, it is probable that stakeholders and their cost target areas relevant for MedCMs against OP agents could also be deduced. The next section aims to explore and quantify this notion.

4.3.2 Case Examples of Missed Opportunity for MedCMs against OPs

It is reasonable to assume that diversified infrastructures, policies, and costs concerning varying threat levels within a specific geographic area can significantly affect the relevance of stakeholders and their willingness to make available MedCMs against OP agents. To carry out a comprehensive stakeholder and incentive analysis within a given geographical area, substantial data analysis and/or the availability of studies containing relevant data must be available. In the following section are several case examples that illustrate the missed economic opportunities of using cost-effective MedCMs against OP agents.

4.3.2.1 Warfare Exposure – Soldiers in the U.S. Military

According to official reports, 866,181 US soldiers were injured during the Iraq and Afghanistan wars. The associated long-term medical treatment costs per injured soldier are estimated at approximately 2 million USD – or a total of 1.7 trillion USD. These estimates include related costs spent between 2001 and 2013 (e.g. medical, disability), and are then projected forward to 2053 (Bilmes, 2013). When considering the current costs associated with the death of a soldier resulting from hostile combat, the U.S. military includes provisions for death benefits of 100,000 USD (Powers, 2016) and life insurance of up to 400,000 USD (Military Advantage, 2016) for each soldier. Upon projecting the associated costs of an actual military event, as already noted in Section 4.2.2.1, it was stated that 2,900 Gulf War allied troops reported relevant symptoms of OP poisoning following their destruction of Iraqi munitions (e.g. sarin, cyclosarin). Hence, it is highly conceivable that significant long-term costs for medical treatment and disability could reach 5.8 billion USD (2,900 x 2 million). These figures illustrate the tremendous cost-effective investment potential of the U.S. military for MedCMs against OP agents.

4.3.2.2 Pesticide Poisoning – Farm Workers in Chile

In an analysis of healthcare and economic costs incurred by acute pesticide poisoning in farm workers in Chile (Ramírez-Santana et al., 2014), an average of 311 occupational cases reported annually to the Regional Health Authority were reviewed (e.g. patient registers, costs of health care services, and public information on living conditions). The key influencers of cost were determined to be severity of intoxication, days of sick leave (average duration: seven days), and type of healthcare needed. For example, 77 percent of the cases could be treated ambulatory at an average cost of 330 USD per case whereas 23 percent of the cases were more severe; thus, per case costs for the latter requiring hospitalization climbed to 1,158 USD. A breakdown of both ambulatory and hospitalized costs can be found in Table 28.

All the cases monitored were related to occupational pesticide poisoning and 39 percent of them were specifically caused by OP pesticides. Of the acute poisoning cases, the total annual costs nationwide for all workers were calculated at 185,000 USD. However, because workers tend to fear for their jobs when disclosing information about such symptoms, the real number of poisonings is estimated to be three to four times higher. Hence, this plus the cost underestimations of their public insurance system suggests that the total costs may approach 1.1 to 1.4 million dollars. Preserving health could be achieved by determining and monitoring the baseline ChE levels of these workers with medical diagnostic devices. For instance, if OP exposure reduces the baseline value of the worker – beyond the regulated tolerance limit – to 70 percent, then medical intervention and/or corrective action can be taken. The cost for a single test with the National Institute of Public Health is 72.98 USD. But since achieving a baseline and control measurement requires two tests, this would equal 146 USD. On the assumption that acute poisoning incidence affects 1 in 500 workers in Chile, standard monitoring procedures would cost over 70,000 USD to diagnose 1 case (Ramírez-Santana et al., 2014). Consequently, significance costs could easily discourage the farming industry from implementing bio-monitoring measures. Economic structures in each country would require specific data and analysis; however, it is plausible that barriers to achieve cost effectiveness in such cases could be resolved.

For example, one alternative could be to significantly reduce costs for measuring ChE levels by applying alternative tools (e.g. a MedCM that is a ChE kit for field diagnosis based on the Ellmann method). A study conducted by testing pesticide applicators in the US, State of California (Lessenger, 2005) measured ChE enzyme levels in 366 workers from 45 companies over a 15-year period between 1989 and 2004. While the study determined that the measurement costs to industry were substantial (47,160 USD total at 36 USD per test), it deemed that the cost-effectiveness was plausible because costs incurred were probably less than treating a single pesticide illness in a given worker's compensation system (Lessenger, 2005).

Table 28 – Overall Costs per Day per Case of Occupational Poisonings due to Pesticides (Ramírez-Santana et al., 2014)

Costs of items regarding family care and health care	Ambulatory		Hositalized	
	Per day	Per case	Per day	Per case
Family care/household/farm				
Productivity loss:	20,46	143,22	20,46	143,22
Family cost:	18,12	18,12	12,24	61,2
Family lost income:	20,46	143,22	20,46	143,22
Subtotal:	59,05	304,56	53,16	347,64
Health care services				
Medical consultation at emergency room:	22,6		22,6	
Hospitalization (1-d ICU + 4-d medical ward):	0		550,35	
Ambulance transportation:	0		25	
Pharmacy items (medicines and medical supplies):	2,98		127,79	
Diagnosis support (laboratory, x-ray, ECG):	0		85,25	
Subtotal:	25,49		810,99	
Total cost per case:	330,05		1158,63	

ECG, electrocardiogram; ICU, intensive care unit

4.3.2.3 Pesticide Poisoning – World Farm Projections

It is estimated that more than 90 percent of the world's farms (~500 million) are family run, controlling about 70 percent of the world's agricultural land, with the remaining 30 percent controlled by non-family farms (Lowder, Skoet, & Singh, 2014). Many of these farms provide work for a vast number of family members and seasonal hired workers across the globe. Although it is difficult to accurately predict how many of these farms apply OP pesticides or how many workers may be subjected to OP pesticide poisoning, some data indicates the number could be quite significant. As observed in Section 4.2.2.2, OP pesticides has nearly a 30 percent global market share in terms of

value by types of insecticides and is expected to continue dominating the global insecticides market in volume by 2020 (Allied Market Research, 2014). Moreover, agriculture provides the main source of income and employment for 70 percent of the world's poor living in rural areas (World Bank Group, 2014a) where studies, as previously mentioned, indicate the annual incidence rates of acute pesticide poisoning in agricultural workers range from 18.2 per 100,000 full time workers in developed countries to 180 per 100,000 in more underdeveloped countries such as Sri Lanka (Thundiyil et al., 2008). By applying GDP per capita figures for agriculture and rural populations by various regional scenarios – i.e., world aggregate, lower income, and specific country examples (World Bank Group, 2014b) – and assuming 240 workdays per year, a daily GDP per capita can be calculated as listed in Table 29. In order to project GDP lost for a numeric range (from 1,000 to 10,000) of OP poisoning cases based on the lost GDP per day, an average of seven days of sick leave per case (not considering potential deaths) has been assumed to calculate Table 30. This average had been determined as previously described in Chilean farming case (Ramírez-Santana et al., 2014).

The actual total number of worldwide OP poisoning cases per year is uncertain but is probably in the millions (Vijaya et al., 2010). Hence, Figure 19 projects the corresponding world aggregate GDP lost for up to 1 million cases. This calculation demonstrates that for every 1 million cases of OP poisoning worldwide, over 300 million USD of GDP could be unexploited. While a Ministry of Health and/or various national and state governmental departments may be in the best position to protect government interests for optimizing GDP, other relevant stakeholders – depending on the country – with an interest to preserve worker productivity would likely be industry (e.g. profit optimization, avoidance of worker’s compensation) and insurance companies (e.g. disability, health).

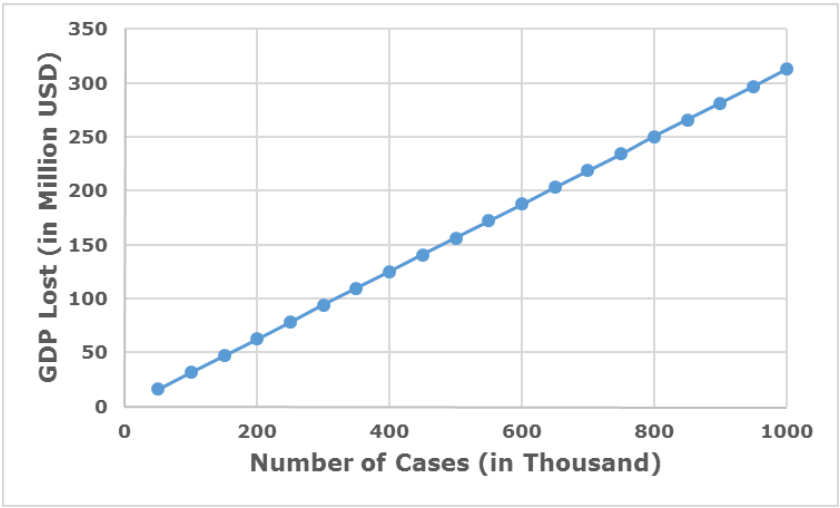
Table 29 – Estimated GDP per capita in 2014 for Agriculture & Rural Populations (in USD)

	World Aggregate	Lower Income	Chile	Sri Lanka	Malaysia
GDP per capita (Year):	10.721	641	14.528	3.819	11.307
GDP per capita (Day):	44,7	2,7	60,5	15,9	47,1

Table 30 – GDP Loss Projection for Numeric Range of OP Poisoning Cases (in USD)

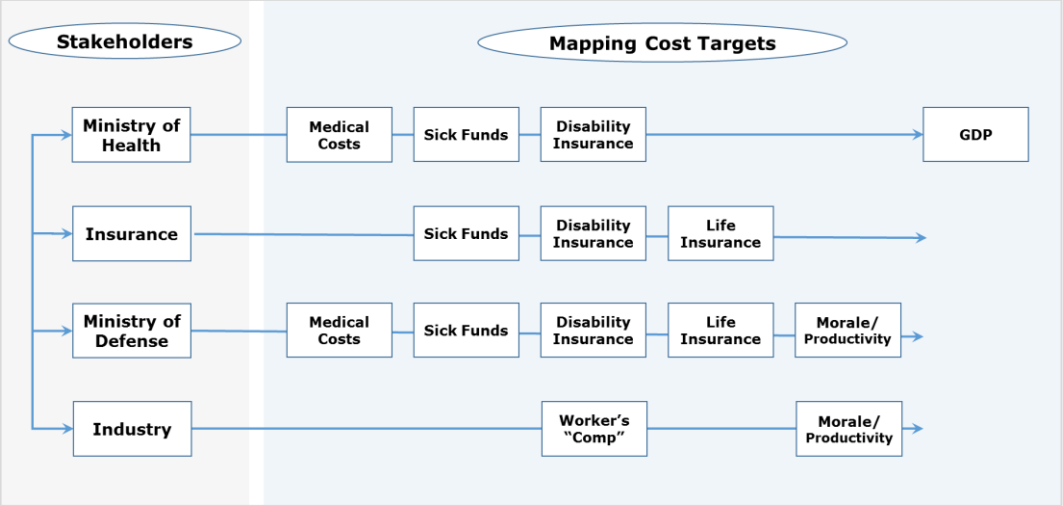
Number of Cases	World Aggregate	Lower Income	Chile	Sri Lanka	Malaysia
1.000	312.708	18.690	423.743	111.392	329.789
2.000	625.416	37.380	847.486	222.784	659.579
3.000	938.124	56.071	1.271.229	334.176	989.368
4.000	1.250.832	74.761	1.694.971	445.568	1.319.158
5.000	1.563.540	93.451	2.118.714	556.961	1.648.947
6.000	1.876.248	112.141	2.542.457	668.353	1.978.736
7.000	2.188.956	130.831	2.966.200	779.745	2.308.526
8.000	2.501.664	149.522	3.389.943	891.137	2.638.315
9.000	2.814.372	168.212	3.813.686	1.002.529	2.968.105
10.000	3.127.080	186.902	4.237.428	1.113.921	3.297.894

Figure 19 – Negative Impact on GDP: World Aggregate (in USD)



Upon considering these case examples of missed opportunity, Figure 20 maps the probable stakeholders and their cost target areas relevant for MedCMs against OP agents.

Figure 20 – Stakeholder Identification and their related Cost Areas



4.4 Conclusion

In terms of best stimulating WTP for the utilization of currently available MedCMs against OPs – or even for the initiation of R&D to create new innovative alternatives – economic proposals that depict the impact of a "real" threat of occurrence (e.g. occupational exposure via acute and/or chronic OP pesticides) will be the most influential. Alternatively, predictable – even if improbable – OP threats such as warfare, terrorist attack or industrial accidents must be well forecasted in order to secure a medium level of WTP. Given the multiple active and potential OP exposure routes that flow throughout civilian and military sectors, quantifiable and cost-effective proposals for funding can be directed at diverse and identifiable stakeholders who may even be unaware of their vested interest in reducing negative financial impact via the availability of cost-effective MedCM solutions. Correspondingly, the determination of each stakeholder's contribution level and its sustainability can be reinforced with business case analysis (e.g. metrics such as ROI, vulnerability presented to GDP).

Because economic infrastructure and the nature of specific OP threats are unique to each country or region, the quantification of economic feasibility must be based on the particular vulnerability characteristics for specific exposure routes within the geographical area for which MedCMs are to be budgeted. Upon determining a cost-

effective investment, the identification of cross-functional and interdisciplinary stakeholders who can share cost/benefits (e.g. various ministries, departments, institutes, private companies, insurance firms) can potentially increase total funding and strengthen sustainability through their combined resources. Similarly, the cost to develop new and innovative MedCMs will be lower for each stakeholder than if paid in full by any single contributor. Moreover, the associated increase in market demand could better secure supply of existing MedCM technologies.

Chapter 5 ECONOMIC EFFICIENCY OF MEDCMS AGAINST RADIOLOGICAL AND NUCLEAR AGENTS

Since the terrorist events on September 11, 2001, new serious threats also include the deliberate release of radiological and nuclear agents (Rosoff & Von Winterfeldt, 2007). There are many scenarios possible; however, those most likely range from hiding a sealed radioactive source at a public location to the use of a radiological dispersal device (RDD) most commonly referred to as a dirty bomb. Scenarios could also include detonation of an atomic bomb (Bushberg et al., 2007). This scenario is nonetheless less likely due to the technical skills required. In 2016, Yukiya Amano, the director general of the International Atomic Energy Agency (IAEA) warned that since terrorism continues to spread, use of nuclear material cannot be excluded. Namely, given it is now old technology, terrorists have the means, the knowledge and the information they need (PressTV, 2016). The director general continued to reinstate such concerns one year later (International Atomic Energy Agency, 2017). Nonetheless, release of radioactive material could also easily be facilitated by accidental events (e.g. radionuclides released during the nuclear disasters in Chernobyl in 1986 and the Fukushima Daiichi plant in 2011) or by deliberate actions such as cyber-attacks with the potential to turn critical infrastructure such as a nuclear power plant itself into a weapon of mass destruction (Unal & Aghlani, 2016). Indeed, worldwide dependency on nuclear power plants is immense. As of April 2017, thirty countries were operating 449 nuclear reactors to generate electricity, while 60 new nuclear plants were under construction in 15 countries. More than 13 of these countries rely on nuclear energy to supply at least one-quarter of their total electricity – with France in the lead with more than 70 percent dependency, followed by Slovakia, Ukraine, Belgium, and Hungary – each with more than 50 percent (Nuclear Energy Institute, 2017).

The origin of radiological material determines whether the associated material is a radiological or nuclear agent. Namely, radiological agents are typically generated as by-products and waste from mineral processing industries or produced for use in industrial applications and medical therapy. They even occur naturally in the

environment. Nuclear agents are generated from nuclear fission or fusion such as those produced by detonation of a nuclear weapon or by releases from damaged nuclear power plants (International Committee of the Red Cross, 2014). Unfortunately, government negligence in developing countries and states that were part of the former Soviet Union has led to the loss of many large sealed sources of radioactive materials (Bushberg et al., 2007). Hence, the availability of such materials to terrorists cannot be ruled out.

This chapter's aim is to illustrate how a radiological or nuclear event (whether accidentally or intentionally) can induce severe economic consequences. To that end, it is strived to determine the probable role that MedCMs can play to reduce these consequences. Accordingly, Section 5.1 presents health implications associated with exposure and briefly introduces types of relevant MedCMs. In Section 5.2, overall adverse economic impact potentially resulting from the release of these agents are first introduced. Then, those areas where costs could be reduced via the availability of MedCMs are identified. Finally, Section 5.3 concludes areas for further analysis which may potentially enhance economic efficiency surrounding the availability of associated MedCMs.

5.1 Health Implications & Measures

Radioactive materials are capable of inflicting hazard in two ways. Firstly, the release of highly penetrating radiation leads to irradiation of individuals (either from a distant source or from external contamination). Secondly, contamination of tissues and organs in the body occurs if the agents are inhaled, absorbed through the skin, or ingested in contaminated food or water – referred to as internal contamination (International Committee of the Red Cross, 2014). Depending on the physical and chemical properties of radioactive materials, different types of ionizing radiation are emitted. Alpha (α) radiation, for example, emits particles consisting of two protons and two neutrons (Helium nucleus). These particles are not able to penetrate human skin because they have only short range and low penetration capability. Nonetheless, alpha-emitting

materials are harmful if entering the body via inhalation or ingestion. Beta (β) radiation emits particles consisting of negatively charged electrons. These particles can travel several feet through the air with moderate capability to penetrate the human body (e.g. the top layer of human skin). However, gamma (γ) radiation and X-rays are highly penetrating forms of electromagnetic radiation that can penetrate many centimetres into human tissue (International Committee of the Red Cross, 2014). This section highlights health impacts associated with various scenarios and introduces the types of MedCMs which address these impacts.

5.1.1 Health Effects

Depending on the dose of radiation and the type (e.g. alpha, beta or gamma), high exposures over a period lasting anywhere from a few minutes to several hours from any source can cause acute, life-threatening injuries. Resulting adverse health effects are known as “deterministic effects”. By contrast, “stochastic effects” are those diseases such as cancer which can develop over time due to significant exposure to lower doses of radiation. Because latency periods can extend to many years, stochastic effects are more difficult to accurately assess (International Committee of the Red Cross, 2014).

5.1.1.1 Radiological Agents

The planting of a sealed radioactive source at a public location may expose many people to irradiation before the source could be noticed. A dirty bomb on the other hand is designed exactly for the purpose (Bushberg et al., 2007). In fact, an attack with radiological material is most likely to be induced through use of dirty bombs. Incidents substantiating this intention can be confirmed as early as June 2002, when the US arrested Jose Padilla for his involvement with Al Qaeda in planning a dirty bomb attack on the US, and in January 2003, British officials secured documents in the Afghan city of Herat which indicated Al Qaeda had successfully built a small dirty bomb. Several factors make use of dirty bombs attractive as a weapon to terrorists. Besides this weapon’s ability to cause health and psychological effects, obtaining radioactive

materials and building a dirty bomb is a fairly simple process (Rosoff & Von Winterfeldt, 2007). It is suggested the chances of a successful dirty bomb attack are about 10-to-40 percent. Were an attack successful, high radiological doses would be expected to be confined to a relatively small area, however. Though not a nuclear weapon, a dirty bomb uses conventional explosives (e.g. dynamite, plastic explosives) to disperse its radioactive material. While the initial explosion itself might kill or injure victims within the blast area, few beyond the immediate zone would be expected to experience health effects (Bushberg et al., 2007).

Through an explosion, lower levels of radioactive dust and debris can be dispersed into the air in the form of a plume where wind would carry it to distances ranging from a few city-blocks to miles. As the radioactive material settled to the earth, it would further contaminate the environment. However, except for a limited number of persons within very close proximity to the initial blast, a dirty bomb is generally not expected to produce enough radiation to cause associated illnesses. External contamination of radioactive material on skin and clothing does not directly subject one to any immediate life-threatening danger. This is especially the case if a victim's clothing is removed quickly and they are showered with soap and warm water. However, a key risk posed by external contamination is that radioactive material could enter the body through inhalation, ingestion, or through a break in the skin. Once contamination becomes internal, the radiation it emits can damage cells and tissues. Depending on the levels of radiation exposure, an increased risk for subsequent development of cancer could take anywhere from years to decades. Although internal contamination does not necessarily lead to cancer (Department of Health and Senior Services - Missouri USA, 2012), an attack involving the release of radioactivity from a dirty bomb is widely recognised to have psychological effects. Those exposed to radiation (or those fearing needlessly that they have been exposed – the so-called "worried-well") experience feelings of vulnerability, anxiety and lack of control. This can trigger signs and symptoms of autonomic arousal such as abnormal rapid breathing (tachypnea) and heart rate (tachycardia), nausea, and diarrhoea for both the exposed and worried-well (Koenig et al., 2005).

5.1.1.2 Nuclear Explosion and Nuclear Accident

The primary consequences of a nuclear explosion are air blasts (shock waves) and thermal radiation which starts fires and burns skin over large areas. Nuclear radiation (i.e. the release of large amounts of neutron and gamma radioactivity) and residual nuclear radiation or fallout (i.e. contamination spread throughout the environment) is the worst scenario (National Research Council, 2005). Whether it is an atomic bomb, an attack or an accident on a nuclear facility (that will not cause a nuclear detonation), survivors exposed to radiation within the vicinity can suffer from bone marrow failure, immuno-suppression, radiation burns, and internal organ damage (Coleman et al., 2009). The gray (Gy) is an international unit of measurement that reflects the absorbed radiation dose. Casualties most necessitating treatment are persons receiving radiation doses in units between 2 and 6 Gy. In the absence of medical treatment, nearly all casualties with exposure doses above 4 Gy will die within 30 days. A large single exposure of gamma radiation to the whole human body can result in various forms of acute radiation syndrome (ARS), also referred to as radiation sickness (Koenig et al., 2005).

ARS has a post-exposure symptom sequence referred to as prodrome, critical and latency phases. The prodromal phase of ARS is typically drawn from occurring symptoms. For example, the occurrence of nausea and vomiting is a key indicator for screening potential victims who may require urgent medical investigation. Other symptoms can include headache, affected consciousness, and higher body temperatures; however, evaluations should be refined in a laboratory setting. The critical phase of ARS embraces many of the clinical manifestations as previously mentioned, but it also includes changes in the blood such as a reduced number of platelets (cells that circulate to clot the blood) and lymphocytes (a type of white blood cell). The latency phase of ARS is marked by further decreases in white blood cells (including granulocytes), but also by diarrhoea and hair loss (Koenig et al., 2005).

When a significant decrease in lymphocytes occurs within the first 6 to 48 hours, prolonged and intensive medical treatment will likely be required. Extremely high

doses of radiation (greater than 30 Gy) are rare but would lead to a deadly cardiovascular/central nervous system syndrome. Reaction to this syndrome occurs almost immediately and symptoms include prostration (extreme exhaustion), ataxia (lack of muscle coordination), hypotension (abnormally low blood pressure) and convulsions. Other syndromes ultimately leading to death include gastrointestinal and hematopoietic (i.e. affecting formation of blood or blood cells). Gastrointestinal syndrome occurs from exposures at roughly 6 to 20 Gy primarily due to death of intestinal mucosal stem cells and hematopoietic syndrome occurs at radiation doses of approximately 2 to 10 Gy as a result of bone marrow depression (Koenig et al., 2005).

To consider potential health consequences of a real event, it may be useful to review heath implications associated with the release of radionuclides during the nuclear disasters in Chernobyl in 1986 and the Fukushima Daiichi plant in 2011. Concerning Chernobyl, an international team of more than 100 scientists concluded that up to 4,000 people could eventually die from long-term effects (i.e. thyroid cancer). However, as of mid-2005, fewer than 50 deaths had been directly attributed to radiation exposure. Many of these victims were rescue workers who were exposed to much higher radiation levels than other members of the population, dying within months of the accident (WHO/IAEA/UNDP, 2005). It is perhaps surprising that the most notable long-term health effect for most of the adult population may be due to perceptions (Lehmann & Wadsworth, 2011). Indeed, the mental health impact of Chernobyl is viewed as the most significant public health problem created by the accident. While perhaps attributed to a lack of accurate information – or even insufficient trust in government (Blair et al., 2017) – the psychological effects include a negative self-assessment of health, belief in a shortened life expectancy, lack of initiative, and dependency on assistance from the state (WHO/IAEA/UNDP, 2005).

Concerning the Fukushima nuclear accident, the WHO reports there were no acute radiation injuries or deaths among the workers or the public (World Health Organization, 2017b). However, there may be a long-term health risk to certain subsets of the population by region (World Health Organization, 2013). Based on age, gender and proximity to the nuclear plant, an increased risk of specific types of cancers over

what would normally be expected have been estimated. For example, for female infants located in the most contaminated parts: all solid cancers (~4 percent), breast cancer (~6 percent), and thyroid cancer (up to 70 percent). Although a 70 percent risk increase over what would normally be expected appears quite high, it is important to note that these percentages represent increases over the baseline rates, and not absolute risks. In the case of thyroid cancer for females, the baseline is very small at roughly 0.75 percent; therefore, a large relative increase represents a small absolute increase. Lastly, an increase over baseline for developing leukaemia is about 7 percent for males exposed as infants. For those located in the second most contaminated location of Fukushima, the aforementioned risks are expected to reduce by about half (World Health Organization, 2013). For 12 workers who are believed to have received the highest absorbed radiation doses to the thyroid, they may be subject to yet a higher risk of developing thyroid cancer and other thyroid disorders. An additional 160 workers received higher levels of whole body doses. Although they could potentially be subject to a higher increased risk of cancer sometime in the future, it will not be detectable by epidemiological studies because of the difficulty of confirming a small incidence against the normal statistical fluctuations in cancer incidence. Hence, from a global health perspective, the health risks directly associated to radiation exposure for this particular event are estimated to be low in Japan and extremely low in neighbouring countries and the rest of the world (World Health Organization, 2017b).

5.1.2 Medical Countermeasures

Medical response to a nuclear detonation have many similarities with other mass casualties such as trauma, burns, bleeding, infection and psychological stress. Other scenarios (dirty bomb, concealed/lost source) will induce contamination/irradiation. More specific to these types of events is the additional requirement to decontaminate the whole-body (Coleman et al., 2009). Although radioactive material which has entered the body can be removed by natural processes such as urination, the use of specialised MedCMs is advisable to reduce the level of internal contamination within

a very limited time window. This depends on the type of radioactive material and the exposure level (Department of Health and Senior Services - Missouri USA, 2012).

There are currently three classes of MedCMs that act against radiation. Radioprotectants are drugs that prevent radiation-induced cellular and molecular damage; radiation mitigators are drugs that accelerate recovery or repair after radiation injury; and radionuclide eliminators are drugs that discorporate or block absorption of internalised radionuclides. Radioprotectants licensed or under investigation include the phosphorylated aminothiols amifostine and phosphonol, Tempol and other membrane-permeable nitroxides, keratinocyte growth factor, the angiotensin-converting enzyme inhibitor captopril, the isoflavone genistein, the nonandrogenic steroid androstenediol, and the vitamin E analogue a-tocopherol succinate (see also listing in Hall et al. 2016). Radiation mitigators currently under investigation include the colony-stimulating factors, androgenic steroid androstenediol, glutamine and pentoxifylline. Radionuclide eliminators currently licensed or under investigation include potassium iodine, ferric hexacyanoferrate (Prussian blue), calcium and zinc diethylenetriaminepentaacetate (Ca- and Zn-DTPA), bicarbonate, barium sulfate, calcium gluconate, penicillamine, the aluminum antacids and sodium alginate (Koenig et al., 2005). Specifically concerning the immediate availability of potassium iodine as a prophylaxis for radiation-induced thyroid cancer, the WHO suggested that pre-distribution to households in the vicinity of nuclear reactors should be seriously considered (World Health Organization, 1999). This is necessary because there is only limited time for implementation following exposure to radionuclides transported in the air. It is interesting to note that over the past few years various news reports have indicated that some countries (e.g. France, Belgium, Holland, Switzerland) are adhering to these guidelines (Nascimbeni, 2015; Imam, 2016; Pieters, 2017; Bosley & Bennett, 2014). Nevertheless, consideration should be given to the psychosocial consequences of iodine prophylaxis, both in terms of the reassurance it may provide and any possible anxiety it may create among the population because it constantly reminds one of a threat (World Health Organization, 1999).

Despite vast research over the last decades, there remains a shortage of non-toxic, safe and effective MedCMs for radiological and nuclear emergency (Singh & Hauer-Jensen, 2016). In addition to the potential use of such drugs in response to a dirty bomb or nuclear fallout, radiation toxicity is a major problem for patients receiving therapy for malignancies. There are only a few radioprotectant agents used clinically to minimise the severity and duration of toxicities associated with radiation therapy for cancer patients (Hall et al., 2016). While innovative research initiatives have been stimulated by the threat of intentional release of radiological and nuclear agents, this also offers an opportunity to better understand the limitations of the current approaches to using radioprotectors and/or mitigators to improve cancer radiation therapy (Prasanna et al., 2012).

5.2 Economic Impact of Radiological and Nuclear Events

This section highlights various types of adverse economic consequences associated with these events. While Section 5.2.1 briefly introduces the wider scope of adverse consequences, Section 5.2.2 strives to determine those specific areas where the availability of MedCMs may offer economic utility.

5.2.1 General Implications

Diverse economic implications can be attributed to the blast of a dirty bomb or a nuclear detonation. For example, independent of potential structural damage, it will likely take months or years to complete the associated decontamination efforts of radioactive material from an affected area. During clean-up/remediation activities and evacuation from the area, relocation will likely be required. Only when radiation in the environment has been reduced to acceptable levels will it be possible for people to return to their homes and places of work. Furthermore, the effects of radioactive contamination are likely to lead to temporary embargos for certain products (e.g. agricultural) and business activities (Department of Health and Senior Services - Missouri USA, 2012). To investigate the potential economic consequences of an attack

with a radiological weapon, a scenario concerning the release of a dirty bomb in the Los Angeles downtown area was evaluated (Giesecke et al., 2012). In the design of this hypothetical event, physical damage (referred to resource loss) was differentiated from behavioural effects. Although an RDD blast is expected to have a low impact on resource loss, substantial short-run resource loss via business interruption would likely dominate. For instance, the short-term impact of business interruption on GDP after shutting down the targeted area for 30 days is estimated to be 1 billion USD. Nonetheless, long-term behavioural effects would be expected to reduce the LA County GDP by 2.6 billion USD. This is because behavioural factors (e.g. fear, risk) would not only increase supply costs of resources to the targeted region, but such factors also diminish market demand for its regional output of goods. The increase in supply costs could be influenced by a chain of new and diverse requirements. These requirements may include investors who expect higher returns and customers who demand price discounts. Because such behavioural effects are bound to impose long-term impact on both the supply-cost of resources of a region and the WTP for regional output, a negative effect to GDP would be far more significant than resource loss effects such as capital damage and life (Giesecke et al., 2012).

Economic analysis (Rosoff & Von Winterfeldt, 2007) of a dirty bomb attack scenario on the ports of Los Angeles and Long Beach suggests that while damage to health would likely be fairly limited (e.g. inducing latent cancers to tens or at most hundreds of persons), the economic impact would be far more significant. Indeed, it is important to note that in the case of radionuclide contamination, the solution does not solely rely on MedCMs but also on other costly remediation actions which are out of the scope of this dissertation. In addition to costs associated with decontamination efforts, business would be severely disrupted due to a lengthy shutdown of the ports before they could be declared as safe by authorities. Because there could be ambiguity as to when and how the term “safe” can be determined, the study assumes that business interruption could extend anywhere from 15 days to one year. At the time of the study in 2007, these business interruption costs corresponded to a rough cost range of 130 million to 100 billion USD. Other adverse economic consequences would arise from evacuations,

depreciated property values and business losses due to the stigma attached to a business location within the plume area. In such a scenario, it is estimated that adverse economic impact would probably approach billions of USD, but not tens or hundreds of billions because a resilient response could be expected. Even if people did relocate due to higher radiation levels, they would likely not stop working. Although the impact on property values could be severe, values would be expected to return to normal after about a year. Moreover, it is even anticipated that businesses would return to their original locations (Rosoff & Von Winterfeldt, 2007).

While economic consequences of a nuclear explosion can include loss of lives/activity, costs to limit the consequences of the accident (e.g. containment buildings), impact to land prices, and population displacement within the blast area, the resulting radioactivity compounds such consequences. Computer modelling of a 10-kiloton (kT) nuclear detonation suggests that the zone of significant infrastructure damage would extend approximately 2 miles from ground zero. Hence, largely leaving infrastructure beyond 2 miles intact with glass breakage and traffic crashes beyond (DiCarlo et al., 2011). Nuclear war being an extreme example, to consider some of these potential consequences, it may be useful to further review the impact of radionuclides that were released during the nuclear disaster from the Fukushima Daiichi plant in 2011. Beyond the adverse economic impacts resulting from physical health issues, several other factors contribute to significant costs. For example, subsequently to the power plant accident, 150,000 residents were evacuated either voluntarily or by force within the event's ~20-kilometer zone (Barletta et al., 2016). This appears to have been very effective in preventing any radiation-induced health-effects to the public thus far (Conca, 2016). Impact of the disaster on land prices due to the radiation effect has been estimated to be as much as roughly 64.1 billion yen (or ~606 million USD), with commercial and business areas being more sensitive to radiation quantity than residential areas (Managi & Tanaka, 2014). In March 2016 (five years after the accident), almost 100,000 people remained evacuated, living in temporary housing, with relatives or beginning a new life elsewhere else (Barletta et al., 2016). Although the Japanese government planned to have two-thirds of all evacuees return to their

homes by March 2017, most of them remain hesitant and sceptical to do so. Their resistance is believed to be based not only on perceived health risks, but on their reluctance to lose the financial compensations they have been receiving. The effect on the population that needed to leave their homes and disrupt their jobs likely created adverse psychological issues such as insecurity, stress and psychosomatic complaints. In addition, the incident led to significant long-term adverse economic effects. Largely due to evacuee compensation payments in the range of hundreds of millions of US dollars, the power plant operator, Tokyo Electric Power Company, was nationalised once it went bankrupt (Barletta et al., 2016).

According to another estimate, direct costs of the Fukushima disaster runs at about 15 billion USD in clean-up over the next 20 years and over 60 billion USD in refugee compensation. In addition, it could cost Japan over 200 billion USD to replace its 300 billion kilowatt hours from nuclear each year with fossil fuels (Conca, 2016). Engineers estimate it could take between 10 and 30 years to complete decommissioning of Fukushima Daiichi's nuclear reactors, costing more than 12 billion USD (Yorucu & Katircioğlu, 2014). As one might expect, the level of domestic and foreign tourists visiting the region has dropped by 50 to 60 percent, while the region's farming and fishing communities have suffered income losses due to the spread of radiation and loss of public trust in food safety. Livestock has also been abandoned within the evacuation zone and with all the entailing economic loss. As reconstruction of the affected region gets underway, there is high competition for financial, material, technical, labour and land resources. Accordingly, all costs will increase, which will likely impede the speed and scope of the recovery. Yet, the nuclear meltdown also questions the integrity of Japan's energy policy based on the belief that economic expansion and advanced technology would provide solutions for accelerated economic development. Ironically, Japan will have a renewed dependency on fossil fuels at least in the short and medium term, and this will increase the cost of electricity production. Moreover, this will also increase carbon dioxide emissions and threaten Japan's environmental contributions associated with global warming. Ultimately, the country would be well-advised to facilitate renewable energy resources. However, shifting

toward renewables will require significant time and costs, and Japan is already heavily burdened by its current recovery and reconstruction efforts. The resulting heavy debt burden will elevate and extend the painful recovery (Yorucu & Katircioğlu, 2014).

5.2.2 Determining Utility for MedCMs

The previous section illustrates that the depicted scenarios can present diverse catastrophic economic consequences that could, although partially, be reduced if very efficient MedCMs were available. To consider specifically which adverse impacts can be minimalized through the availability of MedCMs, relevant points from previous chapter sections are very briefly reiterated and others further explored. For instance, economic analysis from Rosoff & Von Winterfeldt (2007) determined that damage to health from a dirty bomb attack scenario on the ports of Los Angeles and Long Beach would likely be fairly limited (e.g. inducing latent cancers to tens or at most hundreds of persons). Bushberg et al. (2007) suggest that even if a dirty bomb were successful, high radiological doses would be expected to be confined to a relatively small area. Hence, only those survivors within the immediate blast area could eventually experience health effects including an increased risk of cancer.

The nuclear disasters in Chernobyl and Fukushima powerplants also provided evidence that heath implications associated to the release of radionuclides may be somewhat small. Concerning Chernobyl, fewer than 50 deaths as of mid-2005 had been directly attributed to radiation exposure, with up to 4,000 people at risk to long-term effects such as thyroid cancer (WHO/IAEA/UNDP, 2005). Specific to Fukushima, the WHO reported there were no acute radiation injuries or deaths among the workers or the public (World Health Organization, 2017b). However, the highest risk may be a long-term physical health risk to certain subsets of the population by region (World Health Organization, 2013). Yet, as previously reflected, perceptions may again be the most notable long-term health effect for the adult population. Indeed, many of the 150,000 residents that were evacuated following the Fukushima Daiichi power plant accident were reluctant to return to their homes (Barletta et al., 2016).

Up to 70 percent of the casualties of roughly 100,000 in each of the cities of Hiroshima and Nagasaki in August 1945 had combined injury (i.e. radiation plus trauma and/or burns). However, these detonations were airbursts which produce higher rates of combined radiation and burn injury than the more likely threat of ground-level detonation. Moreover, both cities contained primarily wooden structures, so building collapse and secondary fires were more common than would be anticipated in a modern city. As a result, lower rates of combined injury tend to be expected in national planning scenarios. Because little medical care was available in the aftermath of both detonations, it is difficult to estimate the potential benefits of medical interventions (DiCarlo et al., 2011). Likewise, despite extensive long-term follow-up of survivors and their offspring, evidence has failed to show abnormal births, malformations, and extensive mutations among the children of irradiated survivors (Jordan, 2016)

5.3 Conclusion

A review of the adverse event scenarios such as a dirty bomb, nuclear bomb detonation, or nuclear power plant disaster indicates that these events can induce severe economic consequences, with costs running to several billions of USD. However, this assessment also suggests that the role of MedCMs against these agents (e.g. radio-protectants, radiation mitigators, radionuclide eliminators) may play only a limited role when it comes to reducing these costs. The reason is that evidence has not yet shown that a significant number of survivors would likely be affected enough by radiation to increase their risks of immediate illness and delayed cancer. By contrast, other more dominant factors can be expected to induce adverse economic consequences. These include behavioural and infrastructural effects associated with contamination and detonation.

Given some health impact similarities with other mass casualty consequences, the availability of medical response measures for trauma, burns, bleeding, infection, and psychological stress are more likely to be cost-effective and available. This is because of their capability to meet purposes for both radiological/nuclear and accidental

"peacetime" domestic events. Yet, specific to radiological/nuclear events is the requirement to decontaminate the whole body. Depending on the type of radioactive material and the exposure level, the use of specialised MedCMs is recommended to reduce the level of internal contamination to a very limited time window. Pending analysis, it appears reasonable to consider the economic feasibility of a MedCM that could enhance current approaches to the use of radio-protectants and/or mitigators to shield cancer patients during radiation therapy. If a dual-use for both situations (radiological/nuclear events and cancer treatment therapy) could be achieved, market demand alone for conventional therapy use – even in the absence of emergency response to a release of radiological or nuclear agents – would more likely support profitable scenarios.

It is probable, however, that a far greater number of the "worried-well" will suffer from psychological stress factors due to their fear of any long-term development of health problems. To boost the economic efficiency of MedCMs, more research and analysis should be dedicated to this area. There are indications that stress can adversely affect labour market performance, for example. Hence, in addition to a government's communication efforts to establish public trust about health risks, it should also consider the feasibility of an innovative MedCM to reduce the long-term effects of radiation exposure. Through increasing the efficacy of prophylactics and increasing its availability to the wider public following a radiological or nuclear emergency, the psychological effects and their associated adverse economic impact could potentially be reduced.

Part III – Supply and Demand Rationale

Part III defines a more comprehensive approach to gauge and offset the deterrence factors of market supply and demand by applying existing economic models and framework. To achieve this, Chapter 6 introduces components of a risk-informed framework, emphasising the components' utility for systematically shaping demand-side rationale for governments to fund CBRN MedCMs. Whereas case examples in Part II accentuated CBRN events pertaining to natural and accidental exposures, this chapter predominantly focuses intentional release. Finally, assuming there is resolute market demand, Chapter 7 probes the counteraction of supply-side deterrents. Through the establishment of diverse incentives and a decisional framework, a more thorough and insightful strategy can be deployed to better motivate suppliers with proven capability to develop and manufacture CBRN MedCMs.

> *"There is one and only one social responsibility of business – to use it resources and engage in activities designed to increase its profits so long as it stays within the rules of the game, which is to say, engages in open and free competition without deception or fraud"*(Friedman, 1970)

Chapter 6 RISK-INFORMED DEMAND

Besides a natural or accidental release, the likelihood of exposure to CBRN agents also stems from the ability of non-state actors to acquire relevant materials and their financial resources to research, produce, purchase, and sustain them (Unal & Aghlani, 2016). Terrorists have an increased interest in CBRN material and are continuously trying to acquire them, meaning their access to relevant technical information, technologies, and materials can by no means be ruled out (Vicar & Vicar, 2011). Because many technical difficulties have historically hindered a perpetrator's ability to release CBRN agents and generate maximum efficacious exposure, the threat of such a devastating attack is typically referred to as low probability-high impact. Nonetheless, even intentional use of crude and easy to achieve CBRN weapons bear the potential to create maximum panic (Pellérdi & Berek, 2009). One must also consider the recent synthesis and use of sulfur mustard by the Islamic State of Iraq and the Levant, referred to as ISIL (United Nations Security Council, 2017). While new and rapid technologies (e.g. nanostructures, genetic technologies like CRISPR Cas-9, synthetic biology and chemicals, cyber, drone, 3D printing) are becoming readily available and affordable for civilian purpose, their applications are dual-use (Coleman, Ishisoko, Trounce, & Bernard, 2016; Unal & Aghlani, 2016). This means that the technologies, though intended for peaceful domestic use, can also be utilised to facilitate the production and use of CBRN weapons. For instance, nanostructures can be applied to aid the dispersal and delivery process, or even conceal pathogens. CRISPR-Cas-9 makes it possible also for terrorists to perform genome editing in virtually any living organism accessible to experimental manipulation (Haeussler & Concordet, 2016). As such genetic technologies mature, less expertise is required. Hence, the terrorist threat of engineered viruses will increase. Synthetic biology and chemicals may simplify the dissemination of knowledge to enable development of biological and chemical weapons and/or the ability to increase resistance to medical treatment. A cyberattack has the potential to turn critical infrastructure itself (e.g. chemical plant, nuclear power plant) into a weapon of mass destruction. The use of drones could prove effective for executing assassination attempts or terrorist attacks. And 3D printers might provide for the easy

transfer of electronic blueprints to more complex and reliable explosives and detonators. Some of these dual-use developments are so revolutionary that they have not been taken into account in policy which aims to influence appropriate legal and resilience measures (Unal & Aghlani, 2016). Because technology is product-oriented and can be applicable across military and civilian sectors, dual-use policy must ensure its shared access is effectively managed (Merindol & Versailles, 2010). Yet, the more military product specifications fulfil conditions of a commercial market, the more difficult it can become for dual-use policies to circumvent its transfer. Moreover, institutional complexity of military R&D and lack of inter-services coordination can lead to oversights associated with supervision. Policies also require that all public actors share the same policy objectives. Otherwise, significant difficulties in the process of articulating the civilian and military knowledge bases will prevail.

If effectively disseminated, a single release of some CBRN agents could cause tens of thousands of casualties. Protection via MedCMs could help shield human vulnerability to the serious threat posed against health and life. Nonetheless, for some diseases caused by CBRN agents, MedCMs do not exist and many of those that do might not be readily available. Moreover, many existing MedCMs could be upgraded with new ones that offer higher efficacy (Pellérdi & Berek, 2009). To secure availability of CBRN MedCMs at the time of an event, responsible preparedness measures include appropriate stockpiling and distribution methods. As suggested in Part I of this dissertation, however, this necessitates reliable and robust health R&D funding and government procurement efforts. Hence, the forefront of defence is the R&D of new and innovative MedCMs. Besides inducing immunity and providing treatment options, investment in MedCMs may even send a message of deterrence to terrorist groups aiming to use such weapons (Unal & Aghlani, 2016). That is, a perception of preparedness against particular agents may discourage its use as a weapon. However, some critics suggest that if only specific CBRN MedCMs are developed and sustained, the overall threat will not be reduced because terrorists will then simply target alternative agents. This is the reason why a comprehensive description of countermeasures is classified in most of the countries. Ideally, a broad approach to

build resistance against a broad array of agents must be developed and maintained (Pellérdi & Berek, 2009).

Although the position of GHSI would imply that threat of CBRN attack is credible, few governments are willing or able to fund the prerequisites (e.g. R&D, procurement) needed to achieve availability of MedCMs. As Chapter 2 illustrates, in the absence of strong public and international participation, the global business environment offers a limited customer base, not to mention low and unpredictable sales potential for many MedCMs that are rarely needed without the threat of intentional (or accidental) release of CBRN agents. Besides, the regulatory environment is also uncertain (Elbe, Roemer-Mahler, & Long, 2015) and there are alternative opportunities. This results in inappropriate MedCM preparedness that can induce health vulnerability in the case of an event/attack, with the resulting adverse economic consequences (e.g. lost income) far exceeding the costs of strong and comprehensive preparedness initiatives. Hence, there is then need for sustainable public intervention to cope with market failure by providing new sources of timely financing and/or incentives to create more favourable market conditions. Since CBRN exposure can threaten all countries and infectious diseases are likely to extend across borders, in particular through travel (Pavia, 2007), the very costly MedCMs could then be considered as global public goods. However, because no global government or organisation exists to invest in such health-related global public goods, their development requires international cooperation at state level and with international organisations to implement innovative financing mechanisms.

In contrast, adequate market demand for products in free market conditions can motivate profit-oriented developers and manufacturers since engagement in such markets can maximise their own profit and lead to a competitive equilibrium that is Pareto efficient (i.e. a situation where the allocation of goods guarantees that no one will be better off without making it worse for someone else). However, in presence of market imperfections or public goods, the competitive equilibrium is not Pareto efficient. In particular, inefficiencies arise when free rider problems, that is people choosing to receive the benefits of a public good without contributing to its costs of

production, lead to under-production or consumption of public goods and require government intervention (e.g. regulation, taxes). For this reason, these goods, which are non-excludable and non-rivalrous according to Samuelson (1954) definition, are often supplied by governments and paid for collectively. Health is not generally considered a public good since it does not exactly respect the two properties of Samuelson and because non-paying individuals (for health insurance, healthy food, etc.) may not be able to achieve good health. Efforts have been made to introduce universal health coverage in many countries. This entails adoption of social insurance systems or other publicly financed health insurance, where all citizens are insured and can utilize healthcare services regardless of whether they can afford it or not. However, this suggests that insured health services then become non-excludable and non-rivalrous, better approximating a public good.

This chapter aims to challenge the *status quo* concerning CBRN MedCM availability by discussing and compiling existing economic models and tools that may be applicable towards enhancing related government funding initiatives. By integrating these concepts with a risk-informed framework, a more comprehensive approach to gauge and offset deterrence factors of market demand for CBRN MedCMs can be construed. Applying a risk-informed approach, devised by the IAEA can guide systematic and comprehensive evaluation of multiple factors associated with demand. Components of this approach include concepts associated with threat, risk, the cost of doing nothing or something else, implementation, and economic aspects associated with prioritisation and the sustainability of funding. Before related funding and procurement can prevail, however, the level of political motivation must increase. Hence, tools associated with behavioural and political economics are also interpreted for the framework. While this risk-informed framework provides orientation for this construal, it should be noted that specific topics were freely chosen and allocated across its components. Hence, this evaluation is not necessarily (nor intended to be) fully IAEA conform. First, this chapter portrays a generic definition of all risk-informed framework components in Section 6.1. Then, Section 6.2 demonstrates its application by associating behavioural and political economics under the framework's first component, "Set the Context". In

Section 6.3, the next component of "Assess Risk and Threats" is summarised so that hypothesised terrorist threats of low-probability/high events can be better interpreted. Financial impact and evaluation of cost-benefit are discussed in Section 6.4 under the framework component, "Identify Alternative Measures". And in Section 6.5, prioritisation methods are introduced under the component of "Implement". Finally, alternative public health funding mechanisms and global collaborative attributes that may act to increase the effectiveness of political efforts as well as mitigate risks (including political opportunity costs) associated with funding are depicted under the "manage" component in Section 6.6.

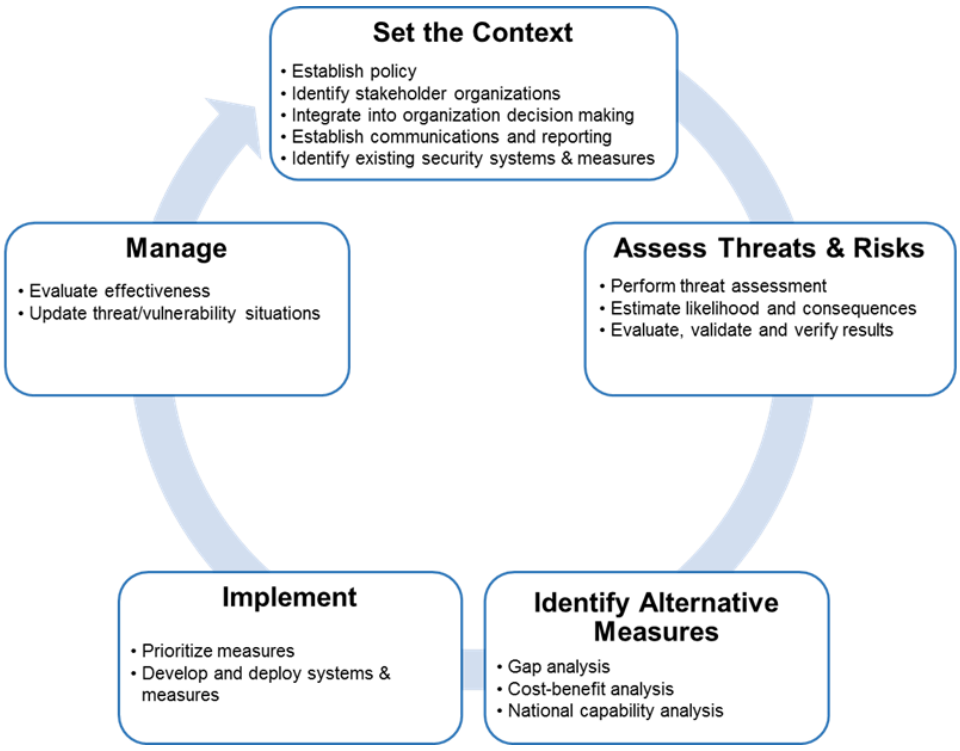
6.1 Risk-Informed Framework

Before new public health policy or programme can be implemented, consideration must go far beyond the intrinsic merit or worth of the proposed intervention (Catford, 2006). In terms of making managerial and political sense, interventions need to be shown to be reliable, valuable, acceptable, affordable, feasible and accountable. Hence, to determine if intervention is "able", factors pertaining to efficacy and safety, potential health impact, policy and political fit, cost and sustainability, capacity for action, and responsibility and monitoring must be evaluated. To help clarify and facilitate such decisional support to promote R&D and procurement for CBRN MedCM, one can refer to risk-informed framework which utilises a systematic and iterative process. The IAEA's risk-informed framework can guide prevention, detection, response, mitigation and recovery efforts to minimise risks (International Atomic Energy Agency, 2015). Given the IAEA's specific mandate, their approach has specifically targeted the low probability-high impact threats of nuclear and other radioactive material threats. However, because many chemical and biological agents also pose low probability-high impact threats, I consider the risk-informed approach to be compatible across the range of CBRN concerning the objectives of this chapter. Key components of this approach include decision-making support within a wider context in areas such as strategic planning; policy making; funding; prioritising R&D; as well as designing operational activities for security. Due to high potential negative impact of a CBRN event,

governments are not only challenged with taking all necessary steps to prevent its occurrence, but to mitigate the impact if such a catastrophic event does take place (International Atomic Energy Agency, 2015). Governments do not have unlimited resources, though. Hence, it is necessary to prioritise those methods that will contribute the most to reducing identified threats. Before focusing on economic solutions of this approach directly associated with CBRN MedCMs, the key components of a generic risk-informed approach are first briefly explained in this section.

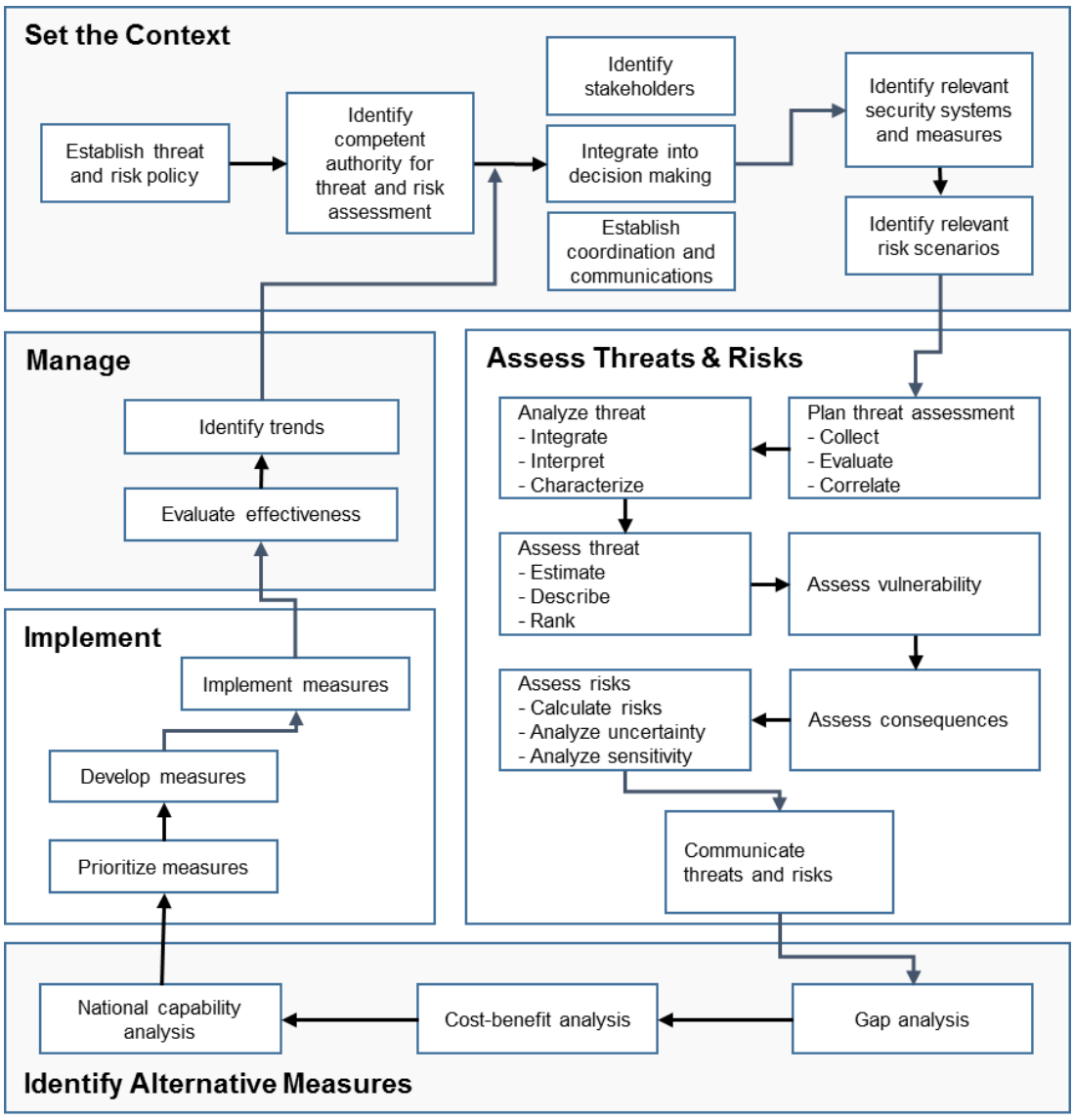
The individual and interconnected components of the risk-informed framework to implement security systems and measures (refer to Figure 21) are labelled as “Set the Context”; “Assess Threats and Risks”; “Identify Alternative Measures”; “Implement”; and “Manage”. Further details are outlined in Figure 22. In the first component, “Set the Context”, key considerations include the identification of which risks will be managed; who will be responsible for managing them; what information is pertinent; and what stakeholders are most central. Also during this step, resources required for the implementation of a risk-informed approach should be identified and estimated (e.g. budget, headcount, organisational structure). The next component of the framework, “Assess Threats and Risks”, aims to evaluate risks with current related policies, systems, and measures. This typically involves the estimation of threat, vulnerability, and consequences of potential actions of adversaries. Depending on decision requirements, evaluation methods to acquire relevant information can range from table top exercises with subject matter experts to detailed risk calculations.

Figure 21 – Risk-informed approach to implement security systems and measures (International Atomic Energy Agency, 2015)



In the next component, "Identify Alternative Measures", results from the risk assessment gained from the previous step are applied to identify potential improvements to best counter high priority risks. Especially concerning defence, attention to identification, prioritisation, and design of relevant security systems must be thorough. Three types of analyses to identify and evaluate alternatives are typically applied (gap, cost-benefit, and national capability). A gap exists when there is inefficient ability to guard against a threat. During analysis, gaps are usually determined by evaluating those threats which pose the highest degree of risk. Then, alternatives for mitigating those threats are identified. A cost-benefit analysis is applied to compare the cost of a proposed measure with the monetary value of its contribution towards the reduction to risk. And a national capability analysis encompasses the evaluation of the whole array of systems and measures aimed to address the threat. This form of analysis can be used to model multiple threat scenarios, especially when the nature of a threat can be altered by an adversary in response to particular security measures.

Figure 22 – Threat assessment and risk-informed approach template (International Atomic Energy Agency, 2015)



After it has been decided which security systems and measures are to be obtained, "Implementation" can be designed and deployed in accordance to project management practices. In addition to their effectiveness to reduce risks, prioritisation of security systems and measures should also consider budgetary and political factors as well as their feasibility and acceptability. Once systems and measures have been implemented and are deployed, the next step to "Manage" them takes effect (e.g. operation, maintenance and sustainment). Throughout this step, systems and measures need to be continually tested and re-evaluated. Adversary developments (e.g. nature of,

objectives, and capabilities) must be monitored to assure that measures remain effectively aligned against threats and vulnerabilities that are posed. New risk analysis information acquired during the monitoring process should flow back into the first step, "Set the Context", so that updates can be considered for the next iteration of the risk-informed approach cycle. To begin interpreting the utilisation of risk-informed framework more specifically relevant to the economics of MedCMs that protect against CBRN agents, the next section presents associated examples for the first component "Set the Context".

6.2 Set the Context

Before framework process can begin, there must be some perception of threat and political will to at least consider the initiation of action. Consequently, this section introduces political and behavioural economic concepts as it relates to initiating public health policy and demand for CBRN MedCMs. Namely, influences of the decisional process such as political interests, fear messages, emotion, and policy nudges are depicted. Correspondingly, it is intended to draw conclusions concerning a potential role that political and behavioural economics may play when setting the context of the risk-informed approach.

6.2.1 Fulfilling Political Interests

Promoting health requires public policy to support its prerequisites. Whilst this often includes sustainable resources, literature indicates a significant gap exists between declared health promotion policy and practice. The potential root cause for this gap is lack of political will to secure healthy environments. Although insufficient willpower could stem from lack of political courage or poor judgement, it can also be attributed to a politicians' inattentiveness to the unique structural conditions associated with the health policy domain (Zalmanovitch & Cohen, 2015). Of course, budget constraints as well as competing priorities might also play a role. As previously indicated, despite GHSI's call for concerted global action to strengthen the public health response to the

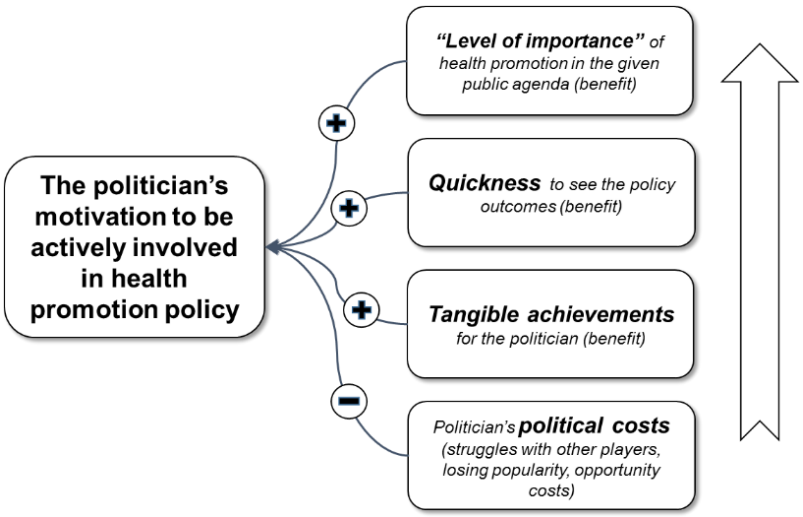
threat of international CBRN terrorism, few governments are willing to procure innovative MedCMs nor fund R&D initiatives needed to ensure availability.

Before undertaking active political involvement in a modern democracy to promote health – or create more demand for MedCMs –, certain conditions of rationality must be met (Zalmanovitch & Cohen, 2015). These are formulated as propositions (see Table 31) and assume that politicians are rational beings acting to optimise their own political self-interest, with the mobilisation of political gain (e.g. more voters) being a cornerstone. Given that promoting health often does not achieve this, then the avoidance of such policy is a rational decision. To illustrate the motivational aspects of such conditions, refer to Figure 23. As an example, one can consider the lengthy, risky, and expensive R&D process associated with developing innovative CBRN MedCMs. When combined with the historically low probability that a release of CBRN agents will occur, none of the conditions as depicted by the four propositions are likely to be met. That is, in the absence of acute perceived threat about a release of CBRN agents, the relevant health policy initiatives tend to lack importance. Secondly, a ponderous and risky development phase of up to 20 years is too long, and its success uncertain. Thirdly, even when successful, the long period's completion is likely to occur outside of one's own political term, meaning the tangible achievements would fall to one's political successors. This imposes political costs to the reigning politician because he or she could have benefited from alternative actions more compatible with the motivational aspects of the propositions.

Table 31 – Politicians' involvement in health promotion policies (Zalmanovitch & Cohen, 2015)

	PROPOSITIONS
1	As the level of importance of health promotion in the public agenda grows, politicians' tendency to be active in the area of health promotion will increase.
2	When the results of the politicians' actions regarding health promotion become evident more quickly, their tendency to be active in health promotion will increase.
3	When the products of the politician's actions regarding health promotion result in tangible achievements, his/her tendency to be active in health promotion policies will increase.
4	As the politicians' political costs for intervening in health promotion increase, their tendency to be involved in health promotion will decrease.

Figure 23 – Motivational Aspects of Propositions (Zalmanovitch & Cohen, 2015)



This leads to a paradoxical situation that can best be portrayed by the boiling frog metaphor. The premise of this scientifically disputed metaphor is that if a frog is suddenly put into boiling water, it will jump out. However, if the frog is put in cold water which is then brought to a boil slowly, it will not perceive the danger and will be cooked to death. The frog jumping out of boiling water symbolises the US response to the "Amerithrax" anthrax letter attacks in 2001 which accelerated its public health policy surrounding the BioShield program. The choice to do nothing and not prepare against CBRN threat symbolically represents the frog slowly cooking to death. By using the comprehensiveness of the risk-informed framework, it derives economic perspectives that can better avoid paradoxes. To review behavioural economic concepts allocated under the component of setting context, the following section clarifies the previously described metaphor of the frog jumping out of boiling water (or not).

6.2.2 Applying Behavioural Economics

Guiding decision based purely on an economic calculation basis may indeed appear rational; however, this approach would assume choice to be fully shielded from the reality of human limitations (e.g. ignorance, emotion, impulsiveness, distraction, and selfishness). Hence, behaviour influence on economics should be considered (Oullier,

Cialdini, Thaler, & Mullainathan, 2010). Indeed, behavioural economics is by no means a new concept and particular aspects were grasped even in the 1700s within the concept of Adam Smith's invisible hand theory (Smith, 1759). Namely, upon laying the foundations of classical free market economic theory, it was noted that the force of the free market would be driven by an entrepreneur's desire to maximise his or her own self-interests of maximised profits. While it was proclaimed that an entrepreneur's greed could motivate one to create innovative products capable of excelling the market standard, counteractions of competitors would assure that prices remain competitive. Within these forces of a free market, a positive condition for both consumers and entrepreneurs could be created (good products at good prices). Since Kahneman and Tversky (1979), behavioural economics study the influence of psychological, social, cognitive and emotional factors on economic decisions, in particular cognitive biases that reflect the bounded rationality of agents and alter their judgment. Thaler and Sunstein (2008) have shown that these biases may be used to improve the decisions of others, especially concerning health, and without restricting their freedom of choice according to their idea of libertarian paternalism. A deliberate use of behavioural biases for the benefit of others is based on three concepts; namely, Libertarian Paternalism, Influence, and Nudge (Oullier et al., 2010). From the term libertarian paternalism, paternalism signifies a policy adapted to guide or shift decision choices in socially desirable directions, while libertarian represents the need to respect an individual's freedom to act in accordance to his or her own belief.

Behavioural economics can play a significant role to set the context about the initiation of CBRN MedCM preparedness activities. Although former President George W. Bush was responsible for signing the US government's BioShield programme into law, for example, there is indication that behavioural response was first prompted by his predecessor, President Bill Clinton. After reading the book, "The Cobra Event" by Richard Preston, President Clinton became alarmed and summoned experts and government leaders to consider the implications of bioterrorism. He also requested his Defence Secretary, William Cohen, to read the book and conduct an intelligence analysis of the viability of a real-life cobra event. Although this book plots the fictitious

occurrence of mysterious deaths caused by a fabricated infectious agent, it references real history, politics, technology and bureaucracy of bioterrorism. Consequently, this reading influences President Clinton as a real example, to perceive and respond to the increasing probability of such an event. Hence, this availability or representativeness heuristic led President Clinton to adjust his federal budget proposal to augment defences against biological weapons (Charatan, 2002; Jacobsen, 2015). To substantiate the ability of political and behavioural economics to set actionable context, the following sections aim to demonstrate the utility of fear messages, emotion, and policy nudges.

6.2.2.1 Fear Messages

If stressing the negative consequences of health-impairing behaviours induces a level of fear, it can – under certain conditions – initiate a positive response to counteract the associated threat. This is referred to as a "fear message", with its potential to engage political action. To positively influence behaviour to counteract threat, Li (2014) suggests fear messages of a high-threat condition can indeed motivate positive attitudes/behavioural changes for those affected. Evaluated in the context of achieving political action against the threat of global warming, it is recommended that a message directed to change behaviour should contain both threat and efficacy content. The concept of creating a "fear message" by no means suggests it should be applied as a manipulative tool; it rather suggests effective and actionable communication can be appropriately applied by competent health authorities and/or even the public community to stimulate the right public health response and policy for self-protection. There are past related incidents where fear messages containing both threat and efficacy content appear to have been successful. For example, historically infectious diseases including plague and smallpox have been the cause of enormous fear and social distress. This often led to immediate and emotional responses to improve failures of public health systems (Smith et al., 2004). Even in the 1950s, cold war fears of bioterrorism were used to convince the US Congress to fund the transformation of a Malarial Control Center into the modern CDC (Richards, O'Brien, & Rathbun, 2002).

Following the 2001 anthrax letter terrorist attacks in the US, bioterrorism became an emotional issue capable of triggering immediate intense reaction. Namely, fear of bioterrorism drove politicians and government agencies to defend themselves from accusations they were unprepared for bioterrorist attack, leading to their BioShield program.

In a democracy, public fears have precedence over what politicians should do, even if the public's view is scientifically inaccurate (Posner, 2002). The power of the state to keep the public safe and protect well-being is based on common law, and politicians facing pressure from voters are keen to exploit it (Risse, 2016). Hence, public outcry can be very beneficial towards enabling federal agencies to pass associated legislation to remedy public concerns (Richards et al., 2002). Yet, unless occurring on a regular basis and/or with substantially high death rates, responses related to unconventional (CBRN) terrorism are likely to be only short-term. This infers that key to effective CBRN terrorism policy is its ability to establish a healthy balance between complacency and fear. While voter complacency poses risk that public health authorities will ignore issues off the radar of its voters, fear is essential to public action. However, response driven by fear bears the risk that when the threat fails to materialize, the credibility of authorities could be damaged.

To observe the relationship between the use of fear appeals, attitudes, and behavioural intentions, principles from available literature (Witte, 1992; 1996) were applied to an analysis, referred to as extended parallel process model (EPPM). EPPM suggests important variables (severity, susceptibility, response efficacy, and self-efficacy) must be perceived if fear appeal messages are to be effective. Perceived "severity" describes the seriousness of the threat and "susceptibility" indicates whether the message recipient feels personally exposed. Perceived "response-efficacy" is how effectively proposed counteraction is believed to be and "self-efficacy" entails the recipient's awareness of their own ability to perform this action. EPPM suggests a high degree of threat is required to sufficiently motivate response to fear messages; thus, evoking two different processes: namely, the danger and fear control processes. On one extreme, the

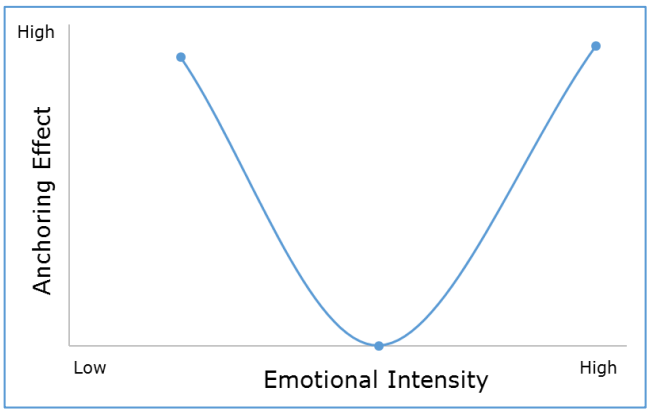
danger control process is an attempt to manage threat by performing the recommended actions which were communicated in the fear message. This process can only be initiated if the severe threat to which the message recipient feels personally exposed is perceived, with any recommended counteraction viewed as effective and self-efficacious. As illustrated in Chapter 3, despite decades of multiple EVD outbreaks, the international community maintained a rather quasi-laissez-faire attitude. However, the outbreak of 2014/2015 shifted the paradigm (Johnson et al., 2017). Namely, response included development of efficacious MedCMs against the deadly EVD. While the "unprecedented extent" of the outbreak introduced susceptibility even to western countries for the first time – constituting a threat to international peace and security –, it is plausible that several countries also viewed the unique adverse impact the EVD could pose within its own borders.

On the other extreme, the fear control process represents the unintended consequences of a fear message. Namely, although the recipient perceives a severe threat and feels personally susceptible, he will attempt to minimise the issue's importance if suggested solutions are interpreted as neither efficacious nor self-efficacious. Though this condition is typically portrayed by lack of response to improve environmental issues believed to cause global warming, it may possibly also be applicable towards the international availability of CBRN MedCMs. That is, because there are multiple potential CBRN threats and a viable solution in terms of making managerial and political sense to achieve fully comprehensive protection is lacking, authorities may choose to do nothing. If so, this would be a key contributor to the market failure and free rider effects which hinder the availability of CBRN MedCMs. Li (2014) concludes that, in a high-threat condition, both high and low-efficacy messages could result in positive attitudes and behavioural changes. By contrast, in a low-threat condition low-efficacy messages lead to negative changes and behavioural intentions.

6.2.2.2 Emotion

Although the previous section gives some indication that fear, in certain cases, can influence behaviour to counteract threats, one can also surmise that such emotion should not be exaggerated. During a decision-making process, there is a tendency for cognitive bias to rely too strongly on the first piece of information offered (the "anchor") or even uninformed random information points. Once an anchor is set, new messages aimed at shaping alternative interpretations which might differ from the anchor will be perceived with bias. Empirical evidence suggests there is a relationship between this anchor and one's emotional state (Araña & León, 2008). Namely, the degree of anchoring declines as emotional intensity increases, reaching a minimum for an average value emotional intensity. Hence, the estimated relationship between emotion and anchoring effect can be best expressed as U-shaped (see Figure 24). This experiment result infers that the optimal point for influencing opinion – with the aim of changing the *status quo* – would be when an intermediate level of emotional intensity can be achieved. This is because when emotional intensity is too low, blockage of short-term memory and lack of attention is dominant. By contrast, if emotional intensity is too high, thinking becomes disorganised and irrational interpretation of cost benefits will prevail. The relationship between emotions and the decision process is quite complex and evidence has not yet differentiated between valuation in the context of private and public or environmental goods. Yet, this suggests that some degree of emotional intensity might help to reduce cognitive load; thus, enhancing human decision-making.

Figure 24 – Relationship between Emotion Intensity and Anchoring Effect (Araña & León, 2008)



Upon interpreting the previous theories of political and behavioural economics and applying it to the real example presented in Section 6.2.2 concerning President Bill Clinton, congruency is given. Namely, it can be surmised that the book communicated a fear message proficient of leading President Clinton to perceive himself as personally susceptible to political high-threat induced by his lack of public health preparedness. Moreover, this message induced some degree of emotional intensity that reduced cognitive load (the lowering of the anchoring effect). The adjustment of the federal budget to augment defences against biological weapons indicates that subsequent review and intelligence analysis not only validated the context of this fear message, but also determined both response- and self-efficacy.

6.2.2.3 Policy Nudges

For a strategy to augment support for policy endorsement, nudging can be applied to sway decision. Nudges are informational interventions that can alter human behaviour in a predictable and beneficial manner without prohibiting alternative options. In fact, to be considered a nudge, the intervention may not be obligatory and must be easy and inexpensive to avoid (Thaler & Sunstein, 2008). To influence one to increase well-being, a nudge is a cognitive strategy to guide a person to make good choices for themselves. The core stimulus created via such behaviour sciences is that the body, mood, desires, and habits of human beings are put at the heart of economic concerns. In other words, given there are human flaws in individual decision-making, nudges can

work by making use of these flaws (Valatin, Moseley, & Dandy, 2016). To do so, relevant human cognitive factors that guide decision and increase involvement can be targeted. In Table 32, behavioural economic elements have been listed and categorised by Easy, Attractive, Social, Timely (EAST) nudges. Empirical evidence demonstrates, in a variety of settings, the potential impact these nudges can have on decision-making (Valatin et al., 2016). To first demonstrate a few generic examples, it has been shown under an EASY nudge that enrolment in a US pension plan aimed to benefit employees by increasing their savings will be higher if this choice is selected by "default"; and the undesirable choice only when one must manually opt-out. This is because people tend to accept the pre-set option. In this case, an increase from 37 to 86 percent could be observed for the beneficial option. Correspondingly, in countries where individuals are required to opt-out of organ donation programs, far higher donation rates can be observed than if an opt-in rule is applied. In other EASY examples, plain and clear simplification of UK tax letters were found to be 2 to 3 times more effective than previous standards and the removal of friction were measured to increase significant participation. To clarify and illustrate the latter, an insulation company determined that a key barrier to business was the issue consumers had with clearing their attics so that they could be insulated. After offering a service to clear the attics at cost, the company saw a five-fold increase in its insulation business (Valatin et al., 2016).

Table 32 – Behavioural Economics Elements of EAST Nudges

NUDGE BY CATEGORY

EASY	***Behavioural Insight*** (Valatin et al., 2016)	***Clarification***
DEFAULTS	Individuals asked to opt-out (rather than opt-in) to schemes	One tends to accept the more beneficial option if this choice is selected by "default"; and the undesirable choice only when one must manually opt-out.
SIMPLIFICATION	Make it clearer and easier	Plain and clear language
REMOVE FRICTION	Identify and remove actual or perceived barriers	Identify key obstacle(s) presented to one for reaching positive decision and offer solution to resolve.
ATTRACTIVE		
SALIENCE	Draw attention to key points	Make key messages in required bureaucratic and/or associated actions clear.
MESSENGER	People are heavily influenced by who communicates information	Careful selection of who is most influential for communicating information
PERSONALIZATION	Personal messages increase response rates	Personal addressed and inclusion of hand-written notes
AFFECT	Use strong feelings to prompt decisions	Reinforce emotional reaction to the real issue at hand (e.g. health impact).
INCENTIVE DESIGN	People focus on short-term rewards	Since people are especially loss-averse, award financial incentive in advance (to be paid back if agreed performance is not achieved).
SOCIAL		
SOCIAL NORMS	Tell people what others are doing so that people are made explicitly aware of other people's good behaviour	Explicit awareness of the good behaviour of others can strongly influence decision-making. Build perception of belonging to a group to develop team dynamic to achieve goals.
NETWORKS	Using social networks to encourage collective behaviour	Convince others by building perception that others are joining the policy; thus, forming a social norm.
COMMITMENT	Public commitment makes action more likely	Keep or lose rewards depending on whether commitments are held.
EXEMPLIFY	Individuals often respond to reciprocity and fairness	Motivate good behaviour by being a role model.
TIMELY		
PRIMING	People are influenced by subconscious cues	Discontinue routine behaviour by changing process; initiating need for new choice.
FRAMING AND MENTAL ACCOUNTS	People assign decisions to different mental accounts	Associate related budgeting with less sensitive "mental account" (e.g. if one budget label is typically not desirable to access, apply a more unprotected label).
KEY MOMENTS	Timing interventions at critical points	In cases of financial support, make payment conditional and payable directly before committed action is to take place.

Matjasko et al. (2016) suggest it could be effective to determine what influences behaviour, then to design nudges which aim to alter them. To illustrate how nudges could be applied towards the availability of CBRN MedCMs, one could revisit the

previous example illustrated in Section 6.2.2.1 concerning fear response. For instance, assuming a politician perceives a severe CBRN threat and feels personally susceptible but minimises the issue's importance because suggested solutions are interpreted as neither efficacious nor self-efficacious, this problem of fear control could potentially be resolved by applying the "remove friction" nudge. Namely, a feasible solution to remove friction could be the offering of a global and feasible approach towards achieving prioritized CBRN MedCMs, such as that witnessed during the EVD outbreak of 2014/2015 (Johnson et al., 2017). Assuming this alternative could be interpreted as efficacious and self-efficacious, applying this nudge would empower those overstrained politicians to transform political response from fear control to danger control. Correspondingly, the shifting of burden to third parties via a global approach would be a feasible solution in terms of making political and managerial sense. To integrate another nudge example, it has been shown under a "default" nudge that participation can be increased if individuals are asked to opt-out (rather than opt-in) to schemes. Hence, the number of countries participating in global CBRN MedCM ex-ante preparedness initiatives (before an event) could be increased if they are opted-in by default (e.g. via the amendment of an international public health agreement). If so, individual costs would most certainly be far lower and much more sustainable than when emergency measures for MedCMs depend on a handful of voluntary donors.

Concerning specific application of nudges to general health policy, the most relevant behavioural economic concepts are listed in Table 33 (Matjasko et al., 2016). The table describes each of these concepts and provides a general example of how it informs public policy.

Table 33 – Key Departures from Rationality and Their Related Applications (Matjasko et al., 2016)

DEVIATION FROM RATIONALITY	POSSIBLE BEHAVIORAL ECONOMIC APPLICATION
Time inconsistent preferences (e.g. Hyperbolic discounting) People tend to prefer more immediate gratification, even at the expense of longer-run well-being. This may lead to preference reversals, such as people repeatedly quitting and then resuming risky health behaviours, and dietary cycles of binging and purging.	Offer pre-commitment devices that allow people to restrict the choices of their future selves in order to increase the probability of adhering to the healthy behaviour. Research suggests that people are more successful in quitting smoking and losing weight when at the outset they post a monetary bond that would be forfeited in the future should they fail.
Bounded rationality Rationality in decision making is curtailed by a lack of information, cognitive limitations, and a finite amount of time to make a decision. People may also have finite amounts of willpower and experience decision fatigue.	Simplify how information is presented in order to make it easy for people to use. Simple checklists for important multistep procedures may be useful in preventing surgical errors and airline crashes.
Status quo bias People exhibit inertia, and tend not to deviate from the default option or reverse their earlier decisions. For example, many people stick with default options for organ donation, retirement savings, and health insurance plans.	Make the healthy option a default option, such as including sliced apples rather than French fries as a side in children's meals. Limit portion sizes.
Framing effects People react to the same trade-off in different ways depending on whether the possible outcomes are presented as losses or gains. Some people respond differently to risk presented as 80 percent chance of survival versus 20 percent chance of death.	Uptake may be improved by using gains-framed messages and incentives for encouraging healthy behaviours and loss-framed messages for encouraging use of health screenings.
Availability heuristic People judge the odds of a given event occurring based on how readily an example comes to mind. Diseases or conditions faced by a friend or which are the topic news coverage and advertising tend to increase individual's perception of their personal risk of the disease.	Prime a behaviour by providing examples relevant for that population. For example, youth may be more responsive to a drug prevention programme after the death of a celebrity from drug overdose.
(Mis)perceptions of social norms People want to conform to social norms but often misperceive the norms/behaviours of others. For example, many college students overestimate how much alcohol their peers drink.	Avoid conveying the message that large fractions of the population are engaged in risky health behaviours (especially to teenagers and others who may be easily influenced by bandwagon or peer effects).

As demonstrated by the example to nudge a danger control response to a fear message, a prerequisite to defining a behaviourally informed policy intervention is to fully understand the decision-making process at the stem of the targeted behaviour. That is, the problem must be recognised, the decision process traced, and deviations from rational decision-making identified (Michie & West, 2013). Yet, before a nudge design is finalised, it should be comprehensively tested to assure the nudge's impact is effective and its results are cost-effective. Pertaining to political motivation surrounding the availability of CBRN MedCM, one must also reiterate that benefits associated with R&D and/or preparedness against a probable attack are likely to

materialize far beyond the political term of an incumbent politician. This suggests that nudges capable of satisfying more short-term behavioural needs could be most effective.

6.3 Assess Threats and Risks

Under the "Assess Threats and Risks" component of the risk-informed framework, the purpose of this section is to clarify hypothesised threats so that low-probability/high impact events can be better interpreted. Because many technical difficulties hinder a maximum efficacious exposure of CBRN agents, most believe chances for a devastating attack to occur are small. "Risk" assessments aim to expose the level of risk presented to a particular asset or group (Gonzales, Schofield, & Herraiz, 2005). To understand risk, Figure 25 highlights that risk is a function of threat, vulnerability, and criticality. Correspondingly, this suggests that understanding risk is dependent on a clear understanding of all three of these components. Brief definitions associated with their assessments are listed in Table 34. Since threat represents the intentions and capabilities of an adversary, threat is guided by the aggressor's perception of the attack's potential consequences – criticality or impact – and likelihood of success – vulnerability (International Atomic Energy Agency, 2015).

Traditionally, to be informed of risk and apply this knowledge toward managing threat, qualitative statements or numerical ratings from each of these individual components are evaluated. Namely, a "Criticality" assessment addresses what impact will likely result if an identified asset is lost or harmed. A "Threat" assessment raises the question as to how probable it is that an adversary will attack those identified assets and a "Vulnerability" assessment evaluates which weaknesses the adversaries will most likely exploit to target identified assets (Gonzales et al., 2005). An assessment matrix example to identify potential ratings for criticality can be found in Table 35 and for threat assessments in Table 36. Although there are multiple methods for ultimately calculating risk, a common methodology utilises results from criticality (or impact),

threat, and vulnerability assessments. Hence, to calculate risk, a basic formula is most often applied:

Risk = Threat x Vulnerability x Criticality

> *"Threat times vulnerability represents the probability of an unwanted event occurring, and criticality equals the consequence of loss or damage to the critical infrastructure or key asset"* (Gonzales et al., 2005).

Figure 25 – Relationship between threat and risk and supporting components (International Atomic Energy Agency, 2015)

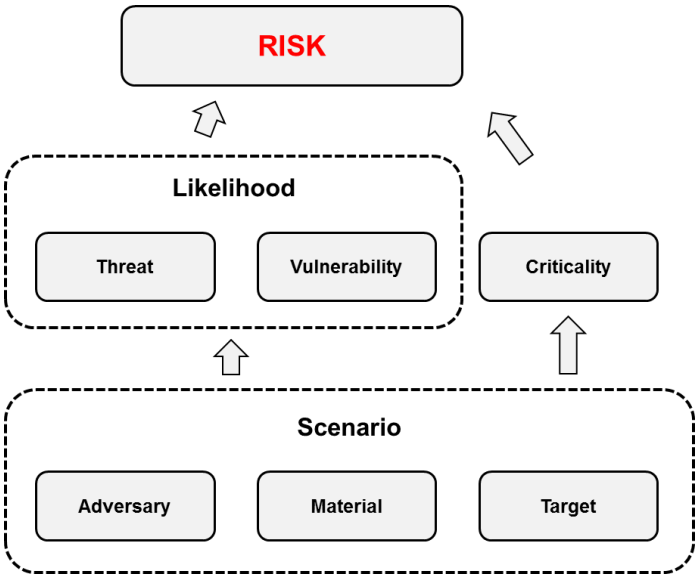


Table 34 – Definition of Risk and Assessments of its Components (Gonzales et al., 2005)

ASSESSMENT	DESCRIPTION
CRITICALITY/ IMPACT	A systematic effort to identify and evaluate important or critical assets within a jurisdiction. Criticality assessments help planners determine the relative importance of assets, helping to prioritize the allocation of resources to the most critical assets.
THREAT	A systematic effort to identify and evaluate existing or potential terrorist threats to a jurisdiction and its target assets. Due to the difficulty in accurately assessing terrorist capabilities, intentions, and tactics, threat assessments may yield only general information about potential risks.
VULNERABILITY	The identification of weaknesses in physical structures, personnel protection systems, processes, or other areas that may be exploited by terrorists. The vulnerability assessment also may suggest options to eliminate or mitigate those weaknesses.
RISK	The combination of all assessments (criticality, threat, and vulnerability).

Table 35 – Example of a Qualitative Impact Matrix (International Atomic Energy Agency, 2015)

IMPACT TYPE	1	2	3	4	5
HEALTH	Likely to produce no casualties	Likely to cause fewer than ten casualties	Likely to cause more than ten casualties	Likely to cause more than 100 casualties	Likely to cause more than 1000 casualties
ECONOMIC	Costs equal to replacement of a building	Costs significant at the city district level	Costs significant at the city level	Costs between 1% and 10% of GDP	Costs >10% of GDP
ENVIRONMENTAL	No significant contamination	Small area or temporary contamination	Significant contamination in a small area	Large area with Measurable contamination or small area with critical resources unavailable	Large area with critical resources unavailable owing to contamination
SOCIETAL	No major change in population behaviour or effects on social functioning locally or nationally	Occasional or minor loss of non-essential social functions in a circumscribed geographical area	Loss of many non-essential social functions in a circumscribed geographical area	Dysfunctional Behaviour and disruption of important social functions for a sustained period	Loss of belief in government and institutions Widespread disregard for official instructions Widespread looting and civil unrest

Table 36 – Example of Word Ladder Describing Overall Threat Levels (International Atomic Energy Agency, 2015)

RATING	DESCRIPTION
VERY HIGH	Adversaries have an established capability and current intention to attack the target It is assessed that an attack is highly likely
HIGH	Adversaries have the capability to attack the target and such an attack is within the group's current intentions It is assessed that an attack is likely
MEDIUM	Adversaries have some capability to attack the target, and such an attack would be consistent with the group's intentions, or they have the capability, but their intention may depend on current circumstances It is assessed that an attack is possible
LOW	Adversaries currently have little capability and/or intention to attack the target It is assessed that an attack is unlikely
VERY LOW	Adversaries currently have no capability and/or intention to attack the target It is assessed that an attack is very unlikely

Since risk of CBRN weapons use by non-state actors is dynamic (actively changing) and not static (as pertaining to a fixed or stationary condition), reliance on historical trends are apt to give a false sense of security when considering current and future threat levels (Unal & Aghlani, 2016). As described in the introduction of this chapter, the rapid development of dual-use technology underscores this risk, yet there are others. For instance, the newly won expertise and capacity to use chemical weapons on the battlefields of Syria and Iraq could be used to plan attacks outside these regional conflicts in the near future. Indeed, a most obvious threat would be the terrorist group, Islamic State (IS), where it is reported that periodic low-level use of chemical weapons has already become relatively routine in Iraq and Syria. In fact, the OPCW confirmed laboratory tests from Iraq had come back positive for sulphur mustard after 35 Kurdish fighters became ill in August 2015. The OPCW did not confirm who used the sulphur mustard, but a diplomat did state under the condition of anonymity that it had been confirmed to be IS fighters (Reuters, 2016). IS not only bears the capacity to acquire and effectively use chemical agents, but it has also demonstrated its intentions to obtain weapons across the whole CBRN range. Although the group may also experiment with radiological and biological means, chemical weapons continue to pose the most likely threat to IS's enemies (House, 2016). Stemming from its high impact, chemical weapons are sometimes referred to as the "poor man's" atomic bomb because they are

inexpensive and relatively easy to acquire. Actually, there are cases where extremists in the US have been convicted for stockpiling deadly chemical agents (Unal & Aghlani, 2016). Since any CBRN attack even with limited casualties and physical damage may stand to cause substantial disruption and uncertainly, there is a claim that no such attack can be deemed as having low impact.

To simplify portrayal of the dynamic characteristics of risk, the matrix in Figure 26 shows conventional weapons (e.g. firearms, explosives) as remaining highly attractive to non-state actors because their degree of difficulty is low (i.e. such weapons are easily obtainable). However, their scale of achievable "impact" can act as a disincentive of use. Hence, these weapons are generally plotted in the lower left quadrant of the matrix due to their more limited damage and disruption. By contrast, the CBRN weapon area occupies the upper-right matrix quadrant of impact and degree of difficulty, meaning they are difficult to obtain, but with high impact. The matrix in Figure 27 plots the incentive of use (scale of achievable impact) vs. disincentive of use (degree of difficulty) for a non-state group for each individual CBRN weapon type. This view is nonetheless somewhat over-simplified as some chemical agents for instance are easily acquired (chlorine for instance). The principles derived from this visual matrix of threat are revisited and expanded in Section 6.5.2 which involves a risk-informed prioritisation of hypothesized threats related to the implementation of specific countermeasures (Unal & Aghlani, 2016).

Figure 26 – CBRN vs. Conventional Threat (Unal & Aghlani, 2016)

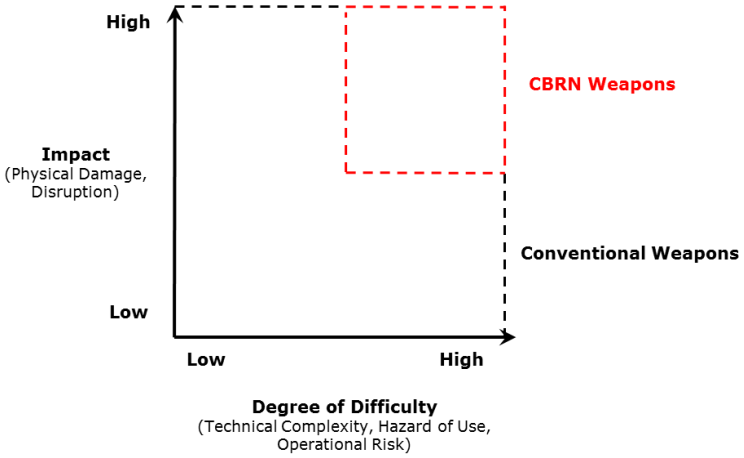
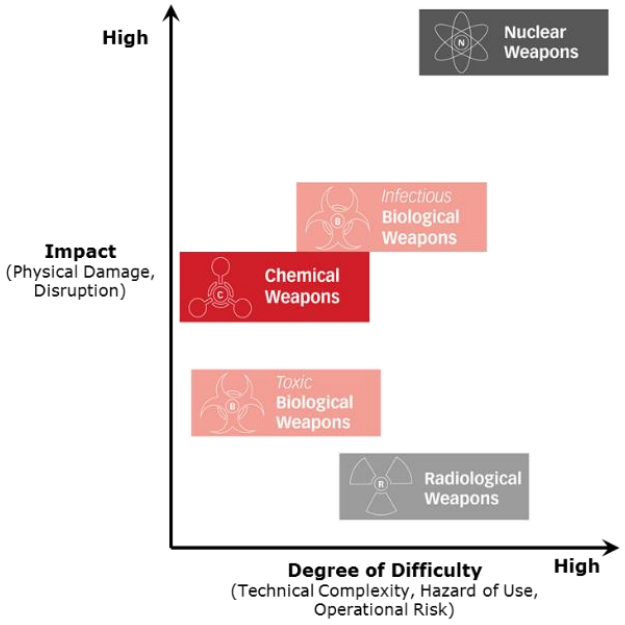


Figure 27 – CBRN Threat Matrix (Unal & Aghlani, 2016)



6.4 Identify Alternative Measures

Under the "Identify Alternative Measures" component, this section aims to clarify and summarize financial impact and evaluation of cost-benefit. Particularly for low probability-high consequence events where the optimisation of public safety is a key

objective, decisional support needs to prioritise those measures most likely to best shelter well-being. Moreover, their cost-effectiveness must also be determined so that such measures can be sustainable (Stewart, 2010). This notion entails that implementation plans to defend against potential terrorist attacks must indeed be executed in a financially responsible manner since there are financial constraints. The safeguarding of vulnerability while satisfying these constraints must be balanced through cost-effective responses (Chapman & Leng, 2004). While continuous focus on economic feasibility may intuitively appear to exhibit immoral characteristics, the distribution of a public good such as MedCMs can only be rationalised through the consideration of cost-benefit analysis. Indeed, when considering public policies and the resolution of ethical conflicts, ethical theory referred to as utilitarianism implies the best action is the one that maximises utility (e.g. for society) and not for affected individual(s). This theory was founded by Jeremy Bentham (and first published in 1789) who described utility as the sum of all pleasure that results from an action, minus the suffering of anyone involved in the action or the greatest happiness of the greatest number (Bentham, 2000). Correspondingly, "fair" is maximising net balance of social satisfaction with a decision-making process which weighs present and future profits with present and future losses (Salazar, 2013). Utilitarianism was substantially modified by his successors, in particular John Stuart Mill, who popularized the word and not only viewed actions as a core part of utility, but as the directive rule of moral human conduct, the rule being that we should only be committing actions that provide pleasure to society (Mill, 1863). Theories related to utilitarianism have been applied to social welfare economics. Yet, despite counteraction that could be achieved against main issues such as the crisis of global poverty or the importance of avoiding existential risks to humanity, there is inability to quantify, compare, or measure happiness or well-being.

6.4.1 Financial Impact of CBRN Events

A cost-benefit analysis can be utilised to measure cost associated with the reduction, avoidance, or transfer of risk (Stewart, 2010). This information can enable a decision

maker to reach risk-informed choices concerning cost utilisation (e.g. to assure proposed countermeasures to risk can make good use of societal resources). However, casualties and physical damage inflicted directly during an event can be compounded with psychological, social, political, and economic damage (Klein, 2007). For this reason, decision support framework of a cost-benefit analysis needs to consider various factors such as threat scenarios and probabilities, value of human life, physical (direct and indirect) damage, risk reduction, and protective measure costs (Stewart, 2010). Because it is probable that threat of terrorism will be driven by an intelligent adversary who will adapt to changing conditions to maximise likelihood of success, uncertainties are high because predicting threat must rely heavily on security expert opinion (e.g. derived from game theory). High reliance on judgement and scenario analysis deems it wise that any cost-benefit analysis be subject to a sensitivity analysis so that impact on a given outcome can be understood from a range of variables. Nonetheless, where there is substantial uncertainty about threat because an actual event may never materialise, it is inevitable there will be uncertainty concerning expenditures for protective measures.

Part II already provided many specific examples of overall economic implications that can result from CBRN attacks due to a variety of reasons which include diminished consumer and company expectations for the future. Yet, further examples can be found. Namely, efficiency of industry such as transportation and trade can be negatively impacted because governments and the private sector may be forced to invest in security measures (Unal & Aghlani, 2016). An increase in terrorism can even erode a sovereign credit rating. According to Procasky & Ujah (2015), an average 2-point increase in terrorism on a 10-point scale can lead to a half notch reduction in a sovereign's credit rating. However, this negative impact is especially pronounced for developing countries: the same 2-point increase in terrorism can lead to a whole notch downgrade in the sovereign credit rating (e.g. from BB to BB-). Even the clean up after a CBRN incident could require that people, buildings, infrastructure and the environment undergo a cost intensive and lengthy decontamination process. Moreover,

response and retaliatory measures directed towards associated attackers can cause further economic disruption associated with geopolitical conflict.

Several cost evaluations have been conducted to represent either real or simulated CBRN attacks. For example, the costs alone to decontaminate anthrax (its spores are extremely resistant to decontamination measures), after the 2001 attacks in the US is estimated at roughly 330 million USD (Schmitt & Zacchia, 2012). In another example, a terrorist attack with anthrax on the central business district in Seattle was simulated to assess its potential impact on real estate prices (Dormady, Szelazek, & Rose, 2014). Economic analysis predicts the median residential real estate sales price could decline by as much as 280,000 USD and by nearly 100,000 USD in nearby communities. If so, this would represent an impact on the residents of Seattle of more than 50 billion USD (a 33 percent overall decline) and likely lead to 70,000 foreclosures. The economic impact of a terrorist attack on the Los Angeles financial district with a chemical weapon, chlorine gas, was simulated to estimate its associated resource losses – e.g. injuries, business interruption, behavioural losses stemming from factors such as fear and social stigma effects (Giesecke et al., 2015). Taking into account the associated economic interdependencies such as migration, capital stock damage, investment, and business relocation, simulation results indicate that behavioural effects are highly dominant. Namely, while 10-year behavioural losses are calculated at 4.78 billion USD, ordinary losses (e.g. business interruption, physical damage, medical expenses) are 135 million USD. This represents a ratio of a total 10-year behavioural to ordinary losses of greater than 35. These ordinary losses are comprised of direct and indirect business interruption (131 million USD), other resource losses (3 million USD), as well as medical expenditure and financing (1 million USD) in the event year. Likewise, the ratio of a total 10-year behavioural to short-run direct business interruption reaches almost 60: 10-year behavioural (4,78 billion USD) / direct business interruption (81 million USD).

6.4.2 Evaluating Cost-Benefit of CBRN MedCMs

Upon evaluating CBRN threats and its associated potential economic impact, the cost of MedCMs to diminish health vulnerability appears quite high in relation to available financial resources (Ramseger, Kalinowski, & Weiß, 2009). For example, although it may be possible to procure some less innovative MedCMs (i.e. antibiotics against anthrax) because they are cheap and readily available on the market for other non-related purposes, some new MedCMs may need to be developed. As discussed in Chapter 1, this entails the associated out-of-pocket R&D costs for new drugs ranging from 850 million to 1.5 billion USD and a time period from 10 to 22 years needed to achieve an approved MedCM. Moreover, as indicated in Chapter 2, market sales opportunity for some MedCMs may not sufficiently incentivise industry to develop new innovative measures or to maintain pertinent manufacturing capabilities that can secure the availability for existing MedCMs. Even if maintained, a sudden peak in demand for a particular MedCM during an unexpected CBRN event or imminent threat is likely to exhaust appropriated supply resources. Consequently, it is advisable to carefully plan each individual MedCM on a case-by-case basis to determine its necessity, efficiency, and effectiveness (Ramseger et al., 2009). Although investment in MedCMs can often be determined as a good investment – with reduction of economic damage generated via use of MedCMs more significant than the cost of the measure itself – this does not necessarily indicate cost-effectiveness. For example, opportunity costs (briefly discussed in the next Section 6.5) – can be presented to the relevant community. Hence, decisions to develop and/or acquire MedCMs should include consideration of low-budget alternatives. Moreover, cost-effectiveness analysis should also consider the benefit even if the event does not happen: that is, if the MedCM can be utilised for other incidents such as natural disaster and accidents or as a deterrent by diffusing the motivations of terrorists (Ramseger et al., 2009).

As a basic orientation for evaluating economic benefit of life-saving MedCMs, a value of statistical life (VSL) can be applied. The VSL represents the amount a given group is willing to pay to reduce fatal risk with the expectation of saving one life. Although it is likely the VSL will deviate from group to group (or country by country), a value

of roughly 120 times the GDP per capita is typically applied (Miller, 2000). According to Viscusi (2016), the bias-corrected estimates of VSL for the all-set US sample is 9.6 million USD. However, given the VSL is subject to a range stemming from factors which include the economical basis of certain geography as well as age of the hypothesized dead, the calculation of a widespan of different values may be beneficial. For example, Hamilton et al. (2015) included a VSL of 9.1 million USD (in 2013 dollars) as a base case concerning decision making for reoccupation of contaminated areas following anthrax release in the US. Nevertheless, the associated sensitivity analysis included a range from as low as 1 million to a high of 10 million USD (Hamilton et al., 2015).

In addition to loss of life, case studies in Part II of this dissertation included depiction of materialized CBRN threats. In one example provided in Chapter 3, a paramount trigger of the international community's united effort to develop a MedCM during the 2014 EVD natural outbreak most probably the growing awareness that EVD could be exported to developed countries where negative GDP impact could claim far greater monetary loss reaching several billion USD. In another example from Chapter 4 involving acute and chronic occupational and environmental exposure to OP, a calculation model indicates that for every 1 million cases of chronic OP poisoning worldwide, over 300 million USD of GDP could potentially go unexploited. In contrast, Chapter 5 provides some indication that although adverse economic impact from radiological and nuclear events can be severe, the cost-effective role that MedCMs can play is less clear. A cost-effective scenario may result; however, this tends to hinge more heavily on their capability to meet purposes for both radiological/nuclear and accidental "peacetime" domestic events. With a view to expand methodology for achieving a more systematic evaluation of MedCM utilisation for mitigating financial risk, selected cost-effectiveness models are depicted in Appendix 1, Section 6.8. This is comprised of a Cost-of-Doing-Nothing Analysis and an approach to augment the more traditional DALY method.

6.5 Implement

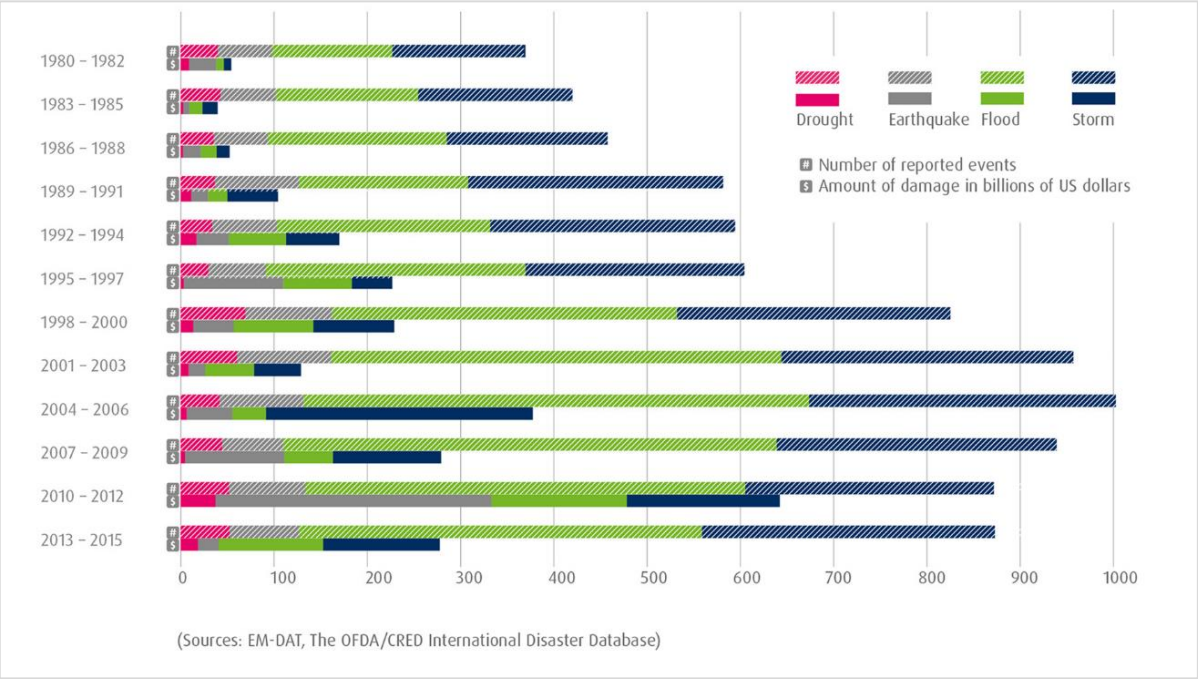
Assuming consideration of previous risk-informed components could provide for some political will, a "reasonable" probability of risk, and economic justification for medical intervention, further progress can be strived. Namely, evaluation of the "implement" component from the risked-informed framework may provide further decisional support towards the availability of particular CBRN MedCMs. To frame key economic considerations that influence access to finite resources, this section begins by highlighting examples of opportunity costs associated with implementation. Secondly, an approach that may potentially help to support the prioritisation of measures which aim to counter hypothesized threat is depicted.

6.5.1 Opportunity Costs

It can often be determined that when indirect losses (e.g. business interruption, GDP) are considered, then protective measures such as MedCMs are often cost-effective even if the probability of such an event is not high. However, opportunity costs can be significant and can render the investment less cost-effective (Stewart, 2010). The opportunity cost of a resource is the value forgone of not using the same resource in its next best alternative. Within the context of a societal perspective, the true cost of a resource used in one healthcare intervention is the loss of not using it in the next most efficient but unused intervention (Hutton & Baltussen, 2002). Concerning MedCMs, it can be evaluated that various CBRN scenarios represent significant adverse economic consequences. However, it is useful to put these negative consequences into perspective with alternative health risks. For example, where CBRN events can be considered as low probability-high impact, natural disasters represent a far higher certainty of occurrence. From a global perspective as illustrated in Figure 28, disaster preparedness measures for natural threats such as drought, earthquakes, floods, and storms are far more likely to express benefit. For instance, historically it can be easily observed that multiple occurrence of natural disasters over the decades have continuously and reliably claimed significant costs (e.g. over 850 natural disasters globally from 2013 to 2015 caused over 250 billion USD in damage). Hence, it is likely preparedness

initiatives against events of high certainty would be more prone to justify budget allocation from the finite resources of government (United Nations University, 2016). The concept of opportunity cost only underscores the importance of prioritising CBRN risk and the agents one should guard against. The prioritisation of CBRN MedCMs is addressed in the following section.

Figure 28 – Numbers of Reported Disasters and Amount of Damages (United Nations University, 2016)



6.5.2 Prioritization of Hypothesized Threat

Since budgetary constraints deem it necessary to prioritise implementation of particular MedCMs, preference should go to those deemed most apt to maximise cost-effective value. Parallel to considering the potential impact of a CBRN attack, one should prioritise those agents representing the most credible and "reasonable" probability of their release. After all, cost-effectiveness analysis assumes the minimalization of costs in the event of occurrence. In the absence of incidence, cost-effectiveness is less likely to prevail. Yet with multiple dangerous CBRN weaponry options now potentially available to terrorists, preparing against the risk of CBRN terrorism can easily

overwhelm those responsible. This is partially due to the difficulty associated with quantifying terrorist intent in relation to the technical ability to carry out an attack (Coleman et al., 2016). Nonetheless, assuming a credible threat is indeed posed by particular CBRN agents, "doing nothing" by avoiding MedCM preparedness could induce more economic cost than would an effective prioritised implementation (Ramseger et al., 2009).

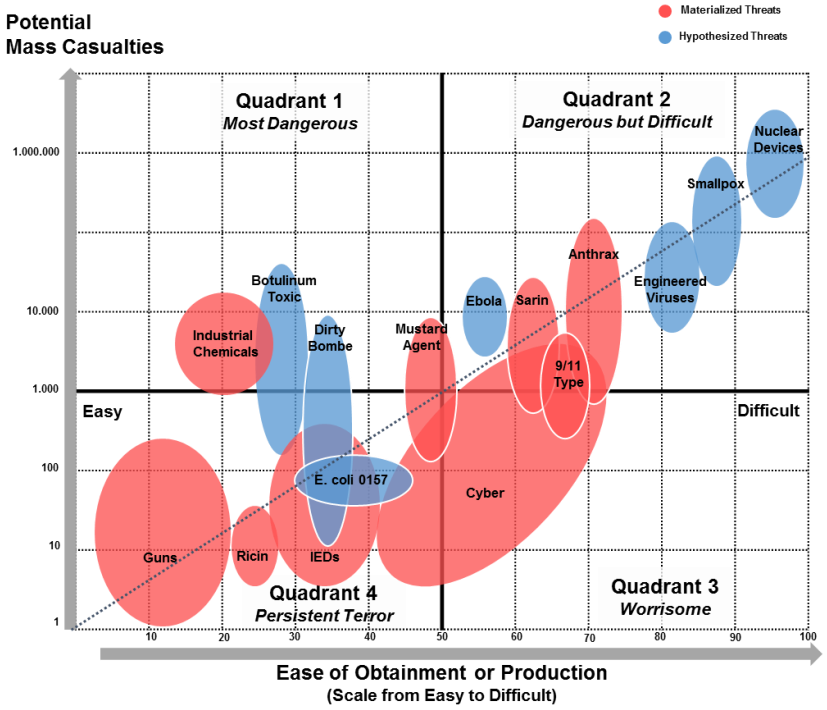
Various factors undercut the validity of applying historic probabilities to which terrorist weapons will be used in present and future. These factors include the fundamental rarity of high impact terrorist events, the changeability of terrorist intent, as well as the widening access to new weapons created via technological development. Assuming terrorist intention, various factors can render the prioritisation of countermeasures difficult. Firstly, there is a wide array of weaponry options with their diverse potential impacts. These options range from easily obtained guns and improvised explosive devices (IEDs) to less probable options with higher impact potential such as 9/11-type attacks and exposure to multiple CBRN agents. While weapons at the lower end of this accessibility range generally cause limited casualties, although the November 2015 terrorist attacks in Paris caused far more victims than the anthrax letters, the others require special MedCM preparedness response initiatives. Secondly, the ranking of ever-changing terrorist threats versus their impact as well as the cost-effectiveness of associated interventions challenge the integrity of prioritization measures on a continual basis. For a comprehensive consideration and synthesis of appropriate counteractions, an approach further developed by Coleman et al. (2016) aims to diminish complexity of these numerous influences by plotting the evolving nature of terrorism on a 2x2 matrix (see Figure 29). The plotting of diverse types of potential terrorist weapons in this way allows characterisation of the most urgent and appropriate countermeasure priorities and a dynamic interpretation of how these threats change over time. Accurately assessing the threat remains difficult. For example, the change in modus operandi in 2015 from explosives to automatic weapons went undetected and some "experts" would have easily rejected this possibility. Using the most dominant parameters applied by policymakers to assess modern terrorist

threats, the x-axis of the matrix represents the "ease of obtainment or production" of a weapon and the y-axis represents the "potential for mass casualties".

6.5.2.1 Characterisation of Terrorist Weapons

To characterise the diverse set of threats, each quadrant of the matrix is numbered clockwise, 1 to 4, to portray the level of threat. Starting with quadrant 1, the threat level begins with "most dangerous" to "dangerous but difficult", "worrisome" and "persistent terror". The weapons plotted in Figure 29 represent common concern; however, these weapons are not intended to represent all possible options. Although plotting is based on qualitative threat analysis from security professionals worldwide, historical information, and public health publications, Coleman et al. (2016) stress that their depiction is for demonstrating the prioritisation matrix only. Hence, it should not be debated here where each threat has been plotted or if each threat is correctly positioned (i.e. refer to previous comment concerning the number of Paris attack casualties versus Amerithrax). Moreover, the evolution of threat is dynamic, meaning such an analysis requires continuous updating before any decisional guidance should be sought (Coleman et al., 2016).

Figure 29 – Characterisation of Terrorist Weapons (Coleman et al., 2016)



Past and current preventative initiatives, including security and non-proliferation, render more catastrophic weapons costly and difficult to obtain. The diagonal line in Figure 29 which runs from the lower left up to the upper right corner of the matrix marks the ratio between the effort to use a weapon and the resulting casualties. Namely, weapons that lie predominantly above the line gain attraction by those with malicious intent because of their ability to cause more casualties and terror for the same unit of effort. However, those weapons below the line are frequently utilized because, although less efficient, they are more readily accessible. Given the limited quantitative precision of the y-axis – for which its determination includes historical events, expert opinion as well as mathematical simulations and modelling – it can only be considered semi-quantitative. To reflect the width of variation in the level of sophistication needed to obtain weapons on the x-axis and the height of potential impact on the y-axis, the borders of each plotted oval is extended accordingly. A key reason the terrorist weapons plotted in quadrant 1 are the "most dangerous" is because, in parallel to being easy to obtain, they can inflict mass casualties. Hence, interpretation of the matrix would suggest that absolute highest priority should be taken to remove threats from

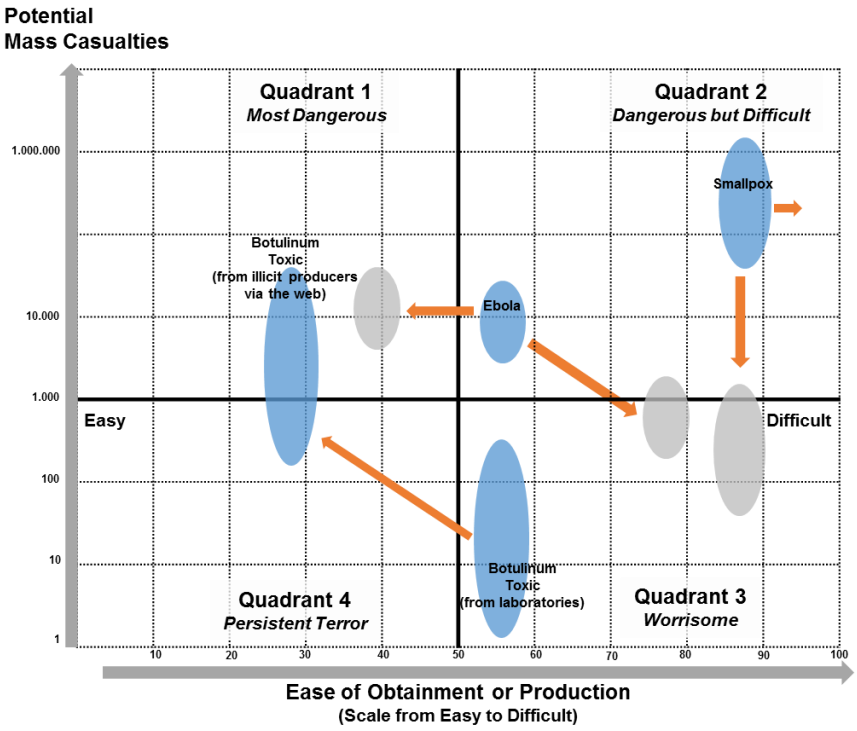
this quadrant. Although weapons plotted in quadrant 2 are most capable of creating mass casualty, they are classified as "dangerous but difficult" because it is believed preventive initiatives have sternly limited their access (Coleman et al., 2016). Nonetheless, as described at the beginning of this chapter, due to the increasingly available and affordable dual-use technologies subject to misuse for terrorist aims, this *status quo* should be viewed with caution (Unal & Aghlani, 2016). Quadrant 3 is dominated by cyberterrorism, labelled as "worrisome". Although its impact would appear more limited than those in quadrant 2, ease of obtainment and associated mass casualties are extremely diversified (Coleman et al., 2016). Also as already described, a more sophisticated level of cyberterrorism bears potential to turn critical infrastructure itself (e.g. chemical plant, nuclear power plant) into a weapon of mass destruction (Unal & Aghlani, 2016).

6.5.2.2 Movement of Terrorist Threats

To reflect the efficacy derived from diverse types of countermeasures already implemented and actively engaged, plotted weapons can be shifted from one quadrant to another (Coleman et al., 2016). To demonstrate qualitative evaluation which reflects specifically R&D for CBRN MedCMs and/or stockpiling, as well as operational mitigation to deter and prevent attacks, three examples are depicted in Figure 30. To portray the first example, hypothesized use of Ebola as a weapon is plotted. As described in Chapter 3, the natural outbreak of Ebola in 2014/15 showed that lack of robust response preparedness could threaten the security and peace of the international community. This learning curve led to improvements which include increased protection, enhanced communications and response within the global health community as well as the development of new Ebola vaccine candidates and treatments (Johnson et al., 2017). Hence, this development enables Ebola as a weapon to be replotted downward to quadrant 3 (Figure 30, diagonal arrow). Nonetheless, although these improvements are likely to reduce mass casualties associated with Ebola, the natural outbreak has also made the virus easier to obtain because increased quantities of live samples have been made available to multiple laboratories and culture

collections throughout the world. Consequently, Ebola as a weapon also warrants a shift to the left in the matrix to quadrant 1 (Figure 30, left-pointing arrow).

Figure 30 – Movement of Terrorist Threats (Coleman et al., 2016)



As a second example, if smallpox were obtained from laboratory stocks – or synthesized as a weapon for terrorist – impact would be far worse than Ebola due to its airborne transmission and high fatality rate. Given that eradication of the smallpox virus has led to a situation where most of the world's population is not immunized against the disease, its impact as a weapon could potentially be catastrophic. However, due to initiatives of the BARDA in the US to develop and stockpile smallpox vaccines and treatments, those responsible for preparedness – at least in the US – can claim associated potential mass casualties has been reduced from quadrant 2 down to quadrant 3 (Figure 30, downward-pointing arrow). In parallel to the availability of efficacious MedCMs to potentially deter use of smallpox as a weapon, Coleman et al. (2016) suggest that campaigns to discard frozen smallpox culture collection samples from laboratory freezers are likely to increase difficulty to obtain the virus. This could

perhaps justify the replotting of smallpox further to the right (Figure 30, right-pointing arrow). However, this can be a short-live change with progress made in synthetic biology. As a third example, it may be interesting to note the regression of prevention associated with a botulinum attack. This is due not only to eased access to the toxic material over the internet from foreign suppliers, but also by the availability of larger quantities. Correspondingly, threat of a botulinum attack moves up as well as to the left; thus, shifting into the most dangerous quadrant 1 (Figure 30, diagonal arrow). Although multiple initiatives aim to counter the threat posed by botulinum toxin, many of these are pending implementation (Coleman et al., 2016).

To proactively manage reduction to threats posed by potential terrorist weapons, the visual matrix could also be applied to effectively direct future actions and investments. For instance, rapid expansion of dual-use genetic technologies (including gene editing) means affordable research can be carried out beyond high-tech laboratories. Thus, access to engineered viruses is eased because persons with access to the internet and even a basic technical education can seize opportunities to study genetic sequences of pathogenic organisms. Moreover, it is increasingly possible to purchase genetic engineering kits which help obtain or produce engineered viruses and toxins. These influences shift the threat of engineered viruses from quadrant 2 to the left towards quadrant 1 “most dangerous”. Given this advancing trend, the matrix would sternly illustrate that initiatives to offset and decrease the ease of obtainment to engineered viruses and toxins should be implemented (Coleman et al., 2016; Unal & Aghlani, 2016).

6.6 Manage

Under the “Manage” component, alternative public health funding mechanisms and global collaborative attributes may act to increase the effectiveness of political efforts as well as mitigate risks associated with funding. Determination to minimalize both political and financial opportunity costs while maximising cost-effectiveness is more likely to draw public health funding resources towards measures that protect against

more predictable and widespread threats. However, ignoring CBRN MedCM preparedness could potentially lead to detrimental economic consequences. To manage this dilemma, it is necessary to move beyond a pure domestic sphere. Indeed, as globalization progresses, it is becoming clear that many public goods and policies that were previously confined to national territory are now issues of global impact and concerns. Examples include carbon emission of global warning, but also health which is an even greater international problem and increasingly considered as a global public good (Smith, Beaglehole, Woodward, 2003). This is especially the case when considering exposure to rare and deadly CBRN agents. For example, given that no single country had the ability nor incentive to stop EVD's natural spread across Western Africa in 2014/2015, need for international cooperation became essential. Correspondingly, it may be advantageous to review alternative public health funding mechanisms and global collaborative attributes that may act to increase the effectiveness of political efforts as well as mitigate associated financial risks. This may shed light on how to strengthen funding towards the international availability of CBRN MedCMs.

6.6.1 Funding and Sustainability

This section highlights international health sector funding mechanisms that compete less with resources routinely allocated to other more certain threats. In addition, lessons learned regarding a single nation's efforts – namely the US – to generate and sustain expenditures for its own CBRN MedCM programme are described.

6.6.1.1 International Health Sector Funding Mechanisms

Insights into alternative public health funding mechanisms and their underlying models can be drawn from the global health sector's past decade. Past funding mechanisms available include those which rely on models such as taxation, bonds, and contracts. However, more recent models also include insurance and auctioning. Despite their common objective of creating supplementary funding to provide medicines that address

unmet needs, the future liabilities created by each of these alternatives must be weighed (Gartner, 2015). Established international mechanisms include UNITAID, International Finance Facility for Immunization (IFFIm), Advanced Market Commitment (AMC) as well as the more recent Pandemic Emergency Financing Facility (PEF).

The organisation, UNITAID, represents a mechanism based on a taxation model. In 2004, the French president Chirac and his advisors proposed that taxation on airline tickets would be the best approach to raise health funding. This conclusion was based on the ease of its implementation, the higher net income of those citizens targeted, and the symbol of globalisation that could be represented without placing undue burden on the air travel market (Gartner, 2015). Subsequently, with the specific objective to lower prices for drugs against HIV/AIDS, malaria, and tuberculosis, UNITAID was established in 2006 by Brazil, Chile, France, Norway as well as the UK to be hosted by the WHO (World Health Organization, 2017a). By 2011, nine countries supported this French driven effort by imposing a tax on air tickets. Tax fees vary by country; however, in France the tax is 1 Euro for domestic flights and 6 Euros for international flights in economy class (10 and 40 Euros in first class respectively). This UNITAID mechanism generated approximately 1.48 billion USD which represents roughly 61 percent of total UNITAID resources (Gartner, 2015).

To summarize a model of bond issuance as a funding mechanism, the IFFIm mechanism can be referenced. Originally proposed by the UK Prime Minister, Gordon Brown, this initiative aimed to prevent the deaths of more than 5 million children from vaccine-preventable diseases. At the 2005 World Summit, the UK, France, Italy, Spain and Sweden committed nearly 4 billion USD to the launch of the IFFIm. These original donors used legally binding commitments of overseas development assistance to issue bonds on international capital markets, repayable over periods of up to 20 years (Gartner, 2015). Funds raised via IFFIm are used by the GAVI, the Vaccine Alliance, a public-private partnership, to purchase and deliver life-saving vaccines as well as strengthen health services in the world's poorest countries. By the end of June 2014,

the Vaccine Alliance had committed 8.7 billion USD in support until 2017 (International Finance Facility for Immunization, 2017).

The idea for yet another mechanism that uses Advanced Market Commitment (AMC) as an incentive for manufacturers to dedicate their efforts to develop vaccines for low-income countries was introduced by an economist of Harvard University, Michael Kremer (Gartner, 2015). In 2007, the Italian government led the launch of the AMC which partners included the UK, Canada, Norway, Russia, and the Bill and Melinda Gates Foundation (Gartner, 2015). Under the AMC, sponsors legally commit – prior to product development and licensure – to guarantee a price for a maximum number of predefined purchases of a vaccine that fulfils a set of previously defined technical specifications. If no suitable product is developed, then no AMC payments would be payable (Kremer & Williams, 2010). This funding option allows one to fend against free-rider issues (other stakeholders benefiting without contributing). Namely, higher prices can be imposed upon parties outside of the contract (Mossialos et al., 2010). By 2010, it could be announced that donors committed to providing a 1.5 billion USD AMC for a *Pneumococcus* vaccine suitable for children in the developing world (Gartner, 2015).

The UNITAID, IFFIm, and AMC mechanisms (outlined in Table 37) shared the common goal of creating supplementary funding. However, attributes concerning their objectives, models, and governance influence their effectiveness and impact on market-shaping. Market-shaping can be defined as actively influencing markets for health products to optimise price, quality, design, and sustainable supply (The Global Fund, 2015). Although France, the UK, and Italy are among those countries most competitively promoting their innovative funding mechanism initiatives, it is inevitable that only with the participation of others would their initiatives be likely to succeed. Yet, in addition to other state actors contributing to the success of these mechanisms, the role of non-state actors ultimately fosters the desired outcomes concerning market impact. Governance characteristics were identified that contribute to better performance. These include independency, participation, and accountability. Such

attributes could be better achieved within the context of multi-stakeholder governance as defined under the UNITAID mechanism than within an expert governance as in the case for IFFIm and AMC. For example, while French officials impose taxes under the UNITAID mechanism, governance structures include multiple stakeholders. Besides the inclusion of representatives from leading donor country governments and the WHO on its board, members also encompass governments from areas affected by the targeted diseases (e.g. government representatives from Africa and Asia). This enhances potential to efficiently and successfully channel funds appropriately to impact the market (Gartner, 2015). The specific UNITAID objectives that target market-shaping interventions include the definition of funding priorities, alignment with effective health partners, enhancement of strategic approach to funding, and engagement of country level stakeholders and partners to enhance the long-term. Subsequently, an evaluation (ITAD Limited, 2012) validated UNITAID's ability to identify, select, and fund market-shaping interventions through the implementation of its partners.

Table 37 – Earlier Established International Health Sector Funding Mechanisms

MECHANISM	MODEL	GOAL	BASE FUNDING CONCEPT	MAIN DONORS	CONTRIBUTIONS
UNITAID **2006**	Tax	Leverage innovation for global health, make medical innovation more accessible, lower prices for drugs against HIV/AIDS, malaria, and tuberculosis (Gartner, 2015)	Automatic and sustainable funding through taxation on airline tickets. Success factors are its ease of implementation, the higher net income of those citizens targeted, and the symbol of globalisation that can be represented without placing undue burden on the air travel market (Gartner, 2015)	Initiated by French President Chirac France, UK, Brazil, Norway, Chile, the Republic of Korea, Mauritius, Madagascar, the Bill & Melinda Gates Foundation (World Health Organization, 2017a) Hosted by WHO	Since its establishment, over 2.5 billion USD (World Health Organization, 2017a)
INTERNATIONAL FINANCE FACILITY FOR IMMUNIZATION (IFFIM) **2006**	Bonds	Purchase and deliver life-saving vaccines and strengthen health services in the world's poorest countries, prevent the deaths of more than 5 million children from vaccine-preventable diseases (Gartner, 2015)	Predictable funding through issue of bonds on international capital markets, repayable over periods of up to 20 years. Hosted by UNICEF until 2009 until the GAVI Alliance was recognized as an independent institution (International Finance Facility for Immunization, 2009). Funds raised are used by the GAVI, the Vaccine Alliance, a public-private partnership (PPP).	Initiated by UK Prime Minister Gordon Brown Australia, France, Italy, the Netherlands, Norway, South Africa, Spain, Sweden and the UK (International Finance Facility for Immunization, 2017). Hosted by GAVI Alliance	IFFIm benefits from long-term pledges of 6.5 billion from donor contributions over a total period of 25 years (International Finance Facility for Immunization, 2017)
ADVANCED MARKET COMMITMENT (AMC) **2007**	Contract	Guarantee a market for the pneumococcal vaccine suitable for children in low-income countries	Conditional funding. Sponsors legally commit – prior to product development and licensure – to guarantee a price for a maximum number of predefined purchases. If no suitable product is developed, then no AMC payments would be payable (Kremer & Williams, 2010).	Initiated by Italy Donors are the Bill & Melinda Gates Foundation, Canada, Italy, Norway, Russia, UK, the World Bank, Gavi, and UNICEF. Hosted by Gavi, the World Bank and UNICEF	From the total of 1.5 billion USD committed, donors have paid 1,2m as of end of 2016 (Gavi, 2016).

As opposed to multi-stakeholder governance, IFFIm and the AMC are more dependent on experts for shaping the strategic direction of their mechanisms. For instance, IFFIm demands the support of the financial industry to design and implement bonds and the AMC requires the involvement of experts in health and economics. Correspondingly, it could be expected that IFFIm financial experts specialised in identifying bond attributes may tend to display less passion and aptitude towards vaccine outcomes. In fact, five years after the launch of IFFIm, it was reported that although flow of global health resources could be accelerated, the ability to influence the market for vaccines was considered limited (Gartner, 2015). Fairly stated, there remained a lack of consensus concerning which framework could be used to evaluate this performance, and even whether market shaping had been defined as a specific objective. Nonetheless, since IFFIm funds could increase participation of manufacturers, evaluation did acknowledge that increased market competition provoked lower prices (Pearson et al., 2011). Yet its impact on the vaccine market was considered much smaller relative to its overall resources.

For the AMC, one might expect that health and economic experts could effectively re-shape the vaccine market through its governance, but this model did not adequately test the supposition. This is because the objectives initially aimed to support R&D. Yet, as a result of growing G8 pressure, refocus was later cast on the stockpiling of existing vaccines (Gartner, 2015). Subsequent evaluation determined (Dalberg, 2013) that, especially for those products which are almost market ready, the AMC mechanism as initially conceived may not be most suitable for dealing with market failure. For instance, manufacturers have expressed their preference for individual purchase guarantees to offset the risks incurred for their significant long-term investments. Thus, programmes need to better consider the specific realities of individual markets while assuring that a comprehensive approach can create overall benefit, striking a balance between reducing risk and the provision of sufficient market rewards.

In addition to participatory governance, another foremost success factor attributed to these funding mechanisms is the automatism of financing. Again, these conditions are best met by the UNITAID mechanism. For instance, once the airline ticket tax is implemented, further actions to sustain financing are not necessary. In contrast, financing for both the IFFIm and the AMC mechanisms are predictable, but both remain dependent on national government donors to fulfil their commitments (Gartner, 2015). And since the political cycle of donor countries rarely extends throughout the duration of the contractual commitments, these are not long-term mechanism of funding and their durability is uncertain. Besides, any doubts associated with honouring commitments is of utmost concern particularly in the developing world where infrastructural weaknesses undermine procurement and delivery capabilities (Mossialos et al., 2010). Since UNITAID funds could increase bulk purchase potential, its position for negotiating lower drug prices with manufacturers was strengthened. In fact, overall the UNITAID model achieved the highest level of market impact. By contrast, it was reported that market impact realised by the AMC model was the lowest (Gartner, 2015). Table 38 provides a summary of all three funding mechanisms and their relevant attributes concerning model, governance, financing, and market impact.

Table 38 – Global Health Sector Funding Model Summary (Gartner, 2015)

Mechanism:	**UNITAID (2006)**	**IFFIm (2006)**	**AMC (2007)**
Model:	Tax	Bond	Contract
Governance:	Multi-Stakeholder	Expert	Expert
Financing:	Sustainable	Predictable	Predictable
Market Impact:	High	Medium	Low

To improve pandemic response, an innovative financing scheme inspired by the natural outbreak of EVD in 2014/15 was to create a new collaboration with the World Bank Group (WBG) and the insurance industry. Key features of the Pandemic Emergency Financing Facility (PEF) were briefly summarized in Chapter 3. An outline (see Table 39) and further details are provided in the following paragraphs.

Table 39 – More Recent International Health Sector Funding Mechanism

MECHANISM	MODEL	GOAL	BASE FUNDING CONCEPT	MAIN DONORS	CONTRIBUTIONS
PANDEMIC EMERGENCY FINANCING FACILITY (PEF) **2016**	Insurance / Bond / Contract	Bridge the critical financing gap that begins in the early stages of an outbreak (e.g. influenza pandemic virus, SARS, MERS, Ebola, Marburg, and other zoonotic diseases) (World Bank Group, 2016b)	Involves collaboration with the WBG, the insurance industry, and capital markets. Coverage purchase in both insurance and capital markets helps to lower costs and increase the amount of coverage the PEF can obtain. Private risk-takers, bond investors or insurance companies, are paid a premium proportionate to the risk they are taking (World Bank Group, 2016c).	During G7 Meeting in Sendai, Japan and Germany committed as donors (World Bank Group, 2016b). Pledges are required to pay insurance premiums and interest on catastrophe bonds (e.g. Japan committed the first 50 million USD) (World Bank Group, 2016b). Hosted by the WBG	A maximum of 500 million USD over three years (e.g. capped at 300 million USD for influenza and 200 million USD for Filovirus (World Bank Group, 2016c)

Initially following the EVD event, it was thought that low-income countries could build their own preparedness with the support of high income countries. Middle income countries could contribute to this by purchasing an insurance policy for particular health risks and/or epidemics (Ugwumadu, 2015). More recently, the WBG announced in 2016 that it was collaborating with the WHO and the insurance industry (e.g. Munich Re [Münchener Rückversicherung], Swiss Re [Schweizerische Rückversicherung]) to launch an insurance fund to protect the world against deadly pandemics (Lawder, 2016). This fund of a maximum of 500 million USD over three years is referred to as the Pandemic Emergency Financing Facility (PEF) and covers outbreaks of the infectious diseases most likely to cause major epidemics. Currently foreseen diseases include new Orthomyxoviruses (influenza pandemic virus A, B and C), *Coronaviridae* (SARS, MERS), *Filoviridae* (EVD, Marburg) and other zoonotic diseases such as Crimean Congo, Rift Valley and Lassa fever (World Bank Group, 2016b). Pay-outs are triggered when an outbreak meets pre-defined threshold values such as number of deaths or infections within a given timeframe (Estrada et al., 2016). Pay-ins from the

insurance window vary by disease, severity, and geographic spread. For example, maximum payments under the PEF per event is capped at 300 million USD for influenza and 200 million USD for Filovirus such as EVD (World Bank Group, 2016c).

Typically, response funds are not available until a major pandemic outbreak has reached more catastrophic levels. However, the provision of early funding can significantly limit adverse effects. As stated in Chapter 3, if the PEF would have been in place before the natural EVD outbreak of 2014/15, surge funding could have been available in the early Summer of 2014 instead the autumn when the crisis had already skyrocketed. In fact, the WBG cites that if 100 million USD could have been mobilised for emergency response as early as July 2014, EVD cases would not have increased by tenfold (World Bank Group, 2016b). The availability of early surge funding could have not only prevented deaths, but it could also have saved billions of USD. Indeed, as a direct consequence of late funding, the international community ended up committing more than 7 billion USD for response and recovery initiatives. In addition, the impact on GDP of the main countries hit (Guinea, Liberia and Sierra Leone) exceeded 2 billion USD. To avoid such consequences, a quicker and more effective response against pandemics is economically advisable. Correspondingly, the PEF aims to bridge the critical financing gap which begins in the early stages of an outbreak up to the point where the crisis level rallies further monetary support. Under the PEF, funding is provided to qualified international response agencies as well as those countries currently eligible for financing from the International Development Association (IDA). The IDA is part of the WBG that helps the world's poorest countries. In the event of pandemic outbreak, these countries are characteristically faced with frail health systems and lack of monetary capabilities (World Bank Group, 2016b).

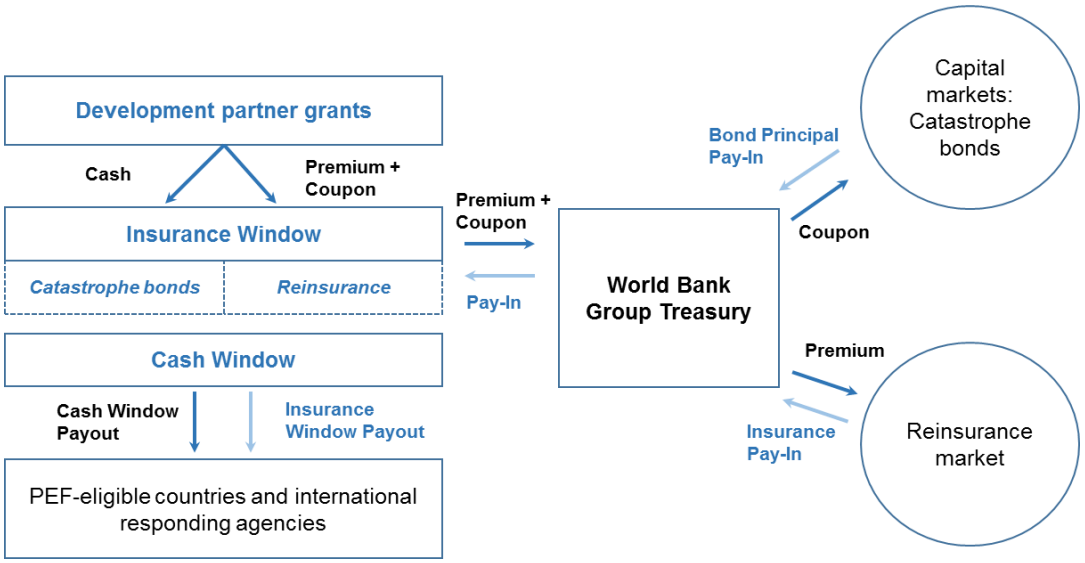
The monetary basis for the PEF is provided via both insurance and cash. Insurance funding is acquired in combination with payments from the reinsurance industry as well as capital market proceeds from catastrophe bonds (World Bank Group, 2016b). Catastrophe bonds (also known as cat bonds) are risk-linked securities that transfer a specified set of risks from a sponsor to investors. Catastrophe bonds were created and

first applied following two disasters in the mid-1990s: Hurricane Andrew and Northridge earthquake (Rode, Fischhoff, & Fischbeck, 2000). In the case of the PEF, these bonds are issued by the WBG Treasury to sell to a wide range of investors (e.g. private risk-takers, bond investors, insurance companies) via the International Bank for Reconstruction and Development (IBRD) (World Bank Group, 2016b; 2016c). The IBRD is owned by the governments of its 189-member countries (middle-income) and provides a variety of services to developing countries. These services include financing as well as technical and strategic advice (World Bank Group, 2014c).

To generate the required surge funding resources, the WBG Treasury issues catastrophe bond(s) in parallel with agreeing contracts with major insurers and reinsurers on the market. An overview of the PEF mechanism is depicted in Figure 31. Pay-ins stemming from insurance contracts or catastrophe bonds are transferred within their financial structure to the PEF in the form of a financial intermediary fund (FIF). The combined income secured through capital markets and insurance coverage help to lower costs, while simultaneously increasing coverage. This is achieved by offering broader risk diversity to investors. For example, while some investors target larger premiums which can be obtained when coverage is associated with higher risk (e.g. bonds that target events which occur more frequently), other investors may target coverage for highly rare occurrences. Concerning capital markets, a "bond principal" is paid into the WBG treasury. Throughout the duration of the bond maturity phase, the WBG treasury is obligated to make interest payments to the investors, referred to as "Coupon", which is proportionate to the risk they are taking. If the designated pandemic outbreak does not trigger pay-out by the time the bond has matured, the principal is returned in full to the investor. On the contrary, if the specified catastrophe does occur, a portion of the principal amount corresponding to the risk taken is retained (World Bank Group, 2016c). To stimulate the insurance mechanism, re-insurers are paid a "premium" which compensates the associated risk that coverage will be triggered. Thus, in the event an outbreak should fulfil criteria as pre-agreed, the re-insurance partners provide an "insurance pay-in". Through installation and clarification of such contractual and

bureaucratic conditions prior to an outbreak, this mechanism allows funds to reach affected countries in as little as 10 days (Estrada et al., 2016).

Figure 31 – Overview of the PEF Mechanism (World Bank Group, 2016c)



The PEF mechanism also requires long-term pledges from development partners. Their grants provide funding for the premium and bond coupons established within the insurance window. The contributions from Japan and Germany through their legally binding pledges during the 2015 G7 Leaders' summit allowed for the PEF's insurance window to be operational in July 2017. To enhance flexibility for resources that can be directed towards outbreaks not covered under insurance contracts, a cash window was scheduled to be operational in early 2018 (World Bank Group, 2016b; 2017b). The PEF is compatible with the WHO's International Health Regulations (IHR). The IHR aims to prevent future outbreaks from becoming epidemics by relying on international collaboration to detect, assess, and respond to public health emergencies of international concern (World Health Organization, 2005b). To gain further support, the G7 also encouraged expansion of this agenda to the G20 level. Annual premiums are estimated to fall between 55 and 65 million USD. Where payment levels fall within this range will depend on the trade-off between coverage and costs. For example, larger and earlier pay-ins from the insurance window will provoke higher premiums as

opposed to smaller and later pay-ins (World Bank Group, 2016c). Although the PEF financing mechanism is the first to cover pandemic risk via the support of an insurance window, it draws from experience gained from well-established risk models associated with climate and disaster risk. One example is the Caribbean Catastrophe Risk Insurance Facility which provides coverage against natural disasters. Other examples include the risk insurance pool which was created for five small Pacific islands under the Pacific Catastrophic Risk Facility and the Turkish Catastrophe Insurance Pool which helped homeowners mitigate against the adverse consequences of earthquakes (World Bank Group, 2016b).

As concluded in Chapter 3, a more careful prioritisation of MedCM development and availability can be viewed as a sort of international health insurance policy. Should global consensus for prioritized MedCMs be achieved by a separate entity (e.g. an international non-profit association), it is plausible that the adoption of an insurance model concept similar to the PEF could also contribute to filling R&D financing gaps for CBRN MedCMs created by market failure (Johnson et al., 2017). Hence, insurance pay-outs to global policyholders upon outbreak of specified naturally occurring diseases that can also be weaponized (or intentionally released) could be fulfilled by the provision of associated R&D progress and eventually the availability of MedCMs. As an alternative to the adoption of an insurance model concept similar to the PEF for MedCMs; however, it could be evaluated if sole reliance on the purchase of insurance coverage can suffice. Namely, to fortify investment cases and create more direct incentive for national governments to purchase insurance coverage, a country's bond ratings and investment criteria could reflect the status of its economic vulnerability to prioritized agents. Because the *status quo* of preparedness (i.e. in this case, insured versus uninsured) could impact financial markets and businesses' investment decisions, political interest to prioritize associated healthcare standards would extend far beyond the Health Minister (World Bank Group, 2017a). Previous review of the UNITAID, IFFIm, and AMC mechanisms would suggest that a taxation model could be considered to supplement insurance purchase funding if required. This might help to avoid the

potentially less advantageous characteristics associated with dependency on other models such as long-term donor pledges (contracts) and bonds.

6.6.1.2 Proposed US Health Sector Funding Mechanism

Recent US initiatives were specifically designed to raise funding for CBRN MedCMs. Based on taxation and auctioning models, some of these initiatives might have a significant potential. The first one, proposed a taxation model to raise innovation funds for new antibiotics via a surcharge referred to as Antibiotic Usage Fee (see Table 40). Given that use of antibiotics eventually contributes to the development of antimicrobial resistance (AMR) to classes of antibiotics (e.g. carbapenems), its usage constitutes consumption of a limited natural resource and renders it vital to develop new antibiotics. Hence, it is feasible that applying a tax could not only raise associated funding but doing so could also be justified.

Table 40 – US Tax Proposal to Raise Funding Capacity

MECHANISM	MODEL	GOAL	BASE FUNDING CONCEPT	MAIN DONORS	CONTRIBUTIONS
TAX ON ANTIBIOTICS (PROPOSED)	Tax	Create funding to reduce risk to manufacturers of innovative antibiotics that are subject to market failure	Because use of antibiotics eventually contributes to the development of antimicrobial resistance (AMR), its usage constitutes consumption of a limited natural resource. Hence, it is proposed in the US to charge a surcharge (Antibiotic Usage Fee) (PCAST, 2014).	If adopted, national government Host not established	With estimated annual sales of antibiotics in the US at ~12 billion USD, a tax of 5 percent, for example, would generate 600 million USD.

These funds could be used to reduce risk to those manufacturers associated with developing the new antibiotics and to enhance market rewards for those companies that have achieved successful approval (PCAST, 2014). Although the imposition of taxes may in some cases carry downsides (e.g. increasing healthcare costs, limiting patient access), it also offers upsides: parallel to raising funding capacity, the inappropriate uses of antibiotics might be better restrained if structured appropriately – e.g. targeting

generic antibiotics used in the outpatient setting (Sciarretta, Røttingen, Opalska, Van-Hengel, & Larsen, 2016). Assuming the sale of alternative products could be linked to contributing to specific CBRN threats, it is plausible it could be justified to adopt this taxation model to source CBRN MedCMs. For example, it was cited in the chapter introduction that new dual-use technology (e.g. nanostructures, genetic technologies like CRISPR Cas-9, synthetic biology and chemicals, drone, 3D printing) is becoming readily available and affordable for civilian purpose. Given such technologies can also facilitate the production and use of CBRN weapons, the taxation of some of these technologies to fund CBRN MedCM mechanisms could be evaluated and debated.

Although an approach to positioning industry incentives to counteract supply-side deterrents for CBRN MedCMs is described in Chapter 7, it is necessary to briefly foreshadow two of these incentives here (outlined in Table 41). This is because they may dually offer a platform to raise significant capital to fund CBRN MedCMs. One of these incentives is a wildcard patent extension – also referred to as transferable intellectual property (IP) protection or tradable patent voucher – that allow the recipient to extend the patent of another more profitable drug (e.g. blockbuster) within its portfolio approaching patent expiration (Mossialos et al., 2010; Renwick, Brogan, & Mossialos, 2016). The other is a Priority Review Voucher (PRV) which grants a fast-tracked regulatory review for another more profitable drug within its portfolio. Achieving time reduction for marketing approval via priority review does not directly increase income but enabling the manufacturer to sell the product earlier does allow revenues to be reaped in the short-term. This increases net present company revenues and thus its Net Present Value (NPV) which represents total development costs and expected present value of future revenues, given the relevant discount rate (Sharma & Towse, 2011). Under the provisions of both incentives, recipients can either utilise their earned vouchers directly to benefit drugs in their own product portfolios or sell them to another company (University of Pittsburgh Medical Center, 2007; Matheny, Smith, Courtney, & Mair, 2009; Renwick, Brogan, & Mossialos, 2016).

Table 41 – US Health Sector Funding Mechanisms

MECHANISM	MODEL	GOAL	BASE FUNDING CONCEPT	MAIN DONORS	CONTRIBUTIONS
PRIORITY REVIEW VOUCHER (PRV) **2007**	Auction	Created to encourage development of drugs for neglected diseases (alternatively, to raise funding for this cause)	Developers of an approved targeted drug receive a voucher for priority regulatory review of another drug. Alternatively, a PRV can be auctioned to the highest corporate bidder (Outterson & McDonnell, 2016)	N/A Hosted by US FDA	As of 2016, four vouchers have sold for an average price of 200 million USD (Ridley, 2017a).
WILDCARD PATENT EXTENSION VOUCHER **(PROPOSED)**	Auction	Proposed to encourage development of drugs for neglected diseases (alternatively, to raise funding for this cause)	If introduced, a patent extension voucher for another drug (e.g. blockbuster) could offer high value to manufacturers because significant sales volume could be shielded against erosion. Hence, it can be auctioned to the highest corporate bidder.	N/A If adopted, hosted by US FDA	Value would be significant e.g. AbbVie's top biotechnology drug, Humira®, represented roughly 8.5 billion USD in 2015 (EvaluatePharma, 2016)

To offer government an option to raise significant capital for funding initiatives surrounding CBRN MedCM preparedness such as R&D and/or stockpiling, it is proposed that government could also auction wildcard patent extensions and/or PRVs to the highest corporate bidders (Outterson & McDonnell, 2016). While this approach would provide industry with the alternative to obtain these vouchers by purchasing them instead of developing specified drugs, it could also raise capital for CBRN MedCM preparedness. Indeed, depending on the drug for which these vouchers would be applied and the relevant sales turnover in the country issuing them, their value can be significant. For example, if the patent of AbbVie's top biotechnology drug, Humira®, were to be extended by a wildcard patent extension in the US, its annual US market sales of roughly 8.5 billion USD in 2015 could be shielded against generic erosion (EvaluatePharma, 2016). This is because patent extension would enable the manufacturer to maintain its higher price associated with market exclusivity. Nonetheless, this extension would also bear significant social costs. For instance, when companies apply the extension to disease areas that are not related to CBRN MedCM funding purposes, patients suffering from those non-related diseases would bear the costs of the extension. Those patients would continue to pay higher prices than would have been the case if the extension had not been applied. This unjustly transfers costs

from one non-related disease area, for which the incentive was established, to a more profitable disease area for which it was applied. In this case, generic manufacturers would also be disadvantaged because the launch of their low-cost alternatives would be delayed in the market via the extension's protection. Consequently, the auctioning of patent extensions has been stalled and remains subject to controversy (Mossialos et al., 2010). In contrast to wildcard patent extensions; however, PRVs are very cost-effective because they create almost zero social costs: only those expenses associated with extra personnel needed to conduct a priority regulatory review are incurred (University of Pittsburgh Medical Center, 2007). An example from the US that represents the potential value of a PRV is reflected by the biotechnological company, United Therapeutics Corporation, which sold the PRV it earned to a subsidiary of AbbVie for 350 million USD. In another case, Retrophin Inc sold theirs to Sanofi for roughly 245 million USD (Dulaney, 2015).

6.6.1.3 US BARDA Sustainability Efforts

By 2016, the US BARDA could announce that in addition to MedCMs that target radiological agents, its CBRN MedCM programme supported 21 MedCMs against biological agents and that it added 14 of these to the USA's national stockpile (Lurie, 2016). However, a lack of preparedness against EVD during the crisis might represent a missed opportunity for the BARDA programme in terms of demonstrating the clear economic value of its programme to US government donors. Specific reasons were not spelled out, but a representative of BARDA did express that donor fatigue was becoming an issue. Moreover, there was increasing pressure to emphasize the economic value of its CBRN MedCM preparedness programme so that substantial use of taxpayer funding could be better defended (Robinson, 2015).

To reinforce its own sustainability, BARDA strives to increase the efficiency of its approach. For example, there is higher priority to target MedCMs capable of broadening usage to commercial areas. This entails increasing focus on MedCMs that have the capability to meet both CBRN and "peacetime" conventional purposes. For

instance, instead of protecting against specific chemical and radiological agents, new strategies are to treat injuries. This is because many pathologies resulting from exposure to these agents are like those observed with more common diseases. This can include pathogen reduction technologies for blood, silver-impregnated dressing for thermal (and other) burns, artificial skin substitutes and debridement technologies for thermal burns (and diabetic ulcers), and antibiotics for resistant organisms. To fortify ROI, BARDA has set a goal that 80 percent of its stockpile should include broader usage MedCMs that extend to commercial areas (Disbrow, 2016; Hatchett, 2016; Lurie, 2016). However, this will not answer the need for all specific MedCMs.

Other BARDA efficiency initiatives include the enhancement of existing MedCMs, cost containment, utilisation of existing technologies as well as the exploitation of less costly stockpiling alternatives (Hatchett, 2016). Enhancements of MedCMs can include increasing yield and/or potency, extending shelf-life, and simplifying storage (Hatchett, 2016). In addition, since one-agent, one-drug approach is not suited for new diseases, BARDA is shifting focus to platform technologies (Lurie, 2016). Concerning cost containment measures, BARDA launched a tool in 2013 to improve financial planning and portfolio management. This tool is referred to as Total Life Cycle Cost (TLCC) and aims to track the total cost to the US Government and sponsor of a MedCM over its full life – e.g. discovery, development, acquisition, infrastructure, operations, support, and disposal (Merkeley, 2016). Utilization of existing technologies entails supporting the development of diagnostic assays which are compatible with existing commercial platforms (Hatchett, 2016) and/or assessing viability of utilizing MedCMs already approved for other diseases. For example, the active ingredient midazolam to treat nerve agent exposures is a benzodiazepine typically used to treat conditions such as seizures or to induce sedation. Silverlon® burn contact dressings can be applied to sulfur mustard burns and Alteplase® (originally indicated for the treatment of acute ischemic stroke) can treat sulfur mustard inhalation (Hatchett, 2016; Laney, 2016). Stockpiling alternatives include exploiting less expensive alternatives to traditional stockpiling such as vendor-managed inventory – i.e. industry guarantees specified quantity for government use in their own inventory (Hatchett, 2016).

As outlined in Chapter 2, because the market rewards associated with CBRN MedCMs are drastically lower than commercial disease markets, BARDA providers are typically eager but less experienced smaller biotechnology companies (usually start-ups) that depend on government largesse to finance the development of CBRN MedCMs (Maher et al., 2012). Consequently, BARDA challenges include sustainment of these manufacturers following initial procurements (Disbrow, 2016). Failure to do so could potentially restrict future availability of prior MedCMs successfully developed. However, to help curtail this resource-intensive requirement to sustain the manufacturing capabilities of smaller companies, contract manufacturing with companies that are already part of a more robust industrial manufacturing base can be agreed. This allows small developers to reap benefits in the form of royalties while manufacturing is secured by self-sustained sources.[5]

6.6.2 Collaborative Risk Mitigation and Effectiveness Models

As revealed from review of the international health sector funding mechanisms in Section 6.6.1, lessons from the past can be drawn to further refine innovative financing for the long-term. Whether using models such as taxation, bonds, contracts, insurance, or auctioning to raise capital, the solutions best capable of avoiding donor fatigue are more likely to persevere. While there is indication that the effort involved to acquire funding via these mechanisms may have some influence (e.g. automatism vs. donor commitments), there is also value in clearly defined objectives and multi-stakeholder governance. As highlighted under the UNITAID mechanism, the combination of a more automatic fund collection via taxation and the participatory nature of their multi-stakeholder governance vastly contributed to this approach's ability to shape the market by lowering prices for drugs against HIV/AIDS, malaria, and tuberculosis (Gartner, 2015). Built upon its success, a high-level task force which included World Bank President Robert Zoellick and UK Prime Minister Gordon Brown recommended the extension of the airline tax to include more countries (Mccoy & Brikci, 2010).

[5] Acknowledgment to Reeves, S. V. (2017, May 18). Major General, US (Ret) for providing comment

Although individual countries such as France, the UK, and Italy strongly championed their chosen funding initiatives, it was inevitable that only with the participation of others would their initiatives be likely to succeed (Gartner, 2015). Indeed, the financial burden and responsibility to provide long-term funding for R&D and stockpile acquisitions remains enormous. For example, to better secure development, access, and response capabilities in the US under the BARDA programme, it is of increasing importance for BARDA to extend its partnerships beyond the US borders. This section introduces two further international partnering models to emphasise extended benefits associated with a unified multinational response. These models offer guidance directly applicable towards strengthening international availability of CBRN MedCMs. The first model depicts specific aspects associated with the Transatlantic Multi-Public-Private Partnerships which enabled the development of the Galileo space-based navigation system project. The second model describes lessons learned during the 2009 H1N1 influenza pandemic concerning international infrastructural deficits.

6.6.2.1 Transatlantic Multi-Public-Private Partnerships

Public Private Partnerships (PPPs) are commonly applied to situations where market conditions do not adequately entice industry to get involved. This is especially the case when new public goods or services must be financed, and public debt is already important or when demand for private goods and services is low, but governments want to encourage technological innovation and demand. Common themes of PPPs are the sharing of risk and the development of innovative, long-term relations between the public and private sectors. Perhaps less known is that this concept can be extended to include multi-public-private partnerships (MP^3) such as involving various EU Member States or cooperating with the US to form a transatlantic multi-public–private partnership (TMP^3). The main advantage of a multi-public-partnership (MPP) is avoidance of duplication in civil/scientific programs amongst the member states. Upon collaborating with private industry to transform the partnership to a MP^3, the financial risk associated with high-technological requirements can be spread. Moreover, investors are enabled to feel more reassured about engagement due to the shared views

of several countries (and higher number of committed customers); especially over politically sensitive security issues (Zervos & Siegel, 2008).

To best understand the nature and potential advantages of these concepts and their variations, it is useful to refer to lessons learnt from the EU's Galileo space-based navigation system project. According to Zervos & Siegel (2008), the most notable MPP was created at the European level in 1970 when the European Space Agency (ESA) was formed. A key lesson drawn was that even though some knowledge and technology had already been developed in other parts of the world (e.g. US, Russia), the European-only collaboration project did not have access to it. While it would have been possible to develop such technologies independently, doing so would have added significant costs and time to the project. Furthermore, there was certainly no guarantee that the newly developed European technology would be superior to foreign technologies based on long learning curves. To quickly gain such technology and avoid delays in achieving the main goal – i.e., creation of the Galileo space-based navigation system – expansion of the MP³ model to TMP³, which included transatlantic support from the US, was determined as advantageous. This lesson may also be valuable when considering availability of technology surrounding CBRN MedCMs.

6.6.2.2 International Access Infrastructure

Despite it becoming clear since April 2010 that most of the vaccine produced in response to the 2009 H1N1 influenza pandemic was not needed and millions of doses had to be destroyed, this event provided an opportunity to learn much about infrastructure needed to achieve international access to MedCMs. While the intensity and quickness of the vaccination campaign reached an unprecedented level, it was rapidly apparent that several barriers hampered the efforts of the WHO as well as various governments to deploy and/or receive a vaccine. The nature of these barriers concerned poor pre-agreements on associated legal, regulatory, and logistical issues. These are summarised in Table 42. To accelerate GHSI efforts to strengthen health preparedness and response for CBRN threats and pandemic influenza (Marinissen, Barna, Meyers, & Sherman, 2014), the Global Health Security Agenda (GHSA) was

launched in 2014. GHSA partners include an expanded network of international organisations and over 50 countries. The aim of both the GHSI and the GHSA builds upon the objectives set by the WHO's IHR. Hence, it includes the improvement of global access to MedCMs. Fortunately, the 2009 H1N1 influenza pandemic did not become more severe; thus, the consequences posed by MedCM access barriers were not detrimental. Although the high cost of unnecessary vaccines could have been better used, lessons learnt from this event call for concerted collaboration of relevant organisations, policymakers, regulatory and legal experts as well as logisticians of the international community to narrow the global preparedness gap by improving infrastructure (Marinissen et al., 2014).

Table 42 – Barriers to Availability of MedCMs

BARRIERS	NATURE	DESCRIPTION
NATIONAL STOCKPILE GOVERNANCE	Legal	National legal guidelines for procurement, stockpiling, and use of MedCMs may limit a countries ability to share with foreign governments or international organizations (Marinissen et al., 2014).
LIABILITY PROTECTION	Legal	The limitation the liability of manufacturers and physicians in the event of adverse effects resulting from new medicinal products. Such protection can be funded from excise tax imposed on e.g. vaccine doses (Mossialos et al., 2010; Elbe et al., 2015; Renwick et al., 2016).
EMERGENCY USE AUTHORIZATION (EUA)	Regulatory	When evidence deems it reasonable to believe the product is effective, its benefits outweigh the risks, and there is no alternative, a prequalification process to use a MedCM even if it is not approved needs to be formally agreed internationally (Marinissen et al. 2014; Elbe et al. 2015).
ANIMAL EFFICACY RULE	Regulatory	Because patients exposed to rare and highly dangerous CBRN agents are often not available to test MedCM efficacy, regulatory authorities must recognize the "animal rule" which bases safety and efficacy on animal models (Elbe et al., 2015).
MASS DRUG ADMINISTRATION SYSTEMS	Logistical	New systems able to execute mass administration of medicine outside of the normal clinical settings are necessary in order to protect significant numbers within a given population within a short period of time (Elbe et al., 2015).
IMPORT AND EXPORT REGULATIONS	Logistical	Potential donor and recipient countries need to conduct thorough review of import and export regulations to assure restrictions with custom authorities do not impede shipments (Marinissen et al., 2014).
LOGISTICAL GUIDANCE	Logistical	The movement of MedCMs across international borders can require refrigeration, arrival reports, and shipping containers may be too large for some commercial flights. In addition, several players may be involved. To help reduce corresponding impediment, the WHO published guidelines (World Health Organization, 2005a; Marinissen et al. 2014).
DATA SHARING	Logistical/ Legal	Globally sharing information about the pathogens causing lethal infectious diseases would better support development of new MedCMs. Yet, various factors hinder such data exchange (e.g. scientists withholding their data pending publications, lack of government will to be associated with a major new outbreak). Hence, new mechanisms aimed to incentivize and promote the international sharing are needed (e.g. Global Initiative on Sharing All Influenza Data [GISAID] (Elbe & Buckland-Merrett, 2017).
AGREEMENTS	Legal	Agreements on funding to cover various costs (e.g. MedCMs, shipping, storage, cold-chain requirements, ancillary supplies) must be in place before associated public health emergencies are triggered (Marinissen et al., 2014).

6.7 Conclusion

Compiling and applying existing economic models and tools guided by components of a risk-informed framework can challenge the *status quo* concerning the funding of CBRN MedCMs. Though the cost-benefit of government investment can often be determined, the venture remains risky. This is because expenditures (e.g. R&D, procurement, opportunity costs) are certain, yet benefits are likely and (as of now) only

in the future if the rare and uncertain event occurs. Alternatively, at the least, it would need to be conceivable that preparedness measures against a specific threat could demotivate terrorist intentions and deter attack. To safeguard and enhance the sustainability of investment, a reduction of political and economic opportunity costs as well as avoidance of donor fatigue can be pursued.

Demand-side rationale for CBRN MedCMs ultimately requires acknowledgement and resource allocation by politicians with the relevant responsibility. Thus, enhancement of political motivation is key to enabling the availability of this public good. In setting this context, a global approach to achieve MedCM solutions appears to offer significant advantages, with a team of world leaders best placed to raise the political importance. Likewise, sharing the overall burden for developing solutions would reduce the individual political costs of each member. If coordinated globally (e.g. via TMP[3]) it is conceivable that policy nudging could be induced. For example, friction would be removed because solutions are executed externally, while team dynamics, awareness of good behaviour, and social norms would be created. This approach would also enable the global community to establish required legal, regulatory, and logistic infrastructure, as well as create access to a pool of the best available technologies. Hence, a keystone for knowledge sharing and the design of infrastructure compatibility could promote further risk mitigation and effectiveness of government efforts.

Partnering with credible institutions to communicate “fear messages”, together with viable countermeasure solutions, may further increase political motivation because anchoring effects could be diminished, and danger control responses triggered. Since it is rational to expect politicians to seek opportunities that attract voter support, enhancing civilian appreciation for CBRN investment could further raise the issue’s importance while lowering the political costs. This could be achieved through better communication of CBRN threats and associated preparedness requirements to civilian communities.

Concerning the reduction of economic opportunity costs, funding sources that use taxation (e.g. of dual-use technology), auctioning (e.g. of priority regulatory review vouchers), and insurance models (e.g. opt-out charging for coverage that allows access to latest MedCM technology) may be best. In some cases, the probability of cost-benefit can also be increased (as applicable) by scaling the evaluation of adverse economic impact caused by the release of CBRN agents via events which may be more prone to occur (e.g. laboratory and industrial accidents/pollution, natural outbreak).

Through use of economic tools, it is suggested that government leaders could deem it rational to allocate sufficient investment to develop and procure CBRN MedCMs appropriately. Yet, this alone may not be enough. To further reinforce investment cases and create even more direct political incentive, CBRN threats must be prioritized via global consensus. If each individual country's vulnerability to these specified risks could be reflected in financial markets and business investment decisions, this would transform CBRN MedCM preparedness initiatives from being solely a public healthcare issue to a more mainstream political agenda item. Correspondingly, collaboration between governments, academia, private endeavours, and even institutions could expand. Likewise, this could incentivize membership to an insurance concept that aims to provide availability of MedCMs that can mitigate the risks that prioritized CBRN agents can pose to social and economic structures.

6.8 Appendix 1: Models for Assessing Cost-Effectiveness

This is a supplement to Section 6.4.2 which addresses the evaluation of CBRN MedCM cost-benefit. Under the risk-informed framework component, "Identify Alternative Measures," two models, a Cost-of-Doing-Nothing Analysis and an augmentation to the DALY approach are depicted. These aim to optimise methodology for achieving a more systematic assessment.

6.8.1 Cost-of-Doing-Nothing Analysis

Meltzer, Cox, & Fukuda (1999) defined a study including categories of medical cost, value of lost lives, value of lost workdays, and net cost of vaccination to better understand the economic impact of pandemic influenza. Although the analysis is based specifically on a natural outbreak of pandemic influenza in the US – not a terrorist attack – the targeted categories measured, and the nature of its outbreak offer compatibility. Namely, in contrast to its seasonal variant, influenza pandemics pose a substantial hypothesized threat because such an event is rare and human populations often lack immunity to it. Compounding the problem is that seasonal influenza outbreaks tend to mostly affect infants and the elderly, while influenza pandemics are more likely to weaken and kill the young and healthy. Consequently, there is a general lack of preparedness and public health initiatives in place. The development and administration of vaccines across large populations would need to be executed reactively as opposed to proactively. Influenza pandemics have killed significant numbers of people worldwide even recently (e.g. H1N1 contributed to an estimated 8,870–18,300 deaths in 2009/2010). However, other examples demonstrate that these pandemics are known to kill far more: the Russian Flu of 1889–1890 which killed an estimated 1 million; the 1918 Flu in the US resulted in an estimated 20–100 million deaths (Prager, Wei, & Rose, 2016). According to the World Bank, it is highly probable that a severe outbreak could destabilise societies and economies somewhere in the world within the next 10 to 15 years. While global annual costs of moderate to severe pandemics are estimated at roughly 570 billion USD (or 0.7 percent of global income), the cost of a severe pandemic influenza similar to the 1918 Spanish outbreak could cost

up to 5 percent (or more than 4 trillion USD) of the global GDP (Fan, Jamison, & Summers, 2015; World Bank Group, 2016b).

Based on a Monte Carlo mathematical simulation, Meltzer et al. (1999) indicated that a pandemic influenza outbreak alone in the US could lead to 207,000 deaths, from 314,000 to 734,000 hospitalisations and as many as 42 million outpatient visits. Calculated in 2012 USD, this study estimated that the total economic losses of such a pandemic would fall between 90 and 220 billion USD (Prager et al., 2016). Over 80 percent of the loss would be linked to loss of life (measured as present value of expected future lifetime earnings). Interestingly, it was determined that while vaccinating 60 percent of the population could reap the highest economic returns, obtaining this coverage was not necessarily deemed as realistic since too much time is required for the vaccine to become effective (Meltzer et al., 1999). However, this study did not consider general equilibrium impacts nor associated resilience and behaviour responses. To clarify these impacts, corresponding evaluation – a cost-of-doing-nothing analysis – is summarised in the next section.

To understand general equilibrium impacts and resilience and behavioural responses to rare, but deadly events, a cost-of-doing-nothing analysis can be applied. For example, a particular computable general equilibrium (CGE) analysis (Prager et al., 2016) targeted pandemic influenza and appears quite compatible for recognising a broad range of potential economic impacts stemming from outbreaks (e.g. including changes in medical expenditures, workforce participation). The CGE approach can be applied for understanding economic impact of natural disasters, technological accidents, and terrorist attacks. In fact, research team members of this particular study have already applied it to other bio-threats (Rose, Oladosu, Lee, & Beeler Asay, 2009; Dixon et al., 2010; Oladosu, Rose, & Lee, 2013). And this approach has been utilised for a diverse range of disasters and countermeasures (Rose, Avetisyan, & Chatterjee, 2014) and even travel behaviour (Prager, Rose, Wei, Roberts, & Baschnagel, 2015).

CGE analysis has proven to be effective at modelling the two major consequence types that influence economic impact the most. These are resilience (Rose & Liao, 2005; Rose et al., 2007) and behavioural responses (Rose et al., 2009; Giesecke et al., 2012). Resilience effects represent the recapture of production via overtime or extra shifts following an adverse event where behaviour of avoidance can include economic loss due to a reduction of tourism, leisure events, educational activity, and use of public transportation. Including these influences creates a broader perspective of individual causal factors by obtaining more accurate and transparent estimates of the total economic impacts. It also provides actionable items that policymakers and public health officials can execute in their attempt to mitigate associated economic risk. To better understand the aforementioned CGE analysis which targets influenza pandemics (Prager et al., 2016), the following sections briefly depict the scenarios, methodology and results of the approach.

6.8.1.1 Scenarios and Methodology

To conduct analysis for general equilibrium impacts, resilience and behavioural impacts, two influenza outbreak scenarios (seasonal and pandemic) were considered. Since it is known that vaccination can reduce the spread of the virus and hinder corresponding economic impacts, four cases (see Table 43) were defined to distinguish between disease severity with and without the utilisation of vaccination. Then a multimarket model of producer and consumer behavioural responses was simulated for each one of the individual cases by impact category (see Table 44) in 2012 USD. Given 10 distinctions within the impact categories, this led to impact calculations for 40 individual factors (10 distinctions times four cases). Data and parameters for this analysis were obtained from the US Centers for Disease Control (US CDC), general literature, and published data on travel expenditures.

Table 43 - Cases to Distinguish Disease Severity (Prager et al., 2016)

CASE 1: NO VACCINATION, SEASONAL OUTBREAK
CASE 2: NO VACCINATION, PANDEMIC OUTBREAK
CASE 3: VACCINATION, SEASONAL OUTBREAK
CASE 4: VACCINATION, PANDEMIC OUTBREAK

Table 44 – Impact Categories: Producer/Consumer Behavioural Responses (Prager et al., 2016)

IMPACT CATEGORY	CGE DISTINCTIONS
WORKFORCE PARTICIPATION	Reduction in labour workforce participation
MEDICAL EXPENDITURES	Increase household spending on medical services
AVOIDANCE BEHAVIOUR	Staying home from work (reduction in labour workforce participation)
	Keeping children from school (reduced attendance)
	Keeping children from school (caregiver avoidance; reduction in labour workforce participation)
	Reduction in inbound international travel (via exports)
	Reduction in outbound international travel
	Reduction in domestic travel/leisure activities
	Reduction in public transportation use
ECONOMIC RESILIENCE	Recapture production through overtime or extra shifts

6.8.1.2 Results

In the event of no vaccination against pandemic influenza, this analysis concluded that a negative impact on the US GDP of 25.40 billion USD could be expected. However, vaccination could reduce the losses to 19.94 billion USD – a reduction of over 5 billion USD. But when avoidance behaviours and resilience effects are considered, a pandemic influenza outbreak has the potential to cause economic losses of 45.32 billion USD without vaccination, and 34.43 billion USD with vaccination (see Table 45) – a reduction of almost 11 billion USD. The substantial difference in these ranges highlights the importance of considering behavioural and resilience factors.

Although the total CGE analysis summations in Table 45 show that vaccinations can result in economic savings for both seasonal and pandemic scenarios, two extremes can be noted. The first is a scenario where there is no vaccination for pandemic outbreaks,

which would likely inflict the most substantial negative impact on GDP. The second entails vaccination against seasonal influenza where there would be slightly less negative financial impact than without.

Table 45 – Influenza Outbreak Simulation Results in 2012 billion USD (Prager et al., 2016)

Impacts	No Vaccination		Vaccination		Description
	Seasonal	Pandemic	Seasonal	Pandemic	
GDP (w/o avoidance & resilience)	-4.95	-25.40	-4.71	-19.94	Includes reduced workforce participation due to illness, death, caring for family, or vaccination as well as medical expenditures
Avoidance	-6.19	-33.39	-4.59	-25.12	Individuals avoiding activity due to fear of being infected (e.g. reduction of inbound & outbound international tourism; domestic travel and tourism [incl. attendance of public gatherings]; use of public transportation; and attendance of public educational facilities)
Resilience	2.22	13.47	2.31	10.63	Refers to production recapture or the ability of U.S. firms to work overtime or extra shifts to make up lost production.
Summation	**-8.92**	**-45.32**	**-6.99**	**-34.43**	Includes resilience

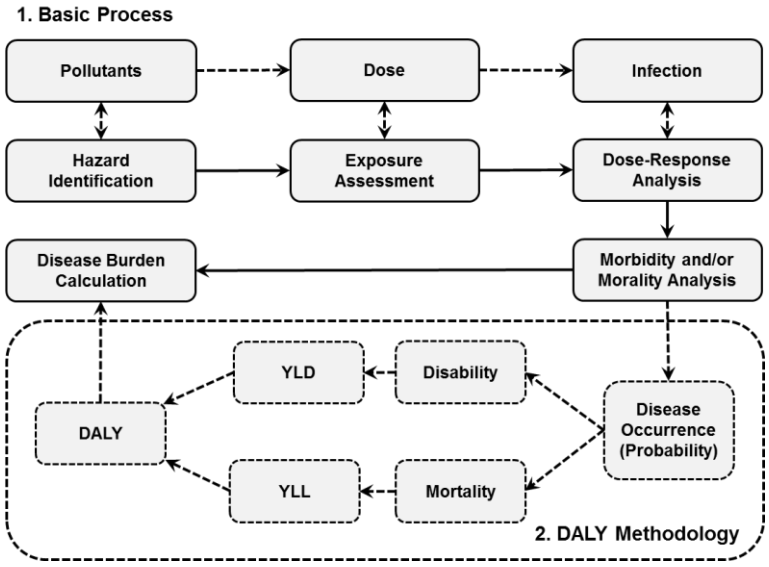
6.8.2 Augmentation to the DALY Approach

As described in Chapter 3, the WHO and WBG developed the DALY approach to prioritise medical intervention for materialised threats. This approach has been widely used since the 1990s to evaluate global and/or regional burden of diseases (Murray, 1994; Gao, Wang, Chen, Ngo, & Guo, 2015). Over the years, multiple revisions have enhanced its applicability to guide health resource allocation based on cost-benefits associated with the implementation of appropriate medical intervention. Although this model does not consider behavioural or resilience factors, it may be applicable for scenarios where these factors may be less pronounced. As presented in Chapter 4, for example, there is widespread environmental exposure to OP chemicals due to its multiple exposure routes. This section demonstrates the potential utility of applying DALYs towards pollutants.

The use of time as a unit enables DALYs to quantify disease burden by measuring a reduction of life years and quality following the outbreak of diseases. Because many environmental pollutants, namely inorganic substances (e.g. lead, mercury), organic substances (e.g. OP pesticides), and microorganisms (e.g. Escherichia coli, salmonella) are also known to inflict disease, their impact on health can also be interpreted as a disease burden. Although this might imply compatibility of the DALY tool, further methodologies referred to as "environmental burden of disease study" are first required before DALYs can be applied. The corresponding framework which illustrates the joining of these two separate methodologies is illustrated in Figure 32. The basic process depicted in Part 1 of this framework is analogous to what is already utilized and is referred to as human health risk assessments of hazards from environmental pollutants. However, instead of obtaining only a probability of risk as outcome, the estimates of morbidity and/or mortality are derived to serve as input for disease burden and DALY calculations as illustrated in Part 2. Exposure assessment encompasses the identification of hazardous exposure routes as well as a calculation of the dose received. Ideally, dose-response analysis is based on epidemiological study and determines the probabilistic relationship between the exposure dose and the health risk. This then leads to the morbidity/mortality analysis which classifies the associated

health effect. To obtain DALY, YLD is calculated via a disability analysis and YLL via a mortality analysis (Gao et al., 2015). Whereas this approach is potentially more effective than conventional environmental pollution risk assessments, Gao et al. (2015) conclude further study is needed so that health-effect evaluation methods about pollutants under various circumstances can be standardised.

Figure 32 – Environmental Burden of Disease Study with Usage of DALY (Gao et al., 2015)



Using environmental burden of disease study methods with usage of DALY has been effectively engaged for a variety of chemicals. For example, it could be estimated that more than 8 million persons in India, Indonesia, and the Philippines suffered disease, disability, or death from exposures to industrial contaminants (e.g. lead, mercury) from toxic waste sites in 2010, resulting in 828,722 DALYs (Chatham-Stephens et al., 2013). Another study concluded that because the burden of disease caused by low but widespread environmental exposure to lead is often underestimated, the environmental burden of disease approach is a useful tool to support decision making process in public health and in environmental management (Jarosińska, Biesiada, & Muszyńska-Graca, 2006). However, Grandjean & Bellanger (2017) suggest that while useful, the DALY metric disregards subclinical dysfunctions, adheres to stringent causal criteria, and is hampered by gaps in environmental exposure data, especially from industrializing countries (Grandjean & Bellanger, 2017). Therefore, calculations to derive exposure-

related health costs for comparison with DALY estimates should be encouraged to obtain more comprehensive and valid conclusions on the environmental burden of disease.

Chapter 7 COUNTERACTION OF SUPPLY-SIDE DETERRENTS

In Part I, "Components of Market Failure", it is indicated that if diverse governments deem it wise to create availability of CBRN MedCMs, then industry must clearly perceive the associated market demand as being compatible with their "financialised" business model approaches. As illustrated, however, the corresponding market rewards are drastically lower than for alternative commercial disease markets. Hence, the industry base that is willing to dedicate its R&D and manufacturing capabilities to the supply of solutions embraces few manufacturers with proven abilities. To address consequential market failure, governments must find new ways to further enhance market rewards and their characteristics. This means that some form of public intervention (e.g. a variety of incentive tools to counteract supply-side deterrents) is required. The aim of this chapter is to highlight key examples of existing tools and how they can be systematically directed towards achieving specific objectives associated with incentivizing supply. Three incentive tools, Priority Review Voucher (PRV), Wildcard Patent Extension, and Advanced Market Commitment (AMC) were already foreshadowed in Chapter 6 because of their dual ability to raise funding. Nonetheless, these are briefly included here together with additional tools that can counteract supply-side deterrents. In Section 7.1, the utility of traditional incentives such as orphan drug and public R&D funding programmes that have been used to foster innovation for various conventional rare diseases and unmet needs are first assessed. Then, it is demonstrated in Section 7.2 that a compilation of multiple incentives can be placed along the R&D value chain to exceed the impact of more traditional approaches.

7.1 Traditional Incentives

One main category that justifies health promotion policy is market failure (Zalmanovitch & Cohen, 2015). This infers that when decentralised behaviour within the free market does not incentivise industry to develop and manufacture products

associated with necessitated health protection, public policy is needed. There are several generic policy tools that can be applied to promote health (see Table 46).

Table 46 – Policy Tools in the Context of Health Promotion (Zalmanovitch & Cohen, 2015)

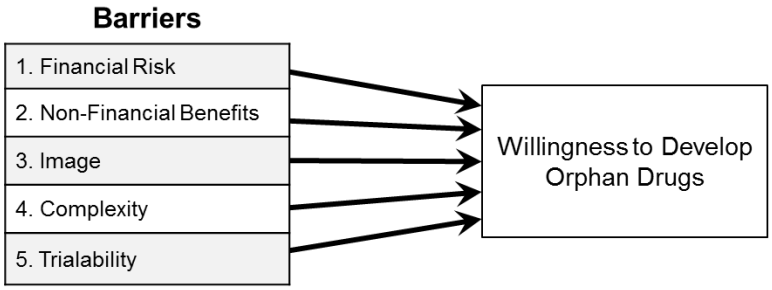
THE TOOL	EXPLANATION	IMPLICATION FOR HEALTH PROMOTION
LEGISLATION	The act of making or enacting laws	To legalize or prohibit unhealthy behaviour (e.g., prohibit the sale of food with saturated fat)
REGULATION	A principle, rule or law designed to control or govern conduct	To control human activity with regard to health promotion (e.g., nutritional requirements for food and drink in schools)
DEREGULATION	The act of freeing from government Regulations	To control human activity with regard to health promotion (e.g., nutritional requirements for food and drink in schools)
TAXATION	The act or practice of imposing taxes. Taxation refers to the institutions that both enforce tax collection and the methods of using the tax code to encourage socially desirable behaviours	Enforcing tax collection and the methods of using the tax code to encourage healthy behaviours (e.g., setting a high tax on cigarette consumption—a "sin tax")
SUBSIDIES	Monetary assistance granted by a government to a person or group in support of an enterprise regarded as being in the public interest	Providing financial support for healthy behaviour (e.g., subsidizing whole wheat bread)
STIPENDS AND GRANTS	A fixed and regular payment, such as a salary, for services rendered or an allowance or money to support a worthy person or cause	Payment or an allowance to support healthy behaviour (e.g., grants for schools that include safe sex programs as part of the school's curriculum)
PRODUCTION	The creation of value or wealth through the production of goods and services by the government	The government produces and supplies goods and services that promote the healthy behaviour of citizens (e.g., developing "healthy behaviour workshops" in order to increase public awareness about the importance of healthy behaviour)
PRIVATIZATION	Relying more on the private institutions of society and less on government to satisfy people's needs	Relying more on the private sector to establish health promotion policies in society (e.g., privatization of health promotion programs and centers at the national or regional level)
NATIONALIZATION	To convert from private to governmental ownership and control with or without compensation	To take a private health promotion asset into government ownership. To convert organizations from private to government ownership and control in order to advance health promotion (e.g., government takeover of privately owned advertising and using it for the promulgation of health promotion ideas)
REFORM	To significantly change an existing institution (rules of the game) by altering or correcting it	To significantly change a given social constraint by altering or correcting health promotion abuses (e.g., reform aimed at establishing a new agency that will be in charge of health promotion)

7.1.1 Orphan Drug Programmes

To circumvent the supply-side market failure of CBRN MedCMs, the potential effectiveness of more traditional orphan drug incentive programmes should not be ignored. These programmes are based on legislation that offers taxation credits, subsidies and public financing by governments to encourage companies to develop and manufacture the medical products deemed as offering insufficient profitability for industry (e.g. low number of people affected). According to the European Medicines Agency (EMA), the criteria to qualify for an orphan drug programme include a life-threatening or chronic debilitating condition whose prevalence in the EU is 5 or fewer persons per 10,000 (European Medicines Agency, 2016). The 1983 Orphan Drug Act of the US government and the EU's European Orphan Drug Regulation of 1999 both aimed to increase innovation by enhancing orphan drug programmes. They offered benefits such as quick regulatory review, technical assistance, short approval times, extension of market exclusivity and exemptions from drug registration fees (Moors & Faber, 2007). Although there are between 5,000 to 7,000 orphan diseases, only 50 of these (i.e. developed to treat orphan diseases) received market authorisation in the EU by the end of 2008. Nonetheless, the programme policy demonstrates effectiveness. These policies can be considered a success. To wit: the number of orphan designations and marketing authorisations granted by the EMA from end-2005 to end-2008 increased from 270 to 570, and from 22 to 50, respectively. More recently, it has been estimated that the worldwide market for orphan drugs will grow by a compounded annual growth rate of 11.7 percent during 2015-2020, reaching total annual sales of 178 billion USD. This growth rate is almost double that of the overall prescription drug market, which is predicted to grow only by 5.9 percent during the same period (EvaluatePharma, 2015a). Based on their projected growth curve, orphan drugs are expected to account for 20.2 percent of global prescription sales in 2020 (excluding generics), a substantial increase over its 6.1 percent share in 2000. However, the case for drugs that target rare conventional diseases is different than for CBRN MedCMs. For example, in the US alone, annual sales in 2014 for the top 10 leading conventional orphan drugs ranged from 805 million USD to 3.6 billion USD per drug. Unlike rare orphan drug diseases whose patient numbers offer at least some level of market

opportunity to industry, the number of patients suffering from diseases caused by some CBRN agents can be virtually nil. Consequently, as detailed in Chapter 2, market demand for associated MedCMs is extremely low to non-existent in the absence of an industrial accident, terrorist attack or acute rare natural outbreak. Nonetheless, various elements of an orphan drug incentive programme may bear some applicability. For example, Figure 33 depicts a conceptual model that represents the independent barriers that can inhibit industry's willingness to develop orphan drugs (Moors & Faber, 2007).

Figure 33 – Conceptual Model of Willingness to Develop Orphan Drugs (Moors & Faber, 2007)



Moors & Faber (2007) formulate the following about each of the barriers:

1. If the financial risk decreases, the willingness will increase.
2. If the non-financial benefits are perceived to be low, willingness is decreased.
3. If image is an important factor, willingness will increase.
4. If R&D is more complex, willingness will decrease.
5. If trialability increases, willingness will increase.

Interpretations for summarising these barriers within the context of CBRN MedCMs are listed in Table 47. Upon using this framework to identify willingness, one could speculate that the barrier regarding complexity might offer incentive to develop some CBRN MedCMs. However, the characteristics of financial risk, image and trialability combine to work against incentivisation. The key recognisable differences of each

barrier to the development of orphan drugs (conventional rare diseases vs. CBRN agents) are surmised in Table 48.

Table 47 – Barriers to Willingness to Develop Orphan CBRN MedCMs

BARRIER	CHARACTERISTICS RELEVANT FOR CBRN MEDCMS
FINANCIAL RISK	As surmised in Chapter 2, market opportunity represents few customers, severely limited market potential, unknown time that governments will remain committed to procurement plans. In addition, market volume is unlikely to trigger necessary investor mechanisms (e.g. low ROI, impact to stock prices).
NON-FINANCIAL BENEFITS	While regulatory and scientific advice could be valuable to both large and small companies by increasing competence, non-financial benefits would likely only have a minimal impact on willingness in the absence of acute and sufficient procurement opportunities. Nonetheless, reduction of time till marketing approval would increase some net present company revenues (University of Pittsburgh Medical Center, 2007).
IMAGE	Good public exposure could be valuable for building image campaigns especially for large corporations as some sense of patriotic duty at a time of emergency has been witnessed in the past (Hoyt, 2012). However, this is likely the case only when the disease area is popular (e.g. EVD Outbreak 2014). Nonetheless, rare diseases are seldom popular and CBRN threat is almost never widely supported in the absence of an acute event.
COMPLEXITY	Due to historical military R&D surrounding defensive and offensive use of CBRN agents, there may already be a valuable knowledge base available on the pathogenesis of various diseases caused by CBRN agents (Oppenheimer, 2009). Hence, collaboration with military departments is apt to reduce complexity.
TRIALABILITY	Standard clinical trial procedures are difficult to nearly impossible due to a low (or even nil) number of patients suffering from diseases caused by CBRN agents. Consequently, there is a strong dependence on animal data and/or surrogate markers which regulatory authorities and public do not always deem as satisfactory (Elbe et al., 2015).

Table 48 – Willingness to Develop Orphan Drugs (Conventional Rare Diseases vs. CBRN Agents)

BARRIER	CONVENTIONAL RARE DISEASES	CBRN AGENTS
FINANCIAL RISK	High R&D costs and low market sales potential on continuous basis.	High R&D costs and nil to barely measurable market sales in the absence of a rare acute outbreak, accident, or terrorist attack. Even if R&D costs are paid for by government, it is unattractive for a company to maintain manufacturing capabilities for a threat that may never occur.
NON-FINANCIAL BENEFITS	--	--
IMAGE	Kind corporate nature to help families whose lives have been devastated by diseases of low prevalence can gain sympathy and admiration.	Civilians and even governments rarely appreciate manufacturer efforts to develop medical solutions for a disease not widely perceived as a threat.
COMPLEXITY	There is likely tendency that diseases of low prevalence have not previously been on the commercial radar. Hence, it is probable that basic R&D knowledge is lacking.	Given historical military focus (and US CDC efforts) on CBRN MedCMs, a R&D knowledge base may be more likely available.
TRIALABILITY	Although patients are rare, in many cases patients are likely to be available.	In many cases, no patients are available.

As in the case for current orphan drug policies that address rare conventional diseases, patients may discover that – although therapies have become available – access to care could remain restricted. Even though industry may respond to orphan drug incentives and develop new corresponding drugs, governments and/or healthcare systems may not necessarily consider the administration of them as cost-effective. Hence, parameters that include societal views and priorities, pricing and reimbursement, as well as research priorities must be congruent. In the absence of these factors' harmonisation, the reaction of industry to orphan drug incentives decreases due to concerns that local access to these drugs will undermine investor expectations about associated market rewards (Drummond & Towse, 2014).

7.1.2 Public R&D Funding

For CBRN MedCMs, a paramount example of public funding in the US, BARDA, was already described in Chapter 2. Therefore, the purpose of this section is to highlight a more conventional example that demonstrates the ability of public R&D funding to stimulate industrial innovation. In Section 7.1.2.1, the effect is first described, then the cause in Section 7.1.2.2.

7.1.2.1 Effect

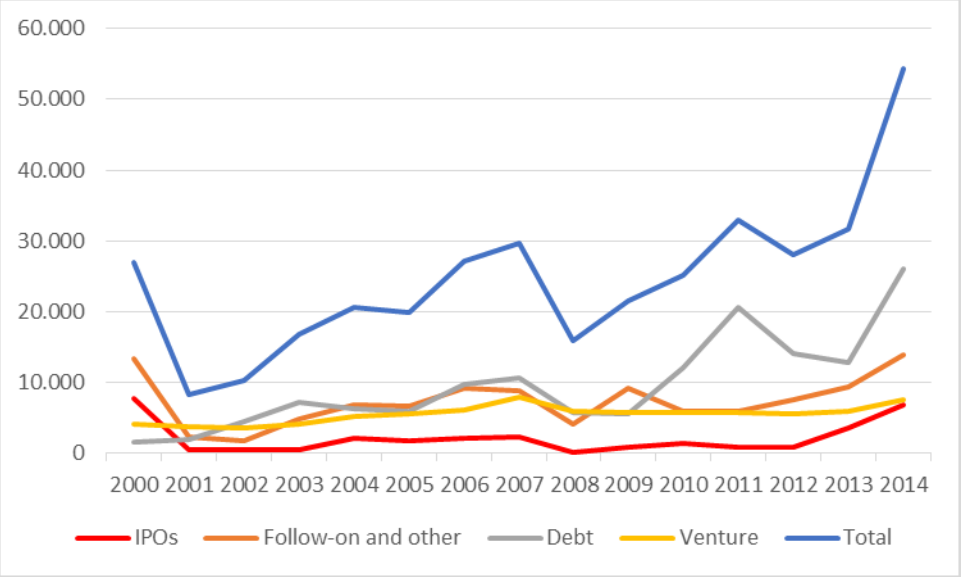
Due to the high probability that any one early-stage compound will fail (see Chapter 1), it is reasonable to expect that small biotechnology companies would have difficulties in raising capital. Yet this is not the case. In fact, as illustrated in Figure 34, and observed: "Fundraising totals in 2014 broke all-time records in both the US and Europe, resulting in a total of 54.3 billion USD raised, a 72 percent increase over 2013, which itself had been a remarkably strong year" (Ernst & Young, 2015). The channels used to attract this significant funding include Initial Public Offering (IPO), debt, and venture capital. Indeed, congruent with the "financialised" business model as described in Chapter 2 and its inferred interdependency between the pharma and biopharmaceutical industry, pharma's strategy to secure future products from new biotechnology companies can function because biotechnology companies are meeting the prerequisite of raising these funds for their early and highly risky cost of innovation. Typically, upon formation of ventures with established pharmaceutical companies, the pharmaceutical partner supports the biotechnology company with funds via an R&D alliance which secures its intellectual property and marketing rights upon successful marketing approval (Lazonick & Tulum, 2011).

7.1.2.2 Cause

Many governments across the globe are likely to directly or indirectly contribute to public funding and incentives to strengthen R&D investment for biotechnology. Examples include the provision of tax credits in France (Deloitte, 2015) as well as the

funding that Germany provides to its industrial biotechnology clusters (Philp & Winickoff, 2017). Yet, Lazonick & Tulum (2011) suggest the central driver of investment for the global biotechnology industry stems from the role of the US National Institutes of Health (NIH). If not for the enormous NIH direct public funding of research by the US government, the biotechnology industry across the world would simply not see the impressive investment levels of venture capital and public equity funds. Indeed, between 1999 and 2014, the NIH awarded 556.9 billion USD (an average of ~35 billion USD per year) for research project grants (National Institutes of Health, 2015). The top three of 26 NIH centers/institutes – the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases and the National Heart, Lung, and Blood Institute – are highly relevant to biotechnology and they consistently receive almost 40 percent of the NIH annual budget. Additionally, the Bayr-Dole Act of 1980 allows biotechnology start-ups to tap the NIH's knowledge base by giving researchers (e.g. universities, hospitals) property rights of knowledge created via NIH federal funds. If the transfer of IP rights were too restrictive, it is very probable that newly created biotechnology knowledge would go unexploited (Lazonick & Tulum, 2011). To increase public access to research paid via government grants, the US passed a bill in 2009 referred to as the Federal Research Public Access Act. This bill required that relevant manuscripts of journal articles be openly available on the internet within 6 months of publication (Mossialos et al., 2010).

Figure 34 – Capital Raised in US and Europe (USD millions), 2000 – 2014 (Ernst & Young, 2015)



7.2 Developing Comprehensive Strategy to Incentivize Supply of CBRN MedCMs

To challenge today's severe lack of attractive business proposition that engage mainstream industry with CBRN MedCMs (even less than orphan drugs), push and pull incentives can be supplemented and utilized. "Push" incentives aim to reduce industry's cost for R&D while "pull" ones increase the financial rewards to companies that successfully develop targeted drugs (Matheny et al., 2007). It can be surmised from Chapter 2 and the previous section that to diminish the forces that deter industry from developing CBRN MedCMs, one must move beyond traditional incentive programmes. Hence, additional contemporary incentives are required to further reduce barriers such as financial risk, image and trialability. Designing and directing such measures can be derived from more recent BARDA efforts (Larsen, 2016a). For example, a significant learning curve associated with antimicrobial resistance has led to a plethora of highly compatible options. In addition to bringing forth elements from previous traditional incentive models, this section introduces more recent embellishments and decisional frameworks that have developed related efforts to incentivise R&D for antimicrobial resistance medical solutions. Although detailed analysis is beyond the scope of this

section, it introduces and reviews some primary examples of these supply-side enticements and conceptionally depicts their application within related decisional frameworks. To reduce barriers such as financial risk and trialability, the nature of these push-and-pull incentives spans across monetary, regulatory, legal and logistical pathways.

7.2.1 Enhancement of Supply-Side Incentives

Economic costs associated with the increasing antimicrobial resistance to classes of antibiotics (e.g. carbapenems) is potentially catastrophic. However, market failure associated with today's poor commercial returns prevents industry from developing new antibiotics. Carbapenems are often the best line of defence against potentially life-threatening lung (e.g. pneumonia) and bloodstream infections. Yet, despite the alarming resistance to carbapenems already seen in some countries, there is incongruity between medical solutions needed by the world and the industry pipelines aimed at addressing these needs (Review on Antimicrobial Resistance, 2015). This predicament with antimicrobial resistance has led to multiple evaluations to reveal new paths and decisional frameworks for stimulating the development of new and innovative drug solutions, resulting in 47 different push and pull incentives (Renwick et al., 2016). The core learnings from these efforts create a strong basis also applicable to the market failure of CBRN MedCMs. Due to the high level of associated complexity, Renwick et al. (2016) conclude that a decisional framework is needed to compile a package of effective incentives. Namely, in parallel to enticing large mainstream companies and small and medium-sized enterprises (SMEs) by addressing the deficiencies that lead to market stagnation, optimal incentive solutions must be sustainable over the long-term.

Complementary to more traditional incentives such as orphan drug programmes and public R&D funding, new tools and concepts must increase access to knowledge, augment its dissemination and foster more collaborative efforts (Chorzelski et al., 2015). By shifting the focus away from the financialised business model's growth parameters (e.g. stock prices) as outlined in Chapter 2, industry can evaluate the risks

and benefits of development opportunities by including consideration of applying Net Present Value (NPV). Whereas a NPV in the range of 720 million to 1.15 billion USD can be achieved for neurological or musculoskeletal drugs, antibacterial drugs currently reach the estimated NPV of only 42.61 million USD. Since it is estimated that industry would be willing to invest in R&D for new antibiotics if a risk-adjusted NPV of approximately 200 million USD could be achieved as a minimum (Sciarretta et al., 2016), the significant NPV opportunity gap clearly emphasises the root cause of market failure for antibiotics. To increase NPV opportunities, push and/or pull supply-side incentives can be applied. Several examples of such incentive options are described in Table 49 and Table 50. For the sake of completeness, Table 50 lists the three incentive tools – PRV, Wildcard Patent Extension, and AMC – already introduced in the last chapter due to their dual role as funding mechanisms. However, additional points relevant to their use as supply-side incentives are raised.

Similarly, when considering examples of push and pull incentives, it is also important to include note of Table 42 in Chapter 6 which lists barriers to availability of MedCMs as learned during the 2009 H1N1 Influenza pandemic. These barriers include legal, regulatory, and logistical pathways. As described under the “Manage” component of the risk-informed framework, addressing these barriers serve to mitigate risk associated with MedCM availability. Yet, the removal of these barriers could also positively influence market rewards of approved MedCMs and/or trialability associated with R&D. Hence, these could be considered as additional push and pull incentives respectively.

Table 49 – Examples of Push Incentives

INCENTIVE	PATHWAY	DESCRIPTION
PUBLIC R&D FUNDING	Monetary	Monetary tools (e.g. project grants, subsidies, fellowships, career establishment grants) to stimulate basic research and preclinical development at different levels (e.g. individuals, research groups, institutions) (Chorzelski et al., 2015).
TAX INCENTIVES	Monetary	Raise the NPV of targeted research projects by awarding tax incentives – e.g. credits, allowances and deferrals (Mossialos et al., 2010; Chorzelski et al., 2015; Renwick et al., 2016).
PUBLIC-PRIVATE PARTNERSHIPS (PPPS)	Monetary	Known also as product development partnerships (PDPs), these voluntary collaborations between state and non-state organizations (e.g. pharmaceutical, biotechnology industry) aim to transfer R&D risk to government via public funding of early and late R&D. Typically, the private company provides industry expertise and the public organization secures most funding (U.S. Department of Health and Human Services, 2004; Russell, 2007; Gronvall, 2008; Marinissen et al., 2014; Chorzelski et al., 2015; Elbe et al., 2015; Renwick et al., 2016).
RESEARCH PRIZES & TOURNAMENTS	Monetary	The awarding of prestigious prizes with monetary values for innovative contributions towards qualified MedCMs (Mossialos et al., 2010; Chorzelski et al., 2015; Renwick et al., 2016).
INNOVATION VOUCHERS	Monetary	Modelled in 2009 by the Czech Republic government in the city of Brno, government set out to increase technology transfer between industry and universities by issuing innovation vouchers to SMEs. These vouchers give companies credit to purchase services from public knowledge providers with the objective of introducing innovative new products, processes or services in their business operations. Since their introduction, the concept spread to 11 other regions in the Czech Republic and by 2013, 462 vouchers were issued. Although the largest number of companies that used innovation vouchers were focused on machinery as well as information and communications technology, this example also included life science companies (Matulova, Stemberkova, Zdralek, Maresova, & Kuca, 2015).
SCIENTIFIC PERSONNEL	Monetary	Assure appropriate scientific specialization and expertise by government funding of doctorate programmes and grant awards (Mossialos et al., 2010; Renwick et al., 2016).
SIMPLIFYING CLINICAL TRIAL REQUIREMENTS	Regulatory	As an example, the EMA changed its guidelines to simplify clinical antibiotic trials by making it easier to recruit trial patients (allowed organism-specific as opposed to disease-specific studies). In addition, it accepted smaller studies and permitted “niche” indications for drug licensing that could be expanded over time to other relevant therapeutic areas (Chorzelski et al., 2015).
INCREASING ACCESS TO IP AND RESEARCH	Monetary	Allow developers (e.g. universities, hospitals) to tap government knowledge bases and receive property rights (Lazonick & Tulum, 2011) as well as assuring manuscripts of relevant journal articles that were paid via public grants to be readily and freely available on the internet within 6 months of publication (Mossialos et al., 2010).

Table 50 – Examples of Pull Incentives

INCENTIVE	PATHWAY	DESCRIPTION
WILDCARD PATENT EXTENSION	Monetary	This incentive (also referred to as transferable IP protection or tradable patent voucher) allows recipient to extend the patent of another more profitable drug (e.g. blockbuster) within its portfolio that is approaching patent expiration – alternatively, the extension could be sold (Mossialos et al., 2010; Renwick et al., 2016).
PRIORITY REVIEW VOUCHERS (PRV)	Monetary / Regulatory	Voucher grant priority regulatory review for another more profitable drug (e.g. blockbuster) within its portfolio. Reduction of time till marketing approval would increase net present company revenues – alternatively, the voucher could be sold (UPMC, 2007; Matheny et al., 2009; Renwick et al., 2016).
DE-LINKAGE AND PARTIAL DE-LINKAGE MODELS (OR HYBRID)	Monetary	To transfer market demand risk to government, tools that utilize IP mechanisms can be applied e.g. a buyout fee can be payable to developers upon successful product approval, regardless of demand. This is referred to as a de-linkage model because the developer is fully protected from poor market conditions. Upon putting drug IP into a patent pool, developers wanting to use the patent to create stocks of a new drug can seek a license against the payment of royalties. When developers retain some IP rights, then it is referred to as a partial de-linkage model (Mossialos et al., 2010; Wizemann et al., 2010; Chorzelski et al., 2015; Renwick et al., 2016).
ADVANCED MARKET COMMITMENT (AMC)	Monetary	Known also as advanced purchase commitment (APC) is an agreement with government to purchase a pre-set amount at a given price upon successful product approval (Mossialos et al., 2010; Renwick et al., 2016).

In addition to considering the ability of diverse push and pull incentives to sufficiently increase NPV and to incentivize SMEs, their desired impact must be counterbalanced against their probable adverse effects. For example, despite the potential of wildcard patent extensions to enormously incentivize manufacturers with blockbuster products, the effects of this incentive are bi-polar as preluded in Chapter 6, Section 6.6.1.2. Yet, because this scheme would offer significant monetary reward at levels fully compatible with a financialised business model, large companies with blockbuster portfolios could be incentivized. Moreover, small innovative biotechnology companies with no blockbuster products could sell their awarded extension to large companies or even utilize the latter to embellish their own company's profile to attract M&A offers. However, such benefits could also be accompanied by significant drawbacks. These include the generation of substantial social costs, concerns about equity and transparency and, finally, a delay of generic entry into the marketplace. These drawbacks as previously explained in Chapter 6 are summarized in Table 51 (Mossialos et al., 2010).

Table 51 – Drawbacks Associated with Wildcard Patent Extensions

DRAWBACK	DESCRIPTION
SUBSTANTIAL SOCIAL COSTS	Costs for allowing 10 wildcard patents were estimated to exceed 40 billion USD (not including costs of other economic incentives – e.g. orphan drug programmes, government grants). If included, this scheme would be expected to result in costs several times higher than current R&D. Moreover, company stacking of multiple extensions onto one blockbuster could further inflate expenses (Mossialos et al., 2010).
CONCERNS OF EQUITY AND TRANSPARENCY	Shifting costs of developing a new drug from one disease to patients with another disease raises ethical implications and could potentially kindle negative publicity. In fact, this led organizations such as the PhRMA to no longer advocate wildcard extensions (Mossialos et al., 2010).
DELAY OF GENERIC ENTRY	For markets where a patent extension is applied, generic companies anticipating patent expiry would be suddenly blocked from market entry. This would act as a disincentive for their early R&D investment to demonstrate bioequivalence with generic drugs because they would be well-advised to wait until patent expiration was final and no longer extendable. Since applying patent extensions to the most lucrative markets would exploit the highest profitability, patent extensions could substantially decrease competition by triggering delayed generic entry. Hence, generic manufacturers would suffer severe setback. In fact, when a wildcard patent extension was proposed for stimulating MedCM R&D for the US Biodefence and Pandemic Vaccine and Drug Development Act of 2005 (also known as BioShield II Programme), strong opposition from the generic industry led to patent extensions being removed before the act could be signed (Mossialos et al., 2010).

Despite the downsides, continued attention could be given to wildcard patent extensions as a plausible option. For instance, to evaluate the economic feasibility of extensions regarding social costs, one particular assessment reviewed its impact on new treatments for priority bacterial diseases (Spellberg et al., 2007). In this case, it was determined that one new antibiotic drug to treat multi-drug-resistant *Pseudomonas aeruginosa* would cost 7.7 billion USD during the first two years and 3.9 billion USD during the following 18 years. However, Spellberg et al. (2007) further suggest that economic viability could be achieved and, moreover, estimate that a new drug could lead to a reduction of 50 percent in the annual cost associated with *P. aeruginosa* infections. If so, then cost neutrality could be obtained in 10 years after drug approval and cost savings of 4.6 billion USD after 20 years. Suggestions for containing social costs include capping the amount of profit that the recipient company could earn and/or a condition that requires 10 to 20 percent of the earnings achievable via the extension to be invested in related target drug R&D (Spellberg et al., 2007).

Advantages of a PRV extend beyond increasing net present company revenues associated with an earlier launch as previously described in Chapter 6. Namely, in some cases it may also offer a direct competitive advantage (e.g. launching before a rival product). For small companies holding a PRV, the value of the PRV itself may represent the sole value of the company because they tend to lack anything else of significant worth (Ridley, 2017b). Since the monetary benefit realised by using a PRV is significantly lower than that expected from a wildcard patent extension, it is fair to assume that a PRV would be less capable of driving financialised business models. Nonetheless, it is plausible that news of a swift regulatory review via PRV could at least contribute to creating entry and exit milestones for stock investors within the context of the financialised business model. And, in some cases, the income obtained via PRV may suffice to cross minimal NPV thresholds required by company investors.

To portray one new example, the use of IP mechanisms as pull incentives entails the rewarding of financial benefits at regulatory approval (or at various milestones). By providing manufacturers with a known and guaranteed ROI payable for services rendered to achieve an approved CBRN MedCM, poor market demand and conditions become irrelevant. Thus, under a full de-linkage model, the company agrees to sell its IP rights to the government but continues to manufacture the drug (or at least maintain a warm base manufacturing level) under the stipulations of receiving guaranteed revenue. However, the company is required to comprehensively refrain from endorsing and marketing the drug. Under a partial de-linkage model (or hybrid), the company may be allowed to retain its IP rights. Nevertheless, related annual revenues could be subject to restrictions (e.g. capped amounts) and responsibilities associated with approval, manufacturing and sales are also resumed. While both de-linkage models may represent the lowest probability of adverse secondary effects, it demands substantial and sustained funding. Not only must an agreed ROI or NPV be sufficient enough to draw industrial engagement, but manufacturers must also perceive long-term funding promises as reliable (Sciarretta et al., 2016).

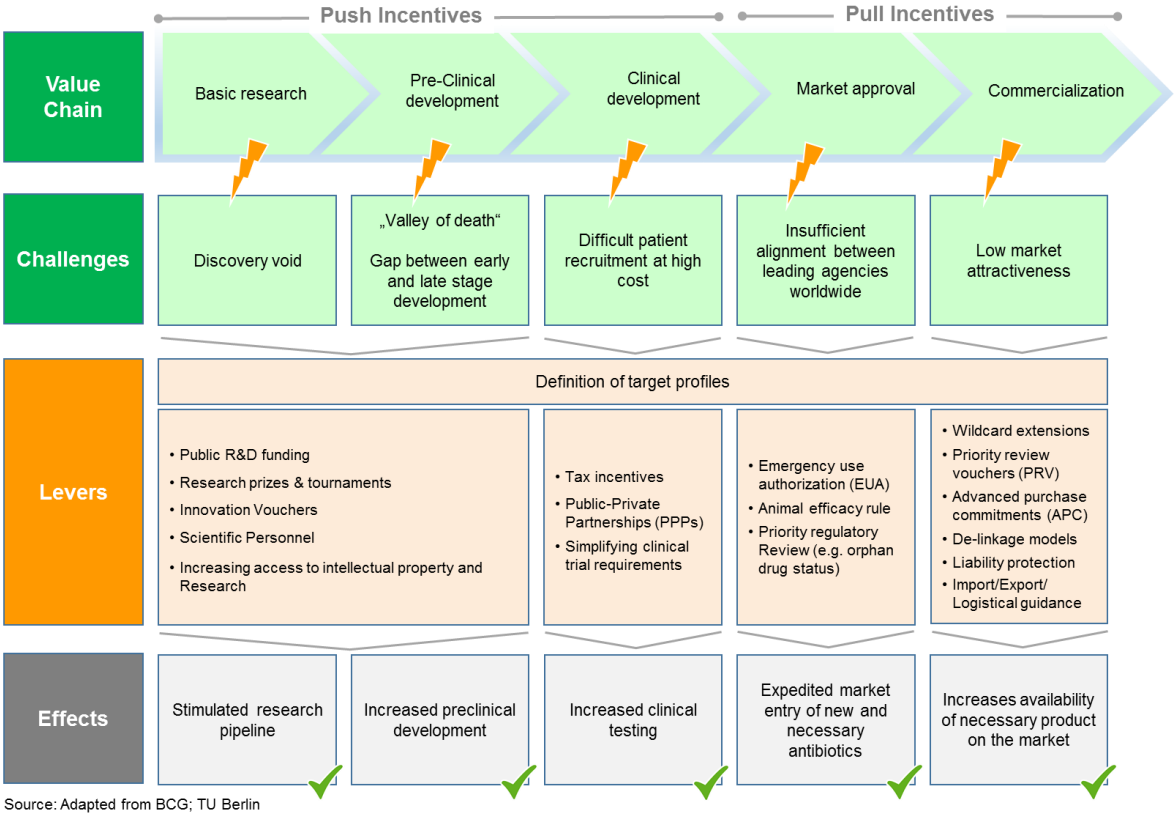
7.2.2 Decisional Framework

As demonstrated by free market mechanisms in healthy markets, government incentives are not required to draw industry resources towards commercially viable products. Hence, logic would lead one to believe that for products plagued with market failure, the more that market potential and/or pull incentives are present, the less need there will be for push incentives. Likewise, depending on the unique balance of economic feasibility associated with various CBRN MedCMs, it is plausible that each disease area will require its own individual mix of push and pull incentives. Moreover, the area of the drug development process (or value chain) that requires the impact of each selected incentive will be fundamental to persuading investors that an opportunity is economically feasible. Figure 35 conceptionally demonstrates the compilation of multiple individual incentive options (alternatively termed "levers") into a package that comprehensively addresses market failure along the whole value chain. In this figure, Chorzelski et al. (2015) decisional framework has been altered to allow more relevant adaptation to CBRN MedCMs. To illustrate, example incentive options from Table 49 and Table 50 are positioned within the value chain. As previously revealed, there is also value to consider improved the legal, regulatory, and logistical infrastructure listed in Table 42 – Barriers to Availability of MedCMs – as supplier incentives. Whilst these barriers can impede the international availability of MedCMs associated with government distribution purposes, removing them can enhance market rewards for manufacturers. Examples of these are positioned as pull incentives. However, it is fair to state that in some of these cases dual positioning also as push incentives would be justified because trialability could also be improved.

As depicted, push incentive levers extend across the earlier phases of the value chain (e.g. basic research, preclinical and clinical development). This is so because they lower the barriers of market entry for developers by reducing R&D costs and associated financial risk. Analogously, pull incentive levers address the challenges associated with later stages (e.g. market approval, commercialisation) since they tend to directly increase market rewards associated with successful drug development and approval (Chorzelski et al., 2015). For simplicity, these incentives are positioned directly under

the value chain's various areas. However, it should be noted that these incentives often target phase transitions and/or can extend across a variety of value chain phases (e.g. research prizes & tournaments are often applied for basic research, preclinical, and clinical development).

Figure 35 –Prolonged Approach along the Value Chain



Source: Adapted from BCG; TU Berlin

Particularly in the case of innovative antibiotics, the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) set out in 2015 to assess and recommend economic incentives for the potential global implementation of antibacterial drug development. This case is outlined in Appendix 2, Section 7.4.

7.3 Conclusion

Assuming governments have the ability and WTP, the creation of an efficacious package of push and pull incentives may sway more industrial resources towards CBRN MedCMs. History suggests that national urgency associated with acute threat can summon support from large corporates all on its own. However, these leaps of faith to ostensibly improve one's public image and/or make patriotic gestures fall short of securing CBRN MedCM readiness before such rare and unexpected events occur. Moreover, once a given crisis has taken its course and the public eye has been redirected to other topics, the basis for any sustainability of the effort is likely to crumble. In the continued absence of sufficient market demand for CBRN MedCMs, government interventions must fortify incentives to make areas such as financial risk, image and trialability much more attractive to industry. The force of incentives must reach beyond the stamina of traditional orphan drug and public R&D funding programmes.

More recently derived to encourage R&D efforts surrounding antimicrobial resistance, abundant literature depicting incentives and decisional framework provides a significant learning curve and starting point for the evaluation of CBRN disease areas. By considering the unique aspects of market failure associated with some CBRN MedCMs (e.g. required ROI and/or NPV that preferred manufacturers would be willing to accept), a blend of numerously drafted push and pull incentives could be compiled and positioned along the value chain to remedy associated market failure. A paramount outcome would be a customized package that offers a reliable and guaranteed reward which adequately respects the economic measures that drive corporate business models. Especially for those mainstream companies that have departed from a "productionist" mindset to seize sales growth via a "financialised" business model, these incentives must forcefully signal to investors the milestones of when to buy and/or sell a company's stock. Because manufacturers have limited resources are must remain committed to its investors' expectations for growth, they will undoubtedly continue to maximise their product portfolios and minimise the opportunity costs associated with investments that offer less attractive market rewards. Hence, the level

of rewards achieved via a mix of market demand and supplier incentives will directly influence which companies (start-ups vs. those with proven capabilities) respond to government proposition.

7.4 Appendix 2: TATFAR Cooperation Initiative

To supplement Section 7.2.2 as referenced concerning the case to increase innovative antibiotics, the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) reviewed numerous relevant sources on the topic (European Commission, 2011; PCAST, 2014; BEAM Alliance, 2015; Carlet & Le Coz, 2015; Cecchini, Langer, & Slawomirski, 2015; Chatham House Report, 2015; Chorzelski et al., 2015; Review on Antimicrobial Resistance, 2015; World Health Organization, 2015b; Innovative Medicines Initiative, 2016; Jackson, 2016; Renwick et al., 2016). Given the continued market failure that constrains industry from developing new efficacious antibacterial drugs, it became urgent to encourage academics and small, medium, and large companies to develop innovative new drugs. Here the initial trend of consensus indicated that numerous push, pull, and de-linkage economic incentives would be necessary to support all phases of development. On the push side, it was concluded that incentives such as grants, contracts, product development partnerships (PDPs) and/or tax credits early in the development phase would be needed. Although early stage investment is highly risky due to excessive product failures associated with these stages, these push incentives could have a stronger impact on NPV. On the pull side, it was determined most critical to establish an adequate and reliable ROI. This could best be achieved by administering a de-linkage model (Sciarretta et al., 2016).

Although BARDA non-US partnerships target various disease areas (e.g. burns, pandemic influenza, EVD, Zika, antibiotics), their approach for shaping the antibiotics market may represent their most novel model (Larsen, 2016b). For instance, to combat antimicrobial resistance a new global public–private partnership known as CARB-X was introduced in July 2016 to address deficits in antibiotic innovation (Outterson et al., 2016). CARB-X stands for Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator. This partnership is expected to include investments of more than 450 million USD over five years to accelerate the development of at least 20 antibacterial products, moving at least two of them into human trials. Funding is provided by BARDA and the Wellcome Trust, a London-based global biomedical

research charity. At the end March 2017, the first major funding of 48 million USD from this global partnership was announced, with 24 million USD in immediate funding for 11 companies. These firms can receive up to 24 million USD in additional payments over three years if specific milestones are met. The partnership also includes academic, industry and other nongovernmental organisations and was created as part of the U.S. and British governments' calls for global efforts to tackle antibiotic resistance (Sun, 2017).

Diverse challenges to the concept of achieving global leadership include the determination of the coordinating institute, alignment of regulatory requirements and the setting of priorities. Nonetheless, the ultimate vision could include the creation of one unified approach for global development and market approvals. Perhaps contributing to this goal, the TATFAR targeted its objective in 2015 to counteract market failure by balancing market rewards associated with the development of new antibiotics. Government members of TATFAR include US, EU, Canadian and Norwegian agencies. To demonstrate cooperation readiness on the supply-side, over 80 manufacturers from 16 countries signed a declaration during the World Economic Forum in Davos, Switzerland. Published in January 2016, the declaration confirms supply-side rationale in view of the proposed market reward incentives as described in Chorzelski et al (2015) and the Review on Antimicrobial Resistance (2015) reports, which aim to increase NPV and revenue certainty for developers (Sciarretta et al., 2016).

To achieve a catalogue of market reward incentives providing supply-side rationale, multiple advisory initiatives were launched during the previous few years. The specific aim of these efforts was to understand how to stimulate industrial activity to develop new and innovative antibiotics by reducing barriers such as financial risk and trialability associated with R&D. The nature of corresponding incentives spanned across monetary and regulatory pathways and are discussed in Chapter 7. Beyond devising individual incentives, however, the declaration emphasized that sustaining such efforts required global leadership. For example, the Chatham House Report (2015)

recommended global coordination of a particular de-linkage model incentive designed to detach low market volume demand for new antibiotics from the more substantial market reward levels required by manufacturers. This de-linkage model can be engaged when market demand risk is transferred to government. To achieve this, tools that utilise IP mechanisms can be applied. For instance, a buyout fee which guarantees sufficient ROI can be payable to developers upon successful product approval, regardless of demand. Hence, this de-linkage model protects the developer from poor market conditions. Once drug IP rights are placed into a patent pool, manufacturers that wish to use the patent can create stocks of a new drug by paying royalties as required by licensing agreements. In cases where developers retain some IP rights, then it is referred to as a partial de-linkage model (Mossialos et al., 2010; Wizemann et al., 2010; Chorzelski et al., 2015; Renwick et al., 2016). Suggestions from the Review on Antimicrobial Resistance (2015) went a step further to suggest the establishment of a global innovation fund and a global purchaser (Sciarretta et al., 2016). Other reports concerning the need for global collaborative effort to drive innovation were echoed by Cecchini, Langer, & Slawomirski (2015) as well as the Boston Consulting Group (Chorzelski et al., 2015). The latter advocated global R&D coordination regarding clinical trials, alignment of regulatory approvals, and drug profile targets.

General Conclusion

This dissertation defines a path to public health economic policy to enhance the international availability of MedCMs against CBRN agents. By strengthening the rationale for supporting both market supply and demand, corresponding resources can be better justified by both government and industry.

The contributions of each chapter are highlighted below.

Part I – Components of Market Failure

Part I explores root causes of market failure by identifying and depicting features of the R&D process and market mechanisms that fail to incentivize, and thus deter industry from developing MedCMs against many CBRN agents.

In Chapter 1, "Clarifying Drug R&D Effort and Cost", the lines of argument linked to controversies surrounding the length, risks and costs of the R&D process are demarcated via a clear understanding of cost definitions. After offering a standard R&D paradigm derived from more robust drug development studies targeting conventional diseases, the chapter describes the R&D characteristics unique to CBRN MedCMs. Whilst some factors can hinder the development of MedCMs applied to CBRN agents, it is argued that other factors are more favourable compared to the standard R&D paradigm. Correspondingly, R&D risk and a range for out-of-pocket cost for both disease areas (conventional versus CBRN MedCMs) could be generalised as being at equilibrium. In view of the need for governments to cooperate with industry to create funding mechanisms that encourage the discovery and successful approval of CBRN MedCMs, this chapter argues that a clear understanding of cost and effort associated

with drug development could be highly conducive to building more trustful partnerships.

In Chapter 2, "Supply-Side Deterrents Related to MedCMs", the key economic levers that motivate industry and influence its business models are highlighted. To portray the root causes of market failure, a contrast is drawn between market rewards and characteristics offered for drugs that target conventional diseases and those that protect against CBRN agents. Because the market rewards and incentives for MedCMs as opposed to drugs for conventional diseases differ much more than their respective R&D process and costs, this chapter confirms that mainstream industry clings to the conventional market. Also described are the emerging market challenges that threaten sustainability of the classical "productionist" bio-pharma business model and, moreover, influence the evolution of a "financialised" business model to secure company revenue growth. These trends further widen the gap for achieving the international availability of CBRN MedCMs. It is also demonstrated that, without intervention that goes beyond public R&D funding, marketing authorisation alone is not sufficient to ensure a ROI. This leaves the typically willing but less experienced smaller biotechnology companies – usually start-ups that depend on government largesse – to shoulder the bulk of the development costs for CBRN MedCMs. Finally, the transparency of market characteristics and business models portrayed underscores the market reward values that can incentivise industry.

Part II – CBRN Case Studies

In Part II, case study examples reveal the characteristics and economic consequences of CBRN incidents. Whether agents are naturally, accidentally or intentionally released, Part II argues that support for MedCM availability can be strengthened by considering multiple exposure routes. The scenarios for each case are outlined to show where availability of MedCMs in these situations could potentially be cost-effective.

Chapter 3, "Strengthening Cost-Effectiveness of MedCM Development against Rare Biological Threats – The Ebola Outbreak", reveals that the implications associated with rare but deadly, naturally occurring biological diseases with epidemic potential include a wide range of political, geostrategic, socially disruptive and emotional factors that affect GDP. Taking the EVD (Ebola virus disease) outbreak of 2014 as a case study, this chapter posits that a more careful prioritisation of MedCM development and availability should be considered as a form of international health insurance policy. This should entail protection for human and economic health irrespective of whether an event occurs in a particular country or not. It argues that an insurance concept could fill the financing gaps invoked by market failure to develop MedCMs. However, the prerequisites to implementing such a concept require international cooperation. They include forming a global consensus for prioritized MedCMs as well as aligning interests across different government agencies, philanthropic organisations and profit-driven sectors (e.g. insurance and biopharmaceutical industry, capital markets). This concept may not apply to all biological agents (such as those causing more limited damage). In addition, further economic and governance analysis is needed to determine various cost-effective and feasible case scenarios.

Chapter 4, "Evolution of Chemical Weapons to Modern Day Exposure and Funding of MedCMs", describes the history of chemical weapons and discloses how exposure to OP, the most potent of all chemical agents, can happen along multiple routes, given its civilian and military applications. Taking OP as an example, multiple stakeholders who stand to gain from improving protection against OP exposure are determined. These include governments (health, defence ministries), industry (insurance) and agriculture sectors which may be unaware of their shared vested interest to reduce an incident's financial impact by making cost-effective MedCM solutions more available. This chapter also demonstrates that the level of each stakeholder's contribution and its sustainability can be reinforced with business case analysis (e.g. metrics such as ROI, vulnerability presented to GDP).

Chapter 5, "Economic Efficiency of MedCMs against Radiological and Nuclear Agents", illustrates how radiological and nuclear events (whether accidentally or intentionally) can induce severe economic consequences. However, it is likely that the MedCMs associated with such incidents would play only a limited role in reducing their consequences. Hence, more analysis in two areas is required. First, assessment indicates there may be more potential for expanding MedCM usage for domestic peacetime applications. If, for example, improved therapy approaches for both radiological/nuclear events and cancer treatment therapy could be achieved by the same MedCM, then profitable scenarios are more likely – even in the absence of emergency response to radiological or nuclear events. Second, the feasibility of an innovative prophylactic to lessen the long-term health effects of radiation exposure should be considered. This could reduce associated psychological effects and their associated adverse economic impacts.

Part III – Supply and Demand Rationale

To weigh the supply-and-demand rationale, Part III turns to the supply and demand levers that influence the availability of CBRN MedCMs.

Chapter 6, "Risk-Informed Demand", seeks to counterbalance the lack of government will to pay for CBRN MedCMs against credible threats of CBRN attack. To challenge this quasi-laissez-faire *status quo*, contemporary funding models and economic tools are explored. Before addressing financial economic principles, consideration is first given to increasing the level of political motivation. This includes concepts associated with behavioural and political economics. Then it is demonstrated that risk-informed framework can guide evaluation concerning the cost-benefit of prioritized CBRN MedCMs. Thus, a sustainable WTP for MedCMs against hypothesized threats could potentially be enabled. However, it is also noted that an element of risk remains for associated investment. This is because expenditure (e.g. R&D, procurement, opportunity costs, sustainability) is certain, but cost-benefit is likely only if the rare

and hypothesized event occurs. To minimise these remaining risks, an array of models for sustainability, collaborative public health funding mechanisms and global partnering are outlined.

Chapter 7, "Counteraction of Supply-Side Deterrents", aims to better balance market reward levels for MedCMs against CBRN agents and conventional diseases. First, the use of traditional incentive approaches such as orphan drug and public R&D funding programmes is reviewed. This analysis determines that the impact of such incentives is not sufficient enough to signal viability to investors whose targets include more substantial and reliable market rewards than can be offered by CBRN MedCMs. Consequently, a more comprehensive strategy is outlined to better motivate suppliers to carry out R&D that targets CBRN agents. Learning curves from more recent push and pull incentives are referenced. Also addressed are the unique aspects of market failure associated with certain CBRN MedCMs such as mandatory ROI and/or NPV that preferred manufacturers would be willing to accept. A decisional framework is also introduced to develop a more comprehensive strategy for positioning incentives along the value chain and to remedy associated market failure. A paramount outcome of this would be a package offering a reliable and guaranteed market reward which respects the economic measures that drive corporate business models. This is especially the case for mainstream companies that have departed from a "productionist" mindset to seize sales growth via their "financialised" business model.

As a general conclusion, this dissertation determines that an economic-based path to public health policy could enhance the international availability of MedCMs prior to a CBRN incident. This approach's readiness against certain rare agents can help minimise loss of human life and the impact on socio-economic structures. The first step to achieving responsible preparedness is to clarify this impact and then raise awareness about it. In addition to describing the characteristics of such incidents, it must be understood that the availability of relevant CBRN MedCMs can, in many cases, be cost-effective. Equally important, however, are approaches that identify and reduce the political and financial opportunity costs associated with MedCM funding across

diverse sectors (e.g. scientific, medical, institutional, industrial, governmental). Although CBRN experts and stakeholders naturally tend to specialise in their field of expertise, there is need to boost cross-functional and interdisciplinary interoperability. Thus, a common understanding that bridges the broad complexities (e.g. R&D, supply, demand, national governance) must be improved so that mutually beneficial collaboration can be established, while achieving comprehensive and responsible preparedness. Because lack of demand is a primary root cause for the failure of the CBRN MedCM market, government officials with responsibility for preparedness should challenge the appropriateness of their own demand levels. By depicting the diverse characteristics, frameworks and tools for managing the levers of supply and demand, this dissertation's scope was defined to support such requirements.

Whilst economic feasibility can often support the demand argument, only in few countries does public health policy reflect the will and capability to robustly fund associated R&D and procurement capacities. Hence, the rationale for supply and its incentivization is stalled. On the one hand, this situation appears to reflect an illogical reaction to healthy fiscal investment. That is, it suggests that many governments continue to ignore a cost-effective means to protect their citizens against CBRN threats. On the other, the economic feasibility of such investment remains at risk. It is, however, possible in some cases to mitigate this risk (e.g. via improved prioritisation of hypothesized threat, broadening usage to commercial areas and sizing response plans to history of accidental and/or actual incidents). Yet unknown risk factors, both in terms of financial and political opportunity costs, are likely to prevail.

This risk can be characterised by at least four main aspects. Firstly, before cost-effectiveness can be achieved, the relevant CBRN incident that was predicted and prepared against must occur (and they rarely do). Alternatively, at the least, it would need to be conceivable that preparedness measures against a specific threat could de-motivate terrorist intentions and deter attack. Secondly, given the numerous CBRN agents proficient enough to cause harm to individuals, a response preparedness plan would likely necessitate a comprehensive portfolio of diversified MedCMs. Therefore,

cost-effectiveness calculations must also consider the total costs (e.g. R&D, procurement, stockpiling) of a broad portfolio versus the economic benefits of a well prepared MedCM response to nil-to-few isolated CBRN incidents that might occur. Thirdly, even if cost-effectiveness can be achieved, government resources are not infinite. Financial constraints may make it economically more beneficial (and even more morally justifiable) for some governments to invest in alternative measures that reap far greater returns, benefit more of its civilians and represent a significantly higher probability of doing so. And fourthly, the adverse economic consequences (or "cost-of-doing-nothing") to justify resources are based only on a range derived from semi-quantitative data for which its determination includes historical events, expert opinion and mathematical simulations and modelling. Hence, the impact of a real event entails no small measure of uncertainty.

To overcome the restraints of supply and demand that lead to market failure, international cooperation strategies have the potential to reduce the risk and opportunity costs of associated political efforts and financial investments. In addition to sharing cost burdens and knowledge, the efficiency and comprehensiveness of a MedCM portfolio can be increased and its sustainability reinforced. If only one nation independently invests in innovative MedCM preparedness for itself, a central value of R&D and procurement efforts is contingent on an actual CBRN attack happening in that nation. Yet, as the size of a prepared geographic region increases beyond the borders of one nation, the probability of an attack happening, for example, anywhere in the world, is more likely probable than its occurrence within the boundaries of one single nation. Moreover, assuming international cooperation and readiness led to higher demand levels (and more customers), this could proportionately reduce supply-side deterrents, or at least fortify current supply-side incentive programmes. To further encourage supportive international public health economic policy, it is recommended that new research initiatives be directed towards the refinement and practical adaptation of such international cooperation and funding mechanisms. Priority research areas include:

- identification of existing international treaty and process required to amend its support of funding models (e.g. opt-out insurance coverage, taxation)
- institutional composition and governance for achieving global consensus on health priorities specifically for MedCMs against CBRN agents
- compensational pathways that encourage sharing of targeted IP/technologies
- access procedures to shared stockpiles and production facilities (especially during peak demand)
- process and means to create a transparent CBRN MedCM market that can be perceived (also by mainstream industry) as robust and reliable.

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