Medical Countermeasures

When investment in medical countermeasures against rare but highly dangerous agents becomes cost effective – the Ebola case

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There are countless chemical, biological, and radiological (CBR) agents that are proficient enough to harm individuals. Examples include viruses (eg influenza) and bacteria which are widely distributed by nature, but also some which are far less common, such as the Ebola virus. Cases include chemical (eg organophosphates) and radiological agents which have been birthed by humans. Although some CBR agents pose low prevalence (the proportion of individuals in a population at risk that are adversely affected) and incidence (number of new cases of a disease caused by CBR agents over a given period divided by the population at risk), or even lack probability of emerging at all, some bear the potential to cause catastrophic impact to society.

The US Centers for Disease Control and Prevention (CDC) has classified such biological agents as Category A biological threats. Examples include those which cause anthrax, plague, smallpox, tularemia, and viral hemorrhagic fevers such as Ebola (CDC 2015). Indeed, in addition to potential exposure via natural release (excepting smallpox which was declared eradicated by the World Health Organisation (WHO) in 1980), the pathogens responsible for many such diseases have been militarised in the past by such nations as the US, UK and former Soviet Union.

While rarely seen in nature within the boundaries of the US and European countries, they pose a high risk to national security because they could be disseminated, although not necessarily easily. In some cases they may only be transmitted from person to person. They may result in high mortality rates and have the potential to make a major impact on public health. They will always cause public panic if the human hand is proved to be behind the event and may induce social disruption; and require special action for public health preparedness.

Similarly, some chemical and radiological agents are high on the threat list of possible agents that could be used by terrorist organisations, non-state actors or even state-sponsored groups (eg the Tokyo subway attack in 1995 by the new religious movement AUM Shinrikyo with the highly toxic nerve agent sarin).

Even so, their release could easily be facilitated accidentally as in the case of radiation released during the nuclear disasters in Chernobyl in 1986 and the Fukushima Daiichi plant in 2011, or even via industrial pollution. While there are no reliable estimates as to how many people suffer from pesticide-related health effects each year (eg via organophosphate chemicals), studies indicate 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, for example, 180 per 100,000 in Sri Lanka (WHO 2008).

Assuming diligent medical research and development, populations could be protected via new prophylactic drugs and vaccines or post-exposure treatment with antidotes and antimicrobials. Nonetheless, developers and manufacturers of such medical countermeasures (MCM) are not empowered to address all these threats sufficiently because it is expensive to develop MCM. Depending on the agent targeted and type of MCM, the cost of developing one MCM probably lies between $25m and $150m. Of course, this estimate does not include other cost factors (eg cost of capital, opportunity cost, failure rates) that industry portrays as a vital part of its financial/investment planning.

The medical costs are generated during a development process of up to 20 years which is heavily affected by uncertainty as to whether or not the new MCM can successfully be determined by the regulatory authorities to be both efficacious and safe for human consumption. Consequently, not only does prevalence and incidence of the disease have to be high enough to provoke industry consideration for MCM development, but industry must also be confident that a sufficient number of MCM recipients will be willing and able to pay its set price. Only by targeting disease areas with high market sales volume, can the survivability and vitality of industry business models be safeguarded.

Concerning protection against highly dangerous, but rare agents, previous *CBRNe World Directory* chapters on MCM have highlighted the need to have international policy in place, which can effectively drive responsible preparedness plans. Only


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through the commitment of appropriate government incentives can the necessary free market characteristics be generated in order to motivate and engage industry adequately – attracting private investment and other resources away from products with higher sales and earnings potential.

Although several signs of policy development in Europe could be traced, Europe's ability to impact business feasibility and spark large and wide industry commitment has yet to be accomplished. Consequently, MCM development initiatives remain minimal outside the US and it remains unclear who the international buyers of such MCM may be.

In fact, ever since the first outbreaks of Ebola, the US identified this virus as a potential threat and in the year 2000, a CDC strategic planning workgroup had listed Ebola as a top Category A biological threat. Fourteen years later, however, in March 2014, the outbreak of Ebola virus in Guinea made it evident that a MCM had not been sufficiently progressed; hence there was no vaccine. Although the US Bioshield programme was launched back in 2004, its initial efforts focused on securing next-generation vaccines for anthrax and smallpox.

While the US and a handful of other countries included MCM against anthrax and smallpox in their national stockpiles, Ebola emerged in 2014 as a top of the news killer. This perhaps goes to show the difficulty of prioritisation versus threat assessment. With unprecedented magnitude, the latest Ebola outbreak which began in March 2014 claimed over 10,000 lives in Guinea, Liberia and Sierra Leone by March 2015. Consequently, hindsight has driven an urgent response to prioritise the availability of innovative MCM against Ebola.

Powerful reaction to the Ebola threat included the formation of the world's first international consortia to accelerate developmental progress of two vaccines. These are cAd3-EBOZ, being jointly developed by GlaxoSmithKline and the US National Institutes of Health (NIH) and rVSV-EBOV, from NewLink Genetics, developed by researchers at the Public Health Agency of Canada. During the most recent Ebola outbreak, the experimental drug, ZMapp, received much attention, but the ability to scale up supply in the short term was extremely limited and its efficacy remains uncertain (Claire M Tully 2015).

In response, the Department of Health and Human Services' (HHS) office of the assistant secretary for preparedness and response (ASPR) announced in September 2014, that the ASPR's biomedical advanced research and development authority (BARDA) would provide funding, and other technical support, through a $24.9 million, 18-month contract with Mapp Biopharmaceutical Inc, of San Diego, California. The contract can be extended up to a total of $42.3 million (HSS 2014).

The project with Mapp Biopharmaceutical was the first BARDA programme supporting the development of a MCM against viruses that cause viral hemorrhagic fevers, such as Ebola. So, given that the brutal Ebola killer virus was discovered in 1976 and reemerged on numerous occasions, why didn't the international community initiate a MCM programme earlier and what exactly drove the decision to do so now? Using Ebola as an example, it is perhaps useful firstly to explore what may have led to the international community's *laissez faire* attitude toward the disease, then highlight possible reasons for a re-evaluation of its status as a threat worthy of high levels of concern and action.

To understand the situation which led to the laisser *laissez faire*, it is important to put the threat into perspective. One must remain aware that many African nations are still burdened with several widespread diseases which cause far higher fatality rates, e.g. pneumonia, HIV, malaria, diarrhoea, tuberculosis, measles, whooping cough, tetanus, meningitis and syphilis. In many instances developed countries are already trying to upgrade Africa's current medical management programmes closer to state-of-the-art capabilities.

So, even if international responsibility and partnership could have evoked a strong will to support Ebola MCM programmes, establishing financial priority over other international programes aimed at basic, unmet medical needs would have remained challenging. Thus, a paramount reason why a MCM could not be adequately prepared is that, in comparison, Ebola is still a fairly rare disease. Consequently, current economic tools and metrics used in allocating funding did not determine monetary levels sufficient to develop MCM.

Indeed, in order 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. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability". (WHO 2015.)

DALYs may be used to evaluate health policies, compare intervention alternatives and to assess risk factors. When evaluating cost effectiveness, the WHO 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. Intervention becomes less and less cost effective the more the investment exceeds the GDP per capita – no longer being cost effective once a value of three times the GDP per capita is exceeded (WHO 2015).

While the use of DALYs attracts criticism, as results are not presented in a way that allows researchers or policymakers to recalculate and reinterpret findings for use in an alternative context (JA Fox-Rushby 2001), it nonetheless influences how much money donors are

willing to invest in medical intervention. When considering their application in determining appropriate investment for Ebola, one must bear in mind that even 10,000 deaths is low compared to other major diseases; thus, the number of DALYs is low.

In strong contrast, worldwide annual epidemics of influenza are estimated to result in three to five million cases of severe illness, and 250,000 to 500,000 deaths (WHO 2014). Besides the influence of low Ebola incidence, and thus, DALYs, in restricting funding for Ebola medical intervention, the cost effectiveness calculation benchmarks GDP per capita in the African nations affected, and this, too, is particularly low. For example, the average GDP per capita in countries most recently hit by Ebola is roughly $600 as against a figure of roughly $50,000 in developed countries, such as Germany, France, and the US.

To avoid placing a substantially lower value on human life in developing countries using the DALY approach, an expert from the Center for Global Development (CGD) argues that a cost effectiveness threshold of $10,000 per DALY averted should be applied. This would have justified a spend of at least $1.25bn on the development of a vaccine against Ebola (Barder, Owen 2014). While cost effectiveness issues may have contributed to the lack of MCM for Ebola, new awareness appears to have sparked new and urgent Ebola MCM projects as previously outlined. With both the GDP per capita in the affected African countries and the number of disease incidents still comparatively low, what has changed to thrust Ebola onto the international community's radar and attract significant investment?

Most probably, that high reaction to the Ebola threat is linked to the realisation that not responding could generate severe economic consequences. In other words, enduring the high costs of medical intervention and development of MCM became more attractive than ignoring the Ebola threat. As the spread of Ebola outpaced response, more forceful international support was summoned by the UN Security Council in September 2014 when it adopted resolution 2177 (2014).

This resolution called on member states to respond urgently to the crisis and refrain from isolating the affected countries. While the unprecedented extent of the Ebola outbreak was perceived to constitute a threat to international peace and security, it is plausible that member states viewed the Ebola threat with more specific content. Namely, at least two major reasons had emerged which possibly led to robust initiation of MCM. Their influence appears to stem from emotional and financial factors which are often interconnected.

The first reason was certainly the growing awareness that the Ebola virus could be exported to developed countries, bringing its substantial economic impact with it. For example, the spread of Ebola to developed countries could not only lead to higher outbreak incidence (thus, increased DALYs), but also significantly raise the GDP per capita of those affected in developed countries. As previously discussed, with DALYs and GDP per capita elevated, higher investment in medical intervention can be recognised as cost effective.

Of course, it can be argued that the robustness of the healthcare infrastructure in developed countries would be capable of quickly containing the imported cases of Ebola virus. If so there would not be a significant change in incidence. Thus the cost effectiveness model could not really be expected to increase investment. Nonetheless, just the fear of possibly being exposed to the Ebola virus might negatively influence economic productivity in developed countries.

For example, in October 2014, the World Bank publicly warned that Ebola could cause up to $33bn of losses for west Africa's economy (Talley 2014). This economic damage is influenced by reduced output caused by changes to behaviour in various economic sectors, for instance when workers/farmers don't show up for work, shop owners close their stores and tourists stay away. Fortunately, international efforts could improve treatment capabilities in the three African countries hit; thus, economic damage has, more recently, been estimated at $1.6bn.

Nonetheless, this still represents over 12% of the three countries' combined GDP which is quite significant. Besides the economic damage in countries directly hit by Ebola, it is estimated that a further financial loss of $0.5bn will accumulate for surrounding countries such as Gambia through Kenya to South Africa, due to reduced tourism there. This would deliver a total hit to the region of $2.1bn in economic damage (Thomas 2015). In comparison, if only a fraction of this fear were to reach the combined economies of France, Germany and the US, a negative impact of just 1% of GDP would mean a total economic loss of over $200bn.

The second reason the international community may have applied pragmatic force to establish a MCM programme for Ebola could be based purely on economic defence mechanisms to reduce direct costs. That is, beside the role and interests of governments in protecting the health of their people as well as their economic growth rates and stability, there are other financially sound reasons why the international community may have heeded the Ebola threat. Specifically, when considering return on investment (ROI) calculations for previous vaccination projects, supportive guidance for Ebola may be presented.

For example, costs of the WHO's enormous smallpox eradication programme between 1967 and 1979 totalled around $300m. This price has been repaid many times in saving human lives and in the elimination of costs for vaccines, treatment and international surveillance activities. The savings are estimated to be more than $2bn each year (Ehreth 2003). Since eradication in 1980, the US has recouped nearly 500-fold the value of its contribution to that effort (Kenny 2014).

While the immensity of these savings does not necessarily apply directly to Ebola, which has a higher mortality rate but is less contagious, they demonstrate that the potential for substantial savings may have been underestimated.

Indeed, to address the impact of Ebola, the World Bank Group announced in January 2015 that it had mobilised nearly $1bn, comprising $518m for emergency response and $450m to enable trade, investment and employment in Guinea, Liberia and Sierra Leone (World Bank 2015).

Back in September 2014, the UN had already announced that it would need nearly $1bn for an exceptional, international response to the Ebola outbreak in west Africa (United Nations 2014). This money was needed for everything from paying health workers and buying supplies to tracing people who had been exposed to the virus. About $23.8m was just to pay burial teams and buy body bags, since the bodies of Ebola victims are highly infectious and workers must wear protection suits (WHO 2014). In fact, the US Department of Defense (DOD) alone spent a total of $384.9m for Ebola related activities as of December 2014 (DOD 2014). While these examples may represent only the tip of the iceberg, clear argument already surfaces to justify investment in innovative MCM against the Ebola virus.

Given the need to set priorities, it quickly becomes self-evident that a holistic blanket of protection with MCM against all potential CBR agents is not realistic. A formal array of current and future medical intervention programmes will inevitably continue to compete for finite time and financial resources, as well as diverse interests. Since it takes several years to develop new MCM, governments remain challenged over setting timely and appropriate priorities that can add most value to the protection of their populations and in some cases, economic stability.

For diseases currently causing high prevalence and incidence, industry will continue to identify widespread human vulnerability as high sales potential; accordingly it will intercept accountability to develop and provide innovative MCM solutions within the context of free markets. This does not apply to several highly dangerous, but rare CBR agents, however. While the application of current influential metrics may affect the amount donors are willing to spend on diseases deemed as non-profitable by industry, lack of MCM preparedness for the Ebola outbreak in 2014 suggests there is room for improvement.

Analysis of cost effectiveness may indeed be a good parameter when allocating resources for achieving sustainable MCM solutions against CBR agents in a timely and effectively manner. It is vital, however, that the international community agrees on further prioritising metrics which are capable of capturing unique threat characteristics as presented by some of these diseases. For example, the Ebola case demonstrates that the direct costs of emergency response as well as the interconnection between economic growth and emotional factors should not be ignored. While tremendous foresight will be needed from the international community if there are to be sufficient incentives for responsible MCM development programmes, investment must go beyond the development of new MCM.

Public procurement contracts must be identified because it is unprofitable for businesses to simply develop a MCM and wait for events of low prevalence and/or probability to occur. New sources of timely financing and/or incentives, as well as alternative approaches to evaluating the real threat which specific CBR agents can present to the security and peace of the international community, must be developed and utilised. Undeniably, hindsight shows that lack of preparedness for Ebola led to significantly more costs than if a responsible MCM were available when it was needed. Moreover, the Ebola experience demonstrates that although the virus appeared to threaten only Africa, it became necessary to share the considerable costs of response across the wider international community.

In this context, more careful prioritising of MCM 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. While traditional insurance policies potentially benefit everyone in society at a reasonable price, most are willing and able to pay for the ability to mitigate financial risk from specified threats. Insurance companies are good at coordinating sufficient membership to secure a substantial capability for making payouts.

Focusing more tightly on health threats as posed by CBR agents, and given the massive cost of MCM development and related stockpiling, parallels can be drawn with the concept of global public goods. This means that national leaders need to realise that everyone is worse off without cooperative and aggregate efforts to create well-funded and effective MCM capability against CBR agents that may indeed some day pose risks to the security and peace of the international community. Although this concept may not apply to all CBR agents (eg those causing more limited damage), further economic analysis is required in order to determine various cost effective case scenarios.

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