Mark Lawrence Johnson writes about the need for long term planning in CBRN Medical Countermeasures

Pay Now or Pay More

Some rare, but deadly CBRN events, whether natural, accidental, or intentionally released, can cause social disruption that adversely impacts economic performance, causes human suffering and loss of life, and has political and geostrategic implications. While appearing to be mere intellectual theory in recent decades, the most recent natural biological outbreaks have made this a reality beyond doubt. In the case of the 2014 Ebola virus disease (EVD) outbreak in West Africa, for example, it was originally estimated that losses of up to $33bn could be incurred for West Africa's economy (World Bank Group, 2014). Such economic damage would have been induced by the lower output due to changed behaviour in various economic sectors (eg 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).

Thanks to international efforts to improve treatment capabilities in the three West African countries affected, the economic damage was subsequently estimated at $1.6bn. Nonetheless, this still represented over 12% of their combined gross domestic product (GDP). Given that Covid-19 is widespread and can also easily affect large and developed economies, GDP impact for them is far higher. There is no way to tell exactly what the economic damage will be, but early estimates predict most major economies will lose at least 2.4% of their GDP over 2020 as a whole (OECD 2020). To put this number in perspective, global GDP was estimated at around $86.6tn in 2019. Every single 1% drop in global economic growth amounts to almost $1tn in lost economic output. Of course, GDP estimates for both of these disease outbreaks do not take into account further GDP losses from previous and/or future impacts and recurring outbreaks.

Protection via medical countermeasures (MCMs) such as a vaccine could have helped shield human vulnerability to the serious threats to health and life. Correspondingly, adverse economic impact could have been minimised. Given there was no vaccine available for either EVD or Covid-19, it appears that the international community did not heed early warning signs appropriately. Since the first known outbreak of EVD in 1976, for instance, there have been multiple natural outbreaks in Africa over the years. In March 2014, however, the outbreak of EVD in Guinea showed that a MCM had not been sufficiently fostered. Likewise, it could be debated whether more preparatory activity could have been undertaken to advance knowledge of the pathogen and strategies for achieving MCMs against emerging forms of the coronavirus. The first cases of severe acute respiratory syndrome (SARS) are thought to have occurred in China's Guangdong province in November 2002. The first nationwide alert was issued in early April 2003 and a coordinated and effective campaign to combat SARS in China began in mid April 2003 (The World Bank, 2008). Even middle east respiratory syndrome (MERS) introduced itself back in 2012.

The R&D process to develop MCMs is extremely lengthy, risky and expensive. Under normal circumstances, it can take 10 to15 years at an average out of pocket cost of $1.5bn to develop one new drug. When funded by private investors, expenses can almost double due to the cost of capital (ie returns investors expect for taking financial risk). These R&D costs accrue from the time a drug is discovered to it being available for patients. Contributing to these high costs is the low probability that any candidate will succeed. The overall success rate of candidates entering the first clinical trial phase of development has fallen from 21.5% to 11.8%.

This means that just over eight candidates on average are needed to successfully develop one drug (DiMasi et al, 2016). In an environment with acute and widespread exposure to a CBRN agent for which no MCMs are available, R&D costs to develop a single drug are likely to be higher. This is because political policy to save lives, and thus the economy, requires faster R&D results as well as an extremely high probability of success. To achieve the latter, significantly more candidates are typically needed. The costs associated with drug development and uncertainty surrounding CBRN outbreaks lead 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 slowly brought to a boil, it will not perceive the danger and will be cooked to death.

The EVD and Covid-19 outbreaks make it more apparent than ever that it is far more costly to respond to acute outbreaks than to apply foresight and build robust preparedness measures. Although the average $1.5bn out of pocket cost of developing one new drug may appear expensive, it represents only a fraction of the cost of doing nothing until an outbreak occurs. Besides the previously mentioned estimated negative GDP impacts, further costs are incurred. For example, in its attempt to end the 2014/15 EVD epidemic in West Africa and to finally strengthen its own domestic preparedness, the US announced the passage of legislation that included $5.4bn in emergency funding on 11 February 2015 (US White House, 2015). Later estimates suggest the international community ended up committing more than $7bn for response and recovery initiatives (World Bank Group, 2016). In the case of the Covid-19 outbreak, costs continue to skyrocket. To start with, it has been reported that there are now 224 candidates in development as the world races to create the first vaccine (*The*

Pay Now or Pay More

Telegraph, 2020). An excessive, frenzied, and uncoordinated approach to developing new candidates must be extremely inefficient, with costs running far into the double digit billions. In addition, mounting expenditures associated with response as well as health and economic recovery initiatives across the globe are likely to exceed anything known in modern times.

But who must pay for timely development and availability of prioritised CBRN MCMs? Fuelled by the Amerithrax letter attacks of 2001 in the US, the government there launched its own BioShield initiative in 2004 with the aim of developing and stockpiling targeted CBRN MCMs. They were quick to realise that industry (US CDC, 2000) would not provide sufficient technology and availability of MCMs against newly perceived rare, but deadly health threats. The reason is that in the absence of an acute threat of a natural, accidental, or intentional release, demand for CBRN MCMs that are rarely needed in a free market environment would be exceedingly low to nil. A marketplace with few customers and low and volatile sales potential, results in market failure.

Exacerbating the lack of profitable appeal is that there is frequent need to develop vaccines that offer long-term immunity. Correspondingly, unless mutation does not make it necessary to constantly adapt the vaccine in the future, the use of such vaccines can dramatically reduce the market sales potential even further. The best example of this is the smallpox vaccination campaign, which allowed the WHO to declare the eradication of the disease in 1980. With that declaration, the market potential for smallpox vaccines evaporated. Hence, the US government appropriated $5.6bn in 2004 for its BioShield programme against perceived threats (ie intentional release of anthrax and smallpox). Despite their efforts, manufacturers of CBRN MCMs could only hope – at best – to realise sales a mere fraction of the size achievable for drugs to treat conventional diseases.

It is also worth mentioning that despite government grant support for R&D and guaranteed procurement following a successful launch, it usually remains a challenge for large manufacturers with proven capabilities to recoup their own direct and opportunity costs. To maximise shareholder value within a marketplace plagued by low, unpredictable, and/or short term demand, excessively high prices for medicines can in some cases offer a solution. Nonetheless, this can easily lead to public outcry and erosion of company images. While scrutinising the actions of industry lobbyists and costs of specialised medicines on a case by case basis is undoubtedly warranted, mutual understanding of the costs and effort associated with drug development could be highly conducive to building more trustful relations. Moreover, consensus regarding prioritised health threats, and access to shared stockpiles and production facilities, as well as opportunities for public private partnerships must be held fair and transparent.

Without further intervention from a broader international public health community, or until a foreseeable outbreak emerges in real time, trends indicate that established companies with proven R&D capability will generally continue to focus exclusively on financially rewarding mainstream drugs. Over recent decades, various analyses and studies have addressed key components needed to achieve MCM preparedness against prioritised CBRN agents. These include risk assessments, the root causes of market failure and its characteristics, economic consequences of different types of CBRN incidents, as well as comprehensive approaches to gauge and offset deterrence factors of market supply and demand. Nonetheless, lack of international CBRN MCM preparedness against the EVD and Covid-19 outbreaks may suggest it has been politically inconvenient to tackle this topic. It is, however, high time to pay now, instead of later. Adverse health and economic impacts realised particularly via the coronavirus pandemic have raised the importance of health promotion on the worldwide political and public agenda. This creates a political environment where voters may be quick to reward or punish the robustness of government response capability.

To overcome the constraints on supply and demand that lead to market failure, and hence lack of CBRN MCM availability, international cooperation strategies can potentially reduce the risk and opportunity costs of associated political efforts and financial investments. Besides sharing cost burdens and knowledge, the efficiency and comprehensiveness of a MCM portfolio can be increased and its sustainability reinforced. Assuming international cooperation and readiness can lead to higher demand (and more customers), this could proportionately reduce supply side deterrents, or at least fortify current supply side incentive programmes. To further encourage progress towards international public health economic policy, new research initiatives must be directed towards the refinement and practical adaptation of international cooperation and funding mechanisms. Priority research and implementation areas to achieve MCM readiness against prioritised CBRN agents include:

- Identification of existing international treaty and process required to amend its contribution to funding models (eg opt-out insurance coverage, taxation)
- Institutional composition and governance for achieving global consensus on health priorities
- Compensation pathways that encourage sharing of intellectual property/technologies
- Access procedures to shared stockpiles and production facilities (especially during peak demand)
- Process and means to create a transparent CBRN MCM market that can be perceived (also by mainstream industry) as robust, reliable, and sufficiently rewarding.

While public health and economic resilience can present a key political battleground domestically, it can also influence foreign relations and geostrategy. Hence, the capability of nations and their alliances to protect themselves against prioritised CBRN agents, whether naturally, accidental, or intentionally released, should be a vital component of national security policy.