Doctor and the medics

Mark Johnson on the international availability of medical countermeasures (MCM).

Ratification of the 1925 Geneva Protocol, which prohibits the use of chemical and biological weapons, symbolised a broad determination not to engage in offensive war strategies that deploy weapons of mass destruction (WMD). Further inspired by the end of World War II, as well as limited historical use of WMD, there arose a cause for governments around the world to abandon their offensive ambitions and adapt more defensive strategies that were aimed towards protecting themselves, just in case a WMD attack should happen. By 1955-1956, for example, work at the two Porton Down establishments in the UK had become solely defensive and Britain had abandoned moves to establish any offensive capabilities. Thereafter, the UK continued to work on biological defense.

It has to be noted that for many years in the military the bulk of the research was on chemical countermeasures. While there was an offensive biological weapons program in both Nato and the Warsaw Pact the bulk of operations was likely to utilize chemical weapons. Biological weapons were categorized as too difficult to control, that their release could not be contained, or restrained, within the target area. As such the weapon de jour for fifty years remained chemical, and within this the MCM manufacturers were provided with a gift: while blood (cyanide) and blister (mustard) were dangerous the most likely military choice would be some form of nerve (VX, sarin, soman, tabun etc). All the nerve agents worked on the body in the same way, inhibiting the acetylcholinesterase enzyme, which meant that there was only one pathway that had to be examined. Both sides of the Iron Curtain devised autoinjectors for this, most recently atropine based, while, more recently, kits were also devised for cyanide (Cyanokit) and mustard.

Radiation countermeasures were slightly more complicated. The military didn't see radiation, for decades, as an end in itself – a Radiological Dispersal Device is a relatively new invention – it was (quite literally) fallout from a much larger incident – a nuclear detonation. The military focus was on the latter, rather than the former, and in strictly strategic geopolitical ends, once the "buckets of instant sunshine" appeared it was "EndEX" – the end of the world as we know it. In the civilian sector, however, radiation was something to be measured, managed and, when things went wrong, medicated. While there was a civilian requirement, mainly Prussian Blue from the 1960s, the military did not need to do much more to improve it. Recently BARDA has started research on new MCM, but between 2010 and the 1960s there has been very little work.

When building and maintaining defense capabilities to protect military and civilian populations against WMD, the availability of medical countermeasures (MCMs) such as vaccines, antiviral drugs, antibiotics, diagnostics and medical equipment is a vital part of defensive preparedness plans. The need to offensively acquire WMD has decreased over the years and for many nations the perceived necessity to fully prepare defense capabilities to mitigate them, such as modern Medical Counter Measures (MCMs), has simultaneously diminished. When considering a lack of global demand for new and innovative MCMs against agents across the broad spectrum of WMD, i.e., chemical, biological, radiological, and nuclear (CBRN), it quickly becomes apparent that many governments do not sense a reasonable likelihood that its military and civilian populations will be exposed to such agents. Regardless of how they are released the novel MCMs required to respond to an incident are expensive to develop and involve a lengthy process to be ready for use.

This low-probability and high-risk characteristic of CBRN threats makes structuring any viable development and manufacturing base that would enable sufficient availability of MCMs during emergency demand very difficult. The level of complexity increases especially for MCMs that are rarely needed in a natural environment without the threat of intentional release. For example, the World Health Organisation's (WHO) success in their 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 (WHO 2001). Likewise, when considering other biological agents such as Anthrax, Botulism and Plague, which belong to top bioterrorism threats as classified by the United States Centers for Disease Control and Prevention (CDC), prevalence of natural occurrence hardly justifies significant investment by government and industry to development modern MCMs. As a result, many such MCMs will only be

developed, licensed, manufactured and made readily available when governments define a policy which reflects a threat perception level worthy of requiring associated defensive preparedness measures.

In December 2011, the US Secretary of State, Hillary Clinton, read a statement at the United Nations during the Biological and Toxin Weapons Convention (BTWC) that included the following remarks: “Now, I know there are some in the international community who have their doubts about the odds of a mass biological attack or major outbreak. They point out that we have not seen either so far and conclude the risk must be low. But that is not the conclusion of the United States, because there are warning signs, and they are too serious to ignore.” While the US might heed warning signs and drive initiatives to take preparedness steps, such as initiating the development and stockpiling of CBRN MCMs, many international institutions also advocate the need for prevention and medical readiness.

To strengthen and extend controls so that state defensive MCM capabilities against WMD, if available, do not require deployment, the United Nations Security Council adopted Resolution 1540 in 2004, which imposes binding obligations on all states to establish domestic controls to prevent the proliferation of nuclear, chemical and biological weapons. The UN stated

that national preparedness contributes to international capabilities for response, investigation and mitigation of outbreaks of disease, including those due to alleged uses of biological or toxin weapons (UN, BWC 2007), also that capabilities to detect, quickly and effectively respond to and recover from the alleged use of a biological or toxin weapon need to be in place before they are required (UN 2010). Nato delegates have also called upon governments and parliaments of the North Atlantic Alliance to properly fund research and development of WMD detection technology and countermeasures such as vaccines and drugs, as well as to ensure sufficient availability of them (NATO 2011). But are governments reacting responsibly by reviewing their defence policies and ensuring that they remain attuned to the evolution of science?

Hillary Clinton pointed out in her address to the BWC that, "The advances in science and technology make it possible to both prevent and cure more diseases, but also make it easier for states and non-state actors to develop biological weapons. A crude but effective terrorist weapon can be made by using a small sample of any number of widely available pathogens, inexpensive equipment and college-level chemistry and biology." The US Human Health Services (HHS) Secretary, Kathleen Sebelius, has stated that, "Increasingly, the range of dangers we face is widening to include biological, chemical, nuclear and radiological hazards. Today, we really don't know where our next public health crisis can come from. It could be a dirty bomb set off in a subway car. It could be a naturally-occurring 'super bug' that is resistant to all treatments. It could be a biological weapon we've never seen before assembled from the building blocks of life by a terrorist in a lab" (ASPR 2010).

To address the problem of potential CBRN agent exposure to deployed military, it is widely known that several governments and their military defence departments maintain and operate varying defense capacities to develop MCMs. Nonetheless, it is often not appropriate for these governments to communicate the focus, comprehensiveness or success of its efforts. Moreover, while military forces are historically acknowledged for protecting the population against conventional threats, it is likely that in most cases military resources and infrastructure are not adequately scaled to meet the requirements associated with providing MCMs such as development, manufacturing and licensing. When considering the development of MCMs for civilian use, significant differences are posed.

Typical soldiers are healthy, young adults, while civilians encompass a broad spectrum from infants to the elderly, who may have pre-existing health problems. For such groups, treatment courses and/or reduced dosages for vaccines and drugs may be required. Phillip Russel, in Project BioShield: What It Is, Why It Is Needed, and Its Accomplishments So Far noted, "After the anthrax attacks in the United States (US) in 2001, the HHS placed the responsibility for the development and acquisition of MCMs against biological threat agents in the newly created Office of the Assistant Secretary for Preparedness and Response (ASPR). Initial efforts focused on securing next-generation vaccines for two CDC category A threats: anthrax and smallpox. It was soon recognised that a secure funding source would be a key component in attracting industry to meet US government requirements. To encourage the development of new MCMs against CBRN agents and to speed their delivery and use in the time of an attack, President George W. Bush proposed Project BioShield in his 2003 State of the Union address. In 2004, President Bush signed into law Project BioShield, which provided new tools to improve medical countermeasures protecting Americans against a CBRN attack".

In the fiscal year 2004/5, appropriation for the Department of Homeland Security included $5.6 billion over ten years for the purchase of next generation countermeasures against anthrax and smallpox, as well as other CBRN agents (HHS 2004). While the US has recognised the value of industry's role in developing and manufacturing MCMs, it has also recognised key components necessary to activating its engagement. These include clarity surrounding product definition and market predictability, regulatory environment and funding mechanisms.

To highlight the need for clarity surrounding product definition and market predictability, it is vital to understand that the process required to develop MCMs is not only expensive and lengthy but it is also commercially risky. Furthermore, in many instances governments will be the only purchasers of MCMs due to the lack of disease prevalent in a natural environment. To stimulate industry activity toward developing and manufacturing them therefore, there must be clarity regarding which threats governments perceive, which relevant MCMs they want to include in their stockpiles and associated market characteristics such as predictability and size. It should be decided in early stages of the product development process in which context products will be stockpiled, e.g., prophylactic vs. post-exposure, mode of administration, shelf-life, conservation, packaging, multilingual labeling and formulation requirements. Similarly, it is essential that agencies responsible for preparedness possess an adequate understanding of the difficulties, timelines and expenses associated with developing the products which their procurement may wish to target. The general risks of failure and costs associated with developing MCMs are comparable to those aimed at more common diseases. Upon addressing key issues concerning clarity of the regulatory environment, it is given that many CBRN MCMs cannot undergo the classical clinical development process that is applied to traditional pharmaceutical products. This is due to the fact that, for many MCMs, the diseases that they aim to prevent or cure simply occur rarely in nature outside the onset of a terrorist attack. For obvious ethical reasons, the efficacy of many MCMs cannot be tested on humans. To illustrate this point, it was indicated previously that smallpox had been eradicated. As a result, it is not

possible to find and recruit humans who are infected with smallpox and conduct efficacy studies on them to see if a newly developed MCM against smallpox is efficacious, nor would it be ethical to infect them for study purposes. Hence, indirect proof of efficacy, e.g. appropriate animal models and surrogate markers, need to be widely recognised by international regulatory authorities. Lastly, to incentivise and mitigate risk for industry, it is critical that governments clearly outline its provision of funding mechanisms that will better enable product development to cross the so-called 'Valley of Death', between early stage developments and commercialisation.

The US plans to continue their stimulation package for development and stockpiling of MCMs, is reviewing its product portfolio and revising its approach to strengthen factors such as the regulatory science, flexible manufacturing, and strategic investment fund for new countermeasure technologies. It appears to industry, however, that most other countries in the world are maintaining a passive stance, i.e., little market demand outside the US can be perceived. Although reasons for complacency could possibly include satisfaction with existing products, differing threat and risk perception and prioritisation of other more acute health needs, it is also possible that many countries are merely depending on the efforts of few countries that are actively preparing their MCMs. If the latter is the case, tapping the resources of such countries might not prove to be a viable strategy. During the "Amerithrax" Anthrax letter attacks in the US in 2001 for example, many countries attempted to purchase the US manufactured Anthrax vaccine in response to potential threat in their own countries. Foreign access to the US stockpile was not possible for two reasons however: the US required a full stockpile for its own protection and export was restricted in the name of US strategic national interest.

Although past and future US budgeting for modern MCMs is highly significant and commendable for one government to put forward, the overall global market for CBRN MCMs is viewed by industry to have few customers with a severely low sales potential compared to traditional pharmaceutical/biotech markets. A business environment with a limited customer base, as well as inadequate and unpredictable sales potential, signifies a market that is volatile and unprofitable. At most, the efforts of a few niche developers and manufacturers can be supported and major industry activity is unlikely to flourish. In strong contrast, according to data provided by IMS Health, the global market for a traditional market such as oncology (cancer) reached almost $56 billion for the single year of 2010. Given the fact that mass customer demand for therapeutic solutions to such naturally and frequently occurring diseases is predictable and reliable, the full force of industrial attention bares superior worthiness when it comes to attracting the competencies and resources of major industry. This example makes it clear that one government alone with a budgeted few billion US dollars per year will be less effective at developing and assuring availability of MCMs than if a true global market were to be achieved.

The European Commission has shown particular foresight as demonstrated by its CBRN action plan (EU 2009) by requesting that each Member State assess the required amounts and types of medical countermeasures in case of an incident involving high-risk CBRN materials, as well as the possibility of sharing medical counter-measures across borders in case of an incident. It even sets out to address the regulatory issues associated with MCMs. Despite this encouraging action plan however, the situation with regard to the 27 Member States of the EU and MCM funding remains unclear. As a result, the industrial stakeholders who develop and manufacture MCMs continue to scale their capacities almost exclusively to the US market, where their business models stand a better chance of survival. This situation leaves many countries unprepared for the worst that CBRN threats may inflict. As John Abbott, chairman of the bioterrorism prevention steering group at Interpol, stated, "The threat of bioterrorism is for real and it is deadly as it has the potential to kill hundreds, thousands or even millions, but many nations still underestimate the need to prepare for such an attack" (*Gulf News* 2009).

To create a situation where industry can address the international availability of CBRN MCMs with its full capacity, governments around the world need to clearly communicate their perceived threats of WMD terrorism. If such threats are regarded as credible, it is pertinent that they enter into binding agreements with industry and decide which corresponding MCMs are needed and how much they require to stockpile as part of their preparedness plans. Until international governments can more broadly agree on an appropriate threat perception and counterbalance it with associated defense capabilities, the MCM industry will not be in a position to deliver its full potential.

So, how can the global community balance this unpredictable demand with a clear need for solutions? Firstly government needs to call industry to the table and communicate their requirements for MCMs. Equally, if offered this opportunity then industry will have to clearly indicate to governments how and when such requirements can be fulfilled. If the threat estimates and the current capabilities do not match, then governments will then need to partner with industry to develop and manufacture those MCMs that are vital to a responsible WMD preparedness plan. Supply cannot simply be turned on when governments are ready to receive, and dialogue alone will not create industry response to global demand. In many cases, governments will have to find ways to encourage businesses to develop and make their MCMs readily available. Only through an open public-private dialogue between governments internationally and industry can the right balance be found. The necessary exchange of view can best happen in a neutral, balanced and nonbiased environment, where the voice of industry is representative and diverse expertise across the range of CBRN can be given.