
EDITORIALS

The risk of selective investment in downstream pandemic planning

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Introduction

Whilst we recognize an increase in emerging infections and serious epidemics in recent years(1), there has been a lack of investment in upstream prevention and mitigation (2). There has been investment in development of diagnostics, drugs and vaccines, with formation of important organisations such as the Coalition for Epidemic Preparedness Innovations (3). If drugs and vaccines are available, they are important tools for epidemic control but come into play when an epidemic is already established. Equally important are the abilities to prevent epidemics altogether, to identify epidemics early, to ensure excellent triage and hospital infection control, surge capacity of space, and resources and personnel within health systems. Failures in any of these could cause health system failure and blow out of epidemics. Recognising the genesis of epidemics and all points where prevention or mitigation can be achieved is critical. Currently, investment is heavily focused on diagnostic tests, drugs and vaccines, which come into play well after an epidemic has occurred, but these are late in the timeline of epidemic emergence (Figure 1). Our ability to prevent and mitigate serious epidemics will be improved by ensuring an equal focus on governance, preparedness planning, surveillance and early diagnosis.

Many failures of epidemic control have been due to delayed or poor surveillance, lack of physical or human resources, weak health systems, failures in diagnosis and triage, poor coordination of response or breakdown in vaccination programs. Measles, for example, can be controlled with an effective vaccine, but is causing epidemics in the Asia-Pacific region, Africa, Europe and North America (4). Conversely, epidemics such as Ebola, MERS Coronavirus and SARS have been controlled with non-pharmaceutical measures such as infection control, isolation and contact tracing and quarantine (5).

The nature of true epidemics

Epidemics have an impact which is immediate, acutely disruptive and requires surge capacity in health systems and human resources. Whilst the term “epidemic” is widely misused, it refers to a specific pattern of exponential growth over a short timeframe, over and above the expected incidence (6). Epidemic control can be achieved at many points along the timeline of emergence, including prevention, surveillance and early detection (7), clinical diagnosis and triage, rapid diagnostics, patient isolation, hospital infection control, contact tracing and social

distancing, treatment and vaccination programs. An epidemic detected early using good surveillance is much easier to control, because case numbers are less. Epidemics are defined by an exponential rise in cases over a short time period (days to weeks) and characterised mathematically by the reproductive number, R_0 (6). The epidemic threshold is defined as R_0 equals 1, and any infection with an $R_0 > 1$ has epidemic potential. Ebola, for example, was estimated to have a R_0 of about 2 during the 2014 West African epidemic (8). Diseases such as smallpox and Ebola are epidemic in nature and a delay in response of even weeks can be critical because of the exponential growth in case numbers. This rapid surge in case numbers differentiates true epidemic diseases from endemic infectious diseases such as malaria or HIV. For example, the Ebola epidemic of 2014, was recognized in March of that year, when it was still small in scale. Within the 5 months of delay in response the epidemic grew exponentially, as predicted by a R_0 of approximately 2 (9), to an unprecedented scale of over 25,000 cases, most of which could have been prevented if the response had occurred immediately in March (Figure 2).

Governance

Governance, legislation and regulation can influence the risk of emergence of epidemics, particularly those which may arise in the era of genetic engineering and synthetic biology (10). Technology has advanced at a more rapid pace than legal or regulatory frameworks and the risks posed by technologies such as synthetic biology and dual-use research of concern are not fully understood. The risk of emergence of engineered or synthetic epidemics has increased due to increasing accessibility and reducing cost of CRISPR Cas 9 technology and synthetic biology. Gene synthesis has dropped in cost by more than 250-fold in a decade (11). The synthesis of an extinct orthopox virus called horsepox in 2017 (12), whether wise (12) or not (13), proves that variola, the virus that caused smallpox, could equally be created in a lab. Preparedness planning must include regulation of synthetic biology, which is presently unregulated and subject to a voluntary code of conduct. Do it yourself (DIY) biology, too, is expanding rapidly and self-regulated (14). The popularity of DIY biology means lab-in-a-box and other equipment are readily available for purchase online, along with open access scientific publications. The potential for a small group of actors to acquire all the necessary means to produce and then deploy a biological weapon is real.

Figure 1. Genesis of epidemics and opportunities for prevention and mitigation.

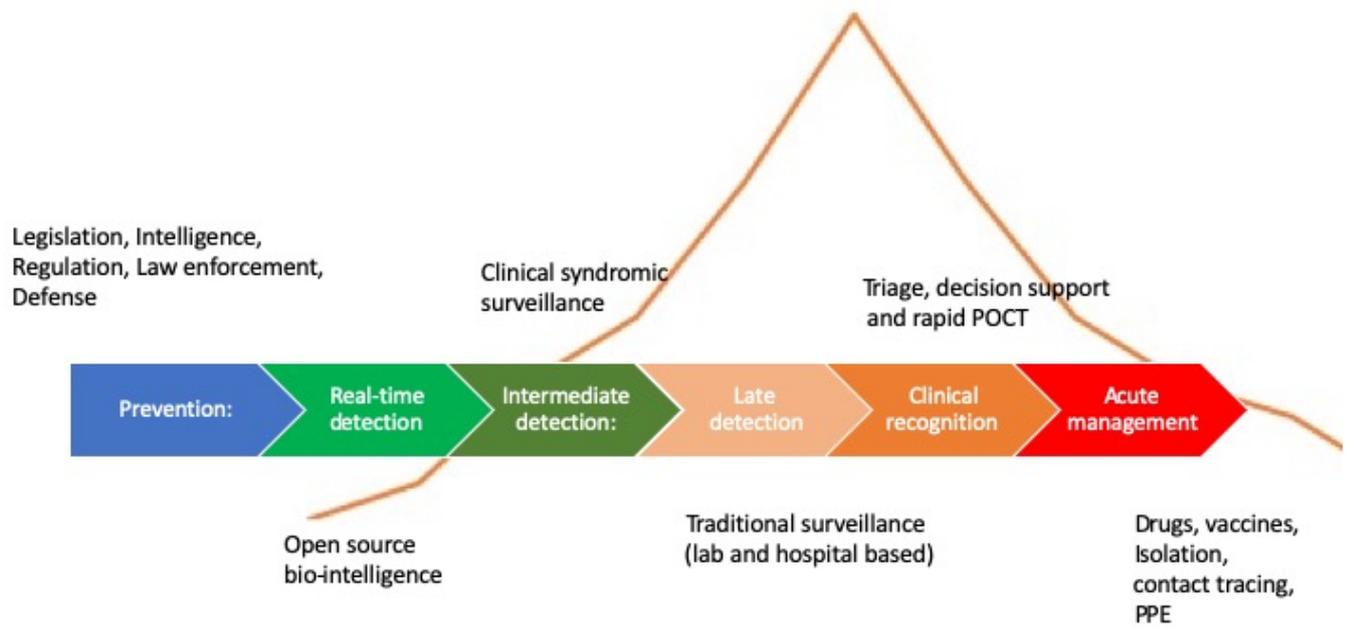
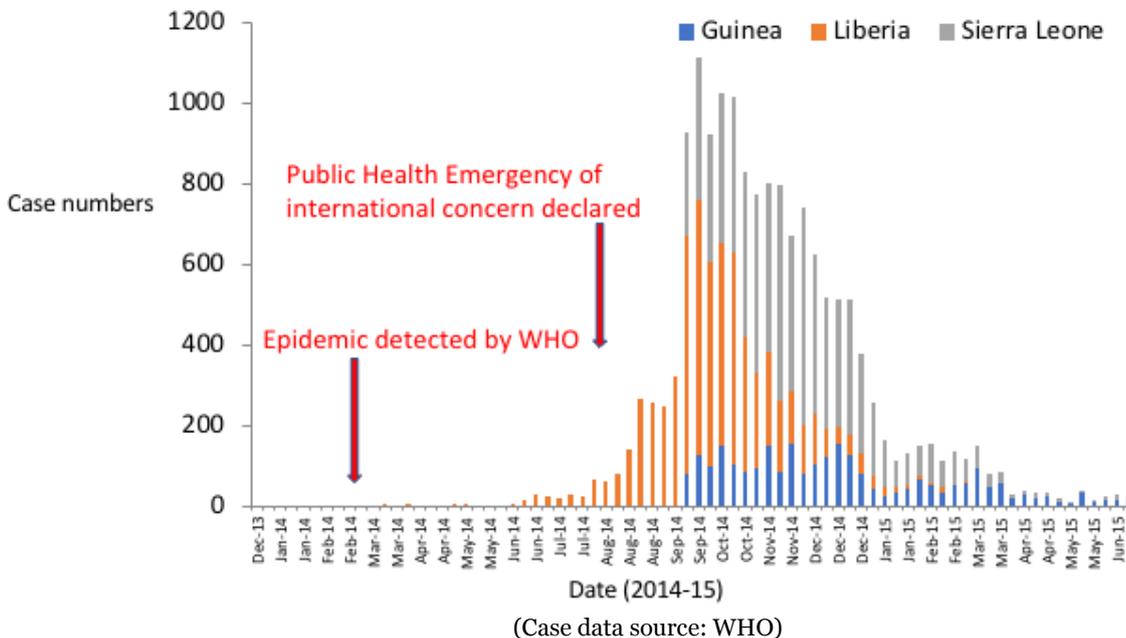


Figure 2. The time critical nature of epidemics – Ebola 2014-15



There is also the recognized threat of highly skilled insiders colluding with terrorist groups or hostile states within regulated laboratories, not just in the highest security laboratories (BSL 4) but in BSL 2 and 3 laboratories, which are far more numerous and less stringently regulated. Currently, most countries do not have adequate legislation to urgently remove a suspected rogue scientist from a lab. In terms of other laws and regulations, such as the Biological Weapons Convention (BWC), the Cartagena Protocol, local gene

regulation laws and the International Health Regulations (IHR), none adequately address the need arising from the rapid expansion of genetic engineering and synthetic biology. The BWC focuses on nation states as actors rather than rogue, small group non-state actors and differs from the Chemical Weapons Convention in that it is not enforceable or auditable. The Global Health Security Agenda (GHS) Action Package touches on some relevant aspects, but is more attuned to response than prevention and is a

voluntary framework that remains health-centric in scope. The IHR are relevant only after a full blown epidemic is apparent and was last fully revised in 2005. It is well understood that many countries cannot comply with the IHR, and the IHR has not made any apparent difference to recent serious epidemics, such as Ebola in 2014. It would seem timely to revise the IHR to better meet the needs of a very different landscape than when it was last revised 15 years ago. The role of legislation, regulation and governance on epidemic control is more important than ever, but finding enforceable, global mechanisms to assist disease prevention and control is a priority.

Surveillance and early detection of epidemics

If we could have detected and acted on the 2014 Ebola epidemic earlier, it would be even easier to prevent a large-scale epidemic. Epidemic control depends on surveillance, which in turn requires human resources, systems, capacity, communication and strong networks, which are often inadequate in low income countries. Traditional public health surveillance relies on data from the health system or laboratories, which is validated but may be significantly delayed. In some instances, official surveillance data from countries may be absent altogether due to fear of adverse impacts on tourism or trade. Surveillance data provide insights into trends over time, allow comparison between time periods, and can signal an unusual rise in a disease incidence. Enhanced rapid surveillance and intelligence using novel methods to complement (not replace) traditional surveillance can improve health security. There is a vast array of open source data, including social media and news reports, which capture the concerns and discussions of the community and can provide early signals of epidemics, prior to official detection by health authorities (15, 16). Public health has been slow to adopt this capability, which is particularly useful in low income countries because automated rapid epidemic intelligence systems mitigate the lack of human resources for surveillance. An automated system could reduce the required human resources and increase the efficiency of existing resources by providing early signals for public health investigation. Rapid epidemic intelligence can be developed using data algorithms for mining social media (15), and epidemics can be detected months earlier than by using traditional laboratory or hospital based surveillance (17). To further enable rapid response, risk analysis tools which take into account country-specific, disease specific and other predictors of risk, can be used to flag the need for urgent intervention (18).

Recognition, triage and diagnostics

The focus of investment is on diagnostics tests, rapid point of care tests and other novel diagnostic aids. Point of care tests that can be used in the field or at the bedside will improve infection control by

providing rapid diagnosis. However, if POCT are not available, suspected contagious cases should be isolated while waiting for a confirmatory laboratory test. In practice, this often does not occur, with outbreaks of measles commonly resulting from undiagnosed cases waiting for prolonged periods in the emergency room(19).

With low probability, high impact cases in an emergency department, such as Ebola, MERS Coronavirus or monkeypox, triage protocols and clinical decision aids, including travel history, are critical. However, failure of triage and missed diagnosis occurs repeatedly, from Ebola in Dallas, USA(20) and Nigeria (21) to MERS Coronavirus in South Korea (22) and smallpox in Yugoslavia (23). There is a need to invest in mandated decision aids and triage protocols to avoid the missed diagnosis of high-consequence infections. Without a clinical suspicion of a disease, the best diagnostic tests are useless because the prompt to using a diagnostic test is awareness of the possibility of the diagnosis – which appears to be the most consistent shortcoming in nosocomial epidemics.

Health systems, surge capacity and first responder protection

Many descriptive publications on the magnitude and mortality of the Ebola epidemic were generated in 2014, whilst concerted research efforts began for development of a drug or a vaccine against Ebola. Yet while waiting for drugs and vaccines, no concrete disease control goals were expressed in the first six months of the epidemic. One of the pressing problems in all three affected countries was a lack of hospital beds and isolation facilities for cases of Ebola. It was estimated only 15-20% of Ebola patients were in treatment units at the peak of the epidemic, because of a lack of both hospital beds and health workers (24), which contributed to uncontrolled transmission of infection in communities. Case isolation is an exceptional infection control intervention and can stop transmission of infection effectively. A modelling study published in September 2014 showed that in the absence of any pharmaceutical interventions, isolating 70% of patients could control the epidemic (25). A concerted public health response by local governments and responding military forces expanded the capacity to isolate infectious patients by building of field hospitals. This and other non-pharmaceutical efforts such as improved infection control, burial practices and waste management resulted in eventual control of the epidemic. The lessons of the 2014 Ebola epidemic were very much about understanding the importance of non-pharmaceutical measures, infection control and health system capacity in epidemic control. The Ebola epidemic of 2014 was further characterized by conflict over PPE protocols for health workers (26). The root of the problem is that hospital infection control as a discipline developed around patient safety and

remains focused on patient safety. The occupational health and safety of health workers is the domain of occupational safety experts, but infection control guidelines are generally written by infection control experts. It is essential that we give the highest priority to the safety and protection of health workers and other essential first responders such as paramedics, police, military and emergency services workers. In addition to the occupational health and safety obligations to first responders, any emergency response will be seriously compromised if first responders are not adequately protected – not only because they may succumb to illness, but because they may refuse to work under conditions of poor occupational safety.

Preparing for high-consequence epidemics

Smallpox was eradicated in 1980, but is a renewed concern because of new methods which make it possible to create the virus in a lab (13). In contrast to Ebola, we have effective vaccines against smallpox, yet health systems capacity and planning are equally important, even in high income settings. A new study we published in 2019 (27) looked at the impact of a hypothetical bioterrorism attack with smallpox in Sydney, Australia, on the health system. Using a mathematical model of smallpox transmission, we determined requirements for hospital beds, contact tracing and health workers (HCWs) in Sydney, Australia, during an epidemic of smallpox. We found that every day of delay in response increases the epidemic size. The public health response should commence within about a week after the first case of smallpox becomes symptomatic, or a severe epidemic may result. This relies on rapid diagnosis, but many outbreaks of smallpox have not been recognised until second generation cases occurred (23), which means that in practice, delays in response are likely. In terms of surge capacity, the requirement for extra hospital beds could range from 4% to 100% of all available beds in best and worst-case scenarios (27). This means that care of other urgent patients, such as people with heart attacks or strokes, may be affected due to shortage of beds and staff (27). The surge in beds requires a corresponding surge in doctors and nurses to treat smallpox-infected patients, as well as adequate PPE for these clinicians. Most stockpiling provides short-term supplies, but an epidemic could go on for months or years, in which case standard stockpiles (which typically provide a few weeks supply) will be rapidly depleted. Vaccination is critical for epidemic control (28), but the process of vaccination requires more than the vaccine. Smallpox control using ring vaccination (finding and vaccinating close contacts of each case of smallpox) requires contact tracing, with the number of contacts expected to be an order of magnitude greater than cases (27) – yet the public health workforce available to conduct contact tracing is much smaller than the clinical workforce. We estimated that there are about 100,000 clinical HCWs in Sydney, but only

about 300 public health workers. Even worse, trained public health workers are not registered as health practitioners in Australia, which means identifying the available pool of qualified workers is difficult. In our modelled smallpox epidemic, it is likely that community volunteers would be required to assist with contact tracing, as was the case during eradication of smallpox. Countries without civil preparedness programs or national service would be more vulnerable if surge capacity needs require community volunteers. There is a strong case for offering civil preparedness courses, training and certification to enable rapid community surge capacity.

In the case of a large-scale epidemic of a serious emerging infection, it is important to have back up plans for pop-up treatment centres (rather than treating cases in general hospitals). This not only reduces the risk of nosocomial infection but can reduce the number of staff exposed to infection and enable better cohorting of patients and rostering of staff. Failure to diagnose Ebola in Nigeria in 2014 during the height of the West African epidemic resulted in a nosocomial epidemic which caused the deaths of several HCWs. After making the diagnosis, Nigeria did this well to control the outbreak, drawing on extensive experience with polio control campaigns (29). They immediately established a separate designated Ebola treatment centre in an abandoned building and moved patients out of the general hospital environment. One surviving doctor, Ada Igonoh, wrote an account of the management of the epidemic in Nigeria through her personal experience of becoming infected and being taken to a makeshift facility for Ebola care. She detailed the meticulous infection control measures taken, including on exit from the facility (30). Aside from the initial missed diagnosis, Nigeria did an exceptional job of containing and stopping the nosocomial epidemic and preventing a larger scale epidemic in the community. A large-scale epidemic in the capital city of the most populous country in Africa would have been a disaster.

In summary, a holistic view of epidemic control from prevention at one end to pharmaceutical interventions at the other is ideal. Forethought, legislation, surveillance, planning, capacity building, training and the ability to effect rapid surge capacity in physical space and human resources can prevent or control an epidemic. Planning should focus on identifying influential factors we can control to mitigate epidemics (31), which are present along the entire spectrum depicted in Figure 1. There is much we can do to prevent and mitigate epidemics, and all opportunities for prevention are equally important. Improving global governance, legislation and regulation, use of rapid epidemic intelligence and risk analysis tools, health systems planning, and systematic triage and diagnosis protocols, can all be achieved. Within health systems, this includes plans for rapid establishment of “pop-up” dedicated

treatment facilities, rostering plans, surge capacity for staff and volunteers, infection control plans and ensuring health workers are protected with vaccination and adequate PPE. Together with availability of diagnostics, drugs and vaccines, these are the full repertoire of strategies for epidemic control.

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