

Quest for Outbreak Preparedness: Advancing Research Response to the Next Infectious Threat



Explosive human population growth and international travel, combined with a shrinking habitat for animal species and increased interaction between humans and animals, are just some of the contributing factors that have led to an environment ripe with potential infectious threats. While the development of antimicrobials and vaccines over the last 70 years has played an important role in the fight against infectious diseases, their unpredictable nature means the next threat will emerge; it is only a matter of time. Outbreaks like the 2009 H1N1 “swine flu” pandemic and the recent West African Ebola epidemic may offer clues to what steps need to happen to enable a more rapid response to the next threat.

The Zika virus, which is spread to people through mosquito bites, is just one example of a disease that has likely emerged in the Americas from ecologic changes that have increased human exposure to infected insects. Virtually unknown outside the medical community until a few weeks ago, Zika is now in the headlines of every major news outlet. In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed Zika virus infection in Brazil. The outbreak in Brazil has now spread to other regional countries and has led to reports of Guillain-Barre syndrome and increasing numbers of newborns with birth defects and other poor pregnancy outcomes. Today, more than 30 cases of Zika virus infection have been reported in the United States, most in subjects returning from affected areas, although cases of sexual transmission have also been documented. In response, the US Centers for Disease Control and Prevention (CDC) has issued a travel alert (Level 2 - Practice Enhanced Precautions) for people, particularly pregnant women, travelling to regions and certain countries where Zika virus transmission is ongoing.

There is currently no vaccine to prevent Zika; however, funding for vaccine research has been gaining momentum. In January, the US National Institute of Allergy and Infectious Disease (NIAID) announced it would make grants available for Zika vaccine research, while the UK Medical Research Council (MRC) announced a ‘Rapid Response’ call for research applications aimed at tackling the risk posed by the Zika virus.¹ Several companies have already begun working on the development of vaccines for Zika virus, but the World Health Organization (WHO) has warned that it will be at least 18 months until the first candidates are ready for trials.²

It Takes a Village

As infectious agents continue to evolve, vaccines must as well, but vaccine development isn’t easy. In addition to the usual clinical development challenge of reducing spiralling costs, outbreaks like Ebola, H1N1 influenza A

and Zika present critical time issues. Time is crucial not only to protect patients, but also to ensure launch before a new strain emerges. Even after a vaccine is developed, clinical trials to test a vaccine during a pandemic demand extreme speed in start-up, a rapid operational tempo, and access to subjects in high-risk areas for the targeted disease.

The global response to preventing, identifying, managing, and containing emerging infectious threats has included everything from strengthening general infrastructure, healthcare infrastructure and diagnostic capacity to improving treatment capacity and containment techniques, as well as epidemiologic and control capacity, particularly in the most vulnerable geographic areas. Stockpiling diagnostic, prophylactic and therapeutic countermeasures for the most likely potential threats, such as influenza, has also been proposed and undertaken.

While these are all valid recommendations, the most important lesson that has emerged from pandemics of the past is that true collaboration among government agencies, academia, pharma, international groups, and local healthcare workers is essential.

Lessons Learned from 2009 H1N1 Influenza A Pandemic and Ebola Outbreak

During the 2009 H1N1 influenza A pandemic in North America, the CDC worked with other US government agencies including the Food and Drug Administration (FDA), the NIAID, the US Department of Defense (DOD) and the US Department of Health and Human Services (DHHS) to conduct research during the pandemic. Most of this research was sponsored by the US DHHS through the Biomedical Advanced Research and Development Authority (BARDA). Additionally, the CDC also collaborated with academia, the pharmaceutical industry, the WHO, and other international partners to help with diagnosis, treatment, prevention, and control in the US and abroad.

In addition to conducting research aimed at obtaining approval of vaccines or antimicrobials for biological threats, the FDA allows for the distribution of experimental antimicrobials through the emergency IND process (eIND). Licensed prescribers can request the drug through the manufacturer after obtaining FDA approval for individual patients. While the data collected during this process is not comprehensive and not collected under GCP guidelines, valuable lessons can be learned during this process.

During the emergent threat, and depending on the

phase of drug development for the antimicrobial, the FDA may grant an emergency use authorisation (EUA) that allows the distribution of the unapproved product to treating physicians in the US. Although the collection of clinical data is not possible with this mechanism, assessment of safety and tolerability of the product in general terms is possible. Finally, formal clinical research to supplement the NDA package and strengthen the safety database is also possible and can provide useful data.³

BioCryst, the manufacturer of IV peramivir (a neuraminidase inhibitor for influenza), completed, presented and published an emergency IND case series of patients treated with IV peramivir during the 2009 influenza pandemic, enabling distribution of peramivir to individual clinicians under the eIND process.⁴ BioCryst also achieved the only emergency use authorisation (EUA) for an unapproved drug in the United States, allowing the use of IV peramivir during the 2009 influenza pandemic in North America. Approximately 1600 courses of IV peramivir were distributed by the CDC to individual clinicians in the US; these activities were coordinated in close collaboration with the NIAID, the FDA and the DHHS in the US.⁵ IV peramivir was approved by the FDA late in 2014.⁶

Several companies conducted research to develop and obtain approval of new diagnostic methods and vaccines for 2009 H1N1 influenza A during the pandemic; some of this research was delayed and resulted in the identification of a need to increase vaccine production capacity worldwide.

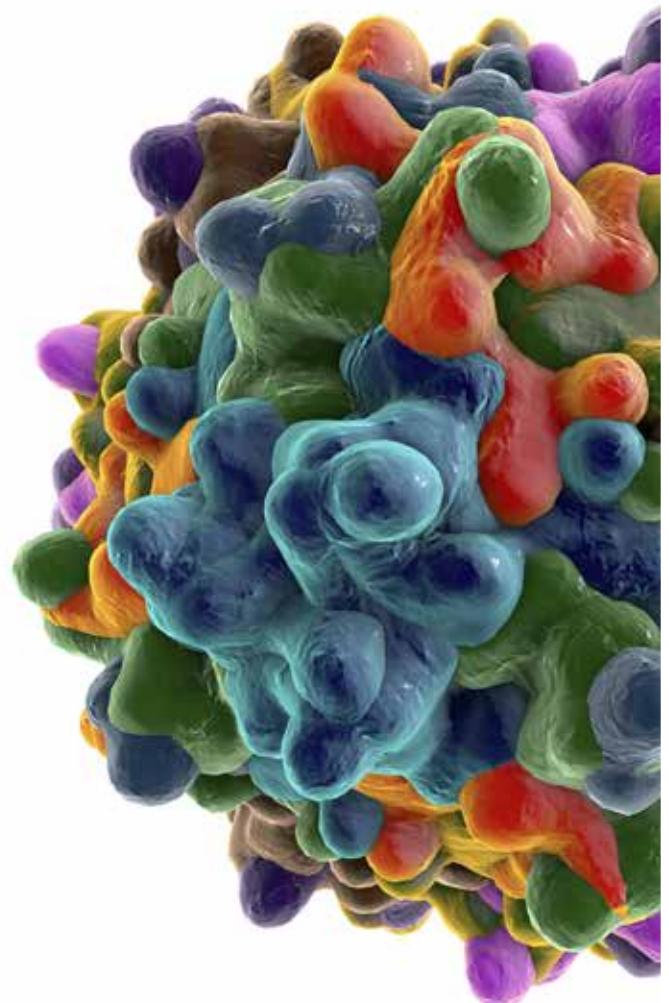
The 2014 Ebola epidemic in West Africa, the largest outbreak in history, claimed thousands of lives and is still having ramifications on the region's ability to provide adequate healthcare today. Like the H1N1 influenza pandemic, the main takeaway that has come out of the efforts to control the Ebola outbreak has been the need for collaboration.

During the outbreak, the CDC, together with other US government agencies, the WHO and international partners worked to establish protocols for monitoring and screening subjects flying from Liberia, Sierra Leone and Guinea to prevent importation of additional cases into the US and other countries. Protocols to evaluate the ability to respond to Ebola in neighbouring countries were established along with infection control practices for US healthcare facilities. Additionally, the CDC, FDA, NIAID, BARDA, DOD, and others worked with other country agencies (Health Canada, Swiss Government, MOHs from affected West African countries, etc.), and international groups (WHO, Doctors Without Borders, Wellcome Trust, etc.), deploying dozens of experts to the affected areas to collaborate with local and external healthcare workers on finding a vaccine.

Several Ebola vaccines are currently in development.

The two most advanced are from GSK and the NIAID (ChAd3-ZEBOV) and NewLynk/Merck and the Canadian Public Health Service (rVSV-EBOV). Both are in Phase III and are being investigated in various countries, including West Africa. Other vaccines in development include one each from Novavax and Protein Sciences.

While many government agencies and aid organisations, both in Africa and internationally, came together in an effort to stop the Ebola virus from spreading and finding a vaccine, funding for trials wasn't made available until more than six months after the official outbreak began. A £3.2m (\$4.9m) Wellcome Trust grant was used to conduct fast-tracked studies of investigational treatments in what were the first ever clinical trials done during an Ebola outbreak. Despite this effort, many Ebola researchers have expressed frustration about the pace and scope of the response and believe that clinical trials need to become a matter of course as opposed to an afterthought. Additionally, funding for trials has proven to be more difficult once the threat of an epidemic is no longer present or perceived.⁷



Following the Ebola outbreak, the WHO created the R&D Blueprint for infectious diseases with epidemic potential.⁸ The Blueprint calls for submissions on how to improve R&D readiness for priority infectious disease threats and is currently being followed in an effort to combat the Zika virus.⁹

The Next Threat

Despite the unpredictability of infectious disease, new threats like Zika and reemerging threats like Ebola are almost certain. In fact, just in January this year, hours after the WHO declared the West Africa outbreak over, Sierra Leone officials confirmed a death from Ebola. The country had been declared free of the virus last November, and the region as a whole was cleared when Liberia was pronounced Ebola-free in January, but the WHO has warned that West Africa may continue to see flare-ups.¹⁰

In addition to applying some of the lessons learned from previous outbreaks, preemptive measures to strengthen local infrastructure, and improve sanitation, triage and isolation practices, as well as more advanced healthcare facilities in the developing world, are needed to allow for more rapid identification and control of future threats. Continued collaboration will remain crucial. Significant headway has been made in a number of areas designed to improve approaches to vaccine, drug and diagnostic development during an infectious disease threat.

Efforts to streamline clinical trials are also underway and will likely become a more accepted part of responding to infectious threats, such as Zika, Ebola and others. However, it is critical that members of the international community remain steadfast and continue to do their part in accelerating research on experimental treatments so that immediate, actionable results can be collected and interpreted and treatments can be brought to bear in affected areas.

References

1. in-Pharma Technologist.com. "WHO: Zika vaccine still at least 18 months from clinical trials," by Gareth MacDonald, February 12, 2016. <http://www.in-pharmatechnologist.com/Regulatory-Safety/WHO-Zika-vaccine-still-at-least-18-months-from-clinical-trials>
2. Outsourcing-Pharma.com, "Future epidemic trials must cut through red tape, says Ebola researcher," by Dan Stanton, November 19, 2015. <http://www.outsourcing-pharma.com/Hot-Topics/Ebola-outbreak/Ebola-researcher-Future-epidemic-trials-must-cut-through-red-tape>
3. Michael G Ison, Joseph Fraiz, Barry Heller, Luis Jauregui, Graham Mills, William O'Riordan, Brian O'Neil, Geoffrey Playford, Douglas Rolf, Eduardo Sada-Diaz, Jenna Elder, Phil Collis, Jaime E Hernandez and William Sheridan: Intravenous peramivir for treatment of influenza in hospitalized patients. *Antivir Ther.* 2014;19(4):349-61. doi: 10.3851/

IMP2680. Epub 2013 Aug 28.

4. Jaime E. Hernandez, MD, Raghavendra Adiga, MD, Robert Armstrong, MD, Jose Bazan, DO, Hector Bonilla, MD, John Bradley, MD, Robin Dretler, MD, Michael G. Ison, MD MS, Julie E. Mangino, MD, Stacene Maroushek, MD, PhD, MPH, Avinash K. Shetty, MD, Anna Wald, MD, MPH, Christine Ziebold, MD, Jenna Elder, PhD, Alan S. Hollister, MD, PhD, William Sheridan, MD, on behalf of the eIND Peramivir Investigators: Clinical Experience in Adults and Children Treated with Intravenous Peramivir for 2009 Influenza A(H1N1) under an Emergency IND Program in the United States. *Clin Infect Dis*, 2011; 52 : 695-706.
5. Yu Y, Garg S, Yu PA, Kim HJ, Patel A, Merlin T, Redd S, Uyeki TM. Peramivir use for treatment of hospitalized patients with influenza A(H1N1)pdm09 under emergency use authorization, October 2009-June 2010. *Clin Infect Dis*. 2012 Jul;55(1):8-15. doi: 10.1093/cid/cis352. Epub 2012 Apr 5.
6. US Food and Drug Administration. FDA approves Rapivab to treat flu infection (2014). Press Release: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427755.htm
7. Medical Research Council (MRC). "MRC launches Rapid Response to fast-track Zika research," February 3, 2016. <https://www.mrc.ac.uk/news/browse/rapid-response-launched-to-fast-track-zika-research/>
8. WHO R&D Blueprint http://www.who.int/medicines/ebola-treatment/public_consult_platform-tech021115.pdf
9. WHO: A research and development blueprint for action to prevent epidemics, "WHO to fast-track availability of diagnostics for Zika virus," February 15, 2016. <http://www.who.int/csr/research-and-development/en/>
10. BBC News. "Ebola virus: New case emerges in Sierra Leon," January 15, 2016. <http://www.bbc.com/news/world-africa-35320363>



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