THE NEXT TIME

THE WORLD IS ILL-PREPARED FOR THE NEXT EPIDEMIC OR PANDEMIC. BUT THE HORROR OF THE EBOLA OUTBREAK IN WEST AFRICA MAY DRIVE CHANGE.

By Declan Butler

If there was one point last year when public-health experts held their breath, it was when a Liberian man infected with Ebola virus flew to Lagos, Nigeria, in July. Ebola was already raging uncontrolled through impoverished countries in West Africa, killing half of those it infected. Now a vomiting man had carried it straight to the heart of Africa's largest megacity — with 21 million inhabitants, many of whom live in slums. Experts were horrified at the prospect that the virus might rip through the city — and then, because Lagos is an international travel hub, spread farther afield.

"The last thing anyone in the world wants to hear is the two words, 'Ebola' and 'Lagos' in the same sentence," said Jeffrey Hawkins, the US consul general in Nigeria, at the time.

In the end, this apocalyptic scenario did not play out. Because Nigeria is a focus of global efforts to eradicate polio, it has a decent infrastructure of virology labs and epidemiologists and the capacity to run large public-awareness campaigns. Authorities quickly repurposed this toolbox to tackle Ebola, and the outbreak was contained with just 20 cases in all. The number of infections from Ebola in Guinea, Liberia, and Sierra Leone has dropped from its peak of hundreds of cases per week, to 20 or 30. But what has not faded is the fear that, at some point in the future, the world will face an outbreak of a deadly disease that spreads much more easily between people than Ebola does, and so results in an epidemic or pandemic that is even more terrible than that in West Africa.

Quite what that disease will be, no one knows. One worst-case scenario is that of an influenza virus as deadly as the one behind the 1918 pandemic, which raced across the world killing as many as 50 million people. Other virus families also keep researchers awake. Poxviruses are one: smallpox was eradicated in 1980 after killing some 300 million people in the twentieth century, but there are many animal poxviruses that could evolve to replace it. Paramyxoviruses are another major worry: the family includes Nipah virus and Hendra virus, both of which have triggered small outbreaks that caused serious illness and death. But uncertainty prevails. "Second on the list is the one we haven't thought of, and at the very top is the one we can't imagine," says infectious-disease specialist David Morens at the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland.

Graves dug in Freetown, Sierra Leone, to cope with those dying from Ebola in late 2014.

MADS NISSEN/PANOS

The Ebola epidemic has spurred researchers and public-health experts to call for a major overhaul of the world's approach to epidemic threats. What's needed, they argue, is better monitoring for the emergence and re-emergence of pathogens, and beefed-up health systems in the many poor countries that are often on the frontline of epidemics. They want to see nimble task forces that are able to respond rapidly and forcefully to outbreaks, and a multibillion-dollar global fund to quickly develop countermeasures such as drugs and vaccines.

At the same time, the risks need to be kept in perspective, say researchers. History shows that new pathogens that pose a large epidemic threat are "very rare", says Adrian Hill, a specialist in infectious diseases and director of the Jenner Institute in Oxford, UK. So are those that quickly kill many of those infected — the type that film plots thrive on. Many emerging epidemics, such as that of multidrug-resistant tuberculosis, move more slowly, yet cumulatively can kill many more people than the acute outbreaks that attract most of the media and political attention. But when they happen, large, acute epidemics can cause devastating loss of life and major economic damage, and the panic and chaos they generate can do more harm than the pathogen itself. The Ebola epidemic is not over, and there are concerns it could spike again.

"Ebola has been a wake-up call, not just for Africa, but for the world," said Margaret Chan, director-general of the World Health Organization (WHO) in March. "The world must never again find itself in such a position."

The greatest new epidemic threats are unknown pathogens that spread easily — for example, through the air — and to which humans have little or no immunity. The world's last brush with anything coming close was in late 2002, when the virus causing severe acute respiratory syndrome (SARS) caused a outbreak in humans in Guangdong province, China, then quickly fanned out into 29 countries — infecting at least 8,098 people and killing 774 of them — before a massive international response brought it under control. If that virus had spread just a bit more easily, it might have killed many more. "SARS probably came close to becoming an out-of-control pandemic," says Morens. "I think of SARS as one of our scariest close calls."

HOW TO DETECT THREATS

Like SARS, which is thought to have originated in bats, most future infectious diseases will come from animals; some three-quarters of new human diseases have emerged this way. Scientists suspect that the current Ebola outbreak originated when the virus passed from fruit bats to a two-year-old boy playing in a forested region of southern Guinea; Middle East respiratory syndrome (MERS), a viral disease that emerged in 2012, is probably transmitted by camels. And just last month, researchers reported that three squirrel breeders in Germany who had died of encephalitis were killed by a novel bornavirus that had been carried by the animals.

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In theory, this knowledge could help the world to prepare. Scientists could carefully monitor viruses in animal populations and in people living nearby to identify potential threats, such as any that show some ability to cross the species barrier. Such basic research might allow scientists to get a head start on developing vaccines and drugs. But the science of predicting such threats is in its infancy. Scientists know little about what allows an animal pathogen to infect humans or to then spread between them, processes that depend on many factors, including its ability to enter human cells and replicate there. "Of all our gaps in knowledge, the worst gap is how little we know about the mechanisms of emergence," says Morens.

To make matters worse, the vast majority of infectious-disease research and surveillance is in developed countries, but most emerging and re-emerging diseases are in the developing world. "We need to be where the diseases are, and where they are likely to emerge, studying them at their source, not sitting in labs in US science buildings," says Morens, who is currently working on Ebola in Guinea.

Robert Garry, a virologist at Tulane University in New Orleans, Louisiana, is working with African scientists in an international project — the African Center of Excellence for Genomics of Infectious Diseases, based at Redeemer's University in Redemption City, Nigeria. The project, which began in May last year, is taking blood samples from villagers in the region who have fevers, and using next-generation genetic sequencing of the samples to discover new pathogens, as well as developing diagnostics for both new and known ones. Supported by the US National Institutes of Health and the World Bank, it has an initial four-year budget of around US$8 million.

Researchers do have some clues to guide their search for threats. They know that factors such as geography, climate and culture can help to identify hotspots of disease emergence, with most at lower latitudes. And it is clear that a major driver is contact between animals and humans. The EcoHealth Alliance, an international network of scientists centred in New York City, and the US Agency for International Development's Emerging Pandemic Threats programme are carrying out viral sampling

from animals and people in hotspots across the world, and trying to tease out how farming, trade, deforestation and hunting and consumption of bushmeat influence the emergence of diseases.

Such projects have led to the discovery of hundreds of viruses including arenaviruses, phleboviruses, coronaviruses and rhabdoviruses — and are likely to yield many more in the future, says Garry. But even when researchers do find new viruses, it is difficult to say which of them might pose a major threat. Few people would have anticipated that HIV/AIDS, the world's largest recent pandemic, would be caused by a retrovirus, part of a viral family that had not previously been associated with major infectious disease, Garry says (see 'Emerging threats').

Some hints can be found by examining the affinity of viruses for receptors on human cells and assessing how well they spread between animals in the lab. These approaches are perhaps most advanced for flu viruses, which cause pandemics every few decades, of varying severity. Researchers around the world try to rank the potential pandemic risk of flu viruses using a battery of criteria, including the pathogens' ability to infect or transmit between ferrets, whether they can bind to human receptors, and to what extent the human population has immunity. This information is used to prioritize the development of vaccines against those that seem more threatening. But it cannot predict which flu viruses might go pandemic.

Researchers know that more could and should be done. One of the most important tasks is to establish local medical and research systems that can quickly analyse what is going on when a cluster of people suddenly comes down with serious disease. Such systems, which are often underdeveloped in poorer countries, require a trained local workforce of microbiologists, epidemiologists and clinical scientists, and diagnostics laboratories capable of testing clinical samples for a wide range of diseases. These could be implemented in a low-income country for as little as $12 million annually, according to Jeremy Farrar, director of the UK biomedical charity the Wellcome Trust, who helped to establish such a system in Vietnam.

But right now, surveillance systems are just as limited as scientists' knowledge of emerging threats. So the current reality is that we will probably be alerted to the next human epidemic or pandemic only once it is well under way.

HOW TO RESPOND

At that point, the world must respond — fast. For Ebola, it did not. The initial outbreaks occurred in December 2013, but Ebola was only identified as the cause at the end of March 2014, by which point the outbreak had already spread. Early alarms by the humanitarian organization Médicins Sans Frontières (MSF; also known as Doctors Without Borders) were ignored, and the international response did not kick into high gear until September (see *Nature* **513,** 469; 2014). "Ebola spun out of control because of a lack of political leadership, will and accountability — not because of insufficient funding, early-warning systems, coordination or medical technologies," Joanne Liu, international president of MSF, told a gathering of health leaders in May.

This was not how it was meant to be. In 2005, all 196 countries adopted a set of laws called the International Health Regulations, which were designed to improve the response to disease outbreaks. The regulations — effectively the world's emergency action plan — were spurred by the SARS epidemic, and by outbreaks of H5N1 avian flu virus.

But Ebola revealed how weak the regulations are. They mostly tasked individual countries with dealing with outbreaks — setting targets for them to reinforce their capacities for disease surveillance and response by 2012 — but did not include support to help the poorest countries reach those goals. This weakness has long been recognized, but not acted on — an "elephant in the emergency room", says David Fidler, a specialist in international and national security law at Indiana University Bloomington. Ten years after the treaty was adopted, two-thirds of its signatories have yet to meet the targets.

The regulations also failed to create an international rapid-response group to deal with a major outbreak. The WHO has never had outbreak-response teams on the scale needed to deal with an epidemic as large as Ebola, says Fidler, and what capacity it had has been slashed by budget and staff cuts. "What we are seeing in the Ebola crisis is the lack of a global public-health expeditionary capability that can handle something on a country or regional scale," he says.

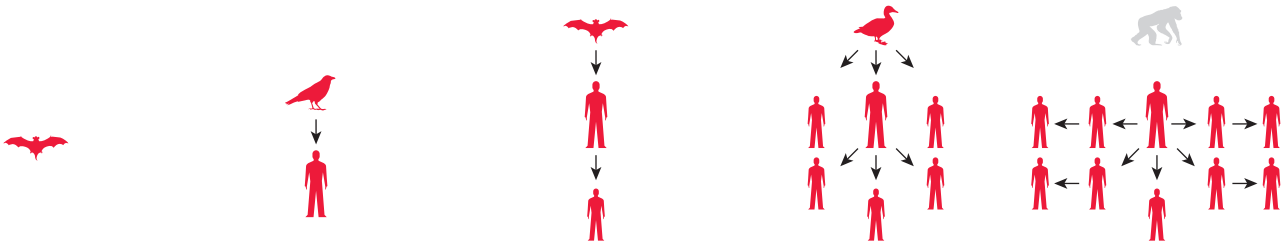
Governments and international organizations are now considering a raft of proposals to prevent the next serious outbreak from growing into an epidemic. These include boosting financial support for surveillance and outbreak response in low- and middle-income countries, and reform of the WHO, which has come under fire for its slow response to Ebola. One idea is to create a Centre for Emergency Preparedness and Response within the WHO but autonomous from it to avoid the agency's notorious politicization and bureaucracy. The body would link to other United Nations' agencies, the World Bank, philanthropic organizations, non-governmental organizations and industry. It would create an international reserve force that could be rapidly deployed to an outbreak, and be able to call up the planes and helicopters often needed to quickly ship large amounts of medical equipment to regions in need.

The World Bank, the WHO and other organizations are also working on the idea of a Pandemic Emergency Facility that could swiftly send contingency funds to cover the efforts of the WHO, governments and other bodies in the event of a serious outbreak.

The question now is whether these grand plans will become a reality. Many people hoped that these and other measures to reinforce outbreak

EMERGING THREATS

The size and severity of disease outbreaks depends on where the causal agent sits in an evolutionary spectrum, ranging from animal viruses that have yet to leap to humans, to pathogens that have evolved to spread easily between humans.



1. Animals only
Potential threats, including pathogens from families that have caused human disease in the past.

Examples:
poxviruses, paramyxoviruses.

2. Limited spread
Pathogens that pass from animals to humans but do not spread further.

Examples:
H5N1 flu, Nipah, rabies.

3. Small outbreaks
Pathogens that spill over and then spread between just a few people.

Examples:
MERS, Marburg.

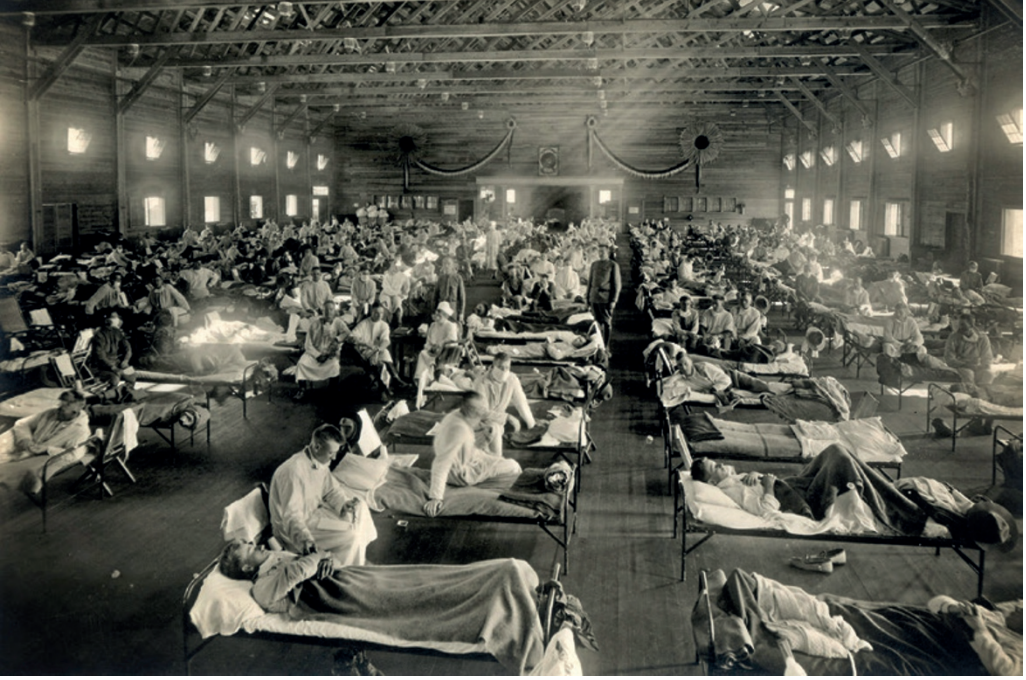
4. Large outbreaks and epidemics
Pathogens that spill over into large numbers of people, or spread between many people.

Examples:
Chagas disease, cholera, Ebola.

5. Human only
Animal pathogens that have evolved to become human viruses.

Examples:
HIV/AIDS, measles, tuberculosis.

ADAPTED FROM N. D. WOLFE *ET AL. NATURE* **447,** 279–283 (2007)



NATIONAL MUSEUM OF HEALTH AND MEDICINE/SPL

Public-health experts fear a repeat of the 1918 flu pandemic which killed as many as 50 million people.

preparedness and response would receive firm pledges at the June summit of G7 industrialized countries in Germany. But although the summit produced supportive language, it did not make concrete decisions, something that disappoints Manica Balasegaram, executive director of MSF's Access Campaign in Geneva, Switzerland. "We need money put on the table, we need political commitment and funding," he says.

But Farrar says that the high-level political attention is a good sign. He notes that the G7 has previously delivered on major public-health initiatives, such as helping to create the multibillion-dollar Global Fund to Fight AIDS, Tuberculosis and Malaria in 2002, two years after it was first proposed. What emerged from the G7 this year "has to be seen as setting a tone and a direction," Farrar says. "What's key is what then comes out of the language."

HOW TO GET VACCINES AND DRUGS

Even if the world reacts quickly to an emerging outbreak, it has to have effective tools to deploy. A vaccine could have stopped Ebola in its tracks, but the only ones available had not been tested in humans. Drugs, too, were stuck in the experimental phase. In this and other outbreaks, healthcare workers often have to rely on centuries-old public-health measures, such as quarantine, chemical disinfection and encouraging hand washing — essential, but often not enough.

If a worst-case epidemic hit tomorrow, the script would probably be the same. The problem, say public-health officials, lies in how global drug and vaccine development is set up. The process is left largely to major pharmaceutical companies, which are geared towards treating those who can pay — developed-world inhabitants with mostly developed-world diseases — rather than to addressing the most pressing global health needs, which are often infectious diseases in the developing world. "What humanity actually needs isn't part of the equation," says Morens. "It's what can make big bucks."

That there were even candidate vaccines and drugs for Ebola was largely down to spending on biodefence rather than concerns about global health, says Balasegaram. And there are few, if any, effective drugs and vaccines for a host of other epidemic threats and neglected diseases ranging from SARS to dengue — leaving the world defenceless against almost all the pathogens most likely to cause the next epidemic.

After Ebola, "there is a real opportunity to change the status quo", says Jean-François Alesandrini, a spokesman for the Drugs for Neglected Diseases Initiative (DNDi), a non-profit body working on long-ignored diseases such as leishmaniasis.

In a paper published in May, leading researchers and public-health officials proposed the creation of an international not-for-profit pharmaceutical body, bringing together research organizations, governments, charities and private pharmaceutical companies that would research, develop and manufacture medical countermeasures for the many global-health threats for which there is little or no market (M. Balasegaram *et al. PLoS Med.* **12,** e1001831; 2015).

Such efforts have precedent in public–private partnerships (PPPs) that have sprung up over the past 15 years, including the DNDi. The proposed initiative would be similar, but writ large: with proposed funding of $10 billion annually, it would focus not only on emerging epidemic threats, but also on existing neglected diseases and developing much-needed new antibiotics. This would share limited resources, ensure sustained financing, and allow more coherent long-term planning. "There is no PPP for outbreak pathogens. It is time to create one," says Hill. "If this doesn't happen soon, the opportunity will be lost as global attention moves on."

Pharmaceutical companies are generally supportive of the proposal — which is crucial, because such ventures typically need access to the vast drug libraries, vaccine-technology platforms and manufacturing capacity that only industry possesses.

Within such a scheme, Hill favours the immediate and accelerated development of vaccines against priority threats such as MERS and Marburg — a virus from the same family as Ebola that kills most of those it infects. He suggests foregoing the slow, costly animal studies that require high biosafety and biosecurity labs to contain the viruses, and instead developing small batches of vaccine that could be put directly through phase I safety and dosage testing in humans. If the vaccines were safe, and generated a good immune response, it is likely they would work, he says. Stockpiles could then be created, ready for phase II efficacy trials to start as soon as an outbreak occurs — so that it "can be nipped in the bud", Hill says. Researchers are encouraged by the announcement this week that a clinical trial of an Ebola vaccine has had positive results (see page 13).

But that still leaves the unknown pathogens, which are harder to prepare for. One option in such an outbreak would be to transfuse patients with the plasma of survivors, whose blood is often rich in antibodies specific to the virus, says Ian Lipkin, a virologist and outbreak specialist at Columbia University in New York. In many cases, this technique could provide a quick, ready-made therapy to an unknown pathogen, bypassing the years of research it can take to find drugs or vaccines.

The approach gained prominence during the Ebola outbreak: clinical trials of 'convalescent plasma' for Ebola began in West Africa in December (see *Nature* http://doi.org/6dr; 2014), and results are expected in coming months (*Nature* **517,** 9–10; 2015). Lipkin would like to see the infrastructure for collecting and processing blood and plasma improved in poorer countries, where it is often lacking.

Ideally, say researchers, clinical-trial designs would also be approved by regulators before an outbreak so that a trial could launch straight away (see page 29). This is already being done by researchers in the International Severe Acute Respiratory and Emerging Infection Consortium, an international network of outbreak specialists based in Oxford that aims to develop generic clinical-trial protocols that can be adapted to any epidemic threat.

Reforming the world's epidemic response systems is not going to be easy, and public-health specialists are well aware that impetus might be lost as the Ebola epidemic fades from the limelight. But they also think that the shocking events in West Africa — bodies on the streets, nationwide quarantines, economies collapsing — have left an indelible mark.

The West African epidemic has been a "game-changer" in how the world prepares for a serious epidemic, says Morens. The era after Ebola, he hopes, will be very different from the one before it. ■

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