Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Known unknowns and unknown unknowns

WHO's latest list of priority infections includes Disease X, an unknown illness. But how do we prepare for such a disease? Talha Burki reports.

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The 2014–16 west African Ebola virus disease outbreak caused mayhem. People had thought Ebola was a rural phenomenon. Previous outbreaks had been readily contained. But this time, the disease struck countries that had not been hit before and it tore through cities. At least 11 000 people died. The Liberian president wondered whether her country would survive intact. Vaccines were rushed into production and several clinical trials were arranged and done in less than a year. But by the time the vaccines were ready for protection trials, cases were tailing off.

The outbreak laid bare the shortcomings in international epidemic preparedness. In response, WHO has set up the R&D Blueprint, which aimed to "fast-track the availability of effective tests, vaccines and medicines that can be used to save lives and avert large scale crisis". The Blueprint is focused on a list of priority diseases that have the potential to cause destructive epidemics and for which there are currently no adequate countermeasures.

The list was first published in 2015. It included Crimean–Congo haemorrhagic fever, Ebola virus disease, Marburg virus disease, Lassa fever, Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), Nipah virus disease, and Rift Valley fever. An annual review in January, 2017, added Zika virus. The same month saw the newly formed Coalition for Epidemic Preparedness Innovations (CEPI) announce its intention to bring four to six vaccine candidates for Lassa fever, MERS-CoV, and Nipah disease to the end of phase 2 trials by 2022.

In February, 2018, WHO added Disease X to the list. "Disease X could be a completely brand new pathogen, something we have never seen before, or it could be a pathogen that we already know but is presenting itself in a modified or unexpected way", explains Marie-Pierre Preziosi (WHO, Geneva, Switzerland).

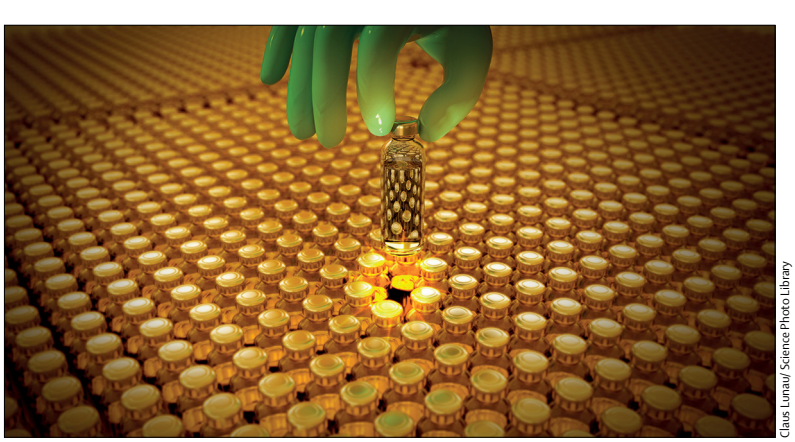
Zika virus, for example, took experts by surprise by causing a surge in cases of microcephaly. When it spread to the Americas, the US Biomedical Advanced Research and Development Authority and other partners launched a rapid vaccine development programme. They started in early 2016, more or less from scratch, with the aim of having a Zika vaccine ready for emergency use within 29 months. Such a time-line would represent a marked improvement over the 10–15 years taken by a conventional development process, but it is not quick enough to prevent many cases in the midst of an emergency.

"If you are faced with an unknown pathogen and you need to make a vaccine very quickly, you must not try to invent a new type of process or technology; you have to have something off-the-shelf", explains Adrian Hill (University of Oxford, UK). "The leading approach for that type of vaccine is viral vectors; the technology platform will apply to most new viruses or bacteria."

Richard Hatchett, CEO of CEPI, agrees that a vaccine for Disease X is likely to be a viable proposition. "But it would require a significant push to respond rapidly", he said. He cites the example of the 2009 H1N1 influenza pandemic. By the time vaccine production had been scaled up, 4–5 months after the beginning of the outbreak, the epidemic had peaked.

"We had the infrastructure already in place, and years of planning for the pandemic", points out Hatchett. "We knew how to develop the vaccine, there was an available platform, and we acted quickly as soon as the disease had been recognised." The vaccine is thought to have prevented 1 million cases and around 12 500 deaths. But H1N1 caused an estimated 60–65 million cases of influenza. "If that had been a truly deadly virus, we would have been much too late", Hatchett told *The Lancet Infectious Diseases*.

CEPI have put out a call for proposals for vaccine platform technologies for novel or previously unknown pathogens. They are targeting a time-frame of 16 weeks from identification of the antigen to product release for clinical trials, 6 weeks from administration of the first dose to clinical benefit, and 8 weeks to scale up production to 100 000 doses. "If we can achieve these goals, it would be a



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substantial advance", said Hatchett. "But we will also need to forge a new understanding with regulatory authorities about the kind of data they are going to be looking for in the event of a large outbreak with a brand new pathogen."

The only vaccine platform widely accepted by regulators is for influenza. "The authorities understand the platform and are comfortable with producers changing the strain of the virus", stated Hatchett. "We would like to get to the point that regulatory authorities are comfortable moving rapidly even with brand new diseases on a platform they have understood."

Diagnosing and treating Disease X pose a different set of problems. Nigeria, for example, is currently experiencing a spike in cases of Lassa fever. It has only two laboratories where the disease can be definitively diagnosed and the only available antiviral, ribavirin, is barely adequate. "The idea behind the Blueprint is to develop R&D roadmaps, target product profiles, and go on to the development of the products themselves", said Preziosi. She notes that there are similarities between several pathogens on the prioritised list. "One recommendation would be to look into having antivirals that can work in a range of diseases and test them in clinical trials, perhaps in combination with other antivirals", she said.

Once an epidemic has taken hold, clinical diagnosis tends to become reasonably accurate, although that still leaves the problem of diagnosing the first cases. "We have to ensure that countries that could be exposed to Disease X have sufficient laboratory capacity, including the mechanisms for rapid data and sample sharing", said Preziosi. Manufacturing capacity is another issue. Even the UK has no good manufacturing practice-certified vaccine development and manufacturing facility.

Ebola virus was eventually brought under control by the mobilisation of health care alongside public education and behaviour change. A range of measures were deployed, such as isolation of patients, quarantine of household contacts, safe burial practices, and cancellation of mass gatherings. "On their own, none of these would have been sufficient, but taken together, they form a whole", said Hatchett. "The concept of a multimodal response is extremely important as a general principle." Nonetheless, the availability of an effective vaccine against Ebola virus would have made an enormous difference. "Even for a lot of diseases which can be addressed without specific countermeasures, we still need vaccines", said Hatchett.

Talha Burki

Infectious disease surveillance update

For more on **Lassa fever in Nigeria** see http://www.who.int/csr/don/01-march-2018-lassa-fever-nigeria/en/

For more on **yellow fever in Brazil** see https://www.promedmail.org/post/5662410

For more on **hepatitis E in Namibia** see https://www.promedmail.org/post/5656294

For more on **diphtheria in Yemen** see http://outbreaknewstoday.com/yemen-diphtheria-cholera-situation-update-84297/

For more on **influenza H7N4** see http://www.who.int/csr/don/22-february-2018-ah7n4-china/en/

Lassa fever in Nigeria

Between Jan 1, 2018, and Feb 25, 2018, 1081 cases of Lassa fever have been reported in Nigeria, including 90 deaths. 317 cases have been confirmed and eight have been classified as probable, including 72 deaths—a case fatality rate of 22% for confirmed or probable cases. Cases have been reported across 18 states, with 2845 contacts having been identified. 14 cases have been reported in health-care workers, including four deaths. Four Lassa fever case management centres have been set up in Anambra, Abakaliki, Edo, and Ondo states.

Hepatitis E virus in Namibia

Since an outbreak of hepatitis E virus was declared in December, 2017, 894 suspected cases have been reported in Windhoek, Namibia as of Feb 28. 90 cases have been laboratory confirmed. Six patients have died in this period, four of whom were women who had recently given birth. Transmission is occurring mainly in areas of informal settlement, with Havana, Goreangab, and Hakahana being the most affected.

Yellow fever in Brazil

Between July 1, 2017, and Feb 28, 2018, 723 cases of yellow fever were reported in Brazil, including 237 deaths. In the same period in 2016–17, 576 cases were reported, including 184 deaths. The majority of cases have been reported in three states: Minas Gerais (314 cases), São Paulo (307 cases), and Rio de Janeiro (96 cases). As of Feb 27, an estimated 5·5 million people have been vaccinated in these three states—23% of the target population for the vaccination campaigns.

Diphtheria in Yemen

As of Feb 10, a total of 1032 probable cases of diphtheria have been reported in Yemen, including 64 deaths. The cases have been reported in 161 districts across 20 governorates in Yemen. 30% of the probable cases were in children aged under 5 years, who account for 47% of the reported deaths.

Influenza H7N4 in China

On Feb 14, 2017, the first ever human infection with avian influenza A (H7N4) was reported from Jiangsu Province by the National Health and Family Planning Commission of China. The patient was a 68-year-old woman with pre-existing health conditions who developed symptoms on Dec 25, 2017. She reported having exposure to poultry before symptoms developed. 28 close contacts of the patient are under observation; however, all have so far tested negative and remain asymptomatic.

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