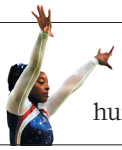
COMMENT

AI Robot designers should work with dancers, animators and more **p.422**



EVOLUTION How planetary processes have shaped human history **p.425**

WATER We know it is running out, so why don't we use less? **p.426**

BULLYING Investigations need a code of conduct or nothing will change **p.429**

SVEN TORFINN/PANOS

Health workers in the Democratic Republic of the Congo screen people for Ebola symptoms using an infrared thermometer.

Where are the Ebola diagnostics from last time?

Analysis reveals commercial tests for Ebola are too hard to come by in the current outbreak — sustain investment, urge **Lieselotte Cnops**, **Kevin K. Ariën** and colleagues.

The Democratic Republic of the Congo (DRC) is in the grip of its worst Ebola outbreak since 1976. It's the second-largest the world has seen, and could escalate into an even greater crisis as a result of conflict, political instability, poor infrastructure and socio-economic weaknesses.

The largest outbreak so far (from 2014 to 2016, in West Africa) spurred companies, including Cepheid in California[1,2] and Altona in Germany[3], to develop new diagnostics. And 14 tests have been approved by either the US Food and Drug Administration (FDA) or the World Health Organization (WHO), or both.

Yet health workers and organizations trying to stem the current outbreak cannot obtain diagnostic tests fast enough. Even when funds from international donors are available to pay for them, it is taking staff at laboratories or health centres two to eight weeks to get hold of the tests.

There are two types of diagnostic test for Ebola. Rapid diagnostic tests detect a viral protein; those based on the polymerase chain reaction (PCR) identify the virus's genomic material. By filling out company request forms, e-mailing manufacturers and searching their websites, we established that, of the recently approved tests provided by companies, only four are readily available to buyers (see 'What's available?'). All of these are PCR-based tests. OraSure Technologies in Bethlehem, Pennsylvania, has made its rapid diagnostic test OraQuick available to the WHO and the US Centers for Disease Control and Prevention (CDC), which are distributing the test to health workers in the current outbreak. But it is not available to other buyers.

Our analysis reveals that research and scaled-up production have been sustained for only a few of the company-provided tests that were developed and approved during the 2014–16 emergency. Indeed, we were co-developers of a diagnostic test for Ebola[4] that is no longer available because the manufacturer decided to focus exclusively on oncology.

Diagnostics are fundamental to containing outbreaks. Without such tests, it is impossible to trace whether people with the disease have infected others, whether the virus persists in survivors, or to investigate the cause of deaths. In our view, the various Ebola diagnostic approaches need to be evaluated and the best ones prioritized. Most importantly, developers must be incentivized to sustain their investment in diagnostics during and after epidemics, so that health workers are not scrambling to obtain tests when the next outbreak arrives.

EMERGENCY MEDICINE

In August 2014, almost six months into the West Africa Ebola outbreak (which killed more than 11,000 people), the FDA created an 'Emergency Use Authorization' procedure for Ebola diagnostic tests. This permits medical products that the agency has not yet approved to be used in an emergency — to diagnose, treat or prevent serious diseases or conditions when there are no available alternatives (see go.nature.com/2vbkhhd).

The following month, the WHO instigated an Emergency Use Assessment and Listing procedure, to enable faster review of diagnostics in a public-health emergency (see go.nature.com/2vcgjjd). It also called on manufacturers to develop diagnostics that would be easy to use and give quick results at the sites where people were being tested, and in countries lacking health infrastructure and trained personnel.

As the outbreak raged, researchers, manufacturers and other organizations, such as the Foundation for Innovative New Diagnostics (FIND) and Médecins Sans Frontières (MSF, also known as Doctors Without Borders), both in Geneva, Switzerland, strove to accelerate the development, evaluation, production and deployment of Ebola diagnostics. Over the next 2 years, the FDA approved 11 tests and the WHO approved 7 (see 'Success story').

Health workers in the DRC don't need 14 different tests for Ebola. What they do need is a handful of reliable, easy-to-use PCR-based and rapid diagnostic tests that are consistently available. Why are so few of the approved company-provided diagnostics in stock and on sale?

Developing diagnostics for unpredictable infectious diseases such as Ebola is a high-risk strategy for manufacturers. Compared with the millions of tests consistently needed for diseases such as malaria and tuberculosis, relatively few are required for viral haemorrhagic fevers such as Ebola — even during outbreaks that typically affect hundreds or thousands of people. This means that the costs of manufacturing a test, stockpiling the raw materials and final product, and addressing the logistical and distribution challenges to get it deployed on the ground, far exceed gains made from sales.

As fears about Ebola waned at the end of the West Africa outbreak, so did public and private funds available to manufacturers. Companies struggled to get enough samples to evaluate their tests even during the emergency[5]. But with fewer people infected, it becomes even harder to evaluate tests in the field, and to obtain national and local permissions to share samples and transport clinical specimens.

We think that two actions are urgently needed to improve the availability of diagnostics — both in the current DRC Ebola outbreak and in future crises.

Evaluate and prioritize specific diagnostics. Stakeholders need to evaluate tests and pick the winners. For Ebola, health workers need two or three PCR-based tests and two or three rapid diagnostic tests that can be used in tropical settings where resources are scarce. PCR-based tests tend to be more accurate, so are preferable if the necessary infrastructure and expertise are available. Rapid diagnostic tests are simpler to conduct, and so easier to use in the field. Competition between multiple manufacturers can drive down prices, and having alternative options might provide a safeguard if there are problems with supply.

To maximize the chances of health workers making a correct diagnosis in an epidemic, prioritized tests should include those that can simultaneously identify co-circulating pathogens that cause similar symptoms. For Ebola, this might be other Ebola virus strains, such as the Sudan or Bundibugyo virus; the protozoan that causes malaria; or other haemorrhagic-fever viruses, such as Marburg and yellow fever.

In selecting the most promising candidates, various factors will need to be considered besides reliability and ease of use in the field — such as whether the associated infrastructure already exists. Thousands of the PCR GeneXpert machines needed to run the Xpert Ebola test have already been installed across Africa — for diagnosis of HIV and multiple-drug-resistant tuberculosis[6]. Although the machines are not always located in the right places to be useful in an Ebola outbreak, people are used to handling them (see *Nature* **558**, 172; 2018). Indeed, their widespread installation has already enabled the deployment of the Xpert Ebola assay in the two recent DRC outbreaks.

Incentivize developers. Various programmes have demonstrated that companies can be encouraged through incentives to develop diagnostics for infectious diseases that mainly affect low- and middle-income countries (LMICs). In 2006, for example, the GeneXpert PCR platform was made available in LMICs at around half of its original cost[6], thanks to FIND leveraging millions of dollars of donor funding. Many more such programmes are needed — particularly ones that focus on disease outbreaks.

Greater investment in surveillance could be another way to assure markets for developers and manufacturers. Establishing national and regional surveillance programmes for viral haemorrhagic fever, for example, throughout central and West Africa would require thousands of diagnostic tests. In Uganda, a national surveillance programme has confirmed 16 independent viral haemorrhagic-fever outbreaks since 2010, reduced the time of response to outbreaks from 2–3 weeks to 1–3 days, and resulted in shorter and less severe outbreaks[7].

Much can also be learnt from the vaccine community. For example, a public-health organization and a government authority might commit to purchasing a vaccine before it has been licensed. This provides an important incentive for the vaccine industry, in which licensing remains the biggest bureaucratic barrier. In 2016, for instance, Gavi, the Vaccine Alliance in Geneva,

SUCCESS STORY

The first WHO-approved diagnostic test for Ebola

The first Ebola diagnostic test to be approved by the World Health Organization (WHO) was a PCR kit developed by Altona Diagnostics in Hamburg, Germany. Over the past 20 years, the company has developed and commercialized nearly 50 molecular diagnostic assays in response to emerging infectious diseases.

Altona owes its success partly to its close ties with research centres such as the Bernhard Nocht Institute for Tropical Medicine in Hamburg. These relationships have enabled it to become highly specialized in the marketplace for tropical and emerging infectious diseases. And because Altona produces the main components of its diagnostic itself, it can ramp up production rapidly.

Despite this, getting the kit to health workers in the current Ebola outbreak and in other poor settings is problematic. Barriers include the need to first extract Ebola virus RNA from a person's blood plasma and the need for the kit to remain frozen in transport. It is encouraging that the company plans to incorporate several of its assays into a system that could be used *in situ* in field laboratories to identify multiple pathogens in parallel. L.C., K.K.A. *et al.*

WHAT'S AVAILABLE?

Few approved Ebola diagnostics are accessible

We questioned manufacturers and searched their websites to try to understand why health workers in the Democratic Republic of the Congo (DRC) are struggling to obtain diagnostics.

In our analysis, we focused on approved Ebola tests that are provided by companies. Three tests can be obtained only from the US Centers for Disease Control and Prevention (CDC) or from US Department of Defense laboratories. We searched for the brand name of the test kit on the manufacturer's website. We filled out company request forms and e-mailed contacts at the companies to ask how many kits each provider could send. We also asked for expiry dates, costs and delivery time to our lab in Belgium. (The lab is a national reference centre for tropical infectious diseases, including Ebola, and a representative client of those companies in the European Union.)

Of the seven PCR-based tests we investigated, only four were readily available — meaning that they could be sent to our lab in less than two weeks. For the others, we either got no responses to our online order forms or would have needed to have waited 14 weeks (see table).

Four rapid diagnostic tests for Ebola have been approved. For undisclosed reasons, the manufacturer of one requested that it be taken off the lists of approved diagnostics in May 2018. OraQuick is available to health workers in the DRC but only through the CDC or the World Health Organization. For the remaining two tests, we received no response to requests, and couldn't find information on the manufacturers' websites about prices, shipping time or shelf life. **L.C., K.K.A. *et al.***

Test name and provider	Test type	Approved by	Price per sample (US$)	Available within two weeks	Used in the DRC 2018 outbreak
EZ1 test (DOD)	PCR	FDA	?	✘	✘
NP RT-PCR (CDC)	PCR	FDA	?	✘	✘
VP40 RT-PCR (CDC)	PCR	FDA	?	✘	✘
FilmArray NGDS BT-E (BioFire)	PCR	FDA	?	✘	✘
FilmArray Biothreat-E (BioFire)	PCR	FDA, WHO*	?	✘	✘
RealStar Ebolavirus (Altona)	PCR	FDA, WHO	18–79†	✔	✘
LightMix Ebola Zaire (Roche)	PCR	FDA	10–30†	✔	✘
Xpert Ebola (Cepheid)	PCR	FDA, WHO	22.5‡, 79.5§	✔	✔
Ebola Real Time RT-PCR (Liferiver)	PCR	WHO	19–64†	✔	✘
Idylla Ebola (Biocartis)	PCR	FDA	114	✘	✘
ReEBOV (Corgenix)	RDT	FDA*, WHO*	?	✘	✘
OraQuick (OraSure)	RDT	FDA, WHO	?	✘	✔
SD Q Line Ebola (SD Biosensor)	RDT	WHO	?	✘	✘
DPP Ebola Antigen (Chembio)	RDT	FDA	?	✘	✘

CDC, US Centers for Disease Control and Prevention; DOD, US Department of Defense; DRC, Democratic Republic of the Congo; FDA, US Food and Drug Administration; RDT, rapid diagnostic test; WHO, World Health Organization. *Test delisted in 2018. †Estimated cost when testing 20 samples (in batch) or 1 sample per run, and excluding cost of RNA extraction; ‡Cost under Cepheid's High Burden Developing Country programme; §Cost to United States and countries in Europe.

announced that it would pay US$5 million to the manufacturer Merck to ensure the supply of 300,000 doses of its VSV Ebola vaccine to people in West Africa. The vaccine had not been approved by regulators at that stage. The same kinds of deal should be made for diagnostics.

The deployment of diagnostics and surveillance programmes in LMICs requires sustained funding: from international organizations and funders, such as the United Nations and the Africa Centres for Disease Control and Prevention; the ministries of health of G20 countries; public–private partnerships; and the governments of the countries at risk. And, just as for vaccines, we think that some kind of global alliance is needed.

FIND's Diagnostics for Epidemic Preparedness strategy, an effort to streamline the development of diagnostics, was conceived in 2017 with this in mind[8]. But in our view, it lacks the financial support and heft to convene stakeholders from across the diagnostics field. Since 2016, the Coalition for Epidemic Preparedness Innovations (CEPI) in Oslo has drawn up a priority list for vaccines against epidemic diseases. It is also liaising with funders to help push promising vaccine candidates for LMICs into clinical trials. We urge CEPI to incorporate diagnostics into its programme.

Together, these steps will help to ensure that investments made during one outbreak are not wasted. Such efforts must be sustained so that they can help people to tackle the next crisis. ■

Lieselotte Cnops *is a postdoctoral researcher in the neglected tropical diseases unit at the Institute of Tropical Medicine, Antwerp, Belgium.* **Birgit De Smet** *is a laboratory scientist in the outbreak research team at the Institute of Tropical Medicine, Antwerp, Belgium.* **Placide Mbala-Kingebeni** *is head of the viral haemorrhagic fever unit in the virology department at the National Institute of Biomedical Research (INRB), Kinshasa, Democratic Republic of the Congo.* **Johan van Griensven** *is head of the neglected tropical diseases unit at the Institute of Tropical Medicine, Antwerp, Belgium.* **Steve Ahuka-Mundeke** *is professor of virology and head of the virology department at the INRB, Kinshasa, Democratic Republic of the Congo.* **Kevin K. Ariën** *is professor of virology and head of the virology unit at the Institute of Tropical Medicine, Antwerp, Belgium.*
e-mails: lcnops@itg.be; karien@itg.be

1. Semper, A. E. *et al. PLoS Med.* **13**, e1001980 (2016).
2. Raftery, P. *et al. PLoS Negl. Trop. Dis.* **12**, e0006135 (2018).
3. Rieger, T. *et al. J. Infect. Dis.* **214** (Suppl. 3), S243–S249 (2016).
4. Cnops, L. *et al. J. Infect. Dis.* **214** (Suppl. 3), S192–S202 (2016).
5. World Health Organization. *Ebola/Marburg Research and Development (R&D) Roadmap. May 2018 — Draft for Public Comment* (WHO, 2018).
6. Albert, H. *et al. Eur. Respir. J.* **48**, 516–525 (2016).
7. Shoemaker, T. R. *et al. Lancet Infect. Dis.* **18**, 373–375 (2018).
8. Foundation for Innovative New Diagnostics. *Diagnostics For Epidemic Preparedness: Outbreak Strategy 2018* (FIND, 2018).