

▶ thousands of enhancers, they typically have only a few hundred super-enhancers. As a result, researchers now use super-enhancers as a signpost for important genes, says Hennighausen. Understanding how they work could shed light on how cells adopt their identities. But researchers don't know whether the enhancers in a cluster act independently, or whether they work together in a new form of gene regulation.

That question arose right from the start, says Richard Young, a biologist at the Whitehead Institute for Biomedical Research and a co-founder of Syros — both in Cambridge, Massachusetts. “There were investigators who questioned whether or not they should have the term ‘super’, because it implied some function that typical enhancers didn't have,” he says. “To be frank, at the time we didn't know if they had some special function.”

Since then, researchers have scrutinized a few super-enhancers, studying the function of each enhancer in the cluster. But the results are inconclusive: some enhancers show signs of working together, whereas others seem to work independently. “It's a very intense debate,” says Denes Hnisz, a molecular biologist at the Max Planck Institute for Molecular Genetics in Berlin.

Hnisz notes that the discrepancy might arise in part from the algorithms used to identify enhancers in genomic data: the algorithms could be mislabelling some sequences as super-enhancers. And different labs use different assays to test for super-enhancer activity, he adds, which could introduce another source of conflict.

Resolving the debate might have to wait until more scientists have studied more super-enhancers, says Douglas Higgs, a haematologist at the University of Oxford, UK. “At the current time, it is hard to be sure if they represent a new type of fundamental regulatory element.”

For Syros, the debate is largely academic, says Nancy Simonian, the company's president and chief executive. “From our point of view, it doesn't really matter,” she says. “We're just saying it's a marker for a hotspot that we know is associated with genes that are really important for controlling the cell.”

The next few years could bring some answers. Studies of enhancers fell out of favour in the early 2000s, says Hennighausen. But technological advances are bringing them back into fashion. The ability to use relatively simple gene-editing tools, such as CRISPR–Cas9, to alter enhancer sequences has made it easier to study their function, he notes. An experiment that once took two years can now be done in a few months for much less money.

“The questions were always there, but the technology was needed to answer them,” he says. “The whole field is emerging right now.” ■

## EPIDEMIOLOGY

# Scientists seek hidden sources of Ebola

*Two-thirds of new infections in the Democratic Republic of the Congo cannot be linked to known cases.*



An Ebola health worker carries a child at a hospital in the Democratic Republic of the Congo.

BY AMY MAXMEN

As the epicentre of the Ebola outbreak in the Democratic Republic of the Congo (DRC) shifts into the war-weary city of Butembo, public-health workers are trying to stamp out new infections from an unforeseen source: unregulated health centres.

Decades of political instability in the north-eastern DRC, the site of the epidemic, have fostered an increase in informal clinics that offer traditional and modern medicine. These centres treat people for malaria and other common illnesses, filling the vacuum left by the lack of a functional health system. But they are not designed to prevent the spread of a virus as dangerous as Ebola — which has put their patrons at high risk, according to the World Health Organization (WHO). Health officials have begun trying to lessen the centres' load by pre-emptively giving out malaria medication.

The push highlights a central challenge to ending the epidemic, which is now the second-largest on record: although experimental drugs

and a vaccine have helped to limit Ebola's reach, two-thirds of new infections cannot be linked to existing cases. That has left epidemiologists racing to identify overlooked routes of infection. And conventional prevention measures have been thwarted by conditions in the north-eastern DRC, where decades of severe conflict have left millions of people dead, and millions more traumatized and homeless.

“I have lived through many outbreaks, but this is the worst one,” says Jean-Jacques Muyembe-Tamfum, director-general of the National Institute for Biomedical Research in Kinshasa.

Already, 494 people have been infected with the virus, and 283 of those have died, the WHO said on 10 December. “This is as tough and complex as it gets,” says Peter Salama, head of the WHO's health-emergency programme in Geneva, Switzerland.

In the city of Beni in North Kivu province, health workers have been struggling to identify and monitor people who might have been touched by someone in the throes of an

GORAN TOMASEVIC/REUTERS

infection. This work is crucial to containing the epidemic, but many people with Ebola will not name those they might have infected, says Annick Antierens, a strategic adviser at the humanitarian group Médecins Sans Frontières (also known as Doctors Without Borders).

“People are afraid and mistrust the system, so the contact lists are not very good,” Antierens says. And some people with Ebola die without seeking medical help, or receive care only after they are too ill to communicate.

As a result, 66% of Ebola cases are springing up outside known chains of transmission. “When you look at a proportion like that, this outbreak should really be out of control,” says Salama. But, on average, each person with Ebola in Beni is infecting just one other person, a success that Salama attributes to extensive vaccination. More than 40,000 people have received the experimental rVSV-ZEBOV Ebola vaccine since 8 August.

Analyses of patient data exposed the unregulated health centres as one unexpected source of cases, the WHO says. During some weeks in September and October, more than half of new Ebola infections were in children under the age of 16. Epidemiologists deduced that parents were taking their feverish children to the health centres for treatment, unwittingly exposing them to Ebola.

For years, the informal clinics have served

communities that lack reliable, regulated health-care facilities. Caretakers rarely have sterile equipment or even enough beds for patients, who must share, says Ibrahima Socé-Fall, director of the WHO’s emergency operations for Africa, in Brazzaville in the neighbouring Republic of Congo. “Someone who has malaria will go to these facilities and drink from the same cup as the patient before them, or get an injection with the same needle,” he

**“I have lived through many outbreaks, but this is the worst one.”**

are attempting to support the clinics. They offer anyone who treats people — including traditional healers — the Ebola vaccine and training on basic measures for preventing the spread of infection, such as isolating people who are vomiting blood or showing other signs of Ebola. The task is enormous. There are an estimated 300 unregistered clinics in Beni alone, and outreach takes time, Antierens says: “We aren’t just dropping off soap.”

Ebola responders are also distributing anti-malaria drugs broadly across Beni. The DRC saw rising rates of malaria in 2017, with 435,000 deaths from the disease.

says. “But you cannot tell people not to go there, since there is no alternative.”

Instead, the WHO, the DRC government and aid organizations

But greater challenges lie ahead as the centre of the outbreak moves from Beni to Butembo, an even more dangerous part of North Kivu. After years of arson, rape, murder and hunger, some communities in the area question the intentions of outsiders who are there to fight Ebola, Salama says. And some people distrust treatment centres because roughly half of their patients die in the first couple of days — in part, Antierens says, because many arrive too late for help.

Violence has also hindered response efforts directly. The WHO evacuated some staff members after a shell hit the hotel where they were staying in Beni on 16 November. Since then, Ebola responders who take temperatures and search for patients’ contacts have been threatened. For their own safety, doctors must leave Ebola-treatment centres at sunset, says Muyembe-Tamfum. “We lose patients because they die in the night,” he adds.

Political rallies organized in advance of the DRC presidential election, set for 23 December, could further complicate the Ebola response, by sparking violence and drawing people with the virus to mingle with those who do not carry it.

Salama predicts that the outbreak will continue for at least another six months. “I think we can stop this as long as security holds,” he says, “but that’s the big ‘if.’” ■

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