As an unprecedented outbreak of plague sweeps Madagascar, health experts see unsettling parallels with West Africa’s Ebola epidemic of 2 years ago. Again, a fearsome disease is spreading from person to person, abetted by local customs and a broken health care system. And like Ebola, this outbreak of plague has moved from the countryside to the cities, where it is flashing out of control. “Exactly like Ebola, it is very challenging to contain urban outbreaks,” says Eric Bertherat, a plague expert with the World Health Organization (WHO) in Geneva, Switzerland, which is helping Madagascar coordinate its response.

In contrast with Ebola, plague can be treated with antibiotics, and so far the case numbers are relatively small. As of 20 October, WHO reported that 1297 people in Madagascar had been infected with plague and 102 had died. (Those numbers include confirmed, probable, and suspected cases.) But cases are doubling almost weekly. In the capital, Antananarivo, schools are shuttered and public gatherings banned. Last week, Madagascar’s health minister implored health workers not to take vacations. And hundreds of epidemiologists and technical experts are pouring into the island nation, one of the poorest in the world.

Not only is the disease hitting densely populated urban areas, including Antananarivo and the port city Toamasina, but it has taken an unusual and especially menacing form: pneumonic plague, which is spread from person to person through coughing or sneezing. Without treatment, pneumonic plague is 100% fatal, usually within 48 hours. “I don’t think any other disease kills so fast,” Bertherat says. “I personally saw a person in the [Democratic Republic of the Congo] get infected in the morning and die that night.” Madagascar is one of the few countries still afflicted by plague, the Black Death of the Middle Ages. The disease, caused by the bacterium Yersinia pestis, is endemic in remote areas, erupting during the rainy season and typically infecting perhaps 400 people. These outbreaks are mostly bubonic plague, which lurks in rats and is occasionally spread to humans by fleas. But when bubonic plague is untreated, it can reach the lungs and morph into the pneumonic form, capable of racing from person to person.

One reason the outbreak spiraled out of control is that health care workers in the capital were not used to seeing plague, which starts with flulike symptoms. “There was a delay in diagnosis, so the chains of transmission were not broken,” Bertherat says. One reason the outbreak spiraled out of control is that health care workers in the capital were not used to seeing plague, which starts with flulike symptoms. “There was a delay in diagnosis, so the chains of transmission were not broken,” Bertherat says.

**On high alert**
The World Health Organization deems nine countries at high risk of a plague outbreak because of trade and travel ties with Madagascar.
Children in Madagascar’s capital city wear masks to protect themselves from pneumatic plague.

transmission continued,” Bertherat says. At least 39 health workers have been infected.

Pastor has distributed thousands of rapid diagnostic tests. The institute confirms each case with the polymerase chain reaction, which takes about 8 hours, and its plague lab is seriously backed up, Pasteur scientists say. All Y. pestis strains isolated so far are susceptible to antibiotics.

International partners have helped set up nine plague treatment centers and isolation wards, but WHO says more are urgently needed as symptomatic people crowd into clinics and hospitals, risking further spread.

“You want to make sure a suspected plague case does not walk through the clinic,” says Nyka Alexander, WHO’s communications chief in Madagascar. WHO and its partners, among them the U.S. Centers for Disease Control and Prevention, UNICEF, and the European Centre for Disease Prevention and Control, are positioning supplies around the country, including more than 1.2 million doses of antibiotics and 150,000 sets of personal protective gear for health workers.

Disinfection and rat and flea control are key to curbing bubonic plague. But for pneumonic plague, health workers need to find and prophylactically treat everyone who has come into contact with an infected person. WHO has already trained almost 2000 community health workers in Antananarivo in contact tracing, which began 12 October. Of some 2500 contacts identified to date, 66% have been given oral antibiotics. (For confirmed cases, treatment is far more harrowing—40 antibiotic shots given over 7 days.)

Contact with the dead can be risky. But as in the Ebola epidemic, efforts to reduce risk during burials conflict with deep cultural beliefs and traditions such as washing the body and returning it to the person’s birthplace, Bertherat says. “If we don’t respect [those traditions], we risk that people will hide deaths.”

WHO is also worried that the outbreak will spread beyond Madagascar; it considers nine neighboring countries and territories at very high risk (see map, p. 430). Departing passengers are closely screened at Madagascar’s international airport. And technical advisers are helping at-risk countries set up systems for surveillance and contact tracing, and are positioning medical supplies.

To infectious disease experts, the outbreak underscores the lesson of the Ebola epidemic. As cities burgeon and populations become more mobile, once-isolated diseases are increasingly likely to reach cities, where they can race out of control. “Next time,” Bertherat says, “we need to be ready to manage [plague] in an urban setting.”

HUMAN GENETICS

Neandertals gave ‘lost’ African DNA back to moderns

Eurasians acquired genes linked to smoking and waist size

When Neandertals mated with modern humans, they shared more than an intimate moment and their own DNA. They also gave back thousands of ancient African gene variants that Eurasians had lost when their ancestors swept out of Africa in small bands, perhaps 60,000 to 80,000 years ago. Restored to their lineage, this diversity may have been a genetic gift to Eurasian ancestors as they spread around the world. Today, however, some of these ancient variants are a burden: They seem to boost the risk of becoming addicted to nicotine and having wider waistlines.

In talks last week at the annual meeting of The American Society of Human Genetics, researchers announced that some “Neandertal” genetic variants inherited by modern humans outside of Africa are not peculiarly Neandertal genes, but represent the ancestral human condition. The work highlights just how much diversity was lost when people passed through a genetic bottleneck as they moved out of Africa.

“They left many beneficial variants behind in Africa,” says evolutionary genomicist Tony Capra of Vanderbilt University in Nashville, who reported the results. “Interbreeding with Neandertals provided an opportunity to get back some of those variants, albeit with many potentially weakly deleterious Neandertal alleles as well.”

His team found the ancient African variants when they scrutinized the genomes of more than 20,000 people in the 1000 Genomes Project and Vanderbilt’s BioVU data bank of electronic health records. They soon noticed a strange pattern: Stretches of chromosomes inherited from Neandertals also carried ancient alleles, or mutations, found in all the Africans they studied, including the Yoruba, Esan, and Mende peoples.

The researchers found 47,261 of these single-base changes across the genomes of Europeans and 56,497 in Asians, Capra says.

In Eurasians these alleles are only found next to Neandertal genes, suggesting all this DNA was acquired at the same time, when the ancestors of today’s Eurasians mated with Neandertals roughly 50,000 years ago.

The most parsimonious explanation is that these alleles represent the ancestral human condition, inherited by both Neandertals and modern humans in Africa from their common ancestor, Capra says. When people migrated out of Africa, their small numbers resulted in a bottleneck, in which they lost many alleles that remained in larger populations in Africa. Later, the Neandertals reintroduced these alleles—along with distinct Neandertal genes—to the ancestors of Eurasians, Capra says.

Some of these ancient alleles were beneficial, such as one that boosted immune responses. But today’s humans might prefer to shed others. So far, Capra’s team has found three functional variants, which are associated with addiction to nicotine, a wider waistline, and skin pigmentation.

The data are “very compelling that Neandertals bring back some of the lost ancestral variance,” of modern humans, said geneticist Mait Metspalu of the Estonian Biocentre in Tartu, who heard the talks.

Geneticists at the meeting also zeroed in on archaic DNA “deserts,” where living humans have inherited no DNA from Neandertals or other archaic humans. One of these regions includes the site of the FOXP2 “language” gene. The absence of archaic DNA suggests that in our ancestors, natural selection flushed out the Neandertal version of this gene.

Using software that evaluates gene expression, Vanderbilt graduate student Laura Colbran found that Neandertal versions of FOXP2 would have pumped out much less of its protein than is expressed in modern brains. A rare mutation that causes members of a family to produce half the usual amount of FOXP2 protein also triggered severe speech defects, notes Simon Fisher, director of the Max Planck Institute for Psycholinguistics in Nijmegen, the Netherlands, who discovered the gene. Boosting FOXP2 expression may have been key to modern human language, he says.
Echoes of Ebola as plague hits Madagascar
Leslie Roberts

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