Epidemics of plague past, present, and future

Thierry Berrod, Mona Lisa Production

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See Articles page 537

Plague has a deservedly bad reputation. The disease killed over 20 million people in India during the early 1900s, and even more people during the so-called Black Death that swept Europe beginning in 1346. The causative agent, *Yersinia pestis*, circulates on five continents, infecting a range of animal reservoirs living in diverse ecological settings. Human disease is typically acquired through flea bites and takes the form of bubonic plague; however, infection can also spread to the lungs, producing pneumonic infection. Pneumonic plague is rapidly fatal and can spread from person-to-person through respiratory droplets. In 1910, an outbreak of pneumonic plague in Manchuria killed nearly 60 000 people in just 7 months.[1]

Understandably, it was with some alarm that health authorities reported an outbreak of pneumonic plague in September, 2017, in Antananarivo, the capital city of Madagascar. Antananarivo is home to more than 2 million people, densely packed and largely impoverished, with little public-health and health-care infrastructure. A large and complex response was mounted with the assistance of the international community and 2 months later, on Nov 27, 2017, local health officials declared the outbreak contained.[2] The immediate danger had passed; however, the risk of future outbreaks remains, and it is important to learn all that is possible from this event.

In *The Lancet Infectious Diseases*, Rindra Randremanana and colleagues[3] report a detailed, systematic analysis of this exceptional outbreak of pneumonic plague in an urban setting. The authors should be commended for their diligence—this assessment required refining diagnostic protocols, retesting samples, and reclassifying cases. Along with other important findings, the analysis revealed that the outbreak was considerably smaller than initially feared. Among 1878 clinically suspected cases of pneumonic plague, nearly all of which received laboratory testing, only 32 (2%) were laboratory confirmed as plague, with eight (24%) of these leading to death. Another 386 (21%) cases were classified as probable plague, but only a portion of these are likely to have been true infections.

Given the circumstances, it is natural to assume that this outbreak was comprised of one or two extended chains of person-to-person transmission. However, considering the smaller number of cases and their distribution over time, it is possible that the outbreak was in fact a series of small clusters and individual pneumonic cases arising independently from bubonic infections. Aided by molecular tools, investigators have found an alternative framework for zoonotic diseases, in which outbreaks result from simultaneous spillover of multiple strains from the environment rather than extensive transmission of a single clone.[4,5] This distinction is crucial for pneumonic plague because it speaks to the efficacy of control efforts. Pneumonic plague is not highly contagious, and it should be possible to interrupt person-to-person transmission through education campaigns and simple social distancing.[6] In this instance, control of person-to-person transmission could have been more effective than might be surmised from the overall epidemic curve. Molecular analysis of isolates from the outbreak should shed light on this possibility.

Although the Madagascar outbreak was smaller than feared, the event was no less significant. In an already impoverished area, the cost and social disruption were considerable, and it is impossible to know what would have happened had the response been less robust. Nevertheless, it should be feasible to contain and control outbreaks of pneumonic plague with relative ease given our understanding of transmission and the availability of effective treatment. This outbreak underscores the need to develop and validate new diagnostics for use in resource-limited settings, to move toward less toxic and easier to administer treatments, and perhaps most importantly of all, to enhance public health messaging and communication. In the modern era, public fear and mistrust might be the greatest obstacles when combating plague outbreaks. Plague has a bad reputation, but the days of panic should be well in the past.

Paul Mead
Bacterial Diseases Branch, Division of Vector-Borne Diseases, National Centers for Emerging and Zoonotic Diseases, Centers for Disease Control and Prevention, Fort Collins, CO 80521, USA
pmead@cdc.gov

I declare no competing interests.

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The remarkable tenacity of sulfadoxine-pyrimethamine

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See **Articles** page 546

Plasmodium falciparum infection during pregnancy causes low birthweight in the newborn, which is a risk factor for infant mortality.[1] Intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine was introduced with the primary aim of ameliorating the effect of malaria on birthweight. At the time of its introduction 15–20 years ago, many countries were still using sulfadoxine-pyrimethamine as the first-line treatment for malaria. Concerns immediately arose about the spread of sulfadoxine-pyrimethamine-resistant malaria and the effect of resistance on the effectiveness of the drug combination for both the treatment and prevention of malaria. Over the past decade, all countries in sub-Saharan Africa have changed their first-line treatment of malaria to an artemisinin-based combination therapy, raising the possibility that sulfadoxine-pyrimethamine resistance might begin to decrease in prevalence. However, in contrast to the re-emergence of chloroquine-susceptible malaria after the removal of drug pressure,[2] sulfadoxine-pyrimethamine resistance seems to be fixed in the parasite population in Africa, despite its withdrawal from use as the first-line treatment for uncomplicated disease.[3] This fixation might be due to the use of sulfadoxine-pyrimethamine for IPTp, or the frequent use of another antifolate drug combination, co-trimoxazole (trimethoprim-sulfamethoxazole), for the treatment of bacterial infection and for prophylaxis among people living with HIV. Regardless of the mechanism of its persistence, sulfadoxine-pyrimethamine resistance seems to be here to stay.

In *The Lancet Infectious Diseases*, Anna Maria van Eijk and colleagues[4] report results of a meta-analysis of aggregated-data from 57 studies (involving 59 457 births) and of individual-patient data from 13 surveys (42 394 births), assessing the effect of sulfadoxine-pyrimethamine resistance on sulfadoxine-pyrimethamine IPTp effectiveness. van Eijk and colleagues collected data on molecular markers of sulfadoxine-pyrimethamine resistance from published reports, individual authors, and population prevalence maps compiled by the Worldwide Antimalarial Resistance Network (WWARN). Data on transmission intensity were collected from the Malaria Atlas Project. The investigators categorised study areas as having low, moderate, or high resistance by exploring various thresholds of prevalence of three mutations in the *P falciparum dhps* gene: Lys540Glu, Ala437Gly, and Ala581Gly. The distribution of sulfadoxine-pyrimethamine-resistant genotypes differed: in east and southern Africa, the high prevalence of *dhps* Lys540Glu defined high-level resistance to sulfadoxine-pyrimethamine, but was rarely identified in central and west Africa, where *dhps* Ala437Gly prevalence distinguished low from moderate levels of resistance. Pooled estimates from the aggregated-data meta-analysis suggested that protection from low birthweight decreases with increasing prevalence of *dhps* Lys540Glu (P_{trend}=0·0060), but is unaffected by the prevalence of *dhps* Ala437Gly mutations (P_{trend}=0·35). The individual-participant analysis of survey data, however, shows the resilience of sulfadoxine-pyrimethamine IPTp, with a protective effect even in areas with a *dhps* Lys540Glu prevalence of more than 90% and Ala581Gly prevalence of less than 10% (relative risk reduction [RRR] 10% [95% CI 7–12%]). This protection waned in areas with both a high prevalence of *dhps* Lys540Glu and a *dhps* Ala581Gly prevalence of 10% or higher (RRR 0·5% [–16 to 14]), but this most extreme resistant genotype was only found in a small number of locations in east Africa.

The need for such a large meta-analysis to link sulfadoxine-pyrimethamine resistance to its protective