

The reemergence of yellow fever

Since 2016, yellow fever outbreaks have become a major public health concern

By Alan D. T. Barrett

Yellow fever is a viral hemorrhagic fever with a case fatality rate up to 50%. It is caused by yellow fever virus (YFV), a mosquito-borne flavivirus that is related to dengue and Zika viruses. Despite an effective vaccine (17D), the virus still causes major outbreaks, as occurred in Brazil between December 2016 and March 2018 where there were >2000 confirmed cases, including >500 deaths, as well as >4000 epizootics (yellow fever in nonhuman primates) (1). On page 894 of this issue, Faria *et al.* (2) provide a genetic investigation of the outbreak in Brazil from December 2016 to October 2017, demonstrating the origins and movement of YFV during the outbreak. They determined that the outbreak originated in northeastern Brazil and moved southward to areas where the virus had not been found previously. Surprisingly, YFV moved at a rate of 4.25 km/day, which probably explains the magnitude of the outbreak. Modeling infectious disease outbreaks with phylogeographic tools (based on the geographic distribution of viruses according to viral genome sequence) as well as phylodynamic tools (based on the interaction of epidemiologic, immunologic, and evolutionary factors in viral genetics) has played a critical role in understanding outbreaks and developing public health countermeasures.

To date, there has been little modeling of YFV outbreaks because few isolates have been available to study, and we have instead relied on vaccination strategies. The study of Faria *et al.* demonstrates the potential of mapping viral incidence and spread almost in real time and their potential to contribute to control strategies, such as the current World Health Organization (WHO) program called Eliminate Yellow Fever Epidemics (EYE) that aims to eliminate the disease by 2026 (3).

However, the investigation of yellow fever outbreaks in real time is not straightforward. YFV has a sylvatic, or forest, transmission cycle involving tree hole-breeding mosquitoes and nonhuman primates. Human cases usually occur in forested areas; hence, other than during large outbreaks, it is difficult to obtain

virus samples for analysis (4). For these reasons, until June 2016 there were only 42 YFV genomic sequences available for study. Today this has increased to ~135 genomes, with most of the additional sequences coming from the outbreak in Brazil. YFV is found in 44 countries in sub-Saharan Africa and tropical South America, and seven virus genotypes have been identified (5, 6); many additional genomic sequences are needed to understand virus activity within the geographic range of the virus, especially because RNA viruses such as YFV continually evolve. Nonetheless, it is clear that the capabilities are now becoming available as the genome database expands over time and space.

WHO, the Pan American Health Organization, and related sponsors have been successful at controlling yellow fever through mass vaccination campaigns such that there were no outbreaks in West Africa in 2015, a region where historically the most cases of disease have been recorded. However, dramatic increases in yellow fever incidence have occurred recently, and they are occurring in

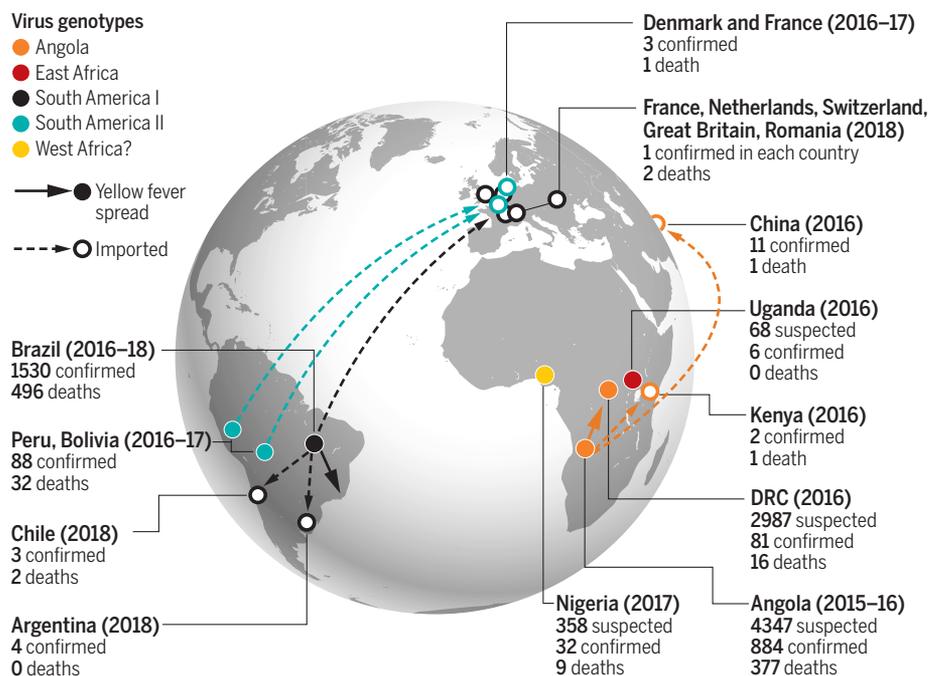
areas that had been considered free of yellow fever (see the figure).

The most dangerous form is urban yellow fever, where the transmission cycle involves domestic *Aedes aegypti* mosquitoes and humans. Urban yellow fever occurred in 2016 in both Angola and the Democratic Republic of Congo (DRC), and 11 Chinese workers infected in Angola returned to China, where they developed yellow fever (7). This was the first time that any cases of yellow fever had been reported in Asia, but these were imported cases and there were no secondary cases in China. Furthermore, there was a concurrent outbreak in Uganda caused by a virus genotype different from that in Angola (8). World vaccine supplies were exhausted twice during early 2016, and a dose-sparing regimen of 17D had to be used whereby one-fifth of a full dose was administered (9, 10). The concurrent clinical trial of dose-sparing vaccination has shown that the immune response is not inferior to a full dose 4 to 5 weeks after immunization (10). The epidemic in Africa was controlled by September 2016. Unfortunately, yellow fever was then reported in Brazil in December 2016 (1). Again, 17D supplies were exhausted and dose sparing was used to immunize 24 million individuals in Brazil.

Whereas urban yellow fever outbreaks periodically occur in Africa, such as in Angola and the DRC in 2016, they are rare in South America. Faria *et al.* provide persuasive evidence that the recent Brazilian

Yellow fever outbreaks

In 2016–2018, there have been numerous outbreaks of suspected and confirmed cases of yellow fever, resulting in imported cases to other countries (dashed arrows), but these did not result in secondary cases.



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outbreak was due to the forest yellow fever transmission cycle and not the urban cycle. The last documented large urban yellow fever outbreak in the Americas was likely in Brazil in 1928; subsequent urban yellow fever outbreaks in South America have been very small, each involving no more than nine cases. This suggests that the epidemiologies of urban yellow fever in Africa and South America are different and require further investigation.

The exhaustion of vaccine supplies on multiple occasions, together with the resurgence of YFV activity in the past 3 years, is a cause for concern. There were many outbreaks between 2016 and 2018, and in addition, international travelers caused multiple importations into countries outside these outbreaks (see the figure). Notably, the Brazil outbreak resulted in travelers transporting YFV to seven countries during 2018, including five in Europe (11, 12). By comparison, only three cases were imported into Europe during the previous 16 years. Clearly, we cannot rely on YFV control by vaccination alone, and modeling is a critical component.

There are reasons to be optimistic. Advances in genomic sequencing technology of YFV isolates have enabled modeling of YFV activity, which has been routinely undertaken for other pathogens such as influenza virus. As the database improves, so will our understanding of YFV movement and our ability to identify areas where the virus has potential to cause outbreaks. Concurrent activities of the EYE strategy will result in production of vaccine that can be appropriately distributed with input from YFV modeling. Therefore, it may be possible to eliminate yellow fever epidemics by 2026, as planned. ■

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CANCER

Fusion oncogenes—genetic musical chairs

Ewing sarcoma–driver fusion genes can result from complex genomic rearrangements

By Marcin Imielinski^{1,2} and Marc Ladanyi³

The cytogenetic definitions of many cancers predate the genome sequencing era. Indeed, some classes of cancers (largely subtypes of sarcomas, lymphomas, and leukemias) have long been defined by simple and distinct patterns of chromosomal changes, or karyotypes, that, in many cases, feature a single pathognomonic somatic translocation of two genomic regions that creates a fusion oncogene (for example, the Philadelphia chromosome translocation in chronic myelogenous leukemia results in the *BCR-ABL1* fusion oncogene) (1). Whereas many common cancers display genomic complexity consistent with multistep oncogenesis, such as carcinomas of breast and lung, cancers that are defined by translocations typically display simple karyotypes, suggesting that they were shaped by a single translocation. However, the cytogenetic simplicity of these cancers may mask more complex genomic events. On page 891 of this issue, Anderson *et al.* (2) report whole-genome sequencing (WGS) of 50 Ewing sarcomas (EWSs), an aggressive sarcoma that is defined by fusion between the EWS RNA binding protein 1 (*EWSRI*) gene on chromosome 22 and an E26 transformation-specific (ETS) family transcription factor gene, either *FLI1* at 11q24 or *ERG* at 21q11 (3). Anderson *et al.* show that ~40% of *EWSRI-FLI1* fusions and all *EWSRI-ERG* fusions arise via a complex rearrangement pattern called chromoplexy, which was first identified in prostate cancer (4). They suggest that chromoplexy “bursts” may be early initiating events in Ewing sarcomagenesis and mark a more aggressive form of the disease.

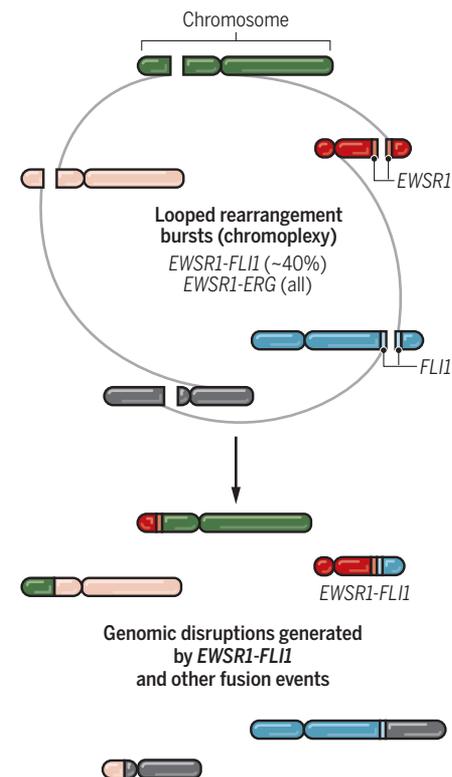
Whereas standard reciprocal translocations involve DNA breaks in two fusion partners, chromoplexy involves three or

more breakpoints in the genome. Like the children’s game of musical chairs, in which players are forced to stand up and find a new seat, three or more broken chromosome ends are forced to find a new partner. Unlike musical chairs, during which one of the chairs is removed at each round of play, every broken end finds a new partner, resulting in a loop pattern (see the figure). Chromoplexy is thus a complex means to an end: the formation of functional *EWSRI-FLI1* or *EWSRI-ERG* fusions that, upon expression, provide a selective growth or survival advantage.

Although *EWSRI-ERG* fusions were known to require more complex rearrangements because their opposing chromosome orien-

Fusions via chromoplexy

Bursts of complex rearrangements can generate Ewing sarcoma oncogenic fusion genes and are associated with genomic complexity, more frequent *TP53* mutations, and increased risk of relapse.



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