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Responding to the threat of urban yellow fever outbreaks

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When in April, 2016, WHO declared the yellow fever epidemic in Angola a global threat, it was because yellow fever appeared in Luanda, the capital city of Angola, causing a rapidly spreading urban outbreak due to the massive movement of people to and from the city and easy access to international airports, with daily connections to Asia, Europe, and the Americas. Nearly 45 years had elapsed since a similar urban yellow fever epidemic occurred in Angola in 1971 (a smaller one occurred in 1988); in that interval, urbanisation has increased at record rates, with more than 62% of the population now living in urban areas.[1] For reasons that are still poorly understood, the yellow fever virus, which is maintained in a transmission cycle involving non-human primates and arboreal mosquitoes, crosses into a far more threatening human-to-human transmission cycle involving urban and domestic *Aedes aegypti* mosquitoes. The distribution of *A aegypti* is now the widest ever recorded and it is extensive in all continents, including parts of North America and Europe, with more than 3 billion people at risk.[2] Urbanisation with resulting increased population densities, further enhanced by man-made larval habitats, amplifies *A aegypti*-transmitted diseases, including those caused by the dengue, chikungunya, and Zika viruses.[3] Among these viral infections, yellow fever is of major concern because the lethality of this haemorrhagic fever is 20–50%, rivalling that of Ebola virus disease. Of particular concern is that urban yellow fever has the potential for rapid spread via international travellers to vulnerable countries where *A aegypti* mosquitoes are present. Indeed, for the first time, such spread happened during the Angola outbreak when travellers infected with yellow fever in Angola entered China between March and April, 2016, thereby putting 1·8 billion largely unvaccinated people in Asia at risk. Fortunately, no autochthonous cases occurred.

In late 2015 and the first months of 2016, the yellow fever outbreak in central Africa had a high reproductive rate (4·8 new people infected for every case). Although an effective vaccine, which protects against infection within 7–10 days after vaccination, has been available since the 1930s, implementation of an emergency vaccination campaign to contain the rapidly expanding outbreak was hampered by limited vaccine supplies and problems in the delivery of vaccinations. In such a setting it is essential to identify the areas at greatest risk of infection, to inform vaccine prioritisation decisions. Consequently, the analyses by Moritz Kraemer and colleagues[4] reported in *The Lancet Infectious Diseases* provide an important contribution with many practical implications.

Although a WHO working group had previously identified a set of mainly ecological criteria relevant to the transmission of yellow fever virus and systematically applied these criteria to classify areas with risk for transmission of yellow fever virus,[5] the model developed by Kraemer and colleagues adds mobility patterns and demographic determinants that govern transmission and spread of the virus in the region. The investigators used standard logistic models that discriminated districts with high risk of invasion from others. Notably, population density was a dominant predictive factor for onward transmission, corroborating previous findings.[6] The spread of yellow fever in Angola was driven by high population density, including in locations that were distant from the origin of the outbreak in Luanda. Furthermore, the team

captured different aspects of connectivity and were able to infer regular daily commuting patterns, longer-term movements, and general human diffusion processes. Their gravity model assumed that relative flow between districts is a log-linear function of the population sizes of the districts and the distance between them,[7] thereby emphasising large population centres such as the capital cities Luanda (Angola) and Kinshasa (DR Congo), which were the epicentres of the epidemic. A radiation model additionally took account of the draw from other populations within the same radius of the districts considered, as well as the population sizes and distance of the origin and destination locations. Models based on travel volumes as shown by Kraemer and colleagues are increasingly used to predict international spread and identify the most vulnerable receiving areas or countries for infectious diseases such as influenza H1N1,[8] polio,[9] dengue,[10,11] Zika virus,[12–14] and yellow fever,[15] and should become the basis for similar studies aiming to predict regional and international spread.

The modelling techniques used by Kraemer and colleagues allowed the analysis of near real-time data to inform the control of an ongoing outbreak. If, in mid-February, the 50 districts with the highest calculated probability of infection had been targeted, their model would have correctly identified 27 (84%) of the 32 districts that were eventually affected. This approach, if applied in the future, could speed up prioritisation of areas to be targeted for rapid deployment of vaccines in the context of finite resources. However, the Article does not address how generalisable to other settings the pattern of spread was in this particular outbreak in which urban transmission initiated in a major city and radiated outward. Moreover the model does not account for the fact that yellow fever virus was introduced from Angola into densely populated parts of the southern DR Congo without the extent of spread seen in Angola.

Yellow fever virus has caused substantial outbreaks in Africa (eg, in The Gambia in 1978–79, Nigeria in 1969, and Ethiopia in 1962) where sylvatic mosquito vectors have been mainly responsible for inter-human virus transmission, and where human population movements, population density, and A aegypti distribution have not clearly determined the pattern of the epidemic at the time. These occurrences emphasise the complex ecology of yellow fever and the importance of determining the role of specific mosquito vectors in each yellow fever epidemic. Nevertheless, in an increasingly urbanised Africa, application of Kraemer and colleagues' model will allow rapid assessment of the predicted pattern of spread and logistical approach to containment. Notably, the investigators found that the epidemic in Angola slowed around the time that vaccination was initiated in February, 2016, or even before it was implemented, suggesting that other factors, such as a possible change in human behaviour, slowed transmission as word spread of the dangers of yellow fever. In a 2013 epidemic of dengue in Luanda, mosquito avoidance strategies (such as application of mosquito repellent or sleeping under a bed net) were associated with reduced infections.[16]

Urban yellow fever poses a substantial threat and large A aegypti-borne outbreaks have occurred despite the constrained transmission dynamics resulting from the relatively low competence of this vector for yellow fever,[17] the early recognition of the striking clinical presentation, and the availability of a safe and efficient vaccine. The main lesson learned from the recent Angolan yellow fever outbreak is that control efforts should not rely on reactive vaccination campaigns, which are always associated with delays that result in preventable deaths. The mainstay for yellow fever control remains adequate vaccine coverage. To achieve high vaccination coverage on a long-term basis, the best strategy is to incorporate yellow fever vaccination into routine infant immunisations and to implement catch up campaigns in the older population. To that end, a new effort led by WHO (Eliminating Yellow fever Epidemics [EYE]) is planned to roll out during the next 5 years. Until it is implemented, outbreaks will continue to arise from the enzootic cycles, with potential spread by urban transmission.

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Quantifying the fitness of antiviral-resistant influenza strains
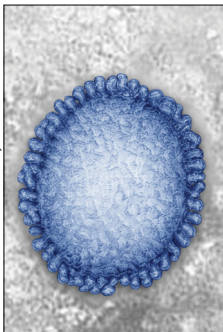
Influenza remains a serious public health threat, causing recurrent outbreaks of respiratory virus infections on a global scale every year. Occasional pandemics mark the establishment of a novel virus in the population.[1] Vaccination and antiviral treatment can mitigate influenza morbidity and mortality, particularly among high-risk populations.[2] However, viral evolution promotes escape from population immunity to natural infection or vaccination, and facilitates acquisition of antiviral resistance.

The adamantane class of antivirals has been available for decades but are no longer used due to frequent adverse events and high resistance in circulating viruses. Oseltamivir (Tamiflu; Roche, Basel, Switzerland) belongs to a newer class of antivirals approved for influenza treatment and prophylaxis in 1999 in the USA. It was believed that oseltamivir resistance came at a high fitness cost for the virus, precluding effective onward transmission, and hence was not considered an issue. This honeymoon period for oseltamivir ended abruptly with the rapid global spread and fixation of resistance in influenza A H1N1 viruses in 2007–08, including in countries that used little or no antivirals.[3,4] Several years later, experimental studies revealed that compensatory mutations had facilitated the rise of resistance.[5] In 2009, the emergence of a pandemic A H1N1 virus susceptible to oseltamivir displaced the resident strains, conveniently setting a clean slate for oseltamivir use against A H1N1 infection. Sporadic emergence of resistant A H1N1 viruses since 2009 suggests that the threat is still there, and that careful monitoring is essential. In *The Lancet Infectious Diseases*, Kathy Leung and colleagues[6] introduce a practical statistical method to predict the potential of antiviral-resistant strains to outcompete susceptible strains, and help re-evaluate the arsenal of tools for fighting influenza in near real time.

Leung and colleagues'[6] method relies on minimal surveillance data on the incidence of resistant and susceptible strains and information on the generation interval (the interval between successive cases, typically well-known for influenza) to quantify the relative fitness of the resistant virus over sensitive strains. The method is shown using both theoretical simulations and empirical data. Simulations show that unbiased fitness estimates are obtained after about ten generations of disease transmission when at least five influenza specimens are tested daily for resistance, and the sensitivity and specificity of the test are greater than 90%. However, the method is sensitive to assumptions about the distribution of the generation interval and stochastic effects. In applying their method to empirical data from ten regions in 2007–08, the authors found that the antiviral-resistant strain exhibited, on average, a 3–5% higher transmissibility than the susceptible virus, in line with a previous global mechanistic model.[7] However, much heterogeneity in country-level estimates of fitness remained unexplained: as a case in