25.1 Case Study: Modeling Fractional-Dose Emergency Vaccination Campaigns for Yellow Fever

Joseph T. Wu and Corey M. Peak

Contents

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Learning Objectives

This chapter should enable readers to understand and discuss:

- Why WHO warned against cutting mosquito control programs when the incidence of yellow fever (YF) dropped around the world.
- The basis of the proposal to provide one-fifth of the normally recommended YF vaccine dose in response to a 2016 YF outbreak in Central Africa.
- How a dose-sparing immunization regimen could reduce the infection rate even if the smaller dose is less effective in preventing infection and disease.
- The mathematical modeling used by the authors to assess the impact of potentially reduced vaccine efficacy with fractional dosing on the YF infection attack rate.
- How the conclusions of the modeling study were applied in urban Kinshasa.
- Conference recommendations for further research on the efficacy of fractional doses in outbreaks.

1 Modeling Fractional-Dose Emergency Vaccination Campaigns for Yellow Fever

Yellow fever (YF) is a mosquito-borne disease with no specific treatment (WHO 2019b). During the 1950s, mass vaccination and intensive mosquito-control programs largely eliminated YF, except in sub-Saharan Africa and sporadic hotspots in South America. However, as the burden of YF subsided, many mosquito control programs were dismantled. The World Health Organization (WHO) has been warning for decades that such policy failure, together with changes in demography, land use patterns, and international air travel, would set the stage for explosive outbreaks of urban YF.

This premonition was realized when YF resurged and spread widely in urban Angola in late 2015 (Chan 2016). By May 2016, more than 2500 suspected cases, including 301 deaths, had been reported from all 18 provinces of Angola. Cases had been exported to Kenya, China, and the Democratic Republic of the Congo (DRC), and the risk of further international spread was escalating. Although WHO maintained a YF vaccine stockpile of about six million doses for emergency use in reactive campaigns, the stockpile was intended for responding to sylvatic spillovers and was therefore insufficient in size for controlling sustained urban outbreaks. Facing severe shortages of YF vaccines, WHO proposed dose fractionation for an emergency YF vaccination campaign in August 2016 to vaccinate eight million people in Kinshasa, three million in anterior Angola, and 4.3 million along the DRC-Angola corridor (Schnirring 2016).

Although empirical evidence suggested that a fivefold fractional dose was not inferior to a standard dose in terms of safety and immunogenicity (largely due to the excess of infectious viral particles in routine YF vaccine batches) (Visser 2019), it was not known whether equal immunogenicity implies equal vaccine efficacy (VE) for YF vaccines. To strengthen the evidence base for the public health benefit of dose fractionation of YF vaccines, we used mathematical modeling to assess the impact of reduced VE in fractional dose vaccines on the infection attack rate (IAR), defined as the proportion of the population infected over the course of an epidemic (Wu et al. 2016). Such an assessment would be particularly useful if the pathogen was not highly transmissible (e.g., the basic reproductive number R_0 of influenza is below 2 (Riley et al. 2007)) because even if dose fractionation reduced VE, the resulting higher vaccine coverage (VC) might confer higher herd immunity, in which case the number of infections could be significantly reduced by the indirect effect of large-scale vaccination. However, the transmissibility of YF in urban settings had never been adequately characterized before due to limited data, and hence the importance of herd immunity for YF vaccination was unknown. As such, the first step of our study was to estimate the R_0 of YF in urban settings by analyzing the epidemic curve of YF in Luanda, Angola. We found that in the absence of interventions, the R_0 of YF was around 5–7, which suggested that the intrinsic transmissibility of YF was not low. Therefore, the

herd effect would not likely be substantial unless the immunization coverage (VC x VE) was close to the control threshold $1-\frac{1}{R_0}$.

Let VE(n) and IAR(n) be the VE and IAR under n-fold dose fractionation. We assumed that vaccine action was all-or-nothing, i.e., vaccines provided 100% protection against infection in a proportion VE(n) of vaccinees and no protection in the remainder. Under this assumption,

$$\mathrm{IAR}(n) = S_0\left(1-\mathrm{VE}(n)\mathrm{nV}\right)\left[1-\exp\left(-R_0\cdot\left(I_0+\mathrm{IAR}(n)\right)\right)\right]$$

where V was the vaccine coverage achievable with standard-dose vaccines, and S_0 and I_0 were the initial proportion of population that were susceptible and infectious. This simple model indicated that n-fold dose fractionation reduced IAR if and only if $\mathrm{VE}(n) > \frac{\mathrm{VE}(1)}{n}$ regardless of the transmissibility of the pathogen and pre-existing population immunity.

Having established the minimum requirement on VE(n) for n-fold dose fractionation to be non-inferior, we then considered VE(5) = 1, 0.9, 0.6 and 0.3 and compared the IAR when vaccines were administered in standard dose only versus according to the fivefold dose-fractionation proposed by the WHO for its vaccination campaign in Kinshasa. We parameterized the population demographics and pre-campaign vaccine coverage in the model using (1) the age distribution of Angola and Kinshasa from the World Factbook (CIA 2020); (2) the annual routine immunization coverage among children aged 12–23 months between 1997 and 2015 from WHO/United Nations Children's Fund (UNICEF) immunization estimates (WHO 2019a); and (3) vaccine coverage conferred by the emergency vaccination of around one million people in Kinshasa during May–June 2016. We estimated that the dose-sparing strategy would avert 7.1, 7.1, 5.4, and 1.3 million infections if R_0 = 4, and around 7.9, 7.9, 4.0 and 1.0 million infections if R_0 = 8–12. These figures were based on the assumption of a sustained epidemic, such that transmission declined when the population of susceptible hosts was depleted.

In conclusion, our rapid risk assessment model, shared via preprint in May 2016, showed that the proposed WHO dose-sparing strategy for the YF vaccination campaign in Kinshasa, DRC, would be a robust and effective strategy for reducing infection attack rate; it would prevent many more infections than using the vaccine at standard dosage, even with a large margin for error in case fivefold fractional-dose vaccine efficacy turned out to be lower than expected. WHO formally recommended the dose-fractionation strategy in July 2016 (WHO 2016a), and it was implemented in August 2016 (◘ Fig. 1), during which nearly 7.5 million residents of urban Kinshasa received fivefold fractional dose vaccines and nearly 0.5 million children under two and pregnant women received standard dose vaccines, achieving an estimated 98% coverage of the target population (WHO 2016b). In June 2017, WHO published an addendum to its 2013 position paper on YF vaccine stating, "As a dose-sparing strategy, a fractional YF vaccine dose meeting the WHO minimum requirement for potency is expected to be equivalent to a standard YF vaccine dose with respect to safety, immunogenicity, and effectiveness" (WHO 2013, 2017c). Research conferences in 2017 and 2019 drew on several clinical studies that supported the efficacy of fractional doses in outbreak circumstances, while recommending further research on the duration of immunity and potential need for booster doses (WHO 2017a, 2020; Casey et al. 2019).

Here, mathematical modeling (▶ Chaps. 24 and 25) provided insights into the tradeoffs between individual-level vaccine efficacy and population-level herd immunity conferred by dose-sparing strategies. This approach bears relevance for questions of dose-sparing for other vaccines, e.g., inactivated polio vaccine

Fig. 1 Dose-sparing yellow fever vaccination campaign underway near Kinshasa. (Courtesy of WHO/E. Photo: Soteras Jalil)

(WHO 2017b), as well as dose-spacing approaches, for example with coronavirus disease 2019 (COVID-19) vaccines (Kadire et al. 2021; Tuite et al. 2021). With respect to the latter, delaying the administration of the second dose of a two-dose vaccine regimen has been implemented in some countries as a means to accelerate population coverage with the first dose, at the potential, uncertain cost of lower and/or waning efficacy during the time between when the second dose would be administered under the standard regimen and the second injection under the dose-spacing regimen. In principle, if during this period the average vaccine efficacy of the first dose remains above one-half of the vaccine efficacy following the second dose, then a dose-spacing regimen may reduce the infection attack rate.

Discussion Questions

1. During the 1950s, mass vaccination and intensive mosquito-control programs largely eliminated YF except in sub-Saharan Africa and sporadic hotspots in South America. As the burden of YF subsided, WHO warned against dismantling many mosquito control programs. Why?
2. Following YF's resurgence and spread in urban Angola in late 2015, cases were exported to Kenya, China, and the DRC, escalating the risk of further international spread. What prompted WHO to consider a fivefold fractional vaccine dose for an emergency YF vaccination campaign in August 2016?
3. The transmissibility of YF in urban settings had never been adequately characterized, so the importance of herd immunity in YF was also largely unknown. Briefly summarize the mathematical modeling used by the authors to assess the potential impact of vaccine efficacy being reduced by an uncertain amount by fractional dosing.
4. Briefly state the conclusions of this study and their application in urban Kinshasa.
5. Research conferences in 2017 and 2019 drew on several clinical studies that supported the efficacy of fractional doses in outbreak circumstances. What were

some recommendations for further research?

6. The mathematical modeling of this study provided insights into the tradeoffs between individual-level vaccine efficacy and population-level herd immunity conferred by dose-sparing strategies. Beside YF, this approach also bears relevance for questions of dose-sparing for inactivated polio vaccine and dose-spacing for COVID-19 vaccines. How could a dose-spacing regimen reduce the infection attack rate?

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