

Fractional dosing of yellow fever vaccine to extend supply: a modelling study



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Summary

Background The ongoing yellow fever epidemic in Angola strains the global vaccine supply, prompting WHO to adopt dose sparing for its vaccination campaign in Kinshasa, Democratic Republic of the Congo, in July–August, 2016. Although a 5-fold fractional-dose vaccine is similar to standard-dose vaccine in safety and immunogenicity, efficacy is untested. There is an urgent need to ensure the robustness of fractional-dose vaccination by elucidation of the conditions under which dose fractionation would reduce transmission.

Methods We estimate the effective reproductive number for yellow fever in Angola using disease natural history and case report data. With simple mathematical models of yellow fever transmission, we calculate the infection attack rate (the proportion of population infected over the course of an epidemic) with various levels of transmissibility and 5-fold fractional-dose vaccine efficacy for two vaccination scenarios, ie, random vaccination in a hypothetical population that is completely susceptible, and the Kinshasa vaccination campaign in July–August, 2016, with different age cutoff for fractional-dose vaccines.

Findings We estimate the effective reproductive number early in the Angola outbreak was between 5·2 and 7·1. If vaccine action is all-or-nothing (ie, a proportion of vaccine recipients receive complete protection [VE] and the remainder receive no protection), *n*-fold fractionation can greatly reduce infection attack rate as long as VE exceeds 1/*n*. This benefit threshold becomes more stringent if vaccine action is leaky (ie, the susceptibility of each vaccine recipient is reduced by a factor that is equal to the vaccine efficacy). The age cutoff for fractional-dose vaccines chosen by WHO for the Kinshasa vaccination campaign (2 years) provides the largest reduction in infection attack rate if the efficacy of 5-fold fractional-dose vaccines exceeds 20%.

Interpretation Dose fractionation is an effective strategy for reduction of the infection attack rate that would be robust with a large margin for error in case fractional-dose VE is lower than expected.

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Introduction

Yellow fever has resurged in Angola and threatens to spread to other countries with lower yellow fever vaccine coverage. As of July 8, 2016, yellow fever has spread from Angola to Kenya (two cases), China (11 cases), and Democratic Republic of the Congo (59 cases), raising concern that yellow fever could resurge in other populations where competent vectors are present and vaccine coverage is low.^{1,2} Indeed, Democratic Republic of the Congo has already declared a yellow fever epidemic in Kinshasa and two other provinces. A broad band of sub-Saharan Africa north of Namibia and Zambia is at risk, as is much of the northern portion of South America. The global community is concerned about the risk of yellow fever emergence in Asia, where the disease has been curiously absent despite seemingly amenable conditions.

There is a safe, highly effective live-attenuated vaccine against yellow fever.³ However, the global emergency stockpile of yellow fever vaccines, which was maintained at approximately 6·8 million doses before 2016, has already been used up completely twice by the Angola outbreak. With a throughput of only 2–4 million doses per month, yellow fever vaccine supply is inadequate for the large urban populations at risk for yellow fever

infection. In response to such a shortage, dose fractionation has been proposed to maximise the public health benefit of the available yellow fever vaccines.⁴ Under dose fractionation, a smaller amount of antigen would be used per dose to increase the number of people who can be vaccinated with a given quantity of vaccine antigen.³ This strategy was previously proposed to extend pre-pandemic influenza vaccine supplies.⁵ If dose fractionation were consistently adopted, equity of yellow fever vaccine access would also be enhanced both within and across countries at risk, as more people could benefit from vaccination without depriving others.⁶

Following the Strategic Advisory Group of Experts (SAGE) endorsement on June 17, 2016, WHO recommended dose fractionation in its emergency yellow fever vaccination campaign in July–August, 2016, to vaccinate 8 million people in Kinshasa, 3 million in anterior Angola, and 4·3 million along the Democratic Republic of the Congo–Angola corridor.⁷ 2·5 million standard-dose vaccines were allocated to Kinshasa, with 200 000 standard-dose vaccines given to children aged 9 months to 2 years and the remaining allocation to be fractionated 5-fold and given to the rest of the population.

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For US Centers for Disease Control and Prevention yellow fever maps see <http://www.cdc.gov/yellowfever/maps/>

Research in context

Evidence before this study

We searched PubMed and Google Scholar on June 10, 2016, with the terms “yellow fever” and “vaccine” or “dose sparing”. We did not find any reports of randomised trials of yellow fever vaccine efficacy, at full or lower doses. Some studies since 2008 suggest similar immunological responses at 5-fold, or more, fractionation as compared with current dose antigen concentrations. Although several perspective articles propose the dose-sparing strategy in response to the shortage, to our knowledge this is the first study to test the robustness of this strategy (in terms of its epidemiological effect) against the uncertainties surrounding fractional-dose yellow fever vaccine efficacy and method of action (eg, “all-or-nothing” and “leaky”). There were no restrictions by language.

Added value of this study

We estimate that the reproductive number of the yellow fever epidemic in Angola during 2016 is 5.2 to 7.1. Our study is the

first to provide an estimate of the transmissibility of yellow fever in urban settings. We characterise the threshold of vaccine efficacy above which dose-sparing can drastically reduce the number of yellow fever cases. We show how the benefits of dose fractionation are influenced by the transmission intensity of the setting, the target coverage, and the fractional-dose vaccine efficacy and method of action. We show that the WHO dose-sparing strategy for the Kinshasa vaccination campaign in July–August, 2016, is a robust and effective strategy for reducing infection attack rate that would be robust with a large margin for error should 5-fold fractional-dose vaccine efficacy turn out to be lower than expected.

Implications of all the available evidence

Our results support the growing evidence that dose-sparing strategies should be adopted as an option for extending the sparse yellow fever vaccine supply.

The evidence base for fractional-dose yellow fever vaccines is built upon two studies that compared the safety and immunogenicity of standard-dose and 5-fold fractional-dose yellow fever vaccines. The first is a randomised, non-inferiority trial that showed that 0.1 mL intradermal (ID) vaccination with the 17D yellow fever vaccine was equally safe and immunogenic compared with the standard 0.5 mL subcutaneous vaccination.⁸ The second is a randomised trial of subcutaneous administration of the 17DD vaccine given in Brazil that showed that there was no significant difference in immunogenicity and viraemia kinetics when the vaccine (containing 27 476 IU of virus) was given at subdoses as low as 11% of the full dose (3013 IU).⁹ Even lower doses produced non-inferior immune responses, but not equivalent viraemia kinetics.⁹ For comparison, the WHO minimum for yellow fever vaccines is 1000 IU per dose at the end of shelf life.¹⁰

No efficacy trial of yellow fever vaccines, however, has ever been done in human beings,¹¹ so the comparative efficacy of different doses and routes of administration remains uncertain. In particular, it is not known if equal immunogenicity implies equal vaccine efficacy for yellow fever vaccines. Moreover, the findings of equal immunogenicity of reduced doses are limited to healthy adults; no comparable data exist in children (thus the age cutoff of 2 years for fractional-dose vaccines in Kinshasa), or elderly or immunocompromised individuals. As such, although non-inferior immunogenicity of fractional-dose vaccines provide a strong basis for an initial consideration of dose-sparing strategies for yellow fever vaccines, it would be prudent to ensure the robustness of this strategy by careful assessment of the risks and epidemiological effect of reduced vaccine efficacy in fractional-dose vaccines. Such an assessment is non-trivial because even if

dose fractionation reduces vaccine efficacy, higher vaccine coverage might confer higher herd immunity, in which case the number of infections could be substantially reduced by the indirect effect of large-scale vaccination.¹² The lower the transmissibility, the larger the number of infections that can be averted by indirect protection, as illustrated by the previous study of dose fractionation for pre-pandemic influenza vaccines.⁵ The importance of herd immunity for yellow fever vaccination is unknown because transmissibility of yellow fever in urban settings has never been adequately characterised due to scarcity of data.

To strengthen the evidence base for the public health benefit of dose fractionation of yellow fever vaccines, we use simple mathematical models to assess the potential reduction in infection attack rate (IAR, defined as the proportion of population infected over the course of a sustained epidemic) conferred by 5-fold dose fractionation under different epidemic scenarios and reductions in vaccine efficacy. We find that all dose-sparing strategies are likely to provide substantial benefit epidemiologically, and that the best policy will be established by balancing logistical and regulatory considerations against the extent of epidemiological benefit. In particular, we conclude that the WHO Kinshasa dose-sparing vaccination campaign in July–August, 2016, would be an effective strategy for reducing infection attack rate, and the results would be robust against a large margin for error should 5-fold fractional-dose efficacy turn out to be lower than expected.

Methods

Estimation of the epidemiological parameters for yellow fever

To set parameters for realistic epidemic scenarios for our analysis, we estimate the reproductive number of yellow fever over the course of the Angola outbreak and use the

estimates during the early epidemic stages (before large-scale vaccination affected transmission) as the range of basic reproductive number (R_0) for future outbreaks in other populations. To this end, we use the Wallinga and Teunis method¹³ to estimate the reproductive number of yellow fever from the daily number of confirmed yellow fever cases recorded in the WHO Angola Situation Report of April 17, 2016,¹⁴ assuming that all cases were attributed to local transmission (ie, no importation of cases). When estimating the extrinsic incubation period, we assume that the average temperature in Angola was 28°C during the outbreak. To estimate the serial interval distribution, we assume that the extrinsic incubation period follows the Weibull distribution estimated by Johansson and colleagues¹⁵ that has mean 12.7 days at 28°C; the intrinsic incubation period follows the lognormal distribution estimated by Johansson and colleagues,¹⁵ that has mean 4.6 days; the infectious period in human beings is exponentially distributed with mean 4 days;¹⁶ and the mosquito lifespan is exponentially distributed with mean 7–14 days.¹⁷ We estimate the initial reproductive number of the yellow fever outbreak in Angola as the average reproductive number among all patients who developed symptoms one serial interval before vaccination campaign began to affect disease transmission (figure 1).

Dose-response for fractional-dose vaccines

Let S_0 be the proportion of population susceptible just before the vaccination campaign begins and V_0 be the vaccine coverage achievable with standard-dose vaccines. Suppose each standard-dose vaccine can be fractionated into n , n -fold fractional-dose vaccines (ie, each of which contains $(1/n)$ th the amount of the antigen in a standard-dose vaccine) with vaccine efficacy $VE(n)$. That is, the vaccine efficacy of standard-dose vaccines is $VE(1)$, which was assumed to be 1. Given V , the highest fractionation sensible is $n_{\max} = S_0 / V$ if the susceptible population can be identified for targeted vaccination and $n_{\max} = 1 / V$ otherwise, ie, the fractionation n must lie between 1 and n_{\max} . To avoid overstating the benefit of dose fractionation, we assume that vaccine efficacy of n -fold fractional-dose vaccines for n between 1 and 5 increases proportionally with the amount of antigen in the vaccines (appendix). Potential increases in vaccine wastage during dose-sparing would be mostly due to unused, reconstituted vaccines¹⁹ or increased vaccine failure due to inexperience with intradermal administration among vaccinators. In the setting of mass vaccination campaigns, wastage due to unused vaccine doses will probably be negligible, because vaccination sessions will be large.

We use IAR as the outcome measure for assessment of the effect of dose fractionation. We calculate IAR using the classic final size approach, which is accurate for directly transmitted SIR (number susceptible–number immune–number recovered)-type diseases²⁰ but only an

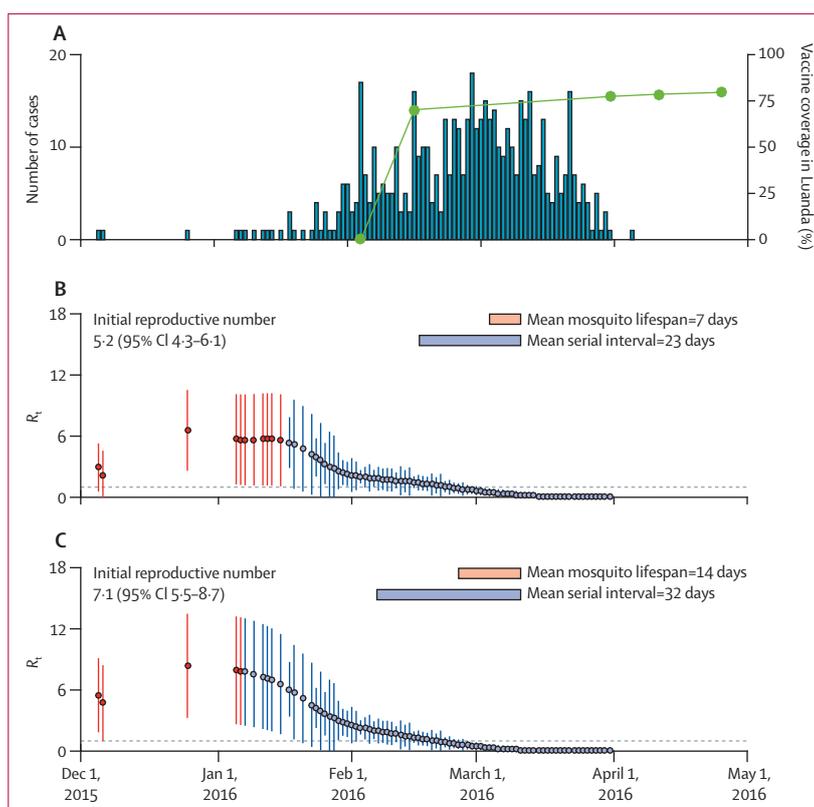


Figure 1: Estimates of the reproductive number over the course of the Angola outbreak

(A) Epidemic curve of confirmed cases by dates of symptom onset in Angola and vaccine coverage (green line) in Luanda province achieved by the reactive yellow fever vaccination campaign that started on Feb 2, 2016.¹⁸ The first cases of this yellow fever outbreak were identified in Luanda province, which accounted for 90 of the 121 cases confirmed in Angola up to Feb 26, 2016. (B, C) Estimates of the daily reproductive number (R_t) assuming that the mean mosquito lifespan was 7 days (B) or 14 days (C). The red datapoints correspond to the cases that were used to estimate the initial reproductive number. These patients had symptom onset one mean serial interval before the vaccination campaign began to affect disease transmission (assumed to be 7 days after the start of the campaign to account for the time it takes for adaptive immunity to develop). The orange horizontal bar indicates the length of the mean mosquito lifespan and the purple horizontal bar indicates the serial interval on the scale of the x-axis.

approximation for vector-borne diseases.²¹ Nonetheless, this approximation is appropriate for realistic parameter ranges because only a small proportion of mosquitoes are infected with yellow fever virus even during epidemics (necessitating pooled testing; appendix).²²

We denote the IAR under n -fold dose fractionation by $IAR(n)$. To assess the outcome of fractional-dose vaccination against that of standard-dose vaccination, we calculate the absolute reduction in IAR as $IAR(1) - IAR(n)$ and relative reduction in IAR as $1 - IAR(n) / IAR(1)$. We assume that the vaccination campaign is completed before the start of the epidemic.

We assume that vaccine action is all-or-nothing, ie, n -fold fractional-dose vaccines provide 100% protection against infection in a proportion $VE(n)$ of vaccinees and no protection in the remainder. In this case, n -fold dose fractionation results in lower IAR if and only if the vaccine efficacy of n -fold fractional-dose vaccines is at least $1/n$ times that of standard-dose vaccines, ie, $VE(n) > VE(1) / n$ (appendix). We term this the benefit

See Online for appendix

threshold for dose fractionation. We also consider the alternative case in which vaccine action is leaky, ie, n -fold fractional-dose vaccines reduce the hazard of infection (the probability of disease transmission per mosquito bite) of each vaccinee by a proportion $VE(n)$.^{23,24} We present our main results in the context of all-or-nothing vaccine action. In principle, disease transmission can be halted if the effective vaccine coverage, defined as the proportion of population immunised (eg, $V \times n \times VE(n)$ if vaccination includes n -fold fractional-dose vaccines only), exceeds the herd immunity threshold $1 - 1/R_0$.

We consider two vaccination scenarios with various levels of transmissibility and efficacy reduction in fractional-dose vaccines.

Random vaccination in a hypothetical population

To illustrate the potential effect of dose fractionation, we first consider a hypothetical scenario where the entire population is susceptible ($S_0=1$) and each individual has the same probability of receiving vaccination. We compare the outcome of using the entire vaccine stockpile for either standard-dose or 5-fold fractional-dose vaccination. If some individuals are immune ($S_0 < 1$, due to previous exposure or vaccination) and vaccination can be targeted at susceptible individuals only, then the resulting IAR within the susceptible population would be the same as that for random vaccination in a completely susceptible population with coverage V/S_0 and basic reproductive number $R_0 S_0$.

The Kinshasa vaccination campaign, July–August, 2016

The population of Kinshasa is estimated to be around 12.46 million people, and around 2.5 million standard-dose vaccines were expected to be administered to the Kinshasa population during this vaccination campaign (personal communication, Bruce Aylward and Alejandro Costa, WHO). Under the WHO dose-sparing strategy, 200 000 standard-dose vaccines were to be given to children aged between 9 months and 2 years (sufficient for vaccinating all unvaccinated children in this age range) and the remaining allocation fractionated to one-fifth of the standard dose and given to the rest of the population. We compare the outcome when the vaccines are administered in standard dose only (strategy S), and according to the WHO dose-sparing strategy with alternative age cutoffs for fractional-dose vaccines ranging from 2 to 20 years (strategy F). For strategy F, let Z be the age cutoff and $p(Z)$ be the proportion of population targeted for standard-dose vaccination. For a given standard-dose vaccine coverage V , the proportion of population receiving standard-dose is $\min(V, p(Z))$, and the proportion of population receiving fractional-dose vaccines is $5 \max(V - p(Z), 0)$. Therefore, the effective vaccine coverage after the vaccination campaign is $B + \min(V, p(Z)) \times VE(1) + 5 \max(V - p(Z), 0) \times VE(5)$, where B is the vaccine coverage immediately before the campaign (ie, at the end of June, 2016; appendix).

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, writing of the report, or the decision to publish. All authors had access to the data; the corresponding authors had final responsibility to submit for publication.

Results

The initial reproductive number of yellow fever in Angola was 5.2 (95% CI 4.3–6.1) if the mosquito lifespan was 7 days and 7.1 (5.5–8.7) if the mean mosquito lifespan was 14 days (figure 1). Although these estimates might reflect partial immunity due to prior vaccination or exposure in some of the population (we estimated that around 28% of the Angola population had been vaccinated before the yellow fever epidemic; appendix), we assume that the basic reproductive number of a future outbreak in another population would range between 4 and 12, due to varying vector ecology and levels of pre-existing immunity in the population.

Figure 2A–B shows the effective vaccine coverage and IAR under standard-dose and fractional-dose vaccination as a function of standard-dose vaccine coverage V given varying levels of transmission and 5-fold fractionation vaccine efficacy when vaccine action is all-or-nothing. The corresponding absolute and relative reduction in IAR are shown in figure 2C–D, and support our earlier claim that fractional-dose vaccination reduces IAR when $VE(5) > VE(1)/5 = 0.2$. Fractional-dose vaccination substantially reduces IAR if $V > 10\%$ and such reduction only diminishes to insignificance when V is close to the herd immunity threshold $1 - 1/R_0$ (eg, 75% for $R_0=4$ and 88% for $R_0=8$). Dose fractionation reduces IAR when the standard-dose vaccine supply is insufficient to halt disease transmission and fractional-dose vaccine efficacy is above 0.2.

If vaccine action is leaky, then the benefit threshold (the efficacy of n -fold fractionated doses necessary to reduce IAR) is higher than $1/n$ and increases with transmission intensity (figure 3). This occurs because under the leaky model each infectious bite is assumed to be less likely to cause infection if the host is vaccinated, but the probability of infection grows as the person receives more infectious bites. Dose fractionation is much less beneficial if vaccine action is leaky, efficacy is modest, and R_0 is high (figure 3; appendix).

A 2014 study²⁵ suggested that the mosquito biting rate for individuals aged 20 or above is 1.22 times higher than for those aged less than 20 years. We did a sensitivity analysis to show that our results are unaffected by such heterogeneity (appendix).

We estimate that the vaccine coverage in Kinshasa was 20% at the end of June, 2016, before the vaccination campaign began. The WHO vaccination campaign would increase the effective vaccine coverage to 37% if all the vaccines were administered only in standard dose. Under the WHO dose-sparing strategy, the effective vaccine

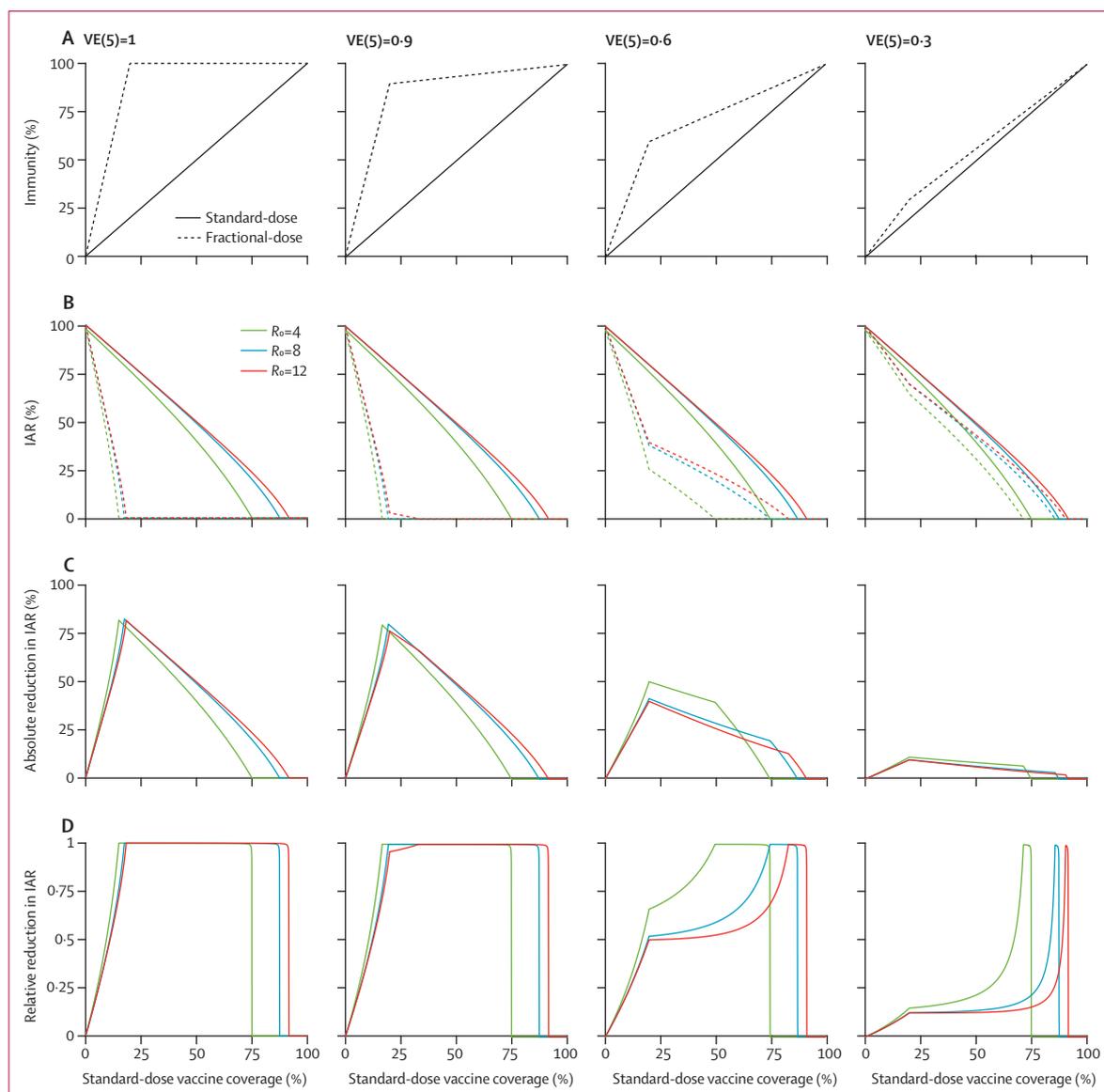


Figure 2: The effect of 5-fold fractional-dose vaccination with different vaccine efficacy and reproductive numbers

We assume that the whole population is susceptible, vaccine action is all-or-nothing, and standard-dose vaccine efficacy is 1. If the standard-dose vaccine coverage V exceeds 20%, then everyone in the population can be vaccinated under 5-fold fractionated-dose vaccination, in which case the fractionation would only be $n=1/V$. (A) The effective vaccine coverage ($VE(n) \times nV$), which is essentially the percentage of population immunised, as a function of standard-dose vaccine coverage V under standard-dose vaccination (solid curves) and 5-fold fractional-dose vaccination (dashed curves). (B) Infection attack rate (IAR) under standard-dose vaccination and 5-fold fractional-dose vaccination. IAR is reduced to 0 when the effective vaccine coverage reaches the herd immunity threshold $1-1/R_0$. (C) Absolute reduction in IAR. As V increases from 0, a kink appears when the herd-immunity threshold is attained or everyone is vaccinated under 5-fold fractional-dose vaccination (ie, $V=20\%$). If 5-fold fractional-dose vaccination at 100% coverage cannot attain the herd immunity threshold (because of low fractional-dose vaccine efficacy), then a second kink appears when V is large enough such that fractional-dose vaccination attains herd-immunity threshold due to the increase in $VE(n)$ resulting from lower fractionation ($n=1/V$). (D) Relative reduction in IAR.

coverage can be increased to 99%, 91%, 68%, and 44% if the vaccine efficacy of 5-fold fractional-dose vaccines $VE(5)$ is 1, 0.9, 0.6, and 0.3, respectively (figure 4). The corresponding absolute reduction in IAR is 57%, 57%, 43%, and 10% if $R_0=4$ and around 63%, 63%, 32% and 8% if $R_0=8-12$. These IAR reductions correspond to 7.10, 7.10, 5.36, and 1.25 million infections averted if $R_0=4$ and around 7.85, 7.85, 3.99, and 1.0 million infections

averted if $R_0=8-12$. The age cutoff for fractional-dose vaccines chosen by WHO (namely, 2 years) provides the largest reduction in IAR as long as $VE(5)$ is above 0.2. That is, the WHO dose-sparing strategy is optimal as long as 5-fold fractional vaccines are at least 20% efficacious. These figures are based on the assumption of a sustained epidemic such that transmission declines when the population of susceptible hosts is depleted.

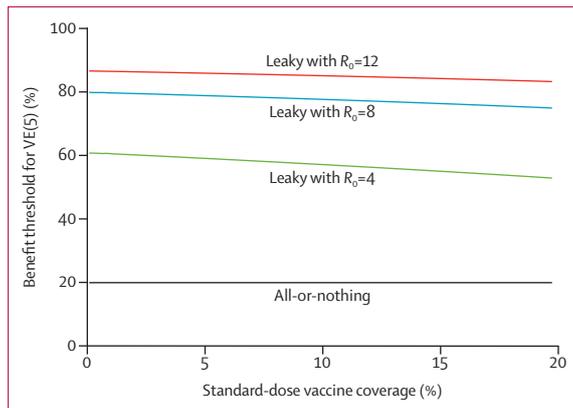


Figure 3: Benefit thresholds for leaky vaccines as a function of standard dose vaccine supply V and basic reproductive number R_0
5-fold fractionated dosing reduces infection attack rate compared with standard dosing if the leaky vaccine efficacy of fractional-dose is above the threshold. This threshold becomes high for large values of R_0 , because under the leaky vaccine action model, multiple exposures eventually overcome vaccine protection and lead to infection of vaccinated individuals.

Discussion

Our primary analysis shows that dose fractionation of yellow fever vaccine, if there is no loss of efficacy as assumed, could provide a substantial benefit to reducing the attack rate of yellow fever in a population. We consider this assumption of full efficacy for 5-fold fractionation to be the most likely scenario, despite the paucity of efficacy data on any yellow fever vaccine. First, two studies of 5-fold, or more, fractionated vaccination doses have shown indistinguishable immunogenicity in human beings. Second, at least some preparations of yellow fever vaccine substantially exceed the WHO minimum standard for potency of 1000 IU/dose, so fractionation could be done without dropping below that threshold; and finally, yellow fever vaccine is live attenuated virus, so a biological rationale exists that if a productive vaccine-virus infection can be established by a fractionated dose, protection should be similar to that with a higher dose. Nonetheless, to assess the robustness of the statement that dose fractionation is likely to be beneficial, against the possibility that in fact efficacy of fractionated doses is lower than anticipated, we consider the possibility that 5-fold fractionated dosing does not immunise a proportion $(1-VE(5))$ of recipients. We find that as long as at least 20% of recipients are fully immunised by the vaccine, more people would be immunised by vaccinating five times as many people with one-fifth of the dose, and so the population-wide benefits of higher coverage would outweigh the lower efficacy of fractionated dosing for individual vaccine recipients.

Even more unlikely, in our opinion, is that fractionated doses would be substantially less efficacious according to a leaky model, in which all vaccinated individuals were imperfectly protected against infection from each infectious bite, with the same probability of infection from

each bite, reduced by the vaccine by a proportion VE (appendix). However, we found that especially in high-transmission areas, the fractionated-dose vaccine would need to be 80–90% efficacious to provide a benefit over standard dosing.

Our analysis is not intended to recommend extending coverage to the point of knowingly compromising efficacy. Rather, our analysis indicates that a strategy of fractionation to a dose that provides equivalent immunogenicity to standard dosing would be greatly beneficial if efficacy is equivalent to standard dosing, and would still be beneficial if, unexpectedly, efficacy were somewhat lower than for standard dosing.

We have used 5-fold fractionation as an example because it is the strategy with the best evidence base of equal immunogenicity. However, some data suggest that more than 5-fold fractionation could be equally immunogenic, and of course the benefits of fractionation would be greater if more than 5-fold fractionation were logistically possible and of similar efficacy.

We have considered fractional dosing for residents of areas at high risk for transmission. Another group of interest are travellers, for whom we must also consider longevity of response, lower exposure, and more detailed discussions on equity outside the scope of this modelling paper. The cost of fractional-dose strategies will depend on the route of administration, but could potentially be substantially less expensive per vaccine recipient.¹⁹

Our simple model has several limitations. We assume homogeneous mixing of the population (reasonable at least locally for a vector-borne disease). We also fix a particular value of R_0 for each calculation, and assume this value is maintained until the epidemic has swept through a population. In reality, R_0 will vary seasonally as vector abundance, extrinsic incubation period, and other factors vary. The existence of a high-transmission season might enhance the benefits of fractional-dose vaccination. Most importantly, achieving high vaccine coverage before the peak of transmission is important to maximise the effect, and this will be limited by supply constraints that could be partially relieved by fractionation. However, the estimates of cases averted might not all be achieved in a single transmission season if seasonal declines in mosquito abundance abrogate transmission before most of the population has become infected.

We have focused on the benefits of increasing vaccine coverage within a single population. Given the global shortage of yellow fever vaccines, an additional benefit of fractionated dosing is to extend coverage to a wider geographic area, covering more populations with vaccine than could be achieved with standard dosing. Indeed, part of the WHO plan is to vaccinate border areas between Angola and Congo,²⁶ providing benefit to that population and a so-called immune buffer to slow movement of disease toward Kinshasa.²⁷

We conclude that dose fractionation could be an effective strategy for improving coverage of yellow fever

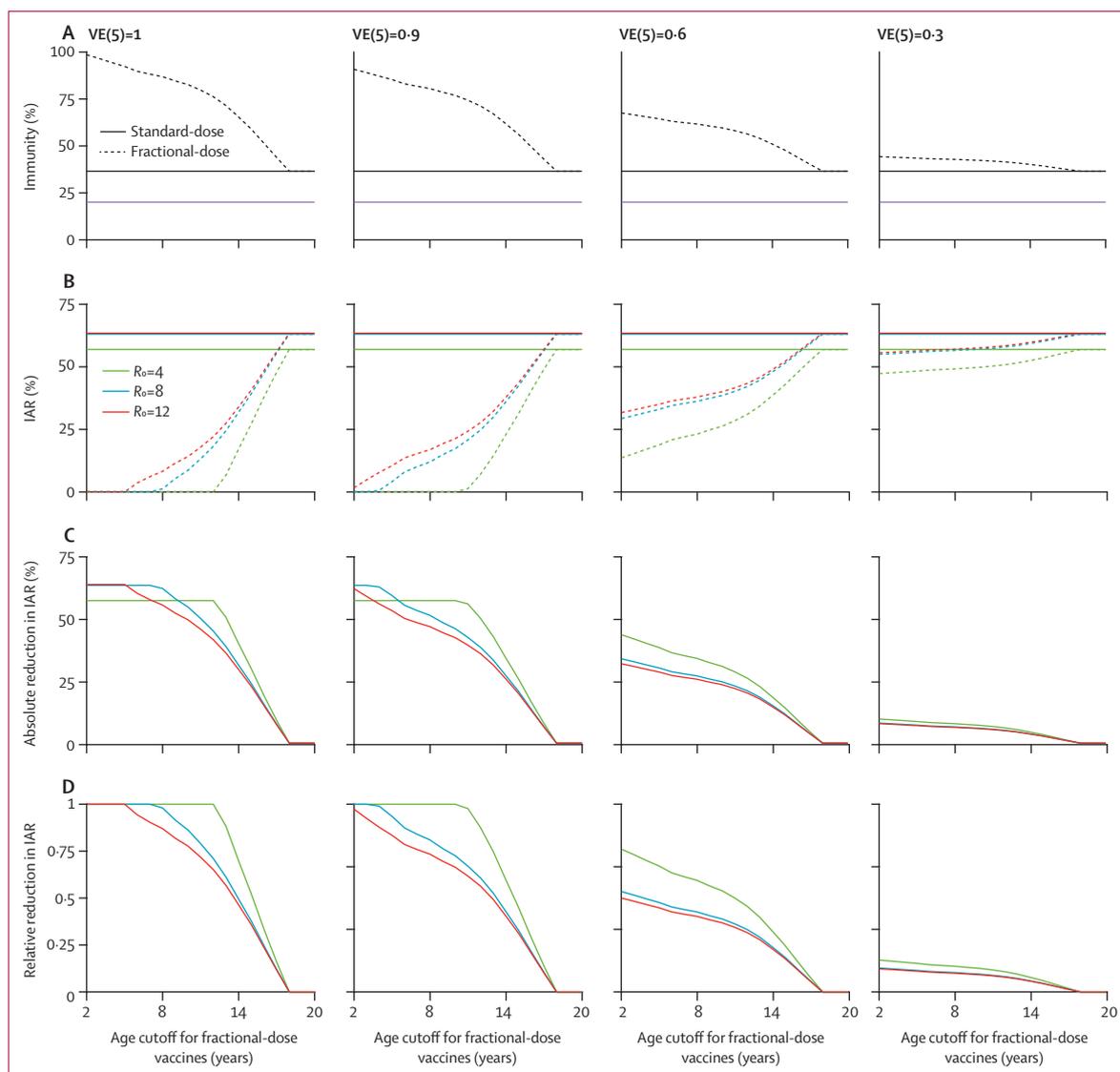


Figure 4: Assessing the WHO dose-sparing strategy in the Kinshasa vaccination campaign in July–August, 2016

IAR=infection attack rate. (A) Effective vaccine coverage (ie, the percentage of population immunised). The purple line indicates the pre-campaign coverage. The black solid and dashed lines indicate the post-campaign coverage if vaccines are administered in standard dose only (strategy S) and according to the WHO dose-sparing strategy with alternative age cutoffs for fractional-dose vaccines (strategy F). (B) IAR under strategy S and F for different R_0 . (C) Absolute reduction in IAR. (D) Relative reduction in IAR.

vaccines and reducing infection attack rate in populations—possibly by a large absolute and relative margin—if high to moderate efficacy is maintained by reduced-dose formulations. For vaccines with standard formulations that exceed WHO minimum concentration of virus particles,¹⁰ this dose fractionation could be accomplished without changing the WHO recommendations. In particular, the WHO plan to use fractional dosing to extend the coverage of vaccination within Kinshasa and in surrounding areas is robust in the sense that it is expected to provide greater benefit than the use of full doses, even if efficacy of fractionated doses were substantially lower than that of standard doses.

Roll-out of fractionated dosing should perhaps be preceded or accompanied by non-inferiority studies of the intended vaccine's immunogenicity at fractional doses in the intended populations. Ongoing programmes should be monitored by observational studies of safety, immunogenicity and, if possible, effectiveness¹⁹ to assure that the assumptions underlying the rationale for such programmes continue to be met. However, it is worth noting that if full-dose vaccine efficacy is indeed almost 100% as believed, estimating the relative efficacy of fractional versus standard doses in a comparative study would be difficult or impossible, as there might be few or no cases accrued in the standard-dose group.

Contributors

JTW, CMP, and ML reviewed the literature and designed the study. JTW and ML developed the mathematical model. JTW ran the mathematical model. JTW, CMP, GML, and ML interpreted the model results and approved the final version.

Declaration of interests

ML reports consulting honoraria (that have been donated to charity) from Pfizer and Affinivax, consulting payments from Antigen Discovery, Inc, and research funding through his institution from Pfizer and PATH Vaccine Solutions, all unrelated to yellow fever. JTW, CMP, and GML declare no competing interests.

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