Fractional Dosing of Yellow Fever Vaccine to Extend Supply: A Modeling Study

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Background
The ongoing yellow fever (YF) epidemic in Angola is placing strain on the global vaccine supply. In order to extend vaccine supply and reduce the cost of mass-vaccination, dose sparing by fractional-dose vaccination has received heightened consideration. Five-fold fractionation is similar to the standard dose in safety and immunogenicity. However, no YF vaccine efficacy trials have been performed in humans, so it is possible that fractional-dose vaccines may be less efficacious even if equally immunogenic. There is an urgent need to study under what conditions fractional dosing could provide epidemiologic benefits in reducing transmission.

Methods
We estimated the effective reproductive number for YF in Angola using disease natural history and case report data. Using these results and simple mathematical models of YF transmission, we calculated the expected final size of an epidemic under varying levels of vaccine coverage with standard-dose vaccines and up to five-fold fractionation with varying efficacy. We consider two allocation scenarios: random and whereby children receive standard-dose vaccines while adults receive fractional-dose vaccines.

Findings
The effective reproductive number early in the outbreak ranged from approximately 5·2 to 7·1 transmission events per infectious individual. Intuition dictates, and we confirm with modeling analysis, that five-fold fractional-doses can dramatically reduce the final epidemic size. If vaccine efficacy is all-or-nothing, as we expect, the conclusion holds that *n*-fold fractionation is beneficial as long as the efficacy is greater than 1/*n*. We quantify how the threshold becomes more stringent if fractional vaccines instead provide partial protection to every recipient (i.e. “leaky” vaccine action).

Interpretation

We conclude that dose fractionation could be a very effective strategy for reducing infection attack rate in populations with a large margin of error in case fractional-dose efficacy turns out to be lower than expected.

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53 INTRODUCTION

54 Yellow fever (YF) has resurged in Angola and threatens to spread to other countries with
55 relatively low YF vaccine coverage. As of June 16, YF cases have been exported from Angola to
56 Kenya (2 cases), China (11), and DRC (53), raising concern YF could resurge in other populations
57 where competent vectors are present and vaccine coverage is low, especially during the rainy
58 season which is beginning in West Africa.[1,2] A broad band of sub-Saharan Africa north of
59 Namibia and Zambia is at risk (http://www.cdc.gov/yellowfever/maps/africa.html), as is much
60 of the northern portion of South America
61 (http://www.cdc.gov/yellowfever/maps/south_america.html). The global community is
62 increasingly concerned for the risk of YF emergence in Asia, where the disease has been
63 curiously absent despite seemingly amenable conditions.

64 There is a safe, highly effective live-attenuated vaccine against YF.[3] However, the global
65 emergency stockpile of YF vaccines is low, with approximately 6.8 million doses currently
66 available and 2-4 million more doses expected per month.[1] Given the large populations at risk
67 for YF infection, the stockpile is expected to be inadequate to meet the need.[4] For this reason,
68 the WHO is considering the possibility of dose-sparing by fractional-dose vaccination,[5] in which
69 smaller volumes of vaccine would be used per dose in order to increase the number of persons
70 who can be vaccinated with a given quantity of vaccine.[3] This strategy was previously proposed
71 to extend pre-pandemic influenza vaccine supplies.[6] If dose-fractionation were consistently
72 adopted, equity of YF vaccine access might also be enhanced both within and across countries
73 at risk, as more people could benefit from vaccination without depriving others.[7]

74 A randomized, noninferiority trial has shown that 0·1 ml intradermal (ID) vaccination with the
75 17D YF vaccine was equally safe and immunogenic compared to the standard 0·5ml
76 subcutaneous vaccination.[8] Another randomized trial of subcutaneous administration of the
77 17DD vaccine given in Brazil showed that there was no significant difference in immunogenicity
78 and viremia kinetics when the currently administered vaccine (containing 27,476 IU of virus)
79 was given at subdoses as low as 11% of the full dose (3,013 IU).[9] Even lower doses produced
80 noninferior immune responses, but not equivalent viremia kinetics.[9] For comparison, the WHO
81 minimum for YF vaccines is 1,000 IU per dose at the end of shelf life.[10]

82 No efficacy trial of YF vaccines has been performed in humans,[11] so the comparative efficacy of
83 different doses and routes of administration remains uncertain. In particular, it is not known
84 whether equal immunogenicity implies equal vaccine efficacy for YF vaccines. Moreover, the
85 findings of equal immunogenicity of reduced doses are limited to healthy adults; no
86 comparable data exist in children, elderly or immunocompromised individuals (e.g. HIV-infected
87 people, pregnant women, etc). As such, while noninferior immunogenicity of fractional-dose
88 vaccines provide a strong basis for an initial consideration of dose-sparing strategies for YF
89 vaccines, it is unlikely that decision makers would change dosing recommendations without
90 carefully evaluating the risk and implications of reduced vaccine efficacy in fractional-dose
91 vaccines. Such an evaluation is nontrivial because even if dose fractionation reduces vaccine
92 efficacy, higher vaccine coverage may confer higher population-level herd immunity in which

case the number of infections could be significantly 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 has been illustrated by the previous study of dose-fractionation for pre-pandemic influenza vaccines.[6] The importance of herd immunity for YF vaccination is unknown because transmissibility of YF in urban settings has so far been poorly characterized due to limited data.

To strengthen the evidence base for the public health impact of dose-fractionation of YF 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 an epidemic) conferred by five-fold dose-fractionation under different epidemic scenarios and reductions in vaccine efficacy. We first estimate the transmissibility of YF during the recent Angola outbreak in order to parameterize realistic epidemic scenarios. We then show that even if vaccine efficacy for five-fold fractional-dose vaccination were considerably lower, higher vaccine coverage could achieve significant reduction in IAR despite lower individual-level efficacy, with the break-even point being 20% efficacy under the assumption that reduced efficacy represents a mix of complete efficacy in some individuals and failure in others ("all-or-nothing"), but higher if vaccines are partially effective in all individuals ("leaky"). Next, given the lack of comparative immunogenicity data for fractional-dose YF vaccination in children, we consider the results of a strategy that provides standard-dose vaccines to children and fractional-dose vaccines to adults. We find that all dose-sparing strategies considered could provide significant benefit epidemiologically, and that the best policy will be determined by balancing logistical and regulatory considerations against the extent of epidemiologic benefit.

METHODS

Estimating the epidemiologic parameters for YF

To parameterize realistic epidemic scenarios for our analysis, we estimate the reproductive number of YF 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 for future outbreaks in other populations. To this end, we use the Wallinga and Teunis method[13] to estimate the reproductive number of YF from the daily number of confirmed YF cases recorded in the 17 April 2016 WHO Angola Situation Report,[14] assuming that all cases were attributed to local transmission (i.e. no importation of cases). When estimating the extrinsic incubation period, we assume that the average temperature in Angola was 28 degrees Celsius during the outbreak. To estimate the serial interval distribution, we make the following assumptions: (i) the extrinsic incubation period follows the Weibull distribution estimated by ref. [15] which has mean 12·7 days at 28 degrees Celsius; (ii) the intrinsic incubation period follows the lognormal distribution estimated by ref. [15] which has mean 4·6 days; (iii) the infectious period in human is exponentially distributed with mean 4 days;[16] (iv) the mosquito lifespan is exponentially distributed with mean 7 to 14 days.[17] We estimate the initial reproductive number of the YF outbreak in Angola as the average reproductive number among all cases who developed symptoms one serial interval before vaccination campaign began to affect disease transmission (see 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 be the vaccine coverage achievable with standard-dose vaccines. Suppose each standard-dose vaccine can be fractionated into *n*, *n*-fold fractional-dose vaccines (i.e. 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, i.e. 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 linearly with the amount of antigen in the vaccines (see appendix for more details). Potential increases in vaccine wastage during dose-sparing would be mostly due to unused, reconstituted vaccines[18] 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 likely to be negligible because vaccination sessions will be large. Increased vaccine failure is effectively the same as reduced vaccine efficacy if vaccine action is all-or-nothing (as we have assumed in the main text). As such, for simplicity, we do not explicitly model wastage.

Infection attack rate

We use infection attack rate or IAR (defined as the proportion of population infected over the course of an epidemic) as the outcome measure for evaluating the impact of dose-

fractionation. We calculate IAR using the classical final size approach which is exact for directly transmitted SIR-type diseases[19] but only an approximation for vector-borne diseases.[20] Nonetheless, this approximation is excellent over realistic parameter ranges because only a very small proportion of mosquitoes are infected with YF virus even during epidemics (necessitating pooled testing).[21] See appendix for the mathematical details.

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

Vaccine action

We assume that vaccine action is all-or-nothing, i.e. *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 are at least 1/*n* times that of standard-dose vaccines, i.e. $VE(n) > VE(1)/n$ (see appendix for details). We term this the benefit threshold for dose-fractionation. We also consider the alternative case in which vaccine action is leaky, i.e. *n*-fold fractional-dose vaccines reduce the hazard of infection (the probability of disease transmission per mosquito bite) of each vaccinee by a proportion $VE(n)$.[22,23] Compared to all-or-nothing vaccines, leaky vaccines have substantially higher benefit thresholds, especially when transmissibility is high (see Results). However, we postulate that vaccine action is much more likely to be all-or-nothing than leaky (see Discussion). As such, we present our main results in the context of all-or-nothing vaccine action.

Dose-sparing strategies

We consider two dose-sparing strategies with at most five folds of dose fractionation:

1. *Random vaccination.* Each individual in the population has the same probability of receiving vaccination regardless of their susceptibility. That is, the susceptible and immune population are indiscernible, so targeted vaccination is not possible. If susceptible individuals can be identified, then targeted vaccination has the same epidemiologic outcome as random vaccination with vaccine coverage V / S_0.
2. *Standard-dose vaccination of children, fractional-dose vaccination of adults*. We assume that children have vaccine priority. That is, all children receive standard-dose vaccines before adults begin to receive fractional-dose vaccines. Let p be the proportion of adults in the population. For a given standard-dose vaccine coverage V, the proportion of children vaccinated is $V_{children} = \min(V, 1-p)$. If the stockpile is large enough to vaccinate all children (i.e. $V > 1-p$), then adults receive n-fold fractional-dose vaccination where $n = \min(5, p/(V-1+p))$. The proportion of adults vaccinated is $V_{adults} = 1$ if $n < 5$ and $V_{adults} = 5(V-1+p)/p$ otherwise. Given the vector-borne nature of yellow fever we assume that transmission between children and adults is well-mixed.

We assume that all individuals are susceptible before vaccination ($S_0 = 1$) unless specified otherwise.

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The sponsors 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

Reproductive number of yellow fever in Angola. Figure 1 shows that the initial reproductive number of YF in Angola was 5·2 (95% CI 4·3, 6·1) and 7·1 (5·5, 8·7) if the mean mosquito lifespan was 7 and 14 days, respectively. While these estimates may reflect partial immunity due to prior vaccination or exposure among some of the population, we assume that the possible basic reproductive number (R_0) in a future outbreak in another population would range between 4 and 12 due to varying vector ecology and levels of preexisting immunity in the population. In principle, disease transmission can be halted if the effective vaccine coverage (defined as vaccine efficacy times vaccine coverage) exceeds the herd immunity threshold 1-1/R_0.

Random vaccination. Figure 2A shows the IAR under standard-dose and fractional-dose vaccination as a function of standard-dose vaccine coverage *V* given varying levels of transmission and five-fold fractionation vaccine efficacy. Figures 2B-C show the corresponding absolute and relative reduction in IAR when vaccine action is all-or-nothing and confirm our earlier claim that fractional-dose vaccination reduces IAR when $VE(5) > VE(1)/n = 0.2$. Fractional-dose vaccination substantially reduces IAR if $V > 10\%$ and such reduction only diminishes to insignificant levels when *V* is close to the herd immunity threshold (1-1/R_0)x100% (e.g. 75% and 88% for $R_0 = 4$ and 8, respectively). In short, dose-fractionation reduces IAR when (i) the standard-dose vaccine supply is insufficient to halt disease transmission and (ii) fractional-dose vaccine efficacy is above 20%.

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. 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. Figure 3 shows, under the leaky model of vaccine action, dose fractionation is much less beneficial if vaccine action is leaky, efficacy is modest, and R_0 is high.

A recent study suggested that the mosquito biting rate for individuals aged 20 or above is 1.22 times higher than those age under 20.[24] We performed a sensitivity analysis to show that our results are unaffected by such heterogeneity. See "Hetereogeneity in biting rates" in the appendix for details.

Vaccination of adults with fractionated doses and children with standard doses. Given the lack of immunogenicity data for fractionated doses in children and evidence of lower seroconversion rates to standard doses,[25] a conservative strategy would be to fractionate doses only for adults while providing full doses to children. Figure 4A shows the fold-increase in vaccine coverage that could be achieved with five-fold fractionation in adults only, as a function of proportion of adults in the population (*p*). Adult fractionation increases coverage more if a larger fraction of the population is adults. In Angola in 2015 approximately 57% of the population was adults (15 and older). If there were enough standard-dose vaccine supplies to cover 70% of such a population, fractionation of only the adult doses would increase the coverage by a factor of 1.43 to 100%. Figure 4B-C shows the same calculations as Figure 2A-B where the five-fold fractional-dose vaccine efficacy is 60%. These calculations all assume that there is no preexisting immunity in children or adults; if preexisting immunity existed mainly in adults, then prioritizing children would have a greater benefit than projected here.

248 **DISCUSSION**

249 Our primary analysis shows that dose-fractionation of YF vaccine, if there were no loss of
250 efficacy, could provide a substantial benefit to reducing the attack rate of YF in a population.
251 We consider this assumption of full efficacy for five-fold fractionation to be the most likely
252 scenario, despite the lack of efficacy data on any YF vaccine, for several reasons: 1) two studies
253 of five- or greater-fold vaccination doses have shown indistinguishable immunogenicity in
254 humans; 2) at least some preparations of YF vaccine substantially exceed the WHO minimum
255 standard for potency of 1,000 IU/dose, so fractionation at some level could be performed
256 without dropping below that threshold; 3) YF vaccine is live attenuated virus, so a biological
257 rationale exists that if a productive vaccine-virus infection can be established by a fractionated
258 dose, protection should be comparable to that with a higher dose. Nonetheless, to assess the
259 the robustness of the conclusion that dose-fractionation is likely to beneficial, against the
260 possibility that in fact efficacy of fractionated doses is lower than anticipated, we consider the
261 possibility that five-fold fractionated dosing fails to immunize a proportion (1-*VE*(5)) of
262 recipients. Consistent with intuition, we find that as long as at least 20% of recipients are fully
263 immunized by the vaccine, more people would be immunized by vaccinating five times as many
264 people with one-fifth the dose, and so the population-wide benefits of higher coverage would
265 outweigh the lower efficacy of fractionated dosing for individual vaccinees. Even more unlikely,
266 in our opinion, is that fractionated doses would be less efficacious according to a "leaky" model,
267 in which all vaccinated individuals were imperfectly protected against infection from each
268 infectious bite, with the same probability of infection from each bite, reduced by vaccine by a
269 proportion VE. If this were the case, then especially in high-transmission areas, the
270 fractionated-dose vaccine would need to be 80-90% efficacious to provide a benefit over
271 standard dosing.

272 Based on the limited evidence on immunogenicity of fractional doses of YF vaccine to date, we
273 consider it unlikely that reducing the dose five-fold or perhaps further from current
274 preparations would result in dramatically lower efficacy of the leaky type. Visual inspection of
275 the data from a dose-fractionation trial of the 17DD vaccine in Brazil shows that for doses down
276 to 47x below the standard dose, the distribution of serologic responses was indistinguishable
277 from those for the standard dose, suggesting that efficacy should be nearly equivalent to that
278 for full doses. This was confirmed by the analysis of peak viremia, which was equivalent for
279 standard dose and for doses down to 11% of the full dose (9-fold fractionation). It was further
280 confirmed by peak cytokine responses, which were comparable to the standard dose for all
281 cytokines tested, down to at least a 9-fold fractional dose. For even lower doses, the proportion
282 seroconverting after vaccination was lower than the 97% observed for the full dose, but the
283 antibody response among the seroconverters appears to be similar at all doses.[9] These data
284 collectively suggest that down to approximately 9-fold fractional dosing of this vaccine the
285 response should be equivalent, and that for further fractionation there may be a failure to
286 induce any substantial response in a fraction of recipients, but the neutralizing antibody titres
287 in those who do respond should be comparable. This pattern is consistent with an all-or-
288 nothing model.

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 was somewhat lower than standard dosing.

We have used five-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 five-fold fractionation could be equally immunogenic, and of course the benefits of fractionation would be greater if more than five-fold fractionation were logistically possible and comparably efficacious.

On programmatic grounds a simpler strategy -- such as fractionated dosing for all -- may be preferred to a more complex strategy that gives different doses to different groups, say age groups. While either would provide epidemiologic benefit, the choice between such strategies would be influenced by the number of available doses, logistical barriers, and location-specific regulations regarding specific groups, such as children. Another group of interest are travelers, for whom we must also consider longevity of response, lower levels of exposure, and more detailed discussions on equity outside the scope of this modeling paper. The cost of fractional-dose strategies will depend on the route of administration, but could potentially be substantially less expensive per vaccine recipient.[18]

Our simple model has several limitations. We assume homogeneous mixing of the population (reasonable at least locally for a vector-borne disease) and neglect preexisting immunity in our main results, though the Methods show how our calculations could be modified to consider preexisting immunity. The purpose is to provide basic calculations for the most at-risk populations, those with little preexisting immunity. 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, there will be a premium on achieving high vaccine coverage before the peak of transmission to maximally impact transmission, and this will be limited by supply constraints that could be partially relieved by fractionation.

We conclude that dose fractionation could be a very effective strategy for improving coverage of YF 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 whose standard formulations exceed WHO minimum concentration of viral particles,[10] this dose-fractionation could be accomplished without changing the WHO recommendations. Even if the efficacy of fractionated doses were substantially lower than expected, increasing coverage by a factor greater than the reduction in efficacy would still be predicted to reduce the population-wide infection attack rate. Substantial benefits could also be achieved if fractional doses were given only to adults while providing standard-dose vaccines to children. We urge consideration of means to implement dose-fractionation as a component

329 of a YF response strategy for the current situation. Rollout of fractionated dosing should
330 perhaps be preceded or accompanied by noninferiority studies of the intended vaccine's
331 immunogenicity at fractional doses in the intended populations. Ongoing programs should be
332 monitored by observational studies of safety, immunogenicity and, if possible, effectiveness[18]
333 to assure that the assumptions underlying the rationale for such programs continue to be met.
334 However, it is worth noting that if full-dose vaccine efficacy is indeed 100% or nearly so as
335 currently believed, estimating the relative efficacy of fractional vs. standard doses in a
336 comparative study would be challenging or impossible, as there might be few or no cases
337 accrued in the standard-dose arm.

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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.

415
416 **Declaration of interests**
417 ML reports consulting honoraria (which have been donated to charity) from Pfizer
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430

Panel: Research in context

Systematic review

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 randomized trials of yellow fever (YF) vaccine efficacy, at full or lower doses. Three relatively recent studies suggest similar immunological responses at five-fold, or more, fractionation as compared to the current dose antigen levels.[8,9,26] While several recent perspective articles propose the dose-sparing strategy in response to the current shortage,[2–4] to our knowledge this is the first study to test the intuition behind the strategy and assess the implications of uncertainties surrounding fractional-dose YF vaccine efficacy and mode of action (e.g. “all-or-nothing” and “leaky”).

Added value of the study

Our study provides a formal confirmation of intuition that dose-sparing can drastically reduce the number of YF cases if high vaccine efficacy is retained. 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 mode of action.

Interpretation

Our results support the growing evidence that dose-sparing strategies should be explored as an option for extending the currently sparse YF vaccine supply.

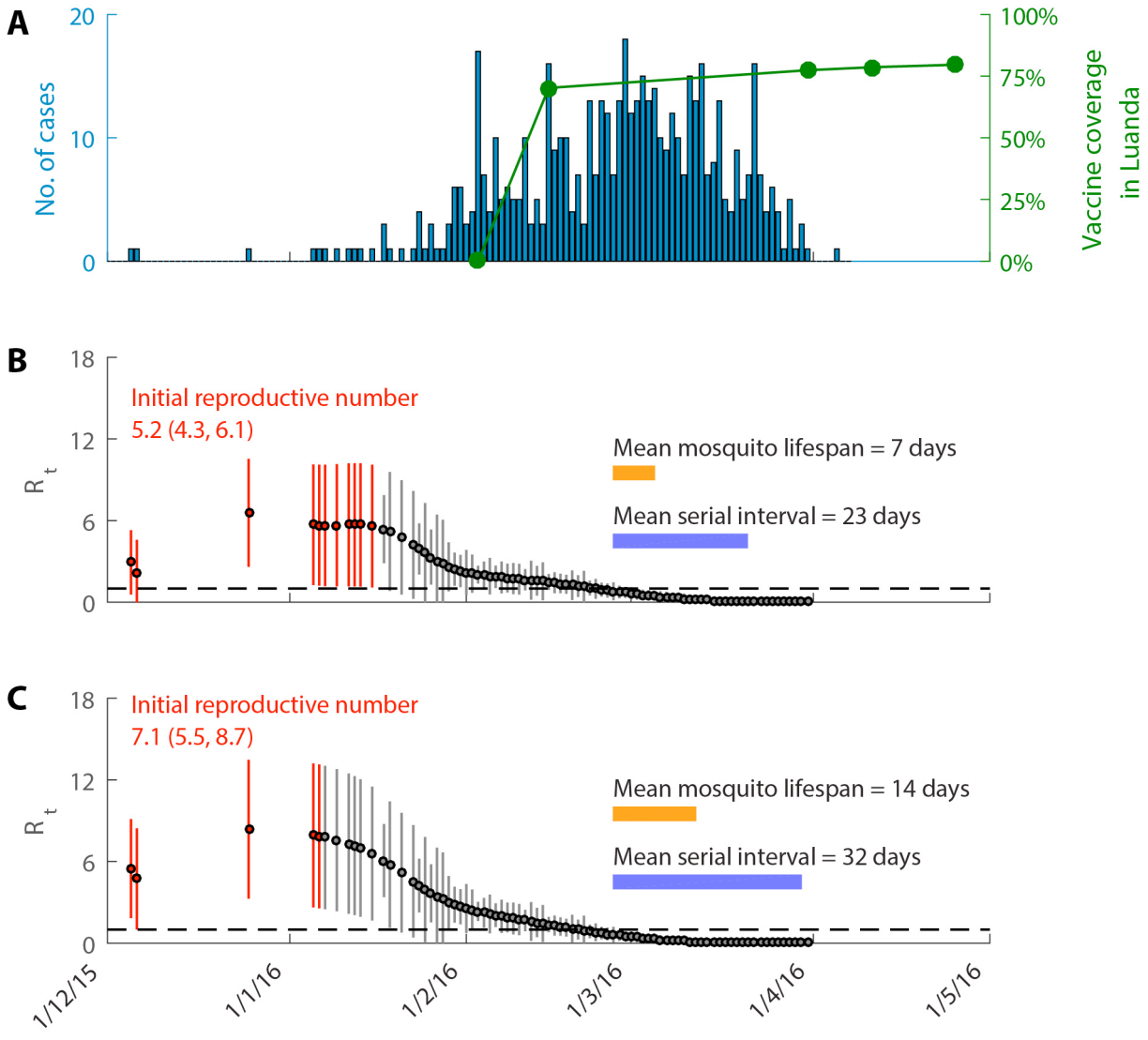

***Figure* 1: Estimates of reproductive number over the course of the Angola epidemic. A** Epidemic curve of confirmed cases by dates of symptom onset in Angola and vaccine coverage in Luanda province achieved by the reactive YF vaccination campaign that started on 2 February 2016.[27] The first cases of this YF outbreak were identified in Luanda province which accounted for 90 of the 121 cases confirmed in Angola up to 26 February 2016. **B-C** Estimates of the daily reproductive number (R_t) assuming that the mean mosquito lifespan was 7 and 14 days, respectively. The red data points correspond to the cases that were used to estimate the initial reproductive number. These cases had symptom onset one mean serial interval before the vaccination campaign began to affect disease transmission (which was 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 and purple horizontal bars indicate the length of the mean mosquito lifespan and serial interval on the scale of the x-axis, respectively.

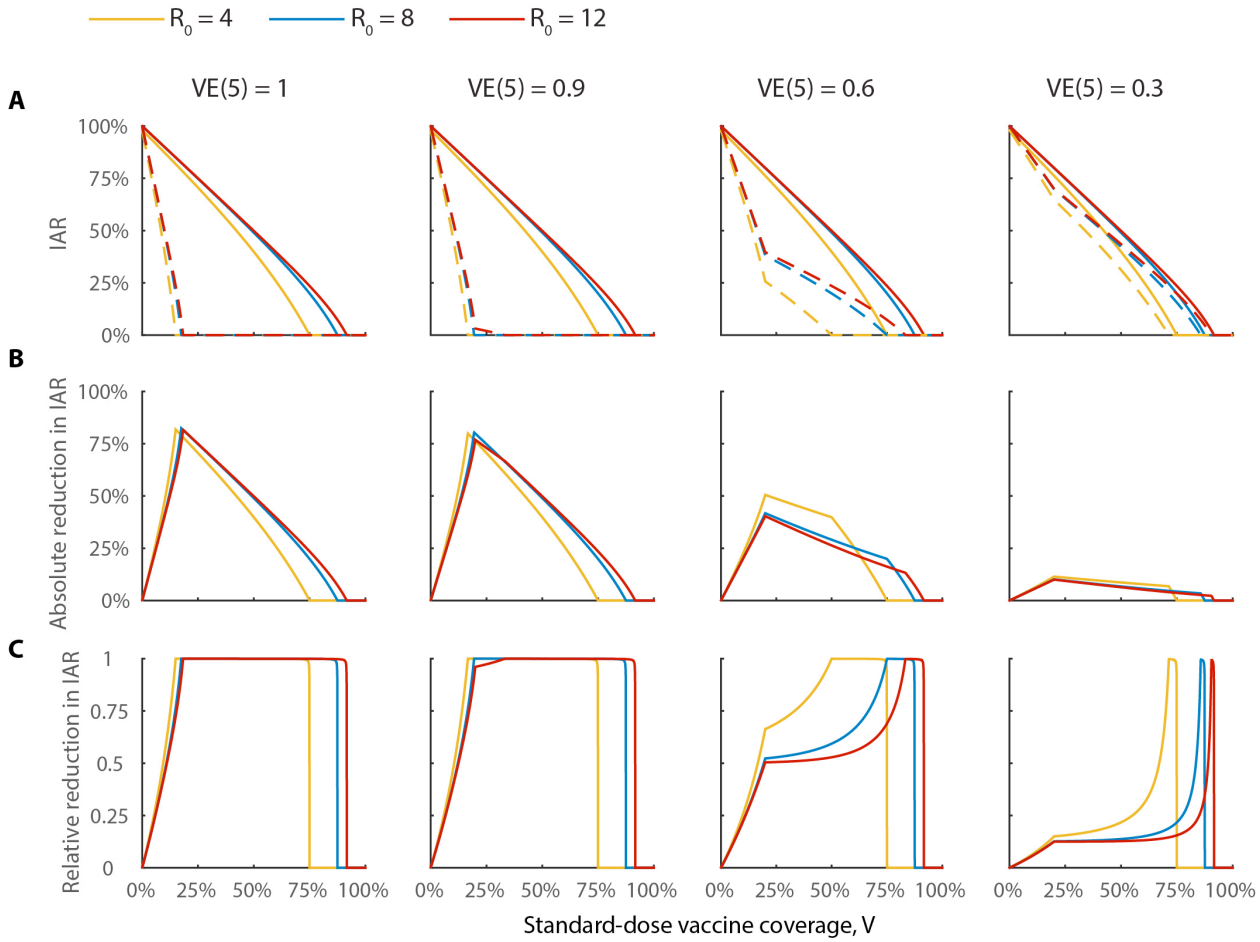

***Figure* 2: The impact of five-fold fractional-dose vaccination with different vaccine efficacy and reproductive numbers.** Vaccine action is assumed to be all-or-nothing and standard-dose vaccine efficacy is assumed to be 1. If the standard-dose vaccine coverage V exceeds 20%, then everyone in the population can be vaccinated under five-fold fractionated-dose vaccination, in which case the fractionation would only be n = 1/V. **A** Infection attack rate (IAR) as a function of standard-dose vaccine coverage, V. The solid and dashed curves correspond to standard-dose and five-fold fractional-dose vaccination, respectively. IAR is reduced to 0 when the effective vaccine coverage (V for solid curves, $VE(n) \times nV$ for dashed curves) reaches the herd immunity threshold $(1-1/R_0)$x100%. **B** Absolute reduction in IAR. IAR reduction is maximum when the five-fold fractional-dose effective vaccine coverage $VE(5) \times 5V$ reaches the herd immunity threshold $(1-1/R_0)$x100%. As V increases from 0, a kink appears when the herd-immunity threshold is attained or everyone is vaccinated under five-fold fractional-dose vaccination (i.e., V = 20%). If five-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 factors (namely $n = 1/V$). **C** Relative reduction in IAR.

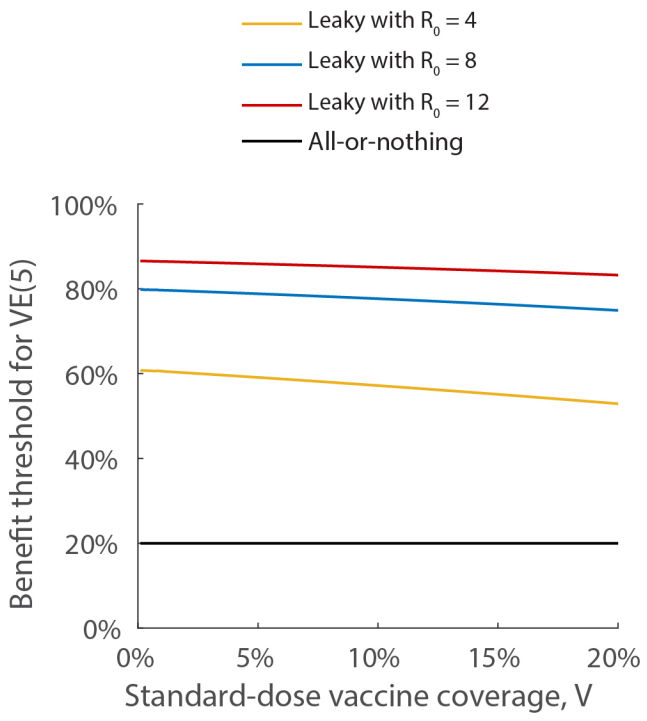

***Figure* 3: Benefit thresholds for leaky vaccines as a function of standard dose vaccine supply *V* and basic reproductive number R_0.** Five-fold fractionated dosing will reduce IAR compared to standard dosing if the leaky vaccine efficacy of fractional-dose is above the line corresponding to the basic reproductive number. This threshold becomes high for large values of R_0 because under the "leaky" model of vaccine efficacy, multiple exposures eventually lead to infection of vaccinated individuals, overcoming their protection from the vaccine.

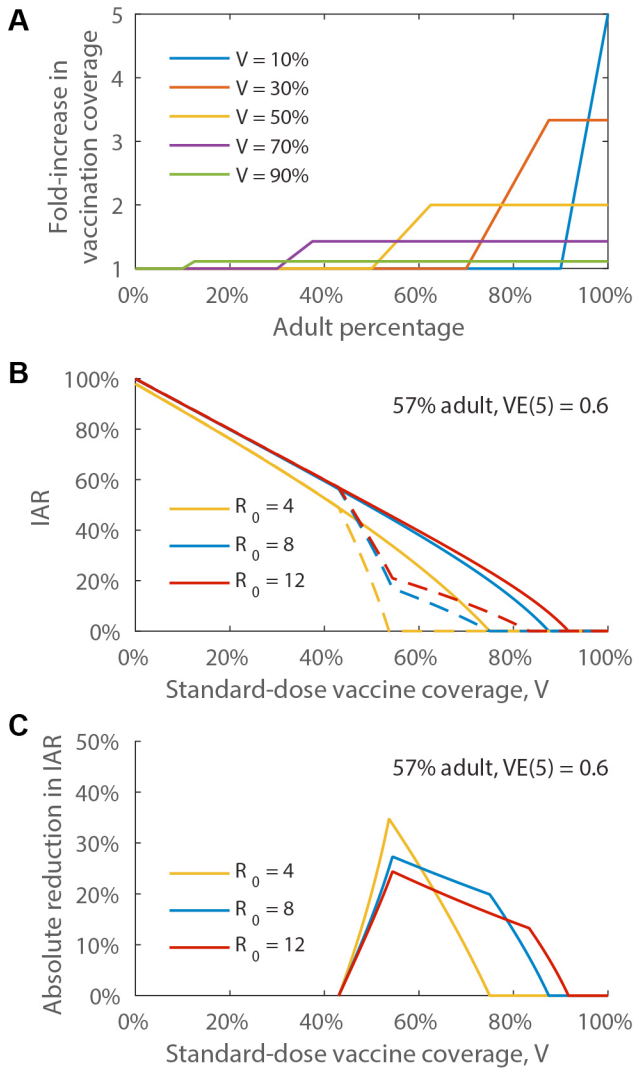

***Figure* 4: Vaccination of adults with fractionated doses and children with standard doses.** All children are vaccinated with standard-dose vaccines before any adults receive vaccination. **A** Fold-increase in the proportion of individuals vaccinated conferred by five-fold fractionated dose vaccination. **B-C** Same as Figure 2A-B when 57% of the population are adults and five-fold fractional-dose vaccine efficacy is 60%.

Appendix

Estimation of the effective reproductive number for YF in Angola

We use the Wallinga and Teunis method[13] to estimate the reproductive number over the course of the YF outbreak in Angola from the daily number of confirmed cases recorded in the 17 April 2016 WHO Angola Situation Report.[14] We assume that all cases were attributed by local transmission, i.e. no importation of cases. Let t_i be the date of symptom onset for case *i*. The relative likelihood that case *i* has been infected by case *j* is

$$p_{ij} = \frac{w(t_j - t_i)}{\sum_{k \neq j} w(t_j - t_i)}$$

where $w(\cdot)$ is the probability density function of the serial interval. Assuming that the probability of case *j* infecting case *i* is independent of the probability of case *j* infecting any other case, the reproductive number for case *j* is a Bernoulli random variable with mean $\sum_i p_{ij}$. The reproductive number on day t, namely R_t, is approximated as the average of the reproductive number of all cases who have symptom onset on day *t*, in which case the mean and standard deviation of R_t are

$$E\left[R_t\right] = \frac{1}{n_t} \sum_{j:t_j=t} \sum_i p_{ij}$$

$$s(R_t) = \frac{1}{n_t} \sqrt{\sum_i \left(\sum_{j:t_j=t} p_{ij}(1-p_{ij}) - \sum_{j,k:t_j=_k=t, j\neq k} p_{ij} p_{ik} \right)} .$$

Assuming that R_t is normally distributed, the approximate (1−α)×100% confidence interval is $E\left[R_t\right] \pm z_{1-\alpha/2} s(R_t)$.

Estimation of the serial interval distribution for YF

We assume that the latent period is the same as the incubation period for all human infections of YF. Suppose an infected individual becomes infectious at time 0. Let t_1 be the time at which the infectious individual is bitten by a competent mosquito which becomes infected, t_2 be the time at which this mosquito becomes infectious, and t_3 be the time at which this mosquito bites and infects a human host. The probability distribution function for the serial interval is

$$f(a) = \frac{h(a)}{\int_0^\infty h(u)du}$$

where

$$h(a) = \int_0^a \int_0^{t_3} \int_0^{t_2} \underbrace{P(I > t_1)}_{\substack{\text{Probability that the} \\ \text{human infectious period} \\ \text{exceeds } t_1 \text{ days when} \\ \text{the mean infectious duration} \\ \text{is mean 4 days.}}} \cdot \underbrace{f_V(t_2 - t_1)}_{\substack{\text{Extrinsic incubation period} \\ \text{at 28 degree Celsius; Weibull} \\ \text{distributed with mean 12.7 days} \\ \text{and CoV 0.61}}} \cdot \underbrace{e^{-d(t_3 - t_1)}}_{\substack{\text{Probability that the} \\ \text{mosquito is still alive} \\ t_3 - t_1 \text{ days after getting} \\ \text{infected}}} \cdot \underbrace{f_H(a - t_3)}_{\substack{\text{Intrinsic incubation period;} \\ \text{Lognormal distributed with} \\ \text{mean 4.6 days and CoV 0.36}}} \, dt_1 dt_2 dt_3$$

In this calculation, we assume that the infectious period in humans is exponentially distributed with mean 4 days,[28] and mosquito lifespan is exponentially distributed with mean varying over 1-2 weeks (http://www.dengue.gov.sg/subject.asp?id=12;[17]). We assume that the extrinsic incubation period follows the Weibull distribution with parameters $\nu = 1.7$ and $\lambda_i = \exp(-7.6 + 0.11T)$ where *T* is the temperature (28 degrees Celsius) as estimated by ref. [15] We assume that the intrinsic incubation period follows the lognormal distribution with parameters $\mu = 1.46$ and $\tau = 8.1$ as estimated by ref. [15].

Dose-response relationship

We assume that vaccine efficacy of n-fold fractional-dose vaccines for n between 1 and 5 increases linearly with the amount of antigen in the vaccines which is proportional to $1/n$. In general, if vaccine efficacy of n-fold fractional-dose vaccines for n between n_1 and n_2 increases linearly with the amount of antigen in the vaccines, then $VE(n) = VE(n_2) + \frac{1/n - 1/n_2}{1/n_1 - 1/n_2}\left(VE(n_1) - VE(n_2)\right)$. We make this assumption to avoid overestimating the benefit of dose-fractionation because:

1. If $VE(5)$ is at the all-or-nothing benefit threshold, namely $VE(1)/5$, then $VE(n)$ is also at the benefit threshold (i.e. $VE(n) = VE(1)/n$) for all n between 1 and 5. That is, if five-fold dose fractionation is not beneficial, then dose-fractionation is not beneficial for all fractionation below five-fold.
2. The reduction in vaccine efficacy as fractionation increases from 1 is likely to be more gradual than what we have assumed here given that standard dose vaccine efficacy appears to be close to 100%.

Appendix Figure 1 illustrates this dose-response relationship for different values of $VE(5)$ with $VE(1) = 1$.

Infection attack rate

We first provide mathematical details on IAR calculations for the case where the population is not stratified into subgroups. If vaccine action is all-or-nothing, then IAR with fractionation n, denoted by $IAR(n)$, is obtained by solving the equation

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

where R_0 is the basic reproductive number, S_0 and I_0 are the initial proportion of population that are susceptible and infectious. As such, dose-fractionation reduces IAR if and only if $VE(n) > VE(1)/n$. If vaccine action is leaky, then $IAR(n)$ is obtained by solving the equation

$$\begin{aligned} IAR(n) = {} & S_0\left(1-Vn\right)\left[1-\exp(-R_0\cdot(I_0+IAR(n)))\right] \\ & + S_0Vn\left[1-\exp(-(1-VE(n))R_0\cdot(I_0+IAR(n)))\right] \end{aligned}$$

In this case, dose-fractionation reduces IAR if and only if

$$VE(n) > 1+\frac{\ln(1-Z)}{R_0(I_0+IAR(1))} \quad \text{where } Z = \frac{IAR(1)}{S_0Vn} - \left(\frac{1}{Vn}-1\right)\left[1-\exp(-R_0\cdot(I_0+IAR(1)))\right]$$

In the special case where $VE(1)=1$, the benefit threshold can be simplified as

$$VE(n) > 1-\frac{\ln\left(1-\left(1-1/n\right)\dfrac{IAR(1)}{S_0(1-V)}\right)}{\ln\left(1-\dfrac{IAR(1)}{S_0(1-V)}\right)}.$$

Next, we provide mathematical details on IAR calculations for the general case where there are *m* groups. Let $S_{0,i}$ and $I_{0,i}$ be the proportion of susceptible and infectious people in group *i* just before the vaccination campaign begins. Let V_i be the vaccine coverage of standard-dose vaccines for group *i*. If n_i is the fractionation for group *i*, then vaccine coverage of fractional-dose vaccines for group *i* is V_in_i. Let $R_0^{j,i}$ be the expected number of secondary infections in group *j* caused by one infection in group *i* in a completely susceptible population. If vaccine action is all-or-nothing, the group-specific IARs are obtained by solving the equations

$$IAR_i(n_i) = S_{0,i}\left(1-V_in_iVE(n_i)\right)\left[1-\exp\left(-\sum_j R_0^{j,i}(I_{0,j}+IAR_j(n_i))\right)\right]$$

If vaccine action is leaky, then the group-specific IARs are obtained by solving the equations

$$\begin{aligned} IAR_i(n_i) = {} & S_{0,i}\left(1-n_iV_i\right)\left[1-\exp\left(-\sum_j R_0^{j,i}(I_{0,j}+IAR_j(n_i))\right)\right] \\ & + S_{0,i}n_iV_i\left[1-\exp\left(-\left(1-VE(n_i)\right)\sum_j R_0^{j,i}(I_{0,j}+IAR_j(n_i))\right)\right] \end{aligned}$$

578 **Heterogeneity in biting rates**

579 A recent study suggested that the mosquito biting rate for individuals aged 20 or above is 1.22
580 times higher than those age under 20.[24] To test the robustness of our results against such
581 heterogeneity, we repeat the calculations in Figure 2 and 3 using a model in which the
582 population is stratified with age 20 as the cutoff. For illustration, we use the demographic
583 parameters of Angola where around 55% of the population are under 20. Appendix Figures 2-3
584 show that our results are unaffected by heterogeneity in biting rates.

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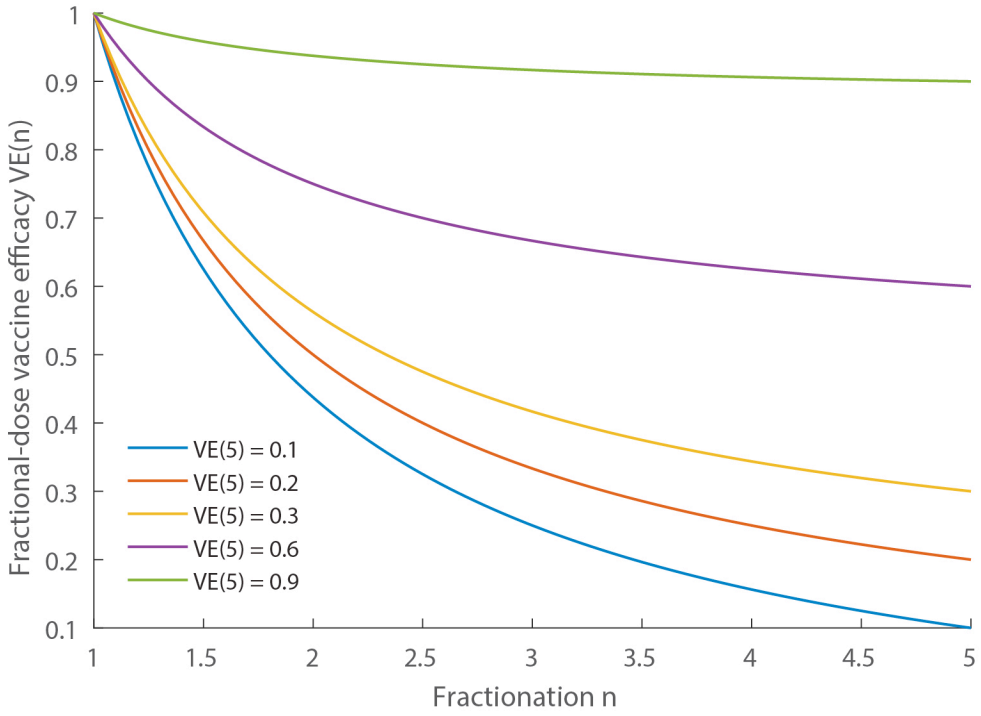

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587 **Appendix Figure 1. The dose response relationship assumed in the model with *VE*(1) = 1.**

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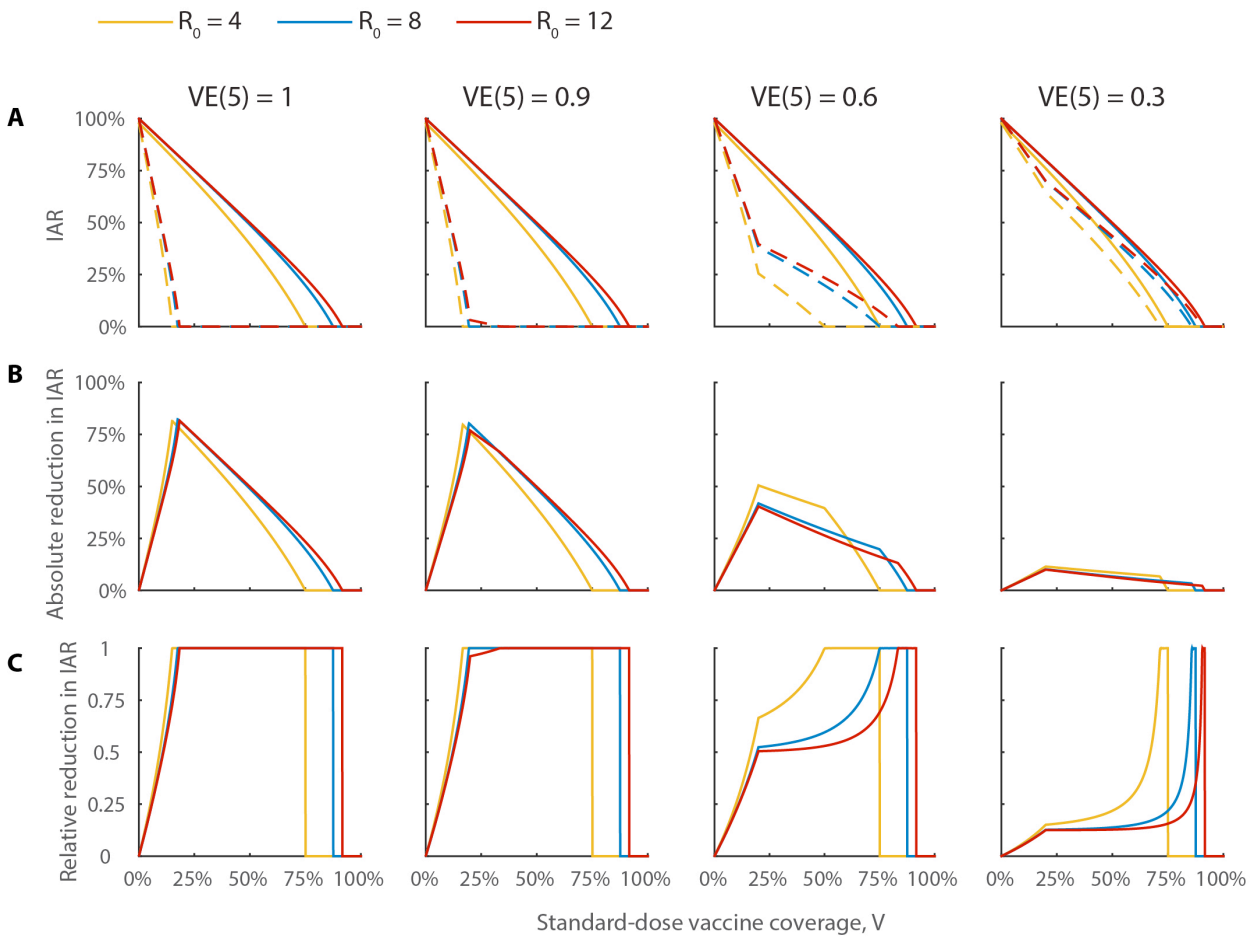
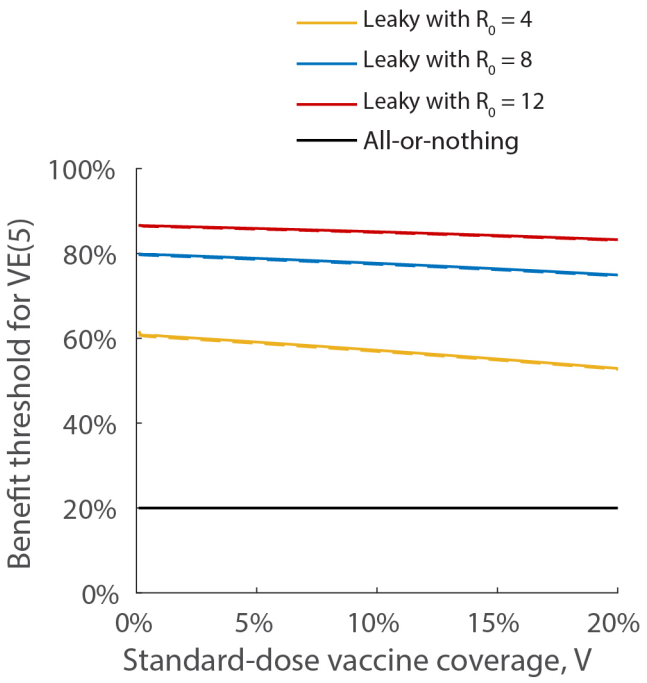


Appendix Figure 2. Repeating the calculations in Figure 2 using a 2-age-group model in which those 20 or older were 1.22 times more likely to be bitten by mosquitos compared to those under age 20. The results are essentially the same as that in Figure 2.



Appendix Figure 3. Repeating the calculations in Figure 3 using a 2-age-group model in which those 20 or older were 1.22 times more likely to be bitten by mosquitos compared to those under age 20. The solid and dashed curves show the results without and with age stratification, respectively.