

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

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19 **Background**

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

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28 **Methods**

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

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36 **Findings**

37 The effective reproductive number early in the outbreak ranged from approximately 5.2 to 7.1
38 transmission events per infectious individual. Intuition dictates, and we confirm with modeling
39 analysis, that five-fold fractional-doses can dramatically reduce the final epidemic size. If
40 vaccine efficacy is all-or-nothing, as we expect, the conclusion holds that n -fold fractionation is
41 beneficial as long as the efficacy is greater than $1/n$. We quantify how the threshold becomes
42 more stringent if fractional vaccines instead provide partial protection to every recipient (i.e.
43 “leaky” vaccine action).

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46 **Interpretation**

47 We conclude that dose fractionation could be a very effective strategy for reducing infection
48 attack rate in populations with a large margin of error in case fractional-dose efficacy turns out
49 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

93 case the number of infections could be significantly reduced by the indirect effect of large-scale
94 vaccination.¹² The lower the transmissibility, the larger the number of infections that can be
95 averted by indirect protection, as has been illustrated by the previous study of dose-
96 fractionation for pre-pandemic influenza vaccines.⁶ The importance of herd immunity for YF
97 vaccination is unknown because transmissibility of YF in urban settings has so far been poorly
98 characterized due to limited data.

99 To strengthen the evidence base for the public health impact of dose-fractionation of YF
100 vaccines, we use simple mathematical models to assess the potential reduction in infection
101 attack rate (IAR, defined as the proportion of population infected over the course of an
102 epidemic) conferred by five-fold dose-fractionation under different epidemic scenarios and
103 reductions in vaccine efficacy. We first estimate the transmissibility of YF during the recent
104 Angola outbreak in order to parameterize realistic epidemic scenarios. We then show that even
105 if vaccine efficacy for five-fold fractional-dose vaccination were considerably lower, higher
106 vaccine coverage could achieve significant reduction in IAR despite lower individual-level
107 efficacy, with the break-even point being 20% efficacy under the assumption that reduced
108 efficacy represents a mix of complete efficacy in some individuals and failure in others (“all-or-
109 nothing”), but higher if vaccines are partially effective in all individuals (“leaky”). Next, given the
110 lack of comparative immunogenicity data for fractional-dose YF vaccination in children, we
111 consider the results of a strategy that provides standard-dose vaccines to children and
112 fractional-dose vaccines to adults. We find that all dose-sparing strategies considered could
113 provide significant benefit epidemiologically, and that the best policy will be determined by
114 balancing logistical and regulatory considerations against the extent of epidemiologic benefit.

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118 METHODS

119 Estimating the epidemiologic parameters for YF

120 To parameterize realistic epidemic scenarios for our analysis, we estimate the reproductive
121 number of YF over the course of the Angola outbreak and use the estimates during the early
122 epidemic stages (before large-scale vaccination affected transmission) as the range of basic
123 reproductive number for future outbreaks in other populations. To this end, we use the
124 Wallinga and Teunis method¹³ to estimate the reproductive number of YF from the daily
125 number of confirmed YF cases recorded in the 17 April 2016 WHO Angola Situation Report,¹⁴
126 assuming that all cases were attributed to local transmission (i.e. no importation of cases).
127 When estimating the extrinsic incubation period, we assume that the average temperature in
128 Angola was 28 degrees Celsius during the outbreak. To estimate the serial interval distribution,
129 we make the following assumptions: (i) the extrinsic incubation period follows the Weibull
130 distribution estimated by ref.¹⁵ which has mean 12.7 days at 28 degrees Celsius; (ii) the
131 intrinsic incubation period follows the lognormal distribution estimated by ref.¹⁵ which has
132 mean 4.6 days; (iii) the infectious period in human is exponentially distributed with mean 4
133 days;¹⁶ (iv) the mosquito lifespan is exponentially distributed with mean 7 to 14 days.¹⁷ We
134 estimate the initial reproductive number of the YF outbreak in Angola as the average
135 reproductive number among all cases who developed symptoms one serial interval before
136 vaccination campaign began to affect disease transmission (see Figure 1).

137 Dose-response for fractional-dose vaccines

138 Let S_0 be the proportion of population susceptible just before the vaccination campaign begins
139 and V be the vaccine coverage achievable with standard-dose vaccines. Suppose each
140 standard-dose vaccine can be fractionated into n , n -fold fractional-dose vaccines (i.e. each of
141 which contains $1/n$ -th the amount of the antigen in a standard-dose vaccine) with vaccine
142 efficacy $VE(n)$. That is, the vaccine efficacy of standard-dose vaccines is $VE(1)$ which was
143 assumed to be 1. Given V , the highest fractionation sensible is $n_{\max} = S_0/V$ if the susceptible
144 population can be identified for targeted vaccination and $n_{\max} = 1/V$ otherwise, i.e. the
145 fractionation n must lie between 1 and n_{\max} . To avoid overstating the benefit of dose-
146 fractionation, we assume that vaccine efficacy of n -fold fractional-dose vaccines for n between
147 1 and 5 increases linearly with the amount of antigen in the vaccines (see appendix for more
148 details). Potential increases in vaccine wastage during dose-sparing would be mostly due to
149 unused, reconstituted vaccines¹⁸ or increased vaccine failure due to inexperience with
150 intradermal administration among vaccinators. In the setting of mass vaccination campaigns,
151 wastage due to unused vaccine doses will likely to be negligible because vaccination sessions
152 will be large. Increased vaccine failure is effectively the same as reduced vaccine efficacy if
153 vaccine action is all-or-nothing (as we have assumed in the main text). As such, for simplicity,
154 we do not explicitly model wastage.

155 Infection attack rate

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

158 fractionation. We calculate IAR using the classical final size approach which is exact for directly
159 transmitted SIR-type diseases¹⁹ but only an approximation for vector-borne diseases.²⁰
160 Nonetheless, this approximation is excellent over realistic parameter ranges because only a
161 very small proportion of mosquitoes are infected with YF virus even during epidemics
162 (necessitating pooled testing).²¹ See appendix for the mathematical details.

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

167 **Vaccine action**

168 We assume that vaccine action is all-or-nothing, i.e. n -fold fractional-dose vaccines provide
169 100% protection against infection in a proportion $VE(n)$ of vaccinees and no protection in the
170 remainder. In this case, n -fold dose fractionation results in lower IAR if and only if the vaccine
171 efficacy of n -fold fractional-dose vaccines are at least $1/n$ times that of standard-dose vaccines,
172 i.e. $VE(n) > VE(1) / n$ (see appendix for details). We term this the benefit threshold for dose-
173 fractionation. We also consider the alternative case in which vaccine action is leaky, i.e. n -fold
174 fractional-dose vaccines reduce the hazard of infection (the probability of disease transmission
175 per mosquito bite) of each vaccinee by a proportion $VE(n)$.^{22,23} Compared to all-or-nothing
176 vaccines, leaky vaccines have substantially higher benefit thresholds, especially when
177 transmissibility is high (see Results). However, we postulate that vaccine action is much more
178 likely to be all-or-nothing than leaky (see Discussion). As such, we present our main results in
179 the context of all-or-nothing vaccine action.

180 **Dose-sparing strategies**

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

- 182 1. *Random vaccination*. Each individual in the population has the same probability of
183 receiving vaccination regardless of their susceptibility. That is, the susceptible and
184 immune population are indiscernible, so targeted vaccination is not possible. If
185 susceptible individuals can be identified, then targeted vaccination has the same
186 epidemiologic outcome as random vaccination with vaccine coverage V / S_0 .
- 187 2. *Standard-dose vaccination of children, fractional-dose vaccination of adults*. We assume
188 that children have vaccine priority. That is, all children receive standard-dose vaccines
189 before adults begin to receive fractional-dose vaccines. Let p be the proportion of
190 adults in the population. For a given standard-dose vaccine coverage V , the proportion
191 of children vaccinated is $V_{children} = \min(V, 1 - p)$. If the stockpile is large enough to
192 vaccinate all children (i.e. $V > 1 - p$), then adults receive n -fold fractional-dose
193 vaccination where $n = \min(5, p / (V - 1 + p))$. The proportion of adults vaccinated is
194 $V_{adults} = 1$ if $n < 5$ and $V_{adults} = 5(V - 1 + p) / p$ otherwise. Given the vector-borne nature of
195 yellow fever we assume that transmission between children and adults is well-mixed.

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

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

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204 **RESULTS**

205 **Reproductive number of yellow fever in Angola.** Figure 1 shows that the initial reproductive
206 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
207 lifespan was 7 and 14 days, respectively. While these estimates may reflect partial immunity
208 due to prior vaccination or exposure among some of the population, we assume that the
209 possible basic reproductive number (R_0) in a future outbreak in another population would range
210 between 4 and 12 due to varying vector ecology and levels of preexisting immunity in the
211 population. In principle, disease transmission can be halted if the effective vaccine coverage
212 (defined as vaccine efficacy times vaccine coverage) exceeds the herd immunity threshold $1 -$
213 $1/R_0$.

214 **Random vaccination.** Figure 2A shows the IAR under standard-dose and fractional-dose
215 vaccination as a function of standard-dose vaccine coverage V given varying levels of
216 transmission and five-fold fractionation vaccine efficacy. Figures 2B-C show the corresponding
217 absolute and relative reduction in IAR when vaccine action is all-or-nothing and confirm our
218 earlier claim that fractional-dose vaccination reduces IAR when $VE(5) > VE(1) / n = 0.2$.
219 Fractional-dose vaccination substantially reduces IAR if $V > 10\%$ and such reduction only
220 diminishes to insignificant levels when V is close to the herd immunity threshold $(1 - 1/R_0) \times 100\%$
221 (e.g. 75% and 88% for $R_0 = 4$ and 8, respectively). In short, dose-fractionation reduces IAR when
222 (i) the standard-dose vaccine supply is insufficient to halt disease transmission and (ii)
223 fractional-dose vaccine efficacy is above 20%.

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

230 A recent study suggested that the mosquito biting rate for individuals aged 20 or above is 1.22
231 times higher than those age under 20.²⁴ We performed a sensitivity analysis to show that our
232 results are unaffected by such heterogeneity. See “Heterogeneity in biting rates” in the
233 appendix for details.

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

247

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 be 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.

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

294 We have used five-fold fractionation as an example because it is the strategy with the best
295 evidence base of equal immunogenicity. However, some data suggest that more than five-fold
296 fractionation could be equally immunogenic, and of course the benefits of fractionation would
297 be greater if more than five-fold fractionation were logistically possible and comparably
298 efficacious.

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

308 Our simple model has several limitations. We assume homogeneous mixing of the population
309 (reasonable at least locally for a vector-borne disease) and neglect preexisting immunity in our
310 main results, though the Methods show how our calculations could be modified to consider
311 preexisting immunity. The purpose is to provide basic calculations for the most at-risk
312 populations, those with little preexisting immunity. We also fix a particular value of R_0 for each
313 calculation, and assume this value is maintained until the epidemic has swept through a
314 population. In reality, R_0 will vary seasonally as vector abundance, extrinsic incubation period,
315 and other factors vary. The existence of a high-transmission season might enhance the benefits
316 of fractional-dose vaccination. Most importantly, there will be a premium on achieving high
317 vaccine coverage before the peak of transmission to maximally impact transmission, and this
318 will be limited by supply constraints that could be partially relieved by fractionation.

319 We conclude that dose fractionation could be a very effective strategy for improving coverage
320 of YF vaccines and reducing infection attack rate in populations -- possibly by a large absolute
321 and relative margin -- if high to moderate efficacy is maintained by reduced-dose formulations.
322 For vaccines whose standard formulations exceed WHO minimum concentration of viral
323 particles,¹⁰ this dose-fractionation could be accomplished without changing the WHO
324 recommendations. Even if the efficacy of fractionated doses were substantially lower than
325 expected, increasing coverage by a factor greater than the reduction in efficacy would still be
326 predicted to reduce the population-wide infection attack rate. Substantial benefits could also
327 be achieved if fractional doses were given only to adults while providing standard-dose vaccines
328 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, effectiveness¹⁸
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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411 **Contributors**

412 JTW, CMP, and ML reviewed the literature and designed the study. JTW and ML developed the
413 mathematical model. JTW ran the mathematical model. JTW, CMP, GML, and ML interpreted
414 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
418 and Affinivax, and research funding through his institution from Pfizer and PATH Vaccine
419 Solutions, all unrelated to yellow fever. JTW, CMP, and GML have no conflicts of interest.

420

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427 The content is solely the responsibility of the authors and does not necessarily represent the
428 official views of the National Institute Of General Medical Sciences or the National Institutes of
429 Health.

430

431 **Panel: Research in context**

432

433 **Systematic review**

434 We searched PubMed and Google Scholar on June 10, 2016, with the terms “yellow fever” and
435 “vaccine” or “dose sparing”. We did not find any reports of randomized trials of yellow fever
436 (YF) vaccine efficacy, at full or lower doses. Three relatively recent studies suggest similar
437 immunological responses at five-fold, or more, fractionation as compared to the current dose
438 antigen levels.^{8,9,26} While several recent perspective articles propose the dose-sparing strategy
439 in response to the current shortage,²⁻⁴ to our knowledge this is the first study to test the
440 intuition behind the strategy and assess the implications of uncertainties surrounding
441 fractional-dose YF vaccine efficacy and mode of action (e.g. “all-or-nothing” and “leaky”).

442

443 **Added value of the study**

444 Our study provides a formal confirmation of intuition that dose-sparing can drastically reduce
445 the number of YF cases if high vaccine efficacy is retained. We show how the benefits of dose
446 fractionation are influenced by the transmission intensity of the setting, the target coverage,
447 and the fractional-dose vaccine efficacy and mode of action.

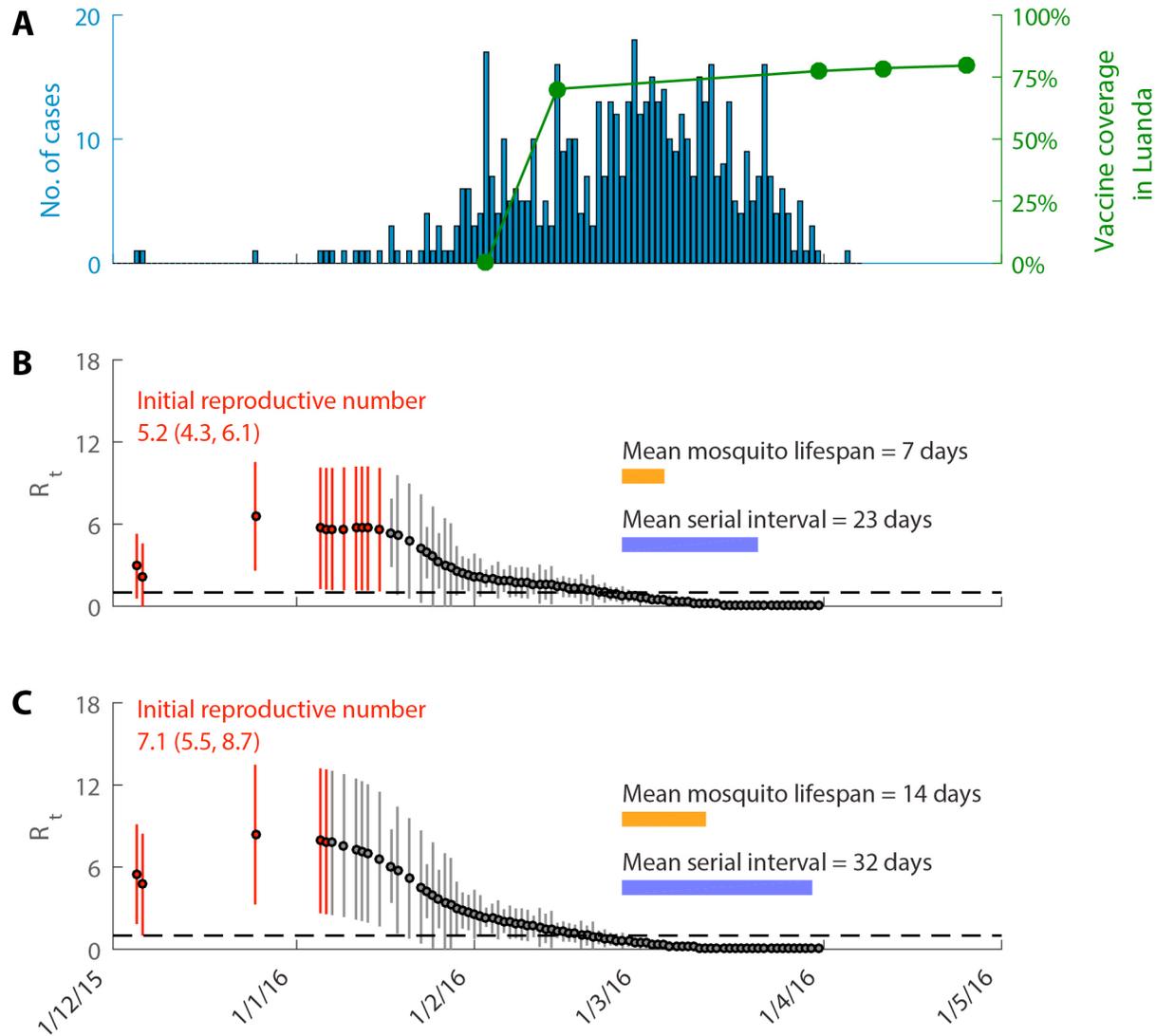
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449 **Interpretation**

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

452

453

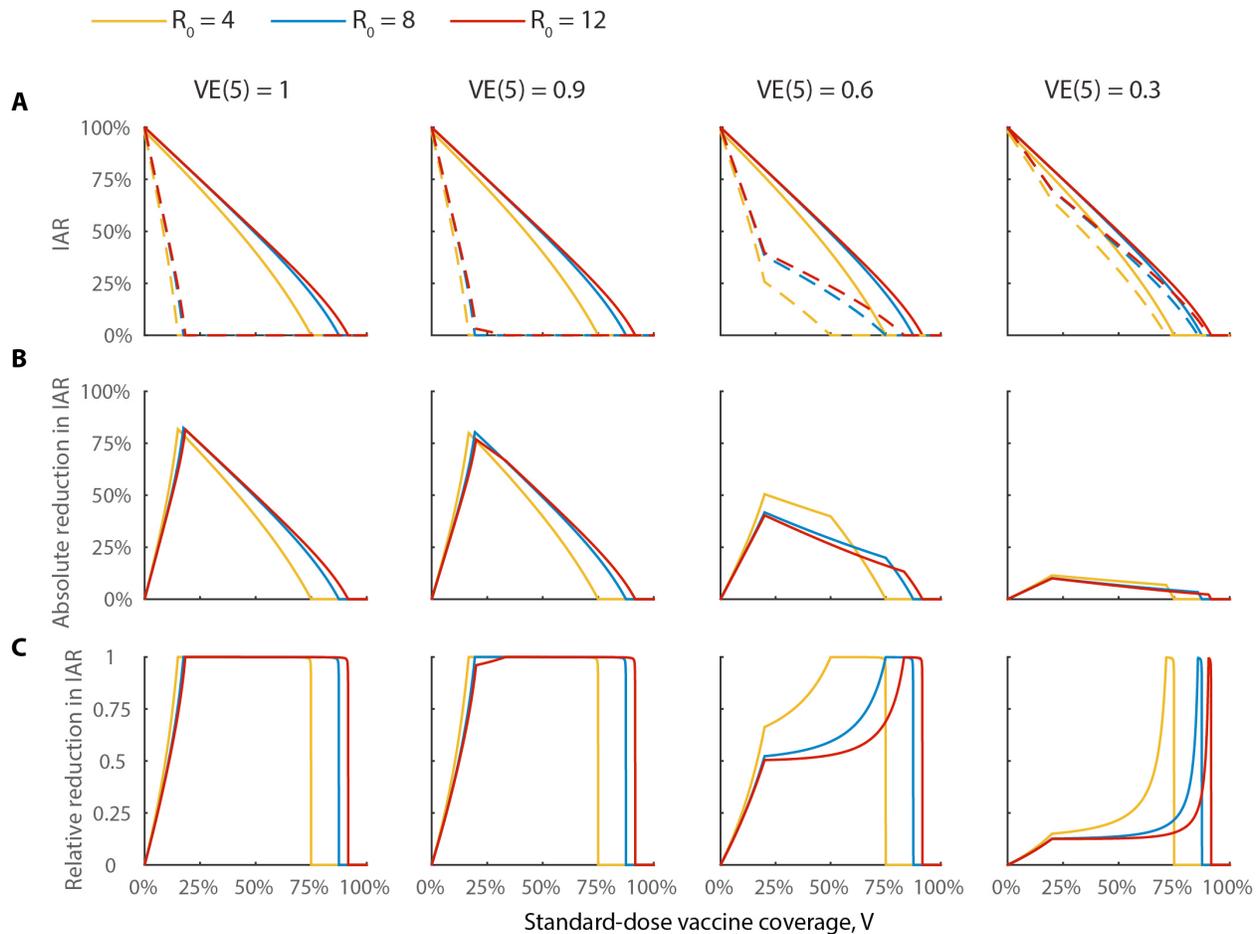


454

455 **Figure 1: Estimates of reproductive number over the course of the Angola epidemic. A**
456 Epidemic curve of confirmed cases by dates of symptom onset in Angola and vaccine coverage
457 in Luanda province achieved by the reactive YF vaccination campaign that started on 2 February
458 2016.²⁷ The first cases of this YF outbreak were identified in Luanda province which accounted
459 for 90 of the 121 cases confirmed in Angola up to 26 February 2016. **B-C** Estimates of the daily
460 reproductive number (R_t) assuming that the mean mosquito lifespan was 7 and 14 days,
461 respectively. The red data points correspond to the cases that were used to estimate the initial
462 reproductive number. These cases had symptom onset one mean serial interval before the
463 vaccination campaign began to affect disease transmission (which was assumed to be 7 days
464 after the start of the campaign to account for the time it takes for adaptive immunity to
465 develop). The orange and purple horizontal bars indicate the length of the mean mosquito
466 lifespan and serial interval on the scale of the x-axis, respectively.

467

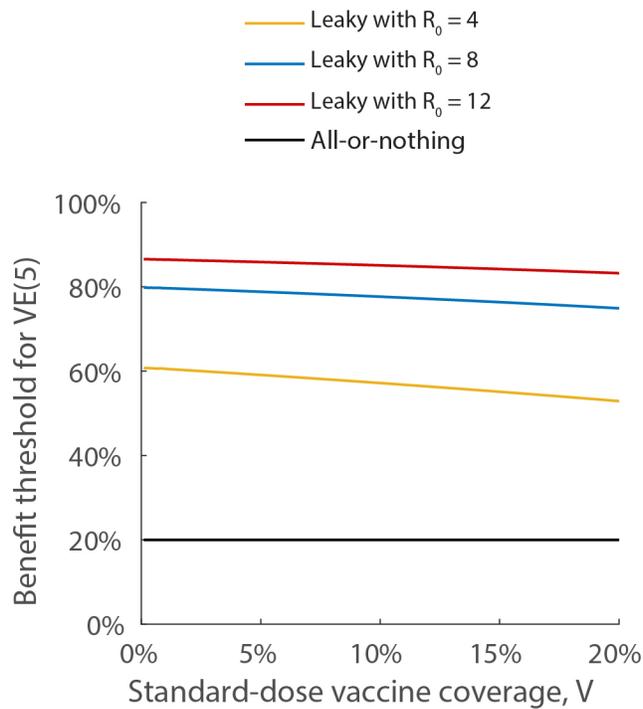
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469

470 **Figure 2: The impact of five-fold fractional-dose vaccination with different vaccine efficacy**
 471 **and reproductive numbers.** Vaccine action is assumed to be all-or-nothing and standard-dose
 472 vaccine efficacy is assumed to be 1. If the standard-dose vaccine coverage V exceeds 20%, then
 473 everyone in the population can be vaccinated under five-fold fractionated-dose vaccination, in
 474 which case the fractionation would only be $n = 1/V$. **A** Infection attack rate (IAR) as a function of
 475 standard-dose vaccine coverage, V . The solid and dashed curves correspond to standard-dose
 476 and five-fold fractional-dose vaccination, respectively. IAR is reduced to 0 when the effective
 477 vaccine coverage (V for solid curves, $VE(n) \times nV$ for dashed curves) reaches the herd immunity
 478 threshold $(1-1/R_0) \times 100\%$. **B** Absolute reduction in IAR. IAR reduction is maximum when the
 479 five-fold fractional-dose effective vaccine coverage $VE(5) \times 5V$ reaches the herd immunity
 480 threshold $(1-1/R_0) \times 100\%$. As V increases from 0, a kink appears when the herd-immunity
 481 threshold is attained or everyone is vaccinated under five-fold fractional-dose vaccination (i.e.,
 482 $V = 20\%$). If five-fold fractional-dose vaccination at 100% coverage cannot attain the herd
 483 immunity threshold (because of low fractional-dose vaccine efficacy), then a second kink
 484 appears when V is large enough such that fractional-dose vaccination attains herd-immunity

485 threshold due to the increase in $VE(n)$ resulting from lower fractionation factors (namely $n =$
486 $1/V$). **C** Relative reduction in IAR.

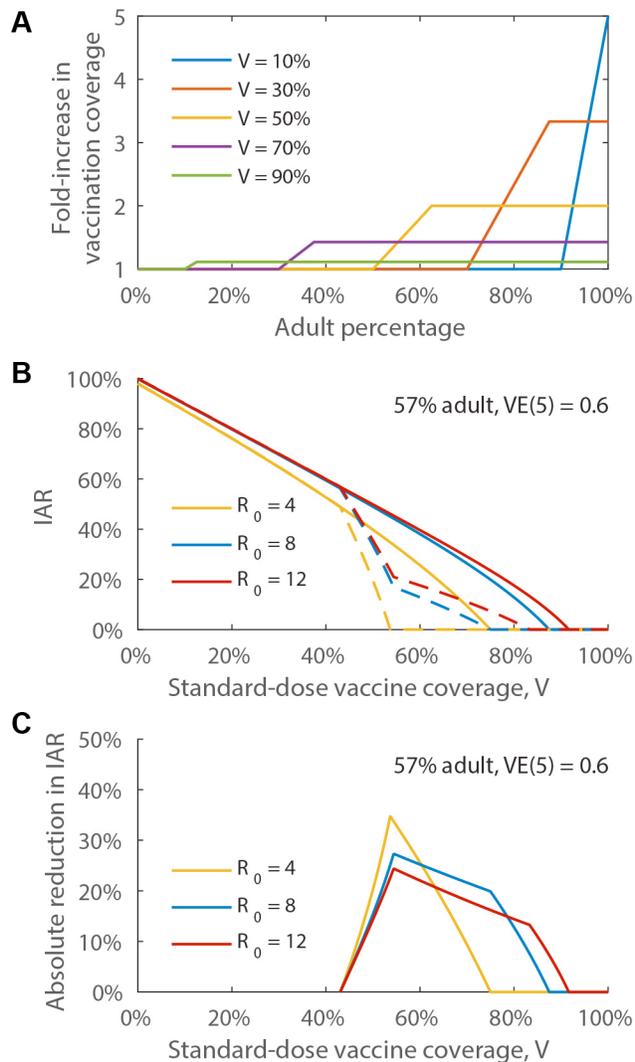


487

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

494

495



496

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

502

503 **Appendix**

504 **Estimation of the effective reproductive number for YF in Angola**

505 We use the Wallinga and Teunis method¹³ to estimate the reproductive number over the
 506 course of the YF outbreak in Angola from the daily number of confirmed cases recorded in the
 507 17 April 2016 WHO Angola Situation Report.¹⁴ We assume that all cases were attributed by
 508 local transmission, i.e. no importation of cases. Let t_i be the date of symptom onset for case i .
 509 The relative likelihood that case i has been infected by case j is

510
$$p_{ij} = \frac{w(t_j - t_i)}{\sum_{k \neq j} w(t_j - t_k)}$$

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

517
$$E[R_t] = \frac{1}{n_t} \sum_{j:t_j=t} \sum_i p_{ij}$$

518
$$s(R_t) = \frac{1}{n_t} \sqrt{\sum_i \left(\sum_{j:t_j=t} p_{ij}(1-p_{ij}) - \sum_{j,k:t_j=t_k=t, j \neq k} p_{ij}p_{ik} \right)}$$

519 Assuming that R_t is normally distributed, the approximate $(1-\alpha) \times 100\%$ confidence interval is
 520 $E[R_t] \pm z_{1-\alpha/2} s(R_t)$.

521

522 **Estimation of the serial interval distribution for YF**

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

528
$$f(a) = \frac{h(a)}{\int_0^\infty h(u) du}$$

529 where

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

531 In this calculation, we assume that the infectious period in humans is exponentially distributed
 532 with mean 4 days,²⁸ and mosquito lifespan is exponentially distributed with mean varying over
 533 1-2 weeks (<http://www.dengue.gov.sg/subject.asp?id=12>; ¹⁷). We assume that the extrinsic
 534 incubation period follows the Weibull distribution with parameters $\nu = 1.7$ and
 535 $\lambda_t = \exp(-7.6 + 0.11T)$ where T is the temperature (28 degrees Celsius) as estimated by ref. ¹⁵
 536 We assume that the intrinsic incubation period follows the lognormal distribution with
 537 parameters $\mu = 1.46$ and $\tau = 8.1$ as estimated by ref. ¹⁵.

538 Dose-response relationship

539 We assume that vaccine efficacy of n-fold fractional-dose vaccines for n between 1 and 5
 540 increases linearly with the amount of antigen in the vaccines which is proportional to $1/n$. In
 541 general, if vaccine efficacy of n-fold fractional-dose vaccines for n between n_1 and n_2
 542 increases linearly with the amount of antigen in the vaccines, then

$$543 \quad VE(n) = VE(n_2) + \frac{1/n - 1/n_2}{1/n_1 - 1/n_2} (VE(n_1) - VE(n_2)). \text{ We make this assumption to avoid}$$

544 overestimating the benefit of dose-fractionation because:

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

552 Appendix Figure 1 illustrates this dose-response relationship for different values of $VE(5)$ with
 553 $VE(1) = 1$.

554 Infection attack rate

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

$$558 \quad IAR(n) = S_0 (1 - VE(n)nV) [1 - \exp(-R_0 \cdot (I_0 + IAR(n)))]$$

559 where R_0 is the basic reproductive number, S_0 and I_0 are the initial proportion of population
 560 that are susceptible and infectious. As such, dose-fractionation reduces IAR if and only if
 561 $VE(n) > VE(1)/n$. If vaccine action is leaky, then $IAR(n)$ is obtained by solving the equation

$$562 \quad IAR(n) = S_0(1-Vn) \left[1 - \exp(-R_0 \cdot (I_0 + IAR(n))) \right] \\ + S_0Vn \left[1 - \exp(-(1-VE(n))R_0 \cdot (I_0 + IAR(n))) \right]$$

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

$$564 \quad VE(n) > 1 + \frac{\ln(1-Z)}{R_0(I_0 + IAR(1))} \quad \text{where } Z = \frac{IAR(1)}{S_0Vn} - \left(\frac{1}{Vn} - 1 \right) \left[1 - \exp(-R_0 \cdot (I_0 + IAR(1))) \right]$$

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

$$566 \quad VE(n) > 1 - \frac{\ln \left(1 - (1-1/n) \frac{IAR(1)}{S_0(1-V)} \right)}{\ln \left(1 - \frac{IAR(1)}{S_0(1-V)} \right)}$$

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

$$574 \quad IAR_i(n_i) = S_{0,i} (1 - V_in_i VE(n_i)) \left[1 - \exp \left(- \sum_j R_0^{j,i} (I_{0,j} + IAR_j(n_j)) \right) \right]$$

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

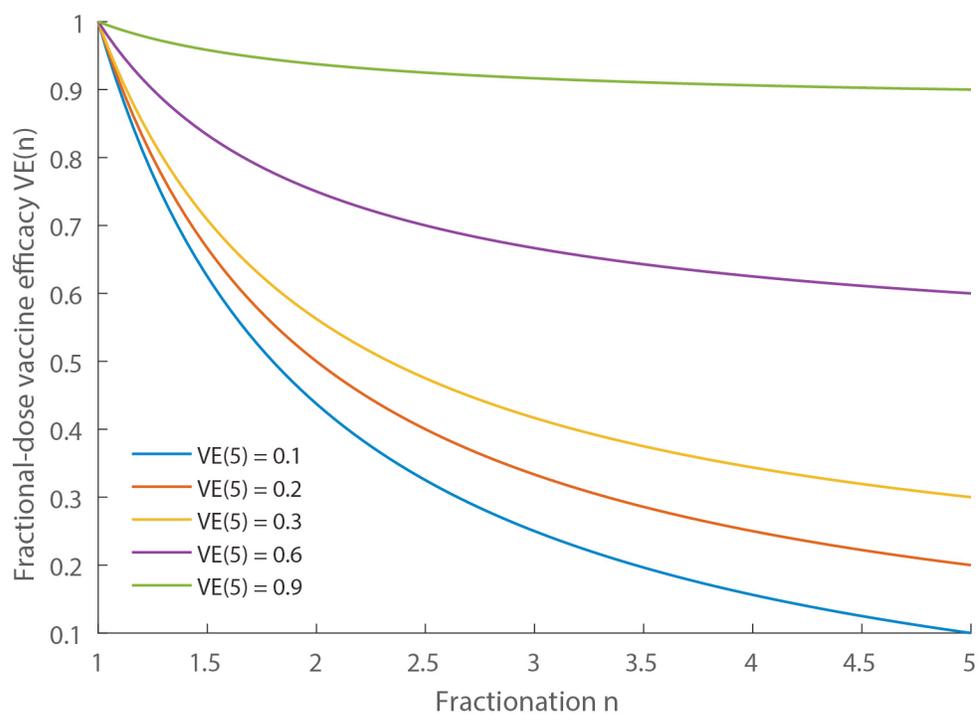
$$576 \quad IAR_i(n_i) = S_{0,i} (1 - n_i V_i) \left[1 - \exp \left(- \sum_j R_0^{j,i} (I_{0,j} + IAR_j(n_j)) \right) \right] \\ + S_{0,i} n_i V_i \left[1 - \exp \left(-(1-VE(n_i)) \sum_j R_0^{j,i} (I_{0,j} + IAR_j(n_j)) \right) \right]$$

577

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.

585

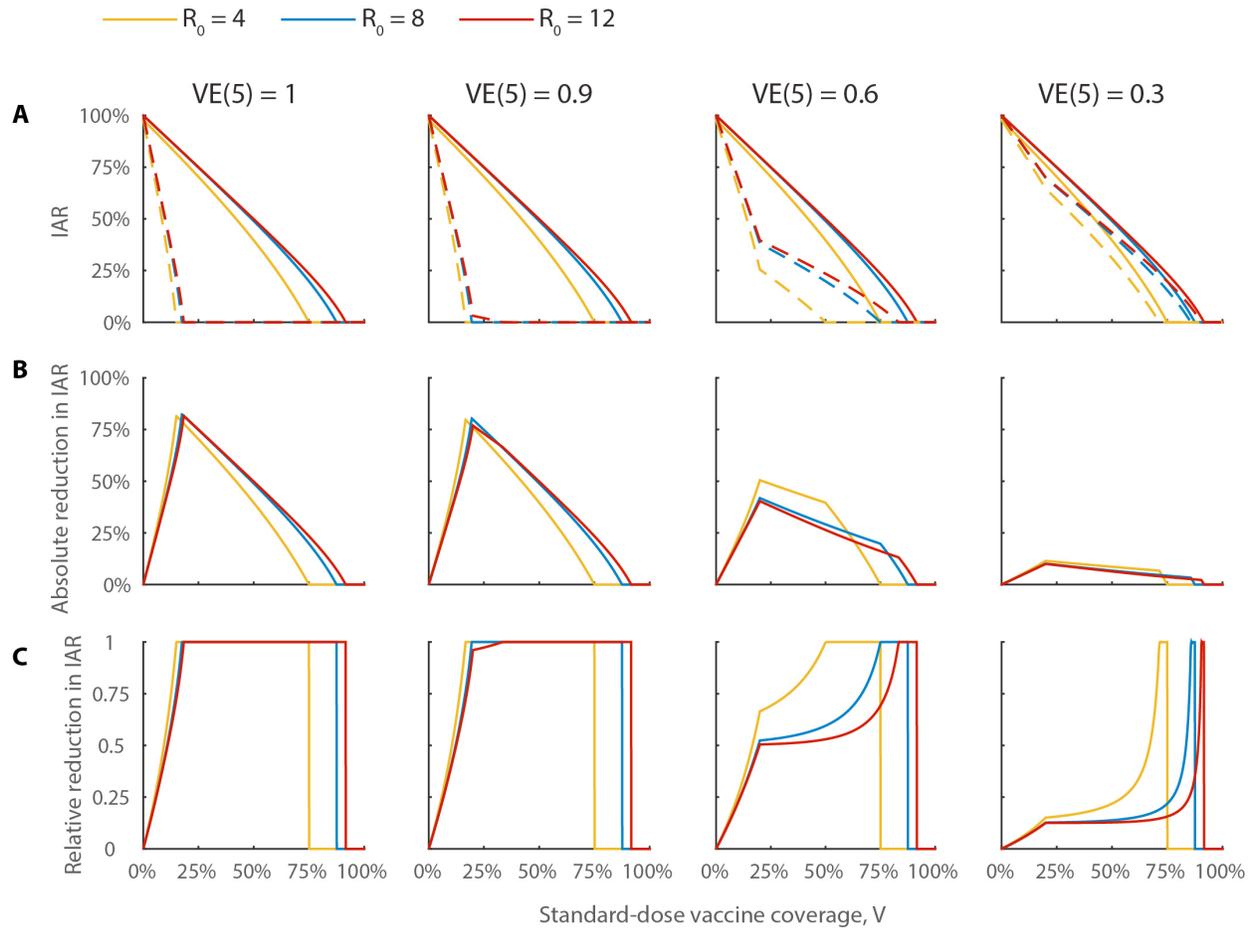


586

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

588

589



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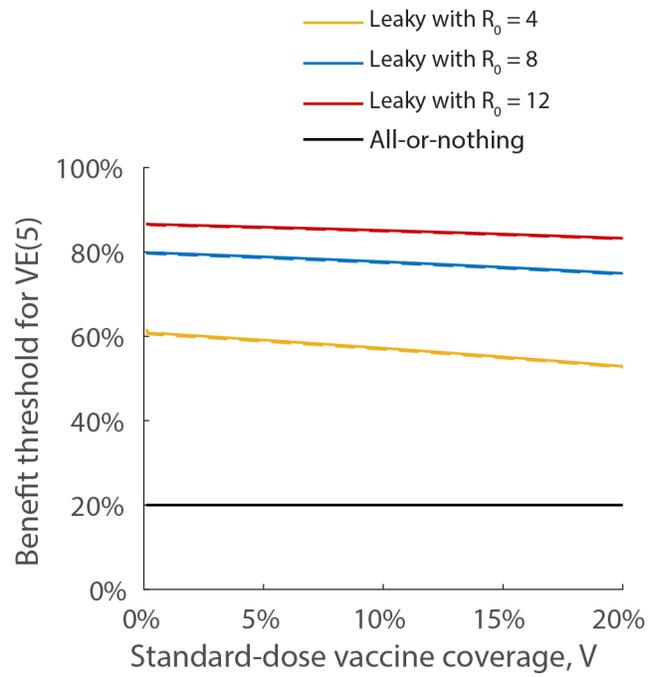
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592 **Appendix Figure 2. Repeating the calculations in Figure 2 using a 2-age-group model in which those 20**

593 **or older were 1.22 times more likely to be bitten by mosquitoes compared to those under age 20. The**

594 **results are essentially the same as that in Figure 2.**

595



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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.