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Force of infection: a determinant of vaccine efficacy?

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Vaccine efficacy (VE) can vary in different settings. Of the many proposed setting-dependent determinants of VE, force of infection (FoI) stands out as one of the most direct, proximate, and actionable. As highlighted by the COVID-19 pandemic, modifying FoI through non-pharmaceutical interventions (NPIs) use can significantly contribute to controlling transmission and reducing disease incidence and severity absent highly effective pharmaceutical interventions, such as vaccines. Given that NPIs reduce the FoI, the question arises as to if and to what degree FoI, and by extension NPIs, can modify VE, and more practically, as vaccines become available for a pathogen, whether and which NPIs should continue to be used in conjunction with vaccines to optimize controlling transmission and reducing disease incidence and severity.

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INTRODUCTION

Lower apparent vaccine efficacy (VE) in low resource settings, when compared to VE observed in high resource settings, has been reported for several pathogens, most notably poliovirus, typhoid, and rotavirus[1–5]. Observed VE also varied when evaluating a malaria vaccine candidate in different parasite transmission settings[6–8]. Numerous economic, social, and biological factors have been proposed to explain these setting-dependent variations in VE[3,9–11]. Many, if not most, of the proposed economic and social determinants of VE, such as, country income status, living conditions, access to healthcare, appear to act indirectly and non-specifically on VE; whereas many but not all biological factors, such as co-infections, malnutrition, and enteropathy, presumably act directly and proximally on VE. More practically, identification of direct and proximal determinants of setting-dependent VE that hold the promise of actionable intervention(s) seem a most urgent need in efforts to enhance and/or sustain VE.

The COVID-19 pandemic has highlighted the contribution of non-pharmaceutical interventions (NPIs) in controlling transmission and reducing disease incidence and severity[12], particularly in the absence of highly effective pharmaceutical interventions, such as vaccines. NPIs also contribute to controlling other major human diseases, including use of condoms for HIV/AIDS[13], bed nets for malaria[14], and hand washing for diarrhea[15]. By reducing the number of (susceptible) individuals effectively contacted by each (infected) person, e.g., through physical barriers, distancing, and masking, NPIs reduce λ, the force of infection (FoI) (see Box 1, Glossary of Key Terms). As vaccines become available for a pathogen, the question arises as to if and which NPIs should continue to be used, if not prioritized[16]. This then begs the broader use-inspired scientific question, as raised previously[8]: after optimizing the vaccine immunogen, formulation, dose level, and regimen, what remaining determinants of VE are amenable to intervention? More specifically, given the role of NPIs in reducing the FoI, if and to what degree is FoI, and by extension NPIs, a determinant of VE?

Interrogating the potential relationship of FoI and setting-dependent VE

A two-step approach was taken to interrogate the potential relationship between FoI and VE. The first explored three mathematical scenarios of VE as a function of various FoI settings. The second followed up on the decades-old observations of lower apparent efficacy of oral poliovirus[1] and oral typhoid vaccines[5] in low resource settings when compared to high resource settings. This empiric interrogation assessed the correlation between the incidence of disease in the placebo population (as a surrogate of FoI in the study population) and the observed VE in different geographical settings. Recent Phase 3 studies of malaria and rotavirus vaccine candidates across a number of settings, including low and high resource settings[6,17], provided data for empirically assessing if and how FoI might be a determinant of VE.

Both the thought experiment of setting-dependent VE of a hypothetical vaccine and the retrospective analyses of rotavirus and malaria Phase 3 efficacy results make a multitude of assumptions that limit the robustness and soundness of any conclusions. For simplicity, factors previously shown or hypothesized to influence transmission, susceptibility, VE, and/or FoI, such as, country income status, age, underlying medical conditions, co-infections, access to healthcare, seasonality, NPI use, spreading events, and strain differences across different settings, and pre-exposure effect were excluded from consideration in both the hypothetical VE or observed VE analyses.

Given these significant limitations in the analyses, the primary goal of the present study was not to provide a definitive answer to the questions of if and to what degree FoI determines VE in different settings. Rather the goal of these analyses was to continue to raise the awareness of the potential impact of FoI on VE[8,18], and to prompt prospective studies designed to assess if and how NPIs might reduce FoI and enhance VE when vaccines are introduced and scaled up. Ultimately well-designed studies that directly evaluate the potential relationship of FoI and setting-dependent VE will provide the evidence needed for well-informed policy recommendations on the continued use or not of NPIs during vaccine introduction and scale-up.

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Box 1 Glossary of key terms

Force of infection: Rate at which susceptible individuals in a population acquire an infectious disease in that population, per unit time. It is also known as the incidence rate or hazard rate[36].

$$\lambda_t = \frac{c_e I_t}{N_t} \quad (1)$$

(see equation 2.13, ref. [36]) where λ_t is the force of infection at time t, c_e is the number of individuals effectively contacted by each person per unit time, I_t is the number of infected in the population at time t, and N_t is the number in the population at time t.

Efficacy: The direct protection provided by vaccination against a defined clinical endpoint; it excludes any indirect (herd) effect[36]. Vaccine efficacy reflects the relative reduction between the vaccinated and control groups for one or more specific clinical endpoints. Calculations of the relative reduction typically use a hazard ratio, a risk ratio, or most simply, as shown below, an incidence ratio[37];

$$\mathrm{VE} = \frac{\mathrm{ARU} - \mathrm{ARV}}{\mathrm{ARU}} \times 100 = 1 - \frac{\frac{I_V}{N_V}}{\frac{I_U}{N_U}} \times 100 \quad (2)$$

(see equations, ref. [38]) where VE is the vaccine efficacy, ARU is the attack rate in the unvaccinated population, ARV is the attack rate in the vaccinated population, I_V is the number of infected in the vaccinated population, N_V number in the vaccinated population, I_U is the number of infected in the unvaccinated population, and N_U is the number in the unvaccinated population.

Herd immunity: The proportion of a population immune to infection or disease[2,36].

Herd immunity threshold: The proportion of the population required to be immune in the population for the infection incidence to reach steady state, i.e., the infection level is neither growing nor declining. To eliminate an infection in the population, the proportion of the population that is immune to infection must exceed this threshold value[36].

Indirect (Herd) effect: The reduction in the rate of infection or disease in the unimmunized portion of a population as a result of immunizing a proportion of the population[2].

Box 2 Vaccine efficacy as a function of force of infection

The following equations define mathematical relationships between vaccine efficacy (VE) and force of infection (FoI) shown in Fig. 1, when the relationship of VE is: (1) independent of FoI ($\mathrm{VE}_{\mathrm{constant}}$); (2) linear to FoI ($\mathrm{VE}_{\mathrm{linear}}$); or (3) logarithmic to FoI ($\mathrm{VE}_{\mathrm{natural\ log}}$):

$$\mathrm{VE}_{\mathrm{constant}} : \mathrm{VE}_S = -0 * \boldsymbol{FoI_S} + \mathrm{VE}_{\mathrm{max}} \quad (3)$$

$$\mathrm{VE}_{\mathrm{linear}} : \mathrm{VE}_S = -\left(\frac{\boldsymbol{FoI_S} - \mathrm{FoI}_{\mathrm{min}}}{\mathrm{FoI}_{\mathrm{max}} - \mathrm{FoI}_{\mathrm{min}}}\right) \times (\mathrm{VE}_{\mathrm{max}} - \mathrm{VE}_{\mathrm{min}}) + \mathrm{VE}_{\mathrm{max}} \quad (4)$$

$$\mathrm{VE}_{\mathrm{natural\ log}} : \mathrm{VE}_S = -\left(\frac{\ln \boldsymbol{FoI_S} - \ln \mathrm{FoI}_{\mathrm{min}}}{\ln \mathrm{FoI}_{\mathrm{max}} - \ln \mathrm{FoI}_{\mathrm{min}}}\right) \times (\mathrm{VE}_{\mathrm{max}} - \mathrm{VE}_{\mathrm{min}}) + \mathrm{VE}_{\mathrm{max}} \quad (5)$$

Where VE_S is the VE in setting S, $\mathrm{VE}_{\mathrm{max}}$ is the highest observed VE, and $\mathrm{VE}_{\mathrm{min}}$ is the lowest observed VE.

And where FoI_S is the FoI in setting S, $\mathrm{FoI}_{\mathrm{min}}$ is the lowest observed FoI, and $\mathrm{FoI}_{\mathrm{max}}$ is the highest observed FoI.

Three scenarios of the potential mathematical consequences of FoI on setting-dependent VE

The potential effects of FoI on the level of VE were explored in three mathematical scenarios: (1) $\mathrm{VE}_{\mathrm{constant}}$, where VE is independent of FoI; (2) $\mathrm{VE}_{\mathrm{linear}}$, where VE decreases linearly as a function of increasing FoI; and, (3) $\mathrm{VE}_{\mathrm{natural\ log}}$, where VE decreases logarithmically as a function of increasing FoI. As noted above, multiple simplifying assumptions were made when considering the mathematical consequences of FoI on VE, including homogeneity in the population with respect to a number of factors, such as, pathogen transmission, host susceptibility to infection and disease (be it genetic or acquired), FoI over time in a specific setting, and protective immunity as a result of vaccination across settings.

With these simplifying assumptions in mind, equations that define the three mathematical scenarios (see Box 2, VE as a function of FoI) are shown graphically in Fig. 1, using the example of a hypothetical vaccine that has a maximum VE of 83% studied under conditions of FoI that vary across two orders of magnitude, from 0.03 to 3.50 infections/person-year. While other more complex mathematical relationships between VE and FoI merit consideration, these three simple equations seemed a reasonable starting point from which to interrogate observed data from Phase 3 VE studies conducted in multiple epidemiological settings.

Empiric evidence of FoI on observed setting-dependent VE

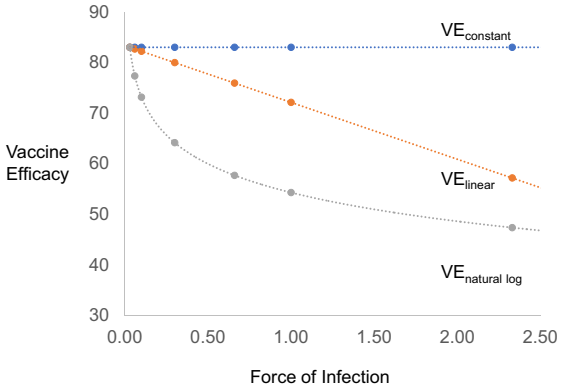
Results from recent placebo-controlled Phase 3 studies of vaccine candidates for two diverse pathogens, *Plasmodium falciparum* and rotavirus, provided a database to determine which, if any, of the three mathematical scenarios best explained any setting-dependent differences in VE. The selection of malaria and diarrhea as clinical endpoints provided an opportunity to analyze FoI and VE for both vector-transmitted and fecal-oral-transmitted pathogens, as well as parenterally and orally administered vaccine candidates, respectively. In addition to the assumptions mentioned above, several additional assumptions noted below facilitated the analyses of these multi-setting VE studies of two pathogens.

First and foremost, the analyses of both pathogens assumed that the intent-to-treat (ITT) incidence of the most sensitive definition of the mildest disease endpoint in the youngest age cohort in the placebo arm best served as an internal Phase 3 study surrogate of λ, the FoI. The validity of this assumption relies upon several other assumptions, including the absence of any significant herd effect (see Box 1, Glossary of Key Terms) on the control from the vaccinated arm of the Phase 3 study. The rationale for making this herd effect assumption, typically also assumed for the control group used in estimating VE in the context of Phase 3 efficacy studies, relies upon: (1) the relatively small proportion of the total population in the study setting enrolled in the vaccinated group in the Phase 3 study; and, (2) the timing of incident disease in the control group relative to eliciting herd immunity and reaching the herd immunity threshold (see Box 1, Glossary of Key Terms) in the study population.

A third key assumption relied upon a comparison of trendlines from the three mathematical scenarios described above to the closest fit trendline of observed VE ($\mathrm{VE}_{\mathrm{observed}}$) as a function of observed FoI ($\mathrm{FoI}_{\mathrm{observed}}$, incidence in the placebo group) in each epidemiologic setting to determine if and how VE varied as a function of FoI. In this regard, because the Phase 3 VE results for both pathogens were known a priori to vary by epidemiologic setting, the posterior probability was low of selecting the $\mathrm{VE}_{\mathrm{constant}}$ mathematical scenario to categorize $\mathrm{VE}_{\mathrm{observed}}$ as a function of $\mathrm{FoI}_{\mathrm{observed}}$. As noted below for each specific analysis, the observed trendline may not necessarily reflect a statistically significant association between $\mathrm{VE}_{\mathrm{observed}}$ and $\mathrm{FoI}_{\mathrm{observed}}$, as assessed by a regression analysis.

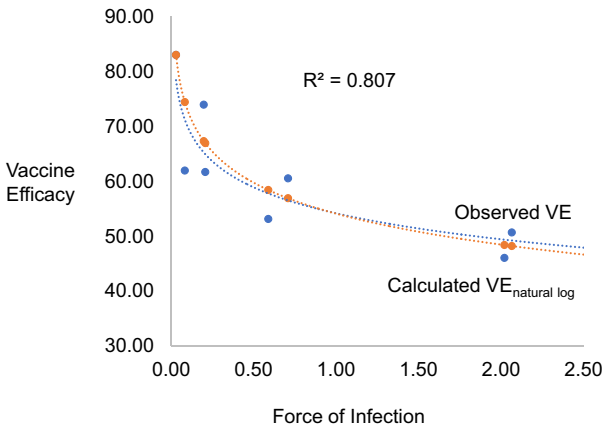
Malaria parasite VE and FoI

A single pivotal Phase 3 VE study (NCT00866619) enrolled 15,459 participants in two age categories (young children aged 5–17 months and infants aged 6–12 weeks at the time of enrollment) across 11 clinical research sites in seven African countries (one site in Burkina Faso, Gabon, Malawi, and Mozambique; two sites in Ghana and Tanzania; and three sites in Kenya). The trial assessed, as a primary aim, VE of a three-dose regimen of $\mathrm{RTS,S/AS01_E}$ against clinical malaria



VE_{max}: 83.0 VE_{min}: 44.0			FoI_{min}: 0.03 FoI_{max}: 3.50
$VE_{constant}$	VE_{linear}	$VE_{natural\ log}$	FoI
83.0	83.0	83.0	0.03
83.0	82.7	77.3	0.06
83.0	82.2	73.1	0.10
83.0	80.0	64.1	0.30
83.0	75.9	57.7	0.66
83.0	72.1	54.3	1.00
83.0	57.1	47.3	2.33
83.0	44.0	44.0	3.50

Fig. 1 Vaccine Efficacy (VE) as a function of force of Infection (FoI) for hypothetical vaccine. Equations that define three mathematical scenarios (see Box 2, Vaccine efficacy as a function of force of infection) are shown graphically, using as an example a hypothetical vaccine with a maximum vaccine efficacy (VE_{max}) of 83.0% and minimum VE (VE_{min}) of 44.0% studied under conditions of force of infection (FoI) that vary across two orders of magnitude, from a minimum FoI (FoI_{min}) 0.03 to a maximum FoI (FoI_{max}) of 3.50 infections/person-year.



VE_{max}: 83.0 VE_{min}: 44.0		FoI_{min}: 0.03 FoI_{max}: 3.46
$VE_{observed}$	$VE_{natural\ log}$	$FoI_{observed}$
83.0	83.0	0.03
62.0	74.4	0.08
74.0	67.3	0.20
61.7	67.0	0.21
53.2	58.4	0.59
60.6	56.9	0.71
46.0	48.4	2.02
50.7	48.2	2.06
44.0	45.1	3.04
49.9	44.0	3.46

$VE_{observed}$ v ln $FoI_{observed}$ Significance F: 0.006

Fig. 2 Vaccine Efficacy (VE) as a function of Force of Infection (FoI) for malaria vaccine. Best fit trendline analysis of observed vaccine efficacy ($VE_{observed}$) as a function of observed force of infection ($FoI_{observed}$) is shown as a logarithmic relationship (blue dotted line) with a R^2 of 0.807. A regression analysis of $VE_{observed}$ as a function of ln $FoI_{observed}$ shown in the embedded table has a Significance F of 0.006. Using the $VE_{natural\ log}$ equation (see Box 2, Vaccine efficacy as a function of force of infection), the observed VE_{max}, VE_{min}, FoI_{max}, FoI_{min}, and $FoI_{observed}$ were used to calculate the $VE_{natural\ log}$ in the embedded table and the calculated $VE_{natural\ log}$ shown graphically (orange dotted line).

over 12 months follow-up[7]. In the per-protocol population of the 5–17 months age category, $VE_{observed}$ was 51.3% (95% CI: 47.5–54.9; *p*-value < .0001) with a $VE_{observed}$ range from 83.0% (95% CI: 37.2–95.4; *p*-value 0.0079) in a low parasite transmission site (Kilifi, Kenya) to 44.0% (95% CI: 36.8–50.3; *p*-value < .0001) in a high parasite transmission site (Nanoro, Burkina Faso) (see Annex 6 Table 23, ref. [19]). As noted above, the intent-to-treat (ITT) incidence of the more sensitive secondary definition of clinical malaria in the control group of infants aged 6–12 weeks at the time of enrollment (see Annex 7 Table 177, ref. [20].) served as the internal Phase 3 study $FoI_{observed}$, the surrogate of λ in the analyses.

The best fit trendline analysis of $VE_{observed}$ as a function of $FoI_{observed}$ revealed a logarithmic relationship (Fig. 2, Observed VE) with an R^2 of 0.807. Regression analysis of $VE_{observed}$ as a function of ln $FoI_{observed}$ revealed a Significance F of 0.006. Using the $VE_{natural\ log}$ equation (Box 2), the observed VE_{max}, VE_{min}, FoI_{max}, FoI_{min}, and the $FoI_{observed}$ from each site generated a logarithmic relationship between the calculated site-specific VE and $FoI_{observed}$ (Fig. 2, Calculated VE). These analyses suggest that malaria parasite FoI functions as a determinant of RTS,S/AS01$_E$ VE.

Rotavirus VE and FoI

Multiple Phase 3 studies of two rotavirus vaccines, RV1 (Rotarix®) and RV5 (RotaTeq®), evaluated VE in diverse epidemiologic settings[17]. In comparison to the analyses conducted for malaria VE, the analyses of rotavirus $VE_{observed}$ as a function of rotavirus $FoI_{observed}$ was complicated by the evaluation of two different vaccine candidates, with two different regimens, in several different clinical protocols. Some of the Phase 3 studies conducted in low resource settings did not collect data on the incidence of rotavirus gastroenteritis (RVGE) of any severity. The analyses excluded these studies due to the absence of an intent-to-treat incidence of any severity RVGE in the placebo group to serve as a surrogate of λ. The analyses also excluded data from countries in which the placebo group

Table 1. Rotavirus vaccine Phase 3 study settings by country, World Bank country income classification, and surrogate observed force of infection.

Country	Economy[a]	$FOI_{observed}$	(RV#)	NTC	References
Finland	H	16.3	RV5	Not available	39
Brazil	UM	16.1	RV1	NCT00140673	24,40
Malawi	L	14.4	RV1	NCT00241644	26,41
Mexico	UM	13.8	RV1	NCT00140673	24,40
South Africa	UM	12.2	RV1	NCT00241644	26,41
EU/USA	H	11.2	RV5	NCT00092443	27
China	UM	10.6	RV1	NCT01171963	23,42
France	H	10.0	RV1	NCT00140686	22,43
Japan	H	10.0	RV1	NCT00480324	25,44
Finland	H	8.8	RV1	NCT00140686	22,43
Japan	H	7.1	RV5	NCT00718237	28
Ghana	LM	7.1	RV5	NCT00362648	29
Venezuela	UM	6.0	RV1	NCT00140673	24,40
China	UM	5.4	RV5	NCT02062385	31
Czech Republic	H	4.1	RV1	NCT00140686	22,43
Kenya	LM	3.7	RV5	NCT00362648	29
Bangladesh	LM	n/a	RV5	NCT00362648	32
Vietnam	LM	n/a	RV5	NCT00362648	32

[a] See ref. [21]

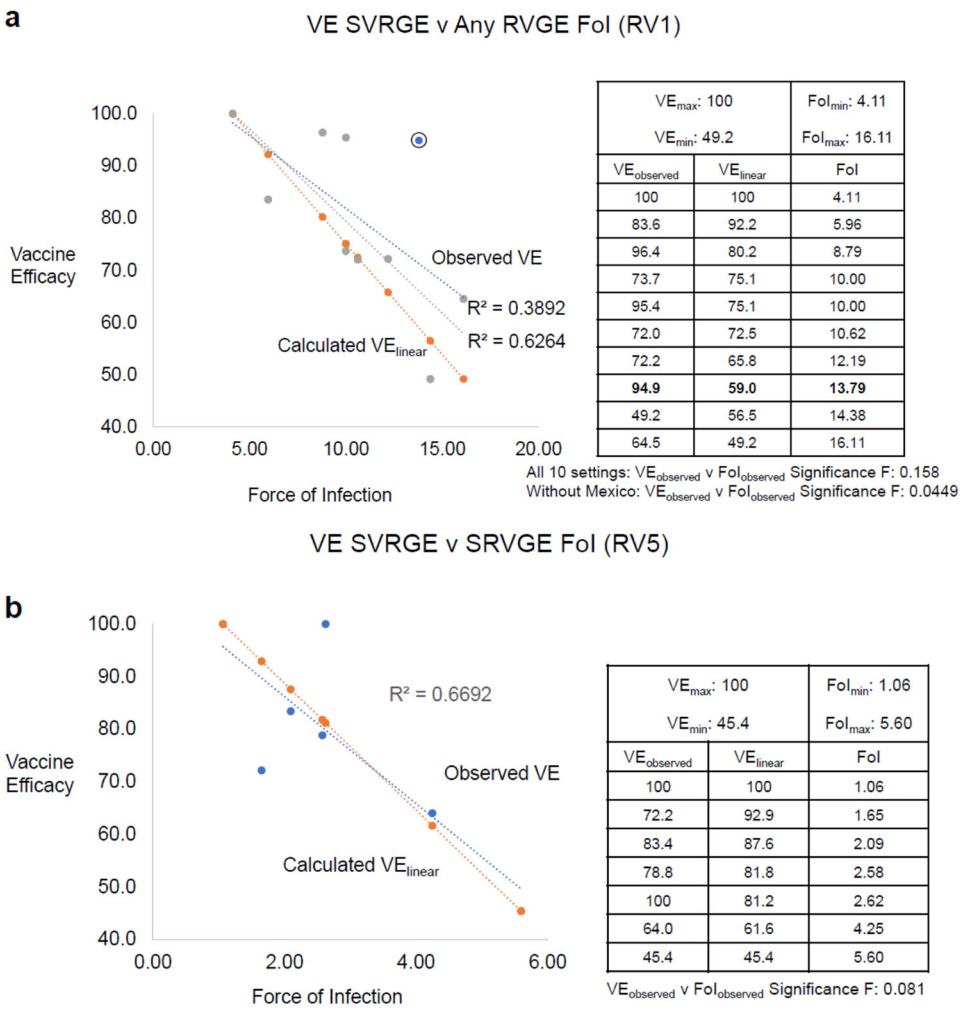
had no or just a single case of RVGE of any severity. From those studies that collected sufficient incidence of any severity RVGE in the placebo group, an Analysis of Variance failed to detect a statistically significant difference (p-value = 0.749) when categorizing $FOI_{observed}$ by 2020 World Bank country income classifications (i.e., upper- v upper middle- v lower middle/lower-income country)[21] (Table 1).

For RV1, results from 10 countries in five independent Phase 3 studies[17,22–26] (see Table 1) met the above $FOI_{observed}$ criteria for interrogation. The best fit trendline analysis of $VE_{observed}$ as a function of $FOI_{observed}$ revealed a linear relationship (Fig. 3a upper line, Observed VE) with an R^2 of 0.3892 and regression analysis with a Significance F of 0.158. The $VE_{observed}$ of 94.9% in one setting (Mexico) with $FOI_{observed}$ of 13.79 appeared to be a significant outlier. Reanalysis absent the data from Mexico revealed a linear relationship (Fig. 3a middle line, Observed VE), with an R^2 of 0.6264 and regression analysis Significance F of 0.0449. Using the VE_{linear} equation (Box 2), the observed VE_{max}, VE_{min}, FOI_{max}, FOI_{min}, and the $FOI_{observed}$ from each of the 10 countries generated a linear relationship between the calculated site-specific VE and $FOI_{observed}$ (Fig. 3a lower line, Calculated VE). These analyses suggest that rotavirus FOI may function as a determinant of RV1 VE.

For RV5, results from five settings in three independent Phase 3 studies[17,27–31] (see Table 1) met the above $FOI_{observed}$ criteria for interrogation. The best fit trendline analysis of $VE_{observed}$ as a function of $FOI_{observed}$ revealed an independent relationship (data not shown but provided for review) with an R^2 of −0.215 and regression analysis Significance F of 0.9838. Interrogating results from 7 settings in five independent Phase 3 studies[17,27–32] (see Table 1) by using the incidence of SRVGE in the placebo group as the $FOI_{observed}$ and surrogate of λ in the analyses, the best fit trendline analysis of $VE_{observed}$ as a function of $FOI_{observed}$ revealed a linear relationship (Fig. 3b, Observed VE) with an R^2 of 0.6692 and regression analysis Significance F of 0.081. Using the VE_{linear} equation (Box 2), the observed VE_{max}, VE_{min}, FOI_{max}, FOI_{min}, and the $FOI_{observed}$ from each of the 7 settings in the reanalysis generated a linear relationship between the calculated site-specific VE and $FOI_{observed}$ (Fig. 3b lower line, Calculated VE). These analyses suggest that rotavirus FOI may function as a determinant of RV5 VE, when the incidence of SRVGE, rather than RVGE of any severity, in the placebo group serves as the $FOI_{observed}$ in the analyses.

CONCLUSION

That a relationship between FOI and VE appears logarithmic for a parenterally administered malaria vaccine candidate and linear for two orally administered rotavirus vaccine candidates may reflect different routes of infection, routes of vaccine administration, fold differences between the FOI_{max} and FOI_{min} (i.e., more than a hundred-fold for malaria and less than ten-fold for rotavirus) or other differences between the pathogens, host responses, or vaccines. If a causal relationship rather than an indirect (e.g., pre-exposure effect[33]), misleading[34], or chance association between FOI and VE exists, then of the many proposed determinants of setting-dependent VE, FOI provides one of the most direct, mechanistically proximate potential determinants. Furthermore, for many but not all pathogens, modifying the FOI provides one of the most actionable interventions to enhance or sustain VE. While improving indirect or distal VE determinants, such as poverty, gut pathology, co-infections, malnutrition, and the microbiome[35] could significantly enhance efforts to control and eliminate simultaneously many pathogens, implementing interventions that effectively mitigate these VE determinants is complex and not immediately achievable. In contrast, modifying the FOI through the concomitant use of affordable, accessible, available, acceptable, and sustainable NPIs provides a proximate and actionable approach to optimizing VE. Considering and then prospectively verifying the speculation that introduction or continued optimal use of NPIs in an effort to reduce the FOI and thereby enhance or sustain VE,



VE_{max}: 100 VE_{min}: 49.2		FoI_{min}: 4.11 FoI_{max}: 16.11
$VE_{observed}$	VE_{linear}	FoI
100	100	4.11
83.6	92.2	5.96
96.4	80.2	8.79
73.7	75.1	10.00
95.4	75.1	10.00
72.0	72.5	10.62
72.2	65.8	12.19
94.9	**59.0**	**13.79**
49.2	56.5	14.38
64.5	49.2	16.11

All 10 settings: $VE_{observed}$ v $FoI_{observed}$ Significance F: 0.158
Without Mexico: $VE_{observed}$ v $FoI_{observed}$ Significance F: 0.0449

VE_{max}: 100 VE_{min}: 45.4		FoI_{min}: 1.06 FoI_{max}: 5.60
$VE_{observed}$	VE_{linear}	FoI
100	100	1.06
72.2	92.9	1.65
83.4	87.6	2.09
78.8	81.8	2.58
100	81.2	2.62
64.0	61.6	4.25
45.4	45.4	5.60

$VE_{observed}$ v $FoI_{observed}$ Significance F: 0.081

Fig. 3 Vaccine Efficacy (VE) as a function of Force of Infection (FoI) for rotavirus vaccines. a RV1: Best fit trendline analysis of observed vaccine efficacy ($VE_{observed}$) as a function of observed force of infection ($FoI_{observed}$) is shown as a linear relationship for all 10 countries (blue dotted line) and for 9 countries (exclusion of the outlier, encircled blue dot; gray dotted line) with a R^2 of 0.3892 and 0.6264, respectively. Regression analyses of $VE_{observed}$ as a function of $FoI_{observed}$ in the embedded table have Significance Fs of 0.158 and 0.0449. Using the VE_{linear} equation (see Box 2, Vaccine efficacy as a function of force of infection), the observed VE_{max}, VE_{min}, FoI_{max}, FOI_{min} and $FoI_{observed}$ were used to calculate the VE_{linear} in the embedded table and the calculated VE_{linear} shown graphically (orange dotted line). **b** RV5: Best fit trendline analysis of observed vaccine efficacy ($VE_{observed}$) as a function of observed force of infection ($FoI_{observed}$) is shown as a linear relationship (blue dotted line) with a R^2 of 0.6692. A regression analysis of $VE_{observed}$ as a function of $FoI_{observed}$ in the embedded table has a Significance F of 0.081. Using the VE_{linear} equation (see Box 2, Vaccine efficacy as a function of force of infection), the observed VE_{max}, VE_{min}, FoI_{max}, FOI_{min} and $FoI_{observed}$ were used to calculate the VE_{linear} in the embedded table and the calculated VE_{linear} shown graphically (orange dotted line).

respectively, upon vaccine rollout seems prudent and, in the context of a pandemic, quite urgent.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

DATA AVAILABILITY

All data used in the analyses can be publicly accessed. The sources and web links for all the data have been cited in the references.

CODE AVAILABILITY

All analyses conducted using Microsoft® Excel® for Microsoft 365 version 2101.

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D.C.K. conceived, wrote, reviewed, approved and is accountable for this paper.

COMPETING INTERESTS

D.C.K., an employee of PATH (a not-for-profit organization), has no financial interest in any for-profit organization, and declares no competing interests.

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