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Association between COVID-19 vaccine efficacy and epidemic force of infection

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The association between vaccine efficacy (VE) and force of infection (FoI) remains incompletely understood. Previous analyses have been primarily based on trial-level summary data—not accounting for the effect of time and constrained by the number of trials. Here, we leverage individual-level data from three phase 3 randomized, placebo-controlled COVID-19 vaccine trials—the COVE trial (Moderna, CoVPN3001), the AZD1222 trial (AstraZeneca, CoVPN3002), and the ENSEMBLE trial (Janssen/Johnson & Johnson, CoVPN3003)—and contemporaneous geographic-location-specific SARS-CoV-2 surveillance data from the start of the pandemic through November 14, 2021 (including the blinded follow-up periods of the trials) to conduct five cohort- and vaccine-specific analyses: COVE (U.S.), AZD1222 overall (U.S. + non-U.S.), AZD1222 U.S., ENSEMBLE overall (U.S. + non-U.S.), and ENSEMBLE U.S. In AZD1222 U.S., higher VE was associated with higher FoI ($p = 0.01$). In ENSEMBLE overall, lower VE was marginally associated with higher FoI ($p = 0.21$), further supported by a region-specific analysis. In COVE, AZD1222 overall, and ENSEMBLE U.S., no VE-FoI association was found. These findings highlighted a new perspective: the VE–FoI association appears complex, potentially influenced by FoI levels, with patterns suggesting an inverted U-shaped relationship, showing a positive association at low FoI levels and a negative association at high levels.

As of September 2025, more than 40 COVID-19 vaccines have been authorized for use in at least one country[1], with variation in population-level vaccine efficacy (VE) reported across vaccine platforms and studies[2,3]. Such variation likely reflects not only differences between vaccines themselves, but also susceptibility-related population characteristics and exposure-related factors, including regional lifestyle, non-pharmaceutical interventions, seasonal effects, and the prevalence of circulating variants[4]. These exposure-related factors can be summarized as Force of Infection (FoI), defined as the incidence rate among susceptible individuals[5–7]. The interplay between VE and FoI is often bidirectional. For example, the widespread use of an effective vaccine with high efficacy can significantly curb pathogen transmission within the population, thereby reducing FoI[8,9]. Conversely, in a high-FoI environment, individuals face a higher load of pathogenic exposure, which may result in more breakthrough infections and a lower VE[10]. Additionally, VE may be lower in such settings due to the more rapid depletion of susceptible individuals[11,12].

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Table 1 | Number of participants and number of accrued COVID-19 endpoints by treatment group in each study

	COVE (Jul 27,2020-Mar 26,2021)		AZD1222 (Aug 28,2020-Jul 30,2021)		ENSEMBLE (Sep 21,2020-Jul 9,2021)	
Treatment group	**Placebo**	**mRNA-1273**	**Placebo**	**AZD1222**	**Placebo**	**Ad26.COV2.S**
Number of Participants						
U.S. + non-U.S. (overall)	14,164	14,287	8528	17,617	13,203[a]	13,352[b]
U.S. only	14,164	14287	7423	15,389	8663	8829
-With linkable county-level FoI_S (%)	9207 (65.0%)	9297(65.1%)	6826 (92.0%)	14,205 (92.3%)	5536 (63.9%)	5633(63.8%)
-With linkable state-level FoI_S (%)	4957 (35.0%)	4990 (34.9%)	597 (8.0%)	1184 (7.7%)	3127 (36.1%)	3196 (36.2%)
Non-U.S.	-	-	1105	2228	4540	4523
Number of COVID-19 Endpoints						
U.S. + non-U.S. (overall)	744	55	184	141	626	293
U.S. only	744	55	148	96	239	77
-With linkable county-level FoI_S (%)	452 (60.8%)	28 (50.9%)	134 (90.6%)	91 (94.8%)	130 (54.4%)	46 (59.7%)
-With linkable state-level FoI_S (%)	292 (39.2%)	27 (49.1%)	14 (9.4%)	5 (5.2%)	109 (45.6%)	31 (40.3%)
Non-U.S.	-	-	36	45	387	216

For U.S. participants, numbers are also provided for those with linkable county-level or state-level FoI_S estimated from surveillance data. The per-protocol analysis cohort specified in each parent study was considered.

[a] The ENSEMBLE trial included 18,924 participants in the placebo group; our analysis represented 69.8% of this group.

[b] The ENSEMBLE trial included 19,113 participants in the Ad26.COV2.S group; our analysis represented 69.9% of this group.

Human challenge trials[13] offer one way to study this relationship by mimicking different levels of FoI through controlled exposure. Langwig et al.[14] predicted that regardless of host susceptibility heterogeneity, VE likely declines with higher pathogen challenge dose from a single exposure or cumulative exposure over time. However, their review found limited empirical support for this prediction, as only a few studies have tested vaccines across a sufficiently broad range of challenge doses. Meanwhile, a household study from Israel, which focused on infections occurring within 10 days of a SARS-CoV-2 diagnosis in another adult member of the same household, found that BNT162b2 mRNA VE was lower than estimates from broader population studies or randomized clinical trials, likely due to the high-risk real-life exposure scenarios[15].

Vaccine efficacy trials offer another important source to quantify the association between VE and FoI; however, the feasibility has often been limited by the availability of data with sufficient variability in both VE and FoI. Kaslow[16] reported a logarithmic inverse relationship between VE and FoI, i.e., higher VE at lower FoI, for a malaria vaccine, and linear inverse relationships for two orally administered rotavirus vaccine candidates[17,18]. These findings were based on summary data from a limited number of sites or countries where the clinical trials were conducted, with FoI estimated from the incidence in the placebo group aggregated over time within each site or country. Gjini[19] reported an inverse association between VE and FoI for a 7-valent pneumococcal conjugate vaccine using country/territory-level summary data, where FoI was estimated at a single time-point using the prevalence of a capsular serotype of *Streptococcus pneumoniae* at the beginning of the trial. Additionally, Amin et al.[20] observed lower VE of rotavirus vaccine in countries with higher rotavirus burden and noted that adjusting for the rotavirus exposure can reduce the variability in VE estimates across countries.

For COVID-19, Coutinho et al.[21] proposed a mathematical model to calculate VE and demonstrated that spurious inverse relationships between VE and FoI can occur when clinical trials are conducted during an outbreak. They also concluded that VE may vary depending on the timing of a clinical trial relative to the peak of the outbreak. However, no quantitative relationship was developed, as VE was based on model simulations. Lastly, Sharma and Anand[3] compared 20 phase 3 trials across eight COVID-19 vaccine candidates and found that VE declined as COVID-19 prevalence at trial sites increased. Their analysis was based on trial site-level summary data, with VE estimated cumulatively by a certain time and FoI estimated using prevalence rates averaged over time. As a result, temporal variation in FoI could not be captured, and the association with VE could not be disentangled from vaccine effect waning[22–24].

In our analyses, we assessed whether VE was associated with FoI, and whether this association differed by COVID-19 vaccine and FoI levels, while addressing some of the limitations in previous investigations as mentioned above. We utilized well-curated participant-level data collected from more than 35,000 placebo recipients and 45,000 vaccine recipients enrolled in three randomized, placebo-controlled COVID-19 vaccine efficacy trials, which together captured 2043 primary endpoints for the analysis. In addition, we incorporated surveillance-data-based FoI estimates linked by geographic locations of trial participants at enrollment. Our analyses accounted for vaccine effect waning over study time, as well as changes in FoI over calendar time that previously reported analyses did not address.

Results

Data linkage and study cohort

As shown in Table 1, for COVE (U.S. only) and AZD1222 (U.S., Peru, and Chile), 100% of the per-protocol participants from the parent studies were included. The ENSEMBLE trial enrolled participants from eight countries; however, due to the unavailability of FoI_S data, participants from Brazil and South Africa were excluded from the overall analysis. Baseline characteristics were comparable between the vaccine and placebo groups in our analyses, as the randomization was stratified by site within the parent study.

Trends in FoI_S estimates

We found that the trend of FoI_S over calendar time closely aligned with the estimated placebo hazard in each trial (Supplementary Fig. 1). This supported the use of FoI_S as an estimate for the FoI among trial participants. Importantly, we observed a three- to six- fold variation in FoI_S over time in both U.S. and non-U.S. regions, justifying the analyses of its association with VE.

Of note, FoI_S estimates in the U.S. were substantially higher in December and January and declined thereafter. During this period, FoI_S was the highest in COVE, followed by ENSEMBLE, and then AZD1222. Notably, the histograms of participants' last dose dates indicate that only COVE participants fully experienced this winter transmission peak. In contrast, most AZD1222 participants in the U.S. received their second dose around the peak. Since endpoints were counted starting 15 days after the

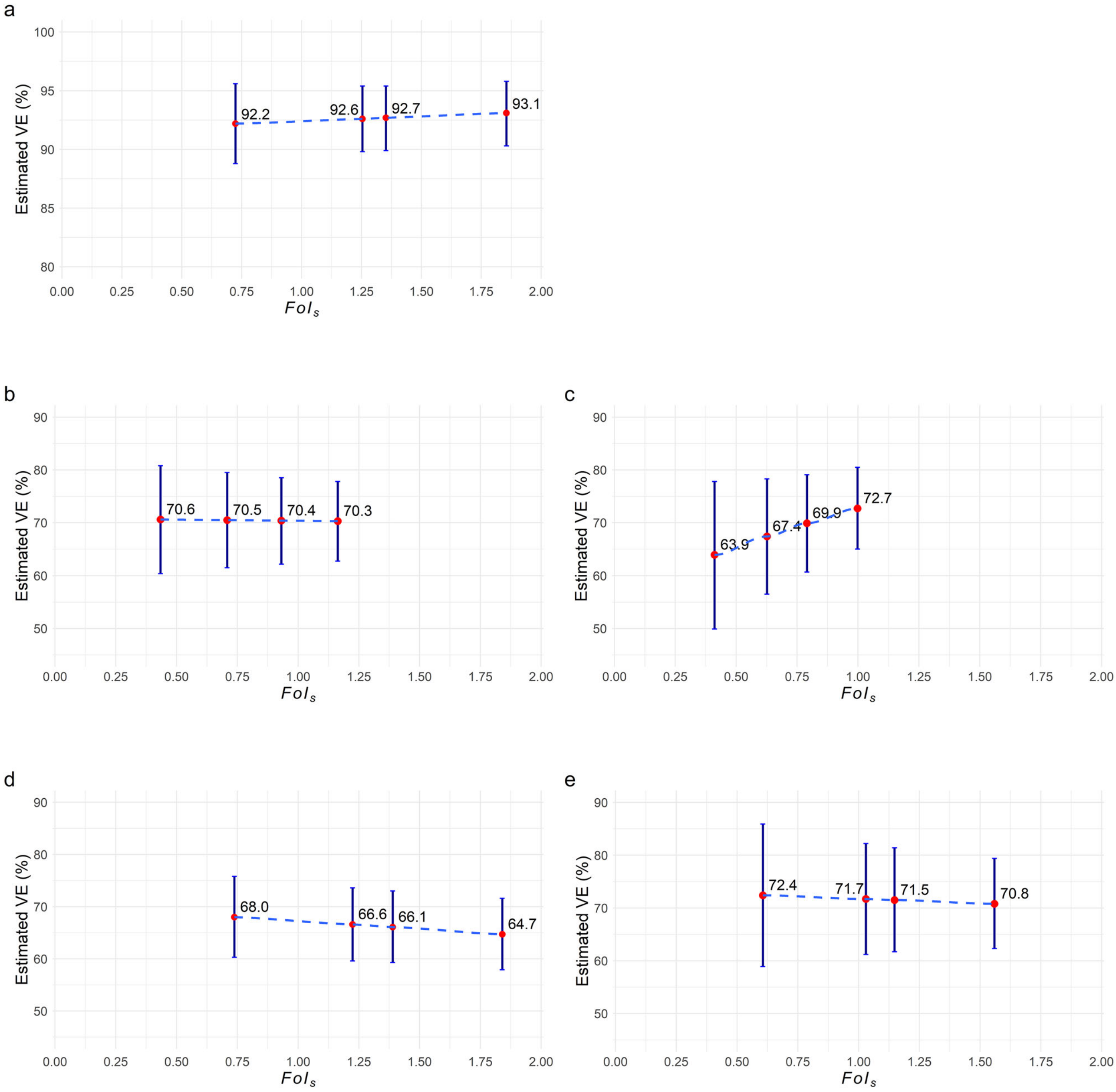

Fig. 1 | Estimated VE at Specific FoI_S Levels and Time Since Vaccination. Panels **a**–**e** corresponds to results from the COVE, AZD1222 (overall and U.S.), and ENSEMBLE (overall and U.S.) Trials. The values of FoI_S in the figure are expressed in units of infections per 1000 person-days. In each panel, from left to right, the values represent the 1st quantile, median, mean, and 3rd quantile. The mean and quantiles were calculated based on daily variations across all participants included in the models. VE was assessed at 45 days since vaccination (post–second dose in COVE and AZD1222 or post–single dose in ENSEMBLE).

second dose, many likely missed the peak period of transmission. This timing difference could explain why the FoI_S quantiles are considerably lower for AZD1222 U.S. compared to COVE and ENSEMBLE U.S. (Supplementary Table 1).

Associations between VE and FoI_S via multivariable Cox modeling

Figure 1 displays the estimated VE at specific FoI_S levels based on Cox models that include interactions of the treatment group with both FoI_S and time since vaccination, with results for the treatment–FoI interactions presented in Table 2. The interaction coefficient reflects how the hazard ratio between the vaccine and placebo groups changes with FoI. A negative interaction coefficient indicates that a lower hazard ratio, and therefore higher VE, is associated with higher FoI, whereas a positive coefficient indicates that a higher hazard ratio, and therefore lower VE, is associated with higher FoI. For all these models, no evidence of violation of the proportional hazard assumption was observed (Supplementary Fig. 2).

Specifically, in the COVE trial, no significant interaction was observed between treatment group and FoI_S, suggesting no detectable association between VE and FoI_S (Supplementary Table 2a). Similarly, no significant interaction was found in the overall AZD1222 analysis (Supplementary Table 3a). In contrast, the AZD1222 U.S. analysis showed a significant negative interaction coefficient ($p = 0.01$, Supplementary Table 4), indicating a lower hazard ratio and thus a higher estimated VE was associated with higher FoI_S after accounting for vaccine waning. In the overall ENSEMBLE analysis, a higher hazard ratio and thus a lower VE was associated with higher FoI_S, as indicated by a positive interaction term between treatment group and FoI_S, ($p = 0.21$, Supplementary Table 5). Figure 2 suggested a similar trend in the ENSEMBLE trial, where lower estimated VE was more evident in regions with higher placebo incidence. No significant trend was observed in the ENSEMBLE U.S. analysis (Supplementary Table 6a). Across all trials, higher FoI_S was consistently associated with higher COVID-19 hazard in both vaccine and placebo groups. Detailed results for each trial are further described in Supplementary Information.

Discussion

To our knowledge, these analyses are the first to investigate the association between VE and FoI using participant-level data from clinical trials and daily FoI estimates derived from surveillance data. The unprecedented COVID-19 pandemic availed such data resources, as part of the necessary public health efforts combating the pandemic via vaccine development and incidence tracking. Another challenge in studying the VE–FoI relationship has been indirect effects[5], where VE influences FoI and, in turn, FoI affects VE. The COVID-19 pandemic offered a unique opportunity to isolate this relationship, as the trials we analyzed were conducted among COVID-19 vaccine-naïve populations and completed before the large-scale vaccine rollout, when such effects were minimal.

Table 2 | Summary of the interaction coefficients between FoI_S and treatment group in Multivariable Cox Models in each analysis cohorts

	Coefficient of interaction	HR (95%CI)	Two-sided *P*-value
COVE	-0.105	0.90 (0.67-1.21)	0.49
AZD1222 overall (U.S. + non-U.S.)	0.016	1.02 (0.81,1.28)	0.89
AZD1222 U.S.	-0.481	0.62[a] (0.42,0.91)	0.01
ENSEMBLE overall (U.S. + non-U.S.)	0.089	1.09 (0.95,1.26)	0.21
ENSEMBLE U.S.	0.057	1.06 (0.72,1.55)	0.77

An interaction coefficient greater than 0 indicates a negative association between VE and FoI_S, while a coefficient less than 0 indicates a positive association (i.e., higher FoI_S, higher VE). HR is the exponentiated interaction coefficient. All models adjusted for Age, Race, and Sex. Details of the model results are included in **Supplementary Tables 2a, 3a, 4, 5 and 6a**.

[a] For each one-unit increase in FoI_S (per 1000 person-days), the hazard in the vaccine group increases only 62% as much as it does in the placebo group. For example, when FoI_S increase from 0.5 to 1.5 infections per 1000 person-days, translating VE at 45 days after vaccination from $1-\exp(-1.18-0.481*0.5+45*0.008) = 65.4\%$ to $1-\exp(-1.18-0.481*1.5+45*0.008) = 78.6\%$.

Leveraging such data from three COVID-19 vaccine efficacy trials and surveillance data of estimated daily SARS-CoV-2 incidence rates, we assessed the association between VE and FoI for these vaccines, accounting for vaccine effect waning and time-varying and location-specific FoI. We summarize these results and provide a brief interpretation below, with further mathematical reasoning provided in Supplementary information. While the interpretations are partly conjectural, the key contribution of the study is the hypothesis that VE-FoI association is complex, varies by vaccine type, and may be influenced by FoI levels.

We found that in the overall (U.S. + non-U.S.) analysis of the ENSEMBLE trial, there was a non-significant inverse association between the estimated efficacy of Ad26.COV2.S and FoI. Such an inverse association aligns with the conclusions presented by Sharma and Anand[3]. A potential interpretation is that the vaccines under consideration behave like "leaky" vaccines rather than "all-or-none" vaccines[25,26]. A "leaky" vaccine does not provide complete immunity against a pathogen but instead reduces the likelihood of infection or disease severity upon exposure. Such vaccines result in some breakthrough infections, and their efficacy tends to decline under repeated exposures[25]. The ENSEMBLE trial included several non-U.S. countries with relatively higher FoI levels during the study period, which may have contributed to reduced VE under sustained exposures.

On the other hand, we found a significant positive association between the estimated efficacy of ChAdOx1 nCoV-19 and FoI in the U.S. cohort of the AZD1222 trial. This was likely due to low FoI_S among participants in the U.S. cohort of the AZD1222 trial, suggesting that repeated exposures were likely not a dominant factor. At these lower FoI levels, increases in FoI potentially raised hazard rates more in the placebo group than in the vaccine group, resulting in higher VE.

In addition, we found no significant associations between VE and FoI in the COVE trial, the overall AZD1222 trial, or the U.S. cohort of the ENSEMBLE trial. These results likely reflect that FoI_S levels in these trials were moderate relative to the efficacy of each vaccine. For instance, although the FoI_S level in the COVE trial was higher than that in the ENSEMBLE U.S. cohort, neither showed an association between VE and FoI_S. This may suggest that mRNA-1273 was able to maintain its efficacy even under relatively higher FoI levels.

Circulating variants should be another important consideration, as they can influence both VE and FoI. In the region-specific VE and placebo incidence analysis of ENSEMBLE shown in Fig. 2, although the placebo incidence in South Africa was comparable to that in Mexico, its VE was noticeably lower. This likely could be related to the emerging Delta variant at

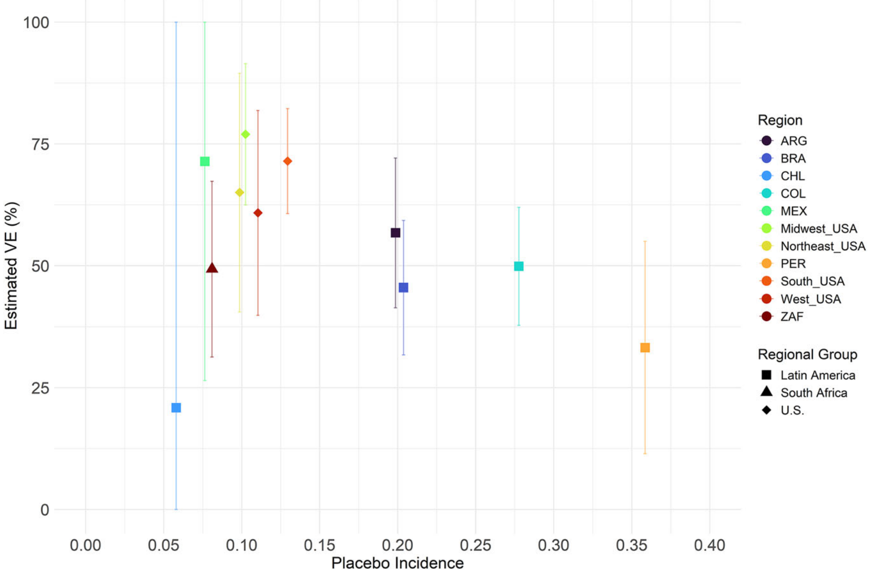

Fig. 2 | Estimated VE and Placebo Incidence Across Regions in the ENSEMBLE Trial. VE was estimated using a Cox proportional hazards model without covariates, with confidence intervals calculated via the delta method. Placebo incidence was defined as the number of cases divided by the total person-years of follow-up in the placebo group.

the time, as nearly all Delta cases during the blinding period occurred in South Africa[27].

In comparing the FoI estimates from external surveillance data and the in-trial placebo data, we found aligned time trends but higher magnitudes in surveillance data. This discrepancy likely arose from differences in estimation methods, populations, and definition of endpoints: surveillance-based FoI_S were estimated, including seroprevalence surveys capturing symptomatic and asymptomatic infections, while placebo hazards were based on participants enrolled in clinical trials capturing only symptomatic infections. Nonetheless, this discrepancy does not affect the interpretation of our findings. Moreover, unlike prior studies, our use of externally estimated FoI based on surveillance data avoids the entanglement of using placebo data for both FoI and VE estimates. An additional advantage of using external FoI is that it preserves both temporal and geographic variation, whereas placebo-based estimates may be unstable (given the smaller number of COVID-19 cases) when aggregated by location and lose spatial resolution when pooled across sites.

Our analyses have several limitations. First, despite the variability observed over time and across regions, the range of FoI_S was still at most six-fold, limiting the statistical power to assess the association between VE and FoI. In the U.S. cohort, more county-level FoI_S estimates were linked in the AZD1222 trial, whereas for COVE and ENSEMBLE, approximately 35% of FoI_S estimates used in the analyses were at the state level, potentially reducing power. In the overall ENSEMBLE analysis, FoI_S for non-U.S. participants were assessed at the country level, and the exclusion of Brazil and South Africa may have further diminished power.

Second, we did not account for variant lineages in the analysis, particularly in the overall analysis of ENSEMBLE, where circulating variants differed across non-U.S. countries. Our interpretation did not explore differences in vaccine platforms (which vary in immunogenicity) or disease severity (which may differ across FoI levels). All cases were treated equally in our analyses once they met the endpoint criteria, regardless of severity.

Third, the multivariable Cox model we used captures only the overall association between VE and FoI, limited by its ability in capturing dynamic changes in this relationship. Future work may apply the method proposed by Bellavia et al.[28], which allows for modeling more complex interaction effects among covariates. Lastly, this study focused on assessing the association between VE and FoI, without establishing a causal relationship[29].

Despite these limitations, this study complements previous investigations of the VE–FoI relationship by using individual-level trial data together with large-scale surveillance data. This is particularly valuable given the unique opportunity provided by the COVID-19 pandemic to revisit this question. Importantly, the findings suggest a new hypothesis that the relationship may vary in direction, potentially influenced by both VE and FoI.

A clear understanding of this relationship can inform both vaccine evaluation and development. Vaccine trials typically include multiple sites, a well-established design feature that accounts for heterogeneity in FoI. However, for single-site trials, the local FoI level should be considered as a potential explanatory variable. Likewise, when translating trial results into public health decisions, it is important to take the local FoI into account to ensure that findings are appropriately adapted to local needs. For the development of vaccines, particularly preventive vaccines against pathogens with relatively low incidence, the initial choice of trial site should carefully consider local FoI. A lower FoI reduces the risk of overwhelming exposure, but also implies that a larger cohort or longer follow-up would be needed to accrue a desired number of cases to achieve sufficient statistical power for VE assessment, making such trials more time- and resource-intensive. In contrast, very high FoI may dampen the efficacy of a candidate vaccine, as shown in our analysis. A moderate-FoI setting may therefore be preferable at the outset, with trials expanded to higher-FoI regions as development progresses.

In summary, we investigated the association between the efficacy of three COVID-19 vaccines and FoI, using individual-participant-level data and incorporating time-varying, location-specific FoI estimates for each trial participant. Our results indicate that the association between VE and FoI may differ by vaccine and FoI level: at lower FoI levels, higher VE was associated with increasing FoI, whereas at higher FoI levels, lower VE was associated with increasing FoI. While these findings require validation in future studies, they suggest that the VE-FoI association may be complex, potentially inverted U-shaped, offering new perspectives on the VE-FoI relationship and on incorporating FoI into future vaccine evaluation and development.

Methods

COVID-19 vaccine trial data

We incorporated data from the Moderna COVE trial of mRNA-1273 (CoVPN3001, ClinicalTrials.gov number: NCT04470427)[30,31], the AstraZeneca/Oxford AZD1222 trial of ChAdOx1 nCoV-19 (CoVPN3002, NCT04516746)[32,33], and the Janssen/Johnson & Johnson ENSEMBLE trial of Ad26.COV2.S (CoVPN3003, NCT04505722)[27]. These trials were funded by the U.S. government and conducted under the Operation Warp Speed program, with operational leadership provided by the COVID-19 Prevention Network (CoVPN)[34–37].

Our analyses focused on the blinded periods of these trials (Table 3), during which participants received either mRNA-1273 (two doses, 28 days apart), ChAdOx1 nCoV-19 (two doses, 28 days apart), Ad26.COV2.S (one dose), or placebo[27,30,33]. The primary endpoint was virologically confirmed COVID-19, with definitions slightly differing across the trials[38]. As reported previously, the VE of mRNA-1273 was 93.2% (95% CI: 91.0–94.8) over a median follow-up of approximately 4 months after the second dose[30]. For ChAdOx1 nCoV-19, VE was 67.0% (95% CI: 58.9–73.5) overall (i.e., among all participants, U.S.+ non-U.S.) and 72.3% (95% CI: 64.1–78.5) among U.S. participants[33], based on a median follow-up of 2.5 months after the second dose. The VE of Ad26.COV2.S was 52.9% (95% CI: 47.1–58.1) overall and 69.7% (95% CI: 60.7–76.9) among U.S. participants[27], based on a median follow-up of 4 and 3.5 months after the single dose, respectively. Local or central institutional review board and ethics committee approvals were obtained by each site; all participants provided written informed consent prior to participating.

FoI estimates from surveillance data

Daily FoI estimates based on surveillance data, denoted as FoI_S, were sourced from the Institute for Health Metrics and Evaluation (IHME)[39,40]. These estimates were derived from a model that integrated data from Johns Hopkins University and national databases[41], incorporating reported COVID-19-associated hospitalizations and deaths, as well as SARS-CoV-2 seroprevalence surveys[39,42]. In this database, FoI_S was defined as the number of new infections on a given day divided by the total population who could possibly get infected that day (at risk) in the region, regardless of vaccination status or prior infection history[42]. In the U.S., state-level estimates were available for all states except Alaska, and county-level data were available for 109 counties, 80 of which had at least one clinical site enrolling participants in one of the trials included in our analyses. Outside the U.S., country-level estimates were available for Peru, Chile, Argentina, Mexico, and Colombia.

Linkage between trial data and surveillance data

To obtain the daily-grid time-varying FoI_S, we linked each participant's trial site with the corresponding location in the IHME surveillance database. For U.S. participants, we used county-level FoI_S when available and state-level FoI_S otherwise. For non-U.S. participants, we used country-level FoI_S. We also estimated hazard rates for the placebo arms in each trial using a non-parametric kernel smoothing method[43] to assess whether the linked FoI_S values captured the temporal incidence patterns observed among placebo recipients.

Multivariable Cox model incorporating daily-varying FoI_S

We modeled the hazard of COVID-19 using a covariate-adjusted Cox regression model, applied separately to data from each of the three trials

Table 3 | Participant characteristics by treatment group in each study among individuals with linked FoI_S Data included in the analyses

	COVE (Jul 27, 2020–Mar 26, 2021)				AZD1222 (Aug 28, 2020–Jul 30, 2021)				ENSEMBLE (Sep 21,2020-Jul 9,2021)			
		Placebo (*N* = 14164)	mRNA-1273 (*N* = 14287)	Total (*N* = 28451)		Placebo (*N* = 8528)	AZD1222 (*N* = 17617)	Total (*N* = 26145)		Placebo (N = 13203)	Ad26.COV2.S (N = 13352)	Total (N = 26555)
Age group	**≥18 to 64 yr**	10,569 (74.6)	10,661 (74.6)	21,230 (74.6)	**≥18 to 64 yr**	6712 (78.7)	13,921 (79.0)	20,633 (78.9)	**≥18 to 60 yr**	8470 (64.1)	8587 (64.3)	17057 (64.2)
	≥65 yr	3595 (25.4)	3626 (25.4)	7221 (25.4)	**≥65 yr**	1816 (21.3)	3696 (21.0)	5512 (21.1)	**≥60 yr**	4733 (35.9)	4765 (35.7)	9498 (35.8)
Sex	**Male**	7494 (52.9)	7439 (52.1)	14,933 (52.5)	**Male**	4814 (56.4)	9885 (56.1)	14,699 (56.2)	**Male**	7450 (56.4)	7553 (56.6)	15003 (56.5)
	Female	6670 (47.1)	6848 (47.9)	13,518 (47.5)	**Female**	3714 (43.6)	7732 (43.9)	11,446 (43.8)	**Female**	5750 (43.6)	5796 (43.4)	11546 (43.5)
									Unknown	0 (0)	1 (0)	1 (0)
									Undifferentiated	3 (0)	2 (0)	5 (0)
Race	**White**	11,273 (79.6)	11,391 (79.7)	22,664 (79.7)	**White**	6735 (78.9)	13,972 (79.3)	20,707 (79.2)	**White**	8814 (66.7)	8877 (66.5)	17691 (66.6)
	Black or African American	1352 (9.6)	1395 (9.8)	2747 (9.7)	**Black**	699 (8.2)	1401 (7.9)	2100 (8.0)	**Black or African American**	1086 (8.2)	1087 (8.1)	2173 (8.2)
	Asian	700 (5.0)	628 (4.4)	1328 (4.7)	**Asian**	355 (4.2)	738 (4.2)	1093 4.2)	**Asian**	530 (4.0)	595 (4.4)	1125 (4.2)
	American India or Alaska Native	113 (0.8)	109 (0.8)	222 (0.8)	**American Indian or Alaska Native**	372 (4.4)	747 (4.2)	1119 (4.3)	**American Indian or Alaska Native**	1580 (12.0)	1614 (12.1)	3194 (12.0)
	Native Hawaiian or Other Pacific Islander	31 (0.2)	36 (0.2)	67 (0.2)	**Native Hawaiian or Other Pacific Islander**	15 (0.2)	50 (0.3)	65 (0.2)	**Native Hawaiian or Other Pacific Islander**	35 (0.3)	47 (0.4)	82 (0.3)
	Multiracial	304 (2.1)	300 (2.1)	604 (2.1)	**Multiple**	203 (2.4)	421 (2.4)	624 (2.4)	**Multiple**	699 (5.3)	699 (5.2)	1398 (5.3)
	Other	274 (1.9)	282 (2.0)	556 (1.9)	**Unknown**	39 (0.4)	82 (0.5)	121 (0.5)	**Unknown**	195 (1.5)	198 (1.5)	393 (1.5)
	Not Reported or Unknown	117 (0.8)	146 (1.0)	263 (0.9)	**Not Reported**	110 (1.3)	206 (1.2)	316 (1.2)	**Not Reported**	264 (2.0)	235 (1.8)	499 (1.9)

overall (U.S. + non-U.S.) and to the U.S. cohorts of the AZD1222 and ENSEMBLE trials. Analyses were conducted in the per-protocol populations, as defined in each parent trial[27,30,33], among baseline SARS-CoV-2-negative participants who received the full vaccine regimen (two doses for COVE and AZD1222, one dose for ENSEMBLE). We adjusted for age, sex, and race as potential confounders, with their distributions summarized in Table 3.

Data were analyzed in the calendar time scale to incorporate daily FoI_S. We included an interaction term between time-varying FoI_S and treatment group (vaccine or placebo) to examine whether VE remained constant across varying levels of FoI_S[44]. To account for potential vaccine effect waning, we also included an interaction term between treatment group and time since the most recent vaccination[45,46]. Interaction terms with p-values greater than 0.05 were excluded from the final models to improve interpretability. Schoenfeld residuals were used to assess the proportional hazards assumption for the time-invariant covariates[47].

Region-specific VE and placebo incidence in the ENSEMBLE trial

For ENSEMBLE, we derived region-specific VE and placebo incidence estimates to examine their relationship. Specifically, U.S. participants were categorized into four regional cohorts: Northeast, Midwest, South, and West, following the United States Census Bureau's classification[48]. Non-U.S. participants from South Africa, Brazil, Colombia, Argentina, Peru, Chile, or Mexico were each treated as a separate regional cohort, resulting in a total of 11 regions. For each region, VE was estimated using a Cox proportional hazards model without covariates, and confidence intervals were obtained using the delta method. Region-specific placebo incidence was computed as the number of cases divided by the total person-years of follow-up among placebo recipients in that region. This analysis was not performed for the COVE and AZD1222 trials, due to the smaller number of regions (4 and 6, respectively).

All analyses were conducted in R version 4.4.1[49] using the survival package[50].

Ethics

The primary clinical trials were approved by their respective institutional review boards, and informed consent was obtained as described in the parent studies.

Data availability

COVE: Requests to use the data can be made to Moderna Inc., 325 Binney Street, Cambridge, MA 02142, USA. A materials transfer and/or data access agreement with the sponsor will be required for accessing shared data. AstraZeneca AZD1222: AstraZeneca's data sharing policy is described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. AstraZeneca Group of Companies allows researchers to submit a request to access anonymized patient-level clinical data, aggregate clinical or genomics data (when available), and anonymized clinical study reports through the Vivli web-based data request platform. Janssen ENSEMBLE: The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/ transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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Author contributions

Xu and Huang had full access to all of the data in the study and took responsibility for the integrity of the data and accuracy of the data analysis. Concept and design: Xu, Halloran, Huang. Acquisition, analysis, or interpretation of data: Xu, Halloran, Moore, El Sahly, Baden, Goepfert, Gray, Grinsztejn, Sobieszczyk, Falsey, Zhou, Dromme, Truyers, Hirsch, Neuzil, Corey, Follmann, Janes, Gilbert, Huang. Drafting of the manuscript: Xu, Robinson, Huang. Critical review of the manuscript for important intellectual content: All authors. Statistical analysis: Xu, Halloran, Zhou, Hirsch, Truyers, Follmann, Janes, Gilbert, Huang. Obtained funding: Neuzil, Corey, Janes, Gilbert, Huang. Administrative, technical, or material support: Garcia, Moore, Huang. Supervision: Neuzil, Corey, Janes, Gilbert, Huang.

Competing interests

Dr Sobieszczyk reported receiving grant support to the institution from the NIH during the conduct of the study and grant support to the institution from the Gates Foundation, Sanofi SA, Merck, Sharpe and Dohme, and Gilead Sciences Inc. outside the submitted work. Dr El Sahly reported receiving grant support from the NIAID during the conduct of the study. Dr Baden reported receiving grant support from the NIH during the conduct of the study. Dr Falsey reported receiving grant support from AstraZeneca during the conduct of the study and grant support from AstraZeneca, Pfizer Inc., and CyanVac LLC, and personal fees for serving on an advisory board from Merck & Co. Inc., GSK, ADMA Biologics Inc., and Moderna Inc. outside the submitted work. Dr Hirsch reported holding stock or stock options in AstraZeneca. Dr Neuzil reported receiving grant support from Pfizer Inc. and the National Institutes of Health (NIH) during the conduct of the study. Dr Janes reported receiving grant support from the NIH during the conduct of the study. Dr Gilbert reported receiving grant support to the institution from the NIAID and NIH during the conduct of the study and serving on the vaccine scientific advisory boards for Moderna Inc. and AstraZeneca. Dr Huang reported receiving grant support from the NIH during the conduct of the study. All other authors declare no competing interests.

Additional information

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