Review

Vaccinating Against a Novel Pathogen: A Critical Review of COVID-19 Vaccine Effectiveness Evidence

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Review

Vaccinating against a Novel Pathogen: A Critical Review of COVID-19 Vaccine Effectiveness Evidence

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Abstract: We study here what can be learned from our experience with COVID-19 vaccination for an initially naïve population, that can inform planning for vaccination against the next novel, highly transmissible pathogen. We focus on the first two pandemic years (wild strain through Delta), because after the Omicron wave in early 2022, few people were still SARS-CoV-2-naïve. Almost all were vaccinated, infected, or often both. We review the evidence on COVID-19 vaccine effectiveness (VE), waning effectiveness over time, and what we should expect about VE and waning from a future pathogen. As a basis for our analysis, we conducted a PRISMA-compliant review of all studies on PubMed through August 15, 2022 reporting VE against four endpoints: any infection, symptomatic infection, hospitalization, and death, for the four principal vaccines used in developed Western countries (BNT162b2, mRNA1273, Ad26.CoV2.S, and ChAdOx1-S). The mRNA vaccines (BNT162b2, mRNA1273) had high initial VE against all endpoints but protection waned after approximately six months, with BNT162b2 declining faster than mRNA1273. Both mRNA vaccines initially outperformed the viral vector vaccines. A third "booster" dose, roughly six months after the primary doses, substantially reduced symptomatic infection, severe disease, and mortality, and in hindsight should be seen as part of the normal vaccination schedule.

Keywords: COVID-19; SARS-CoV-2; vaccine; vaccine efficacy; vaccine effectiveness; vaccine booster; BNT162b2; mRNA1273; Ad26.COV2.S; ChAdOx1-S; SARS-CoV-2 variants

1. Introduction

The COVID-19 pandemic was the first global pandemic in the era of modern air travel, involving a novel, highly-transmissible respiratory pathogen, with significant rates of severe disease and death. Vaccines, developed in record time, became a crucial and highly effective means of preventing severe disease. Other mitigation measures slowed spread and, when used effectively, reduced mortality rates, but in the end were only stopgaps. While the origins of SARS-CoV-2 remain debated, the risk of future zoonotic respiratory pathogens entering the general human population remains high.[1] A future pathogen could have some or all of the features that made COVID-19 so difficult to control, including asymptomatic spread, aerosol spread; high transmissibility, and rapid evolution, including evolution to evade immune response even when the immune system was primed by vaccination or prior infection.

Thus, it is critical to use the experience with COVID-19 to study the effectiveness and timing of vaccination, as a guide to advance planning for responding to the next major respiratory pathogen. With that goal in mind, we review here the COVID-19 pandemic vaccination campaign, including the timing and effectiveness of initial, primary vaccination and a booster dose. The massive body of research on the COVID-19 vaccines provides a unique opportunity to study vaccination practices against a novel respiratory pathogen, vaccine dosage and timing, vaccine waning over time, research

[1] We follow here the standard practice of referring to the virus as SARS-CoV-2, and to the disease as COVID-19.

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designs that can address selection effects when measuring vaccine effectiveness (VE), and how to measure effectiveness, including against which endpoints.

We provide here an installment on the broader project of learning the lessons that one can from this pandemic, as a guide to planning for the next one. We focus on what is now known about initial and longer-term effectiveness for the four principal COVID-19 vaccines used in the U.S. and Europe, against four different endpoints (infection, symptomatic infection, hospitalization, and death). We focus on 2021 – the period dominated by the initial virus variant and the Alpha and Delta variants. We do not study the Omicron-dominant period that began at the end of 2021, both because studying the Omicron period is empirically challenging given limited information about infection rates, due to the widespread use of at-home testing, and the practical reality that by the end of the early 2022 Omicron wave, almost the entire population was vaccinated, infected, or both, and thus no longer naïve to the SARS-CoV-2 virus.[81][82] We study the four COVID-19 vaccines that were widely used in the United States (US), Canada, Israel, the United Kingdom (UK), and the European Union. Two were mRNA-based: BNT162b2 (Pfizer-BioNTech) and mRNA1273 (Moderna). Two used an adenovirus-vector: Ad26.COV2.S (J&J) and ChAdOx1-S (AstraZeneca). BNT162b2, mRNA1273, and ChAdOx1-S are two-dose vaccines; Ad26.CoV2.S is single dose.

This critical review reports vaccine-specific evidence from studies known to us or available on PubMed through August 15, 2022, from clinical trials and observational studies; including evidence on waning VE for the two, primary vaccine doses, and the value of a third, booster dose for the Delta (VoC B.1.617.2) and earlier SARS-CoV-2 variants.

The use and timing of booster doses was initially controversial [1], partly reflecting disagreement on the goals of vaccination. Booster skeptics asserted that the principal goal of vaccination should be to prevent severe disease and death, and wanted to wait for strong evidence of waning against severe disease before authorization of boosters. Proponents of more rapid booster rollout were more willing to accept imperfect evidence on waning in the middle of an ongoing pandemic. The booster proponents were also more willing to provide boosters to younger persons, not at high risk of severe disease, to limit spread to higher risk persons (see [83] for evidence supporting this strategy.) Neither side could draw on experience with a prior, novel, highly transmissible respiratory pathogens with significant rates of severe disease and death. The most relevant prior pandemic, the 1918 influenza pandemic, predated modern air travel and vaccine development. This review provides such evidence by examining COVID-19 vaccine effectiveness from widespread deployment of vaccines at the beginning of 2021 through the emergence of the Omicron variant.

This review assesses VE for four endpoints: any infection; symptomatic infection; hospitalization; and death. It builds on and extends a prior review [58], which covered fewer studies (18) for a shorter period (through December 2, 2021), reported waning VE against infection but only "minimal" waning against "severe disease" (thus supporting the booster-skeptics' view) and did not study death as an endpoint. The review in [73] does not address waning; the review in [84] covers only early-2021 studies; the review in [85] is limited to randomized trials, which did not have sample sizes sufficient to study severe disease.

This review provides strong evidence of progressive waning of VE with time since vaccination against all endpoints, including hospitalization and death. BNT162b2 VE shows a noticeable decline at 4-5 months; mRNA1273 wanes somewhat more slowly. ChAdOx1-S has both lower initial VE than the mRNA vaccines, and substantial waning; Ad26.COV2.S has much lower initial VE but less waning. An mRNA booster substantially increases VE for symptomatic infection, hospitalization, and death. This supports the value of boosters for all adults, starting no later than 5-6 months after vaccination. Less definitive evidence suggests booster waning and the value of a fourth dose for ages 60+.

An innovation in this review is to stress remaining risk (RR = 1 – VE) as a core measure of interest.[79] For highly effective vaccines, a small apparent drop in VE can imply a large percentage change in RR. For example, a drop in VE against death from 95% to 90% implies a doubling in RR

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and thus in mortality among vaccinated persons. RRs can also provide a basis for comparing vaccines that is more sensitive than VE to moderate differences in risk.

2. Materials and Methods

2.1. Scope of Review and Literature Search

To be included in this review, a study needed to report efficacy for full primary vaccination with standard timing between doses, against one or more of the four endpoints. The exclusion criteria were: (i) the source reported vaccine-specific results; (ii) the source reported time since vaccination, so that we could assess evidence for waning; (iii) the sample was large enough to provide reasonable precision for the reported endpoint(s); (iv) the sample did not have apparent biases that could affect generalization (as would be the case for, e.g., studies of healthcare workers or military veterans); and (v) the study included an appropriate control group.

Since early 2021, the authors manually tracked studies of COVID-19 VE. This evidence was combined with a PRISMA-compliant review of all papers indexed by PubMed (including preprints) from December 1, 2020, through August 15, 2022, using search criteria which required the title, abstract, or keywords to refer to: (1) disease or pathogen name; (2) one or more of the studied vaccines; and (3) vaccine efficacy or effectiveness. This initial search returned > 10,000 papers; it was therefore modified to exclude papers with titles referring to adverse effects, specific populations (e.g., children), high-risk conditions, and antibody levels, which are outside the scope of this review. Comments, responses, and reviews were excluded as not providing primary evidence. See Appendix for search details.

The revised PubMed search returned 1169 results, which were screened based on title and abstract. This screening produced 183 candidates (89 new, 94 previously identified in our manual review), which were retrieved and evaluated against the inclusion and exclusion criteria. Sixty-three papers passed this assessment (27 new, 36 previously identified). Of the 18 studies included in [58], 12 are included here; the other 6 did not meet our inclusion and exclusion criteria. The Appendix provides a PRISMA flowchart and details on inclusion decisions.

2.2. Data Limitations; Implications for Inclusion and Presentation of Results

An ideal VE study would: (i) report vaccine-specific and variant-specific evidence; (ii) report time of both "full" primary vaccination (below, simply "vaccination") and infection or other endpoint; (iii) include a matched, unvaccinated control group; (iv) cover a population-representative sample, large enough to provide reasonably tight confidence intervals (CIs); (v) report VE or RR for standard, well-defined endpoint(s); (vi) report results within age ranges; and (vii) study a post-vaccination period long enough to allow more severe endpoints to be reached (for example, studying post vaccination mortality within 30-40 days after vaccination is insufficient)[67,74]. Even the best available studies do not achieve all this. Therefore, compromises are needed in assessing which studies to rely on and which questions they can answer.

The principal analysis addresses the limited granularity of data on time since vaccination by grouping "early" evidence (up to 120 days since vaccination) and "late" evidence (after 120 days). We do not report results by gender or age range. The included studies are consistent with gender having only modest effects on VE and age having only modest effects on VE against the infection endpoints.[2],[75] More recent studies provide evidence that waning VE against hospitalization and death occurred principally for ages 60+.[86][87] VE is evaluated for the whole adult population, without controlling for prior infection. When VE was reported with-versus-without prior infection, we used without-prior-infection data. When multiple protocols were used, the lower VE rate is reported.

3. Results

Our review includes the initial clinical trials, as well as VE data for 2021, including data from late 2021 on booster VE against the Delta variant.

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3.1. Empirical Challenges and Choice of Endpoints

A major challenge in analyzing data across countries, trials, and observational studies is varying definitions of illness severity. These include asymptomatic, symptomatic, mild, requiring medical intervention, moderate, mild to moderate, serious, severe, moderate to severe, hospitalization, admission to an intensive care unit (ICU), critical, and death (among others, not strictly in severity order). Definitions of the same term can vary across nations and studies. Four severity categories emerged from the data as most feasible to examine: (1) any infection (with positive SARS-CoV-2 test); (2) symptomatic infection (infection plus presence of COVID-19 symptoms); (3) hospitalization, defined as symptomatic infection plus inpatient admittance; and (4) mortality with COVID-19 as a primary cause. For studies which report data for "severe disease" but not hospitalization, we generally assume VE for hospitalization equals reported VE for severe disease.

3.2. Evidence from Phase 3 Clinical Trials

The Phase 3 vaccine trials, summarized in Table 1, provide evidence for VE against symptomatic infection against then-prevalent variants. The primary endpoint for all four trials was symptomatic infection. There were too few hospitalizations and deaths to permit more than a rough assessment of efficacy for these outcomes.

Table 1. Vaccine Efficacy Rates Against Harmonized Endpoints in Phase 3 Trials.

	Efficacy vs.			
	Any Infection	Symptomatic Infection	Hospitalization	Death
Vaccine				
BNT162b2 (Pfizer-BioNTech)	NR	95%	100% [b, c, d]	100% [b, c]
mRNA1273 (Moderna)	NR	94·5%	100% [b, c]	100% [b, c]
Ad26.COV2.S (J&J)[a]	59·7%	66·5%	76·7-83·5% [a]	100% [b]
ChAdOx1-S (AstraZeneca)	27·3-64·3% [e]	70·4-74·0%	94·2-100% [b, c]	100% [b, c]

[a] The Ad26.CoV2.S protocol did not distinguish between actual hospitalizations and persons who came to the hospital but were not hospitalized, so the reported percentage understates efficacy against actual hospitalization. [b] Results reported as "100%" indicate no qualifying events in the treatment group, and do not imply actual efficacy of 100%. [c] Inferred from no adjudicated cases in the treatment group requiring hospitalization. [d] The formal Pfizer submission to the FDA reported no hospitalizations among vaccinated persons, but 4 individuals with "severe illness," of whom one was in the vaccine group (not hospitalized). The related academic article [7] reported 6 severe cases, one in the vaccine group. [e] Protocols for defining asymptomatic infection varied across the countries included in the ChAdOx1-S trial, so the reliability of this point estimate is limited. NR = not reported or computable from the reported data. Data for BNT162b2,[3] mRNA1273,[4] and Ad26.CoV2.S[5] is from documents provided by the U.S. Food and Drug Administration (FDA) to Vaccines and Related Biological Products Advisory Committee meetings. Additional data for Ad26.COV2.S from [53],[61], which report lower efficacy against hospitalization than the FDA submission. Data for ChAdOx1-S is from [6],[31].

The Phase 3 trial results were highly promising, especially for the mRNA vaccines. Efficacy against symptomatic disease and apparent efficacy against hospitalization or death were high. The viral vector vaccines (Ad26.CoV2.S and ChAdOx1-S) showed lower efficacy against symptomatic disease, but performed strongly against hospitalization or death, especially ChAdOx1-S.

3.3. Early Observational Evidence

Table 2 summarizes evidence on VE in the general population within 120 days after vaccination. Israeli data on BNT162b2 is particularly compelling, given high-quality, population-level data, and

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several excellent research groups. Qatar also vaccinated principally with BNT162b2 has similar data quality but a much younger (91% under age 50) population. Data on ChAdOx1-S is limited because many UK studies did not report vaccine-specific results and the UK used an extended time interval between doses.

Table 2. Early Observational Evidence on Vaccine Effectiveness (pre-Delta).

	Efficacy vs.			
	Any Infection	Symptomatic Infection	Hospitalization [b]	Death [b]
Vaccine				
BNT162b2	65·1 - 93·8% [a]	86·0 - 97·7%	87·0 - 100·0%	91·1 - 100·0%
mRNA1273	65·1 - 96·4%	84·9 - 96·3%	90·6 - 100·0%	96·0 - 99·0%
Ad26.CoV2.S	64·0 - 74·2%	NR	71·0 - 83·5%	78·0 - 82·8%
ChAdOx1-S	63·1 - 67·0%	44·5 – 74·5%	75·7 - 95·2%	93·0 -94·1%

Table sources: [8], [10],[11],[12],[13],[14],[15],[16],[38],[40],[41].[43],[44],[46],[47],[49],[51],[68],[75]. The samples in [12] and [13] overlap. [a] The value for [11] is an average over 0-4, 5-9, and 10-14 weeks after second dose. [b] Results reported as "100%" indicate no qualifying events in the treatment group and do not imply actual VE 100%. Table reports point estimates from the indicated studies. Where there are multiple studies, the range of point estimates are reported. The principal relevant variants for these studies were the late 2020, Alpha, and Beta variants.

Overall, the evidence for the mRNA vaccines and ChAdOx1-S was consistent with the clinical trials, and provided large-sample evidence on strong performance against hospitalization and death. Anecdotal evidence suggested that most vaccinated persons who required hospitalization were very old or had major comorbidities. The early studies also confirmed superior performance for the mRNA vaccines against symptomatic infection, compared to the viral vector vaccines. Ad26.CoV2.S efficacy against hospitalization and death was below the other vaccines.

3.4. Evidence on Waning, Principally against Delta Variant

By July 2021, the situation had greatly changed. The Delta variant had become dominant, and Israeli data provided evidence that VE for BNT162b2 had declined substantially against all outcomes by 5-6 months post-vaccination. Table 3 summarizes the evidence on VE more than 120 days after vaccination. Delta became dominant over the same period in which VE was waning. We do not attempt to decompose waning into waning against earlier variants versus lower VE against Delta. Both effects are likely present.[3],[17].[56]

The 120-day lower bound was chosen based on evidence of clinically important waning beginning around then, and the small number of studies presenting data for a longer period since vaccination and permitting finer decomposition. Since waning is progressive, the point estimates in Table 3 overstate VE after longer periods.

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Table 3. VE Against Harmonized Endpoints Four-plus Months After Vaccination, Against Delta.

	Efficacy vs.			
	Any Infection	Symptomatic Infection	Hospitalization	Death
Vaccine				
BNT162b2	0·0 – 54·0% [a,b]	0·0 – 70·1% [a,b]	71·5 – 90·7%	83·0 – 90·4%
mRNA1273	0·0 – 80·0% [b]	52·1 – 81·9%	61·0 – 92·3%	88·0 – 93·7%
Ad26.CoV2.S	36·0%	37·5 – 64·3%	65·0 – 80·0%	73·0 – 80·0%
ChAdOx1-S	NR	0·0 – 59·0% [b]	52·3 – 77·0%	78·7 - 82·0%

Table sources: [11], [14],[16],[18],[19],[20],[21],[40],[41],[43],[48],[52],[75]. [a] For BNT162b2, [11] reports negative point estimates for any infection and symptomatic infection as 0.0. Post-approval clinical trial results, not included in Table 3 because they predated Delta, also found waning against symptomatic infection.[32] [b] Insignificant negative point estimates in a few studies are reported in this table as 0%. Table reports point estimates from indicated studies. Where there are multiple studies, the range of point estimates are reported.

Table 3 provides evidence of waning for all vaccines across all outcomes. It also provides evidence for comparative ranking of vaccines. mRNA1273 wanes more slowly than BNT162b2, and the mRNA vaccines outperform the viral vector vaccines.

The VE declines against hospitalization and death may appear small. However, Tables 1-3 adopt the standard practice of reporting VE as percent reduction in risk, relative to no vaccination. An alternative view, adopted in Table 4, would focus instead on remaining risk (RR) = 100% - VE. RR is sharply higher after waning, including against hospitalization and death, for BNT162b2, mRNA1273, and ChAdOx1-S. Ad26.CoV2.S wanes less, but from a much higher base.

Consider mortality and the midpoints of the ranges in Table 4. For BNT162b2, RR against death increases from 4.5% to 13.3% (roughly tripling). For mRNA1273, RR against death increases from 2.5% to 9.2% (more than tripling, but from a lower base). For ChAdOx1-S, RR against death increases from 6.5% to 19.7% (tripling, from a higher base). These RR increases have major implications for mortality of vaccinated persons. Hospitalization risk also rises sharply for all three vaccines.

Table 4. Remaining Risk: < 120 days (Panel A) vs. > 120 days (Panel B) post-vaccination.

	RR vs.			
	Any Infection	Symptomatic Infection	Hospitalization [b]	Death [b]
Panel A: Evidence within 120 days after Vaccination				
BNT162b2	6·2 - 34·9%	2·3 - 14·0%	0·0 - 13·0%	0·0 - 8·9%
mRNA1273	6·3 - 34·9%	3·7 - 15·2%	0·0 - 9·4%	1·0 – 4·0%
Ad26.CoV2.S	25·8 - 36%	NR	15·6 - 29·0%	17·2 - 22·0%
ChAdOx1-S	33·0 - 36·9%	25·5 - 55·5%	4·8 - 24·3%	5·9 – 7·0%
Panel B. Evidence Over 120 days after Vaccination				
BNT162b2	46·0 - 100%	29·9 - 100%	9·3 - 28·5%	9·6 - 17·0%
mRNA1273	20·0 - 100%	18·1 - 48·8%	7·7 - 39·0%	6·3 - 12·0%
Ad26.CoV2.S	64·0%	35·7 - 62·5%	20·0 - 35·0%	20·0 - 27·0%
ChAdOx1-S	NR	41·1 - 100%	23·0 - 47·7%	18·0 - 21·3%

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Panel A reports point estimates for remaining risk (RR) soon after vaccination, based on from Table 2. **Panel B** reports point estimates for remaining risk allowing for waning, from Table 3. RR = (100% - VE).

3.5. Evidence on Booster Effectiveness Against Delta Variant

Data on booster VE is limited to the mRNA vaccines. The most complete data is for BNT162b2 from Israel, which began an aggressive booster vaccination campaign in July 2021, starting 5 months after initial vaccination.[88] Studies with later booster rollouts, cannot separate the booster effects from the large differences in infectiousness and immune evasion between the Delta and Omicron variants.

Table 5 reports evidence on booster VE both versus the vaccinated but unboosted (Panel A) and more limited evidence on booster VE versus the unvaccinated (Panel B). Reduced risk from the booster dose (Panel A) and VE for primary vaccination after waning (Table 3) can also be combined to estimate booster protection relative to the unvaccinated. For example, the low-end BNT162b2 estimate of 86% VE against death (Table 3), plus the low-end 90% risk reduction from the booster imply RR = (1-90%)*(1 - 86%) = 1.4% (98.6% VE). Thus, the booster dose can restore the high protection against hospitalization and death seen soon after vaccination (Table 2).

Table 5. Booster Effectiveness.

	Any Infection	Symptomatic Infection	Hospitalization	Death
Panel A. Risk Reduction (Booster vs. Vaccinated)				
Vaccine				
BNT162b2	86-91%	75-95%	70-95%	81-97%
mRNA1273		86-89%	82%	
Panel B. VE vs. Unvaccinated				
BNT162b2		90-93%	88-99%	99%
mRNA1273		89%	86%	

Table sources: Panel A. [22],[23],[24],[25],[26],[59],[60],[63],[64],[69]. Panel B. [53],[59],[64],[77], **Panel A**. Table reports point estimates for risk reduction for vaccinated plus boosted persons, versus vaccinated without booster, to nearest percent, for the indicated endpoints. Panel B. VE for vaccinated plus booster vs. unvaccinated. **Both panels**. Where there are multiple studies, the range of point estimates are reported. Values for severe illness are treated as equivalent to values for hospitalization.

4. Discussion

4.1. Developing Vaccines for a Novel Pathogen

The vaccines against COVID-19 were developed, tested in randomized trials for efficacy against symptomatic infection and for safety, and approved by regulators, in record time. The rapid approval surely saved millions of lives worldwide. But speed came with tradeoffs. The short interval between first and doses for the two-dose vaccines was established by the manufacturers with an eye to the minimum spacing needed for efficacy, rather than to optimal dose spacing for longer-lasting protection. There was always a likelihood that the initial protection would wane, and that a booster would be needed, even if the extent and speed of waning was yet to be determined. The initial trials were not sized to study efficacy against hospitalization and death, given the population-level rates of those endpoints.

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The initial speed was wonderful, and provides a model to build on. But both vaccine manufacturers and public health authorities fell short in planning for evaluation of waning, and of VE against severe disease. Observational data was potentially available on a massive scale, but in most countries was not systematically collected and analyzed (Israel and Qatar are notable exceptions).

This review offers evidence on VE against severe disease and on the waning that was actually experienced, against both infection and severe disease. It can guide the response to a future novel pathogen.

4.2. Overall Evidence on Booster VE

There is strong evidence of both: (i) vaccine waning against the Delta variant against all endpoints; and (ii) significantly higher VE following a booster. After initial caution,[88] the FDA now strongly supports the value of a booster dose, with the FDA commissioner and head of vaccines unit writing in May 2022, "it is critical that patients and caregivers understand the profound benefit of a booster dose of the mRNA vaccines."[65]

4.3. Re-examining Vaccine Dose Timing

The evidence for waning VE suggests that full vaccination for SARS-CoV-2 should be redefined to include an initial two-dose primary series plus at least one booster, 6 months or so after the first two doses. This vaccination pattern is familiar from recommended schedules for other vaccines.[27] The mRNA vaccines dominate the viral vector vaccines for areas where the cold-chain requirements for these vaccines can be met. Additional doses may be appropriate, at least for ages 60+,[67],[89],[90] but the value of a second or subsequent booster cannot be assessed within the time period of this study.

The interval between primary doses and subsequent (booster) dose(s), and whether that interval depends on vaccine type or patient age, are topics for future research. So is the value of mixing and matching vaccines, either across types (mRNA versus viral vector) or within types.[14] Decisions on when to recommend additional doses need to take into account the time needed for population rollout. A further factor is the risk, illustrated by the emergence of Omicron, of more infectious or immune-evasive variants. Moreover, distributing vaccine doses to a large population takes time. Thus, even if boosting at 6 months were optimal for individuals, earlier *availability* (perhaps at 5 months as Israel decided) would likely be preferable. The optimal number and timing of vaccine doses might be different for the previously infected, who face lower risk of severe disease.[37],[38],[39]

4.4. Comparing Across Vaccines: RR for Hospitalization and Death

For the primary vaccine series, RR against hospitalization or mortality provides a metric for comparing vaccines. A clear preference order emerges for both endpoints, both before and after waning: mRNA1273 > BNT162b2 > ChAdOx1-S > Ad26.CoV2.S. The RRs for mortality, measured at midpoints after waning, are 9.2% for mRNA1273; 13.3% for BNT162b2; 19.7% for ChAdOx1-S , and 23.5% for Ad26.CoV2.S. A similar gradient is seen for hospitalization. When comparing vaccines, the endpoint matters. Ad26.CoV2.S is initially inferior for all endpoints (Table 2) but wanes more slowly and after 120 days is comparable for infection (Table 3),[79] but remains inferior against mortality.

However, differences for the primary series may diminish after a booster. A U.S. study compares BNT162b2 and mRNA1273 and finds a BNT162b2/mRNA1273n odds ratio for mortality of 2.40 (z=4.26) after waning for primary vaccination, but only 1.25 (insignificant, z=0.50) after booster.[87] Whether larger differences between vaccines after booster dose would emerge over a longer time period is outside the scope of our study period. There was also limited evidence on how heterologous boosting compares to homologous boosting; one UK study finds similar VE against infection for ChAdOx1-S boosted with BNT162b2 versus homologous BNT162b2 booster.[35]

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4.5. Population Implications of Booster Use

Our analysis focused on booster benefit for the boosted. But there can also be benefit to others. One benefit is reduced infection spread. The relationship between reduced infection risk and reduced viral load could be supralinear, if boosted-but-infected people have lower viral loads than unboosted people, shorter duration of infectivity, or reduced rates of viral shedding. If R_t (the time-varying mean number of people infected by each initially infected person) exceeds 1, a single infection can lead to a large number of follow-on infections. Even if R_t is modestly below 1, a single infection predicts multiple follow-on infections. For example, for R_t of 0.9, each infection predicts roughly 5 additional infections ($0.9 + 0.9^2 + 0.9^3 + \ldots$). The young, who generally experience less severe illness, can infect the old, who are more likely to experience severe illness.[83] The vaccinated can infect the unvaccinated. The relevant R_t is time-varying and unknown, but greater booster uptake should imply at least some reduction in transmission. Also, at various times during the pandemic, including early 2022, many hospitals were at or beyond normal capacity, leading to higher mortality for COVID-19 and other conditions. Reducing infections also reduces demand for treatments that are in short supply.

4.6. Value of Harmonized Endpoints

There are no standard protocols for VE endpoints. A lesson from this project is the difficulty of reporting data for harmonized endpoints across studies and countries. We propose that useful categories, which researchers should report, should include any infection, symptomatic infection, hospitalization, death, and ideally a category between hospitalization and death (perhaps admission to intensive care). Even here, there will be play in the joints – what symptoms count as symptomatic infection, how to track asymptomatic infection reliably, and different criteria for hospitalization or intensive care. But these categories are more manageable than categories such as "severe" or "critical" disease, which may be feasible in a formal trial,[39] but translate poorly across countries and health systems.

4.7. Behavioral Differences Between the Vaccinated and Unvaccinated

The observational studies we rely on generally cannot address differences between vaccinated and unvaccinated persons in behavior or underlying health. For example, negative VE point estimates against infection after waning could reflect the vaccinated relaxing their guard against infection.[11],[14] Most studies do not match vaccinated to unvaccinated (beyond age and gender); those that do often do not control for prior infection; and matching cannot address behavior differences between the vaccinated and unvaccinated.

5. Conclusions

The mRNA-based COVID-19 vaccines were initially highly effective against all endpoints; the viral vector vaccines were effective but less so (Tables 1-2). However, all vaccines waned substantially against all endpoints and did so over a limited time period after primary vaccination. This is easier to see using RR as the metric (Table 4). Booster data for the mRNA vaccines shows substantial reduction in RR. Vaccine development and VE assessment could have, but did not, included explicit assessment of waning, using the observational data generated by the rollout of primary vaccination.

The experience with COVID-19 suggests that even with two-dose primary vaccination, initial vaccination planning for novel, highly-transmissible respiratory pathogens should reflect the potential value of at least one additional dose, and should include population-level surveillance plans to identify the timing and need for such a dose. Public health authorities also should prepare the ground for a possible additional dose, and not overpromise with regard to the duration of protection from initial vaccination.

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Appendix A

This paper and the Appendix A can be downloaded without charge from SSRN at: http://ssrn.com/abstract=4155493.

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