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COVID-19 Vaccine Efficacy and the Evidence on Boosters

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DRAFT

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Abstract

Background. The need for COVID-19 vaccine booster shots is controversial. Krause et al. [1] and others have argued that need for a COVID-19 booster for all adults has not been sufficiently established. The EU, UK, Canada, and Israel approved boosters for all adults, but U.S. regulators initially limited booster eligibility, waited nearly two months before allowing, and even longer before recommending boosters for all adults, with public health officials sending mixed messages on booster value.

Methods. The authors summarize vaccine efficacy 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 ChAdOxS-1), and evidence for waning efficacy over time, based on review of regulatory submissions and studies which met defined inclusion criteria.

Findings. Evidence on vaccine efficacy across multiple studies supports the conclusions that: (i) the mRNA vaccines experience significant declining efficacy after approximately six months, especially against infection but also against severe disease, with Pfizer declining faster than mRNA1273, but (ii) both mRNA vaccines outperform the Ad26.CoV2.S and ChAdOx1-S viral vector vaccines. Booster doses greatly strengthen antibody levels and reduce both symptomatic infection and severe disease.

Interpretation. Strong epidemiological evidence supports the value of a booster dose for COVID vaccines, roughly 6 months after initial vaccination. Boosters both protect those who receive them and provide large spillover benefits to others, both vaccinated and unvaccinated, by preventing downstream infections, some of which will lead to hospitalization and death; reducing shortage risk for monoclonal antibodies, antiviral medications and other currently scarce COVID treatments; and reducing hospital overload (and thus improving survival rates. The emergence of the Omicron variant strengthens their value. Comprehensive evaluation of vaccination dosage and timing, including boosters, are part of proactive public health response to COVID risk.

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COVID-19 Vaccine Efficacy and the Evidence on Boosters

Bernard Black and David Thaw

1. Introduction

Across the United States (US), Canada, Israel, the United Kingdom (UK), and the European Union (EU), four COVID-19 vaccines have been approved and widely deployed. Two are based on the mRNA platform: BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna). The U.S. and UK/EU each also have approved an adenovirus-vector vaccine: Ad26.COV2.S (Johnson&Johnson) in the U.S., and ChAdOx1-S (Oxford/AstraZeneca) in the UK/EU. BNT162b2 is used in all areas; Ad26.CoV2.S principally in the US; Astra-Zeneca principally in the UK and EU, and mRNA1273 principally in the US and the EU. BNT162b2, mRNA1273, and ChAdOxS-1 are two-dose vaccines; Ad26.CoV2.S is single dose.

A crucial question is whether, when, and for whom these vaccines need an extra (booster) dose. That question must be answered in real time based on available data. This study provides evidence on the waning efficacy of primary vaccination, the need for boosters, and the need to re-evaluate SARS-CoV-2 vaccination timing and dosage schedules as evidence on efficacy evolves and new variants emerge. The evidence reported below is based on review of the principal available studies. We focus on efficacy, because the vaccine safety profiles are excellent. At most, safety profiles might suggest recommending one vaccine over another depending on patient age and gender.

This study focuses, for manageability, on the studies the authors evaluate as most compelling after applying the inclusion criteria specified below. A systematic review is not yet appropriate given the emerging state of the data. We rely instead on our best knowledge of the constant flow of new results. Evidence is drawn from manufacturer submissions to regulators for vaccine approval, published studies, and preprints from reputable research groups. The best studies come primarily from Israel, UK, US, and Qatar. Vaccine efficacy is evaluated for the whole adult population, without controlling for prior infection.

To briefly summarize the results presented below, there is strong evidence that efficacy of the Pfizer-BioNTech vaccine (BNT162b2) against the currently dominant Delta variant (SARS-CoV-2 VoC B.1.617.2) declines with time since vaccination, against both any infection and symptomatic infection. The decline is noticeable at 4-5 months, and becomes progressively stronger after that. Efficacy data is most extensive for BNT162b2. However, there is also evidence for declining efficacy for the other vaccines, and both lower initial efficacy and declining efficacy for the viral vector vaccines (ChAdOxS-1 and Ad26.CoV2.S). This evidence supports the value of boosters for all adults: starting roughly no later than 6 months after vaccination for BNT162b2; perhaps somewhat longer for mRNA1273; and right away for the viral vector vaccines. These declines in protection imply that, as for a number of other vaccines, the concept of full vaccination likely needs to include a third dose after 6 months or so.

Additional factors, beyond the evidence discussed below, support the value of boosters, and of authorizing them somewhat earlier than when efficacy waning becomes significant. A crucial aspect of efficacy is controlling infection, including asymptomatic infection, and thus spread. One infection can lead to many others, depending on the reproduction rate R_t (which depends on multiple population-level factors, including the percentage SARS-CoV-2 naïve, percent vaccinated, percent receiving a booster, time since vaccination or booster, which vaccine(s) are used, and adherence to masking and other non-pharmaceutical interventions (NPIs). If R_t is even close to 1, the number of downstream infections from

each initial infection is large. Preventing infections also reduces the risk of "long COVID," which appears important, apparently at all ages, even after mild infection. Proactive vaccination policy can also reduce the risk from more contagious or vaccine-resistant variants.

Moreover, we are in a pandemic, in which some hospitals are or could be at or beyond normal capacity. As hospitals near capacity, mortality rises both for COVID and other conditions, as does the practical need for economically and socially costly government interventions. For example. Israel's government viewed rapid booster rollout as a way to avoid hospital overload and another lockdown.[2] Reducing infections also reduces the demand for monoclonal antibodies and other treatments that are in short supply.

2. Vaccine Efficacy: Initially and Now

This analysis includes vaccine efficacy data from 2021 (through 8 December), from manufacturer submissions, published articles, and preprints from reputable research teams, at three broad points in time: (i) clinical trials (generally late 2020); (ii) early 2021 shortly after mass vaccination began (prior to the rise of the Delta variant); and (iii) later on, during summer and fall 2021 (principally against the Delta variant).

2.1. Data Limitations

An ideal efficacy study would: (i) report vaccine-specific efficacy; (ii) report time of both vaccination and infection; (iii) report efficacy by variant; (iv) compare the vaccinated to a matched control group of similar unvaccinated persons; (v) cover a population-representative sample; (vi) report efficacy for several well-defined endpoints; (vii) report results after "full" vaccination (below, simply "vaccination"); (vii) report results within age ranges; and (viii) have sufficient sample size to provide reasonably tight confidence intervals. Even the best available studies, while excellent in many ways, do not achieve all this. Therefore compromises are needed in assessing which studies to rely on, and which questions they can answer.

This analysis addresses limited data on time since vaccination by grouping together "early" evidence (up to 120 days since vaccination) and "late" evidence (after 120 days since vaccination). It was not feasible to require that a study report data by age range for inclusion in this analysis, but the available evidence is consistent with patient age having only a modest effect on the results reported below.[3]

A major challenge in analyzing data across countries, trials, and observational studies is varying definitions of illness severity. These terms variously include asymptomatic, symptomatic, mild, moderate, serious, severe, requiring medical intervention, 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 emerge from the data as the most feasible to examine: (1) any infection (with positive SARS-CoV-2 test); (2) symptomatic infection, defined as infection plus the presence of symptoms associated with COVID-19; (3) hospitalization, defined as symptoms associated with COVID-19 resulting in inpatient admittance for treatment and a positive SARS-CoV-2 test; and (4) mortality, adjudicated as including COVID-19 as a primary cause. For studies which report efficacy for "severe" or "critical" disease but not hospitalization, we generally assume efficacy for hospitalization is the same as the reported efficacy for severe or critical disease.

A challenge with no good solution is whether the vaccinated and unvaccinated are similar on medical and behavioral demographics. Many studies do not explicitly match vaccinated to unvaccinated; those that do often do not control for prior infection; and matching cannot address the likely behavior differences between the vaccinated and unvaccinated that affect the likelihood of infection (e.g., adoption of NPIs).

When efficacy for individuals with versus without prior infection was reported, data without prior infection is reported. When multiple protocols were used, the lower efficacy rate is reported. The Appendix provides details on inclusion decisions.

2.2. Initial Evidence from Phase 3 Clinical Trials

The Phase 3 vaccine trials presented promising results indicating vaccine efficacy against symptomatic infection, hospitalization, and mortality, with more limited evidence and lower efficacy against any infection. The results are summarized in the following table. The primary endpoint for all four trials was symptomatic infection, and 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 Initial Phase 3 Trials

NR = not reported or computable from the reported data. Data for BNT162b2,[4] mRNA1273,[5] and Ad26.CoV2.S[6] is from review documents provided by the U.S. Food and Drug Administration (FDA) to Vaccines and Related Biological Products Advisory Committee meetings for each vaccine. Data for ChAdOxS-1 is from Voysey et al.[7]

	Efficacy vs.			
	Any Infection	Symptomatic Infection	Hospitalization	Death
Vaccine				
BNT162b2 (Pfizer)	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% [e]	66·5%	83·5% [a]	100% [b]
ChAdOx1-S (AstraZeneca)	27·3% [e]	70·4%	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 that there were no qualifying events in the treatment group. This does not imply actual expected efficacy of 100%.

[c] Inferred from the lack of adjudicated treatment group cases requiring hospitalization.

[d] The formal Pfizer submission to the FDA reported no hospitalizations among vaccinated persons, but reported 4 individuals with "severe illness," of whom one was in the vaccine group (not hospitalized). The related academic article [8] reported 6 severe cases, one in the vaccine group.

[e] Protocols for defining asymptomatic infection varied across the countries included in the ChAdOxS-1 trial, so the reliability of this point estimate is limited.

The initial Phase 3 trial results were highly promising, especially for the mRNA vaccines. While the mRNA trials did not assess efficacy against any infection, efficacy against symptomatic disease and apparent efficacy against hospitalization or death were high. The viral vector vaccines (Ad26.CoV2.S and ChAdOxS-1) showed lower efficacy against symptomatic disease. However, this could partly reflect the relative prevalence of the B.1.1.7 (Alpha) and B.1.351 (Beta) variants circulating in the UK and South Africa during those trials and both (especially ChAdOxS-1) performed strongly against hospitalization or death.

2.3. Early Observational Evidence

We turn next to evidence on efficacy in the general population within 120 days after vaccination, summarized in Table 2. The inclusion criteria for this table (see Appendix for details) were: (i) results reported by vaccine type for one or more outcomes; (ii) time since vaccination less than 120 days; (iii) the

sample selection criteria have no major biases which might affect generalization to a broader population; (iv) the study compares fully vaccinated to unvaccinated persons, rather than only to earlier or later vaccinated persons; and (v) reasonably large sample size.

The data on BNT162b2 comes principally from Israel and is particularly compelling, given vaccination beginning in early 2021 (Israel and Qatar were leaders in early vaccination), high-quality, population-level data, and several excellent, often competing research groups. Qatar also vaccinated principally with BNT162b2, has a smaller, more diverse, but much younger (91% under age 50) population than Israel, with similar data quality and a strong research group. Data on ChAdOxS-1 is limited due to a number of UK studies not reporting vaccine-specific results.

Although none of the trials measured vaccine efficacy against transmission from the vaccinated to others, the early observational data on incidence rates following vaccination suggests that all four vaccines significantly reduced transmission but did not provide sterilizing immunity.

Table 2: Early Observational Evidence on Vaccine Efficacy (pre-Delta)

Table reports point estimates from the indicated studies. Where there are multiple studies, the range of point estimates are reported.

	Efficacy vs.			
	Any Infection	Symptomatic Infection	Hospitalization	Death
Vaccine				
BNT162b2	65·1% - 93·8% [a]	87·1% - 97·7%	87·0% - 100·0%	95·2% - 100·0%
mRNA1273	NR	88·7% - 96·3%	93·0% - 100·0%	NR
Ad26.CoV2.S	NR	NR	71·0%	NR
ChAdOxS-1	NR	44·5% - 74·5%	95·2%	94·1%

Table sources: [9], [10], [11]; [12], [13], [14], [15], [16], [17]. The samples in [13] and [14] overlap.

[a] [13] reports data for infection without documented symptoms; [14] reports data for asymptomatic infection. The value for [12] is an average over 0-4, 5-9, and 10-14 weeks after second dose; an Appendix to this source reports lower values (average = 52.3) against asymptomatic infection.

Overall, the evidence for the mRNA vaccines and ChAdOxS-1 was consistent with the clinical trials, and provided large sample evidence on strong performance against hospitalization and death. 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 was below the other vaccines.

In addition, an Israeli Health Ministry report (a credible source, but without sufficient detail to warrant inclusion in Table 2) reported 99% BNT162b2 efficacy against hospitalization and death.[18] Moreover, anecdotal evidence suggested that most vaccinated persons who required hospitalization were either very old or had major comorbidities. Much of this evidence involved the initial strains (A, B, and B.1) or (for ChAdOxS-1) the Alpha (B.1.1.7) variant, which was prevalent in the UK in early 2021.

2.4. Later Observational Evidence on Waning Efficacy against the Delta Variant

By July 2021, the situation had greatly changed. The highly infectious Delta variant had become dominant in many countries. And Israel data provided evidence that BNT162b2 efficacy had declined substantially

against all outcomes by 6 months post-vaccination. We summarize the evidence on waning efficacy in Table 3. Because Delta became dominant over the same period in which vaccine efficacy was waning, it is hard to decompose waning efficacy into waning against earlier variants versus lower efficacy against Delta, and this analysis does not do so (Keehner, et al., attempt decomposition[19]).

Table 3 summarizes estimates of vaccine efficacy more than 120 days after vaccination. The inclusion criteria were the same as for Table 2, except for the period since vaccination. The 120-day lower bound was chosen based on evidence of clinically important reduction in efficacy against infection beginning around then, and the small number of studies that present data for a longer period since vaccination. Since waning is progressive, the point estimates and ranges in Table 3 overstate efficacy after longer periods such as six months.

Table 3: Vaccine Efficacy Rates Against Harmonized Endpoints Four-plus Months After Vaccination

Table reports point estimates from indicated studies. Where there are multiple studies, the range of point estimates are reported.

	Efficacy vs.			
	Any Infection	Symptomatic Infection	Hospitalization	Death
Vaccine				
BNT162b2	0·0% - 47% [a]	0·0% - 70·1% [a]	64·0% - 90·7%	88·4% - 90·4%
mRNA1273	NR	67·0% - 81·9%	85·0% - 92·3%	93·7%
Ad26.CoV2.S	NR	37·5% - 64·3%	65·0% - 80%	80%
ChAdOxS-1	NR	0% − 47·3% [b]	77·0%	78·7%

Table sources: [10], [12], [3], [20], [21], [15],[17], [22], [23], [24].

[a] For BNT162b2, [12] reports negative point estimates for any infection and symptomatic infection as 0.0.[12]

[b] For ChAdOxS-1 [15] reports a statistically insignificant negative point estimate against symptomatic infection, which is reported in the table as 0%.[15]

Table 3 provides evidence for a clinically meaningful decrease in efficacy over time for all vaccines, across all outcomes for which there is available data. The decline is not well measured for the any infection outcome, but among the other outcomes, is steepest for symptomatic infection. Thus, a substantial drop in efficacy against any infection is likely. Efficacy against hospitalization and death declined less sharply than against infection, but all four vaccines exhibited a substantial increase in the remaining risk (e.g., going from a 98% to a 90% reduction in risk means going from remaining risk of 2%; to 10%, thus a five-fold increase). Thus, after six months and with Delta as the dominant variant, none of the four vaccines provide sufficient efficacy to support the relaxation of non-pharmaceutical interventions (NPIs) in early summer 2021.

Table 3 also provides evidence for a comparative ranking of vaccines. mRNA1273 appears to wane more slowly than BNT162b2, but both mRNA vaccines outperform the viral vector vaccines in preventing hospitalization and death.

Several additional studies that did not meet the inclusion criteria (lacked time since vaccination) provide further evidence of progressive waning. A UK study reports waning using blended UK data on BNT162b2 and ChAdOxS-1.[15]   A study of U.S. military veterans provides evidence of waning efficacy against

infection (mostly symptomatic infection, since there was no systematic testing of the study population).[25] The figure below reports hazard ratios, using a Cox proportional hazard model. mRNA1273 efficacy decays more slowly, and Ad26.CoV2.S more rapidly, with BNT162b2 in the middle.
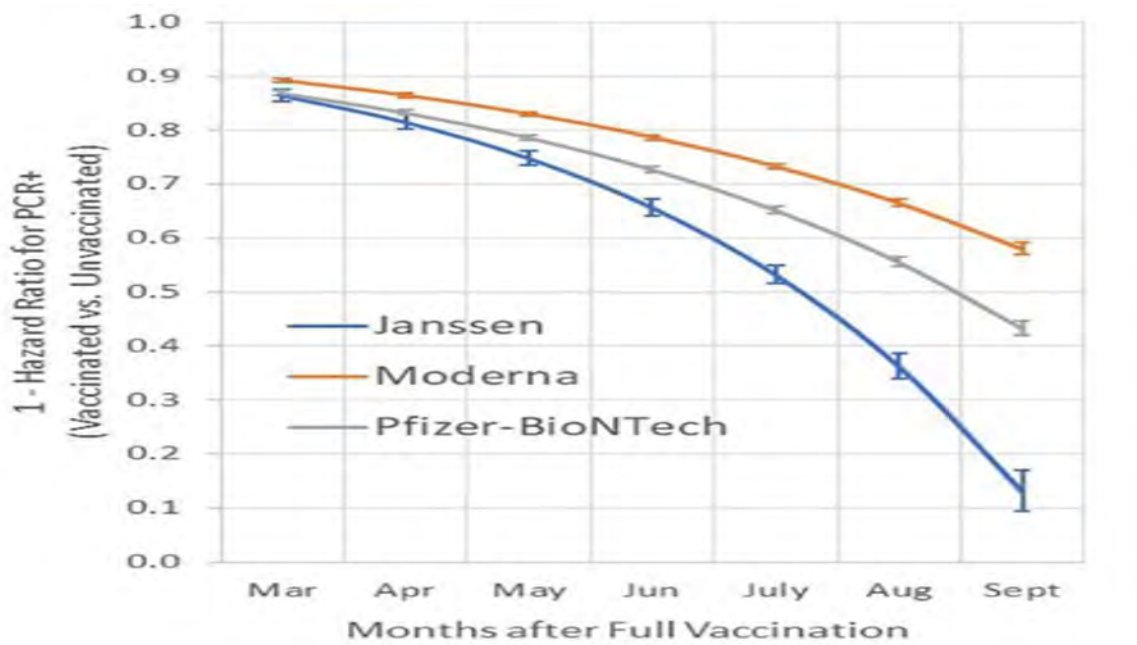

Figure source: [25]

2.5. Evidence on Booster Efficacy Against Delta Variant

There are two sources of evidence on increased vaccine efficacy, after a booster dose. The most direct is evidence on outcomes after the booster dose. To date, the only solid data is for BNT162b2, and comes from Israel, which began an aggressive booster vaccination campaign beginning in July 2021, with boosters available starting 5 months after initial full vaccination. Several studies report relative risk reduction starting 12 days after a booster dose, versus risk for vaccinated persons with no booster. None directly compares risk for persons with three vaccine doses to risk the unvaccinated. We summarize the results on risk reduction from a booster dose in Table 4.

Table 4: Risk Reduction for Vaccinated Plus Booster versus Vaccinated without Booster

Table reports point estimates for risk reduction for vaccinated plus boosted persons, versus vaccinated without booster, from indicated studies, to nearest percent, for the indicated harmonized endpoints. Where there are multiple studies, the range of point estimates are reported. Values for severe illness are treated as equivalent to values for hospitalization.

	Relative Risk Reduction for			
	Any Infection	Symptomatic Infection	Hospitalization	Death
Vaccine				
BNT162b2	86-91%	NR	92-95%	90-93% [a]

Table sources: [26], [27], [28], [29], [30].

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Reduced risk from the booster dose (Table 4) and efficacy of primary vaccination (Table 3) can be combined to provide rough estimates of protection for persons receiving boosters relative to the unvaccinated. For example, the low-end estimates for BNT162b2 of 88·4% efficacy against death from Table 3, plus risk reduction of 81% from Table 4, for booster versus vaccinated, imply remaining risk of (1-88·4%)*(1-81%) = 0.022, and thus efficacy of 97·8%. Thus, the booster dose appears to restore the high levels of protection against hospitalization and death seen in the early observational studies.

A second source of evidence is higher antibody titers after the booster dose, which are likely to correlate with increased protection. A small Israeli study reports a 58-fold increase in median igG antibody levels for patients age 60+, measured 10-19 days after, versus just before, a BNT162b2 booster dose.[31] A second Israeli study of older healthcare workers (median age 67) reports an increase from a median igG level of 3.7 to over 150 (maximum value measured) 10 days after booster.[32] And a U.S. booster study for BNT162b2, mRNA1273 and Ad26.CoV2.S reported strong anamnestic humoral response, with some advantage for heterologous boosting.[33]

3. Discussion

3.1. Need for a Third Dose and for Re-examining Vaccine Dose Timing

The evidence for waning efficacy against infection, observed for BNT162b2, Ad26.CoV2.S and ChAdOxS-1 in Table 3, and likely for mRNA1273 (albeit more slowly), suggests reconsideration of what counts as full vaccination for virus-naïve people to include a third dose, spaced 6 months or so after the first two doses. This vaccination pattern is familiar from recommended schedules for other vaccines.[34] Similarly, the weaker protection from Ad26.CoV2.S casts doubt on the efficacy of a single-dose, as a either a complete vaccine or as a primary series. Collectively, the evidence supports an initial two-dose primary series regime plus at least one booster dose. Additional doses may turn out to be appropriate as well, especially if the virus continue to evolve; perhaps with updating the vaccine structure to address Omicron (B.1.1.529) or other new variants.

The time interval between the primary series dose(s) and subsequent (booster) dose(s), and whether that time 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. Nordstrom et al. report Swedish evidence that one dose of ChAdOxS-1, followed by one does of an mRNA vaccine (principally BNT162b2) provides protection against infection similar to mRNA1273, and superior to two ChAdOxS-1 or two BNT162b2.[15] In assessing when health authorities should recommend a third dose, an important consideration is the need for population-level vaccination in the presence of rapid-transmission variants such as Delta; as well as the risk, illustrated by the recent emergence of Omicron, of new variants which are more infectious or more able to generate breakthrough infections in the vaccinated or repeat infections. Thus, even if boosting at six months were optimal for individuals, earlier *availability* (perhaps at 5 months as Israel decided) is likely preferable taking into account distribution logistics, and the value of reducing transmission.

3.2. Population Implications of Reduced Infection Rates

The analysis in Part 2 focused on booster benefit for the boosted. But there is also important benefit to others. Reduced infection implies reduced infectivity. It is likely that 90% (say) relative efficacy against becoming infected implies similar relative efficacy in transmitting to others – both vaccinated and unvaccinated. The relationship between reduced infection and reduced infectivity could be supralinear, if boosted-but-infected people have lower viral loads than unboosted people, shorter duration of infectivity, or are less likely to be superspreaders. In theory, 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 very large number of follow-on infections. Even if R_t is modestly below 1, a single infection predicts multiple follow-on infections. For example, if R_t is 0.9, each infection predicts roughly 5 additional infections ($0.9 + 0.9^2 + 0.9^3 + ...$). The young, who will mostly survive infection, can infect the old, who may not. The vaccinated, who are more likely to survive, can infect the unvaccinated. The relevant R_t is time-varying and unknown. Still, greater use of boosters implies substantial prevention of onward transmission.

Much of the U.S. discussion of boosters, including the Krause et al. critique, the discussion by the advisory committees to the U.S. Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) focused on severe disease and death as the principal outcomes of concern.[1] Some discussion diverged into whether the same vaccine dose would be more useful if given to the unvaccinated than as a booster, which is not within the FDA's authority to judge.[35] The U.S. initially limited booster availability to the elderly and those at high risk of infection, later authorized boosters for all adults, but recommended boosters only for those aged 50 and above; and still later recommended boosters for all adults. We view the focus on severe disease among the already vaccinated as too narrow, and the almost immediate expansion of the CDC booster recommendation in response to detection of Omicron as evidence of the limitations of reactive booster protocols. Yes, even after six months, the mRNA vaccines still provide substantial protection against hospitalization or death, with younger people at lower risk of these outcomes, vaccinated or not. But vaccinated younger persons can still become very sick or die, and can spread infection to older people and the unvaccinated. The value of reducing infection spread needs to be central to any discussion of the number and timing of vaccine doses.

Boosters for the already vaccinated will not replace vaccinating the unvaccinated, but there is no reason to think that public health messaging on the value of boosters for the vaccinated will undermine other efforts. Nor are booster doses used in more affluent countries likely to displace initial doses in less affluent ones. The central challenge for poor countries is distribution, not supply.[36]

3.3. Vaccine Doses and Timing for the Previously Infected

The available evidence did not allow this study to examine vaccine efficacy conditioned on prior infection. The optimal number and timing of vaccine doses might be different for the previously infected, who face lower risk of infection, especially severe infection 37],[38],[39], [40] and have a strong humoral response to vaccination.[41]

3.4. Value of Reporting Using Harmonized Endpoints

There are currently no global standard protocols for which endpoints vaccine trials or efficacy studies should report. An important lesson from this project is the difficulty of reporting efficacy for even roughly harmonized endpoints across multiple studies in multiple countries. We propose that useful infectious disease categories, which researchers should aim to report, should include any confirmed infection, any

symptomatic infection, hospitalization, death, and ideally a standardized category that would be intermediate between hospitalization and death (perhaps admission to intensive care). Even here, there will be play in the joints – how to handle incomplete population testing, what symptoms count as symptomatic infection, and different criteria for hospitalization or intensive care. But these categories are more manageable than categories such as "severe" or "critical" disease, which translation poorly across countries and health systems.

3.5. Behavioral Differences Between the Vaccinated and Unvaccinated

A limitation of the observational studies we rely on, and thus of this analysis, in addition to the limitations discussed above, is the potential for behavior differences between vaccinated and unvaccinated persons. In particular, negative point estimates of vaccine efficacy against infection after waning in Table 3 for BNT162b2 [12] and ChAdOxS-1 [15] could reflect a tendency of the vaccinated tend to relax their guard against infection, rather than vaccination causing increased infection risk, which is biologically implausible. More generally, the efficacy estimates in Tables 2 and 3 could be biased downwards by behavioral differences.

3.6. Implications of the Omicron Variant

The evidence on vaccine efficacy against the Omicron variant was too preliminary to warrant inclusion in this study. However, there is no reason to believe that public health advice would be different for Omicron than for the currently dominant Delta variant. To the contrary, early evidence suggests greater vaccine escape and reinfection risk for Omicron [42], against which a third dose provides substantial protection [43].

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Appendix for

COVID-19 Vaccine Efficacy and the Evidence on Boosters

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The paper can be downloaded without charge from medRxiv at:
[*url to come]

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Appendix for COVID-19 Vaccine Efficacy and the Evidence on Boosters

Bernard Black and David Thaw

Abstract: This Appendix contains additional details about the studies relied on in Black and Thaw, COVID-19 Vaccine Efficacy and the Evidence on Boosters (2021). It also contains additional details on the study inclusion criteria and definitions of outcome measures.

Appendix for COVID-19 Vaccine Efficacy and the Evidence on Boosters

Bernard Black and David Thaw

1. Countries from Which Data is Drawn: Strengths and Limitations

The studies which satisfied our inclusion and exclusion criteria come principally although not exclusively from Israel, the UK, the US, and Qatar.

Israel. Many of the more compelling studies come from Israel. Israel uses Pfizer nearly exclusively. It had an especially rapid initial vaccine distribution, which allows more time to assess vaccine efficacy over time; was well ahead of other countries in conducting a major booster campaign; and it has rich, population data from its four health networks, for a population of around 9.2 million people. All resident Israeli citizens must belong to one of these networks. High-quality research comes from the Israeli Health Ministry, which has population-wide data; from the Clalit health network, which covers around 60% of the Israeli population of around 9.2 million people; the Maccabi clinic, with around 2.5 million covered lives, the Leumit health network, and major hospitals. The Israeli population is less diverse than some other countries.

Qatar. Qatar also primarily uses Pfizer and has good population data, but for a smaller, albeit highly diverse population (2.9 million), with fewer studies. The ones we rely on come from a single research group. While the Qatar data are high quality, as is the research group studying Qatar, the Qatar population is extremely young, with 91% under age 50 (noted as a limitation in Chemiatelly et al., 2021). This limits the generalizability of the Qatar results.

United Kingdom. The UK used principally AstraZeneca and Pfizer. It has population data from their National Health Service, but many UK studies do not separately study Pfizer versus AstraZeneca. The UK vaccine rollout has other features which limit our ability to draw on UK studies: (i) the time between first and second dose, due to a UK decision in early 2021 to use then-limited supply to extend this time period to provide first doses to more people; (ii) the UK is using Pfizer for booster doses, even for those who initially received AstraZeneca; and (iii) the vaccine rollout was slower than the other countries we draw on (Israel, Qatar, and the US).

United States. The U.S. uses Pfizer, Moderna, and J&J. It lacks population data but has individual health systems with substantial size; also, the Centers for Disease Control has arranged to receive reports from health systems in a number of states which taken together should be reasonably population representative. Data on J&J is limited because the J&J vaccine because available later than the mRNA vaccines, was widely viewed as inferior to the mRNA vaccines, and therefore was infrequently used once there was sufficient vaccine supply to let individuals to choose another vaccine. A notable limitation on U.S. data is the lack of formalized systems for national vaccination recording and infection reporting, which limits the practicality of population-level observational studies (unlike Israel, Qatar, and the UK) and the nature of the research designs and controls for confounding which the available data will permit.

2. Vaccine Safety Profiles

The known significant adverse effects from each of the four vaccines are rare, mostly short-term, almost never fatal, and are far outweighed by vaccine benefit for all adult age groups. At most the relative

incidence of adverse effects might suggest using different vaccines for different groups; for example, one might prefer Pfizer instead of Moderna for young men due to lower myocarditis risk.

All vaccines can produce short-term reactions, including local swelling and soreness at the injection site, fever and fatigue usually for a day or two, and rarely anaphylactic shock (Desai, Desai and Loomis, 2021), which can be addressed by having patients wait for 15-30 minutes after vaccination (to allow for treatment if needed).

For the mRNA vaccines the principal more severe side effects are myocarditis and pericarditis, principally in younger men. However, even for this group, the risk of myocarditis (the more serious of the two side effects is around 1 in 6,000 for the second dose, and the myocarditis usually mild, with only one known fatality. That risk and is far outweighed by the many risks from COVID, including myocarditis (Merovich et al., 2021). The risk of myocarditis from a booster dose is lower than from a second dose; this may be related to the longer time interval between second dose and booster, than between the first and second doses (Buchan et al., 2021).

The viral vector vaccines have small risks of stroke, principally in middle-aged women (Schultz et al., 2021), and Guillain-Barre syndrome. These risks can be addressed by preferring the mRNA vaccines for this group; they reinforce the general efficacy advantage of the mRNA vaccines.

3. Implications of Prior Infection

Most vaccines are administered to uninfected persons, and studied for efficacy for an uninfected population. COVID is unique, because vaccination is occurring concurrent with an active pandemic, with much of the population already infected, often recently so. Especially in a population with many already infected persons (plausible US estimates exceed 50%), the decline in vaccine efficacy for persons who are vaccinated but SARS-CoV-2 naïve could exceed population-level estimates (which do not account for the protective effect of prior infection). Also, vaccine efficacy, optimal vaccine dosing, and dose and timing could differ for the uninfected versus the already infected. This is a fruitful area for further research, which we could not address due to lack of studies attempting this decomposition. At a minimum, it is important for studies of vaccine efficacy to control for known prior infection.

4. Details on Studies Reviewed and Inclusion and Exclusion Criteria

We view our approach – scanning the rapidly developing literature on vaccine and booster efficacy for empirically strong studies, but without conducting a systematic review, as providing a realistic balance between speed and completeness. A comprehensive list of the sources reviewed for potential inclusion is available upon request.

5. Need for Vaccine-specific Evidence

A number of studies did not provide vaccine-specific evidence, and thus could not be included in our review. This was an issue particularly for the UK, which used both AstraZeneca and Pfizer extensively, but also for studies that did not separately assess Pfizer versus Moderna. The vaccines are different enough, however, to deserve separate analysis. For example, the relative underperformance of AstraZeneca led to a U.K. decision to use Pfizer as a booster, regardless of which vaccine people received initially. The underperformance of J&J, which may partly reflect it being a one-dose vaccine, led to J&J obtaining U.S. approval for a booster after two months.

6. Expanded Results Reporting

This Section provides expanded information regarding the results of this analysis, the criteria used, and the data sources involved.

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

The Phase 3 trials were primarily conducted in 2020 (reported data is exclusively so for BNT162b2 (Pfizer), mRNA1273 (Moderna), and ChAdOxS-1 (AstraZeneca)). The trials thus had effectively no inclusion of B.1.617.2 (Delta) and at most limited inclusion of B.1.1.7 (Alpha). Furthermore, the BNT162b2 and mRNA1273 trials primarily relied on U.S.-based participants, and efficacy could have been different in other nations which imposed stricter NPIs, had different public health messaging, and may have had different behavioral characteristics among the study population. These factors might account for some of the differences in efficacy seen between the Phase 3 trials (Table 1) and early observational studies (Table 2).

6.2. Table 2: Early Observational Evidence on Vaccine Efficacy (pre-Delta)

The tables below provide additional detail on the sources used for Table 2. Detailed judgments concerning specific studies, including inclusion decisions and how efficacy was reported, are indicated in the table with small triangular marks in the upper right corners of some cells, and are available from the authors on request.

Table App-2.1: Data Sources Satisfying Inclusion Criteria for Table 2 – BNT162b2 (Pfizer)

Authors	Country	Journal	Variant(s)	Time Since Vaccination	Any Infection	Symptomatic Infection	Death	Mortality
Abu-Raddad, Chemaitelly, et al.	Qatar	NEJM	B.1.1.7	0-30	89.5%		100.0%	100.0%
			B.1.351	0-30	75.0%		100.0%	100.0%
			other	0-30	NR		97.4%	97.4%
Andrews, Tessier, et al.	UK	medRxiv	B.1.617.2	7-63		89.8%	98.4%	95.2%
Bernal, Andrews, et al.	UK	NEJM	B.1.1.7	7-120		93.7%		
			B.1.617.2	7-120		88.0%		
Chemaitelly, Tang, et al.	Qatar	medRxiv		0-84	65.1%		95.4%	
Dagan, Barda, et al.	Israel	NEJM		7-30	92.0%	94.0%	87.0%	
Haas, Angulo, et al.	Israel	Lancet		0-60	91.5%	97.0%	97.2%	96.7%
				0-53	93.8%	97.7%	98.0%	98.1%
Nordstrom, Ballin, et al.	Sweden	SSRN		0-106 (weighted)		87.1%		
Pilishvili, Gierke, et al.	US	NEJM		0-90		88.8%		
Self, Tenforde, et al.	US	MMWR		14-120			91.0%	

Table App-2.2: Data Sources Satisfying Inclusion Criteria for Table 2 – mRNA1273 (Moderna)

Authors	Country	Journal	Variant(s)	Time Since Vaccination	Any Infection	Symptomatic Infection	Death	Mortality
Andrews, Tessier, et al.	UK	medRxiv	B.1.617.2	7-63		94.5%	100.0%	
Nordstrom, Ballin, et al.	Sweden	SSRN		0-106 (weighted)		88.7%		
Pilishvili, Gierke, et al.	US	NEJM		0-90		96.3%		
Self, Tenforde, et al.	US	MMWR		14-120			93.0%	

Table App-2.3: Data Sources Satisfying Inclusion Criteria for Table 2 – Ad26.CoV2.S (J&J)

Authors	Country	Journal	Variant(s)	Time Since Vaccination	Any Infection	Symptomatic Infection	Hospitalization	Death
Self, Tenforde, et al.	US	MMWR		0 to less than 120			71.0%	

Table App-2.4: Data Sources Satisfying Inclusion Criteria for Table 2 – ChAdOxS-1 (AstraZeneca)

Authors	Contry	Journal	Variant(s)	Time Since Vaccination	Infection	Symptomatic Infection	Hospitalization	Death
Andrews, Tessier, et al.	UK	medRxiv	B.1.617.2	7-63		66.7%	95.2%	94.1%
Bernal, Andrews, et al.	UK	NEJM	B.1.1.7	7-120		74.5%		
			B.1.617.2	7-120		67.0%		
Nordstrom, Ballin, et al.	Sweden	SSRN		0-106 (weighted)		44.5%		

Table App-2.5: Weighted Average Calculations for Nordstrom, Ballin, et al. (2021)

BNT-162b2	15-30 (0-16) days	31-60 (17-46) days	61-120 (47-106) days	Early Weighed Mean	121-180 (107-166) days	181-210 (167-196) days	> 210 (> 196) days	Later Weighted Mean	
events (vacc.)	333	1095	1796	3224	631	688	519	1838	*(sum)*
fully adj. VE	92.00%	89.00%	85.00%	**87.08%**	47.00%	29.00%	23.00%	**33.49%**	*(weighed mean)*
weight	0.103287841	0.339640199	0.55707196		0.343307943	0.374319913	0.282372144		

mRNA-1273	15-30 (0-16) days	31-60 (17-46) days	61-120 (47-106) days	Early Weighed Mean	121-180 (107-166) days	> 180 (> 166) days		Later Weighted Mean	
events (vacc.)	20	67	116	203	65	32		97	*(sum)*
fully adj. VE	96.00%	93.00%	85.00%	**88.72%**	71.00%	59.00%		**67.04%**	*(weighed mean)*
weight	0.098522167	0.330049261	0.571428571		0.670103093	0.329896907			

ChAdOxS-1	15-30 (0-16) days	31-60 (17-46) days	61-120 (47-106) days	Early Weighed Mean	> 120 (> 106) days			Later Weighted Mean	
events (vacc.)	33	53	293	379	86				*(sum)*
fully adj. VE	68.00%	49.00%	41.00%	**44.47%**	-19.00%			**-19.00%**	*(weighed mean)*
weight	0.08707124	0.139841689	0.773087071						

Table Source: Nordstrom, Ballin, et al. (2021).

6.3. Table 3: Vaccine Efficacy Rates Against Harmonized Endpoints Four-plus Months After Vaccination

Decomposing efficacy decrease between the effect of waning and the effect of B.1.617.2 (Delta) was beyond the scope of our analysis. However as noted in the main text, Keehner et al. (2021) attempted this decomposition using UK data, and found that waning was the more likely cause. In any event, given the dominance of Delta, public health advice would be the same regardless of whether similar waning would have been seen against earlier variants. As discussed in the text, the recent emergence of the Omicron variant appears to increase the value and urgency of a booster dose.

The selection of 120 days (four months) as the dividing line between early and later evidence on efficacy was based on our analysis of the data sources satisfying the inclusion criteria, the time frames used in those studies and an assessment that statistically significant evidence of waning across endpoints begins at around four months. Some studies, notably Chemiatelly et al. (2021), find evidence of substantial

waning earlier than 4 months against any infection and symptomatic infection. Using an alternate dividing line, such as the 5 months at which a booster is recommended in Israel or the 6 months at which a booster is recommended in the US, would have reduced the number of usable sources, and would not have affected the overall conclusion on progressive waning of efficacy and the value of a third dose at roughly 5-6 months.

Table App-3.1: Data Sources Satisfying Inclusion Criteria for Table 3 – BNT162b2 (Pfizer)

Authors	Country	Journal	Minimum Time Since Vaccination	Any Infection	Symptomatic Infection	Hospitalization	Death
Andrews	UK	medRxiv	140		69.7%	90.7%	90.4%
Chemaitelly, Tang, et al.	Qatar	medRxiv	175	0.0%	0.0%	71.5%	
Israel Ministry of Health	Israel	VRBPAC Slide Excerpt	180	16.0%	16.0%	82.0%	
Lin, Gu, et al.	US	medRxiv	210		70.1%	87.7%	88.4%
Nordstrom, Ballin, et al.	Sweden	SSRN	107		33.5%		
Self, Tenforde, et al.	US	MMWR	120			77.0%	
Tartof, Slezak, et al.	US	Lancet	160	47.0%		88.0%	
Tenforde, Self, et al	US	JAMA IM	120			64.0%	

Table App-3.2: Data Sources Satisfying Inclusion Criteria for Table 3 – mRNA1273 (Moderna)

Authors	Country	Journal	Time Since Vaccination	Any Infection	Symptomatic Infection	Hospitalization	Death
Lin, Gu, et al.	US	medRxiv	210		81.9%	92.3%	93.7%
Nordstrom, Ballin, et al.	Sweden	SSRN	107		67.0%		
Self, Tenforde, et al.	US	MMWR	120			92.0%	
Tenforde, Self, et al.	US	JAMA IM	120			85.0%	

Table App-3.3: Data Sources Satisfying Inclusion Criteria for Table 3 – Ad26.CoV2.S (J&J)

Authors	Country	Journal	Time Since Vaccination	Any Infection	Symptomatic Infection	Hospitalization	Death
Lin, Gu, et al.	US	medRxiv	150		64.3%	80.0%	80.0%
Gray and Becker	South Africa	Sisonke presentation	90 - 120			65.0%	
Tenforde, Self, et al.	US	JAMA IM	120			64.0%	
J&J	multi-national	VRBPAC sponsor presentation	150		49.0%	65.0%	
		Unblinded Phase 3 followup	180		37.5%	65.0%	
			210		37.5%	85.0%	

Table App- 3.4: Data Sources Satisfying Inclusion Criteria for Table 3 – ChAdOx1-S (AstraZeneca)

Authors	Country	Journal	Time Since Vaccination	Any Infection	Symptomatic Infection	Hospitalization	Death
Andrews, Tessier et al.	UK	medRxiv	140		47.3%	77.0%	78.7%
Nordstrom, Ballin, et al.	Sweden	SSRN	107		-19.0%		

Table App-3.5: Weighted Average Calculations for Nordstrom, Ballin, et al. (2021)

Please see Table App-2.5, which covers the calculations for this study that underlie both Tables 2 and 3.

6.4. Inclusion Criteria

We faced the challenge that some Israeli and U.S. studies report efficacy for severe disease, but not for hospitalization. We made the judgment to report efficacy for these studies under the harmonized hospitalization outcome, based on evidence that: (i) roughly two-thirds of hospitalized Israeli patients are classified as having severe disease; and (ii) when efficacy is reported for both hospitalization and severe disease, efficacy is very similar for both outcomes (Barda et al., 2021; Bar-On et al., 2021a)). We used a similar approach for other studies that rely on the U.S. National Institutes of Health "critical illness" category.

Studies report data based on different start times (e.g., 7 days after terminal dose (the second dose for a two-dose regime, the only dose for J&J), date of terminal dose, 14 days after terminal dose). These are normalized to day "0" defined as 14 days after the terminal dose in the primary series. In some cases, we exercised judgment on how to classify results reported in another way. For example, Chemiatelly et al. (2021) report efficacy of Pfizer vaccination for periods of 0-4, 5-9, 10-14 etc. weeks after second dose. We chose to include the 0-4 week period in reporting efficacy during the first 120 days after full vaccination.

The precision of reported estimates depends on a combination of sample size, the outcome being studied, and COVID prevalence in the population during the study period. In light of these complexities, we did not apply a strict numerical size cutoff, but did exclude a number of U.S. studies that, for example, were limited to a single site, to a convenience sample such as healthcare workers, or both.

6.5. Comments on Relevant Studies

We discuss here several additional studies which provide evidence on waning vaccine efficacy, but did not meet the inclusion criteria for Tables 2-4.

> Puranik et al., (2021) provide strong U.S. evidence from matched vaccinated and unvaccinated cohorts, followed longitudinally in the Mayo Clinic of waning for both Pfizer and Moderna, with stronger waning for Pfizer, over January-July 2021. We did not include it in the text because the study does not control for date of vaccination.

> Scobie et al. (2021) report U.S. evidence of waning in 13 states over April-July 2021, but does not control for either vaccine type or date of vaccination. Given that the U.S. used Pfizer and Moderna in similar percentages, with much lower (around 4%) use of J&J, this can be understood as effectively a study of the mRNA vaccines.

A press release from the UK Health Security Agency (2021) reports over 90% reduction in symptomatic infection risk following a booster dose. The press release did not contain sufficient detail to meet the inclusion criteria. Also, the UK is using Pfizer boosters both for people initially vaccinated with Pfizer and those initially vaccinated with AstraZeneca with Pfizer, and the press release does not distinguish between these two groups.

7. Discussion of Data Source Selection

Data regarding vaccine efficacy for COVID-19 is being developed and released at a pace in excess of any observed in the history of modern medical science. Conducting a formal systematic review under such conditions is unrealistic and may defeat the purpose of formalization, since such a review requires selection of a cutoff date. Yet, regardless of the selected date, is it probable (if not certain) that new studies will emerge almost immediately after the selected date which otherwise would satisfy inclusion criteria. Indeed, just before this draft was released, Discovery Health, South Africa's largest private health insurance administrator, announced the results of observational studies of disease severity and vaccine efficacy against B.1.1.529 (Omicron) (Gray 2021b))., and many more studies are expected on the Omicron variant.

The infeasibility of a formal systematic review, satisfying PRISMA criteria, does not argue against the conduct of multi-source analyses such as this one. It remains urgent to conduct such analyses, on a time frame compatible with the evolution of knowledge about COVID-19 and changes in the virus itself. Developing methods for evaluating and contextualizing results across different healthcare systems, with different vaccines and vaccination policies, different clinical classifications of disease, different clinical resources, different access to resources, and different public health demographics is of critical importance to understanding the effect of vaccines.

This analysis combines the general goals of a systematic review with the flexibility of a semi-structured analysis to produce a result that is both scientifically rigorous and useful in practical context. Specifically, rather than attempting to ensure a 100% capture rate of qualifying sources (as a systematic review may demand), it focuses on studies considered to be most compelling as a function of peer review, quality of data sources, quality of the research group, and whether the studies met rigorous inclusion criteria.

For the purposes of completeness, a PubMed keyword search was attempted to scan for potentially-missed sources using the following criteria:

> Keywords = vaccin! AND ("covid19" OR "Covid-19" OR "SARSCOV2" OR "Sars-Cov-2"))

This search produced approximately 23,000 results on 8 December 2021. We then added the secondary limitation:

> (Keywords = ("Pfizer" OR "BNT162b2" OR "BNT-162b2" OR "Moderna" OR "mRNA1273" OR "mRNA-1273", "Johnson & Johnson" OR "J&J" OR "Ad26CoV2S" OR "Ad26.CoV2.S" OR "AstraZeneca" OR "ChAdOx1" OR "ChAdOx1S" OR "ChAdOx1-S")) AND (Title != "child!")

This reduced the results to 2,311, but still included many results unrelated to vaccine efficacy or immunogenicity, and included many studies far too small or narrow to be relevant to the population-level efficacy targeted by this analysis (e.g., "Parsonage-Turner Syndrome Following COVID-19 Vaccination: MR Neurography").

Given the number of results returned, with a likelihood of a similar or larger number for a search of medRxiv, we judged that the approach of beginning with a keyword search, and then reviewing the results for inclusion, was not feasible given the competing needs for speed and for capturing the many additional results that are emerging daily. Accordingly, this analysis relies on the most prominently reported data sources from reputable journals, pre-print results from reputable research groups (generally with prior

successful publication results), official national public health authorities, to which we then applied the inclusion criteria, as well as and official submissions of vaccine manufacturers to regulatory authorities.

Appendix References

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