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REVIEW ARTICLE (INVITED)

COVID-19 Vaccines and SARS-CoV-2 Transmission in the Era of New Variants: A Review and Perspective

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Coronavirus disease 2019 (COVID-19) vaccines have yielded definitive prevention and major reductions in morbidity and mortality from severe acute respiratory syndrome coronavirus 2 infection, even in the context of emerging and persistent variants of concern. Newer variants have revealed less vaccine protection against infection and attenuation of vaccine effects on transmission. COVID-19 vaccines still likely reduce transmission compared with not being vaccinated at all, even with variants of concern; however, determining the magnitude of transmission reduction is constrained by the challenges of performing these studies, requiring accurate linkage of infections to vaccine status and timing thereof, particularly within households. In this review, we synthesize the currently available data on the impact of COVID-19 vaccines on infection, serious illness, and transmission; we also identify the challenges and opportunities associated with policy development based on this data.

Keywords. asymptomatic infection; COVID-19; SARS-CoV-2; viral shedding; transmission; variants

In just over 1 year, >10 billion doses of coronavirus disease 2019 (COVID-19) vaccines have been administered globally [1], with 10 vaccines granted emergency use listing by the World Health Organization so far, including mRNA, adenovirus-vectored, soluble protein, and inactivated virus vaccines [2]. These vaccines have demonstrated efficacy in preventing symptomatic COVID-19 in randomized controlled trials, in the context of both the original severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strains (D614 and D614G) and real-world effectiveness against variants of concern [3]. Economists at Indiana University and the RAND Corporation estimated that COVID-19 vaccination prevented at least 140 000 deaths in the United States alone by May 2021 [4].

While COVID-19 vaccines have yielded definitive prevention and major reductions in morbidity and mortality from SARS-CoV-2 infection, the impact of these vaccines against asymptomatic infection, viral shedding, and secondary SARS-CoV-2 transmission with emerging variants is more nuanced [5]. Real-world effectiveness studies in the context of the Alpha variant suggest that multiple vaccines do reduce infection and onward transmission [6–8], but the coordinated, robust surveillance systems needed to track this in real time for emerging variants of concern are lacking. This dearth of real-time data stymies policy-makers, who are navigating public policy decisions around primary and booster vaccination, the rollout of monoclonal antibodies and small-molecule antivirals, and guidance on nonpharmaceutical interventions like masking. Many misinterpreted reports of increased breakthrough infections as evidence of wholesale loss of vaccine protection against transmission have resulted in public confusion on the topic, and these questions are even more pronounced given emergence of the most recent variant of concern as of November 2021, Omicron (B.1.1.529) [9].

In this review, we outline the literature on the impact of COVID-19 vaccines on SARS-CoV-2 infection, peak and duration of viral shedding, and transmission of SARS-CoV-2 following vaccination, with an emphasis on COVID-19 vaccine effects against variants of concern. COVID-19 vaccines remain a critical tool to in the path to ending the pandemic, even in the context of newer variants and waning immunity. We argue that surveillance of transmission among both vaccinated and unvaccinated populations is woefully inadequate, leaving policy-makers uninformed and vulnerable to poor decision-making in the face of potentially more transmissible variants on the horizon. Prospective studies evaluating vaccine efficacy in the context of evolving variants are necessary for providing definitive answers about the magnitude of reduction in infection and transmission of SARS-CoV-2 variants.

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POLICY IMPLICATIONS OF UNDERSTANDING SARS-COV-2 TRANSMISSION

Our understanding of transmission of SARS-CoV-2 and the impact that vaccines have on reducing risk have significant policy implications. As of January 2022, the Centers for Disease Control and Prevention (CDC) continues to recommend that individuals in areas of substantial or high transmission should wear masks indoors in public regardless of vaccination status, due to the increased transmissibility of SARS-CoV-2 [10, 11], although by February 2022 many states have begun to reverse mask mandates [12]. Given the general overwhelmed state of hospital systems and overworked state of health care workers, ultraconservative isolation and return-to-work policies for infected workers may result in both absenteeism (further overwhelming the system with possible delays in care due to understaffing) or presenteeism (placing patients at risk for being infected when workers come to work sick) [13–15]. In December 2021, the CDC recommended a 5-day isolation after a positive SARS-CoV-2 test for vaccinated, asymptomatic individuals while keeping the 10-day isolation for unvaccinated individuals [16]. Understanding SARS-COV-2 transmission and when individuals can safely return to work, school, and public venues also has economic implications including more businesses remaining open, fewer days off from work for vaccinated sick workers, and less negative employment change overall, which may lead to improved psychological distress and more equitable racial distribution of negative impacts [17].

VACCINE EFFECTS ON TRANSMISSION—A 2-STEP PROCESS

Step 1: Vaccine Protection Against SARS-CoV-2 Infection

The first step in preventing transmission is preventing infection. If an individual is not infected, they cannot transmit virus to someone else. Therefore, when considering how well a vaccine protects against transmission, we must first determine how well it protects against infections, including asymptomatic infections. If a vaccine can prevent an overwhelming majority of infections, it will have a major impact on curtailing the epidemic, protecting the vaccinated as well as their close contacts (Figure 1). Total vaccine protection against infection is sometimes referred to as *sterilizing immunity*, and while it can be achieved in individual cases, it is exceedingly rare for any vaccine to achieve this across a population of vaccinated individuals [18]. The mechanism of sterilizing immunity is typically attributed to the presence of neutralizing antibodies that can bind to surface structures on an infectious particle, such as the spike (S) protein on the surface of SARS-CoV-2, and inhibit entry into cells to block replication before it begins [18]. Neutralizing antibody to mRNA-1273 vaccine has also been shown to be a direct correlate of protection against symptomatic SARS-CoV-2 infection among mRNA-1273 recipients, though whether vaccine-induced neutralizing antibodies are a correlate of protection against all infections and for other vaccine platforms remains unknown [19]. Vaccinated individuals can experience breakthrough infections, which can be either symptomatic or

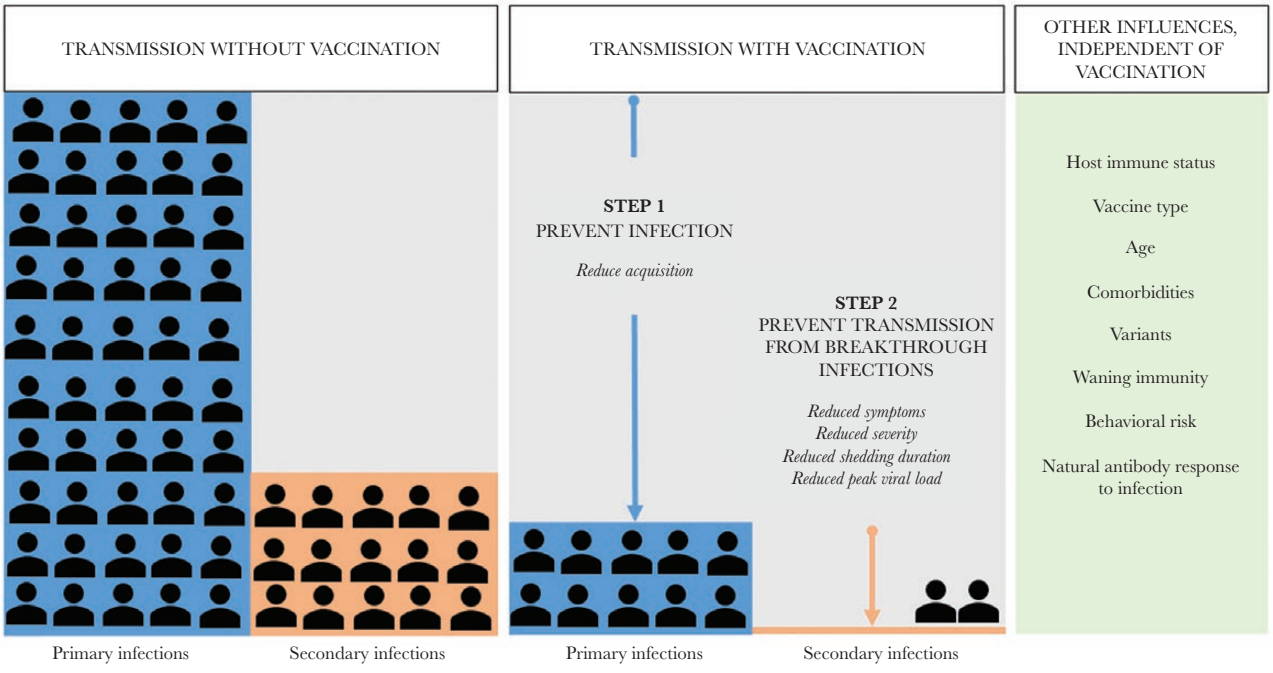

Figure 1. Vaccine effects on reducing SARS-CoV-2 transmission. The left panel demonstrates SARS-CoV-2 transmission with primary infections leading to secondary infections. The middle panel demonstrates 2 steps of transmission reduction through vaccination: reduction of infection acquisition and reduction of breakthrough infections. The right panel describes other factors independent of vaccination status that influence transmission likelihood. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

asymptomatic, people who are immunocompromised may have less robust responses to vaccination and thereby less protection against disease [20–22], and evolution of SARS-CoV-2 variants may interfere with development of neutralizing antibodies, thereby leading to these breakthrough infections or rendering monoclonal antibodies obsolete [23].

Step 2: Vaccine Protection Against Transmission of Breakthrough Infections

In the setting of breakthrough infections, however, vaccines can also reduce the likelihood of onward transmission [24] by decreasing the magnitude and duration of viral shedding, reducing the degree of symptoms, and possibly rendering breakthrough viruses less infectious (Figure 1). Perhaps most significant among these effects is a vaccine-induced reduction in viral shedding. Among those infected with SARS-CoV-2, nasopharyngeal viral load may be a strong direct correlate for human-to-human transmission [25]. Evidence for this is nuanced and based on models [26, 27] or nonhuman primate studies that have shown that COVID-19 vaccines reduce viral load in the lower and upper respiratory tracts [28, 29]. One study found no link between viral load cycle threshold and transmission in a college student cohort [30], and while a large prospective cohort showed no significant difference between cycle threshold peaks of symptomatic vs asymptomatic individuals, vaccinated individuals had faster viral load clearance and therefore lower overall duration of infection [31, 32]. Unfortunately, we have not yet identified the best laboratory method for reliable prediction of infectiousness [33]; therefore, these inferences of the vaccine effect on infectiousness remain indirect and imperfect. From a mechanistic standpoint, vaccines eliciting neutralizing antibodies block the SARS-CoV-2 spike protein from interaction with the ACE2 receptor at the mucosal surface and obstruct viral entry into cells, but not all cells may be protected [34]. While some cells may not escape infection, resulting in brief bursts of viral replication, the total magnitude of viral replication will be reduced. Moreover, vaccine-induced T-cell immunity and other non-neutralizing immune responses can further limit the spread of small pockets of mucosal infection, reducing the duration of infection. In addition to reducing viral shedding, vaccine-induced immune responses may also limit symptoms during breakthrough infections by preventing progression of disease from the mucosal compartment to the lower respiratory tract and the rest of the body. Furthermore, a vaccine may have a "sieve effect," whereby vaccination preferentially blocks infection with viruses that are more transmissible [35, 36].

DRIVERS OF CONTINUED SARS-COV-2 TRANSMISSION

Despite the fact that >60% of world's population has received at least 1 dose of a COVID-19 vaccine [1], nearly all countries have experienced a surge of infections from April to December 2021. The drivers of the continued population transmission of SARS-CoV-2 are multifactorial (Figure 2). The emergence of new, highly transmissible viral variants in January/February of 2021 [37], complete saturation by the Delta variant by July 2021, and subsequent dominance of the Omicron variant toward the end of 2021/early 2022 with concern for even greater vaccine escape [38] are important factors. Potential waning of vaccine-induced immunity, immune evasion by new variants, and increased pathogenicity of variants are others; evasion of the immune response, whether from natural infection or vaccine resistance, has been observed with other infectious diseases [39–41]. A root cause of much of the ongoing transmission is the inequitable distribution of COVID-19 vaccines

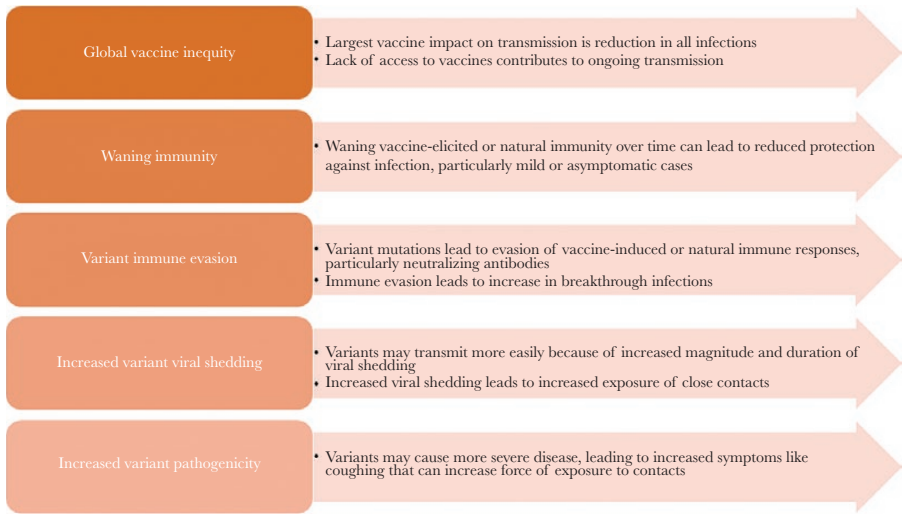

Figure 2. Potential drivers of continued SARS-CoV-2 transmission in the context of vaccines. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

globally, leaving low-income countries particularly vulnerable to unabated infections and attendant onward transmission, as well as the risk for development of new variants of concern [42]. Importantly, in addition to the virus and vaccine effects, several other factors may influence transmission, including individual immune system function and comorbidities, community behaviors (eg, masking, isolation, travel, and large gatherings), seasonal effects (eg, cold weather forcing people indoors), and the impact of natural or hybrid immune response to infection (Figure 1).

VACCINE IMPACT ON TRANSMISSION OF SARS-COV-2 ALPHA VARIANT INFECTIONS

In late 2020, the United Kingdom reported a new SARS-CoV-2 variant, designated Alpha (B.1.1.7) [43]. This variant was found to be 50%–75% more transmissible than previously circulating strains and had a higher secondary attack rate [44, 45]. The Alpha variant contained several mutations in the spike protein, which did not confer significant immune evasion of vaccine-induced neutralizing antibody responses as tested in vitro [46, 47]. Data from both observational cohort studies and randomized controlled clinical trials during the period of time in which Alpha was the predominant circulating strain in the study location (Alpha period) confirmed that COVID-19 vaccines maintained activity against the Alpha variant, including partial protection against infection regardless of symptoms (Table 1) [3, 48–59]. A meta-analysis of 12 studies found that the effectiveness of the adenovirus-vectored vaccines against infection was 73% (95% CI, 69%–77%), and for mRNA vaccines it was 85% (95% CI, 82%–88%) in participants ≥18 years [3]. Some of these data provide evidence of effectiveness against Beta and Gamma variant strains as well [48, 55]. Furthermore, evidence suggested that individuals with vaccine breakthrough SARS-CoV-2 infection during the Alpha period were less likely to transmit to household contacts than unvaccinated individuals with SARS-CoV-2 infection. For example, Prunas et al. analyzed a database of >2 million individuals in Israel who had received 2 doses of BNT162b2 between June 2020 and March 2021, in which positive SARS-CoV-2 tests were linked by addresses, allowing the tracking of index cases and household contacts [8]. Modeling estimated that vaccination reduced susceptibility to infection by ~80% and reduced infectiousness by 41%, resulting in an overall inferred reduction in transmission risk of 88.5% [60, 61].

Data from the United Kingdom also suggested that vaccination led to a 40%–50% reduction in transmission of breakthrough infections following only a single dose of either ChAdOx1 or BNT162b2 in a large centralized database study of households with positive SARS-CoV-2 tests in England during January to February 2021 [62]. Following full vaccination, investigators in the Netherlands calculated that vaccination led to a 70% reduction in transmission of breakthrough infections between February and May 2021 in a study utilizing detailed contact-tracing strategies [63]. Interestingly, when evaluating transmission pairs, the estimated attack rate was 10% if *either member of the pair* was vaccinated, vs 30% for unvaccinated–unvaccinated pairs [60, 61], supporting benefit of vaccination of some household members even when others remain unvaccinated. Investigators also demonstrated reductions in the development of COVID-19 among household members of vaccinated health care workers in Scotland [64] and among nonimmune household members of individuals who demonstrated either vaccine-induced or natural infection-induced immunity to COVID-19 in Sweden [65].

The likely mechanisms behind this reduced transmission of breakthrough infections were decreases in viral shedding and symptoms. In the United States, Thompson et al. looked at a prospective cohort of US health care workers between December 2020 and April 2021 who received weekly nasal SARS-CoV-2 polymerase chain reaction (PCR) [61]. Investigators found that vaccination led to a reduction of mean peak viral load from 3.8 $\log_{10}$ copies/μL to 2.3 $\log_{10}$ copies/μL and a reduction of duration of RNA detection from 9 days to 3 days. Moreover, infected vaccinated participants had a shorter duration of symptoms, and only 25% had fever compared with 63% of unvaccinated participants. Pouwels et al. also showed that vaccination with multiple different platforms significantly reduced viral load in breakthrough infections compared with nonbreakthrough infections in the Alpha period [60].

REDUCED VACCINE IMPACT ON TRANSMISSION OF SARS-COV-2 DELTA VARIANT INFECTIONS

The Delta variant (B.1.617.2 lineage) was first identified in India in December 2020 and became the prevalent variant worldwide by July 2021. The Delta variant is highly transmissible compared with both Alpha and ancestral strains, potentially due to the L452R mutation in the spike protein leading to better binding avidity with the ACE2 receptor [60, 66–68]. Unlike the Alpha variant, the Delta variant also appears to partially evade immune responses in vitro [69], though very high D164 S-specific neutralizing antibody titers can overcome this evasion in laboratory studies [70, 71]. The vast majority of reports regarding protection against Delta infection focus on symptomatic infection.

Real-world data during the period of time in which Delta was the predominant circulating strain in the study location (Delta period) suggest that vaccine effectiveness against symptomatic SARS-CoV-2 infection is attenuated compared with the pre-Delta period, but that protection against moderate to severe disease remains very strong [72]. Observational studies of mRNA-1273 have shown a reduction in protection against symptomatic illness from >93% for Alpha to as low as 84% for Delta, but mRNA-1273 remained >90% effective against moderate to severe disease [51, 73–76]. For ChAdOx1, vaccine

Table 1. Studies Describing COVID-19 Vaccine Protection Against Infection in the Period Before Delta Variant Predominance

Time Period of Enrollment and Follow-up	SARS-CoV-2 Variant(s)	Population	Design	Location	Outcome	Vaccine	VE (95% CI) 1 Dose	VE (95% CI) 2 Dose	Citation
12/2020–2/2021	Alpha[a]	Health care workers	Prospective biweekly PCR screening	England	All infection	BNT162b2	70 (55 to 85)	85 (74 to 96)	Hall et al. [52]
12/2020–1/2021	Original/wild-type[b]	PCR + health care workers	Retrospective medical record review	Israel	All infection	BNT162b2	30 (2 to 50)	75 (72 to 84)	Amit et al. [49]
12/2020–3/2021	Alpha[b]	Health care workers	Prospective weekly PCR screening	USA	All infection	Mix: BNT162b mRNA-1273	80 (59 to 90)	90 (68 to 97)	Thompson et al. [58]
12/2020–4/2021	Alpha[b]	Individuals in health care system	Retrospective medical record review	USA	All infection	BNT162b2 mRNA-1273	61 (51 to 59) 67 (52 to 77)	88 (84 to 91) 92 (82 to 97)	Pawloski et al. [54]
12/2020–2/2021	Alpha[a]	Individuals in health care system	Prospective medical record review	Israel	All infection	BNT162b2	60 (53 to 66)	92 (88 to 95)	Dagan et al. [50]
12/2020–2/2021	Alpha[b]	Individuals in health care system	Retrospective medical record review of preprocedural PCR screening	USA	Asymptomatic infection	BNT162b2	79 (62 to 89)	80 (56 to 91)	Tande et al. [57]
4/2021–8/2021	Alpha[c] Delta	Individuals in national registry	Retrospective medical record review, with sequencing of positive samples	Norway	All infection	Mix: BNT162b2 mRNA-1273 ChAdOx1	Alpha: 55 (50 to 58) Delta: 22 (17 to 27)	Alpha: 84 (82 to 87) Delta: 65 (61 to 68)	Seppala et al. [56]
1/2021–4/2021	Gamma[a]	Health care workers	Retrospective medical record review	Brazil	All infection	CoronaVac	35 (–7 to 61)	38 (–46 to 74)	Hitchings et al. [53]
5/2020–11/2020	Original/wild-type[b]	Clinical trial participants	RCT, weekly PCR screening	UK	Asymptomatic infection	ChAdOx1	N/A	27 (–17 to 55)	Voysey et al. [59]
9/2020–1/2021	Beta[c] Zeta	Clinical trial participants	RCT, N-immunoassay seroconversion	USA, Latin America, South Africa	Asymptomatic infection	Ad26.COV2.S	66 (40 to 81)	N/A	Sadoff et al. [55]
7/2020–3/2021	Epsilon[b] Beta Alpha	Clinical trial participants	RCT, PCR screening at visits, and N-assay seroconversion	USA	Asymptomatic infection	mRNA-1273	N/A	63 (57 to 69)	El Sahly et al. [51]
7/2020–12/2020	Original/wild-type[a]	Clinical trial participants	RCT, any PCR test in study	UAE Bahrain	All infection	WIV04 HB02	N/A N/A	64 (49 to 75) 74 (61 to 82)	Al Kaabi et al. [48]

Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; RCT; randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness/efficacy; VOC, variant of concern.

[a]SARS-CoV-2 variant(s) as indicated by the authors of this manuscript.

[b]SARS-CoV-2 variant(s) not indicated in the manuscript. Variant(s) listed in the table is the dominant sequence at the time and location of the study, as per Nextstrain.org.

[c]SARS-CoV-2 variant(s) as per in-study sequencing.

effectiveness also decreased after 2 doses from 75% for Alpha to 67% for Delta infections, but protection against moderate to severe disease remained much higher at 82% [77, 78]. Preliminary data from South Africa show that Ad26.COV2.S maintains strong protection against moderate to severe COVID-19 [79], as do inactivated COVID-19 vaccines studied in Guangdong, China [80]. BNT162b2 also decreased in effectiveness against symptomatic illness from 94% for Alpha to 88% for Delta infections but maintained effectiveness of 93% against hospitalizations for infections with the Delta variant [77, 81]. It is unclear if these reductions in effectiveness against disease are due to Delta immune evasion or waning immunity, as evidenced by studies that show that attenuation is focused on older age groups or people more remotely vaccinated [75, 82].

While COVID-19 vaccines (particularly mRNA) have maintained robust protection against symptomatic illness and moderate to severe disease from recent variants, there appears to be a more marked attenuation in protection against infection (Table 2) [56, 60, 74, 78, 81, 83–85]. For example, estimates of mRNA-1273 effectiveness against infections among nursing home residents decreased from 74.7% against Alpha to 50.6% against Delta [83], with other studies also estimating mRNA and Ad-vectored vaccine effectiveness in the 50%–60% range against Delta infection, particularly for BNT162b2 [74, 78, 81, 84, 85]. Estimates of Ad26.COV2.S against Delta-predominant COVID-19 disease suggest vaccine effectiveness of 60%–65% for preventing emergency department/urgent care encounters or hospitalizations for COVID-19 [75]. However, not all studies have estimated such sharp reductions in effectiveness against Delta, with other data suggesting rates closer to the 70%–80% range for mRNA vaccines [60, 84, 85].

Because the Delta surge occurred simultaneously with waning immunity for most vaccinated individuals globally, it is difficult to disentangle the precise mechanism for the attenuation of vaccine effectiveness observed during the Delta period. Nevertheless, the evidence suggests a reduced impact of vaccines against transmission by virtue of the increased rate of breakthrough infections (Step 1 of vaccine effects on transmission) (Figure 1). There also appears to be a reduction in vaccine effect on the infectiousness of breakthrough infections (Step 2 of vaccine effects on transmission) (Figure 1), as suggested by data from Singanayagam et al., who performed a prospective, longitudinal study of ambulatory close contacts of confirmed COVID-19 cases [86]. In this study, the secondary attack rate among household contacts exposed to fully vaccinated index cases was no different than the rate among those exposed to unvaccinated index cases (25% vs 23%, respectively). In contrast, Harris et al. and de Gier et al. estimated reductions of 40%–70% in secondary attack rates during the Alpha period [62, 63].

One potential reason for the reduced vaccine effect on infectiousness may be a loss of vaccine effects on peak viral load in breakthrough infections. Brown et al. studied peak viral loads in 469 individuals identified in an outbreak in Massachusetts wherein 74% of cases were in fully vaccinated individuals, and >90% of the viruses were sequenced as Delta variant [87]. Investigators found no difference in viral load (as measured by cycle threshold) between breakthrough infections and nonbreakthrough infections. Pouwels et al. also demonstrated no difference in peak viral load during the Delta period in a prospective study of vaccine recipients in the United Kingdom including individuals vaccinated with ChAdOx1, Pfizer BNT162b2, and Moderna mRNA-1273 vaccines from December 2020 to August 2021 [60]. Singanayagam et al. also reported no difference in peak viral load between vaccinated and unvaccinated individuals [86].

While peak viral load may be the same between breakthrough and nonbreakthrough infections, the total duration of viral shedding may not be the same. Investigators in Singapore found that the viral kinetics of breakthrough infections were significantly different than in unvaccinated infections, with a steeper decline in viral load and accelerated clearance [88]. Singanayagam also found that vaccinated individuals had a faster mean rate of viral load decline than did unvaccinated individuals, as did Kissler et al. [32, 86]. Moreover, Shamier et al. found that breakthrough infections were much less likely to be culture positive (ie, live virus) compared with nonbreakthrough infections, even when samples had the same viral load on PCR) [89]. In contrast, in a study of a subset of 70 symptomatic persons who provided swabs for serial testing in a Texas prison, no significant difference was found in the median interval between reported symptom onset and last positive reverse transcription PCR result in vaccinated vs unvaccinated persons (9 vs 11 days) [90]. Virus was cultured from 42% of unvaccinated samples compared with 38% of fully vaccinated samples (with the limitation that these data may not reflect the viral kinetics of asymptomatic infections).

These data suggest that there may be vaccine effects on the total duration of shedding of infectious virus that may not necessarily translate to meaningful reductions in household transmission, perhaps because most transmission may occur during early, peak shedding periods and during so-called "superspreader events" [91, 92]. A retrospective study in the UK found a more pronounced effect of reduction of onward transmission with vaccination against the Alpha variant compared with Delta; however, although vaccination was associated with higher cycle threshold (Ct) values (aka lower viral loads), differences in Ct values alone did not fully explain the effect of vaccination [93]. Furthermore, breakthrough Delta infections could still be less transmittable at the population level. Phylogenetic evaluation of the Massachusetts outbreak in a highly vaccinated population suggested an overdispersion phenomenon in which a few individuals propagated most transmission events, suggesting that not all cases with high viral load detected by PCR ended up as the source of secondary transmission [92, 94].

Table 2. Studies Describing COVID-19 Vaccine Effectiveness Against Delta, Omicron, and Other Variants of Concern

Time Period of Enrollment and Follow-up	SARS-CoV-2 Variant(s)	Population	Design	Location	Outcome	Vaccine	VE (95% CI) 1 Dose	VE (95% CI) 2 Dose	Citation
4/2021–8/2021	Alpha[c] Delta	Individuals in national registry	Retrospective medical record review, with sequencing of positive samples	Norway	All infection	Mix: BNT162b2 mRNA-1273 ChAdOx1	Alpha: 55 (50 to 58) Delta: 22 (17 to 27)	Alpha: 84 (82 to 87) Delta: 65 (61 to 68)	Seppala et al. 2021 [56]
3/2021–9/2021	Beta[c] Delta	Individuals in national registry	Retrospective medical record review, with sequencing of positive samples	Qatar	All infection	BNT162b2 mRNA-1273 BNT162b2 mRNA-1273	Beta: 19 (–2 to 35) 66 (56 to 74) Delta: 45 (22 to 62) 74 (58 to 84)	Beta: 74 (70 to 78) 81 (69 to 88) Delta: 52 (47 to 56) 73 (68 to 78)	Tang et al. 2021 [85]
4/2021–5/2021	Delta[c]	Individuals in health care system	Retrospective medical record review, with sequencing of positive samples	India	All infection	ChAdOx1	46 (32 to 58)	63 (52 to 72)	Thiruvengadam et al. 2021 [78]
12/2020–8/2021	Epsilon[c] Alpha Delta	Individuals in health care system	Retrospective medical record review, with sequencing of positive samples	USA	All infection	BNT162b2 1 mo 5 mo BNT162b2 1 mo 5 mo	N/A	Non-Delta: 97 (95 to 99) 67 (45 to 80) Delta: 93 (85 to 97) 53 (39 to 65)	Tartof et al. 2021 [81]
7/2021–8/2021	Delta[c]	Male prisoners	Prospective weekly PCR screening	USA	All infection	mRNA-1273	N/A	57 (42 to 68)	Chin et al. 2021 [74]
4/2021–6/2021	Delta[c]	Individuals in national registry	Retrospective medical record review, with sequencing of positive samples	Scotland	All infection	BNT162b2 ChAdOx1	N/A N/A	79 (75 to 82) 60 (53 to 66)	Sheikh et al. 2021 [84]
12/2020–8/2021	Alpha[a] Delta	Individuals in community-based survey across Alpha and Delta periods	Prospective monthly PCR screening	UK	All infection	BNT162b2 ChAdOx1 BNT162b2 ChAdOx1	Alpha: 59 (62 to 65) 63 (55 to 69) Delta: 57 (50 to 63) 46 (55 to 69)	Alpha: 78 (68 to 84) 80 (77 to 83) Delta: 79 (56 to 90) 67 (62 to 71)	Pouwels et al. 2021 [60]
3/2021–8/2021	Alpha[a] Delta	Nursing home residents	Retrospective medical record review	USA	All infection	BNT162b2 mRNA-1273 BNT162b2 mRNA-1273	N/A	Pre-Delta: 74 (69 to 79) 75 (66 to 81) Delta: 52 (48 to 56) 51 (45 to 56)	Nanduri et al. 2021 [83]
11/2021–12/2021	Delta[c] Omicron	Individuals in national registry	Retrospective medical record review, with sequencing of positive samples	Denmark	All infection	BNT162b2 mRNA-1273 BNT162b2 mRNA-1273	N/A	Delta: 87 (85 to 89) 88 (83 to 92) Omicron: 55 (24 to 74) 37 (–70 to 76)	Hansen et al. 2022 [96]

Table 2. Continued

Time Period of Enrollment and Follow-up	SARS-CoV-2 Variant(s)	Population	Design	Location	Outcome	Vaccine	VE (95% CI) 1 Dose	VE (95% CI) 2 Dose	Citation
12/2021	Delta[c] Omicron	Individuals in health care system	Retrospective medical record review, with sequencing of positive samples	USA	All infection	mRNA-1273 +Boost mRNA-1273 +Boost	Delta: 57 (41 to 68) N/A Omicron: 20 (10 to 30) N/A	Delta: 80 (68 to 88) 94 (92 to 95) Omicron: 44 (35 to 52) 72 (70 to 73)	Tseng et al. 2022 [97]

Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness/efficacy; VOC, variant of concern.

[a]SARS-CoV-2 variant(s) as indicated by the authors of the manuscript.

[b]SARS-CoV-2 variant(s) not indicated in manuscript. Variant(s) listed in table is the dominant sequence at the time and location of the study, as per Nextstrain.org.

[c]SARS-CoV-2 variant(s) as per in-study sequencing.

OMICRON AND OTHER VARIANTS OF CONCERN

There is comparatively little data on COVID-19 vaccine effects on transmission of other variants of concern such as Beta and Gamma. Hitchings et al. evaluated CoronaVac (an inactivated vaccine) during the Gamma variant wave in Manaus, Brazil, and found that after 2 doses, the vaccine was 37.9% effective against all SARS-CoV-2 infection [53]. Sadoff et al. found that Ad26.COV2.S was 66% effective against asymptomatic infections that included a large proportion of Beta, given that 15% of the study population was from South Africa during their Beta surge [55]. There are no additional published data on viral dynamics and secondary transmission of breakthrough infections for these variants.

In November 2021, a new variant was reported in South Africa that was noted to overtake Delta sequences in surveillance data and was subsequently designated the variant of concern Omicron (B.1.1.529); as of February 2022, it has been identified in almost every country worldwide and is the predominant circulating strain in the United States since January 2022 [9]. The BA.1 Omicron variant has >30 mutations in the spike protein, including changes associated with increased transmissibility and immune evasion [38, 95]. Available data demonstrate reduced mRNA vaccine effectiveness against Omicron compared with Delta (Table 2) [96, 97]. The full impact of COVID-19 vaccines on transmission of Omicron is still being evaluated; however, data suggest increased transmission with higher secondary attack rates in households compared with rates during the Delta predominant period [98]. Evolving data regarding the clinical impact of Omicron suggest that despite increased infections and hospitalization rates, there is a reduced risk of severe disease and death compared with Delta [99–102]. However, the rates of infection and hospitalization in children and adolescents increased rapidly during the Omicron wave, a feature of Delta but not other variants [103].

The waning effects of vaccines against the Omicron variant are concerning [96]. Preliminary reports suggest that prior infection- and vaccine-induced antibody neutralization response against Omicron is significantly reduced [38, 104–106]—possibly explaining increased infection rates, while vaccine-induced cellular immune responses may remain robust in response to Omicron, possibly explaining protection against severe disease [107]. There is evidence that 3 doses may be needed to maintain a similar level of effectiveness against Omicron as was achieved with 2 doses against prior variants [97, 105, 108, 109], and vaccine effectiveness may be significantly reduced in immunocompromised people even with 3 doses [97]. Vaccinated individuals (and even those boosted) are still at risk of acquisition of SARS-CoV-2; however, unvaccinated people had rates of infection and hospitalization with Omicron that were 3.8 and 23.0 times higher compared with vaccinated people who had received boosters [110]. As such, the CDC still recommends booster doses for people

older than 12 years [111], and a fourth dose for people with immunocompromising conditions [112].

The BA.2 sublineage of Omicron has emerged with additional mutations, distinguishing it from the predominant BA.1 lineage [113]. Preliminary data suggest that BA.2 may be more transmissible than BA.1, even in individuals who have been fully vaccinated; however, the largest secondary attack rates occurred among unvaccinated household individuals [98]. Like BA.1, BA.2 appears to evade neutralizing antibody responses in vaccinated individuals, a finding remedied by introduction of a vaccine boost/third dose, and, importantly, infection with BA.1 in vaccinated individuals may result in hybrid immunity with development of robust neutralizing antibodies against BA.2 [114]. Evolution of mutations leading to future variants of concern continues to be a possibility and should embolden worldwide vaccination efforts to reduce the proportion of individuals susceptible to future infections.

GAPS IN THE DATA: GETTING WHAT WE NEED WITH THE RESOURCES AVAILABLE

This review highlights several limitations to understanding SARS-CoV-2 transmission patterns effectively. First, retrospective observational studies have a delay in providing information, leading to a situation in which the literature applies to a variant that is already out of circulation. However, given the progression of this pandemic with rapidly evolving variants, even prospective studies may find themselves engaging in a race against time to the "next variant," or collecting data prospectively that spans the course of more than 1 variant wave.

Second, many studies rely predominantly on proxy markers of asymptomatic infection (such as seroconversion) or are based on relatively infrequent PCR testing (eg, less than twice weekly). Both incorporate "length bias," with individuals with short-duration infections or who never seroconvert misclassified as uninfected. If missed infections occur more often among vaccinated individuals, due to shortened duration of shedding or reduced seroconversion, this will inflate estimates of vaccine effects against SARS-CoV-2 infection. Furthermore, it will inflate estimates of vaccine effects on secondary transmission to the extent that testing of contacts/household members is triggered by diagnosis of the index case.

A related issue occurs when infection is exclusively or predominantly triggered by an event such as onset of COVID-19 symptoms or potential SARS-CoV-2 exposure. If the frequency of the trigger is not balanced across vaccinated and unvaccinated groups, as in the case of symptom-prompted testing, infections will be differentially misclassified, leading to bias. Symptom-prompted testing is likely to miss more infections among vaccinated individuals and therefore to inflate estimates of vaccine effects on SARS-CoV-2 infection and secondary transmission. Symptom-prompted testing will also miss characterizing the effect of vaccination on shedding of asymptomatic infections.

Evaluating vaccine effects on secondary transmission requires distinguishing primary and secondary infection events within transmission clusters, for example, households. However, even prospective household transmission studies may have challenges. First, it may be difficult to accurately account for possible shared (eg, siblings at daycare or adults with similar friend circles) or other community-acquired exposures and challenging to determine directionality of transmission in a household when community spread is high. Additionally, while frequent testing would provide the most complete viral load trajectory, perfect adherence to daily procedures is difficult, even with incentives, because sometimes participants forget, or perhaps lack motivation to test. Furthermore, it is possible that individuals with more personal concern about COVID-19 may have greater incentive to adhere to testing procedures, which could potentially result in systematic bias when evaluating viral load trajectories. However, even with frequent, systematic SARS-CoV-2 testing of all members of transmission units, inferring transmission chains is challenging, given that individuals are likely infectious only for a few days early in the course of infection and just on or before the onset of any symptoms that develop [31, 115]. When testing is infrequent or triggered by symptoms or potential SARS-CoV-2 exposure, it is considerably more challenging, and misclassification of transmission events is very likely. This misclassification will bias estimates of vaccine effects on secondary transmission.

Finally, uncontrolled studies are subject to confounding, possibly due to differential likelihood of exposure to SARS-CoV-2 status or different behavior influencing transmission conditional on vaccination status. The driving forces of these differences may not be captured in the collected data or adequately controlled for in the design. Confounding is a major concern, especially in settings such as the United States where there has been politicization of vaccines and other prevention measures and in settings where vaccine access is limited by prioritization guidance. Retrospective observational studies are especially subject to uncontrolled confounding given limited capability to retrospectively capture exposure/transmission variables.

Despite the challenges outlined above in accurately measuring vaccine effects on transmission, it is nevertheless critical to push forward and invest in such research. In particular, we recommend increased support for prospective studies that (1) follow individuals with routine, frequent PCR testing for viral quantification, infectiousness testing, and sequencing; (2) simultaneously collect risk behavior information on these individuals, as well as vaccination history, comorbidities, demographic data, and symptomatology; (3) prospectively follow secondary contacts of these individuals (eg, their households) to accurately infer transmission events and calculate secondary attack rates, as well as capture full viral load trajectories on both asymptomatic and symptomatic individuals; and (4) provide rapid, transparent sharing of data to inform real-time evidence-based

public health decision-making. While no study is perfect, this type of prospective "household transmission study" would provide invaluable data on vaccine effects on SARS-CoV-2 transmission that are more robust than most retrospective studies can provide.

With evolving recommendations for booster vaccinations, understanding what the optimal boosting frequency and schedule will be now and into the future to prevent illness, infection, and reduce onward transmission will be an important question to keep future SARS-CoV-2 outbreaks under control. These efforts require considerable support and willingness by federal and local agencies, as well as vaccine developers. As new data emerge and influence policy, transparent communication of these data requires refinement that recognizes the interplay between waning humoral immunity and changing individual/community risk behaviors regarding gathering, masking, and attitudes toward vaccination; this communication will be paramount in framing future public health initiatives.

CONCLUSIONS

Over the last 2 years, we have seen unparalleled scientific collaboration and innovation including rapid sequencing of SARS-CoV-2, vaccine development, new and repurposed treatment agents, and evolving understanding of the epidemiology of transmission. Looking to the future, funding for intensive surveillance for infection and transmission in sentinel cohorts, with real-time reporting of data, would provide opportunities to understand how to best adapt policy and vaccine development to new variants that emerge. Recognition of ongoing transmission possibilities in the face of effective vaccines should not weaken confidence in vaccines, but rather strengthen confidence in a multipronged public health response that include vaccines paired with additional interventions such as masks, physical distancing, and high-quality ventilation, among others, in areas of high community transmission. As we head into the third year of this pandemic with the unfortunate realization that complete eradication of SARS-CoV-2 may be out of reach, the ongoing evolution and inevitable emergence of new variants will continue to present challenges for halting transmission. Enhancing our understanding of transmission dynamics will be pivotal in developing flexible, nimble public health systems operating within the nuance of how and when prevention strategies can be turned on and off to prevent unnecessary illness and death.

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