Indirect Protection by Reducing Transmission: Ending the Pandemic with SARS-CoV-2 Vaccination

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Introduction

Remarkably, in less than a year since the COVID-19 pandemic began, multiple vaccines employing a variety of platforms have demonstrated high efficacy for protection against symptomatic COVID-19 in randomized controlled trials. This protection appears to be especially potent against severe COVID-19, with sizable reductions in severe outcomes now being confirmed in real-world settings at much larger scale.[1,2] The direct protection against disease measured by the clinical trials is important, but whether and to what extent the vaccines provide indirect protection by reducing transmission is also of great consequence in controlling and eventually ending the pandemic.[3] Therefore, understanding the effects of vaccines on transmission is key to deploying evidence-based population vaccination plans, recommendations for the public, and policies for use of nonpharmaceutical interventions with varying degrees of effectiveness in this next stage of the pandemic.[4]

There are two ways a vaccine can reduce transmission risk. First, a vaccine may decrease the probability of a recipient becoming infected in the first place by protecting against both symptomatic (as measured by the primary endpoints of the clinical trials) and asymptomatic infection (which can only be identified using systematic PCR or serology testing). Second, a vaccine may decrease the probability of secondary transmission from an infected vaccine recipient by reducing the duration or degree of infectiousness. Accumulating evidence suggests that SARS-CoV-2 vaccines can substantially reduce transmission through both of these mechanisms.

Evidence of Protection by Vaccines Against Infection (Symptomatic and Asymptomatic)

Three randomized controlled trials to date provide evidence supporting protection against all infection (including asymptomatic infection). In the Moderna mRNA-1273 vaccine trial, all asymptomatic participants underwent PCR testing at the time of the second dose, and the study showed a 61% (95% CI 31-79%) reduction in asymptomatic infection relative to an 85% (95% CI 66-93%) reduction in symptomatic infection prior to the second dose.[5] This is likely to underestimate efficacy against new

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infection because PCR may remain positive for weeks after infection (and thus testing may include residual positive testing prior to the effect of the first dose), and the efficacy was assessed prior to full protection after both doses.[6] The AstraZeneca ChAdOx1 nCoV-19 vaccine was evaluated in a series of pooled trials, one of which included weekly screening by PCR, and showed a 55.7% (95% CI 41.4-66.7%) reduction in all infections, relative to a vaccine efficacy against symptomatic disease of 70.4% (95% CI 54.8-80.6%).[7] By using cross-sectional testing, the estimates from these two studies are actually composite measures of reduced risk of infection and duration of PCR positivity (i.e. duration of infection).[8] Finally, the randomized controlled trial of the Janssen AD26.COV2.S vaccine included a subset of participants with available serology data at day 71, and showed a 65.5% (95% CI 39.9-81.1%) reduction in all infections after day 29, compared to a 66.5% (95% CI 55.5-75.1%) reduction against symptomatic COVID-19.[9] A limitation of serology-based studies is that there may be a reduced sensitivity for identifying asymptomatic infections.[10,11]

Protection against infection has also been shown in observational studies of healthcare workers, community members, patients, and elderly residents of long-term care facilities. These studies include regular or systematic PCR testing, compare SARS-CoV-2 infection risk between otherwise similar vaccinated and unvaccinated individuals, and adjust for confounding variables associated with both the probability of receiving a vaccine and exposure to SARS-CoV-2. One such study included over 23,000 healthcare workers in the United Kingdom who underwent SARS-CoV-2 PCR testing at least every two weeks (twice per week for frontline healthcare workers) during roll out of the Pfizer-BioNTech BNT162b2 vaccine.[12] After controlling for potential confounders (demographic characteristics, comorbidities, job role, frequency of contact with patients with COVID-19, employment in a patient facing role, and occupational exposure), investigators found that receipt of the vaccine was associated with a 70% reduction (95% CI 55-85%) in all SARS-CoV-2 infections 21 days after the first dose and an 85% (95% CI 74-96%) reduction seven days after the second dose. A cohort study of 373,402 community members in the United Kingdom who were regularly tested using SARS-CoV-2 PCR every 1-4 weeks

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found progressively stronger protection from infection with greater time after either the AstraZeneca ChAdOx1 nCoV-19 or Pfizer-BioNTech BNT162b2 vaccines, peaking with a 70% reduction (95% CI 62-77%) after the second dose after adjusting for demographics, neighborhood deprivation, work setting, co-morbidity, and household characteristics, among other confounders.[13] Another study evaluated 39,156 consecutive asymptomatic individuals who had pre-procedural SARS-CoV-2 PCR screening at a large United States healthcare system.[14] After adjusting for demographic characteristics and repeated testing, vaccinated patients had an 80% reduction (95% CI 56-91%) in risk of infection after the second dose of either the Pfizer-BioNTech BNT162b2 or the Moderna mRNA-1273 vaccines, with similar protection seen starting 10 days after the first dose. Vaccine effectiveness against all infections regardless of symptoms has also been shown in long-term care facilities, a particularly high risk setting that was not considered in clinical trials. A study of 10,412 residents in the United Kingdom with a median age of 86 who had regular PCR screening at least monthly showed a 62% reduction in infection risk (95% CI 23-81%) 35 days after the first dose of the Pfizer-BioNTech BNT162b2 or AstraZeneca ChAdOx1 nCoV-19 vaccines after adjusting for sex, age, prior infection, bed capacity, and local SARS-CoV-2 incidence.[15] While all of these studies attempted to adjust for confounding variables, their findings may still be biased if there are large unmeasured differences in vaccinated and unvaccinated populations. Other vaccine effectiveness studies that included regular PCR screening but did not adjust for potential confounding variables have similarly found strong protection against all infections regardless of symptoms.[16-19]

Experimental and observational evidence thus suggests that vaccines across multiple platforms are associated with large reductions in all SARS-CoV-2 infections regardless of symptoms, with protection that is nearly as high as that provided against symptomatic COVID-19. There may be some populations – like certain immunocompromised individuals – where this is not the case, though limited data suggest protection against at least symptomatic infection is broadly preserved.[20] Another caveat is that, with the exception of the Janssen AD26.COV2.S vaccine, these data were not obtained in the context of the variants currently most concerning for immune escape — B1.351 and P1, which predominate in South

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Africa and Brazil, respectively. These variants, and a number of the mutations contained within them, are associated with varying degrees of reduction in neutralizing activity by serum from vaccinated individuals,[21-23] though this does not necessarily correlate with loss in clinical protection. It is not yet known to what degree these variants are associated with a clinically meaningful change in vaccine effectiveness against overall infection.

Evidence of Reduced Transmission Potential for People Infected After Vaccination

The decrease in overall SARS-CoV-2 infection risk after vaccination is the lower bound on a vaccine's effect on transmission. There will be additional reductions in transmission risk if infected vaccine recipients have lower transmission potential relative to infected people who have not been vaccinated. It is already known that people with asymptomatic infection have a shorter duration of viral load shedding and lower secondary attack rates, with a meta-analysis finding a secondary attack rate of 1% (95% CI 0-2%) for asymptomatic index cases relative to 7% (95% CI 3-11%) for pre-symptomatic cases and 6% (95% CI 5-8%) for symptomatic index cases. [24-26] As a result, even in the absence of a decrease in overall infections with vaccination, the reduction in symptomatic infections demonstrated in the clinical trials is expected to result in sizable attenuation in transmission risk.

The most direct way to assess transmission potential of vaccine recipients who become infected is through epidemiological studies directly measuring secondary attack rates among contacts of infected vaccine recipients. In a transmission study of over 550,000 households in England, contacts of index cases who had received the first dose of either the Pfizer-BioNTech BNT162b2 or AstraZeneca ChAdOx1 nCoV-19 vaccine 21 days or more before testing positive were about 50% less likely to become infected after adjusting for confounding.[27] This 50% reduction may be an underestimate for two reasons. First, contact tracing studies like this are most likely to identify index cases with greater symptoms, there is evidence that the vaccines reduce severity of symptoms among those who become infected, and those

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with fewer symptoms have lower secondary attack rates (as discussed below). Second, some contacts may have been infected outside the household.

Though not a direct measure of secondary attack rates, a nationwide cohort study in Scotland found that household members of healthcare workers who were at least 14 days after their second dose of either the Pfizer-BioNTech BNT162b2 or the AstraZeneca ChAdOx1 nCoV-19 vaccine had a 54% reduction in infection risk (95% CI 50-70%) relative to household members of unvaccinated healthcare workers after adjusting for demographic characteristics, socioeconomic deprivation, comorbidity, healthcare worker role, occupation and part-time status.[28] In this case, this result can be thought of as the lower bound in the reduction in transmission risk from the vaccinated household member because exposures may also have occurred from other individuals inside or outside the household.

There are also several proven determinants of SARS-CoV-2 infectiousness that vaccines appear to impact —the magnitude of the peak and rapidity of the decline of the respiratory tract viral load, and severity or number of symptoms.[24,29-33] Altering these determinants is likely to have an important effect in an infection that has a relatively short and intense period of infectiousness with transmission dynamics characterized by overdispersion.[34,35] The clinical trial testing the AstraZeneca ChAdOx1 nCoV-19 vaccine in the United Kingdom included weekly SARS-CoV-2 PCR testing and, among vaccinated participants who became infected, the median minimum cycle threshold value (inversely associated with peak viral load) was 28.8 (IQR 20.5-33.5), compared to 20.2 (IQR 15.5-29.6) ($p<.0001$) for infected participants who had received placebo.[26] They also found that vaccinated participants with infection had one week shorter median duration of PCR positivity. Similarly, an observational study of residents of a United States Veteran's Administration nursing home that conducted twice weekly PCR screening found a 2.4 mean $\log_{10}$ lower viral load at diagnosis among infected residents who had received the first dose of the Pfizer-BioNTech BNT162b2 vaccine relative to unvaccinated residents with infection.[36] The previously mentioned cohort study of community members in the United Kingdom who regularly underwent SARS-CoV-2 PCR testing found a much greater protection after the second dose of either the

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AstraZeneca ChAdOx1 nCoV-19 or Pfizer-BioNTech BNT162b2 vaccines against infections with cycle thresholds values less than 30 (vaccine effectiveness 88%; 95% CI 80%-93%) compared to those with cycle threshold values of 30 or greater (vaccine effectiveness 48%; 95% CI 30%-62%).[13]

Further evidence supporting reduced viral loads during infections after vaccination comes from Israel, which has had the most rapid vaccination implementation per capita in the world. One observational study compared viral loads between people infected with SARS-CoV-2 who had received the Pfizer-BioNTech BNT162b2 vaccine and demographically matched with unvaccinated people, finding a 2.8 to 4.5-fold reduction in viral loads 12-37 days after the first dose.[37] A complementary study took advantage of a national vaccination program that used age-based eligibility and compared viral loads over time in newly-infected individuals 60 years or older (75% of whom were at least 14 days after the first dose of the Pfizer-BioNTech BNT162b2 vaccine at the time of the study) to viral loads in individuals 40 to 60 years old (25% of whom had similar vaccine exposure).[38] Viral loads at diagnosis, initially similar between the two groups, began to separate with vaccine implementation, and the researchers estimated a 1.6 to 20-fold reduction in viral load with vaccination during this early period after the first dose.

In addition to viral load, the severity or number of symptoms is also associated with infectiousness.[24,32] In addition to multiple real-world vaccine effectiveness studies definitively demonstrating strong protection against severe disease by the mRNA vaccines,[1,2] the interim results for the Janssen AD26.COV2.S vaccine presented to the FDA showed a 24% reduction in symptom severity score on day one for infected vaccine recipients relative to those who received placebo, a 47% reduction on day seven, and a 55% reduction on day 14.[39] Infected participants who had received the Janssen AD26.COV2.S vaccine and developed symptoms experienced significantly fewer symptoms compared to those with symptomatic COVID-19 who had received placebo. Taken together, the available evidence strongly suggests that vaccines decrease the transmission potential of vaccine recipients who become infected with SARS-CoV-2 by at least half.

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Evidence from Randomized Controlled Trials of Monoclonal Antibodies

In addition to data from SARS-CoV-2 vaccines, we can also understand vaccines' likely effects on transmission through recent evidence from two randomized controlled trials of neutralizing monoclonal antibodies used for post-exposure prophylaxis.[40,41] Neutralizing antibodies are one important component of the adaptive immune response induced by vaccines, and protection provided by therapeutic neutralizing antibodies are also likely to be present with vaccines that elicit a robust polyclonal antibody response. In one study of 300 nursing home residents, administration of the neutralizing monoclonal antibody bamlanivimab resulted in an 77% reduction (95% CI 52-89%) of SARS-CoV-2 infection relative to placebo during four weeks of follow up that included weekly PCR testing.[40] Infected participants who had received bamlanivimab had significantly lower viral loads at diagnosis and more rapid declines in viral load over time. While this is an important proof of concept, we note that bamlanivimab does not retain neutralizing activity against E484K, one of the key substitutions in B1.351 and P.2.[42]

Similarly, an interim analysis of a study of 409 participants exposed to a household member with COVID-19 had only a small number of events but found a non-statistically significant 48% reduction (95% CI -12%-80%) in overall SARS-CoV-2 infection after receiving the combination of casirivimab with imdevimab compared to placebo, with a 100-fold reduction in peak viral load and a significantly shorter duration of positive PCR testing among those who became infected.[41]

Conclusions

In sum, the data we have reviewed provide compelling evidence that SARS-CoV-2 vaccination results in a substantial reduction in transmission risk, although the exact magnitude of overall transmission reduction is yet to be fully characterized. As a result, the vaccines have much greater potential to decrease population morbidity and mortality than they would in a situation where they only prevented symptomatic disease.[43] These vaccines will thus play a foundational role in curbing and eventually ending the

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pandemic, as evidenced by the recent dramatic reduction in cases in the United Kingdom and Israel, where vaccination campaigns have successfully reached a high proportion of the population. Because of this, efforts to achieve rapid and complete global vaccination coverage are even more essential and urgent. While vaccines remain a scarce resource, the emphasis on vaccinating those with highest risk for adverse outcomes (e.g. older individuals) should continue. However, the indirect protection provided by vaccines also suggests strong population benefit from vaccinating people with lower risk for poor clinical outcome who are in larger networks with higher risk of infection – a population for whom preventing transmission is a key outcome.[44] Large reductions in infection risk and decreased viral replication among infected vaccine recipients will also mean less opportunity for the emergence of new variants. While the great majority of the world remain unvaccinated, non-pharmaceutical interventions will continue to be the fundamental components of strategies to reduce transmission and its consequences.

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Conflicts of Interest

AR, EAM, and MC report no conflicts of interest.

Patient Consent Statement

Patient consent is not relevant to this viewpoint.

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