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Review article

SARS-CoV-2 reinfections: Overview of efficacy and duration of natural and hybrid immunity

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ABSTRACT

Seroprevalence surveys suggest that more than a third and possibly more than half of the global population has been infected with SARS-CoV-2 by early 2022. As large numbers of people continue to be infected, the efficacy and duration of natural immunity in terms of protection against SARS-CoV-2 reinfections and severe disease is of crucial significance for the future. This narrative review provides an overview on epidemiological studies addressing this issue. National surveys covering 2020–2021 documented that a previous SARS-CoV-2 infection is associated with a significantly reduced risk of reinfections with efficacy lasting for at least one year and only relatively moderate waning immunity. Importantly, natural immunity showed roughly similar effect sizes regarding protection against reinfection across different SARS-CoV-2 variants, with the exception of the Omicron variant for which data are just emerging before final conclusions can be drawn. Risk of hospitalizations and deaths was also reduced in SARS-CoV-2 reinfections versus primary infections. Observational studies indicate that natural immunity may offer equal or greater protection against SARS-CoV-2 infections compared to individuals receiving two doses of an mRNA vaccine, but data are not fully consistent. The combination of a previous SARS-CoV-2 infection and a respective vaccination, termed hybrid immunity, seems to confer the greatest protection against SARS-CoV-2 infections, but several knowledge gaps remain regarding this issue. Natural immunity should be considered for public health policy regarding SARS-CoV-2.

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1. Introduction

After the outbreak of SARS-CoV-2 in December 2019 in China, a rapid spread occurred leading to a global pandemic of coronavirus disease 2019 (COVID-19) (Singh et al., 2021; Wu and McGoogan, 2020). Decisions on measures against SARS-CoV-2 infections are challenging and require scientific knowledge on their efficacy and their potential benefits and harms (Ioannidis, 2020a; Kampf and Kulldorff, 2021; Pilz, 2021). Vaccination against SARS-CoV-2 proved to be highly efficacious in short-term randomized controlled trials (RCTs) and effective in real-life settings (Khandker et al., 2021; McIntyre et al., 2022; Polack et al., 2020; Sharif et al., 2021). Reports on waning immunity as early as a few months after vaccination pose a challenge to public health strategies (Chemaitelly et al., 2021b; Goldberg et al., 2021b; Levin et al., 2021; Rosenberg et al., 2022). Evidence is accruing on the extent to which booster vaccinations may help restore a highly efficient protection against SARS-CoV-2 infections and related mortality (Arbel et al., 2021; Bar-On et al., 2021a, 2021b; Chemaitelly et al., 2021b; Goldberg et al., 2021b; Levin et al., 2021; Rosenberg et al., 2022). However, the frequency of needed boosters (if any) in different age groups is unclear and absolute benefits may be far greater among immunocompromised

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and elderly individuals, given the very steep age-gradient of COVID-19 infection fatality rate (Axfors and Ioannidis, 2022). Moreover, with new emerging variants like Omicron the ability to achieve sufficient protection against infection and transmission is contested (Buchan et al., 2022). In the context of increasingly complex vaccination strategies and general measures against COVID-19, natural immunity acquired after SARS-CoV-2 infections may be a crucial, yet often less considered, factor (Ioannidis, 2020b; McIntyre et al., 2022).

Detailed knowledge on the efficacy and duration of natural immunity in terms of protection against reinfections and related morbidity and mortality may be key for the COVID-19 pandemic as more than a third and possibly more than half of the global population may have already been infected (at least once) with SARS-CoV-2 at the beginning of 2022, with the majority of the cases not being officially detected and reported (Bergeri et al., 2021; Hotez et al., 2021; McIntyre et al., 2022). This estimate is based on seroprevalence data suggesting that almost a quarter of the global population had been infected by spring 2021 with substantial further increase thereafter with the advent of the Delta variant waves since mid-2021 and then the massive surges of the Omicron variant starting in December 2021 (Arora et al., 2021; Bergeri et al., 2021; Chen et al., 2021; Ioannidis, 2021c; Jones et al., 2021). While high-income countries with huge testing efforts are capable to detect and report about every second SARS-CoV-2 case currently, the ratio between true cases and reported cases appear to have been about 62 to 1 in low-income countries in a systematic review including data until October 2021 (Bergeri et al., 2021). This ratio has probably decreased over time even in low-income countries, since more testing is being done, but ratios exceeding 10 are likely to be common in these countries. For example, in India, the national serosurvey in August 2021 showed a seroprevalence of almost 70% while the documented cases were only about 2% (Jahan et al., 2021). Therefore, unrecognized asymptomatic cases are very common. A recent meta-analysis reported that even among patients with confirmed COVID-19, 40.5% were asymptomatic (Ma et al., 2021). With the advent of the Omicron variant, the proportion of entirely asymptomatic cases may be even larger. As Omicron shows even larger transmissibility and steep epidemic waves, the proportion of infected individuals is likely to increase further substantially (Christie, 2021; Del Rio et al., 2022; Kupferschmidt and Vogel, 2021). As the pandemic is entering its endemic phase, soon it may be an uncommon exception that an individual has not been infected with SARS-CoV-2 at least once.

The scope of this narrative review is to provide a brief overview on the current knowledge regarding the efficacy and duration of natural immunity derived from large epidemiological studies in general populations, preferably national surveys. Comparisons of natural immunity as opposed to vaccine induced and so-called hybrid immunity, i.e. immunity achieved by SARS-CoV-2 infection plus vaccination, are also covered in this review. Our work is based on a literature search in PubMed until January 1, 2022 using the search terms “SARS-CoV-2” or “COVID-19” in combination with “reinfection” (yielding 891 items). This search procedure was reiterated in medRxiv, but only articles of outstanding interest were included (with due caution) from these not peer reviewed pre-prints. Our work significantly extends and updates previous reviews on this topic (Kojima et al., 2021; Petras, 2021; Shenai et al., 2021). While this manuscript has its focus on epidemiological data regarding natural immunity, we refer the reader to excellent reviews on the detailed immunological responses to SARS-CoV-2 infections and vaccinations as we only briefly touch upon these issues in some sections of our review (Castro Dopico et al., 2022; Cromer et al., 2021; Gussarow et al., 2021; Milne et al., 2021).

2. Efficacy and duration of natural immunity against reinfections

Differentiation between true reinfection and prolonged primary infection with SARS-CoV-2 is challenging due to reports of viral shedding lasting several weeks to a few months (Lee et al., 2021; Long et al., 2021; Yahav et al., 2021). For epidemiological purposes, a SARS-CoV-2 reinfection could be defined as any positive RT-PCR test more than 90 days after the initial positive test result, a definition that has been adopted by many scientists and organizations including the Centers for Disease Control (CDC) in the Unites States (Yahav et al., 2021). Of course, it would be optimal to have negative PCR test results after the initial diagnosis and confirm reinfections based on sequencing results documenting different viral strains, but such an approach is usually not feasible for large surveys. In general, epidemiological data on natural immunity must, of course, be interpreted in light of the various potential sources of bias of these observational studies. These biases include, but are not limited to:

1. Detection bias due to different testing frequencies among those previously infected and those not previously infected, and also between vaccinated and unvaccinated individuals.
2. Misclassifications due to unrecognized infections (both primary and reinfections).
3. Misclassification due to imperfect sensitivity and specificity of molecular and antibody tests.
4. Confounding due to various factors that may differ between infected and non-infected individuals and which may also affect the chances of being re-infected and having a serious outcome after reinfection, e.g. degree of protection and extent of risk/exposures (because of different health consciousness and potential sense of protection given prior infection), different uptake of vaccines, differences in comorbidities, in demographics, occupation, socioeconomic status, living in institutionalized settings, and potentially many other factors that may be difficult to measure or are even entirely unknown.

These considerations apply to all sections of this review. Therefore, the estimates of uncertainty (e.g. 95% confidence intervals (CI)) derived from reinfection studies and presented below should be seen as very conservative. Bias may also affect the estimates themselves and the direction of the impact may not necessarily be predictable. Moreover, estimates may be different with new and emerging variants and under conditions with different vaccination strategies and vaccine uptake.

2.1. Efficacy of natural immunity

First evidence on natural immunity derived from a population based cohort was reported by a study in 133,266 previously SARS-CoV-2 infected patients from Qatar showing that reinfection risk was estimated at 0.02% (95% CI: 0.01%–0.02%), and that reinfection incidence rate per 10,000 person weeks was 0.36 (95% CI: 0.28 to 0.57) (Abu-Raddad et al., 2021e). That study did not include a formal group comparison to previously uninfected individuals but estimated, based on modeling of the general incidence rate in Qatar, that the efficacy of natural SARS-CoV-2 infection against reinfection is about 95%. By the end of 2020 and beginning of 2021, the first cohort studies in specific populations documented a significantly reduced risk of SARS-CoV-2 infections in patients with versus without a prior infection (Breathnach et al., 2021b; Hall et al., 2021; Hanrath et al., 2021; Kojima et al., 2021; Lumley et al., 2021a). Lumley et al. published one of the first investigations on this issue in a cohort of 12,541 health care workers, who were well characterized by PCR and antibody testing (Lumley et al., 2021a). They reported that a previous SARS-CoV-2 infection was associated with an 89% (95% CI: 44%–97%) protection against SARS-CoV-2 infection compared to previously not infected individuals (Lumley et al., 2021a). The first national surveys addressing this issue were from Austria and Denmark, accompanied by a large cohort study from the United States that was based on seroprevalence data (Hansen et al., 2021; Harvey et al., 2021; Pilz et al., 2021). This latter study included 3,257,478 participants and showed a 90% (95% CI: 81%–95%) reduction of SARS-CoV-2 infections comparing patients with a positive versus a

negative antibody test against SARS-CoV-2 (Harvey et al., 2021). In line with this, data from a population based survey in 192,984 individuals with available SARS-CoV-2 antibody test results from Qatar showed a 95.2% (95% CI: 94.1%–96.0%) efficacy of natural immunity based on antibody status (Abu-Raddad et al., 2021d). Additional studies in the general population on this issue were derived from national health data from Qatar, large cohort studies in the United States and population based surveys from Italy and the United Kingdom, and are listed in Table 1 that is restricted to population based studies providing group comparisons for infection risk in individuals with and without previous PCR confirmed SARS-CoV-2 infections (Abu-Raddad et al., 2021a; Abu-Raddad et al., 2021e; Chemaitelly et al., 2021a; Goldberg et al., 2021c; Kim et al., 2021; Sheehan et al., 2021; Spicer et al., 2021). In summary, all these epidemiological studies have consistently documented that a previous SARS-CoV-2 infection confers substantially large protection against reinfections.

All studies in Table 1 are peer-reviewed studies based on PCR confirmed cases at baseline and follow-up, with the exception of one study from the United States including antigen tests in addition to PCR tests, and the study from the United Kingdom that classified infection status at baseline on either PCR or antibody tests (Breathnach et al., 2021b; Spicer et al., 2021). Importantly, the studies listed in Table 1 cover different infection waves including also the Delta variant, but no data on the Omicron variant. Preliminary data suggest that the Omicron variant is associated with substantial ability to evade immunity from prior infection, in contrast to the Beta or Delta variants (Lusvarghi et al., 2021; Rössler et al., 2021, Danza et al., 2022). Therefore, natural immunity has to be reassessed after incorporation of more data from SARS-CoV-2 Omicron variant infections. In this context, a preprint article reporting national data from Qatar suggests that while protection against reinfections may be reduced for Omicron to 56.0% (95% CI: 50.6%–60.9%), the protection against hospitalization or death due to reinfections appears similarly high as for other variants with 87.8% (95% CI: 47.5%–97.1%) (Altarawneh et al., 2022). Preliminary reports on natural immunity regarding Omicron are, however, inconsistent and require cautious interpretation (Eggink et al., 2021; Pulliam et al., 2021). While Table 1 is restricted to studies in general populations including relative risk estimates for infections with SARS-CoV-2 in groups with and without prior infections, there are numerous other studies on this topic in either specific populations (e.g. health care workers) or with other study designs (e.g. solely based on antibodies with thus unclear infection date or missing control groups) that are all in line with the notion that natural immunity significantly protects against reinfections (Abrokwa et al., 2021; Fabianova et al., 2021; Hall et al., 2021; Hanrath et al., 2021; Harvey et al., 2021; Iversen et al., 2021; Jeffery-Smith et al., 2021; Kojima et al., 2021; Leidi et al., 2021; Letizia et al., 2021; O Murchu et al., 2021; Rennert and McMahan, 2021).

Several methodological approaches have been used to evaluate efficacy of natural immunity. A special note may be worthwhile for the test-negative study design (Ayoub et al., 2022). In this design, cases and matched test-negative controls are selected among people who present themselves for testing because of symptoms. Effectiveness of prior infection in preventing reinfections is calculated as one minus the ratio of odds of prior infection in individuals testing positive, to the odds of prior infection in individuals testing negative for the infection. For caveats about the robustness of the test-negative design see Lewnard et al., (2021).

2.2. Duration of natural immunity

Various studies indicate that natural immunity seems to be relatively long-lasting (Chemaitelly et al., 2021a; Flacco et al., 2021; Hansen et al., 2021; Leidi et al., 2021; Peghin et al., 2021; Pilz et al., 2021; Salehi-Vaziri et al., 2021; Sheehan et al., 2021; Vitale et al., 2021). In detail, the national survey in Denmark did not find any evidence that protection against reinfections was waning after 6 months, a finding that is consistent with data from Austria (Hansen et al., 2021; Pilz et al., 2021). Interestingly, some investigations indicate that protection against reinfection is lowest at 4 to 5 months after initial infection and increases thereafter, a finding that might hypothetically be explained by persistent viral shedding, i.e. misclassification of prolonged SARS-CoV-2 infections as reinfections (Kim et al., 2021; Sheehan et al., 2021). Some population based studies with follow-up times exceeding one year reported a sustained efficacy of protection against SARS-CoV reinfections with no

Table 1
Protection against SARS-CoV-2 reinfections in population based studies.

Country (Ref.)	Participants (n)	Infected at baseline (n)	Reinfections (n)	Follow-up time (mean ± SD)	Period of first infection and reinfection follow-up	Protection against reinfection (95% CI)
Austria (Pilz et al., 2021)	8,901,064	14,840	40	212 ± 25 days	First infection from February to April 30, 2020; Follow-up from September 1 to November 30, 2020	91% (87% to 93%)
Denmark (Hansen et al., 2021)	525,339	11,068	72	A total of 1,346,920 person days	First infection from March to May 2020; Follow-up from September 1 to December 31, 2020	80.5% (75.4% to 84.5%)
Qatar (Chemaitelly et al., 2021a)	89,642	44,821	263	A total of 280,835.1 person weeks	First infection in June 2021 (median); Follow-up from March 8 to April 21, 2021	Beta variant: 92.3% (90.3% to 93.8%) Alpha variant: 97.6% (95.7% to 98.7%)
Qatar (Abu-Raddad et al., 2021a)	308,714	158,608	214	A total of 996,341.5 person weeks	First infection before November 1, 2020; Follow-up from January 18 to March 3, 2021	Alpha variant: 97.5% (95.7% to 98.6%) Unknown variant: 92.2% (90.6% to 93.5%)
United States (Kim et al., 2021)	325,157	50,327	40	300 ± 76 days	First infection March 9 to December 31, 2020; Follow-up from July 1 to September 9, 2021	85.4% (80.0% to 89.3%)
United States (Spicer et al., 2021)	550,168	41,647	593	90 to 300 days (minimum to maximum)	First infection from March 6 to August 31, 2020; Follow-up until December 31, 2020	77.3% (75.4% to 79.0%)
United States (Sheehan et al., 2021)	150,325	8845	62	139 ± 46 days	First infection from March 12 to August 30, 2020; Follow-up until February 24, 2021	81.8% (76.6% to 85.8%)
Italy (Vitale et al., 2021)	13,496	1579	5	280 ± 41 days	First infection from February to July 2020; Follow-up until February 28, 2021	94% (92% to 95%)
United Kingdom (Breathnach et al., 2021b)	66,001	10,727	8	Not indicated	First infection from February to July 2020; Follow-up from August to December 2020	94% (88% to 97%)

Table 2
Protection against SARS-CoV-2 reinfections in population based studies stratified by follow-up time.

Country (Ref.)	Follow-up time	Protection against reinfection (%) (95% CI)
Denmark (Hansen et al., 2021)	3 to 6 months	79.3 (74.4 to 83.3)
	7 months and longer	77.7 (70.9 to 82.9)
United States (Kim et al., 2021)	90 to 150 days	63.9
	151 to 210 days	93.2
	211 to 270 days	93.9
	271 to 330 days	91.3
	331 to 390 days	90.8
	After 390 days	87.3
United States (Spicer et al., 2021)	90 to 120 days	70.1 (65.6 to 74.0)
	121 to 150 days	78.7 (75.1 to 81.7)
	151 to 180 days	81.4 (77.5 to 84.6)
	181 to 210 days	74.0 (67.2 to 79.4)
	211 to 240 days	70.4 (59.5 to 78.4)
	241 to 270 days	79.8 (65.0 to 88.4)
	271 to 300 days	Not indicated (no infection in 1335 participants with a prior infection and 77 infections in 10,382 without a prior infection)
United States (Sheehan et al., 2021)	90 to 150 days	60.0
	151 to 210 days	90.6
	After 210 days	93.9

significant decline at the end of the observational period (Flacco et al., 2021; Kim et al., 2021). In this context, Kim et al. showed that more than 390 days after the initial SARS-CoV-2 infection, protection against any infection was 87.3% and against symptomatic infection 95.0% (Kim et al., 2021). Detailed data on population based studies reporting efficacy of protection against reinfections stratified by different follow-up times are shown in Table 2.

Preliminary data from Israel that lack a comparison to uninfected and unvaccinated individuals do, however, suggest that protection against reinfections may decline from 6 to more than 12 months after the first SARS-CoV-2 infection (Goldberg et al., 2021a). In detail, reinfections (95% CI) per 100,000 person days were 10.5 (8.8 to 12.4) at 4 to 6 months and increased to 30.2 (28.5 to 32.0) at more than 12 months after first infection (Goldberg et al., 2021a). Even thus, the rate remains low after more than 12 months in terms of absolute risk (less than 0.1% per month).

Taken together, epidemiological studies indicate that protection against reinfections by natural immunity lasts for over one year with only moderate, if at all, decline over this period. The notion of long-term protection against-reinfections is also underpinned by data on persistance of anti SARS-CoV-2 antibodies and cellular immunity over more than one year in the majority of patients (Chellamuthu et al., 2021; Dehgani-Mobaraki et al., 2021; Gussarow et al., 2021; Lau et al., 2021; Rosati et al., 2021).

2.3. Risk factors for reinfections

Data on risk factors that identify groups with a higher risk for SARS-CoV-2 reinfections are less clear. Some reports indicate that older individuals, in particular those in long-term care facilities, immunocompromised patients and those with certain comorbidities or exposure risk (e.g. health-care workers) may have higher rates of reinfections, but data remain inconsistent (Fakhroo et al., 2021; Hansen et al., 2021; Murillo-Zamora et al., 2021a, 2021b; Ringlander et al., 2021; Spicer et al., 2021). It is plausible that reinfection risk may be a function of exposure risk. With more exposures as societies use less or no lockdown measures and citizens feel more safe to get exposed, higher rates of re-infections may ensue (Ioannidis, 2021a). However, the exact shape of the exposure-reinfection risk function (e.g. whether there is a plateau and many people will not be reinfected regardless of the amount of increased exposure) remains unknown. Moreover, differentiation between persistent COVID-19 and reinfection is challenging, in particular in older persons (Ringlander et al., 2021). It is also not entirely clear whether disease severity of the initial SARS-CoV-2 infection significantly modifies the risk of reinfections, but it should be noted that even asymptomatic SARS-CoV-2 infections elicit a strong immunological response (Boyton and Altmann, 2021; Garrido et al., 2021; Murillo-Zamora et al., 2021a; Schuler et al., 2021; Spicer et al., 2021).

Whether determination of anti SARS-CoV-2 antibodies in patients with known prior infection is useful for risk stratification of reinfections is not clear. A retrospective study from the United Kingdom showed that a group of 224 previously SARS-CoV-2 infected patients who had no detectable antibodies against SARS-CoV-2, still had an 80% protection (95% CI: 19%–95%) against SARS-CoV-2 infections compared to a group of persons with no previous infection and a negative serology (Breathnach et al., 2021a). In the same study, reinfection risk was not significantly different in patients with a prior SARS-CoV-2 infection, when comparing groups with versus without detectable anti SARS-CoV-2 antibodies (Breathnach et al., 2021a). This finding does not question the numerous studies showing that participants with versus without detectable anti SARS-CoV-2 antibodies are at significantly reduced risk of infections, but merely questions the additional prognostic value of antibody measurements in recovered patients (Harvey et al., 2021). More studies on this issue are welcome, but adoption of antibody testing in guidelines for individual personalized care would be precarious or even harmful based on what we know currently. In principle, adding massive antibody testing for clinical use may complicate an already complex milieu where massive testing is being performed for viral tests. This may create more confusion and protract the perception of an ongoing anomaly in the population.

Other aspects of the immune response may also be modifying the risk of reinfection. Besides antibodies, SARS-CoV-2 infections elicit strong cellular immune responses (Havervall et al., 2022; Melenotte et al., 2020; Sekine et al., 2020). The impact of different types of cellular immune response, e.g. Th1 versus Th2 response on modulating reinfection risk, needs better study (Melenotte et al., 2020).

2.4. Clinical severity of reinfections

An even more crucial question is whether natural immunity conferred by previous SARS-CoV-2 infections may mitigate the disease severity of potential reinfections. Using national, federated databases from Qatar, it has been shown in a well matched case control population based study, that reinfections with SARS-CoV-2 had a 90% lower odds

(95% CI: 75%–97%) of resulting in hospitalization or death when compared to primary infections (Abu-Raddad et al., 2021c).

Comparisons of disease severity for each individual patient during the first versus the reinfection episode have also been evaluated in several case series and small cohort studies and have partially, but not consistently, indicated that reinfections are less severe than primary infections (Abu-Raddad et al., 2021e; Fabianova et al., 2021; Hussein et al., 2021; Lo Muzio et al., 2021; Qureshi et al., 2022; Slezak et al., 2021). Taken together, there is accumulating evidence that reinfections may be significantly less severe than primary infections with SARS-CoV-2, a finding with huge implications for the COVID-19 pandemic and its evolution into an endemic phase. Reduced clinical severity of SARS-CoV-2 reinfections makes, of course, also sense from a biological point of view, as a previously primed immune system should be better prepared for a re-challenge with this virus (Boyton and Altmann, 2021; Castro Dopico et al., 2022; Cromer et al., 2021; Milne et al., 2021).

Given that reinfections versus primary infections with SARS-CoV-2 are associated with a significantly lower viral load, as evidenced by the RT-qPCR cycle threshold (Ct) value, they may be less infectious and may thus be associated with reduced transmission (Abu-Raddad et al., 2022). This may have significant implications for the course of the COVID-19 epidemic waves (Abu-Raddad et al., 2022). It should also be noted that human experimental reinfections with endemic human coronaviruses showed milder symptoms and shorter duration compared to primary infections (Callow et al., 1990; Lavine et al., 2021). The primary infections with the four endemic human coronaviruses occur early in life at a mean age between 3.4 and 5.1 years, with frequent but mild reinfections later in life (Lavine et al., 2021). It is speculated whether, once the endemic phase is reached, a similar pattern may apply also to SARS-CoV-2 (Lavine et al., 2021).

One would need to consider also that the comparison of severity between primary infections and reinfections excludes the most severe primary infections that resulted in death. Moreover, the health profile and comorbidities of the same person may differ at the time of reinfection versus the time of primary infection. This may become more relevant many years into the endemic phase, e.g. when reinfection affects a person who is several years older and may have developed various health problems in the interim versus when he/she had the primary infection.

3. Comparison of natural immunity with vaccine induced and hybrid immunity

3.1. Vaccine induced immunity

The high efficacy of vaccines against SARS-CoV-2, e.g. 94.1% for the mRNA-1273 (Moderna) and 95% for the BNT162b2 (BioNTech/Pfizer) vaccine, has already been reviewed and summarized elsewhere (Rotshild et al., 2021; Sharif et al., 2021). In brief, RCTs on vaccines against SARS-CoV2 evaluated time periods less than 4 months and their very high short-term efficacy has been subsequently confirmed in effectiveness studies in real-world settings (Baden et al., 2021; Chemaitelly et al., 2021b; Polack et al., 2020; Rosenberg et al., 2022). Extending the observational periods regarding these vaccines to about 6 months and longer yielded, however, significantly waning protection against SARS-CoV-2 infections (Chemaitelly et al., 2021b; Goldberg et al., 2021b; Rosenberg et al., 2022). In detail, waning efficacy was observed with respect to protection against SARS-CoV-2 infections (e.g. only approximately 20% after about half a year in Qatar), whereas protection against severe disease was either sustained or showed only a moderate decline (Chemaitelly et al., 2021b; Goldberg et al., 2021b; Rosenberg et al., 2022). National data from Israel showed that in individuals who received two doses of the BNT162b2 vaccine at least 5 months earlier, an additional vaccine dose, a so-called booster, significantly lowered mortality and severe illness (Arbel et al., 2021; Bar-On et al., 2021a). These findings suggest that this booster restored and probably exceeded the initial short-term efficacy after the initial vaccination. Data are still emerging as of this writing regarding the efficacy and effectiveness of boosters against the Omicron variants. Preliminary data suggest far lower ability to restore protection from infection and vaccination (Altarawneh et al., 2022; Buchan et al., 2022; Lyngse et al., 2021; Pulliam et al., 2021). However, fatalities and hospitalizations remain distinctively low (Christie, 2021; Kupferschmidt and Vogel, 2021; Ulloa et al., 2022).

3.2. Natural immunity versus vaccine induced immunity

Comparisons of natural immunity versus vaccine induced immunity are restricted to observational studies with all their inherent limitations, as discussed in section 2 above (Bozio et al., 2021; Gazit et al., 2021; Goldberg et al., 2021a, 2021c; Lumley et al., 2021b; Satwik et al., 2021; Shenai et al., 2021; Shrestha et al., 2021). Biases may be even more prominent in these comparisons since they combine the biases of comparisons of infected versus uninfected, plus the biases of comparisons between vaccinated and non-vaccinated, with strong potential selection biases and confounding. Of particular note, the proportion of people previously infected and/or vaccinated may influence estimates of effectiveness. For example, if we hypothesize, for illustrative purposes, that previous infection confers perfect protection from death upon reinfection and all the population has been previously infected, then a vaccine will show zero effectiveness, because there is no room to improve protection any further. Similarly, if all people in a population are vaccinated and vaccination affords perfect protection from death, then reinfection after vaccination will seem to offer zero additional benefit for death outcomes.

A previous systematic review and pooled analyses by Shenai et al. concluded that natural immunity is at least equivalent to the protection afforded by “complete” vaccination against SARS-CoV-2 (without a booster), but additional studies have been published after the literature search of this otherwise excellent review (August 31, 2021) (Bozio et al., 2021; Goldberg et al., 2021a; Shenai et al., 2021). Notably, data from vaccine RCTs on previous SARS-CoV-2 infection status provided only very few cases precluding adequately powered statistical analyses comparing previously infected and unvaccinated patients versus previously not infected and vaccinated participants (i.e. 0.014 versus 0.024 infections per person year) and the comparison is not randomized anyhow (Shenai et al., 2021).

Three nationwide surveys (all pre-prints as of this writing) from Israel with an overall study population of approximately 6 million participants performed, amongst others, a comparison between immunity acquired after SARS-CoV-2 infection and immunity induced by BNT162b2 vaccination (Gazit et al., 2021; Goldberg et al., 2021a, 2021c). Goldberg et al. compared unvaccinated patients with a prior SARS-CoV-2 infection and vaccinated individuals followed up from a week after the second vaccine dose onwards versus a group of unvaccinated and not previously infected individuals (Goldberg et al., 2021c). Follow-up time was from December 20, 2020 (i.e. the date of launching the vaccination program) to March 20, 2021, for all groups, but only patients with a prior infection occurring from June 1 to September 20, 2020 were included in the natural immunity group, as reinfections were only diagnosed when occurring three months or more after the first diagnosis of infection. Compared to unvaccinated and not previously infected individuals, the natural immunity and vaccinated group had a similar protection of 94.8% and 92.8% against infection, of 94.1% and 94.2% against hospitalization, and of 96.4% and 94.4% against severe illness, respectively (Goldberg et al., 2021c). Gazit et al. performed a similar investigation in Israel during the follow-up period from June 1 to August 14, 2021 (Gazit et al., 2021). They compared individuals who received their second vaccine dose prior to February 28, 2021 with patients who had a documented infection with SARS-CoV-2 from January 1 to February 28, 2021, so that both groups had similar follow-up times (Gazit et al., 2021). After adjusting for comorbidities,

the vaccinated versus the previously infected group had a 13 (95% CI: 8 to 21) fold higher risk of SARS-CoV-2 infections and a 27 (95% CI: 13 to 58) fold higher risk of symptomatic disease. Reiterating these analyses by including all patients with documented SARS-CoV-2 infections from March 1, 2020 to February 28, 2021 in the previously infected group, resulted in a 6.0 (95% CI 4.9 to 7.3) fold increased risk of infections and a 7.1 (95% CI: 5.5 to 9.2) fold increased risk of symptomatic disease in the vaccinated versus the previously infected group, suggesting waning natural immunity over time (Gazit et al., 2021). Finally, Goldberg et al. evaluated SARS-CoV-2 infections in Israel during the study period from August 1 to September 30, 2021 by stratifying their analyses according to the last immunity-conferring event, i.e. the last vaccination or SARS-CoV-2 infection (Goldberg et al., 2021a). Protection against SARS-CoV-2 infection was significantly higher in recovered versus vaccinated individuals when a similar time period since the last immune-conferring event was evaluated. In analyses adjusted for age, gender, population group and risk of exposure, infection cases per 100.000 person days (with 95% CI) for recovered patients were 10.5 (8.8 to 12.4) at 4 to 6 months (after infection) and 30.2 (28.5 to 32.0) at more than 12 months. The respective results for vaccinated individuals were 21.1 (20.0 to 22.4) at less than 2 months (after vaccination), 69.2 (68.8 to 69.8) at 4 to 6 months, and 88.9 (88.3 to 89.6) at 6 to 8 months (Goldberg et al., 2021a). Importantly, after receiving a booster (i.e. an additional vaccine dose) in the vaccinated group, the respective infection rate declined to 8.2 (8.0 to 8.5) when the time since the booster was less than 2 months.

In addition to the nationwide data from Israel there are some other investigations on this issue but with significantly fewer participants and with limited generalizability due to the nature of their specific study cohorts deviating from the general population (Bozio et al., 2021; Satwik et al., 2021). In an observational study among 4296 employees of a tertiary care hospital in India, two doses of the ChAdOx1 (AstraZeneca) vaccine showed an efficacy of protection (with 95% CI) versus unvaccinated persons of 28% (10% to 41%) against symptomatic SARS-CoV-2 infection, of 67% (44% to 81%) against moderate to severe disease and of 76% (37% to 89%) against need for oxygen supply (Satwik et al., 2021). Importantly, the respective efficacy for previous SARS-CoV-2 infection versus no infection was 93% (87% to 96%) against symptomatic SARS-CoV-2 infection, 89% (57% to 97%) against moderate to severe disease, and 85% (−9% to 98%) against need for oxygen supply (Satwik et al., 2021). Lumley et al. observed that in 13,109 health care workers two vaccine doses (BNT126b2 or ChAdOx1) reduced SARS-CoV-2 infections by 90% (95% CI: 62%–98%) and seropositivity (i.e. a proxy for a previous infection) by 85% (95% CI: 74%–92%) (Lumley et al., 2021b). In a study among 52,238 health care workers from the United States, no SARS-CoV-2 infection occurred in 1359 participants with a prior infection, who remained unvaccinated during follow-up lasting for a median duration of 143 days (interquartile range from 76 to 179 days) for all previously infected participants (Shrestha et al., 2021). In the same study, only 15 infections (0.7%) occurred in participants who were not previously infected but vaccinated (Shrestha et al., 2021). In another study from the United States, hospitalized patients with COVID-19-like-illness were examined to evaluate whether the odds of having a SARS-CoV-2 positive test result differs in patients who 90 to 179 days before hospitalization received either two doses of an mRNA SARS-CoV-2 vaccine or had a previous SARS-CoV-2 infection (Bozio et al., 2021). Additional inclusion criteria were, amongst others, at least one SARS-CoV-2 test $\geq$14 days before hospitalization, availability of vaccines, and SARS-CoV-2 testing during hospitalization, so that only 7348 out of 201,269 patients who were hospitalized for COVID-19 illness from January 1 to September 2, 2021 were eligible for analysis suggesting a risk of strong selection bias and low generalizability. Laboratory confirmed SARS-CoV-2 infection was detected in 324 (5.1%) out of 6328 vaccinated patients and in 89 (8.7%) of previously infected unvaccinated patients. The adjusted odds ratio (95% CI) of laboratory confirmed SARS-CoV-2 infection in the previously infected versus vaccinated group was 5.5 (2.8 to 11.0) (Bozio et al., 2021).

Taken together, observational studies indicate that natural immunity offers equal or greater protection against SARS-CoV-2 infections compared to individuals receiving two doses of an mRNA vaccine, but data are not fully consistent. It appears to be critical for any analysis to account for the timing of the last immunity-conferring event (i.e. time of infection and vaccination) since there is compelling evidence for relatively rapid waning of protection against SARS-CoV-2 infections by vaccination whereas waning of natural immunity seems to be relatively moderate. It is very difficult to adjust for all the differences of vaccinated and previously infected individuals and results of such analyses may depend substantially on how the study population is selected/filtered and what specific adjustments are made. The proportion of people with prior infection and/or prior vaccination may also affect the results.

3.3. Hybrid immunity

The term hybrid immunity applies to individuals with a prior SARS-CoV-2 infection who were then vaccinated against SARS-CoV-2 or vice versa (Abu-Raddad et al., 2021b; Bates et al., 2021; Cavanaugh et al., 2021; Gazit et al., 2021; Goldberg et al., 2021a; Kim et al., 2021; Kojima et al., 2021; Lumley et al., 2021b; Satwik et al., 2021; Shenai et al., 2021; Shrestha et al., 2021). Data on hybrid immunity from the SARS-CoV-2 vaccine RCTs were limited due to small numbers of previously SARS-CoV-2 infected participants when these studies were done precluding accurate statistical analyses on this issue (Shenai et al., 2021). However, for RCTs done currently and for those that may be done in the future, consideration of prior infection and hybrid immunity will be essential.

In the nationwide investigation in more than 5.7 million residents from Israel that was already mentioned above, it was shown that when the time since the last immunity-conferring event (either primary infection or vaccination) was the same, the rates of SARS-CoV-2 infections were similar in the following groups: (a) individuals who had a previous infection and no vaccination, (b) individuals who had an infection and were then vaccinated with a single dose after at least 3 months and (c) individuals who were vaccinated (two doses) and then infected (Goldberg et al., 2021a). In detail, 4 to 6 months after the last immunity-conferring event, the adjusted rates of SARS-CoV-2 infections (95% CI) per 100,000 days at risk were (a) 10.5 (8.8 to 12.4), (b) 10.3 (9.4 to 11.4), and (c) 12.8 (9.9 to 16.6), respectively. All these latter groups showed waning immunity over time and had significantly lower SARS-CoV-2 infection rates when compared to persons who received two vaccine doses and had an adjusted infection rate per 100,000 days at risk of 69.2 (95% CI: 68.8 to 69.8) (Goldberg et al., 2021a). Severe disease was overall relatively rare: when ignoring the time for the last immunity conferring event, the crude rates for severe disease per 100.000 person days for individuals 60 years and older, were 0.6 for participants with a previous infection and no vaccination, 0.5 for participants who had an infection and were then vaccinated, 1.1 for participants who were vaccinated (two doses) and then infected, 4.6 for participants vaccinated with two doses, and 0.4 for those who additionally received a booster vaccine (Goldberg et al., 2021a). Another earlier investigation from Israel reported that in 14,029 individuals with a previous SARS-CoV-2- infection, those who received a single vaccine dose had a 0.53 fold (95% CI: 0.3 to 0.92) reduced risk of SARS-CoV-2 infections compared to previously infected individuals without receiving a vaccine (Gazit et al., 2021). When restricting the analysis to individuals who were first infected and then vaccinated (i.e. 81% of this group), the odds ratio was 0.68 (95% CI: 0.38 to 1.21) (Gazit et al., 2021).

A large survey in 1,531,736 individuals from Qatar who all received two doses of an mRNA vaccine compared outcomes in those with versus without a prior SARS-CoV-2 infection (Abu-Raddad et al., 2021b). The adjusted hazard ratio (with 95% CI) for SARS-CoV-2 infections at 120 days of follow-up in the group with versus without a prior infection was 0.18 (0.15 to 0.21) for those vaccinated with BNT162b2, and 0.35 (0.25 to 0.48) for those vaccinated with mRNA-1273. Comparing patients who were infected 6 months or more prior to vaccination versus those who

were infected less than 6 months prior to vaccination resulted in an adjusted hazard ratio (95% CI) for SARS-CoV-2 infections of 0.62 (0.42 to 0.92) for the BNT162b2 vaccine and 0.40 (0.18 to 0.91) for the mRNA-173 vaccine (Abu-Raddad et al., 2021b). Severe diseases were very rare in this study with no COVID-19 death. Data from a population based cohort study in 325,157 individuals from the United States showed that among vaccinated individuals receiving two doses, those with versus without a prior infection had an 86.8% (95% CI: 74.5%–93.2%) protection against SARS-CoV-2 reinfections (Kim et al., 2021). A case control study among 738 participants from Kentucky, United States, showed that residents with a prior SARS-CoV-2 infection who remained unvaccinated had an odds ratio of 2.34 (95% CI: 1.58 to 3.47) for reinfections compared to previously infected individuals who received full vaccination by either two doses of an mRNA vaccine or a single dose of the Janssen (Johnson&Johnson) vaccine (Cavanaugh et al., 2021). In 2579 health care workers from the United States who were previously infected with SARS-CoV-2, there was no significant difference in reinfection rates between those with and without vaccination (two doses of an mRNA vaccine) as no infection occurred in this whole group (Shrestha et al., 2021). A cohort study in 13,109 health care workers from the United Kingdom did not report a difference in SARS-CoV-2 infections in seropositive participants comparing those with and without vaccination (two doses of BNT126b2 or ChAdOx1) (Lumley et al., 2021b).

Data on the efficacy of hybrid immunity are inconsistent but point into the direction of hybrid immunity being superior as compared to either vaccine-induced (without a booster) or natural immunity alone. Much of this literature (and this applies also to almost all COVID-19 vaccine studies) uses relative risk measures, which tend to provide more impressive results. However, absolute event rates and absolute risk differences would be more informative to convey the level of risk and how much it changes under different settings. This is even more important for serious outcomes (hospitalization and death). E.g. a 90% relative risk reduction ("vaccine effectiveness of 90% for death") may correspond to an absolute benefit of less than 0.01% or even less than 0.001%. Absolute risks and absolute risk differences depend on the level of epidemic activity. However, in general, absolute risks for people who are already vaccinated or infected are already very low for such serious outcomes, and there is a relatively little window for improving them.

Timing and mode of vaccination of previously infected individuals to achieve optimal hybrid immunity are central questions that remain to be addressed in future studies. Evaluating the nationwide data from Israel as opposed to data from Qatar and the United States one might hypothesize that two versus one dose of an mRNA vaccine might be more efficacious in the setting of previously infected patients, but this is very speculative (Abu-Raddad et al., 2021b; Cavanaugh et al., 2021; Goldberg et al., 2021a; Kim et al., 2021). Regarding optimal timing of vaccination, the survey from Qatar indicates a higher protection when infection and subsequent vaccination are at least separated by 6 months versus a shorter interval, but such data require further investigations (Abu-Raddad et al., 2021b).

Adverse events after vaccination of previously SARS-CoV-2 infected patients have to be carefully evaluated in future studies as well as the overall risk to benefit ratio in this setting (Menni et al., 2021). Focus on absolute risks is essential for such assessments.

3.4. Immunological considerations and future SARS-CoV2 waves and variants

It has been documented that SARS-CoV-2 infections, even with mild or asymptomatic disease, induce a robust humoral and cellular immune response (Kojima and Klausner, 2022). During the COVID-19 pandemic, measurements of antibodies against SARS-CoV-2 have been frequently requested, but it must be emphasized that antibodies are only incomplete predictors of protection and have, for most settings, justifiably not yet been established as part of a decision making processes (Breathnach et al., 2021a; Kojima and Klausner, 2022). Compared to vaccination, antibody responses induced by SARS-CoV-2 infections are usually more variable with lower concentrations, but are targeted not only against the spike protein but also against many other open reading frames encoded by the approximately 29,900 nucleotides of SARS-CoV-2, and also involve mucosal immune responses (Krammer, 2021). The cell mediated response to SARS-CoV-2 infections seems to be even more polyepitopic than the humoral response with long-term persistence of memory T- and B-cells in recovered patients (Milne et al., 2021; Turner et al., 2021).

Regarding protection against reinfections with different SARS-CoV-2 variants, it must be underlined that efficacy of protection was of roughly similar magnitude across various different virus variants in 2020–2021 (Chemaitelly et al., 2021a; Kim et al., 2021). However, data on the Omicron variant are sparse as of the writing of this review. Considering the broad immunological response induced by natural SARS-CoV-2 infections against all parts of the virus, it would appear logical that even future variants may not completely evade natural immunity. Nevertheless, many open questions usually arise with the emergence of new variants (e.g. Omicron) requiring rapid and accurate re-evaluation of our current knowledge (Altarawneh et al., 2022; Christie, 2021; Del Rio et al., 2022; Kupferschmidt and Vogel, 2021). Given that vaccination rates are continuously increasing and that by the beginning of 2022 perhaps half or more of the global population has already been infected with SARS-CoV-2, with the vast majority of this group being not officially detected, it would appear logical that future infection waves, even with highly transmissible variants of SARS-CoV-2, may be limited with respect to their maximum potential health burden. The advent of Omicron suggests that massive surges can occur even in populations with extremely high rates of previous vaccination and variable rates of prior infections. However, even then, the accompanying burden of hospitalizations and deaths is far less than what was seen in 2020 and most of 2021 (Altarawneh et al., 2022; Christie, 2021; Kupferschmidt and Vogel, 2021; Ulloa et al., 2022). However, the true burden of ongoing Omicron infections needs to be thoroughly investigated. One may argue that the pandemic has already transitioned to the endemic phase and that Omicron is an endemic wave occurring in the setting of already widespread population immunity. Future endemic waves may continue to be high-peaked but this would be manageable if they have limited clinical burden.

4. Conclusions

In conclusion, natural immunity acquired after SARS-CoV-2 infections appears to be highly effective in terms of protection against reinfections and, more importantly, against COVID-19 serious outcomes. Efficacy seems to be equal or higher compared to individuals receiving two mRNA doses, but data are not fully consistent. Hybrid immunity, i.e. immunity achieved by SARS-CoV-2 infection plus vaccination, appears to be most protective. These conclusions must be viewed in light of the limitations of our work that was not based on a prespecified and registered systematic review and meta-analysis, but rather attempted to provide an evolving, up-to-date topical overview on several inter-related questions to update and extend the work of previous reviews (Kojima et al., 2021; Petras, 2021; Shenai et al., 2021).

Although we clearly outlined the efficacy of natural immunity, we want to strongly emphasize that nobody should on purpose seek infection to bypass vaccination because SARS-CoV-2 infection, regardless of the underlying variant, is associated with noteworthy adverse outcomes. However, it would be imprudent not to factor previous infections into policy considerations, given their high frequency. This may be even more important for younger age strata where COVID-19 risks of severe outcomes are far lower anyhow (Ioannidis, 2021b).

The efficacy and duration of natural immunity will definitely be crucial for current policy deliberations and even more for the future (Cheng et al., 2021; Dunkle et al., 2021; Gentile et al., 2021; Gupta et al., 2021; Ingram et al., 2021; Krause et al., 2021; Weinreich et al., 2021; Zemb et al., 2020). Nevertheless, huge knowledge gaps regarding

natural immunity remain, that pose a challenge for health policy makers and require additional investigations. It will be of particular importance to address the questions on how to incorporate the protection by prevailing immunity in the general population into decisions on restrictions or related public health measures against SARS-CoV-2, and whether any laboratory measures of protective immunity (e.g. antibody measurements or cellular immunity assays) may have any practical value for decision-making (and, if so, in which settings) regarding vaccination or treatments of COVID-19. It is likely that very soon, an overwhelming majority of people will have been infected with SARS-CoV-2 at least once in their lifetime. It will be essential to understand how to achieve optimal hybrid immunity in terms of the timing and mode of vaccination (including further developments of vaccines) in previously infected patients with SARS-CoV-2.

Author contributions

S.P. and J.P.A.J. performed the literature search and drafted the first version of this manuscript. All authors have reviewed and edited the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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