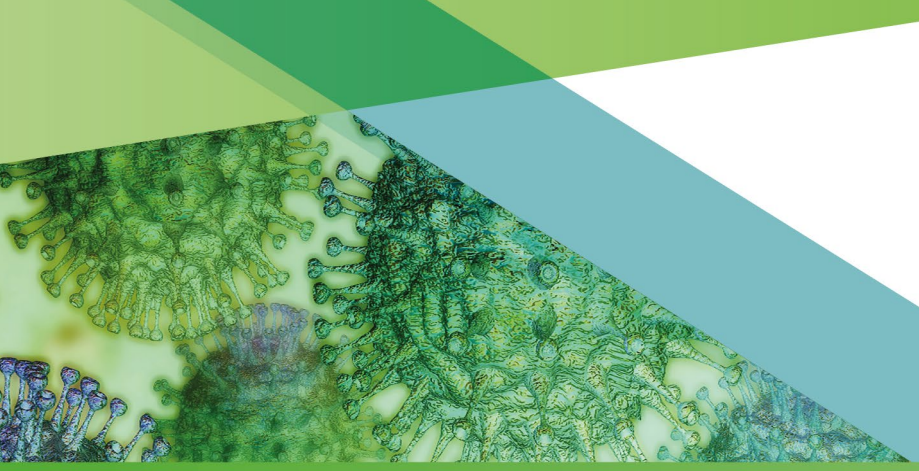

ECDC TECHNICAL REPORT

Risk of SARS-CoV-2 transmission from newly-infected individuals with documented previous infection or vaccination

29 March 2021

Summary

More than one year into the SARS-CoV-2 pandemic, over 120 million people have been infected with the virus across more than 200 countries. Reinfections following natural infections with the same or a new SARS-CoV-2 variant have been reported sporadically and questions remain concerning the duration of immunity following natural infection, and whether asymptomatic reinfected individuals may be able to transmit the virus.

COVID-19 vaccines have been evaluated for their efficacy and effectiveness against symptomatic COVID-19 infection and for reducing and/or preventing mild, moderate, or severe COVID-19 disease, including mortality. However, the vaccine trials have not been designed to measure reduction in transmission risk from infected vaccinated individuals to susceptible contacts.

In this context, it is important to understand the available scientific evidence on the extent to which previous SARS-CoV-2 infection or COVID-19 vaccination prevents onward transmission from infected individuals to susceptible contacts. Therefore, ECDC has conducted a review of published and pre-print literature on duration and characteristics of immunity following a natural SARS-CoV-2 infection due to any variant or after COVID-19 vaccination with any of the EU-authorised vaccines now available.

The review of evidence on natural immunity and possibilities for transmission from previously infected to susceptible contacts found that:

- Evidence from studies specifically designed to assess the impact of previous infection on the risk of transmission is currently lacking. Infection with SARS-CoV-2 does not provide sterilising immunity for all individuals and some who are reinfected might still be able to transmit SARS-CoV-2 infection to susceptible contacts.
- There is evidence that reinfection remains a rare event. Results from cohort studies confirm that the protective effect of previous SARS-CoV-2 infection ranges from 81% to 100% from Day 14 following initial infection, for a follow-up period of five to seven months. Protection against reinfection is lower in individuals aged 65 years and older.
- These studies were carried out before the emergence of SARS-CoV-2 variants of concern (VOCs) and therefore there is limited preliminary evidence that immunity induced against previously circulating SARS-CoV-2 variants may not have the same potency or duration against the VOCs identified to date (in particular the B.1.351 and P.1 variants.)
- As the number of individuals acquiring natural immunity increases, the total number of infections is expected to decrease significantly, leading to decreased transmission overall, unless the genetic changes in the circulating variants induce significant immune escape.

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The review of evidence on immunity and possibilities for transmission from infected, previously-vaccinated individuals to susceptible contacts found that:

- Direct evidence of the impact of vaccination on the risk of transmission is only available from one study, a large register-based household transmission study from Scotland. This study suggests that vaccination of a household member reduces the risk of infection in susceptible household members by at least 30%.
- There is evidence that vaccination significantly reduces viral load and symptomatic/asymptomatic infections in vaccinated individuals, which could translate into reduced transmission, although the vaccine efficacy varies by vaccine product and target group. In light of this fact, the total number of infections is expected to decrease significantly as vaccination coverage increases, provided that there is a match between the vaccine strains and the circulating virus strains. This will lead to decreased transmission overall.
- Follow-up periods for vaccinated persons are not yet sufficiently long enough to draw conclusions on the duration of protection against infection long-term. Antibody titres in vaccinated individuals peak at 3–4 weeks following vaccination.
- Many of the vaccine efficacy studies were carried out before the emergence of SARS-CoV-2 VOCs. In studies that address the variants, there is limited preliminary evidence of reduced vaccine efficacy, in particular for B.1.351 and possibly also for P.1.

Follow-up of cohorts with previous SARS-CoV-2 infection and vaccination is needed to better assess the magnitude and duration of protection from reinfection leading to asymptomatic/symptomatic disease, and the effect of protection against further transmission to contacts.

As an RNA (ribonucleic acid) virus, SARS-CoV-2 will continue to evolve over time and its potential to escape human immune defences induced by natural infection or vaccination has already been documented. It is likely that in the future VOCs will continue to evolve and play a significant role in placing immunological pressure on the circulating viruses. It is not possible to predict when and where this will occur, however, co-circulation of the three VOCs (B.1.1.7, B.1.351 and P.1) has been noted in several EU/EEA countries.

Scope of this document

The aim of this document is to provide a summary of the available scientific evidence on the risk of SARS-CoV-2 transmission to susceptible contacts from infected individuals with documented previous infection or vaccination.

Target audience

This document is intended to support decision-makers in EU/EEA countries, including public health authorities.

Glossary

COVID-19 vaccines
COVID-19 vaccines are pharmaceutical products administered with the aim of preventing disease caused by the novel initial coronavirus SARS-CoV-2. As and when virus variants arise through amino acid substitutions, deletions, or insertions, they may become less susceptible to the immune response evoked by vaccines developed against prior circulating types. Therefore COVID-19 vaccines are expected to be updated at regular intervals and include one or several SARS-CoV-2 variants, similar to influenza vaccines. The regulatory framework for updating COVID-19 vaccines is under development by European Medicines Agency [1].

Vaccine course
The first three EU authorised COVID-19 vaccine products (Comirnaty vaccine developed by Pfizer/BioNTech, COVID-19 Vaccine Moderna and COVID-19 Vaccine AstraZeneca) are recommended to be administered in a two-dose regimen to prime the immune response. A fourth vaccine, COVID-19 Vaccine Janssen, was authorised for use in the EU on 11 March 2021 and is recommended to be used in a one-dose regimen for priming the immune response [2]. This vaccine was authorised by the Food and Drug Administration (FDA) in the US in late February 2021. Additional vaccines currently under rolling review by the European Medicines Agency include vaccine candidates developed by CureVac AG (CVnCov), Novavax (NVX-CoV2373) and Gamaleya (Sputnik V (Gam-COVID-Vac)) [2].

COVID-19 vaccines developed and produced in China (Sinovac) and Russia (Gamaleya) are currently being procured and used in a few EU/EEA Member States (Czechia and Hungary).

It is expected that all COVID-19 vaccinees will need to receive booster doses at regular intervals and it is possible that vaccinated individuals will have to receive repeated immunisations throughout life to provide protection against new emerging variants. Therefore, it is currently difficult to define who is fully vaccinated and protected against COVID-19 disease, in the short and long-term. This means that the assessment of vaccine-induced immune status will always be made on a case-by-case basis, guided by the product characteristics of the vaccine that the individual has received and by circulating SARS-CoV-2 virus variants at the time of assessment.

Infection
Infection is defined as the entry and development or multiplication of an infectious agent in an organism, including the body of humans and animals [3]. In this document natural infection refers to previous infection, or reinfection episodes subsequent to the first infection episode. Often evidence of seroconversion is required to prove that an infection, rather than just contamination with nucleic acid, has occurred. In this document a positive result from a PCR or rapid antigen test is considered as a reasonable proxy of infection for a person, irrespective of symptoms.

Immunity
Immunity is the resistance acquired by a host as a result of previous exposure to a natural pathogen or foreign substance for the host [3]. Immunity may develop either through infection or vaccination. Acquired immunity can be expressed as humoral immunity, measured by specific antibody responses or cellular immunity, measured by T-cell responses. Currently it is understood that most of the virus neutralising antibody activity in previously infected or vaccinated persons is mediated by antibodies targeting the SARS-CoV-2 spike protein, and more specifically, the receptor binding domain (RBD) of that protein.

Transmission of infection
The process, mechanisms, and determinants by which an infectious agent or an infectious disease are spread from a source or reservoir to another person or across communities and countries [3].

Risk of transmission
The risk that an infected person (pre-symptomatic, symptomatic, or asymptomatic) transmits the infectious agent to one or more other individuals.

Variants of concern
This refers to variants of the SARS-CoV-2 virus which, due to recombination or spontaneous mutation, have demonstrated the potential to:

- increase in transmissibility or detrimental change in COVID-19 epidemiology;
- increase in virulence or change in clinical disease presentation; or
- decrease the effectiveness of public health and social measures, available diagnostics, vaccines, and/or therapeutics [4].

Background

More than one year into the SARS-CoV-2 pandemic, over 120 million people have been infected with the virus across more than 200 countries [5].

Reinfections with SARS-CoV-2 have been reported sporadically and questions remain concerning the duration of immunity following natural infection and whether asymptomatic/pre-symptomatic reinfected individuals may be able to transmit the virus.

A range of vaccines have been developed against COVID-19 and vaccine roll-out is in process throughout the EU/EEA and beyond. The vaccines for COVID-19 have been evaluated for their efficacy and effectiveness in reducing either COVID-19 infection or, more specifically, induced mortality, severe outcomes and/or mild or moderate COVID-19 disease. However, these trials have not been designed to measure transmission risk, following exposure to circulating virus, from vaccinated individuals to others. Some populations are not currently eligible for vaccination, such as children, or may be immunocompromised and may need to be given special consideration as regards transmission risk from vaccinated individuals.

Furthermore, since December 2020, SARS-CoV-2 VOCs have been reported, initially from the United Kingdom (variant B.1.1.7), South Africa (B.1.351) and Brazil (P.1). These variants are all associated with increased transmissibility. Information on whether previous infection or vaccination are protective against infection from these variants is discussed below. It is expected that additional VOCs may emerge elsewhere in the near future.

Evidence required to evaluate transmission risk

SARS-CoV-2 virus transmission by an individual that has recovered following a prior infection requires that immunity developed during the first episode of infection is insufficient to prevent reinfection following exposure to SARS-CoV-2. While there may be protection from severe symptoms or death during the reinfection episode, immune responses mounted following the initial infection may not prevent virus replication in the upper respiratory tract to an adequate extent to preclude possible onwards transmission. The vaccines currently available against SARS-CoV-2 do not induce sterilising immunity (i.e. complete protection from subsequent infection) in everyone that is vaccinated. Transmission may still occur if immune responses triggered following completion of the vaccine course do not sufficiently restrict virus replication in the upper respiratory tract following a breakthrough infection.

A large number of vaccine efficacy and effectiveness studies have been conducted or are in progress worldwide. To date, these studies have primarily focussed on estimating product-specific protective efficacy or real-world effectiveness against a range of outcomes, including mild or moderate infection, severe infection, hospitalisation and death. Prospective follow-up investigations of both vaccination and placebo arms are embedded within some of these studies to additionally assess for asymptomatic breakthrough infections. Careful follow-up to estimate the relative reduction of the proportion of asymptomatic breakthrough infections in vaccinated groups, as well as evidence of reduced viral load, duration of viral shedding, culture viability and secondary attack rates among close contacts is essential for a complete evaluation of the transmission risk posed by vaccinated individuals.

Follow-up studies comparing infections in recovered individuals with well-matched naïve individuals are scarce and may become even more so as vaccination programmes expand beyond prioritised risk groups. However, the same principles apply and a comprehensive assessment of transmission risk requires evidence of reduced viral load, duration of viral shedding, culture viability and secondary attack rates among close contacts. Annex 1 summarises the types of studies and levels of evidence required to fully evaluate transmission risk in previously infected or vaccinated individuals.

Immune responses and correlates of protective immunity

Correlates of protective immunity to a pathogen are measurable signs that reliably identify individuals as protected against specific outcomes, such as infection, transmission risk or disease outcome. Following infection with SARS-CoV-2 virus or vaccination, it is the adaptive immune response that ideally delivers long-term protection. The adaptive immune response primarily comprises memory B cells that produce different classes of antibody to neutralise the virus or virus-infected cells, and memory T cells that support antibody production and also have a direct role in killing virus-infected cells. While there is evidence of both memory B cell and T cell immune responses in individuals infected with SARS-CoV-2 as well as in vaccinated persons, clear correlates for protective immunity have yet to be defined [6-9]. However, neutralising antibodies seem to play a role in protective immunity and their activity is assessed against the different SARS-CoV-2 variants in convalescent sera following natural infection and sera from vaccinated individuals having received different COVID-19 vaccine products.

A systematic review of 150 studies describing virus-specific serum antibody responses in individuals infected with SARS-CoV-2 showed IgM is consistently detected before IgG, peaking between weeks two and five and declining over a further three-to-five-week period post-symptom onset. IgG peaks between weeks three and seven post-symptom onset, persisting for at least eight weeks. Neutralising antibodies – with the capacity to restrict virus growth in vitro – are detectable within seven to 15 days of disease onset, and levels increase until Days 14–22, before plateauing and then decreasing. Lower antibody titres have been observed in those with asymptomatic or clinically mild disease. However, the review in question primarily featured observational studies of hospitalised cases, with follow-up periods lasting up to three months post symptom onset. Critically, there is considerable heterogeneity in the types of assays used, as well as the SARS-CoV-2 proteins they target [7].

There is limited data comparing serum antibody responses following primary infection with reinfection episodes. In a recent preprint article from the Netherlands, serum samples from 17 suspected reinfection cases were evaluated against 96 control sera, obtained from 86 PCR-confirmed cases (67 adults, 19 children, seven of which needed hospitalisation). SARS-CoV-2 specific serum antibody responses for suspected reinfection cases showed significantly faster and stronger levels of both RBD-specific serum Ig antibodies and S1-specific IgG antibodies when compared to control sera within the first seven days post infection. The authors also assessed binding avidity to SARS-CoV-2 S1, reporting an avidity index (AI) of approximately 40% two months after primary infection. In contrast, 13 of 17 suspected reinfection cases already showed AI values >40% within the first two weeks, with a median of 49% for serum obtained within 14 days post-onset of disease [10]. As with B cell immunity, T cell immunity develops over a period of at least 10–20 days post symptom onset. A systematic review of 61 studies indicated that increasing disease severity is associated with more robust, virus-specific T cell

responses [8,9]. Studies of T cell responses are affected by heterogeneity in the types of assays used, and there is limited data on infected individuals who are asymptomatic or pauci-symptomatic [8,9].

The assessment of immune responses induced by vaccination has largely focussed on the development of antibodies targeting the S1 domain of the SARS-CoV-2 spike protein. S1 includes the receptor binding domain, and antibodies targeting this domain critically impair virus cell entry. A key benefit of some vaccine regimens is that anti-S IgG titres are higher than for natural infection, with serum from vaccinated individuals showing greater neutralisation capacity against homologous SARS-CoV-2 viruses in vitro [11].

As mentioned above, in the absence of definitive correlates of protective immunity, the presence of neutralising antibodies against SARS-CoV-2 provides the best current indication for protection against reinfection and breakthrough infection for previously infected and vaccinated individuals. A number of studies have shown that the neutralisation ability of polyclonal serum correlates positively with anti-S IgG or anti-RBD IgG [7].

Vaccination has also been shown to result in robust T cell responses, with memory and effector function demonstrated against multiple viral epitopes. Additionally, cross-reactive T cell responses have been demonstrated against variant viruses in vaccinated individuals. However, the significance of T cell responses for protection and susceptibility at population level, independent of memory B cell responses, remains unclear.

Duration of immunity and transmission risk over time

Although virus-specific B cell and T cell responses are evident shortly into the recovery from infection or vaccination, they are prone to wane over time, with decreasing numbers of circulating virus-specific memory T cells, memory B cells and serum antibodies [12]. Consequently, protection against outcomes such as infection, transmission risk or severe disease may also wane over time. Assessing the impact of waning immunity requires careful evaluation of both the quantitative reduction in immune readouts and the qualitative or functional change over time. It is also important to consider the interdependency of readouts assessing T cells, B cells or antibodies. In a long-term follow-up study of 25 individuals infected with SARS-CoV-2, virus-specific memory B cells were identified in the early stages of convalescence. While serum antibodies peaked 20 days post infection before waning, virus-specific memory B cells persisted for over 242 days post-symptom onset [12]. This study highlights that a decline in serum antibodies in convalescence may not reflect waning immunity, but rather a contraction of the immune response, with the development and persistence of virus-specific, long-lived B cells in bone marrow [12-14]. Similarly, the development of memory T cells directed at non-surface SARS-CoV-2 proteins following infection or vaccination may offer a route to durable immunity where virus evolution leads to spike protein mutations that escape pre-existing neutralising antibodies. This will occur either by offering more efficient support to activated naïve B cells responding to the altered spike protein (memory CD4 T cells), or through direct lysis of SARS-CoV-2 infected cells (CD8 T cells) [14,15].

The vast majority of SARS-CoV-2–infected individuals seroconvert following SARS-CoV-2 infection. Reviews of the published literature indicate that >90% patients develop IgG seropositivity and neutralising antibodies following primary infection, ranging between 91 and 99% in large studies [7,14]. A scoping review performed by the Irish Health Information and Quality Authority (HIQA), to evaluate the long-term duration of immune responses following SARS-CoV-2 infection, identified five studies that investigated immune responses at ≥6 months post-infection, including two studies at ≥8 months post-infection. In general, studies reported a waning of antibody responses in the late convalescent period (3−6 months post-infection). However, T-cell and memory B-cell responses were still present, and in many cases increased, up to eight months post-infection in all study participants [15]. A recently published prospective cohort study from Singapore has evaluated the dynamics of SARS-CoV-2 neutralising antibody responses over time. Serum samples were collected at approximately 30-day intervals up to 180 days post symptom onset from 164 patients with PCR-confirmed SARS-CoV-2 infection experiencing mild, moderate, or severe disease. The authors described five distinctive patterns of neutralising antibody dynamics:

- negative - individuals who did not develop strong neutralising antibody responses: 19/164 patients (12%);
- rapid waning - individuals who had varying levels of neutralising antibodies from around 20 days after symptom onset, but seroconverted in less than 180 days: 44/164 patients (27%);
- slow waning - individuals who remained neutralising antibody-positive at 180 days post-symptom onset: 52/164 patients (29%);
- persistent - individuals with varying peak neutralising antibody levels, but minimal neutralising antibody decay: 52/164 patients (32%);
- delayed response - individuals that showed an unexpected increase in neutralising antibodies during late convalescence (at 90 or 180 days after symptom onset: 3/164 patients (2%).

Greater disease severity was associated with persistent neutralising antibody levels, and patients with milder disease appeared to have more rapid neutralising antibody waning. While this study showed that neutralising antibody dynamics can vary greatly among individual patients with COVID-19, development and persistence of

virus-specific, long-lived memory B cells was not studied. However, the authors did analyse 23 randomly selected patients from the five categories described, confirming the presence of virus-specific memory T-cells at 180 days post-symptom onset in patients from each of the five categories [16].

Follow-up periods for vaccinated individuals are not yet sufficiently long to be able to draw conclusions on the duration of protection against infection long-term.

Risks associated with SARS-CoV-2 variants

SARS-CoV-2 is an RNA virus that is prone to frequent mutations, insertions and deletions [17]. Other human coronaviruses are capable of escaping human immune defences through genomic changes and usually the natural immunity that follows infection may prevent further infection for a period between one and two years [6]. Something similar might be expected with SARS-CoV-2, although it cannot be ruled out that vaccines may induce longer protection than natural immunity.

For previously infected persons, documented reinfection with a variant of concern at rates similar to those for people who were not previously infected would be indicative of immune escape. The presence of neutralising antibodies against SARS-CoV-2 provides the best current indication for protection against reinfection and breakthrough infection for previously infected and vaccinated individuals respectively. A reduction in the neutralising capacity of serum polyclonal antibodies against variant viruses may indicate a reduced capacity to protect against reinfection.

Methods

Frameworks for evidence: natural infection and vaccination

Scientific evidence for assessing transmission risks posed by previously infected persons or vaccinated persons may be available from a wide range of biomedical or epidemiological studies. Inferences from such studies can be made with varying levels of confidence. This document categorises the available evidence according to a hierarchical evidence framework (Annex 1) to provide an assessment of the level of confidence ECDC attaches to each of the results.

Literature reviews

Natural infection

The literature used for natural infection was based on a living systematic review on duration of immunity and protection from reinfection following SARS-CoV 2 infection by the Irish Health Information and Quality Authority (HIQA) published on 8 March 2021 [18]. Pre-print and published literature up to 4 February 2021 were included in that review. A search was conducted for the published and pre-print literature from 4 February to 8 March 2021 in ECDC's COVID-19 database, using PubMed search terms from the HIQA protocol [18].

No randomised studies were found on natural immunity, so evidence is described for non-randomised cohort and other observational studies, as well as laboratory studies and selected outbreak investigation studies.

Vaccination

A rapid review of the literature was carried out according to outcome of interest, with evidence of vaccine efficacy and effectiveness against transmission (i.e. reduction of secondary attack rates) considered as the primary outcome. In addition, evidence of vaccine reducing viral load or duration of viral shedding, and evidence of vaccine effectiveness against symptomatic/asymptomatic infection were considered as surrogate outcomes for risk of transmission from fully and partially vaccinated individuals. Evidence of antibody response following vaccination in previously-infected individuals was also reported.

Information from the main vaccine trials was retrieved and reported separately from the evidence collected from non-randomised studies. Non-randomised observational studies were further categorised according to the population of interest (e.g. general population, healthcare workers, residents of long-term healthcare facilities). Any evidence available from reports of breakthrough infection was also described.

A separate search covering both natural immunity and vaccination was carried out for publications on VOCs as part of an ongoing scoping review being conducted by ECDC. This search included all publications on the VOCs B.1.1.7, B.1.351 and P.1 up until 4 March 2021.

Results

Natural infection

Evidence that previous infection with SARS-CoV-2 reduces transmission

No evidence was found of studies specifically designed to assess whether previous infection with SARS-CoV-2 prevents against future transmission. This would require carefully designed follow-up studies of recovered individuals, with regular screening to capture asymptomatic reinfection episodes and onward secondary transmission events. This is further complicated by difficulties in establishing cohorts where recovered individuals are carefully matched with non-infected individuals. Given that no such studies have been carried out, there is currently no strong evidence that previous SARS-CoV-2 infection reduces transmission risk.

Evidence that SARS-CoV-2 infection impacts viral load or duration of viral shedding in reinfected individuals

There was no evidence found to support the assumption that viral load or duration of shedding are reduced when individuals become re-infected with SARS-CoV-2. Such evidence could demonstrate that reduced viral load or duration of shedding may lower the chance of transmitting the infection to other susceptible contacts.

Evidence that a previous SARS-CoV-2 infection protects against future infection

It is very likely that if previous infection is protective against reinfection this will also reduce transmission at the population level. Comparing rates of nucleic acid detection in those who have recovered with rates in those who have not been previously infected is the best available surrogate to estimate transmission risk.

Although the full duration of protective immunity following SARS-CoV-2 infection is still under investigation, there is evidence from cohort studies that the probability of reinfection in the months following a primary infection is low [18]. There may be exceptions to this – for example if the new infection is with a variant of concern, or in the case of immunosuppressed individuals.

There is some evidence from studies that previous SARS-CoV-2 infection reduces the risk of future infection, at least during the five to seven months following the first infection. However, these studies were conducted prior to the emergence of VOCs.

In a cohort study of 12 541 healthcare workers, 1 265 of whom were positive, the adjusted incidence rate ratio of a second positive PCR in healthcare workers with positive anti-spike antibodies was 0.11 (95% CI: 0.03−0.44; P=0.002) after a median follow-up of 139 days at risk after a positive antibody test [19]. Only two infections were diagnosed in anti-spike antibody seropositive participants and both were asymptomatic.

In a large prospective cohort study with more than five months of follow-up of over 20 000 healthcare workers (the SIREN study), 44 reinfections were detected among 6 614 participants who were antibody positive or had a previous positive PCR test for SARS-CoV-2, compared to 318 new PCR positive infections among 14 173 participants who were antibody-negative and did not have a previous positive PCR test (aOR: 0.17−95% CI 0.13−0.24) [20]. The incidence density was 3.3 infections per 100 000 person days in the positive cohort and 22.4 infections per 100 000 in the negative cohort. Among the 44 reinfections, 15 (34%) were symptomatic, while 79% of cases in the negative cohort were symptomatic.

In a cohort study from Qatar, that included 43 044 people positive for SARS-CoV-2 antibodies followed for a median of 16.3 weeks (maximum 34.6 weeks), the risk of viral sequencing-confirmed reinfection was 0.10% (95% CI: 0.08−0.11%) [21]. Compared to the incidence of infection in the general population in Qatar, the effectiveness of natural infection against reinfection was estimated to be >90%.

In a cohort study of 1 038 healthcare workers with evidence of previous SARS-CoV-2 infection (defined as positive PCR and/or serology) and 10 137 without evidence of previous infection, after seven months there were no symptomatic infections in the group with previous infection and 290 (2.9%) in the group without previous infection ($p<0.001$) [22]. In a separate group of 481 healthcare workers who participated in a pilot asymptomatic screening study, there were 0 (0%) positive results among the 106 participants with previous infection, compared to 22 (5.9%) among the 375 participants without previous infection ($p= 0.011$).

A cohort study from the US examined the rates of positivity of nucleic acid amplification test (NAAT) results among a cohort of 2 876 773 antibody-negative and 378 606 antibody-positive individuals [23]. Among the

individuals in the seronegative group, about 3% had a positive NAAT during the 4.5-month follow-up period. Among individuals in the seropositive group, only 0.3% had a positive diagnostic NAAT that occurred at >90 days from the initial positive antibody test, indicating that natural infection has a protective effectiveness of 90%.

A Danish population-level observational study of patients, taken from the Danish Microbiology Database, compared infection rates during the period September to December 2020 among individuals who had positive and negative PCR results between March and May 2020 [24]. Among 11 068 PCR-positive individuals from the first surge of the epidemic, seven (0.65% [95% CI 0.51–0.82]) tested positive again during the second period compared with 16 819 (3.27% [95% CI 3.22–3.32]) of 514 271 who had tested negative during the first period. Infection during the first period was 80.5% (95% CI 75.4–84.5) protective against re-infection. Protection from reinfection was lower among people aged 65 years and older who had tested positive during the first period (47.1%;95% CI 24.7–62.8). The study did not find evidence of waning immunity after six months.

Overall, the results from these cohort studies confirm the protective effect of previous SARS-CoV-2 infection ranges from 81% to 100% during a follow-up period of five to seven months. However, longer follow-up is necessary to better define the duration of immunity for extended periods of time.

An assessment of laboratory test results from Israel assessed reinfection by determining which individuals in the study sample size of 149 735 individuals had a second positive-PCR at least 100 days after the initial infection. They found that 154 persons had second infections of this type, with a reinfection rate of 1 per 1 000 [25].

Less direct evidence on the protective effect of natural infection can also be provided by laboratory studies, including neutralisation experiments. A recent study from Sweden demonstrated that neutralising antibodies persisted after nine months in 96% of 370 participants that had antibodies against the spike protein, while two-thirds of these participants also had measurable specific memory T-cells [26,27].

Further indirect evidence from outbreak investigations is also available. In outbreaks affecting two care homes in the UK, the attack rate among individuals with previously confirmed SARS-CoV-2 infection (by either serology or RT-PCR) was 1.1% (1/88 individuals) compared to 30.1% (22/73 individuals) among those with confirmed seronegative status before the outbreak [27]. The estimated relative risk was 0.038 (95% CI: 0.005–0.273; $p < 0.0001$). In an outbreak at a summer school retreat in the US, where 116 (76%) of 152 participants had confirmed or probable COVID-19, none of the participants who had a positive antibody test before arrival received a positive SARS-CoV-2 PCR result [28].

Evidence for and considerations relating to VOCs

Specific humoral and cellular immunity develops against specific antigens of the virus. For SARS-CoV-2, virus neutralising antibody responses appear to be mainly targeting the spike protein and, more specifically, the receptor-binding domain of the spike protein [7]. Virus evolution due to spontaneous mutations under selective pressure or recombination might also affect these proteins in a way that changes the immune responses in people previously infected with the original strain, or other variants.

For VOCs, there is limited evidence available regarding any differences in the duration of protective immunity from prior infection by a different strain. There is concern that some mutations can lead to increased or even complete resistance to neutralisation by several monoclonal antibodies, as well as reduced neutralisation, or complete resistance to neutralisation by convalescent plasma and sera [28-30]. However, it is not yet known whether there are more reinfections related to one specific variant than for other strains.

There is limited evidence on the effect that emerging SARS-CoV-2 variants with immune escape potential can have on the protection provided by natural infection.

B.1.1.7

While there are no studies that directly address the transmission risk linked to reinfection with this variant, there are several observational studies that provide indirect evidence on reinfection for B.1.1.7.

In a matched case-control study of 1 769 cases of infection with SARS-CoV-2 variant B.1.1.7 in the UK and 1 769 wild-type controls, two reinfections (1.13/1 000 cases) were detected in the variant case group and three reinfections (1.70/1 000 cases) in the comparator group (p=1.00) [32]. These data, which were collected at a time when the B.1.1.7 variant was circulating, but not completely dominant in the UK, suggest that natural immunity to the wild-type virus is similarly effective against B.1.1.7.

An observational study in the UK paired longitudinal COVID Symptom Study mobile application data with regional data during the period when the previously circulating SARS-CoV-2 strain was being replaced with the B.1.1.7 variant. The study found a low reinfection rate of 0.7% (95% CI 0.6−0.8), which was consistent across regions and time, indicating that reinfection is no more likely in the context of B.1.1.7 [33].

A retrospective review of laboratory results at a south-west London laboratory identified 10 727 patients with evidence of SARS-CoV-2 infection (defined as positive PCR and/or serology) and 55 274 patients without

evidence of SARS-CoV-2 infection before the end of July 2020 [34]. Eight (0.07%) patients in the first group had evidence of infection between 1 August and 31 December, compared to 713 (1.29%) in the second group (RR 0.0578, 95% CI 0.0288−0.1160). There were no reinfections during the first seven months of the second study period. All reinfections in the group with evidence of previous infection occurred in December 2020. This observation may be related to the emergence of variant B.1.1.7; the increased risk of infection during the peak of the epidemic around the end of the year and/or progressive waning of immunity.

Laboratory studies present conflicting results, finding that B.1.1.7 is not more resistant to convalescent plasma from previously-infected individuals than the original strain, while other studies find a modest resistance to convalescent plasma, with a majority of serum samples retaining functional activity above neutralising thresholds [34-36].

B.1.351

One study provides information gathered in South Africa from the placebo arm of a phase 2b vaccine trial on risk of reinfection associated with the B.1.351 variant. There was no difference in infection or reinfection between seronegative and seropositive individuals in the placebo arm of the study. This indicates that prior infection was not protective against reinfection with the B.1.351 variant, which was widely circulating in the country during the data collection window (23 November to 30 December 2020) [38].

Some laboratory studies provide weak evidence for possible increased risk of reinfection in individuals with the B.1.351 variant. Several convalescent plasma studies have found that B.1.351 has resistance to neutralisation, with reductions in antibody activity ranging from a factor of six to complete knockout activity [29,34,38].

An analysis of CD4+ and CD8+ T cell responses from COVID-19 convalescent subjects found that the response was not substantially affected by the B.1.351 variant [15].

P.1

There are no observational or cohort studies providing information on transmission or reinfection risk.

Laboratory or case studies provide weak evidence for possible increased risk of reinfection in individuals with the P.1 variant.

Immune plasma of COVID-19 convalescent blood donors in Brazil had 6-fold less neutralising capacity against the P.1 variant than the B-lineage [40]. However, a separate analysis of CD4+ and CD8+ T cell responses from COVID-19 convalescent subjects found that the response was not substantially affected by the P.1 variant [15].

A phylogenetically-confirmed case of SARS-CoV-2 reinfection with the P.1 variant in an otherwise healthy 29-year-old woman, nine months after her first episode of SARS-CoV-2 infection has been reported in a case study. The case had a positive IgG rapid antibody test eight days before symptom onset of the second infection episode. This indicates that reinfection may have occurred, despite pre-existing anti-SARS-CoV-2 antibodies. Low Ct values (<25) during the reinfection episode suggested that the subject could have been infectious and transmitted the virus [31].

Summary and discussion of evidence: natural infection

Annex 1 summarises the types of studies required to fully evaluate transmission risk in previously-infected individuals, categorised according to a hierarchical evidence framework. Overall, evidence on the transmission risk posed by previously-infected individuals is largely based on studies showing lower proportions of asymptomatic reinfection episodes in those who have recovered compared to naïve individuals. This has been scored as low-strength evidence for reduced transmission risk, on account of limited comparative data on viral load, virus culture viability and secondary attack rates among household contacts.

At present, there is no evidence from studies specifically designed to assess the role of natural infection in prevention against the transmission of SARS-CoV-2.

However, there is indirect evidence from cohort studies that natural infection significantly decreases the overall risk of symptomatic and asymptomatic reinfection by 81 to 100% for a follow-up period of five to seven months. However, protection from reinfection is lower in individuals aged 65 years and above. Altogether, as the number of individuals acquiring natural immunity increases, the total number of infections is expected to decrease significantly, leading to reduced transmission overall. However, infection with SARS-CoV-2 does not provide sterilising immunity to all individuals and some who are reinfected might be able to transmit SARS-CoV-2 infection to susceptible contacts.

There is weak evidence that infection with VOCs, in particular B.1.351 and P.1, may impact adversely on the level and duration of immunity developed against the original SARS-CoV-2.

Population-level impact on virus circulation will depend not only on the risk of an individual transmitting the disease, but also the number of susceptible contacts that the person may expose to a virus. The importance of population immunity from natural infection, or as a result of vaccination, should be taken into consideration when assessing how individual risk of transmission affects the circulation of the virus within the community. This could be important when assessing risk in congregate settings, such as long-term care facilities or prisons, or in some occupational settings where the transmission to a large number of individuals can occur rapidly if they are susceptible, and if effective prevention measures, such as the use of face masks and physical distancing, are not in place.

SARS-CoV-2, as an RNA virus, will continue to evolve and has the potential to produce variants that escape human immune defences from natural infection. It is likely that in the future such variants will become dominant. It is not possible to predict when this may occur or to what extent. Data from other human coronaviruses suggest that immunity against clinical disease may be longer-lived than immunity against infection and onward transmission [41].

Knowledge gaps and areas for further research: natural infection

There is still limited evidence on the role of natural immunity generally in preventing transmission of SARS-CoV-2. More specifically, there is very limited evidence on how newly-emerged VOCs may affect the likelihood of reinfection with symptomatic/asymptomatic SARS-CoV-2 and what role these infections will play in further transmission. To fill these gaps, cohorts with SARS-CoV-2 humoral and cellular immunity markers need to be followed up. This will allow better measurement of the magnitude and duration of protection from reinfection and symptomatic disease. It will also enable measurement of the effect of protection on transmission generally and, more specifically, in relation to VOCs. SARS-CoV-2 will continue to change and mutate. ECDC will continue to follow the viral evolution and the resulting scientific evidence on transmissibility, severity and immune escape and evaluate VOCs as they emerge.

Vaccination

Evidence of vaccine effectiveness against transmission

As of 14 March 2021, only one study was identified that directly investigated and reported on the effectiveness of COVID-19 vaccine against transmission of SARS-CoV-2 to susceptible contacts from vaccinated cases. This study is a register-based analysis from Scotland including 144 525 healthcare workers and 194 362 members of their households. This analysis has shown that household members of healthcare workers vaccinated with a single dose of either Pfizer or Astra Zeneca COVID-19 vaccine were at significantly reduced risk (HR=0.70; 95% CI: 0.63−0.78) of PCR-confirmed SARS-CoV-2 infection, and non-statistically significant reduced risk of hospitalisation (0.77; 95% CI: 0.53-1.10), compared to household members of unvaccinated healthcare workers, 14 days after vaccination [42]. As household members of healthcare workers could also have been infected through other routes, the reported 30% risk reduction for infection is probably an underestimate and could in reality be as high as 60%. These findings are consistent with a substantial reduction in transmission risk from fully-vaccinated individuals to susceptible contacts.

Evidence of vaccine effectiveness on reducing viral load and duration of viral shedding

Viral load appears to be a leading indicator of SARS-CoV-2 transmission [43], therefore vaccines that can reduce the viral load in SARS-CoV-2 infections may also reduce the chance of viral transmission.

In the UK Oxford–AstraZeneca COVID-19 vaccine trial, lower viral load and shorter duration of shedding (median reduction of one week with no difference between B.1.1.7 and non-B.1.1.7 infections) was observed in a small group of symptomatic and asymptomatic PCR-positive vaccinated individuals compared to PCR-positive unvaccinated controls [44]. It is interesting to note that neutralising antibody titres following vaccination with COVID-19 vaccine Astra Zeneca were lower for the B.1.1.7 lineage, despite similar efficacy against clinical endpoints.

A preliminary observational study from Israel showed a four-fold reduction of viral load in infections occurring 12−28 days after the first dose of the Pfizer-BioNTech vaccine [45].

It is not yet clear at this stage whether, and how much, these observed reductions in viral load and duration of shedding would make a vaccinated person less infectious.

Evidence of vaccine effectiveness against infection

A vaccine that is highly effective at preventing infection is likely to also be able to reduce transmission.

Evidence for two doses of vaccine

Data from randomised studies

In the UK Oxford-AstraZeneca COVID-19 vaccine trial, the participants performed self-administered nose and throat swabs every week with an overall 54.1% (95% CI: 44.7−61.9%) reduction in PCR-positivity. Specifically, a 67.6% (95% CI: 50.8−78.7%) reduction in PCR-positivity was observed after a low dose, followed by a standard dose of vaccine (LD/SD) and a 49.5% (95% CI: 37.7−59.0%) reduction after two standard doses of vaccine (SD/SD) compared to the placebo group [46]. The average longer interval between doses in the LD/SD compared to the SD/SD group may explain these results, as a consistently increased vaccine efficacy against all study end points was observed in the trial with longer intervals between doses.

As a secondary endpoint, several vaccine trails are assessing the vaccine effectiveness against SARS-CoV-2 infection determined by anti-SARS-CoV-2 NP antibodies, regardless of whether the infection was symptomatic. The trial will assess the proportion of participants (vaccine versus placebo recipients) with SARS-CoV-2 infection determined by anti-SARS-CoV-2 NP antibodies, specifically including asymptomatic infection, across the two years of study follow-up [47].

Data from non-randomised studies

General population

A large observational study of 596 618 individuals from Israel showed that vaccination with the Pfizer-BioNTech vaccine reduces PCR-confirmed infection, irrespective of symptoms, by 92% (95% CI: 88−95%) in individuals who received two doses of vaccine seven days or more after the second dose. The reported vaccine effectiveness against asymptomatic infection (i.e. positive PCR with no reported symptoms used as proxy of asymptomatic infection since mild symptoms may not have been documented) was 29% (95% CI: 17−39%) for the period from 14 to 20 days after the first dose; 52% (95% CI: 41−60%) for the period from 21 to 27 days after the first dose, and 90% (95% CI: 83−94%) seven or more days after the second dose [48]. As people who have previously been infected are currently not eligible for vaccination in Israel, this study could not look at vaccine effectiveness against infection in previously-infected individuals. On 11 March 2021, the company announced that an updated analysis from Israel, with data until 6 March, found a vaccine effectiveness of 94% against asymptomatic infection from two weeks after the second dose of Pfizer-BioNTech vaccine [49]. It is interesting to note that during the analysis period more than 80% of the specimens collected were reported to be B.1.1.7.

A recent retrospective study carried out in the USA among 39 156 patients attending pre-procedural and pre-surgical SARS-CoV-2 screening found that the risk of asymptomatic infection was reduced by 80% among vaccinated patients after the second dose of Pfizer or Moderna COVID-19 vaccines (RR=0.20; 95% CI: 0.09−0.44) [50]. It is important to note that, due to potential unmeasured confounding, this study was only able to show a correlation between vaccination and reduced asymptomatic infection, rather than causation.

Older adults

A national register-based retrospective study was performed in Denmark, including 39 040 residents of long-term healthcare facilities (median age: 84 years) frequently tested with PCR, irrespective of symptoms [51]. After the second dose of Pfizer-BioNTech vaccine, an effectiveness of 52% (95% CI: 27−69%) was reported within seven days of the second dose, and of 64% (95% CI: 14−84%) seven days after the second dose among the residents.

Healthcare workers

The Danish retrospective cohort study also included 331 039 healthcare workers who were offered PCR testing on a weekly basis during the study period. After the second dose of Pfizer BioNTech vaccine, an effectiveness of 46% (95% CI: 28−59%) was reported within seven days of the second dose, and of 90% (95% CI: 82−95%) beyond seven days after the second dose [51]. Data from the SIREN study, a multicentre cohort study carried out in the UK with weekly swabbing of 23 000 healthcare workers, showed a 86% (95% CI: 76−97%) reduction seven days after two doses in the seronegative cohort [20]. It is important to note that the variant B.1.1.7 was the predominant variant in the UK during the performance of this study.

A pre-print study, looking at humoral immunity in individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine, found the presence of large titres of IgG antibodies within the saliva of vaccinated individuals that far exceeded those seen in convalescent individuals with positive PCR. Authors speculate that this might indicate that vaccination confers a sterilising immune response in the oral cavity and thereby lowers virus transmission [52].

Evidence for one dose of vaccine

Data from randomised studies

In the UK Oxford-AstraZeneca COVID-19 vaccine trial, the participants performed self-administered nose and throat swabs every week, with an observed 67% (95% CI: 49−78%) reduction in overall PCR-positivity after 21 days among the subset of individuals vaccinated with a single standard dose [46]. More specifically, in the first 90 days of follow-up, despite providing a significant 76% (95% CI: 59−86%) reduction in symptomatic infections, a single standard dose of vaccine did not significantly reduce asymptomatic PCR-positive infections (vaccine efficacy: 16%; 95% CI: -88−-62%). In the COVID-19 Moderna vaccine trial, investigators swabbed study participants 28 days after

the first dose, just before receiving the second dose, and found a 62% reduction of SARS-CoV-2 infection occurrence among vaccinated individuals (0.10%) compared to placebo (0.27%) after the first dose of vaccine [53]. Data from the Janssen COVID-19 vaccine trial (one-dose regimen) reviewed by the US Food and Drug Authority (FDA) show potential efficacy against asymptomatic infection (defined as positive RT-PCR, or a positive serology with N-specific immunoglobulin assay) developing during the study period, although it did not fulfil criteria for signs and symptoms of COVID-19 29 days after vaccine inoculation (seroconversion rate of 74%). In this study only a non-random fraction of study participants had available serology and the follow-up time was limited [54]. For the Janssen COVID-19 vaccine, an immunological test for seroconversion based on SARS-CoV-2 N protein will be performed to identify cases of asymptomatic infection in samples obtained at Day 1 (pre-vaccination), Day 29, Day 71, six months, and one year after vaccination. Based on preliminary data from a partial dataset, efficacy was 59.7% (95% CI 32.8−76.6%) for the prevention of asymptomatic cases [55].

Data from non-randomised studies

General population

In the large population-based published study from Israel (n=596 618 individuals), vaccine effectiveness against PCR-confirmed infection at Days 14 through 20 after the first dose of Pfizer-BioNTech vaccine, irrespective of symptoms, was estimated at 46% (95% CI: 40−51%) [48].

A separate study of 503 875 individuals from Israel using historical controls (1−12 days following vaccination) showed a 51.4% relative risk reduction of infections 13−14 days after the first dose of Pfizer-BioNTech vaccine [56]. A re-analysis of the data from this study using daily incidence of infection found an increasing vaccine effectiveness from Day 14 following the first dose, which peaked at 91% on Day 21 [57]. As people with previous infection are currently not eligible for vaccination in Israel, these studies could not look at vaccine effectiveness against infection in previously-infected individuals.

A retrospective analysis carried out in the USA among 39 156 patients attending pre-procedural and pre-surgical SARS-CoV-2 screening, found the risk of asymptomatic infection was reduced by 79% (RR=0.21; 95% CI: 0.12−0.37) in vaccinated patients from 10 days after the first dose of Pfizer or Moderna COVID-19 vaccine [50]. It is important to note that, due to potential unmeasured confounding, this study was only able to show a correlation between vaccination and reduced asymptomatic infection, rather than causation.

Older adults

In a Danish population-based pre-print study among residents of long-term healthcare facilities, no statistically significant vaccine effectiveness against SARS-CoV-2 infection was observed at any time between the first and second dose of Pfizer-BioNTech vaccine [51]. The estimated vaccine effectiveness after adjustments was 21% (95% CI -11−44%) in the 14-day period following vaccination and before the second dose.

Healthcare workers

Among healthcare workers from the same Danish retrospective cohort study referred to above, a statistically significant vaccine effectiveness of 17% (95% CI 4−28%) was observed from 14 days after the first dose of Pfizer-BioNTech vaccine until the second dose [51].

In another study from Israel, a single-centre retrospective cohort study of healthcare workers without active surveillance of asymptomatic infections, a reduction in infection rates of 75% (95% CI: 72–84%) was observed in healthcare workers who did not have previous SARS-CoV-2 infection between Day 15 and Day 28 after the first dose of Pfizer-BioNTech vaccine [58].

In the SIREN study from UK (n=23 000 with weekly swabbing), a 72% (95% CI: 58−86%) reduction in all infections was reported 21 days after a first dose of Pfizer-BioNTech COVID-19 vaccine [19,58].

Data from Cambridge's Addenbrooke Hospital in the UK, collected between 18 and 31 January 2021, showed a four-fold decrease in asymptomatic infections among healthcare staff, vaccinated for at least 12 days, after a single dose of the Pfizer-BioNTech vaccine compared to unvaccinated healthcare staff [59]. It is important to note that the variant B.1.1.7 was the predominant in the UK during the performance of these two studies.

Evidence for vaccination of previously infected individuals

Evidence is emerging of vaccine effectiveness in previously-infected individuals. Currently there is early evidence showing a high antibody response after one and two doses of vaccine in previously-infected individuals.

Data from randomised studies

For COVID-19 vaccines AstraZeneca, Janssen and Moderna data from the clinical trials were insufficient to assess vaccine effectiveness in participants with evidence of prior SARS-CoV-2 infection [2]. In the results available from clinical trials for Comirnaty from Pfizer-BioNTech, Novavax, Bharat Covaxin (phase 3) and Sinovac there is no mention of effectiveness in previously-infected individuals. In the clinical trial for the Sputnik V vaccine, previously-infected individuals were excluded from the trial, and there is no mention of the effectiveness in these individuals [59-62].

Data from non-randomised studies

A small, US National Institutes of Health supported study, published as a pre-print, suggests a single dose of mRNA vaccine elicits rapid immune responses in seropositive individuals with post-vaccine antibody titres that are comparable to, or exceed titres found in naïve individuals who received two vaccination doses [64]. The study included 109 individuals (67 seronegative and 41 seropositive) who received mRNA vaccines Pfizer-BioNTech or Moderna. The antibody titres of vaccinees with pre-existing immunity were 10−20 times higher than those of naïve individuals at the same points in time, and also exceeded the median antibody titres measured in naïve individuals after the second vaccine dose by more than 10-fold. The 41 people who tested positive prior to vaccination generated high levels of antibodies within few days of vaccination with first dose, while negative individuals developed low levels within 9−12 days of first dose.

A nested case-control analysis of 51 participants in an ongoing longitudinal observational study of healthcare workers in London (COVID-19 Consortium) suggests a good antibody response to the first Pfizer-BioNTech dose in previously-infected individuals [65]. Among previously-uninfected, seronegative individuals, anti-S titres after one vaccine dose were comparable to peak anti-S titres in individuals with a previous natural infection who had not yet been vaccinated. Among those with a previous SARS-CoV-2 infection, vaccination increased anti-S titres more than 140-fold from peak pre-vaccine levels [66]. This increase appears to be at least one order of magnitude greater than reported after a conventional prime-boost vaccine strategy in previously-uninfected individuals. The authors suggest the findings provide a rationale for serology-based vaccine dosing to maximise coverage and impact.

Another small study also looked at antibody responses to a single dose of the Pfizer-BioNTech or Moderna vaccines in 59 healthcare workers. Those who had previously been infected with SARS-CoV-2 had a clear antibody response, which peaked at 10 and 14 days after vaccination. At all points in time, healthcare workers with previous infection showed statistically significantly higher antibody levels than those who had not been infected [67].

Whether enhanced vaccine-induced antibody responses among previously seropositive individuals will show differential longevity compared to boosted vaccines remains to be seen.

Evidence for breakthrough infections with SARS-CoV-2 matching the vaccine strains and new emerging VOCs

With reported vaccine efficacy for the four EU authorised COVID-19 vaccines (Comirnaty developed by BioNTech/Pfizer, COVID-19 Vaccine Moderna, COVID-19 Vaccine AstraZeneca and COVID-19 Vaccine Janssen) varying in the range of 65−95% against any COVID-19 disease caused by the matching SARS-CoV-2 viruses in the community, breakthrough infections following vaccination are expected. This may either be due to primary vaccine failure, where the individual did not mount an immune response to vaccination, or secondary vaccine failure where an individual developed disease despite evidence of some immune response to vaccination.

There are currently no publications available on breakthrough infections but data are beginning to emerge. For Comirnaty, which was used in Israel, the majority of breakthrough infections were caused by B.1.1.7 but also some B.1.351, which matches the pattern of variant circulation in the country. These data should be interpreted with caution and always in the context of the proportion of circulating variants and the geographical distribution at the time of detection.

Lower vaccine efficacy has been observed for some of the new VOCs, as detailed below.

- For the vaccine candidate developed by Novavax, clinical trial data showed its vaccine was 89% effective in a clinical trial conducted in the UK with matching virus, but only 50% effective at preventing COVID-19 in South Africa where B.1.351 circulated in the community.
- The COVID-19 Vaccine Astra Zeneca, tested in a small study of 18 to 65 year-olds in South Africa, offered only limited or no protection from mild disease with a vaccine efficacy of 10% (95% CI -76.8 to 54.8) against the B.1.351 variant [68].
- A pre-print study on a limited number of healthcare workers receiving the Pfizer-BioNTech COVID-19 vaccine found a nearly identical antibody response in serum samples from vaccinated and infected individuals against the wildtype virus versus the variant B.1.1.7. For the variant B.1.351, virus neutralising tests revealed substantially-reduced neutralisation capacity but still neutralisation was not abrogated [52].
- Sera of participants vaccinated in the Phase 1 trial of the Moderna mRNA-1273 vaccine had reductions in neutralising antibodies by a factor of 1.2 against B.1.1.7, 6.4 against B.1.351, 3.5 against P.1, and 3.1 against B.1.1.7 with the E484K mutation [69].
- Five months after booster immunisation with the Sinovac inactivated vaccine, plasma from vaccinated individuals failed to efficiently neutralise P.1 lineage virus isolates [40].

There are several media reports of outbreaks in long-term care facilities across Europe including breakthrough infections among fully-vaccinated residents and staff [69-73]. The reported outbreaks are often linked to emerging VOCs, but the majority of cases among vaccinated residents have been mild or asymptomatic, with only a minority of cases requiring hospitalisation.

Summary and discussion of evidence: vaccination

The available evidence of COVID-19 vaccine effectiveness against transmission of SARS-CoV-2 is still limited. However, results from ongoing trials and observational studies of vaccine effectiveness against symptomatic and asymptomatic infection, viral load and duration of viral shedding are suggestive of relevant effect, including against transmission. Vaccine effectiveness against infection has been measured only shortly after the second dose of vaccine and not for all available vaccine products and VOCs. Vaccination significantly decreases the overall risk of symptomatic and asymptomatic infection. Therefore, the total number of infections is expected to decrease significantly, leading to reduced transmission overall. It is important to consider that different vaccine products show different effectiveness against infection and therefore risk of onward transmission. Different vaccines may also confer different durations of protection and effectiveness against VOCs.

COVID-19 vaccines do not confer sterilising immunity to all individuals, and some of those vaccinated might still be able to transmit SARS-CoV-2 infection to susceptible contacts if there is substantial viral replication. However, the population-level impact on virus circulation will depend not only on the risk of an individual transmitting the disease, but also on the proportion of susceptible people that the individual may expose to a virus. With mass vaccination programmes, a substantial impact on transmission can probably be anticipated with the currently licensed vaccines. Therefore, the vaccination uptake at population level will contribute critically to determining whether a vaccinated person can transmit the virus to susceptible contacts.

SARS-CoV-2, as an RNA virus, will continue mutating and has the potential to recombine to escape human immune defences in order to replicate and spread. The possibility cannot be discounted that in the future there will be new dominant variants that will be transmitted despite vaccination. It is not possible to predict when this may occur and what will then be the residual effectiveness of currently available vaccines against disease severity, also given the possibility of waning immunity. Data from other human coronaviruses suggest that immunity against the development of clinical disease may be longer-lived than immunity against infection and onward transmission [41].

Annex 1 summarises the types of studies required to fully evaluate transmission risk from vaccinated individuals, categorised according to a hierarchical evidence framework. There is evidence that vaccination significantly reduces PCR-positivity and symptomatic/asymptomatic infection in vaccinated individuals, although the vaccine efficacy varies by product and target group. A limited number of vaccine studies with prospective follow-up show reduced viral load and duration of virus shedding among vaccine recipients compared to placebo groups. This has been scored as moderate-strength evidence for reduced transmission risk, on account of the limited comparative data on culture viability and secondary attack rates among household contacts.

Knowledge gaps and areas for further research: vaccination

SARS-CoV-2 will continue to change and mutate. ECDC will continue to follow the viral evolution and resulting scientific evidence on transmissibility, severity, immune escape and vaccine escape and to evaluate VOCs as they emerge. Cohorts with SARS-CoV-2 humoral and cellular immunity markers need to be followed-up. This will allow better determination of the magnitude and duration of protection from reinfection and symptomatic disease. It will also enable determination of the effect of protection on transmission.

There is still limited evidence on the role of natural immunity against some of the newly-emerged VOCs.

There is incomplete evidence on the effectiveness and duration of protection of the various vaccine products against infection and further transmission of SARS-CoV-2 VOCs.

There is a need to ensure that any outbreak investigations identify the role of vaccinated individuals with infection in the further transmission of SARS-CoV-2 in congregate settings, including long-term care facilities, to provide clearer evidence on vaccine efficacy and transmission risk in these settings.

Finally, data on transmission risk in vaccinated individuals stratified by age group is lacking.

Forthcoming evidence

Vaccine failures will be followed up in many EU/EEA Member States through enhanced surveillance and then reported to the European Surveillance System (TESSy) database. This will include viral sequencing data to identify genetic changes that may be associated with vaccine escape, identifying patient factors or programme delivery factors associated with vaccine failure and monitoring disease outcomes. Data on breakthrough infection will be used to understand whether there is any evidence of vaccine-induced immune enhancement, whereby disease outcomes are more severe in vaccinated cases.

Healthcare workers' household studies are ongoing in the UK and should provide some results in the coming months [75,76]. One such study, carried out by the University of Nottingham, is based on an existing cohort of hundreds of healthcare professionals and their family members who were tested last spring and summer for

antibodies and viral RNA. The investigators are planning to re-test healthcare workers who have now been vaccinated and members of their households who have not received the vaccine. This should show whether the risk of transmission to close contacts within the family has decreased following the vaccination of healthcare professionals.

Household studies are also planned in Israel, involving close family contacts of vaccinated individuals. A cluster randomised trial involving the Sinovac vaccine in the Brazilian town of Serrana will assess the transmission in unvaccinated areas of the town to measure the indirect effects of vaccination on other areas of the town [76,77].

In the COVID-19 Pfizer-BioNTech vaccine trials ongoing in the USA and Argentina, a bi-weekly swabbing programme is foreseen to investigate vaccine effectiveness against infection [76].

Limitations

The uncertainty concerning the findings presented in this report are mainly related to the following:

- the fact that this review was based on emerging evidence, much of it from the pre-print, non-peer reviewed literature. Findings from such studies may be subject to revision as they undergo peer review;
- the fact that this is a relatively new pandemic and vaccines have only been developed and tested very recently. Consequently, there is limited follow-up data on duration of natural immunity or duration of immunity following vaccination;
- the situation concerning VOCs is evolving rapidly. Much of the evidence collected and presented here was generated before the variants started circulating widely and therefore conclusions may be revised as more data becomes available in the future.

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Annex 1

Frameworks for evidence

In this document, available evidence on SARS-CoV-2 transmission risk to susceptible contacts by previously infected and vaccinated individuals has been categorised according to a hierarchical framework to provide an assessment of the level of confidence ECDC attaches to study results. Categories in this framework are described below and summarised in a subsequent table.

Natural infection

1. Prior infection provides sterilising immunity, with little to no reinfections (Strong)

Types of studies required to provide such evidence:

Longitudinal cohort studies of individuals with confirmed prior SARS-CoV-2 infection (RT-PCR, rapid antigen or serology positive), that show little to no asymptomatic or symptomatic reinfections during follow-up, despite sustained virus transmission and infections amongst individuals without prior SARS-CoV-2 infection in the same cohort.

2. Prior infection reduces risk of symptomatic reinfection, but with virus carriage (non-sterilising immunity):

Types and assessed strength of evidence, and studies required to provide such evidence:

A. Reduced transmission by asymptomatic laboratory confirmed SARS-CoV-2-positive reinfected individuals (Strong)

Longitudinal cohort studies of recovered individuals, where household contacts of participants who become RT-PCR or rapid antigen test-positive are also screened. Reduced transmission confirmed if secondary attack rate is lower in recovered individuals versus individuals experiencing a first episode of infection.

Limitations: Difficult study design as hard to establish cohorts where recovered individuals are carefully matched with non-infected individuals; "Strong" only if secondary attack rate is zero or close to zero, otherwise theoretical risk of transmission remains. While rapid antigen tests can be used for screening and detection of SARS-CoV-2 positive individuals, they generally have lower sensitivity than RT-PCR and may generate false negative results [78].

B. Reduced viral titres in asymptomatic laboratory confirmed SARS-CoV-2 positive reinfected individuals AND culture negative (Moderate/Strong)

Longitudinal cohort studies that show reduced viral load in asymptomatic RT-PCR-positive individuals that were reinfected vs individuals experiencing a first episode of infection. Reduced viral RNA shedding duration may also be observed in asymptomatic RT-PCR-positive recovered individuals. This reduces the window for transmission, and if coupled with reduced average viral load, provides stronger evidence of reduced transmission risk.

Limitations: Viral load is only a proxy for infectiousness. Higher average Ct values may be difficult to translate to transmission risk. Strength of evidence improves if productive virus cannot be cultured from asymptomatic PCR-positive recovered individuals.

C. Reduced viral titres in asymptomatic laboratory confirmed SARS-CoV-2 positive reinfected individuals WITHOUT culture negative (Moderate)

Longitudinal cohort studies that show reduced viral load in asymptomatic RT-PCR-positive recovered individuals that were reinfected vs individuals experiencing a first episode of infection. Reduced viral RNA shedding duration may also be observed in asymptomatic RT-PCR-positive individuals after reinfection. This reduces the window for transmission, and if coupled with reduced average viral load, provides stronger evidence of reduced transmission risk.

Limitations: Viral load is only a proxy for infectiousness. Higher average Ct values may be difficult to translate to transmission risk. Strength of evidence improves if productive virus cannot be cultured from asymptomatic PCR-positive recovered individuals.

D. Fewer asymptomatic laboratory confirmed reinfected individuals (Low)

Longitudinal cohort studies that show reduced proportion of asymptomatic RT-PCR or rapid antigen test-positive recovered individuals that were reinfected vs individuals experiencing a first episode of infection.

Assumptions: Lower risk of transmission if fewer asymptomatic RT-PCR or rapid antigen test-positive individuals in recovered group.

Limitations: Need to confirm that viral load in asymptomatic recovered group is actually reduced when compared to individuals experiencing a first episode of infection, otherwise these asymptomatic individuals still pose a transmission risk. While rapid antigen tests can be used for screening and detection of SARS-CoV-2 positive individuals, they generally have lower sensitivity than RT-PCR and may generate false negative results [78].

Vaccination

1. Vaccination provides sterilising immunity, with little to no asymptomatic breakthrough infection (Strong)

Type of studies required to provide such evidence:
Vaccination studies with prospective follow-up that show little to no asymptomatic or symptomatic breakthrough infections in vaccinated individuals, despite sustained transmission and infections among unvaccinated contacts.

2. Vaccination reduces risk of symptomatic disease, but with virus carriage (non-sterilising immunity)

Types and assessed strength of evidence, and studies required to provide such evidence:
A. Reduced transmission by asymptomatic laboratory confirmed SARS-CoV-2-positive vaccinated individuals (Strong).

Vaccination studies where household contacts of participants who become RT-PCR or rapid antigen test-positive are also screened. Reduced transmission confirmed if secondary attack rate is lower in vaccine arm than placebo arm.

Limitations: difficult study design; 'Strong' only if secondary attack rate is zero or close to zero, otherwise theoretical risk of transmission remains. While rapid antigen tests can be used for screening and detection of SARS-CoV-2 positive individuals, they generally have lower sensitivity than RT-PCR and may generate false negative results [78].

B. Reduced viral titres in asymptomatic laboratory confirmed SARS-CoV-2 positive vaccinated individuals AND culture negative (Moderate/Strong)
Vaccination studies that show reduced viral load in asymptomatic RT-PCR-positive individuals in the vaccine arm versus the placebo arm. Reduced viral RNA shedding duration may also be observed in asymptomatic RT-PCR-positive vaccinated individuals compared to placebo. This reduces the window for transmission, and if coupled with reduced average viral load, provides stronger evidence of reduced transmission risk.

Limitations: viral load is only a proxy for infectiousness. Higher average Ct values may be difficult to translate to transmission risk. Strength of evidence improves if productive virus cannot be cultured from asymptomatic PCR-positive individuals.

C. Reduced viral titres in asymptomatic laboratory confirmed SARS-CoV-2 positive vaccinated individuals WITHOUT culture negative (Moderate)
Vaccination studies that show reduced viral load in asymptomatic RT-PCR-positive individuals in the vaccine arm versus the placebo arm. Reduced viral RNA shedding duration may also be observed in asymptomatic RT-PCR-positive vaccinated individuals compared to placebo. This reduces the window for transmission, and if coupled with reduced average viral load, provides stronger evidence of reduced transmission risk.

Limitations: viral load is only a proxy for infectiousness. Higher average Ct values may be difficult to translate to transmission risk. Strength of evidence improves to 'Moderate/Strong' if productive virus cannot be cultured from asymptomatic PCR-positive individuals.

D. Fewer asymptomatic laboratory-confirmed SARS-CoV-2-positive vaccinated individuals (Low)
Vaccination studies showing reduced proportion of asymptomatic RT-PCR or rapid antigen test-positive individuals.

Assumptions: lower risk of transmission if fewer asymptomatic RT-PCR or rapid antigen test-positive individuals.

Limitations: need to confirm that viral load in asymptomatic individuals is actually reduced in the vaccine arm, otherwise these asymptomatic individuals still pose a transmission risk.

While rapid antigen tests can be used for screening and detection of SARS-CoV-2 positive individuals, they generally have lower sensitivity than RT-PCR and may generate false negative results [78].

Natural infection

Grade	Strength	Description
Sterilising immunity		
1	Strong	Prior infection provides sterilising immunity, with little to no reinfections
Non-sterilising immunity: prior infection reduces risk of symptomatic reinfection, but with virus carriage		
2A	Strong	Reduced transmission by asymptomatic laboratory confirmed SARS-CoV-2-positive reinfected individuals
2B	Moderate/Strong	Reduced viral titres in asymptomatic laboratory confirmed SARS-CoV-2 positive reinfected individuals *AND* culture negative
2C	Moderate	Reduced viral titres in asymptomatic laboratory confirmed SARS-CoV-2 positive reinfected individuals *WITHOUT* culture negative
2D	Low	Fewer asymptomatic laboratory confirmed SARS-CoV-2-positive reinfected individuals

Vaccination

Grade	Strength	Description
Sterilising immunity		
1	Strong	Vaccination provides sterilising immunity, with little to no asymptomatic breakthrough infection
Non-sterilising immunity: vaccination reduces risk of symptomatic disease, but with virus carriage		
2A	Strong	Reduced transmission by asymptomatic laboratory confirmed SARS-CoV-2-positive vaccinated individuals
2B	Moderate/Strong	Reduced viral titres in asymptomatic laboratory confirmed SARS-CoV-2 positive vaccinated individuals *AND* culture negative
2C	Moderate	Reduced viral titres in asymptomatic laboratory confirmed SARS-CoV-2 positive vaccinated individuals *WITHOUT* culture negative
2D	Low	Fewer asymptomatic laboratory confirmed SARS-CoV-2-positive vaccinated individuals