

TESTING EN QUARANTAINES VOOR PERSONEN MET EEN VOORGAANDE INFECTIE MET SARS-COV-2

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1.1. AANBEVELINGEN

- Aangezien het Europese herstelcertificaat afgeleverd wordt voor 180 dagen, wordt voorgesteld dat **asymptomatische hoog-risicocontacten** (ongeacht vaccinatiestatus) die in de voorgaande **180 dagen** reeds een initiële positieve SARS-CoV-2 test hadden:
 - worden geïdentificeerd en gebeld door het call center. Omdat het risico op herinfectie gering is en er een risico bestaat van vals-positieve resultaten (“prolonged shedding”), worden ze vrijgesteld van tests en quarantaine op voorwaarde dat ze asymptomatisch zijn.
 - het call center informeert hen dat zodra er symptomen optreden, zelfs milde symptomen, zij getest moeten worden.
 - In het geval van clusters met doorbraakinfecties, wordt geadviseerd alleen degenen die **<90 dagen geleden** zijn besmet vrij te stellen van tests en quarantaine. Het personeel van het clusterbeheer kan de test-/quarantainestrategie aanpassen aan de situatie.
- **Personen die voldoen aan de definitie van een mogelijk COVID-19 geval:**
 - moeten niet worden hertest gedurende 180 dagen na de initiële besmetting zolang ze milde symptomen vertonen. Het beperken van testen gebeurt om vals-positieve resultaten te voorkomen, die het gevolg kunnen zijn van zgn. ‘prolonged shedding’, een fenomeen dat vaak voorkomt.
 - moeten niettemin worden getest als er een epidemiologische link is met een bevestigd COVID-19-geval (d.w.z. contact met een COVID-geval, zelfs bij een laag risico) of in geval van ernstige symptomen. In deze gevallen verdient een PCR-test de voorkeur zodat een eventueel positief staal gesequencet kan worden.
- Voor de verwerking van gegevens op het niveau van Sciensano (dat gewoonlijk niet over klinische gegevens beschikt) wordt aanbevolen het onderscheid te maken tussen een “oude besmetting” en een nieuw geval op basis van een periode van **ten minste 90 dagen** tussen een eerste en een tweede positieve test. Dat wil zeggen dat elke positieve test die zich ten minste 90 dagen na een eerste positieve test voordoet, als een nieuw geval wordt beschouwd en niet als een duplicaat.

1.2. BACKGROUND AND QUESTIONS

Re-positivity is often observed when re-testing for SARS-CoV-2 and can be due to prolonged viral shedding but also to reinfection. As prolonged viral shedding frequently occurs, a time frame between two positive tests was defined to consider a second positive case as a reinfection. Initially set at 8 weeks, this time frame was extended to 90 days following a [RAG advice](#) published on 29 March 2021 and based on data about the duration of protection after a first infection and the scarcity of reinfection events within 90 days.

The consequence of this time frame was that following a COVID-19 positive test, individuals were exempted from testing and quarantine within 90 days of the first positive test, both after a high risk contact and after travelling, except in case of severe symptoms.

As of 1st July 2021, the European digital COVID certificate will be put in place, for which the vaccination status, a negative test or a previous infection will be taken into consideration. For the EU digital green certificate, a recovery certificate, will be issued for a period of **180 days** after the first positive PCR result. (independent of vaccination status).

In addition, given the increasing number of vaccinated individuals in Belgium, testing and quarantine measures for vaccinated high risk contacts will be adjusted. As of 24 June 2021, fully vaccinated individuals will have to be tested only once after high risk contact and, if test negative, they will be exempted from second test and quarantine. A fully vaccinated individual is defined by the Interministerial Committee as having received the full vaccination scheme **or one dose of a two-dose vaccine plus infection within the previous 180 days.**

Given the validity period of a previous infection for travelers and for partially vaccinated high risk contacts, the following questions are asked:

- Should the period during which asymptomatic non-vaccinated HRC are exempt from testing and quarantine be extended from 90 days to 180 days post-infection?
- Should persons that fulfill the COVID-19 case definition but present only mild symptoms be exempted from testing during 180 days post-infection?
- What parameters should be taken into consideration to determine a second positive test as a reinfection episode? (time frame between episodes, symptoms, epidemiological information, ..)
- In terms of data management and contact tracing, what time frame should be applied to define a second positive test as a new infection rather than a duplicate? This is currently set at 90 days in accordance with the previous recommendation.

1.3. ELEMENTS TO CONSIDER

- The immune response following SARS-CoV-2 infection seem to persist for several months (6-12); large cohort studies analyzing the risk of reinfection suggest that SARS COV-2 infection could indeed induce effective immunity to future infections in most individuals.
- Extensive data on immune protection against variants of concern are still lacking
- Current guidelines for asymptomatic travelers and partially vaccinated high risk contacts grant exceptions after a previous infection episode for 180 days.
- Although a certain residual risk of infection remains present in both vaccinated and previously infected persons, testing is more difficult in previously infected individuals because PCR tests can remain positive for a long time after the initial infection.

1.4. INTERNATIONAL GUIDANCE REGARDING REINFECTION, TRAVELING AND CONTACT TRACING

1.4.1. Reinfection

The ECDC published two technical reports, (i) on [March 29](#) about the risk of SARS-CoV-2 transmission from newly-infected individuals and (ii) on [April 8](#) on SARS-CoV-2 reinfection surveillance within the EU/EEA.

The report on risk of infection after previous infection notes that:

- “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.)”

In the report of April 8th, the proposed case definition for a suspected COVID-19 reinfection case is however defined using an interval of only 60 days, without any additional criteria.

- “A suspected COVID-19 reinfection case is a positive PCR or rapid antigen test (RAT) sample **≥60 days** following a previous positive PCR, a previous positive RAT or a previous positive serology (anti-spike IgG).”

The table below summarizes case definitions for reinfection used in neighboring countries, based on publicly available information on their websites. Note that these definitions have not been updated since March 2021.

| Country | Defintion | Latest date of update |
|-----------------|--|-----------------------|
| France | The time period during which the risk of reinfection with SARS-CoV-2 appears negligible is of two months at this time. It may change according to the information available | 16/03/2021 |
| The Netherlands | A time period of 8 weeks after the first day of illness (or after the date of testing) is considered for a possible reinfection. | |
| Germany | After a confirmed SARS-CoV-2 infection, the person has overcome the acute respiratory illness or had an asymptomatic SARS-CoV-2 infection AND The time between the first and the second positive test in at least 3 months AND The number of SARS-CoV-2 genome copies within the scope of the current PCR detection $\geq 10^6$ / ml or Ct value < 30 | 31/03/2021 |
| United Kingdom | Reinfection should be considered in the following circumstances: -a repeat positive SARS-CoV-2 PCR test 90 days or more after a previous positive PCR test -new COVID-19 symptoms in a patient with previous SARS-CoV-2 PCR positive infection after apparent full recovery (resolution of previous symptoms) AND a repeat positive SARS-CoV-2 PCR test (including within 90 days after a previous positive PCR test) | 15/03/2021 |
| USA | Most people with a history of test-confirmed COVID-19 who remain asymptomatic after recovery do not need to retest or quarantine if another exposure occurs within 90 days of their initial infection. | 17/03/2021 |

1.4.2. Travel

- In accordance with the EU Digital Covid Certificate, the ECDC states that individuals that have recovered from a laboratory-confirmed SARS-CoV2 infection within **180 days** prior to travel, could be exempted from quarantine and testing requirements. However, it is still unclear whether a prior infection with one variant protects against other variants.
- The recommendation from the CDC from March 2021, remains unchanged: travellers are exempt from requirement to present a negative test before arrival in the US, during **90 days** after previous infection, unclear with regards to quarantine.

1.4.3. Contact tracing

There are no updates from ECDC or CDC regarding contact tracing recommendation since the previous [RAG advice on reinfection](#).

1.5. LITERATURE UPDATE

For previously discussed evidence, see the [RAG advice on reinfection dd 29/03/2021](#).

1.5.1. Duration of immunological response following SARS-CoV-2 infection

There is a substantial amount of publications describing the antibody response after SARS-CoV-2 infection. The vast majority of SARS-CoV-2-infected individuals seroconvert following infection. While there may be a waning of antibody response over time, T- and B- cell responses could persist for at least 8 months post-infection (1).

In a cross-sectional study by Dan et al, the duration of immunological memory after COVID-19 (CD4 T cells, CD8 T cells and humoral immunity) was analyzed; 188 recovered COVID-19 cases were followed-up to 8 months after infection. Most cases included in the study were symptomatic patients with mild disease. Antibodies declined moderately over 8 months, memory B cells increased between 1 month and 8 month after infection, and memory CD4- and CD8- T cells declined with a half-life of 3 to 5 months. **Heterogeneity in the memory response was observed but 95 % of subjects nevertheless retained an immune memory at 6 months after infection** (2).

Turner et al. described bone marrow plasma cells, a persistent source of protective antibodies, in mild COVID-19 convalescent individuals. Levels of serum anti-SARS-CoV-2 spike protein (S) antibodies declined rapidly in the first 4 months after infection and then more gradually over the following 7 months, but **remained detectable at least 11 months after infection**. Anti-S antibody titres correlated with the frequency of S-specific plasma cells in bone marrow at 7 to 8 months after infection, suggesting that mild infection with SARS-CoV-2 induced robust antigen-specific, long-lived humoral immune memory in humans (3).

The group of Davenport et al analyzed the characteristics of a durable immune control of SARS-CoV-2 and prevention of reinfection. In a modelling study, this group also concluded that antibody neutralization levels could predict immune protection (1,4).

1.5.2. Risk of reinfection and in particular reinfection in context of VOC circulation

In the previous [RAG advice about reinfection](#), several cohort studies were described, that showed a low risk of reinfection for previously infected individuals and confirmed that SARS COV-2 infection could induce effective immunity to future infections in most individuals. In these studies, reinfection was considered if the time frame between the first and second infection episode was > 90 days, the follow-up period was 5 to 7 months (5–8). O'Murchu et al performed a systematic review to synthesize the evidence of the risk of reinfection over time, this analysis included the studies mentioned above. O'Murchu et al calculated **an absolute rate of reinfection of 0 – 1,1 % and no reported increase of reinfection over time** (6-10 months). They also concluded that naturally acquired SARS-CoV-2 immunity does not wane for at least 10 months post-infection (9).

The published studies mentioned above were based on data from 2020, so most did not include patients infected with variants of concern (VOC). In contrast, the SIREN study was carried out in the UK until December 2020, so at a time when the variant B.117 (Alpha) emerged and spread in this region. The effect of this variant was included in the analysis, but no evidence was found that increased prevalence of the Alpha variant adversely affected reinfection rates in the studied cohort (5).

Another observational study performed in the UK evaluated longitudinal symptom and test reports of 36 920 people positive for COVID-19 during a 3-month period (28/09/2020 – 27/12/2020). They found a likely reinfection rate of around 0.7% (95% CI 0.6-0.8). Their data also suggested that the Alpha variant did not substantially alter the risk of reinfection (10).

In the previous RAG advice about reinfection, some evidence suggesting reduced protection of previous SARS-CoV-2 infection against infections with variants Beta and Gamma was also described. To our knowledge, there is still very little information about reinfection rates due to the Beta, Gamma or Delta variants. **Theoretical concerns exist however, in view of the immune escape properties that are attributed to these variants.**

Phenotypic impacts* of VOCs

| | Alpha (B.1.1.7) | Beta (B.1.351) | Gamma (P.1) | Delta (B.1.617.2) |
|---|---|----------------|---------------|-------------------|
| Increased transmissibility risk (change in R or secondary attack rate) | Yes | Yes | Yes+ | Yes ++ |
| Increased severity (risk of hospitalization/death) | Possible | Possible | Possible | Possible |
| Increased reinfection risk (following natural infection by other variants) | No change | Possible | Possible | Possible |
| Impacts on diagnostics (PCR or Ag RDTs) | Limited, largely negated by standard assays | None reported | None reported | None reported |

- Impacts on vaccines to be discussed in later sessions and detailed in the [WHO COVID-19 Weekly Epidemiological Updates](#)

Source: WHO webinar: Global Consultation on SARS-CoV-2 Variants of Concern and their Impact on Public Health Interventions" June 10th 2021

See also the [risk assessment](#) published by ECDC on June 10 about SARS-CoV-2 circulation, variants of concern, non-pharmaceutical interventions and vaccine rollout in the EU/EEA

A few case studies have been published, describing reinfection with the Beta variant in Luxembourg (11) or with the Alpha variant in Italy (12). Staub et al described four reinfection cases in HCW in a cluster of infections with the Beta variant. All reinfections were mild. In the study from Novazzi et al the reinfection was also mild, while the first episode had required hospitalization. Of note, in this study, the reinfection episode happened as soon as one month after the first episode.

It has to be noted that there is in fact a small number of well- documented cases of reinfection with SARS- CoV-2. However, there is likely a significant under- reporting of SARS- CoV-2 reinfections due to several factors. Individuals with low levels of infection who do not have clinically significant symptoms may not present for testing. In addition, once a potential reinfection case is identified, conclusive determination can be confounded by prolonged symptoms following an initial infection, persistent shedding of SARS- CoV-2 RNA, the potential for laboratory false positives, minor evolution of SARS- CoV-2 variants within a host, and the variability and timing of antibody responses to the initial infection (1).

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