

Testen van personen met vroegere COVID-19 besmetting

RAG 23/03/2021 – gevalideerd door de RMG 29/03/2021

VRAAGSTELLING

Met het oog op verdere versoepelingen en in het kader van uitgebreide test-capaciteit, wordt onderzocht welke bijkomende groepen getest kunnen worden en welke implicaties dat eventueel heeft.

Wanneer testen op grotere schaal worden uitgerold, kunnen vals-positieve resultaten een probleem zijn. Aanhoudende excretie van niet-infectieus virus ('prolonged viral shedding') na een initiële positieve test is een gekend probleem. De huidige aanbeveling in België is dat personen met voorgaande COVID-19 infectie niet in quarantaine moeten noch getest moeten worden binnen de 8 weken na een initiële positieve test. Deze uitzondering wordt echter niet aanvaard in het geval van buitenlandse reizen. Discussie zijn lopende op het Europese niveau in verband met **onder welke omstandigheden mensen met een voorgaande infectie vrijgesteld kunnen worden van testen en/of quarantaine.**

AANBEVELINGEN:

- **Het is niet aangeraden om personen opnieuw te testen binnen de 90 dagen na een initiële positieve test, noch om hen aan een quarantaine te onderwerpen.**
 - Deze uitzondering geldt niet indien er ernstige symptomen zijn die kunnen wijzen op COVID-19.
 - Deze uitzondering geldt niet voor reizigers die naar België reizen na verblijf in een regio waar VOCs met mogelijke immune escape veel intenser circuleren dan in België.
 - Voor reizigers die niet uit bovengenoemde zones komen en die hun hoofdverblijfplaats niet in België hebben, wil dit zeggen dat een bewijs van voorgaande positieve test aanvaard dient te worden in plaats van een negatief testresultaat als voorwaarde om het grondgebied te betreden.

1. Testing of previously infected persons

2.1 ELEMENTS OF DISCUSSION

- **The duration of a protective immunity against SARS-CoV-2 is still unclear**, but reinfection within the first 90 days seems rare. From the 16 reinfections cases described in the scientific literature until January 2020, 40 % showed more than 90 days between the first episode and the reinfection; 70 % showed more than 60 days between both episodes. More recent trials following up larger cohorts of people only looked into reinfection after more than 90 days.
- Prior infection might be less protective against re-infection with new variants of concern, especially those with the E484K mutation. Since restrictions in travelers have as one of the main objectives to slow down the introduction of VOCs, this is of particular concern.
 - On the other hand, in the interest of simplicity, it is preferable to have the same rules for re-testing/quarantine asymptomatic individuals after identified exposure and after travel.
- Especially VOCs with a potential immune escape mechanism and not yet widely circulating in Belgium are relevant in the context of travelers.
- With regards to travelers, a uniform European policy is preferable. The current proposal is to accept a previous positive result instead of a negative test result up to 90 days after the first positive test.

2.2 INTERNATIONAL GUIDANCE

ECDC

- **Contact tracing:** reclassify as low-risk contacts if exposure within 90 days after previous infection unless they work with vulnerable populations.
- **Travelers:** “For individuals that have recovered from a laboratory-confirmed SARS-CoV-2 infection within 180 days prior to travel, it can be considered to ease quarantine and testing requirements. However, it is still unclear whether a prior infection with one variant protects against other variants.”
“Alternatively, requiring a RADT at the earliest 48 hours in advance of travel may also be considered for this group of travelers as a means of confirming that that they are not infectious with SARS-CoV-2 at the time of travel since these tests will rule out individuals with a high viral load (i.e. the most infectious cases; see Annex 1). **This approach may be considered to account for the possibility of being re-infected with VOCs.**”

CDC

- **Contact tracing:** exempt from quarantine and testing during 90 days after previous infection, unless presenting symptoms

- **Travelers:** exempt from requirement to present a negative test before arrival in the US, during 90 days after previous infection, unclear with regards to quarantine.

WHO

- **Contact tracing:** “Until more is known about SARS-CoV-2 reinfection and the potential for transmission, contacts who have previously experienced a SARS-CoV-2 infection should be advised individually on the need for quarantine.”
- **Travelers:** “The use of “immunity certificates” for international travel in the context of COVID-19 is not currently supported by scientific evidence and is therefore not recommended by WHO.”

2.3 INTERNATIONAL SCIENTIFIC LITERATURE REGARDING REINFECTION

Risk of reinfection

See the [previous RAG advice on re-infection](#) for a detailed overview of reported cases of reinfection. Another review of 16 published reinfection cases is presented by Babiker et al. (1). **Median duration between the first infection episode and the reinfection was 66 days** (range 19 – 142 days). The immune status of the reinfection cases remains unclear, but little analysis of the cases immune responses during both episodes had been performed. None of the cases had a known immunodeficient state. More recently, cohort studies have tried to evaluate the risk of reinfection. Hall et al (2) showed that a previous exposure to SARS-CoV-2 reduced the risk of infection. This publication presented the intermediate results of the SIREN (SARS-CoV-2 Immunity and Reinfection Evaluation) study, a multi-center prospective cohort study of hospital healthcare workers performed in UK. Between June and November 2020, 44 reinfection cases (2 probable and 42 possible) were identified among the 6 614 participants in the positive cohort (previous positive PCR test or previous positive serology) and 318 new PCR infections and 94 seroconversions were identified among the 14 173 participants in the negative cohort. This is an incidence of 3,3 reinfection per 100 000 person days for the positive cohort compared to 22,4 new infections per 100 000 person days in the negative cohort. The **authors concluded that a prior history of SARS-CoV-2 infection >90 days ago was associated with an 83% lower risk of infection**, with median protective effect observed five months following primary infection. Note that in this study a possible reinfection case was only defined as two PCR positive samples 90 days or more apart, no sequencing was performed to confirm them as true reinfections.

Similar conclusions were drawn by Lumley et al (3), who found that among 11 364 health care workers with negative serology, 223 had a positive PCR test during the study time frame (1,09 per 10 000 days at risk) while among 1 265 health care workers with positive serology, 2 had a PCR positive test (0,13 per 10 000 days at risk). Both were asymptomatic. There were no symptomatic infections in workers with a positive serology.

See also the recent publication of Jeffery-Smith et al who analyzed reinfection rates in two nursing homes experiencing a second COVID-19 outbreak (4). They observed 96 % protection against reinfection for patients with previous COVID-19.

In Denmark, population-wide data was used to assess the risk of re-infection. Rates of positive tests during the second wave were compared between 11,727 individuals testing positive during the first wave and 525,339 individuals testing negative during the first wave (5). The authors only look at possible re-infection >90 days after the initial positive test. They note a protection of 80.5% [75.4-84.5%] against re-infection during the 3-5 months following an initial positive test. To account for behavioral differences (both in terms of exposure as in test-seeking) a subanalysis was done in healthcare workers, which showed similar results. However, **in individuals aged 65 years and older, observed protection was significantly lower, at 47% [24.7-62.8%]. Moreover, the authors warn that during the time of study, no VOCs were known to be circulating.** A similar study-design as in Denmark was used in the US, analyzing a multi-hospital databank containing test-results for 150,325 patients (6). Like in the other studies, a protection from previous infection of 81.8% [76.6-85.8%] was noted. Interestingly, risk or re-infection was highest around 90 days, which led the authors to speculate that this might rather represent ongoing viral shedding and not true reinfection.

Reinfections due to new variants

To our knowledge, there have been no published case reports of reinfection cases due to new variants. However, during the clinical trial performed in **South Africa by [Novavax](#)** (protein based vaccine), serological status of participants was assessed at day 0 (i.e. presence or not of anti-SARS-CoV-2 antibodies “anti-spike IgG” not assessment of neutralizing Ab levels) and no difference was found in the rate of infection during the trial: **3,9 % of the participants were infected in the placebo group whether they had anti-spike IgG or not.** This is a strong indication that reinfection with the 501Y.V2 variant could happen and that prior infection might not be protective against this variant.

Similarly, a pre-print study from Wibmer et al showed that plasma from convalescent patients had a reduced neutralizing activity against variant 501Y.V2 (in vitro assay). However, despite this neutralization escape, a significant proportion of non-neutralizing antibodies remained active against 501Y.V2. The role of such non-neutralizing antibodies and the efficacy of T-cell responses remains to be elucidated (7). See also preprint study from Cele et al (8).

In Manaus, Brazil, the attack rate was estimated to 76 % in October, implying a certain level of immunity in a significant proportion of the population. However, since December 2020, there has been a new rapid increase in the number of cases and hospitalisations in Manaus. In parallel, the variant 501Y.V3 was identified in the region. Several non-mutually exclusive hypothesis are currently being investigated to explain the resurgence of COVID-19 in Manaus: (i) the immunity against infection might have begun to wane between the first and the second episode; (ii) the variant 501Y.V3 might escape immunity generated against a previous infection; (iii) increased transmissibility of new circulating lineages could also explain a resurgence when associated to immune escape (9).

Prolonged viral shedding

Vibholm et al. report repeated testing of a prospective cohort of 203 post-symptomatic participants with a previous RT-PCR-verified SARS-CoV-2 infection (10). **At time point 2, approximately 90 days after recovery (range 85-105 days), 5.3% were still positive.** Assisted contact tracing among persistent PCR positive individuals revealed zero new COVID-19 diagnoses among 757 close contacts. Similarly, the Korean CDC reported 285 re-positive patients where no new cases could be found in 790 close contacts (11).

The following experts contributed to this advice:

Emmanuel André (KU Leuven); Emmanuel Bottieau (ITG/IMT); Laura Cornelissen (Sciensano); Géraldine De Muylder (Sciensano); Olivier Denis (CHU-UCL Namur); Herman Goossens (UAntwerpen); Marie Pierre Hayette (CHU-Liège); Xavier Holemans (GHDC); Frédérique Jacobs (Erasmus); Benoît Kabamba-Mugadi (UCLouvain); Yves Lafort (Sciensano); Barbara Legiest (ZG); Tinne Lernout (Sciensano); Pieter Libin (UHasselt); Bénédicte Lissoir (GHDC); Romain Mahieu (COCOM); Christelle Meuris (CHU-Liège); Roel Van Giel (Domus Medica); Elizaveta Padalko (UZGent); Ann Van den Bruel (KU Leuven); Te-Din Daniel HUANG (CHU Namur – UCL); Olivier Vandenberghe (ULB); Koen Vanden Driessche (UZA).

REFERENCES

1. Babiker A, Marvil C, Waggoner JJ, Collins M, Piantadosi A. The Importance and Challenges of Identifying SARS-CoV-2 Reinfections. *J Clin Microbiol* [Internet]. 2020 Dec 23 [cited 2021 Jan 7]; Available from: <https://jcm.asm.org/content/early/2020/12/21/JCM.02769-20>
2. Hall V, Foulkes S, Charlett A, Atti A, Monk E, Simmons R, et al. Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 2020 [Internet]. *Epidemiology*; 2021 Jan [cited 2021 Feb 4]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2021.01.13.21249642>
3. Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, Howarth A, Hatch SB, et al. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. *N Engl J Med*. 2020 Dec 23;NEJMoa2034545.
4. Jeffery-Smith A, Iyanger N, Williams SV, Chow JY, Aiano F, Hoschler K, et al. Antibodies to SARS-CoV-2 protect against re-infection during outbreaks in care homes, September and October 2020. *Eurosurveillance*. 2021 Feb 4;26(5):2100092.
5. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *The Lancet* [Internet]. 2021 Mar 17 [cited 2021 Mar 18];0(0). Available from: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)00575-4/abstract](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00575-4/abstract)

6. Sheehan MM, Reddy AJ, Rothberg MB. Reinfection Rates among Patients who Previously Tested Positive for COVID-19: a Retrospective Cohort Study. *Clin Infect Dis* [Internet]. 2021 Mar 15 [cited 2021 Mar 18];(ciab234). Available from: <https://doi.org/10.1093/cid/ciab234>
7. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Lambson BE, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. *bioRxiv*. 2021 Jan 19;2021.01.18.427166.
8. Cele S, Gazy I, Jackson L, Hwa S-H, Tegally H, Lustig G, et al. Escape of SARS-CoV-2 501Y.V2 variants from neutralization by convalescent plasma. *medRxiv*. 2021 Jan 26;2021.01.26.21250224.
9. Sabino EC, Buss LF, Carvalho MPS, Prete CA, Crispim MAE, Fraiji NA, et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. *The Lancet*. 2021 Feb;397(10273):452–5.
10. Vibholm LK, Nielsen SSF, Pahus MH, Frattari GS, Olesen R, Andersen R, et al. SARS-CoV-2 persistence is associated with antigen-specific CD8 T-cell responses. *EBioMedicine*. 2021 Feb;64:103230.
11. KCDC. Findings from investigation and analysis of re-positive cases [Internet]. [cited 2020 Jun 11]. Available from: https://is.cdc.go.kr/upload_comm/syview/doc.html?fn=158993708884700.pdf&rs=/upload_comm/docu/0030/