RAG ADVICE
ISOLATION FOR COVID-19 PATIENTS

validated by the RMG 03/12/2020

1. Question

Isolating contagious COVID-19 patients is of crucial importance for infection prevention and control, especially in settings with vulnerable people like elderly nursing homes or hospitals. However, excessively long isolation periods importantly reduce quality of life for patients and put unnecessary strain on limited hospital resources, e.g. in terms of PPE, revalidation possibilities or availability of designated COVID-19 isolation beds. Different durations of isolation might be warranted, depending on factors like disease severity or immune status of the patient. International guidelines have shifted from a heavily test-based to a more symptom-based approach but important differences still exist between the different organizations. It also appears that several Belgian hospitals have developed their own protocols.

Do the current guidelines on ending isolation need to be adapted, especially in ICU / immunocompromised?

2. Current guidelines in Belgium

End of isolation period	For which patients?	Remarks
7d after symptom onset + min. 3d without fever + improvement of respiratory symptoms	Outpatients in home-isolation	- Includes patients discharged from hospital before the end of their 14d isolation - 7d after date of test for asymptomatic cases - Excludes residents of collectivities
14d after symptom onset + min. 3d without fever + improvement of respiratory symptoms	Hospitalized patients/ Residents of residential collectivities	- E.g. elderly nursing homes- - All hospitalized patients, except severe/critical cases (defined as requiring intensive care)
28d after symptom onset OR **14d** after symptom onset **AND 2x negative PCR** with min. 24h interval + min. 3d without fever + improvement of respiratory symptoms	Admitted to intensive care	- Either a test-based or a symptom-based approach can be chosen - In view of concerns of prolonged shedding, no negative test is required if the isolation period is 28 days

3. Aanbeveling

- De huidige aanbevelingen voor patiënten in thuisisolatie en in residentiële voorzieningen worden behouden. Deze gelden enkel voor patiënten die niet ernstig immuungecompromitteerd zijn. Indien er politieke wil is om te komen tot uniforme richtlijnen in heel de Europese Unie, gaat de RAG akkoord met het verlengen van de isolatieduur tot minimum 10 dagen na start symptomen voor patiënten in thuisisolatie. Voor patiënten die volledig asymptomatisch blijven, wordt de dag van afname van de test als startpunt genomen.
- Omwille van het risico op nosocomiale besmettingen en aërosol -genererende procedures, worden symptomatische patiënten in het ziekenhuis steeds geïsoleerd tot minstens 14 dagen na het begin van symptomen. Dat wil zeggen dat een patiënt die symptomen en een positieve test had op dag 0 en waarvoor een ziekenhuisopname gepland was op dag 8 in het ziekenhuis nog een week in isolatie zal moeten blijven (of, indien mogelijk, dat de geplande opname een week uitgesteld wordt). Voor patiënten zonder COVID-19 symptomen (diagnose op basis van screening), volstaan 7 dagen isolatie.
- Voor patiënten die opname op intensieve zorgen vereisen omwille van ernstige COVID-19 symptomen, worden de criteria voor het beëindigen van isolatie als volgt aangepast :

klinische beterschap + 3d koortsvrij	EN	21d na aanvang symptomen[1] OF 14d na aanvang symptomen + 2x PCR (min. 24u interval) met virale lading $<10^5$ copies/ml (per labo te individualiseren met welke ct-waardes dit overeenkomt)

- Voor patiënten die ernstig immuungecompromitteerd zijn (zie criteria hieronder) wordt in het algemeen aanbevolen de isolatie pas te beëindigen 21 dagen na aanvang van symptomen, op voorwaarde dat er duidelijke klinische beterschap is en 3 dagen geen koorts. Van deze regel kan afgeweken worden in overleg met een specialist infectieziekten (bv. vroeger beëindigen van isolatie op basis van herhaalde PCR met virale lading $<10^5$ copies/mL, uitvoeren van PCR ook na 21 dagen indien geplande ziekenhuisopname op afdeling met kwetsbare patiënten of afwezige seroconversie…).
- Het aantal patiënten dat behoort tot de categorie “ernstig immuungecompromiteerd” is beperkt en deze categorie vereist overleg met een specialist infectieziekten. Worden als ernstig immuungecompromitteerd beschouwd:
    - actieve behandeling met chemotherapie, vooral voor hematologische maligniteiten, na gespecialiseerd overleg
    - onbehandelde HIV infectie met CD4-count <200/µL
    - gecombineerde (primaire) immuundeficiëntie, na gespecialiseerd overleg
    - behandeling met Methylprednisolon (Medrol®) >16mg gedurende >2 weken

[1] Indien de patient verder geïntubeerd blijft of invasieve procedures (bv. bronchoscopie) moet ondergaan, wordt verder 28 dagen na aanvang van symptomen als termijn te nemen.

4. Elements of discussion

- The currently recommended duration of isolation for outpatients in Belgium is short in comparison with other international recommendations, but can be extended in case of ongoing symptoms. Prolonging the duration of isolation for all mild cases might limit compliance and willingness to submit to testing.
- A distinction might be useful between “patients hospitalized because of COVID-19” and “patients hospitalized for other reasons, with an incidental diagnosis of COVID-19” as disease severity is likely different in both groups. However, this should be weighed against the advantage of having simple, clear guidelines and the importance of avoiding nosocomial transmission.
- Belgian guidelines currently use “admission to intensive care unit” as a proxy for severe/critical disease, in contrast with more detailed international recommendations.
- A zero-risk approach does not exist and should not be aimed for. However, implications of releasing a still infectious person will be different according to the setting (e.g. residents of elderly nursing homes, hospitals), so a diversified approach might be necessary.
- The RAG reiterates the importance of reporting semi-quantitative results (rather than binary positive/negative) of PCR tests, in a standardized way that help clinicians make decisions. The NRC recently submitted a proposal to the Commissie Klinische Biologie. This process should be continued.
- Case reports probably highlight the exceptions rather than the general rule. A variety of settings and patient characteristics may warrant case-by-case discussions and prolongation of the duration of isolation and/or additional testing (e.g. serology, repeated PCR, quantification of viral load…). This should be done through multidisciplinary consultation including an infectious diseases specialist. The clinical evolution of the patient is an important factor to take into account.

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5. International Recommendations

AUTHOR	MILD/MODERATE	SEVERE DISEASE	IMMUNOCOMPROMISED	COMMENTS
WHO	Min. 10d after symptom onset + extra 3d no symptoms	Consider test-based (including VL/nAb) if prolonged symptoms	NA	**Min. 13d** for symptomatic cases Min. 10d for asymptomatic cases
ECDC	Clinical improvement + no fever for 3d + **10d** after symptom onset OR 2x neg PCR	Clinical improvement + no fever for 3d + **min. 14-20d** after symptom onset OR 2x neg. PCR	Clinical improvement + no fever for 3d + **20d** after symptom onset OR 2x neg PCR	**Residents/staff of LTCF or other vulnerable population** (prison, migrant hosting facility): like immunocompromised
CDC	no fever for 24h **+ 10d** after symptom onset	Consider 20d	Consider test-based	
RKI (DE)	48h no symptoms + **10d** after symptom onset	(defined as requiring O_2) As mild cases + negative PCR	Case-by-case	No symptoms = "significant clinical improvement" high CT-values can be considered "negative PCR" LTCF: like severe
RIVM (NL)	24h no symptoms + **7d** after symptom onset (+ 48h no fever for HCW only)	Only if still hospitalized: 14d after symptom onset + 48h clinical improvement If still mechanically ventilated: 21d after SO + 48h clinical recovery + 2x neg PCR on LRT specimen	24h no symptoms + **14d** after symptom onset + consider 2x neg PCR	If still asymptomatic 72h after test: end isolation in LTCF: 24h no symptoms + 48h no fever + **14d**
SPF (FR)	48h no fever/dyspnea + **7d** after symptom onset	?	48h no fever/dyspnea + 10d after symptom onset	7d from date of test for asymptomatic
PHE (UK)	48h no fever + clinical improvement + **10d** after symptom onset	48h no fever + clinical improvement + **14d** after symptom onset	As severe + consider testing	

N.B. **WHO definitions of disease severity**:
- Mild disease = symptomatic, no evidence of viral pneumonia or hypoxia
- Moderate = clinical signs of pneumonia but no signs of severe pneumonia, including SpO2 on room air ≥90%
- Severe = clinical signs of pneumonia + min. 1 of RR>30/min, severe respiratory distress or Sp02<90% on room air

6. Scientific Background

6.1. KEY POINTS FROM LITERATURE REVIEW

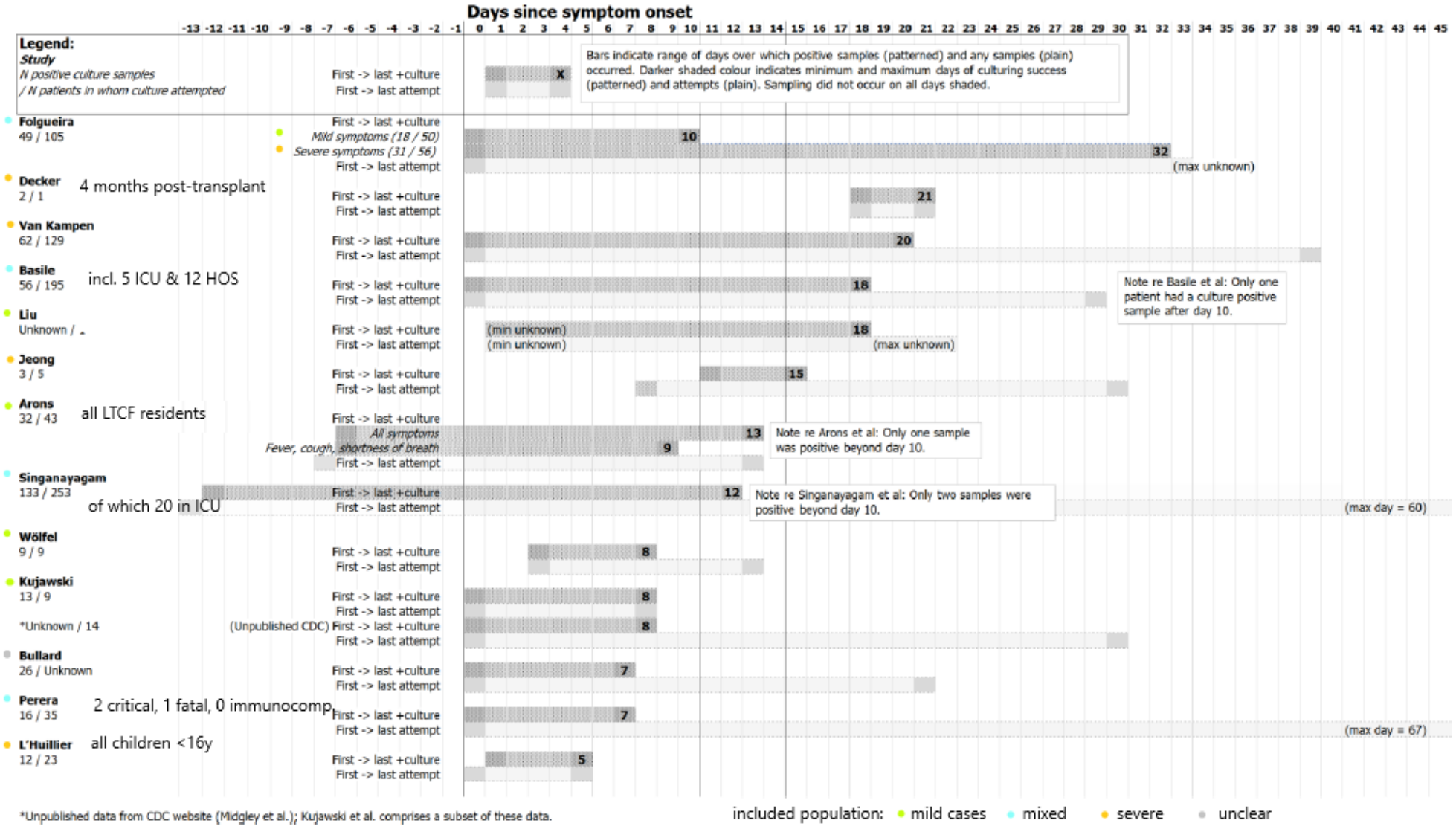
- Data is available from contact tracing studies, modelling of transmission and studies using viral culture. Studied populations are heterogeneous, e.g. with regards to disease severity and immunosuppression. Studies assessing viral culture generally include rather small case numbers especially for time points long after onset of symptoms. No viral culture studies prospectively follow up patients until reaching negative culture, so results should be interpreted with caution.
- Studies on dynamics of viral load, contact tracing and modelling studies are consistent in finding that infectiousness peaks around the time of symptom onset.
- The probability of successfully culturing virus seems limited (<5%) 8-10d after symptom onset in mild-moderate cases and 14-20d (or more) in severe cases. A pre-print article does however describe a positive viral culture in a hospitalized patient (no further details) as long as 32d after symptom onset (1).
- Prolonged infectiousness seems to be associated with immunocompromised status, but data is limited. One case report in a patient with lymphoma and impaired B-cell immunity reports a positive viral culture as long as 116 days after first onset of symptoms (2)
- A test-based strategy is hindered by known prolonged shedding of viral RNA, which does not equate with infectiousness. Assessment of viral load might help in these cases but viral loads are usually semi-quantitatively expressed as *cycle threshold*-values, which differ according to technical lab circumstances and the gene target(s).

6.2. REVIEWS AND EVIDENCE SUMMARIES

The **WHO** Scientific brief on "Criteria for releasing COVID-19 patients" dates from 17th of June (3). The US Centres for Disease Prevention and Control **CDC** last updated their guidance on 19th of October (4). The identified key points by CDC include "For patients with mild to moderate COVID-19, replication-competent virus has not been recovered after 10 days following onset of symptoms. Recovery of replication-competent virus between 10 and 20 days after symptom onset has been documented in some persons with severe COVID-19 that, in some cases, was complicated by immunocompromised state." They do however mention the caveat that replication-competent virus was isolated after mild disease in one case report 18 days after symptom onset on sputum (5) and potentially in another mild case more than 20d after symptom onset (6). The references include the pre-print study of van Kampen et al. (129 patients with severe COVID-19 of which 30 immunosuppressed in the Netherlands, last positive culture day 20) (7) but not of Folgueira et al. (1) (55 severe cases in Spain, last positive culture day 32), see 6.3. Finally, the European Centres for Diseases Prevention and Control **ECDC** issued updated guidance on the 16th of October (8) which contains in large part the same references as the CDC, but advices longer periods of isolation (see point 5).

A review on the topic including 9 viral culture studies and 1 contact tracing study was published end of August by Rhee and colleagues who conclude that "infectivity rapidly decreases to near-zero after about 10 days in mild-moderately ill patients and 15 days in severly-ill and immunocompromised" (9). The most comprehensive recent review of the evidence we found was by the Irish Health Information and Quality Authority Ireland (10). The review includes 13 viral culture studies (all included in Rhee et al + 4 extra e.g. Flogueira) and 2 contact tracing studies. We include the following summary figure of the viral culture studies:

Fig. 1: Days since symptom onset at which virus culture attempts (pale grey) and successful virus culturing (dark grey) took place in each study. *Source: annotated from Health Information and Quality Authority Ireland* (10)

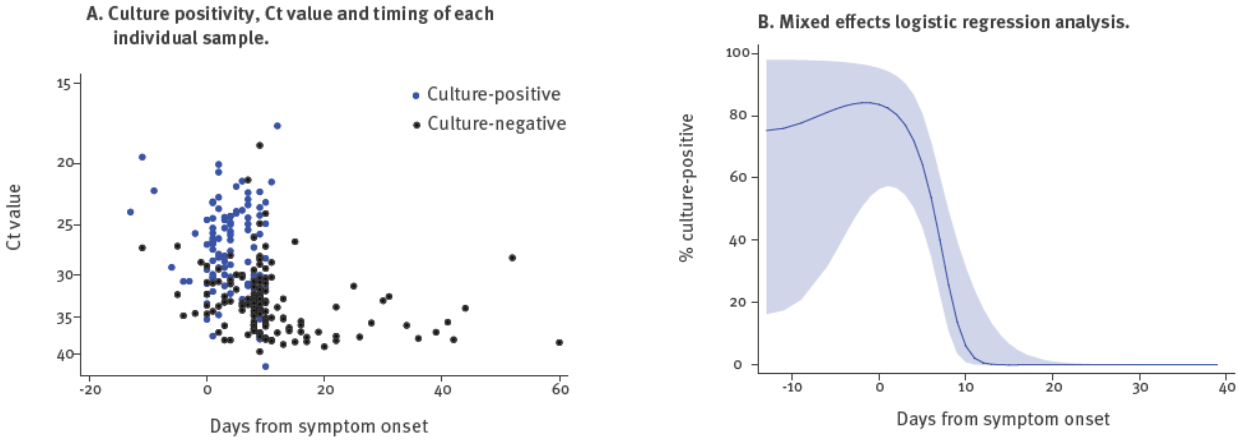


6.3. HIGHLIGHTS OF SELECTED STUDIES

Whilst viral culture studies are difficult to interpret and all studies have important methodological limitations, the contact tracing study of Chen et al (Taiwan) is of high quality. In the study, 100 confirmed cases (of which 6 severe) and their 2,761 close contacts are followed up. Only 22 secondary cases occurred. **No secondary cases were observed in those exposed to the index case more than 5 days after onset of symptoms** (SAR 22/1,818 = 1.0% [0.6%-1.6%] first 5d vs. 0/852 = 0% [0-0.4%]) (11).

The first viral culture data came from a small study of Wölfel et al in 9 patients with mild disease. In these patients, no viable virus was cultured more than 8 days after symptom onset, although viral loads sometimes remained high (12). Since then, the study with the largest sample size that has been published is by Singanayagam et al (13). This group in the UK examined a total of 324 samples from mostly asymptomatic or mild-to-moderate cases (n=233, 92%) and some severe/critical cases (defined as requiring ICU or fatal, unlike the WHO definition of 'severe disease'). All samples were from the upper respiratory tract but sampled in various ways (nasal, oral, combined, nasopharyngeal swab or nasopharyngeal aspirate). Date of symptom onset was available for 246 samples. Culture-positivity was clearly associated with a shorter time after symptom onset. Despite the various sampling techniques, viral load (as expressed by Ct-values) was both associated with days from symptom onset and with culture positivity, as is shown in figure 2. Of note is that the number of samples tested after more than 10 days is low.

Fig.2 Relationship between culture positivity and time between symptom onset and sample collection (n=246) *Source Singanayagam et al.*



The authors also provide a break-down per day of the probability of being culture-positive, based on a mixed effects logistic regression, presented in the table below. There is no break-down by disease severity or information on immunosuppression.

Estimated percentage of SARS-CoV-2 samples culture-positive 7-15 days after symptom onset (n=121) *Source: Singanayam et al.*

Day post symptom onset	Estimateda percentage culture-positive (95% CI)	N (observed number tested)	R (observed number culture-positive
7	40.1 (22.8–60.4)	14	10
8	25.8 (11.0–49.4)	33	9
9	13.7 (3.7–39.6)	34	10
10	6.0 (0.9–31.2)	23	6
11	2.2 (0.2–23.9)	6	1
12	0.7 (0.0–17.9)	3	1
13	0.2 (0.0–13.1)	4	0
14	0.03 (0.0–9.4)	2	0
15	0.006 (0.0–6.7)	2	0

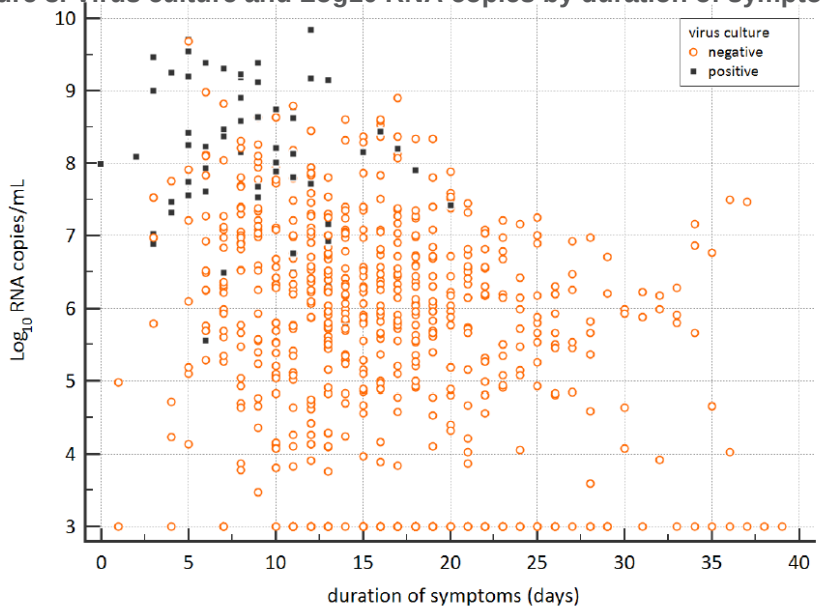
Immunocompromised patients

In June, Decker et al. reported a case in a 62y-old male who was on active immunosuppression 4 months after a cardiac transplant. The course of the illness was generally mild and all symptoms resolved by day 20, viral culture was still positive at day 21. **The patient still presented a positive PCR and high viral load on day 35 post-infection onset, but infectiousness at this stage is unknown since viral culture was not attempted beyond day 21** (14). Another case of prolonged infectiousness was published end of October and concerns a 60y-old man with lymphoma and associated B-cell immunodeficiency (2). Despite mild initial presentation (afebrile with productive cough, no need for supplemental oxygen) the patient required 3 admissions over a 4-month period and was treated twice with remdesivir and convalescent plasma. **Viral culture was still positive at day 116** after initial onset of symptoms. Based on viral genome sequencing, re-infection was highly improbable. The authors argue that it may be reasonable to use Ct thresholds, RT-PCR for replicative subgenomic RNA or seroconversion with titer as surrogates for the presence or absence of infectious virus. Finally, Aydillo and colleagues reported on a sample of 20 immunocompromised patients (recipients of hematopoietic stem-cell transplants (HSCT) or chimeric antigen receptor T-cell (CART) therapy and 2 patients with lymphoma) of which 11 had severe disease. Viable virus was detected for up to 61 days after onset of symptoms. All 3 patients with viable virus for more than 20 days had received either HSCT or CART in the previous six months. (15)

Severe cases

Previously, higher viral loads and prolonged shedding have been described in severe cases compared to mild cases (16–18). Of particular interest are therefore two studies, both not yet peer-reviewed, which include a large sample of severe or immunocompromised cases. The first one, of van Kampen et al describes analysis of 690 respiratory samples of 129 patients with severe COVID-19 (89 admitted to ICU and 40 to medium care) at a hospital in Rotterdam (7). All samples that were sent to the lab during 1 month were included in the analysis (i.e. no repeat testing until negative). The sample further included 30 patients (23%) with some form of immunosuppression, of which 19 (14,7%) were severely immunosuppressed (e.g. HIV with CD4-count <200 cells/µL or use of immunomodulating biologicals). Infectious virus could be isolated from 23 patients (18%) and a total of 62 samples (9%). **The probability of isolating infectious virus was below 5% from day 15 after symptom onset or with a neutralizing antibody titer of 1:80. Of all 4 patients who still had a positive culture on day 15 or beyond, only 1 was classified as non-severely immunocompromised** (personal communication) **No infectious virus was found in samples beyond day 20 after symptom onset.** Results are presented in figure 3. An important caveat is that from some supplementary data (supplementary figure 1), it seems as if for 6 out of 15 patients with a positive culture (data not shown for the other 8 culture+ patients) a negative viral culture was followed by a positive one in the following days, suggesting limitations in the use of a negative viral culture as a proxy for end of contagiousness.

Figure 3. Virus culture and Log10 RNA copies by duration of symptoms. *Source van Kampen et al.*



As mentioned, viral culture as proxy for infectiousness also has its limitations. Technical factors, such as the cell line permissiveness for SARS-CoV-2, might explain the striking difference with results found by the Spanish group of Folgueira. In their analysis of 106 samples of 105 patients (50 mild non-hospitalized and 55 severe cases of which 6 admitted to ICU) they were able to isolate infectious virus up to 32 days post-onset of symptoms. **In severe cases, infectious virus was found in the third week after symptom onset for 6/10 samples and in 2/6 samples beyond the third week.**

7. References

1. Folgueira MD, Luczkowiak J, Lasala F, Perez-Rivilla A, Delgado R. Persistent SARS-CoV-2 replication in severe COVID-19. medRxiv. 2020 Jun 12;2020.06.10.20127837.

2. Baang JH, Smith C, Mirabelli C, Valesano AL, Manthei DM, Bachman MA, et al. Prolonged Severe Acute Respiratory Syndrome Coronavirus 2 Replication in an Immunocompromised Patient. J Infect Dis [Internet]. [cited 2020 Dec 1]; Available from: https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa666/5934826

3. World Health Organization. Criteria for releasing COVID-19 patients from isolation [Internet]. Geneva: World Health Organization; 2020 Jun [cited 2020 Nov 24]. Available from: https://www.who.int/publications-detail-redirect/criteria-for-releasing-covid-19-patients-from-isolation

4. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 Nov 16]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html

5. Liu W-D, Chang S-Y, Wang J-T, Tsai M-J, Hung C-C, Hsu C-L, et al. Prolonged virus shedding even after seroconversion in a patient with COVID-19. J Infect. 2020 Aug;81(2):318–56.

6. Gallichotte EN, Quicke KM, Sexton NR, Fitzmeyer E, Young MC, Janich AJ, et al. Longitudinal Surveillance for SARS-CoV-2 Among Staff in Six Colorado Long-Term Care Facilities: Epidemiologic, Virologic and Sequence Analysis. medRxiv. 2020 Nov 5;2020.06.08.20125989.

7. van Kampen JJA, Vijver DAMC van de, Fraaij PLA, Haagmans BL, Lamers MM, Okba N, et al. Shedding of infectious virus in hospitalized patients with coronavirus disease-2019 (COVID-19): duration and key determinants. medRxiv. 2020 Jun 9;2020.06.08.20125310.

8. European Centre for Disease Prevention and Control. Guidance for discharge and ending of isolation of people with COVID-19 [Internet]. Stockholm: European Centres for Disease Prevention and Control; 2020 Oct p. 7. Available from: https://www.ecdc.europa.eu/en/publications-data/guidance-discharge-and-ending-isolation-people-covid-19

9. Rhee C, Kanjilal S, Baker M, Klompas M. Duration of SARS-CoV-2 Infectivity: When is it Safe to Discontinue Isolation? Clin Infect Dis Off Publ Infect Dis Soc Am [Internet]. 2020 Aug 25 [cited 2020 Nov 20]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7499497/

10. Health Information and Quality Authority Ireland. Duration of infectiousness of SARS-CoV-2 | HIQA [Internet]. 15 September [cited 2020 Nov 25]. Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/duration-infectiousness-sars-cov-2

11. Cheng H-Y, Jian S-W, Liu D-P, Ng T-C, Huang W-T, Lin H-H. Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset. JAMA Intern Med [Internet]. 2020 May 1 [cited 2020 May 11]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2765641

12. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465–9.

13. Singanayagam A, Patel M, Charlett A, Lopez Bernal J, Saliba V, Ellis J, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Eurosurveillance [Internet]. 2020 Aug 13 [cited 2020 Aug 17];25(32). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.32.2001483

14. Decker A, Welzel M, Laubner K, Grundmann S, Kochs G, Panning M, et al. Prolonged SARS-CoV-2 shedding and mild course of COVID-19 in a patient after recent heart transplantation. Am J Transplant. 2020;20(11):3239–45.

15. Aydillo T, Gonzalez-Reiche AS, Aslam S, van de Guchte A, Khan Z, Obla A, et al. Shedding of Viable SARS-CoV-2 after Immunosuppressive Therapy for Cancer. N Engl J Med. 2020 Dec 1;0(0):null.

16. Walsh KA, Jordan K, Clyne B, Rohde D, Drummond L, Byrne P, et al. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. J Infect. 2020 Sep 1;81(3):357–71.

17. Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. BMJ [Internet]. 2020 Oct 23 [cited 2020 Nov 23];371. Available from: https://www.bmj.com/content/371/bmj.m3862

18. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe [Internet]. 2020 Nov 19 [cited 2020 Nov 23];0(0). Available from: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30172-5/abstract