

(10)(2e) – AIOS IZB – stage LCI 24-8-2020 t/m 18-9-2020

Richtlijn herzien, COVID-19: Maatregelen naar aanleiding van een melding van een bevestigde patiënt.

31-8-2020 Overleg met (10)(2e). Welke categorie gaan we uitzoeken:

- Buiten instellingen: Is het nodig om op basis van de huidige (vernieuwde) kennis, de isolatie duur aan te passen voor patiënten met covid in de thuissituatie?
- Het beleid voor immuungecompromiteerden is momenteel 14 dagen, wat is hier over de literatuur in te vinden (algemeen (er zijn namelijk vele groepen te benoemen))? Mogelijk dat hier de FMS (federatie medisch specialisten) informatie over heeft. Omdat er zoveel groepen immuungecompromiteerden zijn is het idee dat de eigen behandelaar hierover beslist.
- Asymptomaten: uitzoeken wat het internationale beleid is.
- Immuungecompromiteerde asymptomaten: uitzoeken wat hier over te vinden is in de literatuur en overleg met (10)(2e).

- o Hoe aan te pakken. Eerst internationale richtlijnen bekijken.



- o Nauwe search op pubmed (vraag zo nodig de bibliotheek)
- o FMS richtlijnen

1. De covid-19 patiënt in de thuissituatie:

WHO: **10 dagen en 3 dagen klachtenvrij** <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/coronavirus-disease-answers?query=isolation+period> 31-08-2020 → geen referentie

How long should people with COVID-19 stay at home and in isolation?

People with COVID-19 who are cared for at home should stay in isolation until they are no longer able to transmit the virus to others:

- Those with symptoms should stay isolated for a minimum of **10 days after the first day they developed symptoms, plus another 3 days after the end of symptoms** – when they are without fever and without respiratory symptoms.
- People without symptoms should stay isolated for a minimum of 10 days after testing positive

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In settings with limited testing capacity, patients can be discharged from isolation when the following criteria are fulfilled: 1. resolution of fever for at least three days, 2. clinical improvement of other symptoms and 3. after eight days from symptom onset for mild cases or 14 days from symptom onset for severe cases [33]. WHO recommends that patients are released from isolation 10 days after symptom onset, plus at least 3 additional days without symptoms. 31-08-2020 → beide referenties (webpagina's) zijn niet te vinden.

(10)(2a)

CDC: **10 dagen en 24 uur koortsvrij en verbetering klachten** <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/isolation.html> 31-8-2020

Duitsland: **milde symptomen: 10 dagen en minimaal 48 uur klachtenvrij. Ernstige symptomen: 10 dagen en minimaal 48h klachtenvrij en PCR onderzoek.**
https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Entlassmanagement.html 31-8-2020

Engeland: **10 dagen (dan mag je nog hoesten, anosmie en ageusie hebben)**
<https://www.gov.uk/government/publications/covid-19-stay-at-home-guidance/stay-at-home-guidance-for-households-with-possible-coronavirus-covid-19-infection#ending-self-isolation-and-household-isolation> 31-08-2020

Denemarken: **48h klachtenvrij, anosmie en ageusie mag dan nog aanwezig zijn.**
<https://www.sst.dk/en/English/Corona-eng/FAQ#uk-corona-faq-syg> en <https://www.sst.dk/-/media/Udgivelser/2020/Corona/Oversættelser/testet-positiv-engelsk.ashx?la=da&hash=9F7371BEF96630436FE2EC71C145BF972C38B843> 31-08-2020

Finland: **14 dagen en 48h klachtenvrij**

<https://thl.fi/en/web/infectious-diseases-and-vaccinations/what-s-new/coronavirus-covid-19-latest-updates/symptoms-and-treatment-coronavirus/treatment-of-coronavirus-and-instructions-for-the-infected> 31-08-2020

Noorwegen: 8 dagen isolatie en arts bepaald hoe lang nodig is. <https://www.fhi.no/en/op/novel-coronavirus-facts-advice/facts-and-general-advice/social-distance-quarantine-and-isolation/> Your doctor will assess how long you need to be isolated. You need to be isolated for at least 8 days after you become ill. 31-08-2020

Zweden: 7 dagen en 48h klachtenvrij (droge hoest, anosmie en ageusie mogen bestaan) <https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/covid-19/> If you have a confirmed COVID-19 infection you should stay at home for at least seven days after falling ill. You should be free from fever for two days and clearly feel well before returning to work or school. A dry cough and loss of smell and taste may remain but if you feel well otherwise and seven days have passed since you fell ill you can return to work or school. 31-08-2020

Canada: 10 dagen tot 14 dagen, geen koorts en klinisch verbeterd. Mag nog hoesten <https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/interim-guidance-cases-contacts.html> For cases with symptoms: Home isolation should continue for a minimum of 10 days from the onset of symptoms or as directed by the PHA. The criteria for discontinuing home isolation includes: at least 10 days or up to 14 days, depending on the situation and PHA direction, have passed since onset of first symptom or laboratory confirmation of an asymptomatic case, the case did not require hospitalization, the case is afebrile and has improved clinically. Absence of cough is not required for those known to have chronic cough or for those who are experiencing reactive airways post infection. 31-08-2020

Search op pubmed: 2-9-2020

Covid duration infectivity → 578 resultaten, scannen van titel op relevantie.

- Int J Infect Dis. 2020 Aug;97:293-295. doi: 10.1016/j.ijid.2020.06.020. Epub 2020 Jun 12.
Duration of viral shedding in asymptomatic or mild cases of novel coronavirus disease 2019 (COVID-19) from a cruise ship: A single-hospital experience in Tokyo, Japan. Although the duration of viral shedding was approximately three weeks, the infectivity and transmissibility period from asymptomatic and mild COVID-19 cases is unclear. Further studies are needed to determine how long such asymptomatic and mild COVID-19 cases have infectivity.--> geen virusweek.
- Int J Infect Dis. 2020 Jul;96:531-537. doi: 10.1016/j.ijid.2020.05.045. Epub 2020 May 17.
Factors associated with the duration of viral shedding in adults with COVID-19 outside of Wuhan, China: a retrospective cohort study. Laat de tijd zien hoe lang iemand een positieve PCR heeft, maar niet of dit ook daadwerkelijk nog infectieus is.
- Clin Infect Dis . 2020 Apr 17;ciaa451. doi: 10.1093/cid/ciaa451. Online ahead of print. The duration of viral shedding of discharged patients with severe COVID-19. Laat de tijd zien hoe lang iemand een positieve PCR heeft na opname, maar geen kweken om te zien of dit ook daadwerkelijk nog infectieus is.
- J Infect. 2020 May 21;S0163-4453(20)30310-8. doi: 10.1016/j.jinf.2020.05.035. Online ahead of print. Asymptomatic infection and atypical manifestations of COVID-19: Comparison of viral shedding duration. Laat de tijd zien hoe lang iemand een positieve PCR heeft na opname, maar geen kweken om te zien of dit ook daadwerkelijk nog infectieus is.
- J Infect . 2020 Jul;81(1):e78-e79. doi: 10.1016/j.jinf.2020.03.053. Epub 2020 Apr 10.
Duration for carrying SARS-CoV-2 in COVID-19 patients. Niet bruikbaar voor deze vraag.

- *Pediatr Infect Dis J* . 2020 Sep;39(9):e249-e256. doi: 10.1097/INF.0000000000002814. Duration of Respiratory and Gastrointestinal Viral Shedding in Children With SARS-CoV-2: A Systematic Review and Synthesis of Data. Alleen PCR, geen virusweek.
- *J Infect* . 2020 Sep;81(3):357-371. doi: 10.1016/j.jinf.2020.06.067. Epub 2020 Jun 29. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. Geen virusweek
- *Euro Surveill* . 2020 Jul;25(30):2001292. doi: 10.2807/1560-7917.ES.2020.25.30.2001292. Duration of SARS-CoV-2 RNA detection in COVID-19 patients in home isolation, Rhineland-Palatinate, Germany, 2020 – an interval-censored survival analysis. Wel PCR analyse maar geen virusweek.
- **Clin Infect Dis. 2020 May 22;ciaa638. doi: 10.1093/cid/ciaa638. DOI: 10.1093/cid/ciaa638 Online ahead of print. Predicting infectious SARS-CoV-2 from diagnostic samples.** Ook virusweek
- *BMC Infect Dis* . 2020 Jun 19;20(1):429. doi: 10.1186/s12879-020-05151-y. Positive results for patients with COVID-19 discharged from hospital in Chongqing, China. Geen virusweek.
- **Infect Dis Health . 2020 Aug;25(3):210-215. doi: 10.1016/j.idh.2020.05.002. Epub 2020 May 20. SARS-CoV-2: The viral shedding vs infectivity dilemma.** Review over infectivity
- *Int J Infect Dis* . 2020 Jul;96:288-290. doi: 10.1016/j.ijid.2020.05.030. Epub 2020 May 11. Viral dynamics in asymptomatic patients with COVID-19. **ASYMPTOMATEN**
- *Emerg Microbes Infect.* 2020 Dec;9(1):1254-1258. doi: 10.1080/22221751.2020.1772677. Dynamic surveillance of SARS-CoV-2 shedding and neutralizing antibody in children with COVID-19. Wel over hoe lang PCR positief blijft maar geen virusweek.
- **Euro Surveill . 2020 Aug;25(32):2001483. doi: 10.2807/1560-7917.ES.2020.25.32.2001483. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020.**
- *Crit Care*. 2020 May 24;24(1):245. doi: 10.1186/s13054-020-02952-0. Duration of SARS-CoV-2 viral RNA in asymptomatic carriers. **ASYMPTOMATEN**
- *Emerg Infect Dis.* 2020 Aug;26(8):1834-1838. doi: 10.3201/eid2608.201097. Epub 2020 May 8. Prolonged Persistence of SARS-CoV-2 RNA in Body Fluids. Geen virusweek alleen PCR
- **Eur J Clin Microbiol Infect Dis. 2020 Jun;39(6):1059-1061. doi: 10.1007/s10096-020-03913-9. Epub 2020 Apr 27. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards.** Mogelijk bruikbaar.
- *Clin Microbiol Infect.* . 2020 Jul 9;S1198-743X(20)30410-9. doi: 10.1016/j.cmi.2020.07.008. Online ahead of print. Virus shedding dynamics in asymptomatic and mildly symptomatic patients infected with SARS-CoV-2. Geen virusweek, wel PCR
- *Nat Med*. 2020 Aug;26(8):1200-1204. doi: 10.1038/s41591-020-0965-6. Epub 2020 Jun 18. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Geen virusweek.
- *Emerg Infect Dis.* 2020 Jun 22;26(10). doi: 10.3201/eid2610.201620. Online ahead of print. Clinical Course of Asymptomatic and Mildly Symptomatic Patients with Coronavirus Disease Admitted to Community Treatment Centers, South Korea. Geen virusweek.

- Pathog Dis 2020 Jun 1;78(4):ftaa031. doi: 10.1093/femspd/ftaa031. Positive SARS-CoV-2 RNA recurs repeatedly in a case recovered from COVID-19: dynamic results from 108 days of follow-up. Geen virusweek, mogelijk heel klinisch.

3-9-2020: nav artikel volkskrant die naar andere artikelen refereert:

Shedding of infectious virus in hospitalized patients with coronavirus disease-2019 (COVID-19): duration and key determinants. doi: <https://doi.org/10.1101/2020.06.08.20125310> Medrx (BMJ)

129 patiënten in ErasmusMC met ernstig covid (opgenomen), tijd van virus uitscheiding is 0-20 dagen. Tevens een associatie met het opkomen van antistoffen en het stoppen van virus uitscheiding. 690 respiratoire samples waarvan 623 opgekweekt konden worden.

The median time of infectious virus shedding was 8 days post onset of symptoms (IQR 5 – 11, range 0 – 20) and probit analysis showed a probability of $\leq 5\%$ for isolating infectious SARS-CoV-2 when the duration of symptoms was 15,2 days (95% CI 13,4 – 17,2) or more (Figure 2). The median viral load was significantly higher in culture positive samples than in culture negative samples (8,14 versus 5,88 Log₁₀ RNA copies/mL, $p < 0,0001$) and the probability of isolating infectious SARS-CoV-2 was less than 5% when the viral load was below 6,63 Log₁₀ RNA copies/mL (95% CI 6,24 – 6,91) (Figure 2).

In conclusion, infection prevention and control guidelines should take into account that patients with severe or critical COVID-19 may shed infectious virus for longer periods of time compared to what has been reported for in patients with mild COVID-19. Infectious virus shedding drops to undetectable levels when viral RNA load is low and serum neutralizing antibodies are present, which warrants the use of quantitative viral RNA load assays and serological assays in test-based strategies to discontinue or de-escalate infection prevention and control precautions.

Eerder artikel van Wolff met 9 patiënten. Virological assessment of hospitalized patients with COVID-2019
<https://doi.org/10.1038/s41586-020-2196-z> Nature.

Samples van München, 2 samenwerkende labs die elkaar confirmeren in de diagnostiek. Geen ernstige casus, allen maar mild. Er wordt benoemd dat er virus isolatie plaatsvindt, maar geen duiding aan gegeven.

The prolonged viral shedding in sputum is relevant not only for the control of infections in hospitals, but also for discharge management. In a situation characterized by a limited capacity of hospital beds in infectious disease wards, there is pressure for early discharge after treatment. On the basis of the present findings, early discharge with ensuing home isolation could be chosen for patients who are beyond day 10 of symptoms and have less than 100,000 viral RNA copies per ml of sputum. Both criteria predict that there is little residual risk of infectivity, on the basis of cell culture.

Temporal dynamics in viral shedding and transmissibility of COVID-19. <https://doi.org/10.1038/s41591-020-0869-5> Nature.

Niet bruikbaar.

→ **Artikel dat van 10 dagen uitgaat.**

Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. <https://doi.org/10.2807/1560-7917.ES.2020.25.32.2001483> Eurosurveillance

Engels onderzoek 324 samples van 253 ptn (233 asymptomatisch danwel mild/matig en 20 ernstig (soms fataal)) die positieve PCR hadden hebben ze geprobeerd te kweken. Geen verschil in Ct-waarde tussen de mild/matig en de ernstige groep.

More than half the samples ($n = 130$, 53%) tested (from 91 cases) were received more than 7 days after symptom onset and 21% of those (27 samples from 18 cases) were culture-positive; none of the 91 patients had severe illness or were immunosuppressed. Most of these late culture-positive samples (25/27) were taken between 8 and 10 days after symptom onset. Based on the real-world data described here, we recommend that infection control measures

for persons with mild-to-moderate COVID-19 be particularly focussed immediately after onset of symptoms and retained for 10 days. Asymptomatic and presymptomatic persons are likely to be a source of infectious virus.

Deze samples zijn uit de FF100 studie uit GB, behoudens 1 case met alleen anosmie heeft iedereen klachten.

Clin Infect Dis. 2020 May 22;ciaa638. doi: 10.1093/cid/ciaa638. DOI: 10.1093/cid/ciaa638 Online ahead of print. Predicting infectious SARS-CoV-2 from diagnostic samples.

Samples uit Canada. Van de 90 samples konden er 26 succesvol gekweekt worden. De mediane Ct waarde van de samples die konden worden gekweekt was 17. Van alle samples was de mediane Ct waarde 23. Geen informatie over de symptomen van de patienten, asymp, mild, ernstig. Mogelijk wel enkele immuungecompromiteerden (discussie). Laat zien dat er langer positieve PCR is dan dat mensen mogelijk besmettelijk zijn.

Here we add to the existing body of literature by presenting viral culture results on a larger cross-sectional group of patients, compared to PCR data and time of symptom onset.

Positive cell culture results in our study were most likely between days one and five. This finding is consistent with existing literature. The probability of obtaining a positive viral culture peaked on day 3 and decreased from that point.

Our study showed no positive viral cultures with a Ct greater than 24 or STT greater than 8 days.

Liu WD, Chang SY, Wang JT, Tsai MJ, Hung CC, Hsu CL, Chang SC. Prolonged virus shedding even after seroconversion in a patient with COVID-19. J Infect. 2020 Apr 10;S0163-4453(20)30190-0.

Case-report: Casus van 1 pte in Taiwan waarbij tot 18 dagen na start symptomen de virus gekweekt kon worden. Ook was er al wel een antistof spiegel opgebouwd. Er is nog een positieve PCR geweest tot 63 dagen na ontstaan klachten.

Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards.

Franse studie uit Marseille, gaat over ptn die opgenomen zijn en medicatie (hydroxychloroquine and azithromycin) krijgen. Van de 183 samples konden ze er 129 opkweken. PCR was bij deze ptn tot 20 dagen na start klachten positief, maar na dag 8 konden ze geen virussen meer opkweken. Boven een Ct waarde van 34 kon geen enkele sample meer opgekweekt worden.

Infect Dis Health . 2020 Aug;25(3):210-215. doi: 10.1016/j.idh.2020.05.002. Epub 2020 May 20. SARS-CoV-2: The viral shedding vs infectivity dilemma.

Review artikel waarin wordt gewezen naar literatuur, geen eigen studie.

(10)26, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al. Viral dynamics in mild and severe cases of COVID-19 [Internet] Lancet Infect Dis 2020 Apr 24. [https://doi.org/10.1016/S1473-3099\(20\)30232-2](https://doi.org/10.1016/S1473-3099(20)30232-2)

Komt voort uit bovenstaande review: The viral shedding vs infectivity dilemma, maar heeft geen viruskweken gedaan en het zijn allemaal ernstige casus.

Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility [Internet] N Engl J Med 2020 Apr 24. <https://doi.org/10.1056/NEJMoa2008457> komt voort uit review artikel The viral shedding vs infectivity dilemma.

Verzorgingshuis waar ze mensen hebben getest 10 dagen nadat er 1 positief was. En vervolgens 7 dagen later weer indien mensen de eerst keer negatief waren of positief met atypische of

asymptomatische symptomen. Er is zowel bij presymptomaten als asymptomaten virus gekweekt.

Viable virus was isolated from specimens collected 6 days before to 9 days after the first evidence of typical symptoms.--> deze zin is niet goed te begrijpen in het kader van fig S1 omdat daar bij 13 dagen na klachten een virus kon worden gekweekt. Onduidelijk of bij sommigen de klachten al over waren toen (2^e keer) virus isolaat kon worden gekweekt.

In pubmed zoeken met Mesh termen:

((COVID-19[MeSH Terms]) AND (infectivity[MeSH Terms])) AND (viral cultivations[MeSH Terms])→ 0 hits

((COVID-19[MeSH Terms]) AND (viral cultivations[MeSH Terms])→ 0 hits

(COVID-19[MeSH Major Topic]) AND (virus cultivation[MeSH Terms]) → 0 hits

COVID-19[MeSH Terms] → 0 hits

Er lijken geen Mesh termen te zijn aangemaakt voor covid-19.

In pubmed zoeken:

covid-19 AND viral shedding AND cell culture → 6 hits

SARS-Cov-2 AND viral shedding AND cell culture → 2 hits, niet bruikbaar

coronavirus AND viral shedding AND cell culture→ 31 hits, bij filter op publication date 1 year → 5 hits, allen niet bruikbaar.

Vrije zoektermen in Pubmed:

viral cell culture covid-19→ 96 resultaten, titels screenen. Slechts 1 mogelijk artikel:

Int J Infect Dis. 2020 Jul; 96: 387–389. Published online 2020 May 14. doi: 10.1016/j.ijid.2020.05.035 PMCID: PMC7224665 PMID: 32417248 SARS-CoV-2 infection diagnosed only by cell culture isolation before the local outbreak in an Italian seven-week-old suckling baby.

Gaat over een 7 weken oud kind waarbij door virusweek corona werd ontdekt. Dit is ook met PCR bevestigd. Gaat niet over hoe lang er besmettelijkheid is.