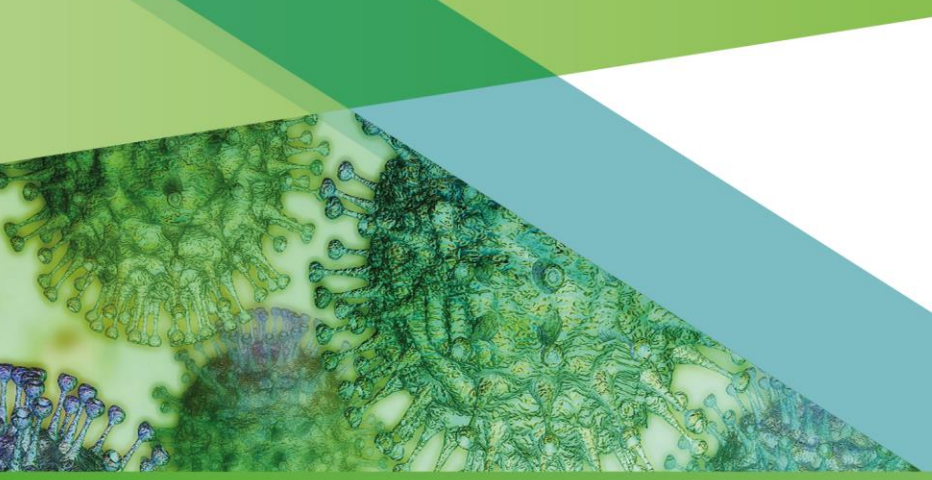


TECHNICAL REPORT

Guidance on ending the isolation period for people with COVID-19, third update

28 January 2022

Scope of this document

This document provides updated guidance for ending the isolation of people with COVID-19, either home-isolated or inpatients.

What is new in this update

This update includes new and emerging evidence on the shedding of SARS-CoV-2 variants including the newly emerged B.1.1.529 (Omicron) variant of concern (VOC), and considers options for modifying isolation periods to address pressures on healthcare systems and/or societal functioning. Evidence on viral shedding by individuals vaccinated with COVID-19 vaccines is also included, with emerging evidence specifically for the Omicron VOC. Rapid antigen detection tests (RADTs) are now included in the testing options for ending isolation with specific advice on self-test RADTs. Guidance on the optimum isolation period for prevention of transmission from asymptomatic and mild or moderate fully-vaccinated cases is provided, as well as options for decreasing the period of isolation for COVID-19 cases when countries face high or extreme pressure on their healthcare system and societies from significant increases of COVID-19 cases. The document also gives consideration to possible reduced isolation requirements in the longer term.

Target audience

Public health authorities in European Union/European Economic Area (EU/EEA) countries.

Background

Since the publication of the first update of ECDC's advice on discharge criteria for and ending of isolation for COVID-19 cases [1], and as of January 2022, all EU/EEA countries are experiencing varying degrees of increased community transmission of SARS-CoV-2. New variants of SARS-CoV-2 emerged during 2020-21 and are monitored by ECDC. Of these, variant B.1.351 (Beta, first detected in South Africa), variant P.1 (Gamma, first detected in Brazil), variant B.1.617.2 (Delta, first detected in India) and variant B.1.1.529 (Omicron, first detected in Botswana and South Africa) are listed as variants of concern (VOCs) for the EU/EEA [2]. As of week 3, 2022 (ending 23 January 2022), the Omicron VOC is the dominant variant in EU/EEA countries [3].

In the context of ongoing community transmission of SARS-CoV-2, increasing testing capacity and the availability of different testing methods, i.e. RADTs, self-test RADTs and RT-PCR, across EU/EEA countries as well as the existing evidence on viral shedding and infectiousness, there is a need to update the guidance for discharge and ending of isolation for people with COVID-19 [1,4].

The current document reflects the information available at the time of publication and may change if more information on the viral shedding and duration of infectiousness of SARS-CoV-2 variants become available.

Suggested citation: European Centre for Disease Prevention and Control. Guidance on ending the isolation period for people with COVID-19, third update, 28 January 2022. Stockholm: ECDC; 2022.

Scientific evidence on SARS-CoV-2 shedding

Viral shedding and transmission with RT-PCR positivity

Some patients with laboratory-confirmed COVID-19 show positive SARS-CoV-2 RT-PCR test results over prolonged periods of time after infection and clinical recovery. In a cohort of about 1 000 mildly symptomatic immunocompetent patients from the first wave of COVID-19 in Brazil, 74% had persistently positive RT-PCR on day 14 after the onset of symptoms. The same study back calculated from their results that roughly 20% of all SARS-CoV-2 positive individuals could have prolonged RT-PCR positivity [5]. Similar results on prolonged RT-PCR positivity were shown from a Korean series of mild or asymptomatic patients [6]. Studies in hospitalised COVID-19 cases found that the RT-PCR test for SARS-CoV-2 in respiratory samples can remain positive up to six weeks from illness onset [7,8], with some evidence that these cases were not linked to secondary transmission [9,10]. In a small series of hospitalised COVID-19 patients from China, older age and continuing chest congestion was associated with persistent RT-PCR positivity, and the median time to negative RT-PCR was 14 days (IQR: 10–18) from the first positive test [11]. In addition, several studies showed that, in some cases, a RT-PCR test could turn positive after a first negative result [12,13]. The presence of viral RNA should, however, not be confused with viral shedding.

The identification of SARS-CoV-2 RNA through RT-PCR (i.e. viral RNA shedding) in a patient does not equate to the presence of infectious SARS-CoV-2 (viral shedding), with the exception of immunocompromised patients, for whom this is still unclear. Prolonged detectability of SARS-CoV-2 RNA has been shown even after seroconversion [10,14]. In patients with a positive SARS-CoV-2 RT-PCR test result over a prolonged period, virus culture or sub-genomic RNA detection can be used to confirm the presence of viable SARS-CoV-2. If viable SARS-CoV-2 is detected, the patient may need to remain in isolation at a designated facility or at home, depending on their work or social mixing patterns and the possibility of mitigating risks of transmission through other measures, such as the use of face masks and physical distancing.

Viral load and infectiousness

The exact duration of when COVID-19 patients are infectious is unknown and is likely to vary between variants as well as between patients. It is dependent on many factors, but in particular, the individual's immune status, disease severity and the viral load to which they have been exposed, as well as the type of contact (e.g. household vs. non-household contact).

Viral load and/or culture of SARS-CoV-2 have been used as proxies to estimate the infectious period. In non-severe cases, SARS-CoV-2 virus was successfully isolated from respiratory samples up to 10 days after the onset of symptoms [15-21]. A systematic review identified 15 key studies and found that individuals with mild or moderate disease were unlikely to be infectious beyond 10 days of symptoms. A systematic review and meta-analysis comparing viral characteristics of other coronaviruses (SARS-CoV-2, SARS-CoV and MERS-CoV) in 2020 reported that none of the studies included in the analysis were able to detect live virus beyond day nine of symptoms, despite persistent RNA shedding [22,23]. Longer viral shedding has been rarely reported in mildly symptomatic patients; in a cohort of about 1 000 immunocompetent patients, 74% had persistently positive RT-PCR on day 14 after the onset of symptoms, while SARS-CoV-2 virus was cultured from 27% of those specimens collected after day 14 from symptom onset [5].

Among hospitalised and/or severe COVID-19 patients, isolation of SARS-CoV-2 virus was possible until day 20 after onset of symptoms, with a median of eight days (interquartile range (IQR) 5-11 days) [20,24]. The probability of detecting infectious SARS-CoV-2 virus decreased to below 5% after 15.2 days post-symptom onset (95% confidence interval 13.4-17.2). In patients with critical or severe disease, virus was isolated up to day 32 in one study, and up to 20 days in immunocompromised patients [25]. Neutralising antibody levels were inversely associated with shedding infectious virus, while the risk of having a positive SARS-CoV-2 culture was three times higher in immunocompromised patients, which suggests that these patients may shed SARS-CoV-2 for prolonged periods [24]. A recently published study on mildly symptomatic immunocompromised individuals was able to isolate virus from nasopharyngeal swabs 14 days or longer after symptom onset [5]. A study from Berlin analysed viral load data from 25 381 cases (mild and severe) tested from February 2020 to March 2021 in Germany and estimated a rate of viral load decline of 0.17 $\log_{10}$ units per day. The mean virus culture isolation probability declined to 50% at five days and 30% at 10 days after peak viral load [21].

A positive viral culture has been correlated with viral loads quantified by RT-PCR and the cycle threshold (Ct) value is used as a proxy of the viral load. The likelihood of a positive viral culture decreases with increasing Ct values [17]. In one study, it was not possible to culture SARS-CoV-2 from samples with a viral load below 1×10^6 copies per mL (approximately Ct 28-30 but will depend on RT-PCR sensitivity) [15]. In other studies, culturing SARS-CoV-2 was not possible when Ct values were > 24 or >34 [16,17]. RADT results also correlate with Ct values. In a study comparing RT-PCR with RADT, the sensitivity of the RADT was 100.0%, 94.4% and 81.1% for Ct ≤ 20 (n=18), Ct ≤ 25 (n=36) and Ct ≤ 30 (n=53), respectively. In all samples with Ct values ≥ 30 (n=23), the RADT was negative [26]. Older age and a more severe infection have been associated with a higher viral load [27,28]. However, it was also recently demonstrated that children have viral loads similar to those of adults [29], and asymptomatic patients have viral loads similar to those of symptomatic patients [30]. Nevertheless, most studies have found faster viral clearance among asymptomatic than among symptomatic individuals [22].

While Ct values can provide a correlate of the infectiousness of the patient, they need to be interpreted with caution due to the variability in the sample collection process and the laboratory methods used that prohibit reliable comparison of results. To ensure comparability, methods need to be standardised for RNA quantification, ideally also performing parallel virus isolation in the laboratory.

Viral load of different SARS-CoV-2 variants

Higher peak viral loads have been reported for individuals infected with the Delta and Alpha VOCs than for individuals infected with the ancestral SARS-CoV-2 [21,31]. A case series from Singapore showed that patients infected with the ancestral virus needed a median of 13 days to reach Ct ≥ 30 from symptom onset, while patients infected with the Delta VOC needed a median of 18 days [32]. On the contrary, a prospective, longitudinal cohort study from the UK did not find any difference in peak viral load among patients infected with different VOCs and estimated that typically a 10-day period was required from peak viral load to undetectable virus. A recent preprint compared the viral dynamics and duration of SARS-CoV-2 infection with the Omicron VOC to the Delta VOC and found that infections with the Omicron VOC exhibited lower peak viral loads and a shorter viral clearance (5.35 days, 95% CI 4.78-6.00) than infections with the Delta VOC (6.23 days, 95% CI 5.43-7.17). However, this study has several limitations, including a homogenous young study population and no indication on the proportion of vaccinated and/or previously infected individuals [33]. It is still unclear how the duration of infectiousness differs between VOCs and it is difficult to disentangle whether differences are attributable to immunity in a largely vaccinated or/and infected population, or due to intrinsic characteristics of the different VOCs.

Transmission by asymptomatic and pre-symptomatic individuals and transmission after onset of symptoms

The incubation period is generally defined as the period between exposure and the first appearance of symptoms. For infection with the ancestral virus, the incubation period was estimated, in 2020, to range from one to 14 days [34-36] based on a meta-analysis, with an estimated mean of 5.68 days (99% CI 4.78-6.59) [37]. However, emerging SARS-CoV-2 VOCs have shown varying incubation periods [38]. A limited number of outbreaks caused by the Omicron VOC indicate a shorter incubation period than for the Delta VOC, with a reported median incubation period of three days [IQR 3-4 days] [39-41].

For the transmission dynamics of SARS-CoV-2, the rate of transmission during the incubation period, i.e. before the appearance of symptoms, is of great importance. Asymptomatic infection at the time of laboratory confirmation has been reported from many settings [42]. Many studies do not distinguish between the pre-symptomatic stage and truly asymptomatic infections, as a large proportion of these cases experience some symptoms of COVID-19 at a later stage of infection. However, the overall proportion of asymptomatic cases has been estimated to be 30–40% of all COVID-19 infections [43-45].

SARS-CoV-2 RNA as well as infectious SARS-CoV-2 have been detected in asymptomatic patients [46-48]. In a study from South Korea, the viral load and the probability of detecting viable SARS-CoV-2 were similar in symptomatic and asymptomatic persons, indicating that asymptomatic persons represent a source of transmissible SARS-CoV-2 [30]. In summary, and as stated in a recent meta-analysis, the high percentage of asymptomatic infections highlights the potential transmission risk from asymptomatic infections in communities [49]. Moreover, the high viral load close to the onset of symptoms in symptomatic patients suggests that SARS-CoV-2 can easily be transmitted at an early stage of infection [27,46,50-52]. Several studies showed that secondary transmissions from an index case could occur as early as three days before the onset of symptoms of the index case and indicated that the pre-symptomatic phase of SARS-CoV-2 is highly infectious [52-55]. One study described that viable SARS-CoV-2 was isolated from specimens collected from six days before, to up to nine days after, the first evidence of typical symptoms of COVID-19 [56]. The proportion of transmission that occurred from the index case in the pre-symptomatic phase of infection was estimated to be as high as 37% (95% CI 16–52%) in one study [57] and 44% in another study [55].

In an analysis of 72 infector-infected pairs in South Korea, the estimated median duration of transmission following the onset of symptoms was 1.31 days (standard deviation 2.64 days), with a peak at 0.72 days before

the onset of symptoms [57]. A population-based cohort study from the first wave in China investigated the transmission potential of 730 index cases to close contacts. The risk of infection was highest between two days before and three days after the onset of symptoms of the index case, peaking at day zero (adjusted relative risk [ARR], 1.3; 95% CI, 1.2-1.5). The risk of infection was not statistically higher among contacts exposed between days three and five (ARR, 2.0; 95% CI, 0.8-4.7) or days six and 10 (ARR, 1.8; 95% CI, 0.7-4.7) after symptom onset of the index case. Additionally, an increased risk of transmission was associated with the severity of disease of the index case [58]. Data from other contact tracing studies have shown that exposure of secondary cases had usually occurred up to five days after onset of symptoms of the index case [59,60]. Household contacts are at higher risk for transmission compared to non-household contacts [61].

The emergence of the Omicron VOC in late 2021, with a growth rate leading to its dominance very quickly in many EU/EEA countries, revived the discussion on transmission dynamics. Indeed, the Omicron VOC seems to cause a much higher rate of asymptomatic infections than other VOCs [62]. This variant emerged in the context of high COVID-19 vaccine uptake, and due to its immune escaping profile, results in a higher incidence of breakthrough infections and reinfections. This could be a contributing factor to the extremely rapid spread of the Omicron VOC as observed globally.

In conclusion, understanding the kinetics of infectious SARS-CoV-2 virus shedding in relation to its potential for transmission is crucial to guide infection prevention and control strategies and decisions on ending isolation of people with COVID-19. Transmission depends not only on the viral load or levels of culturable virus of the index case, but other factors as well, such as contact rates and type of contact, non-pharmaceutical measures in place, vaccination status and others. The relationship between SARS-CoV-2 viral load and infectiousness is poorly understood and the infectious dose of SARS-CoV-2 has not yet been determined. It is generally accepted, that high viral load is associated with transmission, although this relation has not been accurately quantified, yet. Viral loads are highly individual-dependent and in addition, the viral load at the exact time of the contact remains unknown and may greatly differ from that measured several days later, at the time of diagnosis. Detection of infectious virus by demonstration of in vitro infectiousness on cell lines is regarded as a more informative surrogate of viral transmission than detection of viral RNA [61].

Contact tracing and household studies show that the transmission probability of SARS-CoV-2 usually peaks around symptom onset with large individual variations [61,63].The probability of transmission in the days after symptom onset decreases gradually from day three until day 10, but until day 12 probably still remains above a nominal 5% [61,63]. Data to estimate the population impact of transmission after day five from the onset of symptoms are missing.

Viral shedding in vaccinated individuals

There is evidence of viral shedding in vaccinated individuals who were infected with the Delta VOC, and similar Ct values have been reported in vaccinated and unvaccinated individuals in several studies [64-66]. However, viral loads decrease faster in vaccinated than in unvaccinated individuals [64,65]. This may contribute to a relatively less efficient transmission from vaccinated individuals [67], although time since vaccination remains a crucial factor to take into account [65]. Many studies, mostly case-control studies, were unable to account for viral dynamics in the early stages of infection and testing was triggered by the onset of symptoms. In a prospective longitudinal study using almost 20 000 viral samples from 173 study participants collected between December 2020 and August 2021, breakthrough infections showed a more rapid clearance in vaccinated (5.5 days, 95%CI=4.6-6.5) than in unvaccinated individuals (7.5 days, 95%CI=6.8-8.2) [68].

As regards breakthrough infections from different SARS-CoV-2 VOCs, a study from the UK observed a faster decline in viral loads in unvaccinated individuals infected with the Alpha and Delta VOCs than in unvaccinated individuals infected with the pre-Alpha group of SARS-CoV-2 [65]. Clearance times could be different with the Omicron VOC, although the evidence is still scarce. Preliminary emerging evidence does not suggest higher viral loads in vaccinated individuals infected with the Omicron VOC compared with vaccinated individuals infected with the Delta VOC [69]. Preliminary data from a very small study from the US suggest that vaccinated individuals infected with the Omicron VOC can shed SARS-CoV-2 with similar intensity as vaccinated individuals infected with other VOCs [70]. Very recent data from Japan on Omicron VOC viral shedding using 83 specimens taken from 19 vaccinated and two unvaccinated individuals showed that viral RNA load was the highest at three to six days from symptom onset, and gradually decreased over time, with no infectious virus detected in respiratory samples 10 days after symptom onset [71].

Limited real-world data are available about transmission of the Omicron VOC from infected vaccinated individuals. Recent data from 11 937 households in Denmark reported increased transmission (secondary attack rates) in households of unvaccinated individuals and reduced transmission in households of individuals who had received a booster dose of vaccine compared to households of individuals who completed the primary vaccination series without getting a booster. When comparing individuals infected with the Omicron VOC to those infected with the Delta VOC, secondary attack rates for the Omicron VOC were 2.61 (95%-CI: 2.34-2.90) times higher in fully vaccinated and 3.66 (95%-CI: 2.65-5.05) times higher in booster-vaccinated individuals than for the Delta VOC [72]. Similar findings were observed in the UK [73]. The dynamics of viral shedding in vaccinated individuals infected with the Omicron VOC can be used as a proxy for potential of transmission but should be interpreted with caution while waiting for more direct evidence from household transmission studies.

In summary, although limited evidence exists that duration of viral shedding may be shorter and clearance more rapid in vaccinated patients infected with recently emerged VOCs (Delta and Omicron), the exact duration of infectiousness is still unclear, and studies tend to agree that there is limited infectious virus shedding after day 10 from the onset of symptoms in mild or moderate COVID-19 cases.

Reinfection

There are only limited data available on the duration of protection and risk of reinfection after SARS-CoV-2 infection, which ideally are drawn from longitudinal cohort studies comparing infection risk amongst naive and recovered individuals at three- or six- month intervals. Several studies reported a low risk of reinfection; however, it is likely that reinfections are substantially under-ascertained. A recent systematic review identified 10 key studies and reported an average risk reduction against reinfection of 90% up to 10 months post initial infection [74]. Most recently, an analysis on reinfections from 2 July 2020 to 2 December 2021 in the UK showed a low rate of reinfection. A higher risk of reinfection was observed in the later period when the Delta VOC was dominant (17 May 2021 onwards). Reinfections in the Delta VOC-dominated period were characterised by higher viral loads and reinfected cases were more likely symptomatic than in the Alpha VOC-dominated period. However, it is unclear if this effect was due to the characteristics of the Delta VOC or the waning of immunity over time. The median time between primary infection and reinfection was about eight months and reinfections were more likely in unvaccinated than in vaccinated individuals [75].

The emergence of new divergent VOCs might significantly affect the duration of protection conferred by vaccination or previous SARS-CoV-2 infection. Several countries reported an increase in reinfection rates associated with the emergence of the Omicron variant [73,76]. The UK Health Security Agency (UKHSA) estimated the relative risk for reinfection with the Omicron variant at 3.3 (95%CI: 2.8 to 3.8) compared to other variants [77]. In a more recent report, the UKHSA identified that 9.5% of individuals infected with the Omicron variant had previously been infected with another SARS-CoV-2 variant [73]. A study from UK-Scotland found that the rate of possible reinfection with Omicron VOC (7.6%) was higher than with the Delta VOC (0.7%) in individuals who had previously tested positive more than 90 days before) [78]. A recent observational, test-negative, case-control study from Qatar exploring protection against reinfection for the different VOCs showed almost 90% protection if prior infection was with the Alpha and Delta VOCs, but protection dropped to about 60% for the Omicron VOC. Nevertheless, prior infection showed robust protection against hospitalisation and death, in the relatively young population of Qatar [79].

Ending of isolation criteria

Decisions on ending isolation need to balance, on the one hand, the risks that an individual who ceases their isolation following a confirmed episode of infection could still transmit the infection to others and the impact of such a transmission, and on the other hand, the impact of isolation on the individual, essential services and society more broadly. This balance should take into account both the likelihood that a recovering case continues to shed infectious virus and what additional measures can be taken to reduce transmission (such as wearing a suitable face mask) and the vulnerability of those the recovering case will mix with (e.g. vulnerable populations in long term care facilities). When deciding on the guidance for criteria on ending home isolation of COVID-19 cases and discharge of COVID-19 patients from hospitals and other healthcare facilities, health authorities should consider factors such as the existing capacity of the healthcare system, laboratory diagnostic resources and the current epidemiological situation. In addition, factors that may need to be considered by public health authorities when deciding on their guidance for ending isolation of people with COVID-19 include the need to balance the risk of further transmission with the need to ensure continued provision of essential services.

This section of the document, and the guidance set out in Table 1, sets out criteria that provide the greatest level of assurance regarding the mitigation of the risks of transmission from patients recovering from SARS-CoV-2 infection, based on current virological and epidemiological evidence. It considers the fact that there remains a substantial proportion of people within the EU/EEA that are still susceptible to infection, with the possibility of severe disease, although with significant variations between countries (largely according to vaccine coverage levels). They should be considered when resources are adequate at all levels.

However, in recognition of the fact that testing and societal capacities can be severely stretched, particularly at times of high incidence, such as during the current epidemic surge associated with the Omicron VOC, the following section and Table 2 set out options for reducing either the duration or testing criteria to alleviate testing or societal pressures. In view of the evidence on continued, albeit lower levels of transmission up to 10 days post-symptoms onset, reductions in isolation period, especially if not based on repeated negative testing, should be accompanied by reinforced messaging on mask use and other relevant distancing measures. In addition, given the very high attack rate of Omicron infections in the population, and taking into account the fact that 70% of the EU/EEA population has completed its primary vaccination course, it is expected that at the end of the ongoing Omicron wave the vast majority of the EU/EEA population will have built a degree of cellular immunity against SARS-CoV-2, and as such, risks of transmission are likely to be lower and the need for longer isolation periods lessened [80].

COVID-19 patients may end home isolation or may be discharged, if hospitalised, after considering:

- clinical resolution or improvement of symptoms;
- time elapsed since onset of symptoms;
- severity of disease;
- immune status;
- occupational status and/or susceptibility of those with whom they have regular contact,
- social mixing factors;
- evidence of negative RADT or RT-PCR test(s) from the upper respiratory tract (Table 1, Figure 1).

Self-test RADTs could be used as adequate proof of positivity, particularly if countries are facing large increases of incidence of new cases and pressure on their testing capacity. Testing to decide on ending isolation should ideally start after improvement of symptoms and from day three after the symptom onset. Cases can end isolation after two consecutive RADT or RT-PCR negative tests (ideally with 24hr interval). In asymptomatic individuals, testing to end isolation can start on day three after the day the first sample was taken. The validity of self-test RADTs make them less suitable than RT-PCR and non-self-test RADTs for deciding to end isolation, but can be considered if testing capacity is exhausted.

Regarding COVID-19 cases more likely to be self-isolating at home (asymptomatic, mild or moderate cases), the following represent optimum criteria for preventing transmission from recovering cases according to the evidence outlined above for fully and not fully vaccinated individuals, to be considered when public health authorities have sufficient testing capacity and when a substantial proportion of the population remains susceptible to the possibility of severe disease:

- For asymptomatic, mild or moderate COVID-19 cases in not fully vaccinated individuals, self-isolation should be followed until two negative RADT or RT-PCR tests taken at least 24 hours apart, depending on the availability and testing capacity, or until completing 10 days from the date the sample was taken or the date of the onset of symptoms. Isolation should continue if the RADT (even if a self-test RADT) remains positive.
- For asymptomatic, mild or moderate COVID-19 cases in fully-vaccinated individuals, consideration can be given to decreasing the isolation period to six days after the onset of symptoms, if symptoms have resolved and with a negative RADT or RT-PCR SARS-CoV-2 test on day six, as outlined in Table 1. Isolation should continue if the RADT or RT-PCR test is positive on day six. RADT can be repeated daily until negative or until 10 days of isolation are completed. Currently, fully-vaccinated individuals include people who have received a full primary COVID-19 vaccination course within the last six months, not including one-dose vaccines, or have received a booster dose of COVID-19 vaccine. In countries/regions where the Omicron VOC is dominant, the period determining full vaccination (after either a two-dose primary series or booster vaccination) may be reduced to three months [81]. The duration of protection from vaccination is subject to evolving evidence and may impact the duration of this period (see Table 2) [82].

For hospitalised severe COVID-19 cases available evidence indicates that infectious SARS-CoV-2 virus shedding, irrespective of the VOC, may persist up to up to 20 days.

- Any patient needing discharge from a health facility before fulfilling clinical criteria for being unlikely to be infectious and/or without negative SARS-CoV-2 RT-PCR or RADT test results, should be instructed to continue self-isolating at home or at a safe place to complete the necessary duration of isolation (10 days for mild-to-moderate cases, unless two negative RADT or RT-PCR results are obtained before the 10 days elapse; 20 days for severe cases, unless two negative RADT or RT-PCR results are obtained before the 20 days elapse) based on an individual case risk assessment. The assessment should consider the presence of immunosuppression and whether the patient will be in contact with people who are vulnerable to severe COVID-19 and whether they live or work in settings in which there is a risk of large outbreaks (e.g., long-term care facilities (LTCFs), prisons or migrant/refugee hosting facilities). In addition, they should be advised to wear a well-fitting medical or high-efficiency (FFP2) mask for the remainder of that period, respect physical distancing measures (especially with vulnerable people) and use proper hand hygiene and respiratory etiquette. The patients should seek medical advice if they develop symptoms again.

- Two consecutive negative RADT or RT-PCR SARS-CoV-2 test results, ideally with a minimum of a 24-hour interval, are recommended as an option for the discontinuation of isolation of any hospitalised patient, including immunocompromised cases. The second test is confirmatory, to exclude the possibility of a false negative result. Similarly, two consecutive negative RADT or RT-PCR SARS-CoV-2 test results, ideally with a minimum of a 24-hour interval, can be considered for the discontinuation of isolation of severely ill patients, especially if they will be transferred to other units within the hospital or discharged to a LTCF. All patients who are instructed to complete isolation at home or another safe place should follow infection prevention and control guidance with personal hygiene precautions to protect household contacts [83]. Isolation should continue if the RADT or RT-PCR test results remains positive (even if a self-test RADT). In cases with prolonged RT-PCR positivity (RNA shedding), high Ct values (≥30) can be used as a proxy of low likelihood of transmissibility, while low Ct values (<24) indicate a higher likelihood of transmissibility, with the caveat that these are not standardised thresholds and differ across laboratories. In these cases, the decision to discontinue isolation should also include an assessment of the clinical and immune status of the case, as well as the time from the onset of symptoms and/or more specialised genotyping (see above in RT-PCR positivity section).

There is insufficient evidence on viral shedding in individuals with reinfection to enable robust separate recommendations on criteria for ending isolation to be provided for this group.

Adapting the period of isolation and testing requirements

Criteria for ending of isolation and discharge of COVID-19 patients may be adapted by public health authorities with consideration of the residual risk of transmission, the local epidemiological situation, the testing and contact tracing capacity and the socio-economic effects of the pandemic in the specific setting.

EU/EEA countries facing increasing pressure on their healthcare system or other sectors from significant increases of COVID-19 incidence can consider decreasing the isolation period, with or without requiring a negative test to end isolation. When recommending a shorter duration of isolation, especially without testing, particularly regarding healthcare workers or LTCF staff who come in contact with vulnerable populations, the residual risk of onward transmission of SARS-CoV-2 leading to severe disease increases. However, these difficult policy decisions should be balanced against maintaining the essential functions of society, and the use other mitigating measures, such as the appropriate use of face masks.

A UK model using testing with RADTs from day six after the onset of symptoms and requiring two negative tests with a minimum of 24hrs apart estimates that 79% of individuals can end isolation correctly being non-infectious on day seven, while about 6% will need to remain in isolation until day 10 [84]. Another model aiming to address the significant staff shortages in many sectors caused by the spread of the Omicron VOC evaluated 'test-to-release' strategies. It found that requiring two consecutive negative tests with a minimum 24hrs apart significantly reduces the number of infectious days in the community, but it requires the availability of a large number of tests. Interestingly, their finding was independent of the minimum period advised to wait until the first testing attempt to end isolation after the onset of symptoms, i.e. individuals could start testing immediately when improved, even without waiting for three days [85]. Finally, a model examining how testing and vaccine boosters can be used to reduce transmission in various group settings shows that an isolation period of five or six days is adequate if the infectious period is less than six days, and testing to end isolation is not needed when the isolation period is similar with the infectious period. When the isolation period is shorter than the infectious period, then testing becomes important [86,87].

A series of non-evidence-based options for decreasing the period of isolation in fully vaccinated and not fully vaccinated individuals with or without testing in high and extreme pressure situations on healthcare systems and society are provided in Table 2. These can be used to address essential worker shortages but can be expanded to the general population if resources are under strain.

In addition, given the very high attack rate of Omicron infections in the population, and taking into account the fact that 70% of the EU/EEA population has completed its primary vaccination course, it is expected that at the end of the ongoing Omicron wave the vast majority of the EU/EEA population will have built a degree of cellular immunity against SARS-CoV-2, and as such, risks of transmission are likely to be lower and the need for longer isolation periods lessened [80].

Contributing ECDC experts (in alphabetical order)

Agoritsa Baka, Orlando Cenciarelli, Annette Kraus, Favelle Lamb, Katrin Leitmeyer, Angeliki Melidou, Diamantis Plachouras, Natalie Sippl, Carl Suetens, Maria Tseroni.

Table 1. Guidance on ending isolation of people with COVID-19

Description	Guidance
Mild/moderate COVID-19 in a not fully vaccinated individual Probable or confirmed COVID-19 case that is neither immunocompromised nor a resident or staff in a closed vulnerable population setting	The patient can end isolation when the following criteria are fulfilled: • Resolution of fever, if present, for at least 24 hours and clinical improvement of symptoms other than fever[1] **AND** – two consecutive negative SARS-CoV-2 RADT or RT-PCR tests from respiratory specimens with a minimum 24-hour interval.[2, 3] **OR** – 10 days after the onset of symptoms. Mild or moderate cases should be instructed to wear a well-fitting face mask after ending their isolation until day 10 after symptom onset and respect physical distancing and personal hygiene rules.
Mild/moderate COVID-19 in a fully vaccinated individual[4] Confirmed COVID-19 case that is neither immunocompromised nor a resident or staff in a closed vulnerable population setting	The patient can be end isolation when the following criteria are fulfilled: • Resolution of fever, if present, for at least 24 hours and clinical improvement of symptoms other than fever[1] **AND** – two consecutive negative SARS-CoV-2 RADT or RT-PCR tests from respiratory specimens with a minimum 24-hour interval [2, 3] **OR** – six days after the onset of symptoms **AND** one negative RADT or RT-PCR test from respiratory specimen on day 6 or later.[5] Mild or moderate fully vaccinated cases should be advised to wear a well-fitting face mask after ending their isolation until day 10 after onset of symptoms and respect physical distancing and personal hygiene rules.
Severe COVID-19 Probable or confirmed COVID-19 case that is neither immunocompromised nor a resident in a closed vulnerable population setting	The patient can be released from isolation when the following criteria are fulfilled: • Resolution of fever for at least 24 hours and clinical improvement of symptoms other than fever[1] **AND** – two consecutive negative SARS-CoV-2 RADT or RT-PCR tests from respiratory specimens with a minimum 24-hour interval [2, 3] **OR** – minimum 14 and up to 20 days after the onset of symptoms Hospitalised patients who are discharged early based on clinical criteria per evaluation of the treating physician should be instructed to self-isolate at home or in a safe place wear a well-fitting face mask until the above criteria are fulfilled and respect physical distancing and personal hygiene rules.
Immunocompromised patient (e.g., transplant recipient, patient receiving immune-modulating treatment or cancer chemotherapy, patient with HIV and a low CD4 count, patient with an immune deficiency)	The patient can be released from isolation when the following criteria are fulfilled: • Resolution of fever, if present, for at least 24 hours and clinical improvement of symptoms other than fever[1] **AND** – Two consecutive negative SARS-CoV-2 RADT or RT-PCR tests from respiratory specimens with a minimum 24-hour interval [2, 3, 6] **OR** – 20 days after the onset of symptoms

[1] COVID-19 patients can exhibit several symptoms including cough, sore throat, headache, vomiting/diarrhoea and others. Clinical improvement of symptoms other than fever does not refer to complete recovery but an overall improving course. In addition, no evidence until now points to the clinical significance of 72 hours with no fever.

[2] This option can be used when testing capacity is sufficient. First test to end isolation is advised, at the earliest, on day three after the onset of symptoms or the day the sample was taken in asymptomatic cases.

[3] RADTs should preferably be performed by a qualified professional. Self-test RADTs are not considered adequate for ending isolation

[4] Currently, fully vaccinated individuals include people who have received a full primary COVID-19 vaccination course within the last six months, not including one-dose vaccines, or have received a booster dose of COVID-19 vaccine. In countries/regions where the Omicron VOC is dominant, this period may be restricted to three months for the primary COVID-19 vaccination and/or the booster dose.

[5] Isolation should continue if the RADT or RT-PCR test is positive on day six, even if a self-test RADT. If RT-PCR is performed, then high Ct values (≥30) can be used, with caution, as a proxy of low likelihood of transmissibility. RADT can be repeated daily until negative or until 10 days of isolation are completed.

[6] In immunocompromised patients with prolonged positive RADT or RT-PCR, potentially with low Ct values, virus culture or sub-genomic RNA detection can be used to confirm viable SARS-CoV-2 to make decisions on ending isolation.

Description	Guidance
Not fully vaccinated resident or staff of closed vulnerable population settings (e.g., long-term care facility, prison, migrant/refugee hosting facility), **including asymptomatic cases**	The patient can end isolation and return to or resume work in the closed vulnerable population setting when the following criteria are fulfilled: • Resolution of fever, if present, for at least 24 hours and clinical improvement of symptoms other than fever[1] **AND** – two consecutive negative SARS-CoV-2 RT-PCR tests in a 24-hour interval from respiratory specimens [2, 3] **OR** – 20 days after the onset of symptoms Residents of closed vulnerable population settings who are discharged earlier based on clinical criteria per evaluation of the treating physician should be isolated at the facility in a single room until the above criteria are fulfilled.
Fully vaccinated[4] resident or staff of closed vulnerable population settings (e.g., long-term care facility, prison, migrant/refugee hosting facility), **including asymptomatic cases**	Fully vaccinated[4] residents or staff members of closed vulnerable population settings can end isolation when the following criteria are fulfilled: • Resolution of fever, if present, for at least 24 hours and clinical improvement of symptoms other than fever[1] **AND** – two consecutive negative SARS-CoV-2 RT-PCR tests in a 24-hour interval from respiratory specimens [2, 3] **OR** – 10 days after the onset of symptoms **AND** one negative RADT or RT-PCR test from respiratory specimen on day 10[5] Residents of closed vulnerable population settings should be advised to wear a well-fitting face mask after ending their isolation until day 10 after onset of symptoms and respect physical distancing and personal hygiene rules.
Asymptomatic COVID-19 case in not fully vaccinated individuals Person without symptoms who tested positive for SARS-CoV-2 but did not develop symptoms and that is neither immunocompromised nor a resident or staff in a closed vulnerable population setting	Asymptomatic individuals can end isolation when the following criteria are fulfilled: – two consecutive negative SARS-CoV-2 RADT or RT-PCR tests from respiratory specimens with a minimum 24-hour interval [2, 3] **OR** – 10 days after the sample for the positive test was taken. People should be advised to wear a well-fitting face mask after ending their isolation until day 10 after the sample was taken and respect physical distancing and personal hygiene rules.
Asymptomatic COVID-19 case in fully vaccinated individuals[4] Person without symptoms who tested positive for SARS-CoV-2 but did not develop symptoms and is fully vaccinated and that is neither immunocompromised nor a resident or staff in a closed vulnerable population setting	Asymptomatic individuals, who are fully vaccinated[4], can end isolation when the following criteria are fulfilled: – two consecutive negative SARS-CoV-2 RADT or RT-PCR tests from respiratory specimens with a minimum 24-hour interval [2, 3] **OR** – six days after the sample for the positive test was taken **AND** one negative RADT or RT-PCR test from respiratory specimen on day six[5] People should be advised to wear a well-fitting face mask after ending their isolation until day 10 after the sample was taken and respect physical distancing and personal hygiene rules.

Table 2 aims to provide options for isolation of essential workers (e.g. individuals working in healthcare, transportation, law enforcement, critical infrastructures), particularly in the context of the current epidemiological situation, and does not address the isolation of hospitalised patients.

Table 2. Guidance on isolation of COVID-19 cases and non-evidence based options for adaptation for essential workers

Type of COVID-19 case	Standard isolation guidance	Options for adaptation	
		High pressure on healthcare systems and society	Extreme pressure on healthcare systems and society
Not vaccinated or not fully vaccinated, mild or moderate COVID-19 case	**Option 1** Resolution of fever for 24 hours and clinical improvement of symptoms[a] **AND** Two consecutive negative RADT or RT-PCR tests[b,c] from respiratory specimens, with a minimum interval of 24 hours **Option 2** Resolution of fever for 24 hours and clinical improvement of symptoms[a] **AND** 10 days isolation after the onset of symptoms	Resolution of fever for 24 hours and clinical improvement of symptoms[a] **AND** five days isolation[e] after the onset of symptoms and five additional days wearing a high efficiency (FFP2) mask[f] **AND** A negative RADT or RT-PCR test[b] from respiratory specimen on day five after onset of symptoms	Resolution of fever for 24 hours and clinical improvement of symptoms[a] **AND** five days isolation[e] after the onset of symptoms and five additional days wearing a high efficiency (FFP2) mask[f] **AND** If possible, test by RADT or RT-PCR[b] on day five after onset of symptoms[g]
Fully vaccinated[d], mild or moderate COVID-19 case	**Option 1** Resolution of fever for 24 hours and clinical improvement of symptoms[a] **AND** Two consecutive negative RADT or RT-PCR tests[b,c] from respiratory specimens, with a minimum interval of 24 hours **Option 2** Resolution of fever for 24 hours and clinical improvement of symptoms[a] **AND** six days after the onset of symptoms **AND** a negative RADT or RT-PCR test[b] from respiratory specimen on day six[g]	Resolution of fever for 24 hours and clinical improvement of symptoms[a] **AND** three days isolation[e] after onset of symptoms **AND** three additional days wearing a high-efficiency (FFP2)[f] mask **AND** A negative RADT or RT-PCR test[b] from respiratory specimen on day three after onset of symptoms	Resolution of fever for 24 hours and clinical improvement of symptoms[a] **AND** three days isolation[e] after onset of symptoms **AND** three additional days wearing a high efficiency (FFP2)[f] mask **AND** If possible, test by RADT or RT-PCR[b] on day three after onset of symptoms

[a] Asymptomatic COVID-19 cases should follow the same guidance as symptomatic cases. Days should be counted from the date of the sample collection for their diagnostic test.

[b] Testing by either RADT or RT-PCR should preferably be performed by a qualified professional. Self-testing by RADTs is not considered adequate for ending isolation.

[c] First test for ending isolation is, at the earliest, on day three after the onset of symptoms.

[d] In this table, the term 'fully vaccinated' refers to people who:

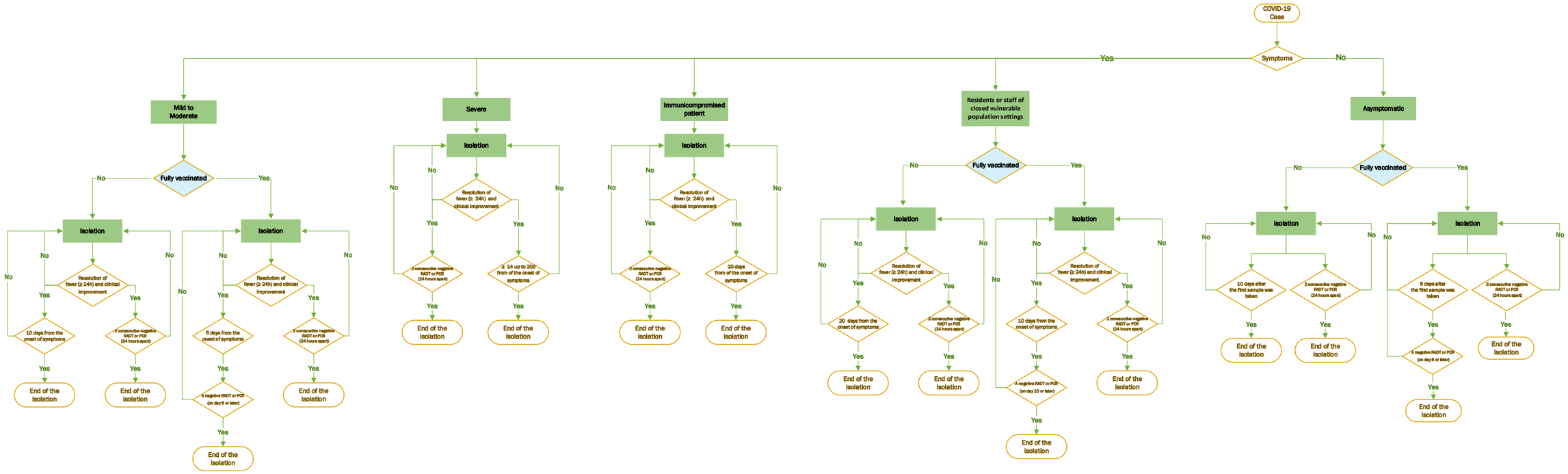
- *have received a full primary COVID-19 vaccination course within the last six months.*
  - *The duration of protection is subject to evolving evidence and this may need to be considered.*
  - *In areas/countries where the Omicron VOC is dominant, this period may be restricted further to three months.*
  - *This does not apply to one-dose vaccines.*
- *have received a booster dose of COVID-19 vaccine.*
  - *In areas/countries where the Omicron VOC is dominant, this period may be restricted further to three months.*

[e] When recommending a shorter duration of isolation, the residual risk of onward transmission of SARS-CoV-2 increases. Therefore, in addition to wearing a mask, COVID-19 cases should be advised to avoid non-essential contact with other people and especially vulnerable individuals. The end of isolation should be differentiated from the potential need for sick leave.

[f] Where a high-efficiency mask is recommended, an FFP2 (or equivalent) without a valve should be used. To be effective, these need to be fitted properly at all times and seal testing should be performed each time the mask is put on. Fit testing is recommended, especially for those working in the healthcare sector, where re-using FFP2 masks should be avoided due to heavy contamination.

[g] Isolation should continue if the RADT (including self-performed) or RT-PCR test is positive on day six. If RT-PCR is performed, then high Ct values (≥30) can be used, with caution, as a proxy of low likelihood of transmissibility. RADT can be repeated daily until negative or until 10 days of isolation are completed.

Figure 1. Algorithm for ending of isolation of people with COVID-19



References

1. European Centre for Disease Prevention and Control (ECDC). Guidance for discharge and ending of isolation of people with COVID-19. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/covid-19-guidance-discharge-and-ending-isolation
2. European Centre for Disease Prevention and Control (ECDC). SARS-CoV-2 variants of concern as of 13 January 2022. Stockholm: ECDC; 2022. Available at: https://www.ecdc.europa.eu/en/covid-19/variants-concern
3. European Centre for Disease Prevention and Control (ECDC). Country Overview Report: Week 01, 2022. Stockholm: ECDC; 2022. Available at: https://www.ecdc.europa.eu/en/covid-19/country-overviews
4. European Centre for Disease Prevention and Control (ECDC). Options for the use of rapid antigen tests for COVID-19 in the EU/EEA - first update. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/options-use-rapid-antigen-tests-covid-19-eueea-first-update
5. Leitão IdC, Calil PT, Galliez RM, Moreira FRR, Mariani D, Castiñeiras ACP, et al. Prolonged SARS-CoV-2 Positivity in Immunocompetent Patients: Virus Isolation, Genomic Integrity, and Transmission Risk. Microbiology Spectrum. 2021;9(3):e00855-21. Available at: https://journals.asm.org/doi/full/10.1128/Spectrum.00855-21
6. Kim S-m, Hwang YJ, Kwak Y. Prolonged SARS-CoV-2 detection and reversed RT-PCR results in mild or asymptomatic patients. Infectious Diseases. 2021;53(1):31-7. Available at: https://www.tandfonline.com/doi/abs/10.1080/23744235.2020.1820076
7. Xiao AT, Tong YX, Zhang S. Profile of RT-PCR for SARS-CoV-2: a preliminary study from 56 COVID-19 patients. Clinical Infectious Diseases. 2020;71(16):2249–51. Available at: https://academic.oup.com/cid/article/71/16/2249/5822175
8. Zhou B, She J, Wang Y, Ma X. Duration of Viral Shedding of Discharged Patients With Severe COVID-19. Clinical Infectious Diseases. 2020;71(16):2240-2. Available at: https://academic.oup.com/cid/article/71/16/2240/5821307
9. Korean Centre for Disease Control (KCDC). Findings from investigation and analysis of re-positive cases. Cheongju: KCDC; 2020. Available at: https://www.mofa.go.kr/viewer/skin/doc.html?fn=20200521024820767.pdf&rs=/viewer/result/202201
10. Molina LP, Chow S-K, Nickel A, Love JE. Prolonged Detection of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA in an Obstetric Patient With Antibody Seroconversion. Obstetrics & Gynecology. 2020;136(4):838-41. Available at: https://journals.lww.com/greenjournal/Fulltext/2020/10000/Prolonged_Detection_of_Severe_Acute_Respiratory.30.aspx
11. Hu X, Xing Y, Jia J, Ni W, Liang J, Zhao D, et al. Factors associated with negative conversion of viral RNA in patients hospitalized with COVID-19. Science of the Total Environment. 2020;728:138812. Available at: https://www.sciencedirect.com/science/article/pii/S0048969720323299
12. Woodruff A. COVID-19 follow up testing. Journal of Infection. 2020;81(4):647-79. Available at: https://www.journalofinfection.com/article/S0163-4453(20)30289-9/fulltext
13. Cento V, Colagrossi L, Nava A, Lamberti A, Senatore S, Travi G, et al. Persistent positivity and fluctuations of SARS-CoV-2 RNA in clinically-recovered COVID-19 patients. The Journal of infection. 2020;81(3):e90. Available at: https://www.sciencedirect.com/science/article/pii/S0163445320304059
14. 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. Journal of Infection. 2020;81(2):318-56. Available at: https://www.sciencedirect.com/science/article/pii/S0163445320301900
15. 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. Available at: https://www.nature.com/articles/s41586-020-2196-x
16. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. Predicting Infectious Severe Acute Respiratory Syndrome Coronavirus 2 From Diagnostic Samples. Clinical Infectious Diseases. 2020;71(10):2663–6. Available at: https://academic.oup.com/cid/article/71/10/2663/5842165
17. La Scola B, Le Bideau M, Andreani J, Hoang VT, Grimaldier C, Colson P, et al. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. European Journal of Clinical Microbiology & Infectious Diseases. 2020;39(6):1059. Available at: https://link.springer.com/article/10.1007%2Fs10096-020-03913-9
18. Weiss A, Jellingsø M, Sommer MOA. Spatial and temporal dynamics of SARS-CoV-2 in COVID-19 patients: A systematic review and meta-analysis. EBioMedicine. 2020;58:102916. Available at: https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30291-7/fulltext
19. Health Information and Quality Authorit (HIQA). Evidence summary for the duration of infectiousness in those that test positive for SARS-CoV-2 RNA. Dublin: HIQA; 2020. Available at: https://www.hiqa.ie/sites/default/files/2020-09/Evidence-summary-for-duration-of-infectiousness-of-SARS-CoV-2.pdf

20. Singanayagam A, Patel M, Charlett A, Bernal JL, 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. Euro Surveill. 2020;25(32):2001483. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.32.2001483
21. Jones TC, Biele G, Mühlemann B, Veith T, Schneider J, Beheim-Schwarzbach J, et al. Estimating infectiousness throughout SARS-CoV-2 infection course. Science. 2021;373(6551):eabi5273. Available at: https://www.science.org/doi/10.1126/science.abi5273
22. 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. The Lancet Microbe. 2021;2(1):E13-E22. Available at: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30172-5/fulltext
23. Yan D, Zhang X, Chen C, Jiang D, Liu X, Zhou Y, et al. Characteristics of viral shedding time in SARS-CoV-2 infections: A systematic review and meta-analysis. Frontiers in Public Health. 2021;9:652842. Available at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.652842/full
24. van Kampen JJ, van de Vijver DA, Fraaij PL, Haagmans BL, Lamers MM, Okba N, et al. Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (COVID-19). Nature Communications. 2021;12(1):1-6. Available at: https://www.nature.com/articles/s41467-020-20568-4
25. Walsh KA, Spillane S, Comber L, Cardwell K, Harrington P, Connell J, et al. The duration of infectiousness of individuals infected with SARS-CoV-2. Journal of Infection. 2020;81(6):847-56. Available at: https://www.sciencedirect.com/science/article/pii/S0163445320306514
26. Poopalasingam N, Korenkov M, Ashurov A, Strobel J, Fish I, Hellmich M, et al. Determining the Reliability of Rapid SARS-CoV-2 Antigen Detection in Fully Vaccinated Individuals. SSRN [Preprint]. 2022. DOI: 10.2139/ssrn.4000128. Available at: Poopalasingam, Nareshkumar and Korenkov, Michael and Ashurov, Artem and Strobel, Janina and Fish, Irina and Hellmich, Martin and Gruell, Henning and Lehmann, Clara and Heger, Eva and Klein, Florian, Determining the Reliability of Rapid SARS-CoV-2 Antigen Detection in Fully Vaccinated Individuals. Available at SSRN: https://ssrn.com/abstract=4000128 or http://dx.doi.org/10.2139/ssrn.4000128
27. To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. The Lancet Infectious Diseases. 2020;20(5):565-74. Available at: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30196-1/fulltext
28. Pan X, Chen D, Xia Y, Wu X, Li T, Ou X, et al. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. The Lancet Infectious Diseases. 2020;20(4):410-1. Available at: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30114-6/fulltext
29. Yonker LM, Neilan AM, Bartsch Y, Patel AB, Regan J, Arya P, et al. Pediatric Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Clinical Presentation, Infectivity, and Immune Responses. The Journal of Pediatrics. 2020;227:45-52.e5. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0022347620310234
30. Lee S, Kim T, Lee E, Lee C, Kim H, Rhee H, et al. Clinical Course and Molecular Viral Shedding Among Asymptomatic and Symptomatic Patients With SARS-CoV-2 Infection in a Community Treatment Center in the Republic of Korea. JAMA Internal Medicine. 2020;180(11):1447-52. Available at: https://doi.org/10.1001/jamainternmed.2020.3862
31. Wang Y, Chen R, Hu F, Lan Y, Yang Z, Zhan C, et al. Transmission, viral kinetics and clinical characteristics of the emergent SARS-CoV-2 Delta VOC in Guangzhou, China. EClinicalMedicine. 2021;40:101129. Available at: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00409-0/fulltext
32. Ong SWX, Chiew CJ, Ang LW, Mak T-M, Cui L, Toh MPH, et al. Clinical and Virological Features of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variants of Concern: A Retrospective Cohort Study Comparing B. 1.1. 7 (Alpha), B. 1.351 (Beta), and B. 1.617. 2 (Delta). Clinical Infectious Diseases [Preprint]. 2021. DOI: 10.1093/cid/ciab721. Available at: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab721/6356459
33. Hay JA, Kissler SM, Fauver JR, Mack C, Tai CG, Samant RM, et al. Viral dynamics and duration of PCR positivity of the SARS-CoV-2 Omicron variant. medRxiv [Preprint]. 2022. DOI: 10.1101/2022.01.13.22269257. Available at: https://www.medrxiv.org/content/10.1101/2022.01.13.22269257v1
34. Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20–28 January 2020. Eurosurveillance. 2020;25(5):pii=2000062. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.5.2000062
35. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. New England Journal of Medicine. 2020;382:1199-207. Available at: https://www.nejm.org/doi/full/10.1056/NEJMOa2001316
36. Wei Y, Wei L, Liu Y, Huang L, Shen S, Zhang R, et al. A systematic review and meta-analysis reveals long and dispersive incubation period of COVID-19. MedRxiv [Preprint]. 2020. DOI:

10.1101/2020.06.20.20134387. Available at: https://www.medrxiv.org/content/10.1101/2020.06.20.20134387v1
37. Dhouib W, Maatoug J, Ayouni I, Zammit N, Ghammem R, Fredj SB, et al. The incubation period during the pandemic of COVID-19: a systematic review and meta-analysis. Systematic reviews. 2021;10(1):1-14. Available at: https://link.springer.com/article/10.1186/s13643-021-01648-y
38. Grant R, Charmet T, Schaeffer L, Galmiche S, Madec Y, Von Platen C, et al. Impact of SARS-CoV-2 Delta variant on incubation, transmission settings and vaccine effectiveness: Results from a nationwide case-control study in France. The Lancet Regional Health-Europe [Preprint]. 2021. DOI: 10.1016/j.lanepe.2021.100278. Available at: https://www.sciencedirect.com/science/article/pii/S2666776221002647
39. Brandal LT, MacDonald E, Veneti L, Ravlo T, Lange H, Naseer U, et al. Outbreak caused by the SARS-CoV-2 Omicron variant in Norway, November to December 2021. Euro Surveill. 2021;26(50):2101147. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.50.2101147
40. Helmsdal G, Hansen OK, Moller LF, Christiansen DH, Petersen MS, Kristiansen MF. Omicron outbreak at a private gathering in the Faroe Islands, infecting 21 of 33 triple-vaccinated healthcare workers. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.12.22.21268021. Available at: https://www.medrxiv.org/content/10.1101/2021.12.22.21268021v2
41. Jansen L. Investigation of a SARS-CoV-2 B. 1.1. 529 (Omicron) Variant Cluster—Nebraska, November–December 2021. MMWR Morbidity and mortality weekly report. 2021;70(5152):1782–4. Available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm705152e3.htm
42. Sah P, Fitzpatrick MC, Zimmer CF, Abdollahi E, Juden-Kelly L, Moghadas SM, et al. Asymptomatic SARS-CoV-2 infection: A systematic review and meta-analysis. Proceedings of the National Academy of Sciences. 2021;118(34):e2109229118. Available at: https://www.pnas.org/content/118/34/e2109229118.short
43. Lavezzo E, Franchin E, Ciavarella C, Cuomo-Dannenburg G, Barzon L, Del Vecchio C, et al. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. Nature. 2020;584(7821):425-9. Available at: https://www.nature.com/articles/s41586-020-2488-1
44. Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection: A Narrative Review. Annals of Internal Medicine. 2020;173(5):362-7. Available at: https://www.acpjournals.org/doi/full/10.7326/M20-3012
45. Tao J, Zhang X, Zhang X, Zhao S, Yang L, He D, et al. The time serial distribution and influencing factors of asymptomatic COVID-19 cases in Hong Kong. One Health. 2020;10:100166. Available at: https://www.sciencedirect.com/science/article/pii/S2352771420302676
46. Cereda D, Tirani M, Rovida F, Demicheli V, Ajelli M, Poletti P, et al. The early phase of the COVID-19 outbreak in Lombardy, Italy. Arxiv [Preprint]. 2020. Available at: https://arxiv.org/abs/2003.09320
47. Hoehl S, Rabenau H, Berger A, Kortenbusch M, Cinatl J, Bojkova D, et al. Evidence of SARS-CoV-2 infection in returning travelers from Wuhan, China. New England Journal of Medicine. 2020;382(13):1278-80. Available at: https://www.nejm.org/doi/full/10.1056/nejmc2001899
48. Luo S-H, Liu W, Liu Z-J, Zheng X-Y, Hong C-X, Liu Z-R, et al. A confirmed asymptomatic carrier of 2019 novel coronavirus. Chinese Medical Journal. 2020;133(9):1123-5. Available at: https://journals.lww.com/cmj/Fulltext/2020/05050/A_confirmed_asymptomatic_carrier_of_2019_novel.21.aspx
49. Ma Q, Liu J, Liu Q, Kang L, Liu R, Jing W, et al. Global Percentage of Asymptomatic SARS-CoV-2 Infections Among the Tested Population and Individuals With Confirmed COVID-19 Diagnosis: A Systematic Review and Meta-analysis. JAMA Network Open. 2021;4(12):e2137257-e. Available at: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2787098
50. Han Y, Yang H. The transmission and diagnosis of 2019 novel coronavirus infection disease (COVID-19): A Chinese perspective. Journal of Medical Virology. 2020;92(6):639-44. Available at: https://onlinelibrary.wiley.com/doi/10.1002/jmv.25749
51. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. New England Journal of Medicine. 2020;382(12):1177-9. Available at: https://www.nejm.org/doi/full/10.1056/NEJMc2001737
52. Weiskopf D, Schmitz KS, Raadsen MP, Grifoni A, Okba NM, Endeman H, et al. Phenotype and kinetics of SARS-CoV-2–specific T cells in COVID-19 patients with acute respiratory distress syndrome. Science Immunology. 2020;5(48):eabd2071. Available at: https://www.science.org/doi/abs/10.1126/sciimmunol.abd2071
53. Pan Y, Zhang D, Yang P, Poon LL, Wang Q. Viral load of SARS-CoV-2 in clinical samples. The Lancet Infectious Diseases. 2020;20(4):411-2. Available at: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30113-4/fulltext
54. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction–based SARS-CoV-2 tests by time since exposure. Annals of Internal Medicine. 2020;173(4):262-7. Available at: https://www.acpjournals.org/doi/abs/10.7326/m20-1495

55. Gudbjartsson DF, Norddahl GL, Melsted P, Gunnarsdottir K, Holm H, Eythorsson E, et al. Humoral Immune Response to SARS-CoV-2 in Iceland. The New England journal of medicine. 2020;383(18):1724-34. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2026116
56. 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. New England Journal of Medicine. 2020;382(22):2081-90. Available at: https://www.nejm.org/doi/full/10.1056/nejmoa2008457
57. Chun JY, Baek G, Kim Y. Transmission onset distribution of COVID-19. International Journal of Infectious Diseases. 2020;99:403-7. Available at: https://www.ijidonline.com/article/S1201-9712(20)30612-3/fulltext
58. Ge Y, Martinez L, Sun S, Chen Z, Zhang F, Li F, et al. COVID-19 transmission dynamics among close contacts of index patients with COVID-19: a population-based cohort study in Zhejiang province, China. JAMA Internal Medicine. 2021;181(10):1343-50. Available at: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2783099
59. 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 Internal Medicine. 2020;180(9):1156–63. Available at: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2765641
60. Bernal JL, Panagiotopoulos N, Byers C, Vilaplana TG, Boddington NL, Zhang X, et al. Transmission dynamics of COVID-19 in household and community settings in the United Kingdom. medRxiv [Preprint]. 2020. DOI: 10.1101/2020.08.19.20177188. Available at: https://www.medrxiv.org/content/10.1101/2020.08.19.20177188v1
61. Marc A, Kerioui M, Blanquart F, Bertrand J, Mitjà O, Corbacho-Monné M, et al. Quantifying the relationship between SARS-CoV-2 viral load and infectiousness. eLife. 2021;10:e69302. Available at: https://elifesciences.org/articles/69302
62. Garrett N, Tapley A, Andriesen J, Seocharan I, Fisher LH, Bunts L, et al. High Rate of Asymptomatic Carriage Associated with Variant Strain Omicron. medRxiv [Preprint]. 2022. DOI: 10.1101/2021.12.20.21268130. Available at: https://www.medrxiv.org/content/10.1101/2021.12.20.21268130v2
63. Edwards DA, Ausiello D, Salzman J, Devlin T, Langer R, Beddingfield BJ, et al. Exhaled aerosol increases with COVID-19 infection, age, and obesity. PNAS. 2021;118(8):e2021830118. Available at: https://www.pnas.org/content/118/8/e2021830118
64. Chia PY, Ong SWX, Chiew CJ, Ang LW, Chavatte J-M, Mak T-M, et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study. Clinical Microbiology and Infection [Preprint]. 2021. DOI: 10.1016/j.cmi.2021.11.010. Available at: https://www.sciencedirect.com/science/article/pii/S1198743X21006388
65. Singanayagam A, Hakki S, Dunning J, Madon KJ, Crone MA, Koycheva A, et al. Community transmission and viral load kinetics of the SARS-CoV-2 delta (B. 1.617. 2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. The Lancet Infectious Diseases [Preprint]. 2021. DOI: 10.1016/S1473-3099(21)00648-4. Available at: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00648-4
66. Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta K-D, et al. Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.08.18.21262237. Available at: https://www.medrxiv.org/content/10.1101/2021.08.18.21262237v1
67. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 breakthrough infections in vaccinated health care workers. New England Journal of Medicine. 2021;385(16):1474-84. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2109072
68. Kissler SM, Fauver JR, Mack C, Tai CG, Breban MI, Watkins AE, et al. Viral dynamics of SARS-CoV-2 variants in vaccinated and unvaccinated persons. New England Journal of Medicine. 2021;385(26):2489-91. Available at: https://www.nejm.org/doi/full/10.1056/Nejmc2102507
69. Puhach O, Adea K, Hulo N, Sattonnet P, Genecand C, Iten A, et al. Infectious viral load in unvaccinated and vaccinated patients infected with SARS-CoV-2 WT, Delta and Omicron. medRxiv [Preprint]. 2022. DOI: 10.1101/2022.01.10.22269010. Available at: https://www.medrxiv.org/content/10.1101/2022.01.10.22269010v1
70. Milton DK, Sheldon Tai S-H, Jennifer German J, Filbert Hong F, Barbara Albert B, Yi Esparza Y, et al. Initial Assessment of SARS-CoV-2 Omicron Variant in Exhaled Breath Aerosol. Available at: https://mfr.osf.io/render?url=https%3A%2F%2Fosf.io%2Fdscy3%2Fdownload
71. National Institute of Infectious Diseases Disease Control and Prevention Center, National Center for Global Health and Medicine (Japan). Active epidemiological investigation on SARS-CoV-2 infection caused by Omicron variant (Pango lineage B.1.1.529) in Japan: preliminary report on infectious period. Tokyo: NIID; 2022. Available at: https://www.niid.go.jp/niid/en/2019-ncov-e/10884-covid19-66-en.html
72. Lyngse FP, Mortensen LH, Denwood MJ, Christiansen LE, Møller CH, Skov RL, et al. SARS-CoV-2 Omicron VOC Transmission in Danish Households. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.12.27.21268278. Available at: https://www.medrxiv.org/content/10.1101/2021.12.27.21268278v1

73. UK Health Security Agency (UKHSA). SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 33. London: UKHSA; 2021. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043807/technical-briefing-33.pdf
74. Kojima N, Shrestha N, Klausner JD. A systematic review of the protective effect of prior SARS-CoV-2 infection on repeat infection. Evaluation & the Health Professions. 2021;44(4):327-32. Available at: https://journals.sagepub.com/doi/10.1177/01632787211047932
75. Office for National Statistics. Coronavirus (COVID-19) Infection Survey, characteristics of people testing positive for COVID-19, UK: 16 December 2021. Newport: ONS; 2021. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurveycharacteristicsofpeopletestingpositiveforcovid19uk/16december2021#glossary
76. Statens Serum Institut (SSI). Reinfektioner indgår nu i Statens Serum Instituts daglige overvågning. Copenhagen: SSI; 2021. Available at: https://www.ssi.dk/aktuelt/nyheder/2021/reinfektioner-indgar-nu-i-statens-serum-instituts-daglige-overvagning
77. UK Health Security Agency (UKHSA). SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 32. London: UKHSA; 2021. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042688/RA_Technical_Briefing_32_DRAFT_17_December_2021_2021_12_17.pdf
78. Sheikh A, Kerr S, Woolhouse M, McMenamin J, Robertson C. Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland. The University of Edinburgh [Preprint]. 2021. Available at: https://www.research.ed.ac.uk/en/publications/severity-of-omicron-variant-of-concern-and-vaccine-effectiveness-
79. Altarawneh H, Chemaitelly H, Tang P, Hasan MR, Qassim S, Ayoub HH, et al. Protection afforded by prior infection against SARS-CoV-2 reinfection with the Omicron variant. medRxiv [Preprint]. 2022. DOI: 10.1101/2022.01.05.22268782. Available at: https://www.medrxiv.org/content/10.1101/2022.01.05.22268782v1
80. European Centre for Disease Prevention and Control (ECDC). Assessment of the further spread and potential impact of the SARS-CoV-2 Omicron variant of concern in the EU/EEA, 19th update. Stockholm: ECDC; 2022. Available at: https://www.ecdc.europa.eu/en/publications-data/covid-19-omicron-risk-assessment-further-emergence-and-potential-impact
81. UK Health Security Agency (UKHSA). SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing: Update on hospitalisation and vaccine effectiveness for Omicron VOC-21NOV-01 (B.1.1.529) London: UKHSA; 2021. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1044481/Technical-Briefing-31-Dec-2021-Omicron_severity_update.pdf
82. European Centre for Disease Prevention and Control (ECDC). Guidance on quarantine of close contacts to COVID-19 cases and isolation of COVID-19 cases, in the current epidemiological situation, 7 January 2022. Stockholm: ECDC; 2022. Available at: https://www.ecdc.europa.eu/en/covid-19/prevention-and-control/quarantine-and-isolation
83. European Centre for Disease Prevention and Control (ECDC). Infection prevention and control in the household management of people with suspected or confirmed coronavirus disease (COVID-19). Stockholm: ECDC; 2020. Available at: https://www.ecdc.europa.eu/en/publications-data/infection-prevention-control-household-management-covid-19
84. Bays D, Whiteley T, Pindar M, Taylor J, Walker BF, Williams H, et al. Mitigating isolation: The use of rapid antigen testing to reduce the impact of self-isolation periods. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.12.23.21268326. Available at: https://www.medrxiv.org/content/10.1101/2021.12.23.21268326v1
85. Quilty BJ, Pulliam JR, Pearson CA. Test to release from isolation after testing positive for SARS-CoV-2. medRxiv [Preprint]. 2022. DOI: 10.1101/2022.01.04.21268372. Available at: https://www.medrxiv.org/content/10.1101/2022.01.04.21268372
86. Color Health, Inc. Omicron Workplace Modeling Tool. Color Health, Inc; 2022. Available at: https://www.color.com/omicron-workplace-tool
87. Bergstrom CT. The plot below shows the average peak number of people in isolation out of 1000. Testing weekly, the longer the isolation period, the more people out at peak. But when testing more often, a longer isolation period can actually decrease the peak number in isolation. Twitter. 8 January 2022 11:14 PM. Available at: https://twitter.com/CT_Bergstrom/status/1479939559622279169