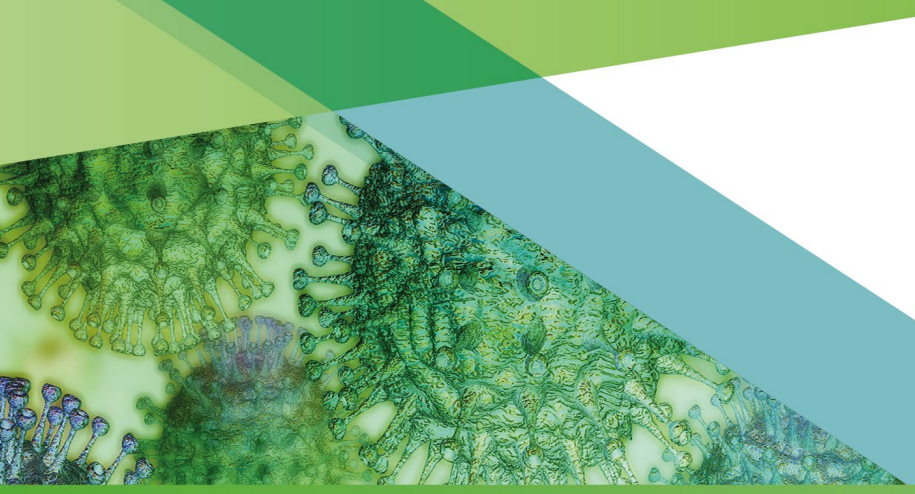


TECHNICAL REPORT

Reinfection with SARS-CoV-2: implementation of a surveillance case definition within the EU/EEA

8 April 2021

Key messages

- Reinfection with SARS-CoV-2 has been reported both within the European Union/European Economic Area (EU/EEA) and globally. This report summarises the available evidence about reinfection and duration of immunity following SARS-CoV-2 infection and describes surveillance practices implemented in EU/EEA countries to document and report suspected reinfection cases.
- Thirteen of 17 EU/EEA countries responding to a survey sent by ECDC on 28 January 2021 about existing surveillance case definitions and reporting systems for reinfection confirmed they had a national case definition, with the minimum interval between episodes described in the definition ranging from 45 to 90 days. In terms of diagnostic testing criteria, countries report different practices for identifying and counting possible SARS-CoV-2 reinfection cases.
- In 2020, a total of 1 887 possible cases of reinfection were reported to be under investigation across 12 responding EU/EEA countries.
- SARS-CoV-2 variants of concern – in particular B.1.351 and P.1 – have demonstrated a capacity to escape protective immune responses mounted by individuals that have recovered from a prior infection. It is possible that reinfections may occur more frequently in areas where there is sustained transmission of these new variants.
- Although reinfection events are rare, they are likely under-reported. In order to better ascertain the burden and impact of SARS-CoV-2 reinfection across the EU/EEA, particularly in the context of emerging variants with immune escape potential, ECDC has established a surveillance case definition for *suspected* reinfection, introducing new case-based and aggregated variables to improve systematic reporting via The European Surveillance System (TESSy).

Scope of this document

The aim of this document is to present the findings of a survey of EU/EEA countries carried out to ascertain surveillance practices implemented to document and report suspected reinfection cases. In addition, this document summarises the available evidence on the duration of protective immunity following infection with SARS-CoV-2, addressing concerns related to reinfection, such as disease severity during a reinfection episode. The survey responses and available evidence are used to underline the rationale for the surveillance case definition proposed for suspected reinfection cases, to be reported via The European Surveillance System (TESSy).

Suggested citation: European Centre for Disease Prevention and Control. Reinfection with SARS-CoV-2: implementation of a surveillance case definition within the EU/EEA. 8 April 2021. ECDC: Stockholm, 2021.

Target audience

Public health authorities in EU/EEA countries.

Background

Since its emergence in December 2019, SARS-CoV-2 – the virus causing Coronavirus disease 2019 (COVID-19) – has spread globally, infecting over 120 million people across more than 200 countries [1].

In September 2020, ECDC published a threat assessment brief in response to a small number of published case reports documenting suspected or possible reinfections in individuals that had recovered from a prior episode of SARS-CoV-2 infection [2]. This brief highlighted the challenges in determining whether such reports represent true reinfections, persistent viral shedding, or recurrence of positive (re-positive) polymerase chain reaction (PCR) diagnostic tests [3]. Additional lines of investigation to support a diagnosis of reinfection were also highlighted and included genetic sequencing to compare virus isolates from the initial and suspected reinfection episode.

A diagnosis of true reinfection with SARS-CoV-2 can only be established when viral clearance is complete for the first episode of infection, and sufficient time has elapsed to allow for immune responses to be mounted. Re-positive PCR tests have been widely reported in convalescent patients. However, in the absence of a documented symptom-free period and supportive diagnostic sequencing, it is difficult to exclude fluctuations in viral shedding or false negative results when viral loads are low [4-7].

To better ascertain the burden and impact of SARS-CoV-2 reinfection across the EU/EEA, it is necessary to establish standardised surveillance reporting protocols for suspected reinfection cases. In order to establish the reporting protocol, a working case definition for suspected reinfection cases is required, which takes into account the time required to mount a neutralising antibody response and the variability of neutralising antibody dynamics following infection with SARS-CoV-2, as well as existing surveillance practices and reporting capabilities among EU/EEA countries.

Duration of immunity and reinfection risk in seroconverted individuals

Following infection with SARS-CoV-2 virus, it is the adaptive immune response that ideally delivers long-term protection. The adaptive immune response primarily comprises memory B cells that produce different classes of antibodies to neutralise the virus or virus-infected cells, and memory T cells that support antibody production and also have a direct role in killing virus-infected cells. While there is evidence of both memory B cell and T cell immune responses in individuals infected with SARS-CoV-2, clear correlates for protective immunity have yet to be defined [8-11].

A systematic review of 150 studies describing virus-specific serum antibody responses in individuals infected with SARS-CoV-2 showed that IgM is consistently detected before IgG, peaking between weeks two to five and declining over a further three to five weeks post-symptom onset. IgG peaks between weeks three to seven post-symptom onset, persisting for at least eight weeks. Neutralising antibodies – with the capacity to restrict virus growth in vitro – are detectable within seven to 15 days following disease onset, with levels increasing until days 14–22 before plateauing and then decreasing. Lower antibody titres are observed in those with asymptomatic or clinically mild disease, however, the review primarily featured observational studies of hospitalised cases, with follow-up periods lasting up to three months post symptom onset [9].

The vast majority of SARS-CoV-2–infected individuals seroconvert following SARS-CoV-2 infection. Reviews of the published literature indicate that >90% patients develop IgG seropositivity and neutralising antibodies following primary infection, ranging between 91 to 99% in large studies [9,12].

In the absence of definitive correlates of protective immunity, the presence of neutralising antibodies against SARS-CoV-2 provides the best current indication for protection against reinfection for previously infected individuals. Several well-conducted studies have shown that neutralisation ability of polyclonal serum correlates positively with anti-spike IgG or anti-RBD IgG [9]. The S1 domain of the SARS-CoV-2 spike protein includes the receptor binding domain, and antibodies targeting this critically impair virus cell entry [13].

A recently published prospective cohort study from Singapore has evaluated the dynamics of SARS-CoV-2 neutralising antibody responses over time. Serum samples were collected at approximately 30-day intervals up to 180 days post symptom onset from 164 patients with PCR-confirmed SARS-CoV-2 infection experiencing mild, moderate, or severe disease. The authors described five distinctive patterns of neutralising antibody dynamics:

- negative: individuals who did not develop strong neutralising antibody responses: 19/164 patients (12%);
- rapid waning: individuals who had varying levels of neutralising antibodies from around 20 days after symptom onset, but seroconverted in less than 180 days: 44/164 patients (27%);

- slow waning: individuals who remained neutralising antibody-positive at 180 days post-symptom onset: 52/164 patients (29%);
- persistent: individuals with varying peak neutralising antibody levels, but minimal neutralising antibody decay: 52/164 patients (32%); and
- delayed response: individuals that showed an unexpected increase in neutralising antibodies during late convalescence (at 90 or 180 days after symptom onset: 3/164 patients (2%).

Greater disease severity was associated with persistent neutralising antibody levels, and patients with milder disease appeared to have more rapid neutralising antibody waning. While this study showed that neutralising antibody dynamics can vary greatly among individual patients with COVID-19, development and persistence of virus-specific, long-lived memory B cells was not studied. However, the authors did analyse 23 randomly selected patients from the five categories described, confirming the presence of virus-specific memory T-cells at 180 days post-symptom onset in patients from each of the five categories [14].

A scoping review performed by the Irish Health Information and Quality Authority (HIQA) to evaluate the long-term duration of immune responses following SARS-CoV-2 infection identified five studies that investigated immune responses at ≥6 months post-infection, including two studies at ≥8 months post-infection. In general, studies reported a waning of antibody responses in the late convalescent period (3-6 months post-infection). However, T-cell and memory B-cell responses were still present, and in many cases increased, up to eight months post-infection in all study participants [15]. Taken together, results from cohort studies confirm the protective effect of previous SARS-CoV-2 infection ranges from 81% to 100% during a follow-up period of five to seven months [16-21], although longer follow-up is necessary to better define the duration of protection for longer periods of time. These studies were largely conducted prior to the emergence of variants of concern (VOCs), for which the World Health Organization established working definitions in February 2021 [22].

Risk posed by emerging SARS-CoV-2 variants

Since April 2020, the emergence of a SARS-CoV-2 variant circulating in mink has highlighted the ability of the virus to adapt in animal species, while retaining transmissibility and pathogenicity among humans [23]. In February 2021, ECDC published a Rapid Risk Assessment focussing on the emergence and increased spread of new SARS-CoV-2 VOCs first identified in the United Kingdom (B.1.1.7), South Africa (B.1.351), and Brazil (P.1) [24]. All three variants have demonstrated increased transmissibility in human populations, with B.1.1.7 associated with increased disease severity. While seroconversion to previously circulating SARS-CoV-2 strains may generate neutralising antibodies that protect against reinfection by a homologous virus, the neutralising capacity of these antibodies is reduced against VOCs, particularly those bearing the E484K mutation [24,25].

Current estimates of reinfection incidence

In Denmark, Hansen *et al.* conducted a population-level observational study, collecting individual-level data on patients who had been tested in Denmark in 2020 from the Danish Microbiology Database. They analysed infection rates during the second surge of the COVID-19 epidemic, from 1 September to 31 December 2020, by comparison to infection rates between individuals with positive and negative PCR tests during the first surge (March to May 2020). During the first surge (before June 2020), 533 381 people were tested, of whom 11 727 (2.20%) were PCR positive, and 525 339 were eligible for follow-up in the second surge, of whom 11 068 (2.11%) had tested positive during the first surge. Among eligible PCR-positive individuals from the first surge of the epidemic, 72 (0.65% [95% CI 0.51–0.82]) tested positive again during the second surge, compared with 16 819 (3.27% [3.22–3.32]) of 514 271 who tested negative during the first surge (adjusted RR 0.195 [95% CI 0.155–0.246]) [21].

In a preprint article from UK, Graham *et al.* evaluated longitudinal symptom and test reports of 36 920 users of the COVID Symptom Study app testing positive for COVID-19 between 28 September and 27 December 2020, estimating the number of possible reinfections (defined as two positive PCR tests >90 days apart with at least seven symptom-free days between tests) and the proportion of B.1.1.7 cases over time, estimating a reinfection rate of 0.7% (95% CI 0.6-0.8), but with no evidence that this was higher compared to older strains [26].

In Czechia, Fabiánová *et al.* evaluated PCR-confirmed COVID-19 cases with onset before 31 October 2020 that were reported to the Infectious Diseases Information System by 9 November 2020. 28 SARS-CoV-2 reinfections with two symptomatic episodes no less than 90 days apart occurred in 0.17% of all patients at risk of reinfection (28 of 16 582). When 54 asymptomatic patients were taken into account, the overall rate of reinfections was higher, reaching 0.49% (82 of 16 582) [27].

While these studies indicate that reinfection events are rare, more population level data to capture the burden of reinfection cases at national and European level is required. As new SARS-CoV-2 variants emerge, it is particularly useful to understand how this burden changes over time and during possible future surges in transmission.

Disease severity in reinfected persons

There is limited available evidence on the severity of confirmed reinfection cases relative to the first episode of infection, although a small number of reports have emerged where suspected reinfection episodes were associated with more severe disease [28-31]. Variables such as the initial dose of virus, possible differences between SARS-CoV-2 variants and changes in a person's overall health could all affect the severity of the reinfection episodes described in such reports [32]. In a systematic review of PCR re-positivity, Gidari *et al.* identified 82 articles, featuring 1 350 re-positive PCR cases. Of these patients, only 27.6% were symptomatic at time of PCR re-positivity. The authors accompanied the systematic review with a case series analysis of nine suspected reinfection cases – defined as PCR re-positivity following improvement of symptoms and two negative swabs collected at least 24 hours apart following the initial infection. None presented severe disease or complications at the time of presumed recurrence. All tested patients (n=8) had antibodies against the S1 and S2 subunit of SARS-CoV-2 spike protein with sufficient titres immediately before or during the presumptive recurrence, and no culture-viable virus could be obtained from these individuals [7]. However, this study did not set a minimum interval between infection episodes and was completed prior to the emergence of new SARS-CoV-2 variants.

The limited availability of population level data on disease severity underscores the value of establishing standardised surveillance reporting protocols for suspected reinfection cases within the EU/EEA in order to assess:

- The total number and incidence of suspected reinfection cases;
- The risk of suspected reinfection by variants; and
- The severity of suspected reinfection cases, as compared to first episodes of infection.

How reinfection is being captured in the EU/EEA – results from the ECDC survey

On 28 January 2021, a survey was sent to EU/EEA countries to gather information on existing case definitions for reinfection, data availability, and reporting capability. The objective of this survey was to better adapt European surveillance to capture reinfection cases across EU/EEA countries, which is particularly important in the context of emerging SARS-CoV-2 VOCs.

In total, 17 EU/EEA countries responded to the reinfection survey (Figure 1), of which 13 reported having a national case definition, with 11 also having a national reporting system in place to collect reinfection cases in their countries. In 2020, 1 887 suspected reinfection cases were under investigation in 12 countries, and in 2021 (up to the date of the survey) 691 suspected reinfection cases were under investigation in six countries (Table 1).

Figure 1. Map of EU/EEA countries responding to the reinfection survey

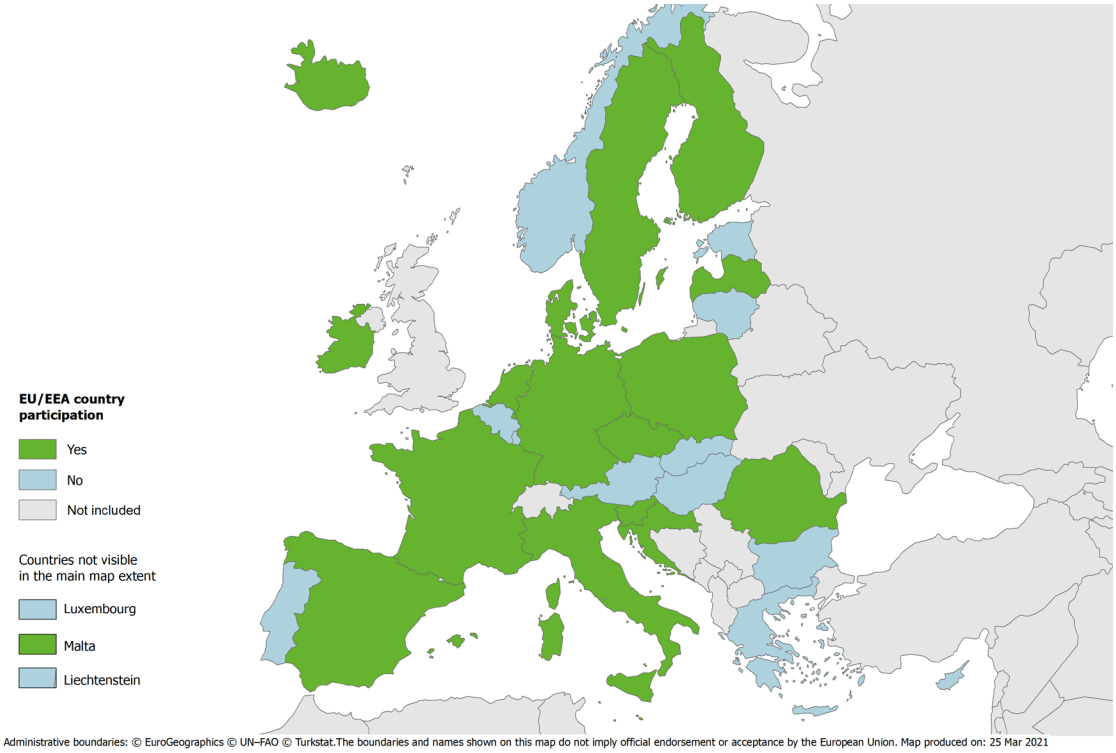


Table 1. Summary of countries with a case definition for reinfection, a national reporting system and reinfection cases under investigation in 2020/2021, EU/EEA countries, February 2021

Country	Case definition	National reporting system	Cases under investigation	
			2020	2021
Croatia	Y	Y	8	6
Czechia	Y	N	281	
Denmark	Y	Y	367	161
Finland	N	N		
France	Y	Y		
Germany	Y	Y	101	169
Iceland	Y	Y	3	
Ireland	Y	Y	140	89
Italy	N	N		
Latvia	N	N	7	4
Malta	Y	Y	90*	
Netherlands	Y	Y	38	
Poland	N	N		
Romania	Y	Y	606	262
Slovenia	Y	N	16*	
Spain	Y	Y		
Sweden	Y	Y	230	
Total	13 (76%)	11 (65%)	1 887	691

Y: Yes. N: No.
Case numbers with an asterisk were not assigned to a specific year but were grouped under 2020 as this was more realistic given that the survey was sent in January 2021.

Of 13 countries (76%) that reported having a case definition, the time interval between episodes 1 and 2 ranged from 45 to 90 days, with the majority (7; 54%) using 90 days (Table 2). Symptom-free periods between episodes 1 and 2 were mentioned in the case definitions from five (38%) countries (Croatia, Czechia, France, Ireland, and the Netherlands), but only specified as 60 days from one country (France). Seven countries (54%) reported using a working case definition based on a minimum interval between positive PCR tests, without the use of rapid antigen diagnostic tests. Latvia provided data on several cases under investigation but did not report having a case definition or a national reporting system (Table 2).

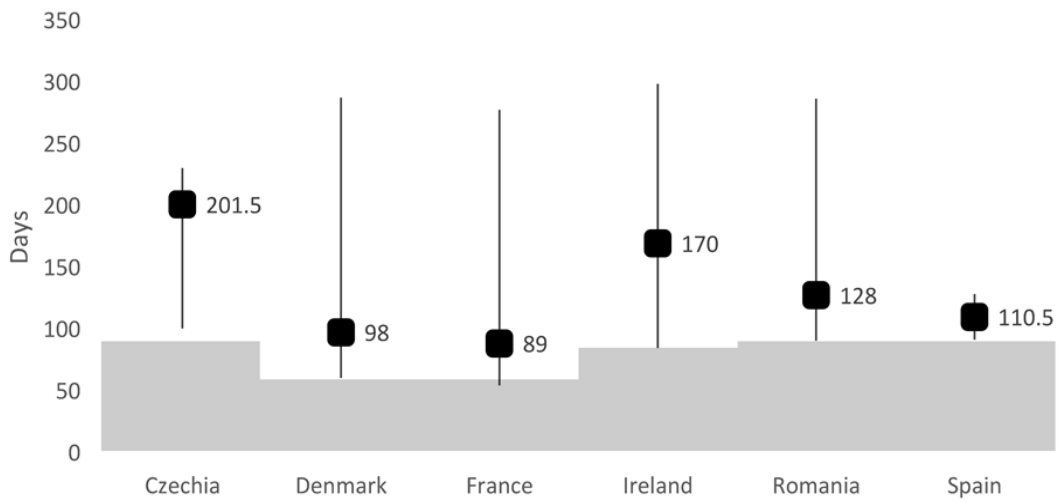
Table 2. Summary of case definition for reinfection, 13 EU/EEA countries, February 2021

Country (n=13)	Case definition				Episode 1 and 2			
	Interval (days)	Symptom-free period	Interval + PCR only	Variant	PCR	Sequence	RAT	Serology
Croatia	90	Y	Y	N	Y	Y	N	N
Czechia	90	Y	Y	N	Y	N	N	N
Denmark	60	N	Y	N	Y	Y	N	N
France	60	Y	N	Y	Y	Y	Y	Y
Germany	90*							
Iceland	60*				Y	Y	N	N
Ireland	84	Y	Y	N	Y	N	N	N
Malta	45	N	Y	N	Y	N	N	N
Netherlands	60	Y	N	N	Y	Y	Y	N
Romania	90	N	N	N	Y	N	Y	N
Slovenia	90	N	Y	Y	Y	Y	N	Y
Spain	90	N	N	Y	Y	Y	Y	N
Sweden	90	N	Y	Y	Y	Y	N	N
Total (%)		5 (38)	7 (54)	4 (31)	12 (92)	8 (62)	4 (31)	2 (15)

Y: Yes. N: No. PCR: Polymerase chain reaction test; RAT: Rapid antigen test.
**Interval specified, with no additional criteria.*

Six countries (Czechia, Denmark, France, Ireland, Romania, and Spain) provided additional information on the time interval between first and second infection for probable and confirmed reinfection cases according to the case definition. The interval ranged from 55 to 299 days (median range 89-201.5) (Figure 2).

Figure 2. Minimum, maximum and median intervals between first and second infections according to the national case definition, six EU/EEA countries, February 2021



Black dot (median); black line (observed minimum/maximum interval); grey box (minimum interval as per case definition). Minimum/maximum range: 55-299; median range: 89-201.5. Figure based on both probable and confirmed reinfection cases.

Of 11 countries with a national reporting system, eight collected information on cases of reinfection according to the case definition, and it is of note that three countries (France, Iceland, and Sweden) reported having a national case definition and reporting system but indicated 'no' for this field. Most variables were collected by the majority of countries, but the date of antibody test for first episode confirmation was only collected by one country and the dates of rapid antigen test for first- and second-episode confirmation by four countries, indicating that these variables could be more problematic for countries to collect systematically (Table 3).

Table 3. Variables collected via national reporting systems, 11 EU/EEA countries, February 2021

Variable	No.	%
Case of reinfection according to national case definition	8*	73*
Date of first episode	10	91
Date of second episode	10	91
Time period between episodes	9	82
Type of test for confirmation of first episode	10	91
Date of antibody positive test for first episode confirmation	1	9
Date of rapid antigen positive test for first episode confirmation	4	36
Date of PCR positive test for first episode confirmation	10	91
Date of rapid antigen positive test for second episode confirmation	4	36
Date of PCR positive test for second episode confirmation	9	82
Sequence data first episode	7	64
Sequence data second episode	7	64

PCR: Polymerase chain reaction test.
**Three countries reported having a case definition and national surveillance system but responded 'no' to this field.*

Of 17 countries that responded to the reinfection survey, nine (Denmark, Finland, France, Germany, Italy, Malta, the Netherlands, Spain, and Sweden) indicated that they have special studies/activities planned on reinfection, five (Czechia, Italy, the Netherlands, Spain, and Sweden) planned studies on reinfection in relation to new variant viruses (e.g. household studies, healthcare workers studies, etc), and 15 countries (all but Romania and Slovenia) planned to sequence and characterise viruses from reinfection cases.

Conclusions

While reinfection events appear to be rare, there is currently limited population level data available that captures the burden of reinfection cases at national level and over time. Following a survey of EU/EEA countries, the majority of responding countries reported having a working case definition and a national reporting system to capture reinfection cases. These definitions, although similar, were not standardised.

In order to better ascertain the burden and impact of SARS-CoV-2 reinfection across the EU/EEA, particularly in the context of emerging variants with immune escape potential, ECDC has established a surveillance case definition for suspected reinfection, introducing new case-based and aggregate variables to improve systematic reporting via The European Surveillance System (TESSy).

Proposal for case definition and TESSy variables

Objectives for reinfection surveillance include describing the epidemiology of reinfection in the EU/EEA and understanding the risk of reinfection for cases infected with VOCs. With this in mind, a case definition was developed for suspected COVID-19 reinfection and published on 15 March 2021 [33] and is as follows:

A *suspected* COVID-19 reinfection case is defined as:

Positive PCR or rapid antigen test (RAT) sample ≥60 days following:

- Previous positive PCR;
- Previous positive RAT;
- Previous positive serology (anti-spike IgG Ab).

This case definition takes into account the time required to mount a neutralising antibody response and the variability of neutralising antibody dynamics following infection with SARS-CoV-2, the potential risk of early immune escape posed by emerging VOCs, as well as existing surveillance practices and reporting capabilities amongst EU/EEA countries.

To collect data on suspected reinfection cases via TESSy, an update to the metadata was implemented on 12 March 2021; more information can be found in the latest reporting protocol [34]. Standardised surveillance reporting protocols for suspected reinfection cases within the EU/EEA will facilitate the assessment of:

1. The total number and incidence of *suspected* reinfection cases;
2. The risk of *suspected* reinfection by VOCs; and
3. The severity of *suspected* reinfection cases, as compared to first episodes of infection.

Depending on the quality of data submitted to TESSy on suspected reinfection cases, these outputs will be considered for inclusion in ECDC's COVID-19 country overview reports [35].

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