

AANBEVELINGEN BETREFFENDE HET TESTEN VAN REIZIGERS

RAG subgroep Testing – 3 Maart 2021

Note: The current recommendations are subject to change depending on new scientific data and/or the evolution of the epidemic.

Aanbevelingen:

- De huidige procedure, waarbij reizigers met residentie in België die terugkeren uit een rode zone zo spoedig mogelijk na hun terugkeer worden getest met een RT-PCR, blijft de voorkeursstrategie.
- Snelle Ag-tests kunnen een alternatief zijn, maar alleen als:
 - het om de een of andere reden (onvoldoende PCR-testcapaciteit, te hoge kosten van PCR-tests) niet langer mogelijk is om alle terugkerende reizigers binnen een redelijke termijn met een RT-PCR te testen;
 - de logistiek voor het testen op de plaats van binnenkomst zorgvuldig wordt georganiseerd om te zorgen voor fysieke afstand, de bescherming van het personeel te allen tijde, voldoende kwaliteit van de uitgevoerde tests en redelijke wachttijden.
- Met het oog op sequentiebepaling, moet steeds een voldoende groot deel van de reizigers die uit een rode zone terugkeren, met een RT-PCR worden getest.
- Het probleem van een slechte naleving van testen, isolatie en quarantaine kan niet worden opgelost door gebruik te maken van snelle Ag-tests in plaats van RT-PCR, en er zijn andere maatregelen nodig om de naleving te bevorderen (ongeacht de gebruikte test).
- Andere mogelijke strategieën, zoals het gebruik van geautomatiseerde Ag-tests, moeten verder worden onderzocht.
- Andere aspecten van de huidige richtlijnen, zoals een quarantaine van 10 dagen voor alle reizigers uit een rode zone (terugkerende inwoners en aankomende buitenlanders) die kan worden verkort als een RT-PCR op dag 7 negatief is, of de eis dat aankomende buitenlanders een negatief RT-PCR-resultaat moeten hebben dat minder dan 72 uur oud is, blijven geldig.
- Een extra test voor niet-inwoners die uit een rode zone komen bij aankomst of zo snel mogelijk na aankomst is een optie, maar geen noodzaak. Dit kan alleen worden overwogen indien:
 - het operationeel haalbaar is;
 - er geen andere prioriteiten zijn voor het gebruik van de huidige ongebruikte testcapaciteit;
 - de test een RT-PCR-test is, die sequencing mogelijk maakt.
- Net als voor terugkerende inwoners is het belangrijkste dat de quarantaineperiode voor buitenlandse reizigers wordt nageleefd. Het is belangrijk een controle uit te voeren met RT-PCR op dag 7. In geval van een positief staal moet dit zo mogelijk door sequencing worden geanalyseerd voor de opsporing van nieuwe varianten.

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CONTEXT

Non-essential travel abroad is currently prohibited for Belgian residents and non-essential travel to Belgium is prohibited for foreigners.

There is a socio-economic pressure to relax the travel restrictions, and the RAG testing was requested to provide advice on the following:

- The current guideline is to test all resident travelers returning from a red zone following a stay longer than 48 hours abroad with an RT-PCR asap after arrival. However, it is not possible to control to what extent travelers follow this guidance. Testing with a rapid Ag test at site upon entry could ensure that travelers are tested and adhere to quarantine/isolation measures.
- Similarly, foreigners are now only allowed entry upon presentation of a recent negative RT-PCR test ≤ 72 hours before departure. Testing with a rapid Ag test upon arrival could give extra assurance.
- The guidelines apply to travelers coming from red zone countries. ECDC makes a distinction between red and dark red zones. The RAG testing was asked its opinion on distinguishing between red and dark red zones in the testing procedures.

CURRENT TRAVELER TESTING PROCEDURES

- Residents returning from a red zone (≥ 6 years):
 - Receive corona test prescription code per SMS to go for a RT-PCR test asap
 - Go in isolation if positive result or in quarantine if negative result (both 10 days)
 - Can leave quarantine after 7 days if the RT-PCR test on day 7 is negative
- Non-residents arriving from a red zone (≥ 6 years):
 - Have to have upon arrival a negative RT-PCR result that is less than 72 hours old
 - Go in quarantine (10 days)
 - Can leave quarantine after 7 days if a RT-PCR test on day 7 is negative.

ECDC COLOR CODES

- Red: the 14-day cumulative COVID-19 case notification rate ranges from 50 to 150/100,000 and the test positivity rate is 4% or more, OR the 14-day cumulative COVID-19 case notification rate is more than 150 but less than 500/100,000.
- Dark red: the 14-day cumulative COVID-19 case notification rate is 500/100,000 or more.

DISCUSSION

Rapid Ag test instead of RT-PCR

Arguments in favor of using a rapid Ag test

- Cost saving
- Can provide a faster result, if tested immediately upon arrival
- If tested immediately upon arrival, more control over adherence to testing, and theoretically possible increased adherence to isolation and quarantine

Arguments in disfavor of using a rapid Ag test

- Sample can no longer be sequenced for the detection of new variants (as is currently indicated for travelers returning from a red zone)
- Lower sensitivity and specificity compared to an RT-PCR, particularly in asymptomatic people
- Advantage of a faster result is less valid if test cannot be performed at the point of entry
- Control over adherence to testing, isolation and quarantine is dependent on many factors:
 - Only applies if test is done upon entry and if measures are in place to ensure that arriving travelers get tested
 - Ensuring adherence to isolation is only possible if a positive person is kept in isolation straight after arrival in e.g. a hotel, as is done in some countries, and there will only be an impact on adhering to quarantine, if a negative result, if the test and quarantine strategy is reinforced
- Is logistically very challenging, and probably only possible in certain settings (airports, high-speed train railway stations) and not in other (travelers returning by car, by normal train, by bus)
- Having a different test used in returning travelers than in high-risk contacts is confusing, considering that both are tested for the same reason (asymptomatic and been at risk for infection)
- If not well organized, implementing a testing procedure at the point of entry may increase crowding, thus creating opportunities for SARS-CoV-2 transmission

Other considerations

- Another test procedure that could be considered is using automated antigen testing, as is currently planned in some airports in Germany. These tests may have a better

performance than rapid Ag tests (although still less than an RT-PCR), and can provide results in one hour time. It implies, however, new infrastructures and skilled staff.

Distinguishing between red and dark red zones

Having different procedures for travelers returning from dark red zones will unnecessarily complicate matters.

Additional testing of non-residents upon entry

- An additional test upon or as soon as possible after arrival offers certain advantages such as early identification of new variants. This assumes that the test is done with an RT-PCR and not with a rapid Ag test. However, this advantage has to be weighed against the additional operational and financial cost. There is currently sufficient test capacity, but there are other test strategies that are being considered and the use of this underused capacity must be based on clear priorities.
- Testing incoming non-residents with a rapid PCR test (such as GeneXpert) upon arrival is not an option, because of the shortage of this type of tests and its cost.
- With regards to reducing the risk of transmission from infected travelers during and after travel, the current test strategy of providing proof of a negative RT-PCR test before departure and a quarantine of 10 days, shortened to 7 days if tested on day 7, is believed to be sufficiently effective. This assumes, however, that the quarantine is strictly adhered to.
- Reducing the pre-travel period in which a test can be done to 48h, instead of 72h, (as recommended by ECDC) is not recommended. For travelers coming from some countries, as the US, it is difficult to get a test result on such short notice

RECOMMENDATIONS

Considering the pro's and contra's of testing returning travelers with a rapid Ag test instead of an RT-PCR, the RAG testing concludes:

- That the current procedure of testing resident travelers returning from a red zone with an RT-PCR, asap after their return, remains the preferred strategy.
- That rapid Ag tests can be an alternative but only if:
 - For some reason (insufficient PCR testing capacity, too high cost of PCR testing) it is no longer possible to test all returning travelers within reasonable time with an RT-PCR;
 - The logistics for testing at the point of entry be carefully organized to ensure physical distancing, the protection of staff at all times, sufficient quality of the tests performed and reasonable waiting times.
- A sufficient proportion of travelers returning from a red zone need to be tested with an RT-PCR for sequencing purposes.

- The problem of poor adherence to testing, isolation and quarantine cannot be resolved by using rapid Ag tests instead of RT-PCR, and other measures are needed to reinforce adherence (regardless of the test used).
- Other possible strategies, such as using automated Ag tests, need to be further explored.
- Other aspects of the current guidelines, such as a 10-days quarantine for all travelers from a red zone (returning residents and arriving foreigners) that can be shortened if an RT-PCR on day 7 is negative, or the requirement for arriving foreigners to have a negative RT-PCR result that is less than 72 hours old, remain valid.
- Adding an additional test for non-resident travelers coming from a red zone upon arrival or as soon as possible after arrival is an option, but not a necessity. It can only be considered if:
 - It is operationally feasible
 - There are no other priorities for using the current unused test capacity
 - The test is an RT-PCR test, allowing sequencing for active genotyping
- Similar as for returning resident travelers, most important is to reinforce the adherence to the quarantine period. To allow sequencing, non-resident travelers should be encouraged to perform a test on day 7 of the quarantine.

BACKGROUND LITERATURE

Literature

Several modelling studies have evaluated different test strategies to reduce the risk of transmission from infected travelers during and after travel.

Johansson et al. found that a quarantine of 7 days combined with symptom monitoring and a test on day 3-4 after arrival is highly effective (95-99%). With effective quarantine after arrival, testing a few days later optimizes sensitivity to detect those infected immediately before or while traveling (1).

Taylor et al. found that, without quarantine, a single RT-PCR taken upon arrival at the airport is only 39.6% effective (2). Alternatively, testing four days after arrival is 64.3% effective whereas a test at the airport plus additional test four days later is 68.9% effective.

Clifford et al. observed that a quarantine period of 8 days on arrival with a PCR test on day 7 can reduce the number of infectious arrivals released into the community by a median 94% compared to a no quarantine, no test scenario (3).

International and national recommendations

ECDC

ECDC published guidelines for COVID-19 testing of air travelers on 2 December 2020 (4), in which they state that if screening of travelers is being considered, Member States should aim for the use of RT-PCR tests or other tests with performance close to RT-PCR. Rapid Ag tests

have by nature of their technology a lower sensitivity than RT-PCR tests for detecting SARS-CoV-2 and therefore a lower positive predictive value. In a low prevalence population, such as travelers, screening of asymptomatic persons by rapid Ag tests is not recommended and therefore, if such screening is to be attempted by Member States, RT-PCR tests should be used instead.

ECDC is currently developing a TECHNICAL REPORT on Guidance for COVID-19 quarantine and testing for travelers. In the draft version, they recommend the following testing strategy in travelers:

1. A pre-departure test, at the earliest 48 hours before departure or at the point of departure. If this is difficult or hardly feasible (e.g. short business or personal trips, tourists, or other non-residents at the place of departure), this could be replaced by a test performed immediately upon arrival at the destination.
2. Testing five-to-seven days after arrival.

ECDC warns that implementing a testing procedure at any point of departure and/or entry will increase crowding, thus creating further opportunities for SARS-CoV-2 transmission. It is therefore crucial that the logistics for testing are carefully organized to ensure physical distancing of travelers and the protection of staff at all times.

With regard to sequencing for the detection of new variants, ECDC suggests that for an early detection and prevalence calculation of known VOCs, alternative methods, such as using diagnostic screening PCR-based assays that generate results in a few hours, with subsequent verification/confirmation by sequencing, can be valuable.

WHO

The latest guidance from WHO with regard to testing in the context of international travel dates from 16 December 2020 (5). It states: 'Nucleic Acid Amplification Testing (NAAT), such as with real-time reverse-transcription polymerase chain reaction (rRT-PCR), is the recommended assay type for confirmation of SARS-CoV-2 infection. Use of Ag-RDTs is not recommended in settings or populations with low expected prevalence of disease where confirmatory testing by NAAT is not readily available. The prevalence of SARS-CoV-2 infection among travelers is expected to be low compared to the general population, considering that symptomatic individuals and case contacts should already have been prevented from travelling. The test population has an influence on the sensitivity and specificity of a test, and evaluations of using SARS-CoV-2 Ag-RDTs at points of entry are limited'.

CDC

The most recent CDC update on testing and international air travel (18 February 2021) (6) recommends that all air passengers, 2 years of age or older, traveling into the US, including US citizens and legal permanent residents, arriving to the US from a foreign country to get tested no more than 3 days before their flight departs.

After return, US residents are recommended to get tested 3-5 days after travel AND stay home and self-quarantine for 7 days after travel. If they don't get tested, it is recommended to self-quarantine for 10 days after travel. This does not apply to non-residents.

Travelers must be tested with a viral test that could be either an antigen test or a nucleic acid amplification test (NAAT). Rapid tests are acceptable as long as they are a viral test acceptable under the Order.

The Netherlands

Travelers to the Netherlands from a high-risk country, aged 13 years and older, must present a negative PCR test result and a negative rapid test result (7).

A molecular PCR test must have been conducted less than 72 hours before arrival. Travelers coming to the Netherlands by aircraft or ferry have to have, in addition, a rapid Ag test no more than 4 hours before boarding.

They must quarantine for 10 days immediately after returning to the Netherlands, and if tested on day 5 can shorten the quarantine period.

France

As in Belgium, non-essential international travel is currently prohibited in France. For essential travel the following procedures apply (8):

All incoming travelers aged 11 or over have to present a negative RT-PCR test result, carried out less than 72 hours before departure. Travelers from outside Europe must, in addition, self-isolate for 7 days upon arrival in France, and submit, if aged 11 years or older, to a RT-PCR test at the end of the isolation period. If traveling from a place where an RT-PCR test cannot be carried out, a virological screening test capable of detecting SARS-CoV-2 (antigen/lateral flow test) can be performed upon arrival.

United Kingdom (England)

All travelers to England, aged 11 years or older, must have proof of a negative COVID-19 test, taken in the 3 days before departure (9). The test must meet performance standards of $\geq 97\%$ specificity, $\geq 80\%$ sensitivity at viral loads above 100,000 copies/ml. This could include tests such as:

- a nucleic acid test, including a polymerase chain reaction (PCR) test or derivative technologies, including loop-mediated isothermal amplification (LAMP) tests;
- an antigen test, such as a test from a lateral flow device.

Upon arrival in England, travelers need:

- to quarantine for 10 days, either in the place they are staying or in a quarantine hotel, depending on where they have been in the 10 days before arrival in England.
- Take two COVID-19 tests, one upon arrival, one to shorten the quarantine period after 5 days of isolation.

Germany

Also in German, non-essential international travel is currently prohibited (10).

Essential travelers, six years or older, who have been in a high incidence area or in a virus variant area in the past ten days prior to entry into Germany must carry proof that they have been tested with them upon entry (11).

Travelers who have visited any other risk area have to furnish proof of a negative test result within 48 hours of entry.

The swab specimen must have been taken at the earliest 48 hours before entry. They enter a 10-day quarantine period, but can lift it earlier with a second negative test.

Rapid antigen tests are recognized if they fulfil the minimum criteria of $\geq 80\%$ sensitivity and $\geq 97\%$ specificity. To optimize the performance of such rapid antigen tests, the antigen tests should not be carried out by laypersons, but exclusively by trained personnel with strict adherence to the manufacturer's instructions.

Persons who have been in areas with a particularly high risk of infection within the last 10 days before entering Germany are obliged to have their tests before the start of the trip to Germany.

Germany will provide testing at international airports (12). At many international airports, testing is already available, usually conducted in the form of a RT-PCR tests, in some cases in the form of other internationally recognized testing procedures for the direct detection of the SARS-CoV-2 (LAMP, TMA as well as WHO-approved antigen tests) (13).

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