RECOMMANDATIONS STATEGIE DE TESTING

RAG sous-groupe testing – 14 Décembre 2020

Note : Les recommandations actuelles sont susceptibles d'être modifié en fonction de nouvelles preuves scientifiques et/ou de l'évolution de l'épidémie.

Principales recommandations selon leur importance :

Niveau 1 - Testing est considéré comme nécessaire et donc fortement recommandé :

- Personnes présentant des symptômes suggestifs
- Contacts à haut risque
- Contacts à faible risque lors de l'investigation de clusters dans les écoles et les entreprises
- Voyageurs de retour d'une zone rouge
- Nouveaux résidents des maison de repos et de soins
  (en fonction de la situation épidémiologique)
- Les patients non-COVID admis dans un service à haut risque d'un hôpital
  (en fonction de la situation épidémiologique)
- Dépistage périodique du personnel des maison de repos et de soins, et des infirmiers à domicile
  (en fonction de la situation épidémiologique)

Niveau 2 – Testing est considéré comme utile mais non nécessaire, et est donc facultatif et dépendent de la situation épidémiologique et des autres conditions à remplir :

- Visiteurs des maison de repos et de soins
- Dépistage ponctuel d'autres personnes susceptibles d'infecter ponctuellement de nombreuses autres personnes et pour lesquelles des mesures préventives efficaces ne sont pas ou sont difficiles à mettre en œuvre
- Dépistage périodique d'autres groupes de population qui peuvent potentiellement infecter beaucoup d'autres personnes de manière continue et pour lesquels des mesures préventives efficaces sont impossibles ou difficiles à mettre en œuvre

Recommandations générales

- Un délai d'exécution (« turn around time ») court (objectif < 24h) reste important, dans toutes les situations de testing.
- La principale priorité en matière de tests reste les personnes présentant des symptômes et l'investigation de clusters. Maintenant que la capacité de test le permet, tester les contacts à haut risque est également une priorité.
- Des nouvelles techniques, telles que le prélèvement de salive et les tests rapides de dépistage d'antigènes, créent des possibilités de nouvelles stratégies de dépistage, comme les tests périodiques et le dépistage ponctuel.

- Les tests ne suffisent pas à eux seuls à contrôler l'épidémie. Tous les efforts déployés pour augmenter la capacité n'ont de sens que si la mesure d'isolement (et la quarantaine pour les contacts) est correctement observée.
- Certaines indications de testing ne sont applicables que dans un contexte de forte circulation du virus (= en fonction de la situation épidémiologique). Pour déterminer une valeur seuil à cet égard, on utilisera les données issues d'études de modélisation. En attendant, les valeurs seuils de la stratégie politique seront utilisées. Dans la phase de contrôle (incidence cumulée sur 14 jours < 100/100 000 et RP < 3 %), le dépistage des individus asymptomatiques, en dehors des contacts à haut risque et des voyageurs revenant d'une zone rouge, est moins utile.
- En raison de la capacité accrue des tests, les tests PCR et les tests Ag rapides peuvent être utilisés plus largement, également pour des raisons socio-économiques, plutôt que pour des raisons de santé publique. La décision de savoir qui doit payer pour un test particulier doit être prise par les autorités politiques, et non par le RAG.
- Cependant, il est important que (au moins) tous les résultats positifs des tests effectués soient communiqués via health/data et Sciensano aux centres de recherche de contact.
- La réalisation d'un test doit également respecter le cadre juridique. Par exemple, un test Ag rapide ne peut être effectué que sur ordonnance et sous la responsabilité d'un médecin.
- Dans le cadre de cet avis, aucune liste exhaustive des applications possibles des échantillons de salive ou des tests Ag rapides pour le dépistage n'a été établie, mais des critères ont été définis pour évaluer l'utilité de ce dépistage. Le RAG propose d'évaluer les demandes d'avis sur le dépistage sur une base hebdomadaire, sur la base d'un document modèle pour la demande d'avis, qui sera établi.

Utilisation des tests PCR

Le test PCR sur un écouvillon naso-pharyngé ou un écouvillon combiné gorge/nez reste actuellement la référence (golden standard) pour le diagnostic d'une infection par le SARS-CoV-2 (sensibilité la plus haute). La capacité de réaliser des tests PCR a entre-temps été augmentée, ce qui offre des possibilités d'utilisation plus étendue.

Le test PCR reste recommandé lorsqu'il n'y a pas encore suffisamment de preuves que l'alternative, le test antigénique rapide, a une fiabilité suffisante. Le test PCR reste recommandé pour le diagnostic dans les cas avec des symptômes qui durent plus de 5 jours et chez les patients admis dans un service d'urgence et nécessitant une hospitalisation immédiate. Le test PCR reste également recommandé pour tester les contacts à haut risque et les voyageurs revenant d'une zone rouge, ainsi que pour les tests répétés d'échantillons de salive.

Comme dans les recommandations précédentes du RAG, pour les contacts à haut risque, un test initial est recommandé dès que possible après l'identification du cas contact, endéans maximum les trois jours qui suivent la dernière exposition. Ce test permet de détecter rapidement les contacts positifs afin de lancer la recherche de contacts secondaires. Si la personne de contact est identifiée tardivement (au-delà de 72h du dernier contact à risque), le premier test n'est plus utile et ne doit donc pas être effectué. Si la quarantaine est arrêtée avant 10 jours, un deuxième test est toujours requis chez tous les contacts au plus tôt 7 jours après le dernier contact à haut risque afin d'exclure toute infection avant la fin de la quarantaine.

Les voyageurs revenant d'une zone rouge sont testés, tout comme les contacts à haut risque, au plus tôt 7 jours après leur retour, afin d'exclure toute infection avant la fin de la quarantaine, si elle est arrêtée avant 10 jours.

Utilisation du PCR multiplex

La recommandation du RAG en septembre reste inchangée. Les tests PCR multiplex, qui détectent simultanément plusieurs agents pathogènes respiratoires, sont utiles pendant l'épidémie de grippe chez les patients présentant des symptômes respiratoires graves. Ces tests ne sont recommandés qu'en milieu hospitalier (patients des services d'urgence et patients hospitalisés) et si les données de surveillance montrent effectivement une épidémie de grippe. Chez les patients présentant des symptômes très graves, il est recommandé d'utiliser si possible un maxi-panel (détection d'un large éventail d'agents pathogènes), tandis que chez les patients présentant des symptômes moins graves, un mini-panel suffit (uniquement pour le SARS-CoV2/influenza A/B, ou uniquement pour le SARS-CoV2/influenza A/B et le RSV).

Utilisation des tests antigéniques (Ag) rapides

Les tests Ag rapides de la deuxième génération sont un complément utile aux tests PCR. Il reste essentiel de limiter la sélection des tests antigéniques aux tests qui sont suffisamment validés. Les tests qui, chez les patients dont la durée maximale des symptômes est de 5 jours, ont une sensibilité inférieure à 80 % ou une spécificité inférieure à 97 % (par rapport à une RT-PCR) ne doivent pas être utilisés. La sensibilité souhaitée est >90 %, et chez les personnes ayant une charge virale élevée (>=10^5 copies de RNA/mL ou valeur Ct <25), qui sont très infectieuses, elle devrait être >95 %. Ces valeurs seuils doivent être confirmées par au moins trois évaluations indépendantes.

Des tests répondant aux conditions ci-dessus sont déjà disponibles et recommandés chez les personnes symptomatiques présentant des symptômes suggestifs depuis ≤ 5 jours dans un cabinet de médecine générale, un centre de triage ou un service d'urgence - voir l'avis du RAG de novembre.

Actuellement, il existe peu de données scientifiques sur la sensibilité des tests rapides Ag chez les individus asymptomatiques, mais ces tests permettent d'identifier en tous les cas les individus très contagieux (>=10^5 copies de RNA/mL ou valeur Ct <25). Par conséquent, les tests Ag rapides sont également recommandés pour l'examen d'un cluster, puisque la prévalence attendue est plus élevée et une détection rapide permet de prendre immédiatement les mesures appropriées pour contenir le cluster. Actuellement, des protocoles ont déjà été mis au point pour l'examen des cluster dans les écoles secondaires et les entreprises. Pour l'examen d'un cluster dans un maison de repos et de soins (MRS), on attend les résultats des recherches en cours dans ce cadre.

Les tests Ag rapides peuvent également être utilisés pour le dépistage immédiat des personnes (asymptomatiques) qui par un contact ponctuel ont le potentiel d'infecter de nombreuses autres personnes (prévalence relativement élevée, et contact étroit avec un grand nombre de personnes ou propagation possible au sein d'une collectivité) ou d'entrer en contact avec des personnes exposées à un risque d'infection grave ; et pour lesquelles des mesures préventives efficaces ne sont pas ou sont difficiles à mettre en œuvre. Ainsi, un MRS peut envisager de proposer un dépistage aux visiteurs afin d'éviter qu'une personne positive

et très contagieuse n'infecte les résidents vulnérables. Toutefois, comme un résultat négatif n'exclut pas la possibilité que le visiteur soit contagieux, les mesures de précaution habituelles en application doivent continuer d'être respectées. En outre, le résultat d'un test Ag rapide ne s'applique qu'au jour même. Pour les personnes qui se rendent au MRS plusieurs fois par semaine, un dépistage périodique peut être envisagé (voir ci-dessous).

L'utilisation des tests Ag rapides pour les enfants de moins de 12 ans dans le cadre d'un dépistage ponctuel n'est pas recommandée. Le prélèvement d'un échantillon de nez/gorge ou nasopharyngé doit être réservé dans ce groupe pour la détection d'une infection ou pour les contacts à haut risque, et seulement chez les enfants >= 6 ans.

Le dépistage ponctuel n'est pas fortement recommandé pour l'instant, mais peut être envisagé s'il est justifié du point de vue de la santé publique. Le dépistage ponctuel ne devrait jamais avoir pour objectif principal un assouplissement des mesures. Toutefois, si les mesures sont assouplies pour d'autres raisons socio-économiques, le dépistage ponctuel peut être un moyen de minimiser les conséquences négatives de ces assouplissements.

Utilisation d'échantillons de salive

- Pour détecter la présence du SARS-CoV-2, les échantillons de salive ne peuvent être analysés que par PCR. Des études sont en cours sur l'utilisation des tests antigéniques rapides sur salive, mais cette combinaison n'a pas été suffisamment validée à ce jour.
- Il n'y a pas encore suffisamment d'évidence scientifique à ce jour pour recommander l'utilisation d'échantillons salivaires comme outil de diagnostic chez un patient symptomatique, ni pour les utiliser chez les enfants. Un échantillon de salive ne peut être envisagé que si un écouvillon nasopharyngé ou un écouvillon combiné gorge/nez n'est pas possible ou difficile.
- Un protocole a été établi pour le prélèvement et l'analyse des échantillons de salive[1].
- La capacité actuelle PCR permet l'utilisation d'échantillons de salive dans le cadre d'un dépistage périodique chez des personnes (>=12 ans) asymptomatiques.
- Étant donné que les conditions proposées pour son lancement sont remplies (protocole et capacité PCR suffisante), le dépistage périodique (au moins hebdomadaire) est maintenant recommandé au personnel du MRS et aux infirmières à domicile s'occupant de personnes à risque d'infection sévère COVID-19.
- Le dépistage périodique d'autres populations n'est pas recommandé actuellement, mais il peut être envisagé s'il est justifié du point de vue de la santé publique, c'est-à-dire chez les personnes susceptibles d'infecter de nombreuses autres personnes (prévalence relativement élevée, et contact étroit avec un grand nombre de personnes ou propagation possible au sein d'une collectivité) ou d'entrer en contact avec des personnes exposées à un risque d'infection grave ; et lorsque des mesures préventives efficaces ne sont pas ou sont difficiles à mettre en œuvre. Le dépistage périodique ne devrait jamais avoir pour objectif principal un assouplissement des mesures. Toutefois, si les mesures sont assouplies pour d'autres raisons socio-économiques, des tests périodiques peuvent être un moyen de minimiser les conséquences négatives de ces assouplissements.

[1] Disponible à: https://covid-19.sciensano.be/sites/default/files/Covid19/20201130_Advice%20RAG_Saliva%20sampling_FR.pdf

- La fiabilité exacte n'étant pas encore totalement connue, l'utilisation d'échantillons salivaires n'est pas recommandée à ce stade pour le testing des contacts proches ou des voyageurs au retour.

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Résumé recommandations de testing

Indication	Échantillon recommandé	Test recommandé	Type de recommandation
Personne symptomatique			
Symptômes<=5 jours	Écouvillon naso-pharyngé ou nez/gorge	Ag RDT	Dans les centres de triage, les cabinets de médecine générale[2] et les services d'urgence
Symptômes>5 jours ou hospitalisation urgente	Écouvillon naso-pharyngé ou nez/gorge	PCR	Généralement recommandé
Gravement malade pendant une épidémie de grippe	Écouvillon naso-pharyngé ou nez/gorge	PCR Multiplex Mini-panel	Uniquement en milieu hospitalier
Très gravement malade pendant une épidémie de grippe	Écouvillon naso-pharyngé ou nez/gorge	PCR Multiplex Maxi-panel	Uniquement en milieu hospitalier
Contacts étroits			
Contact étroit, immédiatement après l'identification	Écouvillon naso-pharyngé ou nez/gorge	PCR	Si dernier contact<=3 jours
Contact étroit, 7 jours après le dernier contact	Écouvillon naso-pharyngé ou nez/gorge	PCR	Si la quarantaine est arrêtée prématurément (<10 jours)
Voyageurs asymptomatiques			
Voyageur de retour d'une zone rouge (jour 7)	Écouvillon naso-pharyngé ou nez/gorge	PCR	Si la quarantaine est arrêtée prématurément (<10 jours)
Investigation d'un cluster			
Contacts à faible risque dans les clusters scolaires	Écouvillon naso-pharyngé ou nez/gorge	Ag RDT	Uniquement dans les écoles secondaires
Contacts à faible risque dans les clusters d'entreprises	Écouvillon naso-pharyngé ou nez/gorge	Ag RDT	Tous les clusters dans un environnement de travail
Dépistage périodique			
Tests périodiques du personnel de MRS et des infirmières à domicile	Salive	PCR	Recommandé en fonction de la situation épidémiologique
Tests périodiques sur d'autres populations	Salive	PCR	Facultatif et seulement si certaines conditions sont remplies
Dépistage ponctuel			
Admission à l'hôpital d'un patient non-COVID	Écouvillon naso-pharyngé ou nez/gorge	PCR	Selon les lignes directrices existantes pour les hôpitaux[3]
Nouveaux résidents MRS	Écouvillon naso-pharyngé ou nez/gorge	PCR	Recommandé en fonction de la situation épidémiologique
Visiteurs MRS	Écouvillon naso-pharyngé ou nez/gorge	Ag RDT	Facultatif
Autres situations	Écouvillon naso-pharyngé ou nez/gorge	Ag RDT	Facultatif et seulement si certaines conditions sont remplies

[2] Dès que les études pilotes en cours seront terminées et si elles ont eu un résultat positif
[3] Disponible à : https://covid-19.sciensano.be/sites/default/files/Covid19/Lettre_Strat%C3%A9gie%20de%20test%20pour%20les%20h%C3%B4pitaux%20g%C3%A9n%C3%A9raux%20et%20psychiatriques%20et%20pour%20les%20h%C3%B4pitaux%20de%20r%C3%A9adaptation.pdf

CONTEXT

The PCR test capacity has substantially improved over the past month, better performing rapid antigen tests have become available and a protocol for sampling and analyzing saliva specimens has been developed. This opened perspectives for new testing strategies.

The current test strategy update focusses on the following topics:

1. TESTING OF ASYMPTOMATIC HIGH-RISK CONTACTS

1.1. Definition of a high-risk contact

The current definition of a contact person is any person who has had contact with a confirmed COVID-19 case within a period of 2 days before the onset of symptoms (symptomatic cases) or before the sample was taken (asymptomatic cases) until the end of the infectivity period of the case - generally 7 days after the start of the symptoms, or longer if symptoms persist, (symptomatic cases) or 7 days after the sample was taken (asymptomatic cases).

A contact person is considered a high-risk contact if any of the following conditions are present[4]:

- a cumulative contact of at least 15 minutes within a distance of <1.5 m ("face to face") without proper use of a mouth mask by either person;
- direct physical contact with a COVID-19 patient;
- direct physical contact with excretions or body fluids of a COVID-19 patient;
- been identified by the "Coronalert" application as a close contact;
- traveled with a COVID-19 patient for more than 15 minutes.

1.2. Past and current recommendations

Recommendations for testing (asymptomatic) high-risk contacts (HRCs) have changed over time in response to the evolution of the epidemic and the available testing capacity. Initially, only HRCs with a high risk of coming in contact with vulnerable populations were tested (with a PCR) at the end of the 14-days quarantine period (between day 11 and 13), to confirm that they are not infected.

In June (12/6), when the incidence had decreased and the contact tracing system had become operational, the recommendation became to test all HRCs, except children under 6, immediate after identification to detect positive cases. HRCs testing negative went into a 14 days quarantine period. The rule to test HRCs in contact with vulnerable populations at the end of the quarantine period was maintained.

At the end of June (23/6), the protocol was revised. If the test was done within 7 days of the last contact, a second test could be performed the earliest 5 days after the first test and 9 days after the last contact. If both tests were negative, the quarantine could be stopped at day 10.

[4] More detailed definition available at: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_procedure_contact_NL.pdf

HRCs in contact with vulnerable populations could also be tested in the first week after exposure, but had to remain in quarantine if testing negative. Only if testing negative on day 11 to 13, the quarantine could be stopped on day 14.

At the beginning of October (1/10), when incidence had increased again and the 14-day quarantine period resulted in some staff shortages, the strategy changed to no longer test HRCs immediately after identification and only test them the earliest 5 days after the last contact. If testing negative, the quarantine could be stopped on day 7.

At the end of October (21/10), testing of asymptomatic HRCs was put on a hold because of the high pressure on the PCR testing capacity.

Since November 23, testing of asymptomatic HRCs has reinitiated. The current recommendation is the same as the October 1st recommendation:

- All asymptomatic close contacts (except children <6 years) should be tested at the earliest 7 days after the last high-risk contact.
    - If the result is positive, the home isolation is extended to 7 days after the test (or start of symptoms). The contact becomes an index case and the detection of his or her closest contacts is initiated.
    - If the result is negative, the quarantine can be lifted as soon as the test result is obtained (minimum 7 days after the last high-risk contact). As the incubation period can be up to 14 days, the general measures must be followed for a further 7 days.

1.3. International recommendations and strategies in other countries

ECDC

ECDC updated its recommendations with regards to contact tracing on November 18[5].

It recommends that high-risk contacts without symptoms are tested as soon as possible after being traced, to enable early identification of any asymptomatic or pre-symptomatic secondary cases among contacts and to start further contact tracing. This also applies to low-risk contacts in settings with vulnerable populations or in which transmission is likely, such as health and social care settings, prisons, certain occupational settings and social events such as choirs or weddings.

Both RT-PCR and Ag RDTs can be considered. Ag RDTs have the advantage of speed which allows for further contact tracing to commence as soon as possible. If more than seven days have passed since the exposure, it is recommended that negative Ag RDTs are confirmed by RT-PCR.

Even if the test is negative, high-risk exposure contacts still need to quarantine, and low-risk exposure contacts still need to observe prevention measures for the remainder of the 14 days after exposure.

Testing at the end of quarantine can also be done, in addition to the test taken upon tracing. A negative RT-PCR test at day 10 can be used to discontinue quarantine earlier than the recommended 14 days.

Testing capacity may be limited and it is important that testing contact persons for the purpose of ending quarantine early should not adversely impact test accessibility and test turnaround time for symptomatic people.

[5] ECDC - TECHNICAL REPORT - Contact tracing: public health management of persons, including healthcare workers, who have had contact with COVID-19 cases in the European Union – third update - 18 November 2020

In the Technical Report for the use of rapid antigen tests (November 19), ECDC recommends to only test contacts with a Ag RDTs if the test positivity is expected to be ≥10%[6].

WHO

WHO has not updated its guidance on contact tracing since August 19. The latest guidance only stipulated that for contacts who do not develop symptoms, WHO no longer considers laboratory testing a requirement for leaving quarantine after 14 days.

France

In France, asymptomatic contacts are advised to immediately get tested if they live under the same roof as the index case[7]. If they do not live under the same roof, the advice is to get tested 7 days after the last contact. The rationale is that testing earlier has a too great chance of giving a negative result. Contacts living under the same roof testing negative in the first test have to test again 7 days after the index case is cured. If the test is negative, the quarantine can be stopped.

Other countries

The Netherlands and England do not recommend to test contacts. No guidelines were found for Germany.

1.4. Discussion

- A first test early after identification enables early detection of any asymptomatic or pre-symptomatic secondary cases among contacts and to start further contact tracing.
- All HRCs >=6 years old should be tested, including those not living under the same roof, because these might be the index case.
- Systematically testing of low risk contacts in settings with vulnerable populations is not indicated. The current guideline is that the health inspector evaluates the situation when a case is detected in a collectivity with a vulnerable population, such as a nursing home, and can decide, if the risk of an outbreak is high, to test low-risk contacts. This guideline remains adequate.
- It will be difficult to return to a longer quarantine period, because this would face too much resistance of the public, the industry and politicians, and the current recommended period of minimum 7 days should be maintained. A second test on day 7 after the last contact remains therefore indicated. However, if the high-risk contact is only identified several days after the last contact, the period between the first and second test may become very short. There should be at least 4 days between the two tests. In this event, it is indicated to skip the first test and only test on day 7.
- A separate quarantine and testing procedure for contacts living under the same roof and contacts not living under the same roof, as in France, makes it too complicated and is not necessary. The current procedure already takes into account situations where it is not possible to isolate household contacts from each other (such as between parents and small children) and considers in those situations the last day of the 7 day isolation period as the last contact.

[6] ECDC - TECHNICAL REPORT - Options for the use of rapid antigen tests for COVID-19 in the EU/EEA and the UK - 19 November 2020. Available at: https://www.ecdc.europa.eu/en/publications-data/options-use-rapid-antigen-tests-covid-19-eueea-and-uk

[7] J'ai été en contact à risque avec une personne malade du COVID-19 [Fiche patients] - Publié le 3 Novembre 2020 - Mis à jour le 06 novembre 2020. Available at : https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/depliant-flyer/j-ai-ete-en-contact-a-risque-avec-une-personne-malade-du-covid-19-fiche-patients

- In both the first and the second test the more sensitive PCR test is indicated, because the contact might still be in an early stage of infection before viral load increases. This also applies to the second test, because the current quarantine period is much shorter than the incubation period.
- In periods that there is pressure on the PCR capacity and long delays in getting the results (>24h hours), an Ag RDT might be considered as an alternative.
- Testing high-risk contacts is only effective if the contact tracing system is effective, which is currently still insufficiently the case. There is therefore a need to further improve the system.

1.5. Recommendations

- To test all HRCs, 6 years old or older, as soon as possible after their identification.
- To re-test HRCs, who tested negative in the first test, on day 7 after their last contact with the index patient
- To skip the first test if the HRC is identified more than 3 days after the last contact. In that event the HRC is only tested on day 7.
- To use a PCR test for both the first and second test episode, unless there is a delay of more than 24 hours in getting the result. In that event an Ag RDT can be used.
- Low-risk contacts are only tested in the context of a cluster investigation, or when the health inspector judges that there is a risk of an outbreak in a collectivity with a vulnerable population (see separate procedures).

2. REPETITIVE SCREENING[8]

2.1. Current recommendation

The current recommendation (November update) with regards to repetitive screening (using saliva samples) is:

- There is an urgent need to establish a protocol for the use of repetitive saliva samples in combination with PCR in various sectors (health care, education, high-risk companies, essential services).
- If there is an increased demand for saliva testing in a setting of repetitive screening, the pressure on PCR testing capacity will further increase. Therefore, before starting repeated screening using saliva samples, the capacity must first be increased.
- If the two conditions mentioned above (sufficient PCR capacity and protocol available) are met, the use of saliva samples for repeated screening (at least weekly) in asymptomatic adults, such as staff of nursing homes, can be considered.

2.2. Literature

Several modelling studies have assessed the effectiveness of repetitive screening in controlling SARS-CoV-2 spread in specific populations. All these models showed that frequent testing with a less sensitive test (rapid antigen test) or a less sensitive sample (saliva) is more effective than one-time testing with the more sensitive RT-PCR on a naso-pharyngeal sample

[8] For the purpose of this advice we define 'repetitive screening' as testing asymptomatic people at frequent regular intervals to rapidly detect an infection by SARS-CoV-2.

(1–3). The recommended periodicity varies across models and is dependent on various factors, such as the sensitivity and specificity of the test, the prevalence, the reproductive number and the compliance to measures taken for positive cases. Most studies recommend a periodicity of at least 2-3 times a week (4–7), but other state that relatively infrequent testing, such as every one or two weeks, is already sufficient to keep controlled outbreaks small (8). One study assessed the effect of regular universal testing and concluded that this strategy would require unrealistic high testing frequencies to reopen society while maintaining control of virus transmission (9).

Atkeson at al. assessed the economic benefits of repeated testing (with a rapid antigen test) and concluded that the fiscal, macroeconomic, and health benefits of rapid SARS-CoV-2 screening testing programs far exceed their costs (10). A weekly testing in a regime with high compliance comes close to suppressing the virus, and moving to a four-day cadence is highly effective. They point out however, that the screening testing program must have high specificity to be credible and to evoke high adherence. If specificity is not close to 100%, the positive predictive value is low in low-prevalence settings, putting many people unnecessary in isolation. They propose therefore confirmation of positive results with an RT-PCR test. The problem of low positive predictive value in low prevalence settings, and therefore a need to confirm positive results, is also addressed in another study (11).

Studies evaluating the effect of repetitive screening in a real-life situation are rare. One study evaluated a longitudinal screening program for critical on-site employees within a research institute, and concluded that it was accepted by employees and can be used to maintain the health of the workforce, potentially keeping positivity rates below community levels (12). Another study screened asymptomatic HCWs in a large hospital over a 3-week period and concluded that such an approach is critical for protecting patients and hospital staff (13). Both these studies used RT-PCR tests.

2.3. International recommendations

Very few countries have issued guidelines on repetitive screening. **ECDC** mentions in their '*Population-wide testing of SARS-CoV-2: country experiences and potential approaches in the EU/EEA and the United Kingdom'* report (19 August 2020) that most EU/EEA countries and the UK regularly test individuals in high-risk settings such as at healthcare facilities[9]. Of the eight countries that responded to the ECDC enquiry that are not currently planning population-wide testing of individuals without symptoms, at least five regularly test individuals without any symptoms in high-risk settings e.g. healthcare workers, individuals working in long-term care facilities, and people in various other settings, such as patients admitted to hospitals, individuals in specific occupational settings, prisons, etc. Testing in these settings was sometimes occurring in response to a cluster of cases reported in that group or setting, or carried out to protect vulnerable populations (i.e. patient groups, health workers, patients or long-term care facility residents).

WHO

In its interim guidance on Prevention, identification and management of health worker infection in the context of COVID-19 (30 October 2020), the World Health Organization lists factors that should be taken into account when deciding on the need for routine testing among health care workers[10]:

[9] Available at: https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-population-wide-testing-country-experiences.pdf

[10] Available at: file:///C:/Users/YvLa1869/Downloads/WHO-2019-nCoV-HW_infection-2020.1-eng%20(2).pdf

- The intensity of transmission in the setting of the health facility(ies), for example in the presence of community transmission or intense outbreaks of COVID-19.
- The capacities of the facility and laboratories to conduct the testing including financial and human resources available, as well as availability of testing materials and laboratory capacity.
- The volume of patients identified as positive for SARS-CoV-2, admitted to the facility or being assessed by health workers.
- The positivity rate among staff.
- The number of staff who are ill but not diagnosed with COVID-19 and in quarantine as contacts for COVID-19, leading to inability to provide adequate and safe staffing levels.

For health workers staffing or working with long-term care facilities, they recommend routine testing irrespective of the COVID-19 transmission scenario.

CDC

The US Centers for Disease Control recommends that staff of nursing homes be serially tested based on the county percent test positivity rate. Approaches may include initial testing of all workers before entering a workplace, periodic testing of workers at regular intervals, and/or targeted testing of new workers or those returning from a prolonged absence.

2.4. Discussion

- The main objective of repetitive screening should be a public health one, namely to early detect positive infections in people whose infection can have serious public health consequences (potentially infect many other people or infect vulnerable people).
- The objective of repetitive screening is not to allow relaxation of preventive measures, or to avoid isolation or quarantine. Nevertheless, if epidemic control measures are alleviated for socio-economic reasons, repetitive screening can be a mean to mitigate the negative impact of these relaxations.
- Lower sensitivity of the test used can be compensated by a sufficiently high frequency.
- The use of saliva samples has the advantage of ease of sample taking, but requires the more expensive RT-PCR.
- The use of rapid antigen tests has the advantage of the lower cost and rapidity in getting results, but requires nasopharyngeal, or at least nasal/oral, specimens.

Criteria to consider when deciding on repetitive screening in a specific population (in order of importance):

- Having contact with people vulnerable to severe COVID-19 disease
  Rapid detection of positive COVID-19 cases is especially important in people who are continuously in contact with persons vulnerable to a severe form of the disease. These are in the first place elderly people. Staff in nursing homes and home nurses attending to elderly at their home are therefore populations eligible for repetitive screening.
- Not being able to take the appropriate protective measures
  Repetitive screening is less meaningful in populations that are perfectly able to correctly protect themselves and the people they come in contact with.
- Potential to rapidly transmit the infection to a large number of people
  Repetitive screening is only meaningful in populations that, if infected, have a potential to rapidly transmit the infection to a large number of people. These can be people who have

a large number of serial close contacts, are come in close contact with large groups of people, or live in social clusters, and who have a substantial risk to be infected.

- Feasibility
  Before initiating repetitive screening in a specific population the feasibility needs to be assessed. This is especially important if the size of the population is large.

Criteria to consider in the choice of the specimen to collect and the test to use:

- Ease of sampling
  Because frequent sampling is inherent to repetitive screening, it is recommended to use as much as possible specimens that are little invasive or painful, and easy to collect. Naso-pharyngeal samples are therefore not recommended. Nasal/oral swabs are acceptable, but saliva is by far the least invasive specimen.

- Cost
  The rapid antigen test is much less expensive than an RT-PCR. Nevertheless, the current PCR capacity allows to perform a large number of tests at relatively little additional cost.

- Rapidity of result
  In settings were a very rapid result is required, a rapid antigen test is indicated. However, in a context of sufficient RT-PCR capacity, the turn-around time to get the PCR result should be sufficiently short in most situations.

Testing frequency

The ideal testing frequency depends on a number of factors, such as the sensitivity of the testing protocol used, the positivity rate in the tested population, the incidence and the reproductive number, and the measures taken for positive cases (and level of adherence to those measures). A European consortium, with UHasselt as one of the members, is currently developing a mathematical model that will provide more exact recommendations on the ideal testing frequency in different situations and prevalence levels. Pending the results, we maintain the recommendation to test at least weekly.

Result interpretation

A sufficiently high frequency of testing compensates for the lower sensitivity of a saliva specimen or an Ag RDT, and a person with a negative test result is therefore considered as not having COVID-19 and/or not being infectious.

The use of RT-PCR guarantees a sufficiently high specificity. If an Ag RDT is used with a lesser specificity, there is a risk of a low positive predictive value if the positivity rate in the tested population is very low. However, testing in populations with a very low prevalence is anyway not indicated and even then have false positive detections few negative consequences.

2.5. Recommendations

- We recommend repetitive screening in populations that are in frequent contact with people vulnerable to severe COVID-19 disease (staff at nursing homes, home nurses attending to elderly clients).

- Repetitive screening in other populations is only justifiable if the following conditions are fulfilled:
  - Risk of rapid spread of the infection to a large number of people; AND
  - No possibility to fully apply effective protective measures; AND

    - The number of people to test is feasible.

- Frequency of testing will be defined by the modelling exercise currently in development. Meanwhile, we recommend a frequency of at least weekly.

- We recommend the use of an RT-PCR test on saliva specimens. The use of Ag RDTs on nasal/oral swabs can be a valid alternative if the delay in getting the result is >24 hours because of reduced RT-PCR capacity.

- People testing negative are considered as not having COVID-19 and/or not being infectious. Basic preventive measures need nevertheless to be maintained. People testing positive are considered as confirmed cases and the procedures with regards isolation and contact tracing is initiated.

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3. ONE-TIME SCREENING[11]

3.1. Current recommendation

Testing of asymptomatic people is currently (RAG advice of November 3) advised in the context of contact tracing, returning travelers, cluster investigations and repetitive screening of nursing home staff.

One-time screening is only advised for non-COVID patients requiring hospitalization, under certain conditions, and new residents of nursing homes. The test to use is an RT-PCR. If the test is negative, it can be repeated according to clinical need.

3.2. Literature

Few studies assessing the effect of routine one-time screening in specific situations were identified.

A Cochrane review of universal screening for SARS-CoV-2 infection, done in September, concluded that the evidence base for the effectiveness of screening is limited. Low-certainty evidence suggests that screening at travel hubs may slightly slow the importation of infected cases. The authors highlight the uncertainty and variation in accuracy of screening strategies. A high proportion of infected individuals may be missed and go on to infect others, and some healthy individuals may be falsely identified as positive, requiring confirmatory testing and potentially leading to the unnecessary isolation of these individuals. Further studies need to evaluate the utility of rapid laboratory tests, combined screening, and repeated screening. More research is also needed on reference standards with greater accuracy than RT-PCR (1).

An update in October, concluded that one-time screening in apparently healthy people is likely to miss people who are infected. The authors are unsure whether combined screenings, repeated symptom assessment, or rapid laboratory tests are useful (2).

3.3. International recommendations

WHO

In their Interim guidance for antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays of 11 September 2020, WHO does not recommend the use of rapid antigen tests in individuals without symptoms unless the person is a contact of a confirmed case, and neither for airport or border screening at points of entry[12].

[11] For the purpose of this advice we define 'one-time screening' as testing asymptomatic people prior to a potential risk of spreading SARS-CoV-2 to others. Screening can occur in the same individual on different occasions, but unlike repetitive screening it is not done on pre-defined regular intervals.
[12] Available at: file:///C:/Users/YvLa1869/Downloads/WHO-2019-nCoV-Antigen_Detection-2020.1-eng%20(1).pdf

ECDC

In the guidelines for the use of rapid antigen tests (19 November 2020) ECDC states: 'In a high prevalence situation, in the context of circuit breaker strategies to detect individuals with high transmission potential in the community and to lower the pressure on health-care settings and laboratories, rapid antigen tests' use can be considered for a targeted population-wide testing approach, e.g. in a local community. In such situation, the risk of not detecting all cases or risk of false negative results is balanced out by the timeliness of results and the possibility of serial testing of individuals.' and 'Rapid antigen tests are not suited for screening incoming travelers to prevent virus (re-) introduction in regions/countries that have achieved zero or very low levels of transmission. In these situations, i.e. in a low prevalence population, only RT-PCR should be used to reduce the risk of false negative results. Air travelers belong mostly to a non-symptomatic sub-population, with variable but lower probability of COVID-19 compared to the general population (estimated prevalence of COVID-19 at <1%)[13].

3.4. Discussion

- The main objective of one-time screening should be a public health one, namely to prevent an infected person to infect others before an at-risk exposure.
- The objective of one-time screening is not to allow relaxation of preventive measures, or to avoid isolation or quarantine. Nevertheless, if epidemic control measures are alleviated for socio-economic reasons, preventive screening can be a mean to mitigate the negative impact of these relaxations.
- Screening is less relevant in children <12 years, because the lesser role they play in spreading the SARS-CoV-2 virus..

Criteria to consider when deciding on routine one-time screening in a specific situation (in order of importance):

- People entering in contact with people vulnerable to severe COVID-19 disease
  These are in the first place elderly people. Routine testing of visitors to nursing homes is therefore a meaningful strategy.
- Not being able to take the appropriate protective measures
  Screening is less meaningful in situations where it is perfectly possible to correctly prevent transmission.
- Important contribution to the chain of transmission
  Screening is most meaningful in situations where an early detection of positive cases can prevent further spread of the virus. It is therefore most useful in populations with a high risk of being infected who enter in contact with many other people, or enter in contact with a person in contact with many other people.
- Feasibility
  Before initiating routine screening in a specific setting the feasibility needs to be assessed. Factors to consider with regards to feasibility include the amount of screening tests to perform and the feasibility to perform a rapid antigen test on site.

[13] Available at : https://www.ecdc.europa.eu/sites/default/files/documents/Options-use-of-rapid-antigen-tests-for-COVID-19.pdf

Criteria to consider in the choice of the specimen to collect and the test to use

- Rapidity of result
  In situations where a very rapid result is required, a rapid antigen test is indicated. This is especially the case when screening is done at the moment of entry.

- Cost
  The low cost of the rapid antigen test is an important advantage for large-scale screenings.

- Ease of sampling
  Because one-time screening is not repeatedly done, ease of sampling is a less important criterion.

Result interpretation

Rapid antigen tests have shown to have a lower sensitivity in asymptomatic people and a negative result does therefore not exclude an infection. Rapid antigen tests have a good sensitivity in people with a high viral load and will detect the most infectious infections. Nevertheless, we cannot exclude that some of the missed infections will be infectious. A negative result does therefore not exempt the tested person from respecting all needed preventive and protective measures.

Rapid antigen tests have overall a high specificity. Nevertheless, in settings with a (very) low positivity rate a very high specificity is necessary to avoid too many false positive results. We therefore only recommend one-time screening using a rapid antigen tests with a very high specificity (>99%) and in populations where the expected positivity rate will be at least 1%.

3.5. Recommendations

- One-time screening of visitors to nursing homes is considered a useful strategy, and can optionally be implemented.

- Systematic one-time screening in other situations is only justifiable if the following conditions are fulfilled:
  - Risk of rapid spread of the infection to a large number of people; AND
  - No possibility to fully apply effective protective measures; AND
  - The number of testing events is feasible.

- In situations where an immediate test result is needed (less than 30 minutes), we recommend the use of an Ag RDT with high specificity (>99%) on a naso-pharyngeal or a nasal/oral swab. A PCR test can be used in settings where their result can rapidly be obtained, such as in hospitals.

- If a rapid antigen test is used, a negative result does not exclude infection or infectiousness, and all preventive and protective measures need to be respected.

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4. USE OF MULTIPLEX PCR ASSAYS

4.1. Current recommendation

The testing strategy update of the RAG on 09/09/20 stated that during the flu season symptomatic patients, especially in severe condition, could be tested with a multiplex PCR panel in order to guide therapeutic care and support:

- Hospitalized patients with respiratory symptoms: multiplex PCR mini panel (SARS-CoV2, RSV, Influenza A and B) on nasopharyngeal or nose/throat sample
- Hospitalized patients with respiratory symptoms and severe condition: multiplex PCR maxi panel (detection of 10 pathogens)
- Symptomatic patients in ambulatory care: only test for SARS-CoV-2

Limitations to the routine use of multiplex PCR highlighted on 09/09/2020 included:

- No commercially available multiplex test in Belgium
- No reimbursement of multiplex test
- Not all labs can perform the multiplex test
- Lab personnel has often no information on the clinical profile (symptomatic or asymptomatic; severity) of the patient

4.2. literature

Multiplex PCRs have been used to analyze transmission patterns of different respiratory pathogens as well as to assess the extent of co-infections of SARS-CoV-2 and other common respiratory pathogens, and its impact on clinical outcomes.

In a recent study, Poole et al. assessed the impact of SARS-CoV-2 in the prevalence of respiratory viruses in hospitalized patients (1). They compared samples from March-May 2020 with samples from the same period in previous years. Before 2020, non-SARS-CoV-2 viruses (such as Influenza, rhinovirus, RSV, seasonal coronaviruses or parainfluenza virus) were detected in 54 % of patients. In 2020 non-SARS-CoV-2 viruses were present in 4,1 % of the samples while 38 % of samples were positive for SARS-CoV-2. The emergence of SARS-CoV-2 was therefore associated with reductions in the circulation of seasonal respiratory viruses. The authors concluded that this observation could be due to the measures taken to fight COVID-19, such as social distancing and lock-down. Another hypothesis points at interactions and interferences between different viruses. This has been shown for other respiratory viruses (2).

Reduction in the circulation of other seasonal respiratory viruses during the first peak of the epidemic was also observed in several regions worldwide (3,4). An early Italian study however did not see different trends for other respiratory viruses in March 2020 compared to the same period in previous years (5).

Co-infections of SARS-CoV-2 and other respiratory viruses have been described in several reports, with variable levels of co-infections. In a study by Leuzinger et al. co-infection was shown to occur in 1,8 % of the samples (6). Poole et al. found co-infections of SARS-CoV-2 and other respiratory virus in 1 % of the samples (1). Also other studies found low levels of coinfection with other respiratory viruses (7). Some studies observed more extended cases of co-infections with bacterial pathogens (8).

COVID-19 patients co-infected with influenza had in one study a 2.27 times greater risk of death than non-co-infected patients (9).

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4.3. International recommendations

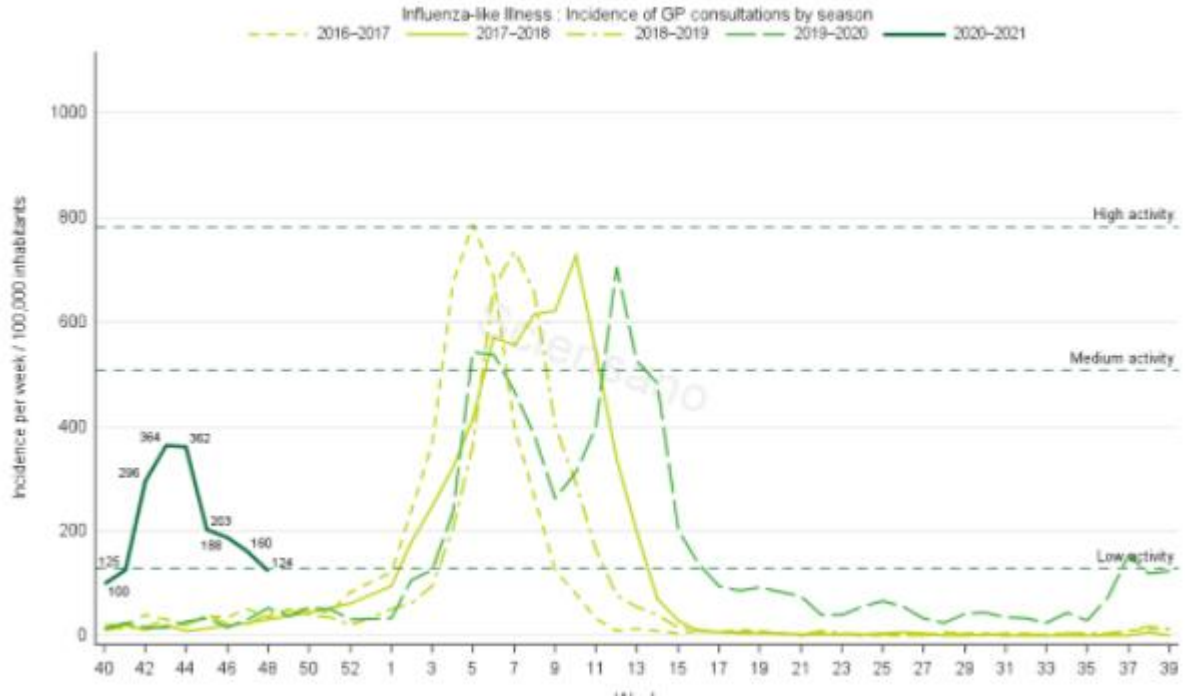
WHO

The World Health Organization recommends in a Policy brief dated 6 November to test patients with severe or complicated disease or those with risk factors (regardless of severity) using a rapid molecular assay when results can be made available within 24 hours preferably[14]. Awaiting test results should not delay empiric treatment, which can be modified subsequently, according to test results. The longer the time lag between sampling and test results, the less the test will benefit clinical management. Empiric treatment without laboratory diagnosis could lead to expanded use of oseltamivir and could contribute to overuse and the development of resistance.

[14] WHO - Readiness for influenza during the COVID-19 pandemic - Policy brief - 6 November 2020. Available at: file:///C:/Users/YvLa1869/Downloads/WHO-2019-nCoV-Influenza_readiness_COVID-19-2020.1-eng.pdf

4.4. Influenza season in Belgium

The figure below presents the trends in influenza like illnesses (ILI) in past years in Belgium. The period with the highest incidence of ILI in general practitioners consultations is from January to April.



4.5. Discussion

- Many of the factors limiting the use of multiplex assays have been resolved. They have become available on the Belgian market, most labs can perform them and lab staff can know what type of multiplex to use from the prescriptions.
- The only persisting barrier is that currently multiplex assays are still not reimbursed by the national health insurance.
- Despite the evidence showing that the emergence of SARS-CoV-2 appears to result in reductions in the circulation of seasonal respiratory viruses and the low levels of co-infection established in several studies, it was agreed that it remains important to use multiplex assays in certain situations. In particular because a co-infection with, for example, influenza can give a more severe pathology. This applies both to adults and children.
- Because of the high cost of a multiplex assay, the use should be reserved for the more severe cases in hospital settings. A broader use in primary care settings is not indicated. Eligible patients include both those requiring hospitalization and those presenting at the emergency department.
- Maxi panels, testing for a broad range of panels, should be reserved for patients with a severe clinical condition. Patients without a severe clinical condition can be tested with a mini panel.
- There are mini panels that only include SARS-CoV-2 and influenza (A and B), and mini panels that also include RSV. Both are acceptable.
- A sequential approach (first test for SARS-CoV-2 and only use a multiplex assay if negative) is not recommended.

- It is not known what the effect of the measures to control the SARS-CoV-2 epidemic will have on the seasonal influenza epidemic. It is therefore important to monitor the incidence of influenza and only initiate the use of multiplex assays once there are clear signs of a seasonal epidemic.

4.6. Updated recommendation for use of multiplex PCR in Belgium

- During the seasonal influenza epidemic patients with respiratory symptoms, especially in severe condition, can be tested with a multiplex PCR panel in order to guide therapeutic care and support.
- The use of multiplex assays is only recommended if there is evidence of a seasonal influenza epidemic, based on the surveillance data of influenza-like illnesses in Belgium or neighboring countries.
- A multiplex assay is only indicated in patients attending hospitals, both hospitalized in-patients and out-patients at the emergency department. Patients in ambulatory care outside a hospital setting (such as in general practice) should only be tested for SARS-CoV-2.
- Patients with respiratory symptoms without severe clinical condition should be tested with a multiplex PCR mini panel (SARS-CoV2/ Influenza A and B, or SARS-CoV2/ Influenza A and B/ RSV).
- Patients with respiratory symptoms and a severe clinical condition can be tested with a multiplex PCR maxi panel (detection of a broad range of pathogens), if available.
- Multiplex assays should be done on specimens that ensure a high sensitivity, such as nasopharyngeal swabs, nose/throat swabs, tracheal aspirate or broncheo-alveolar lavage fluid (BAL); and not on specimens with lower sensitivity, such as salivary samples.