L'UTILISATION D'ÉCHANTILLONS SALIVAIRES ET DES ÉCOUVILLONS NASAUX-OROPHARYNGÉS COMBINÉS AUTO-COLLECTÉS POUR LA DÉTECTION DE SARS-COV-2 AVEC UN RT-PCR

RAG sous-groupe testing –14 Juin 2021

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

Recommandations :

Échantillons salivaires

- Un écouvillon nasopharyngé ou un écouvillon combiné nez-gorge restent les échantillons préférés pour le dépistage du SARS-CoV-2.
- Les échantillons salivaires constituent une alternative valable dans les circonstances suivantes :
  1. Patients symptomatiques avec des symptômes <=5 jours (cependant, un test Ag rapide sur un écouvillon nasopharyngé reste le premier choix)
  2. Lorsqu'un prélèvement nasopharyngé ou un prélèvement combiné nez-gorge est très difficile ou impossible. Exemples : déviation de la cloison nasale, patients très jeunes, patients souffrant de troubles psychiatriques ou patients qui ressentent une douleur ou une gêne excessive lors des examens par écouvillonnage nasopharyngé ou combiné nez-gorge.
  3. Dépistage périodique (hebdomadaire) des personnes asymptomatiques
  4. Dépistage pré-événement des personnes asymptomatiques (mais uniquement sous la surveillance étroite d'un prestataire de soins de santé ou d'une autre personne qualifiée)
- Les échantillons salivaires doivent toujours être testés par RT-PCR
- L'utilisation de la salive n'est pas recommandée chez les contacts asymptomatiques à haut risque et les voyageurs arrivant ou revenant au pays
- L'utilisation de la salive est autorisée pour les voyageurs en partance, sous la surveillance étroite d'un prestataire de soins de santé ou d'une autre personne qualifiée, si elle est approuvée par le pays de destination
- Les échantillons salivaires doivent toujours être collectés, transportés et analysés conformément au protocole approuvé

Auto-collecte combinés nez-gorge

- Un écouvillon combiné nez-gorge auto-collecté est une alternative valable à un écouvillon nasopharyngé ou combiné nez-gorge administré par un prestataire dans les conditions suivantes :
  1. La collecte par le prestataire est difficile (par exemple, en raison d'une charge de travail excessive)
  2. L'écouvillonnage auto-collecté est effectué sous la surveillance étroite d'un prestataire de soins de santé ou d'une autre personne formée
  3. La personne testée n'a aucun intérêt personnel dans un résultat négatif (par exemple, personnes symptomatiques, dépistage répété sur le lieu de travail, etc.)
- Dans un contexte où la personne testée a un fort intérêt personnel à obtenir un résultat négatif, comme le dépistage avant un événement ou chez les voyageurs en partance, l'auto-collecte d'un écouvillon combiné nez-gorge n'est pas recommandé

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CONTEXT

The number of COVID-19 tests performed in a context of screening asymptomatic/ non-high-risk contact people has increased over the past months and is expected to further increase sharply during the holiday season, because of screening departing travelers.

The current recommendation for screening asymptomatic people, other than in a setting of repetitive testing, is to perform an RT-PCR test or a rapid Ag test on either a nasopharyngeal or a combined nose-throat swab. Saliva samples are only recommended in a context of repetitive (weekly) screenings and, exceptionally, when a respiratory swab is very difficult or impossible to obtain, for example, in a deviation of the nasal septum, in some patients with psychiatric disorders, or in some children. Nasal swabs (anterior or mid-turbinate) are only recommended in symptomatic patients with symptoms <=5 days and in a context of self-testing, but not for other screening purposes. No recommendation exists with regards to self-collection of combined nose-throat swab.

Because of the limited capacity to collect nasopharyngeal swabs and the lesser acceptability of this type of specimen, and because several countries agreed to accept saliva specimens for

testing departing travelers, the RAG Testing was requested to review the most recent literature with regards to saliva specimens and assess if the current recommendations are still valid.

In addition, a question was raised if an RT-PCR test can be done on a combined nose-throat swab, self-collected under supervision.

1. SALIVA SAMPLES

DISCUSSION

- While results of studies are often inconsistent, some conclusions can be made:
    1. Among symptomatic patients, RT-PCR on nasopharyngeal swabs has generally a (slightly) higher sensitivity than RT-PCR on saliva specimens
    2. The difference is less when viral load is high or in severe disease
    3. Most reviews conclude that saliva is an acceptable alternative specimen collection method in a context of diagnosis in ambulatory care

- Only few studies specifically assessed the performance of saliva for screening asymptomatic people. Studies that included asymptomatic people show often contradictory results. Overall, sensitivity appears lower among asymptomatic people than among symptomatic people, possibly as a result of the lower viral load in this population.

- Data on the performance of saliva specimens in children, and in particular small children (<6 years) are scarce. In older children (6-18 years) there are some indications that performance is similar to that in adults.

- Most studies evaluated the performance of saliva samples collected under supervision of a health care provider, and few data are available on self-collected saliva. One study found an additional loss in sensitivity if self-collected.

- The great advantage of using saliva samples is the ease of collection, not requiring health staff.

- The disadvantages/risks of using saliva samples are:
    1. Loss of sensitivity
    2. Great variability depending on the type of saliva sample (with gargled and deep-throat saliva performing best), the time of the sampling (early morning) and the influence of eating, drinking, smoking and gum chewing
    3. Difficulties in getting sufficient saliva (in particular in children and elderly people)
    4. Processing challenges at the laboratory

- France and the Netherlands have guidelines similar to the current Belgian guidelines: for repetitive screenings and when respiratory swabs are difficult or impossible. Many countries do not have guidelines. The Netherlands approve saliva for children <6 years. ECDC has recently expanded their indications for the use of saliva specimens and approves it within the first five days after symptom onset.

- The above conclusions only apply to an RT-PCR test on saliva samples, and not to antigen tests on saliva (see separate RAG advice).
- In settings where the highest possible sensitivity is required, such as in high-risk contacts and returning/ arriving travelers, saliva should not be recommended.

RECOMMENDATIONS

- A nasopharyngeal swab and a combined nose-throat swab continue the preferred samples for SARS-CoV-2 testing.
- However, saliva specimens are a valid alternative in the following circumstances:
    1. Symptomatic patients with symptoms <=5 days (but rapid Ag test on a nasopharyngeal swab remains the first choice)
    2. If a nasopharyngeal swab or combined nose-throat swab is very difficult or impossible. Examples are: deviation of the nasal septum, very young patients, patients with psychiatric disorders, or patients experiencing too much pain or discomfort during the nasopharyngeal or combined nose-throat swabbing
    3. Repetitive (weekly) screening of asymptomatic people
    4. Pre-event screening of asymptomatic people
- Saliva samples must always be tested with an RT-PCR
- The use of saliva is not advised in asymptomatic high-risk contacts and arriving/returning travelers
- The use of saliva is permitted in departing travelers, if it is approved by the country destination
- Saliva samples always have to be collected, transported and analyzed according the corresponding protocol[1]

SCIENTIFIC LITERATURE

Sensitivity of RT-PCR on saliva vs. on nasopharyngeal swabs

Numerous studies have evaluated the performance of COVID-19 testing using saliva specimens. Several systematic reviews and meta-analyses of these studies have been published. The table below summarizes the pooled sensitivity of RT-PCR testing on saliva samples calculated in the meta-analyses. The results are consistently around 85% and a loss of sensitivity compared to nasopharyngeal swabs of 2-5% (the consistency being greatly explained by the large overlap of included studies). Important to point out is that most studies were among symptomatic adults at a hospital or in ambulatory care.

[1] See : 20201130_Advice RAG_Saliva sampling_NL.pdf (sciensano.be) or 20201130_Advice RAG_Saliva sampling_FR_0.pdf (sciensano.be)

Table: Pooled sensitivity of RT-PCR on saliva samples calculated through meta-analysis

Review	Nr of studies	Pooled sensitivity of saliva	95%CI	Pooled sensitivity of NPS
Tsang et al. (1)	23	85%	75%-93%	
Khiabani et al. (2)	26	83%	77%-89%	87% (+4%)
Buttler-Laporte et al. (3)	16	83%	75%-91%	85% (+2%)
Moreira et al. (4)	33	84%	77%-89%	
Bastos et al. (5)	37	87%	82%-90%	90% (+3%)
Lee et al. (6)	25	88%	81%-93%	97% (+11%)
Ibrahimi et al. (7)	49	87%	84%-89%	92% (+5%)

Tsang et al. used nasopharyngeal swabs as the gold standard and found that pooled nasal and throat swabs gave the highest sensitivity (97%), followed by saliva (85%) and nasal swabs (86%), and a much lower sensitivity by throat swabs (68%). They concluded that pooled nasal and throat swabs offered the best alternative, but that saliva and nasal swabs give comparable and very good diagnostic performance and are clinically acceptable alternative specimen collection methods.

Khiabani et al. compared sensitivity of saliva and deep throat sputum (DTS) to nasopharyngeal, combined naso/oropharyngeal, and oropharyngeal swabs (using positive with either sample as reference). They found the highest sensitivity (97%) for bronchoalveolar lavage fluid, followed by double naso/oropharyngeal swabs (92%), nasopharyngeal swabs (87%), saliva (83%), deep throat sputum (82%), and oropharyngeal swabs (44%). They conclude that saliva and DTS are valuable diagnostic specimens for COVID-19 diagnosis, although that the methods of sampling, storing, and laboratory assay need to be optimized and validated before introducing it as an appropriate standardized procedure.

Buttler-Laporte et al. compared the sensitivity of naso-pharyngeal swabs and saliva samples using an estimated true disease status based on the results from both tests as reference. The nasopharyngeal swab RT-PCR had a pooled sensitivity of 85% and a specificity of 99%, against 83% and 99%, respectively, for saliva samples. They concluded that saliva RT-PCR diagnostic accuracy is similar to that of nasopharyngeal swab RT-PCR, especially in the ambulatory setting.

Moreira et al. compared the clinical performance of RT-PCR tests using oral saliva and deep-throat saliva/posterior oropharyngeal saliva (DTS/POS) against standard specimens (NPS, OPS, or a combination of both). DTS/POS samples presented the highest sensitivity (90%), but had a low specificity (63%). Oral saliva had a sensitivity of 84% and specificity of 96%. They conclude that saliva samples simply taken from the oral cavity are promising alternatives, but that further assessment and validation is required.

Bastos et al. determined the difference in sensitivity for SARS-CoV-2 detection between nasopharyngeal swabs and saliva, against a reference standard of a positive result on either sample. The sensitivity of saliva was 3.4 percentage points lower than that of nasopharyngeal swabs, but with important differences depending on the context. Among persons without a previous SARS-CoV-2 diagnosis, saliva was 7.9 percentage points less sensitive, while among persons with previously confirmed SARS-CoV-2 infection, saliva's sensitivity was 1.5 percentage points higher than that of nasopharyngeal swabs. The authors conclude that saliva sampling seems to be a similarly sensitive and less costly alternative that could replace nasopharyngeal swabs for collection of clinical samples for SARS-CoV-2 testing.

Lee et al. compared saliva, oropharyngeal (OP) swabs, and nasal swabs versus NP swabs. NP swabs and combined OP/NS swabs had the highest pooled sensitivity (97%), followed by saliva (88%), oropharyngeal swabs (84%) and nasal swabs (82%). They concluded that NP swabs remain the gold standard, although that alternative specimens are promising. Much remains unknown about the impact of variations in specimen collection, processing protocols, and population (pediatric versus adult, late versus early in disease course), such that head-to head studies of sampling strategies are urgently needed.

In a pre-print article, Ibrahimi et al. compared saliva and nasopharyngeal/ oropharyngeal samples and found a pooled sensitivity of 87% for saliva and 92% for NPS. The authors concluded that saliva could be used for frequent testing of COVID-19 patients and "en masse" screening of populations.

Most studies evaluated saliva collected under supervision of a health care provider, few studies assessed unsupervised collection. Fernández-González et al. compared both approaches and found that overall sensitivity in self-collected samples was much lower than in saliva specimens collected under supervision (66.7% and 86%, respectively) (8). However, the difference was less in samples with a Ct value <=25 (93.3% and 100%, respectively).

Performance in asymptomatic individuals

Most studies assessing the performance of saliva specimens were among symptomatic people (hospitalized patients or people attending an OPD or an emergency department).

The review by Khiabani et al. comprised only two studies that included symptomatic combined with asymptomatic patients and one study among asymptomatic patients only. They found that the sensitivity rate was directly related to the severity of the disease and that saliva had an approximately two times higher sensitivity (83%) in symptomatic patients than in asymptomatic patients (46%).

On the other hand, in the review by Bastos et al., that included 2 studies in asymptomatic participants and 7 studies with both symptomatic and asymptomatic participants, the loss of sensitivity was higher among symptomatic persons (4.9 percentage points less) than among asymptomatic persons (1.6 percentage points less). This was mostly the result of the inclusion of one study by Rao et al. in Malaysia (9). They tested 217 asymptomatic male adults in a quarantine center who had tested positive prior to isolation and found a higher sensitivity using saliva samples (93%) compared to NPS (53%). The same authors compared saliva to a combined nasopharyngeal / oropharyngeal swab among 59 asymptomatic detainees who tested positive during a cluster investigation and 6 asymptomatic positive air travelers, and found again a higher sensitivity using saliva (95%) than using NP/OP swabs (72%) (10).

Recently, some studies have been published assessing the performance of saliva sampling specifically in a context of screening asymptomatic people.

Herrera et al. assessed concordance between NPS and saliva among 2017 asymptomatic healthcare and office workers in Mexico (11). 178 (8.4%) tested positive with NPS and 152 (7.2%) with saliva. Using positive with either sample as a reference and excluding inconclusive results, the sensitivity was 94.5% for NPS and 81.4% for saliva. However, saliva had a lower number of inconclusive results and showed a significantly higher concentration of both total RNA and viral copies than NPS.

Norizuki et al. assessed, over a 7 days period, the sensitivity of different tests on nasopharyngeal, anterior nasal and saliva samples taken from 20 asymptomatic air travelers who had tested positive with RT-PCR on a NPS and were under quarantine in Japan (12). On a total of 97 samples tested, the sensitivity compared to RT-PCR on NPS was 69% for RT-PCR on a nasal swab and 64% for RT-PCR on saliva, comparable to the sensitivity of a rapid Ag test (Fujirebio) on a NPS (60%). Sensitivity of an automated Ag test (Lumipulse) on saliva was 55%. Among 33 samples with viral load ≥ 104 copies/sample, sensitivity was 100% for both RT-PCR on a nasal swab and RT-PCR on saliva (which was equal to the sensitivity of the rapid Ag test on NPS), and 91% for an automated Ag test on saliva.

Performance in children

A literature review on the performance of RT-PCR testing on saliva samples in children is available in previous advices. A table in annex summarizes the results, also including a few more recent studies. A problem with most studies is the very small sample size.

A more recent study by Al Suwaidi et al. included a relatively larger number of children. They compared saliva sampling with NPS among school children presenting for testing at a community testing center. Of the 80 children that tested positive (about half symptomatic and half asymptomatic) on either sample, 87.5% had tested positive on saliva and 92.5% on NPS, results that are comparable to most studies in adults. It has to be observed that the median age was 10 years and there were only few children <6 years old.

INTERNATIONAL RECOMMENDATIONS

ECDC

ECDC recently (May, 2021) published a Technical Report on the use of saliva as sample material for COVID-19 testing. For symptomatic patients the report states that saliva may be used as an alternative to nasopharyngeal swabs for RT-PCR tests within the first five days after symptom onset or when practical considerations make nasopharyngeal swabbing difficult.

For screening asymptomatic individuals, saliva specimens can be considered as an option in asymptomatic individuals who are required to self-test frequently for occupational or other reasons. Screening of asymptomatic individuals using saliva as sample material for RT-PCR analysis can also be considered as an alternative method if nasopharyngeal swabs cannot be obtained, e.g. in case of shortages of swabs, in very old or disabled individuals, and to increase acceptance for repeated testing. When using saliva as a sample material, its limitations need to be considered.

Nasopharyngeal swabs should be the preferred sample option for persons with high risk of exposure to a positive COVID-19 case; if saliva needs to be collected instead, and the time of exposure is known, testing should be performed as soon as possible after the contacts have been identified. If more than seven days have passed since the exposure, it is recommended that negative tests are repeated.

With regards to children, the report concludes that the available limited data do not give a clear picture on whether children can be reliably diagnosed based on saliva samples and more studies are needed.

France

The 'Haute Autorité de santé (HAS)' of France had already approved in September 2020 the utilization of saliva samples for COVID-19 testing in symptomatic people for whom nasopharyngeal swabbing is difficult or impossible (deviation of the nasal septum, very young patients, patients with psychiatric disorders...). In February 2020, two indications were added: (1) in high-risk contacts for whom a nasopharyngeal swab is difficult or impossible; (2) in a context of large-scale targeted screenings, especially if they are repeated regularly: in schools, universities, personnel of health establishments...

Based on the recommendations by the HAS, the 'Haut Conseil de la Santé Publique (HCSP)' of France has elaborated a list of populations in which to prioritize the use of saliva samples for either repetitive screening or contact testing. These are (1) health professionals; (2) hospitalized patients; (3) nursing home residents; and (4) nursing home staff and visitors.

The Netherlands

RIVM has approved the use of saliva specimens for testing children under 6 years of age and in exceptional cases for other patients of all ages in the care of the disabled and in (psycho)geriatrics, in whom it is impossible to take naso- and oropharyngeal swabs.

Germany

The Robert Koch Institute does not disapprove the use of saliva specimens for COVID-19 testing, but warns that the sensitivity may be more or less inferior to the reference method. The use of these sample materials should therefore take place taking into account the respective setting and in close consultation with the laboratory.

ANNEX: SENSITIVITY OF RT-PCR ON SALIVA SPECIMENS FOR DETECTING SARS-COV-2 IN CHILDREN

Study	Study population	Sample size	Age range	Me(di)an age	Type of specimen	Compared to	Sensitivity	Comments
Chong et al. (13)	Hospitalized patients (asymptomatic/symptomatic)	18	-	6.6 years	Spitted or syringed saliva	NPS+	52.9% (on day 4-7)	Sensitivity was lower before and after day 4-7
Han et al. (14)	Hospitalized patients (asymptomatic/symptomatic)	11	0-18 years	6.5 years	Saliva (not further specified)	NPS+	73%	Sensitivity was 80% in week 1 after onset
Kam et al. (15)	Hospitalized patients (asymptomatic/symptomatic)	11	0-12 years	-	Buccal swabs	NPS+	81.8%	The 2 missed cases had Ct value>26
Yee et al. (16)	Inpatients, outpatients and high-risk contacts	43	0-18 years	12 years	Spitted saliva	NPS or saliva positive	79.1%	Sensitivity was 88.3% in 4-10 years old Sensitivity of NPS was 88.4%
Brandal et al. (17)	Symptomatic school children	13	5-12 years	-	Saliva (not further specified)	NPS+	84.6%	There was an explanation for both false negative results (one drank milk, one had low viral load)
Felix et al. (18)	Symptomatic out-patients	10	-	10.2 years	Spitted saliva	NPS or saliva positive	60%	Sensitivity of NPS was also only 60%
Al Suwaidi et al. (19)	School children tested at school	80	3-18 years	10.8 years	Spitted saliva	NPS or saliva positive	87.5%	Sensitivity of NPS was 92.5%
Guzmán-Ortiz et al. (20)	Children hospitalized for non-CIVID reasons	23	5-19 years	11 years	Spitted saliva	NPS or saliva positive	87.0%	Sensitivity of NPS was 73.9%

2. SELF-COLLECTED COMBINED NASAL-THROAT SWABS

DISCUSSION

- Studies assessing the performance of self-collected combined nasal-throat swabs have often discordant results, but mostly conclude that it is an acceptable sampling approach.
- Most studies were among symptomatic people with self-collection at the PoC under supervision of a health care provider.

RECOMMENDATION

- A self-collected nasal-throat swab is a valid alternative to a provider collected nasopharyngeal or nasal-throat swab under the following conditions:
    1. Collection by the health care provider is difficult (for example because of too high workload)
    2. The self-collection is done under close supervision of a health care provider or other trained person
    3. The tested person has no personal interest in a negative result (for example symptomatic people, repetitive screening at the workplace,…)
- In a context where the tested person has a strong personal interest in a negative result, such as in pre-event screening or departing travelers, a self-collected nasal-throat swab is not recommended

SCIENTIFIC LITERATURE

Several studies have included self-collected combined nasal-oropharyngeal swabs in the evaluation of the performance of self-collected respiratory samples. The results are summarized in the table below. Two studies compared them to HCP-collected nasopharyngeal swabs, one to saliva and three studies to HCP-collected combined nasal-oropharyngeal swabs. Results varied between studies.

Kandal et al. found that, after adjusting for the random sampling of negative specimens and fraction of individuals with a paired non-nasopharyngeal swab, sensitivity was similar to that of a HCP-collected NPS, and also Shakir et al. found that the loss of sensitivity was minimal. Braz-Silva et al. compared at-home collected saliva with at-home collected combined nasal-oropharyngeal and found that saliva performed better. Tan et al. found that a self-swab from the oropharynx and mid-turbinate detected substantially less infections than a similar swab collected by a HCP, and concluded that self-collected swabs are inferior to HCP swabs. Therchilsen et al. found a loss of sensitivity of 5%, compared to a HCP-collected oropharyngeal/ nasal swab, but concluded that a self-collected swab is reliable enough. Wehrhahn et al. found no loss of sensitivity. Both latter studies had, however, very small sample sizes.

All of these studies were mostly among symptomatic adults.

Table: Sensitivity of self-collected combined oral–nasal swabs

Author	Sample*	Population	N	Sensitivity
Kandel et al. (21)	saline gargle	testing center attendees	65	90%
	oral swab		56	82%
	combined oral–anterior nasal		42	87%
	HCP-collected NPS		163	90%
Shakir et al. (22)	combined anterior nasal-oropharyngeal	testing center attendees	118	96.6%
	HCP-collected NPS			99.2%
Braz-Silva et al. (23)	at-home collected saliva	symptomatic out-patients	70	78.6%
	at-home collected combined nasal-oropharyngeal			74.3%
Tan et al. (24)	saliva	hospitalized patients	373	79.6%
	combined oropharynx - mid-turbinate nasal			80.7%
	saliva + combined oropharynx - mid-turbinate nasal			93.0%
	HCP-collected combined oropharynx - mid-turbinate nasal			90.1%
Therchilsen et al. (25)	combined oropharynx - mid-turbinate nasal	symptomatic out-patients	19	84.2%
	HCP-collected combined oropharynx - mid-turbinate nasal			89.5%
Wehrhahn et al. ** (26)	combined throat-nasal	symptomatic out-patients	25	100%

*Self-collected at the PoC unless otherwise indicated

**Compared to HCP-collected combined throat-nasal

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