Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Is oropharyngeal sampling a reliable test to detect SARS-CoV-2?

We would like to congratulate Nicole Tsang and colleagues on their clinically relevant systematic review and meta-analysis of the diagnostic performance of different sampling methods to detect SARS-CoV-2 by RT-PCR.[1] The authors concluded that, compared with a nasopharyngeal swab, a pooled nasal and oropharyngeal swab offered the best alternative sampling approach to diagnose SARS-CoV-2 infection, followed by saliva and nasal swabs. Oropharyngeal swabs were not recommended for diagnosis because of low sensitivity and positive predictive value.

In the meta-analysis, the gold standard was nasopharyngeal swab, such that any other sample that gave a positive SARS-CoV-2 RT-PCR test (eg, saliva, nasal swab, or oropharyngeal swab) was categorised as a false positive if the nasopharyngeal sample was negative for the same individual. We are concerned that this approach might have introduced bias. To illustrate, we used data from a study by Xiong Wang and colleagues,[2] which was included in Tsang and colleagues' review. In this study,[2] 192 individuals were concomitantly tested using a nasopharyngeal and an oropharyngeal swab, of whom 19 (10%) tested positive by one or both tests. Seven (37%) of 19 patients had tests that were concordant and 12 (63%) were discordant; seven of 12 were positive by nasopharyngeal swab and five were positive by oropharyngeal swab. In their meta-analysis, Tsang and colleagues calculated the sensitivity of the oropharyngeal swab to be 50% (seven of 14) and the specificity to be 93% (178 of 192).[1] However, if the reference had been any positive sample from the upper airway, the sensitivity of a nasopharyngeal swab would have been reduced from 100% to 74%, and the sensitivity of an oropharyngeal swab would have increased from 50% to 63%—ie, the difference would have been 11 percentage points and not the 50 percentage points reported by Tsang and colleagues. Nevertheless, a nasopharyngeal swab would remain numerically more sensitive than an oropharyngeal swab.[1]

Nasopharyngeal swabbing is a challenging procedure and improper sample collection is known to contribute to false-negative results.[3] We think that the reference for assessing different sampling methods must be a sample method that tests positive in any upper airway sample, because RT-PCR has a very high specificity to detect SARS-CoV-2. This view is also that of WHO, which recommends combining nasopharyngeal and oropharyngeal swabs to improve diagnostic accuracy.[4] Further research is warranted to improve the evidence base on, and guide recommendations for, the optimal sampling technique that yields the highest diagnostic accuracy among individuals presenting in ambulatory care.[5]

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*Tobias Todsen, Nikolai Kirkby, Thomas Benfield
tobias.todsen@regionh.dk

Department of Otorhinolaryngology, Head and Neck Surgery and Audiology (TT) and Department of Clinical Microbiology (NK), Copenhagen University Hospital, Rigshospitalet, Copenhagen 2100, Denmark; Copenhagen Academy for Medical Education and Simulation, Capital Region, Denmark (TT); Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark (TT, TB); Department of Infectious Diseases, Copenhagen University Hospital, Amager-Hvidovre Hospital, Denmark (TB)

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Authors' reply

We thank Tobias Todsen and colleagues for their comments on our recent systematic review and meta-analysis comparing the diagnostic performance of different sampling methods to detect SARS-CoV-2 by RT-PCR.[1] Based on the findings of one included study,[2] they questioned whether any positive sample from the upper airway would be a better gold standard than the traditional nasopharyngeal swab. This method corresponds with a practice that has also been used previously by a small number of studies.[3,4] Here, we repeat the random-effects meta-analysis, including all 23 studies and using any positive respiratory sample as the reference gold standard. We calculated the sensitivity and negative predictive value (NPV) for each sampling approach (table).

The updated results are consistent with our previous conclusion, with pooled nasal and throat swabs offering the best diagnostic performance with sensitivity maintained at 97%, followed by nasopharyngeal swab (sensitivity changed from 100% to 94%), saliva (85% to 87%), and nasal swabs (86% to 87%). Throat swab (68% to 75%) still ranked as the least sensitive approach, with a 22% lower sensitivity than pooled nasal and throat swab (table). Similar to our previous analysis,[1] NPVs were comparable and high (range 95–99%) for all sampling approaches.

Although the sensitivity estimate might numerically vary, our results show that the ranking of diagnostic

	Nasopharyngeal swab as reference comparator		Any positive specimen as reference comparator	
	Sensitivity	NPV	Sensitivity	NPV
Pooled nasal and throat swab	0·97 (0·93–1·00)	0·99 (0·98–1·00)	0·97 (0·93–1·00)	0·99 (0·98–1·00)
Nasopharyngeal swab	1·00 (ref)	1·00 (ref)	0·94 (0·91–0·97)	0·99 (0·98–1·00)
Saliva	0·85 (0·75–0·93)	0·97 (0·94–0·98)	0·87 (0·78–0·93)	0·97 (0·94–0·98)
Nasal swab	0·86 (0·77–0·93)	0·95 (0·88–0·99)	0·87 (0·80–0·93)	0·95 (0·88–0·99)
Throat swab	0·68 (0·35–0·94)	0·96 (0·94–0·98)	0·75 (0·52–0·92)	0·96 (0·94–0·98)

Data in parentheses are 95% CIs. NPV=negative predictive value.

Table: **Sensitivity and NPV of sampling approaches using nasopharyngeal swab or any positive specimen as the reference comparator**

performance remained consistent with the use of a different reference standard. However, using any positive sample as the gold standard makes it impossible to assess the issue of false positivity, which carries non-trivial health-related, financial, and psychological implications,[5] and so effectively negates the possibility of doing a proper assessment of test performance through the calculation of specificity and positive predictive value. Together, these reasons might also explain why nasopharyngeal swabbing is being so widely used as the gold standard for diagnosis of SARS-CoV-2 in clinical practice, most studies, and other systematic reviews we examined in our Article.[1]

In summary, our updated analysis using the alternative gold standard of any positive sample reaffirmed our recommendation of pooled nasal and throat swabs as the best sampling approach that gives the highest sensitivity for diagnosing SARS-CoV-2 infection in the ambulatory care setting, followed by nasopharyngeal swabs, saliva, and nasal swabs. Throat swabs gave a much lower sensitivity and should not be recommended.

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*Nicole Ngai Yung Tsang, Hau Chi So, *Dennis Kai Ming Ip*
dkmip@hku.hk

WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, 999077, China

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Is indiscriminate use of medicines the main reason for problems faced during the second wave of COVID-19 in India?

The Comment by Satchit Balsari and colleagues[1] on the second COVID-19 wave in India offers an interesting read. While it is admirable for the authors to propose simple testing and management recommendations, it is disappointing to note that they incriminate the indiscriminate and unwarranted use of several medicines in the tribulations that surfaced during the second wave.

Undoubtedly, the second wave hit India very hard and overwhelmed the health-care system simply by the sheer number of patients. Surprisingly, Balsari and colleagues label favipiravir as an ineffective therapeutic intervention when one of the authors (ZU) was the lead author of the paper that showed efficacy of favipiravir.[2] Likewise, a meta-analysis concluded the efficacy of ivermectin in the prevention and treatment of COVID-19.[3] There are many other publications supporting the use of other medicines (albeit at appropriate time) that the authors mention.

In the tsunami of information, practicing evidence-based medicine is a challenge. When the evidence is lacking, opinions matter, and clinicians were justifiably led by opinions of seniors and experts. To complicate matters, retraction of published evidence leading to change in guidelines is not unknown. The most recent example relates to two papers on angiotensin-converting enzyme inhibitors and hydroxychloroquine that were retracted within weeks of publication.[4] In a desperate attempt to save lives, indiscriminate use might have happened in a few instances (I believe this to be more common with steroids), but to generalise it is a bit far-fetched.

It is also not correct to say that for nearly a year patients were being advised institutional isolation. It is on record that large COVID-19-care centres were urgently commissioned for this very purpose in July, 2020, and a triaging protocol based on simple clinical parameters like oxygen saturation and respiratory rate was successfully used.[5]

I also humbly differ in opinion on the recommendation that patients with moderate disease can be managed at home. We have learnt that these patients worsen suddenly, and timely

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