

COVID-19 Evidence Update

COVID-19 Update from SAHMRI, Health Translation SA
and the Commission on Excellence and Innovation in Health

Updated 4 May 2020 – 2nd Edition

“What is the prevalence, positive predictive value, negative predictive value, sensitivity and specificity of anosmia in the diagnosis of COVID-19?”

Executive Summary

There is widespread reporting of a potential link between anosmia (loss of smell) and ageusia (loss of taste) and SARS-COV-2 infection, as an early sign and with sudden onset predominantly without nasal obstruction. There are calls for anosmia and ageusia to be recognised as symptoms for COVID-19.

Since the 1st edition of this briefing (25 March 2020), there has been a significant expansion of literature on this topic, including 3 systematic reviews.

Predictive value: The reported **prevalence** of anosmia/hyposmia and ageusia/hypogeusia in SARS-COV-2 positive patients are in the order of 36-68% and 33-71% respectively. There are reports of anosmia as the **first symptom** in some patients.

Estimates from one study for hyposmia and hypogeusia:

- **Positive likelihood ratios:** 4.5 and 5.8
- **Sensitivity:** 46% and 62%
- **Specificity:** 90% and 89%

The US Centres for Disease Control and Prevention (CDC) has added **new loss or taste or smell** to its list of recognised symptoms for SARS-COV-2 infection. To date, the World Health Organization has not.

Conclusion: There is sufficient evidence to warrant adding loss of taste and smell to the list of symptoms for COVID-19 and promoting this information to the public.

Context

- Early detection of COVID-19 is key to the ongoing management of the pandemic.
- The prevalence of other symptoms in people who have tested positive for SARS-COV-2 are estimated to be: fever (82.2%); cough (61.7%); fatigue (44.0%); dyspnea (41.0%); anorexia (40.0%); productive sputum (27.7%); sore throat (15.1%); nausea (9.4%); dizziness (9.4%); diarrhea (8.4%); headache (6.7%); vomiting (3.6%) and abdominal pain (2.2%).(1)
- General population prevalence of anosmia and hyponosmia (in the absence of COVID-19) has been estimated to be between 2.7% and 24.5% (1). Prevalence increases with age (2). Olfactory function is also known to be impaired by smoking (3). Population prevalence of dysgeusia is approximately 5%.(2)
- Biological plausibility: Studies in mice have shown that after intranasal inoculation, **SARS-CoV-1** is neuroinvasive with infection directly transmitted through olfactory neurons into the central nervous system.(3-5).

SUMMARY OF KEY EVIDENCE

1. Published evidence

Predictive value

- A study in France (published in Lancet Infectious Diseases) surveyed patients who were tested for SARS-CoV-2, prior to public awareness of the potential link between taste or smell disorders and COVID-19. The diagnostic value of hypogeusia, hyposmia and both for the diagnosis of COVID-19 were then estimated. The table below reports values and shows that the best predictive performance (highest specificity and positive likelihood ratio) was obtained with the combination of hypogeusia and hyposmia in patients with no medical history of ear nose and throat disorders. (6)

	Patients with SARS-Cov-2 (n=68)	Patients without SARS-Cov-2 (n=189)	Odds Ratio [IC95]	P value	Sensitivity [IC95]	Specificity [IC95]	Positive likelihood ratio [IC95]	Negative likelihood ratio [IC95]
All patients								
Hypogeusia (%)	42 (62%)	20 (11%)	13.4 [6.61-28.3]	<0.0001	62% [49-73]	89% [84-93]	5.8 [3.7-9.1]	0.43 [0.31-0.58]
Hyposmia (%)	31 (45%)	19 (10%)	7.44 [3.63-15.6]	<0.0001	46% [33-58]	90% [85-94]	4.5 [2.7-7.5]	0.6 [0.48-0.76]
Hypogeusia and hyposmia (%)	29 (43%)	13 (7%)	9.94 [4.54-22.9]	<0.0001	43% [31-55]	93% [88-96]	6.2 [3.4-11.2]	0.61 [0.50-0.76]
ENT history								
Hypogeusia (%)	14 (56%)	8 (14%)	7.55 [2.31-26.7]	0.0002	56% [35-76]	86% [74-93]	4.0 [1.9-8.2]	0.51 [0.32-0.80]
Hyposmia (%)	12 (48%)	8 (14%)	5.51 [1.68-19.3]	0.0002	48% [28-69]	86% [74-94]	3.4 [1.6-7.3]	0.60 [0.41-0.89]
Hypogeusia and hyposmia (%)	11 (44%)	7 (12%)	5.47 [1.6-20.1]	0.0003	44% [24-65]	88% [76-95]	3.6 [1.6-8.1]	0.64 [0.44-0.91]
No ENT history								
Hypogeusia (%)	28 (65%)	12 (9%)	18.2 [7.27-48.6]	<0.0001	65% [49-79]	91% [85-95]	7.1 [4.0-12.8]	0.38 [0.25-0.57]
Hyposmia (%)	19 (44%)	11 (8%)	8.56 [3.38-22.7]	<0.0001	44% [29-60]	92% [86-96]	5.3 [2.7-10.2]	0.61 [0.46-0.80]
Hypogeusia and hyposmia (%)	18 (42%)	6 (5%)	14.8 [5.02-50.2]	<0.0001	42% [27-58]	95% [90-98]	9.2 [3.9-21.7]	0.61 [0.47-0.79]

ENT: ear, nose, and throat

Table 1. Diagnostic value of hypogeusia, hyposmia, and both, for the diagnosis of COVID-19

Systematic reviews

- A systematic review (7) including 19 studies concluded that:
 - The sinonasal cavity may be a major site of infection by SARS-CoV-2
 - Viral shedding appears to be highest from the nose, reflecting a major source for transmission, and as a result, rhinology and otolaryngology societies from Europe and America around the world are recommending that endonasal surgeries be approached as high-risk procedures for the transmission of COVID-19.(8, 9)
 - While sinonasal symptomatology appears to be a rarer symptom, anosmia without nasal obstruction appears to be a highly specific predictor of COVID-19.
- A systematic review of studies of hospitalised patients (5 studies) found that the most common symptoms of COVID-19 are fever (85.6%), cough (68.7%), and fatigue (39.4%). Pharyngodynia was quite common (12.4%), nasal congestion was not (3.7%), and rhinorrhea was rare. None of the included reports reported on loss of smell.(10)

The review notes another study of hospitalized patients with COVID-19 at Sacco hospital (Milan, Italy), which was excluded due to not matching the inclusion criteria. That study found that among 59 interviewed patients, 33.9% reported at least one taste or olfactory disorder and 18.6% reported both. 'Twelve patients (20.3%) presented the symptoms before the hospital admission, whereas 8 (13.5%) experienced the symptoms during the hospital stay. Taste alterations were more frequent (91%) before hospitalization, whereas after hospitalization taste and olfactory alterations appeared with equal frequency.' (11)

- A systematic review of 92 studies found that patients with COVID-19 may present with neurological symptoms such as headache, impaired mental state, confusion, dizziness, nausea and vomiting, anosmia/hyposmia, dysgeusia/hypogeusia as initial symptoms. To a more severe manifestation such as seizures or coma. The neurologic signs are clinical symptoms similar to those reported for SARS-CoV and MERS-CoV.(12)

Primary studies that indicate prevalence

- In the UK, 1,573,103 subscribers to the RADAR COVID-19 app reported their symptoms. 26% reported having one or more symptoms of COVID-19. Of those, 1702 had a COVID-19 test and within this group, **loss of smell and taste** were present in **59% of COVID-19 positive individuals vs 18%** who received a **negative COVID-19** test result. The authors concluded that loss of taste and smell is a strong predictor of having been infected by the COVID-19 virus. The study found that a combination of loss of smell and taste, fever, persistent cough, fatigue, diarrhoea, abdominal pain and loss of appetite was predictive of COVID-19 positive test with sensitivity 0.54[0.44; 0.63], specificity 0.86[0.80; 0.90], ROC-AUC 0.77[0.72; 0.82] in the test set, and cross-validation ROC-AUC 0.75[0.72; 0.77].(13)
- In the US, 59 COVID-19 positive and 203 COVID-19 negative participants completed an online survey. Symptoms (self-report) associated with Covid-19-positivity in order of descending frequency were: fatigue (81%); **ageusia (71%)**; fever (70%); **anosmia (68%)**; myalgia or arthralgia (63%); diarrhea (48%), and nausea (27%). Fever was the most common presenting symptom (54%), while **22%** reported **anosmia at initial presentation** of Covid-19-positive illness. Compared to other symptoms, loss of smell and taste (**which tended to be profound rather than mild**) showed the largest association with Covid-19 positivity (**anosmia: OR 10.9, 95% CI: 5.6-21.0; ageusia: OR 11.9 95% CI 6.1-23.2**). (14)

Primary studies that support an association between COVID-19 and anosmia and dysgeusia

- A retrospective observational study at a French (Nord Franche-Comté) hospital reported that 54 of 114 patients (47%) with confirmed COVID-19 reported anosmia. Anosmia was never the first or second symptom to develop, but it was the third symptom in 38% (22/52) of cases. Anosmia was associated with dysgeusia in 85% of cases (n = 46). 70% of those with anosmia did not present with nasal obstruction. Anosmia began 4.4 (\pm 1.9 [1–8]) days after infection onset. The mean duration of anosmia was 8.9 (\pm 6.3 [1–21]) days.(15)
- Preliminary analysis of a COVID-19 Anosmia Reporting Tool for Clinicians in the US revealed that of the first 237 entries (of patients who were diagnosed with COVID-19 and had anosmia), anosmia was noted in 73% of subjects prior to COVID-19 diagnosis and **was the first symptom in 26.6% of patients**. Overall it was reported that anosmia was the contributing factor for testing among 40%. (16)
- A study of 45 patients admitted to an isolation unit in Israel with mild COVID-19 infection indicated that fifteen patients (35.7%) reported anosmia and 14 (33.3%) reported dysgeusia and 14 reported both (with one reporting only anosmia).(17)
- An observational study of 23 participants with confirmed COVID-19, and chief complaint of anosmia in Iran found that anosmia could be the only clinical presentation of COVID-19 without any other significant symptoms (apparent in 16 cases). The authors conclude that **new onset anosmia** should be considered in screening for COVID-19 infection.(18)
- A study of 10,069 participants in Iran indicated a highly statistically significant correlation between the olfactory disorder and COVID-19 in patients in all 31 provinces, to 16th March 2020. The authors reported a surge in outbreak of olfactory dysfunction in Iran during the COVID-19 epidemic.(19)
- A survey of 72 physicians in Italy found that the most common symptoms observed were headache, myalgia, taste and smell abnormalities.(20)
- In a study of 59 COVID-19 positive patients with influenza-like symptoms in Europe, loss of smell and taste was reported by 71% of patients.(21)

- A case study report indicated that an 85 year old man with sudden anosmia and an 80 year old woman with loss of taste and smell. Neither had history of fever, cough or dyspnoea indicating that anosmia and dysgeusia in the absence of other respiratory conditions should be carefully evaluated.(22)
- One early published study reported on a study of 214 patients admitted to hospital in Wuhan with severe SARS-CoV-2 infection. 5.1% of patients reported loss of smell, 5.6% of patients reported loss of taste. However, the data were collected retrospectively from medical files, and therefore, is likely to underestimate prevalence.(4)

Plausible biological mechanism:

- In a Letter to the Editor BMJ (31 Jan 2020) Gulistan Bahat MD, Professor, Internal Medicine, Geriatrics, Istanbul University) suggested that the ACE inhibition that is present in COVID-19 infections may be the cause of the loss of smell/taste symptomatology, which seems to be specifically common in COVID-19 infections. (Note: The letter cites no primary observations, and referred to the reports from ENTUK).(23)
- In an RACGP news piece (22 April 2020) focussed on the impact of neurological impact of COVID-19, it was reported that “One of the emerging tell-tale signs of SARS-CoV-2 infection is anosmia, and neurologist Dr Robb Wesselingh, noted the biological plausibility of virus entering the olfactory bulb, and concerns for potential to infect the nerve or the brain.(24)

2. Professional correspondence from medical professionals and associations

Prof Claire Hopkins (BMBCh, MA FRCS(ORLHNS) DM(Oxon)), President of British Rhinological Society & Prof Nirmal Kumar (President of ENT UK) Publisher: ENT UK (25)

Professional correspondence indicates that there is:

- ‘Good evidence from South Korea, China and Italy that significant numbers of patients with proven COVID-19 infection have developed anosmia/hyposmia.
- In Germany it is reported that more than 2 in 3 confirmed cases have anosmia.
- In South Korea, where testing has been more widespread, 30% of patients testing positive have had anosmia as their major presenting symptom in otherwise mild cases.’
- ‘there is a chance the apparent increase in incidence could merely reflect the attention COVID-19 has attracted in the media, and that such cases may be caused by typical rhinovirus and coronavirus strains, it could potentially be used as a screening tool to help identify otherwise asymptomatic patients, who could then be better instructed on self-isolation’.

The American Academy of Otolaryngology – Head and Neck Surgery position statement (26)

*‘Anecdotal evidence is rapidly accumulating from sites around the world that anosmia and dysgeusia are significant symptoms associated with the COVID-19 pandemic. Anosmia, in particular, has been seen in patients ultimately testing positive for the coronavirus with no other symptoms. **We propose that these symptoms be added to the list of screening tools for possible COVID-19 infection. Anosmia, hyposmia, and dysgeusia in the absence of other respiratory disease such as allergic rhinitis, acute rhinosinusitis, or chronic rhinosinusitis should alert physicians to the possibility of COVID-19 infection and warrant serious consideration for self-isolation and testing of these individuals.**’*

This academy also has a COVID-19 Anosmia Reporting tool to accumulate data on anosmia in the US and more broadly <https://www.entnet.org/content/reporting-tool-patients-anosmia-related-covid-19>

Stanford University School of Medicine Departments of Otolaryngology-H&N Surgery and Neurosurgery statement (27)

In a statement focused on excess risk to ENTs of COVID-19, there was inclusion of information received from an Italian colleague Dr. Puya Deghani-Mobaraki, reporting “the possible loss of smell and taste that this virus brings. They are not only seeing it in their patients, but they have noticed it within their own ranks, in otherwise healthy asymptomatic doctors, at rates far above what could be considered normal.”

3. Adoption as symptom of COVID-19 by US Centers for Disease Control and Prevention (CDC) (28)

[News](#) media from 24 April 2020 cover the US CDC expanding its list of symptoms (from fever, cough and shortness of breath) to the following:

People with these symptoms or combinations of symptoms may have COVID-19: Cough, Shortness of breath or difficulty breathing.

*Or at least two of these symptoms: Fever, Chills, Repeated shaking with chills, Muscle pain, Headache, Sore throat, **New loss of taste or smell.***

4. Selected News Reports of Clinician Observations

- Iran News (09 March 2020) reports on *Loss Of Sense Of Smell Among Iranians Coinciding With Coronavirus Epidemic*, citing Deputy Chairman of **Iran's Rhinology Association (and ENT Surgeon)** Dr. Ebrahim Razmpa "During the last month there is a sudden, unexpected and unbelievable jump in cases of weak sense of smell and difficulty with vision", reported across the country." "The first theory revolves around the impact of coronavirus, which seems to be more probable". "The second possibility is that the phenomenon is related to increasing exposure to chemicals in washing and disinfecting materials, which are being used frequently in recent weeks as a preventive measure against the deadly virus."(29)
- Frankfurter Allgemeine Hendrik **[In German]** reports on **Virologist** (Hendrik StreeckBonn) who went from house to house and to every infected person in the district of Heinsberg, particularly affected by Covid-19. "Almost all infected people we interviewed, and this applies to a **good two thirds, described a loss of smell and taste lasting several days.**" They reportedly interviewed 100 infected but non-hospitalised cases. They also noted that diarrhea also occurred in our infected people in 30 percent of the cases, which is more common than previously thought.(30)
- Liberoquotidiano (In Italian) reported from Sacco hospital in Milan: out of **100 patients recovered, 87 of them had three symptoms: loss of smell, taste and diarrhea** (the first two very common) "in the final stage".(31)
- It has been reported that members of the Association for Chemoreception Sciences (AChemS) have created a working group, the Global Consortium for Chemosensory Research (GCCR), to help pool expertise and resources for other researchers to further understand the role between anosmia and COVID-19 carriers.(32)

Authors: Prof Caroline Miller, Dr Jacqueline Bowden, Jo Dono

Searchers: Nikki May and Dr Ingrid Lensink (CEIH), Aimee Brownbill

Expert input: Prof Steve Wesselingh, Prof David Lynn

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