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Breath diagnostics in the era of SARS-CoV-2 – clinical and research arena.

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Abstract

The emergence of the SARS-CoV-2 pandemic has transformed not just healthcare, but also economic systems on a global scale. Despite significant efforts to contain the infection, it continues to spread. Stringent infection control measures have been taken to minimise the transmission between individuals and healthcare workers, especially those undertaking aerosol generating medical procedures. The uncertainties surrounding infection transmission through breath tests in particular, and to some extent faecal testing, will invariably cause concerns amongst both the patients and healthcare workers. It is therefore pertinent that all of the necessary measures are adopted to minimise risk of spreading. In this article, we summarise the physiology and virulence of SARS-CoV-2 and discuss the implications for breath testing (in both the clinical and research arena) as well as outlining methods to mitigate these risks.

Introduction

On the 11th of March 2020, the World Health Organization declared the Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) infection to be a pandemic. Originating from the city of Wuhan in China, the SARS-CoV-2 virus has engulfed 210 countries and territories in the world. Healthcare systems are currently undergoing a massive overhaul, in order to tackle this unprecedented crisis of an air borne pathogen. Once the pandemic settles down, a few of these changes are likely to remain in place for good – at least in order to be better prepared with measures against highly transmissible viruses.

SARS-CoV-2 is a single stranded RNA virus, belonging to the beta coronavirus family. Over the past few decades, coronavirus outbreaks have occurred from time to time and efforts made to sustain the infections. SARS-CoV emerged in 2002 and spread to 26 nations which resulted in 774 deaths with a case fatality rate of 9.5%.[1] The Middle East Respiratory Syndrome coronavirus (MERS-CoV) was first identified in 2012 which resulted in 858 deaths and case fatality rate of 34.4%.[2] SARS-CoV-2, at the time of writing this article (28th of April 2020) has resulted in 202,733 deaths out of 2,959,929 confirmed cases in 210 countries/regions.

SARS-CoV-2 usually causes mild respiratory symptoms (sub-clinical), but on occasion leads to severe pneumonitis.[3] The most common transmission routes include inhalation of airborne droplets and contact transmission to the mucus membranes. Of particular concern is the fact that asymptomatic people can also shed the virus.[4,5] It's high reproductive number (R0 - defined as the average number of secondary infections produced by a typical case in a wholly susceptible population)[6] and shorter serial interval (the time interval between the symptom onset in a primary case and symptom onset in a secondary case)[7] testifies of its high virulence.

Breath tests

Detection of biomarkers in an exhaled breath has drawn a lot of attention in recent times; particularly as an emerging non-invasive modality of diagnosis for various diseases. It's relative low cost and feasibility for point of care testing has made them an attractive complementary diagnostic tool.

Human exhaled breath consists of aerosols, volatile and non-volatile organic compounds, phospholipids[8], proteins, oxidation products and microbiomes.[9–11] Different pathological conditions cause distinct compositions of these mixtures which results in a unique pattern ('fingerprint'), specific for that disease process. Various breath recipient devices (e.g. Tedlar® bags [E. I. du Pont de Nemours and Company, Wilmington, DE, USA], aluminized Mylar bags, Tenax® cartridges [Buchem B.V., Apeldoorn, The Netherlands], Bio-VOC™ bottles [Markes International Ltd., Llantrisant, UK] and more recently the EBC condenser, ReCIVA™ [Owlstone Ltd., Cambridge, UK], RTube™ [Respiratory Research Inc., Austin, TX, USA] and QuinTron™ samplers [QuinTron, Milwaukee, WI, USA] and analytical methods (e.g. gas and liquid chromatography mass spectrometry, ion-mobility spectrometry, electronic noses, ultra violet and infra-red spectroscopy) have been described in literature largely determined by the disease of interest. Gas phase breath sampling has been used widely within day-to-day clinical practice (such as H-pylori breath tests, hydrogen breath tests) and in the research domain-breath volatile organic compound tests for detection of lung cancer[12], tuberculosis[13] and others. Exhaled breath condensate (EBC) is collected by passing breath through a condensing device. EBC sampling has shown some use in assessing pulmonary inflammation, genotyping of pulmonary microbiome etc.[14]

Breath tests and the risk of SARS-CoV-2 transmission - A conundrum?

Most of the breath tests currently used in clinical practice are based on tidal volume breathing. The droplet generation during this type of breathing and the risk of virus spread are minimal.[15] However, repeated inhalation and breath holding during a breath testing procedure could result in rapid breathing, forced expiration, cough and possibly deep breathing. The latter effects increase the generation of aerosols. A study by Johnson and Morawska[16] showed that, following inhalation to normal end-tidal lung volume, deep exhalation can increase the aerosol generation up to 6-fold. Furthermore, cough can expel more aerosol through its wind shear effect in the respiratory tract. Another study showed that inhalation to total lung capacity (deep breaths) can result in 70-fold increase in particle concentration.[15] More recently, it has been shown that virus particles can be detected in the saliva of infected patients.[17] This suggests that even at normal tidal volume breathing (as in diagnostic testing), SARS-CoV-2 could be detectable and therefore transmissible. Moreover, a large proportion of the particles generated by the above-mentioned breathing activities were below the mean diameter of 0.8 microns.[18] Hence, these smaller particles, known as aerosols, remain suspended in air for longer periods and could result in airborne transmission.

The R0 for SARS-CoV-2 appears to be higher than that of other droplet transmissible infections, such as SARS-CoV-1 and Tuberculosis. The world Health Organisation declared the R0 for SARS-CoV-2 as in the range of 1.4 – 2.5.[19] However, a recent review showed that the mean R0 value for SARS-CoV-2 was 3.28, which is higher in comparison to other similar infections.[6] The high virulence factor of SARS-CoV-2 poses a risk of infection transmission especially to health care workers undertaking diagnostic tests.

Although many of the currently used breath tests kits are single use (e.g. urea breath test, tests for small bowel intestinal overgrowth), reusable devices are still widely in use in low income countries. Whilst the mouthpieces and masks are disposable, the exhalation particle filter and a one-way valve are not. The filtration efficiency of these filters, varies with the size of the particles they come into contact with. The efficiency is less for particles in the range 0.05 -0.5 microns.[20] The performance of these filters in the setting of SARS-CoV-2 is unknown. Moreover, use of particulate filters before condensers are not recommended in EBC collection devices, as the volatile compounds can be affected by the filters.[21] The reusable part of the device and the tubing are mostly made of plastic. After each use, these devices are usually decontaminated by using antimicrobial wipes. However, not all the areas are easily accessible or effective against viruses. As SARS-CoV-2 can survive on plastic surfaces for up to 72 hours[22], there is a sobering possibility that the use of plastic based reusable kits can play a role in the transmission of these highly contagious viruses.

What is a safe approach in the current pandemic?

Moving away from breath tests could be counterproductive as these diagnostic technologies are beneficial. Hence, mitigating the risks would be a logical way forward. This would entail adopting a model of preventive measures, within a multifaceted strategy (Figure 1). Patient selection is key and a negative swab for SARS-CoV-2 would enable departments to follow existing protocols. Conversely, if positive and clinically not feasible to postpone such testing, then adoption of enhanced decontamination techniques and the modification of the procedure room environment (e.g. negative pressure rooms and safe disposal of used samples in line with the local infectious waste disposal guidance) would considerably

minimise the non-human related risk of infection. It is noteworthy that disinfection should be carried out with extra caution (in line with the manufacturer's accepted standards), as the residual disinfectants in the devices may alter the subsequent sample testing.

Human mediated transmission can effectively be tackled by the adoption of standard infection control measures and the risk categorisation of patients undergoing those procedures. Administration of a simple questionnaire prior to these tests could be useful in risk categorisation. Personal protective measures with at least FFP3 or N95 masks should be used for those staff involved in the procedures for high risk patient categories. Equally, health education for both patients and health care workers would immensely help to alleviate the anxiety related to these procedures.

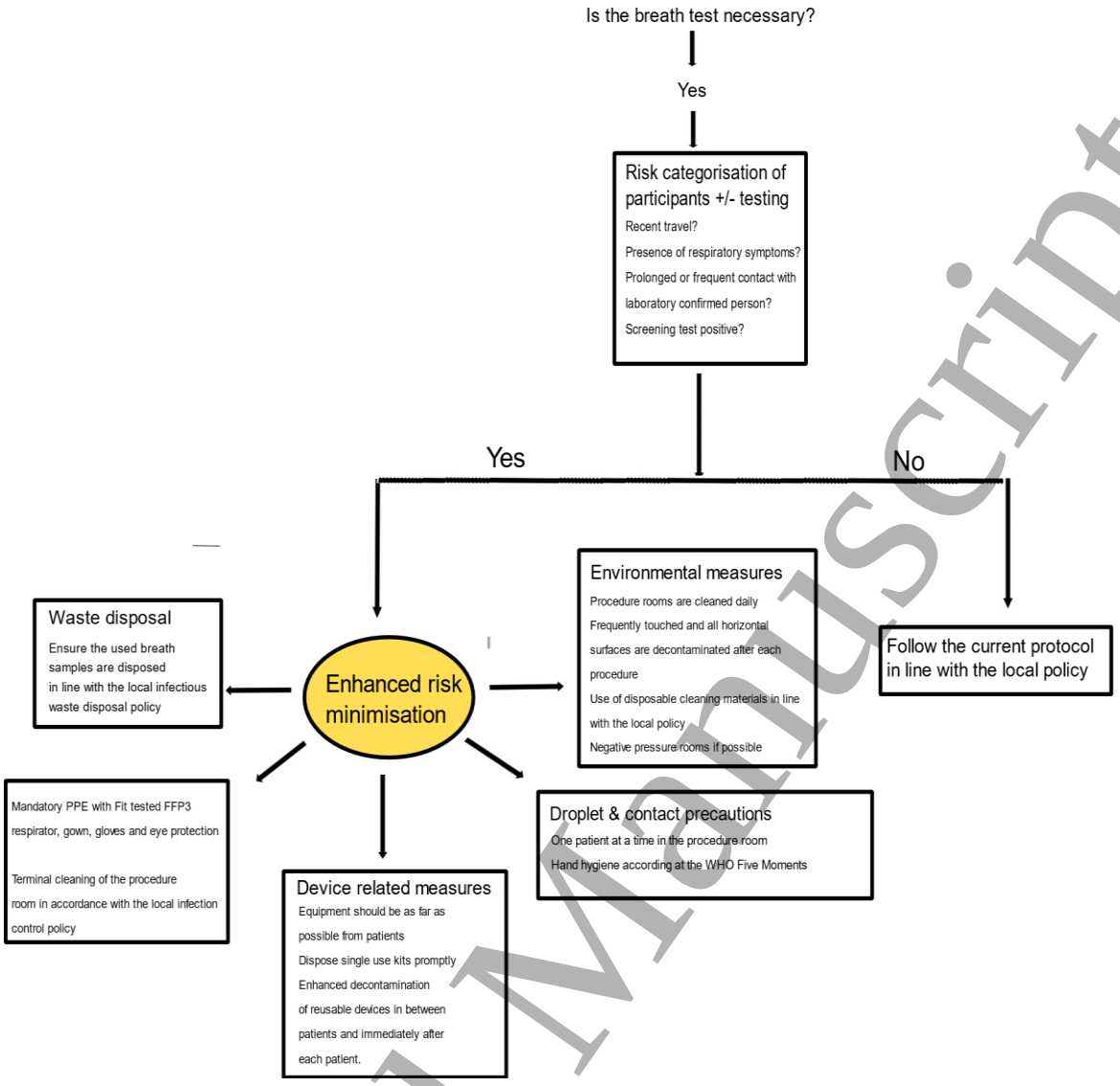

Figure 1: An illustration showing the different aspects of the measures need to be adopted to minimise the transmission of breath test associated SARS-CoV-2. The initial step is risk stratification of participants. For a high-risk participant, enhanced risk minimisation measures, to include PPE for staff, device and environmental measures to reduce contamination as well as waste disposal to be implemented contemporaneously.

It is worth noting that if breath tests are to be used in a mass screening setting, these measures could potentially slow down the process significantly. Moreover, financial implications of providing PPE should be borne in mind. The use of disposable kits and devices would be an alternative approach but again adds to the cost. An alternative would be a centralised model, where disposable breath bags or single use 'tenax' tubes are collected at home and samples are either processed in a central laboratory or using patients' hand held devices – rather similar to that undertaken for diagnosing carbohydrate intolerance or bacterial overgrowth.[23,24] Volatile diagnostic tests involving other types of body fluids (such as faeces) where there is concern of 'faecal aerosol' would also require careful consideration and the above recommendation in Figure 1 may help circumvent problems.

As an additional perspective, we need to consider is how comfortable will participants be to undergo these tests in the future? It is therefore imperative that appropriate measures are put in place to protect and reassure participants. Participants should be informed about the small possibility of infection transmission and the measures taken to minimise this risk. At present, it is not possible to quote a number as the level of risk for each device is unknown. The SARS-CoV-2 pandemic should not deter clinicians or participants from breath diagnostics, but rather strive to implement precautionary measures as outlined in Figure 1. Future guidelines on any breath test device will likely require added stringent data to support CE marking in particular safety against air borne viruses. For now, it would appear that home testing using disposable aerosol kits, coupled with digital applications for diagnosis, is likely to be viewed as priority.

References

1. World Health Organization. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. *Online 2004*. 2004;2(July):1-3.

2. *World Health Organization Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (2019)*. https://www.who.int/emergencies/mers-cov/en/.

3. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med*. 2003;348(20):1953-1966. doi:10.1056/NEJMoa030781

4. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. 2020;382(13):1199-1207. doi:10.1056/NEJMoa2001316

5. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-NCOV infection from an asymptomatic contact in Germany. *N Engl J Med*. 2020;382(10):970-971. doi:10.1056/NEJMc2001468

6. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med*. 2020;27(2). doi:10.1093/jtm/taaa021

7. Nishiura H, Linton NM, Akhmetzhanov AR. Serial interval of novel coronavirus (COVID-19) infections. *Int J Infect Dis*. 2020;93:284-286. doi:10.1016/j.ijid.2020.02.060

8. Bake B, Larsson P, Ljungkvist G, Ljungström E, Olin AC. Exhaled particles and small airways. *Respir Res*. 2019;20(1). doi:10.1186/s12931-019-0970-9

9. Groves WA, Zellers ET. Investigation of Organic Vapor Losses to Condensed Water Vapor in Tedlar® Bags Used for Exhaled-Breath Sampling. *Am Ind Hyg Assoc J*.

1996;57(2):257-263. doi:10.1080/15428119691014981

10. Goncharova VA, Mamedov DT, Dotsenko EK. Biologically active substance levels in exhaled air from patients with pre-asthma and bronchial asthma. *Sov Meditsina*. 1989;(5):22-24.

11. Carpenter CT, Price P V., Christman BW. Exhaled Breath Condensate Isoprostanes Are Elevated in Patients with Acute Lung Injury or ARDS. *Chest*. 1998;114(6):1653-1659. doi:10.1378/chest.114.6.1653

12. Nardi-Agmon I, Peled N. Exhaled breath analysis for the early detection of lung cancer: Recent developments and future prospects. *Lung Cancer Targets Ther*. 2017;8:31-38. doi:10.2147/LCTT.S104205

13. Soobratty MR, Whitfield R, Subramaniam K, et al. Point-of-care urine test for assessing adherence to isoniazid treatment for tuberculosis. *Eur Respir J*. 2014;43(5):1519-1522. doi:10.1183/09031936.00132613

14. J. H. Exhaled breath condensate: An evolving tool for noninvasive evaluation of lung disease. *J Allergy Clin Immunol*. 2002;110(1):28-34. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2003048662.

15. Fabian P, Brain J, Houseman EA, Gern J, Milton DK. Origin of exhaled breath particles from healthy and human rhinovirus-infected subjects. *J Aerosol Med Pulm Drug Deliv*. 2011;24(3):137-147. doi:10.1089/jamp.2010.0815

16. Johnson GR, Morawska L. The mechanism of breath aerosol formation. *J Aerosol Med Pulm Drug Deliv*. 2009;22(3):229-237. doi:10.1089/jamp.2008.0720

17. To KK-W, Tsang OT-Y, Yip CC-Y, et al. Consistent Detection of 2019 Novel Coronavirus in Saliva. *Clin Infect Dis*. February 2020. doi:10.1093/cid/ciaa149

18. Morawska L, Johnson GR, Ristovski ZD, et al. Size distribution and sites of origin of droplets expelled from the human respiratory tract during expiratory activities. *J Aerosol Sci*. 2009;40(3):256-269. doi:10.1016/j.jaerosci.2008.11.002

19. WHO (World Health Organization). Statement on the meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). *WHO Newsletter*. https://www.who.int/news-room/detail/23-01-2020-statement-on-the-meeting-of-the-international- health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019- ncov)?from=singlemessage&isappinstalled=0. Published 2020.

20. Hinds WC. Properties, Behavior, and Measurement ofAirborne Particles. *J Aerosol Sci*. 1999;14(2):175. doi:10.1016/0021-8502(83)90049-6

21. Horváth I, Hunt J, Barnes PJ, et al. Exhaled breath condensate: methodological recommendations and unresolved questions On behalf of the ATS/ERS Task Force on Exhaled Breath Condensate. *Eur Respir J*. 2005;26:523-548. doi:10.1183/09031936.05.00029705

22. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N Engl J Med*. March 2020. doi:10.1056/NEJMc2004973

23. Maceira A, Vallecillos L, Borrull F, Marcé RM. New approach to resolve the humidity problem in VOC determination in outdoor air samples using solid adsorbent tubes

followed by TD-GC–MS. *Sci Total Environ*. 2017;599-600:1718-1727. doi:10.1016/j.scitotenv.2017.05.141

24. Richter V, Gonzalez JO, Hazan S, et al. The validity of breath collection bags method in detecting Helicobacter pylori using the novel BreathID ® Hp Lab System : a multicenter clinical study in 257 subjects . *Ther Adv Gastrointest Endosc*. 2019;12:263177451984340. doi:10.1177/2631774519843401

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