References

1. Echternach M, Gantner S, Peters G, Westphalen C, Benthaus T, Jakubaß B, *et al*. Impulse dispersion of aerosols during singing and speaking: a potential COVID-19 transmission pathway. *Am J Respir Crit Care Med* 2020;202:1584–1587.
2. Jones NR, Qureshi ZU, Temple RJ, Larwood JPJ, Greenhalgh T, Bourouiba L. Two metres or one: what is the evidence for physical distancing in covid-19? *BMJ* 2020;370:m3223.
3. Philip KEJ, Lewis A, Buttery SC, McCabe C, Fancourt D, Orton C, *et al*. The physiological demands of Singing for Lung Health compared to treadmill walking [preprint]. *medRxiv*;2020 [accessed 2020 Dec 15]. Available from: https://www.medrxiv.org/content/10.1101/2020.12.08.20245746v1.
4. Russell BA, Cerny FJ, Stathopoulos ET. Effects of varied vocal intensity on ventilation and energy expenditure in women and men. *J Speech Lang Hear Res* 1998;41:239–248.
5. Hoit JD, Lohmeier HL. Influence of continuous speaking on ventilation. *J Speech Lang Hear Res* 2000;43:1240–1251.
6. Guallar MP, Meiriño R, Donat-Vargas C, Corral O, Jouvé N, Soriano V. Inoculum at the time of SARS-CoV-2 exposure and risk of disease severity. *Int J Infect Dis* 2020;97:290–292.
7. Chu H, Chan JF, Wang Y, Yuen TT, Chai Y, Hou Y, *et al*. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an *ex vivo* study with implications for the pathogenesis of COVID-19. *Clin Infect Dis* 2020;71:1400–1409.

Reply to Philip *et al.*

From the Authors:

In the comment by Philip and colleagues, the authors state that the special inhalation patterns are also important in the transmission of coronavirus disease (COVID-19). We absolutely agree that every part of the transmission pathway, specifically *1*) the absolute aerosol production during singing and speaking (1), *2*) the special aerosol impulse dispersion and expansion (2), *3*) the accumulation and convectional spreading of aerosols in rooms (3), and *4*) the special inhalation patterns during singing (4) contribute to person-to-person transmission of the COVID-19 virus.

Although our understanding of the COVID-19 pandemic has grown recently, to the best of our knowledge, the main question remains unclarified: How high a virus dose is needed to infect a person? Whereas the transmission factors (1–3) contribute to the necessary infectious dose, factor 4 represents the rate of admission by a receiving person. In agreement with Philip and colleagues, we do believe that it is very important to understand phonation-related differences in breathing patterns. With regard to this, it has been shown that ventilation patterns differ between types of phonation, showing higher $\dot{V}_E$ for singing in contrast to breathing (4). However, many open questions remain with regard to ventilation. For example, to the best of our knowledge, it has not yet been clarified in detail if an infection is more likely if a virus cloud has been inhaled more deeply, thereby reaching deeper parts of the breathing apparatus, nor if there is any difference between transoral and transnasal breathing. With deep breath inhalation used, for example, for louder speaking, typically the fraction of transoral inhalation increases, which does not have the same immune competence as the nose. However, as far as we know, most virus dose at the beginning of the infection is found in the nasopharynx (5), a part of the breathing system that is only encountered by transnasal breathing patterns.

Nevertheless, exhalatory characteristics such as impulse dispersion appear more important for estimating safety distances because they draw the volume and regions of the highest potential viral dose within the transmission process, inoculated in a direct compact stream. Such a stream reaches significant distances, exceeding 1.3 m (2). By contrast, during inhalation, aerosol particles must enter a person's near field, which shows much less distance from the mouth than for exhalation. The inhalatory near field can be assumed to originate from a hemispherical volume around the mouth and nose with a small radius. In a single-subject side experiment of our study, the radius of the region from which inhaled vapor for a sustained phonation came was determined at approximately 6.5 cm. Thus, the cloud has to be quite near to the mouth of the recipient to be inhaled. To illustrate, it is quite easy to blow out a candle at a distance of 10 cm by the compact exhaling stream, but it is nearly impossible to do the same by inhalation. To provide estimations of safety distances (2), we analyzed phonation-related differences in the impulse dispersion of aerosols while not disregarding that all other parts of the transmission pathway are important for understanding the COVID-19 pandemic. ■

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References

1. Alsved M, Matamis A, Bohlin R, Richter M, Bengtsson P-E, Fraenkel C-J, *et al*. Exhaled respiratory particles during singing and talking. *Aerosol Sci Technol* 2020;54:1245–1248.
2. Echternach M, Gantner S, Peters G, Westphalen C, Benthaus T, Jakubaß B, *et al*. Impulse dispersion of aerosols during singing and speaking: a potential COVID-19 transmission pathway. *Am J Respir Crit Care Med* 2020;202:1584–1587.
3. Prather KA, Marr LC, Schooley RT, McDiarmid MA, Wilson ME, Milton DK. Airborne transmission of SARS-CoV-2. *Science* 2020;370: 303–304.
4. Philip KEJ, Lewis A, Buttery SC, McCabe C, Fancourt D, Orton C, *et al*. The physiological demands of Singing for Lung Health compared to treadmill walking [preprint]. *medRxiv*;2020 [accessed 2021 Feb 17]. Available from: https://www.medrxiv.org/content/10.1101/2020.12.08.20245746v1.
5. Walsh KA, Jordan K, Clyne B, Rohde D, Drummond L, Byrne P, *et al*. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. *J Infect* 2020;81:357–371.

Aspergillosis in the ICU: Hidden Enemy or Bogeyman?

To the Editor:

Loughlin and colleagues (1) report on the important possibility of pulmonary aspergillosis in patients with suspected ventilator-associated pneumonia. Aspergillosis is increasingly reported as a potential pathogen in nonimmunocompromised ICU patients, as the authors and editorialist point out (1–4). However, many of these reports have unavoidable but significant methodological limitations that make their conclusions provisory, and the current report is no exception. The authors purport to establish the estimated prevalence of *Aspergillus* infection in nonimmunocompromised ICU patients with ventilator-associated pneumonia, using a combination of tests with imperfect specificity for pathologic disease (microscopy, culture, galactomannan assays, etc.). The test most commonly leading to "probable diagnosis" was the BAL fluid galactomannan assay (BALF GM). The authors claim that the specificity of the BALF GM assay is on the order of 95–100% citing two studies showing some of the highest specificities reported (5, 6); other studies report more modest specificities within a range of confidence limits (7, 8). All studies of BALF GM have a tendency to overstate specificity because they do not require a gold standard for true disease classification, instead lumping proven, probable, and possible invasive aspergillosis together in different combinations. Furthermore, most studies are in immunocompromised patients, and the assumption that sensitivity and specificity are independent of prevalence is not always fulfilled; if they are not, tests may have worse performance in low-prevalence populations, such as nonimmunocompromised patients. These major caveats notwithstanding, even if the specificity is as high as 95% (with a corresponding sensitivity of 65%) (6), but the true base rate of aspergillosis is 1%, the posterior probability of aspergillosis with a positive BALF GM test would be just 12% according to Bayes' Theorem. However, the authors would dichotomize this as a "probable" case, falsely inflating the prevalence in the cohort. This is a form of base rate neglect: in low prevalence populations, the majority of positive tests represent false positives. The problem will be worse if the specificity is a more modest 85% (the lower end of the confidence limit in the most widely referenced meta-analysis [7, 9]), with the posterior probability falling to a mere 4%. The crux of the problem is that with tests of imperfect specificity it is impossible to determine the prevalence of disease in the population because it requires knowing the prevalence of disease in the population! An ancillary problem arises from the policy of allowing any of multiple positive components of the mycological criteria to count for diagnosis (3). This increases the overall sensitivity of the diagnostic strategy at the expense of specificity, amplifying the aforementioned problems. Histology was among the criteria for diagnosis, but it appears that no cases were diagnosed using histopathology of tissue samples. The only way to reliably diagnose aspergillosis in a low-prevalence cohort is to use a gold standard, in this case a biopsy (or necropsy) specimen showing fungal invasion (9). We worry that if the immanent methodological limitations of this and similar studies are not adequately acknowledged—they are not listed among the possible explanations for the results enumerated by the editorialist (2)—an avalanche of testing for aspergillosis in ICUs may ensue, resulting in an epidemic of overdiagnosis and overtreatment. We caution readers of this report that it cannot establish the true prevalence of *Aspergillus* infection in patients with ventilator-associated pneumonia in the ICU, but it does underscore the fact that when tests with imperfect specificity are applied in low-prevalence cohorts, most positive results are false positives (10). Prospective cohort studies using tissue sampling and histopathology, perhaps guided by tests such as BALF GM, are necessary to establish the true prevalence of this disease in nonimmunocompromised patients in the ICU. ■

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