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.

inhaler triple therapy in COPD did not enrol patients already treated with triple therapy.[9] With its smaller size compared with those in the IMPACT and ETHOS trials, the TRIBUTE trial did not report on mortality.

Second, this design does not provide the relevant evidence for the escalation from dual bronchodilators to triple therapy, but rather of treatment withdrawal for many patients.[3] Escalation would randomise patients exclusively receiving LAMA–LABA, in need of ICSs.

Third, abruptly withdrawing ICSs, an effective treatment for the subset of patients who respond to ICSs, such as those patients with an asthma-COPD phenotype, and switching to LAMA–LABA can produce an early effect on mortality. This occurrence was shown in a cohort study of ICS use on asthma mortality, in which asthma mortality was increased in the first 3 months after ICS discontinuation by five times that of the asthma mortality associated with ICS continuation.[8,10] This early pattern is apparent in the IMPACT and ETHOS trials, with the remarkably low HRs (0·24 and 0·37, respectively) in the first 3 months after randomisation. Moreover, the HRs of mortality, among the subgroup of non-users of ICSs, of 1·25 (95% CI 0·60–2·59) and 1·49 (0·49–4·55) in the IMPACT and ETHOS trials, respectively, comparing triple therapy with dual bronchodilators, support a withdrawal effect.

Overall, the IMPACT and ETHOS trials, in assessing the escalation from dual bronchodilators to triple therapy in COPD, noted major benefits of triple therapy on all-cause mortality.[4–6] However, the approximate 50% reduction in mortality reported with triple therapy is inconsistent over the 1-year follow-up. This reduction is exclusively confined to the first 3 months after treatment initiation, during which mortality was reduced by up to 75%, with the reduction disappearing entirely during the subsequent 9 months. These inconsistencies probably result from the study population chosen and the unselected randomisation, and are compounded in trials involving ICSs and the inclusion of patients with a history of asthma or asthma-like symptoms. To circumvent such inconsistencies and related biases, the trial design should adapt the treatment randomisation to the treatment already used by study participants, thus avoiding the treatment withdrawal effects that have plagued major trials, such as the IMPACT and ETHOS trials.

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Samy Suissa
samy.suissa@mcgill.ca

Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal H3T 1E2, QC, Canada (SS); Department of Epidemiology, Biostatistics, and Occupational Health and Department of Medicine, McGill University, Montreal, QC, Canada (SS)

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SARS-CoV-2 antigen testing: weighing the false positives against the costs of failing to control transmission

Lateral flow device (LFD) rapid tests for SARS-CoV-2 antigens are used for asymptomatic testing (including for people who are presymptomatic or paucisymptomatic) in various settings, including in the UK. As of April 9, 2021, LFD tests were made available for twice per week rapid testing to the general

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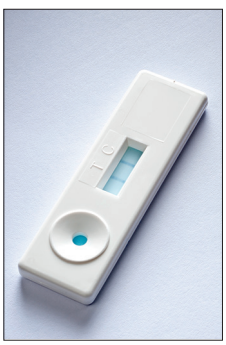

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population in England. News articles reported pressures within the UK Government to rescind asymptomatic testing due to concerns that, despite high specificity (estimated to be 99·9%),[1] the proportion of people testing positive who had COVID-19 (ie, the positive predictive value) was falling in line with the reducing prevalence, leading to greater proportions of individuals having to unnecessarily isolate because of a false-positive test result.[2] Asking people to isolate on the basis of what might be a false-positive result is associated with a perceived unfairness and, in some cases, moral indignation.

The risk of people without COVID-19 self-isolating due to false-positive test results is a cost to the individual, their household, and their workplace that needs consideration and mitigation. However, this cost should be considered in the context of the costs of failing to identify true-positive results. In the UK, the epidemic control strategies implemented during the past year, including lockdowns, have all, to varying extents, required people who do not have COVID-19 to isolate or quarantine and to greatly restrict their social contacts, while shutting down entire economic sectors. These restrictions have had massive implications for the incomes, education, and wellbeing of many people, including children and young people.[3] Any discussions concerning LFD testing policy should incorporate the trade-off between the negative effects of false positives and the onwards transmission prevented. This trade-off is particularly pertinent when considering the contribution of LFD testing to preventing the need for additional widespread restrictive measures.

Keeping COVID-19 prevalence low is of great public benefit. During the pandemic, all people in the UK have been asked to take measures, which might be personally challenging, to mitigate risk to others, even when they have no symptoms and low likelihood of transmitting the virus. People in the UK generally wear a mask over their nose and mouth in enclosed spaces and self-isolate if they have been in contact with someone known to have COVID-19, even if just an estimated 10–15% of people who come into contact with someone with COVID-19 become infected during a period of high prevalence.[4] These measures could be considered analogous to responses to a false-positive test, but the public recognises their value in the reduction of transmission. Most people also recognise that reducing the risk of transmission to others is of benefit to themselves, and the same applies to asymptomatic or community testing.

No measures to control SARS-CoV-2 transmission are without cost or harm, and these costs and harms are not experienced equally across society. If asymptomatic testing is to work and be equitable, it is imperative that more is done to ensure that isolation or quarantine is not an undue sacrifice that disproportionately affects people who cannot work from home and might lose their jobs, incomes, or ability to care for family members.[5,6] A crucial part of the problem is distinguishing between false-positive results and true-positive results and their consequences as an end-to-end system. Much of the harm of false-positive results can be mitigated by taking a second test if the first is positive; if this is done via LFD, it would add only 30 min, and varying test batches (or even tests that detect different antigens) could help address concerns that the chance of receiving a false-positive result might be correlated across tests delivered together, especially if they are from the same batch.[7,8] Although a second test increases specificity of the testing procedure, it can only lower overall sensitivity as neither LFD nor PCR testing is 100% sensitive. The accompanying reduction in true-positive results could also have an effect on transmission.

If COVID-19 prevalence is low and the proportion of false-positive results is judged too high for mass asymptomatic population testing, when considered with the appropriate trade-offs, then LFD testing might be well suited to other applications, including: testing subpopulations with high prevalence, such as people who have been in contact with someone with COVID-19;[9,10] testing in high-transmission settings or where physical distancing is impossible; and testing in areas where variants of concern have been detected. The role of LFD testing in society can, and should, be subject to continuous study (including cost-effectiveness), review, and communication, with policy modifications made accordingly. Furthermore, messaging about LFD test accuracy, interpretation, and importance should be clear, should reach underserved groups, and should be based on the most up-to-date evidence.

Asymptomatic testing interventions should not be dismissed on the basis of numbers of people isolating after false-positive test results alone without assessing

their worth in preventing both onwards transmission and more widespread restrictive interventions.

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Elizabeth Fearon, Iain E Buchan, Rajenki Das, Emma L Davis, Martyn Fyles, Ian Hall, T Deirdre Hollingsworth, Thomas House, Caroline Jay, Graham F Medley, Lorenzo Pellis, Billy J Quilty, Miguel E P Silva, Helena B Stage, Tom Wingfield
elizabeth.fearon@lshtm.ac.uk

Department of Global Health and Development, Faculty of Public Health and Policy (EF, GFM), Centre for the Mathematical Modelling of Infectious Diseases (EF, GFM, BJQ), and Department of Infectious Disease Epidemiology (BJQ), London School of Hygiene and Tropical Medicine, London WC1H 9SH, UK; Institute of Population Health, University of Liverpool, Liverpool, UK (IEB); Department of Mathematics (RD, MF, IH, TH, LP, HBS), and School of Computer Science (CJ, MEPS), University of Manchester, Manchester, UK; Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, Oxford, UK (ELD, TDH); The Alan Turing Institute, London, UK (MF); Emergency Response Department, Public Health England, Salisbury, UK (IH); IBM Research, Warrington, UK (TH); Department of Clinical Sciences, and Department of International Public Health, Liverpool School of Tropical Medicine, Liverpool, UK (TW); Tropical and Infectious Disease Unit, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK (TW); WHO Collaborating Centre in Tuberculosis and Social Medicine, Department of Global Public Health, Karolinska Institutet, Solna, Sweden (TW)

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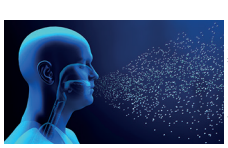
Aerosol generating procedures: are they of relevance for transmission of SARS-CoV-2?

It is now generally accepted that SARS-CoV-2 can be spread by aerosols as well as larger droplets from the upper respiratory tract, although the relative importance of aerosol transmission remains incompletely answered.[1] Despite this, current UK infection control guidance for hospitals is centred on the premise that aerosols are only generated by specific medical interventions designated as aerosol generating procedures (AGPs).[2] This draws from epidemiological observations during the 2003 outbreak of severe acute respiratory syndrome, during which certain procedures appeared to be associated with an increased risk of staff infection (particularly tracheal intubation), and these procedures had a theoretical risk of viral aerosolisation.[3] However, the evidence supporting aerosolisation during these procedures was, before the pandemic, remarkably slim, with aerosolisation being assumed on the basis of the precautionary principle and low quality mechanistic studies.[4]

This view of aerosol generation subsequently led to a dichotomisation—later codified in international guidance[2]—that categorised all medical activities into either AGPs, where potentially infectious aerosols are generated, versus everything else, where the risk of potentially infectious aerosol is presumed to be negligible. The logical extension of this dichotomy has resulted in health-care workers in many countries undertaking interventions classified as AGPs wearing higher levels of personal protective equipment (PPE), such as FFP3 or N95 masks, whereas those health-care workers providing other medical care have not been afforded the same protection, as infectious aerosol is not considered a risk outside of AGPs.[5]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