
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.

translate into longer-term mortality benefit, and we look forward to the preplanned analyses at 6 months.

In summary, the RECOVERY trial provides the most definitive evidence thus far to address the controversy over whether tocilizumab should be added to our armamentarium of treatments for severely ill patients with COVID-19. The answer is yes. Questions remain about tocilizumab's efficacy and safety in other settings, such as those with C-reactive protein concentrations of less than 75 mg/L and among paediatric patients (the RECOVERY group is doing a separate trial in children, which is ongoing), and among more gender and racially diverse populations. Importantly, the 28-day mortality rate of 31% in the tocilizumab group, although lower than the placebo group, remains unacceptably high, and thus additional therapies are urgently needed to further reduce mortality in severely ill patients with COVID-19. Several treatments, including other immunomodulators and antibodies against the spike protein of SARS-CoV-2, are under investigation.[12]

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*Shruti Gupta, David E Leaf
**sgupta21@bwh.harvard.edu**

Division of Renal Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA (SG, DEL); Harvard Medical School, Boston, MA, USA (SG, DEL)

1 Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020; **26:** 1636–43.
2 Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med* 2021; **384:** 693–704.
3 Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA* 2020; **117:** 10970–75.
4 Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with covid-19. *JAMA Intern Med* 2021; **181:** 41–51.
5 Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with covid-19. *N Engl J Med* 2020; **383:** 2333–44.
6 Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021; **181:** 32–40.
7 Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021; **181:** 24–31.
8 Leaf DE, Gupta S, Wang W. Tocilizumab in Covid-19. *N Engl J Med* 2021; **384:** 86–87.
9 Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe covid-19 pneumonia. *N Engl J Med* 2021; published online Feb 25. https://www.nejm.org/doi/10.1056/NEJMoa2028700.
10 Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically Ill patients with Covid-19-preliminary report. *N Engl J Med* 2021; published online Feb 25, 2021. https://www.nejm.org/doi/full/10.1056/NEJMoa2100433.
11 RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397:** 1637–45.
12 Wang C, Wang Z, Wang G, Lau JY, Zhang K, Li W. COVID-19 in early 2021: current status and looking forward. *Signal Transduct Target Ther* 2021; published online March 8. https://doi.org/10.1038/s41392-021-00527-1.

# Hospital admissions due to COVID-19 in Scotland after one dose of vaccine

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The BNT162b2 mRNA vaccine from Pfizer–BioNTech[1] and the ChAdOx1 nCoV-19 vaccine from Oxford–AstraZeneca[2] were the first two products deployed in the UK's COVID-19 vaccination programme. In accordance with the strategy set by the nation's Joint Committee on Vaccination and Immunisation (JCVI), vaccines were initially prioritised for care home residents and staff, individuals older than 80 years, and front-line health-care and social care workers. In December, 2020, in response to surging transmission of SARS-CoV-2, JCVI advised delaying the second dose of these vaccines to achieve broader population coverage with the first dose.[3]

In *The Lancet*, Eleftheria Vasileiou and colleagues[4] report the interim findings following COVID-19 mass vaccination with a first dose in Scotland. The analysis includes 1 331 993 individuals vaccinated between Dec 8, 2020, and Feb 22, 2021. The authors constructed this comprehensive cohort by linking vaccination, primary care, laboratory testing, hospital admission, and mortality datasets covering 5·4 million people in Scotland. By Feb 22, 2021, an impressive 78·6% of adults aged 80 years and older, 85·9% of adults aged 65–79 years, and 13·9% of adults aged 18–64 years had received at least one dose of the vaccine. Uptake was higher in women than in men, with 35·1% of women and 25·0% of men vaccinated by this date.

Randomised vaccine trials of these products reported only small numbers of severe COVID-19 cases and hospital admissions. In contrast, the real-world data from Scotland captured 723 hospital admissions due to COVID-19 among

Russell Cheyne/Reuters

individuals who had received a first dose of vaccine, and 7854 hospital admissions in unvaccinated individuals. Furthermore, the randomised trials were unable to assess vaccine efficacy in narrow subgroups, such as adults aged 80 years and older, a group prioritised for vaccination.

To estimate vaccine effectiveness, Vasileiou and colleagues compared COVID-19 hospital admissions in vaccinated and unvaccinated individuals who had not previously tested positive with real-time RT-PCR. In observational studies, fundamental differences between vaccinated and unvaccinated populations might occur, reflecting differential access or uptake. To address potential confounding, the authors report model-adjusted and propensity score-weighted estimates, incorporating individual-level data on age, sex, socioeconomic status, calendar time, underlying medical conditions, and number of previous rtPCR tests (as a proxy for exposure risk).

The benefit of vaccines reducing hospital admissions takes time to show in a population. Given the time for an immune response to develop, and the time from infection to onset of disease and progression to severe disease, individuals who were admitted to hospital shortly after their first dose were likely to have been infected before vaccination. Focusing on 28–34 days after a single dose, the authors report an estimated vaccine effect of 91% (95% CI 85–94) for COVID-19 hospital admissions for BNT162b2, and an estimated 88% (75–94) vaccine effect during the same period for ChAdOx1.

Although the first dose of each vaccine probably provides substantial benefit, the exact magnitude and timing are less clear. Estimated vaccine effectiveness during the period 0–6 days after the first dose is 75% (95% CI 71–79) for both vaccines combined, but such a rapid benefit against hospital admission is not plausible. The authors posit that this occurred because individuals were advised to take precautions around the time of vaccination and to defer their appointments if they experienced symptoms or were self-isolating. Per the authors, "the later (>14 days) observed effects are much more likely to be mainly driven by traditional vaccine effects". However, early differences might also reflect non-transient sources of bias.

Another challenge is in making direct comparisons between the two vaccines, although the authors are cautious not to do so. Because of storage requirements, BNT162b2 was provided mainly through community vaccination centres. The highest uptake was in patients younger than 65 years, including health-care workers. ChAdOx1 was mainly administered at general practices, targeting care home residents and patients aged 80 years and older. ChAdOx1 was also deployed later, available only from Jan 4, 2021, enabling less time for follow-up. Therefore, the sources of bias for the two vaccines might differ. For example, the estimated 7–13 day vaccine effects are much higher for adults aged 65 years and older than for adults aged 18–64 years, even though we expect these to be similarly low. In a study of these two vaccines done by Public Health England, different early vaccine effects were observed before compared with after Jan 4, 2021, potentially reflecting a programmatic shift to vaccinate lower-risk patients.[5]

Large population cohorts support the real-world impact of COVID-19 vaccines. Given the UK's decision to increase the spacing between doses, longer single-dose person-time follow-up beyond 42 days will be forthcoming and particularly valuable. These assessments rely heavily on observational data, but with the strength of large numbers comes the limitations of bias. Bias-indicator checks, such as estimating effectiveness immediately after vaccination[6] or assessing effectiveness against an unrelated disease,[7] are advisable. The benefits of these vaccines are substantial, and their rapid roll-out is an important achievement for public health.

I declare no competing interests.

*Natalie Dean*
**nataliedean@ufl.edu**

Department of Biostatistics, University of Florida, Gainesville, FL 32611, USA

1 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383:** 2603–15.

2 Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; **397:** 99–111.

3 Joint Committee on Vaccination and Immunisation. Optimising the COVID-19 Vaccination Programme for Maximum Short-Term Impact. 2020. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=103741 (accessed April 6, 2021).

4 Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet* 2021; published online April 23. https://doi.org/10.1016/S0140-6736(21)00677-2.

5 Bernal JL, Andrews N, Gower C, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. *medRxiv* 2021; published online March 2. https://doi.org/10.1101/2021.03.01.21252652 (preprint).

6 Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021; published online Feb 24. https://doi.org/10.1056/NEJMoa2101765.

7 Franke MF, Jerome JG, Matias WR, et al. Comparison of two control groups for estimation of oral cholera vaccine effectiveness using a case-control study design. *Vaccine* 2017; **35:** 5819–27.

# Ten scientific reasons in support of airborne transmission of SARS-CoV-2

Heneghan and colleagues' systematic review, funded by WHO, published in March, 2021, as a preprint, states: "The lack of recoverable viral culture samples of SARS-CoV-2 prevents firm conclusions to be drawn about airborne transmission".[1] This conclusion, and the wide circulation of the review's findings, is concerning because of the public health implications.

If an infectious virus spreads predominantly through large respiratory droplets that fall quickly, the key control measures are reducing direct contact, cleaning surfaces, physical barriers, physical distancing, use of masks within droplet distance, respiratory hygiene, and wearing high-grade protection only for so-called aerosol-generating health-care procedures. Such policies need not distinguish between indoors and outdoors, since a gravity-driven mechanism for transmission would be similar for both settings. But if an infectious virus is mainly airborne, an individual could potentially be infected when they inhale aerosols produced when an infected person exhales, speaks, shouts, sings, sneezes, or coughs. Reducing airborne transmission of virus requires measures to avoid inhalation of infectious aerosols, including ventilation, air filtration, reducing crowding and time spent indoors, use of masks whenever indoors, attention to mask quality and fit, and higher-grade protection for health-care staff and front-line workers.[2] Airborne transmission of respiratory viruses is difficult to demonstrate directly.[3] Mixed findings from studies that seek to detect viable pathogen in air are therefore insufficient grounds for concluding that a pathogen is not airborne if the totality of scientific evidence indicates otherwise. Decades of painstaking research, which did not include capturing live pathogens in the air, showed that diseases once considered to be spread by droplets are airborne.[4] Ten streams of evidence collectively support the hypothesis that SARS-CoV-2 is transmitted primarily by the airborne route.[5]

First, superspreading events account for substantial SARS-CoV-2 transmission; indeed, such events may be the pandemic's primary drivers.[6] Detailed analyses of human behaviours and interactions, room sizes, ventilation, and other variables in choir concerts, cruise ships, slaughterhouses, care homes, and correctional facilities, among other settings, have shown patterns—eg, long-range transmission and overdispersion of the basic reproduction number ($R_0$), discussed below—consistent with airborne spread of SARS-CoV-2 that cannot be adequately explained by droplets or fomites.[6] The high incidence of such events strongly suggests the dominance of aerosol transmission.

Second, long-range transmission of SARS-CoV-2 between people in adjacent rooms but never in each other's presence has been documented in quarantine hotels.[7] Historically, it was possible to prove long-range transmission only in the complete absence of community transmission.[4]

Third, asymptomatic or presymptomatic transmission of SARS-CoV-2 from people who are not coughing or sneezing is likely to account for at least a third, and perhaps up to 59%, of all transmission globally and is a key way SARS-CoV-2 has spread around the world,[8] supportive of a predominantly airborne mode of transmission. Direct measurements show that speaking produces thousands of aerosol particles and few large droplets,[9] which supports the airborne route.

Fourth, transmission of SARS-CoV-2 is higher indoors than outdoors[10] and is substantially reduced by indoor

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