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Effectiveness of England's initial vaccine roll out

Both vaccine candidates offer protection to older adults

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In its human host, the spread of SARS-CoV-2 has followed unusually volatile and seemingly unpredictable patterns that are often driven by statistical extremes, such as superspreading events.¹ These drivers of infection range from household, through local, to community events and beyond,² in which multiple chains of infection coalesce into the regional and highly volatile epidemic waves that characterise this pandemic.

Fluctuating in both space and time, such waves are difficult to predict and occur largely independent of past SARS-CoV-2 incidence or incidence in neighbouring regions.³ Thus, little more than a year after the pandemic began, many regional outbreaks have rapidly generated a broad spectrum of complex genetic variants (including variants of concern) that have already begun to obstruct our view of the pandemic's past, including attempts to unambiguously pinpoint its origin.⁴ Also, these unpredictable patterns of transmission make the development, implementation, and retrospective evaluation of essential public health interventions such as vaccination a particular challenge, because observed short term effects can be strongly biased by random fluctuations in incidence.⁵

In this rapidly changing environment, mass vaccination has emerged internationally as a constant and leading initiative against covid-19. In a linked paper, Lopez Bernal and colleagues (doi:10.1136/bmj.n1088) report evidence of vaccine effectiveness from England's first covid-19 mass vaccination campaign.⁶ Vaccination began on 8 December 2020, and for the first time nucleic acid based vaccine candidates were administered to the UK population—Pfizer's messenger RNA based BNT162b2 and Oxford-AstraZeneca's adenoviral DNA based ChAdOx1-S. Only Pfizer's vaccine was administered until 4 January 2021, then both vaccines were used.

Vaccine effectiveness, which during recent clinical trials^{7 8} measured the reduction in incidence of cases among vaccinated people relative to unvaccinated controls, was here estimated against three different outcomes in adults older than 70 years: symptomatic SARS-CoV-2 infections confirmed with standard polymerase chain reaction testing, admissions to hospital, and deaths. Outcomes were monitored after a first dose (BNT162b2 and ChAdOx1-S) and second dose (only BNT162b2).

During the study period between 8 December 2020 and 19 February 2021, the variant of concern VOC 202012/01 (also referred to as B.1.1.7) became dominant in the UK. After encouraging results from phase III clinical trials, Lopez Bernal and colleagues' data provide much needed real world evidence of

vaccine effectiveness against a novel and now common variant of concern. Indeed, their results indicate significant protection from both vaccine candidates against symptomatic SARS-CoV-2 infection, admissions to hospital, and death—with effectiveness levels near those already seen in clinical trials, or in similar observational reports from other countries.^{9 10}

For adults aged 70 years and older, the authors report vaccine effectiveness of 61% (95% confidence interval 51% to 69%) for BNT162b2 and 60% (41% to 73%) for ChAdOx1-S from 28 days after the first dose. This close similarity in effectiveness is somewhat unexpected since both vaccines encode structurally distinct antigens: BNT162b2 includes a double proline modification that structurally stabilises the spike antigen and favours a stronger immune response, whereas ChAdOx1-S does not.¹¹ Without this stabilisation, the spike protein alone may cause cellular abnormalities such as the formation of syncytia (fusion of cells),¹² so an increase in pharmacovigilance might be indicated for ChAdOx1-S.

The increased odds of a positive test result within 20 days of an initial dose of Pfizer's vaccine among adults aged 80 years and older should perhaps also attract more attention. The authors suggest that this increased risk was probably due to the selection of high risk individuals for vaccination during the campaign's earliest stages. If so, the effect size would be expected to decrease steadily with time—but instead the odds ratio for a positive test result first increased to a peak of 1.47 (95% confidence interval 1.23 to 1.76) after nine days, and then decreased back to baseline (odds ratio 1.00) before 21 days post-vaccination. This pattern remains unexplained.

The study has a test negative design, meaning that the authors compared the vaccination status of individuals according to their observed clinical outcomes. For symptomatic SARS-CoV-2 infection, the study's primary outcome, this comparison is given as odds ratios, which are bias-free if the incidence of concurrent non-SARS-CoV-2 respiratory virus infections is the same in vaccinated and unvaccinated groups.¹³ Such co-infections are not uncommon among people with SARS-CoV-2,^{14 15} and future studies should test more directly whether the above condition is met, and that rates of concurrent viral infections do not depend on vaccination status.

Overall, Lopez Bernal and colleagues' findings strongly support a protective effect among older adults during the initial stages of the UK's first covid-19 vaccination programme. It is, however, important to emphasise that both vaccine types remain vaccine candidates that are still being

evaluated for effectiveness and safety during ongoing confirmatory phase IV trials.

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- 1 Wong F, Collins JJ. Evidence that coronavirus superspreading is fat-tailed. *Proc Natl Acad Sci U S A* 2020;117:29416-8. doi: 10.1073/pnas.2018490117. pmid: 33139561
- 2 Liu Y, Eggo RM, Kucharski AJ. Secondary attack rate and superspreading events for SARS-CoV-2. *Lancet* 2020;395:e47. doi: 10.1016/S0140-6736(20)30462-1. pmid: 32113505
- 3 Hébert-Dufresne L, Althouse BM, Scarpino SV, Allard A. Beyond R0: heterogeneity in secondary infections and probabilistic epidemic forecasting. *J R Soc Interface* 2020;17:20200393. doi: 10.1098/rsif.2020.0393. pmid: 33143594
- 4 Pipes L, Wang H, Huelsenbeck JP, Nielsen R. Assessing Uncertainty in the Rooting of the SARS-CoV-2 Phylogeny. *Mol Biol Evol* 2021;38:1537-43. doi: 10.1093/molbev/msaa316. pmid: 33295605
- 5 Lisewski AM. Interim estimates in null models of COVID-19 vaccine effectiveness. *Int J Infect Dis* 2021;106:169-70. doi: 10.1016/j.ijid.2021.03.050. pmid: 33746095
- 6 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* 2021;373.
- 7 Polack FP, Thomas SJ, Kitchin N, et al C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med* 2020;383:2603-15. doi: 10.1056/NEJMoa2034577. pmid: 33301246
- 8 Voysey M, Clemens SAC, Madhi SA, et al Oxford COVID Vaccine Trial Group. 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. doi: 10.1016/S0140-6736(20)32661-1. pmid: 33306989
- 9 Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021;384:1412-23. doi: 10.1056/NEJMoa2101765. pmid: 33626250
- 10 Torjesen I. Covid-19: First doses of vaccines in Scotland led to a substantial fall in hospital admissions. *BMJ* 2021;372:n523. doi: 10.1136/bmj.n523. pmid: 33619037
- 11 Sanders RW, Moore JP. Virus vaccines: proteins prefer prolines. *Cell Host Microbe* 2021;29:327-33. doi: 10.1016/j.chom.2021.02.002. pmid: 33705704
- 12 Theuerkauf SA, Michels A, Riechert V, et al. Quantitative assays reveal cell fusion at minimal levels of SARS-CoV-2 spike protein and fusion from without. *iScience* 2021;24:102170. doi: 10.1016/j.isci.2021.102170. pmid: 33585805
- 13 Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine* 2013;31:2165-8. doi: 10.1016/j.vaccine.2013.02.053. pmid: 23499601
- 14 Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. *JAMA* 2020;323:2085-6. doi: 10.1001/jama.2020.6266. pmid: 32293646
- 15 Singh V, Upadhyay P, Reddy J, Granger J. SARS-CoV-2 respiratory co-infections: incidence of viral and bacterial co-pathogens. *Int J Infect Dis* 2021;105:617-20. doi: 10.1016/j.ijid.2021.02.087. pmid: 33640570

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