Single-dose Oxford–AstraZeneca COVID-19 vaccine followed by a 12-week booster

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Vaccines to prevent COVID-19 infection are crucial for an effective global pandemic response. In *The Lancet*, Merryn Voysey and colleagues[1] report the updated primary efficacy results for the Oxford–AstraZeneca ChAdOx1 nCoV-19 (AZD1222) vaccine from three single-blind, randomised controlled trials in the UK and Brazil and one double-blind study in South Africa.[2–4] The ChAdOx1 nCoV-19 vaccine was granted emergency use authorisation in adults by the UK Medicines and Healthcare products Regulatory Agency[5] in December, 2020. A subsequent report, based on an interim analysis of four randomised controlled trials done in Brazil, South Africa, and the UK,[4] suggested an overall vaccine efficacy of 70·4% (95·8% CI 54·8–80·6), with a higher efficacy of 90% (95% CI 67·4–97·0) in those who received a low dose ($2·2 \times 10^{10}$ viral particles per dose) followed by a standard dose (5×10^{10} viral particles per dose), and a vaccine efficacy of 62·1% (95% CI 41·0–75·7) in those who received two standard doses (4 weeks apart).

As a result of these interim data, and to achieve the greatest health benefit rapidly, the UK Government decided on a policy of administering as many first doses as possible and delaying the second dose of the ChAdOx1 nCoV-19 vaccine until 12 weeks after the first dose.[6,7] Although this policy was criticised, the latest results reported by Voysey and colleagues provide a necessary evidence-based justification for the decision.[1]

The study is based on an updated analysis of 17 178 participants (9696 [56·4%] were women, 12 975 [75·5%] were white, and 14 413 [83·9%] were aged 18–55 years, 1792 [10·4%] aged 56–69 years, and 973 [5·7%] aged 70 years or older) from the four trials.[2–4] The pooled results from these trials (including participants who received two standard doses and those who received a low dose followed by a standard dose) showed an overall vaccine efficacy against symptomatic COVID-19 more than 14 days after the second dose of 66·7% (95% CI 57·4–74·0). Vaccine efficacy was 63·1% (51·8–71·7) in those who received two standard doses and 80·7% (62·1–90·2) in those who received the low dose plus standard dose. Notably, in exploratory analyses, vaccine efficacy after a single standard dose was 76·0% (59·3–85·9) from day 22 to day 90, and antibody levels were maintained during this period with minimal waning. Supporting a longer-interval immunisation strategy, vaccine efficacy was significantly higher at 81·3% (60·3–91·2) after two standard doses given at an interval of 12 weeks or longer, compared with 55·1% (33·0–69·9) when given less than 6 weeks apart. These findings were supported by immunogenicity studies done in participants who were younger than 55 years, showing anti-SARS-CoV-2 spike IgG antibody responses more than two-fold higher in those who had a dose interval of at least 12 weeks than in those who had an interval of less than 6 weeks (geometric mean ratio 2·32 [95% CI 2·01–2·68]).

Modelling analyses showed an increase in vaccine efficacy after two standard doses from 55·1% (95% CI 33·0 to 69·9) with an interval of less than 6 weeks to 81·3% (60·3 to 91·2) with an interval of at least 12 weeks. A single standard dose had an efficacy against symptomatic COVID-19 in the first 90 days of 76·0% (59·3 to 85·9), yet provided no protection against asymptomatic infection (vaccine efficacy −17·2% [−248·6 to 60·6]). Notably, efficacy against any nucleic acid amplification test-positive cases, including symptomatic and asymptomatic or unknown cases, was 63·9% (46·0 to 75·9) after a single standard dose, suggesting the possibility of reducing viral transmission.

Important study limitations include the fact that these studies were not prospectively designed to establish whether vaccine efficacy would differ by dose interval; therefore, these post-hoc exploratory findings could be biased. Other limitations are that participants were not randomised to dosing interval, only one of the four trials was double-blind, and the single-dose recipients were self-selected. Furthermore, baseline characteristics between the single-dose and two-dose cohorts were substantially different, with an older median age, higher proportion of men and non-white participants, and a smaller proportion of health or social care workers in the two-dose cohort than in the single-dose cohort. Also, worth considering is whether these results would hold up with widespread circulation of more transmissible and lethal viral variants.

Overall, the value of this study is in providing evidence that a single dose of the ChAdOx1 nCoV-19 vaccine is

highly efficacious in the 90 days after vaccination, that a longer prime-boost interval results in higher vaccine efficacy, and that protection against symptomatic COVID-19 is maintained despite a longer dosing interval. It offers much-needed evidence for the UK policy of extending the dosing interval to 12 weeks and for rapid mass-immunisation campaigns worldwide. Further studies are warranted to assess whether a longer-interval strategy would also offer higher vaccine efficacy against the new variants[8] and could be applicable to other types of COVID-19 vaccines.[9–11]

IFNH is a member of the Advisory Panel on COVID-19 Vaccines for the Government of the Hong Kong Special Administrative Region. GAP receives personal fees from AstraZeneca for consultative advice on COVID-19 vaccine messaging. GAP is the chair of a Safety Evaluation Committee for novel non-COVID investigational vaccine trials being conducted by Merck Research Laboratories. GAP offers consultative advice on non-COVID vaccine development to Merck, Medicago, GlaxoSmithKline, Sanofi Pasteur, Emergent Biosolutions, Dynavax, Genentech, and Genevant Sciences. GAP has offered consultative advice on COVID vaccine study design and safety to Eli Lilly and Company, Janssen Global Services, and AstraZeneca. GAP holds patents related to vaccinia and measles peptide vaccines. GAP has received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine.

*Ivan F N Hung, *Gregory A Poland*
poland.gregory@mayo.edu

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong Special Administrative Region, China (IFNH); Mayo Vaccine Research Group, Mayo Clinic, Rochester, MN 55905, USA (GAP)

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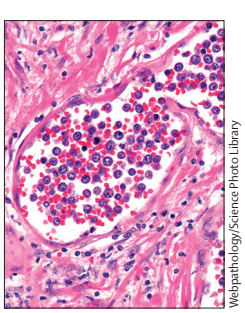
Pirtobrutinib shows evidence to inaugurate a third generation of BTK inhibitors

The Bruton's tyrosine kinase (BTK) protein is a crucial component of antigen-dependent B-cell receptor signalling that regulates B-cell development and maturation. BTK is also implicated in major processes of malignant B non-Hodgkin lymphoma (NHL-B) and chronic lymphocytic leukaemia (CLL) cells such as proliferation, survival, and trafficking. BTK inhibition has a profound effect on malignant cell survival.[1]

BTK inhibitors have been a considerable therapeutic advance in the treatment of NHL-B and CLL. The three BTK inhibitors approved to date, namely ibrutinib, acalabrutinib, and zanubrutinib, are all covalent and irreversible inhibitors at an energetically important area of the protein—the C481 binding site.[1] Ibrutinib was the first approved drug.[2] The second-generation inhibitors, acalabrutinib and zanubrutinib, were designed to be more BTK selective.[3,4] Covalency and irreversibility are therapeutics strengths for these drugs; however, this covalency bond had induced resistance mutations occurring at the covalent binding site C481, rendering the drugs inactive.[1,5]

In *The Lancet*, Anthony Mato and colleagues[6] report the results of a phase 1/2 study with pirtobrutinib (working name; formerly known as LOXO-305), as part of a new BTK inhibitor class via non-covalent and reversible inhibition, in patients with relapsed or refractory B-cell malignancies. The study included 109 (34%) women and 214 (66%) men, with a median age 68 years



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