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.

Efficacy of antivirals and bivalent mRNA vaccines against SARS-CoV-2 isolate CH.1.1

SARS-CoV-2 subvariants BQ.1 (a BA.5 subvariant) and XBB (a BA.2 subvariant) are currently the most widespread variant globally, according to Nextstrain; however, other variants are being closely monitored as they emerge in specific regions. For example, XBB.1.5 (a BA.2 subvariant) is dominant in the USA as of February, 2023, with greater immune-evasion capabilities than earlier variants, including BA.5 and BA.2,[1–3] and CH.1.1 (a descendant of BA.2.75) has rapidly increased in prevalence in the UK.[4] Compared with BA.2.75, CH.1.1 has an additional four substitutions (R346T, K444T, L452R, and F486S) in the receptor-binding domain of the spike protein, which is the principal antigen for vaccines and therapeutic monoclonal antibodies against SARS-CoV-2 (appendix p 5). Although previous studies evaluated the neutralising activity of monoclonal antibodies or plasma from people who have had the COVID-19 vaccines by using a pseudotyped virus possessing the CH.1.1 spike protein,[5,6] the efficacy of antivirals and COVID-19 vaccines against clinical isolates of CH.1.1 remain unknown.

Accordingly, we assessed the efficacy of therapeutic monoclonal antibodies against a clinical isolate of omicron CH.1.1 (the sequence is registered with the Global Initiative on Sharing Avian Influenza Data and GenBank). To test the reactivity of these monoclonal antibodies against the CH.1.1 isolate, we did a focus reduction neutralisation test and determined $FRNT_{50}$ values (ie, the titre of monoclonal antibodies required for a 50% reduction in the number of infectious foci) using Vero E6-TMPRSS2-T2A-ACE2 cells. None of the monoclonal antibodies tested (REGN10987 [known as imdevimab], REGN10933 [known as casirivimab], COV2-2196 [known as tixagevimab], COV2-2130 [known as cilgavimab], S309 [known as the precursor of sotrovimab], and LY-CoV1404 [known as bebtelovimab]) neutralised the CH.1.1 isolate even at the highest $FRNT_{50}$ value (>50 000 ng/mL) tested in Vero E6-TMPRSS2-T2A-ACE2 cells (appendix p 6). All these antibodies, except REGN10987, neutralised BA.2.75, which differs from CH.1.1 by only four amino acids in the S protein, suggesting that these amino acid substitutions contribute to the reduced neutralising activity of the monoclonal antibodies against CH.1.1. Studies have suggested that the use of cells overexpressing host proteins underestimates the activity of monoclonal antibodies.[7,8] Therefore, we also identified $FRNT_{50}$ values in Vero E6-TMPRSS2 cells. The $FRNT_{50}$ values of the tested antibodies in Vero E6-TMPRSS2 cells were lower than those in Vero E6-TMPRSS2-T2A-ACE2 cells. Among the tested antibodies, S309 failed to neutralise any tested omicron variant in ACE2-expressing cells, but neutralised BA.2.75 in Vero E6-TMPRSS2 cells with an $FRNT_{50}$ value of 24 319 ng/mL. However, the $FRNT_{50}$ values of all tested antibodies against CH.1.1 were higher than the detection limit (>50 000 ng/mL) in Vero E6-TMPRSS2 cells and Vero E6-TMPRSS2-T2A-ACE2 cells (appendix p 6). Although in vitro neutralising activity can provide insights into antibody efficacy, it might not always reflect the protective potential of the antibody in humans, due to the other functional activities of the antibody, such as antibody-dependent cellular cytotoxicity. Therefore, additional studies are needed to evaluate the therapeutic efficacy of antibodies against this omicron variant in clinical settings.

The US Food and Drug Administration has authorised three antiviral drugs for COVID-19 treatment: remdesivir (an RNA-dependent RNA polymerase [RdRp] inhibitor), molnupiravir (also an RdRp inhibitor), and nirmatrelvir (a main protease inhibitor). In Japan, ensitrelvir (a main protease inhibitor) received regulatory approval in November, 2022, for emergency use. To assess the efficacy of these antiviral drugs against CH.1.1, we determined the in vitro 50% inhibitory concentration (IC_{50}) values. The CH.1.1 isolate has one substitution (P3395H) in its RdRp and two substitutions (P314L and G662S) in its main protease (appendix p 5), which are also present in the BA.2.75 and XBB variants in which sensitivities against the antivirals tested here are similar to those of the ancestral strain.[9,10] The susceptibilities of CH.1.1 to these four antivirals were similar to those of the ancestral strain (ie, IC_{50} values for remdesivir, molnupiravir, nirmatrelvir, and ensitrelvir that differed by factors of 0·7, 1·3, 0·7, and 0·4, respectively; appendix p 7). These results suggest that remdesivir, molnupiravir, nirmatrelvir, and ensitrelvir are effective against CH.1.1 in vitro.

Last, we evaluated the neutralising ability of plasma from three different cohorts against the CH.1.1 isolate: individuals who received four doses of either the monovalent mRNA vaccine BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna), or both; individuals who received the bivalent (ancestral, BA.4, and BA.5) mRNA vaccine as a fifth dose; and individuals who had a BA.2 breakthrough infection after receiving three doses of mRNA vaccine. The $FRNT_{50}$ geometric mean titres against CH.1.1 after a fourth dose of mRNA vaccine were 69·8-fold, 12·0-fold, and 8·4-fold lower, respectively, than those against the ancestral strain or BA.2 or BA.2.75 clinical isolates (appendix pp 8–9). For plasma from individuals who received the bivalent mRNA vaccine as a fifth vaccine, the neutralising activities against CH.1.1 were also 24·6-fold, 6·5-fold, and 3·5-fold lower, respectively, than those against the ancestral strain,

Published **Online** March 7, 2023 https://doi.org/10.1016/S1473-3099(23)00132-9

For more on **Nextstrain** see https://nextstrain.org/ncov/gisaid/global/all-time

See **Online** for appendix

For the **CH.1.1 sequence on the Global Initiative on Sharing Avian Influenza Data** see https://gisaid.org/hcov19-variants/

For the **CH.1.1 sequence on GenBank** see https://www.ncbi.nlm.nih.gov/genbank/

Published Online
March 17, 2023
https://doi.org/10.1016/
S1473-3099(23)00179-2

BA.2, or BA.2.75 (appendix pp 8, 10). For plasma samples from vaccinees with BA.2 breakthrough infection, the $FRNT_{50}$ geometric mean titres against CH.1.1 were 50·1-fold, 13·2-fold, and 8·9-fold lower, respectively, than those against the ancestral strain, BA.2, or BA.2.75 (appendix pp 8, 11), which were similar to the results with the samples from individuals who received the bivalent mRNA vaccine as a fifth vaccine. Notably, the bivalent vaccine administered as a fifth dose augmented the neutralising titres against CH.1.1 by a factor of 3·6 (appendix pp 8–11), which is greater than the change in neutralising titres against the ancestral strain (1·5-fold), BA.2 (2·1-fold), and BA.2.75 (1·8-fold). These results suggest that although CH.1.1 effectively evades humoral immunity induced by mRNA vaccines or natural infection, the bivalent vaccine can enhance neutralising activities.

Overall, our data suggest that therapeutic options, such as the antiviral drugs remdesivir, molnupiravir, nirmatrelvir, and ensitrelvir, are still valid against the omicron sublineage CH.1.1, and that an additional vaccine dose with the bivalent mRNA (ancestral, BA.4, and BA.5) vaccine might be beneficial in preventing CH.1.1 infection.

YoK has received funds in the form of grants from the Center for Research on Influenza Pathogenesis and Transmission (75N93021C00014) by the National Institutes of Allergy and Infectious Diseases, and a research programme on emerging and re-emerging infectious diseases (JP21fk0108552 and JP21fk0108615), a project promoting support for drug discovery (JP21nf0101632), the Japan Program for Infectious Diseases Research and Infrastructure (JP22wm0125002), and the Japan Initiative for World-leading Vaccine Research and Development Centers (JP223fa627001) from the Japan Agency for Medical Research and Development. YoK has also received unrelated funding from Daiichi Sankyo Pharmaceutical, Toyama Chemical, Tauns Laboratories, Shionogi, Otsuka Pharmaceutical, KM Biologics, Kyoritsu Seiyaku, Shinya, and Fuji Rebio. TK is employed by Nihon Sumo Kyokai. All other authors declare no competing interests. RU, MIt, and MKi contributed equally.

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Risk of omicron infection for high-risk older adults in long-term care facilities

We commend the study by Niklas Bobrovitz and colleagues,[1] which systematically reviewed the evidence for the protective effect conferred by hybrid immunity (combination of infection and immunisation) in context of the SARS-CoV-2 omicron (B.1.1.529) variant.[1] The UK SARS-CoV-2 vaccine programme was a massive undertaking requiring substantial financial, personnel, and logistical resources. Booster vaccines are recommended for high-risk of severe disease, including residents in long-term care facilities and people older than 80 years.[2] The study by Bobrovitz and colleagues might be integral to building an evidence base for targeted immunisation of individuals at high-risk of severe disease.

However, data are scarce for long-term residents in care facilities and people older than 80 years, with continued reliance on data from young adults (18–65 years) and health-care workers. Although individualised risk assessments for those with considerable immune suppression is realistic through regular health-care interactions, older adults are more challenging to reach. Meanwhile, data from the UK Office for National Statistics shows that people admitted to hospital with COVID-19 during the 2022–23 winter period were predominantly individuals aged 85 years and older (peak 154·67 older people with COVID-19 per 100 000 people during the week ending).[3] When studies included in the analysis by Bobrowitz and colleagues did include clear demographic data, older adults were typically classified together as older than 65 years or older than 70 years, reducing our insight into the extremes of age.[1] Bobrovitz and colleagues[1] suggested the scarcity of data in older adults might make