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.

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Urgency of COVID-19 vaccination in adolescents: Androgen and estrogen receptors view

Dear Editor,

Given that international and domestic flights now require only adults to be vaccinated or have negative PCR test results, adolescents' vaccination of COVID-19 for safe travel needs urgent consideration. As adults benefit from vaccination policies that give them priority, now children may become a source of infection transmission leading to new COVID-19 wave outbreaks [1].

With the new cases surging, 12–17 years old adolescents are recommended for vaccination (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/adolescents.html). However, the hesitation and decreasing roll-out make further worrisome because adolescents' immune system development or the elevation of hormones may let them become more vulnerable to the infection of SARS-CoV-2 and emerging variants.

Hormones and in particular, estrogen can disrupt SARS-CoV-2 Spike-ACE2 binding to restrict the viral entry [2]. In addition, androgen receptors (ARs) upregulate transmembrane protease serine 2 (TMPRSS2) which is essential in Spike priming and viral entry [3]. Thus, we wonder whether in adolescents, elevated hormone and activation of receptors (estrogen, androgen receptors, ER and AR respectively) can potentially bind to Spike for vulnerable infection.

Simulation of wild type (WT) or Omicron Spike receptor binding domain (RBD) interacted modeling with the ligand-binding domain (LBD) of the ER and AR, indicated that the ER slightly showed better binding with the Omicron compared to the WT Spike RBD (ΔG, −10.9 $kcalmol^{-1}$ and -10.6 $kcalmol^{-1}$, respectively). However, both the complexes have retrieved identical dissociation constant (Kd) of 1.0E-08 at 25 °C. Similarly, there is minor difference for AR, binding to Omicron RBD as −11.9 $kcalmol^{-1}$ compared to −11.8 $kcalmol^{-1}$ to WT. However, in comparison we found that the Spike RBD retained better affinity of binding with the AR than the ER (Figs. 1A–D). It might be related to some controversial reports that males are more prone compared to females but more clinical investigations would warrant the simulation and hypothesis. The decline of hormones is related to age in both genders suggesting a higher rate in adolescence. Thus, to minimize the risk factors, vaccination in adolescents is especially needed.

There is a significant drop in pediatric vaccination which reflects a similar global pattern (https://www.who.int/news/item/22-05-2020-at-least-80-million-children-under-one-at-risk-of-diseases-such-as-diphtheria-measles-and-polio-as-covid-19-disrupts-routine-vaccination-efforts-warn-gavi-who-and-unicef). Moreover, the international Vaccine Alliance Gavi, UNICEF, and WHO warned that about 80 million children from 68 countries are at risk of vaccine-preventable diseases including polio, meningitis, measles, pertussis, tetanus, and diphtheria because of the COVID-19's disruption of their preventive mass vaccination campaigns. Such increasing hesitancy of both pediatric and COVID-19 vaccination amid pandemic puts adolescents traveling associated with infection in a dangerous position especially in a scenario of reduced restrictions and the emergence and widespread of new variants.

Although COVID-19–associated hospitalizations are mainly linked to adults, its severe cases occur across all age groups. According to a 14-state-data from COVID-2019-Associated Hospitalization Surveillance Network, though overall average infection incidence among children and adolescents during March 2020 to August 2021 was relatively lower than that of the world average, as about 5 per 2000 vs 0.028% of world infection, the rate of Intensive Care Unit (ICU) admission reached about 23.2%–26.5% among hospitalized children and adolescents [4]. About 6–9% hospitalized children and adolescents needed invasive mechanical ventilation during March 1st, 2020–August 1st, 2021 [4]. Moreover, there is no significant conclusion drawn from summer travel or school opening gatherings induced ICU admission rate, death during hospitalizations, vasopressor and highest level of respiratory support [4]. However, the age group distribution data suggest that the 12–17 years old group is at higher risk compared to the 5–11 age group [4]. Thus the adolescents urgently need to be taken into consideration as the vaccination priority groups when adults are completing. As on-board SARS-CoV-2 transmission may be caused by vaccinated adults, children and adolescents are still vulnerable to the infection despite vaccination passports and safety measures implemented by airports [5].

Currently, more emerging variants appear to be related to the shift of COVID-19 infection from elder population to children and young adults. One news report on the different COVID-19 waves data showed that the age shift from 40 years older to 19 years younger was not significant because about 79% of elder people remain as the main infected population (https://www.livemint.com/news/). However, one study reported since the Delta (B.1.617.2) had been spread as the most predominant variant, the overall emergency department (ED) visits and hospital admissions of COVID-19 patients aged 0–17 years increased (during August 14–August 27 with 2 weeks, 2021). In particular, among the older than 12 years old population, the ED visits and hospital admissions were higher among the lower vaccination children compared to that of the higher vaccinated [6]. Therefore, the broad community-based vaccination would be recommended for prevention of SARS-CoV-2 infection and deterioration of COVID-19 illness [5,6].

Based on the recent reports of efficiency of the vaccines on adults and children, the vaccine may be the most effective tool to protect adolescent passengers. Pfizer-BioNTech COVID-19 vaccine's Phase II/III clinical trial results demonstrated clinical efficacy of 100% in adolescents aged 12–15 years with 0.4% adverse events among vaccine recipients that did not statistically differ from that of the placebo group with 0.2% [7]. Similarly, a Spikevax vaccine's clinical trial on 3732 children aged 12–17 years displayed similar efficacy to adults. Thus it was approved to be used in children aged 12–17 years by the European Medicines Agency (https://www.ema.europa.eu/en/news/covid-19-vaccine-spikevax-app

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Abbreviations

WHO	World Health Organization
AR	androgen receptor
TMPRSS2	transmembrane protease serine 2
RBD	receptor binding domain
LBD	ligand binding domain
ICU	intensive care unit
UNICEF	United Nations Children's Fund
ED	emergency department
MIS-C	multisystem inflammatory syndrome in children

roved-children-aged-12-17-eu). Clinical trials of the other vaccines are also ongoing for the similar age group. Thus, given that about 21.5% of 12–17 years aged COVID-19 patients showed multisystem inflammatory syndrome in children (MIS-C), the vaccination would be recommended [5].

The assessment of the advantage-risk balance of vaccines in adolescents shows that the benefits of COVID-19 vaccination outweigh the risks. Even though the side effects may occur for vaccination, the incidence rate is much lower (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/adolescents.html). More clinical data would be considered for safety and efficacy of COVID-19 vaccines while implementing policies that suggest adolescents to be vaccinated. In addition, age group specified and more safe vaccines should be developed urgently through large scale research investment. As children and adolescents are the most urgent groups for school reopening shifted from

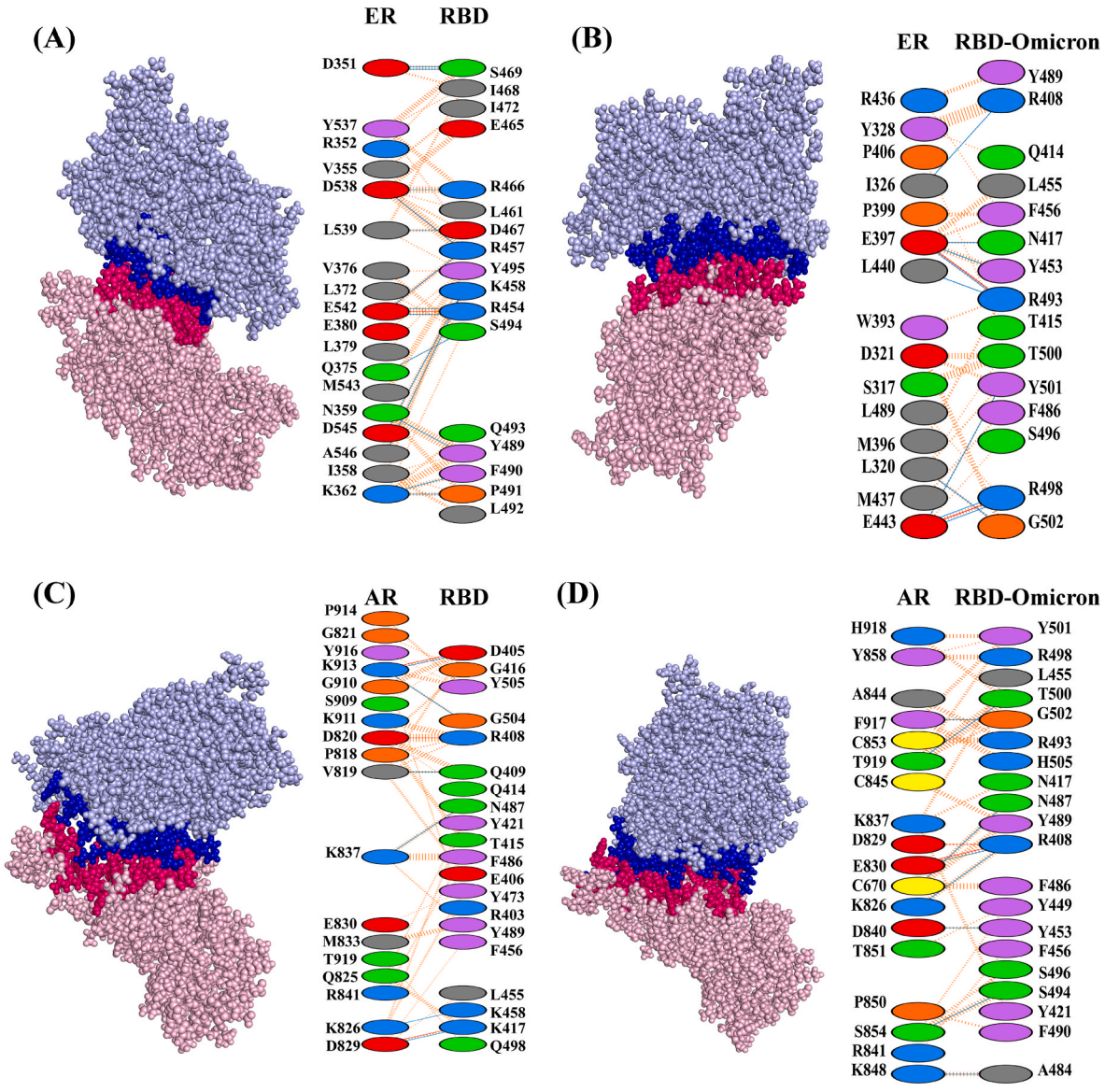

Fig. 1. Interaction complexes of the estrogen receptor (ER) and androgen receptor (AR) with the wild type and Omicron Spike receptor binding domain (RBD). (A and B), indicates the ER complex with wild type Spike RBD and Omicron Spike RBD and (C and D) the androgen complex with wild type Spike RBD and Omicron Spike RBD. Interface residues are indicated by circles of charged based colors. The lines between them shows the respective interaction type, like salt-bridges (red), hydrogen bond interaction (blue) where the pink doted lines represent non-bonded interactions. Ligand binding domain (LBD) in both AR and ER were simulated for docking to RBD. In AR the LBD applied is from 670 to 900 amino acids and ER LBD used is from 311 to 547 amino acids. We have applied a template based modeling followed by building multimeric complexes by AlphaFold_Multimer. For ER templates from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (https://www.rcsb.org/) with PDB IDs are 1AKF, 1A52, 1ERE, 1ERR used. For the AR, PDB IDs 1E3G, 1T5Z, 1XJ7 are used.

online education, the field study and travel related infection risks would be increased without fully vaccination among the population.

Owing to the complexity of the issue discussed, implementation of policies that would require COVID-19 vaccination in adolescents for safe travel would be challenged. For example, the hesitated attitude to the pediatric vaccination, serious health consequences of COVID-19, and the shift of infection towards the younger population due to new variants may outweigh the vaccination risks [8]. In addition, increased risk of on-board infection among adults indirectly associated with adolescents would be a potential transmission stimulator. Although not every country has a designated vaccine available for adolescents and there is a huge variation in global adolescent vaccine policy, the implementation of policies that would require adolescent passengers to be vaccinated might be applied as soon as the most updated, most efficient and most safe vaccines are available. Up to date data suggests the vaccination rate is increasing in many countries either one dose or fully vaccinated, while booster shots and new types of vaccines of variants are developing which gives more hope to protect adolescents in case androgen or estrogen signaling promotes the infection.

Ethics approval and consent to participate

N/A.

Consent for publication

N/A.

Availability of data and materials

N/A.

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Authors' contributions

Bexultan Kazybay collected data, analyzed the results, discussed the data, and wrote the paper. Ashfaq Ahmad developed the simulation of binding with Figure and legend, described the results. Yingqiu Xie raised the question, developed the idea and hypothesis of AR and ER in COVID-19, supervised the project, reviewed literature and wrote the paper.

Declaration of competing interest

There is nothing to declare.

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Bexultan Kazybay
Department of Biology, School of Sciences and Humanities, Nazarbayev University, Nur-Sultan, 010000, Kazakhstan
E-mail address: Bexultan.kazybay@nu.edu.kz.

Ashfaq Ahmad
Department of Bioinformatics, Hazara University, Mansehra, 21300, Pakistan
E-mail addresses: ashfaqahmad82@hotmail.com, ashfaq.binfo@hu.edu.pk.

Yingqiu Xie*
Department of Biology, School of Sciences and Humanities, Nazarbayev University, Nur-Sultan, 010000, Kazakhstan

* Corresponding author. 53 Qabanbay Batyr Ave, Nur-Sultan, 010000, Kazakhstan.,
E-mail addresses: xieautumnus@yahoo.com, yingqiu.xie@nu.edu.kz (Y. Xie).