DYNAMICS OF CHILDHOOD RESPIRATORY INFECTIONS DURING THE COVID-19 PANDEMIC: THE EFFECT OF QUARANTINE AND BEYOND

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Abstract
Monitoring epidemic processes and the dynamics of the spread of infectious diseases is essential for predicting their distribution and effective planning in healthcare. The importance of studying seasonal trends in the spread of respiratory viral infections and the specific effects of non-pharmaceutical interventions in nationwide scales and the use of available vaccines stand out even more in the context of the coronavirus disease-19 (COVID-19) pandemic. Even if the dynamics of pediatric respiratory viral infections show some variation at the national and local levels, depending on health regulation, respiratory viral pathogens follow a typical pattern of incidence. Therefore, we hypothesize that anticipated reduction of the incidence of common respiratory viral infections would undoubtedly exert positive effects, such as ease of burdening healthcare that combats the COVID-19 pandemic. However, we suspect a shift in familiar seasonal characteristics of common respiratory viral infections. We also speculate that strict long-term limitations of the natural spread of respiratory viral infections can lead to the development of hard-to-predict epidemiological outliers. Additionally, the tricky balance between humanity's natural impulse to return to normalcy and control the new and still dynamically evolving infection could lead to new threats from old and well-known pathogens. Finally, we hypothesize that the absence of regular influenza virus circulation may lead to a high mismatch rate and a significant reduction in flu vaccine efficacy.

Keywords: COVID-19, SARS-CoV-2, Hypothesis, Respiratory viral infections, Influenza, RSV, Rhinovirus, Children

INTRODUCTION
Lower respiratory tract infections are a leading cause of morbidity and mortality in children and adults worldwide. Pneumonia and bronchiolitis are the sixth leading cause of death at all ages and the leading cause in children under five years of age [1]. However, we still have limited pharmaceutical measures to prevent viral respiratory infections, including the use of palivizumab in high-risk children under two years of age, the seasonal influenza vaccine, and neuraminidase inhibitors [2,3]. Therefore, non-pharmacological interventions (NPIs) that public health undertakes continue to be extremely important [4]. On the other hand, monitoring epidemic processes and the dynamics of the spread of infectious diseases is essential both for predicting the distribution of material and human resources in healthcare and for planning effective measures to prevent the development of local epidemic outbreaks, epidemics, pandemics, and their consequences [5]. The importance of studying seasonal trends in the spread of respiratory viral infections, the specific effects of NPIs in nationwide scales, the use of available vaccines and the study of collective immunity stand out even more in the context of the coronavirus disease-19 (COVID-19) pandemic.

At the height of the 2019/2020 flu season, the WHO officially announced the pandemic with SARS-CoV-2 [6]. Shortly after the pandemic declaration, even countries with single cases of COVID-19 introduced strict measures such as quarantine and social isolation. These measures have led to a sharp and rapid reduction in influenza cases, as well as a significant drop in visits to emergency and urgent pediatric clinics. There has also been a dramatic reduction in pediatric hospitalizations for non-COVID-19 respiratory diseases [4,7,8]. Fear of COVID-19 resulted in a restriction of visits to emergency for self-limiting conditions, but not for severe and urgent health problems [7-9]. There was a sharp decline in the incidence of typical respiratory infections in the Northern and Southern hemispheres in the following months [10-14].

The new coronavirus has become a strong incentive to carry out targeted studies to establish the exact time and mechanism of transmission of respiratory infections and the effectiveness of various hygienic and other NPIs [15]. In addition, attempts to control the new pandemic have led to the creation of mathematical and statistical models to determine the transmissibility of respiratory viruses, with which to predict future epidemic peaks, both for SARS-CoV-2 and for other socially significant viruses such as influenza and respiratory syncytial virus (RSV) [15,16].

HYPOTHESIS
THE EFFECT OF NPIs ON SEASONAL RESPIRATORY INFECTIONS
The significant morbidity caused by respiratory viruses in infancy, childhood, and adolescence affects the health and well-being of children themselves and the functioning of society as a whole. Therefore, drawing from the previous experience in monitoring and studying the spread of leading respiratory viral pathogens such as influenza, RSV, and seasonal coronaviruses, and on the verge of a pandemic with the new SARS-CoV-2, several anti-epidemic non-pharmacological measures have been proposed and introduced such as compliance with social distance, quarantine of the sick and contact subjects, wearing face masks, frequent hand washing and use of disinfectants, regular ventilation, and cleaning of the premises. Unfortunately, all NPIs used to limit the pandemic spread of SARS-CoV-2 have led to a significant change in the normal dynamics of seasonal respiratory infections [6].

In the 2020/2021 season, there was neither an epidemic increase in influenza cases nor an usual increase in RSV cases during the cold months of the year [6]. Therefore, based on these observations and previous analyses, we propose a hypothesis following the guidance for writing, promoting, and predicting the implications of scientific hypothesis by Gasparyan et al. [17].

VICTORY OVER PATHOGENS OR LULL BEFORE A STORM?
We suggest that reducing the incidence of common respiratory viral infections has undoubtedly had its positive effects, burdening the health systems that have been busy with the increasing number of COVID-19 cases. On the other hand, we hypothesize that signals are beginning to show that this is a lull before a storm and a shift in our familiar seasonal characteristics of common respiratory viral infections.

We can also speculate that strict long-term limitation of the natural spread of respiratory viral infections can lead to the development of hard-to-predict epidemiological outliers (faults). Furthermore, we hypothesize that the tricky balance between humanity’s natural impulse to return to normalcy and control a new and still dynamically evolving infection could potentially lead to new threats from old and well-known pathogens.
WILL THE RENEWED VIGORS RE-EMERGE?
However, due to the shallow circulation of respiratory infections in the winter of 2020/2021 following the introduced measures to limit SARS-CoV-2, we could expect acute viral respiratory infections to re-emerge with renewed vigor this winter. Those epidemiological tendencies could be explained by the relaxation of measures and the accumulation of a more susceptible population due to the limited exposure to these viruses in the previous winter [18].

INFLUENZA DURING COVID-19 PANDEMIC: WHAT IS NEXT?
Additionally, preparations for the 2020/2021 flu season remain challenging to predict. For now, we can speculate whether physical distance measures and other NPIs will continue to suppress the spread of influenza or whether we will face a more severe influenza season due to reduced population immunity to flu [19-20]. Furthermore, considering the dramatic global reduction in circulating influenza viruses, we have significantly fewer data to predict the influenza strains for the coming winter. Finally, we hypothesize that this may lead to a higher mismatch rate and a significant reduction in vaccine efficacy for flu shots, as shown by Tricco et al. [19].

HYPOTHESIS TESTING
THE EFFECT OF NPIs ON SEASONAL RESPIRATORY INFECTIONS
The results of epidemiological, virological, and sentinel studies worldwide show unanimously that the application of NPIs, particularly social distancing in 2020, led to a reduction not only in SARS-CoV-2 cases but also in other circulating respiratory infections such as influenza and RSV.

Although different respiratory viruses cause similar clinical symptoms, they belong to different families. In addition, they have different viral and genomic structures (composition and structure of the virus envelope, capsid, internal proteins, and genomes and the formation of viral aggregates), and to some degree, vary in tropism and life cycle [21]. However, respiratory viruses can generally spread through 4 main models - direct (physical) contact, indirect contact (contaminated surfaces - fomite), large droplets, and fine aerosols [22]. The primary transmission route of SARS-CoV-2 is by air, which requires close contact and aerosols. However, whether droplets or aerosols are the dominant transmission route is not yet fully understood, and the debate continues [23]. In addition, some respiratory viruses, including influenza viruses, coronavirus, and rhinoviruses (RVs), can be recovered from feces and can infect gastrointestinal tract cells [24-25]. Thus, transmission of infection through the feces is also possible, for example, by aerosolization during toilet flushing [26].

Additionally, studies have shown the presence of SARS-CoV-2 in eye secretions and possible influenza infection through spray contact with the ocular conjunctiva, which suggests another route of transmission - through ocular exposure [26,27]. Thus, we can argue that knowledge of the leading models of transmission of various respiratory viruses, including SARS-CoV-2, is crucial for the selection of NPIs that have the potential to limit viral transmission in society significantly. Most studies of transmission pathways are conducted for influenza viruses, which annually lead to local epidemics, cyclically in the Northern and Southern hemispheres, and have the pandemic potency over time. Therefore, as we suggested, NPIs used to limit the spread of SARS-CoV-2 already have significant visible effects on the transmission of other endemic and epidemic respiratory diseases.

BRONCHIOLITIS AND RSV CIRCULATION: VICTORY OVER PATHOGENS OR LULL BEFORE A STORM?
In 2020 for the Southern Hemisphere and 2020/2021 for the Northern Hemisphere, the flu season was almost completely suppressed [28]. A Belgium study by Daan Van Brusselen et al. reported 92.5% fewer hospitalizations for acute bronchiolitis [13]. In addition, the authors reported a non-existent peak in cases of bronchiolitis associated with NPI compliance by adolescents and adults. However, they suggest a delayed peak in the spring/summer of 2020/2021, when the measures are relaxed [13]. The potential causes and impacts of this drastic change in public health are still unclear and uncertain. However, they provide essential conclusions and lessons for the future control of viral respiratory diseases [29].

Similarly, Wang et al. reported a significant reduction in detecting four of the most common respiratory viruses (influenza virus, parainfluenza virus, adenovirus, and RSV) in Xiamen City, China, related to measures taken to limit the spread of SARS-CoV-2 [30]. This effect was most prominent for RSV [30]. Indeed, reports worldwide show up to a 98% reduction in RSV cases during the 2020 pandemic [11,12]. The spread of SARS-CoV-2 occurred just as the Southern hemisphere expected to begin the flu and RSV seasons [31].

Additionally, Australia and New Zealand have reported record low levels of influenza in the 2020 winter with 98% and 99.4% respective reductions in the RSV and influenza detection in children regardless of the school opening [32]. Until recently, it has been unclear whether
the RSV 2020-2021 season would continue to be significantly suppressed or slowed down [13].

WILL THE RENEWED VIGORS RE-EMERGE?
According to data from Australia and several states in the USA, there is a sharp rise in cases of RSV among children under five years of age, unusual for the summer season. In addition, an advisory group of the Academy of Medical Sciences in the UK pointed out that the easing of measures in the spring of 2021 has led to a summer surge of infections typically seen in the winter, such as RSV bronchiolitis, parainfluenza, and RVs [18]. These claims are also supported by published data from Australia and South Africa on the increase in RSV cases in the summer following the previous RSV-free winter during the lockdown [15, 33-35]. In the worst scenario for the 2020/2021 winter with rapid relaxation of measures (behavioral and environmental interventions), the Academy of Medical Sciences predicts a rapid increase in RSV cases with 1.5 to 2 times higher autumn peak (between 1.5 and 2 times the magnitude) strength from regular previous RSV seasons [18]. That could lead to a potential increase in RSV cases by 25% to 65% for children under five and 30% to 100% for the youngest infants. Such a scenario could lead to an overload of children’s wards and pediatric intensive care units (PICU) [18].

In a study by Baker et al., evaluating the effects of SARS-CoV-2 NPIs on two endemic infections circulating in the US (RSV and seasonal influenza), a simulation epidemic model was used to predict the future trajectory of RSV and influenza. Shorter periods of NPI administration may be required outside the disease’s peak season, but this may still lead to increased morbidity rates in future outbreaks. The RSV results in the US suggest that these outbreaks may still peak in the winter of 2021-2022. The authors conclude that the accumulation of a susceptible population during periods of stricter NPIs may lead to large outbreaks in the coming years [43]. Following the disruption of the usual dynamics of RSV spread due to the active actions of the health authorities, we could expect RSV to return to its endemic attractor role. However, more complex behavior is also possible, as other authors suggested [43].

The above-mentioned epidemiological data confirmed that NPIs have significantly limited the spread of the most common respiratory viral pathogens due to similar transmission routes. With this in mind, we suggest that any relaxation of the measures after a long period of physical isolation would lead both to an increase in the incidence of COVID-19 and an increase in the incidence of common respiratory viruses. We anticipated that such analyses are necessary to take timely action by public health authorities to ensure sufficient capacity of the PICU and to provide additional amounts of monoclonal antibodies and combined rapid antigenic tests for SARS-CoV-2, RSV and influenza.

CAPSID OR ENVELOPE: ADVANTAGES AND DISADVANTAGES
In contrast, several studies report continued circulation of RVs despite compliance with NPIs, probably due to their chemical structure. In addition, viral interactions between influenza A and RVs at the individual and population levels have been reported in the literature [36,37]. Following the onset of SARS-CoV-2, there has been a significant increase in RV infections in children under ten years of age, probably due to the lack of circulating influenza viruses.

Unlike influenza viruses, RSV, coronaviruses, including SARS-CoV-2, enveloped viruses, RVs have a capsid instead of an envelope. That makes them resistant to skin and surfaces and resistant to disinfectants and detergents. According to the study by Takashita et al., conducted in Tokyo from January 2018 to September 2020, a significantly increased incidence of RV infections in children was observed despite compliance with the recommended precautions [38]. According to Takashita et al., no enveloped viruses have been detected since May 2020 (including influenza viruses; human metapneumovirus; human parainfluenza virus 1, 2, 3, and 4; and RSV). However, non-enveloped viruses such as RVs, coxsackievirus A and B, and human adenovirus (ADV) still circulated. The authors explain this difference in the prevalence between enveloped and uncoated viruses as being related to their stability [38].

The same trend described studies from Germany. For example, the results of a national sentinel study of the etiology of acute respiratory infections (ARI) for the first 38 weeks of 2020 show that the introduction of NPIs leads to a sharp restriction in the circulation of respiratory viruses [39]. Djin-Ye Oh et al. also observed the recurrence and prevalence of RV infections, potentially associated with the opening of schools and kindergartens [39].

On the other hand, a study by Leung et al. evaluated the effect of wearing a surgical mask on the spread of human coronaviruses (HKU1, NL63, and OC43), influenza viruses, and RVs in children and adults with ARI. The results showed that wearing surgical masks could prevent the transmission of seasonal human coronaviruses and influenza viruses from symptomatic subjects, but not RVs [40]. The above facts appear to
explain why RVs do not follow the same epidemiological patterns as other respiratory viruses.

Interestingly, RV infection elicits an antiviral immune response associated with increased interferon production, which has been shown to protect human airway epithelial cells from influenza A infection [36,37]. This immunological phenomenon supports the potential role of the RV-induced innate immune response in driving the asynchronous circulation of influenza and RV. In addition, data from several European countries suggest that the RV epidemic may have interrupted and slowed the spread of the pandemic virus during the 2009 influenza A (H1N1) pandemic [41,42].

FUTURE STUDY DIRECTIONS TO TEST THE HYPOTHESIS
In the future, the practical applicability of etiological tests for seasonal respiratory infections is becoming increasingly important. The widespread penetration of RT-PCR identification of the most common circulating viral pathogens and the introduction of combined rapid antigen tests is becoming increasingly important for clinical practice in the context of the COVID-19 pandemic. Active and dynamic monitoring of the circulation of respiratory viruses through sentinel studies allows collecting and analyzing objective epidemiological information, which will be a solid basis for economic and political decisions in healthcare. Collecting sufficient epidemiological information makes it possible to create mathematical models predicting different scenarios for the epidemiological processes development, directly and indirectly, related to the COVID-19 pandemic. Widespread application of virology and immunology diagnostic tests could clarify the in-vivo and in-vitro viral-viral interaction, delayed viral clearance processes, and the clinical significance of individual viruses in case of co-infection.

ETHICAL CONSIDERATIONS
Anti-vaccination trends among parents, skepticism about vaccines against COVID-19, and information programs will determine the level of vaccination coverage among children over 12 years. Moreover, this trend can influence the subsequent COVID-19 waves and the distribution of other common respiratory infections. Parents must report all cases of respiratory and other infections, although this does not always happen due to different socioeconomic, individual and other reasons. The main ethical considerations according to COVID-19 vaccination in children and adults are its necessity and being mandatory, sufficient evidence for vaccine safety, efficacy and effectiveness and the ethical aspects of decision-making (https://apps.who.int/iris/handle/10665/340841).

CLINICAL CONSIDERATIONS
Due to the unpredictable dynamics of the prevalence of respiratory viruses in the context of a pandemic and the tightening and relaxation of anti-epidemic measures, the routine prevention of RSV infections in at-risk groups of infants remained unchanged [30]. In the study by Foley et al., an increase in RSV cases is reported in Australia in the spring months, peaking in the summer instead of the typical autumn-winter predominance [44]. The US health authorities are warning about a similar trend [34]. In a study by Agha et al. in New York, the typical peak of RSV cases is missing in the autumn and winter of 2020. However, there has been a sharp rise in RSV cases since April-May with more severe disease in younger infants, probably due to reduced immunity due to lack of RSV contact in the previous season [45]. This epidemiological abnormality poses a severe risk to children who have already passed the immunization program, in whom declining titers of protective antibodies are not sufficient to protect them during the "late" RSV season. (Government of Australia, Communicable Disease Intelligence, Vol 45) [46]. We also can expect the same trends for other respiratory infections.

OTHER IMPLICATIONS
Justified concerns of a more severe co-infection between SARS-CoV-2 and seasonal influenza in 2020/2021 have led to greater interest in annual influenza immunization and a higher level of immunized population. However, studies on the severity and frequency of COVID-19 in influenza-immunized patients and control groups of patients did not show a higher incidence of COVID-19 in those immunized with influenza vaccine than in controls [47]. In addition, a study by Conlon et al. demonstrated that immunization with influenza vaccine is associated with lower levels of positive tests for COVID-19 and improved clinical outcomes. Their results give further evidence that the seasonal influenza vaccine should be promoted, and the indications for its use to reduce the burden of COVID-19 should be expanded [48].

Acquired immunity to influenza weakens with age, with the humoral immune response weakening with a gradual decrease in protective antibodies. At the same time, T-cell memory can provide some degree of protection, including cross-over, for many years [49-51]. Therefore, the weakening of immunity may not have significantly changed the population’s susceptibility during the relatively mild flu season in 2019/2020 and was virtually
absent in 2020/21 [51]. On the other hand, a larger population of infants who have never encountered the flu will accumulate, suggesting a higher incidence of infection in the younger age group [16]. Additionally, we must consider that children might have some protection based on the previous infection with SARS-CoV-2 if we assume that there is cross-reactivity between the infectious agents and the immune responses against each of them. For example, in some countries, such as India, children have a considerable degree of seroprevalence to SARS-CoV-2 (https://www.hindustantimes.com/india-news/kids-adults-have-similar-antibodies-sero-survey-101623953000262.html).

CONCLUSION
The worst-case scenarios predict a summer peak of SARS-CoV-2 and a significant RSV peak in early autumn 2021. The highest incidence and severity are predicted in immunologically virgin infants and young children with secondary effects on adults with chronic lung disease. A more severe flu wave is also expected. In the event of a more significant and time-delayed peak of RSV infections, the lack of adaptation of the palivizumab prevention program may lead to a sharp decrease in efficacy. This may lead to an increased risk of premature infants and those with chronic comorbidities. Other concerns under the pessimistic scenario are the emergence of significant overlapping epidemic peaks of influenza and RSV, in parallel with the spread of SARS-CoV-2 with its new variants/mutants and the existing vaccine skepticism. Therefore, it could potentially lead to triple infection with the three pathogens (SARS-CoV-2, influenza and RSV) or to sequential illness with unpredictable health consequences, both from an immunological and a clinical point of view. Whether these hypothetical scenarios will become part of our daily lives in the coming months greatly depends on the preparation of health systems. They should provide high vaccine coverage for SARS-CoV-2, and promote and expand the indications for influenza vaccination. Besides, they have to dynamically adapt the severity of NPIs according to the epidemiological situation concerning the three leading pathogens and provide adequate bedding in pediatric wards and pediatric intensive care units in the event of high RSV pressure.

A more severe influenza season will depend on compliance with NPIs, duration and effectiveness of the population's anti-influenza immune memory, degree of mismatch of the strains included in the influenza vaccine, and degree of vaccine coverage. Even if the dynamics of pediatric respiratory viral infections show some variation at the national and local level depending on health regulation, respiratory viral pathogens follow a typical pattern of distribution in temperate latitudes. This statement was confirmed by the epidemiological data published since the pandemic, with pandemic conditions and global human movement.

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AUTHOR CONTRIBUTIONS
SL formulated the hypothesis and drafted the manuscript. SL and TV revised the manuscript. SL and TV take full responsibility for the integrity of all aspects of the work.

CONFLICTS OF INTEREST
The authors have completed the ICMJE Disclosure Form (http://www.icmje.org/disclosure-of-interest/); available on request. SL and TV declare that there are no potential conflicts of interest associated with this article.

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COVID-19 ПАНДЕМИЯСЫ КЕЗІНДЕГІ БАЛАЛАРДЫҢ РЕСПИРАТОРЛЫҚ ИНФЕКЦИЯЛАРЫНЫҢ ДИНАМИКАСЫ: КАРАНТИН КЕЗІНЕ ДЕЙІНЕ ОДАҢ ТЫС

Түйіндеме
Респираторлық вирустарың инфекциялардың таралуының маусымдық тенденциялары және ұлтық ауқымда фармацевтикалық емес арасылардың асерін зерттей, сондай-ақ вакциналарды қолдану COVID-19 пандемиясының әсіндә эрекет болып табылуы. Егер балалардың респираторлық вирустарың инфекциялардың динамикасы дәнеаульқа қатысты нормативтик таңбаларға байланысты ұлтық және жергілікті денеілердегі қеііріш анықтауының өзінің ерекшелігін зерттей, ұлтық вирустарың патогендерін аурудың түпкі қаріпшілігіне ие. Осылышға, жалпы респираторлық вирустарың инфекциялардың қуәтлерінің тұмендешеуі, мысалы, COVID-19 пандемиясымен құралуының денсаулыққа сақтау ұқсаметінен және іс-әрекетінде деңе асер етеді деп болмайыңыз. Алайда, біз жалпы респираторлық вирустарың инфекциялардың әдеттегі маусымдық сипаттамаларының өзгеруіне құмандамаймыз. Сондай-ақ, респираторлық вирустарың инфекцияларының табиғы таралуына қақпа үәқ мерзімді шектеуде болмаймыз. Эпидемиологиялық іздетті түнъыдауына алып келуі мүмкін деп ескереміз. Сондықтан қатар, адамдардың қалпына көмірге оралуға деген табиғы қалауы мен жаңа, қарқыңдың дамып қеле жатқан инфекцияны бақылауға деген ұмтылысы арасындағы құрделі төмендік ескі және бәлгілі қозырғыштардың жаңа қауіптіргене қелуі мүмкін. Қорытындылай келе, тұмау вирустарың тұрақты айналымының болмасы сыйкесіздікті жоғары денеі мүмкін, және тұмауға қарсы вирустарың әуілділігінің айырымдамасы тарандығына қелуі мүмкін деп болмайыңыз.

Түйіндез сөздер: COVID-19, SARS-CoV-2, гипотеза, респираторлық вирустар, инфекциялар, тұмау, PCV, риновирус, балақаралар


ДИНАМИКА ДЕТСКИХ РЕСПИРАТОРНЫХ ИНФЕКЦИЙ ВО ВРЕМЯ ПАНДЕМИИ COVID-19: ВО ВРЕМЯ КАРАНТИНА И ВНЕ НЕГО

Резюме
Изучение сезонных тенденций распространения респираторных вирусных инфекций и эффектов нефармацевтических вмешательств в национальном масштабе, а также использование вакцин становятся более актуальными в контексте пандемии COVID-19. Если динамика детских респираторных вирусных инфекций демонстрирует некоторые различия на национальном и местном уровнях, в зависимости от нормативных требований, касающихся здоровья, респираторные вирусные патогены имеют типичную картину заболеваемости. Таким образом, мы предполагаем, что ожидаемое снижение частоты распространенных респираторных вирусных инфекций, несомненно, окажет положительное влияние, например, на облегчение нагрузки на здравоохранение, которое борется с пандемией COVID-19. Однако мы предполагаем изменение привычных сезонных характеристик распространенных респираторных вирусных инфекций. Мы также предполагаем, что строгие долгосрочные ограничения естественного распространения респираторных вирусных инфекций могут привести к появлению трудно предсказуемых эпидемиологических вспышек. Кроме того, сложный баланс между естественным желанием человечества вернуться к нормальной жизни и желанием контролировать новую, динамично развивающуюся инфекцию может привести к новым угрозам со стороны старых и хорошо известных патогенов. Наконец, мы предполагаем, что отсутствие регулярной циркуляции вируса гриппа может привести к высокому уровню несоответствия и значительному снижению эффективности вакцины против гриппа.

Ключевые слова: COVID-19, SARS-CoV-2, гипотеза, респираторные вирусные инфекции, грипп, RSV, риновирус, дети