Canadian Covid Care Alliance
Alliance canadienne pour la prévention et prise-en-charge de la covid
CCCA

Website: www.canadiancovidcarealliance.org
E-mail: info.canadiancovidcarealliance.org

Request to Halt COVID-19 Vaccinations of Children

July 14, 2022

Dear Health Official,

The COVID-19 crisis has been filled with uncertainty since early 2020 that resulted in unprecedented measures adopted by the federal and provincial health agencies and officials to mitigate the impacts of a novel respiratory pathogen on vulnerable groups in our country. A key part of this national effort was Health Canada's approval of the first two-dose series of COVID-19 mRNA novel vaccines for use in children 12 to 15 years of age on May 5, 2021[1] followed by their approval for children 5 to 11 years of age on November 19, 2021,[2] and more recently recommendation of boosters by the National Advisory Committee on Immunization for use in high-risk children 12 to 17 years of age.[3] On June 15, 2022 the Food Drug Administration authorized these vaccines for children 6 months or older,[4] an indication that is currently under review by Health Canada and the National Advisory Committee on Immunization.[5,6]

We are a group of independent Canadian scientists consisting of pediatricians, immunologists, vaccinologists, health policy experts, and evidence-based methodologists from the Canadian Covid Care Alliance who share your concern for the well-being of Canadians. We understand the challenges inherent in ensuring that public health policy remains up-to-date in a field where the science is rapidly evolving. Given the decades of quality life years that our children have ahead of them,[7,8] we firmly believe it is our duty as adults to work together to ensure that our children are protected not only from sickness but also from unnecessary or harmful medical interventions. We are reaching out today, to share with you, *the most up-to-date evidence on COVID-19 mRNA vaccines used in children (aged < 18 years)*. The data shows that, in the Omicron era, when population-based immunity is widespread, the risks associated with COVID-19 mRNA vaccines far outweigh the benefits in children. Please consider the following:

1. **In the Omicron era, there is widespread naturally acquired immunity. Therefore, there is no medical need for children to receive COVID-19 mRNA vaccines**
    a. In the Omicron era when there is widespread naturally-acquired immunity and where the virus produces a milder form of COVID-19 than earlier strains, healthy children are even less at risk of severe disease or death from COVID-19.
    b. In the Omicron era, there is widespread immunity and where the vaccines cannot halt transmission (*i.e.,* non-sterilizing) and likely require perpetual updates, children pose no significant risk to adults.
    c. The vast majority of severe illness and deaths from COVID-19 have impacted frail and older persons having multiple co-morbidities who can better benefit from more targeted protection.

2. **COVID-19 mRNA vaccines do not work well relative to other forms of protection**
    a. Naturally acquired immunity is the gold standard for immunity – it is robust, comprehensive, durable, and provides appropriate protection against a respiratory infection.
    b. There is mounting evidence that the real-world effectiveness of the COVID-19 vaccines is extremely poor and short lived in children under 12 years of age.
    c. There are now potential treatments to prevent severe COVID-19 including new anti-virals, corticosteroids, antiseptic nasal/oral rinses and re-purposed drugs that can be used selectively unlike a global mass vaccination campaign where to be 'fully immunized' is not achievable.

3. **The potential risks of COVID-19 mRNA vaccines outweigh their benefits in the Omicron era**
    a. Both non-inoculated and inoculated individuals with COVID-19 transmit SARS-CoV2 equally with little difference (less than a day) in sickness, eliminating the basis for the mass vaccination of children as a means of protecting society or ICU capacity.
    b. In the Omicron era, where there is widespread naturally acquired immunity, current data shows that COVID-19 vaccines are neither particularly effective nor acceptably safe for children.
    c. There is growing concern related to the adverse long-term impacts on immune function from repeated injections of now obsolete COVID-19 products that paradoxically increase susceptibility to infection and illness via antigenic imprinting, and antibody-dependent enhanced disease.

Kindly allow us to expand on the extensive evidence supporting our claims.

Children do not need COVID-19 mRNA vaccines

a. Healthy children are not at substantial risk of severe disease or death from COVID-19

A recent meta-analysis estimated that 60% of individuals <20 years-old with confirmed COVID-19 diagnosis are asymptomatic.[9] For healthy children ages 0 to 19, the risk of severe disease or death from COVID-19 is virtually zero.[10] This is likely due to fact that children have a lower concentration of the cell entry receptors for SARS-CoV-2 on the cells in their airways compared with adults[11] and that they have very robust natural innate immunity.[12–14] Although rare cases of multi-inflammatory syndrome (MSI, less than 1 out of 1,800 pediatric infections)[15,16] or long-COVID[17–21] in children were initially reported, these studies were not controlled and it is well established that severe COVID-19 outcomes are associated with known risk factors such as advanced age, obesity, and other comorbidities.[22–25] In Canada, the risk of death or hospitalization from identified cases of SARS-CoV-2 infection with the original strain in 0- to 19-years-old was 0.005% and 0.5%, respectively, by mid-May 2021, and given that most infections are not identified, the risk is likely considerably lower than reported.[26] Regardless of prior risk, with the advent of Omicron, the risk of COVID-19 hospitalization and death is considerably lower – by up to 65% relative to Delta according to Ontario data –[27,28] and cases of MSI as low as 1 in 26,000.[15] Even more, it has come to light that many jurisdictions including Ontario, have been over estimating the rate of COVID-19 pediatric hospitalizations and deaths by as much as 60%, which underscores that the true risk to children is substantially lower than originally estimated.[29] A recent seroprevalence study observed that about 75% of US children had infection-induced antibodies following Omicron, meaning that there is now widespread naturally-acquired immunity in this population (Figure 1).[30–32] Furthermore, in England, SARS-CoV-2 antibody testing of unvaccinated school pupils from January to February 2022, showed that 62.4% and 97% of primary and secondary students, respectively, were serologically positive for previous infection with the virus.[33] Similar high rates of SARS-CoV-2 specific antibodies have also been found in over 85% of tested Canadian children two and a half years into an ongoing clinical study led by Dr. Steven Pelech at Kinexus Bioinformatics (personal communication). Currently available data now clearly shows that the risk of severe disease due to COVID-19 in healthy children who are immune to COVID-19 is next to non-existent.

b. Children pose no significant risk to adults

Early in the pandemic, there were concerns that children might be at increased risk of transmitting the virus to adults who were at risk of severe disease. However, it is now recognized that children are less likely to transmit the infection to adults in the household, and very unlikely to transmit the infection to adults in schools.[34] This is due to their low susceptibility to infection from lower levels of the ACE2 receptor to which SARS-CoV-2 binds in the upper airways of children as well as their robust innate immunity, which allows them to quickly clear infections, thus limit transmission.[35,36] Also, in early 2021, prior to the rise of widespread naturally acquired immunity, another nationwide Swedish study showed that leaving schools open did not lead to higher rates of COVID-19 among teachers.[37] Similar findings were recorded by researchers at the University of BC, and the BC Children's Hospital Research Centre in a 2021 study that found that approximately only 40 of the nearly 1,700 teachers tested contracted COVID-19 and that contact tracing showed that these were largely identified as acquired outside of the schools.[38,39] Well into the third year of the COVID-19 pandemic, with widespread immunity from either infection[40] or vaccination,[41] along with less aggressive variants in circulation,[42–44] the risk of severe COVID-19 posed to adults does not justify vaccination of children. Given that neither adults nor children remain at high risk of severe disease from COVID-19, there is no longer a compelling reason to continue with COVID-19 vaccinations in children.

Current vaccinations do not work well relative to other forms of protection

a. <u>Naturally-acquired immunity is the gold standard of immunity – it is strong, comprehensive and durable, and is demonstrably superior to immunity conferred by the current vaccines</u>

At the outset of the pandemic, there were concerns that a deficiency in population-wide immunity against SARS-CoV-2 would result in high rates of COVID-19 deaths. In the Omicron era, immunity is now widespread and, as of February 2022, approximately 75% of US children and adolescents had already demonstrated serologic evidence of a previous infection with SARS-CoV-2.[30] We also now know that young healthy immune systems produce rapid and robust serological and cellular responses to a broad spectrum of SARS-CoV-2 proteins[45,46] and that these responses confer protection throughout the entire respiratory tract.[46–48] Emerging evidence also shows that naturally acquired immunity is long-lasting, with immune responses to the highly related SARS-CoV-1 coronavirus still evident decades after the initial infection back in 2002-2004.[49,50] The Kinexus SARS-CoV-2 clinical study has similarly shown persistence of antibodies against this virus in their participants more than two years after their initial infection (Dr. Steven Pelech, personal communication) Figure 2 shows the high maintenance of SARS-CoV-2 antibodies from the first COVID-19 wave through to after the second COVID-19 wave in the Kinexus serological

study). This durability of the natural immune response is in sharp contrast to vaccination-derived immunity, which is narrow, focusing exclusively on the spike protein,[51] short-lived, and according to the six-month results of the pivotal Pfizer phase III trial, peaking in less than two months after injection and diminishing by 6% every two months thereafter.[52] Additionally, vaccination against COVID-19 generates antibodies that are present at *low concentrations* in the upper airways, which is the primary site of infection.[48] In short, these vaccinations designed to target the original strain of SARS-CoV-2 offer waning and sometimes negative protective immunity against infection with variants such as Omicron, which have 32 or more mutations in the spike protein.[53] Importantly, naturally-acquired immunity bears *little to no risk in itself*, as healthy children usually experience infections that are either asymptomatic or develop into generally very mild forms of disease: with Omicron, no more than a common cold.[46] A randomized controlled trial comparing vaccination-derived immunity to naturally acquired immunity has yet to be conducted, thus claims regarding the superiority of vaccination-derived immunity relative to naturally-acquired immunity, especially in the *Omicron era and beyond are speculative at best*, unsupported by the evidence, and contrary to past experiences with viral and bacterial infections.[54–56] In sum, in contrast with vaccination-derived immunity, naturally-acquired immunity is strong, broad and durable with virtually no safety concerns,[55,57–62] and is therefore the best option for ensuring long-lasting protection for children from future SARS-CoV-2 infections.

b. <u>An increasing number of agents are available to treat those who continue to be at risk of severe COVID-19</u>

Nutraceutical and dietary supplement can aid an individual's immune system providing support against acute respiratory viral infections by assisting normal maintenance and function.[63,64] For the very few non-immune individuals who remain at risk of severe COVID-19 – for instance, those with comorbidities or immunosuppression[65] – Health Canada has approved a number of outpatient drugs for adults including anti-virals like nirmatrelvir/ritonavir (Paxlovid)[66] and remdesivir (Veklury),[67] and monoclonal antibodies.[68–71] Additionally, the Ontario Science Table has recommended fluvoxamine and budesonide for preventing severe disease in adults at low risk of hospitalization.[72] As more is now known about how to bolster the immune system and treat SARS-CoV-2 infections,[72] there is even less of a need for vaccinations that provide negligible incremental protection in a population that is already largely immune to a now treatable disease. Even vulnerable sub-groups of children, who are immunosuppressed, have poor respiratory function (i.e., cystic fibrosis) or are undergoing surgery may benefit from simple, safe and cost-effective

prophylactic alternatives, such as virucidal povidone-iodine nasal rinses[73,74] than increasingly obsolete COVID-19 vaccine products.

The potential benefits of COVID-19 vaccinations do not outweigh their risks

a. COVID-19 vaccinations do not stop acquisition or transmission of SARS-CoV-2

The promise of mass vaccinations to achieve herd immunity and protect those at risk of severe COVID-19 has not come to pass: *abundant evidence confirms that COVID-19 vaccinations neither prevent infection nor stop viral transmission, and that both inoculated and non-inoculated individuals carry equal viral loads, i.e., can equally transmit SARS-CoV-2.*[75–78] Large studies of community transmission have found *equal secondary attack rates among the inoculated as among the non-inoculated*. A large study in the United Kingdom found that 25% of household contacts of fully inoculated individuals who had experienced breakthrough infections contracted COVID-19 vs. 23% of household contacts of unvaccinated individuals who had experienced COVID-19.[76] As shown by a landmark Israeli study, vaccinations have also failed to stop transmission *even in medical institutions with fully vaccinated staff and patients*.[79]

It has been suggested that vaccinated individuals recover from COVID-19 sooner than unvaccinated individuals, and so they are transmissible for a shorter period of time. However, a recent scientific study reported by the US CDC with post-marketing release of the Pfizer/BioNTech vaccine conducted primarily in Denver found that vaccinated participants with Omicron infection spent an average of one half day less sick in bed than did unvaccinated participants with Omicron infection.[80]

It is noteworthy that no gold standard, placebo-controlled disease endpoint trials, large enough (*n*=800,000) to categorically establish the clinical safety and long-term efficacy of the Pfizer COVID-19 mRNA vaccinations in children 12- to 15-years-old, 5- to 11-years-old, 2- to 4-years-old, and 6-months-old to 23-months-old have been undertaken. Instead, Pfizer vaccination approvals for these age groups were based on the preliminary results of four very small *immuno-bridging trials*, enrolling fewer than 3,000 participants each. They were *not designed to establish the superiority of vaccination compared to naturally acquired immunity,* but only the non-inferiority of "neutralizing" antibody concentrations in the blood of a small number of 12- to 15-years-old (*n*=190), 5- to 11-years-old (*n*=264) children, 2- to 4-years-old (*n*=143), and

6-months-old to 23-months-old (*n*=82) compared to young adults.[4,81,82] Because antibody titers in the blood are not a clinically validated measure of efficacy for mucosal infections of the respiratory tract, *study claims regarding efficacy are speculative at best*. Moreover, in these studies, assessment of "neutralizing" antibodies only focused on those antibodies that block the binding of the original strain of SARS-CoV-2 to the ACE2 receptor and entry into test cells. Many of the mutations in Omicron occur within the receptor binding domain of the spike protein. Furthermore, over 95% of antibody responses to the SARS-CoV-2 spike protein in both vaccinated and SARS-CoV-2-infected individuals are directed toward other regions of the spike protein, and the vast majority of the immune protective response is not measured by "neutralizing" antibody tests.

Starting 7 days after the last dose and less than 3 months post-vaccination for those under 12 years, the aforementioned studies provided descriptive relative risk reductions (RRR) in symptomatic cases of COVID-19 of 100%, 91%, 82%, and 76% for children aged 12 to 15 years, 5 to 11 years, 2- to 4-years-old, and 6-months-old to 23-months-old, respectively. Moreover, when outcomes were analyzed to reflect the net benefit of the vaccinations in these groups, the absolute risk reduction (ARR) in mild symptomatic COVID-19 was a mere 2% or lower for all groups, results which lack clinical relevance for the 60% of children and adolescents (<20 years) who experienced asymptomatic infections.[9] In addition, the vaccines did not demonstrate an ability to reduce severe COVID-19 or halt transmission, rendering claims regarding protection in the vast majority of children speculative at best. Of great concern, however, were findings in the 2- to 4-years-old cohort that showed that following the first dose the vaccine was associated with a 199% relative risk increase in severe COVID-19 and a 149% relative risk increase in multiple COVID-19 infections compared to placebos.[4] Moreover, the 76% RRR noted for 6 to 23 month old infants was astonishingly based on just three participants in this age group (1 vaccinated and 2 placebo), and the 82% RRR on just seven participants in the older 2–4-year-olds (2 vaccinated and 5 placebo), and was only after triple vaccination of these children.

The pivotal child vaccination studies were too short to establish vaccinal efficacy and did not control for natural immunity. Natural immunity was only assessed by the detection of antibodies against the nucleocapsid protein of SARS-CoV-2, which often fails to be measurable in people that have recovered from COVID-19. The child vaccine trials were designed to test vaccines developed against the original strain of SARS-CoV-2, which is no longer in circulation. Not surprisingly, COVID-19 vaccinations have demonstrated a lack of effectiveness against Omicron, which has spread widely through mostly inoculated

– even boosted – populations.[83] Real world studies conducted during the Omicron surge in New York State and Denver found that the effectiveness of COVID-19 mRNA vaccination ranged from 51% to 59% for children 12 to 17 years of age and from 12% to 31% for children aged 5 to 11 years.[80,84–85] In the New York State study, efficacy decreased to negative values by 5-6 weeks post second vaccine dose.

Following Omicron, and despite having a very high rate of vaccination (87%) for eligible Ontarians aged five years and older,[41] the Government of Ontario reported ***a negative dose-response effect for the COVID-19 vaccinations***. In other words, the proportion of cases of COVID-19 were highest among those who had been 'boosted', lower among the 'fully inoculated' and least among the 'not fully inoculated' (which includes the 'uninoculated' (Figure 3 panel A). A similar pattern was observed in the 12 to 17 years-old and the 5 to 11 years-old age groups (Figure 3 panel B &C). Additionally, a greater proportion of "boosted" Ontarians have died, revealing that the vaccinations may be associated with serious secondary effects (Figure 4). A concern has been expressed by researchers in Denmark who conducted a meta-analysis of all COVID-19 vaccine randomized controlled trials and found that the mRNA vaccinations were associated *with a significant increase in all-cause and cardiac-related mortality compared to the adenovirus-vector vaccines*.[86] These findings indicate the potential for vaccination-induced adverse effects, including vaccination-enhanced COVID-19 disease,[87,88] development of T-cell[89–91] and vaccine exhaustion[92] especially in the context of multiple and frequent boosters.[93] This alarming data supports epidemiological evidence from Nordic countries of an elevated risk for myocarditis and pericarditis that is dose and mRNA vaccine product dependent, particularly for young males (16-24 years).[94]
Similarly, another recent report has confirmed no significant increase in the incidence of myocarditis or pericarditis in patients recovering from COVID-19 infection.[95] Importantly, there is now documented autopsy analysis from young adult fatalities that support an autoimmunological response to the COVID-19 vaccination among susceptible individuals as reflected by SARS-CoV-2 spike protein expression within the heart with extensive CD4+ lymphocytic infiltration.[96] In sum, there is a lack of quality evidence supporting COVID-19 vaccination efficacy in an Omicron era and a concerning signal of harm with mechanistic evidence supporting a causal link to COVID-19 vaccination as compared to natural infection and recovery among otherwise healthy young adults/adolescents.

The mechanisms by which vaccination may cause negative efficacy in boosted individuals remains unclear, although several hypotheses have been advanced based on prior vaccine prototypes developed for SARS-CoV-1 and MERS, including antibody-dependent enhancement (ADE) and original antigenic sin (or

antigenic imprinting).[97, 98] ADE occurs when antibodies may hasten the destruction of immune cells via the antibody-dependent binding of viruses to these cells and facilitates their entry. Original antigenic sin arises when an initial antibody response against an earlier version of the virus predominates over subsequent responses to mutated versions of the same virus. There is clear evidence that prior COVID-19 RNA vaccines apparently blunts the natural immune response following a COVID-19 infection. Moderna's 30,000-participant study of persons 18 years or older for its RNA vaccine has indicated that subsequent production of antibodies against the Nucleocapsid protein of SARS-CoV-2 was evident in only 40% of previously vaccinated individuals with COVID-19 compared to 93% of unvaccinated peoples that acquired COVID-19.[99] Even an unvaccinated person with a mild case of COVID-19 had a 71% chance of showing Nucleocapsid antibodies in their blood compared to a 15% chance with a vaccinated person that recovered from mild COVID-19.

b. <u>COVID-19 vaccinations demonstrate a concerning increase in all-cause morbidity and absence of established long-term safety</u>

The best available data for assessing the safety of the Pfizer COVID-19 vaccinations in children has come from the phase III trials. These trials provided *important preliminary descriptive data for the level of safety of COVID-19 vaccinations for children,* revealing *dramatic increases in dose-dependent all-cause morbidity.* While the trial demonstrated a 2% reduction in the absolute risk of acquiring a mild COVID-19 infection in both 12- to 15-year-old children and 5- to 11-year-old children, it was associated with a *dramatic net increase in all-cause morbidity relative to placebo which increased with each dose.*[81,82] In the older group, the vaccination was associated with net increases in injection site pain for the first and second dose (63% and 61%) as well as increases in fatigue (19% and 42%), headache (19% and 40%), chills (18% and 35%) and muscle pain (10% and 24%) despite a net increase in the use of anti-pyrectics (26% and 42%) compared to placebo (Figure 5).[81] As no cases of severe COVID-19 were reported in either study,[79,80] claims regarding protection against severe disease in children and adolescents *remain unsubstantiated*. In addition, the studies showed an *absolute risk increase for both severe* (0.4%) *and serious* (0.3%) *adverse events for the COVID-19 vaccinations* compared to placebo in adolescents. These findings were in line with the six-month results of the Pfizer COVID-19 mRNA vaccine trial in adults, which showed significantly more all-cause illness in the vaccinated compared with placebo arms (262 vs 150, $p<0.0001$, Table 1). The study, which has a protocol-specified plan to unblind the trial and offer crossover to the vaccine at six months, is unlikely to yield quality long-terms safety data.[81,82] Even more concerning were the rates of severe adverse

events associated with booster administration. A real world study conducted by the US Centers for Disease Control showed that 25.8% of the 3,418 adolescent booster vaccination recipients aged 12 to 17 years were unable to perform daily activities; 20.0% were unable to attend school or work; and ~0.9% required medical care (Figure 5).[100] The vaccinations were associated with dramatic increases in dose-dependent short-term all-cause morbidity with no current evidence of long-term safety.

Additionally, the phase III trials were insufficiently powered to detect less common safety signals in the study population and were not designed to assess safety in the COVID-19-recovered, those with multiple co-morbidities, or the immunocompromised.[81,82] As a result health officials primarily relied upon passive pharmacovigilance systems, which notoriously underreport vaccination-suspected adverse outcomes.[101] Despite their lack of sensitivity of such passive surveillance systems, a wide range of vaccination-suspected adverse events of a cardiovascular, neurological and immunological nature have been reported.[102] The most concerning of these adverse events has been myocarditis/pericarditis, along with cardiac emergencies, which have been observed in multiple recent population-based studies particularly in male adolescent and young adults.[103-107] The risk of symptomatic myocarditis and pericarditis arising after the second dose of COVID-19 mRNA vaccination in 18- to 24-years-old men in Ontario was originally estimated at 1 in 17,000 for Pfizer and 1 in 3,000 for Moderna from June 1 to Sep 4, 2021,[108, 109] but is now approaching 1 in 5,000 (19.8 events per 100,000 vaccine doses) for mRNA vaccines overall following the second vaccination.[110] These rates likely under-estimate overall heart damage as they do not account for asymptomatic myocarditis, which can be three-times higher than symptomatic[111] myocarditis, and both of which have been linked to long-term cardiovascular disease and premature death.[112, 113]

In addition, a recent Pfizer pharmacovigilance report released from the FDA showed that within the first two months of the worldwide COVID-19 vaccination rollout, 42,086 cases of vaccination-suspected adverse events were processed by Pfizer, of which 1,223 were fatal.[114] A total of 1,077 immune-mediated adverse effects including nerve pain, swelling in the brain and myocarditis and pericarditis were reported, of which 780 were serious and 12 were fatal. Moreover, a total of 34 adverse event cases were reported in children less than 12 years of age of which 24 were serious. Both clinical trial and real world findings point to a concerning increase in dose-dependent all-cause morbidity and concerning immune-mediated safety signals, which increase with each vaccine dose.

In conclusion, the COVID-19 vaccinations were developed to protect children from severe COVID-19 outcomes from the Wuhan strain of SARS-CoV-2 at a time when population-wide immunity was limited. Now that Omicron has displaced the original strain and that there is presently widespread naturally acquired immunity, it is abundantly clear that: children are at extremely low risk of severe COVID-19; further vaccinations do not stop transmission; vaccinations are demonstrating negative-effectiveness; each dose is associated with dramatic increases in all-cause illness including life-altering complications; and there is still no long-term safety data. Considering that children have decades of quality life years ahead of them and that the first principle in medicine is to "Do no harm," it is imperative that every public health official do whatever is in their power to immediately halt the vaccination of children until the long-term efficacy and safety of these vaccinations is either definitively established or disproved.

Finally, we note that the Children's Covid Vaccine Advisory Council of the Health Advisory and Recovery Team in the UK has recently made similar concerns to those provided here by the Canadian Covid Care Alliance regarding the vaccination of children in an open letter dated June 30, 2022 with over 60 Ph.D. and M.D. signatories.[115] Likewise, Søren Brostrom, the director of the Danish Health and Medicines Authority has concluded that it was a mistake to vaccinate children for COVID-19.[116] A safety report published in September 20, 2021 by the Federal Institute for Vaccines and Biomedicine at the Paul-Ehrlich-Institut in Germany already concluded that for children age from 12 to 17 years, the number of reported cases of mis-understood COVID-19 vaccine side effects exceeded the total number of COVID-19-related hospitalizations in this age group.[117]

Thank you for taking the time to review our findings. We trust that our research has provided you with evidence needed to adjust Canadian health policy to protect our children from undue harm. We would be happy to meet you to discuss findings documented in this letter in greater detail.

Respectfully,

Dr. Eric Payne, MD, MPH, FRCPC, Pediatric Neurologist; Canadian COVID Care Alliance, Science and Medical Advisory Committee member

Dr. Robert Rennebohm, MD, MSc, Pediatric Rheumatologist, Cleveland Clinic (OH, U.S.)

Dr. Byram W. Bridle, PhD, Immunologist, Associate professor of Viral Immunology (specializing in vaccinology), University of Guelph; Leader of the Vaccine Task Force of the Scientific and Medical Advisory Committee, Canadian COVID Care Alliance

Dr. Bonnie Mallard, PhD, Immunologist, Professor of Immunology and Immunogenetics, University of Guelph; Canadian COVID Care Alliance, Scientific and Medical Advisory Committee member

Dr. Niel Karrow, PhD, Immunologist, Professor of Immunotoxicology, Department of Animal Sciences, University of Guelph; Canadian COVID Care Alliance, Scientific and Medical Advisory Committee member

Dr. Bernard Massie, PhD, Microbiology and Immunology (specializing in adenoviral vector technology for cancer therapy and vaccines); former Direct General of the Human Health Therapeutic Research Center of the National Research Council; Canadian COVID Care Alliance, Scientific and Medical Advisory Committee member

Dr. Karen Northey, MD, Family physician

Dr. Christopher Shoemaker, MD, CCFP

Dr. Steven Pelech, PhD, Biochemistry, Professor of Neurology, Medicine, University of British Columbia; Canadian COVID Care Alliance, Science and Medical Advisory Committee member and Co-Chair; President and Chief Scientific Officer, Kinexus Bioinformatics Corporation

Dr. Claudia Chaufan, Health policy and Global health, MD, PhD, Associate Professor of Health Policy, York University; Canadian COVID Care Alliance, Scientific and Medical Advisory Committee member

Deanna McLeod, BSc, Evidence-based medicine analyst; Principal, Kaleidoscope Strategic Inc.; Canadian COVID Care Alliance, Scientific and Medical Advisory Committee member.

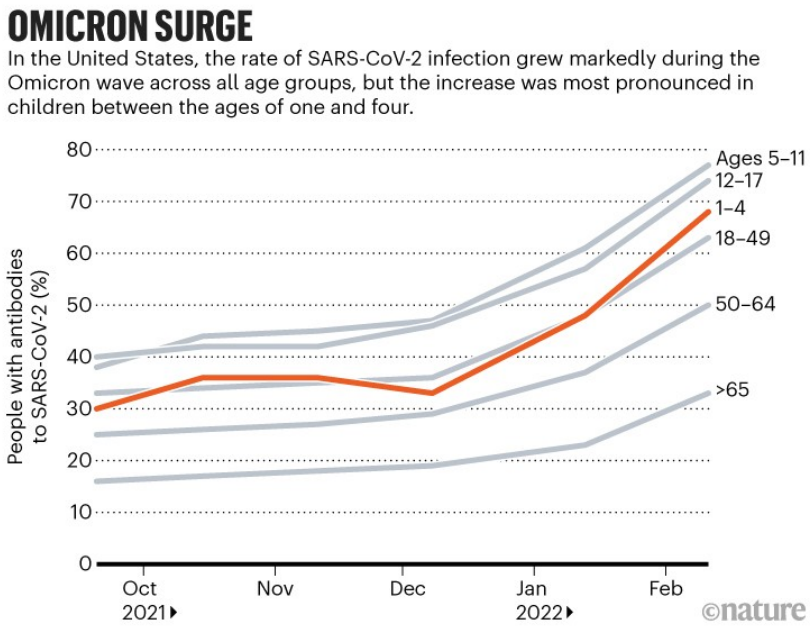
Dr. John Hardie, BDS, MSc (Path), PhD, FRCDC, Oral pathologist (Ret.); Canadian COVID Care Alliance, Scientific and Medical Advisory Committee member

Dr. Christopher Pinto, MD, Physician, Independent practice; Canadian COVID Care Alliance, Scientific and Medical Advisory Committee member

Dr. Philip Britz-McKibbin, PhD, Bioanalytical chemist, Professor of Chemistry and Chemical Biology, McMaster University; Canadian COVID Care Alliance, Scientific and Medical Advisory Committee member

Dr. Christopher Shaw, PhD, Professor of Ophthalmology, University of British Columbia; Canadian COVID Care Alliance, Scientific and Medical Advisory Committee member and Co-Chair

Figure 1: Seroprevalence of infection-induced SARS-CoV-2 antibodies, by age group — United States, September 2021–February 2022



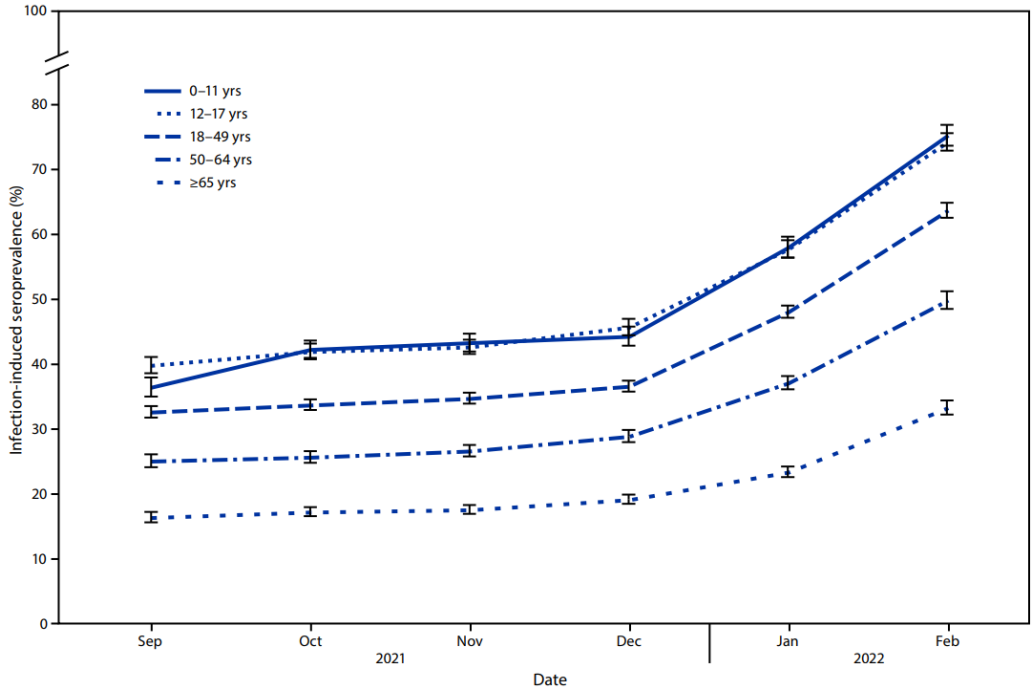


Figure 2: Stability of SARS-CoV-2 antibody patterns in serum samples of twelve COVID-19 recovered individuals tested with the Kinexus 110 marker SARS-CoV-2 antibody screen. The locations of peptides within the various SARS-CoV-2 proteins are indicated in the map shown immediately below. A detectable spot corresponds to the presence of antibodies in the serum that specifically recognize a portion of the target

SARS-CoV-2 proteins. Spot D26 corresponds to a positive control to ensure that the test was working properly. The same participant was tested approximately 10 months later with the results shown in the right panel as compared to when originally tested as shown in the corresponding left panel, and the columns of panels are from the different participants that were tested.

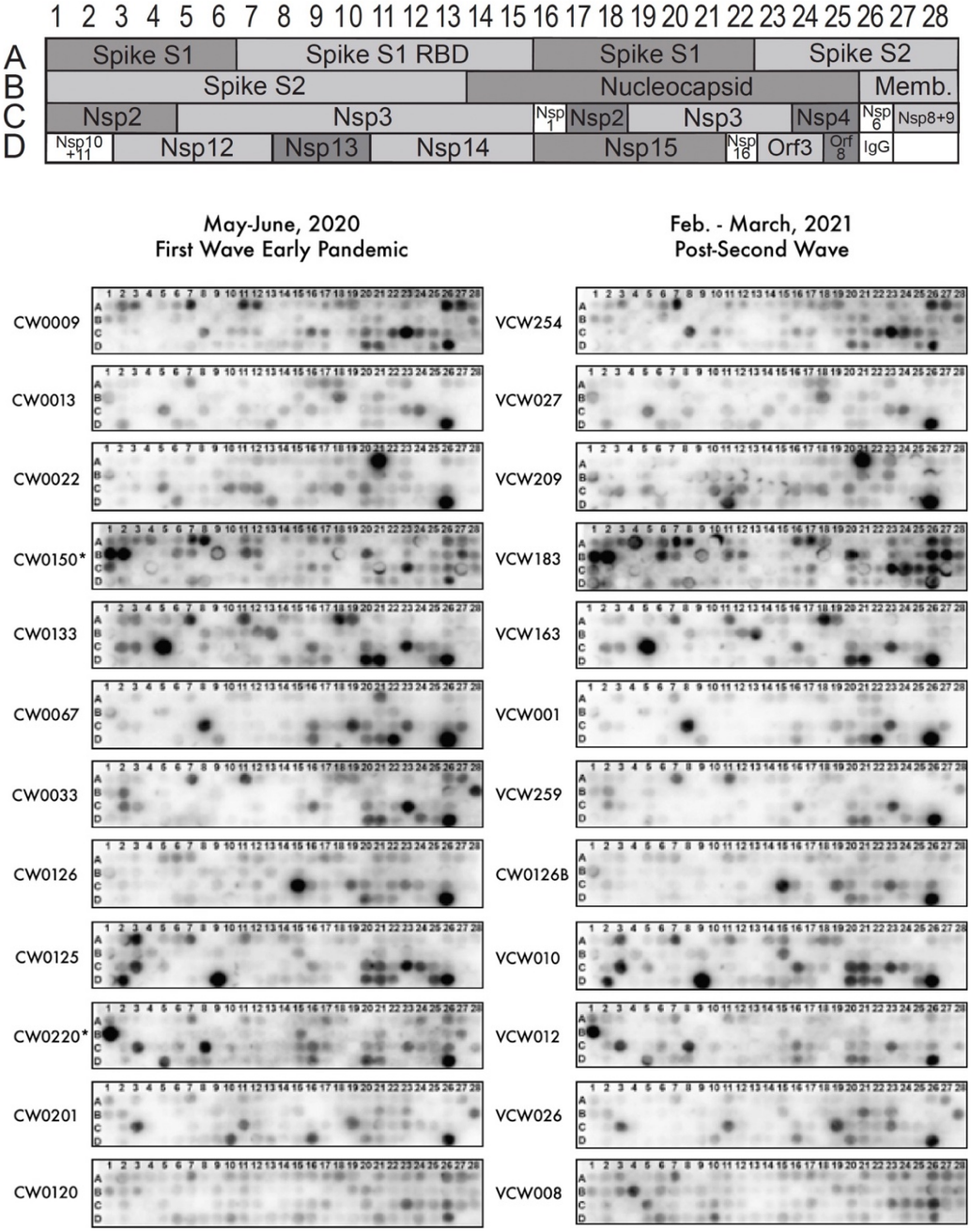


Figure 3: Proportional of daily cases of COVID-19 occurring among A) Ontarians of all ages B) those 12 to 17 years and C) those 5 to 11 years who were 'not fully vaccinated' (i.e., unvaccinated or a single dose; purple line), 'fully vaccinated' (i.e., two doses; pink line), or 'vaccinated with booster dose' (i.e. three or more doses; green line). This graph was copied from Public Health Ontario website on April 30, 2022 (https://covid-19.ontario.ca/data). No data for this graph are available prior to March 17, 2022.

Figure 4: Proportional of daily COVID-19 deaths occurring among Ontarians of all ages who were 'not fully vaccinated' (i.e., unvaccinated or a single dose; green line), 'fully vaccinated' (i.e., two doses; blue line), or 'vaccinated with booster dose' (i.e. three or more doses; pink line). This graph was copied from Public Health Ontario website on April 30, 2022 (https://covid-19.ontario.ca/data). No data for this graph are available prior to March 17, 2022.

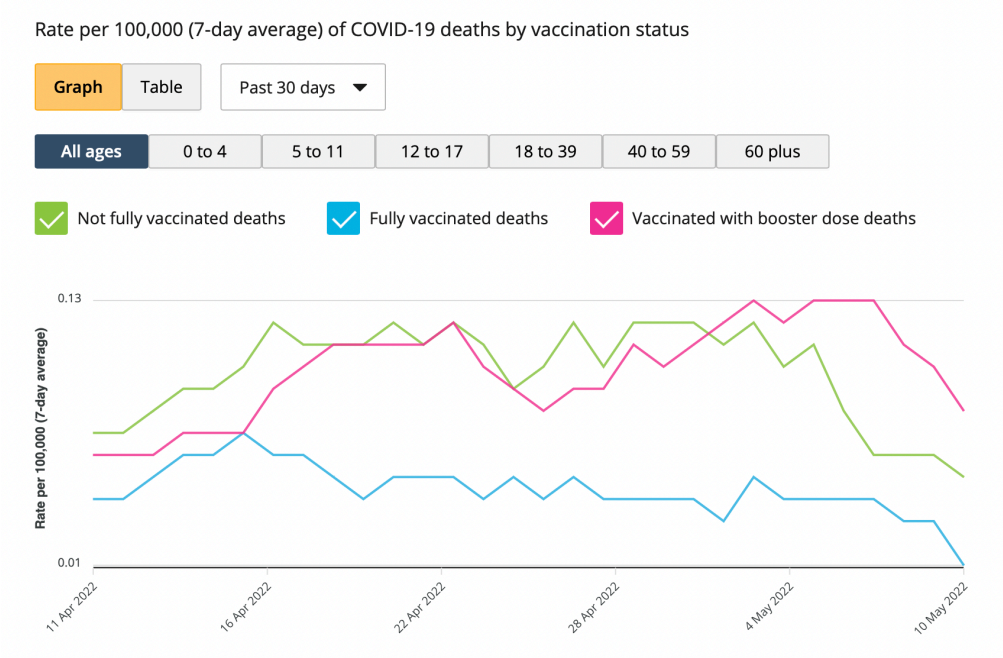


Figure 5 - Local reactions and systemic events reported in 12-to-15-year-olds within 7 days after administration of dose 2 of BNT162b2 or placebo all participants[78] Symptom severity: Mild-green, Moderate-blue, Severe-orange.

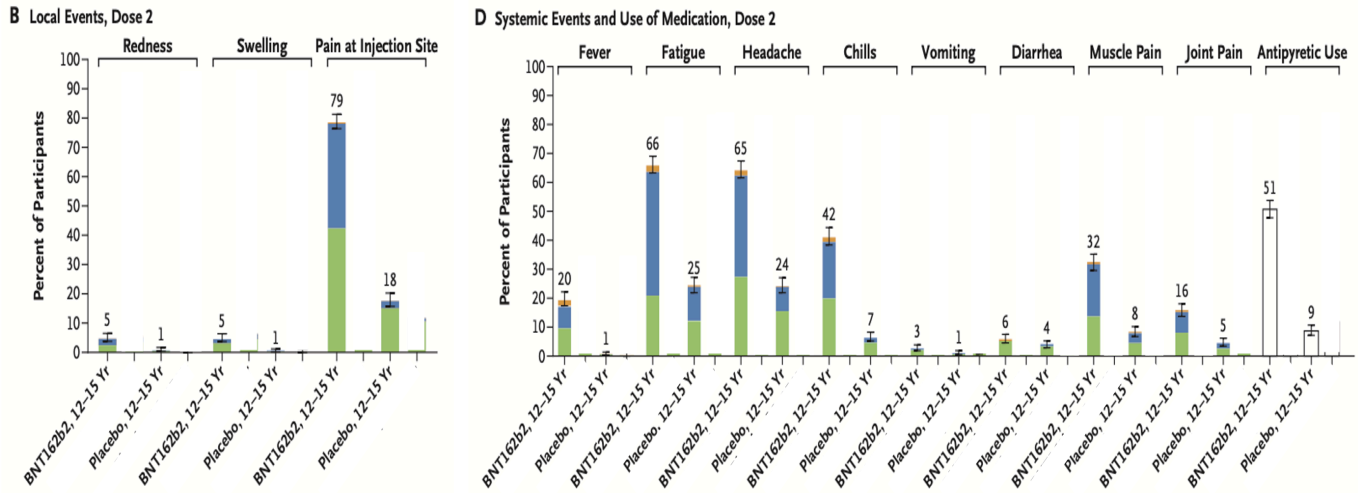


Figure 6 - Adverse reactions and health impacts reported* among persons aged 12–17 years (N = 3,274) who received a homologous Pfizer-BioNTech COVID-19 vaccine booster, by vaccine dose — United States, December 9, 2021–February 20, 2022.

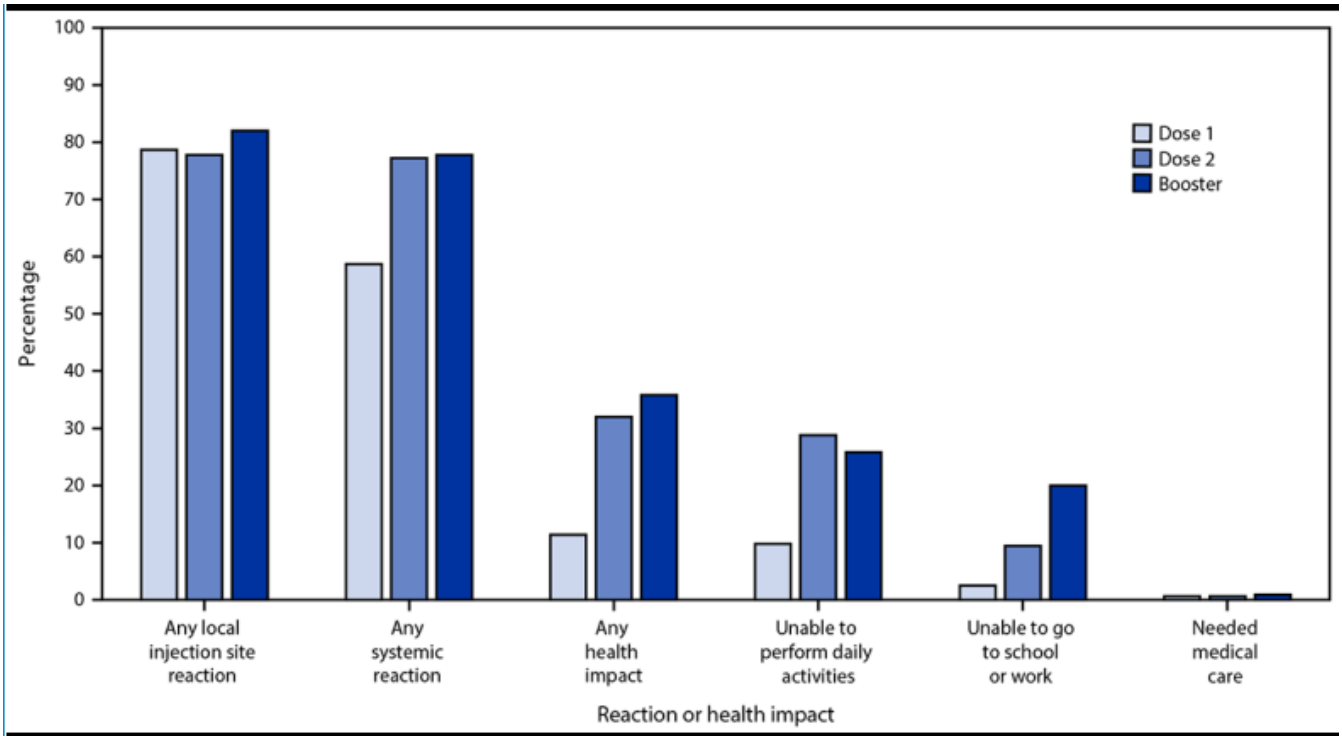


Table 1 - Differences in efficacy and safety events reported in the six-month update of the BNT162b2 mRNA COVID-19 vaccine.[52]

Table 1. Differences in the number of efficacy and safety events in eligible populations[¥] reported in the 6-month update of the BNT162b2 mRNA Covid-19 vaccine

Event	BNT162b2 (n)	Placebo (n)	Absolute Difference (p-value)[?]	Absolute Risk Change* (%)	Relative Risk Change* (%)
Cases Adults and Adolescents 7 days after 2nd dose[$]	77	850	-773 (p<0.00001)	-3.7	-90.9
Any Unsolicited Treatment-Related Adverse Event Adults[#]	5,241	1,311	+3,930 (p<0.00001)	+17.9	+299.7
Any Severe Event Adults[/]	390	289	+101 (p=0.0001)	+0.5	+34.9
Severe Cases in Adults 7 days after 2nd dose[&]	1	23	-22 (p<0.00001)	-0.1	-95.7
Unsolicited Severe Adverse Events[~] Adults Prevents daily routine activity or requires intervention or worse	262	150	+112 (p<0.00001)	+0.5	+74.6
Serious Adverse Event Adults[§] Requires hospitalization or results in permanent injury or death	127	116	+11 (p=0.5)	+0.05	+9.5
Deaths during placebo-controlled period [additional deaths during open-label period in vaccine recipients or placebo-only][%]	15 [+5]	14 [NR]	+1 [+5] (p=0.9)	+0.005	+7.1
Deaths due to cardiovascular events[^]	9	5	+4		

¥ For the purpose of this table and in accordance with the terminology used in the study report, adult and adolescent populations are defined as ≥16 years old and 12-15 years old, respectively;

? Significance figures (p-values) estimated using chi-square calculator available at https://www.socscistatistics.com/tests/chisquare. P values are without the Yates correction. This procedure was applied following the framework used by Classen in his analysis of "All Cause Severe Morbidity" based on data from the initial reports of the vaccine Phase III trials;[107]

** Authors estimated vaccine efficacy using total surveillance time as denominator, however, as this value was unavailable for all the events analyzed, our calculations used the common statistical definition, i.e., number of events relative to total number of eligible patients for each event analysis reported[108] similar to previous analyses of this nature;[107,109]*

$ ≥7 Days after dose 2 among participants without evidence of previous infection;

 # Adverse events reported outside of the reactogenicity subgroup and assessed by the investigator as related to investigational product / In calculations combining efficacy and safety events, the number of patients randomized that received any dose of vaccine or placebo was used as the study population in the statistical calculations, following the framework used by Classen in his analysis of "All Cause Severe Morbidity".[107] Differences in the total (event-incident) population (randomized vs efficacy vs safety) used as denominator are relatively small and are expected to have minimal impact on the relative differences between groups. Without access to individual patient data, these calculations were performed under the assumption that efficacy and safety events were non-overlapping;

& ≥7 Days after dose 2; confirmed severe COVID-19 defined as PCR-positivity and "presence of at least one of the following: • Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg); • Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO); • Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors); • Significant acute renal, hepatic, or neurologic dysfunction;• Admission to an ICU; • Death";

~ Severe (grade ≥3) adverse events were generally defined as those that interfere significantly with participant's usual function, those that affect daily living or require medical care; grade 4 events were generally defined as those that required emergency room visit or hospitalization;

§ Serious adverse events were defined as any untoward medical occurrence that, at any dose: a. Results in death; b. Is life-threatening; c. Requires inpatient hospitalization or prolongation of existing hospitalization; d. Results in persistent disability/incapacity;

% Deaths during the open-label period were reported only in vaccine recipients, 3 participants in the BNT162b2 group and 2 in the original placebo group who received BNT162b2 after unblinding;

^Those with reported cause of death due to: aortic rupture, arteriosclerosis, cardiac arrest, cardiac failure congestive, cardiorespiratory arrest, hypertensive heart disease, or myocardial infarction

References

1. Health Canada. Health Canada authorizes use of the Pfizer-BioNTech COVID-19 vaccine in children 12 to 15 years of age. Published May 5, 2021. Accessed May 17, 2022. https://www.canada.ca/en/health-canada/news/2021/05/health-canada-authorizes-use-of-the-pfizer-biontech-covid-19-vaccine-in-children-12-to-15-years-of-age.html

2. Health Canada. Health Canada authorizes use of Comirnaty (the Pfizer-BioNTech COVID-19 vaccine) in children 5 to 11 years of age. Published November 19, 2021. Accessed May 17, 2022. https://www.canada.ca/en/health-canada/news/2021/11/health-canada-authorizes-use-of-comirnaty-the-pfizer-biontech-covid-19-vaccine-in-children-5-to-11-years-of-age.html

3. Public Health Agency of Canada. Guidance on booster COVID-19 vaccine doses in adolescents 12 to 17: NACI rapid response. Published February 4, 2022. Accessed May 17, 2022. https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/rapid-response-guidance-use-booster-covid-19-vaccine-doses-adolescents-12-17-years-age.html

4. Vaccines and Related Biological Products Advisory Committee June 14-15, 2022 Meeting Announcement - 06/14/2022. FDA. Published June 15, 2022. Accessed June 21, 2022. https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-14-15-2022-meeting-announcement

5. Public Health Agency of Canada. National Advisory Committee on Immunization (NACI): Meetings. Published June 17, 2022. Accessed June 21, 2022. https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/meetings.html

6. Health Canada. Drug and Health Product Submissions Under Review (SUR): Supplemental submissions under review. Published June 20, 2022. Accessed June 21, 2022. https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/submissions-under-review/supplemental-submissions-under-review.html

7. Tulchinsky TH, Varavikova EA. Measuring, monitoring, and evaluating the health of a population. *New Public Health*. Published online 2014:91-147. doi:10.1016/B978-0-12-415766-8.00003-3

8. Force LM, Abdollahpour I, Advani SM, *et al.* The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. *Lancet Oncol*. 2019;20(9):1211-1225.

9. Ma Q, Liu J, Liu Q, et al. Global percentage of asymptomatic SARS-CoV-2 infections among the tested population and individuals with confirmed COVID-19 diagnosis: A systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(12):e2137257. doi:10.1001/jamanetworkopen.2021.37257

10. Ledford H. Deaths from COVID 'incredibly rare' among children. *Nature*. 2021;595(7869):639-639. doi:10.1038/d41586-021-01897-w

11. Nuttall AG, Hedrich C, Semple C, *et al.* S57 Expression of the SARS-CoV-2 receptors ACE2 and TMPRSS2 in the respiratory tract of children and adults. *Thorax*. 2021;76(Suppl 2):A39-A39. doi:10.1136/thorax-2021-BTSabstracts.63

12. Loske J, Röhmel J, Lukassen S, *et al.* Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children. *Nat Biotechnol*. 2022;40(3):319-324. doi:10.1038/s41587-021-01037-9

13. Yoshida M, Worlock KB, Huang N, *et al.* Local and systemic responses to SARS-CoV-2 infection in children and adults. *Nature*. 2022;602(7896):321-327. doi:10.1038/s41586-021-04345-x

14. Dioguardi M, Cazzolla AP, Arena C, *et al.* Innate immunity in children and the role of ACE2 rxpression in SARS-CoV-2 infection. *Pediatr Rep*. 2021;13(3):363-382. doi:10.3390/pediatric13030045

15. Levy N, Koppel JH, Kaplan O, *et al.* Severity and incidence of Multisystem Inflammatory Syndrome in children during 3 SARS-CoV-2 pandemic waves in Israel. *JAMA*. Published online May 19, 2022. doi:10.1001/jama.2022.8025

16. Payne AB, Gilani Z, Godfred-Cato S, *et al*. Incidence of Multisystem Inflammatory Syndrome in children among US persons infected with SARS-CoV-2. *JAMA Netw Open*. 2021;4(6):e2116420. doi:10.1001/jamanetworkopen.2021.16420

17. Zimmermann P, Pittet LF, Curtis N. How common is Long COVID in children and adolescents? *Pediatr Infect Dis J*. 2021;40(12):e482. doi:10.1097/INF.0000000000003328

18. Zimmermann P, Pittet LF, Curtis N. Long COVID in children and adolescents. *BMJ*. 2022;376:o143. doi:10.1136/bmj.o143

19. Molteni E, Sudre CH, Canas LS, e*t al*. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. *Lancet Child Adolesc Health*. 2021;5(10):708-718. doi:10.1016/S2352-4642(21)00198-X

20. Gurdasani D, Akrami A, Bradley VC, *et al.* Long COVID in children. *Lancet Child Adolesc Health*. 2022;6(1):e2. doi:10.1016/S2352-4642(21)00342-4

21. Stephenson T, Pereira SMP, Shafran R, *et al*. Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLoCk): a national matched cohort study. *Lancet Child Adolesc Health*. 2022;6(4):230-239. doi:10.1016/S2352-4642(22)00022-0

22. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infect Dis*. 2021;21(1):855. doi:10.1186/s12879-021-06536-3

23. European Centre for Disease Prevention and Control. Risk factors and risk groups. Accessed May 12, 2022. https://www.ecdc.europa.eu/en/covid-19/latest-evidence/risk-factors-risk-groups

24. Centers for Disease Control and Prevention (U.S.). COVID-19 information for specific groups of people. Accessed May 12, 2022. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html

25. Centers for Disease Control and Prevention (U.S.). Underlying medical conditions associated with higher risk for severe COVID-19: Information for healthcare professionals. Accessed May 12, 2022. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

26. Joffe AR, Redman D. The SARS-CoV-2 Pandemic in High Income Countries Such as Canada: A Better Way Forward Without Lockdowns. *Front Public Health*. 2021;9. Accessed June 8, 2022. https://www.frontiersin.org/article/10.3389/fpubh.2021.715904

27. Ulloa AC, Buchan SA, Daneman N, Brown KA. Estimates of SARS-CoV-2 Omicron Variant Severity in Ontario, Canada. *JAMA*. 2022;327(13):1286-1288. doi:10.1001/jama.2022.2274

28. Ulloa AC, Buchan SA, Daneman N, Brown KA. Early estimates of SARS-CoV-2 Omicron variant severity based on a matched cohort study, Ontario, Canada. *medRxiv*. Published online January 1, 2022:2021.12.24.21268382. doi:10.1101/2021.12.24.21268382

29. Canadian Nosocomial Infection Surveillance Program. COVID-19 pediatric (<18 years) hospitalizations. Published May 12, 2021. Accessed July 4, 2022. https://albertaworker.ca/wp-content/uploads/2021/06/CNISP-Pediatric-COVID-19-Descriptive-Report_12May2021_v2.pdf

30. Clarke KEN, Jones JM, Deng Y, et al. Seroprevalence of infection-induced SARS-CoV-2 antibodies - United States, September 2021-February 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(17):606-608. doi:10.15585/mmwr.mm7117e3

31. Clarke KEN, Kim Y, Jones J, *et al.* Pediatric infection-induced SARS-CoV-2 seroprevalence estimation using commercial laboratory specimens: How representative is it of the general U.S. pediatric population? SSRN.com. Published April 26, 2022. Accessed May 13, 2022. https://papers.ssrn.com/abstract=4092074

32. Mallapaty S. Most US kids have caught the coronavirus, antibody survey finds. *Nature*. 2022;605(7909):207-207. doi:10.1038/d41586-022-01231-y

33.https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/covid19schoolsinfectionsurveyantibodydataengland (release date April 1, 2022)

34. Lee B, Raszka WV. COVID-19 in children: Looking forward, not back. *Pediatrics*. 2021;147(1):e2020029736. doi:10.1542/peds.2020-029736

35. Filippatos F, Tatsi EB, Michos A. Immune response to SARS-CoV-2 in children: A review of the current knowledge. *Pediatr Investig*. 2021;5(3):217-228. doi:10.1002/ped4.12283

36. Sørensen CA, Clemmensen A, Sparrewath C, Tetens MM, Krogfelt KA. Children naturally evading COVID-19—Why children differ from adults. *COVID*. 2022;2(3):369-378. doi:10.3390/covid2030025

37. Ludvigsson JF, Engerström L, Nordenhäll C, Larsson E. Open schools, Covid-19, and child and teacher morbidity in Sweden. *N Engl J Med*. 2021;384(7):669-671. doi:10.1056/NEJMc2026670

38. McSheffrey E. Spread of COVID-19 very low in Vancouver schools in 2021: data - BC | Globalnews.ca. Accessed May 27, 2022. https://globalnews.ca/news/8509433/covid-transmission-vancouver-schools-2021/

39. BC Children's Hospital Research Institute. Tracking COVID-19 for Safer Schools - Preliminary Study Results and Key Findings. Accessed June 21, 2022. https://www.bcchr.ca/sites/default/files/group-tracking-covid/preliminary-study-results-and-key-findings-school-study-may-15-2021.pdf

40. Majdoubi A, Michalski C, O'Connell SE, *et al.* A majority of uninfected adults show preexisting antibody reactivity against SARS-CoV-2. *JCI Insight*. 2021;6(8). doi:10.1172/jci.insight.146316

41. Government of Canada. COVID-19 vaccination in Canada. Published 2022. https://health-infobase.canada.ca/covid-19/vaccination-coverage/

42. Wolter N, Jassat W, Walaza S, *et al.* Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. *Lancet*. 2022;399(10323):437-446. doi:10.1016/S0140-6736(22)00017-4

43. Abdullah F, Myers J, Basu D, *et al.* Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in Tshwane, South Africa. *Int J Infect Dis*. 2022;116:38-42. doi:10.1016/j.ijid.2021.12.357

44. Madhi SA, Kwatra G, Myers JE, *et al.* Population immunity and Covid-19 severity with Omicron variant in South Africa. *N Engl J Med*. 2022;386(14):1314-1326. doi:10.1056/NEJMoa2119658

45. Chou J, Thomas PG, Randolph AG. Immunology of SARS-CoV-2 infection in children. *Nat Immunol*. 2022;23(2):177-185. doi:10.1038/s41590-021-01123-9

46. Garrido C, Hurst JH, Lorang CG, *et al.* Asymptomatic or mild symptomatic SARS-CoV-2 infection elicits durable neutralizing antibody responses in children and adolescents. *JCI Insight*. 2021;6(17):e150909. https://doi.org/10.1172/jci.insight.150909. doi:10.1172/jci.insight.150909

47. Cohen KW, Linderman SL, Moodie Z, *et al.* Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells. *Cell Rep Med*. 2021;2(7):100354. doi:10.1016/j.xcrm.2021.100354

48. Russell MW, Moldoveanu Z, Ogra PL, Mestecky J. Mucosal immunity in COVID-19: A neglected but critical aspect of SARS-CoV-2 infection. *Front Immunol*. 2020;11. Accessed May 12, 2022. https://www.frontiersin.org/article/10.3389/fimmu.2020.611337

49. Mallapaty S. Decades-old SARS virus infection triggers potent response to COVID vaccines. *Nature*. 2021;596(7873):471-472. doi:10.1038/d41586-021-02260-9

50. Tan CW, Chia WN, Young BE, *et al.* Pan-Sarbecovirus neutralizing antibodies in BNT162b2-immunized SARS-CoV-1 survivors. *N Engl J Med*. 2021;385(15):1401-1406. doi:10.1056/NEJMoa2108453

51. Klausner J, Kojima N. The CDC is finally recognizing 'natural immunity' — legislators should follow suit | The Hill. Accessed May 12, 2022. https://thehill.com/opinion/healthcare/592457-the-cdc-is-finally-recognizing-natural-immunity-legislators-should-follow/

52. Thomas SJ, Moreira ED, Kitchin N, *et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. *N Engl J Med*. 2021;385(19):1761-1773. doi:10.1056/NEJMoa2110345

53. Tian D, Sun Y, Xu H, Ye Q. The emergence and epidemic characteristics of the highly mutated SARS-CoV-2 Omicron variant. *J Med Virol*. 2022;94(6):2376-2383. doi:10.1002/jmv.27643

54. Yewdell JW. Individuals cannot rely on COVID-19 herd immunity: Durable immunity to viral disease is limited to viruses with obligate viremic spread. *PLoS Pathog*. 2021;17(4):e1009509. doi:10.1371/journal.ppat.1009509

55. Gazit S, Shlezinger R, Perez G, *et al.* SARS-CoV-2 naturally acquired immunity vs. vaccine-induced immunity, reinfections versus breakthrough infections: a retrospective cohort study. *Clin Infect Dis Off Publ Infect Dis Soc Am*. Published online April 5, 2022:ciac262. doi:10.1093/cid/ciac262

56. Nordström P, Ballin M, Nordström A. Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden. *Lancet Infect Dis*. 2022;22(6):781-790. doi:10.1016/S1473-3099(22)00143-8

57. Joshi M, Bartter T, Joshi A. We must stop ignoring natural immunity - it's now long overdue! BMJ. Published September 13, 2021. Accessed June 17, 2022. https://www.bmj.com/content/374/bmj.n2101/rr-0

58. Hall VJ, Foulkes S, Charlett A, *et al.* SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). *Lancet*. 2021;397(10283):1459-1469.

59. Harvey RA, Rassen JA, Kabelac CA, *et al.* Association of SARS-CoV-2 seropositive antibody test with risk of future infection. *JAMA Intern Med*. 2021;181(5):672-679. doi:10.1001/jamainternmed.2021.0366

60. Turner JS, Kim W, Kalaidina E, *et al.* SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans. *Nature*. Published online 2021:1-5.

61. Wang Z, Yang X, Zhong J, *et al.* Exposure to SARS-CoV-2 generates T-cell memory in the absence of a detectable viral infection. *Nat Commun*. 2021;12(1):1-8.

62. Cohen C, Lustig Y, Levin E, *et al.* Long-term humoral immunity of COVID-19 recovered and BNT162b2 vaccinated individuals: a prospective comparative study. European Congress of Clinical

Microbiology & Infectious Diseases (ECCMID 2022). Published 2022. Accessed June 2, 2022. https://drive.google.com/file/d/17Hjiz-d8JXsbTdVpmHQNpmKn_jvSWXIf/view

63. Ooi SL, Pak SC. Nutraceuticals in immune function. *Molecules*. 2021;26(17):5310. doi:10.3390/molecules26175310

64. Lordan R, Rando HM, COVID-19 Review Consortium, Greene CS. Dietary supplements and nutraceuticals under investigation for COVID-19 prevention and treatment. *mSystems*. 2021;6(3):e00122-21. doi:10.1128/mSystems.00122-21

65. Centers for Disease Control and Prevention (U.S.). People with certain medical conditions. Centers for Disease Control and Prevention. Published May 2, 2022. Accessed May 13, 2022. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

66. Health Canada. Paxlovid. COVID-19 vaccines and treatments portal. Accessed May 12, 2022. https://covid-vaccine.canada.ca/paxlovid/product-details

67. Health Canada. Veklury (remdesivir). COVID-19 vaccines and treatments portal. Accessed May 12, 2022. https://covid-vaccine.canada.ca/veklury/product-details

68. Health Canada. Evusheld. COVID-19 vaccines and treatments portal. Accessed May 12, 2022. https://covid-vaccine.canada.ca/evusheld/product-details

69. Health Canada. Bamlanivimab (bamlanivimab). COVID-19 vaccines and treatments portal. Accessed May 12, 2022. https://covid-vaccine.canada.ca/bamlanivimab/product-details

70. Health Canada. Casirivimab (casirivimab) and imdevimab (imdevimab). COVID-19 vaccines and treatments portal. Accessed May 12, 2022. https://covid-vaccine.canada.ca/casirivimab-and-imdevimab/product-details

71. Health Canada. Sotrovimab (sotrovimab). COVID-19 vaccines and treatments portal. Accessed May 12, 2022. https://covid-vaccine.canada.ca/sotrovimab/product-details

72. Clinical practice guideline summary: Recommended drugs and biologics in adult patients with COVID-19. Ontario COVID-19 Science Advisory Table. Published February 23, 2022. Accessed May 12, 2022. https://covid19-sciencetable.ca/sciencebrief/clinical-practice-guideline-summary-recommended-drugs-and-biologics-in-adult-patients-with-covid-19-version-11-0/

73. Chorney SR, Rizzi MD, Dedhia K. Considerations for povidone-iodine antisepsis in pediatric nasal and pharyngeal surgery during the COVID-19 pandemic. *Am J Otolaryngol.* 2020;41(6):102737. doi: 10.1016/j.amjoto.2020.102737.]

74. Pelletier JS, Tessema B, Frank S, Westover JB, Brown SM, Capriotti JA. Efficacy of povidone-iodine nasal and oral antiseptic preparations against severe acute respiratory syndrome-coronavirus

2 (SARS-CoV-2). *Ear Nose Throat J.* 2021;100(2_suppl):192S-196S. doi: 10.1177/0145561320957237.

75. Riemersma KK, Grogan BE, Kita-Yarbro A, *et al.* Vaccinated and unvaccinated individuals have similar viral loads in communities with a high prevalence of the SARS-CoV-2 delta variant. *medRxiv*. Published online July 31, 2021:2021.07.31.21261387. doi:10.1101/2021.07.31.21261387

76. Singanayagam A, Hakki S, Dunning J, *et al.* Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. *Lancet Infect Dis*. 2021;0(0). doi:10.1016/S1473-3099(21)00648-4

77. Acharya CB, Schrom J, Mitchell AM, *et al.* Viral load among vaccinated and unvaccinated, asymptomatic and symptomatic persons infected with the SARS-CoV-2 Delta variant. *Open Forum Infect Dis*. 2022;9(5):ofac135. doi:10.1093/ofid/ofac135

78. Pouwels KB, Pritchard E, Matthews PC, *et al.* Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *Nat Med*. 2021;27(12):2127-2135. doi:10.1038/s41591-021-01548-7

79. Shitrit P, Zuckerman NS, Mor O, Gottesman BS, Chowers M. Nosocomial outbreak caused by the SARS-CoV-2 Delta variant in a highly vaccinated population, Israel, July 2021. *Eurosurveillance*. 2021;26(39):2100822. doi:10.2807/1560-7917.ES.2021.26.39.2100822

80. Fowlkes AL, Yoon SK, Lutrick K, *et al.* Effectiveness of 2-dose BNT162b2 (Pfizer BioNTech) mRNA vaccine in preventing SARS-CoV-2 infection among children aged 5-11 years and adolescents aged 12-15 years - PROTECT cohort, July 2021-February 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(11):422-428. doi:10.15585/mmwr.mm7111e

81. Frenck RW Jr, Klein NP, Kitchin N, *et al.* Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *N Engl J Med*. 2021;385(3):239-250. doi:10.1056/NEJMoa2107456

82. Walter EB, Talaat KR, Sabharwal C, *et al.* Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. *N Engl J Med*. 2022;386(1):35-46. doi:10.1056/NEJMoa2116298

83. CDC COVID-19 Response Team. SARS-CoV-2 B.1.1.529 (Omicron) variant - United States, December 1-8, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(50):1731-1734. doi:10.15585/mmwr.mm7050e1

84. Dorabawila V, Hoefer D, Bauer UE, Bassett MT, Lutterloh E, Rosenberg ES. Risk of infection and hospitalization among vaccinated and unvaccinated children and adolescents in New York after the emergence of the Omicron variant. *JAMA*. Published online May 13, 2022. doi:10.1001/jama.2022.7319

85. Dorabawila V, Hoefer D, Bauer UE, Bassett MT, Lutterloh E, Rosenberg ES. Effectiveness of the BNT162b2 vaccine among children 5-11 and 12-17 years in New York after the emergence of the

Omicron variant. Accessed May 27, 2022. https://www.medrxiv.org/content/10.1101/2022.02.25.22271454v1

86. Benn CS, Schaltz-Buchholzer F, Nielsen S, Netea MG, Aaby P. Randomised clinical trials of COVID-19 vaccines: Do adenovirus-vector vaccines have beneficial non-specific effects? Published April 5, 2022. Accessed May 12, 2022. https://papers.ssrn.com/abstract=4072489

87. Xu L, Ma Z, Li Y, Pang Z, Xiao S. Antibody dependent enhancement: Unavoidable problems in vaccine development. *Adv Immunol*. 2021;151:99-133. doi:10.1016/bs.ai.2021.08.003

88. Gartlan C, Tipton T, Salguero FJ, Sattentau Q, Gorringe A, Carroll MW. Vaccine-associated enhanced disease and pathogenic human coronaviruses. *Front Immunol*. 2022;13. Accessed May 13, 2022. https://www.frontiersin.org/article/10.3389/fimmu.2022.882972

89. Wherry EJ. T cell exhaustion. *Nat Immunol*. 2011;12(6):492-499. doi:10.1038/ni.2035

90. Kaminski H, Lemoine M, Pradeu T. Immunological exhaustion: How to make a disparate concept operational? *PLOS Pathog*. 2021;17(9):e1009892. doi:10.1371/journal.ppat.1009892

91. Johnson PLF, Kochin BF, McAfee MS, *et al.* Vaccination alters the balance between protective immunity, exhaustion, escape, and death in chronic infections. *J Virol*. 2011;85(11):5565-5570. doi:10.1128/JVI.00166-11

92. Azim Majumder MA, Razzaque MS. Repeated vaccination and 'vaccine exhaustion': relevance to the COVID-19 crisis. *Expert Rev Vaccines*. 2022;0(0):1-4. doi:10.1080/14760584.2022.2071705

93. Regev-Yochay G, Gonen T, Gilboa M, *et al.* 4th Dose COVID mRNA vaccines' immunogenicity & efficacy against Omicron VOC. Published online February 15, 2022:2022.02.15.22270948. doi:10.1101/2022.02.15.22270948

94. Karlstad Ø, Hovi P, Husby A, *et al.* SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. *JAMA Cardiol.* 2022;7(6):600-612. doi:10.1001/jamacardio.2022.0583

95. Tuvali O, Tshori S, Derazne E, Hannuna RR, Afek A, *et al.* The incidence of myocarditis and pericarditis in post COVID-19 unvaccinated patients—A large population-based study. *J. Clin. Med.* 2022; *11*(8), 2219; https://doi.org/10.3390/jcm11082219

96. Baumeier C, Aleshcheva G, Harms D, Gross U, Hamm C, *et al.* Intramyocardial inflammation after COVID-19 vaccination: An endomyocardial biopsy-proven case series. Int. J. Mol. Sci. 2022; 23(13), 6940. https://doi.org/10.3390/ijms23136940

97. Lee WS, Wheatley AK, Kent SJ, DeKosky BJ. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. Nat Microbiol. 2020 Oct;5(10):1185-1191. doi: 10.1038/s41564-020-00789-5

98. Noori M, Nejadghadaderi SA, Rezaei N. "Original antigenic sin": A potential threat beyond the development of booster vaccination against novel SARS-CoV-2 variants. Infection Control & Hospital Epidemiol., 2021: 1-2. doi:10.1017/ice.2021.199

99. Follmann D, Janes HE, Buhule OD, *et al.* Anti-nucleocapsid antibodies following SARS-CoV-2 infection in the blinded phase of the mRNA-1273 Covid-19 vaccine efficacy clinical trial. medRxiv 2022.04.18.22271936. doi: https://doi.org/10.1101/2022.04.18.22271936

100. Hause AM, Baggs J, Marquez P, *et al.* Safety monitoring of COVID-19 vaccine booster doses among persons aged 12-17 years - United States, December 9, 2021-February 20, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(9):347-351. doi:10.15585/mmwr.mm7109e2

101. Lazarus R. Electronic Support for Public Health-Vaccine Adverse Event Reporting System (esp: Vaers)-Final Report. (Prepared by Harvard Pilgrim Health Care, Inc. Under Grant No. R18 Hs017045). Published 2011. https://digital.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf

102. United States Department of Health and Human Services (DHHS), Public Health Service (PHS), Centers for Disease Control (CDC) / Food and Drug Administration (FDA), Vaccine Adverse Event Reporting System (VAERS) 1990 - 04/29/2022, CDC WONDER On-line Database. Accessed May 12, 2022. http://wonder.cdc.gov/vaers.html

103. Oster ME, Shay DK, Su JR, *et al.* Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US From December 2020 to August 2021. *JAMA*. 2022;327(4):331-340. doi:10.1001/jama.2021.24110

104. Sun CLF, Jaffe E, Levi R. Increased emergency cardiovascular events among under-40 population in Israel during vaccine rollout and third COVID-19 wave. *Sci Rep*. 2022;12(1):6978. doi:10.1038/s41598-022-10928-z

105. Karlstad Ø, Hovi P, Husby A, *et al.* SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. *JAMA Cardiol*. Published online April 20, 2022. doi:10.1001/jamacardio.2022.0583

106. Patone M, Mei XW, Handunnetthi L, *et al.* Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. *Nat Med*. 2022;28(2):410-422. doi:10.1038/s41591-021-01630-0

107. Chua GT, Kwan MYW, Chui CSL, et al. Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents following Comirnaty vaccination. *Clin Infect Dis Off Publ Infect Dis Soc Am*. Published online November 28, 2021:ciab989. doi:10.1093/cid/ciab989

108. Buchan SA, Seo CY, Johnson C, *et al.* Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval. Published online December 5, 2021:2021.12.02.21267156. doi:10.1101/2021.12.02.21267156

109. Government of Ontario. Ontario recommends the use of Pfizer-BioNTech COVID-19 vaccine for individuals aged 18-24 Years old. news.ontario.ca. Accessed June 17, 2022. https://news.ontario.ca/en/statement/1000907/ontario-recommends-the-use-of-pfizer-biontech-covid-19-vaccine-for-individuals-aged-18-24-years-old

110. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Adverse events following immunization (AEFIs) for COVID-19 in Ontario: December 13, 2020 to May 8, 2022. Published May 13, 2022. Accessed May 27, 2022. https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-aefi-report.pdf?sc_lang=en

111 Daniels CJ, Rajpal S, Greenshields JT, *et al.* Prevalence of clinical and subclinical myocarditis in competitive athletes with recent SARS-CoV-2 infection: Results from the Big Ten COVID-19 Cardiac Registry. *JAMA Cardiol*. 2021;6(9):1078-1087. doi:10.1001/jamacardio.2021.2065

112. Grün S, Schäufele T, Derin T, *et al.* Long-term follow-up after viral myocarditis established by endomyocardical biopsy: Predictors of mortality. *J Cardiovasc Magn Reson*. 2011;13(1):M7. doi:10.1186/1532-429X-13-S1-M7

113. Kang M, An J. Viral Myocarditis. In: *StatPearls*. StatPearls Publishing; 2022. Accessed May 27, 2022. http://www.ncbi.nlm.nih.gov/books/NBK459259/

114. Pfizer. 5.3.6 Cumulative analysis of post-authorization adverse event reports (report to the FDA). Published 2021. https://phmpt.org/wp-content/uploads/2021/11/5.3.6-postmarketing-experience.pdf

115. https://www.hartgroup.org/open-letter-regarding-covid-vaccines-for-0-4-yrs/

116. https://europe-cities.com/2022/06/27/denmark-admits-in-retrospect-we-did-not-get-much-out-of-vaccinating-the-children/

117.https://www.pei.de/SharedDocs/Downloads/DE/newsroom/dossiers/sicherheitsberichte/sicherheitsbericht-27-12-bis-31-08-21.pdf?__blob=publicationFile&v=5