Negative COVID-19 Vaccine Effectiveness: Examining the Validity of the Assumptions

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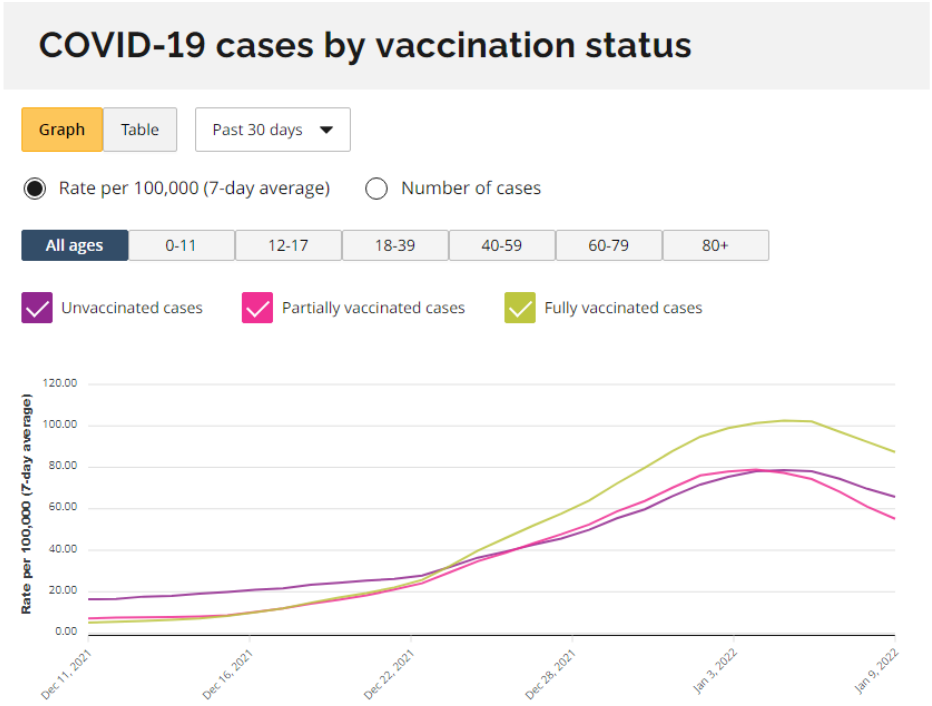
COVID-19 vaccination has been associated with increased rates of SARS-CoV-2 infection (*i.e.*, negative vaccine efficacy). Findings of negative vaccine effectiveness may be due to a number of factors, not all necessarily directly related to a vaccine's performance. When looking at the unadjusted rates of infection and hospitalization related to COVID-19, in such places as Ontario, Canada, and the United Kingdom (UK), some assumptions were put forward to explain the appearance of an enhanced risk of infection that would not be due to the vaccines. However, these assumptions need to be examined in light of evidence to the contrary. Additionally, the possibility of increased susceptibility to SARS-CoV-2 infections among vaccinated individuals is supported by government serological reports and peer-reviewed biological studies.

A. Ontario surveillance data during the first Omicron wave

According to data from the Ontario Ministry of Health, COVID-19 case numbers increased dramatically from December 23, 2021 to January 5, 2022 (see graph below). Of note, the rate of COVID-19 cases was remarkably higher in the vaccinated group compared to the unvaccinated group. Reporting the number of cases as a rate (*i.e.*, number of cases by vaccination status for every 100,000 people with the same vaccination status) increases the comparability between the two groups, regardless of the proportion of vaccinated individuals in the population. This data representation is particularly important given that over 85% of the Ontario population was already fully vaccinated during this period.



[Source: https://covid-19.ontario.ca/data/case-numbers-and-spread]

In December 2021, infections due to the newly emerging Omicron variant quickly exceeded infections due to the Delta variant.[1] Furthermore, the rate of infection rose faster among the vaccinated than among the unvaccinated. Based on infections recorded between December 6 and 26, 2021 (extent of symptoms not yet specified), Buchan and colleagues attempted to explain the observed "negative vaccine effectiveness" of - 38%, for those who had received their last vaccine dose 4 to 6 months earlier, and - 42%, for those who had received their last vaccine dose 6 to 8 months earlier.[2,3,4] Their proposed explanations centered on differential testing practices or differential exposures, rather than vaccine performance, as follows:

- The data could be showing testing bias, where the frequency of testing by certain vaccinated groups such as healthcare workers would be much greater than the frequency of testing within the unvaccinated population; this would mean that a large number of positive cases of infection among the unvaccinated could have remained unidentified;

- Vaccinated individuals were more likely to get infected than unvaccinated individuals, because they were not barred from travelling or from social gatherings under vaccine passport policy, and these activities increased the likelihood of viral exposure—these types of behavior would be expected of a younger population; and

- Cases identified during the early phase of the Omicron wave, and covered by this study, were younger, compared to the negative-test group, supporting the assumption presented above about increased risk exposure among the vaccinated.

The assumption that vaccinated individuals could have been tested more often than unvaccinated individuals is not very strong. There are major accounts of the unvaccinated being subjected to more targeted precautionary measures when exposed to positive cases, and being subjected to regular and frequent testing as an accommodation arrangement for staying on the job, while this directive did not apply to vaccinated staff in workplaces such as healthcare institutions.[5-7] Likewise, in universities and colleges, unvaccinated students were often subjected to PCR and/or rapid antigen testing for SARS-CoV-2 infection, which was not required for COVID-19 vaccinated students. Furthermore, multiple testing samples among frequently tested unvaccinated individuals are likely to yield higher case counts due to the possible inability of data collection systems to avoid overcounting the same cases of infection.[8,9]

The likelihood of a skewed number of positive cases in the direction of the unvaccinated, relative to the vaccinated, is more plausible regarding bias due to differential testing policies. Additionally, test result duplication would lead to an over-representation within the unvaccinated group. Moreover, those that developed COVID-19 within two to three weeks of initial COVID-19 vaccination have been routinely counted as unvaccinated COVID-19 cases by public health authorities. This is despite evidence that in the first two weeks after vaccination there is an increased risk of acquiring COVID-19.[10] Yet, the number of positive cases among unvaccinated individuals has been surpassed by the number of positive cases among vaccinated

individuals, as shown in the graph above. All in all, greater susceptibility of vaccinated people to infection from viral variants, beyond the known initial period of increased risk, cannot be ruled out.

It is possible that vaccinated individuals were more likely exposed to the SARS-CoV-2 virus than unvaccinated individuals, because of vaccine passport policies. However, Buchan and colleagues did also acknowledge that vaccinated individuals may have been more susceptible to infection, when they did get exposed to the virus, due to the biological phenomenon of "antigenic imprinting."[2] When these researchers conducted their analyses using only cases with available symptom information, vaccine effectiveness was no longer negative.[3,4] Nevertheless, they identified similar possible biases, such as differential testing practices, and other limitations like cases being excluded due to missing symptom information. If unvaccinated individuals were more likely to get tested and more likely to have their symptoms recorded when being tested, then vaccine effectiveness would have been overestimated. A more accurate estimate could still yield a negative value.

B. United Kingdom's unadjusted rates of infection and hospitalization per vaccination status

In two samples of UK surveillance reports,[10,11] increased infection rates among the vaccinated were found for all age groups above the age of 17, but to a lesser extent in the older age ranges. A greater risk of exposure among vaccinated people, relative to unvaccinated people, could still be possible. If one assumes that younger vaccinated people would more likely become infected due to increased socializing opportunities, then a reduced trend of infection would be expected among the older vaccinated groups who tend to lead an isolated life more frequently. Although such a finding lends support to the assumption of reduced exposure risk among older people, a negative rate difference was still observed for this segment of the population.

These reports caution against making conclusions based on raw, unadjusted data due to hidden biases. Nevertheless, in the tables shown below, unadjusted rate differences between vaccinated and unvaccinated categories have been calculated for comparison purposes. These rate differences reflect trends within the population, which may be capturing differences in possible contributing factors such as exposure levels, underlying health status, and testing behavior (making up hidden biases), as well as susceptibility to infection, across the two groups.

Table 1. COVID-19 vaccine surveillance report: Week 1, 6 January 2022

	Cases reported by specimen date between week 49 2021 (w/e 8 December 2021) and week 52 2021 (w/e 2 January 2022)			**Cases presenting to emergency care (within 28 days of a positive test) resulting in overnight inpatient admission, by specimen date between week 49 and week 52, 2021**	
	Unadjusted rates among persons vaccinated with 2 doses (per 100,000)	Unadjusted rate differences	Unadjusted rates among persons not vaccinated (per 100,000)	Unadjusted rates among persons vaccinated with 2 doses (per 100,000)	Unadjusted rates among persons not vaccinated (per 100,000)
Under 18	1,827.4	38 %	2,961.6	2.0	7.6
18 to 29	7,221.4	-123 %	3,240.8	6.3	12.7
30 to 39	6,383.9	-138 %	2,686.6	7.1	19.4
40 to 49	5,393.8	-151 %	2,147.2	8.6	33.5
50 to 59	3,738.4	-117 %	1,721.9	10.2	58.8
60 to 69	2,266.3	-90 %	1,194.3	13.0	91.4
70 to 79	1,347.6	-56 %	862.0	20.5	143.4
80 or over	1,055.0	-7 %	981.5	55.0	260.3

[Copied from Table 13, p. 42, in reference #11]

Even recipients of a third vaccine dose follow a similar trend of increased risk of infection, although the gap seems to be worsening, as presented in the next table.

Table 2. COVID-19 vaccine surveillance report: Week 8, 24 February 2022

	Cases reported by specimen date between week 4 2022 (w/e 30 January 2022) and week 7 2022 (w/e 20 February 2022)			**Cases presenting to emergency care (within 28 days of a positive test) resulting in overnight inpatient admission, by specimen date between week 4 2022 (w/e 30 January 2022) and week 7 2022 (w/e 20 February 2022)**	
	Unadjusted rates among persons vaccinated with at least 3 doses (per 100,000)	Unadjusted rate differences	Unadjusted rates among persons not vaccinated (per 100,000)	Unadjusted rates among persons vaccinated with at least 3 doses (per 100,000)	Unadjusted rates among persons not vaccinated (per 100,000)
Under 18	1,416.3	53 %	2,984.6	2.2	11.1
18 to 29	3,089.8	-157 %	1,200.6	5.8	6.5
30 to 39	3,833.8	-204 %	1,260.7	6.3	7.8
40 to 49	3,700.7	-226 %	1,136.8	6.2	8.6
50 to 59	2,244.7	-193 %	765.4	7.1	14.3
60 to 69	1,589.6	-200 %	530.7	11.1	29.8
70 to 79	1,094.8	-143 %	450.2	24.7	72.1
80 or over	1,178.4	-59 %	739.3	79.9	159.8

[Copied from Table 13, p. 45, in reference #12]

Based on the hospital admission data found in Tables 1 and 2, there seems to be a trend of an increased need for emergency care among unvaccinated infected individuals when expressed in relative terms. When considering the unlikelihood of the assumptions used to explain away negative vaccine effectiveness, the unvaccinated do appear less likely to become infected. The most important outcome is a reduction in the risk of symptomatic infection, which avoids hospital admissions altogether. Should symptoms occur, the second most important outcome relates to the recovery process. Lack of early home treatment is actually what is driving the need for emergency care due to COVID-19 in both vaccinated and unvaccinated individuals.[13]

In the UK, COVID-19 surveillance reports, assumptions have been proposed to uncover systematic differences between the vaccinated and unvaccinated groups. Group differences offer possible explanations as to the observed differential rates of infection. In Table 3, these assumptions (as the basis of biases) are examined more closely for their validity, while acknowledging the possibility that the vaccines may be increasing the risk of infection.

Table 3. Critical analysis of assumptions used to explain negative vaccine effectiveness

Proposed explanations for increased infection rates among the vaccinated [11,12]	**Critical analysis**
"many of those who were at the head of the queue for vaccination are those at higher risk from COVID-19 due to their age, their occupation, their family circumstances or because of underlying health issues"	This explanation for a higher rate of infection among the vaccinated (*i.e.*, older, less healthy) would more likely apply in the beginning of the vaccine roll-out, either for the primary series or booster shot. Indeed, there was an observed spike of COVID-19 cases in the elderly coincident with triple vaccination in primarily those over 70 years of age and older in Scotland in the Fall of 2021.[14] The data shown above have not only been stratified according to age but also pertain to late-stage vaccine roll-out, when diverse segments of the population with varied health status and life circumstances would have already been vaccinated from December 2021 through to February 2022. In particular, increased rates of infection among the vaccinated, compared to the unvaccinated, were also found in the younger age groups, where age and pre-existing chronic conditions would not be major contributing factors in the risk of infection.
"people who are fully vaccinated may be more health conscious and therefore more likely to get tested for COVID-19 and so more likely to be identified as a case (based on the data provided by the NHS Test and Trace)"	It cannot be assumed that vaccinated people are more likely to get tested. During test and trace campaigns, the ways in which these programs were undertaken could have influenced the test-seeking behavior of vaccinated people. Testing behavior

"*testing behaviour is likely to be different between people with different vaccination status, resulting in differences in the chances of being identified as a case*"	under these circumstances cannot be generalized to the vaccinated population at large. Health-conscious individuals may just as well have such confidence in the effectiveness of vaccines that they would see no need to get tested once vaccinated, even when having flu-like symptoms. By contrast, unvaccinated people are more likely to have greater motivation to get tested (*e.g.*, job requirements, admission to colleges and universities, visit requirements).[5-7]
"people who are fully vaccinated and people who are unvaccinated may behave differently, particularly with regard to social interactions and therefore may have differing levels of exposure to COVID-19"	Vaccinated people may tend to socialize preferentially with other vaccinated people (either during large family gatherings, where unvaccinated members are being excluded, at venues such as churches, restaurants and movie theatres, or at larger events that require vaccine passports), and choose to physically distance themselves from unvaccinated people. However, this behavior would not solely lead to differences in exposure level. It could just as well bring about opportunities for greater viral transmission among vaccinated individuals, than among unvaccinated individuals, as indication of increased susceptibility to infection following vaccination. As an additional consideration, household exposure is a main way through which the virus spreads, and infected household members have the same peak viral load, regardless of vaccination status, for comparable transmissibility.[15]
"*people who have never been vaccinated are more likely to have caught COVID-19 in the weeks or months before the period of the cases covered in the report. This gives them some natural immunity to the virus which may have contributed to a lower case rate in the past few weeks*"	The matter at hand is how effective are the vaccines under the current circumstances. If a considerable proportion of the population already has natural immunity, vaccination campaigns would thus be required to a much lesser extent. Vaccination requirements need to be based on risk assessments and not be applied universally.

Vaccinated people may be more frequently exposed to the virus than unvaccinated people, but this possibility would not necessarily negate the occurrence of increased risk of infection following vaccination. Indeed, negative vaccine effectiveness is supported by government serological reports and peer-reviewed biological studies.

C. Government serological reports and biological studies supporting the findings of negative vaccine effectiveness

C1. Evidence of immune suppression in vaccinated individuals

Serological reports show immune suppression in vaccinated individuals, pointing to increased susceptibility to infection. Regularly, the UK Health Security Agency participates in efforts to monitor the impact of vaccination campaigns on COVID-19-related antibodies in individuals within their population base. This monitoring includes measuring antibody prevalence among blood donors aged 17 years and older in England. Data on antibody levels yielded evidence of increased risk of vaccine-associated enhanced disease. The data of interest involved antibodies against the SARS-CoV-2 nucleocapsid (N) protein for which presence in the blood indicates a viral infection.[16] Blood donors who were fully vaccinated and then became infected with the virus had lower than expected levels of N antibodies:

> *Seropositivity estimates for N antibody will underestimate the proportion of the population previously infected due to (i) blood donors are potentially less likely to be exposed to natural infection than age matched individuals in the general population (ii) waning of the N antibody response over time and (iii) recent observations from UK Health Security Agency (UKHSA) surveillance data that N antibody levels appear to be lower in individuals who acquire infection following 2 doses of vaccination.*[16 (p. 23)]

The presence of N antibodies in the blood represents an immune response to a viral infection, while antibodies against the spike protein may arise from either infection or vaccination. Vaccinated people who subsequently became infected with SARS-CoV-2 were found to have a diminished ability to produce neutralizing antibodies against the N-protein. The question is, could this reduced immune response contribute to the enhancement of infection, given that the N-protein is hidden within the encapsulated virus and not readily accessible for neutralization by antibodies circulating in the bloodstream?

Novel vaccine development research has targeted the N-protein as a potentially more suitable vaccine antigen candidate, since it is less prone to mutations than the spike protein.[17,18] The immune system's production of antibodies against N-protein could offer another possible way of keeping the infection from spreading further within the body. During the initial stage of infection, Thura and colleagues suggested that the N-protein of incompletely assembled viral particles could be released into the bloodstream following lysis of the infected cells, thereby triggering the production of antibodies against it.[19] It is

thought that these antibodies would contribute to the destruction of other infected cells, displaying the N-protein or its fragments on their surface. Regardless of the role of the N antibodies, lower than expected levels of N antibodies in infected vaccine recipients would be an indication of an impaired immune response, in general.

Serological studies that demonstrate impaired immune responses provide a plausible explanation for negative vaccine effectiveness, especially when such a finding involves epidemiological data on low-risk populations. In a large study of COVID-19 vaccination effectiveness in children and youth living in New York State, the relative risk reduction effectiveness of the Pfizer/BioNTech's BNT162b2 vaccine after double vaccination for 365,502 children aged 5 to 11 years old during the Omicron surge was only 12% for about a month, and for 852,384 teenagers aged 12 to 17 years-old, it was only 51% during the peak of Omicron cases.[20] After just 41 days following full vaccination in the 5-11 years-old cohort, there was already an observable negative 41% relative risk reduction in vaccine effectiveness compared to the unvaccinated, *i.e.*, the vaccinated children were more likely to get infected with Omicron than unvaccinated children.

In view of these studies, the short-term and long-term health implications of a vaccine-associated risk of suppressed immune response to a SARS-CoV-2 infection warrants much further investigation. It would seem that for many people, repeated booster injections of the COVID-19 vaccines may in fact be counterproductive, especially for the younger populations that are at low risk from severe COVID-19.

C2. Evidence of immune imprinting

There exists other supporting evidence of reduced ability to ward off infection among recipients of COVID-19 vaccines. Serological studies on breakthrough cases of COVID-19 have confirmed that immune imprinting (also referred to as antigenic imprinting) can happen.[21] It is a phenomenon known to occur when the body's initial production of antibodies against a specific virus conditions the immune system to produce the exact same antibodies in response to a subsequent exposure to this virus, even after it has undergone substantial mutations and these antibodies are no longer optimal for neutralizing it.[22] Immune, or antigenic, imprinting would be contributing to negative vaccine effectiveness, by causing an inadequate immune response to a mutated form (variant) of the virus that the vaccine was meant to protect against.

The COVID-19 vaccines were based on the spike protein of the original Wuhan strain, which is known to rapidly mutate, and the initial vaccine-generated antibody production against this spike protein may get imprinted at the immune cellular level. This means that upon subsequent exposure to a SARS-CoV-2 variant, the immune system would be set to induce the production of antibodies still aimed at the spike protein of the ancestral Wuhan virus, no longer in circulation. As Röltgen and colleagues reported,

> *We find that prior vaccination with Wuhan-Hu-1-like antigens [spike protein] followed by infection with Alpha or Delta variants gives rise to plasma antibody responses with apparent Wuhan-Hu-1-specific imprinting manifesting as relatively decreased responses to the variant virus epitopes, compared with unvaccinated patients infected with those variant viruses. … The extent to which vaccine boosting … [will] increase [ineffective] responses to the epitopes of antigens encountered previously, as in the "original antigenic sin" phenomenon …, will be an important topic of ongoing study.*[21]

Based on these findings, the risk of vaccine-associated enhanced disease is a valid vaccine safety concern. Furthermore, this risk may be greater with variants that are highly mutated, such as the Omicron strain, even though these variants may be milder than their predecessors. A worsening of a SARS-CoV-2 infection due to an inadequate immune response, rather than a more virulent viral strain, could be behind more serious cases of COVID-19 among vaccinated individuals.

C3. Vaccine-associated risk of enhanced disease in vaccinated individuals

COVID-19 vaccines generate antibodies against the spike protein of the original Wuhan virus strain. These antibodies are meant to prepare the immune system to target the spike proteins on the surface of an invading SARS-CoV-2 virus. However, they can either reduce or enhance viral infection. Risk of vaccine-associated antibody-dependent enhancement (ADE) of infection may manifest when, following vaccination, the binding activity of "enhancing antibodies" overwhelm that of "neutralizing antibodies."

Through molecular modeling simulation, Yahi and colleagues studied changes in the binding activity of the two main types of antibodies produced by the vaccines, as the virus mutated.[23] They showed that neutralizing antibodies had a greater affinity for the Wuhan virus' spike protein than enhancing antibodies had. Neutralizing antibodies bind to the virus' spike proteins in such a way as to block it from entering host cells within the body. By contrast, enhancing antibodies had a greater affinity for the Delta variant's spike protein than neutralizing antibodies had. Enhancing antibodies bind to the virus' spike proteins in such a way as to enable it to more firmly attach itself to the surface of the host immune cells; this stabilizing mechanism facilitates viral entry and infection. These researchers concluded the following:

> *ADE may occur in people receiving vaccines based on the original Wuhan strain spike sequence (either mRNA or viral vectors) and then exposed to a Delta variant. … Since our data indicate that Delta variants are especially well recognized by infection enhancing antibodies targeting the NTD [N-terminal part of the spike protein], the possibility of ADE should be further investigated as it may represent a potential risk for mass vaccination during the current Delta variant pandemic.*[23]

Vaccinated individuals who became exposed to the Delta variant may have been susceptible to infection enhancement. This would also have implications for the Omicron variant with its additional mutations. Even Health Canada has acknowledged the theoretical possibility of vaccine-associated enhanced disease.[24]

D. Conclusion

Evidence is accumulating on vaccine-related enhanced risk of infection. Changes in the binding activities of vaccine-generated antibodies according to mutations in the spike protein provide one plausible biological mechanism for enhanced entry of viral variants into host immune cells leading to infection. Adding to this evidence, serological data reveal suppressed or inadequate immune responses among the vaccinated. Epidemiological analyses of vaccine effectiveness that fail to take into account such biological factors may be producing biased results, masking increased susceptibility to infection among vaccinated individuals. Direct findings of negative vaccine effectiveness signal the need to look beyond vaccination for more effective ways to control the spread of COVID-19.

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