Review

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Pre-Existing Immunity to COVID-19: Overview and Implications — Part 3

Rachel Nicoll[1]

Abstract

This review article is comprised of three parts; Part 1 introduced the subject and investigated how other coronaviruses provided pre-existing immunity to SARS-CoV-2, Part 2 looked at pre-existing immunity from other micro-organisms and this part (Part 3) investigates pre-existing immunity from non-COVID vaccinations and discusses the article as a whole. Observational studies found that the prior administration of live attenuated vaccines (BCG, influenza, oral polio, herpes zoster, MMR and DTP) were associated with lower incidence and/or severity of COVID-19. Clinical trials of vaccination during the COVID-19 pandemic, however, showed mixed results, with BCG trials proving to be indeterminate although a trial of MMR vaccination showed it was associated with reduced risk of symptomatic infection. More research is required to explain anomalous results and to determine the precise mechanism(s) of pre-existing immunity. Overall, the presence of pre-existing immunity from coronaviruses, malaria, commensal bacteria and vaccines has implications for the development of vaccines against COVID-19; if a significant proportion of the population already has some immunity, the need for those vaccines is reduced. Furthermore, it is unknown whether pre-existing immunity will enhance the anti-COVID-19 vaccines or will work against them to create adverse reactions.

Keywords: COVID-19, SARS-CoV-2, pre-existing immunity, cross-reactivity, vaccines

Pre-existing immunity from vaccination

Since 1796, vaccines have been used to help prevent disease by injecting an inactivated strain of the virus in question, but few studies have examined whether these vaccines might protect against other viruses as well. In fact, certain live attenuated vaccines may indeed protect against SARS-CoV-2. (1,2)

[1] London, UK

Corresponding author:
Rachel Nicoll, PhD
London, UK
Email: covidtherealscience@gmail.com

Bacillus Calmette-Guerin (BCG) vaccine

A wealth of studies have reported that countries with pre-existing BCG vaccination had fewer confirmed COVID-19 cases and mortality, both at the population and the individual level. (3-29) A 2022 meta-analysis found significantly lower SARS-CoV-2 incidence in those with prior BCG vaccination compared to the control group, (30) and several studies have shown decreased severity, duration of illness and viral load with prior BCG vaccination. (23,29,31,32) Curiously, two studies found that the BCG vaccine may not protect against severe COVID but could reduce mortality. (33,34) In elderly patients prior BCG vaccination was associated with reduced pro-inflammatory cytokines, (35) suggesting that it could also protect against the hyper-inflammation commonly seen in the elderly with severe COVID. Several authors suggest, however, that in these studies there may have been been inadequate adjustment for bias and confounding factors.

It has been suggested that the BCG strain may influence results (successful trials were carried out using the Japan strain), while the definitions of COVID-19, severe COVID-19 and end points may differ between trials. (38,39) Furthermore, age at BCG vaccination may make a difference; it is known to have a protective effect against other viruses when given to neonates and infants when the immune system is more susceptible to modulation. (39)

Because prior BCG vaccination appeared to confer protection, several trials of vaccination were carried out during the pandemic; meta-analyses and reviews showed conflicting results or no protection. (38,40,41) It is worth noting that studies showing BCG vaccination to be protective against COVID-19 were all observational studies and not clinical trials. Other potential explanations include the recipients being adults, whereas normally this vaccine is given to infants, as well as the COVID-19 vaccines themselves, since although the BCG trials began on the unvaccinated, most of the trial participants received the COVID-19 vaccine during the course of the trial. (40) Additionally, because the vaccine induces a pro-inflammatory state with strong cytokine responses, it could make recipients temporarily more susceptible to severe COVID-19, whereas if vaccination occurred prior to the pandemic, the inflammation would have had time to resolve.

Influenza

Most influenza vaccine studies demonstrate a significantly reduced incidence of COVID-19 infection compared to those who had not been vaccinated. (42–48) as well as reduced disease severity, including mortality. (43–52) Although one study only found benefit for those aged <65 years, (53) others showed that the elderly also had lower incidence and less severe disease, (47–49,54) as well as children and adolescents. (55) A meta-analysis of 38 observational studies found that seasonal influenza vaccination was associated with a lower risk of COVID-19 infection, although it did not protect against ICU admission and death and some of the studies may not have adjusted for all confounders. (56) Interestingly, although the influenza vaccine was largely protective, pre-exposure through influenza infection was not protective, as discussed in Part 2. Nevertheless, a couple of studies have shown that prior influenza vaccination was not associated with a lower incidence or severity of COVID infection or a shorter duration of symptoms. (57,58)

Recent vaccination may be necessary; patients who had not been vaccinated in the last year had 2.44 times greater odds of hospitalisation and 3.29 times greater odds of being transferred to ICU, compared with those vaccinated against influenza in the previous 12 months. (52)

Again, while the majority of studies cited here included subjects who had not had the COVID-19 vaccines, many of those who regularly have the flu vaccine are likely also to have the COVID-19 vaccine, introducing a confounding factor which has not yet been studied.

Oral polio vaccine

Population studies show that countries with effective polio vaccination programmes had fewer COVID-19 infections and/or less severe disease, (48) which was echoed in observational studies. (59,60) Conversely, a Saudi Arabian study using World Heath Organisation (WHO) data showed a significant positive correlation between live attenuated polio vaccine coverage and total COVID-19 cases, as well as deaths. (61)

Measles, mumps, rubella (MMR)

MMR is a live attenuated vaccine, containing enveloped RNA viruses that have glycoprotein spikes similar to those of SARS-CoV-2, and also share other sequence homologies. (62) Immunisation records and studies show that it is more recent MMR vaccination that is associated with decreased COVID-19 infection rates. (48,63–65) Nevertheless, among Egyptian patients, there were high levels of measles and mumps antibody titres in worsening cases, suggesting that antibodies were not protective. (66)

In contrast to BCG vaccination, a randomised control trial of MMR vaccination of healthcare workers during the pandemic found that MMR reduced the risk of symptomatic infection. (67)

Diphtheria, tetanus, pertussis (DTP)

The DTP vaccine induced SARS-CoV-2 cross-reactive B and T cells (203,316), which were associated with reduced COVID-19 severity. Among >70,000 COVID-19 patients, hospitalisation, transfer to intensive care or death were reduced by 20%-23% in DTP-vaccinated individuals. (68) Two large records studies showed that vaccination with DTP in the previous four years (in Spain) or 10 years (in the UK) led to significantly reduced COVID-19 hospitalisation and death rates, although there might have been a slight increase in infection rates. (69,70)

Herpes Zoster

A large study of immunisation records found that live attenuated herpes zoster (varicella) vaccination in the last five years was associated with reduced COVID-19 infection rates. (48) Similarly, a US study of subjects aged ≥50 years, who received at least one recombinant zoster vaccine dose before March 2020, found that vaccination was associated with a 16% lower risk of COVID diagnosis and a 32% lower risk of hospitalisation compared to those unvaccinated. (71) Furthermore, receipt of both the DTP and Herpes Zoster vaccination was associated with lower risk for COVID-19 hospitalisation compared with DTP or Herpes Zoster alone. (72)

As **Table 1** shows, the BCG, influenza, polio, MMR, DTP and herpes zoster vaccination studies generally suggested a protective effect on COVID-19 incidence and/or severity. These studies are all observational and rarely account for confounding factors such as vaccine strain, age at vaccination, co-morbidities, socio-economic status or whether the subjects have received the COVID-19 vaccine.

Clinical trials of vaccination during the COVID-19 pandemic show mixed results. BCG trials generally show no protection, while an MMR vaccination trial, however, showed reduced risk of symptomatic infection.

Discussion of Parts 1–3

These three papers have investigated to what extent COVID-19 incidence and severity was influenced by pre-existing immunity and shows that several prior infections and vaccines may affect both. There is close genetic identity and high homology between SARS-CoV-2 and other human coronaviruses, but other viruses and bacteria with no such similarity to SARS-CoV-2 also appear to impact incidence and severity of COVID-19, so clearly the degree of homology is not necessarily relevant.

Paper 1 shows that although small, there are numerous studies showing cross reactivity between the common cold coronaviruses and SARS-CoV-2. The proportion of the population with pre-existing cross-reactivity to coronaviruses varies by study within a range of 17% to 90%. However, there have been no large-scale prospective studies or clinical trials investigating the impact of cross-reactivity on real-world COVID-19 outcomes, including duration and extent of protection.

Although fewer studies investigate pre-existing immunity, it seems that memory T cells are generally protective against COVID-19 incidence and/or severity, while antibodies may be protective or pathogenic. More research is required to investigate this antibody conundrum. Furthermore, there is over-reliance on serum antibodies, whereas mucosal secretory IgA antibodies in the respiratory tract may provide a better indicator of full respiratory disease protection. Few studies consider confounding factors such as genetics, the proportion of urban to agrarian populations or access to healthcare, which may impact the associations. Nevertheless, several have shown that age is important, with children having twice as many memory T cells as the elderly.

The trained immunity of the innate immune system can also induce a protective inflammatory response or, occasionally, one which worsens COVID-19; the result may depend upon the individual's current inflammatory state. It is not surprising to find that the innate immune system is involved in immune memory when one considers the interconnectedness of the various immune system elements.

Paper 2 showed that pre-existing protective immunity may also be derived from dengue virus and malaria, while cross-reactivity from cytomegalovirus, influenza and viral hepatitis increased COVID-19 risk and severity. The association with dengue virus is in doubt as this may be due to failing to take account of malaria exposure as a confounding factor.

Dysbiosis of the gut, oral and respiratory tract microbiomes, such as poor diversity, lower levels of beneficial bacteria, especially short-chain fatty acid (SCFA)-producing bacteria, and increased inflammation, are all associated with COVID-19 severity, while supplementation with beneficial oral bacteria was associated with protection. Yet some studies show that the presence of traditionally pathogenic bacteria in the microbiome may correlate with less severe disease; further investigation of this phenomenon is required before definite conclusions can be drawn.

Furthermore, we should question the common statement in studies that SARS-CoV-2 alters the microbiome. This is of course possible, but since no study had measured the microbiome prior to COVID-19, it is equally likely that the pre-existing microbiome affects the course of COVID-19, or maybe both could be occurring together. These microbiome studies suggest that individual variation among pre-existing bacteria may have a greater impact on COVID-19 infection and severity than previously considered and supports a case for trialling oral or nasal probiotics to prevent or treat COVID-19 and other respiratory infections.

Paper 3 investigated the prior administration of cer-

tain live attenuated vaccines (BCG, influenza, polio, MMR, DTP and herpes zoster) and found them also to be protective against COVID-19, although trials of vaccination during the pandemic had mixed results, with the single MMR trial being successful, while several trials of the BCG vaccine were inconclusive.

Since the influenza vaccine and prior infection by other coronaviruses appear protective, while prior infection by the influenza and other viruses can worsen COVID-19, there is clearly much that we do not yet understand about the mechanisms of pre-existing immunity. Maybe the success of vaccination has little to do with the specific virus injected but hinges upon the fact that any live attenuated virus is injected. This would suggest that a 'universal vaccine' for any respiratory virus might be possible.

Although far from being the only determinant of COVID-19 outcome, the number of studies demonstrating some form of pre-existing immunity from prior infection or vaccination suggests that this is an important phenomenon, which should have been taken into account in the pandemic planning. The possibility that pre-existing cross-reactivity from other coronaviruses would provide some protection against SARS-CoV-2 was known well before the advent of the pandemic and studies showing that it did indeed provide some protection were available early on. When added to the WHO post-swine flu statement that "the vulnerability of a population to a pandemic virus is related in part to the level of pre-existing immunity to the virus," (73) it is disappointing that governments and health authorities did not think to factor pre-existing immunity into the modelling and pandemic response decisions; several scientists have pointed out that this could have considerably improved decision-making. (74,75) It is hoped that in future pandemics, our health authorities might recognise the presence and importance of pre-existing immunity to viruses and possibly screen for memory T cells, respiratory tract IgA antibodies, microbiome dysbiosis and prior vaccination in order to highlight those most at risk.

There are also implications for the development of the vaccines against COVID-19. If a substantial proportion of us have pre-existing immunity from other pathogens or through earlier vaccination, the need for specific anti-COVID-19 vaccines may be reduced in those least at risk. Furthermore, we have no idea how vaccines manufactured specifically against COVID-19 will be affected by pre-existing immunity: will it enhance their effect or negate it? Sette *et al* have pointed out that pre-existing CD4+ memory T cells may influence vaccination outcome and recommend factoring pre-existing immunity into the COVID-19 vaccine phase I clinical trials. (75) Considerably more research is needed in this area to determine the effect and duration of post-vaccination immunity to other pathogens for clinical practice and its effect on breakthrough infections or unexpected post-vaccination immune responses. This is particularly important when it comes to prioritising specific groups. As Peter Doshi pointed out in the British Medical Journal, if we don't study the question, we won't know. (73)

Table 1. Vaccination conclusion

VACCINE	PROTECTIVE AGAINST COVID-19 INCIDENCE	PROTECTIVE AGAINST COVID-19 SEVERITY
BCG	Yes, per meta-analysis	Mostly yes, several studies
BCG clinical trials during pandemic	Inconclusive	Inconclusive
Influenza	Yes, per meta-analysis	Mostly yes, several studies
Oral polio	Mostly yes, several studies	Mostly yes, several studies
MMR	Mostly yes, several studies	Not studied
MMR clinical trial during pandemic	Yes, reduced symptomatic infection	Yes, reduced symptomatic infection
DTP	Not studied	Yes
Herpes zoster	Yes but few studies	Yes but few studies

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