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COVID-19 in children: Could pertussis vaccine play the protective role?

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ABSTRACT

While COVID-19 continues to spread across the globe, diligent efforts are made to understand its attributes and dynamics to help develop treatment and prevention measures. The paradox pertaining to children being the least affected by severe illness poses exciting opportunities to investigate potential protective factors. In this paper, we propose that childhood vaccination against pertussis (whooping cough) might play a non-specific protective role against COVID-19 through heterologous adaptive responses in this young population. Pertussis is a vaccine-preventable infectious disease of the respiratory tract and it shares many similarities with COVID-19 including transmission and clinical features. Although pertussis is caused by a bacterium (*Bordetella pertussis*) while COVID-19 is a viral infection (SARS-CoV-2), previous data showed that cross-reactivity and heterologous adaptive responses can be seen with unrelated agents of highly divergent groups, such as between bacteria and viruses.

While we build the arguments of this hypothesis on theoretical and previous empirical evidence, we also outline suggested lines of research from different fields to test its credibility. Besides, we highlight some concerns that may arise when attempting to consider such an approach as a potential public health preventive intervention against COVID-19.

Background

The novel coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed challenging questions to researchers about the dynamics of its interaction with the immune system of the human host. One of the main questions concerns the consistent observation that the disease is less frequent and severe in children and adolescents than in adults [1–4]. Indeed, current epidemiological evidence shows that this young population has accounted for only 1%–5% of diagnosed COVID-19 cases, with significantly milder clinical presentations and extremely rare deaths [2].

Several explanations have attempted to explain why adults who have mature immunity seem to be more strongly hit than children whose immunity is incompletely established. These include, (i) potential cross-protection conferred by infection with other Coronaviruses [1] (ii) common presence of other respiratory viruses in children leading to direct virus-to-virus competitions [5], (iii) less potent virus-induced immune response in children, (iv) healthier pediatric respiratory tract due to limited exposure to pollutants and smoking [6] (v) Differential expression levels of the SARS-CoV-2 functional receptor Angiotensin-converting enzyme 2 (ACE2) between children and adults, (vi) the constitutional high lymphocyte count in children, and (vii) the "trained immunity" boosted by several pediatric viral infections and able to confer a cross-protection against a variety of pathogens [7]. However, the exact reasons for this differential protection between children and adults against COVID-19 are still unclear. Nevertheless, the possibility of a non-specific protective effect (also known as 'heterologous' or 'off-target' effect) of a vaccine taken during childhood and providing cross-protection against severe forms of COVID-19 is appealing [8–10].

Non-specific (heterologous) effects of vaccines

Heterologous immunity is that resulting from an encounter with a specific pathogen, providing protection against another unrelated pathogen [11,12]. Such non-specific immunity can, therefore, broaden the protective effects of vaccinations and natural resistance to infections [12]. Non-specific heterologous immunity is normally not as effective as specific homologous immunity, but it may decrease the severe course of heterologous infections, thus reducing their related morbidity and mortality [12,13].

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The longstanding concept of vaccine heterologous effects can be virus-induced, as in the case of measles and oral polio vaccines [14,15], or bacteria-induced as resulting from the Bacille Calmette-Guérin (BCG) vaccine [16]. Possible explanations underlying the beneficial non-specific effects of vaccines include two immunological mechanisms: heterologous adaptive lymphocyte responses and innate trained immunity [11,12,17–19].

Heterologous adaptive lymphocyte responses

Heterologous adaptive lymphocyte responses generally mediate long-term effects. They may be induced by several potential mechanisms including (i) activation of lymphocytes with cross-reactive antigen receptors due to molecular mimicry between unrelated microbial antigens (antigen cross-reactivity), (ii) bystander activation of unrelated lymphocytes that are specific for non-targeted antigens and (iii) Lymphocyte-dependent activation of innate immune cells, via the production of pro-inflammatory cytokines (e.g interferon-gamma (IFN-γ) [11,12,17,20,21]. To note, this latter state of lymphocyte-dependent induction of a heightened innate immune response against a secondary infection wanes rapidly once the initial pathogen is cleared [22]. However, as it is mediated by adaptive immunity induced against a primary pathogen, exerting beneficial collateral effects on the innate host responses to a secondary pathogen, it can be characterized as being by-products of adaptive immunity [23].

Innate trained immunity

Innate trained immunity is mediated by the induction of a non-specific immunological memory in prototypical innate immune cells, especially monocytes, macrophages, or natural killer cells [24,25]. This enhances responsiveness to subsequent triggers. Molecular mechanisms underlying this type of non-specific immunity involve both epigenetic reprogramming, specifically through histone modifications, as well as metabolic rewiring (e.g. the shift from oxidative phosphorylation toward aerobic glycolysis) [11,24]. However, the duration of trained immunity effects is highly unlikely to be as long-lived as classical immunological adaptive memory [24]. Indeed, the immunological phenotype of trained immunity may last at least 3 months and up to one year [25,26]. However, for example, the non-specific protection of neonatal BCG vaccination may extend until adolescence [27]. Consequently, it was proposed that heterologous adaptive lymphocyte responses may take over non-specific infant protection from childhood infections once the trained immunity effect wanes [19].

Hypothesis

Recent reports and pre-print papers suggested that non-specific effects of the BCG [28–31] and measles, mumps, and rubella (MMR) [32] vaccines might protect against COVID-19. BCG-mediated non-specific protective effects on a variety of viral infections were previously documented and this vaccine has a well-known heterologous effect against respiratory pathogens [21]. However, it is unble to fully explain the paradox. Indeed, epidemiological data show children are more protected from COVID-19 than adults consistently across countries where BCG vaccination rates are high or low; children who have not been vaccinated with BCG are also protected. Moreover, the current thinking is that BCG-mediated non-specific protection against COVID-19 relies on innate trained immunity [30,31]. However, as mentioned above, this latter exerts short-time effects lasting for months and subsiding by one year post-immunization. Yet, young adolescents are also markedly less severely affected by COVID-19 than adults [3,4], reflecting that this feature is not restricted to the early childhood months or years. Hence, short-lived trained immunity induced by BCG maybe not able to completely explain the non-specific protective effect against COVID-19. To note, the same logic also applies to short-term trained immune responses that may be possibly induced by other vaccines or stimuli.

Concerning MMR, this vaccine is known to provide specific long-term adaptive immunity that lasts in adults. Indeed, according to the Centers for Disease Control and Prevention (CDC), people who received two doses of MMR vaccine are usually considered protected for life. Consequently, a possible non-specific anti-COVID-19 effect mediated by MMR heterologous adaptive responses may be questionable, as such long-lasting protection should be not only seen in children but must also be maintained in adults. Here again, other vaccines and stimuli inducing similar life-long protection may be unable to fully explain the enigma.

In this line of thought, the candidate vaccine should be one that is routinely used worldwide but which provides relatively “medium-term” adaptive immunity that confers temporary protection during childhood and adolescence, but fades away when reaching adulthood, thus requiring boosters. Potential candidates for this description may be pertussis vaccines, globally included in recommended immunization schedules, and known to induce such kinds of “medium-term” immune adaptive responses [33].

To note, pertussis, caused by the bacterium *Bordetella pertussis,* is a vaccine-preventable infectious disease of the respiratory tract, and it shares many similarities with COVID-19, including transmission dynamics (respiration and droplets) and some clinical features (incubation time, asymptomatic carrier cases, and dry cough) [34]. Although pertussis is bacterial while COVID-19 is viral, both cross-reactivity and heterologous adaptive lymphocyte responses are still possible. Indeed, it was reported that such features can be seen with unrelated agents of highly divergent groups, such as between bacteria and viruses [12,13]. In this context, cross-reactive antibodies or T cells able to recognize both bacterial and viral antigens were previously reported. For example, antibodies directed against HIV’s viral envelope glycoprotein, gp41, cross-react with commensal bacterial antigens [35]. Similarly, Höhn *et al.* identified cross-reactive $CD8^+$ T cells recognizing both HIV envelope gp120 and *Mycobacterium tuberculosis* 19-kDa antigens [36]. Sequence similarities and cross-reactive antibodies between these two pathogens have been also reported [37]. Likewise, Kashala *et al.* previously showed that IgM antibodies to *Mycobacterium leprae* lipoarabinomannan and phenolic glycolipid I in sera from leprosy patients yielded significant cross-reactivity with *pol* and *gag* proteins of HIV-1 [38]. In the same vein, BCG immunization of mice confers protection against the infection with vaccinia virus, but not with lymphocytic choriomeningitis virus, and this non-specific protection seems potentially dependent on heterologous cross-reactive $CD4^+$ T lymphocytes [39]. Additional examples of heterologous protection between bacteria and viruses include that of BCG against human papillomavirus as well as that of herpesviruses against *Listeria monocytogenes* and *Yersinia pestis* [40,41]. However, although these effects are mediated by heterologous adaptive responses, they are not consequences of cross-reactivity.

Overall these data showed that cross-reactivity occurs between bacteria and viruses and that heterologous adaptive responses are involved in non-specific immunity between these two different types of microorganisms.

Pertussis vaccines and their-induced immunity

Pertussis vaccines

Two generations of protective vaccines against pertussis have been developed: whole-cell pertussis (wP) and acellular pertussis (aP) vaccines. wP vaccines consist of detoxified, killed *B. pertussis*. They were developed in the 1940s and strongly contributed to the reduction of the incidence of clinical pertussis. However, due to their association with many serious side-effects, they were widely replaced by aP vaccines in the 1990s–2000s. aP vaccines are composed of 1–5 *B. pertussis* antigens including inactivated pertussis toxin (PT), filamentous hemagglutinin

(FHA), pertactin (PRN), and Fimbriae (FIM) types 2 and 3 [42,43].

Both wP and aP vaccines are generally administered in combination with diphtheria and tetanus antigens (DTwP or DTaP vaccines). Schedules for primary pertussis vaccination differ among countries. However, the World Health Organization (WHO) recommends a 3-dose primary series ideally completed by 6 months of age, with a booster dose for children aged 1–6 years. Additional doses of aP-containing vaccines are also used in several countries as adolescent and/or adult boosters. According to the Global Health Observatory (GHO) data, 86% of infants were globally vaccinated with 3 doses of DTP containing vaccine in 2018 [44]. However, it should be noted that booster DTP vaccine doses are not usual practices in many countries, especially in the developing world. Besides, increasing numbers of reported pertussis cases in adults in developed countries [45] reflect poor compliance with booster recommendations. In this way, a study showed that more than 70% of United States adults ≥ 18 years had not received Tdap vaccinations, by 2013 [46].

Pertussis vaccine-induced immunity

Immunization with both wP and aP vaccines induces potent human IgG antibody responses against pertussis antigens. Yet, wP vaccines induce strong Th1 responses in humans, and recent data in baboon and mouse models suggest that it may induce a mixed Th1/Th17-polarized immune response. In contrast, strong Th2 and weak Th1 responses are induced by the aP vaccines in humans and baboons, while strong Th2 and low-level Th17 responses were observed in the murine model. However, the exact role of Th17 responses in humans is unclear [43,47].

Pertussis infection-induced immunity wanes after 4–20 years while that induced by wP or aP vaccination wanes after 4 to 12 years [33]. However, aP-induced protection is less complete and sustained compared to that conferred by wP vaccines [48]. The faster waning of protection after aP than after wP vaccination was documented in several studies enrolling children who received a three- or four-dose series [49].

The exact mechanisms and correlates by which pertussis vaccination confers protection are complex, multiple, and still not fully understood [50,51]. Storsaeter *et al.* previously showed that IgG antibodies against PT, PRN, and FIM were correlated with protection [52]. However, although vaccine-induced production of anti-pertussis antibodies is essential to protection, vaccinated individuals with waning humoral antibody responses could be still protected due to the presence of cellular immunity. Protection is therefore suggested to be mediated by both humoral and cellular immunity [50,51].

Evaluation of the hypothesis

In order to test the plausibility of a protective effect of pertussis vaccination against SARS-CoV-2 infection, several suggestions can be proposed. First, epidemiological case-control studies can be conducted to examine whether children with severe disease were more likely those without or with incomplete pertussis vaccination. On another note, it is necessary to investigate whether a more severe form of the disease is more likely in people who have not received the booster shots of DTP. Furthermore, comparing COVID-19 epidemiological data between countries using wP and aP containing vaccines may clarify if the proposed protective effect is a feature shared by both vaccine types.

Second, surrogates of protection for the pertussis vaccine (e.g anti-PT, PNR, and FIM antibodies) can be compared among the different subsets of COVID-19 patients (asymptomatic, mild/moderate, severe/critical). As cited above, actors of the cellular immune response are also involved in anti-pertussis protection. However, although under investigation, well-defined correlates of cell-mediated protection are not identified [53] thus hindering comparison of such actors among COVID-19 patients subsets.

Third, biological and bioinformatics studies may provide molecular evidence on whether there exists a plausible foundation that relates SARS-CoV-2 proteins and pertussis vaccine antigens on the phenotypic level. However, while a recent pre-print report has found homologous protein domains between SARS-CoV-2 and measles, mumps, and rubella [54], all viruses, the same could be more difficult with pertussis bacteria. Nevertheless, here again, potentially reported/suggested cross-reactivity and/or sequence similarities between HIV and *Mycobacterium tuberculosis/Mycobacterium leprae* [36–38], HIV and commensal bacteria [35] or BCG and vaccinia virus [39] indicate that such possibility cannot be excluded. In order to shed light on possible sequence similarities and potentially related epitopes between antigens included in the DTP vaccine and those of SARS-CoV-2, we used a bioinformatics approach largely similar to that employed by Swaminathan *et al.* [37] who investigated these features between HIV and *Mycobacterium tuberculosis*. To note, we particularly focused on acellular pertussis-containing vaccines (e.g.DTaP) since they are widely in use for almost 20 years, especially in developed countries, which are currently most affected by COVID-19. In this context, reference protein sequences of antigens included in DTaP vaccines (PT, FHA, PRN, FIM types 2 and 3, Diphtheria toxin and Tetanus toxin) were downloaded from the UniProt database (https://www.uniprot.org/) and then individually compared to the amino acid sequences encoded by the reference genome SARS-COV-2 (NC_045512.2) using the blastp available at NCBI (https://blast.ncbi.nlm.nih.gov/) with the default parameters. Similar peptides identified in both DTaP antigens and SARS-CoV-2 sharing a minimum of 9 identical amino acids and any number of conservative substitutions within a total of 30 amino acid sequences, as previously described [37], were screened for the presence of potential epitopes that could bind to the HLA class II alleles. The TepiTool [55] developed by the Immune Epitope Database (IEDB) team and accessed directly at http://tools.iedb.org/tepitool, was used to predict the ability of identified similar peptides for binding on the 26 most frequent alleles of HLA class II. Although the binding groove of the HLA class II molecules can accommodate long peptides (up to 25 amino acids), only a binding core of 9 amino acids in length could interact or bind to these molecules. Neighboring or flanking residues of the binding core (other amino acids of peptides with a typical length from 15 to 23 amino acids) could also interact outside the binding groove [56]. The Tepitool predicts the 15-mer peptides able to interact with HLA class II using the Consensus method [57,58] and default parameters (peptides with predicted consensus percentile rank ≤ 10). As shown in Table 1, the program predicted several similar peptides from the DTaP vaccine and SARS-CoV-2 could interact with the same HLA-II molecules. Overall, this suggests the existence of sequence similarities and possible related epitopes that could induce similar human immune reactions, probably resulting in cross-reactive responses. These preliminary findings seem promising and may merit further investigations in the future.

Fourth, the presence of antibodies and T cells elicited by pertussis vaccines and having probable cross-reactivity with SARS-CoV-2 can be tested by neutralization and T cell proliferation assays, respectively. As cited above, cross-reactive antibodies or T cells able to concurrently recognize both bacterial and viral antigens were previously reported [35,36,38]. However, a previous study found no significant cross-reactivity between children's vaccines, including DTP, and SARS-CoV [59]. Nonetheless, the study was conducted using the mouse model which may not exactly reflect human responses. Also, it is not clear which type of pertussis vaccines was exactly used. Besides, it is not necessarily discouraging if that was the case for SARS-CoV as, although SARS-CoV-2 shares around 70–80% of its genome with SARS-CoV, these two viruses show genetic and clinical differences [60]. To note, cross-reactive antigen binding is common between SARS-CoV and SARS-CoV-2 [61]. However, even SARS-CoV-2 stimulate SARS-CoV cross-binding antibodies, it was unable to induce the cross-neutralizing antibodies against SARS-CoV, thus suggesting that epitope or immunogenicity between these two viruses are different [54]. Therefore, although this

Table 1
Potential HLA-II molecules binders (15-mer peptides) present in related peptides of DTaP vaccine antigens and SARS-CoV-2 proteins.

Serial number	DTaP vaccine Ag (UniProt accession number)	SARS-CoV-2 protein (NCBI accession number)	Location of matching peptide in DTaP vaccine Ag	Location of matching peptide in SARS-CoV-2 protein	HLA binders# in SARS-CoV-2	Type of shared HLA allele between HLA binders in SARS-CoV-2 and DTaP vaccine Ag
1	Filamentous hemagglutinin (P12255)	ORF1ab polyprotein (YP_009724389.1) 3′-to-5′ exonuclease (YP_009725309.1)	1207–1236	6229–6258 (ORF1ab); 304–333 (3′-to-5′ exonuclease)	KAALLADKFPVLHDI	HLA-DRB3*01:01
2	Serotype 3 fimbrial subunit (P17835)	ORF1ab polyprotein (YP_009724389.1) ORF1a polyprotein (YP_009725295.1) nsp6 (YP_009725302.1)	77–106	3675–3704 (ORF1ab, ORF1a); 106–135 (nsp6)	RKVQHMVVKAALLAD	HLA-DQA1*01:02/DQB1*06:02
					DCVMYASAVVLLILM	HLA-DPA1*02:01/DPB1*05:01
					ASAVVLLILMTARTV	HLA-DRB1*15:01
3	Serotype 3 fimbrial subunit (P17835)	ORF1a polyprotein (YP_009725295.1) 3′-to-5′ exonuclease (YP_009725309.1)	3–30	6236–6263 (ORF1a); 311–338 (3′-to-5′ exonuclease)	KAALLADKFPVLHDI	HLA-DPA1*01/DPB1*04:01; HLA-DPA1*03:01/DPB1*04:02
					KVQHMVVKAALLADK	HLA-DQA1*01:02/DQB1*06:02; HLA-DRB1*01:01; HLA-DRB1*07:01; HLA-DRB1*08:02; HLA-DRB1*15:01
					DKFPVLHDIGNPKAI	HLA-DRB1*03:01
4	Diphtheria toxin (P00587)	ORF1ab polyprotein (YP_009724389.1) ORF1a (YP_009725295.1) nsp2 (YP_009725298.1)	295–321	531–557 (ORF1ab, ORF1a); 351–377 (nsp2)	ARVVRSIFSRTLETA	HLA-DRB1*07:01; HLA-DRB1*09:01
					AFASEAARVVRSIFS	HLA-DQA1*01:02/DQB1*06:02; HLA-DQA1*05:01/DQB1*03:01; HLA-DRB1*07:01
5	Diphtheria toxin (P00587)	ORF1ab polyprotein (YP_009724389.1) ORF1a (YP_009725295.1) nsp3 (YP_009725299.1)	490–515	1273–1298 (ORF1ab, ORF1a); 455–480 (nsp3)	DITFLKKDAPYIVGD	HLA-DRB1*13:02; HLA-DRB3*02:02

Ag for antigen, # for the 15-mer predicted peptides by TepiTool able to bind to HLA class II molecules.
The accessions numbers of DTaP vaccine Ag compared to SARS-CoV-2 proteins using blastp are Pertussis toxin subunit 1 (P04977), Pertussis toxin subunit 2 (P04978), Pertussis toxin subunit 3 (P04979), Pertussis toxin subunit 4 (P0A3R5), Pertussis toxin subunit 5 (P04981), Filamentous hemagglutinin (P12255), Pertactin autotransporter (P14283), Serotype 2 fimbrial subunit (P05788), Serotype 3 fimbrial subunit (P17835), Diphtheria toxin (P00587), Tetanus toxin (P04958).

was not the case with SARS-CoV, cross-reactivity between unique epitopes specific for SARS-CoV-2 and pertussis vaccines remains possible.

Fifth, *in vivo* infection experiments will allow the assessment of potential resistance to SARS-CoV-2 after the administration of pertussis vaccines in a suitable animal model. This latter must be able to mount immune responses to the vaccine and, simultaneously, can be infected by the virus. One possibility is to use transgenic mice that express human ACE2, recently developed by Bao *et al.* [62]. After SARS-CoV-2 infection, these mice showed virus replication in the lungs, interstitial pneumonia, and weight loss. Such features can be therefore compared between pertussis-vaccinated SARS-CoV-2-infected mice and their infected non-vaccinated counterparts.

Finally, clinical trials evaluating a potential protective role of pertussis vaccines against SARS-CoV-2 can be also conducted as done with BCG. For example, the latter is currently under investigation in two independent clinical trials assessing its effects against COVID-19 in vaccinated health care workers [63,64].

Concerns

Some concerns may arise with the hypothesis of a protective heterologous effect of pertussis vaccines against COVID-19. Indeed, it was suggested that beneficial heterologous effects are most often associated with live vaccines (e.g. BCG and measles), while non-live vaccines such as DTP may have negative heterologous effects [11,65,66]. For example, according to a systematic review by Higgins *et al.*, the receipt of DTwP may be associated with an increase in all-cause childhood mortality [67]. However, another meta-analysis published in 2019 shows that risk ratios of all-cause mortality after DTwP were most likely exaggerated due to biases in the studies and that most studies are pertaining to the situation in Africa and therefore cannot give a representative generalization of the estimates [68]. Moreover, independent studies noticed significant beneficial effects reflected by a substantial non-specific reduction of overall mortality among children who received DTP vaccine [69,70]. However, a recent study showed that the Tdap vaccine induces immunotolerance to unrelated antigens and this effect was partially restored by concurrent or subsequent BCG vaccination [71]. Though, the exact components and mechanisms by which such suggested undesirable modulatory effects may occur as well as the degree of implication of pertussis vaccine alone in such consequences are unknown. To note, earlier studies in mice reported a beneficial antiviral role of pertussis vaccine against several viruses including adenovirus and vesicular stomatitis virus [72–74]. However, using a mouse model, a report showed that DTP administration increases mortality after challenge with the respiratory syncytial virus (RSV) and it was suggested that detoxified pertussis toxin may be involved in this effect [75]. Nevertheless, RSV triggers wheezing disease in later childhood [76], but no evidence was found that pertussis vaccination increases the risk of wheezing episodes in children [77]. More importantly, clinical data showed that human immunization with a pertussis-containing vaccine is neither a risk factor for hospitalization for RSV infection nor associated with a more severe clinical course [78].

Conclusion

In conclusion, a possible explanation of the difference of COVID-19 frequency, severity, and mortality rates between children and adults may lie in a potential heterologous adaptive effect of childhood pertussis vaccines. Epidemiological, immunological, molecular, and clinical approaches discussed above can be used to test the credibility of such a probable protective effect.

Overall, our hypothesis forms a potential “another brick in the wall” of the largely obscure COVID-19/children enigma. However, it doesn’t rule out either the possibility of an overlapped, early but short-term protection mediated by non-specific innate trained immunity or additional potential heterologous roles of other vaccines or stimuli.

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Conflict of interest statement

Authors declare no conflict of interest.

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