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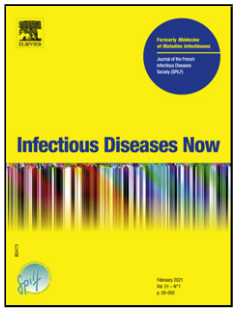

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Pediatric Infectious Disease Group (GPIP) position paper on the immune debt of the COVID-19 pandemic in childhood, how can we fill the immunity gap?

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Highlights

- Since the beginning of the COVID-19 pandemic, a decreased incidence of many viral and bacterial infections has been reported in children.
- Non-pharmaceutical interventions limited the transmission of SARS-CoV-2 and reduced the spread of other pathogens despite school re-opening.
- The lack of immune stimulation due to the reduced circulation of microbial agents and to reduced vaccine uptake induced an "immunity debt" with a growing proportion of susceptible people.
- Vaccination program delay and decreased viral and bacterial exposure lead to a rebound risk of vaccine-preventable diseases.
- As the French vaccination schedule does not include vaccines against rotavirus, varicella, and serogroup B and ACYW *Neisseria meningitidis*, stronger epidemic rebounds could be observed.

Abstract

Since the beginning of the COVID-19 pandemic, reduced incidence of many viral and bacterial infections has been reported in children: bronchiolitis, varicella, measles, pertussis, pneumococcal and meningococcal invasive diseases. The purpose of this opinion paper is to discuss various situations that could lead to larger epidemics when the non-pharmaceutical interventions (NPI) imposed by the SARS-CoV-2 epidemic will no longer be necessary.

While NPIs limited the transmission of SARS-CoV-2, they also reduced the spread of other pathogens during and after lockdown periods, despite the re-opening of schools since June 2020 in France. This positive collateral effect in the short term is welcome as it prevents additional overload of the healthcare system. The lack of immune stimulation due to the reduced circulation of microbial agents and to the related reduced vaccine uptake induced an "immunity debt" which could have negative consequences when the pandemic is under control and NPIs are lifted. The longer these periods of "viral or bacterial low-exposure" are, the greater the likelihood of future epidemics. This is due to a growing proportion of "susceptible" people and a declined herd immunity in the population. The observed delay in vaccination program without effective catch-up and the decrease in viral and bacterial exposures lead to a rebound risk of vaccine-preventable diseases.

With a vaccination schedule that does not include vaccines against rotavirus, varicella, and serogroup B and ACYW *Neisseria meningitidis*, France could become more vulnerable to some of these rebound effects.

Keywords. Covid-19 pandemic, VZV, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Bordetella*, vaccination.

Introduction

The current COVID-19 pandemic imposed a number of hygiene measures unprecedented in history (distancing, masks, hand washing, reduced number of contacts, etc.). These personal non-pharmaceutical interventions (NPI) contributed to limiting the transmission of SARS-CoV-2, but they also reduced the spread of other pathogens. Thus, in hospital emergency rooms and in private practices, the number of visits for community-acquired pediatric infectious diseases decreased significantly, not only during the lockdown periods [1] but also beyond, despite the re-opening of schools [2]. This includes numerous diseases such as gastroenteritis, bronchiolitis (especially due to respiratory syncytial virus), chickenpox, acute otitis media, non-specific upper and lower respiratory tract infections, and also serious ones such as invasive bacterial diseases. These severe diseases due to *Streptococcus pneumoniae*, *Haemophilus influenzae* b or *Neisseria meningitidis* are also associated with mucosal carriage and human-to-human transmission through the respiratory tract. Conversely, no decrease in the number of reported cases of *Streptococcus agalactiae* or urinary tract infections was reported between January and June 2020 compared with the same period in 2018 and 2019. This confirms that the reduction in reported *S. pneumoniae, H. influenzae,* and *N. meningitidis* invasive diseases in 2020 reflects true decreases in incidence rather than underreporting [3]. This is not surprising because the transmission modes of these pathogens are often the same as those of SARS-CoV-2 (essentially by large droplets, aerosols, and hands), often with a lower transmissibility for many of them (based on lower R0). Personal NPIs imposed by the COVID-19 pandemic were thus able to slow down transmission and contagion, and therefore disease incidence. This positive collateral effect in the short term is welcome as it prevents additional overload of hospital emergency rooms, wards, and intensive care units during the SARS-CoV-2 epidemic. However, triggers of these invasive infections are early childhood infections, most often viral, which are almost unavoidable in the first years of life. A lack of immune stimulation due to personal NPI induces an "immunity debt" and could have negative consequences when the pandemic is under control. Mathematical models suggest that respiratory syncytial virus (RSV) and possibly influenza epidemics may be more intense in the coming years [4]. Finally, through the possible role of "trained" innate immunity in the defense against infections and a possible return of the hygienist theory, other consequences could be observed. For some of these infections, negative consequences could be balanced by vaccinations (reinforcement of

compliance with immunization programs in place, or even widening of vaccination target populations).

The purpose of this paper is to discuss various situations that could lead to larger epidemics when personal NPIs imposed by the SARS-CoV-2 pandemic are no longer necessary. We will discuss in turn specific natural immunity to a number of viral and bacterial diseases, and other possible immunological consequences of the various constraints imposed by the pandemic.

I. Specific (adaptive) immunity

I.A. Viral diseases

I.A.1. Varicella

In the absence of an immunization program, chickenpox is considered an unavoidable childhood disease as all individuals contract varicella during their lives, most often in childhood [5]. Late varicella onset, after puberty, is associated with greater severity, justifying the recommendation to vaccinate individuals over 12 years of age who have not yet contracted it in countries where general vaccination of toddlers is not implemented. According to data from the French national agency for health (Santé publique France, French acronym SPF) and the Sentinel Network [6], the varicella annual incidence rate in France in 2019 was 822 cases per 100,000 inhabitants, or approximately 540,000 cases per year. Similar trends were observed in 2017 and 2018, with 557,000 cases and 561,000 cases per year, respectively. Stable rates were thus observed over time, except in 2020 with only 230,000 total cases reported (about 40% lower than usual) [6]. These figures confirm data obtained from outpatient pediatricians via the French Pediatric and Ambulatory Research in Infectious diseases (PARI) network, which observed a decrease in varicella visits in 2020 [7]. Personal NPIs and population containment are clearly involved in this decrease. Due to the unavoidable nature of varicella, young children who should have contracted chickenpox in 2020 will be added to the susceptible population and will possibly contribute to a higher incidence in the coming years. In addition, the population that has not had chickenpox in 2020 will have "aged" and this may lead to a greater number of severe and complicated cases. In France, vaccination against varicella is targeted at specific populations at risk of severe forms. However, since varicella vaccination offers protection similar to that conferred by the natural infection [8] and protects against herpes zoster, this vaccination policy could be reconsidered in this new

context to avoid an epidemic rebound by implementing broader vaccination guidelines already adopted in many high-income countries [9].

I.A.2. Respiratory syncytial virus infections

Illnesses due to RSV range from benign upper respiratory tract infections including ear infections, to potentially serious lower respiratory tract infections (severe bronchiolitis and pneumonia [10]). In 2015, RSV was responsible for 33.1 million episodes of acute lower respiratory tract infections in children under 5 years of age worldwide [11]. RSV infections in young children are a major cause of hospitalization and mortality in low-income countries and a major cause of hospitalization in high-income countries. Bronchiolitis is the most characteristic clinical syndrome, although not the most common. It is the best marker of RSV epidemics. It affects children under 2 years of age during seasonal winter epidemics in northern countries and is the leading cause of hospitalization among RSV-related illnesses [12–14]. All 2-year-olds have been infected at least once [5]. Transmission of RSV occurs by large droplets and contact with contaminated surfaces and is thought to occur more frequently among children in day-care centers and schools [16]. RSV and SARS-CoV-2 have similar baseline R0 reproduction rates (approximately 3) [17,18]. As for the reservoir and transmission of RSV, the role of adults and older children during winter epidemics is still not clearly defined [10]. However, bronchiolitis in infants aged below 3 months of age, which generates numerous hospitalizations for acute respiratory failure each winter and overloads pediatric services, is mainly the result of intrafamilial transmission. It often involves parents who can also be infected during winter by RSV. The experience of the great transport strike of 1995, which abruptly interrupted the epidemic curve of bronchiolitis in the pediatric emergency rooms of the Paris area, was an illustration of this pattern [19].

In the first six months of the COVID-19 pandemic, initial epidemiological data from the Southern Hemisphere and particularly from Australia, showed the virtual absence of RSV infection and influenza epidemics, more than three months after the usual start of annual epidemics [20]. In contrast, Australia reported as early as October 2020 (corresponding to mid-spring in the Southern Hemisphere) a larger RSV epidemic [21] than in previous seasons, without any influenza virus epidemic.

In France, during the 2020-2021 winter season bronchiolitis was characterized by an epidemic cycle that occurred three months later than the second epidemic peak of COVID-19 and was

strongly reduced in intensity (more than a third) compared to the previous years, both in ambulatory and hospital settings.

The absence of strong RSV epidemic will have increased the proportion of RSV-susceptible children that may increase their risk of RSV infection over time. In the absence of an RSV vaccine, partial and transient immunity is naturally and spontaneously achieved each year by two mechanisms: infection or transplacental transfer of maternal RSV antibodies.

Due to the decreased spread of RSV this year as a result of anti-COVID-19 measures, the natural protection of the population against RSV at the end of winter will be lower than usual, raising fears of a more important RSV epidemic in the future [4]. The evolution of NPIs, and particularly their lifting, will have major effect on the incidence. Continued surveillance of RSV infections will be necessary to detect early epidemic in order to adapt the prophylaxis of young infants at risk (especially very premature infants) with palivizumab and to prepare the healthcare system.

I.A.3. Rotavirus

The incidence of acute diarrhea illnesses followed the same downward trend as other viral infections since the beginning of the SARS-CoV-2 epidemic. Even if the sentinel network notes a slight increase in the number of consultations for acute diarrhea in recent weeks, the rate remains much lower than the figures usually observed at this period. The incidence rate of acute diarrhea cases seen by family physicians was 367 cases per 100,000 inhabitants [22] during the second week of January 2020, before the beginning of the epidemic (similar rate to those of previous years), while it is only 98 cases per 100,000 inhabitants in 2021. Data provided by the PARI network confirm this decrease [7]. Rotavirus is the main pathogen responsible for acute diarrhea in children because of its frequency but also because of its potential severity in infants [23]. Indeed, rotavirus is frequently responsible for acute gastroenteritis with severe dehydration and usually causes more than 200,000 child deaths per year worldwide. Most of these deaths mainly occur in developing countries, but it should be noted that the number of deaths in France is significant, with an estimated 20 cases per year [23,24].

It is almost unavoidable to have had rotavirus infection before the age of 3, i.e. the age group in which most severe forms are reported [25]. Reinfections are also common but associated with milder forms. Rotavirus vaccination prevents severe forms and also reduces the overall

number of cases in countries where the vaccine is widely administered. Similar to varicella, we can fear an epidemic rebound after the current pandemic.

I.A.4. Measles

As in most countries, France has seen a rapid decline in the number of measles cases since April 2020, whereas 2019 was an epidemic year [26]. This requires optimal measles, mumps, and rubella (MMR) vaccination coverage if we wish to avoid significant epidemic rebounds in the coming years. Coverage was however not optimal in 2020.

I.A.5. Other viruses

The situations described above represent a significant proportion of pediatric consultations and seasonal epidemics, but the decrease in various viral infections is observed with many other viruses.

Seasonal influenza usually occurs from the end of December onwards. No such epidemic has been observed so far this year [27]. With an R0 much lower than that of SARS-CoV-2 and an identical mode of transmission, the absence of influenza epidemic was expected as long as NPIs were maintained. However, future epidemics are less predictable because many other factors could play a role: virus variability over time, role of population migration, and annual vaccination of at-risk subjects with a vaccine which matching patterns to the circulating viruses and related effectiveness vary every year. The potential role of animal influenza viruses is also at stake.

Enteroviruses are no exception: reports of enterovirus infections by pediatric emergency rooms and by the pediatrician network also decreased [7,28]. These viruses are responsible for numerous cases of pharyngeal, cutaneous, and digestive infections in infants and children, which are generally benign. More severe forms may however be observed, such as sepsis-like syndrome in newborns and meningitis, leading to frequent hospitalizations of younger children.

I.B. Bacterial diseases

While the rate of visits for ambulatory pediatric infectious diseases has decreased, the same is true for invasive infections with encapsulated bacterial species such as *S. pneumoniae,*

N. meningitidis and *H. influenzae* b. A significant decrease in the number of lower and upper respiratory tract infections, but also bacteremia and meningitis, was observed in 2020-2021.

I.B.1. *Streptococcus pneumoniae*

This was confirmed by a large study conducted between January 2018 and May 2020 across 26 countries in six continents [3]. The authors compared the rates of invasive pneumococcal disease in 2020 vs 2018-2019, week by week. The same conclusion was reached in all countries: significant decrease in invasive pneumococcal diseases, regardless of NPIs (school closures, telecommuting, lockdown, etc.). The PARI network also reported a 50% decrease in the number of visits for acute otitis media or pneumonia as compared to previous years [7]. This result was expected as *Streptococcus pneumoniae* is mainly carried in the nasopharyngeal and oropharyngeal microbiota of children aged under 6 years. Transmission occurs by droplets and is either leading to healthy carriage or less frequently to infection. No study investigated the impact of the pandemic on pneumococcal carriage, but one can hypothesize that the decreased incidence of invasive pneumococcal disease may be related to an overall decrease in carriage. Moreover, pediatric pneumococcal carriage and infection are favored by viral infections, but the incidence of such infections has also decreased. Since the 1980s, following the work of Gray [29,30], it has been known that all infants will be colonized by various serotypes of *Streptococcus pneumoniae* in the first years of life. Most of them progressively develop mucosal and systemic immunity against these various serotypes without showing clinical signs of infection, underlining that asymptomatic or paucisymptomatic carriage can induce protective effect. The decreased circulation of pneumococcal strains due to NPIs will probably be associated with a higher proportion of children susceptible to these strains. Although vaccination with conjugate vaccines significantly reduced the risk of vaccine serotype pneumococcal infections, the risk of non-vaccine serotype carriage has increased.

However, despite the protective role of some serotypes able to limit colonization by more virulent serotypes, serotypes with high disease potential (24F, 12F, 8, etc.) which were predominant before the pandemic are likely to remain so after the pandemic [31].

This period of low circulation or low carriage could be followed by an increase in invasive infections if we assume that more children or adolescents are immunologically "naive" to pneumococcal serotypes with high invasive potential and not covered by vaccines. The

availability of new generations of conjugate vaccines, covering more serotypes, may limit the extent of such rebound effects.

I.B.2. *Neisseria meningitidis*

The number of pediatric serogroup C invasive meningococcal disease (CIMD) cases has declined since 2017, driven successively by the implementation of the 5-month vaccination dose in 2017 and the extension of mandatory vaccines in 2018, while IMDs due to other serogroups remained stable (serogroups B and Y) or increased (serogroup W) throughout 2019 [32]. The first lockdown was associated with a significantly lower number of IMD reports compared to the corresponding periods in 2018 and 2019 both in France and in 25 other countries worldwide. This trend was observed regardless of the stringency of NPIs taken by countries [3]. Moreover, in France, this decrease during the lockdown period mainly involved isolates of hyperinvasive genotypes, regardless of the serogroup, whereas the circulation of less invasive isolates did not vary.

Clinical presentations of these invasive infections were also found to have changed during the lockdown period with an increase in respiratory forms, a higher proportion of elderly people affected, and involvement of unusual isolates. This suggests that these isolates, although less virulent, could be carried for a longer period [33]. The average duration of asymptomatic carriage can be as long as four months [34]. Hyperinvasive isolates have a high acquisition/transmission/attack rate compared to carriage isolates (less invasive but carried for a longer time) [35]. In the short term, hyperinvasive isolates would therefore be more impacted by anti-COVID-19 measures. However, an impact on asymptomatic meningococcal carriage could be observed if these measures were to be continued. Asymptomatic carriage of *N. meningitidis* or closely related species such as *Neisseria lactamica* contributes to the development of herd immunity to *Neisseria meningitidis* in the general population [34]. This potential decline in natural immunity could be exacerbated by declining vaccination coverage as observed in France and in the United-Kingdom [36] with an uncontrolled delay in vaccination in 2020 that will increase in 2021. These changes in the circulation of isolates, the reduced carriage, and the delay in vaccination may thus be a sign of a decline in meningococcal herd immunity and an increase in the number of individuals susceptible to meningococcal infections. This raises concerns about a rebound effect in the incidence of IMDs. Preventive action should therefore be prepared immediately. A plan to boost vaccination is necessary for

meningococcal C conjugate vaccination (infant vaccination but also catch-up vaccination in children, adolescents, and young adults) and a vaccination strategy extended to other serogroups (A, Y, and W or even B) could be considered.

I.B.3. Pertussis

Pertussis is also strongly impacted by the SARS-CoV-2 epidemic. According to the unpublished data of the PARI and ACTIV networks (pertussis cases diagnosed in outpatient settings by pediatricians) and the PCR results from the main laboratory in France performing pertussis a 90% drop in the number of cases was observed [7]. This is once again probably due to the decreased circulation of *B. pertussis* due to anti-COVID-19 measures. However, even if the incidence of the disease strongly decreased since the introduction of booster vaccines, the bacterium is still circulating especially in adults and the elderly as shown by sero-epidemiological studies conducted in various countries. This may be due to non-optimal vaccination coverage in these populations.

Unlike other infections, pertussis is not an unavoidable childhood disease [37], and the rebound effect associated with an "immunity debt" built up in 2020 will probably not be observed in this disease if vaccination coverage remains high. However, delays in vaccination were observed in France among infants since the beginning of the pandemic. Such delays are particularly detrimental to children under 3 months of age, in whom pertussis can have a very serious course (malignant pertussis). To mitigate this risk, vaccination of mothers against pertussis during pregnancy should be implemented in France as soon as possible, especially as its effectiveness has been widely demonstrated in several European, North and South American countries and in Australia [38,39]. In addition, delays in vaccination are also observed with the booster shots administered at the age of 6, 11-13, and 25 years which coverage rates must absolutely be increased. Finally, the cocooning strategy must be reinforced because grandparents can transmit pertussis to non-immunized adults and young infants [40]. Acellular pertussis vaccines are very effective against the disease but seem to have little effect on carriage and induce immunity that rapidly declines over time [41]. Vaccination recommendations should be strictly followed and could even be strengthened by introducing a pertussis booster after the age of 25 years to increase herd immunity.

II. Other collateral effects of the pandemic

II. A. Impact on immunization programs and vaccine delays

Prior to the pandemic, infant and young children vaccination coverage rates were usually good in many countries. In France, a significant improvement was reported over the last years, because of the extension of mandatory vaccination implemented in January 2018 [42]. Vaccination coverage (at least three doses by 15 months) was over 94% for the hexavalent vaccine and 93% for the 13-valent pneumococcal vaccine. Vaccination coverage figures for hepatitis B (three doses by 15 months), MMR (one dose at 15 months), and meningococcal C (two doses by 15 months) were admittedly lower and insufficient, but a significant increase in 2017 was observed compared with 2019. However, vaccination coverage for booster shots, particularly DTPaP (diphtheria, tetanus, poliomyelitis, and acellular pertussis) at 6 and 11 years of age, and for HPV vaccination remained insufficient. This insufficiency increases with increasing age (population of 25 years and older), with less vaccinations performed and poor compliance with the recommendations of the French High Council for Public Health (French acronym HCSP) (pertussis not performed).

The COVID-19 pandemic had an impact on all vaccination coverage rates [43] as they all decreased, sometimes even sharply, particularly during the lockdown periods and were not fully restored afterwards [44]. Indeed, during the first lockdown implemented in March 2020, a strong decrease in physician visits was observed, including well-baby visits. The health crisis impacted all consultations for DTPaP booster vaccination, including pediatric appointments at 6 and 11-13 years.

Vaccine delivery has also drastically been reduced since 2020 despite improvement in August 2020, and the overall downward trend continued into early 2021. According to the data from Epiphare [44], for an annual birth cohort of approximatively 780,000, the number of missed vaccinations since March 2020 is:

- 70,000 for hexavalent (Diphtheria-Tetanus, inactivated poliomyelitis, Pertussis, *Haemophilus* B and hepatitis B) vaccines;
- 150,000 for Measle-Mumps-Rubella vaccines;
- 230,000 for papillomavirus vaccines;
- 720,000 children, adolescents, and adults not vaccinated with a tetanus containing vaccine.

Compared to many high-income countries, France has a less extended childhood vaccination scope, i.e., lacking rotavirus, varicella, *Neisseria meningitidis* serogroup B and *Neisseria meningitidis* serogroup ACYW vaccination program (Table 1).

II.B. Impact of the immunity debt on trained immunity

Children seem to be less often infected with SARS-CoV-2 than adults and present with less severe forms than adults [45]. Various hypotheses have been raised to explain this relative resistance of children to SARS-CoV-2: less ACE2 receptors, frequency of infections with common coronaviruses likely to induce cross immunity, role of trained innate immunity [46]. Indeed, one of the first lines of natural defense against pathogens is the innate immunity which role is to produce an immediate, rapid but non-specific response to an infectious aggression (phagocytosis, production of cytokines, etc.) and which effectiveness has limits. The immune system also develops an adaptive immune response, specific to the pathogen, allowing more effective protection during subsequent exposure to the same pathogen thanks to the development of an immune memory. In recent years, several studies suggested that frequent stimulations and "training" of innate immunity would increase its effectiveness [47]. This stimulation by exposure to various pathogens is undoubtedly more frequent in children than in adults. The concept of trained immunity corresponds to a kind of long-term functional reprogramming of innate immune cells, stimulated by pathogens and which would lead to a reinforced response during subsequent exposures. This process would have great advantages for host defense. Thus, this trained immunity would be established in children particularly exposed to viral infections in the first years of life and would be more effective in them than later in adulthood. The probable role of live vaccines, administered in childhood, on this trained immunity is being studied. The reduction of infectious contacts secondary to hygiene measures imposed by the pandemic may have led to a decreased immune training in children and possibly to a greater susceptibility to infections in children.

II.C The hygienist theory

The hygienist theory is based on observations made over the past decades: the decreased incidence of infections in Western countries is temporally associated with an increasing incidence of autoimmune and allergic diseases [48]. Studies also suggested the involvement of the microbiota, particularly the intestinal microbiota, in the increased incidence of these allergic and secondary autoimmune diseases [49]. In the era of lockdowns and NPIs, it seems

legitimate to hypothesize and assess the impact prolonged adoption of NPIs and reduction of infectious diseases as a whole may have on the imbalance of the intestinal microbiota and the related occurrence of allergic and autoimmune pathologies.

Conclusions

Low viral and bacterial exposures due to NPIs imposed by the COVID-19 pandemic raise concerns as we may witness strong pediatric epidemic rebounds once personal protection measures are lifted. In addition, the decrease in vaccination coverage and the potential increased number of cases of vaccine preventable diseases are of concern. This should lead to the implementation of reinforced catch-up vaccination programs. The French vaccination schedule does not include vaccines against rotavirus, varicella, and *Neisseria meningitidis* serogroup B and ACYW; France could thus be more vulnerable to some of these epidemic rebounds. This should lead to advocacy for the expansion of the French vaccination schedule. Finally, for diseases for which there is no vaccine, rapid screening, timely re-enforcement of hygiene measures, and adaptation of healthcare systems should be implemented.

Contribution of authors

RC, MA, MKT, EV, FA, CL, AR, NO, NG, and EG drafted the article. All authors revised and approved the article.

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Table 1. Additional vaccines included in childhood vaccine schedules in high-income countries

	Rotavirus	***Neisseria meningitidis* serogroup B**	***Neisseria meningitidis* serogroup ACYW**	**Varicella**
United-States	+	-	+	+
Canada	+	-	+	+
United-Kingdom	+	+	+	-
Ireland	+	+	+	-
Belgium	+		+	
Netherland	+		+	
Switzerland			+	
Italy*	+	+	+	+
Spain	+	+/-**	+	
Portugal	+	+	+	
Israel	+			+

* According to the region these vaccines could become mandatory or recommended and reimbursed

** According to the region