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RESEARCH ARTICLE

Vaccination against Pertussis in the era of acellular and whole-cell vaccines

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ABSTRACT

Pertussis in a highly infectious respiratory disease, and even though vaccination has been globally implemented since the 1940s, we are far from elimination, and even still suffering from many outbreaks throughout the world.

This comprehensive review is tailored primarily for clinicians and healthcare practitioners, aiming to deepen their insights into the evolving dynamics of Pertussis over time since the first whole-cell Pertussis vaccine was started. It delves into the high reactogenicity and alleged severe neurologic effects, which were later conclusively disproven. The ensuing repercussions of these early challenges manifested in multiple outbreaks, compelling the scientific community to respond proactively. This led to the development and subsequent implementation of acellular Pertussis vaccines, marked by an improved safety profile.

Moreover, the exclusive adoption of acellular Pertussis vaccines for widespread immunization in certain countries resulted in a notable surge in Pertussis cases. Subsequent investigations, conducted through both animal models and epidemiological studies, elucidated that acellular Pertussis vaccines exhibited a considerably diminished mucosal immunity. Consequently, nasopharyngeal carriage showed minimal reduction, leading to a substantial decline in indirect or herd immunity when compared to whole-cell Pertussis vaccines. Conversely, numerous developing countries presently incorporate whole-cell Pertussis vaccines either independently or in conjunction with acellular formulations. In light of this, precise recommendations must be systematically addressed to cultivate a more unified and pragmatic landscape for immunization strategies. These recommendations should be rooted in the latest scientific data and aligned with the guidelines articulated by both the World Health Organization and the Global Pertussis Initiative.

This concerted approach aims to optimize immunization practices on a global scale, fostering a harmonized and evidence-based framework for combating Pertussis. Relevant and updated issues concerning maternal, adolescent and adult vaccination are addressed, as well as the ongoing pipeline of new intramuscular and mucosal vaccines, and finally emphasizing the continuous need for improved surveillance and pharmacovigilance systems.

Introduction

Bordetella pertussis is an aerobic Gram-negative bacillus, which unlike other *Bordetella* species (e.g. *Bordetella bronchiseptica* or *Bordetella parapertussis*) is only transmitted among humans[1].

Pertussis, also known as "whooping cough," has been identified since at least the Middle Ages as a disease that affects mostly infants and children but can also affect teenagers and adults. The symptoms are divided in three distinct stages: the catarrhal phase, which symptoms are similar to a common cold; succeeded by the paroxysmal phase hallmarked by a characteristic cough accompanied with paroxysmal gasping breaths ('whoops') that may last for six weeks; followed by a convalescence period that can last another four weeks[1,2].

With a R0 of 15-17, Pertussis is among the most transmissible airborne infectious diseases. Infants under the age of one year are particularly vulnerable to the impacts of this condition, experiencing a higher rate of complications and mortality. However, it can also lead to significant morbidity in adolescents and adults, especially those aged 60 and above, or individuals with underlying medical conditions like asthma and chronic obstructive pulmonary disease[1,2].

Outbreaks were first described in written records in the 16th century by Guillaume de Baillou in France[3], however, in the prevaccination era, millions of cases occurred globally, with mortality rates ranging from 3.3 to 1500 per million, both in developed and developing countries[1-3].

This comprehensive review, centered on Pertussis, Pertussis vaccination, and their impact on public health, is specifically tailored for clinicians and healthcare practitioners. It aims to achieve the following objectives:

1. Chronological Understanding: Develop a chronological understanding of Pertussis vaccination, starting from the initiation with whole-cell Pertussis (wP) vaccines. Explore the cessation of widespread vaccination in various countries due to alleged, albeit unconfirmed, serious neurologic side effects. Examine the subsequent implementation of acellular Pertussis (aP) vaccines, that proved to have a better safety profile.

2. Manufacturing influence between different wP vaccines: Recognize the potential impact of variations in the manufacturing of wP vaccines on immunogenicity and/or safety.

3. Increased number of Pertussis cases after aP vaccine implementation: Understand why the exclusive implementation of aP vaccines was linked to an increased number of Pertussis cases, even with adequate vaccination coverage. Explore the immunologic mechanisms behind this phenomenon, drawing insights from both animal models and epidemiologic studies.

4. Understand current vaccination strategies: Develop a pragmatic rationale for vaccination strategies and schedules based on three categories: countries utilizing only wP, exclusively aP, or a combination of aP and wP vaccines. Align these strategies with recommendations from both the World Health Organization and the Global Pertussis Initiative.

5. Future Vaccine Platforms: Gain insight into potential future vaccine platforms for Pertussis.

6. Enhancing Surveillance: Strengthen the imperative to improve both surveillance and pharmacovigilance systems for enhanced public health outcomes.

Vaccination with whole-cell Pertussis vaccines:

a. HISTORY AND SUCCESS.

In the late 1940s, Pearl Kendrick, Grace Eldering, and Loney Gordon developed a combined vaccine containing Diphtheria and Tetanus toxoids, as well as the whole-cell Pertussis (wP) component to obtain the Diphtheria, Tetanus, and Pertussis (DTP) vaccine, which was widely adopted[4]. The Committee on Infectious diseases of the American Academy of Pediatrics suggested in 1944, and recommended in 1947, the routine use of this vaccine, and the recommendation was later adopted in other countries[5]. Vaccination coverage improved when the Expanded Program on Immunization (EPI) was established in 1974[5]. By the early 1980s, mass vaccination against Pertussis drastically reduced the morbidity and mortality associated with the disease[5].

b. WHOLE-CELL PERTUSSIS VACCINATION CONCERNS REGARDING SAFETY, ITS INTERRUPTION, AND PERTUSSIS RESURGENCE.

In the 1980s, just as the risks from having Pertussis decreased markedly, attention shifted from the risk of the disease to the fear of vaccine side effects. Doubts began to arise about the safety of wP vaccines, but not to Diphtheria and Tetanus toxoids, which led to a reduction of acceptance to the vaccine by the population, furthermore, in some countries, its use was completely rejected[6]. For instance, in the United Kingdom and the US, concerns about the safety of this vaccine were widely reported in the press as in television programs[5], resulting in decreasing vaccination coverages[7].

In England and Wales, before the introduction of wP immunization in the 1950s, the average annual number of notifications exceeded 120,000. By 1972, when vaccine coverage was around 80%, there were only 2,069 notifications of Pertussis. The professional and public anxiety about the safety and efficacy of the wP vaccine caused coverage to fall to about 60% in 1975, and around 30% by 1978. Major epidemics occurred in 1977–79 and 1981–83. In 1978 there were over 65,000 notifications and 12 deaths[8].

In Japan, the government decided to suspend Pertussis vaccination in 1975, mostly due to two suspected vaccine-related deaths in children and the publicity that came afterwards, however, two years later, the cessation of vaccination resulted in an increase in Pertussis cases with 40 deaths[8].

These major epidemics illustrate the impact of a fall in coverage of an effective vaccine. The actual number of deaths due to these Pertussis outbreaks was indeed higher, since not all cases in infants are recognized[8].

The reactogenicity of wP was extensively evaluated in DTP, and the Pertussis component, particularly the lipooligosaccharide proved to be the main factor responsible for the toxicity. Reported adverse reactions have ranged from local (redness, swelling, and pain at the injection site) to systemic reactions (low to high fever, persistent crying and irritability, and even, though rarely, seizures and encephalopathy)[5,8].

c. DISPELLING THE MISCONCEPTION OF ENCEPHALOPATHY AND SEIZURES LINKED TO WHOLE-CELL PERTUSSIS VACCINE.

Following the 1980s widespread publicity of wP vaccines causing seizures and/or encephalopathy, a raised concern in the scientific community questioned whether these allegations were in fact real:

- In 1994, Jale G et al, performed a population-based control study[9]. A total of 424 confirmed cases of neurological illness were identified prospectively during a 12-month period by statewide active surveillance from the population of 218,000 children 1 to 24 months of age living in Washington and Oregon (estimated 368,000 DTP immunizations given). Each case child was matched to two population control children by birth date (±5 days), gender, and county of birth. Odds ratios (OR) for specific neurologic diagnoses seven days after vaccination varied, but all confidence intervals (CI) included 1, in addition, there was neither elevated risk observed for nonfebrile seizures (OR, 0.5; 95% CI, 0.2 to 1.5).

-Barlow WE et al, in 2001 calculated the relative risks (RR) of febrile and nonfebrile seizures among 679,942 children after 340,386 vaccinations with DTP vaccine, 137,457 vaccinations with Measles, Mumps, and Rubella (MMR) vaccine, or no recent vaccination. Receipt of DTP vaccine was associated with an increased risk of febrile seizures only on the day of vaccination (adjusted RR, 5.70; 95% CI, 1.98 to 16.42). Neither vaccination was associated with an increased risk of nonfebrile seizures. As compared with other children with febrile seizures that were not associated with vaccination, the children who had febrile seizures after vaccination were not found to be at higher risk for subsequent seizures or neurodevelopmental disabilities[10].

-Ray P, et al, in 2006, performed a retrospective case-control study at 4 health maintenance organizations in the US, involving more than 2 million children. The cause of the encephalopathy was categorized as known, unknown, or suspected but unconfirmed. Up to 3 controls were matched to each case. Conditional logistic regression was used to analyze the RR of encephalopathy after vaccination with DTP or MMR vaccines in the 90 days before disease onset as defined by chart review compared with an equivalent period among controls indexed by matching on case onset date. Four-hundred and fifty-two cases were identified. When encephalopathies of known etiology were excluded, the OR for case children having received DTP within 7 days before onset of disease was 1.22 (95% confidence interval [CI] = 0.45-3.31, P = 0.693) compared with control children[11].

Accordingly, the above studies finally failed to yield any evidence between wP vaccination related seizures and/or encephalopathy.

d. DIFFERENCES BETWEEN WHOLE-CELL PERTUSSIS VACCINES MANUFACTURING IN RELATION TO REACTOGENICITY AND IMMUNOGENICITY.

The wP vaccine contains various amounts of whole nonviable bacterial cells that include all major pertussis antigens such as pertussis toxin (PT), adenylate cyclase toxin, lipooligosaccharide, filamentous hemagglutinin (FHA), and agglutinogens. The vaccine is prepared by growing *Bordetella pertussis* bacteria in a liquid medium, and a specific

cellular concentration is aliquoted after bacterial inactivation. Despite the simplicity of the procedure, the antigen content and perhaps vaccine immunogenicity and reactogenicity of wP vaccines varies between different manufacturers[12].

Clinical head-to-head scientific data:

-Steinhoff MC, et al., in 1995 compared the reactogenicity of two wP vaccines. A prospective, randomized, double-blinded assessment of two licensed DTP vaccines was performed in a multicenter clinical trial evaluating 13 acellular Pertussis (aP) vaccines in the US. Infants were immunized at 2, 4, and 6 months of age with a single lot of Lederle® (309 infants) or Massachusetts Public Health Biologic Laboratories (MPHBL®; 94 infants) vaccine. The group receiving the Lederle® vaccine demonstrated significantly higher antibody titers to PT by enzyme-linked immunosorbent assay (ELISA) as well as higher mean agglutinin titers. In contrast, the group receiving the MPHBL® vaccine demonstrated higher ELISA antibody levels to filamentous hemagglutinin and pertactin. In addition, the MPHBL® vaccine was significantly less reactogenic in nearly all clinical categories[13].

-In 2013, Zarei S, et al, in Iran, performed a randomized, double-blind and multicenter prospective study, in which 672 children aged 4-6 years were administered with either a local DTP vaccine (DTP- "Local") (n = 337) or a "commercial" vaccine (DTP-Pasteur°) (n = 335). The geometric mean titers (GMTs) of antibodies produced against Pertussis were 30.2 EU/ml for DTP- "Local" and 47.9 EU/ml for DTP-Pasteur° vaccines ($p<0.001$). Pain and fever were the most frequent local and systemic reactions observed after the vaccination. All local and systemic reactions observed after vaccination were significantly higher in subjects immunized with DTP- "Local" vaccine[14].

In conclusion, though not widely published, the current real-life evidence strongly suggests that manufacturing methods and/or technologies may affect both immunogenicity and/or reactogenicity of wP vaccines.

Vaccination with acellular Pertussis vaccines:

a. REASONS FOR ACELLULAR PERTUSSIS VACCINE INTRODUCTION.

As mentioned before, safety concerns with wP during the 1970s and 1908s ultimately led to the development of the first aP vaccine, namely the Japanese vaccine developed by Sato et al., containing purified antigens from *B. pertussis* mixed with Aluminum as an adjuvant[15]. This aP vaccine had an improved safety profile over the Japanese wP vaccine, while demonstrating comparable efficacy and was, therefore, implemented for use in children[16]. The effectiveness of this vaccine was evidenced by the steady decline in the incidence of the disease in Japan[17]. The first randomized controlled study on aP vaccines was conducted in Sweden, where two Japanese vaccines, one containing formaldehyde-inactivated PT and FHA and the other only with PT toxoid, were investigated and compared to a placebo control. Accordingly, the study confirmed the improved safety profile of aP over wP vaccines and demonstrated comparable culture-confirmed pertussis prevention efficacies of about 80% after two doses. Similar methods to produce aP vaccines were adopted in other

countries, generally with additional antigens, such as pertactin and serotypes 2 and 3 fimbriae, being combined with Diphtheria and Tetanus toxoids (DTaP)[18,19]. Preparations containing up to five components were developed, and several efficacy trials clearly demonstrated that the aP vaccines were able to confer short-term protection that was comparable to that of the most effective wP vaccines, with fewer local and systemic reactions[20]. By the late 1990s, most high-income countries had switched to DTaP, although the cheaper DTP has remained the vaccine of choice in low- and middle-income countries[21].

b. TYPES OF ACELLULAR PERTUSSIS VACCINES.

As mentioned, the main responsible for wP related toxicity is the lipooligosaccharide, hence, several purified antigens of *Bordetella pertussis* are currently present in many vaccines. The specific antigens: PT, FHA, pertactin (PRN), and fimbriae (FIM) vary on both the presence of all or some antigens, and in concentrations (µg) for each commercially available aP vaccine. In addition, some of these vaccines contain immunogens for other diseases such as Polio, *Haemophilus influenzae* type b, etc. Examples of these aP vaccines are in Table 1.

Table 1 Composition of the Pertussis components of selected acellular Pertussis vaccines,[22].

Vaccine	Manufacturer	Age licensed	Pertussis Toxin µg	Filamentous Hemagglutinin µg	Pertactin µg	Fimbrae µg
Infanrix	GSK°	6 weeks to 7 years	25	25	8	–
Boostrix	GSK°	older than 10 years	8	8	2.5	–
Daptacel	Sanofi Pasteur°	6 weeks to 7 years	10	5	3	5
Adacel	Sanofi Pasteur°	11 to 64 years	2.5	5	3	5
Pediacel	Sanofi Pasteur°	6 weeks to 4 years	20	20	3	5
Infanrix-IPV+Hib	GSK°	from 2 months	25	25	8	-
Repevax	Sanofi Pasteur°	from 3 years	2.5	5	3	5
Infanrix-IPV	GSK°	16 months to 13 years	25	25	8	-
Boostrix-IPV	GSK°	from 4 years	8	8	2.5	-

Concerns with acellular Pertussis vaccines:

a. REDUCED DURATION OF IMMUNITY COMPARED TO WHOLE-CELL PERTUSSIS VACCINES.

Various studies support the fact that immune protection against Pertussis persists for 10 and 20 years following natural infection and up to 12 years after wP vaccination, as compared to only 3 to 5 years following immunization with aP vaccines[23,24]. The latter makes school aged children more susceptible, requiring booster doses in younger ages. In addition, cohort-based efficacy studies conducted in several countries in Europe and in Senegal on infants and toddlers who received 3- or 4-dose series of Pertussis vaccines suggested that protection waned faster following aP than after wP vaccination[25,26]. Furthermore, after both three-dose and five-dose primary series of aP vaccination, the OR of Pertussis increases by a factor of 1.33 (95% CI 1.23–1.43) for every year after administration of DTaP,[24]. Clark et al, showed that fully vaccinated young children with aP were more likely to develop Pertussis compared to children vaccinated with wP[27]. Another study by Klein, et al during an outbreak of Pertussis in the US between 2010 and 2011 in school age children and adolescents, showed that children vaccinated with wP vaccines in early childhood was associated with five times the protection when compared to children immunized with aP vaccines[28]. The decrease in immunity was also reported in those who had completed a full immunization schedule with aP-containing vaccines[29]. Even though there are two studies (from Germany and Sweden) not showing differences in the long-term protection between aP and wP vaccines[25,26], it is difficult to estimate a reliable comparability between studies due to the differences of manufacturing that, as shown before, may change the immunogenicity of wP vaccines. In addition, surveillance methods may vary between geographic areas in the globe.

Indeed, the scientific data supporting the longer immunity of wP over aP vaccines is overwhelming, and not too different to natural immunity.

b. REDUCED MUCOSAL IMMUNITY COMPARED TO WHOLE-CELL PERTUSSIS VACCINES.

The pragmatic definition of mucosal immunity is relatively simple, but immunologically complex. We will define it as the ability of a vaccine to activate Th17 cells leading to secretion of IL-17 and IL-22 (cytokines secreted in epithelia including mucosae and directed to eliminate extracellular pathogens such as *Bordetella pertussis*) and produce IgA, the so called "mucosal antibody".

Bordetella pertussis can form biofilms that allow it to adhere to abiotic surfaces as well as to murine nasal and tracheal mucosa[30].

Warfel, Merkel, et al, assayed T-cell phenotypes in baby baboons before and after challenge- infection with *Bordetella pertussis*, and wP or aP vaccination. As expected, *Bordetella pertussis* infection triggered a purely TH17 response, as expected, also wP vaccination led to a predominantly TH17 response, with a lesser TH1 response, resulting in production of both IgG and IgA antibody production. In contrast, aP vaccinated baboons had only TH2 responses, with mostly IgE antibody production, hence,

protection on mucosae would not be expected[31].

These data, along with other studies[5], suggest different immunologic mechanisms between wP and aP vaccines, mostly on mucosal immunity, leading to distinct effects on nasopharyngeal (NP) carriage, and indirect or herd immunity.

c. REDUCED NASOPHARYNGEAL CARRIAGE AND INDIRECT IMMUNITY COMPARED TO WHOLE-CELL PERTUSSIS VACCINES.

NP carriage is the key for transmission of encapsulated respiratory bacteriae that causes not only respiratory infections, but severe life threating diseases, its best examples are *S. pneumoniae, N. meningitidis and Haemophilus influenzae* type b[32]. For these diseases, the overall impact of vaccination always involves its effect on reducing NP carriage, hence, induction of indirect immunity to non-vaccinated individuals, as proven when immunized infants against S. *pneumoniae* confer protection to older adults, also in high risk for invasive pneumococcal disease[33]. With wP and aP vaccines, neither NP carriage or colonization reduction studies (either in late phase 3 clinical trials or as part of phase 4 cohorts) were performed, therefore, indirect immunity following vaccination has not been well studied, until recently:

Warfel, Merkel, et al, again, brilliantly illustrated NP colonization and indirect protection or immunity with either natural infection, wP and aP vaccination, with the baboon model in four different publications:

The first study involved groups of infant baboons vaccinated with aP vaccines and with wP vaccines and subsequently infected with *Bordetella pertussis*[34]. In each case, vaccine-naive baboons developed clinical illness, whereas aP or wP vaccinated animals did not. However, the animals also underwent serial NP sampling for weeks, accordingly, among the wP vaccinated animals, NP carriage was detectable for a mean of 18 days (low bacterial densities) versus 30 to 35 days (at high bacterial densities), furthermore, NP carriage eradication in aP vaccinated baboons was not quicker than in non-immunized animals.

Baboons immunized with aP vaccines and then infected with *Bordetella* were co-nested with vaccine-naive animals who had not been exposed to the *Bordetella pertussis,* the outcome was that unvaccinated cage mate animals also became infected, showing that aP vaccinated animals remained contagious due to persistent NP colonization. The investigators then infected a vaccine-naive animal with and then co-housed it with both an aP-vaccinated animal and a second vaccine-naive animal[35]. Both animals acquired NP carriage at the same colonization density. In a final experiment, female baboons were vaccinated with aP vaccines during pregnancy. After delivery, the newborn baboons were exposed to *Bordetella pertussis,* but were fully protected from clinical disease, nonetheless, 100% became colonized at similar densities as the infant baboons born from unvaccinated mothers[36]. In summary, these animal experiments prove that aP immunization prevents disease, confers vertical protection (from mother to infant) to clinical Pertussis (disease), but does not prevent NP colonization, neither indirect protection to non-vaccinated animals. By

contrast, wP vaccinated baboons had much lower NP carriage in both duration and bacterial density, as the investigators data comparing *Bordetella pertussis* NP shedding: wP vaccinees shedding was more than 1,000-fold lower than aP-vaccinated baboons[37].

We lack most of this essential information in humans, however, a longitudinal study published in 2003 in Senegal supports these interpretations. Only by looking at secondary attack rates among vaccine failures, the investigators showed that wP vaccination reduced secondary infections by 86% compared with only 6% from aP vaccinees[38].

Acellular Pertussis vaccine implementation related to the increased number of Pertussis cases in developed countries.

In the US, wP widespread vaccination was introduced in infants in the 1940s, and, as shown in Figure 1, its effect was impacting, with a reduction of over 200,000 yearly reported cases of Pertussis. The licensure of aP was first started in 1991 as 4th and 5th doses only, followed by recommendation for all five doses in childhood by 1996-1997, as DTaP[8]. Accordingly, a rise in Pertussis cases rose significantly in 2005, and was markedly increased by 2010. Similar trends occurred also in Australia, the Republic of Ireland, and England/Wales, with reemergence of Pertussis cases between 3 to 6 years of aP vaccine introduction (see Figure 1)[39].

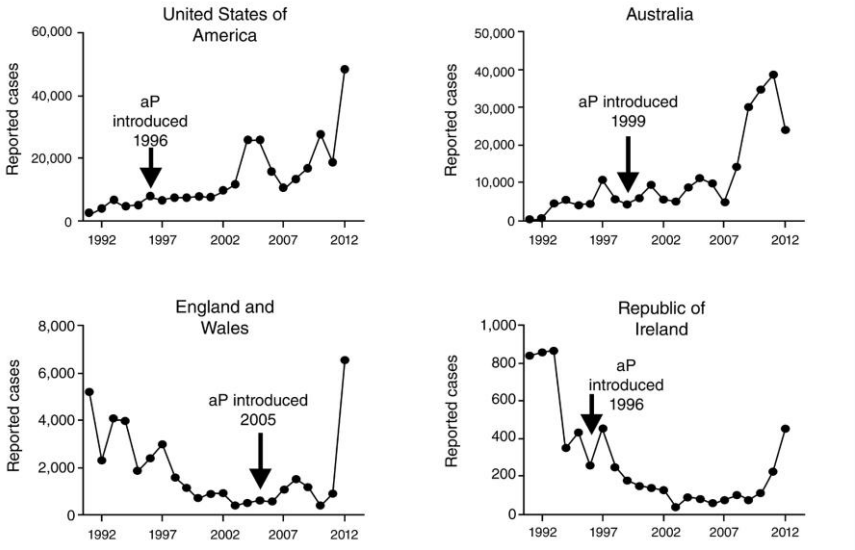

Figure adapted from Mills KHG et al, Trends in Microbiological Sciences, 2014 22(2): 49-52.

- US data from The Center for Disease Control and Prevention, Atlanta, GA, USA (http://www.cdc.gov/pertussis/fast-facts.html);
- Australia data from the National Notifiable Diseases Surveillance System, Office of Health Protection, Department of Health and Ageing, Canberra, Australia (http://www9.health.gov.au/cda/source/rpt_2_sel.cfm);
- UK data from The Health Protection Agency, London, UK; http://www.hpa.org.uk/hpr/archives/2013/hpr14-1713.pdf);
- Ireland data from The Health Protection, Surveillance Centre, Dublin, Ireland (http://www.hpsc.ie/hpsc/A-Z/VaccinePreventable/PertussisWhoopingCough/)-

FIGURE 1 Trends of Pertussis incidence in US, Australia, England/Wales, and the Republic of Ireland 1992 – 2012 Taken from Gil GJ, et al.[39]

Nevertheless, many other factors can be influencing the rise of Pertussis cases after aP vaccine implementation, hence, the following questions were formulated and very well addressed and described by Gill, et al.[39].

1. Detection bias: In the United Kingdom, PCR was used as an elemental tool to confirm Pertussis cases in 2006, one year after aP vaccine introduction. As seen in Figure 2, there was a slight rise on the overall Pertussis incidence, however, starting in 2011, with the same surveillance, the total incidence rose eight times more, from ~2 to more than 25/100,000.

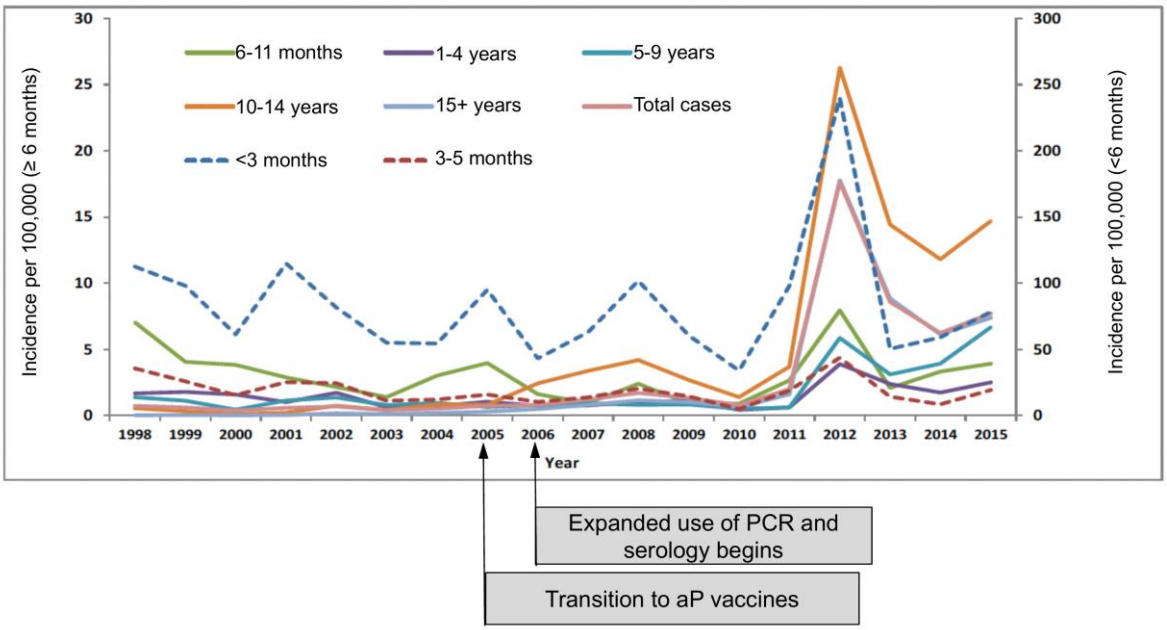

FIGURE 2 Pertussis incidence in the United Kingdom, by age group, 1998–2015. Taken from Gil GJ, et al.[39].

2. Lower vaccination coverages after aP vaccine introduction: Only in the US, aP vaccine coverage in children (five doses) not only did not decrease, but also has been significantly improved by implementing aP vaccination in adolescents, older adults, and more recently pregnant women[40].

3. Evolutionary immunological shifts of *Bordetella pertussis*: Bart et al published a series of phylogenetic analyses among global *Bordetella pertussis* isolates collected during the pre- vaccine, the wP vaccine, and the aP vaccine era[41,42]. Results were impressive. The introduction of aP vaccines, and to a lesser extent wP vaccines, resulted in shifts of the specific allelic isoforms of genes coding for most of the aP vaccine antigens. More studies have identified disease causing *Bordetella pertussis* isolates that stopped expressing one or more of the aP antigen genes, indeed, a definitive strategy for evading antibodies targeting these proteins, which can be a factor of aP vaccine decreased long-term protection, but lesser with wP.

In summary, switching from wP to aP widespread vaccination was indeed the main (though not the only) factor associated with the rise of Pertussis cases in developed countries where wP was completely suspended.

New vaccine platforms against Pertussis:

a. INTRAMUSCULAR VACCINES:

Third generation Pertussis vaccines are indeed needed. Potential approaches for new intramuscular vaccines would be to develop less reactogenic wP vaccines (not yet done), change in aP antigens (uncertain effect), increase quantities of current circulating antigens (would require large trials), genetically inactivate PT (advisable since would increase immunogenicity, however, large trials needed), and add adjuvants to aP (would require large trials), among others.

To date, results from a phase 2/3 randomized-controlled clinical trial with a monovalent Pertussis vaccine containing recombinant, genetically inactivated pertussis toxin (aPgen) alone, or as DTaPgen, versus a chemically detoxified comparator vaccine (DTaPchem) were recently published[43]. Three years post-vaccination, the seroconversion rates for PT-neutralizing antibodies were 65.0% (95% CI 44.1–85.9) and 55.0% (95% CI 33.2–76.8) in aPgen and DTaPgen recipients, respectively. Based on these results, the genetically detoxified monovalent aPgen and DTaPgen vaccines can be expected to induce longer-lasting protection than chemically inactivated DTaP vaccines, but larger clinical trials are needed.

b. NASAL VACCINES.

Mucosal (nasal) vaccines against Pertussis would be the ideal way to immunize since, by delivering the immunogens thru the natural form of infection, both mucosal immunity and reduction on NP colonization would potentially be stronger than with any intramuscular vaccine, leading to a better indirect or herd immunity, and an overall higher impact.

Nasal vaccines are in the pipeline, there are several studies in animals, and others at initial steps in human clinical trials. Examples for these platforms are live attenuated, aP with adjuvants, and nasal wP with outer membrane vesicle pertussis vaccines, we need to wait for results on phase 3 clinical trials[44].

Proposed indications for Pertussis vaccination in infants and toddlers:

a. COUNTRIES USING ONLY WHOLE-CELL PERTUSSIS VACCINES.

The World Health Organization (WHO) recommends a 3-dose primary series, with the first dose administered as early as 6 weeks of age; subsequent doses should be given 4–8 weeks apart, at age 10–14 weeks and 14–18 weeks. The last dose of the recommended primary series should ideally be completed by 6 months of age with either wP or aP vaccines[45]. Many countries often switch from one producer to another, complicating the comparability of surveillance data, if there are any. The WHO recommends that "any change in vaccine or vaccine strategies should be informed by data", whereas in many cases it is unclear whether a comparison between vaccines took place before changing to another manufacturer[45]. Since there is lack of clinical studies showing changes in immunogenicity and safety profiles by switching wP vaccine manufacturers, but many countries do so, the Pertussis Global Initiative strongly recommends enhancing both surveillance and pharmacovigilance[46].

b. COUNTRIES WITH MIXED ACELLULAR AND WHOLE-CELL PERTUSSIS VACCINES SCHEDULES.

In the European Union, Poland is the only country using a primary series with aP vaccine, followed by wP vaccination for boosters,[5], this same approach is used in many other countries[47].

No accepted serological correlate of protection after vaccination with either wP- or aP-containing vaccines has been established, although various parameters have been suggested,[5], hence, interchangeability between wP and aP vaccines is difficult to assess in a non-large clinical trial. Nonetheless, few studies have addressed this issue, as an example, a novel liquid hexavalent DTwP-containing vaccine (EasySix, Panacea Biotec°) was compared with Pentavac° + inactivated poliovirus (IPV) in a small study of around 300 infants in India, and it was reported that the immunogenicity would be similar[48].

The lack of robust data resulted in a general recommendation from the WHO not to interchange wP or aP vaccines from different manufacturers during the primary series,[45], though this recommendation is not universally followed.

Countries only using acellular Pertussis vaccines.

Most developed countries use solely aP vaccines for primary immunization in infants. Returning to wP vaccines is not feasible since would most likely carry out significant criticism by the media, and, particularly, antivaccination groups. Both the Pertussis Global Initiative and the WHO strongly recommend high vaccination coverages and enhancing surveillance[45,46].

Other essential measures:

a. VACCINATION DURING PREGNANCY.

In the US, one year after the FDA approved TdaP (a formulation only for adolescents and adults) post-partum vaccination in pregnancy was implemented, followed by antepartum vaccination in 2011, and vaccination on all pregnant women in the third trimester in 2012[49]. Based on many clinical trials, and real-world evidence (meta-analysis), Tdap vaccines induce pathogen specific antibodies, and those antibodies are known to be transferred from mother to the fetus *in utero* and to the newborn via milk (in a lesser extent), conferring passive immunity, and rapid protection to the newborn and infant[49]. Nevertheless, transferred antibodies may impair the immune response to some *Bordetella pertussis* antigens and even to pneumococcal conjugate vaccines[49,50]. The latter has been shown with aP vaccines, and data of this phenomena with wP containing vaccines are mixed, but also very suggestive[49,50]. Furthermore, a very recent study published in 2024 by Briga M, et al.[51], by implementing a new mathematical model, transient dynamics showed to potentially mask blunting for at least a decade after rolling out maternal immunization. Hence, the current epidemiological evidence may be insufficient to rule out modest reductions in the effectiveness of primary vaccination. However, irrespective of this potential collateral the authors predicted that maternal immunization would remain effective at protecting unvaccinated newborns, supporting current public health recommendations.

In summary, the clinical relevance of these potential immune interferences is unknown, and both the WHO and the Pertussis Global

Initiative strongly recommend vaccination during pregnancy preferably on the third trimester, and continuing primary Pertussis vaccination in infants as scheduled.[40,45,46].

b. VACCINATION IN ADOLESCENTS, ADULTS, AND IN ELDERLY:

Adolescents and adults with asthma, chronic pulmonary obstructive, and adults > 60 years of age are of high risk of complications after infected with *Bordetella pertussis*[45], hence, vaccination to these populations is highly recommended by the WHO. In addition, family members not previously vaccinated benefit by receiving a dose of TdaP (the cocooning strategy).

Only aP-containing vaccines should be used for vaccination of persons aged ≥7 years[45].

In some countries, including Australia, Canada, France, Germany and the US, adolescents and adults are offered boosters of TdaP vaccine[52].

The dilemma comes when widespread Pertussis vaccination is indicated in health adolescents and adults. The study published by Ward JI, et al in 2005 in a phase 3 clinical trial with 1,391 healthy adults enrolled, vaccine efficacy by TdaP on preventing case-definition Pertussis was of 92%[53], additionally, a meta-analysis published in 2019 by Xu J, et al, showed a vaccine protective effect of 88.89%, with a very acceptable safety profile,[52]. Finally, a pharmacoeconomic publication by Lee GM, et al, concluded that routine vaccination of adults aged 20 to 64 years with TdaP is cost effective if Pertussis incidence in this age group is greater than 120 per 100,000 population[54].

In summary, even though the WHO states that decisions concerning vaccination programs in this population should be based on incidence and cost–effectiveness data, and that high coverage of routine immunization in infants must be in place prior to the introduction of vaccination of adolescents and adults, both scientific and pharmacoeconomic data strongly support the vaccination of all adolescents and adults, irrespective of health status.

c. COVERAGE, SURVEILLANCE, PHARMACOVIGILANCE:

High vaccination coverages, irrespective of the type of Pertussis vaccine implemented, is necessary to prevent the dissemination and resurgence of outbreaks. In addition, high immunization coverage can induce the decrease of virulent strains[55].

Almost all countries differ from epidemiologic surveillance and pharmacovigilance methods for Pertussis, varying from hospital-referred passive to prospective-active surveillance systems, leading to misconceptions of Pertussis incidence, and vaccine related toxicity. Indeed, avoidance to vaccine hesitancy is crucial, and should be address individually per country or region.

Conclusions:

Pertussis, despite being a vaccine-preventable disease, remains far from eradication across various regions of the globe. In a landscape where both whole-cell Pertussis and acellular Pertussis vaccines coexist, adherence to established recommendations becomes imperative to optimize both protection and safety across all populations. While prioritizing the immunization of young infants is paramount, it is equally crucial to strongly recommend vaccination for adolescents and adults.

In accordance with guidelines from esteemed entities such as the Global Pertussis Alliance and the World Health Organization, the necessity to enhance surveillance systems and pharmacovigilance is deemed obligatory. Moreover, allocating resources to support the clinical development of novel and improved vaccines is crucial for addressing the evolving challenges associated with Pertussis.

The imperative for continuous medical education on Pertussis and Pertussis vaccines, coupled with fostering societal awareness of this potentially lethal disease, cannot be overstated. Such concerted efforts are vital in sustaining a comprehensive approach toward the prevention and control of Pertussis on a global scale.

Conflict of Interest:

None

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