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Review

Pertussis vaccination in mixed markets: Recommendations from the Global Pertussis Initiative

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ABSTRACT

The Global Pertussis Initiative is an expert scientific forum that publishes consensus recommendations concerning pertussis for many regions of the world. Here, we give recommendations for the primary vaccination of infants in those countries where whole-cell pertussis (wP)- and acellular pertussis (aP)-containing combination vaccines are used in parallel. A selective literature review was performed concerning the influence on safety, immunogenicity, and effectiveness of mixing wP- and aP-containing vaccines for primary immunization of infants. In addition, local data were collected from various countries and the results discussed in a face-to-face meeting. Very few data addressing issues of mixing combination vaccines were identified, and no data were available concerning the effectiveness or duration of protection. It was also found that pharmacovigilance data are scarce or lacking in those countries where they would be needed the most. We then identified frequent problems occurring in low- and middle-income countries (LMICs) where both vaccine types are used. Relying on local knowledge, we give practical recommendations for a variety of situations in different settings. Specific needs for additional data addressing these issues were also identified. International bodies, such as the World Health Organization (WHO), as well as vaccine producers should try to find ways to highlight the problems of mixing wP- and aP-containing combination vaccines with robust data. Countries are urged to improve on their pharmacovigilance for vaccines. For practicing physicians, our recommendations offer guidance when wP- and aP-containing vaccines are used in parallel during primary immunization.
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Introduction

The Global Pertussis Initiative (GPI) is an expert scientific forum that seeks to raise awareness of pertussis and publishes consensus recommendations for pertussis monitoring, prevention, and treatment across many regions of the world. The GPI has now developed recommendations for those countries where whole-cell pertussis (wP)- and acellular pertussis (aP)-containing combination vaccines are used in parallel. This article presents the recommendations put together by a working group and discussed during a face-to-face meeting in Bangkok, Thailand, May 2–3, 2019.

Combination vaccines containing wP (i.e., detoxified killed whole *Bordetella pertussis* bacteria) produce an immune response against a multitude of antigens presented as particulate matter on the bacteria. Combination vaccines with aP contain between one and five purified, stabilized, and chemically or genetically modified (detoxified) *B. pertussis*-derived protein antigens. wP vaccines were developed first, and the broad use of these vaccines

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significantly reduced pertussis morbidity and mortality. However, wP-containing vaccines induce significantly more injection site and systemic (mainly febrile) reactions than aP-containing vaccines (Cherry and Heininger, 2018; Patterson et al., 2018). As expected, the vaccine-induced immune responses are different, with bacterial virulence factors becoming the major target after immunization with aP vaccines (Edwards and Decker, 2017). In respect to the type of cellular immunity, wP-containing vaccines induce a Th1 and Th17 skewed response and, in the mouse model, also CD4 T-memory cells that reside in the lungs (Allen et al., 2018), whereas aP-containing vaccines mostly induce a Th2 leaning response (Edwards and Berbers, 2014). This may also cause differences in the effectiveness of the vaccines and in the duration of protection induced. Priming with one type of vaccine defines the overall characteristics of the cell-mediated immune response, and this type might not be changed by subsequent immunizations or infections (Bancroft et al., 2016).

The aP-containing combination vaccines were developed in high-income countries and are also mainly used in these countries (Figure 1), whereas most infants worldwide today are still primed with wP-containing combination vaccines. These are primarily used in low- and middle-income countries (LMICs) (Figures 1 and 2), and it is astonishing to see how income and the use of wP-containing combination vaccines overlap. However, in many LMICs, wP- and aP-containing vaccines share the market. Parents may decide to vaccinate their children with either wP or aP combination vaccines based on their paediatrician's recommendation, including the different pricing for wP- and aP-containing vaccines, the availability of vaccines, media coverage on unwanted effects, the more 'modern' image of aP-containing vaccines, and additional reasons, and the two types may be mixed during the vaccination process. Therefore, recommendations are needed to advise vaccinating physicians regarding if and how wP and aP combination vaccines can be interchanged during the primary course and the first booster.

Combination vaccines containing wP or aP components are regarded as two rather homogeneous entities, irrespective of the individual brand of the vaccine. However, already in the 1950s, differences between brands of vaccine had become evident, and this still holds important information for today, such as "(i) it is difficult to forecast the field performance of any whole-cell pertussis vaccine without randomized placebo controlled trials using clinical outcome measures; and (ii) it is impossible to extrapolate from the result of an assessment of one type of whole-cell vaccine to reliable assessments of the effects of another vaccine" (Jefferson, 2007). These findings were reiterated in the efficacy trials of aP vaccines, where a licensed US-produced vaccine had a surprisingly low point estimate of efficacy of 36% (Italy) and 48% (Sweden) (Edwards and Decker, 2017). Thus, distinguishing different brands of wP-containing combination vaccines must be

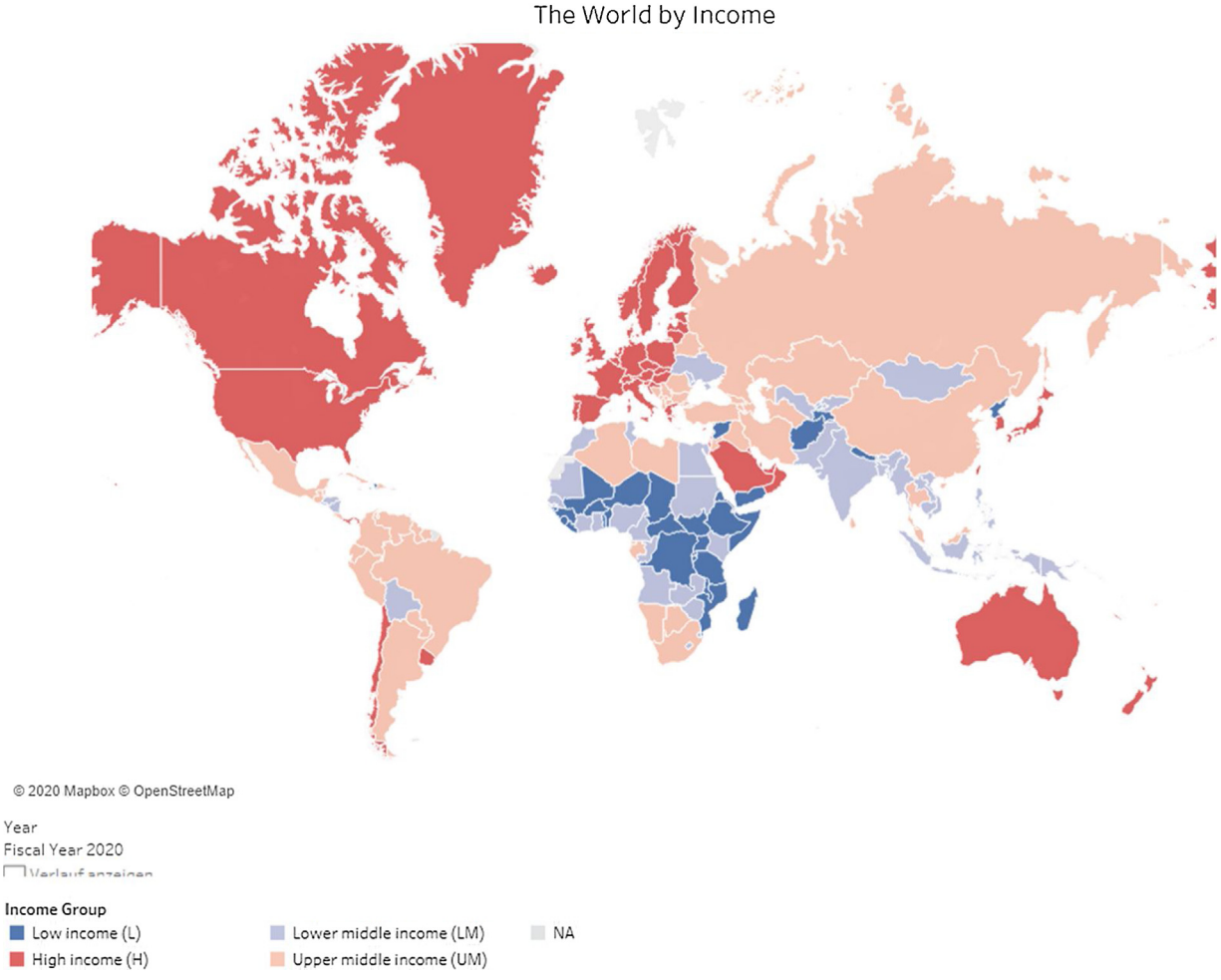

Figure 1. Distribution of high-, middle-, and low-income countries worldwide.
Data source: The World Bank: http://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html.

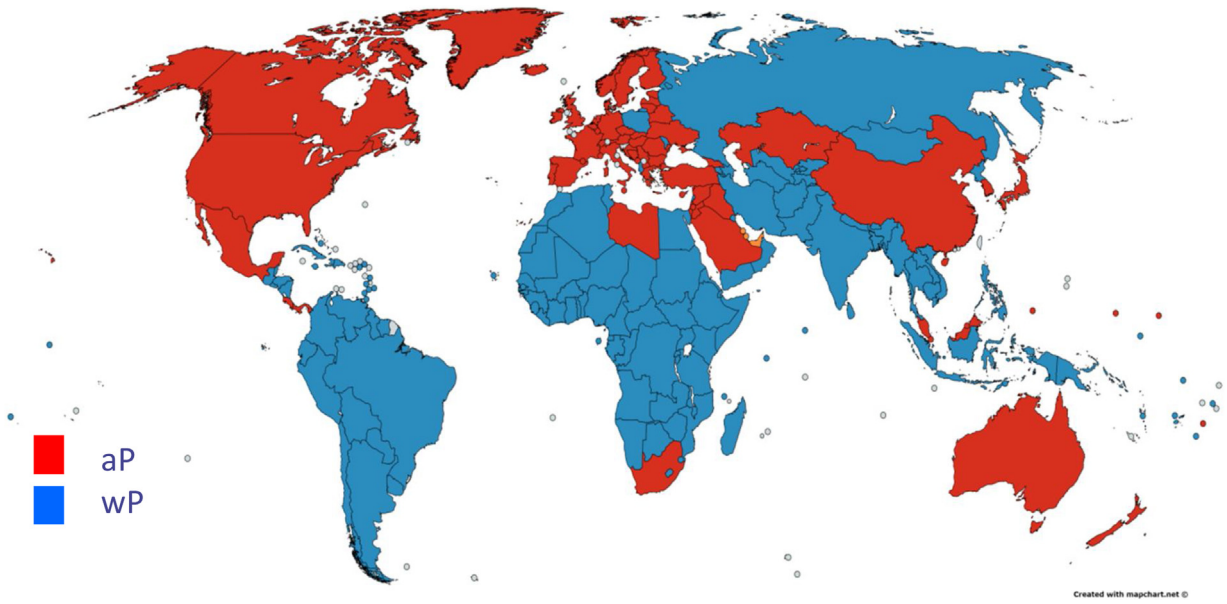

Figure 2. Countries using acellular pertussis (aP)- and whole-cell pertussis (wP)-containing combination vaccines in 2016.
Red: aP combination vaccines used (>95%). Blue: wP combination vaccines used.
Data sources: "WHO vaccine-preventable diseases: monitoring system. 2016 global summary" (http://apps.who.int/immunization_monitoring/globalsummary/schedules, accessed October 16, 2017) and reports from individual countries.

done by measuring their protective efficacy/effectiveness against disease, which may be estimated by controlled studies, but also by pertussis surveillance systems (Guiso and Wirsing von König, 2016).

Immunogenicity data for wP vaccines, when available, have also shown that big differences exist among brands of wP vaccine. Edwards et al. (1995) showed that one US-licensed wP vaccine produced a 46-fold increase in antibodies to pertussis toxin (PT) in infants after three immunizations, whereas another only induced a 2.4-fold increase. Similar findings were also reported at that time from South Africa (Ramkissoon et al., 1991) and elsewhere. Comparing wP-containing vaccines, we thus must rely on surveillance systems to estimate effectiveness of wP and aP vaccines, which are virtually absent in most countries where both vaccines are used.

Safety issues arising from the parallel use of wP- and aP-containing vaccines would require an effective system for monitoring adverse events after vaccination, which also rarely exists in many of the respective countries (Kumar et al., 2016).

Finally, almost all wP- and aP-containing vaccines are administered in combination with diphtheria and tetanus toxoids, but in many cases they are also combined with polyribosylribitol phosphate from *Haemophilus influenzae* type b (Hib), inactivated poliovirus, or the hepatitis B virus surface antigen (HBsAg). In considering interchangeability, possible effects for all vaccine antigens have to be taken into account (Decker et al., 2018).

We tried to address the following queries regarding sequential use of wP and aP vaccines in the same individual:

(1) Is the safety impaired? We assumed that we could get information from regulatory and pharmacovigilance data.
(2) Is the immunogenicity impaired? We tried to find immunogenicity studies that compared different brands of vaccine.
(3) Is the effectiveness altered? Without any trials or studies to base this on, this could only be analysed by a sustained surveillance of pertussis.
(4) Is the duration of protection altered? As before, without any trials or studies, this could only be based on a sustained surveillance of pertussis.

Data basis

The PubMed database was searched using the terms "pertussis" AND "acellular" AND "whole-cell" to identify studies reporting the use of wP- and aP-containing vaccines concomitantly. We also benefitted from the local knowledge of all authors in their jurisdictions. A list of World Health Organization (WHO) prequalified brands of wP- and aP-containing combinations is available at: https://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/ (accessed January 16, 2019). For practical reasons, our recommendations are summarized in 'question and recommendation' boxes (Q/R).

Regulation and release of vaccines

The WHO provides guidance to manufacturers for the prequalification process and sets various requirements for vaccines (https://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_manufacturers_guidance/en/). However, regulatory processes differ from country to country, and the procedures for emerging countries have recently been summarized (Dellepiane et al., 2018). Irrespective of the many attempts to standardize the documents needed for licensure, the requirements for dossiers differ significantly between countries, and only 17% of countries regard a WHO prequalification as sufficient.

Q: Can I use all WHO-prequalified vaccines in my country?
R: No, you should use only vaccines that are properly licensed in your country.
Q: Can I extend the age bracket of licensed vaccines when the vaccine is licensed for this age group in other countries?
R: As a general rule you should only use the vaccines according to the insert relevant for your country. If you think that a vaccination is needed but it

would be 'off-label' in your country, you have to balance the benefits of vaccination and the risk of your personal responsibility.

Q: Does the WHO prequalification ensure sustained quality, immunogenicity, safety, and efficacy for different products?

R: Prequalification data are not resubmitted on a regular basis, and no efficacy/efficiency data are requested.

Safety and pharmacovigilance

Although few data are available on the safety aspects of interchanging various brands of wP-containing and aP-containing combination vaccines in individuals, it can be assumed that in daily routine this happens quite often. Both wP- and aP-containing combination vaccines have been used in parallel in many countries of the world, including many high-income countries. As no specific safety signal has been detected until now, we assume that wP- and aP-containing combination vaccines have been interchanged without significantly endangering patient safety.

Pharmacovigilance systems in five Asian countries were compared by a WHO study group in 2013, and big differences in the effectiveness of the systems were described, with Thailand having the most advanced and functional system (Nwokike et al., 2020). For India, a position paper of the Indian Academy of Pediatrics is available (Chitkara et al., 2013). 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. As an example, India introduced a pentavalent vaccine (diphtheria, tetanus, and whole-cell pertussis (DTwP)–Hib–hepatitis B (HepB)), and some sudden unexplained deaths occurred 72 h after vaccination (Puliyel et al., 2018), which called for a prospective population-wide analysis. In 2013, Vietnam suspended Quinvaxem when deaths in infants were reported days after receiving the vaccine. The WHO reviewed these cases and found "that no unusual reaction could be attributed to pentavalent vaccines" (World Health Organization, 2020), but overall trust in vaccines was significantly impaired. In Uruguay, events classified as severe due to hypotensive hyporesponsive episodes (HHE) increased (Ministerio de Salud Uruguay, 2020), and subsequently the vaccine brand was changed.

Q: When an infant experiences a HHE or any other severe adverse event after a wP combination vaccine dose, should the immunization series be continued with an aP combination vaccine for which the probability of these episodes is lower?

R: You may consider giving an aP combination vaccine as they have a lower risk of HHE compared with wP vaccine, although the overall recurrence rate is low. It may, however, be sensible to give any additional dose in a specialized environment (Crawford et al., 2018). Unfortunately, many of these infants receive no additional doses (Zafack et al., 2017). Additionally, you should report all HHE episodes to your local pharmacovigilance system.

Interchangeability of pertussis-containing vaccines: formal aspects

Many countries, jurisdictions, and international organizations tender for vaccines, and by doing so they regard all licensed wP- or aP-containing combination vaccines and/or all WHO-prequalified wP- and aP-containing vaccines as equal and interchangeable in respect to safety, effectiveness, duration of protection, and immunogenicity. This aspect is important when shortages of available vaccines occur or when the switch from one brand to another during tendering causes an interruption in vaccine supply. Thus, jurisdictions in many countries often switch from one producer to another, complicating the comparability of surveillance data, if there are any.

Q: If one wP combination is actually unavailable in my country, should I postpone the next dose or continue with whatever combination vaccine is available?

R: Delaying doses puts infants at risk of disease. In the absence of sufficient data, it is probably better to give on-time doses than to postpone and stick rigidly to the same manufacturer.

Q: After a jurisdiction changes to a new brand of combination vaccine, is there a minimum recommended time for both brands to remain available in parallel?

R: For practical reasons, both brands should be available at least for the time needed to finish the primary series.

Interchangeability: immunogenicity data

No accepted serological correlate of protection after vaccination with either wP- or aP-containing vaccines has been established, although various parameters have been suggested (Table 1), such as anti-PT, anti-pertactin (PRN), anti-fimbriae (FIM) or anti-filamentous haemagglutinin (FHA) serum antibody levels. However, it is unlikely that a simple correlate of protection exists (Plotkin, 2013). Immunization with wP-containing combination vaccines results in an increase in antibody titres to a variety of antigens of *B. pertussis* organisms, and the pattern depends on the type of wP vaccine and the immunization schedule (WHO Immunological Basis for Immunization Series, 2017). A trial in the 1990s (Edwards et al., 1995) measured antibodies to wP vaccines with standardized methods, but the results of immunogenicity studies on wP vaccines still suffer from using non-standardized methods, although the use of ELISA tests with purified antigens measuring in international units per millilitre (IU/ml) has been recommended repeatedly (Guiso et al., 2011). As explained above, the primary immune response to either wP- or aP-containing combination vaccines defines the type of cellular immune response for all subsequent booster vaccinations (Bancroft et al., 2016).

Few studies have addressed the interchangeability of aP and wP combination vaccines from different manufacturers during primary vaccination. A wP-containing combination vaccine from Crucell (Quinvaxem) was compared with a three-component wP combination vaccine from GlaxoSmithKline (Tritanrix) in the Philippines, and the authors suggested that the vaccines could be readily interchanged (Capeding et al., 2014). 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 (Mohanty et al., 2018).

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 (World Health Organization, 2015). Similarly, the Canadian Immunization Guide stated that, for primary immunization, a vaccine from the same manufacturer should be used whenever possible. For the 18-month booster, and for the preschool booster, experts agreed that aP-containing combination vaccines can be interchanged without loss in immunogenicity (Canadian Immunization Guide, 2006). Similar recommendations are given in the Centers for Disease Control and Prevention (CDC) Pink Book (Centers for Disease Control and Prevention, 2020): "Series should be completed with same brand of vaccine, if possible; limited data suggest that 'mix and match' [diphtheria, tetanus, and acellular pertussis] DTaP schedules do not adversely affect safety and immunogenicity; use different brand of DTaP if necessary."

Table 1
Suggested correlates of protection after vaccination with wP or aP vaccines (adapted from World Health Organization (WHO Immunological Basis for Immunization Series, 2017)).

Antibody type	Study type	Vaccine type	Correlation
Agglutinins (anti-FIM)	Vaccine trial	wP	High titres protect
Agglutinins (anti-FIM)	Household contact study	wP (?)	High titres protect
Anti-PRN	Household contact study	wP (?)	High titres protect
Anti-PRN	Vaccine trial	aP	High titres protect
Anti-PRN + anti-PT	Vaccine trial	aP	High titres protect, especially when combined
Anti-PT	Household contact study	aP	Low titres make susceptible
Anti-PT	Household study	aP	High titres protect
Anti-FIM	Household contact study	aP	High titres protect
Anti-FHA	Cohort study	wP	High titres protect

aP, acellular pertussis; wP, whole-cell pertussis.

Q: Are pertussis immunogenicity data from combination vaccines relevant for my choice of vaccine?
R: It is important to remember that there is no reliable serological correlate or surrogate of protection. Immunogenicity data have to be interpreted with caution and should not be the primary criterion to choose a vaccine.

Interchangeability: priming with wP-containing vaccines and boosting with aP-containing vaccines

Many high-income countries have switched from priming with wP- to aP-containing vaccines. Recent studies, mainly from North America and Australia, showed that the duration of protection after booster vaccination with aP vaccines in adolescence was longer when the primary vaccination was done with wP-containing vaccines that were licensed in the United States or Australia (Klein et al., 2012; Sheridan et al., 2012), and a decreasing number of doses of DTwP was significantly associated with an increased risk of contracting pertussis (Sheridan et al., 2012). Based on the lower duration of immunity induced by aP vaccines, the WHO position paper on pertussis vaccines highlights that "National programmes currently using aP vaccine may continue using this vaccine but should consider the need for additional booster doses and additional strategies such as maternal immunization in case of resurgence of pertussis" (World Health Organization, 2015).

Q: In an aP-primed infant, should I give an additional dose of wP combination vaccine to prolong the duration of protection?
R: There are no robust data to support this, and it is not advisable.

Interchangeability: priming and boosting with aP-containing vaccines

Many countries in the world (Figure 1) use aP-containing vaccines for priming and boosting, and so far no safety issues have emerged from these countries.

Q: Can I freely interchange aP combination vaccines depending on their price?
R: As mentioned in the recommendations above, the same brand should be used for primary immunization if possible; if unavailable, another brand should be used. Interchanging is less critical for the reinforcing dose in the second year.

Concomitant use of wP- and aP-containing vaccines during primary immunization

Very few countries have recommended starting with two doses of aP-containing vaccines and using a wP-containing vaccine as the third dose. There are no pharmacovigilance data available from Saudi Arabia where this sequential use was recommended between 2013 and 2016.

Mixing different brands of wP for primary and booster immunization

In clinical practice, mixing different brands of wP depending on the local situation may occur quite frequently, but apart from very few studies (Capeding et al., 2014), effects on reactogenicity and immunogenicity were not sufficiently addressed for most available wP products.

Q: Can differing wP-containing vaccine brands be used in the same individual?
R: Yes. It is better to give on-time vaccination than delay in the hope of sourcing a previous wP brand.

Duration of protection against pertussis after interchanging wP- and aP-containing vaccines

As before, mixing different brands of wP- and aP-containing combination vaccines depending on the local situation may occur quite frequently, but no formal studies have addressed this question in relation to the duration of protection provided by the sequential use of different vaccines.

Q: Does mixing of brands reduce protective efficacy?
R: There is an absence of data. However, if the vaccines used are effective, a significant impairment of efficacy through using different vaccine brands is unlikely.

Interchangeability in countries with immunization in pregnancy programmes

Immunization with aP-containing vaccines during pregnancy (tetanus, diphtheria, and acellular pertussis (Tdap)) has become a valuable means for protecting young infants, and it is recommended as the primary strategy for prevention of infant disease by the GPI (Forsyth et al., 2015). Until now, most vaccinated pregnant women were primed as infants either with wP-containing vaccines or by natural infection. With prolonged use of aP-containing vaccines in many countries, it has to be proven that aP-primed women will also produce sufficient levels of passively transferred antibodies to pertussis antigens following an aP vaccine booster dose during pregnancy. Another concern is the potential 'blunting' of the immune response to homologous vaccine antigens (contained in Tdap) and heterologous vaccine antigens (not contained in Tdap) during the primary immunization series with wP and aP vaccines in infancy (Campbell et al., 2018). Its clinical relevance remains to be demonstrated, and no negative signs have

been detected until now in the United Kingdom. Limited data from wP-using countries in respect to blunting are available (Vietnam and Pakistan), and it seems to be less relevant for pertussis antigens; no data are available for other vaccine antigens (Maertens et al., 2016; Ibrahim et al., 2018).

Q: May I use a wP combination vaccine to immunize pregnant women?
R: No. You should only use aP-containing vaccines for pregnant women.
Q: May I use Tdap to immunize pregnant women in my country when this is still off-label?
R: No. Although it is registered and recommended in many countries, you should not use Tdap for pregnant women if it is off-label in your country.

Logistic problems in countries with mixed markets

Q: A newly tendered wP combination vaccine is not yet available. What shall I do in infants? Wait or use aP combination vaccines?
R: Don't delay immunization, but use what is available.
Q: When a DTwP–Hib–HepB combination is no longer available, could I use a trivalent DTwP combination vaccine instead?
R: Yes, but you should remember that completing HepB and Hib vaccinations is also necessary later on.
Q: Could I use Tdap instead of DTaP or DTwP combination vaccines at 2 years of age in case of shortage?
R: Yes. If neither DTwP nor DTaP combination vaccines are available, you may use Tdap; however, no Tdap product is licensed for this purpose, and you may need to boost the diphtheria response later on.
Q: Could I use Tdap for the preschool booster when DTaP is not available and DTwP is known to be more reactogenic?
R: While Tdap is being used as a preschool booster in some countries, it may be inferior to DTaP but still better than not receiving a fifth dose.
Q: When no standalone IPV is available, may I use two primary wP pentavalent doses and the third dose as a wP or aP hexavalent combination vaccine to guarantee protection against poliomyelitis?
R: You may do so for protection against poliovirus type 2; however, no robust immunogenicity data are available.

Summary of recommendations and future needs

Our recommendations are made irrespective of the almost complete absence of relevant study data. Table 2 summarizes the perceived basic information and study data needed concerning the interchangeability of wP- and aP-containing combination vaccines.

Lacking robust data, we primarily recommend that brands of wP- or aP-containing combination vaccines should not be interchanged during primary immunization whenever possible. For the fourth dose in the second year of life, aP-containing vaccines may be interchanged, if necessary.

Table 2
Data needed to make evidence-based recommendations for interchanging wP- and aP-containing combination vaccines.

Pharmacovigilance data for currently available wP combination vaccines
Protective effectiveness of currently available wP-containing combination vaccines during priming and first booster
Antibody response of pertussis antigens in actually available wP-containing combination vaccines during priming and first booster, measured with purified antigens and expressed in IU/ml
Effects of mixing brands of actually available wP-containing combination vaccines on immunogenicity and safety
Effects of mixing brands of actually available aP-containing combination vaccines on immunogenicity and safety
Effects of the administration of actually available wP-containing combination vaccines used after priming with aP-containing combination vaccines

aP, acellular pertussis; wP, whole-cell pertussis.

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Conflict of interest

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Author contributions

All authors were responsible for idea generation, critical review, and input into the manuscript drafts, as well as approval of the final draft for submission. All authors had full access to the study data and take full ownership of the integrity of the data and accuracy of the data analysis.

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