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# A worldwide overview for hexavalent vaccines and a glimpse into Turkiye's perspective

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**ABSTRACT**

The surge in recommended vaccinations for child's has spurred the development of combination vaccines, notably hexavalent vaccines, which provide multiple immunizations in a single dose. These vaccines offer various advantages, such as streamlining vaccination schedules, minimizing injection-related pain and exposure to preservatives, expanding vaccine coverage, and reducing administration costs. However, the intricate and expensive development of these vaccines presents substantial challenges, requiring increased investment and healthcare provider education to optimize their utilization and sustain high vaccination rates. Turkey, known for its robust vaccine coverage, strategic geographic location, and the influx of refugees, is at a critical juncture for integrating hexavalent vaccines into national programs. This transition is especially relevant given the rising vaccine hesitancy and the potential resurgence of vaccine-preventable diseases. This review assesses the deployment of hexavalent vaccines, examining their benefits and challenges through clinical trials and global experiences, with a specific emphasis on Turkiye's public health context.

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## Introduction

The number of vaccinations recommended for children in the first 2 years of life has dramatically increased over time. Therefore, combining multiple vaccines into a single syringe has been an emerging strategy to make the schedule easier and simpler and to allow incorporation of new vaccines.[1] Although there are some challenges to be considered such as risk of any potential shortage, possibility of combination chaos and concerns for safety and efficacy, combination vaccines can reduce the number of injections, minimize injection pain, decrease gathered exposure to the preservatives and the stabilizers that may cause some adverse events. Moreover, combination products may boost vaccine coverage by saving time and increasing parental acceptance and compliance and also reduce the costs for administration, handling and storage.[2] This review article with expert opinions aimed to look into the hexavalent vaccines by highlighting the benefits as well as the challenges based on the clinical trials and experiences from different countries with a glimpse from Turkiye on an emphasis of current and future demand.

## Methodology

An Expert Group Meeting, involving 6 experts in related fields (public health,[1] pediatrics,[3] pediatric infectious diseases[1]) from both public and private healthcare institutions in Turkiye, was convened in March 2022 to assess the interest and feasibility of using hexavalent vaccines and to introduce hexavalent vaccines in Turkiye. Prior to that meeting a literature review was performed to explore the background and history of combination vaccines, clinical data of hexavalent vaccines, current positioning of hexavalent vaccines from a global and national perspective. To identify relevant articles, we searched the MEDLINE® (via the PubMed interface), Web of Science, Google Scholar and EMBASE databases. An electronic search of the literature published from 2000 to 2023 was conducted in these databases by using MeSH (Medical Subject Heading, Medline) and EMBASE terms, as well as free text words. The search included the terms "combination vaccines," "childhood immunization programmes," "hexavalent vaccines" and "childhood immunization Turkiye." The inclusion criteria were: (1) peer-reviewed articles and scientific reports, (2) original research articles, review articles and conference papers including information about combination and hexavalent vaccines (3) articles published between 2000 and 2023 The exclusion criteria were: (1) articles not in English or Turkish language, (2) case reports. The reference lists of all manuscripts were manually reviewed for further eligible articles. Most recent and up to date publications were chosen. According to this literature review, experts declared a national perspective and established brief

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recommendations for future immunization landscape in Turkiye focused on hexavalent vaccines.

## Journey of the combination vaccines

Since the onset of the vaccination, the number of vaccine-preventable diseases have been expanding at a fast pace. Developing combination vaccines is a significant way to decrease the number of injections and to provide a higher vaccine coverage.[2] There are two main groups of combination vaccines. Multi-disease combination vaccines include individual vaccines for different diseases, whereas multivalent combination vaccines are directed to several types of the same viral or bacterial pathogen.[4]

Increasing number of multi-disease combination vaccines are being developed, especially for pediatric utilization. According to the immunization recommendations from WHO, five new antigens (Hepatitis B (HBV), *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, rotavirus, and Rubella) have been added to the initial six proposed ones (Bacillus Calmette-Guerin (BCG), Diphtheria, Tetanus, Pertussis, Poliomyelitis and Measles.[3] Combination vaccines have been used in adults and children for more than half a century. In 1948, DTP (diphtheria-tetanus-pertussis) vaccine was licensed in the US and widely used for primary infant vaccination.[2,5] Based on the decreased number of cases and deaths by the introduction of DTP vaccine, WHO had started the "Expanded Programme on Immunization (EPI)" in 1974 to increase vaccine coverage.[6]

Although four hexavalent vaccines have been licensed in the last two decades, as Hexavac® was later suspended in 2005 and withdrawn in 2012 by the European Medicines Agency (EMA) due to concerns about its immunogenicity against HBV, there are currently three different combination hexavalent vaccine preparations available for administration in the market; DT3aP-HBV-IPV/Hib (Infanrix®hexa); DT2aP-HBV-IPV-Hib (Hexyon/Hexacima/Hexaxim®); and DT5aP-HBV-IPV-Hib (Vaxelis®).[7–10] DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib are the ones that are broadly registered including Turkiye, DT5aP-HBV-IPV-Hib is only licensed in US, EU, UK, Switzerland, & Australia. The three licensed hexavalent vaccines were established independently, and none are biosimilars. DT2aP-HBV-IPV-Hib and DT5aP-HBV-IPV-Hib have a fully-liquid formulation, DT3aP-HBV-IPV/Hib requires reconstitution prior to administration by adding the suspension containing DTaP, HBV, and IPV antigens from a pre-filled syringe to a vial supplementing the Hib lyophilized powder.[7]

## Benefits of combination vaccines

Simultaneous administration of vaccines is a safe and effective strategy to improve the vaccination coverage in children. They not only simplify the immunization schedule and increase compliance for children and parents, but they also provide significant benefits such as reduce the time spent on preparation, administration, and recording as well as decrease the administrative costs.[8,9]

Combination vaccines are preferred both by parents and healthcare providers due to a reduced number of injections in each visit. Three injections were accepted to be "too many" at a single office visit by 71%, 76%, and 59% of parents, nurses, and physicians, respectively. Only 15% of physicians were recorded to give DTP, MMR, and Hib vaccines concomitantly to a 15-month-old infant at the same visit.[10] In another study, the proportion of children receiving all recommended vaccinations during the same visit decreases from 99.5% for 2 injections to 88.9% for 5 injections.[11] Combination vaccines may reduce the number of injection site reactions such as pain, fever and swelling.[12] Several health authorities such as the Robert Koch Institute in Germany and the Public Health Agency of Canada recommend combination vaccines to enhance vaccine coverage.[2] A study from Turkiye reported that the reduction in the number of injections and reactogenicity of pertussis vaccine contributed to an increase in the compliance to the vaccination program.[13]

Combination vaccines also contribute to improve timeliness of immunization. A study from Germany revealed that while only 13.3% of children born in the era of predominantly monovalent vaccines completed a full Hib vaccine series at the recommended age of 12 months, the ratio was 17.8% and 27.7% in the cohorts vaccinated with tetra- and penta-valent vaccines, respectively. And there was a 3-fold increase in the group who received hexavalent vaccinations compared to monovalent vaccines, whereas 39.1% of children were vaccinated on time.[14] Combination vaccines may also help the children to catch-up when they are behind the schedule.[2]

Moreover, combination vaccines were shown to improve immunization rates and parental satisfaction. A questionnaire study revealed parents' demand for reducing their children's pain and psychological distress from simultaneous injections given at the same visit.[15] Combination vaccines can also reduce the time spent by parents at the healthcare practice and may even reduce indirect costs related with parental work loss as well as travel costs to the healthcare center.[2]

In addition, the use of combination vaccines provides a convenient and easy solution by decreasing shipping, handling, and storage needs, and thereby reducing the likelihood of human error.[9] Also, fully-liquid hexavalent vaccines require less time for preparation, this may be time-saving for healthcare professionals. Almost all health care professionals (97.6%) stated they would prefer to use fully-liquid vaccines in their daily practice.[7] Record keeping and immunization tracking will also be straightforward, effortless, and more accurate.

Handling fewer syringes reduces the potential for accidental needle sticks. It is estimated that 2 million needle stick injuries occur per year among the healthcare workers.[16] Needle stick injuries and blood exposures comes up with an average cost of $500 to $3,000 per injury.[17] Giving combination vaccines is also preventive for possible administrative errors made during the preparation or mixing processes.[18]

They also have a potential economic impact by minimizing the cost of treating vaccine-preventable disease. These vaccines reduce total vaccine administration charges, and possibly the number of health-care visits. Moreover, by increasing immunization compliance, they may also decrease communicable

diseases and reduce the need for hospitalization of severely ill children. Therefore, overall healthcare costs will be lower in the long-term follow-up.[19] By reducing the number of injections and the cost of vaccination, combination vaccines could become an important argument for the introduction of new vaccines in a vaccination program.

## Challenges of combination vaccines

Although combination vaccines have many remarkable benefits for both society and the healthcare system, there are still concerns about the safe and effective development and production of these vaccines.

The complexity of the development, evaluation, and licensure of DTaP-backboned combination vaccines brings several manufacturing challenges. Compatible antigens should be mixed in the same vaccine to maintain same immunogenicity provided by the single vaccines. This harmony is based on the antigens involved and on the types of adjuvants, buffers, preservatives, pH, and tonicity of the solution. For instance, adjuvants in a combination vaccine could decrease the activity of one antigen and increase the immunogenicity of another antigen. Thus, before licensing and manufacturing, combination vaccines must be widely tested to prove their lot-to-lot manufacturing consistency, safety, and immunogenicity.[20] Due to the biological characteristics, there is a potential risk of failure at any time of the process. The addition of each antigen require careful testing to make sure the combination vaccine is as safe and effective as each of the individual vaccines given separately. Therefore, more batches need repeat-testing, which causes extensive testing processes. This complexity may cause delivery deficiencies.[2,21]

As combination vaccines become more puzzling regarding the multiple antigenic abbreviations used, risks for administration errors have been increasing. While the abbreviations get longer to include all components of vaccines, health care professionals should be more careful in checking the syringes before administration.[22]

When more antigens are included into a single combination, antigen overload and interference should be considered. Extra doses of some antigens may be given with combination vaccines (e.g., a provider who administers 4 doses of DTaP-HBV-IPV vaccine will give an extra dose of hepatitis B component), however, no adverse events were recorded in three-fourth of reports and among the individuals who had an adverse event, injection site reactions and mild systemic symptoms (pyrexia, headache, etc) were the most common ones.[23] A comprehensive preclinical and clinical development program must be developed to meet these challenges and demonstrate consistent performance across different programs and populations.[20]

## Hexavalent vaccines: immunogenicity and safety

Immune responses to diphtheria, tetanus and polio components of the three different hexavalent combinations (DTaP – HBV-IPV – Hib (Hexavac®); DT3aP-HBV-IPV/Hib (Infanrix hexa™); DT2aP-HBV-IPV-Hib (Hexyon/Hexacima/Hexaxim®) are non-inferior to monovalent or fewer component combinations (DTaP).[24] While there are several differences in immune responses against D, T and poliovirus types 1, 2, and 3, antibody levels were remarkably higher than the established seroprotection thresholds with these three vaccines.[25–31] Variability has also been reported for post-primary and/or post-booster antibody concentrations of pertussis, Hib, and HBV antigens.[25–31]

"DT3aP-HBV-IPV/Hib (Infanrix hexa™) generated a good immune response and was well-tolerated regardless of the dosing schedule. One month after the finalization of a three-dose primary immunization schedule in the first 6 months of life, seroprotection rates ranged between 91.0% and 100% for D, T, HBV, IPV, and Hib antigens, and seroconversion for pertussis was between 85% and 100%.[32–40] Moreover, 1 month after a booster in the second year of life, seroprotection was between 96.8% and 100% for D, T, HBV, IPV, and Hib antigens, and seroconversion was 86.0–100% for pertussis antigens.[40–42] At 4–6 years of age, children who had received a booster dose at 12–18 months of age remained seropositive for D, T, HBV, IPV, and Hib antigens between 75.0 and 98.9%, while seropositivity varied from 34.5 to 98.9% for the pertussis antigens.[41] Moreover, DT3Pa–HBV–IPV/Hib set up a response to a HBV vaccine challenge dose, illustrating that long-lasting immune memory to HBV continues for more than 6 years after the fourth dose of DT3aP-HBV-IPV /Hib.[43,44] In a study involving adolescents aged 12 and 13, long-term protection against HBV was confirmed.[45] A review of 7 different studies with a 3-5-11 schedule over a 12-year period, showed that adequate immunogenicity was acquired after the primary and the booster dose for all the antigens in the vaccine with a clinically acceptable safety.[46] Data from 11 clinical trials showed that using hexavalent DT3aP-HBV-IPV /Hib vaccine to replace simultaneous administration of each antigen, does not affect the immunogenicity or safety profile of the vaccination schedule.[47]

DT2aP-HBV-IPV-Hib also led to a strong immune response and long-lasting immune memory with a good safety profile. In terms of primary series, a phase III infant trial at 2 centers in Colombia and Costa Rica dosing infants at 2,4,6 months of age, revealed that seroprotection rates were high in all subjects (≥ 99.1% for anti-D, anti-T, anti-FHA, antipolio 1, 2, and 3 and anti-HB; ≥95.9% for anti-PT; and ≥ 94.1% for anti-Hib).[27] Seroprotective antibody titers for anti-D; anti-T; antipolio 1, 2, and 3; anti-Hep B; and anti-Hib- ranged from 94.6% to 100%, and ≥ 90% of infants reached a 4-fold or higher antibody increase for anti-PT and anti-FHA in a phase II trial from Argentina with the same 2,4,6 months schedule. The anti-Hep B geometric mean titer was similar to the monovalent Hep B control.[48] Similar seroprotection rates were achieved with same schedule in various other clinical trials from Mexico, Thailand, Peru, South Korea, Spain.[25–27,50–52] A Phase III trial from Turkiye compared primary series of DTaP-IPV-HBV-Hib (without Hepatitis B at birth) with licensed control vaccines (DTaP-IPV//Hib and standalone HB and DTaP-IPV-HBV-Hib booster). Postprimary series noninferiority of anti-HB ≥ 10 mIU/mL was demonstrated for the DTaP-IPV-HBV-Hib vaccine (94.0%) compared to the licensed control

(96.1%). Postprimary series primary seroprotection and seroconversion rates were high and similar for both groups.[53] Overall, seroprotection rates after primary schedules were 95–100% for anti-D and anti-polio, 99–100% for anti-T, 94–100% for anti-HB, and 91–100% for anti-Hib. For anti-PT and anti-FHA, seroconversion rates were 88–97% and 82–98%.[32] Following a 2-dose primary series in a phase III trial conducted in Sweden and Finland, seroprotection rate for Hib was 72% and vaccine response rates were 91–100% for all other antigens whereas the seroprotection rate was 58% for Hib and 95–100% for the remaining antigens with control vaccine (DTaP-IPV//Hib).[29]

A single booster dose of DT2aP-HBV-IPV-Hib at 11–24 months created a remarkable immunogenic response, regardless of the primary vaccine type and schedule. Seroprotection rates after the booster were 96–100% for anti-D, anti-T, anti-polio types 1–3, anti-HB, and anti-Hib, and seroconversion rates were 79–97% for anti-PT and 60–97% for anti-FHA.[26,28,54–56]

In comparison with other hexavalent vaccines, DT2aP-HBV-IPV-Hib was noninferior to DT3aP-HBV-IPV/Hib with respect for vaccine response against all antigens in 3-dose primary series and for anti-D, anti-T, anti-PT, anti-FHA, anti-IPV3, anti-HB and anti-Hib in 2-dose primary series.[26,29] Furthermore, in terms of seroprotection/seroconversion, DT2aP-HBV-IPV-Hib booster was similar to DT3aP-HBV-IPV/Hib booster for all antigens when the same vaccines had been used for a 3-dose primary series.[55] There was no difference in the response to a booster of either DT2aP-HBV-IPV-Hib or DT3aP-HBV-IPV/Hib after a primary series of the DTaP-IPV-Hep B-Hib vaccine (Hexaxim®), and both were similar regardless of the primary vaccine.[26,28]

Regarding coadministration with other vaccines, meningococcal serogroup C conjugate vaccine (MenC) was one of the investigated vaccines. Although MenC vaccines are not in routine immunization programs in all countries, they are obtainable with private prescription and recommended for individuals who travel to epidemic areas. In a phase III trial from Finland, infants received DT2aP-HBV-IPV-Hib either with a MenC vaccine co-administered at 2 and 4 months or without MenC vaccine. In both groups, infants had PCV13 at 2 and 4 months of age, and rotavirus vaccine 2, 3, and 4 months of age. Seroprotection rates for HBV was 97.5% [95%CI: 93.1–99.3] in the coadministration group and 96.1% [95%CI: 91.8–98.6] in the group without MenC vaccine. There was no difference for all other antigens in both groups.[54] These infants were further randomized to have either DT2aP-HBV-IPV-Hib with meningococcal serogroup ACWY conjugate (MenACWY) booster or DT2aP-HBV-IPV-Hib booster alone. Following booster vaccination, no differences were observed in both groups (seroprotection rates in coadministration and DT2aP-HBV-IPV-Hib booster alone groups were 97.7–100% and 98.9–100%, retrospectively).[57] Coadministration of primary series with PCV7 and/or rotavirus and coadministration of booster with PCV7, PCV13 or MMRV did not adversely affect immune responses to any vaccines.[27–29–49 58]

Primary and booster vaccination with DT2aP-HBV-IPV-Hib vaccine lead to similar seroprotection/seroconversion rates in preterms compared to term infants against all antigens except anti-HBs ≥ 10 mIU/mL and anti-Hib ≥0.15 µg/mL post-primary vaccination (higher for term [98.31% and 90.91%, respectively] versus preterm infants [89.80% and 79.41%, respectively]).[59]

A three-dose primary schedule of DT5aP-HBV-IPV-Hib at 2,4 and 6 months with HBV at birth showed that more than 97% seroprotection was achieved for all antigens except pertussis. While 98.9% of participants demonstrated a vaccine response against PT, values for other pertussis antigens ranged from 84–90%. This response was shown to be as non-inferior to the comparators.[60,61] A study of 2-3-4 months schedule of DT5aP-HBV-IPV-Hib (without HBV at birth) and a booster at 12 months revealed satisfying antibody responses after the primary and the booster doses and met all the non-inferiority criteria. In almost all cases (>97%), seroprotective vaccine response was reached for D, T, IPV, HBV, and Hib, and seroconversion was achieved for PT and FIM.[31] Even with a two-dose priming schedule (2 and 4 months without HBV vaccine at birth) and a booster at 11–12 months, more than 92% of the infants developed a strong immunogenic response against most of the antigens and vaccine response levels were accepted as adequate for long-term protection.[30] Anti-HBV antibody concentrations were higher than 10 mIU/mL in 70.2% and 65.8% of the children approximately 4 years after completion of a 3 + 1 and 2 + 1 schedules, respectively.[62]

A slightly better immune response was achieved with 3 + 1 schedules compared to 2 + 1 schedules however there are no studies comparing 2 + 1 to a 3 + 1. Considering all hexavalent vaccines, seroprotection/seroconversion rates against most antigens were ≥ 84.0% and ≥ 80.3%, after 3 and 2 primary doses, respectively. However, post-booster seroprotection/seroconversion rates were ≥ 88.9% against all antigens and were almost similar for both schedules.[29,30,63]

Hexavalent vaccines, either as a primary vaccination or as a toddler booster dose, have generally been tolerated well.[64–67] The occurrence of serious adverse events (SAEs) varied between 2.4% and 6.0% in different trials for DT2aP-HBV-IPV-Hib.[26,29] The proportions of children who experienced 1 or more SAEs were 2.8% and 0.8% in DT5aP-HBV-IPV-Hib recipients and 2.2% and 1.1% in DT3aP-HBV-IPV/Hib vaccines in 3 + 1 and 2 + 1 doses, respectively.[30,31] Overall, administration of combined hexavalent vaccines is safer whereas the frequency of adverse reactions is lower with one injection compared to six consecutive applications.[22,65,66] In terms of sudden infant death syndrome (SIDS), it has been shown that there is no relationship between exposure to vaccines and SIDS, and the incidence is the same regardless of the vaccination status.[68]

With regards to co-administration with other vaccines, there are no immunogenicity and safety concerns for any of three hexavalent products to be co-administered with anti-pneumococcal, anti-rotavirus, anti-measles, mumps, rubella, anti-varicella vaccines and anti-meningococcal C conjugate vaccines.[29,47,68,69] Only four vaccine-related SAEs (urticaria, febrile seizure, hypotonic-hyporesponsive episode and Kawasaki disease) were reported when hexavalent vaccines were administered with other pediatric vaccines among more than 6000 children.[67]

### Hexavalent vaccines as a part of national immunization programmes

Europe has been the first region in the world to adopt hexavalent vaccines as part of the routine immunization program. Four hexavalent vaccines have been licensed and three of them are currently in the market in Europe. Eighteen European countries routinely use hexavalent vaccines in children in immunization schemes (Table 1).

Hexavalent vaccines are implemented into the 2017–2019 Italian National Immunization Plan (NIP) for the primary immunization dose and for two booster doses during neonatal age (according to the schedule 2, 4 and 11–13 months or 61, 121, and 301 days of age).[70] And the vaccination rate in Italy was almost 95% in 2019.[71] In Germany, hexavalent vaccines have been used since 2006 (2-, 3-, and 4-months schedule with 11–14-month booster) with coverage rates between 93 and

**Table 1.** Use of acellular hexavalent vaccines in immunization schemes.[71]

| Counrty | Use of hexavalent vaccines |
|---|---|
| South Africa | 6,10,14w, 18 m |
| Argentina | 2,4,6 m |
| Bahamas | 2,4,6 m |
| Barbados | 2,4,6 m |
| Canada | 2,4,6 m |
| Chile | 2,4,6,18 m |
| Mexico | 2,4,6,18 m |
| Panama | 2,4,6,18 m |
| United States of America | 2,4,6 m |
| United Arab Emirates | 2,4 m |
| Bahrain | 2,4 m |
| Jordan | 3,4,5 m |
| Libya | 2,4,6 m |
| Oman | 2,4 m |
| Qatar | 2,4 m |
| Saudi Arabia | 2,4,6 m |
| Andorra | 2,4,12 m |
| Armenia | 6,12,18w |
| Austria | 2,4,10-11 m |
| Belgium | 8,12,16w and 15 m |
| Bulgaria | 2,3,4 m |
| Czech Republic | 3,5,11 m |
| Croatia | 2,4,18 m |
| Estonia | 3, 4.5, 6 m and 2y |
| France | 2,4,11 m |
| Georgia | 2,3,4 m |
| Germany | 2,3,4,11 m |
| Ireland | 2,4,6 m |
| Italy | 3, 5, 11 m |
| Kazakhstan | 2,4 m |
| Luxembourg | 2,3 m |
| Latvia | 2,4,6,12-15 m |
| Monaco | 2,4,11 m |
| North Macedonia | 2,6 m |
| Malta | 2,3,4,18 m |
| Netherlands | 2*,3,5,11 m |
| Norway | 2,5,12 m |
| Portugal | 2,6 m |
| Russian Federation | 3,4.5,6,18 m |
| Romania | 2,4,11 m |
| San Marino | 3,5,11 m |
| Slovenia | 3,5,11-18 m |
| Slovakia | 2,4,10 m |
| Spain | 2,4,11 m |
| Sweden | 3,5, 12 m |
| Switzerland | 2,4,12 m |
| UK (United Kingdom of Great Britain and Northern Ireland) | 8,12,16w |
| Australia | 2,4,6 m |
| Brunei Darussalam | 2,4,6 m |
| Malaysia | 2,3,5,18 m |
| New Caledonia | 2,11 m |
| Niue | 6w, 3,5 m |
| New Zealand** | 6w, 3,5 m |
| French Polynesia | 2,10 m |
| Wallis and Futuna | 2,11 m |

w: week; m: month; y: year

*Additional vaccination at month 2 when mother is not vaccinated against pertussis during pregnancy and in some other special situaions.

**Revaccination for children aged < 10y post HSCT or chemotherapy, pre- or post- splenectomy, pre- or post-solid organ transplant, dialysis, or other severely.

94% and was shown to have a high effectiveness especially against invasive Hib disease.[72] In the UK, tetravalent vaccine (DTP-Hib) was replaced with pentavalent vaccine (DTaP-IPV-Hib) in 2004, and with acellular hexavalent vaccine (DTaP-Hib -IPV-HBV) in 2017 (2-,3-, and 4- months schedule).[73]

According to the February 2020, issue of the Morbidity and Mortality Weekly Report from the Centres for Disease Control and Prevention (CDC), a hexavalent vaccine that includes DTaP-IPV-Hib-HBV has been included in the Federal Vaccines for Children program in the USA.[74] Hexavalent combined vaccines are also recommended in Canada at routine immunization schedule.[75]

Since 2009, the combined vaccine against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and *Haemophilis influenzae* type b has been used for childhood immunization in Australia according to a two-, four-, six-month schedule and followed by booster doses of DTaP vaccine at 18 months and 4 years. Between 2009 and 2018, vaccine coverage for children age of 12 months rose from 91.7% to 94.0% and from 84.9% to 92.6% for all and for Indigenous infants, respectively. Over the same time period, there were no reports of poliomyelitis, diphtheria, or tetanus in infants under 12 months of age. The incidence of hepatitis B among infants <12 months of age were 10 to 20-fold lower than the national average. The annual frequency of the 10 most commonly reported adverse events per 100,000 doses is similar with the safety profile reported in clinical trials and the product information.[76]

In Mexico, DTwP-HB/Hib pentavalent vaccine was introduced in 1999 and was replaced by DTaP-IPV/Hib pentavalent vaccine during 2007, which was replaced by hexavalent aP-containing vaccine including hepatitis B virus (DTaP-IPV-HBV-Hib) in 2019. A retrospective study from Mexico revealed that vaccine coverage rate was highest for the first dose in the primary series, decreasing for each subsequent dose over a 19-year period (2000–2019). The vaccine effectiveness against pertussis was 96.4% (95% CI: 94.7, 97.6) for the first three doses of wP vaccine (2000–2007) and 95.7% (95% CI: 95.1, 96.2) for the first three doses of aP vaccine (2008–2019).[77]

## National immunization program in Turkiye

In Turkiye, diphtheria and pertussis immunization was initiated in 1937, routine childhood pertussis immunization with DTwP was started in 1968 and replaced with DTaP-IPV /Hib since 2008.[78] The pentavalent vaccine has been administered in the 2nd, 4th, and 6th, months of age, in combination with a booster dose administered in the 18th month, according to the national vaccination scheme. The aim was to decrease the number of vaccinations and to replace the wP vaccine with the safer aP.[79] Since 2010, a single-dose diphtheria, tetanus toxoid, acellular pertussis, and inactive polio vaccine (DTaP-IPV) has also been administered to children at seven years of age.[80] And after 2020, DTaP-IPV dose was moved to the age of 48 months. Turkiye's National Childhood Immunization Program is shown in Table 2.[81]

According to the data released by the Turkish Ministry of Health, very high vaccination coverage rates of 97–99% were reported for the vaccines in the national immunization programme in 2019 [for DTaP-1-2-3, measles, mumps, rubella (MMR), 7-valent pneumococcal conjugate vaccine (PCV7) and HBV-1-2-3], enough to provide herd immunity for these diseases.[79]

A phase III open-label trial compared the immunogenicity and safety of DTaP-IPV-HBV-Hib vaccine (Hexaxim/Hexyon/Hexacima) with DTaP-IPV//Hib (Pentaxim/Pentavac) co-administered with a standalone HB vaccine (Engerix B) in Turkiye. The primary and booster studies took place between June 2006 and June 2007 and December 2007 and July 2008, respectively. Levels of anti-HBs ≥10 mIU/mL was reported for the 94% of infants vaccinated with DTaP-IPV-HBV-Hib vaccine primarily and the ratio was in 96.1% of infants for the control group. After the completion of primary doses, antibody persistence was high for other antigens and similar with controls. Safety was good for primary and booster series and similar between groups. Therefore, DTaP-IPV-HBV-Hib vaccine was found to be immunogenic and safe when administered in a challenging primary schedule without HBV vaccination at birth among Turkish children.[53] The primary and booster studies took place between June 2006 and June 2007 and December 2007 and July 2008, respectively.

Despite the success of the national vaccination programs, recent COVID-19 pandemic has had an impact on infant vaccination coverage rates both regionally in Turkiye and globally. There was an unfortunate decline in the number of children receiving life-saving vaccines. This was due to disruptions in the delivery and uptake of immunization services caused by the pandemic. Worldwide, approximately 80 million children under the age of 12 months in 68 countries

**Table 2.** Turkiye's national childhood immunization program.

| Active Ingredients | At birth | End of the 1st month | End of the 2nd month | End of the 4th month | End of the 6th month | End of the 12th month | End of the 18th month | End of the 24th month | End of the 48th month | 13 years |
|---|---|---|---|---|---|---|---|---|---|---|
| Hepatitis B | I | II | | | III | | | | | |
| BCG | | | I | | | | | | | |
| PCV-13 | | | I | II | | B | | | | |
| DTaP-IPV-Hib | | | I | II | III | | B | | | |
| OPV | | | | | I | | II | | | |
| VAR | | | | | | I | | | | |
| MMR | | | | | | I | | | II | |
| Hepatitis A | | | | | | | II | II | | |
| DTaP-IPV | | | | | | | | | B | |
| Td | | | | | | | | | | B |

BCG: Tuberculosis, PCV: Pneumococcal Conjugated Vaccine D: Diphtheria; aP: Acellular Pertussis; T: Tetanus; IPV: Inactivated Polio Vaccine; Hib: *Haemophilus influenza*e type B; OPV: Oral Polio Vaccine; VAR: Varicella Vaccine, MMR: Measles, Mumps, Rubella; B: Booster; Td: Tetanus, Diphtheria.

are reported to be in risk due to the setbacks in vaccination during the COVID-19 pandemic.[82] In terms of Turkiye, vaccination rates in Ankara have decreased 2–5% during the pandemic, and the most prominent decline was in vaccines administered after 18 months of age.[83]

Moreover, Turkiye's geographical location, its close proximity to countries in a state of war and with low vaccination coverage, and receiving extensive immigration always comes up with a possibility of an outbreak.[84] Turkiye has the largest number of Syrian refugees and among these children, the ratio of unvaccinated children were; 54.7% for HBV; 62.5% for BCG; 64.6% for DTaP-IPV-Hib; 58.0% for PCV7; 70.8% for OPV and 76.6% for MMR.[85]

### *Interpretation of literature from a national perspective and future recommendations for Turkiye*

The efficacy and safety of hexavalent vaccines has been proven by both clinical data and real-life observations.[32] Although the transition from pentavalent vaccines to hexavalent vaccines is observed in different parts of the world, especially in Europe, there are significant differences in vaccination schemes in line with the conditions and health system of each country.[67]

Since the Hep B vaccine is applied at birth and in the 1st month in Turkiye, switching to hexavalent vaccines may either lead to the application of an extra Hep B vaccine or that the place of the Hep B vaccine in the current vaccination calendar will need to be changed. Data show that the administration of up to 5 doses of Hep B vaccine does not cause any safety problems and some European countries already apply additional Hep B vaccines.[24,86] However, swapping 1st month Hepatitis B vaccination with a hexavalent vaccine may have some drawbacks in routine child care practices. Children may experience delays in having vitamin D supplementation and weight and height monitoring may be interrupted. Therefore, before applying hexavalent vaccinations into national vaccination schemes, several adjustments should have been done to maintain the best possible child care such as replacing the vaccination visit to a growth check at 1 month of age.

Transitioning from individual vaccine schedules to hexavalent vaccine schedules means that the second dose of HBV vaccine would be delivered at 2 months of age rather than 1 month of age. A recent report from the USA revealed that there is no evidence of immunoprophylaxis failure when HBV vaccine is administered in a 0-, 2-month regimen compared to 0, 1 months (odds ratio: 0.77).[87] Furthermore, HBV surveillance in Australia has shown a consistent decline of Hepatitis B in children after the transition to a 0-, 2-, 4-, 6-month schedule from the previous 0-, 1-, 6-month schedule.[88]

There is a significant decrease in the incidence and prevalence of Hep B in Turkiye with the current vaccination scheme. However, it is not known whether this existing immunity can be maintained against the increasing number of refugees. More evidence is needed to change the current vaccination scheme in Turkiye, especially discontinuation of the Hep B vaccine at birth should be avoided without adequate data. In the meantime, the increase in the awareness of the hexavalent vaccines in private institutions and the spread of its positioning at the 6th month and 18th month may provide a meaningful experience before considering a change in the national vaccine scheme. As there is a high immunity against hepatitis B in Turkiye, Anti-HBs, and HBsAg screening can be used in the follow-up of pregnant women. Depending on this screening, the Hep B vaccine may not need to be given at birth, the 2-4-6 and 18 calendar can be applied as western countries and excess Hep B dosage can be avoided.

Hexavalent vaccines prices are higher than pentavalent vaccines as they include more antigens and require advanced technology. In response to direct costs, there are cost savings driven by administration advantages and logistics including cold chain storage, vaccine wastage, and disposal. Health economics studies from South Africa and Malaysia revealed cost savings by switching from pentavalent + hepatitis B vaccines to fully liquid hexavalent vaccine.[89,90] Excluding the cost of procurement of the individual vaccines, these studies found that fully liquid hexavalent vaccines could lead to direct cost reductions of up to US$3 and US$3.6 per dose, respectively, equivalent to approximately US$10.7 per fully immunized child. Additional cost reductions with hexavalent vaccines were demonstrated in Malaysia from a social perspective by considering direct non-medical costs and indirect costs. This study also highlighted other benefits of fully liquid hexavalent vaccines for the healthcare provider, the families and the healthcare system, including reduction of vaccination errors and time savings allowing more attention and education for parents on child health.[90]

A cost-minimization analysis of a new hexavalent combination vaccine in France revealed that the public price of this vaccine associated with a break-even point would be € 53.77. The annual additional reimbursed cost of protecting an infant against hepatitis B would be €28.20 per child, or about € 21 million for an annual cohort of 760,000 births (total cost, €35 million). However, the number of infants protected against hepatitis B could go up from 230,000 to about 600,000 with this hexavalent vaccine.[91] Another budget impact analysis from Slovenia showed that applying an alternative 2 + 1 hexavalent vaccination schedule could decrease the total vaccination costs in Slovenia by up to 0.47 million euros whilst potentially leading to a better HBV immunization coverage.[92] It should be noted that country-based economic evaluation for specific vaccine formulations is important for vaccine schedule modernization to ensure access to high-quality vaccines at an affordable price.

## Conclusions

Development of combination vaccines is a precious technological advancement in the prevention of infectious diseases and public health due to their significant health and economic impacts. In this respect, hexavalent DTaP back-boned vaccines including IPV, HBV, and Hib has been in the market since 2000.[22]

Combination vaccines have decreased the burden of multiple injections and brought a solution for other challenges including storage and shipment, increasing number of visits, injection of more adjuvants and difficulties in implementing new vaccines into the calendar.[22]

The hexavalent vaccines have been replacing the existing pentavalent ones after they have been widely tested for their immunogenicity and safety. While the three available aP hexavalent

vaccines have some differences due to their formulations, they are generally considered similar and found to be safe and effective.[63]

Although Turkiye is a country with a high vaccine coverage and pentavalent combined vaccine (DTaP-IPV-Hib) has been implemented into the national immunization program, it's geographical location and high number of refugees is always a risk for potential outbreaks. Therefore, simple and more applicable vaccination schemes which provide more vaccinations at the same visit may be an important advantage to maintain high vaccination rates. Moreover, in the era of pandemic with the increasing vaccine hesitancy and presence of the risk for the outbreaks of vaccine preventable diseases, implementing hexavalent vaccines into the national immunization program can sustain high coverage rates for vaccines and avoid vaccine hesitancy by minimizing the physical and psychological burden of multiple injections.

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## Author contributions

All authors made equal contributions to the design of the work, provided input and revised and approved the final manuscript.

## Disclosure statement

**MO** has acted as a consultant and keynote speaker for Sanofi Pasteur Vaccines, Pfizer Vaccines, Biogaia, HiPP, Nestlé Nutrition, Sanofi CHC, Nobel Pharma and Abdi Ibrahim Pharma. **EU** has acted on the advisory board of Sanofi and has received speaker honorarium from Sanofi. **AY** has acted in the advisory board of Sanofi and has received speaker honorarium from Sanofi. **HA** has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals and Bristol Myers Squibb and has received speaker honorarium from Novartis. **SM** and **TP** report there are no competing interests to declare.

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