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A White Paper To Understand The Market Structure Of Pediatric Pertussis Combination Vaccines

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Glossary

Antigen

Any substance that produces immune response in the body against a foreign substance.¹

Schedule

The number of hexavalent vaccines doses (3 or 4) recommended in each country in their national immunization schedule.²

DTP Vaccine

A vaccine that produces immunity against three deadly diseases - namely diphtheria, tetanus, pertussis.³

DTP3 Immunization Rate

The percentage of one-year-olds who have received three doses of the combined diphtheria, tetanus toxoid and pertussis (DTP3) vaccine in a given year.⁴

DTaP Vaccine

DTaP is a combined vaccine against diphtheria, tetanus, and pertussis, in which the pertussis component is acellular (contains purified components of *B. pertussis*).⁵

DTwP Vaccine

DTwP is a combined vaccine against diphtheria, tetanus, and pertussis, in which the pertussis component is a whole-cell, which is an entire *B. pertussis* organism that has been inactivated.⁶

GAVI

The Global Alliance for Vaccines and Immunizations (GAVI), is an international organization, bringing together public and private sectors with the shared goal of creating equal access to new and underused vaccines for children living in the world's poorest countries.⁷

Hexavalent Vaccine

An hexavalent vaccine (DTaP-Hib-HepB-IPV) is a six-in-one vaccine recommended in three or four doses to protect babies against diphtheria (D), tetanus (T), pertussis (aP) (whooping cough), poliomyelitis (IPV), Haemophilus influenza type B (Hib) and hepatitis B (Hep B). All hexavalent vaccines are intended for pediatric use.⁸

Hexaxim®/Hexyon®/Hexacima®

Hexaxim® is a fully liquid, ready to use hexavalent vaccine, manufactured by Sanofi-Pasteur.⁹

Infanrix Hexa®

Infanrix Hexa® is a hexavalent vaccine which needs to be reconstituted before the injection, manufactured by GlaxoSmithKline.¹⁰

Public Markets (Hexavalent Vaccines)

Public markets include countries where hexavalent vaccines are included under national immunization schedules and supplied to the entire nation by the government or governmental agencies. These vaccines are generally procured through tenders, and distributed to healthcare practitioners (HCPs).¹¹

Private Markets (Hexavalent Vaccines)

Private markets include countries where hexavalent are given by private practitioners and not included in the national immunization schedule. The price for this vaccine may be partially or completely reimbursed by insurance companies, or entirely to be borne through out-of-pocket expenditure.¹²

Pertussis vaccines (aP and wP)

Pertussis, also known as whooping cough, is a highly contagious respiratory disease caused by the bacterium *Bordetella pertussis*. Pertussis vaccine is available in two forms namely acellular pertussis (aP) or whole-cell pertussis (wP).¹³

Surviving Infants

Surviving infants is the number of children reaching their first birthday during a given year.^{14, 15}

Statutory Insurance

Statutory health insurance is financed by funds, which are financially and organizationally independent, contributed by employees and employers through payroll taxes.¹⁶

UNICEF

The United Nations International Children's Emergency Fund works in 190 countries and territories to protect the rights of every child.¹⁷

Vaxelis®

Vaxelis® is a fully liquid hexavalent vaccine, manufactured by MCM Vaccine Company, a joint venture between Sanofi Pasteur and Merck.¹⁸

V3P/MI4A Database

V3P/MI4A database contains information on vaccine prices, volumes, manufacturers, procurement modalities, contract length, and more as reported by over 150 countries. This database is published by the World Health Organization (WHO).¹⁹

WHO

The World Health Organization is a specialized agency of the United Nations working in 194-member countries. This organization deals with issues related to public health.²⁰

WHO Regions

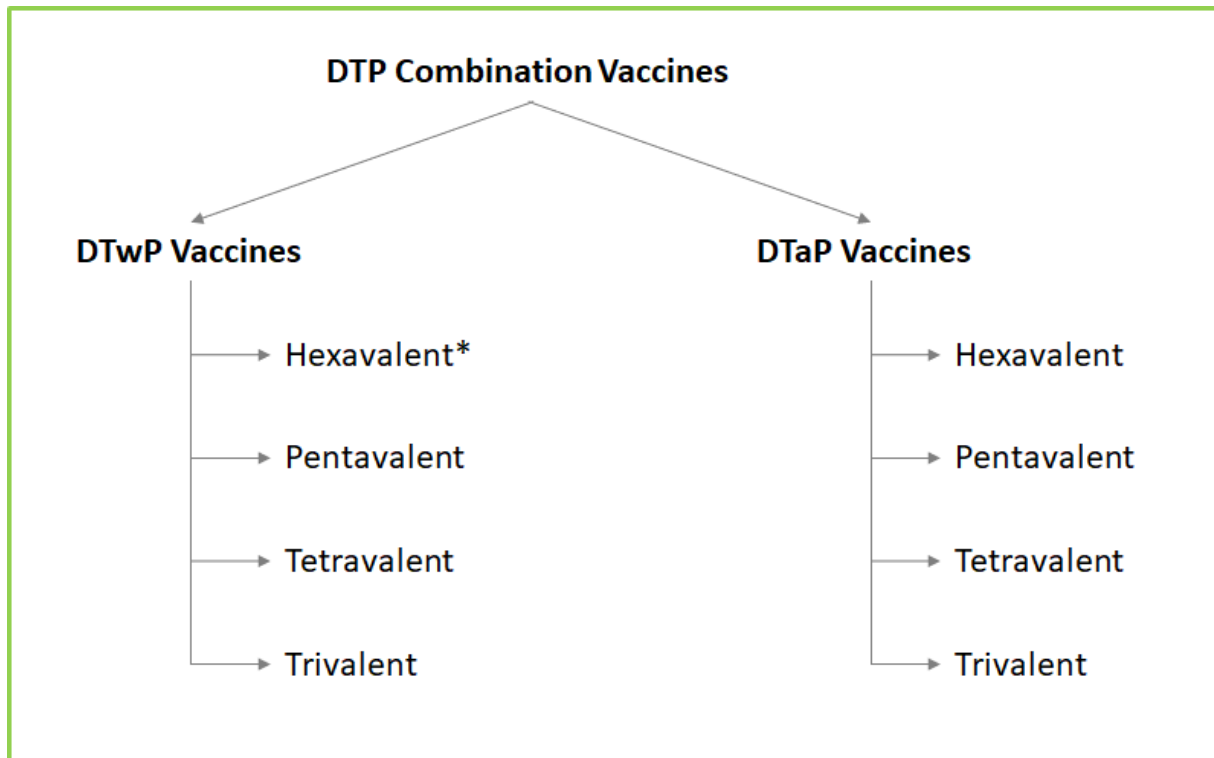
All regions mentioned in this report are according to WHO countries classification. For instance, countries under EUR are the WHO classification of EUR, not limited to the countries which represents European Union

WHO Vaccine Prequalification (Prequalified vaccine)

WHO prequalification ensures vaccines used in immunization programs is safe and effective. It provides the Member States and procurement agencies, such as GAVI and UNICEF, with the information required to purchase vaccines matching the specific needs of the program.²¹

Market Structure Of the DTP Combination Vaccines

The below schematic is to give a background understanding of the hexavalent vaccines market.



*One wP hexavalent vaccine called easy six produced by panacea biotech but with registration and sales limited to India.

A White Paper To Understand The Market Structure Of Pediatric Pertussis Combination Vaccines

Abstract

The objective of the present study is to understand usage patterns for pediatric aP (acellular pertussis) hexavalent vaccines, and to identify the market structure (by volumes administered) among hexavalent aP vaccines. Hexavalent vaccines are (six-in-one ready to use) (or 5+1) combination vaccines recommended for administration in three or four doses to protect babies against diphtheria (D), tetanus (T), pertussis (P) (whooping cough), poliomyelitis (IPV), haemophilus influenza type B (Hib) and hepatitis B (Hep B). Hexavalent vaccines form a part of the DTaP based combination vaccines market (which also include pentavalent and tetravalent vaccine). DTaP vaccines together with DTwP based vaccines compose the DTP backbone combination vaccines market.

In order to meet the study objectives, we analyzed key indicators such as vaccine immunization schedules, vaccination coverage rate, and population of surviving infants for all the 102 target countries, across the globe, in 2019. Qualitative and quantitative data gathered through the application of these key parameters were used to estimate market volumes for hexavalent vaccines in each target country. We referred to UNICEF, WHO, and other country-specific sources for data gathering.

Our results show that DTaP combination vaccines (acellular pertussis) have only a small presence in the DTP based combination vaccines market with a 23% share of the total 326 million doses in 2019. Hexavalent vaccines account for 50% of the DTaP market with approximately 38 million doses consumed in 2019. The study found that hexavalent vaccines are more often utilized in public markets. By region, hexavalent vaccines are consumed more in the European region (EUR). The three countries using the highest volumes of hexavalent vaccines are Mexico, South Africa, and Germany.

Based on our estimations, Hexaxim®, the hexavalent vaccine from Sanofi Pasteur, holds the leading position in the hexavalent vaccines market with 62% of the volumes consumed across the globe. Infanrix Hexa®, manufactured by GlaxoSmithKline (GSK) accounts for 32% of the hexavalent vaccines market, and Vaxelis®, manufactured by MCM (European joint venture formed between Sanofi Pasteur and Merck & Co., Inc.) accounts for 6% of the hexavalent vaccines market based on volumes distributed in 2019. In the public markets analyzed, Hexaxim® has a 69% market share and is the most used hexavalent vaccine.

The adoption of hexavalent vaccines is high in the EUR region, with 30 of the 52 European countries using hexavalent vaccines in their national immunization schedule. In Latin America (LATAM) countries the adoption of hexavalent vaccines is low with only 4 (Argentina, Chile, Mexico, and Panama) of 30 countries adopting this vaccine in their immunization schedules. Panama was the first LATAM country to introduce hexavalent vaccines in its immunization schedule, whereas Chile decided to implement four doses of hexavalent vaccines from 2019 in its national immunization schedule.

Among the top 35 hexavalent vaccine markets, Hexaxim® is the most used vaccine. In 2019, 22 million doses of Hexaxim® were distributed for all infants. Hexaxim® is the most used hexavalent vaccine for Pre-term infants. In 2019, 1.7 million doses of Hexaxim® are distributed for pre-term infants.

Hexaxim® is the only vaccine used in the pre-terms among 16 countries including 5 countries in the Europe: Austria, Belgium, Croatia, Macedonia, and Norway. More than 90 million doses of Hexaxim® have been administered worldwide since its launch, including the estimated 164 000 preterm infants in the 9 European countries (Austria, Belgium, Bulgaria, Croatia, Denmark, Italy, Macedonia, Norway, and Romania).

Key Words: Hexavalent Vaccine, Immunization, Schedule, Hexaxim®, Infanrix Hexa®, Vaxelis®, Acellular Pertussis, Whole-cell Pertussis, Combination Vaccine

1. Introduction

This introduction section describes the evolution of hexavalent vaccines and provides information on the type of hexavalent vaccines and commercially available brands

Combination Vaccines Evolution

Combination Vaccines are used to overcome the problems associated with multiple administration of monovalent vaccines. The use of combination vaccines, which include several antigens in a single administration, offer benefits such as reduced complications associated with multiple intramuscular injections, decreased costs of stocking and administering separate vaccines, and a lowering of the risk of delayed or missed vaccinations.²²

The combined diphtheria, tetanus, and pertussis (DTP) vaccine, which includes a whole-cell pertussis component (DTwP) or two or more acellular pertussis components (DTaP) has already been incorporated into the national immunization schedules in most countries.²³ These DTP based vaccines serve as the backbone of several other combination vaccines such as tetravalent, pentavalent, and hexavalent vaccines.

The trivalent (DTP) and tetravalent (DTP-HepB) vaccines have been replaced with pentavalent vaccines (DTP-Hib, HepB) in most countries.²⁴ Pentavalent vaccines with a whole-cell pertussis component (wP) are used by most low-middle income countries (LMIC),²⁵ whereas pentavalent & hexavalent vaccines with acellular pertussis component (aP) are increasingly used by high-income countries.²⁶

Hexavalent Vaccines

Hexavalent vaccines are a way to increase the compliance with the full primary schedule and the coverage rate of these 6 antigens, assuring simplification of administration and better control of vaccination program costs.²⁷

Hexavalent vaccines have replaced pentavalent vaccines in most European countries, and are the preferred vaccines in this region. In Europe, 30 countries of total 52 countries (according to WHO definition) are using hexavalent vaccines, whereas in LATAM only 4 countries of 30 countries have included hexavalent vaccines in their

immunization schedule. The inclusion of hexavalent vaccines in the immunization schedule of a country is a potential approach to global inactivated polio vaccine (IPV) access, which supports the commitment of the World Health Organization (WHO) to eradicate the poliovirus.²⁸

Middle-income group countries (MIG) countries are increasingly adopting hexavalent vaccines in their national immunization schedule. For instance, two upper-middle-income countries such as South Africa and Mauritius in the AFR region have introduced hexavalent vaccines in their national immunization program. South Africa was the first country in the AFR region to replace the pentavalent vaccine and adopt hexavalent vaccines in 2015, followed by Mauritius in 2017. Other middle-income group countries including Mexico, Romania, and Jordan have also included hexavalent vaccines in their national immunization program.

Types Of Hexavalent Vaccines

The acellular Hexavalent vaccine (DTaP Hib HepB IPV) is a six-in-one (all the antigen in the same container with no reconstitution) (or 5+1) vaccine recommended in three or four doses schedule to help protect babies against diphtheria (D), tetanus (T), pertussis (aP) (Whooping cough), poliomyelitis (IPV), *Haemophilus influenzae type B* (Hib) and hepatitis B (Hep B).²⁹ To date, there is only one hexavalent vaccine with a whole-cell pertussis component available only in India.

Hexavalent Vaccine Brands

There are three hexavalent vaccine preparations commercially available for administration to children; namely Hexaxim®/Hexyon®/Hexacima® (Sanofi Pasteur), Infanrix Hexa® (GlaxoSmithKline, GSK), and Vaxelis® (manufactured by MCM). Hexaxim® and Vaxelis® are fully-liquid formulations available in ready to use syringes or vials, while the Hib component in Infanrix Hexa® is supplied as a lyophilized white powder that has to be reconstituted with the components present in the pre-filled glass syringe.³⁰

Infanrix Hexa® has three purified antigens of *Bordetella pertussis* namely pertussis toxoid (PT), filamentous haemagglutinin (FHA), and pertactin (PRN), whereas

Hexaxim® includes two purified antigens (PT, FHA), and Vaxelis® includes five purified antigens (PT, FHA, PRN, FIM (*Fimbriae*) type 2, 3)³¹ (Table 8). Though the number of pertussis antigens differs by the brand of hexavalent vaccine, the WHO position paper on pertussis states "There is no sufficient evidence to establish any significant difference in vaccine effectiveness of aP vaccines with differing numbers of pertussis antigen components"³²

Hexaxim® is the only hexavalent vaccine having the World Health Organization (WHO) prequalification status and also the only one available in both pre-filled syringe or mono-dose vial presentation.

The primary goal of this white paper is to understand the utilization trends for hexavalent vaccines.

2. Methodology

The study is based on the worldwide demand estimates for the hexavalent vaccines. The potential size of the worldwide hexavalent vaccine market is determined by three factors — the annual worldwide birth cohort, the proportion of children receiving the hexavalent vaccine, and the number of doses of vaccine a child receives as per the recommended schedule. The stakeholders influencing the hexavalent vaccine demand include governments of industrialized and developing countries and the private sector.³³

2.1 Volumes of DTP vaccines by Type of Pertussis Antigens (wP and aP)

The global volumes for wP & aP DTP combination vaccines are taken from a global market study conducted by the WHO on diphtheria and tetanus-containing vaccines.³⁴ The further split of aP vaccines into hexavalent, pentavalent, and others is based on inputs from the Vaccine Product, Price, and Procurement (V3P) database.³⁵

2.2 Public And Private markets For Hexavalent Vaccine

A total of 194 countries were selected from WHO Global Health Observatory (GHO) data and public and private markets for hexavalent vaccines are identified based on the inclusion or otherwise of the hexavalent vaccine in the

government supply and the national immunization schedule of the country. The countries having a hexavalent vaccine in their national immunization schedule are designated public markets. The government bears a part or all of the expenditure for immunization in the public markets whereas vaccine expenditure in most of the private markets is through out-of-pocket expenditure or reimbursement by private insurance payers.

All 194 countries selected from WHO are classified as high income, Upper middle income, lower middle income, and low-income countries based on World Bank classification,³⁶ which is adopted by the WHO.³⁷ Low-income countries are excluded in this analysis, based on the assumption that governments in low-income countries cannot afford the supply of hexavalent aP vaccines and that the consumption of hexavalent vaccines is also limited among private markets in these countries.³⁸ Countries in which hexavalent brands are not registered are also excluded from the study. Finally, 102 countries are considered for the current study which includes 42 countries with public markets for hexavalent aP vaccines (Table 2) and 60 countries with hexavalent aP vaccines administered through private markets (Table 3). Compared to the previous year (2018) three countries namely Jordan, Myanmar, and Russia have shifted from the private to the public market based on the inclusion of hexavalent vaccines in their national immunization schedule. In Russia, hexavalent vaccines are only used for their at-risk population which includes premature and small babies, children with cancer, abnormalities of the intestine and other pathologies.³⁹ In 2019, Denmark removed hexavalent vaccines from its immunization schedule.

For each of the countries in the public and private markets, data for the following indicators (surviving infants, immunization rate, and schedule) are collected to estimate the volumes of hexavalent vaccines consumed in a year. In this study, all the indicators and the volumes of the vaccines are estimated for 2019.

2.3 Indicators For calculating Hexavalent vaccine Volumes

2.3.1 Surviving Infants: The doses of hexavalent vaccines are administered to children less than 12 months of age.⁴⁰ Hence the surviving infant population below 12 months of age is the target population for this study. The data on the surviving children (birth cohort) is obtained from WHO, GAVI, UNICEF, UN population data, and national statistics from CIA Factbook (Table 2 & Table 3).

2.3.2 Immunization Rate for Hexavalent vaccines: The DTP₃ vaccine immunization rate was considered for estimating the hexavalent vaccine immunization rate. For public markets with only a hexavalent vaccine supplied through a national schedule, the total immunization rate of DTP₃ is considered as the immunization rate of the hexavalent vaccine (Table 2).

For public markets having hexavalent vaccines along with other multivalent vaccines, the immunization rate for hexavalent vaccines is estimated based on the consumption of hexavalent vaccines as a proportion of all the available multivalent vaccines (Table 2).

For private markets, the immunization rate for hexavalent vaccines is estimated, based on data collected from secondary sources such as WHO,⁴¹ and the Center for Disease Control and Prevention (CDC).⁴² Parameters such as private healthcare vaccine trends, the income status of a country sourced from WHO are also considered for estimating private hexavalent vaccine market volumes for some of the countries. Private vaccines market shares obtained from WHO surveys⁴³ and research publications are also used for estimating private market volumes for hexavalent vaccines. (Table 3)

2.3.3 Schedule: The number of doses of hexavalent vaccines suggested under each country's immunization schedule is obtained from the WHO (Table 2). For countries under private markets, the standard number of doses suggested by recognized authorities and the European Union is considered (Table 3).

2.4 Calculation Of Volumes Of Hexavalent Vaccine:

The hexavalent market volumes are calculated using these parameters— surviving infants' population, hexavalent vaccine immunization rate, and recommended vaccine dose schedule. The objective is to find the utilization of hexavalent vaccine by region, by country, and by individual brand.

2.5 Brand Analysis of Hexavalent Vaccines

Brand preference among the hexavalent brands is estimated for the top 35 countries having high sales volumes for the hexavalent vaccines.

Our criterion for identifying the top 35 countries is that these countries account for more than 90% of the hexavalent vaccines market by volume. On average, the brand of vaccine that is consumed more in these 35 countries will be a market leader in the overall hexavalent vaccine market. (Table 4)

The consumption patterns for each brand of vaccines across the target countries is obtained through information gathered by various sources as below-

1. National and Regional Tenders
2. Ministry Of Health (MOH) and National Health Authorities
3. Primary Interviews with key members in national immunization programs, medical advisors, university professors, UNICEF members, pediatricians, and immunization researchers.

The method by which vaccines are purchased and financed in each country influences the proportion of individual brands of vaccine consumed. In hexavalent public markets, the government finances and procures vaccines in large quantities through tenders. In hexavalent private markets, where individual consumers pay for the vaccine through out-of-pocket or private insurance, hexavalent vaccines are procured by either GP/ pediatricians offices or by pharmacies, directly from the manufacturer and/or through wholesalers.

National and Regional Tenders

Governmental vaccine procurement departments under the country's Ministry of Health generally procure vaccines through national or regional tenders. For instance, hexavalent vaccines are procured by national tenders in Mexico, Australia, South Africa, Romania, Netherlands, Iraq, Chile, Libya, Norway, Austria, Panama, and Bulgaria. Italy and Spain procure vaccines through regional tenders. In Saudi Arabia, vaccines are procured through the Gulf Cooperation Council (GCC) unified tenders coordinated by Gulf Health Council. Tendering information details and their outcomes in terms of brands purchased are as below-

- In Mexico, the Ministry of Health (MOH) procures tenders for the hexavalent vaccines. Only Hexaxim® is procured by the MOH in 2019.⁴⁴ Around 99% of hexavalent vaccines administered in Mexico are of Hexaxim®.⁴⁵
- In South Africa, the national department of health (NDoH) procures hexavalent vaccines.⁴⁶ Hexaxim® is the only brand of vaccine included in South Africa's national immunization schedule. Around three million doses of Hexaxim® were procured during 2019.⁴⁷
- In the UK, only Infanrix Hexa® is centrally procured to be included in the national immunization schedule. The UK is a national tender market, where Infanrix Hexa® was the awarded vaccine in 2019.⁴⁸
- In Saudi Arabia, the Gulf Health council procures vaccines, through annual GCC tenders. In 2019, the tender for hexavalent vaccines is awarded to Sanofi's Hexaxim®.⁴⁹ More than 90% of the hexavalent vaccine administered in Saudi Arabia is through the national immunization schedule and is of 'Hexaxim®' brand.⁵⁰
- In Australia, Infanrix hexa® is the only brand of hexavalent vaccine procured by the Department of Health through national tenders.⁵¹ Around one million doses of Infanrix hexa® vaccine are procured in 2019.⁵²
- In Chile, The National Health Service System (CENABAST), under the Ministry of Health procures vaccines, and it procured the 'Hexaxim®' vaccine for public immunization in 2019.⁵³
- Romania Ministry of Health procured both Infanrix hexa® and Hexaxim® brands of hexavalent vaccines in 2019⁵⁴. Around 60% of the hexavalent vaccine doses procured are of Hexaxim®⁵⁵ and the remaining market constitutes Infanrix Hexa®.
- In the Netherlands, vaccines are procured through national tenders in the country by the national institute for public health and the environment (an agency of the Dutch Ministry of Health).⁵⁶ Infanrix Hexa® has been replaced by Vaxelis® in 2019.⁵⁷
- In Italy and Spain, vaccines are procured through regional tenders. In 2019, Hexaxim®,⁵⁸ and Infanrix hexa®,⁵⁹ and Vaxelis® are procured by regional tenders in both countries.
- In Canada, Infanrix Hexa® is procured for public immunization by Health Canada for only 5 provinces/territories including British Columbia, Alberta, Quebec, Prince Edward Island, and Yukon.⁶⁰ In 2019, around 0.5 million doses of Infanrix Hexa® were procured by the Government of Canada.⁶¹
- In Libya, vaccines are procured through national tenders by the ministry of health supreme committee for supervision of tender.⁶² Hexaxim® is the only hexavalent vaccine included in its national immunization schedule for public immunization.⁶³
- In Austria, vaccines are procured through national tenders by the Federal Ministry of Labour, Social Affairs, Health, and Consumer Protection.⁶⁴ Hexaxim® is the only hexavalent vaccine included in the free children's vaccination program.⁶⁵
- In Panama, vaccines are procured through national tenders by Ministerio de Salud de la República de Panamá.⁶⁶ Hexaxim® is the only hexavalent vaccine included in the national immunization schedule for public immunization.⁶⁷
- In Bulgaria, vaccines are procured through national tenders by the Ministry of health. Infanrix Hexa® is the only hexavalent vaccine included in the immunization schedule for public immunization in 2019.⁶⁸
- In Norway, vaccines are procured through national contract open tenders through the Norwegian Institute of Public Health.⁶⁹ Hexaxim® is the only hexavalent vaccine used in the national immunization program in Norway in 2019.⁷⁰

- In Belgium, vaccines are procured solely by each Belgian community.⁷¹ Pharmacies directly procure vaccines from manufacturers or wholesalers.⁷² Hexaxim® is the only vaccine used in the immunization program in Belgium in 2019.⁷³
- In Sweden, vaccines are procured through centralized regional public tenders.⁷⁴ Hexaxim® and Infanrix Hexa® are used in the immunization program in Sweden in 2019.⁷⁵
- In Iraq, The State Co. For Marketing Drugs and Medical Appliances (KIMADIA), under the Ministry of Health procures vaccines through annual tenders. The latest tender for the hexavalent vaccine (for the consumption in 2019), is awarded to Sanofi's 'Hexaxim®'.⁷⁶

Ministry Of Health (MOH) and National Health Authorities

The information on brands of hexavalent vaccine administered in national immunization schedules in the different countries is gathered through authentic secondary sources such as the Ministry of Health (MOH) sites, publications by government health authorities among others. For instance, the Swedish public health authority publishes information on the hexavalent brands and the volumes consumed in the country. This along with the information from the regional tenders awarded for 2018 in the country is used to assess the hexavalent vaccines brand utilization in the country.⁷⁷

In 20 public markets namely, the UK, Switzerland, Chile, Netherlands, Belgium, Bulgaria, Canada, Australia, Russia, Libya, South Africa, Saudi Arabia, Mexico, Iraq, Jordan, Panama, Kazakhstan, Austria, Norway, and Georgia are the countries where only one brand of vaccine is administered or available in the public markets, the entire public market consists of this brand of vaccine. For instance, in the UK⁷⁸, Switzerland⁷⁹, and Canada⁸⁰, Infanrix hexa® is the only brand of vaccine available and administered to all the target children. In Libya⁸¹ and Belgium⁸² 'Hexaxim®' is the brand of hexavalent vaccine available and administered to the target children. The National Center for Disease Control (NCDC) provides medical supplies and vaccines in Libya.

According to the United Nations Industrial Development Organization (UNIDO), South Africa, has allocated around 40% of its vaccine supplies budget for the procurement of the hexavalent vaccine from Sanofi (Hexaxim® brand).⁸³ The vaccinator's manual published by the National Department of Health, recommends only Hexaxim® under hexavalent vaccines, to be administered to children.⁸⁴ The reasons for South Africa including the hexavalent vaccine in its national immunization schedule are⁸⁵ lower healthcare provider cost by simplifying logistics and delivery infrastructure, reduced visits to clinics, lower vaccination errors, fewer injections compared to individual vaccines, and reduction in vaccine adverse events.⁸⁶

Primary Interviews

In some of the countries, especially in countries with hexavalent private markets, data on vaccine procurement by pharmacies or clinics, and or wholesaler sales data is not publicly accessible. Primary interviews with key members in national immunization programs, medical advisors, university professors, UNICEF members, pediatricians, and immunization researchers were conducted for such countries to know the brand utilization.

Insights on the brand split of vaccines in Germany, Italy, France, Spain, Poland, Brazil, Indonesia, Greece, Thailand, Jordan, and Saudi Arabia were obtained through primary interviews. (Table 7)

3. Findings & Discussion

3.1 DTP Combination Vaccines by Type of Pertussis Antigens (wP and aP)

In China, the USA, and Japan no hexavalent vaccines were commercialized at the time of the study. In China, only the trivalent DTaP vaccine is being used in the national immunization schedule, whereas in the USA pentavalent vaccines are used and the market is shared between Sanofi Pasteur and GSK. The global DTP-based combination vaccine market in this study excludes DTP vaccines consumed in China.

In 2019, the global demand for DTP-based combination vaccines was 326 million doses.^{87, 88} DTP combination

vaccines with a whole-cell pertussis component (DTwP) had a 77% share of the total DTP combination vaccines market in 2019, which accounts for 250 million doses. DTaP combination vaccines (acellular pertussis) had only a 23% share of the DTP combination vaccines market, which accounts for 76 million doses.

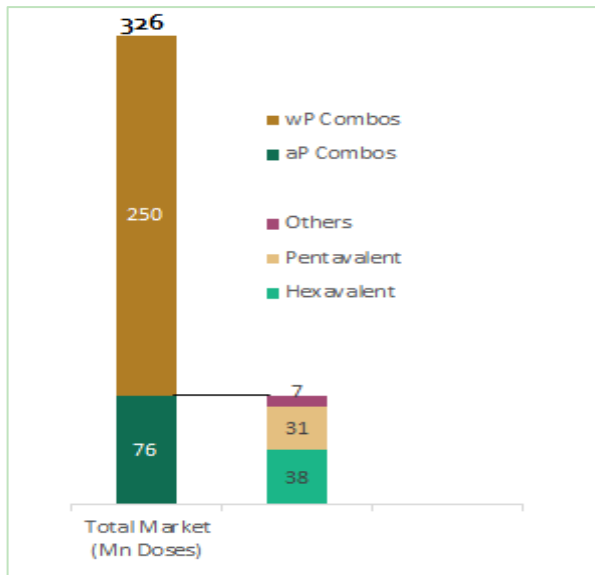


Fig 1: aP and wP Vaccine split; (Others Include tetraivalent)
Global DTP combination market volumes excluding China

The total DTaP combination vaccine market (as shown in Figure-1) is split into hexavalent, pentavalent, and other vaccines. Based on our assumptions, in 2019 the global hexavalent vaccine demand was 38 million doses, which is 50% of the total DTaP market.

The demand for pentavalent vaccines and other vaccines was 31 million doses and 7 million doses respectively. The high share of hexavalent vaccines among DTaP based vaccines can be attributed to a shift to hexavalent vaccines by high-income countries, particularly among the European countries.

3.1.1 Countries Using DTwP and DTaP Vaccine

Among the 194 WHO countries around 118 countries have DTwP combination vaccines and 75 countries have DTaP combination vaccines in their national immunization schedule.⁸⁹ Monaco is using DTIPV (Diphtheria, Tetanus, IPV combination vaccine) in their immunization schedule.⁹⁰

Among 118 countries using DTwP vaccines, 75 countries are of low income and lower-middle-income status. There are only six high-income countries namely Uruguay, Kuwait, Trinidad and Tobago, Seychelles, Antigua, and Barbuda, and Saint Kitts and Nevis are using DTwP vaccines in their national immunization schedule.⁹¹ Most of the wP vaccines are being used by Africa, SEAR, and AMR regions. For instance, in Africa, 44 countries out of 47 countries (according to WHO classification) are using whole-cell pertussis vaccines and in AMR 27 out of 35 countries are using wP vaccines in their national immunization schedule.⁹²

Among the 75 countries using DTaP vaccines, 50 are of high-income status. There are only two lower-middle-income countries: Bhutan and Micronesia, using DTaP vaccines in their national immunization schedules. There are 23 upper-middle-income countries using acellular pertussis component vaccines.⁹³

Most of the EUR countries use aP vaccines, for instance in Europe, among 52 countries (according to WHO classification) 40 countries are using DTaP vaccines in their national immunization schedule. Only three African countries namely Algeria, Mauritius, and South Africa are using DTaP vaccines in public immunization.⁹⁴

DTaP based combination vaccines are more expensive than DTwP vaccines. Pooled procurement agencies such as UNICEF and GAVI procure pentavalent vaccines with whole-cell pertussis (wP) components for supply to low- and middle-income countries. Also, developing countries that procure by self-financing methods procure wP based DTP combination vaccines for the supply in their countries.⁹⁵ Acellular component (aP) based DTP vaccines are supplied to the public by governments of upper-middle-income and high-income countries or consumed in private markets in some high- and middle-income countries through out-of-pocket expenditures.⁹⁶

The above reasons explain the consumption of higher volumes of DTwP vaccines than DTaP vaccines.

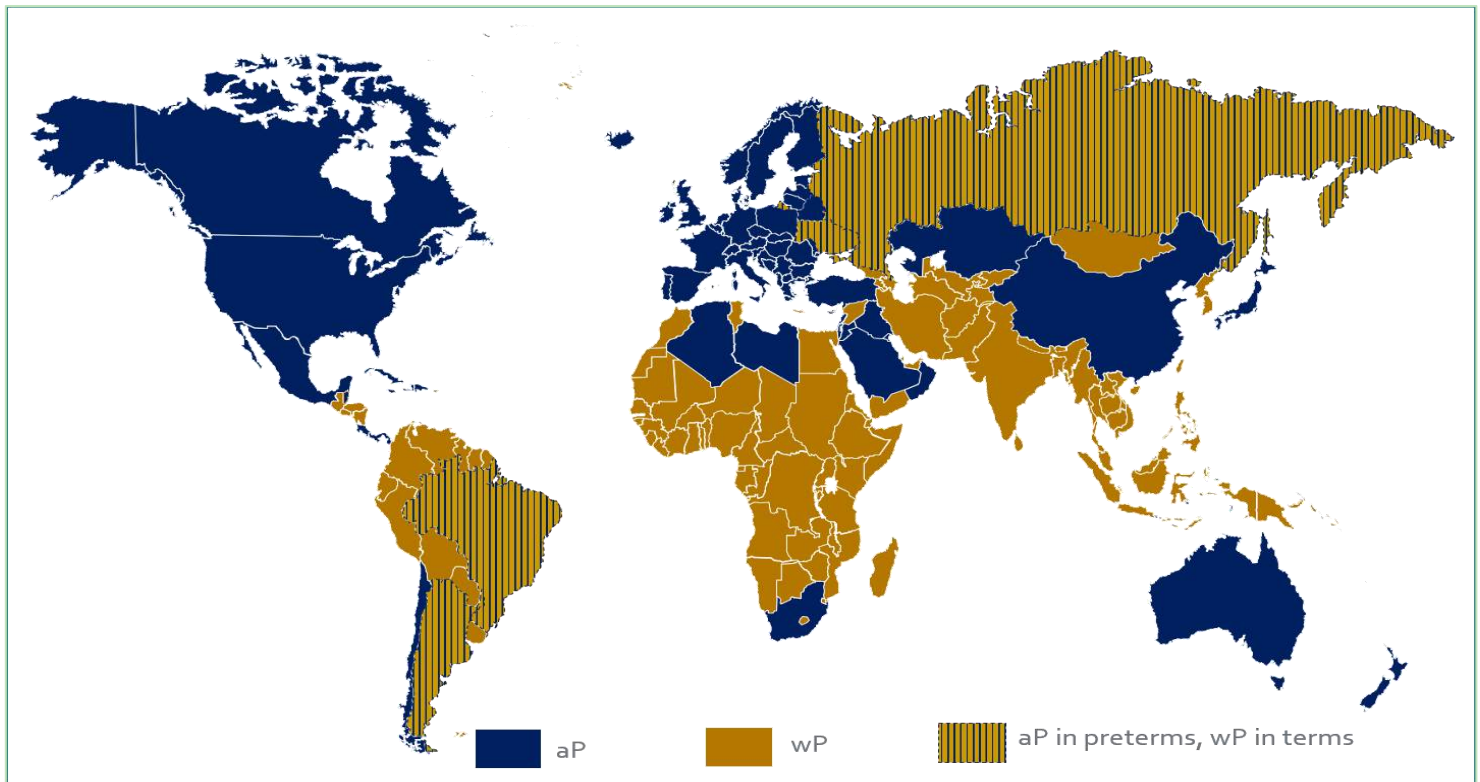


Fig 2: Countries using aP & wP vaccines

The initial cost of implementing hexavalent vaccines through public immunization programs is high compared to whole-cell pertussis vaccines such as pentavalent vaccines.

However, several studies prove the cost-effectiveness of hexavalent vaccines based on the following parameters: reduction in costs associated with the administration of multiple vaccines, decreased cost of vaccine stocking, reduced complications associated with multiple IM (intramuscular) injections⁹⁷ which helps in better vaccine acceptability, convenience, and increased compliance.⁹⁸

According to a study conducted by Demarteau N et.al. in Slovenia the implementation of a hexavalent 2+1 immunization schedule with co-administration of 4th dose MMR or Tdap/MMR at 7 years old leads to annual budget saving of €259,776 and €470,950 as compared to the budget associated with the pentavalent vaccine schedule.⁹⁹

Another study conducted by M. Mogale et.al. in South Africa estimates the cost savings of implementing hexavalent vaccines to be \$0.5 to \$1.5, compared to administering pentavalent vaccines. These cost savings are attributed to reduced cold storage space, reduced hazardous waste disposal, and a reduced number of vaccines administered.¹⁰⁰

According to WHO's MI4A database (market information for access to vaccines), most of the wP vaccines are manufactured in developing countries including India, Brazil, Venezuela, Indonesia, Iran, and Serbia.¹⁰¹ In contrast, most of the aP vaccines are manufactured in developed countries (high-income groups) including the USA, France, Belgium, and Denmark.¹⁰²

Hexaxim® is manufactured in France,¹⁰³ Infanrix Hexa® is manufactured in Belgium,¹⁰⁴ and Vaxelis® is manufactured in the USA.¹⁰⁵

3.2 Global Market For Hexavalent Vaccines

The global market for the hexavalent vaccines section describes the use of hexavalent vaccines in public and private markets, and hexavalent vaccine utilization trends in Europe and LATAM regions.

3.2.1 Public & Private Markets For Hexavalent Vaccines

Based on government supply and inclusion of hexavalent vaccines in the immunization schedule, the countries are split into public and private markets. Out of 102 countries considered for the study, 42 countries are public markets for hexavalent vaccines and the remaining 60 countries are private markets, as shown in Figure 2.

The hexavalent vaccines are used in 42 countries for public programs which include 29 high-income countries, 12 upper-middle-income countries, and one lower middle-income country. The high proportion of high-income countries among these public markets is due to the affordability of the hexavalent vaccines by the governments of these countries.

Hexavalent vaccines are provided by private services in 60 countries, of which 14 are high income, 25 are upper middle income, 20 are lower-middle-income countries, and only one country is from the low-income group.¹⁰⁶

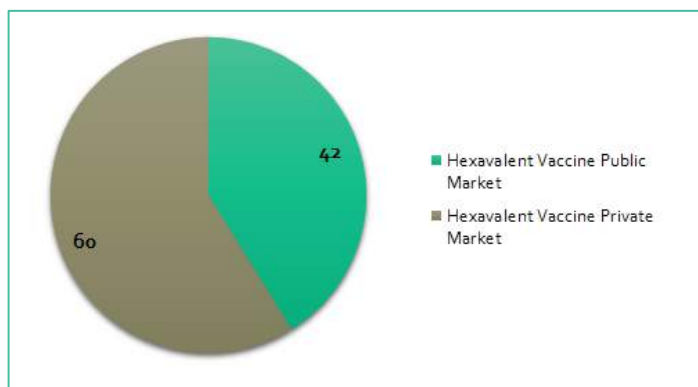


Fig 3: Hexavalent public & private markets
(refer to Table 2 & Table 3 in appendix)

3.2.1.1 Hexavalent Vaccine Trends in EUR Region

EUR region is one of the first regions in the world to use hexavalent vaccines.^{107, 108, 109} This region has high adoption of hexavalent vaccines, and more EU countries are shifting

toward these vaccines. The hexavalent vaccine trends in the European region are described below.

EU Countries Shifting From Mixed Vaccination Schedules To Full Hexavalent Vaccine Schedule

Some European countries have been using hexavalent vaccines along with pentavalent vaccines in their national immunization schedule for primary vaccinations. A trend toward shifting to a full hexavalent vaccine schedule from mixed vaccine schedules (using Hexa/Penta) is observed in European countries. For instance, a few countries such as France (shifted to full hexavalent schedule in 2013) and Spain (shifted to full hexavalent schedule in 2016) have shifted entirely to Hexavalent vaccines.

During 2018 and 2019, some European countries have made changes to their national immunization schedules pertaining to hexavalent vaccines. Countries including Greece¹¹⁰ and Sweden¹¹¹ are progressively replacing pentavalent vaccines with hexavalent vaccines in their immunization schedule.

High Adoption of Hexavalent Vaccines Among High-Income European Countries

Among 52 European countries, 28 countries have adopted hexavalent vaccines in their national immunization schedules of which 22 countries belong to high-income status, 5 countries belong to the upper-middle-income status which includes Russia, Kazakhstan, Romania, Bulgaria, Georgia, and Macedonia. It is evident that the adoption of the hexavalent vaccine in the EU is high in high-income status countries compared to upper middle income and lower-middle-income countries.

Preference Towards Fully Liquid Hexavalent Vaccine

European countries including Germany, France, Italy, Spain, and Belgium prefer a fully liquid hexavalent vaccine compared to a reconstituted hexavalent vaccine.^{112, 113} This trend might be explained by a combination of factors including the willingness of healthcare professionals to reduce reconstitution errors, reduced vaccine preparation time, and ease of use.

In the Netherlands, National Institute for Public Health and the Environment (RIVM) has replaced Infanrix Hexa® with Vaxelis® starting from 2019.¹¹⁴ All children born from December 2018, are being administered with Vaxelis® according to the immunization vaccine schedule.¹¹⁵

According to a survey conducted by Ilse De Coster et.al. in Belgium, the average preparation time for a fully-liquid hexavalent vaccine is 38 seconds, whereas it is 70.5 seconds for a non-fully liquid hexavalent vaccine. The research also reports that the time saved using fully liquid hexavalent vaccines was 34.5 seconds.¹¹⁶

A study conducted by Mathijssen DAR et.al. in the UK demonstrated that the introduction of a fully liquid vaccine in the UK's immunization schedule for infants can save £1.17 million to £1.21 million per year, compared to using a vaccine requiring reconstitution.¹¹⁷

According to a survey conducted by Pierre Bakhache et.al in France, 28% of pediatricians and general practitioners reported occasionally omitting to reconstitute a pentavalent or hexavalent vaccine in error, and 60% of respondents not fully reconstituting the vaccine. According to this study vaccine reconstitution as a complicating factor is reported by 70% of pediatricians, and 57% of general practitioners.¹¹⁸

According to a study conducted in Germany by Lloyd et.al on patient preference and adherence to the hexavalent vaccine, healthcare providers prefer a fully liquid hexavalent vaccine compared to a reconstituted hexavalent vaccine.¹¹⁹ This preference is due to reduced preparation time, and low probability of administration errors with fully reconstituted vaccines.¹²⁰

According to an open-label randomized Belgian study conducted by I. De Coster et al., the preparation time and immunization errors were low in a fully liquid hexavalent vaccine compared to a non-fully liquid vaccine. The same study reported that around 98% of healthcare professionals preferred a fully -liquid hexavalent vaccine (this study samples 96 health care professionals).¹²¹

Georgia Transitioned To Fully Self-Financing Hexavalent Vaccine

Georgia procures many vaccines through the UNICEF supply division. During 2018 – 2019, Georgia introduced hexavalent vaccines in their national immunization schedule. As hexavalent vaccines are not available through UNICEF procurement, the country shifted to self-financing for the procurement of this vaccine.¹²² Georgia was able to procure hexavalent vaccines at a competitive and affordable price despite its market size (smaller market compared to other European countries using hexavalent vaccine). The country has evaluated several reasons for introducing hexavalent vaccine which includes, reduction in vaccine rejections, high trust and acceptance of hexavalent vaccine in Georgia's private sector, and can overcome the potential global supply shortage of IPV vaccine.¹²³

3.2.1.2 Hexavalent Vaccine Trends in Latin America (LATAM)

LATAM countries have low adoption of hexavalent vaccines. Among 30 LATAM countries only 4 countries namely Mexico, Chile, Panama, and Argentina, have adopted hexavalent vaccines in their immunization schedule. Pentavalent vaccines are being used in 26 LATAM countries as of 2019.

In Mexico, the hexavalent vaccine was approved in 2018 for inclusion in the national immunization schedule. During 2018 the hexavalent vaccine was used by the Ministry of Health as a strategy against the shortage of acellular Pentavalent vaccine. In 2019, both pentavalent and hexavalent vaccines co-exist in the Mexican immunization schedule, however by 2020 there will be a complete transition to hexavalent vaccines.¹²⁴ Jalisco, a Mexican state, has incorporated the hexavalent vaccine in the state medical units with a goal to provide immunization for 90,000 children under 5 years of age.¹²⁵ Other Mexican states including Tlaxcala, Guerrero, Quintana Roo and Guanajuato also accepted the hexavalent vaccine in their state medical units.¹²⁶ The reasons for introducing the hexavalent vaccine in Mexico is attributed to increased

vaccine protection and reduced number of multiple vaccine doses.¹²⁷

According to WHO-SAGE recommendations, Chile introduced one dose of IPV vaccine to replace the 2-month OPV dose. As a continuation, the country introduced a hexavalent vaccine (which contains IPV dose) in 2018 for 2- and 4-months intervals, and had 2 OPV doses along with a pentavalent vaccine at 6 and 12 months.¹²⁸ Starting from 2019, the Chilean Ministry of health recommended hexavalent vaccine to provide polio vaccine doses at 2, 4, 6, and 18 months replacing both OPV and pentavalent vaccines.¹²⁹ The reason for Chile shifting to the hexavalent vaccine is to overcome the supply shortages of the IPV vaccine and to reduce the adverse events related to wP pentavalent vaccine in the immunization schedule.¹³⁰

Panama was the first country in the LATAM region to introduce hexavalent vaccines in its immunization schedule. Unlike other LATAM countries, Panama offers only a hexavalent vaccine for infants. According to the Panama ministry of health at least 50,000 children out of 70,000 births, a year are benefited from this immunization.¹³¹

Argentina is using hexavalent vaccines only for risk infants, for instance in preterm newborns weighing less than 1500 grams at birth and <6 months.¹³² According to the Center for Fetoneonatal Studies, Argentina, there are around 1.1% annual pre-term births, or 8,400 are born per year weighing less than 1,500 grams.¹³³

3.3 Analysis Of Indicators For Calculating Hexavalent Vaccine Volumes In Public And Private Markets

Three indicators that are used for the estimation of the hexavalent vaccine market in each target country are the annual worldwide birth cohort (surviving infants), the proportion of children receiving the hexavalent vaccine (vaccine coverage rate), and the vaccine schedule.

3.3.1 Surviving Infants

The countries with high surviving infant's population demand for more volume of hexavalent vaccine doses. Some hexavalent public markets, namely those of Mexico, Iraq, South Africa, and the UK have high levels of surviving infant population. In 2019, Mexico had a surviving infant population of around two million, whereas Iraq and South Africa each had around one million, and the UK had a surviving infant population of 0.7 million. The consumption of hexavalent vaccines is high in these public market countries, due to the supply of free or subsidized hexavalent vaccines by government agencies to the target population (Table 2).

In private markets, countries such as India, Nigeria, Pakistan, and Indonesia have a high surviving infant population. In 2019, India and Nigeria had surviving infant populations of 23 million and seven million respectively, whereas Pakistan and Indonesia each had five million. (Table 3). But only a tiny fraction of the population in these countries have access to private vaccination.

3.3.2 Vaccine Schedule

Most of the countries with hexavalent public markets have implemented the three-dose hexavalent vaccine schedule. Only seven countries have recommended two doses of hexavalent vaccine in their immunization schedule.

In these seven countries, a dose of pentavalent vaccine is administered instead of a third dose of the hexavalent vaccine (Table 2).

In the public markets, mostly three doses of hexavalent vaccines are recommended by the national immunization programs. However, two and four doses of hexavalent vaccines are recommended in few public markets. The public markets in which four doses of hexavalent vaccines are recommended by national immunization programs include South Africa, Chile, Netherlands, Belgium, Russian Federation, Latvia, and Estonia.

Similarly, the public markets following two doses of hexavalent vaccines as per the national immunization programs include Oman, Qatar, UAE, Bahrain, Portugal, Kazakhstan, and Macedonia.

The WHO recommends 2 primary doses plus a booster (2p+1) or 3 primary doses with a booster (3p+1) in vaccine immunization schedule for hexavalent vaccines.

The difference in vaccine scheme is mainly due to serious cases of Hib disease that occurs most commonly in children aged between 4 months and 18 months (countries with low Hib prevalence use fewer hexavalent primary doses compared to countries with high Hib prevalence). The number of primary doses in the immunization schedule is set after consideration of the local epidemiology, vaccine presentation (Hib conjugate monovalent vaccine versus Hib conjugate vaccine in combination with other antigens), and its coordination into the overall routine immunization schedule.

In some countries with the greatest Hib disease burden after the routine use of the Hib vaccine, are recommended to give a booster dose by following either a 2p+1 or 3p+1 schedule.

Countries following the two doses hexavalent vaccine schedule use two doses of either pentavalent or other DTP combination vaccine in their national immunization schedule. For countries with hexavalent private markets, three doses of a hexavalent vaccine are considered as suggested by recognized authorities and/or the European Union (Table 3).

3.3.3 DTP₃ Immunization Rate For Hexavalent Vaccine Market

DTP₃ immunization rate i.e. the third dose immunization rate for Diphtheria, Tetanus, and Pertussis is considered for the hexavalent vaccine immunization rate

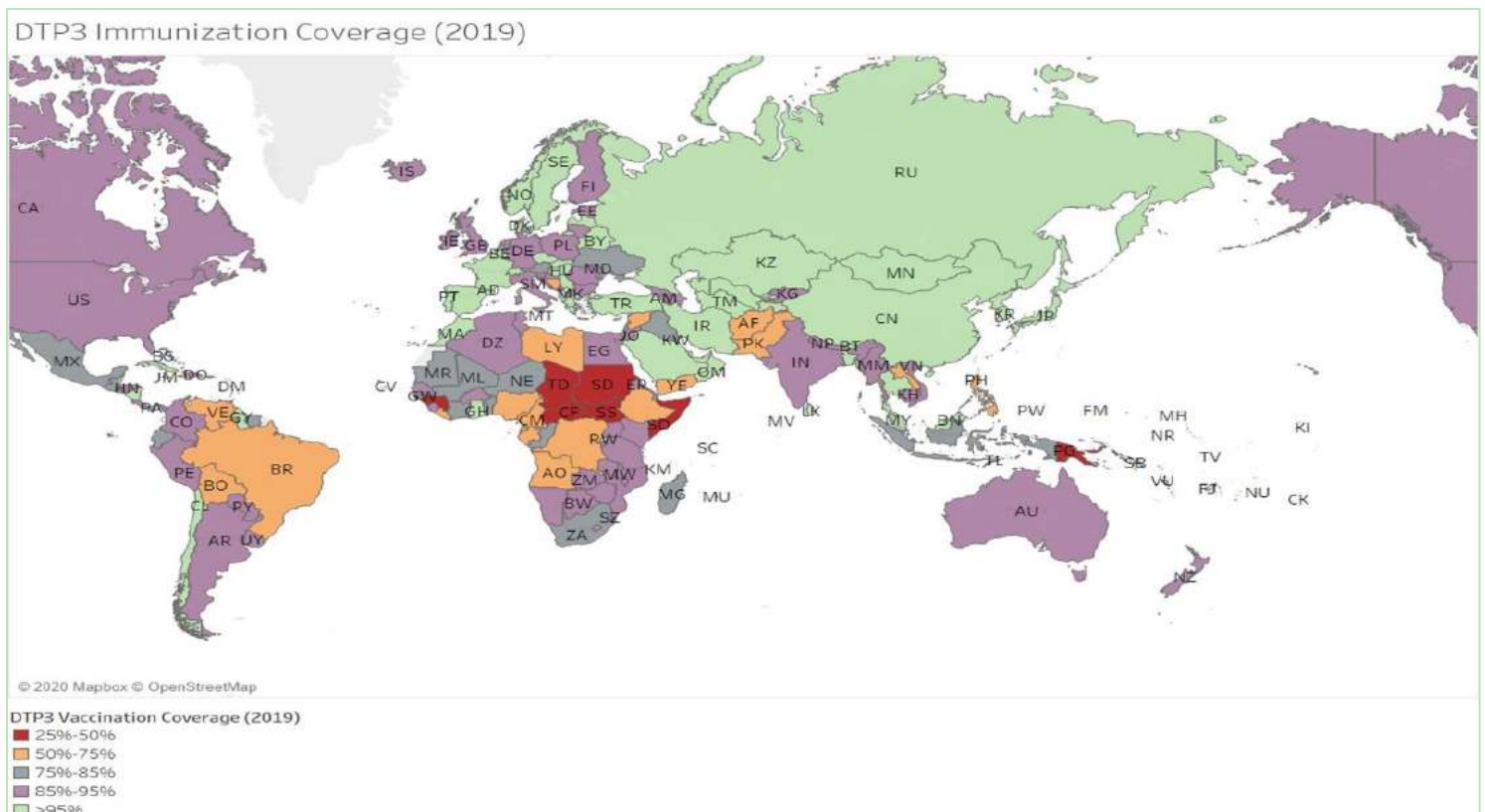


Fig 4: DTP₃ immunization coverage (WHO Immunization Database)¹³⁴

Globally, hexavalent vaccines are consumed more in public markets than in private markets. For public markets where hexavalent is the only vaccine supplied through the national immunization schedule, the rate of immunization is high, ranging from 90% to 99% among those countries.

For public markets where both hexavalent and other multivalent vaccines are used, the immunization rate for hexavalent vaccines varies by country depending on specific factors such as geographical distribution and availability of vaccines within the country, or particular conditions under which hexavalent vaccines are administered.

The immunization rate for hexavalent vaccines ranges from 70%-90% in most of these countries. However, Argentina and Canada have hexavalent vaccine immunization rates of 8% and 50% respectively (Table 2).

Even though the overall immunization rate is high in Argentina and Canada the coverage rate for the hexavalent vaccine is low due to local conditions. In Argentina, hexavalent vaccines are only administered to children weighing less than 1500 grams (or pre-term born infants). In Argentina Public market Hexaxim® was the only Hexavalent vaccine used for pre-term born infants (in 2019), which is about 1.1% of the total infant population.¹³⁵

In Canada, hexavalent vaccines are available only in five provinces out of the ten provinces.¹³⁶ These reasons explain the low immunization rates of the hexavalent vaccine in both countries.

The immunization rate for hexavalent vaccines is low in private markets and ranges from 1-50%, excluding France and Germany which have 95% immunization rates (thanks to public funding or reimbursement). In private markets, most of the high-income countries have hexavalent vaccine immunization rates ranging from 10-20%, whereas upper-middle-income countries and lower-middle-income countries have hexavalent vaccine immunization rates ranging from 2-5% and 1-2% respectively.

The high immunization rates in France and Germany are due to the administration of more than 90% of all the vaccines through private reimbursement. In France, the

high immunization rate (vaccine coverage rate) is reinforced by mandating a hexavalent vaccine from the end of 2018. In these countries, the vaccines are reimbursed through social security (la sécurité sociale) and private health insurance policies making them free of charge to the public.¹³⁷ (Table 3).

3.4 Volumes Of Hexavalent Vaccines:

In 2019, 26 million doses (68.4%) of hexavalent vaccines were administered in public markets through national immunization programs (NIPs), and 12 million doses (31.6%) were administered to infants in private markets (see Figure 3).

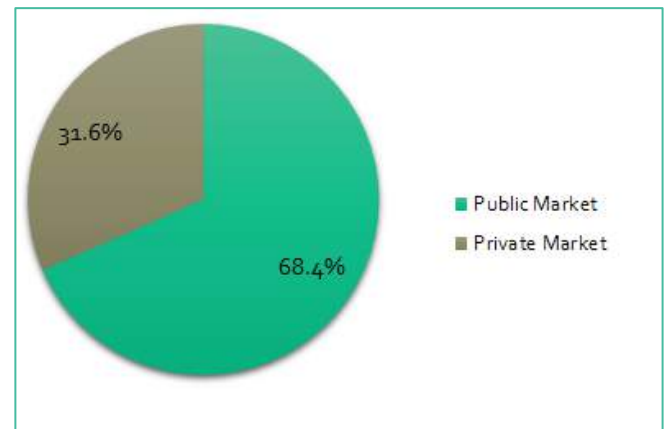


Fig 5: Public and Private Hexavalent Market Share

Hexavalent vaccines were included in the national immunization schedules of many high-income and upper-middle-income countries, due to the strong public immunization financing in these countries. The higher cost of hexavalent vaccines is a hindrance to the supply of these vaccines in low- and middle-income countries.

3.4.1 Hexavalent Vaccines Volume Analysis, By Region

As shown in Figure 4, in 2019 Europe accounted for the major share of the hexavalent vaccines market by volume at 42%, followed by American Region (AMR) with 20%, Eastern Mediterranean Region (EMR) with 13%, African Region (AFR) and Western Pacific Region (WPR) regions accounted for 11% and 9% respectively, followed by Southeast Asian Region (SEAR) with the lowest share at 5% of the hexavalent vaccine market.

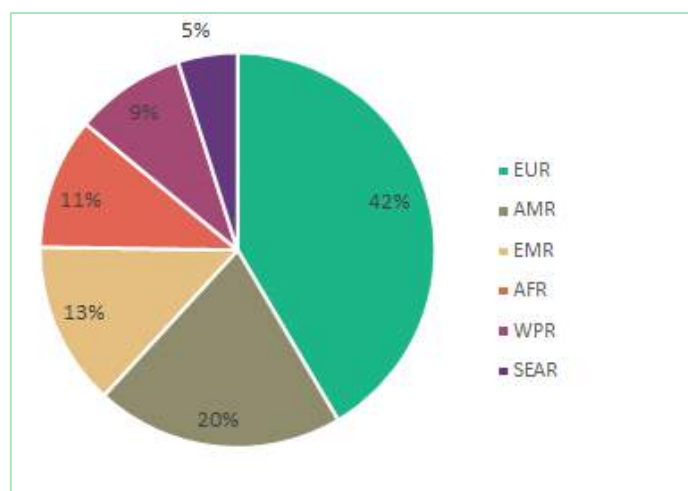


Fig 6: Hexavalent vaccine volume analysis by region

The high share for EUR is due to the early approval and adoption of hexavalent vaccines by most European countries. In 2019, the major European countries such as Germany, UK, France each consumed more than two million doses of hexavalent vaccine, whereas Spain and Italy each consumed more than one million doses of hexavalent vaccine. In France, the use of hexavalent vaccines is mandatory for children born from January 1st, 2018. Some EU countries, such as Italy, France, and Romania, adopted strategies like policy changes and enforcing mandatory vaccination to protect the community when vaccination coverage levels were at risk.

In EMR Saudi Arabia, Iraq, and Libya, are the top countries in hexavalent vaccine consumption. In 2019, more than 1.5 million doses of hexavalent vaccines were used in Saudi Arabia, while around one million doses of hexavalent vaccines were used in Iraq and Libya.

In AMR, only five countries, namely Mexico, Canada, Argentina, Chile, and Panama have included hexavalent vaccines in their national immunization schedules. The low consumption of hexavalent vaccines in the AMR region compared to the EUR region can be attributed to the use of hexavalent vaccines only in special situations. In Argentina, hexavalent vaccines are used only in preterm newborns weighing less than 1500 grams at birth and aged less than 6 months.¹³⁸

In Canada, only 5 out of 10 provinces use hexavalent vaccines. Recently hexavalent vaccines have been approved in the USA (December 2018); this is expected to launch by 2020.¹³⁹

In AFR, South Africa was the first country to introduce hexavalent vaccines in its immunization schedule replacing the pentavalent and HepB Vaccines.¹⁴⁰ More than 80% of hexavalent vaccine volumes consumed in Africa are in South Africa.

In the WPR region only two countries, namely Australia, New Zealand, have hexavalent vaccines in their immunization schedule.

In SEAR hexavalent vaccines are available only through private markets and are not included in the countries' immunization schedules.

3.4.2 Hexavalent Vaccine Volume Analysis, By Country

In 2019, the top 35 countries consumed 35 million doses of hexavalent vaccines which are 92% of the hexavalent vaccine global consumption (see Table 1).

Country Name	Type of Market	Hexavalent Vaccine (Volume, mn)	(% Share among top 35 markets)
Mexico	Public	5.36	14.2%
South Africa	Public	3.53	9.4%
Germany	Private	2.77	7.3%
VietNam	Private	2.29	6.1%
UK	Public	2.15	5.7%
France	Private	2.08	5.5%
Saudi Arabia	Public	1.69	4.5%
Italy	Public	1.27	3.4%
Spain	Public	1.11	2.9%
India	Private	1.09	2.9%
Australia	Public	0.91	2.4%
Chile	Public	0.88	2.3%
Iraq	Public	0.83	2.2%
Libya	Public	0.81	2.2%

Kazakhstan	Public	0.73	1.9%
Netherlands	Public	0.65	1.7%
Poland	Private	0.63	1.7%
Canada	Public	0.58	1.5%
Jordan	Public	0.57	1.5%
Romania	Public	0.49	1.3%
Belgium	Public	0.48	1.3%
Indonesia	Private	0.48	1.3%
Sweden	Public	0.35	0.9%
Russia	Public	0.33	0.9%
Czech Republic	Public	0.32	0.8%
Thailand	Private	0.31	0.8%
Ukraine	Private	0.29	0.8%
Greece	Private	0.25	0.7%
Switzerland	Public	0.24	0.6%
Austria	Public	0.23	0.6%
Brazil	Private	0.22	0.6%
Panama	Public	0.21	0.5%
Norway	Public	0.17	0.5%
Bulgaria	Public	0.17	0.5%
Georgia	Public	0.15	0.4%

Table 1: Hexavalent vaccine volumes for the top 35 countries

Of these 35 countries, 25 have public hexavalent markets, and 10 have private hexavalent markets. In 2019, of the top 35 countries, Mexico had the highest consumption of hexavalent vaccines at 5.3 million doses which is 14.2% of the total volumes of hexavalent vaccines consumed, while Georgia had the lowest consumption of 0.15 million doses which is 0.4% of the global hexavalent vaccines consumed.

In public markets, the top three countries with high volumes of the hexavalent vaccine include Mexico, South Africa, and the UK.

In private markets, the top three countries with high volumes of hexavalent vaccine consumption include

Germany, Vietnam, and France. Germany and France although having high immunization rates are included in the private market category because of the need for health care professional (HCP) prescription for administering vaccines as opposed to national vaccination centers in the UK and Italy. In Germany, the vaccines are reimbursed under the social security reimbursement program, whereas in France the vaccines are reimbursed by primary health insurance fund (CPAM- Caisse Primaire d'Assurances Maladie).

3.4.3 Preterm Hexavalent Vaccine Volume Analysis

In 2019, there are 14.1 million preterm births across the world, which is 11% of the total surviving infant population.

Among the global preterm births in 2019, the SEAR region had a high preterm birth rate of 31.9% followed by AFR, WPR, EMR, AMR, and EUR regions. The top five countries with a high number of preterm births include India, China, Nigeria, Bangladesh, and Indonesia. In 2019, India and China had 3 million and one million preterm births respectively, followed by Nigeria, Bangladesh, and Indonesia with more than 0.5 million preterm births.

In 2019, around 2.6 million doses of hexavalent vaccines were consumed by preterm infants in the top 27 markets (private markets among the top 35 countries are excluded for pre-term analysis except for Germany and France, as private markets do not include the hexavalent vaccine in their immunization schedule) (Table 6). Among these top markets except for the Czech Republic, all other countries are using the same brand of hexavalent vaccines for both pre-term and term infants. In the Czech Republic, although Hexaxim® (actual brand name is Hexacima®) is recommended to use in term infants as per the national immunization program, only Infanrix Hexa® is used in preterm infants.¹⁴¹ In France, hexavalent vaccines are recommended to both term and preterm infants.¹⁴² Hexaxim® is the only vaccine used in the pre-terms among 16 countries (Table 9) including 5 countries in the Europe: Austria, Belgium, Croatia, Macedonia, and Norway.¹⁴³

Argentina uses hexavalent vaccines only for preterm infants weighing less than 1,500 grams at birth and <6 months of age.

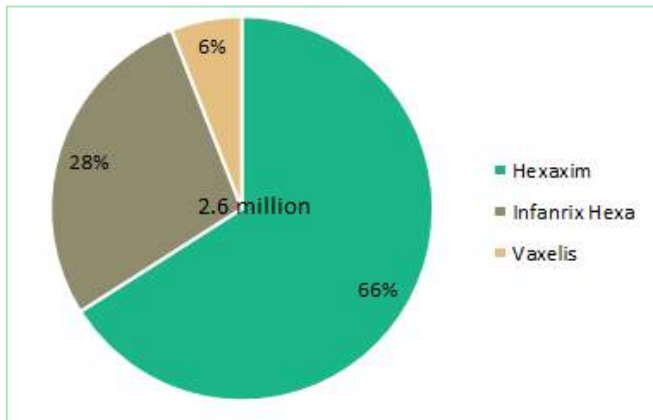


Fig 7: Pre-term infants hexavalent vaccine market by brand

Among the top 27 markets analyzed for pre-term infants, Hexaxim® is the most used vaccine with a share of 66% (1.7 million doses) of the pre-term hexavalent vaccine market followed by Infanrix Hexa® with 28% (0.7 million doses) and Vaxelis® with 6% share (0.1 million doses) of the market.

More than 90 million doses of Hexaxim® have been administered worldwide since its launch, including the estimated 164 000 preterm infants in the 9 European countries (Austria, Belgium, Bulgaria, Croatia, Denmark, Italy, Macedonia, Norway, and Romania).¹⁴⁴

3.5 Brand Analysis of Hexavalent Vaccines

In 2019, Hexaxim® has the highest share of the hexavalent vaccines market by volume with 62%, followed by Infanrix Hexa® with 32%, and Vaxelis® with 6% (see Figure 5). In 2019, around 22 million doses of Hexaxim® were distributed followed by Infanrix Hexa® with 11 million doses, and Vaxelis® with two million doses.

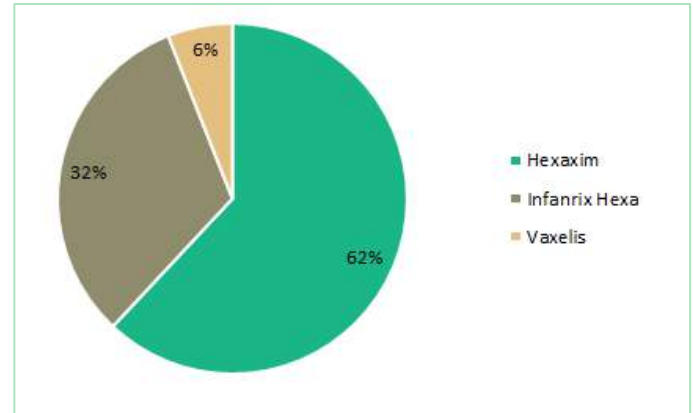


Fig 8: Share of different hexavalent vaccine brands in the top 35 countries

Brand Analysis In Public Markets

There are 25 public markets among the top 35 countries for hexavalent vaccines. These 25 public markets account for a 94% share of the global hexavalent vaccine public market.

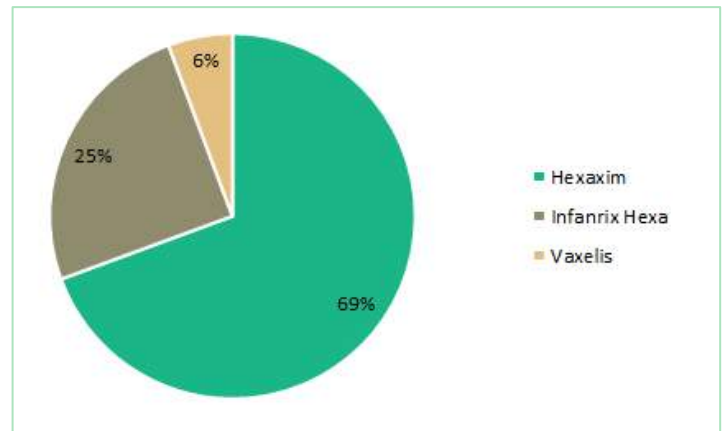


Fig 9: Share of different hexavalent vaccine brands in the top 35 countries among public markets

In public markets, Hexaxim® is the most used hexavalent vaccine with 69% of market share, followed by Infanrix hexa® with 25%, and Vaxelis® with 6% of market share.

In 12 public markets, namely those of South Africa, Saudi Arabia, Mexico, Iraq, Libya, Chile, Panama, Kazakhstan, Belgium, Austria, Norway, and Georgia Hexaxim® is the only brand used in their national immunization schedule. The market for Hexaxim® in these countries is more than 95% of total hexavalent vaccines consumed in those countries.

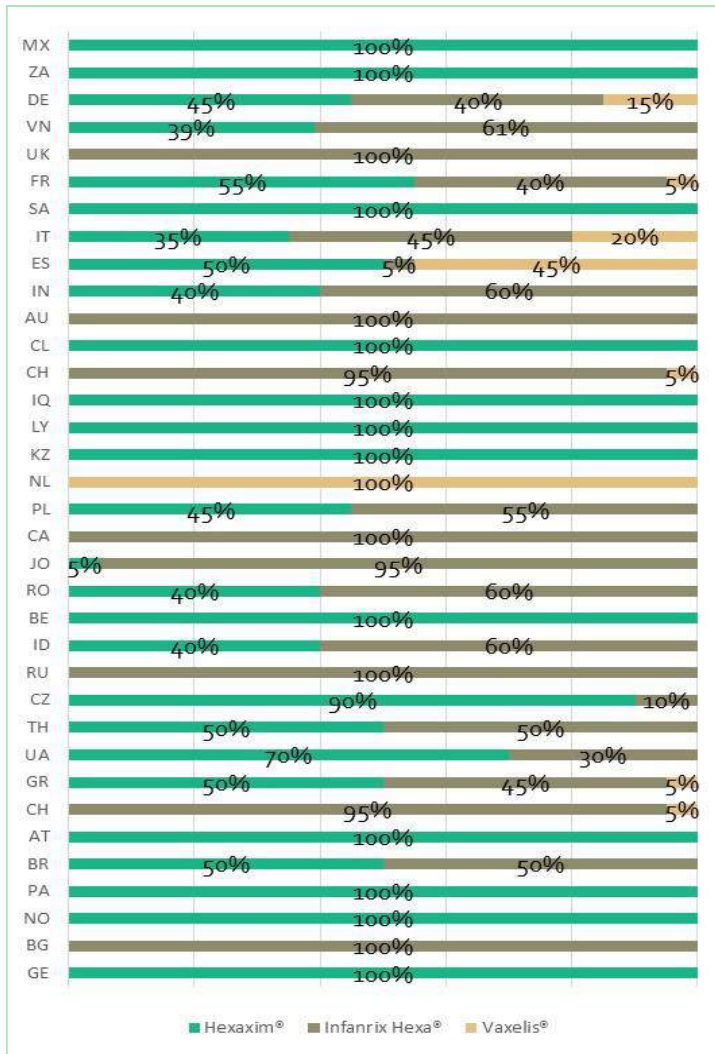


Fig 10: Volume share of hexavalent vaccines by brand, detailed description is given in Table 4 in the Appendix

In seven public markets, namely those of the UK, Australia, Canada, Switzerland, Russia, Bulgaria, and Jordan Infanrix Hexa® is the only brand used in their national immunization schedule. More than 90% of hexavalent vaccines consumed in these countries are of Infanrix Hexa®.

Vaxelis® was approved in the EU in 2016 and was launched in six European countries, namely those of Germany, France, Italy, Spain, Greece, and the Netherlands from 2017 to 2019. Of the total hexavalent vaccine doses consumed, Vaxelis® is the only vaccines used in the Netherlands, 45% in Spain, and 20% in Italy, 15% in Germany, 5% each in France and Greece in 2019.

Brand Analysis By Region

Among the top 35 countries which constitute 92% of the global hexavalent vaccine market, 20 markets (countries) are of EUR, 5 markets are of AMR, 4 markets are of EMR, 3 markets are of SEAR, followed by two WPR and one AFR markets.

In the top 21 EUR markets (all EUR markets are among the top 35 countries) 15.4 million doses of hexavalent vaccines are consumed in 2019. Among these hexavalent vaccine doses, 42% are of Hexaxim®, 46% are of Infanrix Hexa®, and 13% are of Vaxelis®.

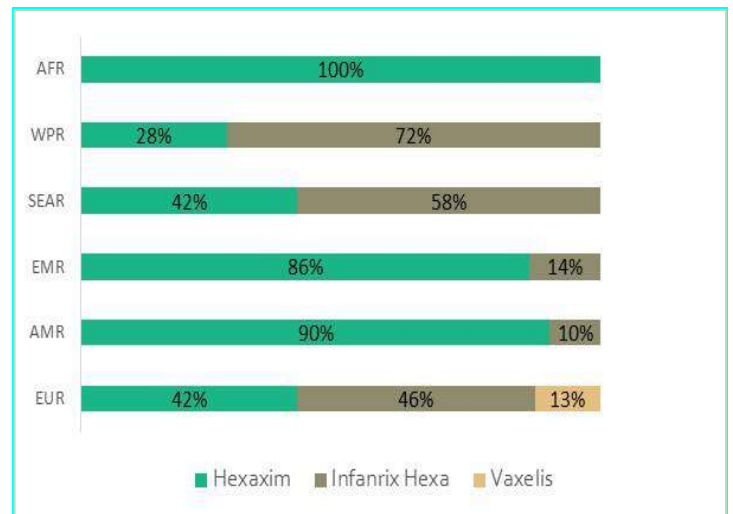


Fig 11: Volume share of hexavalent vaccine brands by regions (top 35 markets)

Among the top 35 countries, only 5 countries namely Mexico, Chile, Brazil, Panama, and Canada are using hexavalent vaccines in the AMR region. These countries consumed 7.2 million hexavalent vaccine doses in 2019. In the AMR region, Hexaxim® is the most used vaccine with a 90% share of the market followed by Infanrix Hexa® with a 10% share of the hexavalent vaccine market.

In the EMR region, only 4 countries namely Saudi Arabia, Iraq, Libya, and Jordan (among the top 35 countries) have consumed 3.9 million doses of hexavalent vaccine in 2019. In this region, Hexaxim® and Infanrix Hexa® are used at a proportion of 86% and 14% respectively.

In the WPR region, only 2 countries namely Australia, and Vietnam are using hexavalent vaccines (among the top 35 countries). In 2019, these countries consumed 3.2 million doses of hexavalent vaccines of which Infanrix Hexa® being the most used vaccine with 72% of the market share in the WPR region. This can be attributed to Australia using solely Infanrix Hexa® in their national immunization schedule.

In the AFR region, South Africa is the major country using the Hexavalent vaccine (among the top 35 countries). In 2019, around 3.5 million hexavalent vaccine doses were consumed of which Hexaxim® is the only vaccine being used under South Africa's national immunization schedule.

4. Value Of the Study

The current study evaluates the volumes of hexavalent vaccines administered across the globe. The proportion of hexavalent vaccines administered among the other DTP based multivalent vaccines is also analyzed. Information on utilization of hexavalent vaccines by region, by country, and by the individual brand is also analyzed as one of the major objectives of the study (not all countries were included also missing the USA, China, and Japan, but those are the countries where no hexavalent were available at the time of the study).

Major indicators that drive the demand for hexavalent vaccines such as immunization rate, surviving infants' population, and schedule, are studied and the correlation between these indicators and the vaccine volumes are described. These indicators directly affect the volumes of hexavalent vaccines consumed.

Different factors drive the demand for hexavalent vaccines among the public and private markets. Government financing and inclusion of the hexavalent vaccine in the immunization schedule drive the vaccine consumption in public markets whereas availability and affordability of the vaccines drive the vaccine consumption in private markets.

5. Conclusions

In 2019, DTaP combination vaccines account for a 23% share of the DTP combination vaccines market for primary vaccination (excluding China), with 76 million doses of the 326 million DTP vaccine doses distributed.

Most public markets occur in high and upper-middle-income countries and most private markets in lower-middle- and low-income countries. The study summarizes that hexavalent vaccines were consumed more in public markets than in private markets in 2019.

Europe accounts for the major share of the hexavalent vaccines market by volume at 42%, followed by AMR at 20%, and EMR at 13%. In 2019, the top 35 countries consumed 35 million doses of hexavalent vaccines which are 92% of global consumption.

Among the commercially available brands of vaccines, Hexaxim® is most administered followed by Infanrix Hexa® and Vaxelis®. In 2019, Hexaxim® has the highest market share in volumes with 62%, followed by Infanrix Hexa® with 32%, and Vaxelis® with 6% of the hexavalent vaccine market by volumes. In public markets analyzed, Hexaxim® has 69% of the market share and is the most used hexavalent vaccine.

Hexaxim® is the market leader among the hexavalent vaccines based on the preterm volumes distributed in 2019 across the globe, which is 1.7 million doses. More than 90 million doses have been administered worldwide since its launch, including the estimated 164 000 preterm infants in the 9 European countries (Austria, Belgium, Bulgaria, Croatia, Denmark, Italy, Macedonia, Norway, and Romania). Hexaxim® is the only vaccine used in the pre-terms among 16 countries (Table 9) including 5 countries in the Europe: Austria, Belgium, Croatia, Macedonia, and Norway.

The fully liquid hexavalent vaccines held a market share of 68% by volumes and reconstituted hexavalent vaccines held a share of 32% of the top 35 countries analyzed (which constitutes 92% of the global hexavalent vaccine market).

The research concludes that the fully liquid hexavalent vaccines are more utilized globally compared to reconstituted hexavalent vaccines, and could be considered a standard of care for hexavalent vaccines worldwide.

Hexaxim® was launched in 2013 and holds its hexavalent market leadership in 2019, already established in 2018, based on our 2019 report.

Conflict of Interest

The research study reported in this whitepaper was sponsored by Sanofi Pasteur. The author of the study serves as an employee of the entity ReportLinker, which conducted the research for Sanofi in return for a consultancy fee. As the consultancy conducted the research through an independent study and the consultancy fee for the research was not affected by the results of the research, a conflict of interest was not found to exist.

Limitations Of The Study

The methodology is very robust to size public market dynamics which represents 92% of the total hexavalent vaccine volumes consumed globally, which constitutes 68.4% of the total public hexavalent vaccine volumes and 31.6% of the total private hexavalent vaccine volumes. The methodology followed for the private market is also robust with both available secondary information and extensive primary research.

The hexavalent vaccine volumes covered by region include 99% in Europe, 95% in AMR, 98% in SEAR, and above 85% in other regions. The vaccine volumes covered in this study represent 92% of worldwide consumption volumes, and so the conclusion of 'Hexaxim®' as the market leader will not alter due to the remaining 8% of uncovered vaccine volumes that are statistically insignificant.

The brand analysis of vaccines in some of the hexavalent private markets is not precise as the information on the exact volumes of the brands administered is not publicly available. (Also, not all countries were included such as the USA, China, and Japan, but these are countries where no hexavalent vaccines were available at the time of the study.) The methodology for hexavalent vaccine preterm volume estimates is not highly robust but based on multiple parameters such as WHO preterm birth rate, surviving infant's population, similar immunization rates used for term babies, private market share of hexavalent vaccines (same information used for term infants). However, we did extensive secondary research to find specific countries that use different brands of vaccines for preterm to estimate the brand proportions split.

Appendix

Table 2-Hexavalent Vaccine Public Markets

The table below shows the parameters considered for hexavalent vaccine volume estimation in the public market

S.No	Country Name	Income Status ¹	Region	# Vaccines ²	Hexavalent Vaccine Immunization Rate ³	Surviving Infants Population ⁴	Schedule
1	Mexico	Upper middle income	AMR	1	62%	2,177,000	3
2	Russian Federation	Upper middle income	EUR	4	5%	1,818,709	4
3	South Africa	Upper middle income	AFR	1	77%	1,147,000	4
4	Iraq	Upper middle income	EMR	1	25%	1,098,000	3
5	United Kingdom	High income	EUR	1	93%	766,596	3
6	Argentina	Upper middle income	AMR	2	1.10%	746,000	3
7	Saudi Arabia	High income	EMR	2	96%	588,000	3
8	Italy	High income	EUR	8	95%	446,000	3
9	Spain	High income	EUR	2	96%	386,000	3
10	Canada	High income	AMR	2	50%	386,000	3
11	Kazakhstan	Upper middle income	EUR	2	97%	374,000	2
12	Australia	High income	WPR	1	95%	318,000	3
13	Chile	High income	AMR	4	96%	228,000	4
14	Jordan	Upper middle income	EMR	2	89%	212,000	3
15	Romania	Upper middle income	EUR	1	88%	185,000	3
16	Netherlands	High income	EUR	1	94%	172,000	4
17	Belgium	High income	EUR	1	98%	124,000	4
18	Libya	Upper middle income	EMR	2	73%	123,000	3
19	Sweden	High income	EUR	1	98%	119,350	3
20	Czech Republic	High income	EUR	1	97%	109,000	3
21	United Arab Emirates (the)	High income	EMR	2	99%	100,000	2
22	Oman	High income	EMR	2	99%	90,000	2
23	Austria	High income	EUR	1	85%	89,000	3
24	Switzerland	High income	EUR	2	70%	88,000	4
25	Portugal	High income	EUR	2	99%	79,000	2
26	Panama	High income	AMR	1	88%	78,000	3
27	Bulgaria	Upper middle income	EUR	2	80%	62,000	3
28	Ireland	High income	EUR	1	94%	60,000	3

29	Norway	High income	EUR	1	97%	59,000	3
30	New Zealand	High income	WPR	1	92%	59,000	3
31	Slovakia	High income	EUR	1	97%	56,000	3
32	Georgia	Upper-Middle Income	EUR	1	94%	52,000	3
33	Croatia	High income	EUR	1	94%	36,000	3
34	Qatar	High income	EMR	2	98%	26,000	2
35	Macedonia	Upper middle income	EUR	2	92%	22,000	2
36	Bahrain	High income	EMR	3	40%	22,000	2
37	Latvia	High income	EUR	2	99%	17,782	4
38	Estonia	High income	EUR	3	91%	14,500	4
39	Mauritius	Upper middle income	AFR	1	96%	13,000	3
40	Luxembourg	High income	EUR	2	99%	6,000	3
41	Andorra	High income	EUR	1	99%	1,000	3
42	San Marino	High income	EUR	1	88%	<1000	3

1. Income Status: Data for the type of country income classification, such as High Income, Upper middle income, Lower middle income & Low-income country were collected from World Bank (WHO follows World Bank classification).

2. #Vaccines: Number of DTP vaccine within the national immunization schedule followed in each country

3. The immunization rates for countries 1-21 are taken from WHO (having only hexavalent in immunization schedule). From countries 19-42 the immunization rates are taken from sources such as WHO, country-specific MOH sites, News articles, and other secondary sources. For instance, in Argentina, children weighing <1500 grams should be administered a hexavalent vaccine, these children are around 1.1% of the total surviving infant population. Hence the hexavalent immunization rate is considered 1.1% for Argentina. In Canada, hexavalent vaccines are used only in 5 provinces out of 10 provinces. In Latvia infants who receive HepB mono vaccine due to hepB risk exposure from mothers will use the pentavalent vaccine, all others are given Hexavalent vaccines. According to the infectious diseases department of Italy's Higher Health Institute (ISS), the immunization rate for a 6 in 1 vaccine has reached 95%.

4. WHO vaccine-preventable diseases: monitoring system (Global summary 2020), GAVI-Country Hub, The World Factbook 2019, UNICEF child survival, and sustainable development goals (SGD), United Nations (UN) Population data.

Table 3-Hexavalent Vaccine Private Markets

The table below shows the parameters considered for hexavalent vaccine volume estimation in the private market

S.No	Country Name	Income Status ¹	Region	# Vaccines	Hexavalent Vaccine Private Share in the market ²	Surviving Infants Population ³	Schedule
1	India	Lower Middle Income	SEAR	1	1.5%	23,390,000	3
2	Nigeria	Lower middle income	AFR	1	0.02%	7,086,000	3
3	Pakistan	Lower middle income	EMR	1	0.5%	5,670,000	3
4	Indonesia	High Income	SEAR	1	3.0%	4,715,000	3
5	Brazil	Upper middle income	AMR	1	3.2%	2,854,000	3
6	Bangladesh	Lower middle income	SEAR	1	0.2%	2,840,000	3
7	Egypt	Lower middle income	EMR	1	5.0%	2,539,000	3
8	Philippines	Lower middle income	WPR	1	3.5%	2,141,000	3
9	Vietnam	Lower Middle Income	WPR	1	37.5%	1,559,000	3
10	Iran	Upper middle income	EMR	1	3.0%	1,506,000	3
11	Kenya	Lower middle income	AFR	1	10.0%	1,439,000	3
12	Turkey	Upper middle income	EUR	1	0.2%	1,297,000	3
13	Algeria	Upper middle income	AFR	1	0.0%	992,000	3
14	Myanmar (Burma)	Lower middle income	SEAR	1	0.5%	907,000	3
15	Ivory Coast	Lower middle income	AFR	1	2.5%	860,000	3
16	Cameroon	Lower middle income	AFR	1	2.0%	851,000	3
17	Germany	High income	EUR	1	95.0%	784,000	4
18	Colombia	Upper middle income	AMR	1	3.5%	725,508	3
19	France	High Income	EUR	1	96.0%	721,000	3
20	Thailand	Upper middle income	SEAR	1	15.0%	702,000	3
21	Uzbekistan	Lower middle income	EUR	1	0.2%	674,000	3
22	Morocco	Lower middle income	EMR	1	1.2%	662,000	3
23	Peru	Upper middle income	AMR	1	3.0%	568,000	3
24	Malaysia	Upper middle income	WPR	1	10.0%	528,000	3
25	Guatemala	Upper middle income	AMR	1	1.0%	418,000	3
26	Ukraine	Lower middle income	EUR	2	20.0%	405,000	3
27	Poland	High income	EUR	2	45.0%	366,000	4

28	South Korea	High income	WPR	3	7.0%	366,000	3
29	Cambodia	Lower middle income	WPR	1	2.0%	355,000	3
30	Ecuador	Upper middle income	AMR	1	1.5%	333,000	3
31	Sri Lanka	Upper middle income	SEAR	1	0.3%	329,000	3
32	Haiti	Low income	AMR	1	0.5%	256,000	3
33	Bolivia	Lower middle income	AMR	1	1.0%	240,000	3
34	Honduras	Lower middle income	AMR	1	0.5%	205,000	3
35	Dominican Republic	Upper middle income	AMR	2	1.3%	201,000	3
36	Tunisia	Lower middle income	EMR	1	10.0%	197,000	3
37	Israel	High income	EMR	1	6.0%	170,000	3
38	Azerbaijan	Upper middle income	EUR	1	4.0%	159,000	3
39	Paraguay	Upper middle income	AMR	1	1.0%	141,000	3
40	Nicaragua	Lower middle income	AMR	1	10.0%	130,000	3
41	Lebanon	Upper middle income	EMR	1	7.0%	116,000	3
42	El Salvador	Lower middle income	AMR	1	1.8%	115,000	3
43	Belarus	Upper middle income	EUR	1	35.0%	109,000	3
44	Hungary	High income	EUR	1	1.0%	91,000	3
45	Serbia	Upper middle income	EUR	1	1.0%	82,000	3
46	Greece	Upper middle income	EUR	1	80.0%	80,000	4
47	Costa Rica	Upper middle income	AMR	1	2.5%	69,000	3
48	Namibia	Upper middle income	AFR	1	12.0%	68,000	3
49	Singapore	High income	WPR	1	25.0%	50,000	3
50	Finland	High income	EUR	1	0.5%	50,000	3
51	Jamaica	Upper middle income	AMR	1	2.4%	46,000	3
52	Armenia	Upper middle income	EUR	1	20.0%	40,000	3
53	Albania	Upper middle income	EUR	1	7.0%	33,000	3
54	Lithuania	High income	EUR	1	10.0%	28,000	3
55	Trinidad and Tobago	High income	AMR	1	15.0%	17,000	3
56	Guyana	Upper middle income	AMR	1	2.4%	15,000	3
57	Cyprus	High income	EUR	1	40.0%	12,000	3
58	Montenegro	Upper middle income	EUR	1	2.0%	7,000	3
59	Malta	High income	EUR	2	10.0%	4,000	3

60	Iceland	High income	EUR	1	10.0%	4,000	3
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1. Income Status: Data for the type of country income classification, such as High Income, Upper middle income, Lower middle income & Low-income country were collected from World Bank (WHO follows World Bank classification).

2. Hexavalent Vaccine Private Market Share: The share of hexavalent vaccine in these countries of total DTP immunization rate. Data taken from WHO private vaccine shares, primary interviews

3. WHO vaccine-preventable diseases: monitoring system (Global summary 2020), GAVI-Country Hub, The World Factbook 2019, UNICEF child survival, and sustainable development goals (SDG), United Nations (UN) Population data.

Table 4-Hexavalent Vaccines Brand Consumption in Top 35 Countries

The table below shows the volumes of hexavalent vaccines consumed in the top 35 countries by brand

S.No	Country Name	Country Code	Type of Market	Volumes (Million doses)	Hexaxim®	Infanrix Hexa®	Vaxelis®
1	Mexico ¹	MX	Public	5.36	5,339,354	16,066	NA
2	South Africa ²	ZA	Public	3.53	3,532,760	NA	NA
3	Germany	DE	Private	2.77	1,246,795	1,108,262	415,598
4	Viet Nam ³	VN	Private	2.29	895,849	1,393,543	NA
5	United Kingdom ⁴	UK	Public	2.15	NA	2,148,300	NA
6	France ^P	FR	Private	2.08	1,142,064	830,592	103,824
7	Saudi Arabia ⁵	SA	Public	1.69	1,693,440	NA	NA
8	Italy ^{6, P}	IT	Public	1.27	444,885	571,995	254,220
9	Spain ^{7, P}	ES	Public	1.11	555,840	55,584	500,256
10	India ^{8, P}	IN	Private	1.09	434,212	651,318	NA
11	Australia ⁹	AU	Public	0.91	NA	906,300	NA
12	Chile ¹⁰	CL	Public	0.88	875,520	NA	NA
13	Iraq ¹¹	IQ	Public	0.83	830,088	NA	NA
14	Libya ¹²	LY	Public	0.81	814,800	NA	NA
15	Kazakhstan ¹³	KZ	Public	0.73	725,560	NA	NA
16	Netherlands ¹⁴	NL	Public	0.65	NA	NA	646,720
17	Poland ^P	PL	Private	0.63	281,637	344,223	NA
18	Canada ¹⁵	CA	Public	0.58	NA	577,500	NA
19	Jordan ^P	JO	Public	0.57	28,302	537,738	NA
20	Romania ¹⁶	RO	Public	0.49	195,360	293,040	NA
21	Belgium ^P	BE	Public	0.48	481,120	NA	NA
24	Indonesia ^{17, P}	ID	Private	0.48	192,372	288,558	NA
22	Sweden ¹⁸	SE	Public	0.35	174,930	174,930	NA
23	Russia ¹⁹	RU	Public	0.33	NA	325,920	NA
25	Czech Republic ²⁰	CZ	Public	0.32	283,708	30,893	NA
26	Thailand ^{21, P}	TH	Private	0.31	153,212	153,212	NA
27	Ukraine ^P	UA	Private	0.29	204,120	87,480	NA
28	Greece ^P	GR	Private	0.25	123,552	111,197	12,355
29	Switzerland ^{22, P}	CH	Public	0.24	NA	224,717	11,827
30	Austria ^{23, P}	AT	Public	0.23	226,950	NA	NA
31	Brazil ^{24, P}	BR	Private	0.22	109,380	109,380	NA
32	Panama ²⁵	PA	Public	0.21	205,920	NA	NA
33	Norway ²⁶	NO	Public	0.17	171,690	NA	NA
34	Bulgaria ²⁷	BG	Public	0.17	NA	171,120	NA

35	Georgia	GE	Public	0.15	146,640	NA	NA
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1. Secretaria de Salud, LOTES DE VACUNAS LIBERADAS 2019
 2. National Department of Health, Tender Procurement, 2019
 3. Vietnam – Drug Administration Ministry of Health, DTP Immunization Services 2019
 4. NHS Immunization Schedule, 2019
 5. Gulf Co-operative Council, Tender 2019
 6. Agenzia Italiana Del Farmaco, Vaccini. Dati e analisi su consumi e spesa
 7. Spain Regional Health Tenders, TED Tender Electronic Daily
 8. IDBI Capital Market Report (Includes Hexaxim®), 2018, 2019
 9. Australia Department of Health, Immunization Schedule; AusTender-Department of Health (2019)
 10. National Health Service System (CENBAST), Mercado Público - La plataforma de compras públicas
 11. KIMADIA (State Co. for Marketing Drugs and Medical Appliances) Tenders 2018 & 2019
 12. Ministry of Health – Supreme Committee for Supervision of Tenders 2019
 13. GMP News (Kazakhstan will provide a six-component vaccine by Sanofi Pasteur for children)
 14. National Institute for Public Health and the Environment (an agency of the Dutch Ministry of Health), National Immunization Program
 15. Public Works and Government Services Canada, Tender 2019
 16. Ministry of Public Health Tender Contract 2019
 17. Ministry of Health, Republic of Indonesia Directorate General of Health Services, 2019 & 2020
 18. Regional Health Tenders, National Vaccine Procurement Sweden 2019
 19. Russia Ministry of Health (Allows hexavalent and pentavalent only for risk population)
 20. Ministry of Health of the Czech Republic Vaccination Calendar 2019,
 21. Thailand Department of Disease Control, Vaccine Procurement
 22. Eidgenössische Kommission Für Impffragen, Definitives Protokoll Der 72. Plenarsitzung (Nov. 2018)
 23. Federal Ministry of Labour, Social Affairs, Health, and Consumer Protection
 24. Leader in vaccine in Brazil, GSK expands operation 2019
 25. Panama National Institute of Statistics & Census (Instituto Nacional de Estadística y Censo) 2014 - 2018
 26. Norwegian Institute of Public Health (CTM-KGV portal)
 27. Ministry of Health of Republic of Bulgaria, Immunization Planning 2018
 28. Curatio International Foundation - Georgia's introduction of the Hexavalent vaccine: Lessons on successful procurement and advocacy
- P. Primary Inputs

Table 5-Estimated Global Preterm Births

The table below shows the estimated global preterm births

S.No	Country Name	Country Code	Preterm Births, 2019
1	India	IN	3,183,379
2	China	CN	1,137,119
3	Nigeria	NG	809,221
4	UK	GB	547,785
5	Bangladesh	BD	543,860
6	Indonesia	ID	490,360
7	Pakistan	PK	475,713
8	Ethiopia	ET	413,683
9	United States	US	373,796
10	Egypt	EG	340,480
11	United Republic of Tanzania	TZ	336,611
12	Democratic Republic of the Congo	CD	325,275
13	Brazil	BR	319,077
14	Philippines	PH	284,111
15	Sudan (the)	SD	175,403
16	Turkey	TR	160,958
17	Afghanistan	AF	157,248
18	Russia	RU	154,901
19	Mexico	MX	153,261
20	Angola	AO	144,598
21	South Africa	ZA	142,572
24	Algeria	DZ	133,027
22	Mozambique	MZ	128,438
23	Kenya	KE	124,330
25	Niger	NE	122,094
26	Iraq	IQ	114,192
27	Uganda	UG	104,331
28	Ivory Coast	CI	102,942
29	Madagascar	MG	101,984
30	Cameroon	CM	101,865
31	Viet Nam	VN	101,803
32	Myanmar (Burma)	MM	94,328
33	Iran	IR	90,962
34	Mali	ML	90,733
35	Thailand	TH	89,154
36	Morocco	TH	88,774

37	Yemen	YE	86,736
38	Burkina Faso	BF	86,543
39	Chad	TD	73,975
40	Zambia	ZM	73,376
41	Somalia	SO	71,940
42	Uzbekistan	UZ	70,096
43	Germany	DE	69,541
44	Senegal	SN	64,279
45	Malawi	MW	63,509
46	Argentina	AR	62,515
47	France	FR	60,708
48	Malaysia	MY	54,912
49	Japan	JP	52,448
50	Guinea	GN	52,309
51	Colombia	CO	51,653
52	Zimbabwe	ZW	50,274
53	Peru	PE	49,927
54	Venezuela (the Bolivarian Republic of)	VE	48,845
55	South Sudan	SS	43,571
56	Syrian Arab Republic (the)	SY	43,264
57	Guatemala	GT	41,089
58	Jordan	JO	37,672
59	Cambodia	KH	36,920
60	Democratic People's Republic of Korea (the)	KP	36,504
61	Ukraine	UA	35,316
62	Italy	IT	27,646
63	Canada	CA	31,378
64	Nepal	NP	28,989
65	Sierra Leone	SL	28,369
66	Tajikistan	TJ	28,288
67	Australia	AU	27,348
68	Ecuador	EC	26,707
69	Poland	PL	26,535
70	Tunisia	TN	26,418
71	Spain	ES	24,974
72	South Korea	KR	24,449
73	Bolivia	BO	23,592
74	Saudi Arabia	SA	23,285
75	Sri Lanka	LK	22,964
76	Papua New Guinea	PG	22,555

77	Congo	CG	20,229
78	Honduras	HN	20,152
79	Dominican Republic	DO	19,758
80	Kazakhstan	KZ	19,373
81	Central African Republic	CF	18,434
82	Liberia	LR	18,314
83	Chile	CL	18,080
84	Mauritania	MR	17,117
85	Lao People's Democratic Republic	LA	16,640
86	Azerbaijan	AZ	16,536
87	Libya	LY	16,494
88	Romania	RO	16,177
89	Kyrgyzstan	KG	15,704
90	Turkmenistan	TM	13,624
91	Netherlands	NL	12,797
92	Nicaragua	NI	12,779
93	Belgium	BE	9,280
94	Eritrea	ER	12,090
95	Paraguay	PY	11,379
96	Serbia	RS	9,815
97	Greece	GR	8,900
98	Oman	OM	8,307
99	Czech Republic	CZ	8,295
100	Namibia	NA	8,140
101	Hungary	HU	8,044
102	Gabon	GA	7,781
103	Mongolia	ME	7,696
104	Panama	PA	7,667
105	Guinea-Bissau	GW	7,541
106	Sweden	SE	7,509
107	Austria	AT	6,200
108	Costa Rica	CR	6,783
109	Cuba	CU	6,720
110	Lesotho	LS	6,344
111	Switzerland	CH	6,327
112	Portugal	PT	6,107
113	Bulgaria	BG	6,000
114	United Arab Emirates	AE	5,500
115	Georgia	GE	5,408
116	Slovakia	SK	5,079

117	Equatorial Guinea	GQ	5,027
118	Belarus	BY	4,665
119	Denmark	DK	4,324
120	New Zealand	NZ	4,407
121	Uruguay	UY	4,216
122	Armenia	AM	4,160
123	Ireland	IE	3,816
124	Republic of Moldova	MD	3,488
125	Norway	NO	3,300
126	Finland	FI	2,885
127	Albania	AL	2,878
128	Macedonia	MK	2,100
129	Croatia	HR	2,000
130	Bosnia-Herzegovina	BA	1,750
131	Lithuania	LT	1,518
132	Guyana	GY	1,475
133	Slovenia	SI	1,452
134	Bhutan	BT	1,352
135	Latvia	LV	1,080
136	Suriname	SR	983
137	Estonia	EE	735
138	Luxembourg	LU	578
139	Iceland	IS	349

**Estimated based on WHO 2014 preterm birth rate (value), HEXYON/HEXACIMA – Use in preterm infants in EU countries with exclusive use (up to end DEC-2019)*

Table 6- Preterm Hexavalent Vaccine Volumes

The table below shows the estimated preterm hexavalent vaccine volumes in the top 35 countries

S.No	Country Name	Country Code	Preterm Births, 2019	Preterm Hexavalent Vaccine Volumes
1	South Africa	ZA	142,821	428,462
2	Mexico	MX	153,402	404,980
3	Iraq	IQ	113,984	287,240
4	Germany	DE	70,162	261,002
5	UK	UK	54,074	152,487
6	Russia	RU	158,000	122,608
7	Jordan	JO	38,000	109,440
8	Italy	IT	27,646	78,791
9	Australia	AU	27,348	77,942
10	Spain	ES	24,845	69,317
11	Chile	CL	18,001	68,404
12	Saudi Arabia	SA	23,364	67,288
13	France	FR	60,456	52,234
14	Belgium	BE	9,280	36,378
15	Libya	LY	16,494	47,998
16	Netherlands	NL	12,722	47,327
17	Romania	RO	16,177	41,737
18	Kazakhstan	KZ	19,684	38,581
19	Czech Republic	CZ	8,371	24,360
20	Switzerland	CH	6,327	24,296
21	Canada	CA	31,459	23,594
22	Sweden	SE	7,509	21,851
23	Panama	PA	7,667	20,242
24	Austria	AT	6,200	15,810
25	Bulgaria	BG	6,000	17,820
26	Georgia	GE	5,500	15,345
27	Norway	NO	3,300	9,504

*The estimation of these preterm volumes is not robust but based on multiple parameters such as WHO preterm birth rate, surviving infant's population, similar immunization rates used for term babies, private market share of hexavalent vaccines used for term infants. However, we did extensive secondary research to find specific countries that use different brands of vaccines for preterm to estimate the brand proportions split.

- 1) Global preterm birth estimates - WHO
- 2) World Bank Population Estimates and Projections
- 3) WHO vaccine-preventable diseases: monitoring system. 2020 global summary
- 4) HEXYON/HEXACIMA – Use in preterm infants in EU countries with exclusive use (up to end DEC-2019)

Table 7-Primary Inputs

The table below shows the primary respondents' information

S.No	Designation	University/Organization	Country
1	University Hospital Mainz/STIKO (Standing Committee on Vaccination)	Chairman/Member	Germany
2	Scientific Project Manager (Coordinator at French national immunization technical advisory group at National Authority for Health, Expert in Vaccine activities)	Haute Autorité de santé (HAS), French Health Technology- Assessment (HTA) Agency	France
3	Member of UNICEF & Immunization and Diseases Outbreak Expert	UNICEF, Immunization and Diseases Outbreak Expert Roster	Italy
4	Pediatrician	Istituto Mario Negri, MOH	Italy
5	Pediatrician	Ruber International Hospital	Spain
6	Pharmacovigilance & Drug Regulatory Affairs Consultant/Pharmacology Associate Professor	Universidad of the Complutense de Madrid	Spain
7	Assistant Professor, Department of Pediatrics	Medical University of Warsaw	Poland
8	Medical Advisor, Former pediatrician, University Professor	ClinPart	Poland
9	Head of Pediatric Department	Medicover Hospital	Poland
10	Head of Pediatrics	Mother and Child Care Center	Poland
11	Project Manager, Former Vaccine Technical Officer at The National Vaccine Institute	National Health Security Office (NHSO)	Thailand
12	Pediatrician	Bangkok Hospital	Thailand
13	Program Manager	Immunization Technical Support Unit (ITSU)-MOHFW	India
14	Director at Brazilian society of infectious diseases, Professor of Infectious Diseases & Vaccinology	The University of Caxias do Sul	Brazil
15	Immunization Researcher	Universidade Federal de São João del-Rei (UFSJ)	Brazil
16	Immunization Coordinator, Pediatrician	Dinas Kesehatan Provinsi DKI Jakarta	Indonesia
17	Pediatrician, Assistant Professor of Pediatrics	Aristotle University of Thessaloniki	Greece
18	National Project Officer Gavi Secretariat	GAVI	India
19	Pediatrician	Ilaya International Group S. L	Ukraine
20	Health Project Coordinator	Islamic Relief World Pediatrician/The Islamic Hospital-Amman	Jordan
21	Pediatrician	Medical Centre Friendlic, Ilaya International Group S.L.	Ukraine

Table 8-Characteristics of Hexavalent Vaccine Brands

The table below shows the characteristics of different hexavalent brands

Vaccine Characteristics	Infanrix Hexa®	Hexaxim®	Vaxelis®
Diphtheria toxoid	Not less than 30 UI	Not less than 20 UI	Not less than 20 UI
Tetanus toxoid	Not less than 40 UI	Not less than 40 UI	Not less than 40 UI
Pertussis	PT 25 µg	PT 25 µg	PT 20 µg
	FHA 25 µg	FHA 25 µg	FHA 20 µg;
	PRN 8 µg	-	PRN 3 µg
	-	-	FIM type 2,3: 5 µg
Hepatitis B - HBsAg	Saccharomyces cerevisiae	Hansenula polymorpha	Saccharomyces cerevisiae
Hib -PRP	10 µg Conjugated to Tetanus toxoid	12 µg Conjugated to Tetanus toxoid	3 µg Conjugated to Meningococcal protein
IPV Polio	Poliovirus inactivated type 1, 2, 3	Poliovirus inactivated type 1, 2, 3	Poliovirus inactivated type 1, 2, 3

Table 9-Exclusive Use of Hexaxim® In Preterms By Country

The table below shows the list of countries exclusively using Hexaxim® for preterms in their immunization schedules.

S.No	Countries Exclusively Using Hexaxim®
1	Argentina
2	Austria
3	Belgium
4	Brazil
5	Chile
6	Croatia
7	Georgia
8	Iraq
9	Kazakhstan
10	Libya
11	Macedonia
12	Mexico
13	Norway
14	Panama
15	Saudi Arabia
16	South Africa

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