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Combined hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b vaccine—Infanrix™ hexa

Twelve years of experience in Italy

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Abbreviations: μg/ml, micrograms per milliliter; ATP, according to protocol; CI, confidence interval; DTPa-HBV-IPV/Hib, diphtheria-tetanus-acellular pertussis, hepatitis B, inactivated poliovirus and *Haemophilus influenzae* type b vaccine; ELISA, enzyme-linked immunosorbent assay; EL.U/ml, ELISA units per milliliter; FHA, filamentous haemagglutinin; GMC, geometric mean antibody concentration; IU/ml, international units per milliliter; mIU/ml, milli-international units per milliliter; PRN, pertactin; PRP, polyribosylribitol phosphate; PT, pertussis toxoid; SP, seroprotection; S+, seropositivity; VR, vaccine response; WHO, World Health Organization

Infant vaccination using 2-dose priming at 3 and 5 mo of age with a booster at 11–12 mo of age was pioneered in Italy. The 3-5-11 schedule is now used in a growing number of European countries. Infanrix™ hexa (DTPa-HBV-IPV/Hib, GlaxoSmithKline Vaccines) was first licensed for use in 2000 and has been the only pediatric hexavalent vaccine available since 2005. We reviewed available clinical trial data describing the immunogenicity of DTPa-HBV-IPV/Hib when administered at 3, 5, and 11 mo of age, and conducted an analysis of safety using global and Italian post-marketing surveillance data. In Italy, DTPa-HBV-IPV/Hib has a demonstrated safety record extending over a decade of use, it has been associated with record levels of vaccine coverage, and with sustained disease control in vaccinated cohorts. Hexavalent vaccines will continue to contribute to high vaccine coverage in Italy and across Europe.

Introduction

Combination vaccines allow the administration of antigens that target multiple diseases in a single injection. The potential benefits of combination vaccines over separate administration of the component parts include increased patient and health care professional acceptance of the administration of multiple antigens at one visit; lower vaccination costs as a result of fewer required office visits; greatly reduced storage requirements for vaccines as well as reduced risk of administration errors and of missed doses. Studies from the United States[1-3] and Germany[4] show that the use of combination vaccines is associated with improved coverage of individual antigens and with more timely vaccination: this means that a higher percentage of children receive all their recommended vaccines at the recommended age.

Hexavalent vaccines targeting six diseases are the largest multi-component combination vaccines currently available. Infanrix™ hexa (DTPa-HBV-IPV/Hib, GlaxoSmithKline Vaccines) is a combined hexavalent vaccine containing 10 antigens (diphtheria toxoid, tetanus toxoid, pertussis toxin [PT], filamentous haemagglutinin [FHA], pertactin [PRN], recombinant hepatitis B surface antigen, inactivated poliovirus [IPV] types 1, 2, and 3, and *Haemophilus influenzae* type b [Hib] polysaccharide polyribosylribitol phosphate [PRP]). DTPa-HBV-IPV/Hib is designed to prevent disease due to diphtheria, tetanus, pertussis, hepatitis B (HBV), poliomyelitis, and Hib. DTPa-HBV-IPV/Hib was first licensed for use in Europe in 2000 and is currently licensed in at least 95 countries.[5] Since the end of 2012, more than 90 million doses of DTPa-HBV-IPV/Hib have been distributed globally, with nearly 15 million doses distributed in Italy. All components of the combined vaccine (DTPa, HBV, IPV, and Hib) are licensed separately for use in infants and young children as Infanrix™, Engerix™ B, Poliorix™, and Hiberix™, respectively, and as components of other combined vaccines.

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Table 1. Studies of DTPa-HBV-IPV/Hib conducted using the 3-5-11 mo vaccination schedule

Study NCT* (country)	Design endpoints	Groups	Number of subjects (total cohort)
DTPa-HBV-IPV-031 NCT01457495 (Slovakia)[13-15]	Open immunogenicity and safety	DTPa-IPV/Hib + HBV	156
		DTPa-HBV-IPV/Hib (1:1)	156
DTPa-HBV-IPV-054 NCT01457508 (Italy and Germany)[15,16]	Open immunogenicity and safety	DTPa-HBV-IPV/Hib	220
		DTPa-HBV-IPV + Hib (1:1)	220
DTPa-HBV-IPV-060 NCT01457560 (Italy)[15]	Open immunogenicity and safety	DTPa-HBV-IPV/Hib (+OPV for dose 3)	80
DTPa-HBV-IPV-094 NCT01457547 (Finland, Italy, and Sweden)[15,17]	Single blind immunogenicity and safety	DTPa-HBV-IPV/Hib	246
		DTPa-HBV-IPV-Hib-SP (1:1)	248
Hib-MenC-TT-014/015 NCT00327184 (Italy, Finland)[18]	Open, randomized, controlled immunogenicity and safety	Hib-MenC-TT + DTPa-HBV-IPV	355
		MenC-TT + DTPa-HBV-IPV/Hib (1:1)	354
Esposito et al. (Italy)[19]	Double blind immunogenicity and safety	DTPa-HBV-IPV/Hib + PCV13	303
		DTPa-HBV-IPV/Hib + PCV7 (1:1)	303
Durando et al. (Italy)[20]	Open field trial immunogenicity and safety	DTPa-HBV-IPV/Hib	43
		DTPa-HBV-IPV/Hib + PCV7	151

DTPa-HBV-IPV/Hib, Infanrix™ hexa (GlaxoSmithKline Vaccines); DTPa-HBV-IPV, Infanrix™ penta (GlaxoSmithKline Vaccines); DTPa-HBV-IPV-Hib-SP, Hexavac™ (Sanofi Pasteur); Hib, Hiberix™ (GlaxoSmithKline Vaccines); Hib-MenC-TT, Menitorix™, (GlaxoSmithKline Vaccines); MenC-TT-NeisVac-C™, Baxter; OPV, oral polio vaccine; HBV, Engerix™ B (GlaxoSmithKline Vaccines); PCV7/13, Prevenar™/Prevenar™13 (Pfizer); *If registered at www.clinicatrials.gov/.

DTPa-HBV-IPV/Hib is one of few acellular pertussis vaccines that contain PRN, which appears to be important in protection against pertussis disease.[6] PRN is a *Bordetella pertussis* surface protein thought to promote adhesion and colonization of the respiratory tract.[7] While all pertussis vaccines contain PT and many contain FHA (so-called 1- or 2-component pertussis vaccines), not all contain PRN (3-, 4-, or 5-component vaccines).

DTPa-HBV-IPV/Hib is indicated for primary and booster vaccination of infants and toddlers,[5] and has been studied in a range of commonly used vaccination schedules.[8] Data have been generated in children between 6 weeks of age and less than 36 mo. Much of the clinical data during the development of DTPa-HBV-IPV/Hib were obtained in studies that employed a 3-dose primary vaccination schedule with a booster in the second year of life.[8] However, administration in a 2-dose primary vaccination at 3 and 5 mo of age, with a booster administered at 11–12 mo of age (3-5-11 schedule) is also specifically approved in the Summary of Product Characteristics.[5] Although the magnitude of the immune response to some antigens may be lower after two priming doses than after three doses,[9,10] the percentage of subjects achieving seroprotection/seropositivity for each of the vaccine antigens is similar: ranging between 91.7 and 100% after 2 doses and between 96.4 and 100% after 3 doses.[5] Similarly, seroprotection/seropositivity rates are comparable after the booster dose in infants primed with 2 or 3 vaccine doses (range 99.2 to 100% and 98.4 to 100%, respectively).[5] The 3-5-11 schedule decreases the cost and complexity of the immunisation schedule, and promotes high rates of immunization coverage. The 3-5-11 schedule was pioneered in Italy in the 1970s,[11] and is now also used in Austria, Denmark, Finland, Iceland, Norway, France, and Sweden, and is being considered in Poland and other countries. The 3-5-11 schedule is used in regions where infectious pressure is low and where high uptake of the booster dose is achieved. Alternative 3-dose primary schedules beginning earlier in life with/without neonatal hepatitis B vaccination are used in countries where infectious pressure is high, and where there is a higher risk of exposure to disease early in life.

DTPa-HBV-IPV/Hib has been available for use in Italy since 2001. The introduction of hexavalent vaccines to Italy was followed by increases in vaccine coverage rates, with coverage of 3 doses of Hib vaccine increasing from 54.7% in 2000 to 83.4% in 2002, and coverage of 3 doses of pertussis vaccine increasing from 87.3% in 2000 to 92.9% in 2002.[12] By 2011, vaccine coverage for three doses of DTPa, poliovirus, hepatitis B, and Hib in Italy was more than 95%.[12]

This review summarizes the available immunogenicity, reactogenicity, safety, and effectiveness data after 12 y of experience using DTPa-HBV-IPV/Hib, focusing on the 3-5-11 schedule in the Italian context.

Clinical Studies that Evaluated DTPa-HBV-IPV/Hib Administered to Infants at 3, 5, and 11 Mo of Age

We identified seven clinical trials that evaluated the immunogenicity and/or safety of DTPa-HBV-IPV/Hib administered

Table 2. Seroprotection/seropositivity rates at each blood sampling time point (ATP immunogenicity cohorts*)

Study	Group		D %SP	T %SP	PT %S+	FHA %S+	PRN %S+	HBs %SP	Polio-1 %SP	Polio-2 %SP	Polio-3 %SP	Hib %SP
031 n = 141	DTPa-HBV-IPV/Hib	Post 2	100	100	100	100	99.3	96.4	100	97.6	99.2	93.5
		Pre 3	86.4	96.4	95.7	100	86.4	95.7	94.4	91.9	80.3	92.8
		Post 3	100	100	100	100	99.3	98.6	100	100	100	100
054 n = 177	DTPa-HBV-IPV/Hib	Post 2	97.1	100	100	100	100	98.3	98.8	95.0	99.4	93.7
		Pre 3	84.0	94.4	98.1	100	95.5	96.9	89.3	84.5	95.3	90.1
		Post 3	100	100	100	100	100	98.9	100	100	100	100
060 n = 80	DTPa-HBV-IPV/Hib	Post 2	96.2	100	97.5	98.7	96.1	98.2	100	97.1	94.3	89.9
		Pre 3	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
		Post 3	100	100	100	100	100	100	100	100	100	100
094 n = 228	DTPa-HBV-IPV/Hib	Post 2	NT	NT	NT	NT	NT	94.8	NT	NT	NT	88.3
		Pre 3	71.0	92.4	84.2	99.1	91.0	89.7	NT	NT	NT	79.5
		Post 3	100	100	100	100	98.6	99.1	99.5	98.5	97.9	99.1
014/015 n = 314	DTPa-HBV-IPV/ Hib + MenC-TT	Post 2	NT	NT	NT	NT	NT	95.3	NT	NT	NT	95.5
		Pre 3	NT	NT	NT	NT	NT	94.2	NT	NT	NT	87.4
		Post 3	NT	NT	NT	NT	NT	99.0	NT	NT	NT	100
Esposito n = 275	DTPa-HBV-IPV/ Hib + PCV13	Post 2	92.8	94.2	99.6	100	100	93.8	99.5	95.6	99.5	87.0
		Post 3	100	97.6	100	100	100	98.4	100	100	100	99.6
n = 279	DTPa-HBV-IPV/ Hib +PCV7	Post 2	96.3	92.5	100	100	100	93.1	99.6	96.6	98.9	90.3
		Post 3	100	93.8	100	100	100	98.8	100	100	100	98.2
Durando n = 43	DTPa-HBV-IPV/Hib	Post 3	100	100	NT	NT	NT	97.7	100	100	100	100
n = 151	DTPa-HBV-IPV/ Hib + PCV7	Post 3	100	100	NT	NT	NT	99.3	100	100	100	100

N, number of subjects in ATP cohorts for immunogenicity (total vaccinated cohort for study 060). For Study 094, post-dose-2 blood samples were collected by only 2 centers for testing of anti-PRP and anti-HBs antibodies. NT, blood samples not taken at this time point in the indicated study. SP, seroprotection. For D and T ≥ 0.1 IU/ml, HBs ≥ 10 mIU/ml, poliovirus types 1, 2, 3 ≥1:8, Hib ≥ 0.15 μg/ml. S+, seropositivity, for PT, FHA, and PRN ≥ 5EL.U/ml. *Analysis on the Total vaccinated cohort for study DTPa-HBV-IPV-060.

to infants according to the 3-5-11 schedule (**Table 1**).[13-17,19,20] In three of the studies DTPa-HBV-IPV/Hib was co-administered with another vaccine: either meningococcal serogroup C conjugate vaccine (MenC-TT) or a pneumococcal conjugate vaccine (PCV).

Immunogenicity and Efficacy

Well-established serological correlates of protection exist for antibodies against tetanus, diphtheria, hepatitis B, polio, and Hib. Therefore, for these antigens, efficacy of DTPa-HBV-IPV/Hib in preventing disease is extrapolated from the percentage of subjects who reach serological thresholds accepted as correlates of protection. The exception to this is pertussis, for which no correlate of protection currently exists.

Diphtheria and tetanus

In each study, antibodies against diphtheria and tetanus were measured by enzyme-linked immunosorbant assay (ELISA), with the assay cut-off of 0.1 IU/ml which is at least 10 times the generally accepted threshold for seroprotection.[21,22] In groups that received DTPa-HBV-IPV/Hib, the percentage of subjects that achieved seroprotective (≥0.1 IU/ml) antibody concentrations after the second primary vaccination dose was between 92.8% and 100% for diphtheria and between 92.5% and 100% for tetanus (**Table 2**). After the booster dose, the percentage increased to 100% for diphtheria and was 100% for tetanus in all studies except when co-administered with 7-valent PCV (PCV7) (93.8%) or 13-valent PCV (PCV13) (97.6).[19] Of note, in a field study in Italy in which DTPa-HBV-IPV/Hib was co-administered with PCV7, the anti-tetanus seroprotection rate after the booster dose was 100%,[20] suggesting that co-administration with PCV7 was not responsible for the somewhat lower seroprotection rates observed by Esposito et al.[19]

Pertussis

Antibodies against PT, FHA, PRN were measured by ELISA,[23,24] with an assay cut-off of 5 EL.U/ml. In studies

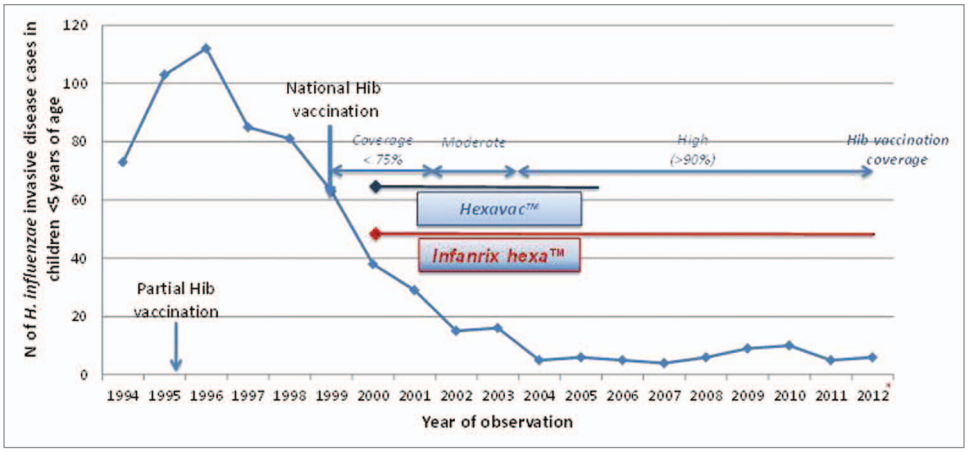

Figure 1. *Haemophilus influenzae* invasive disease in children <5 y of age: Italy 1994–2012. Adapted from publically available data reports of Istituto Superiore di Sanità-Roma, accessed at http://www.simi.iss.it/files/Report_MBI.pdf and http://www.simi.iss.it/files/Report_meningiti_1994-2006.pdf April 2013). *Partial data.

conducted using the 3-5-11 mo schedule, at least 93.1% of subjects were seropositive for antibodies for PT, FHA, or PRN after dose 2 (**Table 2**). After the booster dose, 100% of subjects were seropositive for PT and FHA and at least 98.6% were seropositive for PRN.

No serological correlate of protection against pertussis disease is currently generally accepted. However, efficacy of GlaxoSmithKline Vaccines' pediatric pertussis vaccine (DTPa, Infanrix™) was demonstrated in a German household contact study in the 1990s. Efficacy against World Health Organization-defined typical pertussis after 3-dose primary vaccination was 88.7% (95% confidence interval [CI]: 76.6%; 94.6%).[25,26] Efficacy was also confirmed in a large placebo-controlled prospective cohort study conducted in Italy under the auspices of the United States National Institute of Allergy and Infectious Diseases (Progetto Pertosse). In the Italian setting, efficacy against WHO-defined pertussis after 3-dose primary vaccination was 83.9% (95% CI: 75.8%; 89.4%).[27] Follow-up of subjects for up to 60 mo after vaccination showed no decrease in vaccine efficacy over this period, even though a booster dose was not administered in the second year of life.[28] The pertussis component of DTPa-HBV-IPV/Hib is identical to that of DTPa, and protection against pertussis disease is therefore likely to be of similar magnitude and duration following primary vaccination with either DTPa-HBV-IPV/Hib or DTPa.

Sweden re-introduced pertussis vaccination in 1996 after a 17-y pertussis-vaccine free period, with doses of DTPa administered at 3, 5, and 11 mo of age. Post-marketing data from Sweden attest to the effectiveness of the 3-5-11 schedule, with marked reductions in pertussis disease incidence rates observed in vaccinated cohorts.[29,30] The highest incidences of pertussis disease in settings of high vaccine coverage such Sweden,[29] Italy,[31] as well as countries that use 3-dose primary vaccination schedules,[32] are now observed in infants too young to be fully vaccinated. Ways to reduce the disease burden in vulnerable infants include additional pertussis booster doses in childhood and adolescence, and pertussis vaccination of pregnant women and/or new parents/grandparents, and other adults in contact with newborn infants (the so-called "cocoon strategy").[33] There is growing interest in applying the cocoon strategy in Italy, although a pilot study suggests that good communication with parents and engagement of health care professionals is needed to reach high coverage.[34,35]

Acellular pertussis vaccines prevent severe pertussis disease in young children but recent evidence suggests that immunity wanes rapidly over time[36-39] Maintenance of strong immunization programs that achieve high coverage for primary and booster doses remains important for control of pertussis in countries where acellular vaccines are used. The availability of low antigen-content acellular pertussis vaccines (combined with diphtheria and tetanus) allows for regular boosting against pertussis throughout life. Because the optimal period between booster doses is not known, most countries with adult pertussis booster policies recommend a single life-time dose. However, booster doses administered every 10 y to coincide with recommendations for decennial diphtheria-tetanus boosters have been explored and would improve coverage and require no additional injections.[40,41]

Hepatitis B

The HBV component of DTPa-HBV-IPV/Hib is identical to Engerix™ B, for which efficacy and persistence of immune memory for at least 20 y after vaccination has been demonstrated in endemic regions.[42,43]

An anti-hepatitis B surface antigen (anti-HBs) antibody level of 10 mIU/ml is generally accepted as indicative of protection.[44] In subjects vaccinated with DTPa-HBV-IPV/Hib at 3 and 5 mo of age, between 93.1% and 98.3% had anti-HBs antibodies ≥10 mIU/ml (**Table 2**). After the booster dose, the percentage of subjects with concentrations ≥10 mIU/ml was between 97.7% and 100%. In a key study conducted in Slovakia, the anti-HBs immune response following administration of DTPa-HBV-IPV/Hib at 3 and 5 mo of age was similar to monovalent HBV vaccine (96.4% ≥ 10 mIU/ml vs. 82.6%, respectively), with significantly higher antibody concentrations in the DTPa-HBV-IPV/Hib group.[13] After the booster dose, 98.6% of DTPa-HBV-IPV/

Hib and HBV recipients had seroprotective anti-HBs antibody concentrations. Approximately 10 y after vaccination, administration of a booster dose of HBV vaccine demonstrated persisting anamnestic responses in more than 95% of subjects in both groups.[14] Together these data indicate that administration of DTPa-HBV-IPV/Hib in the 3-5-11 schedule induced long lasting immune memory against HBV that was similar to that induced by monovalent HBV vaccines, for which protective efficacy has been demonstrated. The data are consistent with results observed in children who received three primary DTPa-HBV-IPV/Hib doses or three monovalent HBV doses, and in whom long-term antibody persistence and immune memory was demonstrated.[45-47]

There have been two studies conducted in Italy that assessed long-term anti-HBs antibody persistence in children vaccinated with hexavalent vaccines.[48,49] Hexavac™ (DTPa-HBV-IPV-Hib, Sanofi Pasteur), a fully liquid hexavalent vaccine, was suspended and withdrawn from the market in 2005 because of concerns about long-term protection afforded against hepatitis B.[50] Both studies demonstrated that up to 5 y after vaccination, significantly higher percentages of DTPa-HBV-IPV/Hib-GSK-vaccinated children than DTPa-HBV-IPV-Hib-SP-vaccinated children had persisting anti-HBs levels ≥10 mIU/ml (83.2% vs. 38.4% at year 5[49]). In children boosted with monovalent HBV vaccine, anamnestic responses were observed in the majority of children, regardless of vaccine group.[48,49] The successor product to DTPa-HBV-IPV-Hib-SP was recently approved for use in the European Union.[51]

Table 3. Overview of the 10 most frequently spontaneously reported events for DTPa-HBV-IPV/Hib when co-administered with a PCV, worldwide and in Italy (data from post-marketing passive surveillance reports received between August 23, 2005 and February 4, 2013)

MedDRA preferred term	Number of events		Rate per 100 000 doses of Infanrix™ hexa distributed	
Total doses distributed	Worldwide n = 4102	Italy n = 2167	Worldwide n = 92 302 373 doses	Italy n = 15 395 443 doses
Pyrexia	2113	1337	2.29	8.68
Crying	680	227	0.74	1.47
Hypotonia	367	173	0.40	1.12
Pallor	336	118	0.36	0.77
Vomiting	248	80	0.27	0.52
Urticaria	214	129	0.23	0.84
Erythema	212	110	0.23	0.71
Rash	195	89	0.21	0.58
Cyanosis	185	-	0.20	-
Convulsion	184	-	0.20	-
Irritability	-	93	-	0.60
Decreased appetite	-	76	-	0.49

MedDR, Medical Dictionary for Regulatory Activities.

Poliomyelitis

Antibodies against poliovirus types 1, 2, and 3 were measured by a micro-neutralisation assay, with a 1:8 dilution (assay cut-off) considered seroprotective.[52] In subjects vaccinated at 3-5-11 mo of age, the percentage with seroprotective antibodies for each poliovirus was between 94.3% and 100% after dose 2 and between 97.9% and 100% after dose 3 (**Table 2**). Poliovirus titers, but not seroprotection rates, were observed to be significantly lower (nearly half as low) after vaccination with DTPa-HBV-IPV-Hib-SP compared with DTPa-HBV-IPV/Hib.[53] In Italy, a surveillance study confirmed that lower poliovirus titers (but not seroprotection rates) persisted in DTPa-HBV-IPV-Hib-SP vaccinees compared with DTPa-HBV-IPV/Hib-vaccinees 15 mo after dose 3.[54]

Europe was declared free of poliovirus in 2002.[55] Nevertheless, importation of wild virus strains from areas in which poliovirus continue to circulate remains a theoretical risk, and requires maintenance of immunity throughout life. A recent review of poliovirus seroepidemiology in Italy showed waning immunity with age, supporting the introduction of an adolescent poliovirus booster dose in Italy.[56,57] Thus, induction of high poliovirus titers by hexavalent vaccines may be relevant in children, as they are expected to confer protection until the next IPV booster which is scheduled to be given at pre-school age.

Hib

Antibodies against the Hib polysaccharide, PRP, were measured by ELISA, with a cut-off of 0.15 μg/ml which is considered indicative of seroprotection.[58] The percentage of subjects with seroprotective anti-PRP antibody concentrations was between 87.0% and 95.5% after dose 2, increasing to between 98.2% and 100% after the booster dose (**Table 2**).

The effectiveness of hexavalent vaccines, including DTPa-HBV-IPV/Hib, in preventing invasive Hib disease was investigated through a nation-wide surveillance in Germany over a 5-year follow-up period, the effectiveness of the Hib components of 2 hexavalent vaccines, one of which was DTPa-HBV-IPV/Hib, was 90.4% for a full 3-dose primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).[59]

Long-term effectiveness of Hib vaccine administered in DTPa-based combinations in the 3-5-11 schedule has also been demonstrated in Sweden, where the incidence between 2005 and 2008 was estimated to be 0.4 per 100 000 children 0–4 y of age.[60] In Italy, the incidence of invasive *H. influenzae* disease began to decline when Hib vaccination was first introduced in 1998 (**Fig. 1**).[61] Since 2006, the incidence of invasive *H. influenzae* disease has remained at, or less than, 0.12 per 100 000, with around half of the cases identified as non-typeable and very few as type b.[62]

Reactogenicity and Safety

The reported reactogenicity profile of DTPa-HBV-IPV/Hib is similar to that of other inactivated vaccines, characterized by the

early onset of local reactions and fever that are usually short lived and of minor clinical severity.[5]

GlaxoSmithKline Vaccines receives reports of adverse reactions that occur after vaccination through spontaneous reporting from medical personnel, regulatory authorities, individuals, pharmacists, and literature sources. **Table 3** summarizes the ten most common adverse reactions reported worldwide and in Italy after vaccination with DTPa-HBV-IPV/Hib (primary and booster doses across all schedules) when co-administered with a PCV (since launch until the data lock point of February 4, 2013). Pyrexia after vaccination was the most frequently reported adverse reaction. This is consistent with the established safety profiles of DTPa-HBV-IPV/Hib and PCV7, for which a higher occurrence of fever has been reported when infants receive both vaccines at the same vaccination visit.[5] Adverse reaction values reported from Italy were higher to those of the rest of the world; however, in Italy vaccines undergo a national focused safety monitoring program where HCPs are requested to report all events, even those expected from SmPC such as fever.

More recently GlaxoSmithKline Vaccines performed an analysis to assess the occurrence of severe adverse events (fatalities, cardiorespiratory arrest, hypotonia/ hypotonic-hyporesponsive episode [HHE], and serious neurological disorders) occurring after vaccination with DTPa-HBV-IPV/Hib (co-administered with a PCV) during the period before and after the change from PCV7 to PCV13 in Italy (PCV7 reporting period 01-01-2008 until 31-04-2010; PCV13 reporting period 01-05-2012 until 18-07-2012). The reporting rate (number of reports per doses distributed) for fatalities in period when PCV7 co-administration was in use was 0.03 (95%CI 0.001; 0.14) compared with 0.11 (0.03; 0.29) when PCV13 was in use. The respective reporting rates for cardiorespiratory arrest were 0.31 (95% CI 0.16; 0.54) compared with 0.59 (0.36; 0.90), hypotonia/HHE 3.08 (2.55; 3.68), and 2.10 (1.65; 2.63) and for serious neurological events 4.05 (3.45; 4.74) and 4.56 (3.88; 5.31). The analysis did not show any major difference in the reporting rates of serious adverse events in Italy between the periods when DTPa-HBV-IPV/Hib was co-administered with PCV7 or PCV13.

Historical concerns about a potential temporal association between the occurrence of sudden unexpected death (SUD) and vaccination with hexavalent vaccines have been extensively investigated.[63] In Germany, a population-based evaluation demonstrated a possible safety signal for DTPa-HBV-IPV-Hib-SP but failed to show an imbalance between observed and expected SUD cases for DTPa-HBV-IPV/Hib.[64,65] A large case series conducted in Italy was unable to confirm the presence of a safety signal, but noted that the power of the study was low due to small number of SUD cases that occurred.[66] In 2003 the European Medicines Agency concluded the absence of a cause-effect relationship and no change to the benefit-risk profile of the hexavalent vaccines then available.[67]

Data in Pre-Term Infants

DTPa-HBV-IPV/Hib is specifically approved in the Summary of Product Characteristics for administration to premature infants.[5] In clinical trials DTPa-HBV-IPV/Hib is immunogenic when administered in a 3-dose primary schedule to premature infants (<37 weeks of gestation), with the majority of subjects achieving antibody concentrations consistent with seroprotection after vaccination.[68-70] Furthermore, a booster dose of DTPa-HBV-IPV/Hib induced marked increases in antibody concentrations in toddlers who had been born prematurely, indicative of the development of immune memory and effective priming by DTPa-HBV-IPV/Hib.[71]

In 2007 the Committee for Medicinal Products for Human Use reviewed cases of apnea in prematurely born infants following vaccination with different vaccines, and concluded that the occurrence of apnea following vaccination is increased in infants born very prematurely (≤28 weeks of gestation) due to immaturity of the immune system. This was considered to be an issue for all vaccines administered in this population. The recommendation of the Committee to monitor very premature infants closely for up to 48–72 h after vaccination was included in the Summary of Product Characteristics for DTPa-HBV-IPV/Hib.[5]

Co-Administration

There is extensive clinical trial experience with DTPa-HBV-IPV/Hib co-administered with other routinely recommended pediatric vaccines, including PCVs,[19,72] rotavirus,[73] meningococcal conjugate,[74-76] measles, mumps, rubella, and varicella[77] vaccines. In all studies the immune response was considered adequate. Specifically, clinical trials conducted in Italy showed that the immune response to DTPa-HBV-IPV/Hib antigens was similar when administered alone, or when co-administered with PCV7 or PCV13, with a clinically acceptable safety profile.[19,20] Similarly, DTPa-HBV-IPV/Hib co-administered with a meningococcal serogroup C conjugate vaccine induced seroprotective antibody concentrations against all of the administered antigens, including meningococcal serogroup C, in the majority of subjects.[18] Thus, in line with current recommendations concerning inactivated vaccines,[78] DTPa-HBV-IPV/Hib can be co-administered with other live or inactivated vaccines without interference on the immune response.

Conclusion

DTPa-HBV-IPV/Hib has been licensed for use for 12 y and an extensive body of clinical trial and post-marketing experience attest to its safety and effectiveness in preventing diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive Hib disease when administered alone, or co-administered with other vaccines in infants and young children, including infants born prematurely. A safety record over 12 y provides confidence to health care providers about the acceptable safety profile of DTPa-HBV-IPV/Hib.

In Italy, DTPa-HBV-IPV/Hib has a demonstrated safety record extending over a decade of use and nearly 15 million doses distributed. The use of DTPa-HBV-IPV/Hib in Italy has been associated with record levels of vaccine coverage, and with sustained disease control in vaccinated cohorts. Hexavalent vaccines

will continue to contribute to high vaccine coverage in Italy and across Europe.

Disclosure of Potential Conflicts of Interest

Marchetti F and Castro M are employees of GlaxoSmithKline group of companies and report ownership of stock options. During the last 5 years, Baldo V and Gabutti G have received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, and Pfizer for taking part in advisory boards, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials. Franco E reports grants paid by Sanofi Pasteur MSD and Pfizer to her institution, and payments received from GlaxoSmithKline Biologicals SA, Pfizer, Crucell and Sanofi Pasteur MSD for travel and accommodations for meeting attendance. Prato R reports payments from Sanofi Pasteur MSD, Pfizer, GlaxoSmithKline Biologicals SA for Board membership; payments from Pfizer International Operations SAS for consultancy; payments from Pfizer for lectures including speakers bureaus and from Pfizer, GlaxoSmithKline Biologicals SA, Novartis for travel, accommodations, meeting expenses; grants received by her institution from Novartis, Pfizer and Wyeth Lederle. Vitale F reports no conflict of interest.

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Trademark

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