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REVIEW

The value of booster vaccinations against diphtheria, tetanus, pertussis and poliomyelitis

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Key words

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Introduction

During the last ten years important achievements have been made throughout the world in the fight against infectious diseases, particularly those preventable by vaccination. The combined efforts of researchers, industry and health workers have made it possible to fully exploit the potential of the new vaccines, using them in the most rational way possible on the basis of the latest epidemiological data and objectives to be achieved.

In Italy, in common with other countries, precise objectives have been established in the fight against vaccine preventable disease, appropriate operating strategies have been developed and a vaccination schedule has been defined. This latter harmonises mandatory and recommended vaccinations and indicates the chronological sequence in which they should be performed. The vaccination calendar is an indispensable tool for achieving the objectives of the various immunisations uniformly throughout Italy.

It is vitally important that this vaccination schedule is updated on the basis of the latest scientific knowledge, the changed epidemiological situation of the various infectious diseases, possible changes in organisational requirements and, above all, the availability of new products [1, 2].

The success achieved so far against diseases for which mandatory vaccination exists (diphtheria, tetanus, polio and hepatitis B) is strictly related to the high levels of vaccination coverage reached and maintained nationwide. For recommended vaccinations, the situation is more diversified, although data from the latest ICONA survey show that in the case of antigens included in the hexavalent vaccines, high levels of vaccination coverage have been obtained (pertussis and *Haemophilus influenzae* type b). However, for measles, mumps and rubella, although a significant increase in vaccination coverage, the level critical for eliminating the diseases has not yet been reached [3, 4].

Over and above achievement of the established vaccination coverage objectives, the action taken over the years has influenced the epidemiology of the various diseases with a reduction in morbidity and generally a lower spreading of the corresponding infectious agents.

In some cases, there are also problems associated with the length of protection provided by the vaccines and the consequent need not just to optimise vaccinations in newborns but also to plan booster vaccinations. These latter are essential to avoid the creation of clusters of newly susceptible subjects among adolescents and adults, previously successfully vaccinated, due both to the decay of immunity and the reduced spreading of microrganisms [5].

The 2005-2007 Italian National Vaccination Plan (INVP) has underlined the importance of reaching and maintaining high vaccination coverage rates in childhood; besides, the INVP emphasizes that indications exist for booster vaccinations for tetanus, diphtheria, pertussis and polio, beginning from pre-school age and every ten years in adult life, as indicated by the current Italian national vaccination schedule [6].

The practical indications are backed by Presidential Decree no. 464 of 7 November 2001 [7], which, modifying the provisions of the fourth clause of article 2 of Presidential Decree no. 1301 of 7 September 1965, states:

- *booster vaccinations with administration of tetanus anatoxin, possibly in combination with diphtheria anatoxin and/or other antigens, should be given at 10-year intervals;*
- *in infants and children who begin anti-tetanus vaccination before the age of 7 (aged 6), the first booster should be given, with administration of tetanus anatoxin possibly in combination with diphtheria anatoxin and/or other antigens, 4-5 years after the last dose of the primary vaccination series. Subsequent boosters should be given at 10-year intervals.*

The epidemiological update

Tetanus

As it is well known, tetanus is important not for its incidence (quite low), but for its lethality which approaches about 50% of the cases.

Mandatory vaccination against tetanus was introduced in Italy in 1968, with administration of three doses during the first year of life (3, 5 and 11-12 months) followed by a booster at 5-6 years old.

The available epidemiological data show that since mandatory vaccination was introduced, the Italian tetanus epidemiology has progressively improved and the trend of notifications has dropped dramatically, levelling out at about 100 cases/year [8]. The majority of cases are clustered in the older age groups and in particular in women more than 64 years old. This last figure is related to the fewer opportunities for receiving boosters among the female population (e.g. missing the previous mandatory service in the Army). Noteworthy, stratifying national tetanus notifications by vaccination status, it emerges clearly that the majority of cases are related to incomplete series of vaccinations or no vaccination [9].
The existence of cohorts of susceptible subjects is confirmed by seroepidemiological studies clearly indicating that, while vaccination coverage among infants remains consistently high, the percentage of susceptible or less than optimally protected subjects rises with age, related to the absence of booster vaccinations. The need for catch-up of subjects above the age of mandatory vaccination and of regulations on revaccination and booster doses has recently (as explained above) been sanctioned by Presidential Decree no. 464 of 7 November 2001 [7].

Diphtheria

Diphtheria can cause serious respiratory and heart problems and in the most severe cases prove fatal [10]. From an epidemiological point of view, this infectious disease is worldwide endemic. However, following the introduction of effective vaccination programmes, it is now rare in Western Europe and the industrialised countries. The epidemics, which occurred in the 90's in the former Russia, showed that even severe outbreaks can reoccur if adequate levels of vaccination coverage are not maintained [11].
In Italy, the mandatory vaccination, introduced in 1939, involves administration of three doses during the first year of life (at 3, 5 and 11-12 months) and one booster dose at 5-6 years. Achievement and maintenance of high levels of vaccination coverage have enabled significant results to be obtained with a dramatic drop in the number of notifications and no case reported for many years [10]. This drop can without doubt be interpreted as a success for the vaccination strategy adopted. However, as underlined for tetanus, the seroepidemiological data indicate a progressive accumulation of susceptible or less than optimally protected subjects in the older age groups [12, 13]. These studies confirm the changes induced by the extensive vaccination campaigns on the seroepidemiological trend for diphtheria. As a matter of fact, before vaccination, seroprevalence increased with aging as a consequence of infection; in adolescents and young adults, a plateau was reached as a consequence of persisting contact with *C. diphtheriae* in the environment. After the introduction of vaccination, extensive immunization has enabled high rates of seroprevalence to be obtained by the age of two. However, in the absence of natural boosters, this tends to drop progressively with age [14-17]. Just as described for tetanus, to maintain adequate levels of diphtheria antibodies, it is therefore advisable to administer regular boosters (every 10 years) with adult Td vaccine as sanctioned by Presidential Decree no. 464 of 7 November 2001 [7].

Pertussis

Without vaccination, pertussis is a typical childhood disease with a considerable impact, particularly on infants, involving frequent and serious complications including pneumonia, convulsions and encephalopathy with hospitalisation and deaths. In the world, it is estimated that there are about 20-40 million cases/year of the disease, with about 200,000-400,000 deaths [18, 19].
Pertussis vaccination was recommended by the Italian Ministry of Health in 1962. However, the vaccination coverage has been low for years, particularly in the Southern Regions of Italy. Until 1991, vaccination coverage did not exceed 40% and therefore control of the disease was inadequate [20].
In 1994, the introduction of acellular pertussis vaccines, considerably less reactogenic than whole cell ones, encouraged the spread of vaccination, helped by its inclusion in combined vaccines for administration to infants according to a three-dose schedule (3, 5 and 11-12 months) with a booster at 5-6 years. The percentage of vaccinations in infants aged between 12 and 24 months thus increased rapidly, reaching 88% in 1998 and 95% in 2003 [21].
However, humoral and cellular immunity tends to drop after about three years and to disappear about 10-12 years after vaccination [22, 23]. Thus, the lowering immunity implies a growing number of adolescents and adults susceptible to pertussis and a consequently higher incidence in subjects in these age groups.
Comparison of the epidemiological data from countries with low and high vaccination coverage shows that in areas with low vaccination coverage during childhood, the incidence of pertussis is high in children and low in adolescents and adults. In countries with a high level of vaccination coverage in childhood, incidence is, on the other hand, high in adolescents and adults [24].
All this is paradigmatic of the different immunological pressure on circulation of *B. pertussis*. In the case of no or low vaccination coverage, frequent natural boosters occur and therefore naturally acquired immunity may persist in adolescents and adults. In the case of high vaccination coverage, natural boosters are considerably lower, a decay of immunity occurs in adolescents/adults, and the disease is more frequent in infants (as they are not yet completely vaccinated), adolescents and adults [25].
This fact is particularly important if the different clinical profile of pertussis in relation to the patient's age is considered; noteworthy, in adolescents and adults, pertussis is often mild, with aspecific symptoms, and therefore not diagnosed. As the illness is often not recognised in adolescents/adults, the latest therefore become a significant source of infection for infants [26].
In Italy, the increase in vaccination coverage in childhood is related to an increase of the mean age of in-

fection. During recent years, there has been a greater morbidity in older children, adolescents and adults. Recent epidemiological surveys carried out in Italy have shown an increase in cases in the 5-9 and 10-14 year old age groups, a marked reduction of incidence and an increase in the mean age of cases [21]. More recently, a multicenter study confirmed that the epidemiology of pertussis in Italy is changing in the same way as in other countries with a high level of vaccination coverage [27].
As adolescents/adults may infect infants who have not yet been vaccinated, spreading of *Bordetella pertussis* beyond the age of childhood is not just an obstacle to its elimination but also a limit to controlling the disease as it contributes to transmitting pertussis to the age groups at the greatest risk of complications.
For these reasons, the opportunity of booster vaccinations should be carefully evaluated. This active prophylaxis is today facilitated by the fact that latest generation acellular vaccines can be used on subjects over seven years old. Further, new vaccines are available with acellular pertussis component and reduced antigen content (including for tetanus and diphtheria), suitable for use in adolescents and adults. If the target is to avoid an increase of the mean age of pertussis infection, action must be taken on adolescents and adults by means of a booster dose with a reduced antigen vaccine [28].

Poliomyelitis

Vaccination against polio has enabled extraordinary targets to be achieved [29, 30]. In Italy, vaccination with live and attenuated vaccine (OPV) began with the mass vaccination of 1964, followed by vaccination of all infants with three doses administered during the first year of life and a booster dose in the third year of life. More recently, the strategy against this important infectious disease has been modified, first in 1999 when the vaccination schedule exclusively based on oral polio vaccine (OPV) was replaced by a sequential schedule with administration of two doses of inactivated polio vaccine (IPV) followed by two doses of OPV and subsequently in June 2002, following WHO certification of the eradication of polio from the European Region, with adoption of a schedule based on administration of IPV only. The modifications have not changed the level of vaccination coverage which has remained high throughout Italy. From an epidemiological point of view, circulation of wild poliovirus is currently confined to certain countries in Africa and the Indian subcontinent. This represents an excellent precondition for eradicating this disease. However, as there are still focuses of infection, there is a remote possibility of the disease being reintroduced into safe territories [31].
The certification obtained at national level in Italy in June 2002 was based on the established absence of clinical cases and circulation of wild poliovirus both at human and environmental level. The documented presence of vaccine poliovirus in the faeces of some subjects and in sewage can be correlated to administration of the vaccine. The sustained circulation of vaccine strains between humans has not been demonstrated. Given this epidemiological situation, the immunological pressure exerted by vaccination has eliminated or greatly reduced the possibility of natural boosters and therefore the level of neutralising antibodies in the population has progressively dropped. The exclusive use of inactivated IPV vaccine today also implies a level of mucosal protection considerably lower than in subjects who received the complete series or at least two doses of OPV. It is therefore considered that booster vaccination, already adopted in some countries [32], may enable this negative aspect in cohorts exclusively immunised with IPV to be overcome. With these motivations and the aim of guaranteeing a booster vaccination at a suitable distance from the primary series, in the 2005-2007 INVP it was decided to shift the fourth dose of IPV from the 3rd year of life to the 5th-6th year coinciding with the DTaP booster.

Booster vaccinations

The considerable amount of scientific data collected in the recent years shows that the distinction between vaccination schedules for children, adolescents, adults and the elderly is outdated and we now need to think in terms of a single vaccination schedule covering the various phases of life. It is equally obvious that adoption of well-organised vaccination schemes with thorough coverage of the population has enabled fundamental results to be obtained in the fight against many infectious diseases, substantially modifying the epidemiology of the diseases and circulation of the etiological agents [33].
There is now the need to consolidate the successes obtained, evaluate the consequences of the immunological pressure exerted by vaccination on the pathogenic agents and guarantee continuity of vaccination. Booster vaccinations provide a way of resolving this last point, important in guaranteeing long-term protection of successfully vaccinated subjects, but who may in some cases be exposed to new risks of acquiring the infection and/or disease as a result of the decay of immune protection provided by vaccination, the lower possibility of natural boosters or the reintroduction of a pathogen already eliminated in Italy from areas where it is endemic.
The 2005-2007 Italian National Vaccination Plan (INVP) clearly recognizes the need to plan boosters to avoid creating cohorts of partially or totally susceptible subjects, identifying two timeframes of intervention: 5-6 years (for tetanus, diphtheria, pertussis and polio) and 11-15 years of age (for tetanus, diphtheria and pertussis).

New vaccines available

The possibility of high compliance with booster vaccinations is strictly related to a series of factors, particular important among which are tolerability, efficacy and number of injections.

This last point has always been critical and the availability of combined vaccines has without doubt represented an excellent opportunity as, for the same level of safety and efficacy, they guarantee fewer injections and accesses to services [34].

With reference to the indications in the 2005-2007 INVP, the availability of combined vaccines for tetanus, diphtheria, pertussis and polio boosters is therefore an important resource. GlaxoSmithKline SpA has developed two products derived from the Infanrix family of vaccines, namely PolioInfanrix and PolioBoostrix for booster immunisation against tetanus, diphtheria, pertussis and polio, differing in antigen content and indications for use (Tab. I).

PolioInfanrix has a paediatric antigen content and is indicated for subjects from 16 months to 13 years of age inclusive; PolioBoostrix has a reduced antigen content (of the tetanus, diphtheria and pertussis components) and is indicated for subjects over four years of age. Both vaccines contain three *Bordetella pertussis* antigen components: pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN). The presence of the three antigen components, (mainly PRN), confers them higher efficacy with respect to the other commercially available products with two antigen components (PT and FHA) [35].

PolioInfanrix can be administered in a single 0.5 ml dose by intramuscular injection to subjects who have previously received acellular or whole cell pertussis vaccines and live and attenuated oral polio vaccines or injectable inactivated ones [36, 37]. Clinical studies performed on more than 2000 subjects (15-26 months and 10-14 years of age), previously vaccinated with three or four doses of combined diphtheria, tetanus and pertussis (whole cell or acellular) vaccine and who have completed the primary series, have indicated an excellent safety profile. As expected, booster doses with DTaP vaccines can be more reactogenic in children previously vaccinated with products containing acellular pertussis components. However, the adverse reactions noted during the studies generally occur within 48 hours from immunisation, are light/moderate and resolve spontaneously without sequelae. Immunogenicity is also excellent. The immune responses after the booster with PolioInfanrix, assessed in more than 900 subjects, were irrespective of the number of doses and type of vaccines administered previously. Ninety nine per cent of the immunised subjects had protective levels of antibodies against diphtheria, tetanus and the three types of poliovirus, irrespective of the age of the subjects (15-26 months, 4-7 years or 10-13 years). Although there is no serologic correlate of protection for pertussis antigens, concentrations of PT, FHA and PRN antibodies after administration of PolioInfanrix were always higher than those registered after primary vaccination with the combined paediatric pertussis vaccine, indicating a probable high level of protective efficacy against pertussis.

PolioBoostrix is administered in a single dose (0.5 ml intramuscular) for the booster vaccination against diphtheria, tetanus, pertussis and polio in subjects aged four years or more. It is not indicated for primary immunisation. The principal characteristic of the product is the low antigen content of the diphtheria, tetanus and pertussis components. It can be used to treat wounds at risk of tetanus infection in subjects who received the primary vaccination series with tetanus toxoid and for whom a diphtheria, pertussis and polio booster is indicated [38-42]. Evaluated by administering the vaccine to more than 1500 subjects in various age groups (4-8, 10-14 and more than 15 years) who had previously received four doses of DTaP or DTwP (4-8 or 10-14 years) or at least one primary series of DT with a mean interval of 16.4 years since the last immunisation, the safety profile of PolioBoostrix was found to be excellent. The most frequent adverse events were slight/moderate and local (pain, redness and swelling in the inoculation site) reported in 36.4-66.9% of subjects, generally occurring during the 48 hours following vaccination and clearing up spontaneously without sequelae. Similarly to safety, the immunogenicity profile was also evaluated in clinical studies carried out on subjects of different ages and with different vaccination histories. The seroprotection level and vaccine response to all antigens one month after the booster dose were similar to those observed in controlled studies performed with already registered vaccines (Tab. II). As far as the pertussis components

Tab. I. Qualitative and quantitative composition (1 dose: 0.5 ml).

Ag	PolioInfanrix	PolioBoostrix
Diphtheria toxoid	not less than 30 IU	not less than 2 IU (2.5Lf)
Tetanus toxoid	not less than 40 IU	not less than 20 IU (5Lf)
Pertussis toxoid (PT)	25 μg	8 μg
Filamentous haemagglutinin (FHA)	25 μg	8 μg
Pertactin (PRN)	25 μg	8 μg
Type 1 inactivated polio (Mahoney strain)	40 D	40 D
Type 2 inactivated polio (MEF-1 strain)	8 D	8 D
Type 3 inactivated polio (Saukett strain)	32 D	32 D
Aluminium hydroxide hydrate	0.5 mg Al^{3+}	0.3 mg Al^{3+}
Aluminium phosphate	-	0.2 mg Al^{3+}

Tab. II. Immunogenicity of PolioBoostrix vaccine.

Ag	Response	Subjects 10-93 years n = 690 (% of vaccinated subjects)	Subjects 4-8 years n = 779 (% of vaccinated subjects)
Diphtheria	≥ 0.1 IU/ml*	83.5-100	100
	≥ 0.016 IU/ml^	87.7-100	na°
Tetanus	≥ 0.1 IU/ml	99.6-100	99.9
Pertussis PT	**	94.2-97.1	97.8
Pertussis FHA	**	96.9-97.2	90.1
Pertussis PRN	**	96.6-99.3	96.5
Type 1 polio	≥ 8	99.6-100	100
Type 2 polio	≥ 8	99.6-100	100
Type 3 polio	≥ 8	99.1-100	100

* ELISA assay; ^ Vero-cell in vitro neutralisation assay; ° not available; ** concentration > 5 EU/ml in subjects seronegative before the booster or at least double the antibody concentrations in subjects seropositive before the booster.

are concerned, the antibody concentrations achieved were found to be similar to or even higher than those observed during an efficacy study performed on household contacts with the paediatric acellular combined vaccine, suggesting that PolioBoostrix is expected to provide a high level of protection against pertussis.

Intervention options

Combined vaccines for tetanus, diphtheria, acellular pertussis and polio have been conceived and developed to provide a vaccine suitable for adolescents and/or adults. By guaranteeing high tolerability and immunogenicity, they enable booster vaccinations to be extended from tetanus alone to also include diphtheria, pertussis and polio [34]. The vaccines with a reduced dTap antigen content today available in Europe, the USA, Canada, Australia and many other countries are recommended for adolescents, selected categories of health workers and people in close contact with infants and children [43-46]. Epidemiological data on polio indicate the need to reinforce the immune response in populations vaccinated with IPV and many countries have planned specific action with booster vaccinations [32]. In Italy, the 2005-2007 INVP stresses the need "to maintain over time the high level of immune protection provided by vaccination during childhood … Currently the problem of boosters exists not just for tetanus, but also for diphtheria and pertussis, but there are indications that polio could also be included on this list".

The two new vaccines mentioned about fall within this context. In particular, the PolioInfanrix vaccine has an antigen content similar to that of paediatric vaccines and is indicated for boosters in subjects aged from 16 months

Tab. III. Range of incidence of specifically monitored events observed in clinical trials on adults, who had received the reduced antigen vaccine [dTap; Boostrix™], the adult tetanus and diphtheria vaccine [Td] or the reduced acellular pertussis antigen vaccine [ap], as a booster (from Di Pasquale et al., 2005 [50], mod.).

	dTpa %	Td %	ap %
Pain			
All	72.6-88.5	82.7-85.2	56.4-71.9
Class 3*	0.5-0.9	0.0	3.6-3.7
Redness			
≥ All sizes	32.0-33.3	34.7-38.9	12.5-20.0
≥ 50 mm	2.3-2.7	3.7-11.1	0.0
Swelling			
≥ All sizes	20.8-28.1	26.5-29.6	10.4-10.9
≥ 50 mm	2.3-2.7	3.7-7.4	0.0
***Fever** (≥ 37.5°C)*			
≥ All	5.2-18.5	9.2-33.3	4.2-12.7
≥ 39.0°C	0.0-0.4	0.0	0.0

* class 3 defined as pain preventing normal everyday activities; ** axillary temperature

Tab. IV. Range of incidence of specifically monitored events observed in clinical trials on adolescents, who had received the reduced antigen vaccine [dTap; Boostrix™], the adult tetanus and diphtheria vaccine [Td] or the reduced acellular pertussis antigen vaccine [ap], as a booster (from Di Pasquale et al., 2005 [50], mod.).

	dTpa %	Td %	ap %
Pain			
≥ All	79.0-80.4	78.3-83.3	67.8-68.9
≥ Class 3*	0.0	0.0	0.0
Redness			
≥ Any	17.4-33.0	32.6-53.3	8.9-15.3
≥ 50 mm	0.0	4.3	0.0
Redness			
≥ All sizes	19.6-35.0	37.0-46.7	15.3-15.6
≥ 50 mm	0.0	4.3	0.0
*Fever** (≥ 37.5 °C)*			
≥ All	2.2-8.9	8.3-8.7	5.1-6.7
≥ 39.0 °C	0.0-0.2	0.0	0.0

* class 3 defined as pain preventing normal everyday activities; ** axillary temperature

to 13 years, while PolioBoostrix has a reduced tetanus, diphtheria and pertussis antigen content and is indicated for boosters in subjects since four years of age.

With reference to the above, clearly expressed on the Summary of Product Characteristics (SPC), the booster vaccinations provided for by current Italian legislation at the age of 5-6 years could be performed using either PolioInfanrix or PolioBoostrix.

The 2005-2007 INVP does not support the use of dTpa vaccine formulation in the pre-school children. Such assumption is based on the results of one immunogenicity study carried out in Italy, where the anti-diphtheria adult formulation vaccines generated a geometric mean antibody concentrations lower than those achieved with the paediatric formulation one (14.1 *vs*. 7.7 IU/ml, in DT and dT group, respectively; $p < 0.05$) [47]. On this basis, the Authors speculate that the immune protection is then expected not to last for a sufficient period of time before the subsequent booster is given. It is worth noting that the immunogenicity and reactogenicity results obtained with DT or dT vaccine in six year old children were not similar in the two groups of subjects, as redness and swelling in the inoculation site were significantly more frequent in the DT group. Nevertheless, the Authors' conclusion was that the better immunogenicity and comparable reactogenicity of the DT vaccine suggested it would be more appropriate than dT vaccines for boosters in pre-school age children, in particular as boosters were not routinely given to adolescents and adults [47].

Tab. V. Range of incidence of specifically monitored events observed in clinical trials on pre-school children, who had received the reduced antigen vaccine [dTap; Boostrix™] or the adult tetanus and diphtheria vaccine [Td], as a booster, compared with paediatric combined whole cell vaccine for diphtheria-tetanus and pertussis (DTwP) or acellular diphtheria-tetanus and pertussis vaccine (DTaP) (from Di Pasquale et al., 2005 [50], mod.).

	dTpa %	Td %	DTwP %	DTaP %
Pain				
≥ All	41.8	51.7	67.3	63.3
≥ Class 3*	0.6	2.3	1.5	2.2
Redness				
≥ All sizes	23.6	36.8	33.9	48.9
≥ 50 mm	1.2	17.2	3.6	23.3
Swelling				
≥ All sizes	21.2	34.5	44.2	43.3
≥ 50 mm	0.6	13.8	4.8	15.6
*Fever** (≥ 37.5 °C)*				
≥ All	13.9	32.2	30.9	22.2
≥ 39.0 °C	1.8	4.6	4.8	4.4

* class 3 defined as pain preventing normal everyday activities; ** axillary temperature

Tab. VI. Predicted anti-diphtheria antibody GMC values (extended ELISA measurememt) 10 years after booster vaccination of children aged 4-6 years (from Cheuvart et al., 2004 [52], mod.).

Vaccine	GMC (ELISAext) at year 10	% ≥ 0.0149 IU/ml at year 10 S.D. 0.4
dTpa	0.112	98.6
DTPa	0.170	99.6
Td	0.141	99.3

It should be noted that the above study made no comparison with the dTap vaccine commercially available in Italy today (Boostrix) which has a diphtheria toxoid content of 2.5Lf, higher than in the dT vaccines assessed in the above study.

More recently, a series of articles were published on the excellent safety and immunogenicity profile of Boostrix [48-51] (Tabs. III-V). In 2004, Cheuvart et al. to assess the impact of the two vaccines over the years applied a mathematical model to the results obtained on sera collected from 4-6 years old children and until 3.5 years after administration of DTaP or dTap vaccines. The model predicted that ten years after vaccination (the timeframe indicated at international level as the correct moment to administer the booster) the number of subjects protected against diphtheria did not differ significantly between the two groups of vaccinated subjects (98.6% *vs*. 99.6%, with dTap and DTaP, respectively) (Tab. VI). According to the authors, the differences in GMT noted one month after administration of a booster dose at 4-6 years of age with DTaP or dTap did not exert any clinical relevance in the long-term (10 years) [52].

The combined DTaP-IPV and dTap-IPV vaccines therefore represent an important resource to guarantee vaccination continuity. Considering the unquestionable need to increase booster vaccinations after pre-school age and that health workers and users are always concerned about the safety and reactogenicity of vaccines, the availability of products with a reduced antigen content and guaranteeing excellent immunogenicity and safety and lower reactogenicity than vaccines with a paediatric antigen dosage will help achieve and maintain high levels of coverage from as early as pre-school age.

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