REVIEW

Reducing the risk of pertussis in newborn infants

F. BLANGIARDI, G. FERRERA*
Prevention Department, Ragusa LHA; * Epidemiology Service, Ragusa LHA, Italy

Key words

Bordetella pertussis • Cocoon • Booster vaccination • Italy

Introduction

Pertussis (whooping cough) is a respiratory tract infection characterised by a paroxysmal cough, caused by *Bordetella pertussis*, a gram negative coccobacillus. The disease can affect individuals of all ages, even though the most severe complications and mortality occur more frequently in early infancy. *Bordetella pertussis* is an exclusively human pathogen; hence elimination of the disease by mass vaccination should theoretically be an achievable objective, even though neither natural infection nor vaccination confer permanent immunity. The implementation of well-conducted vaccination strategies in various countries has not prevented the re-emergence of pertussis [1, 2] particularly in 2 age groups: those over 10 years and infants aged less than 5 months [3].
This is the reason why many countries, including Italy, have introduced antipertussis vaccinations for adolescents into the national immunisation schedule.
Among the strategies proposed to control pertussis and decrease pathogen circulation, with the aim of reducing the burden of disease in children that have not yet been vaccinated, the international literature presents a number of strategies. Besides the vaccination of adolescents and the replacement of decennial antitetanus and antidiphtheria booster vaccinations with a trivalent diphtheria, tetanus and pertussis vaccine, the "cocoon" strategy is proposed, with the aim to indirectly protect newborn infants through the immunisation of a target population of adults, represented by parents and other potential close contacts, such as grandparents and healthcare workers [4-6].
The goal of this paper is to evaluate the rationale and potential of "cocooning" as a complementary strategy to universal infant and adolescent's antipertussis vaccination in order to reduce the risk of pertussis in newborn infants, highlighting which healthcare providers are expected to be involved in its implementation.

Epidemiology

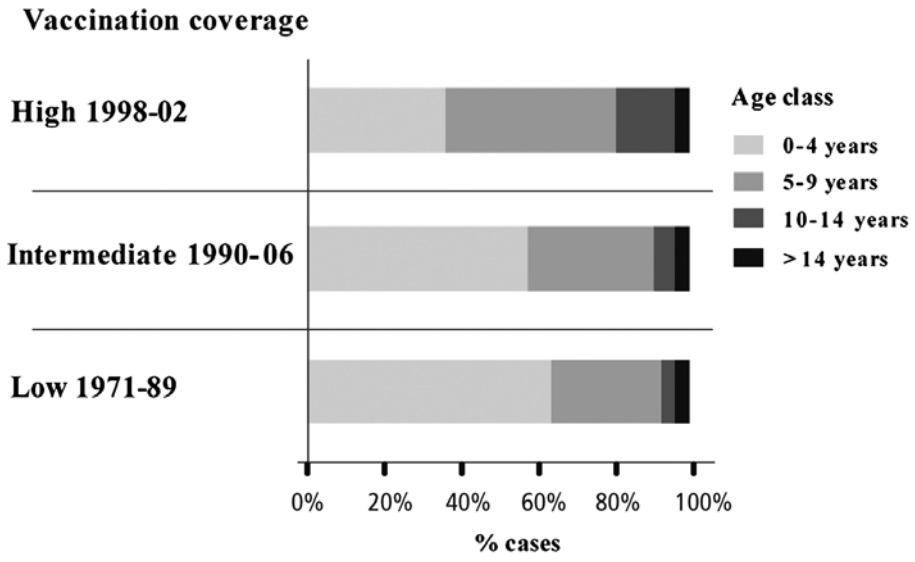
How epidemiology of pertussis in Italy and worldwide has changed with the implementation of universal infant vaccination

Pertussis is a highly-contagious infectious respiratory disease (attack rate greater than 80-90% among non-immunised family contacts [7]). Man is the only known reservoir of the bacterium that is transmitted from person to person through the large respiratory droplets generated by coughing or sneezing (Flugge's droplets). Onset of the actual disease follows an incubation period varying between 5 and 21 days, during which no particular symptoms are shown. The course of the disease is 6-8 weeks, and may be divided into three distinct periods: catarrhal, paroxysmal and convalescence. As shown in Table I, the potential complications of pertussis are represented by hypoxia, pneumonia, convulsions, encephalopathy and death. Children aged less than one year are at high risk of such complications and hospitalisation [5].
The bacterium performs its pathogenic action binding to respiratory tract's epithelial cells through adhesins and above all with the production of highly immunogenic toxins: the pertussis toxin, which causes cellular lesions, filamentous haemagglutinin and pertactin [7].
Notification of pertussis is mandatory in Italy. The introduction of infant vaccination in the 1960s was followed by a reduction in incidence of the disease up until the 1970s, but with increased incidence in the 1980s. This is mainly due to the non-homogeneous offer of vaccination at Region level, which limited vaccination coverage at the national level to around 40% until the 1990s [8, 9]. With the introduction of combined acellular vaccines (less reactogenic compared to whole cell vaccines) in the mid 1990s and the recommendation of a primary cycle with 3 doses, vaccination coverage reached 88% for the cohort born in 1996 [10] and, after the pertussis vaccine became free of charge in 2002, over 96% in 2008 [11].
As a matter of fact higher vaccination coverage influenced pertussis epidemiology in Italy. A retrospective

Tab. I. Complications of pertussis in children aged < 12 months in the USA (2000-2004) [5].

Complication	Number of subjects	%
Hospitalisation	6114	62.8%
Apnoea	5454	55.8%
Pneumonia	1063	12.7%
Convulsions	146	1.5%
Death	92	0.8%

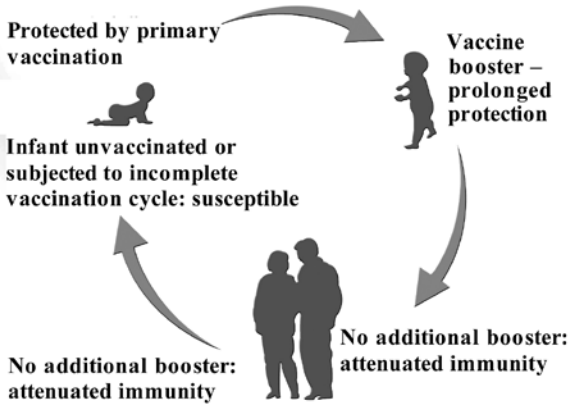
Fig. 1. Proportional distribution of pertussis cases according to age group within low (1971-89), intermediate (1990-1996) and high (1998-2002) vaccination coverage periods (from Rota et al., 2005 [12], by permission).



study [12] has assessed the trend of pertussis incidence rates (ISTAT and Ministry of Health data) within the period 1955-2002 and the seroprevalence of whooping cough using samples of serum collected between 1996 and 1997 for the ESEN (European Sero-Epidemiology Network) project. The results highlight a progressive reduction in the incidence of pertussis among children under the age of 4 years, but a significant increase in the 5 to 9 year old (1.5 fold) and 10 to 14 year old age groups (over 3 fold) (Fig. 1).

The same study documented a shift in the median age of acquiring pertussis, increasing from 3 years in the period 1971-89 to 6 years for the period 1998-2002 [12]. With regard to the serological investigation, the seroprevalence of subjects with levels of IgG antibodies against pertussis toxin (PT) above 2 EU/ml (minimum detection level) has been 77.6%. Furthermore, the high percentage of subjects aged between 10-14 years and 15-19 years with high anti-PT antibody titres suggests that pertussis is still circulating among adolescents. These conclusions have been confirmed by a recent multicentre study conducted in several Italian geographical areas [13] evaluating humoral and cell-mediated immunity in adolescent, adult and elderly subjects, populations that in the past were deemed not to be involved in the circulation of the pathogen, and for which a booster of reduced antigen content vaccine might be something to consider.

Fig. 2. Cycle of pertussis transmission between adults and children.



Although it has drastically reduced the incidence of the disease, the introduction of universal infant vaccination is not in itself enough to eliminate or adequately control pertussis. Inadequate vaccination coverage, loss of immunity and the lack of boosters in adolescents and adults are the main causes [14] (Fig. 2).

In adolescents and adults, diagnosis is frequently delayed due to atypical clinical manifestations, lack of awareness by medical staff with the result of a potential risk of sub-diagnosis [15] and transmission of the infection for several weeks [16]. The increased incidence of pertussis in adolescents and adults results in an increased risk of transmission of the infection to infants before they have initiated or completed the primary vaccination cycle.

The present hypothesis is supported by data reporting number of cases of pertussis hospitalized in the 1st year of life. In fact, according to hospital discharge reports database, in Italy, about 100 hospitalisations are recorded per year in children under the age of one year [17] (Fig. 3), while a retrospective study conducted in Sicily

Region in 2002 [18], found that 72% of hospitalized pertussis cases were in children too young to be fully vaccinated or in those that had received only the 1st vaccine dose (Fig. 4); moreover, among cases of babies too young to be vaccinated, the most important source of infection identified was an household member above 14 years of age (Tab. II).
Italian data are similar to that observed in other countries with high infant vaccination coverage.

In Europe, the EUVAC-NET surveillance project, involving 16 European countries, has recorded a 115% increase in the incidence of cases in adolescents over the age of 14 years between 1998 and 2002 [19].
A retrospective study conducted in Spain analysed hospital discharge reports between 2003 and 2007, concluding that from the 49 pertussis cases hospitalised within the period considered, 47 occurred in children under the age of 6 months, of which 23.4% had a complicated disease course and 3 died. In 65.3% of cases, the source of infection had been identified as a family member [20].
In France, where a pertussis surveillance project has been active within a network of paediatric hospitals since 1996, 2878 cases of pertussis have been recorded in subjects under the age of 16 years between 1996 and 2007. Of these, 1882 were in children under the age of 6 months. An survey conducted among the household members of hospitalized infants showed that in 54% of cases, one of them reported prolonged coughing. The mean age of the family members identified as the source of infection rose from 19.6 years in 1996 to 31.9 years in 2007 (significant difference), while the proportion of siblings reduced from 34% to 19% over the same period [21].
Mortality during the period considered has been 2% (34 children), of which, only 1 had received 1 single dose of vaccine, in 13/16 in which it has been possible to trace the source of infection, it has been confirmed as one of the parents [21].
In the Unites States, where universal infant vaccination was introduced long before than in Italy, these phenomena are well documented. Considering the high levels of Diphtheria Tetanus acellular Pertussis (DTaP) vaccination coverage, it has been estimated that between 2001-2003, on average, there have been 98 hospitalisations due to pertussis each year from every 100,000 children between 0 and 5 months, compared to 12 cases/100,000 children aged between 6 and 11 months [22]. Of the 100 deaths recorded between 2000 and 2004, 76 occurred in children aged less than 1 month [5]. One

Tab. II. Cases of pertussis in children not fully vaccinated due to their age. (from Cuccia et al., 2004 [18], by permission).

	Cases	No contact	Pediatrician	Family member 0-5 years	Family member 6-13 years	Family member ≥ 14 anni
0 months	5	1	2			
1 months	10	3	4	3		
2 months	6	1	2	1	2	
3 months	6	1	3	2		
4 months	3	2	1			
Total	30	7	9	1	3	10

Fig. 3. Number of hospital discharge reports with main diagnosis of pertussis in children aged less than 1 year.

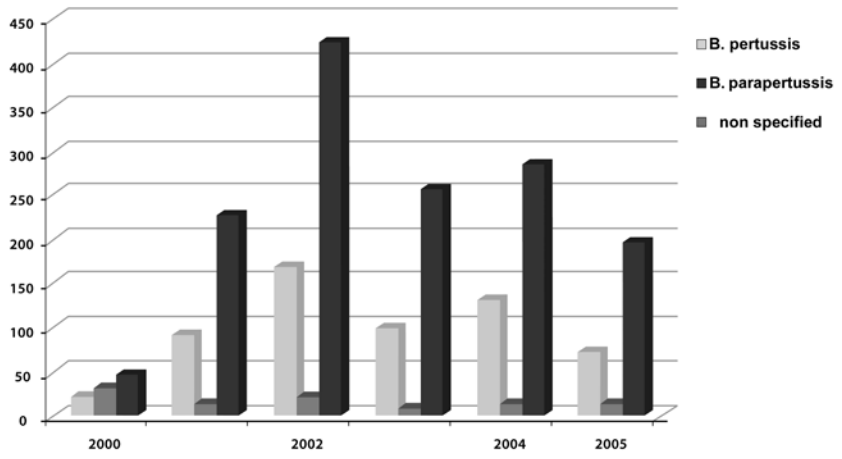
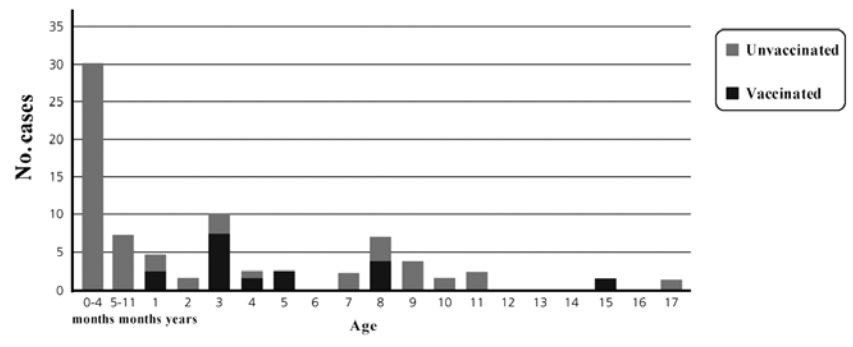


Fig. 4. Hospitalised pertussis cases in Catania province in 2002 (from Cuccia et al., 2004 [18], by permission).

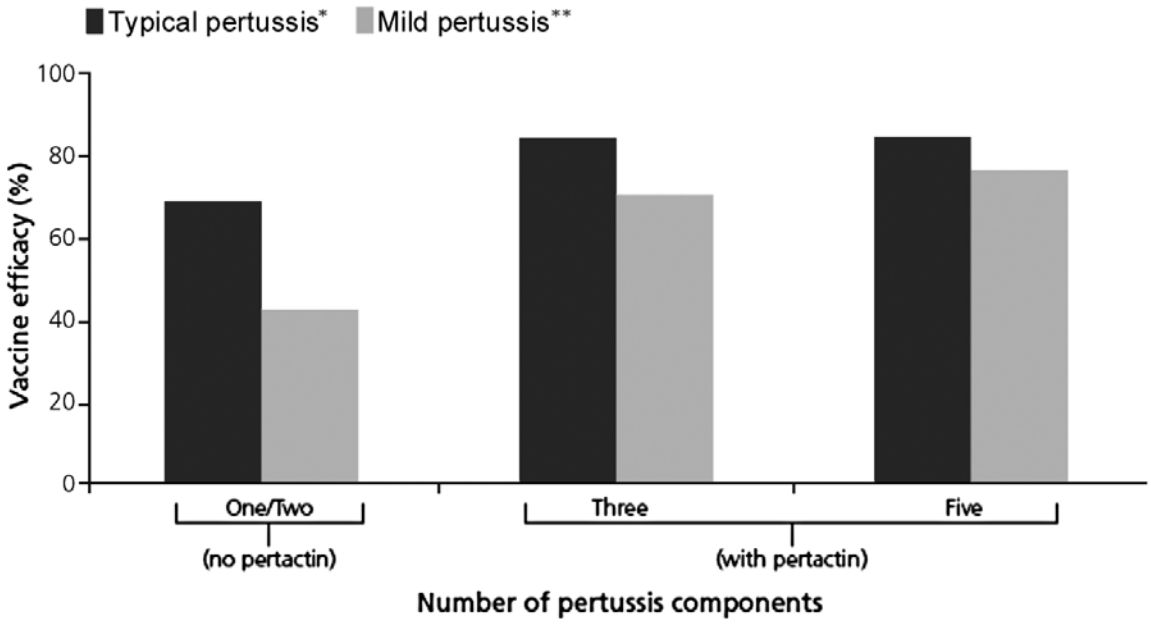


study investigating the source of infection reported that in 32% of cases, this was a family member [5].
Hence, there is growing evidence that adolescents and adults, in particular parents, are the main reservoir of infection for unvaccinated infants [23]. This is mainly associated with loss of immunity, indeed, both vaccination and natural infection cannot succeed in inducing a persistent immune response, as it is now extensively documented in various studies [24, 25]. A recent review of the literature reports that loss of immunity occurs 4-20 years after natural infection, while the immunity acquired after vaccination lasts between 4 and 12 years [26].
The acquisition of this new knowledge regarding how the epidemiology of the disease has changed with the introduction of universal infant vaccination has lead many experts to recommend the administration of periodic pertussis booster, with the aim of interrupting the disease cycle and reducing the frequency of cases of pertussis among adolescents and adults, thus reducing the risk of infection in infants that have not completed the primary vaccination cycle.

Pertussis vaccines

The first vaccines containing whole, inactivated *Bordetella pertussis* cells were developed in the 1950s. However, although they dramatically reduced the incidence and complications of the disease, these vaccines were shown to be very reactogenic. Developing technology allowed the introduction of acellular vaccines, containing only some antigens from the bacterium [27].
Subsequent studies have confirmed that the number of anti-pertussis antigens included in the vaccine formulation (from 1 to 5) is correlated with efficacy. In particular, it has been shown that the addition of pertactin to the pertussis toxin and to phytohaemagglutinin significantly increases the protection conferred by the vaccine [27]. Indeed, various studies have documented that anti-pertactin antibodies have a crucial role in *Bordetella pertussis* opsonisation and phagocytosis [27].
A recent meta-analysis of 52 clinical studies has highlighted how the efficacy of 3-component acellular vaccines, with pertactin, is superior to that of 1 or 2 component vaccines, without pertactin, being equal to 80-84% compared to 67-70% respectively. On the other hand, the addition of other antigens, such as those towards fimbriae 2 and 3, does not seem to further increase protective activity, being equal to 80 and 84% respectively, for 4 and 5 component vaccines (Fig. 5) [27, 28].
Nowadays, acellular pertussis vaccines with reduced antigenic content (dTap) are available for booster vaccinations in adolescents and in adults [5, 29-31].
These vaccines are much more tolerated than those at paediatric dose for which an increased risk of local adverse events has been observed [30, 31] with increasing number of booster dose.
dTpa vaccines are highly immunogenic with regard to seroconversion rates and antibody titre [29, 30] towards pertussis, diphtheria and tetanus antigens. The immunological response to the 3 pertussis antigens in adults and the elderly has been studied in a trial evaluating subjects aged between 15 and 93; in the elderly population, even if the antibody titre level reached was inferior compared to the younger population, a strong booster response was elicited, since titres were raised 6-10 fold compared to the pre-vaccination value, supporting the development of immunological memory. This data show how unvaccinated elderly subjects have a high probability of having been exposed to natural infection throughout

Fig. 5. Efficacy and safety of pertussis vaccines with different pertussis antigen composition in children ≤ 15 years of age: meta-analysis of 52 studies.



*WHO definition: laboratory confirmed pertussis in subjects with ≥ 3 weeks of spasmodic coughing and howling. **Duration of coughing ≥ 1 week, laboratory confirmed.

their lives, and hence pertussis vaccination acts as a booster [30].
With regard to efficacy data in adolescents, a reduced antigenic content vaccine, after a single booster dose, has been shown to induce an antibody response against the 3 pertussis antigens (PT, FHA, PRN) that was no less in comparison to children receiving 3 doses of the primary cycle [31].
Even in adolescents not previously vaccinated against pertussis, the administration of a single dose of dTpa vaccine has been shown to induce high responses in terms of seroconversion and increase in antibody titre against pertussis antigens, in showing that that adolescents have been in contact with the pathogen over the course of their lives and that a single dose of vaccine has boosted the immunological memory and is well tolerated by this population of subjects [32].
The study conducted by Knuf et al. [32] on a group of 123 adolescents (11-18 years), never vaccinated for pertussis, with negative anamnesis for pertussis and low anti-PT IgG titres, has shown that 29-49 days after administration of a single dose of dTpa vaccine, at least 96% of the subjects had an immune response against all three antigens.
Of the 78 initially seronegative for the anti-PT antigen, 84.6% showed an immune response 29-49 das after vaccination. For the other antigens, the immune response was over 90%, regardless of the initial serological state [32].
In addition, a co-administration study has shown that the dTpa vaccine is immunogenic and well tolerated when co-administered, but at separate inoculation sites, with the bivalent anti-HPV vaccine, in youths aged 10-18 years [33] (Figs. 6-8).
Trials conducted in Australia, Belgium and Singapore in adults have shown high seroconversion rates and immune response towards pertussis antigens as well as towards tetanus and diphtheria [30], and antibody titre persistence up to 5 years after vaccination [34]. McIntyre et al. [34] in 2008 reported seroprotection rates towards diphtheria and tetanus of 94.4% and 96.2% respectively and seroconversion towards 3 pertussis antigens of between 89 and 100%. Anti-diphtheria and anti-tetanus antibody titres, up to 60 months after vaccination with dTpa, show how these remain significantly above the protection threshold and their equivalence to titres obtained after vaccination with Td [34].
Finally, the dTpa vaccine has also been evaluated for primary vaccination of adults in a study that enrolled 460 subjects with mean age of 56.9 years, without dT vaccination for at least 20 years, or with an unknown vaccination history (51.5% of the total) [35].
The study has demonstrated that after 3 doses of dTpa vaccine, 99.3% and 100% of the subjects had seroprotective anti-diphtheria and anti-tetanus antibodies, while with regard to pertussis, a sharp increase in anti-pertussis antibody titres has been observed after just 1 dose of vaccine, with rates of seroconversion equal to 92.2% towards all three pertussis antigens (Fig. 9), showing that even in subjects that had never been vaccinated, contact with *Bordetella pertussis* induces an immunological

Fig. 6. Rates of seroconversion/seroprotection towards D, T, P, Polio 1, 2, 3, HPV-16, HPV-18 in 751 youths vaccinated with dTpa-IPV + bivalent HPV 16,18 vaccine.

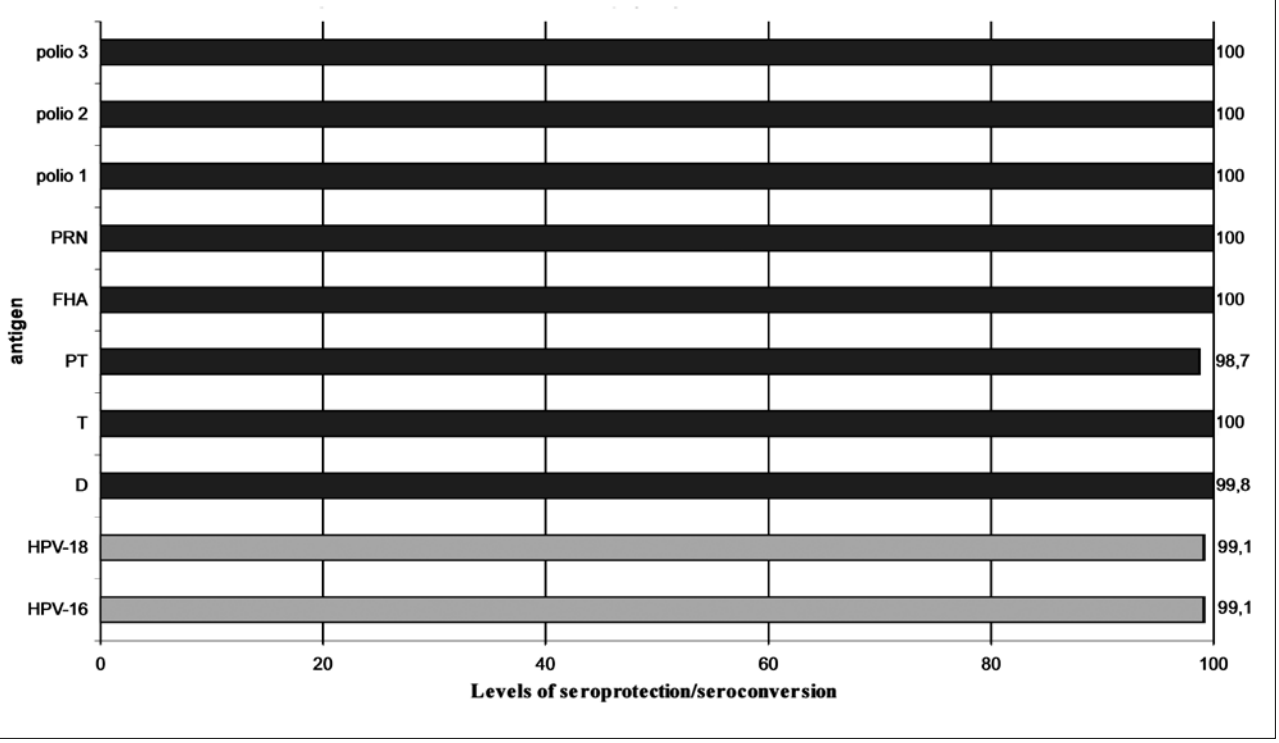
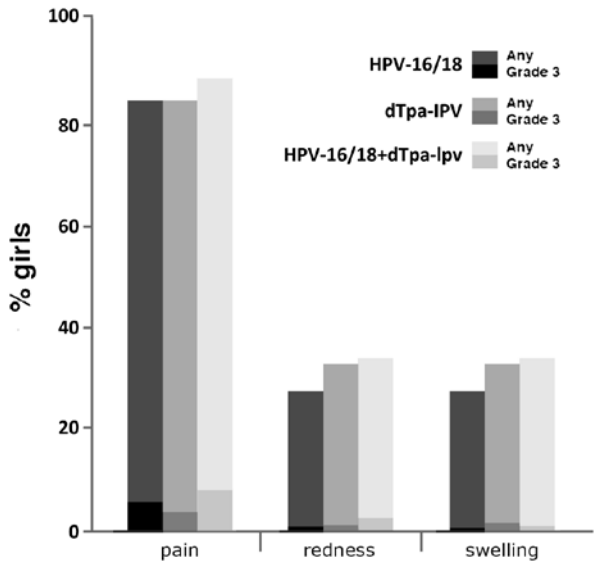


Fig. 7. Local adverse events occurring following administration of dTpa-IPV, HPV 16/18 and dTpa-IPV+ HPV 16/18.



memory that can be successfully boosted with a single booster dose [35].

Preventive strategies

In Italy, the 2005-2007 [36] National Immunization plan recommend a primary anti-pertussis cycle of three doses in the first year of life with a booster doses at 5-6 years of age and evaluation of the opportunity for an additional booster at 11-16 years. The target, with regard to anti-pertussis coverage, is the maintenance of high (> 95%) vaccination coverage, both for newborn infants and for the booster dose at 5-6 years.

In order to achieve the primary objective, which is control of the disease in infants with the greatest risk of complications, the administration of periodic pertussis booster to adolescents and adults, with reduced antigen-content vaccines, in combination with anti-tetanus and anti-diphtheria, is under evaluation.

However, at present, dT and dTpa booster vaccination coverage in adults is very low, as well as those in adolescents, evaluated for the first time in 2008 within the scope of the ICONA study [11].

With regard to the 4th and 5th booster doses of anti-tetanus and anti-diphtheria, coverage is 94 and 48% respectively, while it is definitely low for pertussis, being equal to 22 and 12% for the 4th and 5th doses respectively [11].

Although universal adult vaccination is the most effective strategy for protecting the whole population [4], this does not seem realistically feasible. For this reason, in order to protect the subjects at greatest risk, many countries are implementing strategies based on the vaccination of specific groups of adults (the parents of newborn infants, healthcare workers) as shown in Table III [37-40].

In 2001, the Global Pertussis Initiative (GPI) [4, 41] proposed 7 potential pertussis vaccination strategies, considering that the endemic nature of the disease, despite the good vaccination coverage, can be ascribed to loss of both natural and vaccine-induced immunity in the absence of booster doses. Among those preventive strategies, adolescents vaccination is very important as it has both the objective to protect the single and the community. In fact, it is well documented that the disease has re-emerged among adolescents and that the increasing circulation of *Bordetella* is a frequent cause of pertussis breakthroughs in schools. Moreover, adolescents could be a source of infection for unvaccinated siblings [42].

In Italy pertussis coverage among adolescents is consistently low, even though different between regions. According to ICONA survey, the main reason is lack of information on advantages of vaccination among the families [11], who in the great part of Italy, do not receive any active call for dTap adolescent booster.

However, adolescent booster, despite very important, is not enough to significantly reduce pertussis risk among infants, even with high coverage (> 75%). In fact, according to a recent mathematical modelling study [43], reaching high coverage in adolescents has a direct effect on annual pertussis incidence among 10-19 years

Fig. 8. Systemic adverse events occurring following administration of dTpa-IPV, HPV 16/18 and dTpa-IPV+ HPV 16/18.

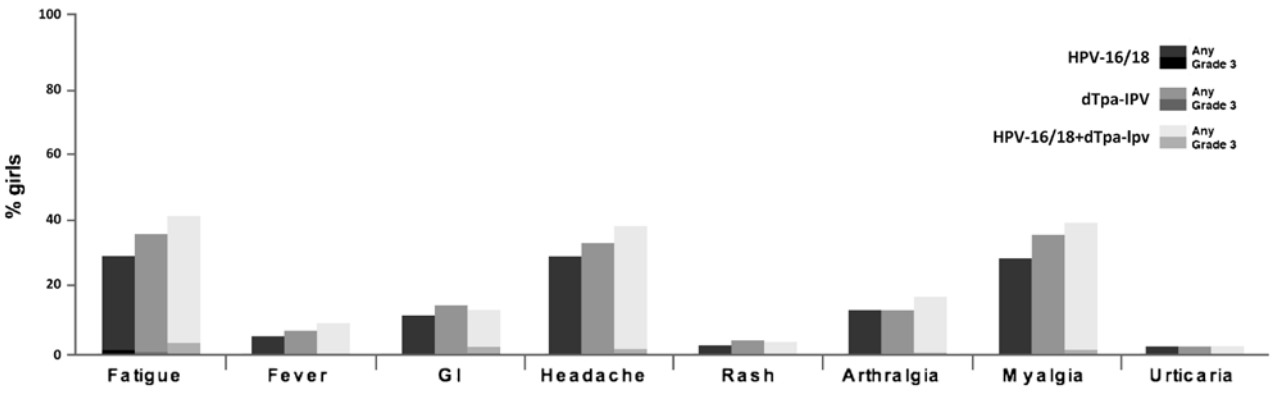
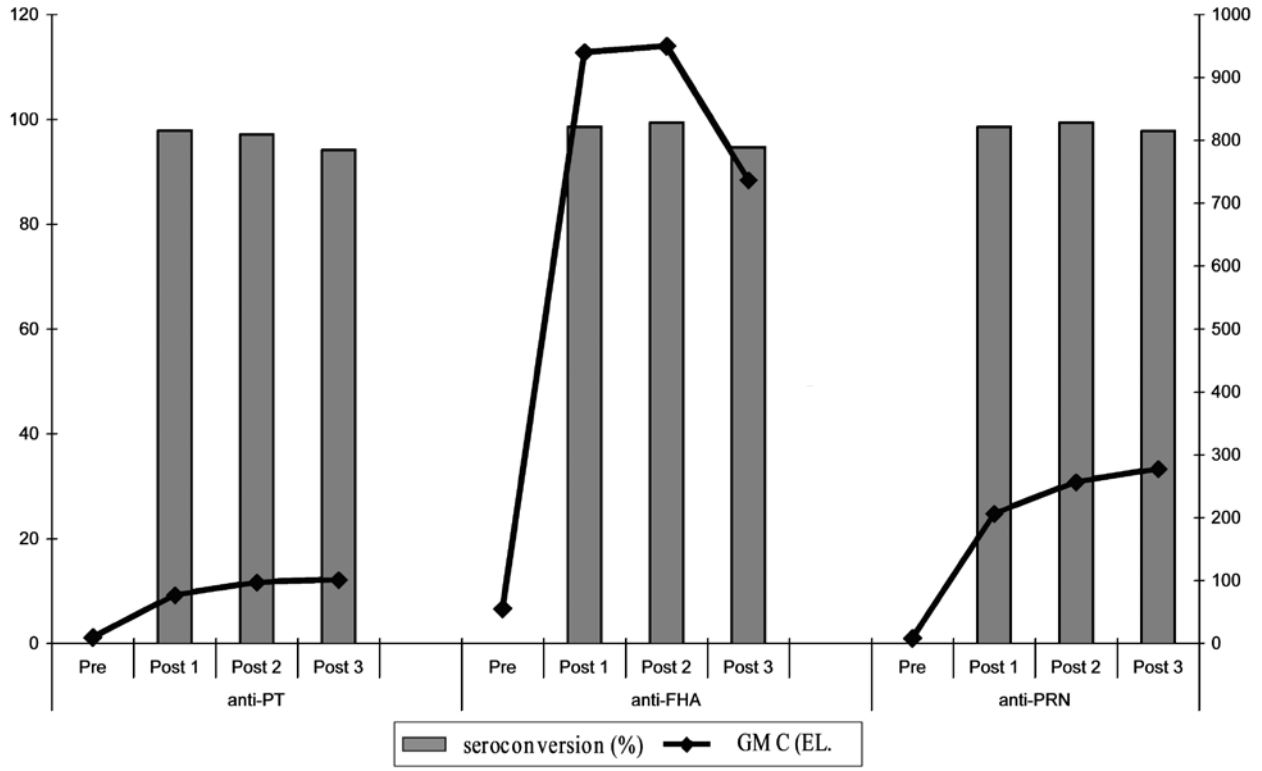


Fig. 9. Immunogenicity of the dTpa vaccine in adults aged >40 years with unknown vaccination history or that had received their last dT booster over 20 years previously. Rates of seroconversion and antibody titres towards the 3 pertussis antigens, prior to beginning the vaccination cycle and following administration of the 3 doses.



Tab. III. Recommendations for pertussis vaccination in adolescents and/or adults in Europe (adapted from Zepp et al., 2009 [40]).

Country	Primary vaccination (age months)	Booster dose	Adult booster
Austria	2–4–6	12–24 months, 13–16 year	
Belgium	2–3–4	15 months, 5–7 years, 14–16 years	Cocoon strategy
Finland	3–5–12	4 years, 14–15 years	-
France	2–3–4	16–18 months, 11–13 years	27–28 years, all health care workers plus Cocoon strategy
Germany	2–3–4	11–14 months, 5–6 years, 9–17 years	≥18 years, Cocoon strategy, health care workers
Italy	3–5–11	5–6 years, 11–15 years	-
Netherlands	2–3–4	11 months, 4 years	-
Poland	2–4–6	16–18 months, 6 years	-
Switzerland	2–4–6	15–24 months, 4–7 years, (11–15 years; catch-up)	-

old subjects as well as a positive impact on newborn cases, but does not reduce the incidence of the disease in adults, that are still the main source of infection for susceptible infants.
Among the strategies proposed [4] to control pertussis, there is the "cocoon strategy", envisaging the immunisation of parents, family members and close contacts of newborns, within the prenatal period and in any case within 4 weeks of birth, with the aim to reduce the risk of transmission to susceptible newborns.
Although this strategy is far from ideal, as do not significantly reduce circulation of *Bordetella* and do not generate a sufficient herd immunity, this strategy could be easier to carry out, compared to universal adult vaccination considering the greater ease of contacting and involving this group of subjects, that anyway are the most probable source in case of an eventual infection of the newborn infant.
The recent recommendations from ACIP [44] (Advisory Committee on Immunization Practices) for the prevention of tetanus, diphtheria and pertussis in pregnant women or during the post-partum period and for newborn infants, consider that the majority of pertussis cases among newborn infants can be traced to parents, mainly the mother, further highlighting how the vaccination of both parents prior to hospital discharge from maternity department, may, according to mathematical models, reduce fatal cases by 38% [45]. The ACIP recommends that all women who have received the last Td vaccination at least 2 years earlier, be administered a Tdap booster dose within the post-partum period [44].
According to the CDC [5], the availability of Tdap vaccines for adults offers the opportunity to reduce the spread of pertussis. In particular, replacement of Td vaccines with Tdap makes it possible to protect adolescents and adults against pertussis, and above all reduce the circulation of the pathogen, allowing reduction of pertussis cases among at-risk subjects (*e.g.* newborn infants) and containment of the costs associated with the disease [5].
A recent mathematical modelling study [43], applied to data available in the Unites States, compared the impact of various pertussis vaccination strategies. The model has shown that vaccination of adolescents alone would lead to an initial reduction in the incidence of pertussis, but with the re-emergence of the disease in subsequent decades. The study shows that the most feasible strategies are represented by infants and adolescents universal mass vaccination and periodic vaccination of all adults every 10 years (with a minimum coverage of 40%), or, as an alternative, in addition to infants and adolescents universal mass vaccination, vaccination of close contacts (at least 65%) of newborn infants, in association with a booster dose for all adults, at the ideal age of 40, according to the model.
The last option could reduce by 2/3 pertussis cases among susceptible newborns [43].
In 2008 the 'Cocoon strategy' has been included in French '*Guide des vaccination*' that, besides booster vaccination against pertussis to preschool children, adolescents and adults, at the time of booster vaccination for tetanus and diphtheria, recommends a dTap booster for adults planning a pregnancy and the household, or alternatively, for the father and households during pregnancy, and, for the mother as soon as possible after delivery, as well as for healthcare workers coming into close contact with infants [37].
Similar recommendations have been inserted in Belgian and German (STIKO) Vaccination Plans [38, 39].
At present, only one experience of implementing Cocoon strategy is available in the literature.
It is a study conducted in France [46] in a university maternity hospital showing that proper counselling of the parents about risks of pertussis infection and the benefits of booster vaccination as long as the recommendation of immunization as soon as possible after discharge, is highly efficacious. After 3 months of active campaign, during which 983 families have been informed during post-partum hospitalization, 68% of mothers and 63% of fathers were vaccinated, mostly in the first month after birth.

Hypothesis of adoption of the cocooning strategy in Italy

As already mentioned, the term "cocooning" means the vaccination strategy envisaging the indirect protection of newborn infants through the immunisation of a target adult/adolescent population, represented by the parents and other potential close contacts, such as siblings/cousins, grandparents and healthcare workers.
Within our organisational structure, the cocoon concept is based on the necessary interaction but in particular the coordination of various professionals, such as the health visitor, gynaecologist, general practitioner and paediatrician, all potentially part of the cocooning strategy, but each operating within a separate healthcare context. Since this is a prevention plan, the local health unit (LHU) Prevention Department should have the responsibility for coordination of the various healthcare departments. On the other hand, the pregnant mother may be identified as the ideal linchpin in this collaboration, being central to its implementation within the territory. Indeed, it is reasonable to consider that the future mother, especially in the final months of pregnancy, centres all her energies on preparation for the birth and the future care of the newborn. Hence, if the pregnant mother is make aware of the problem of pertussis by specifically trained healthcare personnel, she will assume an active role in ensuring that the future contacts of the newborn verify their own vaccination status.
Furthermore, the future mother may be involved more easily than the other contacts of the infant since she undergoes frequent medical check-ups and attends prenatal classes that may become the ideal venue for making her aware of the importance of prevention, through vaccination, against certain infectious diseases that can have severe consequences for the newborn.

Certainly, being among the first contacts, the healthcare personnel involved in the birth (gynaecologist, midwife, hospital paediatrician etc.) and with the infant in the early months (family paediatrician) should also be suitably immunised against pertussis. Finally, if indicated, the pregnant mother herself should receive a booster vaccination, perhaps after the birth [44].

Therefore, if we consider the pregnant mother to be the operational linchpin of cocooning, we must consider the gynaecologist treating her and/or the Maternity Hospital (birth facility or equivalent structure), attended by the pregnant mother, as the healthcare facility where the first "step" in the process begins, namely the training and motivation of the pregnant mother.

The second "step" should envisage the pregnant mother, using the information with which she has been provided, endeavouring to sensitise the future family contacts already identified, inviting them to contact the healthcare authority vaccination clinic.

The third "step" would be the responsibility of the healthcare personnel at the vaccination clinic, who should implement a specific procedure for the administration of dTpa boosters to the future mother, after the birth, and her family members, registering them appropriately.

Naturally, both the family general practitioner and paediatrician should be suitably informed of this strategy, contributing towards the proper operation by providing information on the disease and/or the vaccination to family members interested, or even playing an active role in promoting immunisation in families where there is an ongoing pregnancy.

This organisational framework confirms that the LHU should be the healthcare structure responsible for the coordination of cocooning and evaluating the efficacy of the process. Indeed, the National Immunization Plan (NIP) [36] identifies the LHU as the operational structure allowing the practical implementation of vaccination coverage objectives, at the local level. Despite the organisational diversity existing in various situations, the structure that plans, organises and evaluates vaccination activity is solely the Prevention Department (PD). Indeed, at the entire LHA level, the PD has the responsibility for guaranteeing the attainment of the specific objectives of the various vaccination programmes, both national and regional. Again, according to the NVP, the PD also organises vaccine administration activities through the LHA medical and nursing staff. In particular, the PD is called to preside over priority areas, including vaccination awareness, the active and free offering of the vaccines envisaged in the regional calendar, the management of vaccination coverage and the reporting of infectious diseases, monitoring adverse events potentially attributable to vaccination and also the evaluation of the efficacy of vaccination programmes. Finally, we should remember that with the scope of ensuring the effective operation of the network, the NIP aims to actively involve other LHU services, namely the Districts, family paediatricians, general practitioners, hospital and outpatient specialists.

With regard to the present project, in LHUs opting for the cocooning strategy to reduce the risk of pertussis in newborn infants, the PD might implement the following actions:

- training of a multidisciplinary working party (representing the health worker, gynaecologist, midwife/ Maternity Hospital, general practitioner and hospital and family paediatrician);
- definition of the project and drafting of a process document by the working party;
- definition of the indicators of *management efficiency* (*e.g.* percentage of vaccinated subjects per pregnant mother, number of training operations performed, user surveys ecc.) and *outcome* that are actually measurable (cover, adverse events, degree of user satisfaction);
- the development of cognitive tools (training materials for healthcare staff, booklets for mothers/families);
- presentation of the project within the LHU: staff meetings;
- presentation of the project outside the LHU (meetings with gynaecologists/healthcare staff/GPs, PD/ working party press conference with local/regional press and television);
- vaccination of hospital staff/healthcare staff (in contact with newborn infants) adhering to the project;
- educational materials for pregnant mothers/fertile women distributed through strategic locations (Maternity Hospitals, prenatal courses, LHU clinics, gynaecology clinics/healthcare facilities/GPs);
- evaluation (after a suitable period of time) of the process and outcome indicators envisaged for the project and production of a report;
- periodic communication of the results: publication in relevant scientific journals; PD/working party press conference with local/regional press and television.

By virtue of its scientific content and prerequisites, 'cocooning' might also constitute a training project in accordance with CME criteria. Once accredited, the participants in this project should thus obtain training credits annually, in relation to the operation of the project within the structure of origin in addition to personal learning (as a further incentive). Start-up and operational maintenance of the project requires training meetings and periodic meetings with the participating healthcare workers dedicated to training/ learning and discussion of the operating criteria. The contribution of individual healthcare workers towards the right implementation of the project should be reported to the competent bodies and personnel departments and made public during periodic publishing of the results of the project itself.

Conclusions

European and Italian epidemiological data demonstrate how, despite the high vaccination coverage achieved during the first year of life, pertussis is not perfectly controlled in newborn infants that have not yet been vaccinated due to the circulation of the pathogenic agent and the shift of the disease to adult age.
Besides universal adult vaccination, in order to reduce the risk of pertussis in newborn infants, the subjects at greatest risk of hospitalisation and severe complications, the vaccination of the contacts closest to the newborns (cocooning strategy) has been proposed.
According to this considerations and to the operational models described above, cocooning would appear to be an achievable plan by Public Health Department. Indeed, to put the plan into practice, a great deal of determination by the LHU management, substantial work by the health-care workers involved (especially to start up the project), the availability of the planning and implementation tools identified by the working party, in addition to a positive and capable administration framework, is required.
This project would also have the great additional value of sensitising adults to vaccination boosters and increasing anti-tetanus and anti-diphtheria vaccination coverage, in compliance with Pres. Decree No. 1301 of 7 September 1965, in accordance with which revaccinations, through the administration of tetanus anatoxin, possibly in combination with diphtheria anatoxin and/or with other antigens, are conducted at 10 year intervals [47].
Indeed, recent seroepidemiological data shows that, in Italy, 40% of males over the age of 30 years and 60% of females have anti-tetanus antibody titres that are considered non-protective [48], while, with regard to diphtheria, over 20% of adults over the age of 40 years are unprotected [49].

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■ Correspondence: Giuseppe Ferrera, Epidemiology Service, Ragusa LHA, via Giuseppe di Vittorio 59/c, 97100 Ragusa, Italy - E-mail: servizio.epidemiologia@asp.rg.it