Original article

Vaccine co-administration in paediatric age: the experience of the Local Health Unit of Cuneo-1 (Ambito di Cuneo), Italy

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Abstract. *Background and aim of the work:* The immunization schedule might be continuously updated on the basis of the new scientific and epidemiological knowledge, possible changes in operational requirements and the availability of new products. A high vaccination compliance is strictly related to factors such as tolerability, effectiveness and number of injections. This last has always been a critical point and combined vaccines guarantee high levels of safety and immunogenicity requiring fewer injections and accesses to services. Co-administration should be considered in order to expand the supply of important vaccinations, (eg. meningococcal and pneumococcal), avoiding the increase of the number of accesses to services. *Methods*: Since January 2007, an experience with the co-administration of hexavalent vaccine together with conjugate pneumococcal and meningococcal C vaccines started at the LHU CN1-Ambito di Cuneo. The target of this co-administration, based on scientific criteria, is to provide immunization against St. pneumoniae and N. meningitidis in newborns. *Results:* Considering that the coverage rate (VC%) with hexavalent vaccine has been always high and that, at the end of 2006, the VC% for the pneumococcal and meningococcal C conjugate vaccines were equal to 50.4% and 44.4%, in this first year of experience the compliance to co-administration has significantly increased from 47% of doses administered in the first quarter of 2007 to 65% in the first quarter of 2008. *Conclusions:* Co-administration could be an useful mean to introduce new immunizations into the vaccination schedule and to achieve high vaccination coverage rates. (www.actabiomedica.it)

Key words: co-administration, hexavalent vaccine, heptavalent pneumococcal conjugate vaccine, meningococcal C conjugate vaccine

Background and aim of the work

Vaccination is one of the major discoveries in the health field and has allowed to achieve extraordinary results in the fight against infectious diseases, with a significant reduction of morbidity and mortality (1). Immunization allows to avoid both the targeted disease in the immunized subject (individual protection) and the disease transmission, removing the conditions that allow the spreading of the infectious agent in the population (herd immunity) (2). The immunization schedule, defining the chronological sequence of administration of different doses, is an essential guide for paediatricians, operators of public health and parents. Moreover, it is the most important tool to achieve the coverage rates necessary in order to obtain important goals such as control, elimination or eradication of an infectious disease. The minimum coverage rate required to interrupt the transmission of an infectious agent with specific epidemiological characteristics is a

key point in modern vaccinology (3). The achievement of critical coverage rate for the elimination/eradication of a disease is closely related to the concrete possibility of administering all the necessary doses and to have a high level of acceptance (compliance) by users. The availability of new vaccines is an obvious advantage, but it complicates the definition of the immunization schedule. This latter could become too complex or require too many accesses to services. However, this complexity can be managed by increasing the number of vaccination sessions or of injections at each visit (co-administration), by the use of innovative systems of administration (intranasal or oral), by increasing immunogenicity of vaccines (thus requiring a lower number of administrations) or by the use of combined vaccines. Today, the use of combined vaccines and the co-administration are the strategies most commonly adopted. The benefits consist in a greater acceptance by users and health workers, in the reduction of administration costs, in the simplification of operative procedures and in the possibility to adopt new vaccines. Combined vaccines ensure the same safety and efficacy compared to single products, with a lower number of injections and access to services (4). The possibility of co-administration should be carefully considered when combined vaccines are not available and there is the need to expand the supply of vaccines without increasing the number of accesses, as for immunization against Streptococcus pneumoniae and Neisseria meningitidis. The experience began at the LHU CN1 – Ambito di Cuneo with the co-administration of hexavalent vaccine (DTaP-HBV-Hib-IPV) (Hexa) with heptavalent pneumococcal conjugate vaccine (PNC7) and meningococcal C conjugate vaccine (MenC) fits in this context.

Methods

Geographical area of study

In 2008, the former LHU 15 was reunited with LHU 16 and LHU 17 and became LHU Cuneo 1 – Ambito di Cuneo. It covers an area of 2,462 square kilometers with a population of 159,288 people stratified by age groups as follows: 0-5 yrs.: 8,033; 6-13 yrs.: 11,963; 14-17 yrs.: 5,797; 18-64 yrs.: 98,355; 65-74 yrs.: 17,542; >75 yrs.: 17,598. About 1,450 newborns are registered every year. There is a close co-operation between the Department of Hygiene and Public Health (DHPH) and the Territorial Paediatricians (TPs). Since 2005, a Committee on immunization practices, including 3 Hygienists Doctors and 3 TPs, is active. In addition, the Team of the TPs meets monthly to define and share actions, also regarding vaccination, with the LHU. These meetings allow to activate new programs and to optimize the identification of objectives and strategies of intervention.

Evaluation of immunization coverage rates

Data on the history of both mandatory (Diphtheria, Tetanus, Polio and Hepatitis B) and recommended vaccinations (Haemophilus influenzae type b, Pertussis, St. pneumoniae, N. meningitidis, Measles) were collected and the coverage rates were calculated. Meningococcal and pneumococcal conjugate vaccines are offered at the cost of the vaccine without additional charge and are free for subjects belonging to groups at risk.

Since January 2007, co-administration of Hexa with PNC7 and MenC vaccines started with the objective to immunize newborns with three doses administered in the first year of life according to the schedule adopted at national level (3-5-11 months). Co-administration was performed accordingly to the guidelines given by the World Health Organization (5).

Results

In the considered geographical area, vaccinations against Polio, Diphtheria, Tetanus and Hepatitis B have been used accordingly to the national immunization schedule using firstly single products, and then combined vaccines. In particular, since June 2001 the hexavalent vaccine has been adopted. Regardless of the products used, the vaccination coverage rates have always been high, also for recommended immunizations. Since mid 90's, the coverage rates for compulsory immunizations in newborns in the LHU CN1 –

Ambito di Cuneo have always been higher than 95% (Table 1).

The historical trend of immunization coverage rates for recommended vaccinations is shown in figure 1. VC% has been constantly high for Pertussis and Measles, while the coverage rates for Hib immunization significantly increased since June 2001, with the availability and use of hexavalent vaccine, reaching high levels, similar to the ones obtained for Pertussis and Measles, in the period 2003-2006.

In September 2006 started the use of PNC7 and MenC conjugate vaccines and, since 2007, co-administration of Hexa, PNC7 and MenC vaccines was offered.

Since the availability of these two vaccines, the VC% significantly increased reaching more than 40% for both vaccines. Figure 2 shows the immunization coverage achieved by the co-administration of Hexa, PNC7 and MenC vaccines at the same time: between 01/01/2007 and 03/31/2008 (15 months) an increase of immunization coverage rate from 46.9% to 64.8% was observed.

Discussion

With reference to compulsory immunizations, the results show a high VC% and thus a high degree of participation of the population to mandatory vaccinations (table 1); moreover, high coverage rates have been achieved also for recommended vaccinations (figure 1). These data demonstrate that families are re-

Table 1. Coverage rate for compulsory vaccinations in newborns

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Polio	98.6%	98.8%	98.7%	98.9%	98.1%	98.2%	97.2%	97.9%	97.8%	97.5%	97.0%	96.5%	95.8%
Diphteria	98.4%	98.8%	98.3%	98.4%	97.8%	97.8%	97.2%	97.9%	97.8%	97.5%	96.9%	96.4%	95.9%
Tetanus	98.4%	98.8%	98.3%	98.4%	97.9%	97.9%	97.2%	97.9%	97.9%	97.5%	97.2%	96.5%	95.9%
HBV	98.2%	98.5%	98.3%	98.3%	97.1%	97.6%	96.6%	97.3%	97.3%	96.8%	96.6%	95.8%	95.3%

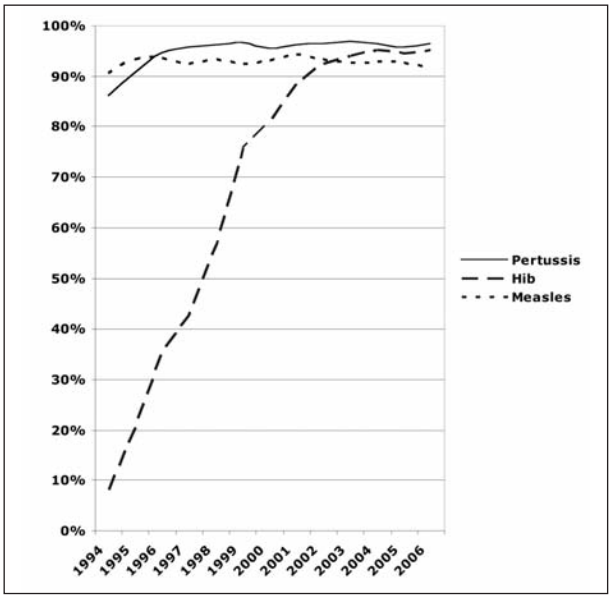

Figure 1. Historical trend of immunization coverage for recommended vaccinations

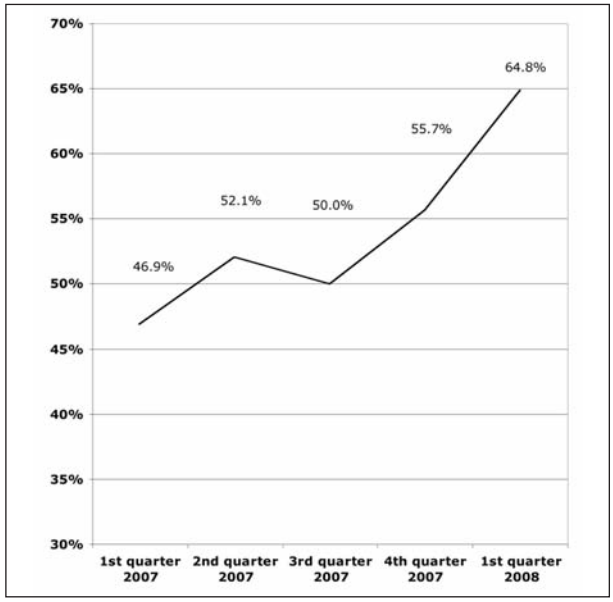

Figure 2. Immunization coverage achieved by the co-administration of hexavalent, MenC and PCN7 conjugate vaccines in the period 01/01/2007 - 31/03/2008

ally interested in preventing infectious diseases, also when immunizations are not compulsory. The achievement of these results is strictly related to a good co-operation and linkage between health workers and parents of children.

As a matter of fact, data related to PNC7 and MenC conjugate immunizations, recently adopted, seem to support this hypothesis. As shown, the rates have steadily increased reaching 50.4% and 44.4% at the end of 2006, respectively for PNC7 and MenC.

The experience of co-administration of Hexa with PNC7 and MenC conjugate vaccines started in this context of high participation by the population to immunizations. The experience is particularly innovative because in Europe few data regarding it are available. In the rest of the world, this type of co-administration is admitted by the Canadian Health System (6). The ground of this strategy is to ensure any child the coverage against major vaccine preventable infectious diseases.

The growing number of available vaccines has increased the complexity of the paediatric immunization schedule, the number of vaccination sessions and related costs. It has also caused a greater difficulty in respecting time of administration, a decrease in coverage and an increase of parents' and children's distress. The use of combined vaccines or, when a combined product is not available, of co-administration, represents a fundamental tool to achieve adequate coverage rates.

As a general rule, vaccines containing different killed or inactivated antigens may be simultaneously administered or after any temporal interval. This kind of administration does not affect the immunogenicity or safety profile of these vaccines. As a matter of fact, the immune system retains the ability to provide appropriate responses to different antigens (7). Concerning live attenuated vaccines, it is necessary to co-administer different products at the same time or to wait at least 4 weeks between immunizations. From an operational point of view, lowering the number of vaccine sessions guarantees the reduction of discomfort for children and families, increases the compliance to new immunizations, decreases costs and allows to improve coverage rates.

A critical point that should be taken into account adopting co-administration is the need to choose the most appropriate time for administration of vaccines and to guarantee a level of immunogenicity and safety at least equal to the one obtained with each vaccine separately administered (8).

Recently, there has been an extensive use of hexavalent combined vaccine and new products, such as conjugate vaccines for St. pneumoniae and N. meningitides, have become available. Considering the epidemiological relevance of these two pathogens in the first months of life, it has been considered the opportunity to include PNC7 and MenC conjugate vaccines in the already adopted immunization schedule guaranteeing the coverage of newborns in a rational manner. Some regions have decided to co-administer Hexa and PNC7 conjugate vaccine with three doses in the first year of life and to give the MenC conjugate vaccine in one dose after the first year of life. Tuscany, on the basis of its available epidemiological data, has initially decided to co-administer Hexa and MenC conjugate vaccine (3 doses in the first year of life) and one dose of PNC7 conjugate vaccine after the completion of the first year of life. These strategies have been adopted on the basis of scientific evidence of their validity (9-15). However, the possibility of co-administration of PNC7 and MenC conjugate vaccines has been amply discussed (16). In July 2005, the National Center for Epidemiology, Surveillance and Health Promotion (CNEPS) of the National Institute of Health issued an advice on the co-administration of PNC7 and MenC conjugate vaccines. According to this advice, the co-administration of Prevenar (PNC7, Wyeth) and Meningitec (MenC, Wyeth) was indicated as possible, as stated on the summary of product's characteristics. In the same advice it was positively evaluated the co-administration of Prevenar and Hexa vaccine and of Hexa and meningococcal conjugate vaccines (17). Concerning other conjugate meningococcal vaccines (MenC Menjugate, Chiron and Meninvact, Sanofi Pasteur MSD), the possibility of co-administration with Prevenar (PNC7, Wyeth) has been stated as possible in September 2006, upon the completion of review process of the summaries of the products' characteristics. In detail, a clinical trial was carried out in order to compare the immune responses obtained in three groups of children with different co-administration protocols: MenC conjugate (Men-

jugate) and Hexa (Infanrix Hexa) vaccines, PNC7 (Prevenar) and Hexa (Infanrix Hexa) vaccines, and MenC (Menjugate), PNC7 (Prevenar) and Hexa (Infanrix Hexa) vaccines. The vaccines were administered according to the schedule 2, 4.5 and 6.5 months of age and the only differences observed between groups regarded the averages of some geometric antibody titres, however, without any clinical relevance. The proportion of children with protective antibody titres in the group that received all three vaccines was similar to the one observed in the other two groups (18).

The main critical point related to triple co-administration is the need to make three injections at the same time; two inocula are made in a thigh (MenC and Hexa) and the third one (PNC7) in the other thigh (5). The need to make three injections in children can imply the risk of a low compliance by parents. However, during the first 15 months of our experience with the triple co-administration the compliance by parents increased from 46.9% of the doses administered in the first quarter of 2007 to 64.8% in first quarter of 2008 (figure 2) contributing to an increase of VC% for these two vaccines.

These data show the growing acceptance by families to an approach to vaccination different from the traditional one after adequate information. Probably, the good compliance obtained is strictly related to the organizational system adopted in LHU CN1 – Ambito di Cuneo. The availability of a team of TPs, which meets monthly and sets out actions that are shared with the Dept. of Hygiene and Public Health (DHPH) allows to optimize the identification of objectives and strategies of intervention and to provide univocal messages to families.

In conclusion, together with the use of combined vaccines, co-administration, when possible on the basis of scientific evidence, is an important tool to introduce into the already complex vaccination schedule new immunizations and it is important to achieve high vaccination coverage. Compliance of parents to triple simultaneous administration can be high if they receive univocal messages on the importance of this intervention by the various health workers that they contact (DHPH and TPs). Of course, besides a high compliance, it must be confirmed that co-administration does not significantly increase the rate and/or severity of adverse events and that it does not affect the immunogenicity of single antigens.

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