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NEWS ON VACCINATIONS

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If we want to make a synthesis of the advantages determined by vaccinations during the millennium ended few years ago, certainly thanks to vaccinations many diseases and their devastating effects disappeared. This led to lose the memory of their severity and of the great usefulness to prevent them. So often we don't realize the great benefits we reached and sometime we invoke their abandonment, forgetting the danger of the reappearance of some diseases, as it happened with the recent epidemics of polio in Albania and some countries of Africa, and of diphtheria in Russia. The importance of the prevention using vaccines is not sufficiently appreciated and recognized, so less than 1% of the total drug charge is devolved to vaccines.

New and old vaccines

The observatory of WHO deputed to plan and survey vaccines divided the world in 6 Regions: Italy takes part of the Europe Region where priorities are represented by the elimination of polio, obtained in 2002, by the surveillance of diphtheria after the serious epidemic in the countries of the East Europe in the second half of years 90, by the elimination of measles and congenital rubella by 2010. As regards polio, since 2002 our new vaccination schedule is based on 4 injections of Salk vaccine in the 3rd, 4th, and 11th month of life with a booster in the 3rd year of age. The substitution of Sabin vaccine with the Salk one is due to the fact that Sabin vaccine provoked polio development in approximately 1 on 700.000 vaccinates. As regards diphtheria, taking into account cases above mentioned and notifications of cases of pertussis in the USA among adolescents and adults, a vaccine against diphtheria, tetanus and pertussis (Tdap) has been prepared for adults of advanced age. The study completed among healthy adolescents and adults between 11 and 64 years of age, treated with either a single intramuscular dose of Tdap vaccine or anti tetanus-diphtheria vaccine (Td) as control, evidenced protective antibody concentrations towards diphtheria and tetanus with both vaccines and antibody titres greatly exceeding protective levels towards pertussis toxoid with the Tdap vaccine. These data support the potential routine use of the Tdap vaccine in adole-

scents and adults in order to maintain valid seroprotection rates (1).

Another objective of OMS is the elimination of measles, a serious infection in the child and still more serious in the adult, through vaccination with the trivalent vaccine measles-mumps-parotitis (MRP). Due to the increased frequency of febrile convulsions as a result of such vaccination and in order to verify the personal or familiar history of convulsions, and/or perinatal factors and/or the socioeconomic state, a survey was conducted in Denmark among 537.171 children born between 1st January 1991 and 31 December 1998. From this survey, the risk of febrile convulsions resulted increased during the first 2 weeks following MRP vaccination (1.56 on 1000 in children). Such risk was greater in siblings of children with a history of febrile convulsions (3.97 on 1000) and higher in children with a personal history of febrile convulsions (19.47 on 1000). Febrile convulsions observed after MRP vaccination led to an increased percentage of recurrent febrile convulsions (RR = 1,19), but not an increased percentage of epilepsy (RR = 0.70) compared to children not receiving the vaccine. Therefore, in spite of the absolute importance of MRP vaccination, this must be carefully administered to children with a personal or familiar history of febrile convulsions (2). Moreover, if vaccination is made in the first year of life, due to the risk to contract the disease, as happened during the epidemics in some Countries, it is necessary a second dose of MRP in the 15th month of life, since children under 12 months are not able to answer adequately to the measles component of the vaccine because of the presence of residual antibodies of maternal origin in the circulation. As regards rubella, a relatively benign infection in children, the objective of WHO is to avoid the disease during pregnancy, in particular in the first weeks, when it often cause spontaneous abortion, intrauterine death or congenital rubella, characterized by serious chronic disabilities of the child such as blindness, deafness, cardiac malformations and mental illness.

In the USA, the production of a vaccine available since 1995 has been favoured by the high infectiousness of chickenpox, leading to frequent admissions to the hospital, complications (streptococcal disease group A) and rarely deaths above all in the adult. Nevertheless, the WHO recommends to administer chickenpox vaccination after the first year of life if it is not possible to guarantee an homogeneous national covering of the 85-90% in order to avoid a higher risk of develop the disease in the adult, where complications and deaths are more frequent (a 30-40% increase) and there is a hypothetical growth in Herpes Zoster cases as a result of the lower circulation of the virus. In the USA, the vaccination led to a decrease in chickenpox cases and admissions to hospitals and till now the

fearful increase of Herpes Zoster cases has not been observed. Finally, taking into account that immunity due to vaccination would be perennial, the economical advantage is also evident (3, 4).

In Italy, the National Vaccine Plan (PNV) recommends to vaccinate people at high risk to develop or to transmit the infection, comprised fertile women and susceptible adolescents, and to estimate the possibility to obtain a vaccination coverage greater than 80%, crucial condition in order to introduce a worldwide vaccination plan. For these last reasons, some regions decided to propose such vaccination free of charge. A new tetravalent vaccine measles-parotitis-rubella-chickenpox will be on the market in a short time: if of reasonable price, it will replace the current MRP leading to remarkable advantages about compliance and vaccination coverage against all pathogens, with positive effects as regards health and economics. The introduction of vaccination, particularly in the first year of life, against pathogens responsible of meningitis markedly reduced the incidence of the infection above all among children under 5 years of age. In Italy, the more evident results were obtained against *Haemophilus Influenzae* type b with a vaccination that led to a decrease in the incidence of the disease and its outcomes (Table 1).

As regards *Streptococcus Pneumoniae*, responsible of serious meningitis in the neonatal age, the WHO recommends to introduce the vaccination if the disease represents a priority problem of health, if there is a good superimposition of serotypes and if the introduction of the vaccination does not interfere negatively with the organizational and economic aspects. In the USA, the conjugate vaccine has been introduced since 2000. A reduction of 69% in the percentage of the disease caused by serotypes contained in the vaccine has been observed in children under 2 years

of age. In adults between 20 and 39 years of age, the disease showed, in 2001, a reduction of 32%, while the decrease was of 8% and 18% respectively in subjects between 40 and 64 years and those over 65 years of age. The incidence of the disease caused by microorganisms not sensible to penicillin was lower than 35% in 2001 compared to 1999 ($p < 0.001$) (5).

In Italy, taking into account the lower incidence of invasive serotypes of *Pneumococcus* in the first five years of life, the cost of the product and the proposals of the WHO, the PNV recommends to vaccinate all children with chronic pathology and to extend the offer to those less than three years of age (free of charge or with participation to the expense according to the regional guidelines) attending the nursery school or other collectivises (approximately 16% of children in the second year of life): three doses from the third month of life with intervals of at least one month are indicated in order to obtain a significant reduction of meningitis, of the invasive pathology and of the serious outcomes. In order to improve the compliance, the vaccine have to be coadministered with an hexavalent vaccine according to the calendar 2-3-4 months and a booster at 12-15 months and according to the calendar 3 - 5 and 11 months for a total of 3 doses of vaccine, with a similar immunization observed both in fullterm and preterm newborns (6, 7).

Although vaccine PCV7 significantly reduced pneumococcal disease, an increase due to serotypes not contained in the vaccine has been observed, so a continuous system of surveillance is mandatory (8). Table 1 - Frequency of meningitis (data updated as of August 1st, 2005)

In Italy, the incidence of meningococcal meningitis of group B and C is less than 1 case on 100.000 with a progressive increase of those of group C from 25% in 2001 to 58% in 2004, cases mostly observed between

Table 1
Frequency of meningitis (data updated as of August 1st, 2005)

	Years	S	P	M	H	T	L	o	n.i.	Total
Total	1994	27	108	164	86	31	27	28	141	612
Total	1995	34	180	200	118	44	25	47	178	826
Total	1996	32	185	169	130	41	37	43	199	836
Total	1997	23	231	182	100	23	50	52	193	854
Total	1998	32	259	155	96	32	33	57	178	842
Total	1999	30	309	275	85	52	36	65	211	1063
Total	2000	26	243	250	57	33	39	66	198	912
Total	2001	29	235	203	54	27	32	57	178	815
Total	2002	31	235	223	42	33	38	77	198	877
Total	2003	21	309	278 [^]	35	18	27	79	202	969
Total*	2004	34	299	342	18	16	35	66	168	978
Total**	2005	9	137	191	13	6	8	26	68	458

S.: *Streptococcus agalactias*; P.: *Pneumococcus*; M.: *Meningococcus*; H.: *Haemophilus influenzae* type B; T.: *Mycobacterium tuberculosis*; L.: *Listeria*; o.: others; n.i.: not identified (derived from: <http://www.simi.iss.it/dati.htm>: *-** data updated as of August 1st, 2005.

the first and the fourth year of age (Table 1-2). So, considering the preliminary data in 2005, *Neisseria Meningitidis* of Group C is the main/first responsible for the bacterial meningitis in childhood.

Currently a vaccine against *Neisseria Meningitidis* of Group B is still under development.

On the other hand a conjugate vaccine against *Neisseria Meningitidis* of Group C is available and it has a long-term protective and effective action even in children below 2 years of age (on the contrary of polysaccharide vaccines).

According to recent data, published on WHO-CISID website, Italy is the European country with the highest cases number of Bacterial Meningitis due to *Neisseria Meningitidis* of group C (Table 2).

As a consequence and on the basis of the worldwide demonstrated safety and tolerability of Meningococcal group C conjugate vaccine, Italian MoH in PN (2005-2007) recommends the administration of 3 doses of vaccine (an interval of at least 2 months) in infants below 12 months of age and a single dose administration in children over 12 months of age (9). The co-administration with hexavalent vaccines is well known and proved also for Meningococcal group C conjugate vaccine.

As regards influenza vaccine, the PN objectives are those to improve the vaccinal covering in children, adults at risk and subjects over 64 years of age. From data of a survey made in 2003, it emerges that in Italy only 8% of children in the 2nd year of life with chronic pathologies were vaccinated against influenza, so it is strongly recommended to increase the vaccinal covering in these subjects.

On 5th august 2005, the Ministry of the Health emanated the circular "Prevention and Control of the influenza. Recommendations for season 2005-2006". In this document the composition, the indications (children over 6 month of age and adults with chronic diseases, subject over 64 years of age) and the different available vaccines (Split, Subunits or adjuvants with MF59 or liposomes) are reported. Dosages

and administration modalities are the following: from 6 to 36 months? Split vaccine or Subunit, half dose (0,25 ml) repeated at a distance of at least 4 weeks for children never vaccinated or a single half dose if already vaccinated; from 3 to 9 years? Split vaccine or Subunit, 1 dose (0,5 ml) repeated at a distance of at least 4 weeks for children never vaccinated or a single dose if already vaccinated; above the 9 years? a single dose of Split vaccine or Subunit (10).

As regards vaccinations in preterm newborns with a low birth weight and in good conditions of health, different studies evidenced that all the above mentioned vaccinations can be regularly applied consistent with the schedule recommended for fullterm neonates, while delayed and/or incomplete vaccinations could lead to an increased risk of disease. The frequently delay observed in beginning vaccinations is above all due to either the prolonged hospitalization or information not adequately supplied to parents (11). According to the American Academy of Pediatrics - Committee on Infectious Diseases, all preterm infants with a low birth weight (LBW) in good conditions should receive immunization at a chronologic age as regards DTaP, Hib, Hepatitis B, Polio and PVC7, as recommended for fullterm neonates and in the 6th month of life should benefit also of influenza vaccine (12).

The occurrence of adverse effects due to vaccinations are similar, also as frequency, in both fullterm and preterm neonates, even if in prematures of very low birth weight (VLBW) more serious (apnea, bradycardia or desaturation) and minor (increased oxygen requirement, altered regulation of body temperature, food refusal) adverse effects have been reported when vaccinations were scheduled before the 70th day of life (13).

Moreover, in preterm newborns with a gestational age < 31 weeks a decreased immune response when completing the primary immunization series against pertussis has been observed compared to that observed in full term newborns: so the administration of a

Table 2

Frequency of Streptococcus Pneum. and Neisseria M. meningitidis (data updated as of August 1st, 2005)

	Streptococcus Pneumoniae			Neisseria Meningitidis			Neisseria Meningitidis Serotypes		
	0	1-4 y of age	Total	0	1-4 y of age	Total	B	C	Total**
2001	16	30	46	16	40	56	27	4	31
2002	23	25	48	22	51	73	26	21	47
2003*	22	31	53	29	56	85	28	23	51
2004*	19	19	38	33	83	116	25	47	72
2005*	7	13	20	15	36	51	13	28	41

* Data updated as of August 1st, 2005

**Note: the sum of group B and C reported cases couldn't overlap with the total number of *Neisseria Meningitidis* reported cases. This is due to the fact that the serotyping of *Neisseria Meningitidis* can be underestimated since sometimes biological samples are missing.

boosterdose before the 5-6 years of age, when it comes regularly made in all children, has been suggested in order to maintain immunization (14).

An indirect confirmation to these statements comes from one study performed in United Kingdom in pre-matures with chronic pulmonary disease (CLD) treated with dexamethasone. Although a reduction in the antibody titles against diphtheria and tetanus has been observed, this resulted in lower normal values, while the antibody response to two of the four antigens of the pertussis vaccine was evidently reduced (15).

New vaccines

A new vaccine protecting against A, C, Y and W 135 meningococcus' type for seven-eight years is interesting. This one is proper for teen-agers who live in and attend crowded places such as schools or colleges where illness can easily spread. In India they are preparing a monovalent conjugated vaccine against A type serum especially for Africa (16, 17). Among all new vaccines we can see the return a vaccine against rotavirus after the withdrawal in 1999 of the one that determined intestinal problems. 4 or 5 rotavirus' serotypes (G1, G2, G3, G4, G9), are responsible of 138 millions cases of pediatric diarrhoea, with 2 millions of hospitalizations every year and about one million deaths, due to the severe dehydration, occurring mainly in developing countries (18,19). In the industrialized countries this problem is not so heavy but it causes a huge economic loss because every child under the age of 3 suffers about 1 or 2 times a year of acute diarrhoea. In the USA rotavirus causes about 3 million diarrhoeas every year with more than 200.000 hospitalizations and about 20-40 deaths. In Italy the social and sanitary damage (estimated in about 10 deaths and 11379 recoveries every year) is about 27 and 68 millions of euro a year (20,21). The liquid form of the pentavalent vaccine is given in three doses beginning from the 6th -12th week with 1-2 months interval. As this trial as shown very good results also in Italy, if the cost/benefits will be confirmed we will introduce it beginning from the second month with the second and third dose given with one month interval at the same time with the beginning of others vaccinations for the children attending communities (such as baby parking) and in other regions for everybody (18,21). This kind of vaccination has a high anticorpal response, does not interfere with the pentavalent or hexavalent vaccine enhancing the vaccine compliance and gives an optimal immunization at the 6th month that is the time when rotavirus' infection is frequent (22). After all is right to mention HPV vaccine. Some among the 100 types of known virus are responsible of dermatologic damage, especially in hands and feet, and more than 40 cause genital and mucosal injury. Infections derivating from types

16,18,31,45 cause cellular alterations that precede genital tumours so they are considered very dangerous as they cause pre-cancerous injuries genital, mucosal and orofaringeal tumours. Two oncogenic proteins named E6 and E7 promote and maintain cellular transformation and are in all HPV carcinoma. This virus are passed as soon as sexual intercourses begin almost in subjects under 25 years of age and it can also be passed from mother to son during pregnancy, birth and even later. A recently published Finnish study done on HPV positive mothers demonstrates that virus was present in newborn children in the 15% of the samples taken from the genital area and in the 10% of those taken from the mouth: at six months it was 18 % and 21% respectively to go down to 10% at 24 months. The persistence of HPV virus in the mother statistically represents a risk for HPV presence in the mouth of the children (23). Newborn infected from birth can show a laryngeal or pulmonary papillomatosis, called youth recurrent papillomatosis, which can cause aphonia and breathing obstruction within fifth year of life. This almost infrequent pathology in paediatric age is often caused by HPV virus 6 and 11 and can infect, in few cases, trachea, bronchi and pulmonary parenchyma turning to a very serious illness (24,25). Considering the early beginning of sexual activity with different partners and the consequent early and frequent infection it would be interesting to have a vaccination for HPV types most frequently causing illness not only to prevent genital oral and orofaringeal tumours in males and females but also to prevent some pathologies not so unusual in childhood. Naturally it would be necessary a proper analysis on infection's frequency, complications on age of development, hospitalization, mortality in adults to have a proper pre and post vaccination picture (27-29).

Conclusions

Vaccinations represent one of the most important steps that have contributed to enhance human's health: some thinks that after water's purifying, no other prophylactic measure has been so successful and cheap as vaccinations are.

All vaccinations, especially those against bacterial invasive infections for whom we need a particular pre and post vaccination control on every circulating kind, become a blind intervention without the proper control made on number and quality of the available data. Furthermore it is very important to consider, on the bases of scientifically evidence, the most convenient use for the vaccines, the vaccines' schedule, the co-provisions and the information to give to the families. Vaccinations policy decisions have to be taken with proper attention because of the money spent on research development and commercialization of vacci-

nes. The fact that a vaccine works will not take to the introduction worldwide because it can solve problems only in certain areas. Working without this approach will lead to serious loss of economic resources that in our field are always lower than those really needed. It is for this reason that many countries have disposed methods to fix vaccinations' priority and recommend their use focusing financial and organizational resources on most important interventions.

We use to say that health has no price, but it has a very high one.

As every choice becomes an economical investment and resources are not ever ending priority goes to worse situations (with higher risk of morbidity and mortality) that have a better opportunity of recover or prevention always considering the community's health.

Vaccination's social priority will emerge much more evidently in contrast with the poor resources devolved them on the basis of scientifically based evidence.

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SESSION 4: A focus on....

Chairman: G. Dore

Moderators: D. Rosatelli, G. Temporin

PREVENTION AND TREATMENT OF NECROTIZING ENTEROCOLITIS OF THE NEWBORN: EVIDENCE AND PRACTICE

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Necrotizing enterocolitis (NEC) is the most serious and devastating acquired intestinal disease of the newborn infants. It affects about 1-3% of babies admitted to a neonatal intensive care unit (NICU), and its overall incidence is about 1-3 cases per 1000 live births. Although it has been reported also in subjects born at term (5-25% of cases), it is predominantly a disease of the preterm infants. In very low birth weight infants (VLBWI) the reported incidence ranges from 5 to 10% (1). In Italy, an incidence of 6.2% has been found in VLBWI (4.2% under 1000 g and 7.0% between 1000 and 1499 g), with a relative risk of 6.7

(95%CI 1.8 to 33.3) in comparison to infants >1500 g admitted to a NICU (2, 3).

NEC is associated with a considerable burden of disease. Mortality ranges from 10% to 30%, but it can be much higher in VLBWI. Between 27% and 63% of affected infants require a surgical intervention, and survivors to the most severe forms have a high incidence of long term adverse outcomes, including developmental delay, respiratory problems, liver disease, intestinal strictures, primarily in the colon, and short bowel syndrome. Moreover, infants with NEC have a longer hospitalization in comparison to those without NEC, ranging from 22 to 60 more days in cases without and with surgical intervention (4).

For diagnosis, NEC is traditionally classified in stages according to the modified Bell criteria: in stages IA and IB NEC is suspected on the basis of suspicious clinical symptoms; in stages IIA and IIB radiological signs of intestinal dilation, pneumatosis intestinalis and portal vein gas are usually found; stages IIIA and IIIB are associated to very ill clinical conditions, in the most severe cases with intestinal perforation and pneumoperitoneum.

Although a lot of variables have been described in association with the development of NEC, prematurity is the only one consistently found in epidemiological studies to be an independent risk factor for the disease. The age of onset appears to be inversely related to gestational age: a large proportion of cases in term infants present in the first days of life, while preterm infants, particularly those born before 30 weeks' gestation, may not develop clinical symptoms for several weeks.

The best strategies for prevention and therapy of NEC are still to be clarified and are object of controversies; just for a few of them a clear evidence of effectiveness has been demonstrated. This uncertainty reflects the fact that the etiopathogenesis of NEC is incompletely understood; the available theories do not explain satisfactorily the full range of clinical manifestations and the epidemiology of the disease. As a consequence, in the absence of a unifying vision of the way in which NEC develops, the suggested interventions are often based only on partial interpretations of laboratory and observational studies. Most likely the spectrum of symptoms is the consequence of a mucosal injury caused by a complex interaction of various predisposing factors and the infant's subsequent response. Among the pathogenetic mechanisms involved, intestinal ischemia is present in NEC, as demonstrated by histopathological observations, although it is difficult to clarify whether it precedes or is a consequence of the development of the disease. A number of variables have been suggested as possible risk factors for the development of intestinal ischemia, such as, for example, perinatal asphyxia. However, many infants with NEC do not have a history of perinatal depression, and do not manifest symptoms until se-