SPECIAL ISSUE

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&

Satellite Meetings

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XXIII CONGRESS “CHILD HEALTH PLAN” - THE NEWBORN

The International Congresses “Child Health Plan”, started in autumn 1982 after a meeting with Prof. Ettore Rossi, at that time Chief of the Pediatric Clinic of the University of Berne, Prof. Giorgio Maggioni, Chief of the Puericultura Institute of the University of Rome, Prof. Gianni Bona, Chief of the Pediatric Clinic of the University of Novara and myself.

During these years the goal of the meetings was to promote constructive comparisons among medical science, technology and medical humanities, focusing on the child’s dignity, since the soul of Medicine, a noble Art, is in the medical/patient relationship.

In the past years the contribution of international authoritative researchers, coming from 28 different nations was determinant in the success of the meetings.

An old aphorism says that “only what becomes tradition has a value”. In this view, the 23rd Congress “Child Health Plan” is included in the prestigious Workshop of Cagliari with the help of renowned colleagues.

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NEW VACCINES AND NEW STRATEGIES IN VACCINATIONS

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Introduction

The remarkable successes achieved with the vaccinations have stimulated many investigators to point out a greater number of vaccines. Such measures control pathologies with remarkable impact on the public health. We here describe the advances on new vaccinations, antipneumocococcus, anti-meningococcus, antivaricella, and antirotavirus, and their potentiality to improving public health.

Antipneumococcal vaccine

Pneumococcus (PNC) is the most frequent agent causing bacteraemia. It can be responsible of the following disease: bacteraemic pneumonia, sepsis, arthritis, osteomyelitis and meningitis.

Important variations of the incidence are observed after the introduction of the conjugated eptavalent vac-
cine (PCV7). Before the employment of the eptavalent conjugated vaccine (PCV7) the total incidence of the invasive diseases from PNC, in the European pediatric population, ranged between 6.6/100,000 and 60/100,000 (1). In Italy recent studies have evidenced an incidence of invasive disease from PNC of 58.9/100,000 in < 3 years-old children and 50.4/100,000 in < 5 years-old children. In North America from the year 2000, a widespread vaccination of more susceptible populations was performed, in particular all the children of < 1 year-old and children until 5 years-old attending the community (asylum or maternal school) underwent vaccination. In New Italian Vaccine Plane of years 2005-2007, the anti-pneumococcocal vaccination have been included between those recommended.

The effectiveness of the vaccination, estimated on the invasive types, ranges between 56% and 80% in several studies. After 2-3 weeks from the vaccination children develop specific antibodies. The polysaccharide antigens are poor immunogenic in the 2-3 years-old children. In addition they do not induce subsequently an immunological memory. The conjugated eptavalent vaccine (PCV7) contains polysaccharides of the 7 stocks. Everyone is conjugated to a carrier represented by CRM-197, a modified difteric anatoxin. Furthermore this conjugation allows to activate the T cells. This determines a specific antibody production also in children of 2 months of age, an immunological memory of long duration and ability to give a fast booster effect with a new dose of vaccine. The protecting effectiveness in vaccinated children is 97.4%, and manifested protection in 85.7 % already in children who have only received 1 or 2 doses of vaccine (2). The regimen of three doses, at 3, 5 and 11-13 months of age, is commonly adopted in countries like Italy (3). The vaccine PCV7, administered at 2, 4, and 6 months with a 4th dose between 12 and 18 months, has reduced dramatically the invasive pathology. In children under the 5 years the reduction of invasive pathology was of 94% for the pathogens included in the vaccine, and of 75% for sierotypes not included in the vaccine (4).

The population immunity of children older then 5 year-old has determined, from 1998-99 to 2003, a reduction of the invasive disease of 62%, for the pathogen included in the vaccine (4). It was observed an increase of disease from sierotypes of PNC not included in the vaccine however. The advantages are obvious because the active balance of the cases has been in 2003 of 24.878 cases. Of these, 12.786 were children of less than children, while the others 12.092 have been the cases of older than 5 years and adults (4).

Some authors, from 1997 to June 2004, have evidenced a reduction of invasive pathology from PNC, in the first 90 days of life. This is because the vaccinated subjects (children), not being carriers of PNC in the pharinn, more difficulty are able to transmit such infection to (sibling) newborn (Table 1). Moreover it was observed a reduction of the number of the PNC resi-

stant to beta-lattamics and macrolids (more frequently employed antibiotics) because of there minor use of the antibiotic (5). In the attempt to widen the spectrum of action of the vaccine in the underdeveloped nations, it is under consideration a vaccine conjugated against a greater number of stocks, nine and eleven, that have demonstrated optimal preventive activity (Table 1). For these new vaccines it will be necessary further and deepened surveying in order to confirm the therapeutic action without adverse effects.

**Antimeningococcus vaccine**

The Meningococcus (Neisseria meningitidis) is a Gram negative bacterium (siero-groups A, B, C, Y, and W135) responsible of serious invasive meningococcal diseases (IMD) like meningitis and sepsis. In general population the number of healthy carriers of the bacterium is 10-25%. However the disease cases are limited. After 2-10 days of incubation, the subject involved develops a clinical evident disease. The symptomatology can evolve towards a disseminated intravascular coagulation, septic shock, insufficiency of organs, and fulminating septic purpura of Waterhouse-Frederiks. The subjects more frequently involved, 30% of the cases, are < 5 years-old but this pathology is frequent also between the 15-19 years children. In Italy the incidence of Meningococcus meningitis (group B and C, both responsible of all the cases of IMD disease) is less than 1/100,000 cases. Moreover a progressive increase of cases has been taken place from siero-groups C (in the year 2004 and 2005 of 57 % and 56% respectively) of cases of meningococcal meningitis.

From few years is available the conjugated vaccine against the meningococcus type C, which has a protecting action for a long time. With the exception of the old polysaccharide vaccines, the vaccine conjugated against the Meningococcus of type C is effective also under the 2 years of age because it stimulates the antibodies reply, and the memory of the immune system. Therefore it protects the subjects vaccinated for a long period of time (6). It is still experimental the vaccine against sierotype B, but within the next few years it could be available. The mass vaccination of children, adolescents and adults until the 24 years of age, performed in Great Britain from November 1999, had the magnitude to reduce the high number of cases of meningococcal disease of group C. Frequently the disease involves the children from 0 to 5 years, and the adolescents of the college from the 15 to the 19 years. England and later other countries such as Ireland, Spain, Nederland, Canada and Australia have adopted the mass vaccination against the disease from Meningococcus type C, for the protection of the groups at risk, namely children and the adolescents. In Italy, the new PNV of 2005-2007 included the vaccination against Meningococcus C in the scheduled new vaccination of infancy. The dosages indicates 2 doses plus 1 under the age 1 year already from the 2nd month of life and at least 2 months from the other vac-
cination (generally 3rd – 5th and 11th month - like recommended in the PNV) or one single dose after 1 year of age. In some regions the vaccine is offered to Pugh risk categories, that are children and adults with particular conditions of hymnuno deficit (asplenia, anatomical or functional, deficit of the complement), and all the newborns, and to children who attend community.

During the year 2006 no case of invasive disease from Meningococcus type C was observed in Tuscany. To the same time it has been showed a reduction of the total number of the invasive diseases from Meningococcus. Moreover recently, it has been confirmed the possibility to associate the vaccine anti-meningococcus of group C with the vaccine evaxalent scheduled in infancy. Vaccine MCV4 is today advised from the American Academy of Pediatrics (7). The vaccine administered in single dose for injective way seems to give a protection in 85% of the cases with duration of effectiveness of 7-8 years. The vaccine is recommended in adolescent with hymnuno-deficiency situations, for those who attend the university colleges, for the pilgrims, for travellers in countries at risk (8).

Antivariella vaccine

The varicella is an infective, exanetmatic, epidemic disease, very contagious with recurrence every 3-4 years, above all in winter and spring. It is caused by a DNA varicella-zoster virus (VZV), more frequently transmitted from direct contagious. In Italy, the varicella virus infect every year about 500,000 subjects, in prevalence during the paediatric age between 0 to 14 years of age, with a peak of incidence between 4 and 5 years of age (9).

The complications in the children are in 3-5% of all cases and in 10% of the subjects with specific pathology (immunodeficiencies, chronic pulmonary or cutaneous diseases, etc.) (10). The more serious complications are the interstitial acute pneumonia, the acute cerebellitis, with an incidence of 1:4,000, characterised by persistent ataxia for several weeks although the outcome is generally benign. The encephalitis is a rare and often fatal extremely severe complication (1:40,000). Other rare complications are the meningitis, the miielitis transversa, the syndrome of Guillain-Barré, and other types of neuritis, and the Reye syndrome. The VZV virus diffuses in all the organs and apparatus. The incidence of the varicella in pregnancy has been estimated in 1:1,000 pregnancy in United States and 2-3 cases every 1,000 pregnancy in United Kingdom. The risk of the infection of the fetus increases with the gestational age (11). Several studies have confirmed that, subsequently the maternal varicella infection, the risk of malformations is of 2%, with a greater risk between 13 and 20 weeks of gestation in comparison to the infection within first 13 weeks (2.4 % versus 0.4%) (11, 12). The maternal infection from varicella in perinatal age, between the 5 days before and 3-5 days after the delivery, determines a neonatal varicella in 20% of the neonates. The rate of mortality of the baby for the infection from varicella in this period of the life is 30% (11). In relation to the several complications reported a great number of hospitalizations are expected. In Italy in the last year 10 death related to varicella were reported (12).

In Sicily, a pharmaco economic evaluation of the cost for varicella infections in the year 2001 has suggested an estimated sanitary cost from 2,6 to 3,6 million of Euros. The estimation included the cost for the Acyclovir consumption. Studies carried out in Germany and USA has demonstrated that the vaccination against Varicella has a good costs/benefits balance. The vaccination introduced in the USA showed a reduction of the cases of varicella and the hospitalization that had exceeded 60% (13). In Italy, to obtain a drastic reduction of the disease, the vaccination should be done in all newborns. The vaccination should be made in limited times to cover almost 80% of infantile population till the 2nd year of life and the adolescents with negative history for the varicella at least to cover 50% of the 12 years old children.

The Italian Plan Vaccine (PNV) suggests to vaccinate, for the varicella, the subjects at high risk to contract or to transmit the infection, including the susceptible women in fertile age or adolescent and those with negative anamnestic history for varicella. Some Italian regions have suggested the free vaccination even the problem will probably resolved, on a national level, which the availability tetravalent vaccine for morbillo, parotitis, rubella and varicella (MMRV). In September 2005, the Food and Drug Administration (FDA) has authorised, after a survey, the commercialization of the tetravalent attenuated vaccine for morbillo, parotitis, rubella and varicella (MMRV) (ProQuad®, Merck & Co) for children aged between 12 months and 12 years. The Advisory Committee on Immunization Practices (ACIP) suggested the administration, at least of one month of interval, of two doses of the vaccine after the 1st year of age or at the 12 years (4).

Besides, in two groups of children of 12 - 23 months of age, were administered two doses of vaccine at 90 days of interval. The MMRV, administered in the first group, and the trivalent MMR plus the vaccine antivaricella Varivax, administered at the second group, were equally tolerated and determined similar high immunity reply (14). Since within short time it will be available the vaccine MPRV for without history of morbillo and varicella and never had been vaccinated for this disease. So it will be advised to administrate two doses of vaccine MPRV. Who had already received a dose of MPRV can use the first dose of the varicella vaccine MPRV and the second dose of the Varivax vaccine after at least one month later.

Anti Rotavirus vaccine

The Rotavirus is a DNA virus of the Reoviridae family. Three serological groups (A, B and C) may infect the humans. They are known like the main causes of
serious acute gastroenteritis, above all in the first infancy. Such pathogens, particularly the group A, may cause serious episodes of diarrhoea in infants and children during the winter and in areas with moderated climate. The period of incubation ranges from 1 to 3 days. Often the first symptom is vomit, followed by diarrhoea for 4-8 days. In some cases, the virus causes an isotonic dehydration with acidosis. From a meta-analysis of 124 studies in 52 different countries between 1973 and 2003, 4 sierotypes (G1P, G2P, G3P and G4P) are responsible in the children of 88.5% of the cases of diarrhoea in the world and more of 90% in Europe. The G4 sierotype is more common in Europe. In Europe every year the acute gastroenteritis from Rotavirus (R-AGE) causes 100,000 hospitalizations in paediatric age. Moreover every year 1 million of children need of specialised visits and rotavirus causes 385 deaths (15). The infection from rotavirus in the European children of less than 5 year-old is responsible, every year, of 3.6 million of episodes of gastroenteritis vists, 87,000 hospitalization, and 231 deaths (16). Therefore the disease remarkably affect on the sanitary costs in Europe. One recent survey has estimated the impact of the costs for patients of less than 4 years. In consideration that the children under the 36 months are near 1.6-1.8 million and that have 1.5-1.7 million episodes of enteritis every year the expensive is about 150-190 million of Euro. The 75% of the costs of such disease are due to the loss of the working time of the parents. Moreover the therapy, administered above all to the children of less than 36 month-old, is consistent for 47% in rehydration and/or probiotics, 26% in re-hydration solutions. 11% in antipyretics, and 11% in anti-emetic drug.

In order to prevent a severe disease, the vaccine anti-Rotavirus has been developed. Two types of oral vaccine have been commercialized, one in the USA and one in Europe, one monovalent and the other pentavalent, with an optimal effectiveness and safety profile. The effectiveness of these two vaccines is quantified in a reduction at least of 85% of the cases of serious disease from rotavirus. Furthermore there is a reduction of beyond 40% of the hospitalization for diarrhoea in South America, USA and Europe and, and a reduction of mortality rate in the developing countries if has been obtained a recombinant virus human-bovine (G1, G2, G3, G4, P1) (PRV) not pathogenic for the human but in degree of induction a high immunity reply. This vaccine employed in a multicentric double blind randomised and controlled international study with placebo on 70,301 children of Italy, Finland, Germany, Sweden, Belgium, Mexico, Guatemala, Costa Rica, Jamaica, Taiwan and United States. Only healthy children to which the dose of vaccine or placebo have was administered at an age ranges between 42 and 84 days. The second and the third dose have been administered at intervals of 4-10 weeks (Pediatric Academic Societies, Washington, 2005). Nobody of vaccinated children has showed serious side effects during the follow-up. Very rarely, the days immediately before the administration of the dose of vaccine/placebo has been showed side effects such as irritability, gaseous cholic, vomit, fever and alteration of the stools (17, 18, 19, 20). At term of the follow-up lasted 2 years the vaccinated children have showed a reduction rate of the hospitalization of 95.8% and the visits at the first aid of 93.4%. The investigation with the human-bovine vaccine (PRV) has showed a reduction in the demand for hospitalization and the sanitary requirement for infection determined gives from Rotavirus. Besides, it appears obvious that the vaccine finds maximal indication in the newborns beginning from the 6 weeks of life with the advantage that it can be administered contemporary with the normal should vaccination. Many authors believe that the vaccine PRV, easy administrable and without side effects, will have in brief time a wide diffusion for the several unsiness and costs that may avoid.

References
7. American Academy of Pediatrics Committee on Infectious Diseases. Recommended childhood

IV SESSION: Round table on malformations
Chairman: M. Silvetti
Moderators: I. Barberi, M. Puddu

INTEGRATED MANAGEMENT OF CHILDREN WITH MALFORMATIONS: THE EXAMPLE OF DOWN'S SYNDROME
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Down's syndrome remains, despite the spread of cytogenetic prenatal diagnosis for pregnancies at risk, the most frequent single cause of mental retardation. Pediatricians, and especially neonatologists, play an important role in the assistance to the newborn with DS, from a medical point of view, as well as a social and human ones. They have to inform parents about it and are involved in all the follow-up programs.

Epidemiology and pregnancy screening
The prevalence of Down's syndrome at birth has recently decreased in different socio-economical nations (from one in 700 to about one in 1000) (1). In Italy the evaluation of the rates of prevalence at birth has shown a progressive and meaningful decrement in time: from 14.4x10.000 born in the period 1978-1984, it has gone down to the 8.7 in the period 1993-1997 (2).

For a long time we have known that the risk of recurrence of Down syndrome increases in proportion to the increasing maternal age: from one in 1.650 in 20 year-old women, to one in 250 in those of 35 years old, one in 50 in women >45 years old). In the past few years in Italy there has been a progressive rise in the average age of conception: on the basis of ISTAT data we can observe an increase in the percentage of pregnant women over 35 years of age. If we submitted all these women to prenatal diagnosis, we could prevent the birth of only around 30% of patients_with Down syndrome (3); therefore, maternal age alone is not a good criteria to select the population at risk. We need of more sensitive and specific screening programs.

In the 1st. trimester of pregnancy the most effective screening test is the combined use of maternal serum screening with Plasma protein A (PAPP-A) and human chorionic gonadotropin (hCG) with fetal ultrasound testing to identify the thickening of the nuchal fold, that may have an 80-86% detection rate with 4-5% rate of false-positives 4. In the second trimester of pregnancy