Are pre-terms born timely and right immunized? Results of an Italian cohort study

Nicola Laforgia, Antonio Di Mauro, Francesco Paolo Bianchi, Federica Di Mauro, Andrea Zizzi, Manuela Capozza, Silvia Intini, Maria Serena Gallone, and Silvio Tafuri

Department of Biomedical Science and Human Oncology, “Aldo Moro” University of Bari, Bari, Italy

ABSTRACT
The aim of this study is to evaluate the vaccination coverage at 24 months of chronological age in a sample of preterm infants discharged by the Neonatal Intensive Care Unit (NICU) of the Bari Policlinico University General Hospital in Italy. The list of infants preterm born discharged during 2013 by the NICU was obtained by hospital database. Vaccination status of each subject at 24 months of chronological age was acquired by the Apulian Regional Vaccination Register (GIAVA). 159 preterm borns were enrolled in this study. 98.1% received the 1st dose of hexavalent vaccine and 98.7% the 1st dose of pneumococcal conjugate vaccine. The 8.8% of hexavalent vaccinations were performed during hospitalization. The percentage of immunized subjects decreased to 91.2% and 87.3% for the 2nd and 3rd dose of hexavalent vaccine and to 90.6% and 86.1% for the 2nd and 3rd dose of pneumococcal conjugate vaccine. Coverage for MMR, MNC and Varicella vaccines were, respectively 76.4%, 86.0% and 80.9%. Pre-terms received the vaccinations later than the age recommended by public health guidelines. Age at the immunization, for all vaccines, seems to increase for lower gestational age and birth weight and for higher length of hospitalization. This study shows a high risk of vaccine delay among pre-terms born. There is a strong need to improve specific vaccination strategies for this group. Neonatologists might play a key role in informing parents about the vaccination schedule at the moment of NICU discharge and during follow-up, also preparing correct time schedule.

Introduction
Preterm infants are at increased risk of infections also for vaccine preventable diseases; in this group, the incidence, the severity and the risk of complication is higher than among full term infants.1

Postnatal immune system maturation begins upon the exposure to environmental antigens without differences between preterm and full term infants; no difference in the immunogenicity of vaccines are reported between these two groups in previous studies.2 Timely and complete immunization of preterm infants is recommended by health authorities, throughout the world.3 Furthermore, the evaluation of the safety and the tolerability of vaccines among preterm new-borns have shown a global incidence of adverse events not different respect to full term babies.4

Public Health guidelines recommended for preterm infants the same vaccination schedule adopted for full term infants; in particular, the delay of vaccine administration is not indicated in case of low birth weight or low gestational age.5-6 Despite timeliness of immunization is essential to achieve the antibody production and to guarantee short- and long-term protection in the large majority of premature infants, several studies showed low vaccination coverage and frequent time delay in this subgroup.

Apulia is a Region of the South of Italy (around 4.000.000 of inhabitants); in Apulia, vaccination schedule for the first two years of life includes three doses of hexavalent vaccines (diphtheria, tetanus, pertussis, Haemophilus influenzae type b, hepatitis B, inactivated polio) at 61, 151 and 331 days of life, a dose of measles-mumps-rubella + varicella (12 months), three doses of conjugate pneumococcal vaccine (using the same schedule of hexavalent vaccine) and a dose of conjugate meningococcal C (12 months). These vaccines are offered free of charge to the entire population.

Recently, the results of the ACTION follow-up project, an Italian area-based prospective cohort study of a large sample of very preterm Italian infants from five Italian regions, have assessed immunization coverage and showed a significant delay of immunizations in Italian preterm, underlining the need of new strategies to increase immunization in this specific population.7

Since 2012, the Neonatal Intensive Care Unit of the Bari Policlinico University General Hospital (the major hospital in the South of Italy, around 1000 beds) has implemented a vaccination strategy for preterm infants through three interventions:

- all stable preterm infants still hospitalized at chronologic age >60 days received vaccinations according the Regional Immunization Schedule;

CONTACT Silvio Tafuri, MD, PhD silvio.tafuri@uniba.it Department of Biomedical Science and Human Oncology, “Aldo Moro” University of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy.
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• at hospital discharge, parents and family paediatricians are informed that, according to public health guidelines, pre-terms should receive the same routine immunization schedule as term new-borns, without any correction for gestational age;
• during outpatient follow-up, neonatologists informed parents about the safety and effectiveness of vaccines, to fight against anti-vaccination mis-informations, to reduce the parental immunization hesitancy and to increase immunization coverage.

This study is aimed to evaluate the coverage and time course of routine immunizations in a cohort of infants born preterm at 24 months of chronological age.

Results

174 preterm newborn discharged in 2013 were found in the hospital database; 3 were excluded because they died at chronologic age < 2 months. 12 newborns were excluded because their vaccination data were not available in the Apulian Regional Vaccination Register; 159 newborns were enrolled in the final analysis study.

At birth, average gestational age and weight of enrolled subjects were, respectively, 32.8 ± 3.2 weeks and 1,817.2 ± 566.2 g. The average chronological age at the hospital discharge was 34.3 ± 38.0 days of life (Table 1).

98.1% (n = 156/159) enrolled subjects received the 1st dose of hexavalent vaccine and 98.7% (n = 157/159) the 1st dose of pneumococcal conjugate vaccine. The 8.8% (n = 14/159) of preterms born received the first dose of hexavalent vaccine during hospitalization. The percentage of immunized subjects decreased to 91.2% (n = 145/159) and 87.3% (n = 138/158) for the 2nd and 3rd dose of hexavalent vaccine and to 90.6% (n = 144/159) and 86.1% (n = 136/158) for the 2nd and 3rd dose of pneumococcal conjugate vaccine, respectively.

The vaccination coverage for MMR, Men C and varicella vaccines were, respectively, 86.0% (n = 135/157), 76.4% (n = 120/157) and 80.9% (n = 127/157).

Overall, vaccination coverage is similar to data of Apulian general population (2012-2014 cohort). A significantly higher coverage is observed in pre-term babies for the 1st dose of hexavalent vaccine (98.1% vs 93.2%; z = 2.5; p<0.05) and for 1st dose of pneumococcal conjugate vaccine (98.7% vs. 92.5%; z = 3.0; p = 0.05; Table 2).

In vaccinated preterm babies, the average age of immunization was higher than the recommended timeline (p < 0.05; Table 3).

Time between the 1st and the 2nd dose and the 3rd and 2nd dose of the hexavalent and pneumococcal conjugate vaccine is significantly higher in the study sample compared to recommended schedule (p <0.05, Table 2).

The correlation coefficient for ranks of Pearson highlights a statistically significant correlation for:
• Age at 3rd dose of hexavalent vaccine and birth weight (rho = −0.2; p = 0.021) and gestational age at birth (rho = −0.3; p = 0.006), age at NICU discharge (rho = 0.3; p = 0.003).
• Age at 3rd dose of pneumococcal conjugate vaccine and birth weight (rho = −0.2; p = 0.038) and gestational age at birth (rho = −0.3; p = 0.001), age at NICU discharge (rho = 0.2; p = 0.007).
• Age at 1st dose of MMR and gestational age at birth (rho = −0.2; p = 0.010).
• Age at 1st dose of anti-varicella and gestational age at birth (rho = −0.3; p = 0.003), age at NICU discharge at limits of statistical significance; rho = 0.2; p = 0.054).

No statistically significant association between outcomes and determinants resulted from multivariate logistic regression model (p>0.05).

Discussion

Our data, including an high quality population-based surveillance system and low “lost at follow-up” (12.7%), shows that, at 24 months of chronological age, vaccination coverage in patients born preterm, discharged by a NICU, is similar to that observed in full term babies.

This result is unexpected because vaccination hesitancy is a well-known phenomenon in children with underlying health problems and another Italian study documented inadequate coverage rate in children affected by chronic diseases. Probably, our vaccination strategy for preterm born infants is consistent with the purpose of overcoming parental immunization hesitancy.

Infact, the most important reasons for immunization refuse or delay are parents’ and paediatricians’ concerns about efficacy and safety of active vaccination in preterm infants, despite the benefits of vaccination are clearly demonstrated and our strategy seems able to increase the compliance of parents to vaccination offer.

Despite the efforts carried out in Apulia to increase immunization coverage, critical coverage for childhood vaccination are vanishing for all preventable disease as shown in Table 2.

The vaccination coverage in our cohort for the 1st dose of hexavalent and pneumococcal conjugate vaccine is higher compared to general population and this picture seems to confirm the importance to guarantee the vaccination offer during hospitalization.

Table 1. Demographical characteristics of children enrolled (n = 159), per gender.

| Characteristics                      | Males (n = 100)                | Females (n = 59)               | Total (n = 159) | test | p  |
|--------------------------------------|--------------------------------|--------------------------------|-----------------|------|----|
| Birth weight, grams                  | 1,867.3±577.4 (720.0–3,280.0) | 1,732.3±541.1 (650.0–2,920.0) | 1,817.2±566.2 (650.0–3,280.0) | t = 1.5 | 0.147 |
| Gestational age at birth, weeks      | 32.9±3.3 (21.3–40.7)          | 32.7±3.0 (21.3–39.1)          | 32.8±3.2 (21.3–40.7) | t = 0.4 | 0.714 |
| Chronological age at NICU discharge, days | 33.3±36.3 (3.0–165.0)       | 36.0±41.0 (2.0–194.0)        | 34.8±39.3 (2.0–194.0) | z = 0.2 | 0.814 |
Immunization coverage in our sample is also higher compared than data from ACTION follow-up project (e.g., percentages of preterm babies who received the first dose of hexavalent vaccine and of PCV in ACTION were 95.9% and 49.7% respectively), probably because, in Regions participating in this project, administration of vaccines in hospital during admission was quite rare.7

Despite the higher percentage for the first dose of hexavalent vaccine, no differences were found in coverage for full schedule between our sample and Apulian general population. Furthermore, coverage resulted little lower than ACTION follow-up project (94.2%). For the first dose of MMR, immunization rates were similar between children born preterm and Apulian population (76.4% vs. 78.7%), and lower respect ACTION follow-up project (84%). According to this picture, we can observe that the premature babies, once cared by territorial structures, are treated as children born at term and this is not a right approach, considering that preterms are an “high risk group” and need particular attentions after hospital discharge.

Our result showed higher immunization rates for MenC and Varicella vaccines respect data from the ACTION follow-up project (respectively 38.5 and 4.1%) while coverage were similar in Apulian general population and in children born preterm.

The great difference in coverage for pneumococcal conjugate, conjugate meningococcal C and varicella vaccines between our cohort and ACTION follow-up project, was due to different immunization policies between Apulia and other Italian Regions. In Apulia, universal mass vaccination (UMV) for PCV, MMR, Varicella started since 2005, while UMV in all Italian Regions was established in 2010.13,14

Regarding the average age at immunization, the first dose administered during hospitalization is often delayed for the need of starting immunization when the newborn baby is clinically stable. Moreover, for other doses, pediatrics and public health physicians attitudes might have had substantial negative effects on time course of routine immunization, because of insufficient knowledge of indications in preterm newborns, i.e. the “dilemma” of considering corrected or not-corrected age. This is considered one of the main reason leading the parents of high-risk children to delay or miss vaccination.15

According to other authors, the delay in vaccination was more pronounced in infants with lower birth-weight or lower gestational age, despite current guidelines, which advise following the same vaccination schedule used in term infants.16

Newborns who have experienced prolonged hospital stay (that may be seen as an indirect measure of morbidity) were significantly more likely to have immunization delayed. Parents of these children probably need intensive education and outpatient medical support to improve correct routine immunizations.

Since data from different study indicate that extremely preterm and low-birth-weight new-borns have higher rates of illnesses and death from vaccine-preventable disease,17,18 delayed immunization in these high-risk categories could be really dangerous.19

However, although our interventions, vaccination coverage investigated is still inadequate and paradoxically significantly more worrying in this population at high-risk of infectious disease-related complications.20

Not only family paediatricians play a central role in educating parents on safety and effectiveness of the vaccines, but also neonatologists can influence the compliance to immunization by answering parents’ questions and addressing common misconceptions. The objective of higher adhesion and correct time course of vaccinations in preterm new-borns is very important in our Region, also because of the decreasing trend of coverage in the general population.

Although the cohort population was quite small due to the mono-centric study design and the findings in terms of coverage may not be generalized, the results of our study highlight how specific educational programs aimed at pediatricians and parents could increase immunization coverage among preterm infants.

One of the most important limitations of our study is the impossibility to analyze from the Apulian Regional Vaccination Register data about the average age at vaccination of general population and, in particular, of children from birth cohort considered

### Table 3. Average age at vaccine administration in preterm borns

| Vaccine | Mean±s of age of immunization (days) | Recommended age (days) | t | p |
|---------|-----------------------------------|------------------------|---|---|
| DTaP-IPV-HBV-Hib 1 dose | 1180 ± 85.1 | 61.0 | 8.4 | 0.000 |
| DTaP-IPV-HBV-Hib 1 dose after NICU discharge | 1240 ± 93.1 | 61.0 | 8.1 | 0.000 |
| DTaP-IPV-HBV-Hib 1 dose during hospitalization | 96.1 ± 17.7 | 61.0 | 7.4 | 0.000 |
| DTaP-IPV-HBV-Hib 2 doses | 195.0 ± 94.0 | 121.0 | 9.5 | 0.000 |
| DTaP-IPV-HBV-Hib 3 doses | 426.0 ± 136.9 | 336.0 | 7.7 | 0.000 |
| PCV 1 dose | 1230 ± 92.1 | 61.0 | 8.4 | 0.000 |
| PCV 2 doses | 196.0 ± 94.3 | 121.0 | 9.5 | 0.000 |
| PCV 3 doses | 423.0 ± 131.7 | 336.0 | 7.7 | 0.000 |
| MMR | 617.0 ± 202.8 | 366.0 | 10.3 | 0.000 |
| Men C | 550.0 ± 239.7 | 366.0 | 8.9 | 0.000 |
| Varicella | 540.0 ± 207.0 | 366.0 | 9.5 | 0.000 |
(2012-2014). Then, it is impossible to understand whether the vaccination delay is due to a mismanagement of the born preterm, or is a common phenomenon in the Apulian infant population, due to structural and organizational problems of the vaccination system. In the future, it would be desirable to repeat the study by expanding the sample and the birth cohorts considered and comparing the average age of vaccination per cohort.

Another limitation is related to the composition of control group, in which three cohorts have been considered. In fact, coverage in each cohort could be different (even if differences registered are small) for many reason (e.g. communication campaigns against vaccination carried out in a particular period, the notice of an adverse events following vaccination, etc) and in general, in recent years a negative trend in vaccination campaigns against vaccination carried out in a particular period, the notice of an adverse events following vaccination, etc) and in general, in recent years a negative trend in vaccination compliance has been noted and average coverage could change in three years.21

Educational interventions and analyses of causes of vaccine hesitancy should be implemented in order to improve vaccination rates and guarantee right immunization timing in this high risk population.22

Neonatologists might play a key role starting immunization during hospitalization, informing parents about the vaccination schedule and their advantages at NICU discharge, checking correct time schedule and appropriately informing pediatricians during outpatient follow-up. These easy, inexpensive and reproducible methods might increase vaccination coverage.

### Methods

This is a cross-sectional study.

The list of infants born preterm discharged by the Neonatal Intensive Care Unit of the Bari Policlinico University General Hospital in 2013 was obtained by hospital database.

For each subject enrolled, gestational age at birth (time between conception and birth), birth weight, chronological age (numbers of days/weeks/months/years of life, that is equal to the time of hospitalization) and weight at NICU discharge, as well as times-of vaccinations were registered in a standardized form.

Vaccination status of each subject was obtained through the Apulian Regional Vaccination Register (GIAVA).

Coverage and time of immunizations of preterm infants, at 24 months of chronological age, were compared with Apulian population (2012-2014 cohort) coverage acquired from GIAVA. Data were included in a database carried out by Ms Excel software and analyzed by STATA MP12 software.

Continuous variables were expressed as mean ± standard deviation and median; categorical variables were expressed as proportions. Z-score test was used to compare proportion and t student test and Wilcoxon rank-sum test to compare continuous variables.

Correlation coefficient for ranks of Spearman was used to analyze the correlation between each of these outcomes:

- age at administration of the 3th dose of exxahavalent vaccine
- age at administration of the 3rd dose of anti-pneumococcal
- age at administration of the 1st dose of MMR
- age at administration of the 1st dose of anti-varicella
- age at administration of the first dose of meningococcal C and these determinants: weight at birth, gestational age at birth, chronological age at hospital discharge.

Multivariate logistic regression models were used to analyze the relationship between each of these outcomes:

- receiving a full-cycle of hexahavalent vaccine (YES/NO)
- receiving a full-cycle of anti-pneumococcal vaccine (YES/NO)
- MMR vaccination (YES/NO)
- anti-varicella vaccination (YES/NO)
- anti-meningococcal C vaccination (YES/NO)

and these determinants: gender, birth weight, gestational age at birth, chronological age at hospital discharge. Adjusted odds ratio (aOR) with CI 95% and z-score test were calculated. A p < 0.05 was considered as significant for all tests.

### Abbreviations

GIAVA  | Apulian Regional Vaccination Register
Men C  | Vaccine against meningococcal serotype C
MMR   | vaccine against measles, mumps and rubella
NICU  | Neonatal Intensive Care Unit
PCV   | Pneumococcal conjugate vaccine
UMV   | universal mass vaccination

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| Variables | Mean ± SD (days) | Gold standard (days) | t  | p   |
|-----------|-----------------|----------------------|----|-----|
| Time between hexavalent 2nd dose – hexavalent 1st dose | 84.4 ± 70.1 | 60.0 | 4.2 | 0.000 |
| Time between hexavalent 3rd dose – hexavalent 2nd dose | 236.0 ± 90.3 | 215.0 | 2.7 | 0.007 |
| Time between anti-pneumococcal 2nd dose – anti-pneumococcal 1st dose | 84.0 ± 69.4 | 60.0 | 4.1 | 0.000 |
| Time between anti-pneumococcal 3rd dose – anti-pneumococcal 2nd dose | 231.9 ± 85.4 | 215.0 | 2.3 | 0.023 |

Table 4. Time intervals between 1st / 2nd dose and 3rd / 2nd dose of hexavalent and anti-pneumococcal vaccine and the gold standard intervals.
N. Laforgia ET AL.

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