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Post-marketing surveillance study of the DTaP2-IPV-HB-Hib (Hexyon) vaccine administered in preterm infants in the Apulia region, Italy, in 2017

Domenico Martinelli, Francesca Fortunato, Giulia Del Matto, Giuseppina Iannelli, Rosa Prato *

Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy
Department of Hygiene, Policlinico Riuniti di Foggia, Foggia, Italy

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ABSTRACT

Recommendations in many countries state that preterm infants (PTIs) should receive the same routine immunization schedule and timing as for full-term births, according to their chronological age. Data regarding hexavalent vaccine safety in PTIs are still limited. We conducted a post-marketing surveillance study of the DTaP2-IPV-HB-Hib vaccine administered to PTIs in Apulia region, Italy.

We identified PTIs by selecting the hospital discharge records of infants born between January and June 2017 using the DRG and ICD-9-CM codes for preterm birth, and we matched these data with records included in the regional immunization registry. We analyzed coverage and timeliness of vaccination. To investigate adverse events (AEs) after the first dose, we interviewed via phone the parents of PTIs vaccinated with at least one dose of the DTaP2-IPV-HB-Hib vaccine.

At the time of our analysis (31.12.2017), 866/936 (92.5%) PTIs received the first dose of hexavalent vaccine and 539/936 (57.6%) were vaccinated by the third month of age, as recommended; 700/866 (80.8%) received the DTaP2-IPV-HB-Hib vaccine. The parents of 339 PTIs vaccinated with the DTaP2-IPV-HB-Hib vaccine reported local pain as the most common reaction (35.7% of the children). Erythema, swelling, induration and nodule were also reported in about 25% of the children. Systemic adverse events were generally rarer than local reactions. No serious AEs were reported.

Our findings showed that more than 40% of PTIs received delayed hexavalent vaccination. This study showed a reassuring safety profile of the vaccine in the preterm population and may be considered as a pilot for further real-world studies.

1. Introduction

The World Health Organization (WHO) defines "preterm birth" as birth before the completion of 37 weeks of gestation. An estimated 15 million babies worldwide are born preterm every year [1].

Preterm birth is the leading cause of death among children under 5 years of age and can aggravate other conditions or cause long-term negative consequences, including cerebral palsy, cognitive disabilities, visual and hearing problems, respiratory illnesses [2]. Preterm infants (PTIs) compared to term-born children are at increased risk of infections during the first months of life, they may also suffer from more frequent and more severe consequences of infectious diseases [3–4]. Vaccines are effective interventions to prevent various infectious diseases in children; evidence suggests that the timeliness of immunization is crucial to achieve the highest probability of prevention [5]. Although PTIs are recommended to receive immunizations according to their chronological age, they may not be receiving their vaccines in a timely manner [6]. The most important reasons for immunization delay are parents' and paediatricians' concerns about efficacy and safety of vaccination in preterms [7], despite the benefits of this preventive intervention are clearly demonstrated.

Numerous studies have already demonstrated that PTIs are able to respond appropriately to vaccines. Rechavi et al. (2015) showed that the development of the immune system in the fetus is already complete for the T-cell component and immunoglobulins starting from the 26th week of gestation, therefore, PTIs can be considered mature with regard to the immune system in response to vaccination [8].

* Corresponding author at: Dipartimento di Scienze Mediche e Chirurgiche, Università degli Studi di Foggia, Ospedale "Colonnello D'Avanzo", Policlinico Riuniti di Foggia, Viale degli Aviatori, 2, 71122 Foggia, Italy.
E-mail address: rosa.prato@unifg.it (R. Prato).

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Both monovalent and combined pediatric vaccines have already been studied in PTIs in terms of safety and immunogenicity. These studies demonstrated that vaccinations are safe and immunogenic in PTIs and that timely vaccination (full schedules completed without delaying) in PTIs confers similar protective immunization, as the one observed for term births [7,9–11]. As a result of these evidences, numerous scientific societies now recommend using the same schedule and timing as for full-term births for routine vaccination in PTIs [12].

Hexavalent combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus, *Haemophilus influenzae* type b conjugate vaccines demonstrated safety, immunogenicity and effectiveness in both clinical trials and real-world evidence studies [13]. Furthermore, clinical trials and phase IV surveillance studies of hexavalents have demonstrated good tolerability in term-born infants [14–15], nevertheless specific data regarding PTIs are still limited, particularly with the 2 + 1 schedule [16].

In Italy, universal vaccination with hexavalent vaccine is actively offered to children from the third month of life; a 2017 law made ten vaccines compulsory for all children aged 0–16 years (antigens contained in the hexavalent vaccine plus measles, mumps, rubella and varicella) [17]. The national regulatory agency has given market authorization to three different combination vaccines [13,18–20]. The "Summary of Products Characteristics" (SmPC) of each of the different vaccines does not give any distinction between term-born and pre-term infants and their use is equally recommended within the National Immunization Plan [21]. A recent study explored the effectiveness of hexavalent vaccine for protection against Hib in PTIs, however the study did not explore safety aspects [22].

The absence of the specific indication of safety of use of hexavalent vaccine in the PTIs, as reported in the SmPC, does not imply a contraindication of use [13]; nevertheless, we think this absence could be one of the causes of the delay in vaccination we often observe in PTIs.

We decided to investigate the safety and timeliness of vaccination in PTIs through a post-marketing surveillance study. The study was conducted in the Apulia region of the southern part of Italy and focused on the use of the Hexyon vaccine (registered in other countries as Hexaxim or Hexacima) administered to PTIs who were born within the period January-June 2017.

2. Methods

We identified children born preterm in the Apulia Region in the period 1 January to 30 June 2017, and we matched these data with records included in the regional immunization registry up to 31 December 2017. We analyzed coverage and timeliness of vaccination. With a survey we investigated the insurgence of adverse events after the first administration of the vaccine.

2.1. Data sources

2.1.1. Identification of preterm population

We identified children born in Apulia in the period 1 January to 30 June 2017 by examining the Hospital Discharge Records (HDRs) of the hospitals of the Region. We identified every child with the date of admission to the hospital equal to the date of birth. We selected the preterm infants by identifying in the HDRs the "International Classification of Diseases, 9th Revision, Clinical Modification" (ICD-9-CM) codes for preterm birth and also the Diagnosis Related Groups (DRGs) codes used by hospitals.

We selected hospital discharges on the basis of the following DRGs for neonatal care:

- Extreme immaturity or respiratory distress syndrome (386)
- Prematurity with a major problem (387)
- Prematurity with no major problem (388).

The ICD-9-CM codes for preterm birth, as indicated in primary or secondary diagnoses, were:

- Extreme immaturity (765.0×)
- Other preterm infants (765.1×)
- From 24 to 35–36 completed weeks of gestation (765.23 to 765.28).

We excluded children that had less than 24 completed weeks of gestation or 24 weeks of completed gestation (ICD-9-CM codes 765.21 and 765.22).

Data were then cleaned to remove multiple hospital admissions for the same child over the same period of time, in order to identify every child only once.

2.1.2. Data on vaccination

Data regarding every vaccine administered in the Region derive from the regional Immunization Information System. Using a unique personal identification number as identifier we linked the list of PTIs with the individual immunization records updated to 31 December 2017.

2.1.3. Data on adverse events

In the period 1 March to 30 June 2018, we interviewed the parents of PTIs vaccinated with at least one dose of Hexyon hexavalent vaccine from 1 January to 31 December 2017. The survey consisted in a structured phone interview, investigating the onset of adverse events (AEs) after the first administration of the vaccine.

The questionnaire collected information regarding: i. Demographics and mothers' behaviours (age at delivery, smoking, alcohol use); ii. Pregnancy and delivery (first baby – yes/no, at least one complication of pregnancy and childbirth, caesarean section); iii. Newborns' health status at birth (jaundice, O_2 desaturation, apneas, respiratory failure, bradycardia, sepsis, other conditions); iv. Breastfeeding (yes/no, duration); v. Infants' health status before vaccination; vi. Local adverse events; vii. Systemic adverse events; viii. Serious adverse events.

The frequency of adverse events with 95% confidence intervals (95% CI) was calculated and compared to the frequencies reported for term-born infants in the SmPC of Hexyon [19].

The study was conducted according to the principles expressed in the Declaration of Helsinki.

2.2. Ethics approval

The study protocol was approved by the Institutional Review Board at the Apulian Regional Observatory for Epidemiology (PROT:19/OER/2017 October 20, 2017). Informed consent was obtained from all participant parents prior to enrolment in the study.

2.3. Statistical analysis

Univariate and multivariate logistic regression analyses were performed to evaluate whether mothers' demographic characteristics, pregnancy status, type of delivery, complications of pregnancy and childbirth, infants' health status after birth and before vaccination were independently associated with reporting vaccination adverse events.

All statistical analyses were performed using the software package STATA version 15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

3. Results

3.1. Preterm vaccination

We identified 1035 hospital discharges with a diagnosis related to pre-term birth in the considered period (1 January to 30 June 2017) in Apulia. After removing multiple hospitalizations as duplicates, 936 PTIs were identified, 53.6% (n = 502) males and 46.4% (n = 434) females, with 2,341.10 g mean weight at birth (SD: 563.7).

At the time of our analysis (31 December 2017), 866 out of 936 (92.5%) PTIs received the first dose of hexavalent vaccine and 539 out of 936 (57.6%) were vaccinated by the third month of age, as recommended. Out of the 866 vaccinated infants, 700 (80.8%) received Hexyon.

3.2. Survey on adverse events

We interviewed the parents of 339 PTIs vaccinated with Hexyon which represented 48.4% of the entire cohort. The majority (n = 332, 97.98%) of the children vaccinated with Hexyon were co-administered with pneumococcal vaccine (PCV13) in the same session; 72.6% (n = 246) of these children were also administered anti-rotavirus in the same session (data based on verified vaccine information).

As for the infants, 86.7% (n = 294) were born between the 32th–38th gestational week (moderate to late preterm), 13% (n = 44) between the 28th–32th gestational week (very preterm) and 0.3% (n = 1) before the 28th week (extremely preterm).

The mothers' mean age at delivery was 33.5 years (SD: 5.5; range: 17–47). Information on demographics and mothers' behaviours, pregnancy and delivery, infants' health status at birth and before vaccination are shown in Table 1.

The adverse events at the injection site after the first dose were generally reported quite commonly (Table 2). The most common reaction was local pain, reported in 121 children (35.7%; 95% CI: 30.7–41%). Other local reactions (erythema, swelling, induration and nodule) were also reported in about 25% of the children. Systemic adverse events were generally rarer than local reactions. Irritability, fever and somnolence were the only reactions that were reported in more than 15% of the children, with proportions affecting from 1 over 6 children (somnolence, 55 cases, 16.2%) to 1 over 4 (irritability, n = 93, 27.4%). Infants experimenting fever (n = 76; 22.4%) were treated with paracetamol and recovered without consequences. Other systemic adverse events were rarer: loss of appetite was reported in less than 10% of children (n = 30; 8.8%), while other reactions concerned 10 children. One child, with a personal history of apnea, experimented an episode 3–4 h after vaccination, without any consequences.

There were no reports of immune system disorders, convulsive disorders, hypotonia, hypotonic reactions or hypotonic-hyporesponsive episodes, extensive limb swelling.

3.2.1. Comparison of frequency of adverse events

Table 2 shows the frequency of adverse events as reported in the SmPC of Hexyon. For local adverse reactions, compared to the frequency of events reported in the SmPC for term-born children, in our preterm population the injection site induration and nodule were reported more frequently. The other reactions were equally frequent compared to the term-born population. Among the systemic adverse reactions, most adverse events had a similar frequency in our sample compared to the term-born infants. We had no report of vomiting, which is considered "very common" (more than 1 event for 10 children) for term-born children. The cutaneous rash was instead more frequent in our sample. We collected 2 reported events of cutaneous rash (0.6%), while the reaction is considered "rare" with frequency of less than one case for 1000 for term-born children.

Reporting at least one complication of pregnancy and childbirth, caesarean section, presence of newborn jaundice, and breastfeeding was independently associated with reporting at least one adverse event following vaccination (Table 3).

Table 1
Information on demographics and mothers' behaviours, pregnancy and childbirth, infants' health status at birth and before vaccination reported for 339 PTIs vaccinated with Hexyon.

Demographics and mothers' behaviours	Number	Frequency (%)	95% CI
Mothers' age at delivery (mean ± SD)	33.5 ± 5.5		32.9–34.1
Smoking	12	3.5	5.3–18.7
Alcohol use	3	0.9	−0.4–6.4
Pregnancy and delivery			
First baby (Yes)	193	56.9	175.1–210.9
At least one complication of pregnancy and childbirth*	99	29.2	82.5–115.5
Caesarean section	239	70.5	222.4–255.5
Newborns' health status at birth			
Jaundice	115	33.9	97.8–132.2
O_2 desaturation	59	17.4	45.2–72.7
Apneas	34	10.0	23.1–44.9
Respiratory failure	19	5.6	10.7–27.3
Bradycardia	2	0.6	−0.8–4.7
Sepsis	2	0.6	0.8–4.7
Other conditions**	15	4.4	0.8–4.7
Breastfeeding			
Yes	209	61.7	191.4–226.6
Breastfeeding duration (weeks; mean ± SD)	20.9 ± 21.4		18.1–23.9
Infants' health status before vaccination			
Use of immunosuppressive drugs***	7	2.1	1.8–12.1

* Twenty-three mothers reported gestational diabetes, twenty-one gestosis, nineteen gestational hypertension, nine placental disorders, four preeclampsia, amniotic fluid abnormalities and cholestasis of pregnancy, three iron deficiency anemia, two renal colic, urinary tract infection, deep vein thrombosis, thrombocytopenia, hyperemesis gravidarum, one HELLP syndrome and cytomegalovirus infection.

** Five newborns had gastrointestinal disorders, three cardiovascular disease, three metabolic disorders, two cerebrovascular disease, one thrombocytopenia, one thermal stress, one necrotizing enterocolitis, one bronchopulmonary dysplasia, one retinopathy of prematurity (ROP).

*** Steroids.

4. Discussion

The present post-marketing surveillance study aimed at investigating the timeliness and safety of the hexavalent vaccine Hexyon in a population of preterm infants. The safety and efficacy of monovalent and combined vaccines for PTIs have already been reported [7,9–11]. Moreover, no contraindications of the use in PTIs of any of the three available hexavalent vaccines are reported in the SmPC [18–20]. Nevertheless, real-world data about safety of

Table 2
Adverse events frequency, as reported by the parents of preterm infants (n = 339) after the first dose of Hexyon vaccination. Comparison to the frequency of adverse events for term-born infants registered in the SmPC.

Local adverse events	Adverse events frequency in preterm infants (n = 339) (A)			Adverse events frequency in term-born infants (B)	A *vs* B
	Number	%	95% CI		
Injection site pain	121	*35.7%*	30.7–41.0%	Very common (≥1/10)	=
Injection site redness	92	*27.1%*	22.6–32.1%	Very common (≥1/10)	=
Injection site swelling	90	*26.5%*	22.1–31.5%	Very common (≥1/10)	=
Injection site induration	84	*24.8%*	20.3–29.7%	Common (≥1/100; <1/10)	>
Injection site nodule	87	*25.7%*	21.1–30.7%	Not common (≥1/1,000; <1/100)	>
Systemic adverse events					
Irritability	93	*27.4%*	22.9–32.4%	Very common (≥1/10)	=
Somnolence	55	*16.2%*	12.5–20.6%	Very common (≥1/10)	=
Loss of appetite	30	*8.8%*	6.1–12.4%	Very common (≥1/10)	<
Vomiting events	0			Very common (≥1/10)	<
Diarrhea	7	*2.1%*	0.8–4.2%	Common (≥1/100; <1/10)	=
Fever (≥38 °C)	76	*22.4%*	18.3–27.2%	Very common (≥1/10)	=
Persistent crying (>3 h)	1	*0.3%*	0.01–1.6%	Common (≥1/100; <1/10)	<
Cutaneous rash	2	*0.6%*	0.1–2.1%	Rare (≥1/10,000; <1/1,000)	>
Serious adverse events	0				

Table 3
Univariate and multivariate analyses of factors associated with adverse events, as reported by the parents of preterm infants (n = 339) after the first dose of Hexyon vaccination.

	AEs (n = 231)		No AEs (n = 108)		Univariate analysis			Multivariate analysis	
	Number	%	Number	%	Odds Ratio (95% CI)	χ^2	p	Odds Ratio (95% CI)	P
Demographics and mothers' behaviours									
Mothers' age at delivery (mean ± SD)	33.5 ± 32.8		33.4 ± 32.4				0.4151		
Smoking	9	3.9	3	2.8	1.4 (0.3–8.3)	0.3	0.6036		
Alcohol use	2	0.9	1	0.9	0.9 (0.05–55.6)	0	0.9561		
Pregnancy and delivery									
First baby (Yes)	130	56.3	63	58.3	0.9 (0.6–1.5)	0.2	0.6531		
At least one complication of pregnancy and childbirth*	79	34.2	20	18.5	2.3 (1.3–4.2)	8.7	0.0031	2.2 (1.2–3.9)	0.008
Caesarean section	173	74.9	66	61.1	1.9 (1.1–3.2)	6.7	0.0095	2.1 (1.2–3.5)	0.008
Newborns' health status at birth									
Jaundice	88	38.1	27	25.0	1.8 (1.1–3.2)	5.6	0.0177	2.1 (1.2–3.6)	0.009
O_2 desaturation	40	17.3	19	17.6	0.9 (0.5–1.9)	0	0.9501		
Apneas	27	11.7	7	6.5	1.9 (0.8–5.4)	2.2	0.1370		
Respiratory failure	14	6.1	5	4.6	1.3 (0.4–4.8)	0.3	0.5935		
Bradycardia	1	0.4	1	0.9	0.5 (0.006–36.8)	0.3	0.5808		
Sepsis	1	0.4	1	0.9	0.5 (0.006–36.8)	0.3	0.5808		
Other conditions**	12	5.2	3	2.8	1.9 (0.5–10.8)	1.0	0.3133		
Breastfeeding									
Yes	156	67.5	53	49.1	2.1 (1.3–3.5)	10.0	0.0015	2.2 (1.4–3.7)	0.001
Breastfeeding duration (weeks; mean ± SD)	21.9 ± 21.6		18.1 ± 20.7				0.1350		
Infants' health status before vaccination									
Use of immunosuppressive drugs***	6	2.6	1	0.9	2.8 (0.3–131.2)	1.0	0.3180		

* Twenty-three mothers reported gestational diabetes, twenty-one gestosis, nineteen gestational hypertension, nine placental disorders, four preeclampsia, amniotic fluid abnormalities and cholestasis of pregnancy, three iron deficiency anemia, two renal colic, urinary tract infection, deep vein thrombosis, thrombocytopenia, hyperemesis gravidarum, one HELLP syndrome and cytomegalovirus infection.

** Five newborns had gastrointestinal disorders, three cardiovascular disease, three metabolic disorders, two cerebrovascular disease, one thrombocytopenia, one thermal stress, one necrotizing enterocolitis, one bronchopulmonary dysplasia, one retinopathy of prematurity (ROP).

*** Steroids.

hexavalent vaccines in PTIs are scarce and this affects the adoption of timelines vaccination in this population.

Our results confirm that vaccination is delayed in the PTIs. In our sample, more than 40% of the population received a delayed vaccination, with the first dose of the hexavalent vaccine received after the third month of age. This proportion is slightly higher than that reported in a large prospective cohort study of very preterm infants, in which immunization start by the third month of age occurred in 67% of children for the hexavalent vaccine [23].

Our results regarding safety show that frequency of different adverse reactions in our sample is quite similar compared to the term-born population presented in the SmPC; in particular, as for the local adverse events, results were comparable for "injection site pain", "injection site redness" and "injection site swelling". These reactions, which are very commonly observed in vaccination and are usually more frequent after the first dose, spontaneously recovered within 24 h. Differently, the "injection site induration" and "injection site nodule" were reported more frequently than expected on the basis of the SmPC. It is remarkable that the "injection site nodule" is reported as "not common", while in our population this event was observed in more than one quarter of children. We cannot exclude the possibility that this finding can be attributable to many reasons, including self-reporting of the events by the parents.

As for the systemic adverse events, we observed equal frequencies compared to those among term-born infants, except for the "cutaneous rash" that in SmPC is reported as rare (≥1/10,000, <1/1,000) and in our study appeared in the 0.6% (n = 2) of the PTIs.

Interestingly, no vomiting events were observed in our population, while they are described as "very common" in the SmPC. It is important to underline that no serious adverse events were reported in the considered population.

We observed one episode of longer gaps than normal between breaths, 3–4 h after the hexavalent vaccination co-administered with pneumococcal vaccine (PCV13), in an infant with personal history of apnea. This event resolved spontaneously without consequences. The adverse event is described in the SmPC of Hexyon [19] as a side effect in babies born very prematurely (at or before 28 weeks of gestation) that can occur for 2–3 days after vaccination. It was not possible to ascertain if this episode was strictly related to hexavalent vaccination due to unavailability of clear information and essential clinical details. However, according to WHO recommendations, at the individual level it is not always possible to establish a definite causal relationship on the basis of a single adverse event case report [24].

In Italy, the post-marketing surveillance on vaccines is summarized in annual reports from the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA). The report assembles the suspected adverse events of vaccines collected through the National Pharmacovigilance Network. These reports do not usually differentiate the PTIs population from the term-born population [25].

The report regarding hexavalent vaccines collects data regarding the three different vaccines present on Italian market (Infanrix hexa, Hexyon, and Vaxelis). The reports of suspected adverse reactions to hexavalent vaccine in Italy in 2018 were 849. As expected according to the vaccination schedule, most reports (77%) refer to the simultaneous administration of hexavalent and other vaccines, in particular with the pneumococcal vaccine. In our sample, the 98% of PTIs were co-administered with PCV13, thus making it difficult to differentiate if the adverse reactions were due to the hexavalent or pneumococcal vaccine.

Among the suspected adverse reactions, in the AIFA report, 130 (15,3%) were reported as serious adverse reactions, of which 94 (72,9%) were correlated with vaccination and included fever, severe local reactions, febrile seizures, irritability, diarrhea, hypotonic hyporesponsive episodes and allergic reactions. Interestingly, we did not collect any serious adverse event in our PTIs population vaccinated with Hexyon.

Our study fills an important gap in the research regarding vaccines use in PTIs. We examined real-world data in a large cohort of newborns from a populous region in Italy. We collected data regarding the timeliness of vaccination and examined through a structured parent interview the occurrence of adverse events. Given the lack of similar studies conducted in Italy, our research may be considered as a pilot for future studies performed in different contexts or involving different vaccines.

Our study has some limitations. By actively interviewing parents of the preterm infants asking for adverse events we could have affected data reliability. The retrospective approach via phone surveys did not permit a high rate of responses, reducing the potential sample and introducing a selection bias. Moreover, although our interviewers were trained not to influence responders, we cannot exclude that their questions may have partially influenced recall of a higher frequency of local and mild adverse events. Similarly, parents who had experienced complications of pregnancy and childbirth (such as caesarean section and newborn jaundice) and mothers who had breastfed their baby may have been more likely to report adverse events following vaccination (Table 3). These parents may need special attention to develop a trusting relationship around the risks and benefits of vaccines in preterms.

Our findings confirm the safety of the Hexyon vaccine among PTIs with real-world data. The similarity of our results with those deriving from term-born infants on the basis of the SmPC confirms that PTIs should not be considered as a different population in terms of vaccines administration. On the contrary, given the high risk of infectious diseases, efforts should be made to educate parents and health care professionals about the importance of timely vaccination in preterm infants, even in case of low birth weight [9]. We envisage that the results of our study will be further confirmed by analogous real-world studies, thus strengthening the evidence supporting the routine hexavalent vaccination for all infants.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Prato reports personal fees and non-financial support for attending symposia and advisory committees from Sanofi Pasteur, during the conduct of the study; personal fees and non-financial support from GSK, personal fees and non-financial support from MSD, outside the submitted work; and RP asserts to be a component of the Apulia Region Immunization Technical Advisory Group, which advises the Regional health authorities on policies of vaccination; advisory and decisional power on vaccines procurement remains solely on the Regional Government. Dr. Martinelli reports non-financial support for attending symposia from Sanofi Pasteur, during the conduct of the study; personal fees and non-financial support from GSK, personal fees and non-financial support from MSD, outside the submitted work. Dr. Fortunato reports non-financial support for attending symposia from Sanofi Pasteur, during the conduct of the study. No other competing interests are to be disclosed.

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Author contributions

RP and DM conceived and designed the study. FF analyzed the data. G.D.M. contributed to the data collection and managed the database. GI provided statistical support. RP, DM and FF wrote the manuscript with contributions from all authors. All authors approved the manuscript.

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