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Infant vaccination against pertussis in Argentina: Parent-reported outcomes on reactogenicity, impact on daily routine and satisfaction after pentavalent whole-cell or hexavalent acellular pertussis vaccines

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A B S T R A C T

Introduction: In Argentina, a pentavalent whole-cell pertussis vaccine (wP) is used in the National Immunization Program, however hexavalent acellular pertussis (aP) vaccines are available in the private market.
Objective: To describe parent or guardianś perceptions on reactogenicity, daily routine and satisfaction after a first or third dose of a wP-pentavalent plus IPV (wP-group) or the fully-liquid aP-hexavalent vaccine (aP-group) in infants.
Material and methods: This was a prospective observational and analytical study. Parents or guardians of infants born at term attending a public or private vaccination center in Buenos Aires City were invited to participate. All parents or guardians had completed 12-year schooling and were asked to fill out an online 7-day post vaccination questionnaire. The questionnaire was validated as the first phase of the study. Descriptive analysis of study variables was carried out, REDCap was used for the online survey, and STATA 14 for data analysis.
Results: 1071 parents or guardians answered the questionnaire (response rate 82%), 530 for wP-group and 541 for aP-group.
Local and systemic adverse reactions, in groups wP and aP respectively, were: pain 83%, 28%; swelling 63%, 16%; redness 52%, 22%; irritability 72%, 52%; fever 37%, 8%; loss of appetite 36%, 19%; drowsiness 38%, 27%; and vomiting 15%, 11%.
Impact on daily life: social activities 36%, 20%; routine 48%, 24%; mood 39%, 23%; vitality 47%, 24%; sleep 50%, 30%; and appetite 22%, 7%.
Parents were satisfied with the vaccination process in 96% and 98% for wP-group and aP-group respectively. Parents reported willingness to bring infant for future vaccine doses in 97% and 99% for wP-group and aP-group respectively.
Conclusions: Reported reactogenicity and impact on family daily routine was higher in infants receiving wP-pentavalent than aP-hexavalent vaccines. Parents in both groups conveyed vaccine acceptance and positive intentions for future immunizations.

Introduction

Immunization is one of the most important tools for the prevention and control of infectious diseases. The success of vaccination programs and the consequent decline in vaccine-preventable diseases reduce the risk perception of diseases and then, concerns about potential vaccine adverse events became more relevant leading to lack of confidence, low vaccine coverage rates and risk of disease re-emergence. [1] Moreover, in recent years, as more vaccines have been developed and approved, vaccination programs have become more complex including an increasing number of injections to comply with immunization schedules. [2]

It is estimated that *Bordetella pertussis* causes 16 million cases of whooping cough and 195,000 deaths in children per year, worldwide. [3] In Argentina, infant immunization against pertussis is included in the National Immunization Program (NIP) using a pentavalent whole-cell pertussis vaccine (DTwP-Hib-HB), in a three dose primary schedule at 2, 4 and 6 months of age. [2] Hexavalent acellular pertussis vaccines (DTaP-IPV-HB-Hib or DTaP-IPV-HB//Hib) are also commercially available on the private market or through private health insurance plans. [4]

Whole-cell pertussis (wP) vaccines are associated with high incidence of adverse events, particularly in infants under 1 year of age; fever, irritability and crying occur in 10–20% of vaccine recipients. [5,6] Febrile seizures and persistent crying are less frequent (<1%), while rates of hypotonic hyporesponsive episode are low (<1 per 1000–2000

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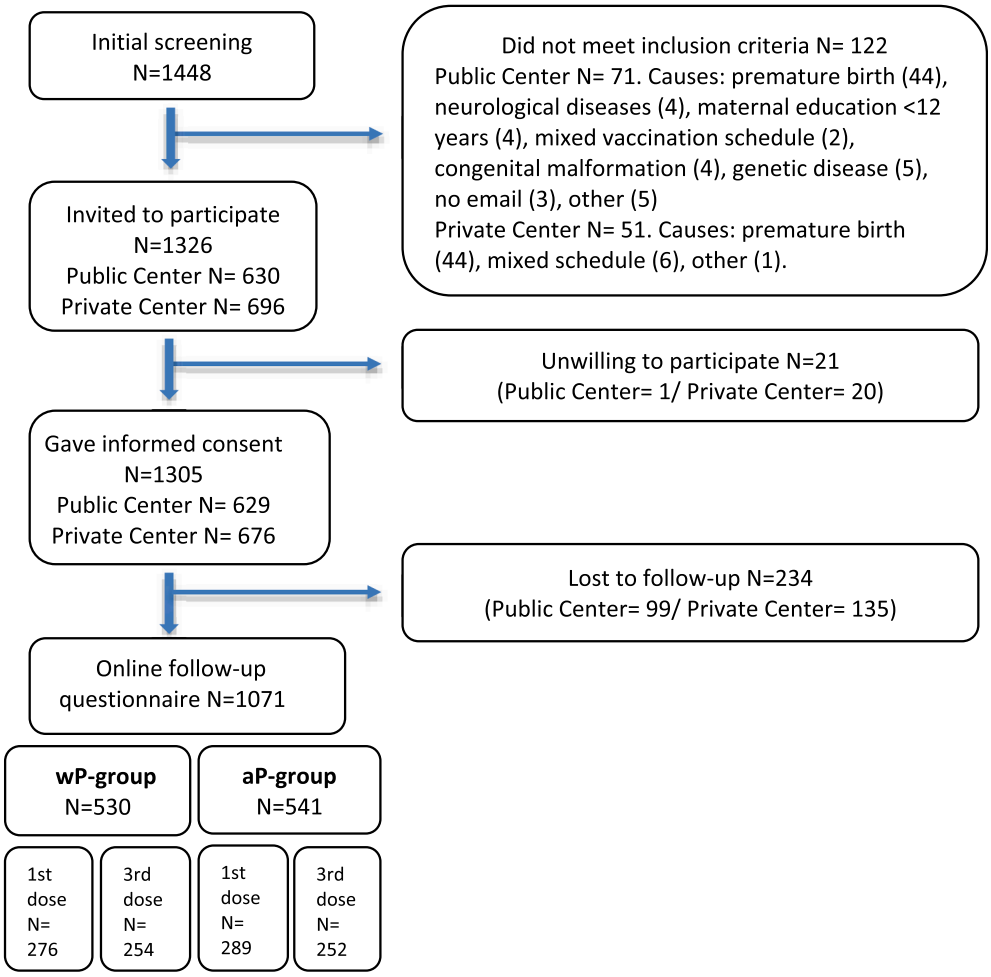

Fig. 1. Flowchart.

doses). [7] Acellular pertussis (aP) vaccines present lower rates of adverse reactions than wP vaccines. [8,9]

Pharmacovigilance systems usually prioritize and report severe and uncommon adverse events; however, mild, more common local and systemic reactions also affect family daily routine and impact healthcare services. [10]

We aimed to describe parent/guardian-reported outcomes on reactogenicity, impact on daily routine and satisfaction, after wP-pentavalent vaccine or fully-liquid aP-hexavalent vaccine administered to infants at 2 and 6 months of age.

Population and methods

Study design

We carried out an observational, prospective and analytical study.

Participants

Parents/guardians of infants receiving either the first dose (at 2–3 months of age) or the third dose (at 6–7 months of age) of pentavalent (DTwP-Hib-HB) vaccine from Serum Institute of India plus IPV from Sanofi or Bilthoven Biologicals (wP-group), according PAHO's Revolving Fund provision; or fully-liquid hexavalent vaccine (DTaP-IPV-HB-Hib; Hexaxim) from Sanofi (aP-group) were invited to participate. wP-group was recruited at a public vaccination center (Ricardo Gutierrez Childreńs Hospital), aP-group at a private center (Stamboulian Vaccines Services), in Buenos Aires City.

We included parents of infants born after at-term pregnancy (37–41 weeks), who had completed 12 years of schooling and who responded to the questionnaire 6–8 days after immunization.

Parents of premature babies were excluded, other exclusion criteria were: history of severe anaphylactic reactions to any pertussis vaccine component, neurological diseases, congenital anomalies, genetic diseases, malnutrition (defined as weight < 3rd percentile), fever (axillary temperature $\geq$ 38 °C) on the day of vaccination, and infants receiving mixed pertussis vaccination schedules (both wP and aP).

Sampling technique and sample size

Non-probabilistic, strategic or convenience sampling was used. Sample size was estimated at 500 participants per group. The enrollment of the subjects ended when the questionnaire response was obtained according to the estimated sample size. Subjects that could not be included were quantified and causes assessed. Response rate for the online questionnaire was calculated.

Study procedures

On the day of vaccination, parents/guardians were invited to participate and signed the informed consent form; the infant's medical history and data about prior vaccines were collected. Subsequently, parents received an online questionnaire to report any adverse events occurring 7 days after vaccination including injection-site reactions: pain, redness and swelling and systemic reactions: loss of appetite, drowsiness, irritability, vomiting, fever (axillary temperature $\geq$ 38 °C)

Table 1
Socio demographic data of study participants.

		wP-group (wP-Pentavalent + IPV) N = 530 N (%)	aP-group (aP-Hexavalent) N = 541 N (%)	p-Value
Infant gender	Male	272 (51.3)	267 (49.4)	
	Female	258 (48.7)	274 (50.6)	0.51 [a]
Age	2–3 months	276 (52.1)	289 (53.4)	
	6–7 months	254 (47.9)	252 (46.6)	0.65 [a]
Mean age of parent/guardian (SD) range		29.65 (SD 6) 18.0–47.0	35.66 (SD 11.01) 20.0–68.0	<0.001[b]
Family relationship	Mother	502 (94.7)	469 (86.7)	<0.001 [a]
	Father	27 (5.1)	71 (13.1)	
	Guardian	1 (0.2)	1 (0.2)	–
Siblings	Yes	302 (57.0)	268 (48.3)	0.01 [a]
Location	BA City*	286 (54.0)	422 (78.0)	<0.001 [a]
	BA Suburbs	240 (45.3)	63 (11.7)	
	Country interior	4 (0.7)	56 (10.3)	
Parent/guardian nationality	Argentina	328 (61.9)	514 (95.0)	<0.001 [a]
	Paraguay	68 (12.8)	0 (0)	
	Bolivia	37 (7.0)	2 (0.4)	
	Perú	53 (10.0)	1 (0.2)	
	Venezuela	23 (4.3)	6 (1.1)	
	Other	21 (4.0)	18 (3.3)	
Motheŕs highest educational level	University	62 (11.7)	491 (90.8)	<0.001 [a]
	High school (complete 12- year schooling)	468 (88.3)	50 (9.2)	
Socio-economic level (Graffar Method) [23]	High	24 (4.5)	425 (78.6)	
	Middle-high	69 (13.0)	106 (19.6)	
	Middle	300 (56.6)	10 (1.8)	<0.001 [a c]
	Low	137 (25.9)	0 (0)	
	Extreme poverty	0	0 (0)	

*Buenos Aires City.
a. Chi-squared test.
b. T-test.
c. Socio-economic level was compared between high/middle-high with ≤ middle level.

Table 2
Concomitant Vaccines stratified by group and age.

	wP-group (wP-Pentavalent + IPV) N = 530 N (%)		aP-group (aP-Hexavalent) N = 541 N (%)	
Concomitant vaccines*	1st dose N = 276	3rd dose N = 254	1st dose N = 289	3rd dose N = 252
IPV	272 (98.5)	243 (95.7)	NA	NA
PCV13	274 (99.6)	3 (1.2)	286 (99.3)	37 (14.7)
Rotavirus	259 (93.9)	1 (0.4)	282 (97.9)	7 (2.8)
ACWY Conjugate Meningococcal	34 (12.3)	55 (21.7)	9 (3.1)	30 (11.9)
Meningococcal B	0	0	5 (1.7)	0
Influenza	NA	134 (52.8)	NA	123 (49.2)

NA: Not applicable.
*Vaccination in the same site: wP-group: IPV (n = 7), ACWY meningococcal conjugated (n = 45), flu vaccine (n = 14). aP-group: PCV13 (n = 3), ACWY meningococcal conjugated (n = 5), flu vaccine (n = 4).

and subfebrile state (temperature between 37 and 37.9 °C). Unsolicited events were not collected, but adverse events following immunization (AEFI) were reported and documented. Use of medical resources and transportation associated with reactogenicity were requested. Impact on family daily activities was assessed, including social activities, routine, mood, vitality, sleep and appetite for the parent/guardian who answered the online questionnaire. In the case of siblings, changes in sleep and leisure activities were evaluated, and whether parental attention had varied. The survey also inquired about household finances (financial expenses related with adverse events) and work (job performance and absenteeism). Finally, parents were asked to rate the degree of satisfaction with the vaccination procedure and to state their attitude and intentions for future immunizations.

Study vaccines (either wP-group or aP-group) were administered in the left limb, preferably alone, to simplify the report of injection-site reactions following routine vaccination guidelines.

Data collection and validation process

To validate the contents of the online follow-up questionnaire, we carried out a pilot test. From October to December 2021, the first 30 participants were interviewed in 3 stages (10 per stage, 5 from each study site). One of the study investigators carried out a video call with the parent or guardian who answered the questionnaire to review if each one of the items was understandable, relevant and appropriate, and whether the length of the questionnaire was adequate (Appendix 1). This was repeated until the vast majority of participants reported comprehension of the questionnaire.

Table 3
Injection-site and systemic vaccine reactions.

		wP-group (wP-Pentavalent + IPV) N = 530			aP-group (aP-Hexavalent) N = 541		
		N	**%**	**95% CI**	**N**	**%**	**95% CI**
Injection-site reactions *							
Pain	No	91	17.2	14.0–20.7	388	71.7	67.7–75.5
	Mild	263	49.6	45.3–53.9	138	25.5	21.9–29.4
	Moderate	146	27.5	23.8–31.6	13	2.4	1.3–4.1
	Severe	30	5.7	3.8–7.9	2	0.4	0.04–1.3
Redness	No	257	48.5	44.2–52.8	421	77.8	74.1–81.3
	Mild	157	29.6	25.7–33.7	100	18.5	15.3–22
	Moderate	86	16.2	13.2–19.6	19	3.5	2.1–5.4
	Severe	30	5.7	3.8–7.9	1	0.2	0.005–1
Swelling	No	198	37.4	33.2–41.6	457	84.5	81.1–87.4
	Mild	254	47.9	43.6–52.2	82	15.1	12.2–18.5
	Moderate	68	12.8	10.1–15.9	2	0.4	0.04–1.3
	Severe	10	1.9	0.9–3.4	0		
Systemic reactions							
Appetite loss	No	340	64.1	59.9–68.2	440	81.3	77.8–84.5
	Mild	144	27.2	23.4–31.2	87	16.1	13.1–19.5
	Moderate	35	6.6	4.6–9	13	2.4	1.3–4.1
	Severe	11	2.1	1.0–3.7	1	0.2	0.005–1
Drowsiness	No	329	62.1	57.8–66.2	395	73.0	69.1–76.7
	Mild	142	26.8	23.1–30.8	113	20.9	17.5–24.6
	Moderate	45	8.5	6.3–11.2	26	4.8	3.2–7
	Severe	14	2.6	1.4–4.4	7	1.3	0.5–2.7
Mood/ Irritability	No	145	27.4	23.6–31.4	261	48.2	44–52.6
	Mild	233	44.0	39.7–48.3	208	38.4	34.3–42.7
	Moderate	90	16.9	13.9–20.5	56	10.4	7.9–13.2
	Severe	62	11.7	9.1–14.8	16	3.0	1.7–4.8
Vomiting	No	448	84.5	81.3–87.7	480	88.7	85.8–91.3
	Mild	59	11.1	8.6–14.2	52	9.6	7.3–12.4
	Moderate	19	3.6	2.2–5.6	8	1.5	0.6–2.9
	Severe	3	0.6	0.1–1.6	1	0.2	0.005–1.0
	Did not respond	1	0.2	0.0–0.9	0		
Fever (≥38 °C)	No	271	51.1	46.8–55.5	461	85.2	81.9–88.1
	Yes	200	37.8	33.6–42	45	8.3	6.1–11
	"Not measured but seemed feverish"	59	11.1	8.6–14.1	35	6.5	4.6–8.9
Mean number of fever days (SD) range		N = 251			N = 79		
		1.52 (SD 0.79) 0–5			1.17 (SD 0.55) 0–4		
Intensity of fever induced reactions		N = 259			N = 80		
	None	45	17.4	13–22.5	19	23.7	14.9–34.6
	Mild reactions	145	56.0	49.7–62.1	36	45.0	33.9–56.5
	Moderate reactions	57	22.0	17.1–27.6	18	22.5	13.9–33.2
	Severe reactions	12	4.6	2.4–7.9	7	8.8	3.6–17.2
Subfebrile state (37–37.9 °C)		N = 271			N = 461		
	No	202	74.5	68.9–79.6	374	81.1	77.3–84.6
	Yes	58	21.4	16.7–26.8	72	15.6	12.4–19.3
	"Not measured but seemed slightly feverish"	11	4.1	2.0–7.1	15	3.3	1.8–5.3

*wP-Pentavalent vaccine was administered preferently alone.

Data analysis

Data were collected in the REDCap system (The REDCap Consortium at Vanderbilt University; Nashville, TN) [11] and analyzed using STATA 14 (Stata Corp LP, College Station, TX, USA). In each group, categorical variables were described as percentages and 95% confidence intervals (95%CI), continuous variables as mean and standard deviation (SD). Items describing adverse events, impact on family daily routine, household economy and work were expressed as percentages, in accordance with the response on a Likert Scale, per group and per dose.

Use of resources associated with reactogenicity, degree of satisfaction with the vaccination procedure and intentions and reasons for future vaccinations were also described as percentages. However, as the populations in the two groups were different, statistical comparison was not carried out.

Ethics

The study was approved by the Ricardo Gutierrez Hospital Research Ethics Committee (N° 2437) and Institutional Review Board. Participation in the study was voluntary, free of charge and confidential. Before entering the study, all participants were asked to sign an informed consent form.

Results

Between January 2021 and April 2022, 1448 parents/guardians were screened, 1326 met the inclusion criteria and 1305 agreed to participate (wP-group: 629 and aP-group: 676). Finally, 1071 participants completed the online follow-up questionnaire (response rate 82.1 %). (Fig. 1).

Socio demographic and vaccination data are shown in Table 1. Participants were evenly distributed as per infantś age and gender in each vaccine group. The following characteristics were significantly

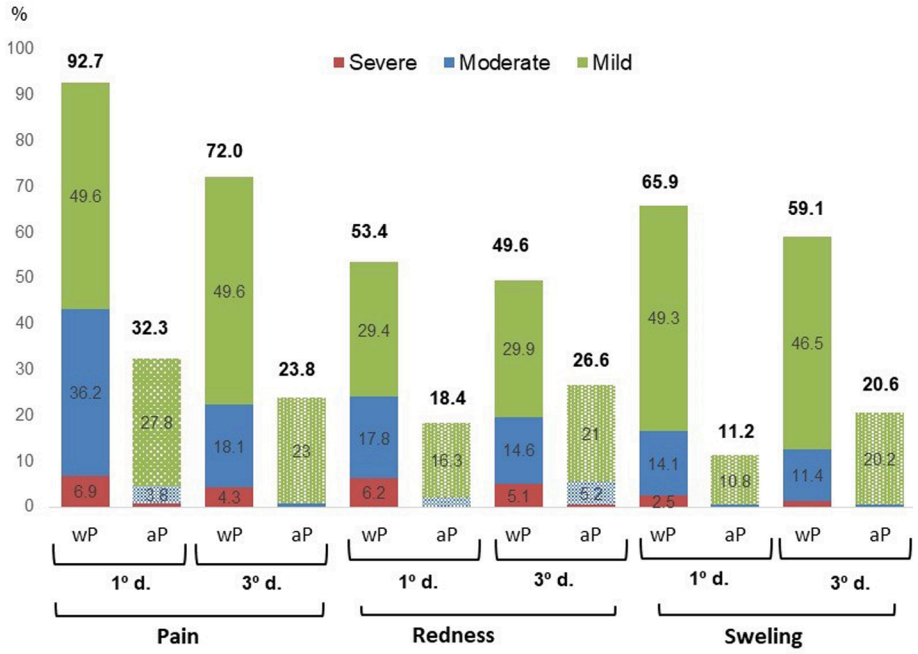

Fig. 2. Injection-site reactions reported by parents/guardians after the first (2–3 months) or third dose (6–7 months) according to vaccine. wP: wP-Pentavalent + IPV. aP: aP-Hexavalent. d.: dose.

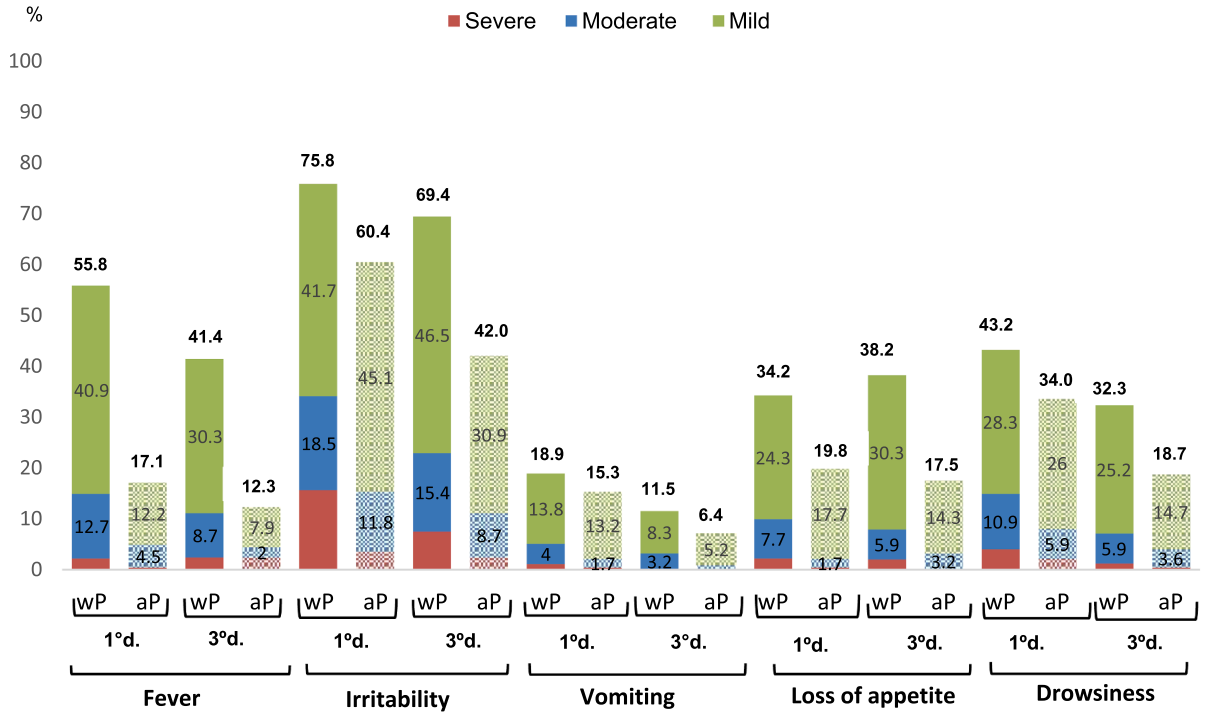

Fig. 3. Systemic adverse events reported by parents/guardians after the first (2–3 months) or third (6–7 months) dose according to vaccine. wP: wP-Pentavalent + IPV. aP: aP-Hexavalent. d.: dose.

more common in wP-group (wP-pentavalent) than aP-group (aP-hexavalent): mother at the vaccine visit, younger age of parent/guardian, siblings, living in the suburbs, foreign nationality, lower maternal educational level and socioeconomic status.

Most infants received concomitant vaccines, 99.6% in wP-group and 83.4% in aP-group; some babies received another vaccine in the same limb (12.5 % wP-group and 2.2 % aP-group) (Table 2).

Adverse events

Post vaccination local and systemic adverse events reported by the parents or guardians associated with vaccination are shown in Table 3. Adverse events were more frequent after the first dose than the third dose, irrespective of the vaccine used. (Fig. 2 and Fig. 3).

Regarding injection-site reactions (without describing level of severity), in wP-group, pain was the most frequent event (83.0%; 95% CI

Table 4
Symptomatic medication, medical resources and transportation.

		wP-group (wP-Pentavalent + IPV) N = 530			aP-group (aP-Hexavalent) N = 541		
		N	**%**	**95% CI**	**N**	**%**	**95% CI**
Use of medication for adverse event	No	233	44.0	39.8–48.2	391	72.3	68.3–76.0
	Yes	297	56.0	51.7–60.3	150	27.7	23.9–31.7
Drug used		N = 297			N = 149		
	Paracetamol	275	92.9	89.4–95.5	140	94.0	88.8–97.2
	Ibuprofen	19	6.4	3.9–9.8	9	6.0	2.8–11.2
	Dipyrone	2	0.7	0.1–2.4	0		
	Not remember drug	1					
Recommended by*	Physician	209	70.6	65.1–75.7	137	91.9	86.3–95.8
	Vaccinator	96	32.4	27.1–38-1	26	17.4	11.7–24.5
	Pharmacist	3	1.0	0.2–2.9	0		
	Relative	4	1.3	0.4–3.4	3	2.0	0.4–5.8
	Nurse	5	1.7	0.6–3.9	1	0.7	0.01–3.7
	Nobody	6	2.0	0.7–4.4	4	2.7	0.7–6.7
	Other	4	1.4	0.4–3.4	2	1.3	0.2–4.8
Need for medical attention	No	519	97.9	96.3–98.9	535	98.9	97.6–99.6
	Yes †	11	2.1	1.0–3.7	6	1.1	0.4–2.4

*Multiple options.
† **wP-group:** Type of consultation: medical consultation by phone (n = 2), at private clinic (n = 2), at private medical office (n = 1), emergency dept. (n = 4), health center (n = 1), other (n = 1). Number of consultation: one (n = 10), two (n = 1). Complementary tests: urine (n = 1). Hospitalization: no (n = 11). Transportation to medical center: car (n = 4), bus (n = 2), taxi (n = 2), other (n = 1). Number of travel: one (n = 7), two (n = 2).
aP-group: Type of consultation: medical consultation by phone (n = 3), at private medical office (n = 1), emergency dept. (n = 1), health center (n = 1). Number of consultation: one (n = 4), two (n = 2). Complementary tests: blood (n = 2). Hospitalization: no (n = 4), yes (n = 2). Transportation to medical center: car (n = 3). Number of travel: one (n = 2), two (n = 1).

79.3–85.9) followed by swelling (62.6%; 95% CI 58.4–66.8) and redness (51.5%; 95% CI 47.2—55.8). In aP group pain (28.3%; 95% CI 24.5–32.3) was the most frequent followed by redness (22.2%; 95% CI 18.7–25.9) and swelling (15.5%; 95% CI 12.6–18.9), but all were less frequent than in wP group.

Systemic adverse events were also more common in wP-group. In this group irritability (72.6%; 95% CI 68.6–76.4) was the most frequent followed by drowsiness (37.9%; 95% CI 33.8–42.2), fever (axillary temperature) (37.7%; 95% CI 33.6–42.0), and loss of appetite (35.8 %; 95% CI 31.8–40.1). In the aP-group, irritability (51.8%; 95% CI 47.5–56), drowsiness (27.0%; 95% CI 23.3–30.9), loss of appetite (18.7%; 95% 15.5–22.2) and fever (8.0%; 95% CI 6.1–11) were also reported more frequently, but less than in the wP-group.

Regarding the use of symptomatic medication 56.0% and 27.7% of children received an antipyretic/analgesic in the wP and aP groups respectively. Type of symptomatic medication, medical resources (consultation, hospitalization, complementary tests) and transportation for consultations are described in Table 4.

Two infants in aP-group were hospitalized due to fever, one was discharged after 24 h because of low risk of severe bacterial infection, and the other had the sixth disease (roseola).

Impact on family activities and daily routines, household finances, and work

Parents/guardians in wP-group reported: sleep disturbance 50.0 % (95% CI 45.7–54.3), changes in daily routine 47.9 % (95% CI 43.6–52.3), vitality 47.2 % (95% CI 42.9–51.5), mood 39.8% (95% CI 35.6–44.1) and social activities 36.6 % (95% CI 32.5–40.9). AP-group participants described sleep disturbance 29.8 % (95% CI 25.9–33.8), changes in daily routine 23.7 % (95% CI 20.1–27.5) and vitality 23.5 % (95% CI 20–27.3). In Table 5 impact on family activities and daily routines are shown.

In wP-group, less parental attention towards siblings was reported by 29.1% (CI95% 24.1–34.6) and sleep disturbance of siblings in 17.2% (95% CI 13.1–22.0) of cases, whereas in aP-group, these were reported in 21.1% (95% CI 16.3–26.5) and 7.3 % (95% CI 4.4–11.1) respectively.

The impact on household finance (expenses) associated with adverse effects was reported by 19.3% (95% CI 16.1–22.8) and 3.0% (95% CI 1.8–4.6) in the wP-group and aP-group, respectively. Work absenteeism of the parent or caregiver was reported in 27.5% (95% CI 21.1–34.7) and 6.3% (95% CI 3.9–9.6) in the wP-group and aP-group, respectively. In Table 6 the impact on household finances and work are shown.

Degree of satisfaction with the vaccination procedure.

Satisfaction with the vaccination process was high in both groups. For the wP-group, 96.4% (95% CI 94.6–97.8) of parents reported being either very satisfied or satisfied, while for the aP-group it was 98.2% (95% CI 96.7–99.1).

Items assessing level of satisfaction with vaccination and attitudes and intentions for future vaccinations are shown in Table 7.

Discussion

In this prospective study we analyzed parent/guardians' reported outcomes of reactogenicity, impact on daily routine and level of satisfaction following the administration of wP-pentavalent and the fully-liquid aP-hexavalent vaccines in infants. In Argentina, access to acellular pertussis hexavalent vaccines is determined by socioeconomic conditions. We observed a different socio-demographic profile for each study group, families of infants receiving hexavalent vaccine had higher socioeconomic status and education, so we were unable to do a head-to-head comparison of both vaccines.

As we used a self-administered online questionnaire to explore parent-reported outcomes, we needed first to validate the instrument in the study population to ensure clarity and understanding. In a similar study, ÓRyan et al. assessed satisfaction, acceptability and impact on daily life after the administration of the same vaccines, however the authors did not inquire about adverse events after vaccination. [12]

Whole-cell and acellular pertussis vaccines have different reactogenicity profiles as reported in literature, wP vaccines exhibit higher rates of local and systemic adverse events, including neurological events. [8,9,13] In our study, parents/guardians of infants receiving wP-pentavalent vaccine reported more local and systemic adverse reactions and greater impact on family daily routine than those receiving the aP-hexavalent vaccine. Reported local or systemic reactions by parents were in the ranged reported in other studies, although in the upper

Table 5
Impact on family routines after vaccination.

		wP-group (wP-Pentavalent + IPV) N = 530			aP-group (aP-Hexavalent) N = 541		
		N	**%**	**95% CI**	**N**	**%**	**95% CI**
Negative impact on parent/guardian							
Social activities	No change	336	63.4	59.2–67.4	434	80.2	76.7–83.4
	Minimum	139	26.2	22.6–30.1	92	17.0	14—20.4
	Moderate	47	8.9	6.7–11.5	12	2.2	1.2–3.74
	Severe	8	1.5	0.7–2.8	2	0.4	0.1–1.2
	No reply	0			1	0.2	0–0.9
Daily routine	No change	276	52.1	47.8–56.3	414	76.5	72.8–80
	Minimum	182	34.3	30.4–38.5	108	20.0	16.8–23.5
	Moderate	60	11.3	8.8–14.2	15	2.8	1.6–4.4
	Severe	11	2.1	1.1–3.6	4	0.7	0.2–1.8
	No reply	1	0.2	0–0.9	0		
Mood	No change	319	60.1	56–64.3	416	76.9	73.2–80.3
	Minimum	159	30.0	26.2–34	99	18.3	15.2–21.7
	Moderate	39	7.4	5.4–9.8	23	4.3	2.8–6.2
	Severe	13	2.5	1.4–4.1	3	0.5	0.1–1.5
Vitality	No change	280	52.8	48.6–57.1	413	76.3	72.6–79.8
	Minimum	172	32.5	28.6–36.5	97	17.9	14.9–21.3
	Moderate	62	11.7	9.2–14.7	26	4.7	3.2–6.9
	Severe	16	3.0	1.8–5.0	5	0.9	0.3–2
Sleep	No change	265	50.0	45.8–54.3	380	70.2	66.3–74
	Minimum	174	32.8	28.9–36.9	112	20.7	17.5–24.3
	Moderate	66	12.5	9.8–15.5	42	7.8	5.7–10.3
	Severe	25	4.7	3.1–6.8	7	1.3	0.6–2.5
Appetite (loss)	No change	416	78.5	74.8–81.8	505	93.3	91–95.2
	Minimum	81	15.3	12.4–18.5	27	5.0	3.4–7.1
	Moderate	24	4.5	3.0–6.6	7	1.3	0.6–2.5
	Severe	9	1.7	0.8–3.1	1	0.2	0–0.9
	No reply	0			1	0.2	0–0.9
Impact on siblings							
		302			**261**		
Sleep	No change	250	82.8	78.2–86.7	242	92.7	89.1–95.4
	Minimum	36	11.9	8.6–16	16	6.1	3.7–9.6
	Moderate	15	5.0	2.9–7.9	3	1.2	0.3–3.1
	Severe	1	0.3	0.-1.6	0		
Recreation activities/play	No change	276	91.4	87.8–94.2	251	96.2	93.3–98
	Minimum	20	6.6	4.2–9.9	10	3.8	2.0–6.7
	Moderate	6	2.0	0.8–4.1	0		
	Severe	0			0		
Parental attention	No change	214	70.9	65.5–75.8	206	78.9	73.7–83.5
	Minimum	70	23.1	18.7–28.2	43	16.5	12.3–21.4
	Moderate	15	5.0	2.9–7.9	11	4.2	2.2–7.2
	Severe	3	1.0	0.3–2.7	1	0.4	0–1.9

Table 6
Impact on family finances and work.

		wP-group (wP-Pentavalent + IPV) N = 530			aP-group (aP-Hexavalent) N = 541		
		N	%	95% CI	N	%	95% CI
Negative impact on expenses		N = 530			N: 541		
	No change	428	80.7	77.1–84	525	97.0	95.2–98.3
	Minimum	87	16.4	13.4–19.8	12	2.2	1.2–3.8
	Moderate	12	2.3	1.2–3.9	3	0.6	0.1–1.6
	Severe	3	0.6	0.1–1.6	1	0.2	0–1
Current job	Yes	178	33.6		315	58.2	
Negative impact on job performance	No change	106	59.6	52–66.8	248	78.7	73.8–83.1
	Minimum	50	28.1	21.6–35.3	52	16.5	12.6–21.1
	Moderate	16	9.0	5.2–14.2	13	4.2	2.2—6.9
	Severe	5	2.8	0.9–6.4	1	0.3	0–1.7
	No reply	1	0.6	0–3.1	1	0.3	0–1.7
Absenteeism	Yes	49	27.5	21.1–34.7	20	6.3	3.9–9.6
Mean (SD) of workdays lost to absenteeism		1.8 (SD 1,09) 1–6			1.31 (SD 0.58) 1–3		

range. [8,9,14,15] One explanation for this finding is the effect of concomitant administration of other NIP vaccines such as PCV13, particularly 2-month-old babies whom had the highest rates. However, in general, reported AEs were lower than in another study in which DTaP-IPV-HB-Hib and PCV-13 and rotavirus were administered in European infants at 2, 3 and 4 months of age. [16] Although this can be seen as a methodological bias, its strength lies in the fact that it shows real-life situations; as this was an observational study, all vaccines were administered according to the NIP schedule. Furthermore, as the wP-pentavalent vaccine does not contain poliomyelitis components,

Table 7
Degree of satisfaction with vaccination.

		wP-group (wP-Pentavalent + IPV) N = 530			aP-group (aP-Hexavalent) N = 541		
		N	**%**	**IC95%**	**N**	**%**	**IC95%**
Level of satisfaction with vaccination procedure	Very satisfied	309	58.3	54.1–62.6	489	90.4	87.8–92.9
	Satisfied	202	38.1	34–42.5	42	7.7	5.7–10.4
	Dissatisfied	10	1.9	0.9–3.4	7	1.3	0.5–2.7
	Extremely dissatisfied	8	1.5	0.7–3	2	0.4	0.04–1.3
	No reply	1	0.2		1	0.2	
Willingness to bring infant for future vaccine doses	Yes	513	97.2	95.3–98.4	537	99.4	98.4–99.9
	No	15	2.8	1.5–4.6	3	0.6	0.1–1.6
	No reply	2			1		
Reasons for coming back for further vaccines*		N = 513			N = 537		
	To follow doctor's recommendations	365	71.2	67.0–75.0	494	92.0	89.4–94.1
	To comply with National Immunization Program	424	82.7	79.1–85.8	489	91.1	88.3–93.3
	To protect son/daughter against diseases	394	76.8	72.9–80.4	503	93.7	91.3–95.6
	Vaccine administration was simple and untroubled	126	24.6	20.9–28.5	189	35.2	31.2–39
	Trust in the safety of vaccines	243	47.4	43.0–51.8	339	63.1	58.9–67.2
	Vaccination will not alter family's daily routine	143	27.9	24.0–32.0	172	32.0	28.1–36.2
	Trust in the vaccination center	242	47.9	42.8–1.6	350	65.2	61–69.2
	Other**	2	0.4	0.04–1.4	4	0.7	0.2–1.9
Reasons for not accepting further vaccines*		N = 15			N = 3		
	Son/daughter cried a lot	5	33.3		0	0	
	Too many injections	4	26.6		1	33.3	
	Concerns about vaccine safety	4	26.6		0	0	
	Economic difficulties	0	0		0	0	
	Unsuitable working hours at vaccination center	0	0		1	33.3	
	Other***	3	20.0		0	0	
	No reply	0	0		1	0	

*Multiple options.
** **wP-group:** "because I want the best for my son/daughteŕs health", "the importance of immunization for society". **AP-group:** "because it involves one injection less", "because herd immunity is important", "because I was allowed to breastfeed my daughter while she received the vaccines, friendly approach", "it would be negligence not to vaccinate my son".
***wP-group:** "The hospital was overcrowded, no social distancing. Had to wait a long time", "I don't know what my son/daughter is receiving" "no more vaccinations until 1 year old".

infants in this group also received stand-alone IPV, which increased the probability of getting two injections in the same site (12.5 % wP-group vs 2.2 % aP-group) and overrating local adverse reactions such as pain.

The current NIP involves a crowded schedule given in a short period of time causing adverse reactions that can negatively impact family daily activities. [2] We observed changes in several features of daily routine among parents/guardians and siblings, as did ÓRyan et al who found significant differences between wP and aP vaccines.[12] A study of adjuvanted flu vaccine in older adults also showed the impact of adverse events on daily life measured with a quality of life score. [17] Another important issue is the effect of reactogenicity on household economy, one fifth of wP-group parents incurred extra expenses and around one third reported job absenteeism, contributing to productivity and income losses in vulnerable populations. These data can be useful for future pharmacoeconomic studies in Argentina and also in Latin America, since similar wP-pentavalent vaccines are provided by the PAHO Revolving Fund in the region.

Use of aP-hexavalent vaccines reduces the number of shots needed thereby reducing discomfort in infants while contributing to improve parentś satisfaction and attitudes towards vaccination leading to increases in vaccination coverage. [18] In our study, most parents/guardians in both groups were satisfied with the vaccination procedure, indeed, 90% in the aP-hexavalent group were "*very satisfied*". Likewise, most parents were willing to continue vaccinating their children, the main reasons were to comply with the immunization program, follow doctorś recommendations and protect against diseases.

These findings are comparable to those of another study in a similar population showing high vaccine confidence levels among parents. [19] In general, vaccine acceptance is high among the population in Argentina and in Latin America where anti-vaccine movements are weak. [20] It is important to point out that NIP vaccination is mandatory in our country which can explain why so many participants responded "to comply with the immunization schedule". [21]

As regards vaccine hesitancy, in the wP-pentavalent group adverse events (mainly crying) and multiple concomitant shots (safety concerns) were the main reasons for doubting future vaccinations, while in the aP-hexavalent group only three participants were hesitant for different reasons.

This study has some limitations, first, it was carried out in vaccination centers in Buenos Aires City and may not represent the situation across the country. Second, selection bias because we excluded parents/guardians with<12 years of schooling. Third, the two populations were inherently different with different sociodemographic characteristics hence direct comparison was not possible. In addition, the vaccines were given at different vaccination centers and the potential adverse event vaccination communication may have been different. Finally, the sample size did not allow for the detection of rare adverse events although this was not a study objective.

Immunization coverage has steadily declined over the last decade in Argentina and has become significantly worse after the COVID-19 pandemic. [22] In countries and regions with low vaccination rates, switching to higher-valent combination vaccines such as hexavalent vaccines can help improve coverage.

Currently, concerns about vaccine safety have grown in the community mainly because of people's experience with novel COVID-19 vaccines. Monitoring adverse events for all vaccines, especially new ones, is crucial, strategies to minimize risks should be strengthened and better communication tools are needed to boost confidence in the community.

Performing a study with a similar approach for booster vaccination may provide additional insights regarding wP and aP-vaccines.

Conclusions

In Argentina, vaccination for *Bordetella pertussis* is mandatory, whole cellular and acellular pertussis vaccines are available according to health system access.

Parents/guardians of children receiving wP-pentavalent plus IPV reported high rates of local and systemic adverse events. Around 50% expressed a negative impact on daily routine, 25% on siblings' daily activities and 19% on expenses. Conversely, parents of infants receiving liquid aP-hexavalent vaccine described lower rates of adverse events, only 25% reported impact on daily routine, very few on siblings' activities and impact on expenses.

Both groups were satisfied with the vaccination process and had positive intentions for future immunizations.

Combined acellular vaccines, such as hexavalent, reduce reactogenicity, impact on daily life and associated costs could improve the families' quality of life and economy after vaccination.

Declaration of Competing Interest

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Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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