Acute adverse events following immunization with DTP-HB-Hib pentavalent vaccine in the first year of life

Shahrokh Izadi,[1] Mahdi Mohammadi,[2] Majid Sartipi,[2] Manoochehr Karami[3] and Hossein Karimi[4]

[1]Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Islamic Republic of Iran (correspondence to: Shahrokh Izadi: izadish@yahoo.com). [2]Department of Epidemiology and Biostatistics; [4]Health Promotion Research Centre, School of Public Health, Zahedan University of Medical Sciences, Zahedan, Islamic Republic of Iran. [3]Department of Epidemiology, Research Center for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Islamic Republic of Iran.

Abstract

Background: Since November 2014, the pentavalent (Diptheria+Tetanus+Pertussis and Hepatitis B and Hib or DTP-HB-Hib) vaccine has been integrated into the Iranian national vaccination programme.

Aims: We conducted a prospective study in Zahedan in the southeast of the Islamic Republic of Iran to determine the incidence of adverse events following immunization (AEFI) with the pentavalent vaccine in children aged under one year.

Methods: Using cluster sampling, 1119 children aged 2–10 months at 15 public health clinics were invited, through their parents, to participate in the study. The parents were trained to register and report any AEFIs in a questionnaire. They were instructed to return the child to the clinic for further examination by a physician if they observed any complications within 3 days of vaccination.

Results: The most commonly reported AEFIs were fever (50.94%), mild (41.46%) and severe (1.70%) injection site complications, persistent crying for 3 hours or more (1.88%), hypotonic hyporesponsive episode (0.36%), vomiting (1.88%), diarrhoea (2.95%), and sterile abscess (0.62%). There were no cases of convulsion, purulent abscess or rash. The work experience of vaccinators (OR = 1.85; 95% CI: 1.4–2.46) showed a significant statistical association with the incidence of mild local complications at the injection site. Those with a history of Bacillus Calmette–Guérin (BCG) lymphadenitis (OR = 3.89; 95% CI:1.04–14.49) had a higher risk of severe local complications at the injection site.

Conclusions: The observed incidence of serious AEFIs following pentavalent vaccine injection in the study population was within the expected range. However, some of the relationships observed in this study require further research.

Key words: DTP-HB-Hib, pentavalent vaccine, adverse event following immunization, Iran

Citation: Izadi S; Mohammadi M; Sartipi M; Karami M; Karimi H. Acute adverse events following immunization with DTP-HB-Hib pentavalent vaccine in the first year of life. East Mediterr Health J. 2023;29(1):6–14. https://doi.org/10.26719/emhj.23.002

Received: 22/10/20; accepted: 19/10/22

Introduction

No drug or vaccine is completely harmless. Adverse event following immunization (AEFI) has been defined as "any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine" (1). There are 5 categories of AEFI: vaccine product-related reaction, vaccine quality defect-related reaction, immunization error-related reaction, immunization anxiety-related reaction and coincidental event (1,2).

Many countries, e.g. India, Indonesia, the Islamic Republic of Iran, Mexico and the United Kingdom, have combined the diphtheria–tetanus–pertussis (DTP) vaccine with the *Haemophilus influenzae* type b (Hib) vaccine and a fifth vaccine, usually hepatitis B or polio vaccine (or both), as part of a penta- or hexa-valent vaccine in their national immunization programmes. Most studies on these multivalent vaccines in these countries have focused on their efficacy and safety; fewer have looked at the AEFIs (3–6).

The pentavalent vaccine, which was integrated into the Iranian national vaccination programme in November 2014 in addition to the diphtheria, tetanus and pertussis vaccines, provides protection against hepatitis B and *H. influenzae* type b (Hib) (4). According to the national vaccination programme, each child must receive the pentavalent vaccine 3 times at intervals of 2 months. The first is usually at the end of the second month of life. Since the introduction of the pentavalent vaccine into the national immunization programme, only a few studies have been conducted on the frequency of AEFIs following administration. Since the vaccine is produced by different manufacturers in different countries, it has not been easy to determine the exact relationship between vaccine quality and vaccine production, and no detailed study has yet been conducted to determine this relationship.

In this study, we measured the frequency and investigated the possible causes of acute complications after the injection of the pentavalent vaccine within the first 72 hours after injection.

Methods

Zahedan is the capital of Sistan-va-Baluchestan province, located in the southeast of the Islamic Republic of Iran. According to the latest national census (2016), the population of Zahedan was about 600 000, with 18 000 children under one year old. In this short-term prospective study, the study population comprised all children aged under one year living in the urban areas of Zahedan who were healthy and eligible to receive the pentavalent vaccine.

In the Islamic Republic of Iran, health workers in charge of urban and rural health centres carry out local household visits at the beginning of each year to refresh information for the population under their coverage. For newborns who do not yet have a file, a vaccination card is issued and an electronic file is created in the health information system, the Integrated Comprehensive Health Information System (locally known as Samaneh SIB). If the parents do not bring their children for immunization on time, the clinic will contact them and may visit their homes if necessary.

The most important criterion for participating in the study was eligibility for the pentavalent vaccine injection. Children with major underlying diseases such as thalassaemia, diabetes or immunodeficiency virus infection were not invited to take part in the study. Other than that, there were no restrictions on children entering the study.

We used 2 questionnaires in this study. The first was the parents' questionnaire, which had 6 questions about the symptoms of localized inflammation at the injection site, the child's axillary temperature, vomiting, seizures, persistent crying attacks that last for 3 hours or more, severe watery diarrhoea and a hypotonic hyporesponsive episode, along with the time and date of each symptom.

In accordance with the national immunization schedule, every child must receive the pentavalent vaccine at least 3 times during the first year of life, preferably at the ages of 2, 4 and 6 months. So, in this short-term prospective cohort study, 3 groups of children were enrolled. One group (mostly about 2 months old) were those receiving their first dose of pentavalent vaccine, the second group (about 4 months old) were receiving their second dose and the third group (mostly around 6 months old) were receiving their third dose. The duration of follow-up for each child was at most 3 days from the time of the injection.

Parents who came with their children for vaccination between July and November 2019 were interviewed and informed about the importance of their participation in this study and asked for their consent for their child to participate in the study. After registering their consent, the training to complete the parents' questionnaire was provided. For parents who were illiterates, consent was verified orally in the presence of a witness. There was no compulsion to participate in the study and routine vaccination services were provided to clients who did not wish to participate. Each of the participating children was followed up to evaluate the AEFI of only one dose of the vaccine that they were receiving for the first, second or third time.

Parents were asked in the parents' questionnaire to record any side-effects they observed in their children within 3 days of their vaccination and to bring the child to the health centre if they noticed fever and/or any other complication so that caregivers could perform more comprehensive examinations and treatments. For parents who were illiterates, a literate relative was requested to help them complete the questionnaire. Parents were asked to submit the completed questionnaire to the vaccinator on the fourth day after vaccination. The vaccinator then completed the second questionnaire, which had more comprehensive questions, during a brief interview with the parents at the health centre. If they did not return the questionnaire for any reason, it was collected during a visit to their home and the second questionnaire was supposed to be completed there. During the 3 days that parents registered their children's complications in the questionnaire, if there was, for any reason, a need for further investigation, the physician in charge of the health clinic was required to examine the children more closely and comprehensively and order any necessary prescriptions and treatments. Primary health care, including the immunization programme and the services for diagnosing and treating AEFIs are free.

The second questionnaire contained 39 questions. The first 20 covered household demographic information, including the child's birth date, their height and weight, sex, education level of parents, type of nutrition during the first 6 months of life, height and weight of the child at birth, nationality of the child, vaccination schedule, work experience of the health worker in charge of her/his vaccination (i.e. the vaccinator) and the serial number and manufacturer of the vaccine.

Unless explicitly stated, all definitions and cut-offs detailed in this study have been adapted from the reference book "Causality assessment of an adverse event following immunization (AEFI)", which was the latest version at the time this study was conducted (1). In the questionnaires, the complications of vaccination (as outcome variables) were divided into 2 categories, topical and systemic complications. Topical complications were further divided into 2 categories, mild and severe. Swelling, redness of the skin and mild pain at the injection site, resolving within a maximum of 2 days, were considered as mild complications, while continuation of these symptoms for 3 days or more or the addition of joint pain and swelling to these symptoms or the need for hospitalization were classified as severe complications. The incidence of abscesses (sterile or infectious) within 3 days of vaccination was recorded separately as a severe complication.

Occurrence of any of the following signs and symptoms within 3 days of vaccination was considered a systemic complication: fever (body temperature 37.5 °C to 38.4 °C as mild; 38.5 °C and above as severe); continuous, persistent crying attack with restlessness

for more than 3 hours, beginning at latest one hour after vaccination; hypersensitivity reactions; frequent vomiting within 3 days of vaccination; seizures; severe watery diarrhoea more than 3 times in 24 hours; and hypotonic hyporesponsive episode (sudden paleness with decreased response and decreased muscle tone, sagging and numbness of the hands and feet) (*1*).

All the injections were given intramuscularly in the anterolateral thigh muscle using 16mm syringes and standard methods and equipment.

To calculate the sample size, we considered the incidence rate of AEFI after a pentavalent injection to be 17% (7). With an accuracy of estimation (d) = 4%, type one error as large as 5%, and the design effect of the cluster sampling (health clinics as clusters) = 1.1, and given that the vaccine is administered 3 times during the first year of life, the sample size was multiplied by 3, so the final sample size was estimated at 1119.

There were 85 health clinics in Zahedan city. To distribute the sample in these centres, Zahedan was first divided into 5 equal zones in terms of population size, then 3 health clinics were selected from the list of centres located in each zone using a random numbers table, each clinic being considered as a cluster, with a total of 15 clusters. Subsequently, sampling was carried out at each facility in a consecutive manner and children under one year who were referred to health centres to receive their first, second or third pentavalent vaccine were invited to take part in the study. In each health clinic, care was taken to enrol an equal proportion of children who were to receive their first, second or third pentavalent vaccines. Most of the children invited were aged 2, 4 and 6 months.

Data collected were entered into a *Microsoft Access* database and analysed using *STATA*, version 11.2. Incidence rates along with their 95% confidence intervals (CIs) were calculated and reported. In monovariate analysis, the independent sample Student *t*-test, Fisher's exact test, Chi-square test and odds ratios were used. In multivariate analysis, logistic regression was used to examine the relationships and eliminate the effect of confounders. The backward elimination procedure was used to select a model. To find confidence intervals for the model parameters, the asymptotic standard errors were used. In all instances, the 95% CIs were calculated and the cut-off for judging the relationship was *P*-value < 5%. Where applicable, the results have been reported as mean and standard deviation.

The ethics committee in medical research of Zahedan University of Medical Sciences reviewed and confirmed the protocol of the study (Ethics code: IR.ZAUMS.REC.1398.115).

Results

In total, the parents of 1119 children aged 2–10 months were invited to enrol their children in the study. One third of these children received the vaccine for the first time, one third for the second time and one third for the third time. Table 1 shows the characteristics of the participants in each group.

Fever was the most common complication after a pentavalent injection (the frequency of axillary temperature < 38.4° C = 42.81% and ≥ 38.5° C = 8.13%). The frequency of mild local complications at the injection site was 41.47% and that of severe local complications 1.70%. Table 2 shows the frequency of all reported AEFIs. Seizures occurred in only one case, 4 hours after the third injection of the pentavalent vaccine in a 6-month-old female child (age 188 days). The diagnosis of seizure in this child was based on the descriptions given by the parents, and the possibility of misdiagnosis could not be ruled out. There was no way for the doctor at the centre to confirm the occurrence of the seizure. In addition to the seizures, the child had a severe localized complication and a mild fever (37.5–38.4° C). According to the parents, she had no previous history of epilepsy or any similar condition.

Table 3 shows the results of crude and multivariate analyses (using logistic regression) of the relationship between AEFIs and participants' characteristics. Two separate models were fitted for 2 different outcomes. Model Number 1 was fitted for mild local injection site complications vs none, therefore, 19 participants with severe local injection site complications were not included in this model. It was not possible to enter the 2 variables in the same model since, due to the high correlation between the level of education of mothers and fathers, the coefficient related to the level of education of the father was calculated and reported from a separate similar model. In this model, of the 3 vaccine manufacturers, the one showing the lowest incidence of the outcome (identified as No. 1) was considered the baseline. The chance of developing a complication for manufacturers Nos. 2 and 3 was more than 2–3 times that of manufacturer No. 1.

In Model Number 1, children without fever were considered as the baseline group. Birth weight and weight for age *Z*-score were the other 2 variables in this model that showed a statistically significant relationship with the chance of mild complications ($P < 0.05$).

Model Number 2 examined the relationship between this AEFI (severe vs mild and no local injection site complications) and other variables. Only 2 variables remained in this model, fever and history of BCG lymphadenitis. Fever over 38.4° C increased the chance of developing a severe injection site complication by more than 7 times (OR = 7.50; 95% CI: 2.23–25.22). Children with a history of BCG lymphadenitis were almost 4 times more likely to have a severe injection site complication (OR = 3.89; 95% CI: 1.04–14.49) (Table 3). Only 19 participants developed severe local injection site complications.

Discussion

In this short-term prospective study, we examined the incidence rate of acute complications associated with pentavalent vaccine in 1119 children aged 2–10 months.

Table 1 Characteristics of the participants, children aged around 2, 4 and 6 months, distributed according to round of pentavalent vaccination, Zahedan, 2019

Characteristic	Round of pentavalent vaccine			Total (*n* = 1119)
	1st (*n* = 373)	2nd (*n* = 373)	3rd (*n* = 373)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (months)	2.21 (0.60)	4.28 (0.41)	6.46 (0.65)	4.31 (1.82)
Birth weight (g)	3092.7 (27.2)	3065.1 (23.2)	3036.4 (25.3)	3064.7 (14.6)
	Median (5th & 95th percentile)	**Median (5th & 95th percentile)**	**Median (5th & 95th percentile)**	**Median (5th & 95th percentile)**
Age (months)	2.07 (2.04 & 2.60)	4.14 (4.07 & 4.96)	6.24 (6.05 & 7.59)	4.14 (2.04 & 6.97)
	%	**%**	**%**	**%**
Sex (male/female) ratio	54.2/45.8	52.0/48.0	52.0/48.0	52.7/47.3
Delivery type (vaginal/caesarean)	63.3/36.7	70.2/29.8	68.1/31.9	67.2/32.8
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**
Father's education level				
Illiterate	16 (4.29)	25 (6.70)	23 (6.17)	64 (5.72)
1–5 years	48 (12.87)	51 (13.67)	77 (20.64)	176 (15.73)
6–12 years	204 (54.69)	188 (50.4)	193 (51.74)	585 (52.28)
University	105 (28.15)	109 (29.22)	80 (21.45)	294 (26.27)
Mother's education level				
Illiterate	26 (6.97)	38 (10.19)	29 (7.77)	93 (8.31)
1–5 years	72 (19.30)	63 (16.89)	93 (24.93)	228 (20.38)
6–12 years	165 (44.24)	172 (46.11)	166 (44.50)	503 (44.95)
University	110 (29.49)	100 (26.81)	85 (22.79)	295 (26.36)
Feeding				
Breast only	280 (75.07)	270 (72.39)	238 (63.81)	788 (70.42)
Breast & formula	71 (19.03)	78 (20.91)	60 (16.09)	209 (18.68)
Formula only	22 (5.90)	25 (6.70)	61 (16.35)	108 (9.65)
Other	0 (0.00)	0 (0.00)	14 (3.75)	14 (1.25)
BMI for age Z-score				
Severe wasting (< −3)	10 (2.68)	7 (1.88)	7 (1.88)	24 (2.14)
Wasting (−3 to −2)	20 (5.36)	19 (5.09)	31 (8.31)	70 (6.26)
Normal (−2 to 1)	286 (76.68)	296 (79.36)	265 (71.05)	847 (75.69)
Risk of over (1 to 2)	34 (9.12)	38 (10.19)	51 (13.67)	123 (10.99)
Overweight (2 to 3)	12 (3.22)	8 (2.14)	16 (4.29)	36 (3.22)
Obese (> 3)	11 (2.95)	5 (1.34)	3 (0.8)	19 (1.70)
Weight for age Z-score				
Severe underweight (< −3)	10 (2.68)	5 (1.34)	5 (1.34)	20 (1.79)
Underweight (−3 to < 2)	28 (7.51)	20 (5.36)	20 (5.36)	68 (6.08)
Normal (≥ −2)	335 (89.81)	348 (93.30)	348 (93.30)	1031 (92.14)
Vaccine producer[a]				
Producer A	7 (1.88)	10 (2.68)	5 (1.34)	22 (1.97)
Producer B	203 (54.42)	242 (64.88)	229 (61.39)	674 (60.23)
Producer C	163 (43.70)	121 (32.44)	139 (37.27)	423 (37.80)
Work experience of vaccinator (years)				
4–7	196 (52.55)	200 (53.62)	174 (46.65)	570 (50.94)
> 7	177(47.45)	173(46.38)	199(53.35)	549 (49.06)

BMI = body mass index.

[a]*The names of the vaccine producers are reserved by the authors.*

Table 2 Distribution of adverse events following immunization in the study population, children aged around 2, 4 and 6 months, according to round of pentavalent vaccination received, Zahedan, 2019

Adverse event following immunization	Round of pentavalent vaccine			Total (*n* = 1119)	*P*-value
	1st (*n* = 373)	2nd (*n* = 373)	3rd (*n* = 373)		
	No. (%)	No. (%)	No. (%)	No. (%)	
Fever (˚C)					
< 37.5	177 (47.45)	187 (50.13)	185 (49.60)	549 (49.06)	0.591
37.5 to 38.4	170 (45.58)	151 (40.48)	158 (42.36)	479 (42.81)	
≥ 38.5	26 (6.97)	35 (9.38)	30 (8.04)	91 (8.13)	
Local injection site complications[b]					
None	215 (57.64)	211 (56.57)	210 (56.3)	636 (56.84)	0.740[a]
Mild	154 (41.29)	156 (41.82)	154 (41.29)	464 (41.47)	
Severe	4 (1.07)	6 (1.61)	9 (2.41)	19 (1.70)	
Diarrhoea					
No	365 (97.86)	359 (96.25)	362 (97.05)	1086 (97.05)	0.453[a]
Yes	8 (2.14)	14 (3.75)	11 (2.95)	33 (2.95)	
Persistent crying					
No	365 (97.86)	367 (98.39)	366 (98.12)	1098 (98.12)	0.961[a]
Yes	8 (2.14)	6 (1.61)	7 (1.88)	21 (1.88)	
Vomiting					
No	366 (98.12)	368 (98.66)	364 (97.59)	1098 (98.12)	0.603[a]
Yes	7 (1.88)	5 (1.34)	9 (2.41)	21 (1.88)	
Hypotonic hyporesponsive episode[c]					
No	370 (99.20)	373 (100.00)	372 (99.73)	1115 (99.64)	0.332[a]
Yes	3 (0.80)	0 (0.00)	1 (0.27)	4 (0.36)	

[a] *P-value based on Fisher's exact test.*
[b] *For definitions look at the Methods section.*
[c] *Paleness, unresponsiveness, decreased muscles tone.*

Fever was the most common complication after a pentavalent injection. The frequency of mild local complications at the injection site was 41.47% and that of severe local complications 1.70%. These findings were more or less similar to those of another study comparing the DTP vaccine with the pentavalent vaccine: fever was reported as the most common complication of the DTP vaccine (47.4%) and mild local complications at the injection site as the most common AEFI of the pentavalent vaccine (31.68%) (*4*). However, these results are slightly different from the findings of a similar study conducted in 2015 in Hamedan. In that study, the frequency of mild fever following injection of the pentavalent vaccine was reported as 12.6%, high fever as 0.1%, and swelling and redness at the injection site as 15.8% and 10.9% respectively (*7*). In a similar study on 173 infants aged 2–6 months in one of the northern provinces of the Islamic Republic of Iran, fever (54.0%) was the most common complication and the incidence of redness (5.7%) and swelling (6.9%) at the injection site were much lower (*8*).

In interpreting the statistical models in Table 3, it should be noted that the main purpose of including some variables, such as parents' education level, birth weight and obesity index, was merely to control for their confounding effects. In most previous similar studies, these variables were not measured and no relationship was reported for them. Perhaps the main reason was that no specific etiological relationship between these variables and the occurrence of complications is conceivable. However, the effect of parent's education level on health literacy, and especially on immunization issues among their offspring, is indisputable, and has been repeatedly reported in other studies (*9–11*).

One of the most important factors showing a relationship with topical complications at the injection site was the vaccine manufacturer. In univariate analysis, the chances of a mild local complication varied from 3.0 to 3.9 times greater than baseline, depending on the manufacturer. In multivariate analysis, after eliminating the effects of confounding factors, the relationship of only one manufacturer with mild local complication remained statistically significant. This relationship between the vaccine manufacturer and complications may be attributed to one of the first 2 types of complications, i.e. vaccine product-related reaction or vaccine quality defect-related reaction (*1,12*). However, to substantiate this relationship and differentiate between relationships, more extensive, controlled studies with appropriate sample size in each group would be necessary. It should be noted that in this observational study, no intervention

Table 3 Crude and multivariate analysis (logistic regression) of the relationship between AEFIs and characteristics of the participants, children aged around 2, 4 and 6 months, Zahedan, 2019

Model/variable	Crude OR (95% CI)	Adjusted OR (95% CI)	*P*-value[a]
Model No. 1 (*n* = 1100[b]) Response variable: local injection site complications (mild vs none)			
Mother's education category College education vs illiterate to diploma	0.44 (0.33–0.59)	0.42 (0.30–0.56)	< 0.001
Work experience (> 7 years vs 4–7 years)	1.48 (1.16–1.88)	1.85 (1.40–2.46)	< 0.001
Vaccine producer			
(Producer B vs producer A)	3.01 (1.01–9.02)	2.07 (0.67–6.42)	0.208
(Producer C vs producer A)	3.93 (1.31–11.82)	3.69 (1.20–11.37)	0.023
Fever within 72 hours of vaccination (°C)			
Mild (37.5 to 38.4) vs normal (≤ 37.4)	2.05 (1.59–2.64)	2.56 (1.94–3.36)	< 0.001
High (> 38.4) vs normal (≤ 37.4)	3.43 (2.14–5.52)	4.36 (2.63–7.23)	< 0.001
Birth weight (≥ 2500g vs < 2500 g)	0.51 (0.34–0.77)	0.45 (0.29–0.70)	< 0.001
Weight for age Z-score (< 1.0 vs ≥ 1.0)	1.59 (1.04–2.42)	1.81 (1.16–2.85)	0.009
Father's education category: college education vs illiterate to diploma[c]	0.48 (0.36–0.64)	0.44 (0.33–0.60)	< 0.001
Model No. 2 (*n* = 1119) Response variable: local injection site complications (severe vs none or mild)			
Fever within 72 hours of vaccination (°C)			
Mild (37.5 to 38.4) vs normal (≤ 37.4)	1.84 (0.53–7.22)	1.58 (0.50–5.00)	0.433
High (> 38.4) vs normal (≤ 37.4)	7.68 (1.90–32.37)	7.50 (2.23–25.22)	0.001
History of BCG lymphadenitis	3.85 (0.70–14.08)	3.89 (1.04–14.49)	0.043

OR = odds ratio; CI = confidence interval.

[a] *P-values from Wald-test logistic regression analysis.*

[b] *Participants with severe complications at the injection site (19 children) were not included in model No. 1.*

[c] *In fitting regression model No. 1, due to the association between level of education among the mothers and fathers (r = 0.73; P < 0.001), these variables were regressed in 2 separate models.*

was carried out to balance the distribution of vaccines from different manufacturers between the participants with respect to their characteristics, and therefore the distribution observed in Table 1 is completely random. We did not find any other study examining such a relationship, and thus, whether this finding implies a causal relationship or is merely a result of chance and random variation remains to be determined in any future observations or studies. In the case of severe local complications, vaccine manufacturer did not show a statistically significant relationship. However, in interpreting and comparing these results, it should be noted that only 19 participants (1.70% of the total sample) had severe vaccine complications, i.e. presumably the sample size may not have been large enough to achieve a convincing conclusion.

There were no statistically significant differences between the children who received the pentavalent vaccine for the second or third time and the children who received the vaccine for the first time in regard to the frequency of any of the AEFIs ($P > 0.05$ for all). Considering the frequency distribution of the types of AEFI in Table 1, even without a statistical test, it is clear that there is no significant difference in this regard. In multivariate analysis, this variable (round of vaccination) did not remain in any of the models. None of the similar studies conducted in the Islamic Republic of Iran or other countries on the pentavalent vaccine, or similar vaccines, have considered this variable (*3–5,7,8,11,13*).

In Model Number 2, the factors associated with the occurrence of severe injection site complications were modelled. Only 2 variables remained, fever and history of lymphadenitis following congenital BCG vaccination at birth. Children with BCG lymphadenitis were almost 4 times more likely to have a severe injection site complication. Regional lymphadenitis is usually the most common feature of BCG-induced disease requiring medical attention; however, this relationship has not been reported in other studies, and whether our finding that it was about 4 times more likely was a chance result or a true relationship requires further study and observation (*13,14*). In Model Number 2, those children having a fever over 38.4° C had 7+ times greater chance of developing a severe injection site complication The association of these 2 complications with each other is probably a result of systemic inflammatory mechanisms.

Another interesting finding in this study was a higher chance of reporting a complication at the injection site among children whose vaccinators had more work experience (OR =1.87; 95% CI: 1.40–2.48, *P*-value < 0.001). The expectation would usually be the contrary. It is possible that those with more work experience need retraining, or perhaps those who are new are more cautious and follow the instructions more accurately. Whatever the reason, this is a finding that system

administrators should take seriously and, on verification, seek to address the causes.

Mild fever (< 38.5° C) and mild local injection site complications were the most common complications observed in this study. Fever ≥ 38.5° C was observed in around 8% of children, and severe injection site complications in < 2%; the incidence of other complications was < 0.4–3.0%.

Comparing the findings of this study with similar studies in the Islamic Republic of Iran and other countries administering the pentavalent vaccine or other similar vaccines, this frequency of AEFIs may be considered to be as expected, and the use of this vaccine can be recommended. Using a pentavalent vaccine helps avoid the need to inject at least 3 types of vaccines differently. This is one of the important advantages of this vaccine.

Given that the follow-up period for children who participated in this study was not more than 3 days, based on our findings, it was not possible to comment on the long-term effects of this vaccine. Likewise, given that this study was not designed to compare vaccines produced by different manufacturers, it was not possible to comment definitively on the differences in the incidence of side-effects between the recipients of vaccines from different manufacturers. However, our results indicate that more detailed studies could provide more definitive information.

In reviewing the research literature, it appears that other studies have rarely addressed the details that have been considered in this study. While this makes the results of our study more interesting, it makes it difficult to find evidence to support them. On most of the issues raised by the study, confirmation or rejection of our findings are dependent on more detailed studies in the future, and many of the findings in this study should be considered as exploratory.

Acknowledgement

The authors and project executives would like to thank all the frontline health care providers, those to whom this work belongs.

Funding: This work was supported by Zahedan University of Medical Sciences, Zahedan, Islamic Republic of Iran (grant number 9070).

Competing interests: None declared.

Manifestations postvaccinales indésirables aiguës liées au vaccin pentavalent DTC-HB-Hib au cours de la première année de vie

Résumé

Contexte : Depuis novembre 2014, le vaccin pentavalent (diphtérie, tétanos, coqueluche, hépatite B et Hib ou DTC-HB-Hib) est intégré au programme national de vaccination iranien.

Objectifs : Nous avons mené une étude prospective à Zahedan, dans le sud-est de la République islamique d'Iran, afin de déterminer l'incidence des manifestations postvaccinales indésirables (MAPI) liées au vaccin pentavalent chez les enfants âgés de moins d'un an.

Méthodes : Au moyen d'un sondage par grappe, 1119 enfants âgés de 2 à 10 mois fréquentant 15 centres de soins de santé publique ont été invités à participer à l'étude, par l'intermédiaire de leurs parents. Ces derniers ont été formés pour enregistrer et signaler toutes MAPI en répondant à un questionnaire. Ils ont reçu pour instruction de reconduire l'enfant au centre de soins de santé pour qu'il soit examiné de manière plus approfondie par un médecin s'ils observaient des complications dans les trois jours suivant la vaccination.

Résultats : Les MAPI les plus fréquemment signalées étaient les suivantes : fièvre (50,94 %), complications bénignes (41,46 %) et graves (1,70 %) au point d'injection, pleurs persistants pendant au moins trois heures (1,88 %), épisodes d'hypotonie-hyporéactivité (0,36 %), vomissements (1,88 %), diarrhée (2,95 %) et abcès stérile (0,62 %). Il n'y a pas eu de cas de convulsions, d'abcès purulent ou d'éruption cutanée. L'expérience professionnelle des agents de vaccination (OR = 1,85 ; IC à 95 % : 1,4-2,46) affichait une association statistique significative avec l'incidence des complications locales bénignes au point d'injection. Ceux qui avaient des antécédents de lymphadénite liée au vaccin Bacille Calmette-Guérin (BCG) (OR = 3,89 ; IC à 95 % : 1,04-14,49) présentaient un risque plus élevé de complications locales graves au point d'injection.

Conclusions : L'incidence des MAPI graves observée dans la population de l'étude après l'administration du vaccin pentavalent se situait dans la fourchette attendue. Toutefois, certaines des relations examinées dans la présente étude nécessitent des recherches plus approfondies.

الأحداث الضارة الشديدة بعد التطعيم باللقاح خماسي التكافؤ في السنة الأولى من العمر

شاهروخ إيزادي، مهدي محمدي، ماجد سرتبي، منوشهر كرامي، حسين كريمي

الخلاصة

الخلفية: أُدرج اللقاح الخماسي التكافؤ (الدفيتريا + السعال الديكي (الشاهوق) + التيتانوس والتهاب الكبد B ولقاح المستدمية النزلية من النوع ب أو اللقاح الثلاثي HB–Hib) في برنامج التطعيم الوطني الإيراني منذ نوفمبر/ تشرين الثاني 2014.

الأهداف: هدفت هذه الدراسة الاستباقية التي أجريت في زاهدان، بجنوب شرق جمهورية إيران الإسلامية، الى تحديد معدل وقوع الأحداث الضارة بعد التطعيم باللقاح الخماسي في حالة الأطفال الذين تقل أعمارهم عن عام واحد.

طرق البحث: باستخدام الطريقة العنقودية لأخذ العينات، دُعي 1119 طفلًا، تتراوح أعمارهم بين شهرين و10 أشهر للمشاركة في هذه الدراسة في 15 عيادة صحية عامة، ووُجهت الدعوة إلى آبائهم. وجرى تدريب الآباء على تسجيل كل حدث ضار بعد التطعيم والإبلاغ عنه في استبيان. كذلك طُلب من الآباء التوجه بالطفل إلى العيادة ليُجري الطبيب المزيد من الفحوص، إذا لاحظوا مضاعفات خلال 3 أيام من تلقّي اللقاح.

النتائج: كانت أكثر الأحداث الضارة بعد التطعيم شيوعًا: الحمى (50.94٪)، والمضاعفات المتوسطة (41.46٪)، والمضاعفات الشديدة (1.70٪) في موضع الحَقْن، والبكاء المستمر 3 ساعات أو أكثر (1.88٪)، ونوبات نقص استجابة الدم لنقص التوتر (0.36٪)، والقيء (1.88٪)، والإسهال (2.95٪)، والخراج العقيم (0.62٪). ولم تُسجل حالات تشنُّج أو خراج قيحي أو طفح جلدي. وأظهرت الخبرة العملية للقائمين على التطعيم (نسبة الأرجحية = 1.85؛ 95٪ فاصل الثقة: 1.4 – 2.46) ارتباطًا إحصائيًّا كبيرًا، مع حدوث مضاعفات موضعية خفيفة في موضع الحَقْن. وأولئك الذين سبق أن أُصيبوا بالتهاب الغدد الليمفاوية بعصيات كاليت جيران (BCG) أكثر عرضة للمضاعفات الموضعية الحادة في موضع الحقن (نسبة الأرجحية = 3.89؛ 95٪ فاصل الثقة: 1.04 – 14.49).

الاستنتاجات: إن معدل ملاحظة وقوع أحداث خطرة ضارة بعد التطعيم بتلقّي حَقْن اللقاح الخماسي التكافؤ بين مجتمع الدراسة ضمن النطاق المتوقع. ورغم ذلك، فإن بعض العلاقات التي لوحظت في هذه الدراسة تستحق المزيد من البحث.

References

1. Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification. Geneva: World Health Organization; 2018.
2. Atkinson KM, Ducharme R, Westeinde J, Wilson SE, Deeks SL, Pascali D, et al. Vaccination attitudes and mobile readiness: a survey of expectant and new mothers. Hum Vaccin Immunother. 2015;11:1039–45. doi:10.1080/21645515.2015.1009807
3. Bavdekar A, Malshe N, Ravichandran L, Sapru A, Kawade A, Lalwani S, et al. Clinical study of safety and immunogenicity of pentavalent DTP-HB-Hib vaccine administered by disposable-syringe jet injector in India. Contemp Clin Trials Commun. 2019 Jan 9;14:100321. doi:10.1016/j.conctc.2019.100321
4. Khazaei Z, Moradi G, Zahraei SM, Gouya MM, Goodarzi E, Yaghini F, et al. The comparison of the adverse events of pentavalent vaccine and DPT vaccine in 2–6 months infants in Iran: a national study. Ann Glob Health. 2020 Feb 3;86(1):11. doi:10.5334/aogh.2449
5. Punjabi NH, Richie EL, Simanjuntak CH, Harjanto SJ, Wangsasaputra F, Arjoso S, et al. Immunogenicity and safety of four different doses of Haemophilus influenzae type b-tetanus toxoid conjugated vaccine, combined with diphtheria-tetanus-pertussis vaccine (DTP-Hib), in Indonesian infants. Vaccine. 2006;24:1776–85. doi:10.1016/j.vaccine.2005.10.023
6. Imran H, Raja D, Grassly NC, Wadood MZ, Safdar RM, O'Reilly KM. Routine immunization in Pakistan: comparison of multiple data sources and identification of factors associated with vaccination. Int Health. 2018 Mar 1;10(2):84–91. doi:10.1093/inthealth/ihx067
7. Karami M, Ameri P, Bathaei J, Berangi Z, Pashaei T, Zahiri A, et al. Adverse events following immunization with pentavalent vaccine: experiences of newly introduced vaccine in Iran. BMC Immunol. 2017;18:42. doi:10.1186/s12865-017-0226-8
8. Sharafi R, Mortazavi J, Heidarzadeh A. Comparison of complications of pentavalent and DTP vaccination in infants aged 2–6 months in Anzali, Iran. Iranian J Neonatol. 2016;7:1–6. doi:10.22038/IJN.2016.7105
9. Sykes S, Wills J, Rowlands G, Popple K. Understanding critical health literacy: a concept analysis. BMC Public Health. 2013;13:150. doi:10.1186/1471-2458-13-150
10. Jani JV, De Schacht C, Jani IV, Bjune G. Risk factors for incomplete vaccination and missed opportunity for immunization in rural Mozambique. BMC Public Health. 2008;8:161. doi:10.1186/1471-2458-8-161
11. Torun SD, Bakirci N. Vaccination coverage and reasons for non-vaccination in a district of Istanbul. BMC Public Health. 2006;6:125. doi:10.1186/1471-2458-6-125
12. Weisser K, Barth I, Keller-Stanislawski B. Sicherheit von impfstoffen [Vaccine safety]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2009;52:1053–64. doi:10.1007/s00103-009-0961-y

13. Lopes SRC, Perin JLR, Prass TS, Carvalho SMD, Lessa SC, Dórea JG. Adverse events following immunization in Brazil: age of child and vaccine-associated risk analysis using logistic regression. Int J Environ Res Public Health. 2018 Jun 1;15(6):1149. doi:10.3390/ijerph15061149

14. Rermruay R, Rungmaitree S, Chatpornvorarux S, Brukesawan C, Wittawatmongkol O, Lapphra K, et al. Clinical features and outcomes of Bacille Calmette-Guérin (BCG)-induced diseases following neonatal BCG Tokyo-172 strain immunization. Vaccine. 2018;36:4046–53. doi:10.1016/j.vaccine.2018.05.098