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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

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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