International Journal of Contemporary Pediatrics
Panda BK et al. Int J Contemp Pediatr. 2021 Feb;8(2):243-247
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20210107

Original Research Article

Safety evaluation following immunization of pentavalent vaccine (multi-dose vial): experiences and comparative study

Bijoy Kumar Panda[1]*, Raveena Bajaj[1], Dipeeka Surve[1], Ruma Deshpande[2]

[1]Department of Clinical Pharmacy, Poona College of Pharmacy, Bharati Vidyapeeth (Deemed to be University), Erandwane, Pune, Maharashtra, India
[2]Department of General Medicine, Bharati Vidyapeeth University Hospital and Research Center, Pune, Maharashtra, India

Received: 20 October 2020
Revised: 28 December 2020
Accepted: 06 January 2021

***Correspondence:**
Dr. Bijoy Kumar Panda,
E-mail: bijoy.panda@bharatividyapeeth.edu

ABSTRACT

Background: Combination vaccines have many benefits but sometimes may result in unexpected side effects which may make the vaccine unfit for administration particularly with multidose vials.
Methods: Healthy infants aged 6-8 weeks who came for routine immunization of liquid pentavalent vaccine were included in the study. All infants were observed for 30 minutes, post vaccination. Telephonic interview was conducted to detect AEFIs at 1 week and 1 month post vaccination.
Results: The common AEFIs were found to be fever and pain at injection site. A comparison of the incidence (per 100 doses) of AEFIs after 1st, 2nd and 3rd dose of pentavalent vaccine showed that AEFIs goes on reducing with dose. Incidence (per 100 doses) of fever and local AEFIs was more (statistically significant) with multi-dose vial pentavalent vaccine.
Conclusions: The multi-dose vial liquid pentavalent vaccine was found to be equally tolerable compared to single-dose vial liquid pentavalent vaccine.

Keywords: Multi-dose vial, Liquid pentavalent vaccine, Clinical trial, AEFI, Comparison, Safety

INTRODUCTION

National immunization programme has achieved remarkable outcome in controlling and eliminating several vaccine-preventable diseases.[1] Over time, the number of immunizations recommended for pediatrics in the first 2 years of life has dramatically increased. Indeed, the increased number of injections a child receives per visit has raised concerns among health workers and parents. Out of this concern arose the concept of combination vaccines.[2] Combination vaccines are beneficial in eliminating the associated pain and trauma, reducing the cost involved and increasing compliance with immunization schedule.

A liquid pentavalent vaccine containing DTwP-HepB-Hib was incorporated in the Universal Immunization Program of India with the funding from Global Alliance for Vaccines and Immunization (GAVI).[3] Currently, this combination vaccine is being used instead of the trivalent vaccine (DPT). Safety profile of combined pentavalent vaccine is not well known and documented. Therefore, some trials and subsequent studies were performed for the vaccine to be added to routine immunization programs.[4-8] However, there were concerns raised regarding safety of pentavalent vaccine administration in other countries.[9,10] Moreover, prior to vaccine licensure, size of the clinical trials is not sufficient to identify rare or deferred AEFIs.[11] Therefore, more attention is being given to the adverse

events that may follow immunization to establish public and healthcare stakeholder confidence and maintain the gains made by such national programs.

Studies have reported that single-dose vial improve vaccine safety.[12] However, in developing countries, multi-dose vial prove to be economical but has challenges like contamination due to frequent transportation and unsafe injection practices.[13]

The aim of this study was to examine the safety of liquid pentavalent vaccine (multi-dose vial) introduced to immunization program compared to single-dose vial.

METHODS

Study design

This was an open label, active surveillance prospective cohort study that evaluated the safety of a multi-dose vial liquid pentavalent vaccine (DTwP-HepB-Hib) in Bharati Vidyapeeth University Medical College and Hospital, a tertiary care teaching hospital, Pune, Maharashtra, India.

The study was undertaken from August 2017 July 2018. Ethical approval for the study was obtained from the Institutional Ethics Committee. Infants receiving the multi-dose pentavalent vaccine were enrolled after the parents/guardians consent.

Sample size

The planned sample size was 636 evaluable infants. This sample size yields 90% power with α=0.05 for a 20% increase in incidence of adverse events in a population.5 This was calculated with the help of online statistics ClinCalc.com calculator.

Vaccinees, vaccines and vaccination

Healthy infants aged 6-8 weeks were enrolled in the study, unless possibly allergic to any component of vaccines, or immunized previously with DTP.

Infants with an acute illness, chronic illnesses at the time of enrolment, congenital disorders, allergic reactions, convulsions and known or suspected to have impaired immune function were excluded.

The infants were included on the basis of their visit to the pediatric OPD according to the immunization schedule provided. All enrolled infants received the government supplied liquid pentavalent vaccine (manufactured by Biological E Pvt. Ltd) for all the three doses administered at age 6, 10 and 14 weeks intramuscularly in the upper thigh, the volume 0.5 ml.

Follow up

All infants were observed for 30 minutes post vaccination.

Potential delayed events were captured via a telephonic interview through a structured questionnaire. Solicited adverse events following immunization (AEFI) occurring within 24-48 hours included local reactions of pain, redness, swelling and nodule at injection site (examined by pediatrician on next day of telephonic interview) and systemic reactions like fever, febrile seizure, irritability, persistent crying, drowsiness, restlessness, vomiting and diarrhea. Fever, redness and swelling were analysed according to standard definitions from Brighton collaboration guidelines.14-16 In addition, parents were also advised to record any other abnormal event following vaccination.

Incidence (per 100 vaccine doses) of the outcomes studied (i.e. the adverse events after pentavalent immunization) was calculated as number of reported AEFIs divided by the total number of administered vaccine doses.

Risk ratio (RR) and chi-square test was used to explore gender differences. Incidence of adverse events after each dose of Pentavac® and Easyfive® reported in a clinical trial5 were summed up and compared with AEFIs reported with multi-dose vial liquid pentavalent vaccine using Chi square test. All statistical analyses were conducted at a significance level of 0.05.

RESULTS

This study included 726 infants who had received 2178 doses of liquid pentavalent vaccine (multi-dose vials).

The mean age of infants in the study group was found to be 52±2.8 days where, 54.1% (n=393) were males. There was no difference in baseline characteristics (age, male to female ratio and birth weight) compared to clinical trial of single-dose vaccine formulation.[5]

Fever was the most common reported AEFI followed by pain, swelling and redness at injection site as shown in Table 1.

Analyses for AEFIs between the doses of liquid pentavalent vaccine (multi-dose vial) revealed that the incidence (per 100 doses) of pain (p=0.03) and fever (p≤0.01) were significantly higher after the first dose compared to the second dose.

Similarly, incidence (per 100 doses) of AEFIs like pain (p=0.0001) and redness (p=0.002) were found to be significantly higher in the second dose compared to the third dose.

Significant gender differences were found with regard to swelling at site of injection where the incidence (per 100 doses) was higher in females (p=0.001) as shown in Table 2. There was no association of any other AEFI with gender.

As shown in Table 3, local AEFIs like pain, swelling and redness at the site of injection and systemic AEFIs like fever was found to be higher with multi-dose vial compared to single-dose vial liquid pentavalent vaccine.

Table 1: Comparison of incidence (per 100 doses) of AEFI after 1st, 2ndand 3rddoses of multi-dose vial liquid pentavalent vaccine.

Variables	Incidence (per 100 doses) of AEFIs				
	After 1st dose (n-726)	After 2nd dose (n-726)	After 3rd dose (n-726)	P value (1st and 2nd dose comparison)	P value (1st and 2nd dose comparison)
Swelling	270 (37.1)	243 (33.5)	23 (32.3)	0.153	0.6549
Pain	338 (46.5)	298 (41.1)	221 (30.5)	0.03	0.0001
Redness	148 (20.4)	124 (17.1)	83 (11.4)	0.121	0.0026
Nodule	2 (0.3)	1 (0.13)	0	1	1
Abscess	1 (0.1)	1 (0.13)	0	1	1
Fever	440 (60.6)	392 (54.0)	364 (50.1)	0.0126	0.1561
Vomiting	4 (0.5)	1 (0.1)	1 (0.1)	0.3741	1
Persistent crying	22 (3)	18 (2.5)	15 (2.1)	0.63	0.72
Irritability	71 (9.8)	64 (8.8)	54 (7.4)	0.58	0.3875
Diarrhoea	4 (0.5)	2 (0.3)	1 (0.1)	0.45	1

n- Number of infants.

Table 2: The incidence (per 100 doses) of adverse events following immunization with liquid multi-dose vial pentavalent vaccine in male and female infants.

Adverse events		Incidence (per 100 doses)		P value	Risk ratio
		Male	Female		(95% CI)
Swelling	Yes	368 (31.2)	379 (37.9)	0.001	0.82 (0.73-0.92)
	No	811 (68.8)	620 (62.1)		
Pain	Yes	458 (38.8)	399 (39.9)	0.62	0.97 (0.88-1.08)
	No	721 (61.2)	600 (60.1)		
Redness	Yes	182 (15.4)	173 (17.3)	0.24	0.89 (0.74-1.08)
	No	997 (84.6)	826 (82.7)		
Nodule	Yes	2 (0.2)	1 (0.1)	1	1.69 (0.15-18.6)
	No	1177 (99.8)	998 (99.9)		
Abscess	Yes	1 (0.1)	1 (0.1)	1	0.85 (0.05-13.5)
	No	1178 (99.9)	998 (99.9)		
Fever	Yes	635 (53.8)	561 (56.2)	0.29	0.96 (0.89 - 1.03)
	No	544 (46.2)	438 (43.8)		
Vomiting	Yes	3 (0.3)	3 (0.3)	1	0.85 (0.17 - 4.19)
	No	1176 (99.7)	996 (99.7)		
Persistent crying	Yes	26 (2.2)	29 (2.9)	0.33	0.76 (0.45 - 1.28)
	No	1153 (97.8)	970 (97.1)		
Irritability	Yes	95 (8.1)	94 (9.4)	0.28	0.86 (0.65 - 1.12)
	No	1084 (91.9)	905 (90.6)		
Diarrhoea	Yes	3 (0.3)	4 (0.4)	0.70	0.64 (0.14 - 2.88)
	No	1176 (99.7)	995 (99.6)		

Number of male infants= 393 (1179 vaccine doses), Number of female infants= 333 (999 vaccine doses).

DISCUSSION

This is one of a rare prospective safety monitoring study of multiple dose vials of pentavalent vaccine under programmatic settings in a tertiary care teaching hospital with a large sample size compared to other studies conducted in western part of Maharashtra, India. The AEFIs reported in the present study were found to be non-serious. This finding is in line with the results obtained in a multicentre clinical trial involving single-dose vial of pentavalent vaccines.[5] Contrary to the above observation, many serious adverse events and deaths were reported following pentavalent vaccine in Sri Lanka, Bhutan and Pakistan.[9] The results obtained in the present study showed that the only significant gender difference was found with regard to swelling at injection site where the incidence (per 100 doses) was higher in females (p=0.001). A study in Iran found significant gender difference with regard to persistent crying, which was significantly more common among males.[17] There are no reasons cited in literature for such significant differences in AEFI based on gender and remains unknown.

Table 3: Comparison of incidence of AEFIs associated with multi-dose vial liquid pentavalent vaccine with single-dose vial liquid pentavalent vaccine.[5]

Adverse events	Incidence of AEFI (%) after 1st dose			Incidence of AEFI (%) after 2nd dose			Incidence of AEFI (%) after 3rd dose		
	Multi-dose vial (n=726)	Single-dose vial (n=484)	p-value	Multi-dose vial (n=726)	Single-dose vial (n=484)	P value	Multi-dose vial (n=726)	Single-dose vial (n=484)	P value
Swelling	305 (42)	216 (44.6)	0.37	287 (39.5)	182 (37.6)	0.50	155 (21.4)	144 (29.7)	0.001
Pain	349 (48.1)	297 (61.4)	<0.0001	286 (39)	272 (56.2)	<0.0001	225 (31)	230 (47.5)	<0.0001
Redness	137 (18.9)	113 (23.3)	0.07	124 (17.1)	90 (18.6)	<0.0001	94 (12.9)	72 (14.9)	0.34
Nodule	3 (0.4)	6(1.2)	0.16	0	1 (0.2)	0.4	0	0	1
Fever	435 (59.9)	215 (44.4)	<0.0001	442 (60.9)	211 (43.6)	<0.0001	319 (43.9)	148 (30.5)	<0.0001
Vomiting	4 (0.55)	15 (3.1)	0.0006	2 (0.3)	12 (2.5)	0.0006	0	8 (1.6)	0.0006
Persistent crying	30 (4.13)	67 (13.8)	<0.0001	12 (1.6)	43 (8.9)	<0.0001	13 (1.8)	29 (6)	0.0002
Irritability	86 (11.8)	140 (29)	<0.0001	60 (8.3)	116 (24)	<0.0001	43 (5.9)	96 (20)	<0.0001
Diarrhoea	5 (0.7)	16 (3.3)	0.001	2 (0.3)	16 (3.3)	<0.0001	0	15 (3.1)	<0.0001

n- Number of infants= number of doses.

A comparison of the incidence (per 100 doses) of AEFI after 1st, 2nd and 3rd dose of liquid pentavalent vaccine showed that incidence of AEFIs goes on reducing with subsequent booster dose. Probable reasons for such reduction in incidences may be increase in muscle mass and deeper intramuscular injections, mothers being more worried about AEFI after 1st dose and the use of acetaminophen in subsequent booster doses due to the experiences mothers gain after the first dose (as conveyed by parents via telephonic interview).

Local AEFIs like pain, swelling and redness at the site of injection and systemic AEFIs like fever were found to be higher with multi-dose vial compared to single-dose vial liquid pentavalent vaccine. Such significant increase with multi-dose vial can be partly accounted for by several factors, including the multi-dose vial leading to increased chances of contamination and challenges due to frequent transportation. The concomitant administration of other vaccines like Rotavirus vaccine, IPV, PCV along with pentavalent vaccine may further increase incidence of fever. On a contrary, systemic AEFI i.e vomiting, persistent crying, irritability, diarrhea were more frequently observed with single-dose vial. Apart from this, few cases of abscess were observed with multi-dose vial. Hindrance of limb movements, loss of appetite and refusal of feeds were also reported with single-dose vial which was not observed in our study.[5]

The limitation includes lack of prospective control group (single dose vials) and follow-up for short duration of period. Long duration follow-up of study cohort is warranted to document rare adverse events. Immunogenicity was not determined as this was not our objective, though it should be a future long-term study as it is said that quality of multiple dose vaccines get

compromised due to inapropriate handling and storage conditions in programmatic settings.

CONCLUSION

The multi-dose vial liquid pentavalent vaccine was found to be equally safe and tolerable compared to single-dose liquid pentavalent vaccines. Fever and local reactions were more but resolved by proper drug therapy and ice application on injection site. No vaccine related serious adverse event were recorded in the study cohort.

ACKNOWLEDGEMENTS

The authors are thankful to the parents for cooperating in the study. The authors also acknowledge the contributions of the clinicians and the paramedical staff.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Vashishtha VM, Kalra A, Bose A, Thacker N, Yewale VN, Bansal CP et al. Indian Academy of Pediatrics, Advisory Committee on Vaccines and Immunization Practices (ACVIP), Indian Academy of Pediatrics (IAP) recommended immunization schedule for children aged 0 through 18 years, India, 2013 and updates on immunization. Indian Pediatr. 2013;50:1095-108.
2. Sreedhar S, Antony A, Poulose N. Study on the effectiveness and impact of pentavalent vaccination program in India and other south Asian countries. Hum Vaccin Immunother. 2014;10:2062-65.
3. UNICEF India. 18 Million Indian Children to Receive Life Saving Five-in-One Vaccine GENEVA. 2009. Available from: http://unicef.in/PressReleases/162/18-Million-Indian-Children-to-Receive-Life-Saving-Five in One-Vaccine-. Last accessed on
4. Dodoo A, Renner L, van Grootheest A, Labadie J, Agyei KOA, Hayibor S et al. Safety Monitoring of a New Pentavalent Vaccine in the Expanded Program on Immunization in Ghana. Drug Saf. 2007;30:347-56.
5. Sharma H, Yadav S, Lalwani S, Gupta V, Kapre S, Jadhav S et al. A phase III randomized, controlled study to assess the immunogenicity and tolerability of DTPw–HBV–Hib, a liquid pentavalent vaccine in Indian infants. Vaccine. 2011;29:2359-64.
6. Schmid D, Macura-Biegun A, Rauscher M. Development and introduction of a ready-to-use pediatric pentavalent vaccine to meet and sustain the needs of developing countries – Quinvaxem®: The first 5 years. Vaccine. 2012;30:6241-48.
7. Sharma H, Yadav S, Lalwani S. Immunogenicity and safety of an indigenously manufactured reconstituted pentavalent (DTwP-HBV+Hib) vaccine in comparison with a foreign competitor following primary and booster immunization in Indian children. Human Vaccines. 2011;7:451-7.
8. Kanra G, Kara A, Demiralp O. Safety and Immunogenicity of a New Fully Liquid DTPw-HepB-Hib Combination Vaccine in Infants. Human Vaccines. 2006;2:155-60.
9. Global Advisory Committee on Vaccine Safety review of pentavalent vaccine safety concerns in four Asian countries. Report from the12 June2013 meeting. Last accessed on 15 October 2013.
10. Deshpande R, Ghongane B. Current status of vaccines against Diphtheria, Pertussis, Tetanus, Hepatitis B and Hib: A Review. Research & Reviews: AHMS. 2014;3:5-13.
11. Kumar A, Garg S, Yadav S. Pharmacovigilance study of vaccine. IJPPS. 2015;4:1187-1201.
12. Y.Lee B, A. Norman B, Marie Assi T, Chen SI, Bailey RR, Rajgopal J et al. Single versus multi-dose vaccine vials: An economic computational model. Vaccine. 2010;28:5292-300.
13. Drain PK, Nelson CM, Lloyd JS. Single-dose versus multi-dose vaccine vials for immunization programmes in developing countries. Bull World Health Organ. 2003; 81:726-31.
14. Kohl KS, Walop W, Gidudu J. Swelling at or near injection site: case definition and guidelines for collection, analysis and presentation of immunization safety data. Vaccine. 2007;25:5858-74.
15. Rothstein E, Kohl KS, Ball L. Nodule at injection site as an adverse event following immunization: case definition and guidelines for data collection, analysis and presentation. Vaccine. 2004;22:575-85.
16. Marcy SM, Kohl KS, Dagan R. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis and presentation. Vaccine. 2004;22:551-6.
17. Karami M, Ameri P, Bathaei J. Adverse events following immunization with pentavalent vaccine: experiences of newly introduced vaccine in Iran. BMC Immunol. 2017;18.
18. Liquid pentavalent combination vaccine (pq_253_254_DTP_HepB_Hib_liquid_BiolE_PI) [package insert]. Hyderabad (Telangana): Biological E Limited; 2014.

Cite this article as: Panda BK, Bajaj R, Surve D, Deshpande R. Safety evaluation following immunization of pentavalent vaccine (multi-dose vial): experiences and comparative study. Int J Contemp Pediatr 2021;8:243-7.