Cross-sectional Retrospective Study on Paracetamol Post Infants’ Vaccination in Malaysia

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Introduction: Practice of dispensing paracetamol (PCM) in post infants’ vaccination remains debatable in Malaysia as the administration of PCM postvaccination in infants was found to cause the vaccine to be less effective, thus requiring appropriate regulation measures. Objective: This research aimed to investigate the prevalence of adverse events following immunization (AEFI) with/without PCM to be prescribed post infants’ vaccination in Malaysia (possible associated factors: age, types and stages of vaccination, concomitant vaccines and drugs, and/vitamins). Materials and Methods: A retrospective cross-sectional study was conducted from 2011 to 2017. The AEFI was extracted from Quests 2, 3, and 3+ System of National Pharmaceutical Regulatory Agency (NPRA). The population of vaccinated infants was obtained from the Ministry of Health (MOH) Malaysia official website. The AEFI data were further categorized into (i) AEFI with possibility for PCM to be prescribed, and (ii) AEFI with no possibility for PCM to be prescribed. The data were analyzed using Microsoft Excel 2013, Portland, USA simple and multiple logistic regression tests, Statistical Package for the Social Sciences (SPSS) software programme, version 22.0 (IBM), New York, USA. Result: Various AEFI cases (359 infants) were reported. DTaP/Hib/IPV and measles–mumps–rubella (MMR) showed higher prevalence of AEFI with/without PCM to be prescribed post infants’ vaccination cases per 100,000 population (2.07 and 2.21, respectively) than other types of vaccinations. DTaP/Hib/IPV (2 months) vaccination showed the highest value (3.00) among other age groups. Backward elimination presented DTaP/Hib/IPV (3–4 months) (95%CI; 0.231, 0.899%; P = 0.023) was the possible associated factor. Hepatitis B (1–5 months), DTaP/Hib/IPV (3–4 months), DTaP/Hib/IPV (5–12 months), concomitant vaccines as well as concomitant drugs and/ vitamins were the identified potential cofounders. Conclusion: Prescribing and dispensing of PCM post infants’ vaccination may be confined to DTaP/Hib/IPV (2–4 months) and 12 months MMR groups.

Keywords: Paracetamol, vaccination, infants
recommended in some countries for vaccination.\[^2\] However, there was lack of evidence that supports this intervention as paracetamol (PCM) was found to cause vaccine to be less effective.\[^2\] Latest study on the relevancy of PCM in post infants’ vaccination revealed that only two studies found significant benefit from prophylaxis PCM in fever and one study found significant benefit from prophylaxis PCM in fussiness, and conversely one study found no significant benefit from prophylaxis PCM in fever.\[^1-4\] This shows that prophylactic administration of PCM in post infants’ vaccination may be uncertain. Thus, this cross-sectional retrospective study was designed to describe the PCM prescribing groups’ prevalence and its possible associated factors by age of the infant upon vaccination, types of vaccination, and stages of vaccination.

**Materials and Methods**

The main sources of information were collected by using a structured data collection sheet developed by the researcher and reviewed by experts. The sources were from the National Pharmaceutical Regulatory Division (NPRA), Ministry of Health (MOH) Malaysia who collects adverse events following immunization (AEFI) in Malaysia, and Public Health Department (PHD), MOH Malaysia who collects the population of infants immunized in Malaysia. Two letters were sent to these government bodies to obtain permission for collecting data from their departments. The approvals from them were received on 23rd April 2014, 15th May 2014, and 25th September 2018.

**Study design and period**

This study involved retrospective cross-sectional design from 2011 to 2017 based in the availability of data provided by the government bodies. The data from NPRA were collected by reviewing the electronic medical records (EMR) of Quests 2, 3, and/3+ System to collect the number of AEFI. The EMR data firstly extracted types of vaccination that included in the Children Malaysian Immunisation Schedule (CMIS) followed by the year of AEFI occurred (i.e., 2011–2017), and finally the age of infants ≤1 year. The number of infants immunized for specific vaccines and age were collected from the PHD by reviewing online Health Indicator Report for each years via MOH Malaysia’s website. The researcher contacted the representative of PHD to collect other data that were inaccessible online.

**Population and sample**

The study sample includes all infants who were immunized with four main types of vaccines (i.e., BCG, Hepatitis B, DTP/Hib/IPV, and measles-mumps-rubella [MMR] vaccines) scheduled in the CMIS for infants ≤1 year old. For the purpose of standardization, measles vaccine and MMR vaccine (9 months) were not analyzed in this study as measles vaccine was injected in the state of Sabah only, and MMR vaccine (9 months) was only implemented in Malaysia since April 2016.

**Inclusion and exclusion criteria**

Any incomplete data on age and gender were excluded in this study. Data that were written AEFI occurred because of suspected vaccine were chosen in this study. The age of immunisation was adjusted according to the acceptable period of the current CMIS.

**Variables (independent and dependent)**

Data collected from the AEFI monitoring form include gender, age of infant upon vaccination, types of immunisation, concomitant vaccines as well as drugs and/ vitamins categorized as independent variables, and the PCM prescribing categorized as dependent variable.

**Paracetamol prescribing grouping**

This study involved discussion by health-care team members (a pediatrician, a statistician, a family medicine doctor, and two pharmacists) for the purpose of PCM prescribing grouping. Group 1 refers to cases of AEFI with possibility for PCM to be prescribed, and Group 2 refers to cases of AEFI with no possibility for PCM to be prescribed. These groupings are also based on the current user manual provided by World Health Organization (WHO) in 2018.

Fever and pain are defined as those mentioned “fever” and “pain” alone, respectively, in the data collected from the EMR of Quests 2, 3 and/3+ Systems. Febrile seizure is defined as those mentioned “fits (non-others specified), seizure and/ tonic-clonic convulsion with fever or febrile seizure” in the data collected from the EMR of Quests 2, 3 and/3+ Systems. PCM prescribing groups refer to groups of AEFI whereby PCM is possibly prescribed or otherwise (i.e., Group 1 and Group 2, respectively), postvaccination in infants. The adverse drug reaction (ADR) terminologies in Quests 2, 3, and/3+ Systems which stated fever and febrile seizure, and/ fever with seizure/ tonic-clonic convulsions/fits were grouped into Group 1 as PCM was prescribed and effectively used. Other ADR terminologies that present pain such as crying (pain score as 3 or 4 for Modified Behavioral Pain Score in Infants) was also grouped into Group 1. The other ADR terminologies not mentioned above found in the extracted data were grouped into Group 2.
**Calculation of paracetamol prescribing groups’ prevalence**

According to the Centre for Diseases Control (CDC) and Prevention, Department of Health and Human Sciences, United States of America, prevalence refers to the number of occurrences of the health indicator during the specified time period divided by the size of the population in which the health indicator occurs. The result is expressed as a percentage as follows:

\[
\text{Prevalence (expressed in \%) = \frac{\text{Persons with a given health indicator during a specified time period}}{\text{Population during the same time period \times 100}}.}
\]

Data collected from the NPRA serve as the numerator; meanwhile, data collected from the PHD serve as the denominator of the formulas above. All data collected from the NPRA include the number of cases of AEFI post types of vaccination analyzed in this study. On the contrary, data collected from PHD include the number of children immunized with the desired type of vaccine (in which DTaP/Hib/IPV vaccine). Both data were collected from the private as well as general health clinics and hospitals in Malaysia. Data were compiled and analyzed thoroughly.

**Statistical analysis**

Statistical analyses consisted of two steps, namely descriptive statistics and multinomial logistic regressions. Descriptive statistics was used for determining the trends of the PCM prescribing groups’ prevalence (Groups 1 and 2). Possible associated factors of the PCM prescribing groups’ prevalence used Simple (Enter Method) and Multiple (Backward Elimination (LR) Method) Logistic Regressions models of the Statistical Package for the Social Sciences (SPSS) software program, version 22.0 (IBM). Furthermore, cofounder was identified by comparing the estimated measure of association before and after adjusting for confounding whereby computing the measure of association both before and after adjusting for a potential confounding factor. If the difference of the two measure of association is 10% or more, then cofounding was present.

**Ethical issues**

This research was referred to Medical Research Ethics Committee (MREC), Secretariat of National Institutes of Health (NIHSEC), Malaysia (NMRR Reference Number: NMRR-17-2573-38799 [IIR]).

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**Figure 1:** Prevalence of Group 1 (AEFI with possibility for PCM to be prescribed) and Group 2 (AEFI with no possibility for PCM to be prescribed) per 100,000 by Age of Infants Upon Vaccination in Malaysia, 2011 till 2017
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RESULTS

Descriptive statistics: prevalence of Groups 1 and 2 per 100,000 population

DTaP/Hib/IPV (2 months) vaccination was the highest prevalence value per 100,000 population (3.00) among other age groups, whereby Group 1 showed only slightly lower value (1.41) than Group 2 (1.59). DTaP/Hib/IPV and MMR vaccination had higher prevalence values per 100,000 population (2.07 and 2.21, respectively) than other types of vaccinations in which both showed that Group 1 (1.17 for DTaP/Hib/IPV vaccination and 1.29 for MMR Vaccination) was only slightly higher than Group 2 (0.9 and 0.92, respectively). In addition, the first dose (i.e., 2 months) DTaP/Hib/IPV vaccination showed the highest values both for Group 1 (1.59) and Group 2 (1.41) than other stages of vaccinations [Figures 1–3].

Statistical analysis: possible associated factors of paracetamol prescribing groups postvaccination in infants (n = 359)

Data extracted from EMR of Quests 2, 3, and 3+ Systems firstly gathered 624 samples of vaccinated with types of vaccines (BCG, Hepatitis B, MMR, and DTaP/Hib, IPV). Then, 105 infants not vaccinated from 2011 to 2017 were excluded from the sample. The samples then filtered age of infants up to 12 months (which excluded 139 infants). Data with missing information (examples: no age, gender, ADR terms, years, and types...
of vaccines), which accounts for a total of 21 AEFI cases, were excluded in this research.

Simple analysis of 359 infants with various AEFI cases reported had revealed that no factor was possible associated with PCM prescribing groups [Table 1]. Multiple logistic regression tests (enter method and backward elimination LR method) presented that DTaP/Hib/IPV (3–4 months) (95%CI; 0.231, 0.899%; \( P = 0.023 \)) was the possible associated factor of PCM prescribing groups. The adjusted odds ratio for DTaP/ Hib/IPV (3–4 months) showed 0.455, which indicated that it is less likely for Group 2 since Group 1 is the reference. Hepatitis B (1–5 months) (91.57%), DTaP/Hib/IPV (3–4 months) (97.8%), DTaP/Hib/ IPV (5–12 months) (95.64%), concomitant vaccines (10.43%) as well as concomitant drugs and vitamins (29.45%) were the identified potential cofounders.

**Discussion**

DTaP/Hib/IPV (which contains diphtheria, tetanus, acellular pertussis, polio, and hemophilus influenza type B vaccines given as one shot) followed by MMR vaccination (which contains MMR vaccines given as one shot) showed the highest prevalence values of PCM prescribing groups than other types of vaccination. These results agreed are parallel with the study by Vesikari (2013), \cite{5} which found that increasing the number of types of vaccines injected at one shot may increase the opportunity of AEFI to be occurred, thus resulting in the increase in prevalence of Group 1 and Group 2. However, both PCM prescribing groups showed a minimum difference and very little prevalence values in 100,000 population. Moreover, Group 2 showed slightly higher value than Group 1. Hence, PCM dispensing practice for Group 1 may not be favorable postvaccination in infants.

Although this research collected data for 7 years, the sample size is deemed acceptable, indicated by the acceptable confidence interval lower and upper values. Coefficient of determination in this model was only 0.025–0.033; therefore, only 2.5%–3.3% of variability in the outcome was explained by gender, age of infants on vaccination, types of vaccination, concomitant vaccines as well as drugs and vitamins.\cite{6,7} In conclusion, there are many other factors such as the storage of vaccines and how the vaccines may be administered which may affect the prevalence values, should be explored. Since confounding was present in this model, the concomitant vaccines as well as drugs and vitamins may be considered for the next research although no significant values in the model was indicated.

**Limitation**

This study did not identify history of febrile seizures by the infants, which may be a factor of AEFI to be occurred. This is because the febrile seizures frequently recur, in which the reoccurrence rate is 30% overall, and increases to 60% if the initial febrile seizure occurs in a child <1 year. Consequently, ibuprofen and PCM have equally been recommended for administration at the time of DTaP immunisation and every 4h and 24h thereafter for children with a history of febrile seizures to reduce the possibility of postvaccination fever.\cite{2,8-10} This study also did not include cases of fever and/pain cured as a result of administering prophylaxis PCM. These factors may be classified into Group 1, which in this present research cannot be analyzed. The data regarding AEFI were limited to the reports from patients and health-care professionals, and the underreporting data were not available during this current research. Thus, the relatively small number of participating subjects may reduce the generalizability of the results.

**Conclusion**

The trends for PCM prescribing groups prevalence varied across years. Thus, it is difficult to make a conclusion regarding the relevancy of PCM postvaccination in infants. However, this study found that the prevalence values for both AEFI with/without PCM to be prescribed post infants’ vaccination in Malaysia groups revealed very small values in 100,000 populations, DTaP/Hib/IPV (2 months), and MMR (12 months) vaccines showed higher prevalence values than other age and types of immunisation groups. DTaP/Hib/IPV (3–4 months [second dose]) prevailed as the possible associated factor. Thus, the use of PCM in post infants’ vaccination may be confined to these groups.

Further research which involves regulatory, educational, and managerial strategies is necessary in deciding PCM to be rational use for postvaccination in infants. The population data for the potential cofounders identified and possible factors discussed are proposed to be used and analyzed for the next research. These factors can be included in the AEFI monitoring form and analyzed in Quest 3 System for the next research.
Table 1: Associated factors of paracetamol prescribing groups post infants’ vaccination (n = 359)

| Variables                              | Simple logistic regression | Multiple logistic regression | Percentage of cofounding (%) |
|----------------------------------------|---------------------------|----------------------------|----------------------------|
|                                        | Regression coefficient (b) | Crude odds ratio (95%) | Wald statistic | P Value | Regression coefficient (b) | Adjusted odds ratio (95%) | Wald statistic | P Value |
| Gender                                 |                           |                           |               |         |                           |                           |               |         |
| Female                                 | 0                         | 1                         | 0             | 1       | 0.123                     | 1.131 (0.742, 1.723)      | 0.328          | 0.567   | 0.163  | 1.178 (0.764, 1.814) | 0.549 | 0.459 | 4.16   |
| Male                                   |                           |                           |               |         | 0.123                     | 1.131 (0.742, 1.723)      | 0.328          | 0.567   | 0.163  | 1.178 (0.764, 1.814) | 0.549 | 0.459 | 4.16   |
| Age of infants upon vaccination, m     |                           |                           |               |         |                           |                           |               |         |         |                           |       |       |         |
| 0 month (first dose) BCG               | 0                         | 1                         | 0             | 1       | 0.123                     | 1.131 (0.742, 1.723)      | 0.328          | 0.567   | 0.163  | 1.178 (0.764, 1.814) | 0.549 | 0.459 | 4.16   |
| 1-5 months (second dose) Hepatitis B   | -20.615                   | 0.000 (0.000, -)          | 0.000         | >0.999  | 21.098                    | (0.000, -)              | <0.001        |         | 0.000  | >0.999                    | -     |       |         |
| 6-12 months (third dose) Hepatitis B   | -21.357                   | 0.000 (0.000, -)          | 0.000         | 0.999   | 1.737 (0.614, 4.916)      | 0.552                    | <0.001        |         | 1.084  | 0.298                      | 91.57 |
| 2 months (first dose) DTaP/Hib/IPV     | -21.323                   | 0.000 (0.000, -)          | 0.000         | 0.999   | b                         | b                       | b             |         | b      | b                          | -     |       |         |
| 3-4 months (second dose) DTaP/Hib/IPV  | -20.664                   | 0.000 (0.000, -)          | 0.000         | 0.999   | -0.786                    | 0.455 (0.231, 0.899)      | 1.084          | 0.298   | 91.57 |
| 5-12 months (third dose) DTaP/Hib/IPV  | -20.536                   | 0.000 (0.000, -)          | 0.000         | 0.999   | -0.111                    | 0.895 (0.410, 1.952)      | 1.084          | 0.298   | 91.57 |
| 12 months (first dose) MMR             | -20.853                   | 0.000 (0.000, -)          | 0.000         | 0.999   | b                         | b                       | b             |         | b      | b                          | -     |       |         |
| Types of vaccination                   |                           |                           |               |         |                           |                           |               |         |         |                           |       |       |         |
| BCG                                    | 0                         | 1                         | 0             | 1       | 0.709                     | 2.033 (0.846, 4.886)      | 2.512          | 0.113   | 0.600  | 1.821 (0.709, 4.681) | 1.550 | 0.213 | 10.43  |
| Hepatitis B                            | -20.881                   | 0.000 (0.000, -)          | 0.000         | 0.999   | -21.162                   | 0.000 (0.000, -)          | -21.162        | 0.000   | 0.999 | -21.162                    | 0.000 | 0.999 | -21.162 |
| MMR                                    | -20.853                   | 0.000 (0.000, -)          | 0.000         | 0.999   | -20.853                   | 0.000 (0.000, -)          | -20.853        | 0.000   | 0.999 | -20.853                    | 0.000 | 0.999 | -20.853 |
| DTaP/Hib/IPV                           | -20.948                   | 0.000 (0.000, -)          | 0.000         | 0.999   | -20.526                   | 0.000 (0.000, -)          | -20.526        | 0.000   | 0.999 | -20.526                    | 0.000 | 0.999 | -20.526 |
| Concomitant vaccines                   |                           |                           |               |         |                           |                           |               |         |         |                           |       |       |         |
| Yes                                    | 0                         | 1                         | 0             | 1       | 0.709                     | 2.033 (0.846, 4.886)      | 2.512          | 0.113   | 0.600  | 1.821 (0.709, 4.681) | 1.550 | 0.213 | 10.43  |
| No                                     | -0.402                    | 0.669 (0.121, 3.700)      | 0.212         | 0.645   | -0.143                    | 0.866 (0.136, 5.530)      | 0.023          | 0.880   | 29.45 |

- BCG = Bacillus Calmette–Guérin
- Enter method
- Excluded in the final model (enter method)
- Included in the final model (backward elimination [LR] method)
- Age of 3-4 months (second dose) DTaP/Hib/IPV showed a significant value [95%CI; 1.141, 2.909%, P = 0.023, R² = 0.025 [Cox & Snell]–0.033 [Nagelkerke]]
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Conflicts of interest
There are no conflicts of interest.

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