RESEARCH PAPER

Study of Common Illnesses Before and After Vaccination: A Risk-interval Approach

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Objective: To compare the proportion of children who developed a specified illness in the 7 day post-vaccination window, with the background rate of the same event in the 7 day pre-vaccination window.

Study design: Risk interval approach (Self-controlled case-series).

Setting: Well Baby Clinic of Christian Medical College, Vellore.

Participants: 1602 healthy infants and under-six children presenting for routine vaccination.

Outcome measures: Episode of any illness.

Methods: The interviewer enquired about any adverse event or illness experienced by the child for each day of the week preceding the administration of age-appropriate vaccines. A second interview (telephonic) was conducted by the same interviewer one week following vaccine administration to enquire about adverse event(s) experienced by the child for each day of the subsequent week using a similar protocol.

Results: With multiple vaccines delivered at appropriate ages, common childhood illnesses that could be reported as adverse events following immunization, except fever (RR=5.7, 95% CI=4.50-7.35), occurred at higher rates pre-vaccination. Risk Ratios of fever following whole cell (RR=9.3, 95% CI=6.43-13.52) and acellular (RR=8.5, 95% CI=3.82-18.91) vaccines were similar, with both showing a decreasing trend with increasing age. The gastrointestinal adverse event profile [diarrhea (RR=0.6, 95% CI=0.14-2.51) and vomiting (RR=1.0, 95% CI=0.14-7.10)] for rotavirus vaccine was similar pre- and post-immunization.

Conclusions: Since most adverse events to vaccines are also common childhood illnesses, estimating the background rates of common illnesses is important to accurately ascertain a causal relationship.

Keywords: *Adverse events, Adverse events following immunization (AEFI) Background rate, Routine vaccination.*

Ensuring safety of vaccines through close monitoring of adverse events helps build community trust, which in turn is the key to the success and long-term sustenance of immunization programs worldwide [1,2]. In particular, acute self-limiting adverse events following vaccination, some of which are also common illnesses in children, are the most frequent illnesses ascribed to vaccines [3]. However, other than data from clinical trials, most published evidence provides limited information about the profile of adverse events, especially in settings where multiple and combination vaccines are administered simultaneously according to a routine immunization program.

The objective of this study was to compare the proportion of children who developed a specified illness in the 7 day post-vaccination window with the background rate of the same event in the 7 day pre-vaccination window using a risk-interval approach, which has the advantage of involving only immunized subjects [4].

METHODS

The study was conducted in the Well Baby Clinic of Christian Medical College (CMC), Vellore from February 2013 to July 2014. As this is a private tertiary care center, where the caretakers have to pay out of pocket for vaccines and services, the clientele for vaccination comprises mostly of the lower and upper middle income groups living in Vellore and its adjoining districts and states [5].

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Study design: The risk-interval (also known as vaccinated cohort) approach is a special case of the self-controlled case series (SCCS) design and is a relatively new statistical methodology to analyze occurrence of acute common self-limiting or rare events resulting from the administration of a vaccine [4]. This design differs from traditional methods (cohort, case-control) in that the classification of exposed and unexposed time intervals occur within the same individual [4,6]. This allows one to

measure the temporal variation in baseline incidence (pre- and post-immunization) of an illness, while controlling for all fixed (time invariant) confounders [7]. Moreover, since cases serve as their own controls, the likelihood of selection bias between exposed and unexposed subjects is effectively eliminated [8]. Although this approach has frequently been applied to a single outcome variable at a time, joint outcomes involving co-administration of multiple vaccines can also be studied [6]. The statistical power of this method closely approximates that of a cohort study when the periods of risk following immunization are short [4,6].

Enrolment: All healthy infants and under-six children presenting to the Well Baby Clinic for routine vaccination were eligible to participate. Infants and children were not eligible if they did not meet the criteria for routine Universal Immunization Program (UIP) / IAP Schedules for Immunization. Infants on intramuscular, oral or intravenous corticosteroid therapy, known/suspected case of impaired immune function, and those with malignancy, chronic diarrhea, growth faltering, hypersensitivity to any component of a routinely administered vaccine, fever (axillary temperature > 99ºF [37.2ºC] / oral temperature >100ºF [37.8ºC] by digital thermometer) on the day of immunization, progressive/ undiagnosed neurological illness or encephalopathy due to prior vaccine administration were excluded from the study. Before vaccination, children whose caretakers were unable or unwilling to recall the adverse events for each of the seven days prior to vaccination were not included in the study. Other reasons for exclusion following screening were children who presented with lapsed immunization that was more than one month overdue, inability to participate due to upcoming travel, lack of time to complete the interview process and respond to the phone calls, and lack of access to either a landline or a mobile phone.

The study protocol was reviewed and approved by the CMC Institutional Review Board. Written informed consent was obtained from parents/guardians of the participating children, prior to enrolment. The protocol required all routine vaccines to be administered as per the IAP Schedule at recommended ages [9-11].

Recording of illness: Information was collected on a wide range of commonly reported adverse events following administration of vaccines using a structured questionnaire.

Following enrolment, the parent/caretaker was asked whether the infant had experienced any of the specified illnesses in the seven days prior to the day of immunization. The interviewer enquired about any adverse event or illness experienced by the child for each day of the week preceding the administration of the vaccine. A second interview (telephonic) was conducted by the same interviewer one week following the vaccine administration to enquire about adverse event(s) experienced by the child for each day of the subsequent week. A set of pre-specified questions were asked during both interviews and no probing questions were asked. Both interviews covered the same set of questions in the same order. This information was recorded in a confidential register which also included study serial number, hospital number, child's name, mother's name, telephone number, address and vaccine(s) given to the child.

All interviews were conducted by nurses working at the Well Baby Clinic, using standard operational definitions [12-14]. Personnel conducting the interviews were trained at the start of the study, and periodically thereafter, to ensure uniformity of data collection. Random check of the interview process was conducted by a pediatrician working in the Well Baby Clinic to cross-validate the data collected.

Sample size: Approximately twenty different relatively common illnesses reported as adverse events were included. These occur at rates between 1-25% of immunized children depending on the vaccine and dose. However, the incidence of these events in the immediate pre-immunization period is unknown. Therefore, a conservative sample size estimate of 1584 infants was calculated, which had adequate power to detect an expected 1% prevalence of pre-immunization adverse events in infants, with a 95% confidence interval (CI) of ±0.5%. Based on this sample size, it was planned to enroll 1600 children for the study.

Statistical analysis: Data were analyzed using STATA for Windows version 10.1 (StataCorp, College Station, TX, USA). The frequency of adverse events in children pre- and post- immunization was compared using the chi-square test or the Fisher's exact test. For the risk-interval analysis, the 7 day post-immunization period was considered as the "exposed" period for each child, whereas the 7 day pre-immunization period was considered as the "unexposed" period contributing to the baseline risk. The association between vaccination and the observed adverse event was investigated using a matched-pair cohort analysis [15], and risk ratios (RR) with 95% CI calculated. Analysis was performed for all children at first, followed by stratified analysis based on the age and the type of vaccine(s) administered.

RESULTS

A total of 2394 children were screened, of whom 1602

children (826 males and 776 females) were included in this study. Reasons for exclusion included upcoming travel (*n*=75), lack of time to complete the interview and respond to phone calls (*n*=57), not having access to landline or mobile phone (*n*=162), lapsed/overdue immunization (*n*= 493) and fever (*n* = 5). The number of infants and children who were vaccinated at different ages and included in the study are presented in ***Table* I**. Of the 1602 children included in the study, all caretakers could be contacted within a fortnight post-immunization with 1537, 1586 and 1602 contacted by the 9th, 12th, and 15th day post-immunization, respectively.

The number of children who did not report any illness either pre- or post-immunization were 725 (45.3%) whereas 877 (54.7%) reported one or more illnesses within 7 days before of after immunization. Of those who reported having illness around the time of immunization, 333 (38%) children reported illness during the pre-immunization period only, whereas 352 (40.1%) reported having illness during the post-immunization period only; 192 (21.9%) children reported having illness both during the pre- and the post-immunization period. The most frequently reported illnesses were upper respiratory illnesses such as rhinitis (347, 21.7%) and cough (134, 8.4%), fever (69, 4.3%), and gastrointestinal illnesses (***Table* II**). None of the children reported hypotonic-hyporesponsive episode (HHE), seizure, pruritus, difficulty in breathing or breath holding, either during the pre- or the post vaccination period.

TABLE I CHILDREN VACCINATED AT DIFFERENT AGES AND INCLUDED IN THE STUDY (*N*=1602)

Completed age	*No.*	*Vaccine*
6 Weeks	(114)	DTwP1, OPV1, IPV1, Hib1, HepB2
	(105)	DTaP1, OPV1, IPV1, Hib1, HepB2,
10 Weeks	(108)	DTwP2, OPV2, IPV2, Hib2
	(50)	DTwP2, IPV2, Hib2, Rotavirus vaccine 1
	(99)	DTaP2, OPV2, IPV2, Hib2
14 Weeks	(110)	DTwP3, OPV3, IPV3, Hib3, HepB3
	(50)	DTwP3, IPV3, Hib3, HepB3, Rotavirus vaccine 2
	(107)	DTaP3, OPV3, IPV3, Hib3, HepB3
6 months	(84)	Flu vaccine
9 months	(110)	Measles
1 year	(110)	Hepatitis A vaccine
15 months	(112)	MMR and Varicella vaccines
18 months	(112)	DTwP B1, OPV4, Hib B1, IPV B
2 years	(111)	Typhoid vaccine and Hepatitis A
5 years	(110)	DTwP B2 / OPV5
	(110)	MMR2 and Typhoid 2

When the entire sample size of 1602 vaccinated infants and children comprising all age groups were analyzed for adverse events 7 days before and after immunization, the only illness with significantly higher reporting during the post-immunization period was fever (RR=5.75, 95% CI=4.50-7.35). On the other hand, gastrointestinal (RR=0.52, 95% CI=0.39-0.68) and respiratory (RR=0.41, 95% CI=0.35-0.48) illnesses were significantly lower during the post immunization period (***Table* III**).

The risk of fever was higher for pertussis containing vaccines post immunization (RR=9.18, 95% CI=6.55-12.86), the risk being similar in children given whole cell (RR=9.32, 95% CI=6.43-13.52) and acellular (RR=8.50, 95% CI=3.82-18.91) vaccines, respectively. When analyzed age-wise, the frequency of fever was significantly higher during the post-immunization period at 6 (RR=16.00, 95% CI=6.10-41.98), 10 (RR=12.20, 95% CI=5.11-29.10), 14 (RR=7.09, 95% CI=3.85-13.05) weeks, at 18 months (RR=6.33, 95% CI=3.24-12.38) and at 5 years (RR=10.40, 95% CI=4.44-24.35) with the administration of pertussis containing vaccines, although the risk of fever following immunization showed a decreasing trend with increasing age.

When analyzed by age separately for whole-cell and acellular pertussis vaccines, children administered whole-cell pertussis vaccine tended to have a higher risk of fever than those administered acellular pertussis vaccine at 6 (RR=20, 95% CI=5-79.97 for whole-cell and 12, 3.18-45.23 for acellular vaccine) and 14 weeks (RR=8, 95% CI=3.96-16.17 for whole-cell and 4.67, 1.34-16.24 for acellular vaccine). At 10 weeks; however, children reported similar risk of fever with both vaccines (RR=12, 95% CI=4.50-31.97 for whole-cell and 13, 1.98-85.46 for acellular vaccine).

Significantly more children reported having fever following simultaneous administration of MMR and varicella vaccines at 15 months of age (RR=2.5, 95% CI=1.02-6.15), typhoid and hepatitis A vaccines at 2 years of age (RR=4.83, 95% CI=2.06-11.35) as well as typhoid and MMR combination (RR=4.33, 95% CI=1.23-15.21) at 5 years of age. However, fever was not significantly reported when measles vaccine (RR=1.86, 95% CI=0.74-4.65) or hepatitis A vaccine (RR=2.00, 95% CI=0.79-5.04) was given alone at 9 months and 1 year of age, respectively.

Among infants given rotavirus vaccine at 10 and 14 weeks, the frequency of GI illnesses such as diarrhea

TABLE II DIFFERENT ILLNESSES REPORTED PRE-VACCINATION AND POST- VACCINATION, NO. (%)

*Illness**	*All children (n=1602)*		*Infants (n=1047)*		*Older children (n=555)*	
	Before vaccination	*After vaccination*	*Before vaccination*	*After vaccination*	*Before vaccination*	*After vaccination*
Crying	11 (0.7)	4 (0.3)	7 (0.7)	4 (0.4)	4 (0.8)	0 (0)
Persistent inconsolable screaming	0 (0)	2 (0.1)	0 (0)	2 (0.2)	0 (0)	0 (0)
Diarrhea	60 (3.8)	38 (2.4)	44 (4.2)	28 (2.7)	16 (2.9)	10 (1.8)
Vomiting	50 (3.1)	24 (1.5)	40 (3.8)	16 (1.5)	10 (1.8)	8 (1.4)
Constipation	26 (1.6)	2 (0.1)	20 (1.9)	1 (0.1)	6 (1.1)	1 (0.2)
Abdominal colic	3 (0.2)	3 (0.2)	3 (0.3)	3 (0.3)	0 (0)	0 (0)
Drowsiness	2 (0.1)	0 (0)	1 (0.1)	0 (0)	1 (0.2)	0 (0)
Cough	134 (8.4)	57 (3.6)	94 (9.0)	42 (4.0)	40 (7.2)	15 (2.7)
Wheezing	2 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)	0 (0)	0 (0)
Hoarseness	4 (0.3)	1 (0.1)	3 (0.3)	1 (0.1)	1 (0.2)	0 (0)
Stridor	0 (0)	2 (0.1)	0 (0)	2 (0.2)	0 (0)	0 (0)
Rapid breathing	1 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)
Rhinitis	347 (21.7)	137 (8.6)	250 (23.9)	88 (8.4)	97 (17.5)	49 (8.8)
Irritability/Restlessness	7 (0.4)	1 (0.1)	4 (0.4)	1 (0.1)	3 (0.5)	0 (0)
Rash	9 (0.6)	3 (0.2)	6 (0.6)	2 (0.2)	3 (0.5)	1 (0.2)
Ear pain	9 (0.6)	3 (0.2)	7 (0.7)	2 (0.2)	2 (0.4)	1 (0.2)
Fever	69 (4.3)	397 (24.8)	40 (3.8)	231 (22.1)	29 (5.2)	166 (29.9)
Watery eyes	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)

**The following illnesses were not reported, either pre- or post-immunization: HHE (hypotonic hyporesponsive episode), difficult breathing, breath holding, seizure, pruritus.*

TABLE III MATCHED-PAIR ANALYSIS OF THE RISK OF SELECTED ADVERSE EVENTS POST-VACCINATION, RELATIVE RISK (95% CI)

	All children (N=1602)	*Infants (n=1047)*	*Older children (n=555)*
Respiratory illnesses[#]	0.41 (0.35 - 0.48)	0.38 (0.32 - 0.49)	0.46 (0.34 - 0.62)
Gastrointestinal illnesses[$]	0.52 (0.39 - 0.68)	0.47 (0.34 - 0.65)	0.66 (0.38 - 1.13)
Neurological illnesses[‡]	0.38 (0.11 - 1.24)	0.75 (0.21 - 2.66)	-
Dermatological illnesses^	0.33 (0.09 - 1.23)	0.33 (0.07 - 1.65)	0.33 (0.03 - 3.20)
Fever	5.75 (4.50 - 7.35)	5.78 (4.18 - 7.98)	5.72 (3.93 - 8.33)
Other illnesses**	0.33 (0.15 - 0.76)	0.43 (0.17 - 1.06)	0.14 (0.02 - 1.16)

*[#]Cough, wheezing, stridor, rhinitis, hoarseness, rapid breathing; [$]Diarrhea, vomiting, constipation, abdominal colic; [‡]Persistent inconsolable screaming, irritability/restlessness, drowsiness; ^ Rash; ** Crying, ear pain, watery eyes.*

(RR=0.60, 95% CI=0.14-2.51) and vomiting (RR=1.00, 95% CI=0.14-7.10) were comparable pre- and post-immunization.

DISCUSSION

This study has documented that common childhood illnesses reported as adverse events following immunization actually occur at similar or higher rates pre-vaccination, with the exception of fever.

Expectedly, pertussis-containing vaccine clusters produced significant fever post-vaccination, although the decrease in relative risk with increasing age is contrary to what has earlier been reported [16,17]. When whole and acellular DPT vaccine combinations were analyzed separately by age, the risk of fever was not found to be as markedly different as previously reported [17-20]. On the other hand, the typhoid Vi-polysaccharide vaccine when administered in combination with hepatitis A was observed to be more pyrogenic, than when administered alone, as observed earlier in Indian children [21].

WHAT IS ALREADY KNOWN?

- The adverse event rates of a single or one combination vaccine, with background rates not factored in.

WHAT THIS STUDY ADDS?

- Common childhood illnesses reported as adverse events following immunization were documented at similar or higher rates pre-vaccination, with the exception of fever.

All the study subjects were vaccinated on the day of appointment, despite their recent history of minor illness. Yet, the significant decline in all adverse events except fever, in the post immunization period suggests the possibility of a "healthy-vaccinee effect" (postponement of immunization due to illness of infant or child in the recent past) [8,22,23]. It has been hypothesized that this healthy-vaccinee effect may occasionally result in lower background rates of adverse events and illnesses in the immediate post-vaccination period [8, 24]. Nevertheless, the study shows that none of these events, except fever, have been precipitated or aggravated by vaccination.

This study has several limitations. It was conducted in a clinic setting where mostly children of affordable caretakers avail of vaccines and services. Also, only caregivers who were able to recall their child's adverse event during the pre-immunization period were interviewed. These may have resulted in this cohort not being representative of all children in the community. However, this lack of representativeness is unlikely to affect the overall study findings, given the study design. Additionally, restricting study participation to such respondents significantly enhanced compliance to protocol, with no dropout. This study was powered to detect illnesses with a 1% or higher prevalence, but some of the illnesses were reported at a much lower frequency than expected, for which the sample size was inadequate. Since the study was designed to ascertain the adverse events profile of a cluster of vaccines as administered in a routine immunization schedule, the contribution of individual vaccines could not always be delineated, although this has been attempted to, where possible. Also, caregivers' decision to not opt for certain vaccines such as the pneumococcal conjugate vaccine (PCV) due to their high cost made it difficult to profile their adverse events. Further, telephonic interview of the caregivers, post-vaccination, could potentially have introduced a reporting bias. Previous studies have; however, shown that telephone encounters can substantially contribute to the detection of possible local and systemic vaccination reactions [25-27]. Moreover, the same nurse who recorded the pre-immunization illness history also conducted the telephonic interview.

A large proportion of events ascribed to and reported as adverse events due to vaccine administration are actually common illnesses in children, coinciding with vaccination. This study highlights the importance of estimating the background rates of common illnesses to accurately ascertain a causal relationship. Large scale studies using similar methodology need to be conducted among infants and children in diverse settings in India for a more accurate estimation of vaccine attributable risk.

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