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ADVERSE EVENTS FOLLOWING IMMUNISATION REPORTED FOR PAEDIATRIC VACCINES IN A DISTRICT HOSPITAL

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1. INTRODUCTION

Vaccines are among the most heavily used medicines in children, and the great majority of doses are given to healthy infants and toddlers at scheduled visits. That fact shapes how safety is judged. A medicine for a sick patient can carry a modest risk if the benefit is large, but a product given to millions of healthy babies must have an exceptionally low rate of serious harm, and any perceived harm tends to spread through families and the media faster than the evidence does [1, 2]. Safety monitoring is therefore built into immunisation programmes in most countries. The World Health Organization (WHO)

Abstract

Adverse events following immunisation (AEFI) are monitored because vaccines are given to healthy infants on a very large scale, and rare or poorly understood events can erode public confidence. This review, which reports no new data, draws on published literature to describe how AEFI are defined, classified and reported, what a district hospital can contribute to surveillance, and what is known about reactions to common paediatric vaccines. It covers case definitions, causality assessment, passive and active surveillance, under-reporting, programmatic errors, immunisation anxiety and communication with families. Most events are mild and self-limiting, serious reactions are rare, and many reports reflect coincidence or error rather than the vaccine. Reporting completeness, data quality and causality assessment remain the main weaknesses.

guidance for immunisation programme managers on AEFI surveillance sets out the framework that national programmes follow, and India has adapted it in national operational guidelines [3, 4]. Hospitals, and

district hospitals in particular, sit at the point where parents bring a child who has become unwell after a vaccine, which makes their records a rich if imperfect source of safety information.

An AEFI is any untoward medical occurrence that follows immunisation and does not necessarily have a causal relationship with the vaccine [3]. The definition is deliberately broad. A child who develops bronchiolitis two days after a pentavalent dose is an AEFI case for reporting purposes, even if the virus was already incubating. This inclusiveness is good for detection and bad for interpretation, because the reports mix true vaccine reactions with coincidence, error and anxiety. This review examines the literature on how such reports are classified, how hospital-based reporting contributes to surveillance, and what is known about the pattern of events with common childhood vaccines. It is a narrative synthesis of published reviews, surveillance reports and studies, and no hospital series is presented. The emphasis is on what a pharmacist or clinician working in a district hospital needs to know to recognise, record and report events well.

Two numbers help to put AEFI reporting in context. The first is the national reporting rate. WHO uses a global indicator based on a minimum of 10 reports per 100,000 surviving infants, and an analysis of reporting trends from 2000 to 2015 found that many countries, particularly low-income ones, still fell short of it even as reporting improved over the period [5]. The benchmark measures system performance rather than vaccine safety: a low rate usually means that events are going unreported, not that few occur. The second is the proportion of reports classed as serious, which depends heavily on what gets reported. Systems that capture only dramatic events show a high share of serious reports, while systems that encourage routine reporting collect many mild events and show a lower share [3, 5]. Interpreting either figure without knowing how the system works is a mistake.

2. CLASSIFICATION AND CASE DEFINITIONS

Classification starts with what kind of event it is. The WHO classification distinguishes five

types: vaccine product-related reactions, which arise from the inherent properties of the vaccine; vaccine quality defect-related events, caused by a fault in manufacture or in the delivery device; immunisation error-related events, caused by inappropriate handling, prescribing or administration; immunisation anxiety-related events, caused by fear of or stress about the injection; and coincidental events that would have happened anyway [3]. Errors are common enough in practice to form a distinct group in passive reports, and many of the reported errors cause no adverse event at all [6]. The scheme is practical because each type has a different remedy. Product reactions are described in the label and handled by clinical care. Quality defects need a batch recall and regulator involvement. Errors need training and supervision, anxiety needs a calmer clinic, and coincidence needs reassurance backed by background-rate data. A district hospital team that records the type correctly sends the report to the right place.

Standard case definitions improve comparability. The Brighton Collaboration was set up to produce consensus definitions for adverse events after immunisation, with levels of diagnostic certainty that allow reports from different settings to be pooled [7, 8]. A report of seizure may mean a febrile convulsion, an afebrile epileptic event or simply a jerky movement during fever, and each has a different meaning for vaccine safety. The definitions specify the clinical features, timing and evidence needed for each level of certainty, and they come with guidelines for data collection. They were designed to work in settings with limited resources as well as in well-equipped centres, so a district hospital can apply the lowest level of certainty with only a clinical record. Fever has its own definition with grading by temperature and method of measurement, which matters when comparing studies that used axillary, rectal or oral readings [9].

Assessment of causality for an individual report is a separate step. The WHO scheme, developed with international experts and tested in several countries, uses a checklist covering the evidence for a causal link, other possible causes, known reactions to the

vaccine, timing, and the presence of a quality or programme error. It leads to one of four categories: a consistent causal association, an indeterminate association, an inconsistent (coincidental) association, or unclassifiable [10, 11]. An earlier algorithm by Halsey and colleagues takes a similar approach through a flow of questions [12]. Neither method proves that a vaccine caused an event in an individual child. They organise judgement, and they make the reasoning visible so that two reviewers looking at the same case can see where they differ. In practice the commonest outcome for individual reports is indeterminate or unclassifiable, because the information is incomplete [10, 11]. That result says as much about the quality of reports as about the vaccine.

3. SURVEILLANCE AND REPORTING IN HOSPITAL SETTINGS

Most national systems rely on passive (spontaneous) reporting. Clinicians, vaccinators or parents send reports to a central unit, which reviews them for signals. The United States Vaccine Adverse Event Reporting System (VAERS) is the best-described example; it accepts reports from anyone, is run jointly by public-health and regulatory agencies, and is valuable for generating hypotheses and detecting unexpected patterns [13, 14]. Its limits are well known. Reports are incomplete, uneven in quality, subject to stimulated reporting after media coverage, and lack the denominators and comparison groups needed to compute risk, so VAERS data cannot by themselves show that a vaccine caused an event [14, 15, 16]. Zhou and colleagues, describing a decade of reports, found that most concerned non-serious events and that the system captured serious ones better [16]. Hospital-based reporting follows the same logic on a smaller scale, with the district hospital forwarding cases to the district immunisation officer.

Under-reporting is the central weakness of any spontaneous system. Evaluations of spontaneous reporting schemes for vaccine events show that only a fraction of events reach the reporting centre, and that the fraction varies with the setting and the type of event [17]. Determinants include ignorance of

what to report, diffidence about whether the event is related, lack of time, belief that only serious events matter, and uncertainty about the reporting channel [18]. A survey of physicians' attitudes to reporting found several reasons for silence, so the reports received are an incomplete picture of what occurs [19]. Vaccines differ from other medicines in that reporting is part of programme duty and parents are often keen to report, but the same barriers apply to busy hospital staff. Simple forms and feedback to reporters are the measures most often recommended [18].

Active surveillance complements passive reporting. The Vaccine Safety Datalink in the United States links vaccination records to health-care encounters in large managed-care populations, which allows comparison of event rates in risk and control periods and quick testing of signals [20]. Sentinel hospital systems play a similar but smaller role in many countries: trained staff review all admissions for specified conditions, such as seizures, anaphylaxis or intussusception, and ask about recent vaccination. Such systems can calculate rates because they know the number of children served. In low-resource settings, a district hospital that records vaccination history for every paediatric admission, and captures batch numbers where available, builds a base from which these rates may eventually be derived [3, 4]. Without such structure, a hospital's reports contribute counts but not risks.

4. REACTIONS TO COMMON PAEDIATRIC VACCINES

Common reactions follow predictable patterns. Local pain, redness and swelling at the injection site, low-grade fever, irritability and reduced feeding are frequent with most inactivated vaccines and appear within a day or two [1, 3]. Whole-cell pertussis-containing vaccines are more reactogenic than acellular products, with higher rates of fever, local swelling and prolonged crying, which is one reason many high-income countries moved to acellular vaccines; Decker and colleagues compared the adverse reactions of 13 acellular pertussis vaccines in a large trial [21]. Live attenuated vaccines such as measles-containing vaccines cause a mild

illness, usually with fever and sometimes a rash, about a week after the dose. *Bacillus Calmette–Guérin* (BCG) commonly produces a local papule and a scar, and abscess or suppurative lymphadenitis is a recognised complication [3, 22]. Knowledge of these patterns lets the clinician tell expected from unexpected.

Combination schedules complicate attribution. In the first year an infant often receives several antigens at one visit, in one or more injections, so an event that follows is rarely attributable to a single component. Reports should list every vaccine given at the visit, with batch numbers, and not only the one the reporter suspects [3, 10]. Studies that compare co-administration with separate administration are few, and even for the MMRV vaccine the difference in febrile seizures was detectable only in a very large population [23]. In practice, a hospital cannot resolve which component was responsible from a single case. What it can do is record accurately, so that reviewers who pool many reports are able to see whether a pattern follows a particular product, a particular batch or a particular combination of vaccines.

Febrile seizures are the most important neurological event discussed in the vaccine literature. A large study of children in the United States found that the risk of seizure rose on the day of whole-cell pertussis vaccination and again eight to fourteen days after measles–mumps–rubella (MMR) vaccine, but that the seizures were mostly febrile and short and were not followed by long-term neurodevelopmental harm [24]. A later study found a modest excess of febrile seizures after the combined measles–mumps–rubella–varicella (MMRV) vaccine compared with separate injections in the second year of life [23]. These findings changed recommendations on the choice of product but not the overall judgement that benefits far outweigh risks. For a district hospital the lessons are practical: take the temperature and onset time accurately, record whether the seizure was febrile and generalised, and avoid labelling a child as epileptic before follow-up [23, 25].

Anaphylaxis is rare, but it is the event for which preparedness matters. Estimates from

large United States studies of children and adolescents put the rate at roughly one case per million doses, with later analyses giving similar figures [26, 27]. Onset is typically within minutes to an hour, and adrenaline must be available in every vaccination room. Mechanisms include immunoglobulin E (IgE) mediated reactions to vaccine components such as gelatin or egg protein, although many reactions have no clear explanation [28, 29]. Intussusception after the first-generation rhesus-based rotavirus vaccine led to its withdrawal in 1999, after an excess of cases appeared in the first week after the first dose [30]. That experience shaped later vaccine trials and surveillance for newer products. Rare events of this kind show why population-level monitoring with denominators is required: no single hospital series, however carefully kept, could reveal them.

Typical events, their timing and the type of evidence behind each are brought together in table 1. Entries are grouped in fig. 1 by event category: expected reactions, neurological events, allergic events, rare serious events and non-vaccine causes such as errors, anxiety and coincidence. The grouping shows that the literature is thickest for expected reactions and for serious but rare events, where large studies have been done, and thinnest for programmatic problems, which are described mostly in guidance documents and case reports instead of in controlled studies [1, 3, 31]. The table is not a list of everything that can happen. It aims to give readers a feel for what is common and benign, what is rare and serious, and what is the fault of the system rather than the vaccine.

5. CAUSALITY, SIGNALS AND COMMUNICATION

Background rates are the yardstick for coincidence. Infants receive several vaccines in their first year, and during the same period they also have their first seizures, first infections and, rarely, other serious illnesses. Statistical work on rare events after licensure shows how many events would be expected by chance alone in a vaccinated population once age-specific background incidence is taken into account [32]. The principle applies to paediatric programmes. If a hospital sees

three cases of encephalitis in a month after vaccination clinics, the question is not whether three is alarming but how many would be expected in the population served. Without denominators and background rates, a cluster of reports can appear worrying and mean nothing, or appear reassuring while hiding a true excess [15, 32].

Reports become signals only when something stands out. Signal detection methods compare the number of reports for a vaccine–event pair with what would be expected from all other reports, or compare rates in risk and control windows in linked databases [14, 25]. When a signal is found, it is examined against biological plausibility, consistency, strength and temporality before a causal conclusion is drawn. The Institute of Medicine review of vaccine adverse effects graded evidence from convincing support for a causal relationship down to inadequate evidence, and it found convincing support for only a small number of vaccine–event pairs, such as anaphylaxis, febrile seizures after measles-containing vaccine and vaccine-strain infection in immunocompromised persons [33]. A systematic review of routine childhood vaccines reached broadly similar conclusions and found serious adverse events to be rare [22]. Those documents are the right references against which a hospital's observations should be read.

Table 1: Adverse events after paediatric immunisation: patterns reported in the literature

Event	Published pattern	Ref.
Local pain, redness, swelling	Common with most injected vaccines; onset within a day or two and self-limiting	[1, 3]
Fever and irritability	More frequent after whole-cell than acellular pertussis vaccines; graded by Brighton definition	[9, 21]
Mild measles-like illness	Fever and sometimes rash about a week after live measles-containing vaccine	[3, 22]
Febrile seizure	Excess on day of whole-cell pertussis dose and 8–14 days after MMR; no long-term harm	[24]

Event	Published pattern	Ref.
Seizure after MMRV	Modest excess compared with separate MMR and varicella vaccines in the second year of life	[23, 25]
Anaphylaxis	About one case per million doses; onset within minutes to hours	[26, 27]
Hypersensitivity, non-anaphylactic	Urticaria and angioedema; components such as gelatin implicated in some cases	[28, 29]
Intussusception	Excess in first week after first dose of first-generation rotavirus vaccine, withdrawn 1999	[30]
Injection-site abscess	Linked to unsafe injection practice, contaminated or reused equipment, and poor technique	[3, 31]
Stress-related responses	Fainting and hyperventilation, sometimes in clusters; not caused by the vaccine product	[34]
Coincidental illness	Infections and other conditions that follow vaccination by chance; judged against background rates	[10, 32]

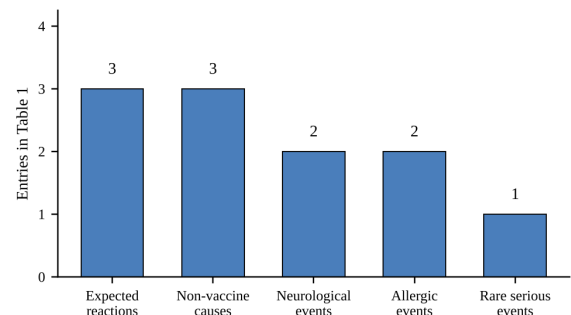


Fig. 1: Number of entries in table 1 by event category

How events are communicated matters almost as much as how they are detected. Parents' concerns arise from the experience of a sick child, from stories heard elsewhere, and from doubts about the number of vaccines. The strategic advisory group on vaccine hesitancy described hesitancy as a spectrum shaped by context, group and vaccine-specific factors, including previous experience with adverse events [2]. Offit and colleagues pointed out that the infant immune system is capable of responding to a very large number of

antigens, so the current schedule is unlikely to overwhelm it [35]. Honest explanation of common reactions beforehand, a clear plan for what to do if fever appears, and respectful follow-up of any unusual event are all supported by the literature on risk communication [1, 2]. For a pharmacist or nurse, this communication is part of the safety system and not an afterthought.

6. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations affect the literature that a hospital reader would use. Studies of AEFI differ in definitions, age groups, follow-up periods and case-finding methods, so rates reported from different places cannot be compared directly. Passive reports provide counts but not risks, and hospital series draw on children who were ill enough to be brought in, leaving out mild events managed at home [15, 17]. Publication favours striking events over routine data. Classification of causality varies between assessors, and many reports remain unclassifiable because batch, timing or clinical details were not recorded [10, 11]. Evidence on newer vaccines and on combination products comes mainly from high-income populations, whereas district hospitals in low- and middle-income countries differ in disease patterns, nutrition, comorbidities and injection practices [4, 5].

Practical improvements are within reach even in modest hospitals. A one-page standard form that captures vaccine, batch, onset time and outcome can be built into admission records. A named focal person, often a pharmacist or nurse, can check weekly for vaccine-related admissions and forward reports. Regular training of vaccinators in injection technique and reconstitution reduces avoidable errors [3, 31]. Feedback from the district AEFI committee to the reporting hospital closes the loop and encourages further reports [4, 18]. Linking hospital records to immunisation registers, where they exist, would allow rates to be calculated, and simple self-controlled designs using risk windows could test signals without needing a separate unvaccinated group [20, 25].

Research priorities are clear. Studies are needed that validate the revised WHO

causality assessment in district settings and show how reproducible it is between assessors of different training [10, 11]. Sentinel sites reporting AEFI with denominators would allow comparison of reaction rates for the vaccines in use locally, including whole-cell pertussis products that remain in widespread use [19, 21]. Qualitative work on why staff and parents do or do not report would guide interventions better than assumption [17, 18]. Evaluation of electronic or mobile reporting tools in resource-limited hospitals is a further priority. Finally, communication research should test messages about vaccine safety in real clinics, since the best surveillance system will not maintain confidence unless families hear about it in terms they understand [1, 2].

7. CONCLUSION

Reports of adverse events following immunisation are common, usually mild, and mostly explained by expected vaccine reactions, programme errors, anxiety or coincidence. Serious reactions such as anaphylaxis and febrile seizures are uncommon, well described and manageable [22, 24, 26, 27]. The typical patterns are collected in table 1. District hospitals contribute by recognising events, classifying them with standard definitions, recording the details needed for causality assessment and forwarding them through the national system [3, 4, 10]. Their reports are not a measure of vaccine safety on their own, but they feed the larger picture that national and international reviewers build.

The weak points are completeness, quality and interpretation. Spontaneous reports undercount events and cannot give risks without denominators and background rates [15, 17, 32]. Better forms, trained vaccinators, active sentinel review and feedback from the district committee are modest measures that can raise the value of hospital data [4, 18, 20]. A review of this kind cannot replace local surveillance, but it provides the framework against which a hospital can read its own reports and talk calmly with families about what they mean [1, 2]. Larger studies with clinical follow-up would also help show how the patterns seen in high-income settings translate to district hospitals.

8. ABBREVIATIONS

AEFI-Adverse events following immunisation,
BCG-Bacillus Calmette–Guérin,
IgE-Immunoglobulin E,
MMR-Measles–mumps–rubella,
MMRV-Measles–mumps–rubella–varicella,
VAERS-Vaccine Adverse Event Reporting
System, WHO-World Health Organization

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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