

## Adverse events monitoring as a routine component of vaccine clinical trials: evidence from the WHO Vaccine Trial Registry

The February 2000 *Bulletin* Round Table Discussion on vaccine adverse events includes a commentary by Clemens on evaluation of vaccine safety before and after licensure (1). Clemens emphasizes that sample sizes in Phase 1–3 vaccine clinical trials are generally too small to assess the potential of vaccines to produce rare side-effects. Another problem in evaluating adverse events in clinical trials is that the population studied is usually healthy and thus may differ from the population routinely administered the vaccine following licensure (2). Nevertheless, Phase 1 and 2 vaccine trials have as their primary objective the short-term evaluation of vaccine safety, while Phase 3 and 4 trials offer the potential for both short-term and long-term safety assessments.

The WHO Immunization Safety Priority Project has set an objective of ensuring that safety is appreciated as a principal endpoint in vaccine clinical trials (3). For trials on pharmaceutical products, including vaccines, safety monitoring is a key requirement of Good Clinical Practice

(GCP) guidelines (4). We used the WHO Vaccine Trial Registry to assess whether and how investigators are monitoring adverse events following immunization (AEFIs) in vaccine trials.

The Vaccine Trial Registry includes all vaccine trials sponsored since 1987 by WHO's Expanded Programme on Immunization, Global Programme for Vaccines and Immunization, and Department of Vaccines and Biologicals (5, 6). For each trial, records include internal documents, reports of visits to trial sites, and publications. As of August 1999, the Registry included 68 trials completed or in progress. The trials concerned vaccines against a wide spectrum of infectious agents and diseases, including cholera, dengue, enterotoxigenic *Escherichia coli*, hepatitis B, *Haemophilus influenzae* type B, measles virus, meningococcus, pneumococcus, poliovirus, tetanus, tuberculosis, and typhoid.

Based on GCP guidelines, an AEFI was defined as "an untoward medical occurrence in a clinical trial subject administered a vaccine; it does not necessarily have a causal relationship with the vaccination" (4). Vaccine Trial Registry records were reviewed to assess (a) whether AEFIs were mentioned; (b) whether AEFI monitoring was short-term (<4 weeks) or long-term (≥4 weeks); and (c) types of AEFIs monitored. AEFIs were classified as local, mild systemic

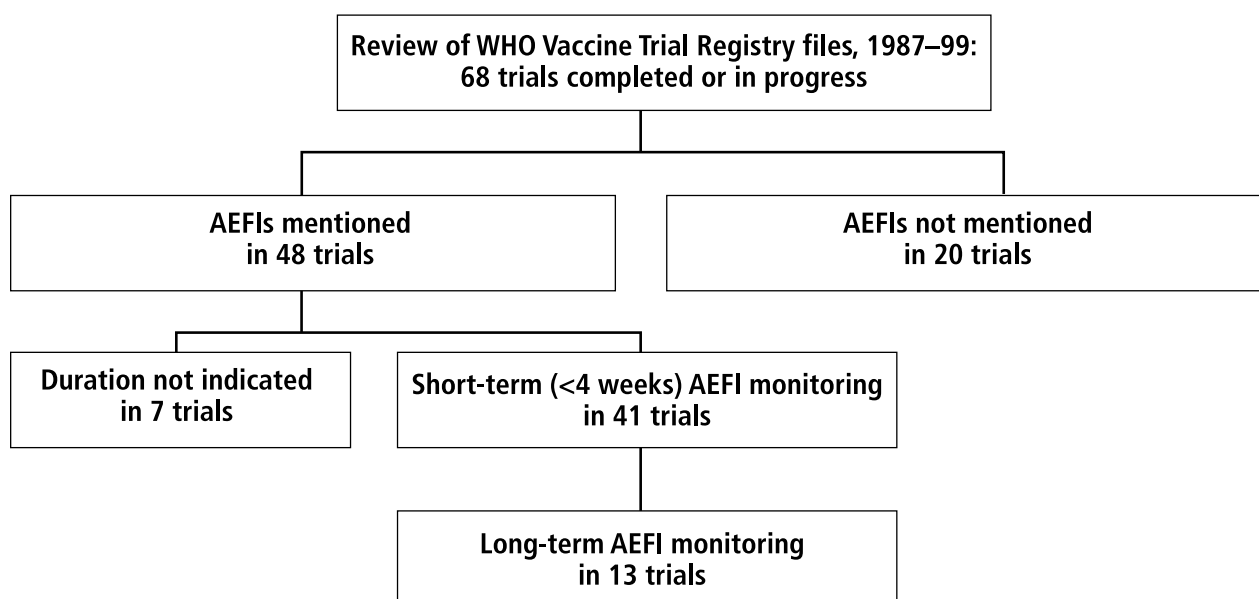
(fever, nausea, malaise, headache), immune-mediated (anaphylaxis), severe systemic toxicity (or other symptoms requiring hospitalization), other (persistent screaming, etc.), death, and not stated.

AEFIs were mentioned in reports from 48 (71%) of the 68 vaccine clinical trials initiated during 1987–99 (Fig. 1). The tendency to report AEFIs increased significantly ( $P=0.01$ ) over time: 54% (14/26) of trials started in 1987–93 mentioned AEFIs, compared with 81% (34/42) of trials started in 1994–99. AEFIs were mentioned in 100% of Phase 1–2, 69% of Phase 3, and 42% of Phase 4 vaccine trials ( $P<0.001$ ).

Forty-one (60%) of the 68 trials conducted short-term AEFI monitoring, but only 17 (25%) detailed the types of events monitored; 13 (19%) trials continued monitoring on a long-term basis (≥4 weeks), but details were reported for only 4 (6%) (Table 1). The type of adverse events most commonly monitored was mild systemic (Table 2).

The increasing trend to include AEFI monitoring in vaccine clinical trials is reassuring, but our analysis indicates that few investigators included detailed AEFI monitoring in their study reports and publications. Ward suggests that ensuring AEFI monitoring in vaccine trials is the responsibility of the vaccine manufacturer and the national control authority (7). However,

Fig. 1. Monitoring adverse events following immunization (AEFI) among trials in the WHO Vaccine Trial Registry (VTR), 1987–99



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Table 1. **Number of vaccine trials conducting short-term (<4 weeks) and long-term (≥ 4 weeks) monitoring of adverse events following immunization (AEFI), WHO Vaccine Trial Registry, 1987–1999**

	AEFI monitored		Details on types of AEFI reported	
	Number of trials	(%) <sup>a</sup>	Number of trials	(%) <sup>a</sup>
Short-term	41	(60)	17	(25)
Long-term	13	(19)	4	(6)

<sup>a</sup> Percentage calculated based on a total of 68 trials completed or in progress.

Table 2. **Number of trials reporting adverse events following immunization (AEFIs) in short-term and long-term monitoring, WHO Vaccine Trial Registry, 1987–99**

Type of AEFI	Number of trials	
	Short-term monitoring (< 4 weeks) (n = 17)	Long-term monitoring (≥ 4 weeks) (n = 4)
None	0	1
Local	5	0
Mild systemic	15	1
Immune-mediated	1	0
Severe systemic toxicity	4	0
Other	2	0
Death	1	3

many vaccine trials are conducted by independent investigators employed by governmental or academic institutions. We believe that study design and public reporting of AEFI monitoring is the responsibility of the study investigators, and that AEFI monitoring methods and results deserve to be included in any publication, along with vaccine efficacy methods and results. Journal editors and reviewers need to be aware that AEFI data, even when negative, are essential information in vaccine trial publications.

We propose the following practical points for monitoring AEFIs in vaccine clinical trials.

- Use of the following standard definition: *An adverse event following immunization (AEFI) is an untoward medical occurrence in a clinical trial subject administered a vaccine; it does not necessarily have a causal relationship with the vaccination.*
- AEFI monitoring should be short-term (<4 weeks) in all vaccine trials and long-term (≥ 4 weeks) in Phase 3 and 4 trials whenever possible.
- Trial publications should report the types of AEFIs monitored, using standard definitions, so that results of different trials will be comparable. A WHO list of AEFI definitions (8) is available, but

needs to be updated in light of new vaccine developments. The absence of AEFIs should also be reported, as this information will contribute to the comprehensive information available for vaccines.

- Where AEFIs are monitored, causality assessment should be carried out for suspected adverse events, using standard WHO criteria which classify causality as: very likely/certain, probable, possible, unlikely, unrelated, and unclassifiable (9). Causality assessment needs to be carried out by an advisory committee independent of the trial investigators. ■

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