Vaccine 36 (2018) 1577–1582

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000–2015 ☆

Jiayao Lei [a], Madhava Ram Balakrishnan [b], Jane F. Gidudu [c], Patrick L.F. Zuber [b,*]

[a] Karolinska Institutet, Stockholm, Sweden
[b] World Health Organization, Geneva, Switzerland
[c] Centers for Disease Control and Prevention, Atlanta, GA, United States

ARTICLE INFO

*Article history:*
Received 28 July 2017
Received in revised form 26 January 2018
Accepted 3 February 2018
Available online 14 February 2018

*Keywords:*
Global vaccine safety blueprint
Global vaccine action plan
Adverse events following immunization
AEFI reporting
Vaccine safety surveillance

ABSTRACT

Reporting of adverse events following immunization (AEFI) is a key component for functional vaccine safety monitoring system. The aim of our study is to document trends in the AEFI reporting ratio globally and across the six World Health Organization (WHO) regions. We describe the number of AEFI reports communicated each year through the World Health Organization/United Nations Children's Fund Joint Reporting Form on Immunization from 2000 to 2015. The AEFI reporting ratios (annual AEFI reports per 100,000 surviving infants) were calculated to identify WHO countries (n = 191 in 2000 and n = 194 by 2015) that met a minimal reporting ratio of 10, a target set by the Global Vaccine Action Plan for vaccine safety monitoring as a proxy measure for a functional AEFI reporting system. The number of countries reporting any AEFI fluctuated over time but with progress from 32 (17%) in 2000 to 124 (64%) in 2015. In 2015, the global average AEFI reporting ratio was 549 AEFI reports per 100,000 surviving infants. The number of countries with AEFI reporting ratios greater than 10 increased from 8 (4%) in 2000 to 81 (42%) in 2015. In 2015, 60% of countries in the WHO Region of the Americas reported at least 10 AEFI per 100,000 surviving infants, followed by 55% in European Region, 43% in Eastern Mediterranean Region, 33% in Western Pacific Region, 27% in South-East Asia Region and 21% in African Region. Overall, AEFI reporting has increased over the past sixteen years worldwide, but requires strengthening in a majority of low- and middle- income countries. The AEFI reporting ratio is useful for benchmarking and following trends over time; but does not provide information on the quality of the reporting system and does not guarantee capacity to detect and manage a vaccine safety problem at a national level. Additional efforts are required to ensure and improve data quality, AEFI reporting and surveillance of immunization safety in every country.


## 1. Background

The benefits of vaccination in saving lives and promoting health through reducing preventable diseases has been recognized worldwide, and vaccines currently prevent more than 2.5 million child deaths each year [1]. Even though vaccines are designed to be both safe and effective, adverse events following immunization (AEFI) do occur and need to be reported in order to identify problems and take appropriate corrective action [2]; examples include a withdraw of the RotaShield vaccine in 1999 after identifying its association with intussusception, and the recall of certain lots of meningococcus type C vaccine in 2009 due to contamination with *Staphylococcus aureus* [3,4]. With progress in improving vaccination coverage and the addition of vaccines to national immunization schedules in recent years, it is estimated that almost twice the total number of doses of vaccine are administered in low- and middle-income countries (LMIC) compared to developed countries [5,6]. As the number of doses administered increases, we can also expect to see an increased number of adverse events following immunizations (both true reactions and temporally coincidental events). Addressing these events requires functional vaccine safety monitoring systems [7,8]. The Global Vaccine Action Plan (GVAP) identifies the establishment and strengthening of AEFI reporting systems as a priority activity for strengthening immunization programs, and defines the AEFI reporting ratio (number of AEFI reports

☆ The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official positions of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry and of the World Health Organization.

* Corresponding author at: Department of Essential Medicines and Health Products, World Health Organization, 20, Av Appia, 1211 Genève, Switzerland.
*E-mail address:* zuberp@who.int (P.L.F. Zuber).

https://doi.org/10.1016/j.vaccine.2018.02.012
0264-410X/

per 100,000 surviving infants) as a performance indicator for monitoring progress [9]. Based on an empirical analysis of Joint Reporting Form on Immunization (JRF) data showing that countries with a sustainable passive vaccine safety surveillance system record at least 10 reports per 100,000 surviving infants per year, the target is currently set at that level [10].

Functional vaccine safety monitoring systems help public health authorities to address vaccine safety concerns in a timely manner, promoting confidence in immunization programs. Previous reports have documented the high variability of AEFI reporting across regions and countries, with a considerable number of countries without any AEFI reporting [11]. An analysis regarding indicators for the post-marketing surveillance of AEFI demonstrated that the global performance of AEFI reporting has shown positive but slow progress from 1997 to 2009 [6]. According to published data, 48% of all people in the world live in countries without functional safety monitoring systems for vaccines [6].

In 2011, the Global Vaccine Safety Blueprint (the Blueprint) was developed by the World Health Organization (WHO) and a group of partners as a strategy to further improve capacity of vaccine safety monitoring in LMIC [5,6]. The mission of the Blueprint is "*to optimize the safety of vaccines through effective use of pharmacovigilance principles and methods*". One of the Blueprint's goals is "*to assist LMIC to have at least minimal capacity for vaccine safety activities*" [5]. The World Health Organization/ United Nations Children's Fund (WHO/UNICEF) JRF provides a mechanism for national authorities to report AEFI to the global level and also provides an opportunity to evaluate country capacity to meet minimal standards for vaccine safety monitoring.

Recently, the Global Advisory Committee on Vaccine Safety (GACVS) proposed that the sensitivity of AEFI surveillance should be assessed through a basic indicator [11]. The GVAP proposed an indicator as the ratio of annual AEFI reports to the number of surviving infants [11]. Our study provides a descriptive analysis of AEFI reporting using data from the WHO/UNICEF JRF [12] over the past 16 years among all WHO countries. The aim of this study is to document trends in the AEFI reporting ratio globally and across WHO regions.

## 2. Methods

### 2.1. Data source

We used data from the WHO/UNICEF JRF, a standard reporting format used to collect information from all Member States in the WHO Regions. The JRF has evolved from a limited set of information collected to capture a wide range of domains of standard performance, planning, financing to quality indicators such an AEFI indicator using aggregate data at global level. For purposes of this analysis, a Member State will be referred to as 'country' in this report. The JRF was developed through a consensus process among UNICEF, WHO, and selected ministries of health (MOH) to monitor immunization systems performance [12]. Information in the JRF is consider as the official report provided by the countries; information about number of AEFI cases in each country reported through the JRF has been available since 2000.

### 2.2. Analysis

Descriptive analysis was used to summarize the number of countries with complete data on AEFI reporting on the JRF from 2000 to 2015 by regions. We tabulated the total number of AEFI reported by all countries in each WHO region annually, from 2000 to 2015. Using JRF data from 2000 to 2015, we also tabulated global and regional ratios of AEFI reporting according to the number of surviving infants. The number of surviving infants was obtained from the United Nations Development Programme (UNDP) statistics on surviving infants [13]. AEFI reporting ratios were further examined by using 2015 data from each region and classifying AEFI reporting ratios into three categories: greater than or equal to 10 per 100,000 surviving infants, less than 10 per 100,000 surviving infants, and no information reported (i.e., country did not report any AEFI information through JRF).

## 3. Results

The number of countries reporting AEFI data through the JRF increased steadily from 32 (17%) of 191 countries in 2000–139 (72%) of 192 countries in 2004. From 2006 onwards, this number fluctuated between 122 (63%) and 134 (69%) (Table 1). By 2015, 124 (64%) of 194 countries reported AEFI data through the JRF. The WHO South-East Asia Region had a higher percentage of countries reporting AEFI data compared to other regions, with at least 10 (91%) out of 11 countries reporting during 2011–2014. The drop in number of Western Pacific countries reporting AEFI during 2005 illustrates how sensitive the JRF system is to completeness of data in a single year.

The global number of AEFI cases reported through the JRF increased during the period studied. This increase, however, was not regular, with four important peaks of AEFI reports apparent in 2004, 2009, 2013 and 2015 (Fig. 1). These peaks corresponded to high numbers of AEFI cases reported by single countries in the European Region during 2004 (Ukraine) and the Eastern Mediterranean Region during 2009 (Lebanon), 2013 (Egypt) and 2015 (Egypt). Individual annual peaks can reflect time-limited increases in AEFI reports because of mass vaccination campaigns or media attention. In the African Region, Region of the Americas, and South-East Asia Region the number of AEFI cases reported between 2000 and 2015 were consistently low with a very small increase in later years. Reported AEFI cases steadily increased in the Western Pacific Region from 2008 to 2015. AEFI cases reported in the European Region varied over time with low numbers of AEFI cases reported before 2004, but large number of AEFI cases reported in 2004 (Ukraine reported 119957 AEFI cases) and in 2013 (Uzbekistan reported 110951 AEFI cases), followed by a decrease in 2014 and 2015. Continuously low numbers of AEFI were reported in the Eastern Mediterranean Region before 2009. The first peak of AEFI cases in the Eastern Mediterranean Region occurred in 2009 (Lebanon reported 14628 AEFI cases), followed by a decrease in 2010, and another peak again in 2013 (Egypt reported 354043 AEFI cases), followed by a lower number in 2014 (Egypt reported 57 AEFI cases) and a new peak in 2015 (Egypt reported 414243 AEFI cases).

In 2015, the Eastern Mediterranean Region had the highest AEFI reporting ratio (2740 per 100,000 surviving infants) of all the regions, followed by the Western Pacific Region (690 per 100,000 surviving infants) (Fig. 2). Globally, the average AEFI reporting ratio in 2015 was 549 AEFI reports per 100,000 surviving infants. For all other regions, the aggregate ratio was lower than this average: European Region (205 AEFI reports per 100,000 surviving infants), Region of the Americas (486), African Region (74), and South-East Asia Region (42). In 2015, the Eastern Mediterranean Region accounted for the majority (60%) of all AEFI reports, followed by Western Pacific Region (22%), Region of the Americas (10%), African and European Regions (each 3%), and South-East Asia Region (2%). The high proportion of AEFI reports from the Western Pacific Region is driven by the figures from China, the most populous country in the Region. During the period studied, the number of AEFI reports from China increased from 1313 in 2005 to 152,066 in 2015 (no data available before 2004 and zero AEFI reports in