Review

Safety reporting in developing country vaccine clinical trials—A systematic review

Susann Muehlhans a, Georgina Richard b, Mohammad Ali c, Gabriela Codarini d, Chris Elemuwa e, Ali Khamesipour f, Wolfgang Maurer g, Edison Mworozih h, Sonali Kochhar i, Gabriella Rundblad k, Dominique Vuittion l, Barbara Rath a.∗

a Department of Pediatrics, Division of Pneumonology-Immunology, Charité University Medical Center, Berlin, Germany
b Department of Preventive Medicine, Tulane University Medical School, New Orleans, LA, USA
c International Vaccine Institute (IVI), Seoul, Republic of Korea
d Stamboulian Vaccination Center, Buenos Aires, Argentina
e National Primary Healthcare Department Agency (NPHCDA), Federal Ministry of Health, Abuja, Nigeria
f Center for Research and Training in Skin Diseases & Leprosy, Tehran University of Medical Sciences, Tehran, Iran
g Center for Public Health, Medical University of Vienna, Austria
h Department of Paediatrics and Child Health, Makerere University Medical School/Mulago Hospital, Kampala, Uganda
i Institute for One World Health, New Delhi, India
j Department of Education & Professional Studies, King’s College, London, UK
k WHO Collaborating Centre, University of Franche-Comté, Besancon, France

A R T I C L E   I N F O

Article history:
Received 5 December 2011
Received in revised form 17 February 2012
Accepted 23 February 2012
Available online 7 March 2012

Keywords:
Vaccines
Safety reporting
Randomized clinical trials
Developing countries
AEFI

A B S T R A C T

With more vaccines becoming available worldwide, vaccine research is on the rise in developing countries. To gain a better understanding of safety reporting from vaccine clinical research in developing countries, we conducted a systematic review in Medline and Embase (1980–2011) of published randomized clinical trials (RCTs) reporting safety outcomes with ≥50% developing country participation (PROSPERO systematic review registration number: CRD42012002025). Developing country vaccine RCTs were analyzed with respect to the number of participants, age groups studied, inclusion of safety information, number of reported adverse events following immunization (AEFI), type and duration of safety follow-up, use of standardized AEFI case definitions, grading of AEFI severity, and the reporting of levels of diagnostic certainty for AEFI.

The systematic search yielded a total number of 50 randomized vaccine clinical trials investigating 12 different vaccines, most commonly rotavirus and malaria vaccines. In these trials, 94,459 AEFI were reported from 446,908 participants receiving 735,920 vaccine doses. All 50 RCTs mentioned safety outcomes with 70% using definitions for at least one AEFI. The most commonly defined AEFI was fever (27), followed by local (16) and systemic reactions (14). Logistic regression analysis revealed a positive correlation between the implementation of a fever case definition and the reporting rate for fever as an AEFI (p = 0.027). Overall, 16 different definitions for fever and 7 different definitions for erythema were applied. Predefined AEFI case definitions by the Brighton Collaboration were used in only two out of 50 RCTs.

The search was limited to RCTs published in English or German and may be missing studies published locally. The reported systematic review suggests room for improvement with respect to the harmonization of safety reporting from developing country vaccine clinical trials and the implementation of standardized case definitions.

© 2012 Elsevier Ltd. All rights reserved.

Abbreviations: AEFI, adverse event following immunization; SAE, serious adverse event; RCT(s), randomized controlled clinical trials; CD, case definition; BC, Brighton Collaboration.

∗ Corresponding author. Tel.: +49 30 450 666664.
E-mail address: Barbara.Rath@gmail.com (B. Rath).

0264-410X/ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2012.02.059
1. Introduction

The success of immunization programs is important to protect the well-being of people living in developed and developing countries alike, and to prevent the spread of diseases in times of international travel and globalization. Safety outcomes and vaccines tested may vary considerably between industrialized and developing countries [11]. With the potential for a significant positive impact on public health and international travel, there is a shared interest in preserving trust in vaccines in both developed and developing countries.

While many vaccines for diseases of global interest have already been developed, the majority of vaccines for diseases most prevalent in developing countries remain under development (Table 1).

Vaccines are mostly administered to healthy individuals, many of whom are children. Serious or even non-serious adverse events following immunization (AEFI) are often deemed unacceptable by vaccinees, parents and the general public [12]. In addition, many vaccines are administered early in life, at a time when childhood illnesses are highly prevalent and may by chance occur following vaccination. Thus, any adverse event occurring after immunization during this early childhood period (as during other time periods) may be interpreted as being vaccine-related. Whether the adverse event was truly caused by the vaccine or was merely temporally related is often difficult to determine [11].

As more and more trials are underway to investigate the efficacy and effectiveness of vaccines in developing countries, it has become increasingly important to pay attention to vaccine safety. In 2001, the CONSORT statement (www.consort-statement.org) provided standard guidelines for the safety reporting in randomized clinical trials (RCTs).

To improve the standardization of safety reporting in vaccine clinical trials, the Brighton Collaboration (www.brightoncollaboration.org) developed pre-defined case definitions for AEFI. Adequate safety reporting in vaccine clinical trials should also include strict adherence to methodological reporting requirements [13] and the use of standardized vaccine nomenclature [14] when documenting immunization events.

To gain better understanding of the current state of safety reporting from clinical research in developing countries, a systematic review of RCTs published from 1989 until 2011 was performed. Lacking a comparable group of RCTs from industrialized countries testing the same vaccines during a similar time period, this analysis will focus on developing country clinical trials and the vaccines outlined in Table 1.

This systematic analysis of safety reporting and the implementation of case definitions in developing country vaccine RCTs aims to provide a first insight into gaps identified and progress made in vaccine safety clinical research in low-resource settings while making suggestions for future developments.

2. Methods

The review was conducted following the proposed structure according to the preferred reporting items for systematic reviews and metaanalyses (PRISMA statement. www.prisma-statement.org [15]).

2.1. Identification of developing country vaccine RCT

Medline and EMBASE were screened for developing country RCTs. 31 October 2011 using the search terms [immunisation or immunization or vaccine] and [safety] and [developing country]; expanded searches were conducted using specific search strategies, such as explosion for the terms implementation, standard, case definition, and geographic terms representing developing countries. The term “developing country” was defined based on the 2006 United Nations World Economic and Social Survey (WESS “developing economy”) [16]. Additional references were added using the same search mechanism, if published before December 31, 2011.

Studies were identified as randomized controlled clinical trials according to the Cochrane Library definition “Glossary of Terms in The Cochrane Collaboration”. A trial was identified as RCT when fulfilling the following criteria: “An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants.” [17].
Table 1
Vaccines of special interest to developing countries.

<table>
<thead>
<tr>
<th>Vaccines for diseases most prevalent in developing countries</th>
<th>Vaccines for diseases of global interest with higher morbidity and mortality in developing countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentine hemorrhagic fever [50]</td>
<td>HPV [62]</td>
</tr>
<tr>
<td>Cholera enterotoxigenic E. coli [51]</td>
<td>Measles [63,64]</td>
</tr>
<tr>
<td>Dengue fever [52]</td>
<td>Meningococcal [38,65]</td>
</tr>
<tr>
<td>Human immunodeficiency virus [53,54]</td>
<td>Norovirus [66]</td>
</tr>
<tr>
<td>Human hookworm [55]</td>
<td>Pneumococcal [67,68]</td>
</tr>
<tr>
<td>Leishmaniasis [56]</td>
<td>Poliomyelitis [69]</td>
</tr>
<tr>
<td>Malaria [57]</td>
<td>Rotavirus [46,70,71]</td>
</tr>
<tr>
<td>Schistosoma [58]</td>
<td>Rubella [72]</td>
</tr>
<tr>
<td>Tuberculosis [59]</td>
<td></td>
</tr>
<tr>
<td>Typhoid [60]</td>
<td></td>
</tr>
<tr>
<td>Yellow fever [61]</td>
<td></td>
</tr>
</tbody>
</table>

* Vaccines that are under development but not yet available.

Non-randomized clinical trials, observational or surveillance studies, animal studies, articles published before 1989, and articles in languages other than English or German were excluded. When multiple publications were derived from the same RCT, sub-analyses of RCTs were excluded from the analysis. Information on safety reporting in methods papers was included if referenced by the authors of the original publication.

RCTs derived from the systematic search were screened individually with respect to the origin or site of the clinical trial. Monocentric trials were included in the analysis if conducted at a developing country site. Multi-center trials were included if ≥50% of participating sites were located in developing countries or if at least half of the study population was recruited in developing countries. The systematic review was registered with the PROSPERO database (http://www.crd.york.ac.uk/prospero; registration number CRD42012002025).

The challenge in identifying vaccine safety RCTs by means of systematic literature searches has previously been highlighted by Price et al. [18]. Not all clinical trials assessing AEFI and safety outcomes are indexed as such. RCTs reporting on vaccine safety were therefore reviewed individually and included if any of the following criteria were met:

(a) Safety outcomes were mentioned in the title of the RCT publication.
(b) Safety outcomes were reported in the RCT original publication.
(c) Safety data were sent to an independent data safety monitoring board.

2.2. Analysis of developing country vaccine RCT

The identified RCTs were analyzed according to the following criteria (if available in the original publication or methods paper):

1. WHO region
2. Date of publication
3. Time of conduct
4. Phase of study
5. Number of subjects participating in the trial
6. Age of trial participants
7. Vaccines tested
8. Assessment of safety outcomes
9. Number of AEFI reported in RCTs
10. Number of vaccine doses administered
11. Use of case definitions in AEFI reporting
12. AEFI reported/defined
13. Grading of AEFI severity
14. AEFI levels of diagnostic certainty
15. Duration of safety follow-up
16. Quality and type of safety follow-up

2.3. Statistical analysis

The majority of data presented are descriptive in nature. Using regression analysis, we analyzed the effect of (a) duration of follow-up, (b) minimum participant age, and (c) use of case definitions for fever, on AEFI reporting rates. The first two tests (a and b) were computed using linear correlation, the latter (c) using binomial correlation. Results were considered significant if the p-value for a specific parameter was <0.05. To adjust for differences in trial size and/or dosing schedules, we used the AEFI/dose ratio as a measure for AEFI reporting rates. Any AE following either vaccine or comparator/placebo were included in the analysis.

3. Results

3.1. Identification of developing country vaccine RCTs

The systematic literature search (January 1989–December 2011) yielded a total number of 227 publications, 50 of which represented individual RCTs conducted predominantly (>50%) in developing countries [16]. Among these 50 publications, all 50 reported safety outcomes according to the inclusion criteria outlined above (Section 2.1.1). In three instances, authors referred to separate methods papers detailing how safety assessments were done [19–21]. For methodological reasons, this review relies on articles published in English or German, which are listed in key electronic literature databases. Individual studies may have been missed due to inconsistent indexing and publication or language bias.

An overview of eligible developing country vaccine RCTs is provided in Table 2, below.

3.2. Analysis of developing country vaccine RCTs

3.2.1. Number of RCTs published per annum

The number of developing country vaccine RCTs has been increasing steadily. Between 1989 and 1999, ten of the published vaccines RCTs were conducted in developing countries. Throughout the following decade, 34 RCTs were published, and 7 in 2011 alone. The increasing number of published RCTs in the last 20 years is illustrated in Fig. 1.

3.2.2. Number of subjects and age of participants in RCTs

A total number of 446,908 participants were enrolled in the 50 vaccine RCTs (median 475, mean 8938).

Among the RCTs listed in this review, only 12/50 trials enrolled more than 3000 subjects, 11 trials had more than 10,000 participants. The highest number of subjects (N = 118,588) was enrolled in a cluster-randomized trial by Yang et al. [22] in China.

The phase of the vaccine clinical trial was specified in no more than 32% of the reviewed RCT publications.

Nearly two-thirds (64%) of the developing country vaccine RCTs were conducted in children (0–18 years) with three out of four pediatric vaccine trial restricted to infants (0–1 year). Of note, 66% of these infant vaccine trials did not report any AEFI during the follow-up period. The effect of age on AEFI reporting rates was tested using...
### Table 2
Developing country vaccine RCTs–study characteristics.

<table>
<thead>
<tr>
<th>Vaccine studied</th>
<th>Number of subjects randomized (n)</th>
<th>Time of conduct (years)</th>
<th>Participant age (years)</th>
<th>Location of study sites (country)</th>
<th>AEFI/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eastern Mediterranean Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Typhoid: Vi polysaccharide [73]</td>
<td>21,059</td>
<td>2003–2003</td>
<td>2–16</td>
<td>Pakistan</td>
<td>0.0093</td>
</tr>
<tr>
<td>3 Leishmaniasis: autolaved L major (ALM) vaccine mixed with BCG [75]</td>
<td>2453</td>
<td>NA</td>
<td>5–72</td>
<td>Iran</td>
<td>8.2503</td>
</tr>
<tr>
<td>4 Leishmaniasis: Leishmania major (ALM) promastigote vaccine [76]</td>
<td>2306</td>
<td>NA</td>
<td>1–65</td>
<td>Sudan</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>South-East Asia Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Cholera: whole cell oral cholera vaccine [77]</td>
<td>66,900</td>
<td>2006–2006</td>
<td>1–17</td>
<td>India</td>
<td>0.0011</td>
</tr>
<tr>
<td>8 Cholera: 1.25 x 10^11 inactivated Vibrio cholera O1 bacteria and recombiantly produced cholera toxin B subunit (rCTB) [78]</td>
<td>330</td>
<td>2010–2010</td>
<td>0–5, 18–45</td>
<td>Bangladesh</td>
<td>0.0260</td>
</tr>
<tr>
<td>9 Cholera: bivalent (O1 and O139) whole-cell oral cholera vaccine [31]</td>
<td>304</td>
<td>1999–2004</td>
<td>16–55</td>
<td>India</td>
<td>0.0132</td>
</tr>
<tr>
<td>10 Cholera: whole cell oral cholera vaccine [41]</td>
<td>120</td>
<td>Begin in 1998</td>
<td>&lt;1</td>
<td>Bangladesh</td>
<td>1.8258</td>
</tr>
<tr>
<td>11 Rotavirus: rhesus rotavirus (RRV)- tetravalent [79]</td>
<td>201</td>
<td>2005–2005</td>
<td>1–40</td>
<td>India</td>
<td>0.0448</td>
</tr>
<tr>
<td>12 Cholera: whole cell oral cholera vaccine [80]</td>
<td>24</td>
<td>NA</td>
<td>20–30</td>
<td>Thailand</td>
<td>0.0000</td>
</tr>
<tr>
<td><strong>European Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Cholera: live oral cholera vaccine strain CVD 103-HgR [81]</td>
<td>75</td>
<td>NA</td>
<td>&lt;1</td>
<td>Israel</td>
<td>2.0897</td>
</tr>
<tr>
<td>14 Pneumococcal: tetravalent (6B, 14, 19F and 23F polysaccharides) conjugated [82]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Western Pacific Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Salmonella typhi Vi-rEPA vaccine [83]</td>
<td>12,008</td>
<td>1997–1997</td>
<td>2–5</td>
<td>Vietnam</td>
<td>0.0138</td>
</tr>
<tr>
<td>17 Rotavirus: pentavalent rotavirus vaccine [42]</td>
<td>2036</td>
<td>2007–2009</td>
<td>&lt;1</td>
<td>Bangladesh (1), Vietnam (2), Korea (1)</td>
<td>0.0000</td>
</tr>
<tr>
<td>18 HPV: quadrivalent (HPV-6, HPV-11, HPV-16, and HPV-18) HPV vaccine [84]</td>
<td>903</td>
<td>2007–2010</td>
<td>11–13</td>
<td>Vietnam</td>
<td>0.7951</td>
</tr>
<tr>
<td>19 Hib: Conjugate Vaccines [37]</td>
<td>319</td>
<td>2005–2005</td>
<td>&lt;1</td>
<td>Korea</td>
<td>1.4399</td>
</tr>
<tr>
<td>22 Cholera bivalent (O1 and O139) killed whole-cell vaccine [86]</td>
<td>153</td>
<td>2005–2005</td>
<td>18–40</td>
<td>Vietnam</td>
<td>0.3199</td>
</tr>
<tr>
<td><strong>American Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 Rotavirus: live attenuated monovalent vaccine RIX4441 [87]</td>
<td>2155</td>
<td>2001–2002</td>
<td>&lt;1</td>
<td>Brazil (1), Mexico (1), Venezuela (1)</td>
<td>0.4417</td>
</tr>
<tr>
<td>24 Rotavirus: pentavalent rotavirus vaccine (RVS) [88]</td>
<td>1804</td>
<td>2002–2005</td>
<td>&lt;1</td>
<td>Jamaica</td>
<td>0.0000</td>
</tr>
<tr>
<td>26 Rotavirus: tetravalent rhesus-human, reassortant rotavirus vaccine (RRV-TV vaccine) [89]</td>
<td>540</td>
<td>1989–1990</td>
<td>&lt;1</td>
<td>Brazil</td>
<td>0.0000</td>
</tr>
<tr>
<td>27 Cholera: live oral bivalent (CVD 103-HgR/CVD 111) [90]</td>
<td>298</td>
<td>1995–1996</td>
<td>18–40</td>
<td>Peru (1), US (1)</td>
<td>0.1812</td>
</tr>
<tr>
<td>28 Malaria: three synthetic peptides (N, R, and C) derived from the P. vivax CS protein [30]</td>
<td>73</td>
<td>NA</td>
<td>18–33</td>
<td>Colombia</td>
<td>1.0514</td>
</tr>
<tr>
<td><strong>African Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 Hib: tetanus protein conjugate vaccine [91]</td>
<td>42,848</td>
<td>1993–1995</td>
<td>&lt;1</td>
<td>Gambia</td>
<td>0.0000</td>
</tr>
<tr>
<td>30 Pneumococcal: 9-valent pneumococcal polysaccharide vaccine conjugated to a noncatalytic cross-reacting mutant of diptheria toxin (CRM197) [92]</td>
<td>39,836</td>
<td>1998–2000</td>
<td>&lt;1</td>
<td>South Africa</td>
<td>0.0000</td>
</tr>
<tr>
<td>31</td>
<td>Malaria: malaria vaccine RTS,S/AS01 [39]</td>
<td>15,460</td>
<td>2009–2011</td>
<td>0–2</td>
<td>Burkina Faso (1), Gabon (1), Mozambique (1), Tanzania (2), Malawi (2), Ghana (2), Kenya (3)</td>
</tr>
<tr>
<td>32</td>
<td>Pneumococcal: nine-valent pneumococcal conjugate [93]</td>
<td>17,437</td>
<td>2000–2003</td>
<td>&lt;1</td>
<td>Ghana (3), Kenya (1), Mali (1)</td>
</tr>
<tr>
<td>33</td>
<td>Rotavirus: pentavalent rotavirus vaccine [43]</td>
<td>5468</td>
<td>2007–2009</td>
<td>&lt;1</td>
<td>Mali (2), Gambia (1), Senegal (1)</td>
</tr>
<tr>
<td>34</td>
<td>Meningococcal: MenA conjugate vaccine (PsA-TT) [38]</td>
<td>1578</td>
<td>2006–2006</td>
<td>0–29</td>
<td>Mali</td>
</tr>
<tr>
<td>35</td>
<td>Pneumococcal pentavalent polysaccharide conjugated to CRM197 with diphtheria, tetanus toxoid, cell pertussis and Haemophilus influenzae type b (TETRAMUNE) [94]</td>
<td>590</td>
<td>NA</td>
<td>&lt;1</td>
<td>Gambia</td>
</tr>
<tr>
<td>37</td>
<td>Pneumococcal: nine-valent pneumococcal conjugate vaccine [95]</td>
<td>500</td>
<td>NA</td>
<td>&lt;1</td>
<td>South Africa</td>
</tr>
<tr>
<td>38</td>
<td>Rotavirus combined with Polio: rotavirus vaccine (RIX4414) and poliovirus vaccines [96]</td>
<td>450</td>
<td>2001–2003</td>
<td>&lt;1</td>
<td>South Africa</td>
</tr>
<tr>
<td>39</td>
<td>Hib: Haemophilus influenzae type b conjugate vaccines [97]</td>
<td>331</td>
<td>NA</td>
<td>&lt;1</td>
<td>South Africa</td>
</tr>
<tr>
<td>40</td>
<td>Rotavirus: human rotavirus vaccine RIX4414 [36]</td>
<td>100</td>
<td>2005–2008</td>
<td>&lt;1</td>
<td>South Africa</td>
</tr>
<tr>
<td>41</td>
<td>Malaria AMA1-based malaria vaccine FMP2.1/AS02A [33]</td>
<td>100</td>
<td>2006–2006</td>
<td>1–6</td>
<td>Mali</td>
</tr>
<tr>
<td>45</td>
<td>Malaria: AMA1-based malaria vaccine AMA1-C1/Alhydrogel [34]</td>
<td>36</td>
<td>2006–2006</td>
<td>2–3</td>
<td>Mali</td>
</tr>
<tr>
<td>46</td>
<td>Malaria: FP9 CS or MVA CS [28]</td>
<td>32</td>
<td>2004–2004</td>
<td>18–45</td>
<td>Gambia</td>
</tr>
<tr>
<td>47</td>
<td>Malaria: Plasmodium falciparum merozoite surface protein-3 long synthetic peptide (MSP3-LSP) [26]</td>
<td>30</td>
<td>2003–2004</td>
<td>18–40</td>
<td>Burkina Faso</td>
</tr>
</tbody>
</table>

**Multi-Regional**

| 48 | Rotavirus: G1P [8] human rotavirus (HRV) [46] | 63,225 | 2003–2004 | <1 | Argentina (1), Brazil (1), Chile (3), Colombia (1), the Dominican Republic (1), Honduras (1), Mexico (12), Nicaragua (1), Panama (2), Peru (1), Venezuela (1), Finland (1) | 0.0002 |

- **a** According WHO regions [98].
- **b** The number in parenthesis reflects the number of sites per country.
linear regression analysis. The relationship between age and AEFI reported/dose was not significant (p-value 0.2877).

3.2.3. Vaccines tested and number of doses
A total number of 735,920 vaccine doses were administered in the reviewed RCTs, with an average of 1.64 vaccine doses administered/participant and 90% of the RCTs using multi-dose schedules (ranging from 2- to 4-vaccine doses).

Overall, 12 different vaccines were tested. The most commonly investigated vaccines in children were rotavirus vaccine (10), followed by malaria (5), pneumococcal (5), Haemophilus influenzae (5), cholera (4), leishmania (3), HPV (2), typhoid (2), meningococcal (1), rabies (1) and salmonella vaccine (1).

Vaccines tested predominantly in adults were cholera – (6) as well as malaria (5), typhoid (2), leishmania (2), HPV (1), HIV (1) and meningococcal vaccine (1)

3.2.4. Quality and type of safety follow-up
Among the 50 identified RCTs, 90% applied active surveillance methodologies. Active surveillance included safety assessments during home/hospital visits (66%) as well as patient diaries (20%) or remote follow-up via Internet (11%) or telephone (1%). The level of structuring in telephone interviews or Internet questionnaires was not detailed in the respective RCT publications.

In 56% of all RCT publications, AEFI assessments and AEFI reporting were conducted by “health care workers” (not further specified), the remaining 44% of RCT publications did not name the profession of the individual responsible for safety surveillance and reporting (Fig. 2).

3.2.5. Duration of safety follow-up
The duration of follow-up was specified in 49/50 vaccine RCT publications. The maximum duration of follow-up ranged from 3 days to 2 years (mean 73 days, median 56 days). Safety follow-up however, was not always differentiated from follow-up for efficacy endpoints, in which case the overall follow-up duration was used for the analysis.

For the purposes of this analysis, long-term follow-up was defined as any surveillance period starting >24h after immunization with the aim to detect delayed AEFI. The majority (62%) of long-term follow-up visits were conducted in person.

In 23/50 developing country vaccine RCT publications, an additional immediate safety observation was performed after immunization ranging from 15 to 60 min (mean 16.9 min, median 30).

The effect of maximum duration of follow-up on AEFI reported/dose was tested using linear regression analysis, which did not yield a significant relationship (p-value 0.37762).

3.2.6. Grading of AEFI severity
In 21 of 50 RCTs the severity of adverse events was graded. In 9 RCTs the MMS scale was used to grade severity of adverse events as follows [23–31]: “mild” (no interference with daily activity), “moderate” (some interference with daily activity) or “severe” (significant, preventing daily activity). Ten RCTs used a 4-graded

Fig. 1. Number of developing country vaccine RCTs published per annum (1989–2011) and publication dates of relevant case definitions*.

Vesikari clinical scoring system for diarrhoeal episodes [5].

BC case definitions for fever [3], seizure [7], intussusception [8] and persistent crying [10].

BC case definition for induration [4] and swelling [6]; WHO case definition for Clinical malaria (incl. fever threshold) [9].

BC case definition for a local reaction [2].

BC case definition for diarrhea [1].
3.2.7. Use of case definitions in AEFI reporting

AEFI definitions were used in 35 out of 50 developing country vaccine clinical trials.

Predefined standardized vaccine safety case definitions by the Brighton Collaboration (BC) were applied in only two instances: to define seizure in a recent malaria vaccine RCT [39] and intussusception in a rotavirus vaccine trial in 2006 [46]. The grading by levels of diagnostic certainty was limited to the two RCTs using the Brighton Collaboration case definitions [39,46].

In 3 instances, case definitions originally designed to measure vaccine efficacy endpoints [5,9] were used.

Of note, 17 of the RCTs not using BC definitions were published prior to the publication of a first set of BC case definitions (incl. fever as an AEFI). The publication dates of the case definitions most commonly used for vaccine safety reporting in the RCTs are illustrated in Fig. 1, above.

3.2.8. AEFI reported/defined – fever as an AEFI

The different types of AEFI reported and the definitions used to describe AEFI in the 50 RCTs are depicted in Table 3, below.

The most commonly defined AEFI was fever with 27 RCTs providing 16 different definitions and temperature thresholds ranging from 36.6 °C (axillary) to 38.5 °C (axillary or rectal). The remaining 23 RCT publications did not provide any definition or threshold for fever (evidently, study protocols were not included in the analysis).

The fever threshold applied most commonly was “≥37.5 °C” (37%), followed by “≥38.0 °C” (29%). Fever definitions in 19 RCT publications required temperatures to be measured at specific body sites. The remaining 8 publications did not specify where body temperatures were to be taken.

Of note, logistic regression analysis (Fig. 3) revealed a positive correlation between the implementation of a fever case definition and the reporting rate for fever as an AEFI (p = 0.027).

4. Discussion

4.1. Summary of the evidence

With increasing numbers of vaccine trials published per annum, fifty developing country vaccine RCTs were identified searching Embase and Medline from 1989 to 2011. For methodological reasons, this review relies on articles published in English or German, which are listed in key electronic literature databases. Individual studies may have been missed due to inconsistent indexing and publication- or language bias.

In the 50 reviewed vaccine RCTs, a total number of 735,920 vaccine doses were administered to 446,908 participants, mostly infants and children. Rotavirus and malaria vaccines were among the most commonly tested. All 50 RCTs assessed the respective vaccine to be safe with 82% reporting ≥1 AEFI during inconsistent follow-up periods ranging from 3 days to 2 years. The variability of AEFI definition criteria used was remarkable with case definitions by the Brighton Collaboration implemented in only 4% RCTs. Fever definitions showed the highest degree of variability, but use of fever definitions significantly increased reporting rates for fever as an AEFI (p = 0.027).

4.2. Gaps identified

The authors have identified several key areas (”gaps”) that might benefit from improved knowledge transfer and standardization: the monitoring of vaccine safety, the reporting of AEFI, and the risk-benefit communication based on vaccine RCTs.
### Table 3
AEFI definitions in 50 developing country vaccine RCTs.

#### Fever

<table>
<thead>
<tr>
<th>Body site for temperature measurement:</th>
<th>Axillary</th>
<th>Oral</th>
<th>Rectal</th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥38.5 °C ≥ 2 days [85]</td>
<td>≥38 °C [90]</td>
<td></td>
<td>≥38.5 °C [36]</td>
<td>≥38 °C [25,79,93,94,97]</td>
</tr>
<tr>
<td>≥38.0 °C [38]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;38 °C [26]</td>
<td>≥37.5 °C [35]</td>
<td></td>
<td>≥38.1 °C [45]</td>
<td>≥37.5 °C [22,28]</td>
</tr>
<tr>
<td>≥37.8 °C [84]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥37.5 °C [21,23,32,37,39,83]</td>
<td>≥37.5 °C [27,33]</td>
<td></td>
<td>≥38 °C [82]</td>
<td>≥37.2 °C [24]</td>
</tr>
<tr>
<td>&gt;36.6 °C [41]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of RCT publications not mentioning any case definition for fever as an AEFI: 3

#### Local AEFI

<table>
<thead>
<tr>
<th>Erythema</th>
<th>Swelling</th>
<th>Local induration</th>
<th>Local pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 mm [83]</td>
<td>≥50 mm [83]</td>
<td>&lt;50mm* [24]</td>
<td>Mild: minor reaction to touch; Severe: cries when moving</td>
</tr>
<tr>
<td>&lt;30 mm [26]</td>
<td>&lt;30 mm [26]</td>
<td>&lt;30mm* [24]</td>
<td>Mild: painful to touch, severe: painful when spontaneously moving</td>
</tr>
<tr>
<td>≥20 mm but &lt;30 mm [85]</td>
<td>≥1 but ≤20 mm [29]</td>
<td>0–20 mm* [28,34]</td>
<td>Mild pain: no restriction of movement; severe pain: no movement possible [28]</td>
</tr>
<tr>
<td>≥1 but &lt;20 mm [29]</td>
<td>≤5 mm [37]</td>
<td>≥10 mm [25]</td>
<td>Limitation of arm motion</td>
</tr>
<tr>
<td>0–20 mm* [28,34]</td>
<td>≤5 mm* [21,32,33,39]</td>
<td>≥5 mm* [38]</td>
<td>Mild: active range of abduction &gt;90° but ≤120°; severe: &lt;30° [28,29,33]</td>
</tr>
</tbody>
</table>

Number of RCT publications not mentioning any case definition for local AEFI: 36

#### Systemic AEFI

<table>
<thead>
<tr>
<th>Seizure</th>
<th>Intussusception</th>
<th>Irritability</th>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Vomiting</td>
<td>Loss of appetite</td>
<td>Body ache</td>
</tr>
<tr>
<td>≥3 uniformed stools over a 24-hour period [45, 80, 86, 90]</td>
<td>Occasional, but able to eat/drink normal amounts [33]</td>
<td>Eating less than usual/interferes with normal activity [21, 33, 36, 39]</td>
<td>Pain (aching) over the entire body [24]</td>
</tr>
<tr>
<td>4-5 looser than normal stools/day [36]</td>
<td></td>
<td>Not eating at all [37]</td>
<td></td>
</tr>
<tr>
<td>3 or more grade 2 stool or 1 or more grade 3 stool [41]</td>
<td>Two episodes vomiting/day [36]</td>
<td>Eating less than usual [32]</td>
<td></td>
</tr>
</tbody>
</table>

Number of RCT publications not mentioning any case definition for systemic AEFI: 36

In several instances severity grading was part of the criteria when defining AEFI.

* Mild; no maximum was defined.

#### 4.2.1. Monitoring of vaccine safety

None of the reviewed RCTs had a sufficient sample size to detect rare AEFI (with “rare AEFI” defined according to CIOMS/WHO as “those with rates of occurrence of less than 1 per 100,000 vaccinees or placebo recipients” or ≥0.01% to ≤0.1%) [47]. Several trials however, were testing vaccines in early phases of development, even if the phase of the clinical trial was not always specified in the publication. While guidance exists on the optimum sample size in clinical trials testing new vaccines [48], there seems to be little consensus on the optimum duration of safety follow up [47]. Certain AEFI, such as anaphylaxis or rash, are expected to appear relatively soon after immunization, while others, such as intussusception or paralysis, will occur with some delay, thrombocytopenia even later. Hence, immediate and mid/long-term safety follow-up are equally important.

#### 4.2.2. Reporting of adverse events following immunization (AEFI)

More than twenty pre-defined case definitions have been developed and published that may be used to standardize the reporting of AEFI in vaccine clinical trials and post-marketing surveillance (www.brightoncollaboration.org). Pre-defined standardized case definitions need to be applied consistently however, to allow for comparability of RCTs, including the pooling of data from multiple trials to detect rare AEFI. Our analysis revealing the implementation of Brighton Collaboration case definitions in only 2/50 developing country vaccine RCTs so far, represents a missed opportunity for extended meta-analyses of vaccine clinical trials in the future.
4.3. Risk-benefit communication based on vaccine RCTs

Public and immunization provider perceptions impact directly on the success of vaccination programs. Some difficult lessons have been learned in countries with longstanding successful immunization programs in terms of how rapidly public confidence can be lost following a public scare regarding vaccine safety and how difficult it is to regain that confidence [41]. More attention should be paid to the communication of vaccine safety research and the awareness of safety methodologies among pediatricians, general practitioners and vaccine providers. Data should be presented in a transparent and systematic manner using safety terminology adhering to international standards.

4.4. Suggestions for further developments

Consistent documentation is key to the successful implementation of international safety standards in resource-poor settings. According to the guidelines outlined by Poland [13], the accurate documentation of the immunization event itself is equally important, including basic information on the ethnicity and any underlying conditions of the subject involved.

The implementation of AEFI definitions may be improved if the complexity of such standards can be reduced. Simple variable checklists may be made available in the public domain to facilitate the use of standardized case definitions in clinical trials and safety surveillance [49]. When case definitions are developed, criteria should be designed such that the required information can be gathered also in low-resource settings. Modern technologies such as SMS and mobile phone applications may facilitate the monitoring of vaccine safety in remote areas where access to Internet connectivity may not always be readily available. In any instances, a high level of sensitivity, openness and serious effort need to be maintained when designing surveillance mechanisms for AEIs.

5. Conclusions

With increasing globalization, and despite the many observed differences, there is much to be gained by both developed and developing countries working together to improve vaccine safety research and reporting in randomized vaccine clinical trials.

Key steps to improving the safety reporting in vaccine randomized clinical trials would include:

(a) Minimization of publication and language bias with respect to clinical trials conducted in low-resource settings.
(b) Improved communication of available standards for the reporting of immunization events, adverse events and safety follow-up.
(c) Consistent implementation of consensus case definitions for the reporting of adverse events following immunization.

Acknowledgments

The authors kindly thank colleagues who reviewed the paper for their advice. They also thank Dirk Wiesenthal for his support with the statistical analysis.

Conflicts of interest: The authors have no conflicts of interest to declare.

References


