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Review

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

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ABSTRACT

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 (1989–2011) 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.

Contents

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

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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 on 31 October 2011 using the search terms [*immunisation* or *immunization* or *vaccine*] and [*safety*] and [*developing*] *countr**; 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.

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

[a] 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, subanalyses 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 [16] 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). 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.

Vaccine studied		Number of subjects randomized (*n*)	Time of conduct (years)	Participant age (years)	Location of study sites (country)[b]	AEFI/dose
Eastern Mediterranean Region[a]						
1	Typhoid: Vi polysaccharide [73]	21,059	2003–2003	2–16	Pakistan	0.0093
2	Leishmaniasis (cutaneous): killed Leishmania major plus BCG [74]	3637	1994–1997	6–15	Iran	1.7534
3	Leishmaniasis: autoclaved L. major (ALM) vaccine mixed with BCG [75]	2453	NA	5–72	Iran	8.2503
4	Leishmaniasis: Leishmania major (ALM) promastigote vaccine [76]	2306	NA	1–65	Sudan	0.000
South-East Asia Region[a]						
5	Cholera: whole cell oral cholera vaccine [77]	66,900	2006–2006	1–17	India	0.0011
6	Hib: lower doses of Hib-polyribosylphosphate (PRP) conjugated with tetanus toxoid (PRP-T) [25]	1294	1996–1999	<1	Indonesia	1.1723
7	Hib: Act-HibTM in combination with BE DTwP [23]	378	NA	<1	India	2.9324
8	Cholera: 1.25 × 1011 inactivated Vibrio cholerae O1 bacteria and recombinantly produced cholera toxin B subunit (rCTB) [78]	340	2005–2007	<1	Bangladesh	0.0111
9	Cholera: bivalent (O1 and O139) whole-cell oral cholera vaccine [31]	330	2010–2010	0–5, 18–45	Bangladesh	0.0260
10	Cholera: whole cell oral cholera vaccine [41]	304	1999–2004	16–55	India	0.0132
11	Rotavirus: rhesus rotavirus (RRV)- tetravalent [79]	120	Begin in 1998	<1	Bangladesh	1.8258
12	Cholera: whole cell oral cholera vaccine [80]	201	2005–2005	1–40	India	0.0448
13	Cholera: live oral cholera vaccine strain CVD 103-HgR [81]	24	NA	20–30	Thailand	0.0000
European Region[a]						
14	Pneumococcal: tetravalent (6B, 14, 19F and 23F polysaccharides) conjugated [82]	75	NA	<1	Israel	2.0897
Western Pacific Region[a]						
15	Typhoid: Vi polysaccharide [22]	118,588	2003–2003	5–60	China	0.0014
16	Salmonella thyphi Vi-rEPA vaccine [83]	12,008	1997–1997	2–5	Vietnam	0.0138
17	Rotavirus: pentavalent rotavirus vaccine [42]	2036	2007–2009	<1	Bangladesh (1), Vietnam (2), Korea (1)	0.0000
18	HPV: quadrivalent (HPV-6, HPV-11, HPV-16, and HPV-18) HPV vaccine [84]	903	2007–2010	11–13	Vietnam	0.7951
19	Hib: Conjugate Vaccines [37]	319	2005–2005	<1	Korea	1.4399
20	Rabies: PVRV–low-dose intradermal rabies vaccination [85]	240	1995–1995	<1	Vietnam	0.4199
21	Typhoid: whole-cell killed (WCK) [24]	239	1997–1998	18–25	Malaysia	0.3159
22	Cholera bivalent (O1 and O139) killed whole-cell vaccine [86]	153	2005–2005	18–40	Vietnam	0.3199
American Region[a]						
23	Rotavirus: live attenuated monovalent vaccine RIX4414 [87]	2155	2001–2002	<1	Brazil (1), Mexico (1), Venezuela (1)	0.4417
24	Rotavirus: pentavalent rotavirus vaccine (RV5) [88]	1804	2002–2005	<1	Jamaica	0.0000
25	Rotavirus: oral rhesus-human rotavirus tetravalent (RRV-TV) vaccine [45]	700	1988–1989	<1	Peru	0.7368
26	Rotavirus: tetravalent rhesus-human, reassortant rotavirus vaccine (RRV-TV vaccine) [89]	540	1989–1990	<1	Brazil	0.0000
27	Cholera: live oral bivalent (CVD 103-HgR/CVD 111) [90]	298	1995–1996	18–40	Peru (1), US (1)	0.1812
28	Malaria: three synthetic peptides (N, R, and C) derived from the *P. vivax* CS protein [30]	73	NA	18–33	Colombia	1.0514
African Region[a]						
29	Hib: tetanus protein conjugate vaccine [91]	42,848	1993–1995	<1	Gambia	0.000
30	Pneumococcal: 9-valent pneumococcal polysaccharide vaccine conjugated to a noncatalytic cross-reacting mutant of diphtheria toxin (CRM197) [92]	39,836	1998–2000	<1	South Africa	0.000

31	Malaria: malaria vaccine RTS,S/AS01 [39]	15,460	2009–2011	0–2	Burkina Faso (1), Gabon (1), Mozambique (1), Tanzania (2), Malawi (2), Ghana (2), Kenya (3)	0.1837
32	Pneumococcal: nine-valent pneumococcal conjugate [93]	17,437	2000–2003	<1	Gambia	0.0091
33	Rotavirus: pentavalent rotavirus vaccine [43]	5468	2007–2009	<1	Ghana (3), Kenya (1), Mali (1)	0.0009
34	Meningococcal: MenA conjugate vaccine (PsA-TT) [38]	1578	2006–2006	0–29	Mali (2), Gambia (1), Senegal (1)	0.2914
35	Pneumococcal pentavalent polysaccharide conjugated to CRM197 with diphtheria, tetanus toxoid, cell pertussis and *Haemophilus influenzae* type b (TETRAMUNE) [94]	590	NA	<1	Gambia	2.1860
36	Malaria: RTS/AS01E candidate malaria vaccine [21]	511	2007–2009	<1	Ghana (1), Tanzania (1), Gabon (1)	2.4967
37	Pneumococcal: 9-valent pneumococcal conjugate vaccine [95]	500	NA	<1	South Africa	0.1145
38	Rotavirus combined with Polio: rotavirus vaccine (RIX4414) and poliovirus vaccines [96]	450	2001–2003	<1	South Africa	0.0000
39	Hib: *Haemophilus influenzae* type b conjugate vaccines [97]	331	NA	<1	South Africa	0.0555
40	Rotavirus: human rotavirus vaccine RIX4414 [36]	100	2005–2008	<1	South Africa	0.8933
41	Malaria AMA1-based malaria vaccine FMP2.1/AS02A [33]	100	2006–2006	1–6	Mali	5.1038
42	Malaria: FMP1/AS02A [27]	40	2003–2003	18–55	Mali	1.4000
43	Malaria: RTS,S/AS02A [32]	60	2002–2002	1–4	Mozambique	1.7545
44	Malaria: Plasmodium falciparum malaria merozoite surface protein FMP1 [29]	40	2002–2003	18–55	Kenya	1.2735
45	Malaria: AMA1-based malaria vaccine AMA1-C1/Alhydrogel [34]	36	2006–2006	2–3	Mali	0.1884
46	Malaria: FP9 CS or MVA CS [28]	32	2004–2004	18–45	Gambia	2.8627
47	Malaria: Plasmodium falciparum merozoite surface protein-3 long synthethic peptide (MSP3-LSP) [26]	30	2003–2004	18–40	Burkina Faso	0.8556
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
49	HPV: (HPV)-16/18 AS04-adjuvanted vaccine [35]	18,644	2004–2005	15–25	Asian Pacific (27), Europe (57), Latin America (4) and North America (54)	1.3824
50	HIV: modified vaccinia virus Ankara with and without DNA priming [40]	115	2003–2004	18–60	Kenya (1), South Africa (2), Switzerland (1), UK (2)	0.3232

[a] According WHO regions [98].
[b] The number in parenthesis reflects the number of sites per country.

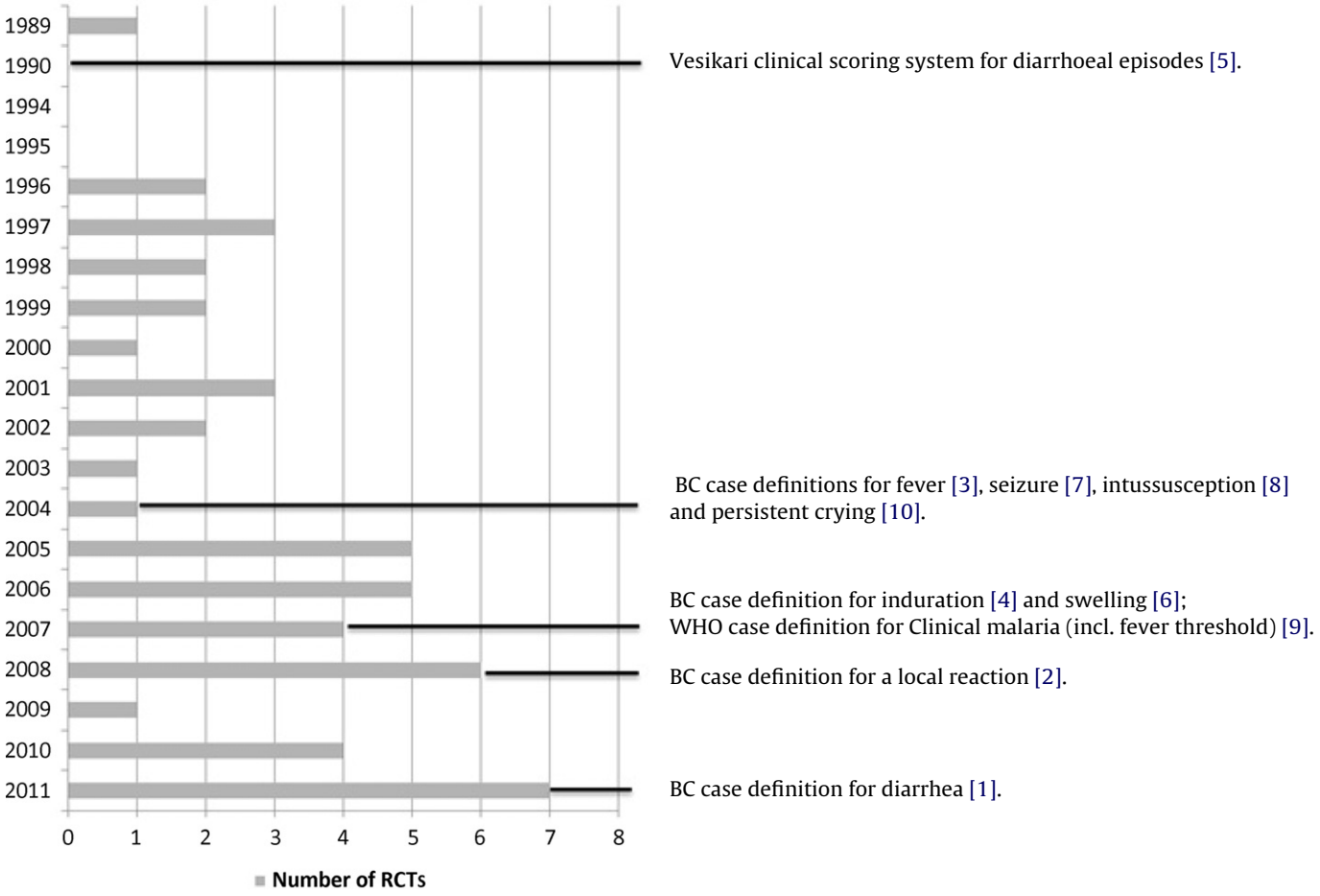

Fig. 1. Number of developing country vaccine RCTs published per annum (1989–2011) and publication dates of relevant case definitions*.

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 >24 h 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

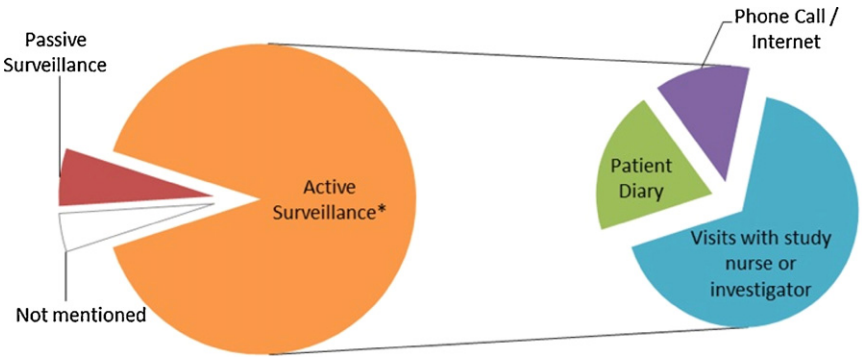

Fig. 2. Quality and type of safety surveillance.
*Specification of active surveillance systems to the right (patient diary, phone call/internet, visits with study nurse or investigator).

scale instead, where "0"was added for "no symptoms" or "VS" for "very severe" [21,32–40].

Mahalanabis et al. [41] used the consistency of stools as well as dehydration as an indirect outcome measure to grade severity of diarrhea as an adverse event. In two rotavirus vaccine RCTs the Vesikari Clinical Scoring System was used instead [42,43]. The Scoring System characterizes "gastroenteritis" as a combination of watery diarrhea, vomiting, fever and dehydration [5]. The scoring system may also be applied as an outcome measure for vaccination failure in cases of rotavirus gastroenteritis following rotavirus immunization. Similarly, Lanata et al. [45] used the WHO definition of dehydration [44] to define diarrhea as an indirect efficacy endpoint in a rotavirus vaccine clinical trial.

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 ($p = 0.027$).

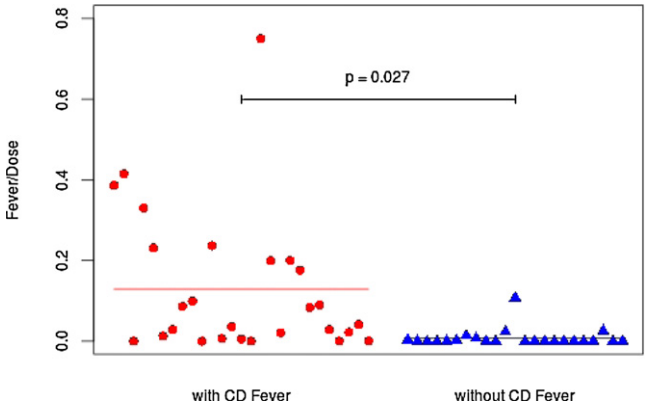

Fig. 3. Reporting rates for fever as an AEFI (per vaccine dose administered) in RCTs with and without use of fever case definitions (CD).

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			
Body site for temperature measurement:			
Axillary	Oral	Rectal	Unspecified
≥38.5 °C ≥2 days [85] ≥38.0 °C [38] <38 °C[a] [26] ≥37.8 °C [84] ≥37.5 °C [21,23,32,37,39,83] >37.5 °C [34] ≥36.6 °C [41]	≥38 °C [90] >37.5 °C [35] ≥37.5 °C [27,33]	≥38.5 °C [36] ≥38.1 °C [45] ≥38 °C [82]	≥38 °C [25,79,93,94,97] ≥37.5 °C [22,28] >37.2 °C [24]
Number of RCT publications not mentioning any case definition for fever as an AEFI: 23			

Local AEFI			
Erythema	Swelling	Local induration	Local pain
≥50 mm [83] <30 mm [26]	≥50 mm [83] <30 mm [26]	<50 mm[a] [24] <30 mm [26]	Mild: minor reaction to touch; Severe: cries when moving [21,32,33,38,39]
≥20 mm but ≤30 mm [85]	≥1 but ≤20 mm [29]	0–20 mm[a] [28,34]	Mild: painful to touch, severe: painful when spontaneously moving [29]
≥1 but ≤20 mm [29] 0–20 mm[a] [28,34]	≥1 but ≤20 mm[a] [34] ≤5 mm [37]	<15 mm or <2 weeks duration[a] [40] ≥10 mm [25]	Mild pain: no restriction of movement; severe pain: no movement possible [28]
≥5 mm [37]			Limitation of arm motion
<5 mm[a] [21,33,39]	<5 mm[a] [21,32,33,39]	>5 mm[a] [38]	Mild: active range of abduction >90° but ≤120°; severe: <30° [28,29,33]
Number of RCT publications not mentioning any case definition for local AEFI: 36			

Systemic AEFI			
Seizure	Intussusception	Irritability	Headache
Brighton Collaboration case definition [39]	Brighton Collaboration case definition [46]	Unusual or inconsolable crying [23] Crying more than usual [21,32,33,39] Crying that could not be comforted or preventing normal activity [37]	Uncomfortable and painful sensations/feelings in the head [24]
Diarrhea	Vomiting	Loss of appetite	Body ache
≥3 unformed stools over a 24-h period [45,80,86,90] 4–5 looser than normal stools/day [36] 3 or more grade 2 stool or 1 or more grade 3 stool [41]	Occasional, but able to eat/drink normal amounts [33] Two episodes vomiting/day [36]	Eating less than usual/interferes with normal activity [21,33,36,39] Not eating at all [37] Eating less than usual [32]	Pain (aching) over the entire body [24]
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.
[a] 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.

4.2.3. 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.

4.3. Progress made

The analysis suggests that the quantity of vaccine safety data derived from developing country RCTs is on the rise with many different vaccines being tested in a variety of settings and diverse patient populations.

The overall quality of safety data from vaccine RCTs is bound to benefit from increasing numbers of trials using active surveillance measures, pre-defined safety standards and levels of diagnostic certainty. Furthermore, pre and post-marketing safety standards, such as case definitions and AEFI terminologies should be harmonized to facilitate the meta-analysis of safety data from different clinical trials in diverse clinical settings. Publication and registration standards have improved the quality of data reported from clinical trials while diminishing publication bias. Additional attention should be paid to the specification of the phase of a clinical trial as well as the duration and quality of follow-up.

New case definitions are issued continuously and implemented with some delay after publication and dissemination. The positive correlation between use of fever case definitions and AEFI reporting rates suggests that the consistent implementation of clearly defined safety outcomes may ultimately improve the sensitivity of vaccine safety assessments.

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 AEFI.

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.

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