



Surveillance for adverse events following immunization (AEFI) in Switzerland—1991–2001

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ABSTRACT

In Switzerland, reporting of adverse events following immunization (AEFI) has been mandatory by law since 1988. The goal of this study was a detailed analysis of reported AEFI received by the Swiss Federal Office of Public Health between 1991 and 2001. Overall, 1013 AEFI were reported which translates to 2.7 reports per 100,000 vaccine doses distributed during the study period. Most AEFI were classified as general systemic reactions (47%), followed by local (26%), neurological (16%) and allergic reactions (13%). The majority of all reported AEFI ($N=513$; 51%) had occurred in individuals 16 years and older. Causal relationship between immunization and AEFI was probable in 91 (10%) of 909 assessable reports and very likely or certain in 194 (21%), the majority of which (88%) were local reactions. Vaccines distributed in Switzerland have proven to be generally safe. Limitations of the passive surveillance system, however, warrant improvements in the future.

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1. Introduction

Collection and assessment of adverse events following immunization (AEFI) are important to monitor potential vaccine safety problems and to maintain public confidence in vaccinations [1,2]. Careful and continuous analysis of such data allows a critical evaluation of the actual vaccine adverse event reporting system. In this respect, unusual increases of previously reported AEFI are as important to be detected as are hitherto unknown AEFI ("signal detection"). Monitoring and evaluation of vaccine safety therefore is an integral part of national immunization programmes.

In Switzerland, reports on AEFI are mandatory by law [3]. Until June 2001, these reports, provided by immunizing physicians, were collected in a central database, administered by the Swiss Federal Office of Public Health (SFOPH).

The goal of this study was a detailed analysis of all AEFI reported in Switzerland between 1991 and 2001.

2. Methods

2.1. Data collection

Based on the Swiss national law on epidemics, established in 1970, an AEFI was notifiable between 1988 and 2001 and had to be reported by physicians if (a) it occurred in reasonable tempo-

ral association (i.e. within 8 weeks after immunization), (b) no other plausible cause explained the event, and (c) it fulfilled one or more of the following criteria: it is serious, previously unknown to occur after immunization, or is the main cause for a physician visit.

Until June 2001, AEFI were to be reported either to the SFOPH or – optionally – to the National Drug Pharmacovigilance Center (SANZ; "Schweizerische Arzneimittelnebenwirkungszentrale"). After June 2001, the reporting system was reorganized by the SFOPH and this task was delegated to a new institution, the Swiss Agency for Therapeutic Products, SWISSMEDIC. Findings of the first 3 years (1988–1990) of AEFI reporting have previously been published [4]. Therefore, this report is based on all reports received by the SFOPH or SANZ between 1991 and June 2001, the final period of surveillance under the auspices of SFOPH.

Reports of AEFI should contain the following information in a standardized fashion: date of report, age and sex of the patient, kind and lot number(s) of vaccine(s) used, description of the adverse event, time interval after immunization, duration of the event, and any additional remarks from the reporter, e.g. final outcome of the AEFI.

For this study, the database provided by the SFOPH (after elimination of duplicate reports) was subdivided by vaccine categories: Bacillus-Calmette-Guérin vaccine (BCG); diphtheria-tetanus-(acellular/whole cell) pertussis DTP(a/wc)/dT±*Haemophilus influenzae* type B (Hib)±poliomyelitis vaccine, oral or inactivated (OPV or IPV); tick-borne encephalitis (TBE); hepatitis A and/or B; measles, mumps, rubella (MMR); yellow fever; influenza; typhoid

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fever; other vaccines; and co-administered vaccines (more than one of the above categories).

For further analyses, each vaccine category was further subdivided in four groups of adverse events by organ systems involved: neurological (e.g. headache, convulsion), allergic (e.g. generalized urticaria, anaphylactic reactions), general systemic (e.g. fever, flu like symptoms), and local reactions (e.g. redness, swelling or pain at the injection site). Assignment into groups of organ systems involved was performed by the responsible officer at the SFOPH (CB) after validation based on all information available in the reports.

The yearly number of distributed doses of various vaccines in Switzerland during the study period was also provided by the SFOPH and allowed an estimation of reporting rates.

2.2. Data analysis

2.2.1. Reporting rates

All data were analysed by the three authors. Reporting rates of AEFI (per 100,000 distributed doses) were calculated by vaccine categories and disease categories. In case of co-administration of two or more vaccines in an individual, we attributed the reported AEFI to the vaccine which most likely caused the event, if possible (e.g. parotitis occurring 15 days after co-administration of MMR, DTP and poliomyelitis vaccines was most likely associated with MMR and therefore attributed to that vaccine). Otherwise, the event was attributed to each administered vaccine (e.g. fever after simultaneous administration of pneumococcal and influenza vaccines).

2.2.2. Age groups

We categorized patients by the following age groups: 0–11 months; 1–7 years; 8–15 years; >16 years; and age unknown.

2.2.3. Causality assessment

We attempted to assess each single report regarding its causal link to the administered vaccine(s) by use of the following categories based on modified (*modifications in italics below*) WHO recommendations on causality assessment of AEFI [5]:

- Unclassifiable: AEFI with insufficient information to permit assessment and identification of the cause.
- Unrelated: AEFI with an incompatible time relationship (*live-attenuated vaccine >30 days, inactivated vaccines >7 days after immunization*) and which could be explained by underlying disease or other drugs or chemicals.
- Unlikely: *unknown (not mentioned in the literature) but in a plausible time interval (live-attenuated vaccine 0–30 days, inactivated vaccine 0–7 days after immunization)*. (WHO definition: AEFI where time relationship to vaccine administration makes a causal relation improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals).
- Possible: AEFI with a reasonable time relationship to vaccine administration, but could also be explained by concurrent disease or other drugs or chemicals.
- Probable: AEFI with a reasonable time relationship to vaccine administration and which is unlikely to be attributed to concurrent disease or other drugs or chemicals. *Local reactions at the injection site with an unknown time relationship to vaccine administration*.
- Very likely or certain: AEFI with a reasonable time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals.

2.2.4. Assessment of severity and seriousness

In pharmacovigilance terminology, severity is intended to describe the clinical severity (or intensity) whereas seriousness is based on patient/event outcome or action criteria that serve as a guide for defining regulatory reporting obligations. In accordance with this, AEFI were assessed as non-serious or serious and further subdivided in categories of severity, including the definition for “serious” AEFI as proposed by WHO [5]:

- non-serious (mild severity): no intervention necessary;
- non-serious (moderate severity): medication given or
 - physician visit or
 - event interfering with daily activities or
 - loss of working hours;
- serious (severe): any untoward medical occurrence that results in death, hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, or is life threatening.

2.2.5. Statistics

For statistical analysis we organized the database as an excel file (Microsoft Office Excel 2003). Reporting rates and 95% confidence intervals were calculated by use of the Excel programme [6].

3. Results

3.1. General aspects

During the 10.5 year study period, 1013 AEFI were reported in 1009 immunized individuals (52.1% in females) and 36,858,216 vaccine doses were distributed in total. On average, 96.5 reports were received per year, i.e. 2.7 reports per 100,000 distributed vaccine doses. As can be seen in Table 1, highest reporting rates were found for tick-borne encephalitis and yellow fever vaccines. AEFI reporting rates by vaccine varied substantially from year to year with up to 10-fold differences. Comparatively low numbers of yearly reports for specific vaccines (leading to wide confidence intervals) account for the great majority of these differences.

AEFI reports by disease categories are demonstrated in Table 2. As can be seen, most AEFI were general systemic reactions, followed by local, neurological and allergic reactions.

3.2. Age distribution

Most AEFI (513 = 50.6%) had occurred in patients 16 years and older, followed by patients 1–7 years (243 = 24.0%), infants (<1 year of age; 155 = 15.3%), and patients 8–15 years of age (85 = 8.4%). In the remaining 17 reports (1.7%) age of patients was unknown. Age distribution on a yearly basis was similar (data not shown). As it was not known to whom distributed vaccines were administered, AEFI reporting rates by age could not be calculated.

3.3. Causality assessment

Each report was assessed by its possible causal relationship to preceding immunization(s). Cases with insufficient information ($n = 104$) were excluded. Among the remaining 909 reports, no causal relationship was found in 154 reports (16.9%), whereas causal relationship was unlikely in 31 reports (3.4%), possible in 439 reports (48.3%), probable in 91 reports (10.0%) and very likely or certain in 194 reports (21.3%). Of 194 AEFI with very likely or certain causal relationship to immunization, 168 (86.6%) were local reactions.

Unfortunately, little information was available on diagnostic procedures applied to exclude other possible aetiologies of most

Table 1

Numbers and incidence (per 100,000 distributed vaccine doses) of reported AEFI by year and vaccine groups.

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	Total
TBE												
<i>N^a</i>	3	6	9	5	4	4	4	5	10	14	9	73
<i>I^b</i>	8.4 [1.7; 24.7]	13.6 [5.0; 29.4]	15.5 [7.1; 29.5]	9.9 [3.2; 23.0]	6.1 [1.7; 15.5]	6.1 [1.7; 15.5]	6.1 [1.7; 15.5]	7.2 [2.3; 16.8]	11.0 [5.3; 20.3]	9.4 [5.3; 16.3]	6.3 [2.9; 11.9]	8.7 [6.8; 11.0]
Yellow fever												
<i>N^a</i>	0	0	0	3	0	1	1	3	0	3	4	15
<i>I^b</i>	0 [0]	0 [0]	0 [0]	6.8 [1.4; 20.0]	0 [0]	78.6 [2.4; 437.6]	3.4 [0.1; 9.1]	11.2 [2.3; 32.6]	0 [0]	9.3 [1.9; 27.3]	13.7 [3.7; 35.1]	5.5 [3.1; 9.0]
BCG												
<i>N^a</i>	9	1	4	7	6	1	6	4	2	1	0	41
<i>I^b</i>	6.6 [3.0; 12.5]	0.7 [0.0; 4.0]	2.4 [0.5; 7.0]	8.5 [3.4; 17.5]	11.5 [4.2; 25.0]	1.4 [0.0; 7.9]	8.7 [3.2; 19.0]	8.5 [2.3; 21.7]	4.3 [0.5; 15.5]	4.6 [0.1; 25.4]	0 [0]	5.1 [3.7; 7.0]
MMR												
<i>N^a</i>	5	6	6	3	1	3	4	16	10	14	21	89
<i>I^b</i>	2.5 [0.8; 5.9]	3.4 [1.3; 7.5]	3.3 [1.2; 7.1]	2.5 [0.5; 7.4]	0.9 [0.0; 5.2]	1.9 [0.4; 5.6]	2.5 [0.7; 6.5]	7.0 [4.0; 11.3]	4.1 [2.0; 7.5]	5.6 [3.1; 9.4]	8.0 [5.0; 12.2]	4.3 [3.4; 5.3]
DTP(a/wc)–Hib–Polio												
<i>N^a</i>	75	51	45	29	51	76	37	44	33	44	64	549
<i>I^b</i>	3.6 [2.9; 4.5]	2.4 [1.8; 3.1]	2.2 [1.6; 2.9]	1.5 [1.0; 2.1]	2.5 [1.8; 3.2]	4.5 [3.5; 5.6]	1.9 [1.3; 2.6]	2.8 [2.0; 3.7]	2.8 [2.0; 4.0]	3.8 [2.7; 5.1]	6.5 [5.0; 8.3]	2.9 [2.6; 3.1]
HepA and/or HepB												
<i>N^a</i>	4	4	8	9	2	7	6	14	6	19	16	95
<i>I^b</i>	3.7 [1.0; 9.5]	1.5 [0.4; 3.9]	2.5 [1.1; 5.4]	4.0 [1.8; 7.5]	0.7 [1.0; 5.2]	2.3 [0.9; 4.8]	1.8 [0.7; 4.0]	2.6 [1.4; 4.3]	0.9 [0.3; 1.9]	3.0 [1.8; 4.7]	3.0 [1.7; 4.9]	2.2 [1.8; 2.7]
Influenza												
<i>N^a</i>	2	1	9	6	14	12	14	18	6	17	22	121
<i>I^b</i>	0.6 [0.1; 2.0]	0.3 [0.1; 1.6]	2.1 [1.0; 4.1]	1.5 [0.5; 3.2]	3.0 [1.7; 5.1]	2.7 [1.4; 4.7]	2.1 [1.2; 3.6]	2.5 [1.5; 4.0]	0.7 [0.2; 1.4]	1.8 [1.0; 2.8]	2.0 [1.3; 3.1]	1.8 [1.5; 2.1]
Typhoid fever												
<i>N^a</i>	1	3	3	2	1	0	1	3	1	1	3	19
<i>I^b</i>	0.4 [0.0; 2.2]	1.1 [0.2; 3.2]	1.2 [0.3; 3.5]	2.5 [0.8; 9.1]	1.3 [0.0; 7.4]	0 [0]	1.3 [0.0; 7.4]	4.3 [0.9; 12.6]	1.4 [0.0; 7.8]	1.3 [0.0; 7.5]	4.4 [0.9; 13.0]	1.3 [0.8; 2.0]
Others												
<i>N^a</i>	0	0	1	0	0	3	0	3	0	2	2	11
<i>I^b</i>	0 [0]	0 [0]	4.4 [0.1; 24.4]	0 [0]	0 [0]	8.4 [1.7; 24.6]	0 [0]	5.4 [1.1; 15.9]	0 [0]	3.3 [0.4; 11.8]	1.3 [0.2; 4.8]	2.1 [1.0; 3.7]
Total												
<i>N^a</i>	99	72	85	64	79	107	73	110	68	115	141	1013
<i>I^b</i>	3.1 [2.5; 3.8]	2.1 [1.6; 2.6]	2.4 [1.9; 3.0]	2.1 [1.6; 2.7]	2.5 [2.0; 3.1]	3.6 [2.9; 4.2]	2.1 [1.7; 2.7]	3.3 [2.7; 3.9]	2.0 [1.6; 2.6]	3.4 [2.8; 4.1]	4.3 [3.6; 5.0]	2.8 [2.6; 3.0]

BCG: Bacillus-Calmette-Guérin vaccine; DTP(a/wc)–Hib–Polio: diphtheria–tetanus–(acellular/whole cell) pertussis component, *Haemophilus influenzae* type B, poliomyelitis combination vaccines; TBE: tick-borne encephalitis virus vaccine; HepA and/or HepB: hepatitis A and/or B vaccines; MMR: measles, mumps, rubella combination vaccines.

^a Number of reported AEFI.

^b Incidence [95% confidence interval].

Table 2
Affected organ system and severity categorization of AEFI by vaccine groups.

Vaccine group ^a	Local reactions, N (%)	General systemic reactions, N (%)	Allergic reactions, N (%)	Neurologic reactions, N (%)	Mild, N (%)	Moderate, N (%)	Serious, N (%)	Unknown, N (%)	Total, N (%)
DTP(a/wc)–Hib–Polio	211 (38.4)	208 (37.9)	57 (10.4)	73 (13.3)	214 (39.0)	217 (39.5)	115 (21.0)	3 (0.5)	549 (53.9)
Influenza	4 (3.3)	78 (64.5)	16 (13.2)	23 (19.0)	14 (11.6)	75 (62.0)	32 (26.4)	0 (0)	121 (11.9)
HepA and/or HepB	5 (5.6)	58 (61.1)	14 (14.7)	18 (18.9)	22 (23.2)	57 (60.0)	16 (16.8)	0 (0)	95 (9.4)
MMR	4 (4.5)	60 (67.4)	10 (11.2)	15 (16.9)	13 (14.6)	53 (59.6)	22 (24.7)	1 (1.1)	89 (8.8)
TBE	0 (0)	42 (57.5)	3 (4.1)	28 (38.4)	4 (5.5)	50 (65.5)	19 (26.0)	0 (0)	73 (7.2)
BCG	40 (97.6)	1 (2.4)	0 (0)	0 (0)	27 (65.9)	11 (26.8)	3 (7.3)	0 (0)	41 (4.0)
Typhoid fever	0 (0)	17 (89.5)	0 (0)	2 (10.5)	0 (0)	15 (78.9)	4 (21.1)	0 (0)	19 (1.9)
Yellow fever	0 (0)	11 (73.3)	0 (0)	4 (26.7)	1 (6.6)	7 (44.7)	7 (44.7)	0 (0)	15 (1.5)
Others	2 (18.2)	4 (36.3)	3 (27.3)	2 (18.2)	3 (27.3)	5 (45.4)	2 (18.2)	1 (9.1)	11 (1.1)
Total	266 (26.2)	479 (47.3)	103 (10.2)	165 (16.3)	298 (29.4)	490 (48.4)	220 (21.7)	5 (0.5)	1013 (100)

^a BCG: *Bacillus-Calmette-Guérin* vaccine; DTP(a)–Hib–Polio: diphtheria–tetanus–(acellular/whole cell) pertussis component, *Haemophilus influenzae* type B, poliomyelitis combination vaccines; TBE: tick-borne encephalitis virus vaccine; HepA and/or HepB: hepatitis A and/or B vaccines; MMR: measles, mumps, rubella combination vaccines.

AEFI, which explains the comparatively high proportion of events possibly related to immunization.

3.4. Assessment of seriousness

Sufficient information for seriousness and severity assessment was available in 1008 (99.5%) of 1013 AEFI reports. Of these, 787 (78.1%) were non-serious (298, 29.4%, were mild and 488, 48.4%, were moderate in severity), and 220 (21.8%) were serious and severe, including 10 deaths, 89 hospitalizations, and 10 events leading to permanent disabilities. There were 18 cases of anaphylaxis (with no deaths): two of them had occurred within minutes after immunization, five within 6 h, four within 6–24 h, and seven after an unknown time interval. The highest reporting rates of serious AEFI were found for tick-borne encephalitis and yellow fever vaccines, although confidence intervals generally were wide due to low numbers (Table 3). Most of the 220 serious AEFI were estimated as possibly causally related ($n = 96$; 43.4%) or unrelated ($n = 70$; 31.7%) to immunization. Eleven serious AEFI (5.0%) were considered to be unlikely related and 11 (4.9%) to be probably related to immunization (three cases of seizures, two cases of lymphadenopathies after BCG immunization, two cases of apnea in infants, two cases of syncope, one case of dyspnea and rash, and one case of bloody diarrhea after typhoid fever immunization); 25 reports (11.3%) could not be assessed concerning their causal relationship to immunization due to insufficient information. Only 7 (3.6%) serious AEFI were assessed as very likely or certainly related to immunization:

- one case of hospitalization because of whole limb swelling at the injection site few days after IPV immunization in a 24 year old person;
- one case of anaphylaxis several minutes after DTP-based combination vaccine in a 22 year old person;
- one case of anaphylaxis in a 22 year old person after MMR;
- one case of elective termination of pregnancy after MMR in a 25 year old woman during the first trimester of pregnancy;
- one case of anaphylaxis 1 min after DTP-based combination vaccines in a 14 year old male;
- one case of anaphylactic shock 1 h after DTP-based combination vaccines in a female and
- one case of anaphylaxis 5 min after DTP-based combination vaccines in a 7 weeks old infant

Similar to the overall age distribution, 101 (45.9%) of 220 serious AEFI occurred in patients >16 years of age, 54 (24.5%) in children 1–7 years of age, 42 (19.1%) in infants, 18 (8.2%) in patients 8–15 years of age, and in the remaining 5 patients (2.3%) age was unknown.

There were 10 (1%) deaths among 1013 reported AEFI (0.03 reported deaths per 100,000 distributed vaccine doses), i.e. one death per year on average:

- Five deaths occurred in association with DTP(a)–Hib–Polio immunizations in infants (all 2–5 months of age) and the time interval between immunization and death varied between 1 and 28 days without any cluster. All of these infant deaths were reported as “sudden infant death syndrome (SIDS)”. None of them were assessed to be causally related to immunization based on data in the literature disproving a causal relationship between sudden unexpected death in infants and immunization [8,9].
- Two further deaths followed 7 and 21 days after yellow fever immunization, respectively. Underlying diseases were cholestatic hepatitis with hepatic necrosis in a 54 year old male and drug-related hepatitis in a 54 year old male. These two deaths were assessed as possibly related to immunization, as they occurred in plausible time intervals after immunization [10].

Table 3

Incidence of serious AEFI by vaccine groups.

Vaccine group ^a	N serious AEFI/N total AEFI (%)	Incidence per 100,000 distributed doses (95% CI)
Yellow fever	7/15 (44.7)	2.5 (1.0–5.2)
TBE	19/73 (26.0)	2.3 (1.4–3.5)
MMR	22/89 (24.7)	1.1 (0.7–1.6)
DTP(a/wc)–Hib–Polio	115/549 (21.0)	0.6 (0.5–0.7)
Influenza	32/121 (26.4)	0.5 (0.4–0.7)
BCG	3/41 (7.3)	0.4 (0.1–1.0)
HepA and/or HepB	16/95 (16.8)	0.4 (0.2–0.6)
Others	2/11 (18.2)	0.4 (0.05–1.4)
Typhoid fever	4/19 (21.1)	0.3 (0.1–0.7)
Total	220/1013 (21.7)	0.6 (0.6–0.7)

^a BCG: Bacillus-Calmette-Guérin vaccine; DTP(a/wc)–Hib–Polio: diphtheria–tetanus–(acellular/whole cell) pertussis component, *Haemophilus influenzae* type B, poliomyelitis combination vaccines; TBE: tick-borne encephalitis virus vaccine; HepA and/or HepB: hepatitis A and/or B vaccines; MMR: measles, mumps, rubella combination vaccines.

- Three deaths were reported after immunization against influenza. All three events occurred in elderly persons (>70 years) with underlying chronic diseases within 5 h to 6 days after immunization. One of the three deaths was a fatal myocardial infarction assessed to be possibly related to immunization [11], the two other deaths were unrelated to immunization because of other plausible causes for death: pneumonia with consecutive multi organ failure in a 75 year old male, and a 72 year old woman with several underlying chronic diseases who was found dead 5 h after immunization.

4. Discussion

Clinical vaccine trials usually involve a limited number of study subjects and thus do not allow detection of rare adverse events. Therefore, post-licensure surveillance of AEFI is an integral part of immunization programmes to continuously monitor safety of vaccines when routinely used in the general population. Usually, this is being done in passive surveillance systems, which have several limitations. These limitations include underreporting, insufficient information on cases reported, lack of denominators (i.e. number of vaccine doses administered in a given population or segments of population), inconsistent diagnoses in the absence of harmonized case definitions, and lack of information on differential diagnoses or diagnoses excluded (e.g. missing details on laboratory investigations performed), which would be needed for adequate causality assessment. Despite these short-comings, passive surveillance systems still can provide useful information as trends and signals can be detected even if reporting is incomplete.

Here we analysed 1013 AEFI reported to the health authorities in Switzerland during an extended period of time, i.e. 10.5 years, which is a strength of our study. The overall rate of AEFI reports (2.7 per 100,000 doses) in Switzerland, varying between 2.04 and 4.38 in individual years under study, is in the lower range of reports from passive surveillance systems in other countries. During the same time period as our study, approximately 5–7 AEFI reports per 100,000 doses were received by the vaccine adverse event reporting system (VAERS) in the USA [12,13]. In Germany, a country with 10-fold population compared to Switzerland and by and large similar uptake of immunizations, 3329 AEFI were reported passively during 3 years (2001–2003) [14]. This translates to an estimated reporting rate of 3.3 AEFI per 100,000 doses. Finally, in Australia in 2005, 11 AEFI per 100,000 doses were reported in children <7 years of age and 2 AEFI per 100,000 influenza doses in adults, similar to figures in previous years [15]. It should be noted that reporting rates in these studies, too, were calculated based on distributed vaccine doses whereas the true denominator – number of doses administered to patients – was unknown. The variation in rates of reported AEFI in these different countries may be explained by vari-

able reporting requirements, case definitions, and settings as well as variable compliance with reporting. Our reporting requirements can be considered stringent (see Section 2.1). Less stringent criteria, i.e. allowance of a longer period of interval between immunization and AEFI and the inclusion of less severe AEFI or AEFI which are not the main cause for a physician visit would increase the likelihood of detection. However, this would also increase the number of reports unlikely to be relevant and the workload for assessment of the reports. Therefore, benefits of changing of reporting requirements in the future need to be balanced against the need for increasing the associated resources in need for that.

The proportion of serious AEFI among all AEFI also varies considerably in national surveillance systems. It was 15% in the USA (1991–1994) [16], 19% in Germany (2001–2003) [14], and 22% in our study. These differences probably reflect variability in reporting regulations but also point to a bias towards reporting serious AEFI which in general have been found to be significantly lower in active surveillance systems and in clinical trials compared to passive surveillance systems [17].

One percent of all AEFI in our study were deaths, which was one death per study year, none of them with very likely or certain causal relationship to the precedent immunization. With a total of approximately 72,000 deaths per year in Switzerland, these single reports do not appear to be of concern.

One interruption of pregnancy was considered causally related to immunization. This procedure was unfortunate in our view, because erroneous MMR immunization in a pregnant woman is not an indication for an induced abortion. One may argue about the appropriateness or not of considering such an event as an AEFI. However, since it was following MMR immunization with the intent to avoid congenital rubella due to rubella vaccine virus we think it truly was an “adverse event”, although clearly avoidable. We are not aware of proven congenital rubella in a newborn caused by precedent rubella immunization in the pregnant mother and this information was communicated at that time to the reporter. This case illustrates a misconception which obviously requires continued education.

There are a number of limitations and strengths regarding this study. As an inherent weakness of passive reporting systems, there was significant variability in the quality of reports, potential for biased reporting (leading to underreporting overall), limited power to establish or disprove a causal relationship to immunization in individual reports, and lack of control groups. Specifically, the Swiss reporting system does not allow calculation of age dependent reporting rates as the number of distributed vaccine doses in different age groups is not known.

With recent publicity regarding the alleged relations between MMR and autism or chronic inflammatory bowel disease [18–20] and hepatitis B vaccine and multiple sclerosis [21–23] one would

have expected this to be reflected in the Swiss monitoring system. However, over the 10.5 year study period no cases of autism or chronic inflammatory bowel disease were reported in association with MMR and only four cases of multiple sclerosis after hepatitis B vaccine, none of which was assessed to be causally related to the precedent immunization because of an incompatible time period between preceding immunization and onset of symptoms.

Although notification of certain AEFI is mandatory by national law for physicians in Switzerland, underreporting is an obvious problem in any passive surveillance system. In the USA, a comparison of AEFI reporting in passive surveillance systems in the private sector and in the public sector revealed higher reporting sensitivities in the public sector, where reports by patients or their parents were included [24]. Giving parents the possibility to report AEFI has advantages (higher rates) but also potential disadvantages (limited quality, potential bias) which need to be weighed carefully.

Regarding causality assessment in general, a causal relationship between preceding immunization and a given AEFI could frequently be classified in cases of injection site reactions it could only be considered as not ruled out in the majority of general systemic reactions, e.g. fever or headaches. In most such cases, relationship was assessed to be “possible” which reflects our conservative approach in light of frequently incomplete clinical information in individual reports. To classify causal relationship between immunization and reported AEFI, we used the WHO guidelines for causality assessment of AEFI. In our opinion, some of the categories in this classification guideline are imprecisely defined. Therefore we modified the classification system to our needs. For example, in the “unlikely” category we added AEFI that were unknown, i.e. not mentioned in the literature, to the original WHO categorization which defined this as “AEFI where time relationship to vaccine administration makes a causal relation improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals.” We did this because in many instances, as mentioned before, documentation of reports was insufficient to rule out underlying disease or other drugs or chemicals as an explanation and a hitherto unknown event in association with a respective vaccine is “unlikely” to be cause and effect. Other modifications in our view added clarity to the WHO categories but admittedly were a subjective interpretation on our side. In the future, the establishment of more precise criteria for causality assessment could lead to higher validity and better efficiency.

Our study also has several strengths. First, data have been obtained nationwide and over an extended period of time. Second, all AEFI reports were scrutinized in a standardized fashion by three investigators for the purpose of this report. Third, the number of distributed vaccine doses in Switzerland was available and allowed calculation of AEFI reporting rates per distributed vaccine doses. Overall, no trend for a significant increase or decrease of reporting was observed during the study period.

In conclusion, despite the acknowledged limitations of a passive surveillance system, this systematic analysis of AEFI reported in Switzerland provides useful information regarding the safety of vaccines used in our country. It will serve as a baseline for repeated analyses of this ongoing surveillance in the future. However, to improve the quality of the current system, several modifications should be considered. These may include the collection of more detailed individual clinical data, use of standardized case definitions [1], monitoring of vaccine administration by age groups, and establishment of a sentinel system for active surveillance of AEFI, e.g. similar to the “Immunization Monitoring Program, Active (IMPACT)” in Canada [25].

Furthermore, follow-up of patients with AEFI, particularly if serious, should be established in a standardized fashion. This would also allow trying to establish alternative diagnoses as an

explanation for a given AEFI, which in the current system is not efficiently possible. All these necessary improvements require time and resources that need to be provided by official authorities. Ultimately, these investments would further improve vaccine safety surveillance.

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