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Real-life versus package insert: A post-marketing study on adverse-event rates of the virosomal hepatitis A vaccine Epaxal® in healthy travellers[☆]

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ABSTRACT

There are various methods to collect adverse events (AEs) in clinical trials. The methods how AEs are collected in vaccine trials is of special interest: solicited reporting can lead to over-reporting events that have little or no biological relationship to the vaccine. We assessed the rate of AEs listed in the package insert for the virosomal hepatitis A vaccine Epaxal®, comparing data collected by solicited or unsolicited self-reporting. In an open, multi-centre post-marketing study, 2675 healthy travellers received single doses of vaccine administered intramuscularly. AEs were recorded based on solicited and unsolicited questioning during a four-day period after vaccination. A total of 2541 questionnaires could be evaluated (95.0% return rate). Solicited self-reporting resulted in significantly higher ($p < 0.0001$) rates of subjects with AEs than unsolicited reporting, both at baseline (18.9% solicited versus 2.1% unsolicited systemic AEs) and following immunization (29.6% versus 19.3% local AEs; 33.8% versus 18.2% systemic AEs). This could indicate that actual reporting rates of AEs with Epaxal® may be substantially lower than described in the package insert. The distribution of AEs differed significantly between the applied methods of collecting AEs. The most common AEs listed in the package insert were reported almost exclusively with solicited questioning. The reporting of local AEs was more likely than that of systemic AEs to be influenced by subjects' sex, age and study centre. Women reported higher rates of AEs than men. The results highlight the need for detailing the methods how vaccine tolerability was reported and assessed.

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1. Background

The rapid escalation in international travel in recent decades has increased the need for effective and well tolerated vaccines in order to minimise travel-related infections. Travellers tend to be sub-optimally vaccinated [1] whether because of fear of needles or other reasons [2]. As with any medical treatment that is not immediately life-saving, a favourable tolerance profile is important for widespread acceptance of vaccination. Patients in general

tend to be less willing to tolerate side effects with elective medical processes, such as vaccination, than in therapeutic or other critical situations [3]. Moreover, good local tolerance is a prerequisite for the concomitant use of several vaccines.

For vaccines, major efforts have been undertaken in recent years to standardize reporting methods of Adverse Events Following Immunization (AEFI). The Brighton Collaboration, an international voluntary collaboration [4], has worked on the development of standardized case definitions and corresponding guidelines for data collection, analysis, and presentation of adverse events (AEs) with vaccines used in human populations. However, while definitions of AE are becoming more standardized, there is no consensus on which AE collection methods to use in clinical vaccine trials in the various stages of the vaccine development. Spontaneous (unsolicited) reporting of adverse events (AEs) data may be biased towards under-reporting. Conversely, soliciting events with a structured checklist or questionnaire may capture more AE, albeit at the risk of over-reporting events

Abbreviations: AE, adverse events; AEFI, adverse events following immunization; HAV, hepatitis A virus; SPC, summary of product characteristics; SOC, system organ classes; MedDRA, medical dictionary for regulatory activities.

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that have little or no biological relationship to the medication studied [5].

The safety information even for similar vaccines may differ considerably in quantity and quality depending on the AE collection and case assessment methods used during the development. This consequently may determine the safety profiles described in the Summary of Product Characteristics (SPC – an extended product information document required for authorization of medicinal products within the European Union) and the package inserts. Subsequently, safety information obtained from phase IV and post marketing observational trials using different AE collection methods may differ from the already presented safety information in the package inserts. We used Epaxal® (Crucell Switzerland AG, formerly Berna Biotech, Berne, Switzerland) as a study case to illustrate the above point. Epaxal® is the first commercially available, aluminium-free hepatitis A virus (HAV) vaccine, and consists of inactivated HAV bound to virosomes by electrostatic forces [6]. Epaxal® has proved to be highly immunogenic, well tolerated in both adults and children [7–12] and with significantly fewer local AEs when compared to aluminium-adsorbed HAV vaccines [12–15]. The frequencies of undesirable effects in the SPC for Epaxal® [16] were derived, by the licensing authorities, largely from studies using solicited AE reporting, without reconciling these rates with those found in studies using unsolicited collection. Hence the SPC data for e.g., the local tolerability of Epaxal® suggests that the AE rates in the Epaxal® SPC may overestimate the real life rates experienced with the product.

To address the difference reporting rates between solicited reporting and unsolicited reporting and to assess the relation of rates of AEs in the SPC to those encountered in medical practice, we performed a post-marketing study to evaluate the effect of different reporting methods on the tolerability profile of Epaxal® in healthy travellers. In addition, we evaluated the effects of age, sex, type of vaccination (priming or booster dose), presence or absence of concurrent vaccination(s) and study centre on prompted and unprompted rates of AE.

2. Methods

Between June 1998 and March 1999, in an open, comparative multi-centre post-marketing safety study, 2675 travellers eligible for HAV vaccination were enrolled at four travel study centres in Switzerland (Medical Department, Swiss Tropical and Public Health Institute, Basel; Institute of Social and Preventive Medicine, University of Zürich, Zurich; Department of Ambulatory Care and Community Medicine, University Hospital, Lausanne; Travel and Migration Medicine Unit, University Hospital Geneva, Geneva). The primary objective was to assess the safety of a single dose of Epaxal® (primary or booster) based on comparison of AE reporting rates generated by solicited and unsolicited (open) questioning. The hypothesis was that soliciting AEs will result in significantly higher rates of AE reporting as compared to unsolicited. The influences of age, sex, type of vaccine, presence or absence of concurrent vaccine(s) and study centre, in terms of AE reporting rates, were also studied. The study was approved by the respective local Ethics committees.

2.1. Study population

Healthy travellers (age ≥ 1 year) consulting one of the study centres for a primary or booster HAV vaccination were considered for enrolment. Subjects who had previously received a complete vaccination for HAV were excluded from the study. Written informed consent from travellers or parents/legal guardians was obtained before study entry.

2.2. Study design

Eligible study subjects at each study centre were assigned by weekly alternation to two different types of AE self-reporting (valid for all subjects enrolled in a given week): based on solicited questions (Group A) or based on unsolicited questions (Group B).

2.3. Vaccine, dosage and administration

The study vaccine was administered intramuscularly. Each 0.5 mL dose contains 24 IU of inactivated HAV (strain RG-SB), adsorbed to the surface of virosomes as the adjuvant systems, composed of highly purified influenza virus surface antigens (10 μ g haemagglutinin) of the A/Singapore/6/86 (H1N1) strain and the phospholipids lecithin (80 μ g) and cephalin (20 μ g).

2.4. Tolerability assessment by diary cards

The travellers or parents/legal guardians were carefully instructed how to record the local and systemic AEs on a numbered, anonymized AE diary card during a four-day period after vaccination. The diary card was to be returned by mail to the study centre using prepaid envelopes. Missing cards, identified via the enrolment log, were requested by a phone call. Additionally, in order to evaluate the health status at the baseline systemic signs and symptoms were assessed by the same types of solicited or unsolicited questioning before the vaccination.

2.5. Adverse event recording

Baseline adverse symptoms were obtained from the solicited group (questions regarding anorexia, diarrhoea, dizziness, fever [$>37.5^\circ\text{C}$], headache, malaise, nausea, skin rash, and vomiting) and from the unsolicited group (open questions regarding well-being, e.g., Do you feel well, yes/no? If no, please describe) in the 24 h preceding the vaccination. The same above listed AEs, which coincided with the Epaxal® SPC listed AEs, were also solicited from group A after vaccination. Only the vaccinees in the solicited group were asked to assess the severity of the reported AEs in the subject diary.

All reported AEs in both study groups were at first assigned preferred terms using MedDRA (version 5.0) terminology. Solicited terms corresponded directly to those used in the SPC for Epaxal®. The main safety evaluation was then carried out based on individual AE preferred terms, sorted by System Organ Classes (SOCs).

Local AEs were assessed by the following solicited questions in Group A: pain, swelling (diameter in cm), and redness (diameter in cm). The severity of AEs following solicited questions was graded on a four-point scale ranging from “0 = none” through “1 = mild” (not interfering with daily activities), “2 = moderate” (interfering with daily activities), and “3 = severe” (preventing normal activities). For Group B (the vaccinees were asked whether they experienced any local discomfort at the injection site), the unsolicited reported local AEs were recorded and assigned preferred terms and were reconciled with the respective SPC term by using MedDRA (version 5.0) high level terms (HLTs). For example the SPC term ‘Pain’ included the MedDRA preferred terms (PTs): pain, tenderness, burning, stinging and movement impaired, all at the injection site.

Systemic AEs were assessed similarly with the following solicited questions for Group A: anorexia, diarrhoea, dizziness, fever, headache, malaise, nausea, skin rash, and vomiting. For Group B (the vaccinees were asked whether they experienced any general disorder), the reported systemic AEs were assigned to PTs and lumped to HLTs and reconciled with SPC terms as described for the local AEs. For example, ‘Skin rash’ included rash, rash pruritic, erythema, pruritus, and exanthema.

Table 1
Baseline characteristics of study population.

	Group A solicited (n = 1274)	Group B unsolicited (n = 1267)
Age		
<18 y	41 (3.2%)	33 (2.6%)
≥18–39 y	755 (59.2%)	761 (60.1%)
≥40–60 y	364 (28.6%)	354 (27.9%)
>60 y	114 (9.0%)	119 (9.4%)
Sex		
Men	597 (46.9%)	616 (48.6%)
Women	677 (53.1%)	651 (51.4%)
Type of vaccination		
Primary	485 (38.3%)	412 (32.8%)
Booster	780 (61.7%)	846 (67.2%)
Concurrent vaccination		
With	887 (69.6%)	889 (70.2%)
Without	387 (30.4%)	378 (29.8%)
Total number of adverse signs and symptoms ^a	311	29
Total number (%) of subjects with at least one sign or symptom ^{a,*}	241 (18.9%)	26 (2.1%)
Headache [*]	127 (10.0%)	11 (0.9%)
Malaise [*]	46 (3.6%)	9 (0.7%)
Diarrhoea [*]	35 (2.7%)	4 (0.3%)
Skin rash ^{**}	33 (2.6%)	0 (0.0%)
Dizziness [*]	27 (2.1%)	3 (0.2%)
Anorexia [*]	19 (1.5%)	0 (0.0%)
Nausea [*]	17 (1.3%)	1 (0.1%)
Vomiting	4 (0.3%)	0 (0.0%)
Fever >37.5 °C	0 (0.0%)	1 (0.1%)

^a Adverse events reported within 24 h prior to vaccination.

* $p < 0.0001$.

** $p = 0.0002$.

2.6. Statistical analysis

All the recorded and assigned PTs for all the individual adverse symptoms at baseline and all post-immunization AEs were evaluated descriptively and in terms of rates. Local AE and systemic adverse symptoms (at baseline) and AE in SPC terms were evaluated descriptively and in terms of rates, separately for each Group A and Group B. The statistical significance of correlations between baseline characteristics and differences in reporting rates was tested by χ^2 analysis. In the sense of exploratory statistics, the rates (%) of subjects with signs and symptoms/AEs in SPC terms recorded in Group A were compared statistically with those in Group B, using the Chi-square test or the Fisher's Exact Test.

3. Results

3.1. Subjects

Of a total of 2675 diary cards distributed, 2541 were returned and could be evaluated (95.0% return rate): 1274 in Group A and 1267 in group B, of whom 387 (30.4%) and 378 (29.8%) received only vaccination against HAV, whereas 887 (69.6%) and 889 (70.2%) received Epaxal[®] and one or more concurrent vaccinations, respectively. The mean age of the study population was 37.5 (range 2–79 years) and slightly more than half of the population were women. The two study groups were comparable regarding age, sex, type of vaccination, concurrent vaccinations and study-centre distribution (Table 1). Baseline characteristics did not differ between the study centres (data not shown).

3.2. Clinical signs and symptoms at baseline

There were significant differences between the study groups in regard to the reported clinical signs and symptoms at baseline (Table 1). A total of 311 systemic signs and symptoms were reported by 241 subjects (18.9% of subjects) in Group A compared

with 29 symptoms by 26 subjects (2.1%) in Group B ($p < 0.0001$). The most dominant systemic clinical signs and symptoms in both groups were headache and malaise.

3.3. Adverse events (AEs) by SPC terms

In total 516 local AE were reported by 377 subjects (29.6%) in Group A, and 285 local AE by 244 subjects (19.3%) in Group B. The percentages of subjects who experienced local AE as defined in the SPC were in Group A significantly higher than in Group B, for overall ($p < 0.0001$) and for individual local AE (Table 2; Fig. 1A). Moreover, the distribution of local AE varied between the groups, with swelling and redness much more prominent in the group where AE were solicited (Fig. 1B).

Table 2

Incidence rates of local and systemic signs and symptoms/adverse events post vaccination, by SPC terms.

	Group A solicited (n = 1274)	Group B unsolicited (n = 1267)
Local adverse events		
Total (≥1 AE) [*]	377 (29.6%)	244 (19.3%)
Pain [*]	288 (22.6%)	231 (18.2%)
Swelling [*]	121 (9.5%)	21 (1.7%)
Redness [*]	92 (7.2%)	13 (1.0%)
Systemic signs & symptoms/adverse events		
Total (≥1 AE) [*]	431 (33.8%)	230 (18.2%)
Headache [*]	199 (15.6%)	58 (4.6%)
Malaise [*]	164 (13.1%)	112 (8.8%)
Diarrhoea [*]	105 (8.2%)	32 (2.5%)
Dizziness [*]	104 (8.2%)	21 (1.7%)
Nausea [*]	87 (6.8%)	34 (2.7%)
Anorexia [*]	82 (6.4%)	1 (0.1%)
Fever >37.5 °C	44 (3.5%)	29 (2.3%)
Skin rash	7 (0.5%)	7 (0.6%)
Vomiting	6 (0.5%)	3 (0.2%)

* $p < 0.0001$.

** $p < 0.01$.

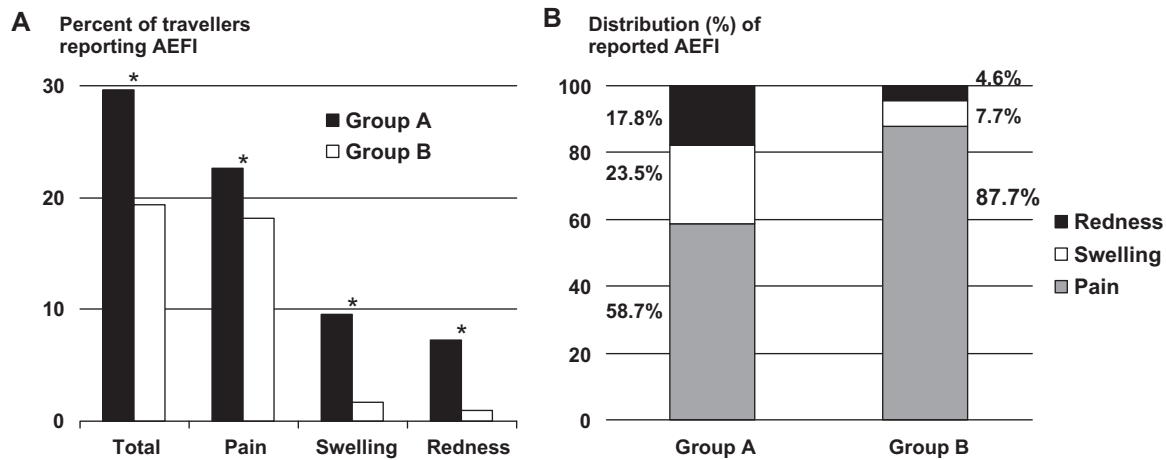


Fig. 1. Incidence and distribution of reported local AEFI: (A) percentages of subjects reporting local AE by SPC terms obtained by solicited (Group A) and unsolicited (Group B) questionnaires, respectively. Asterisks indicate significant differences ($p < 0.01$). (B) Distribution of local AE. The y axis indicates percentage out of the total AE reported for the respective groups. The differences between the groups in distributions of events were statistically significant ($p < 0.007$).

Similar methodology-dependent differences between the groups were seen in systemic AE for which 812 were reported by 431 subjects (33.8%) in Group A, and 305 AE by 230 subjects (18.2%) in Group B. The percentage of subjects who experienced systemic AE as defined in the SPC was in Group A significantly higher than in Group B for overall ($p < 0.0001$) and for most individual symptoms/AE (Table 2; Fig. 2A). The qualitative distribution of systemic AE also varied between the groups (Fig. 2B). Relative rates of headache, dizziness and anorexia were higher amongst the solicited subjects (Group A), whereas rates of malaise and fever were higher amongst the unsolicited subjects (Group B). As with local AE, the absolute rate (%) of subjects who reported systemic AE in SPC terms was significantly higher in Group A than in Group B, for all symptoms/AE ($p < 0.0001$) and for most individual symptoms/AE.

Pain (Fig. 1A), as well as malaise and fever (Fig. 2A) were overall more likely to be reported, whether solicited or unsolicited, while other local and systemic AE were subject to increased reporting bias. Most AE were mild or moderate in nature, whether systemic (96.8%) or local (99.4% regarding pain, tenderness or burning and with 81.2% of redness or swelling being ≤ 2 cm). The median duration of AE, both local and systemic, was 2.0 days (range: 1–4 days). No deaths, other serious AEs, or other significant AEs were reported.

3.4. Factors influencing differences in reporting rates

The distributions of local and systemic AE according to age, sex, type of vaccination and study centre are shown in Fig. 3A and B. Several baseline characteristics were associated with differences in reporting rates in both groups. Whether prompted or unprompted, women reported consistently higher rates of local as well as systemic AE than men. Older subjects reported fewer AE than younger subjects, with the exception of subjects < 18 years of age. The youngest subjects had the highest rates of solicited systemic AE and intermediate rates of other AE. For systemic AE, first vaccinations and vaccinations without concurrent vaccination were associated with greater percentages of subjects reporting systemic AE than booster vaccinations and concurrently vaccinated subjects, but there were no differences in rates of local AE between these groups. Rates of local AE varied with study centre: highest in Basel and Zurich and lowest in Lausanne and Geneva.

Rates of local AE were influenced significantly by subjects' sex, age and centre of administration ($p < 0.01$). Systemic AE were influenced by the type of vaccination (first or booster vaccination) and by whether the vaccine was administered concomitantly with another vaccine ($p < 0.05$). Unsolicited AE rates, local as well

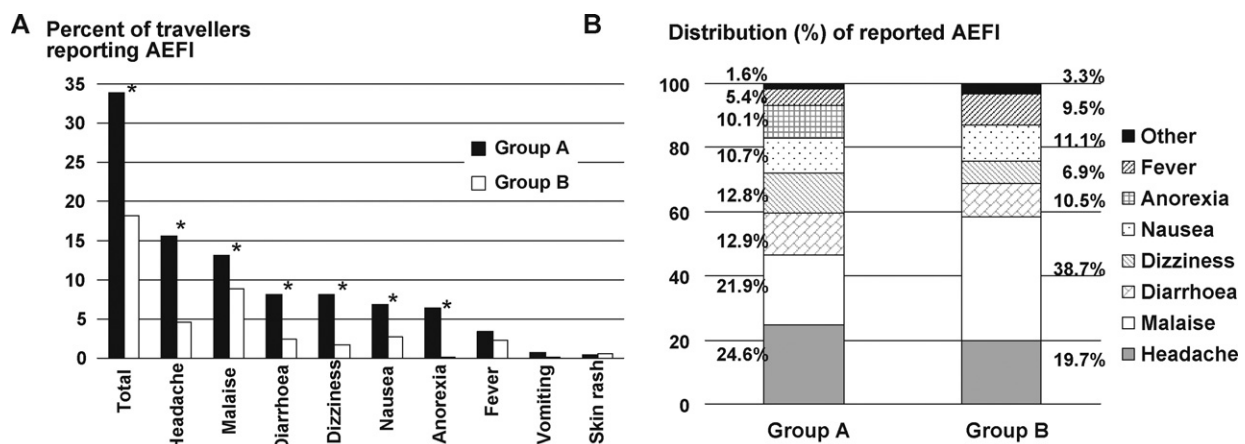


Fig. 2. Incidence and distribution of reported systemic AEFI: (A) percentages of subjects reporting systemic AE by SPC terms obtained by solicited (Group A) and unsolicited (Group B) questionnaires, respectively. Asterisks indicate significant differences ($p < 0.01$). (B) Distribution of systemic AE. The y axis indicates percentage out of the total AE reported for the respective groups. Rates of anorexia were 0.3% in Group B and do not show up on the scale represented. The differences between the groups in distributions of events were statistically significant ($p < 0.007$).

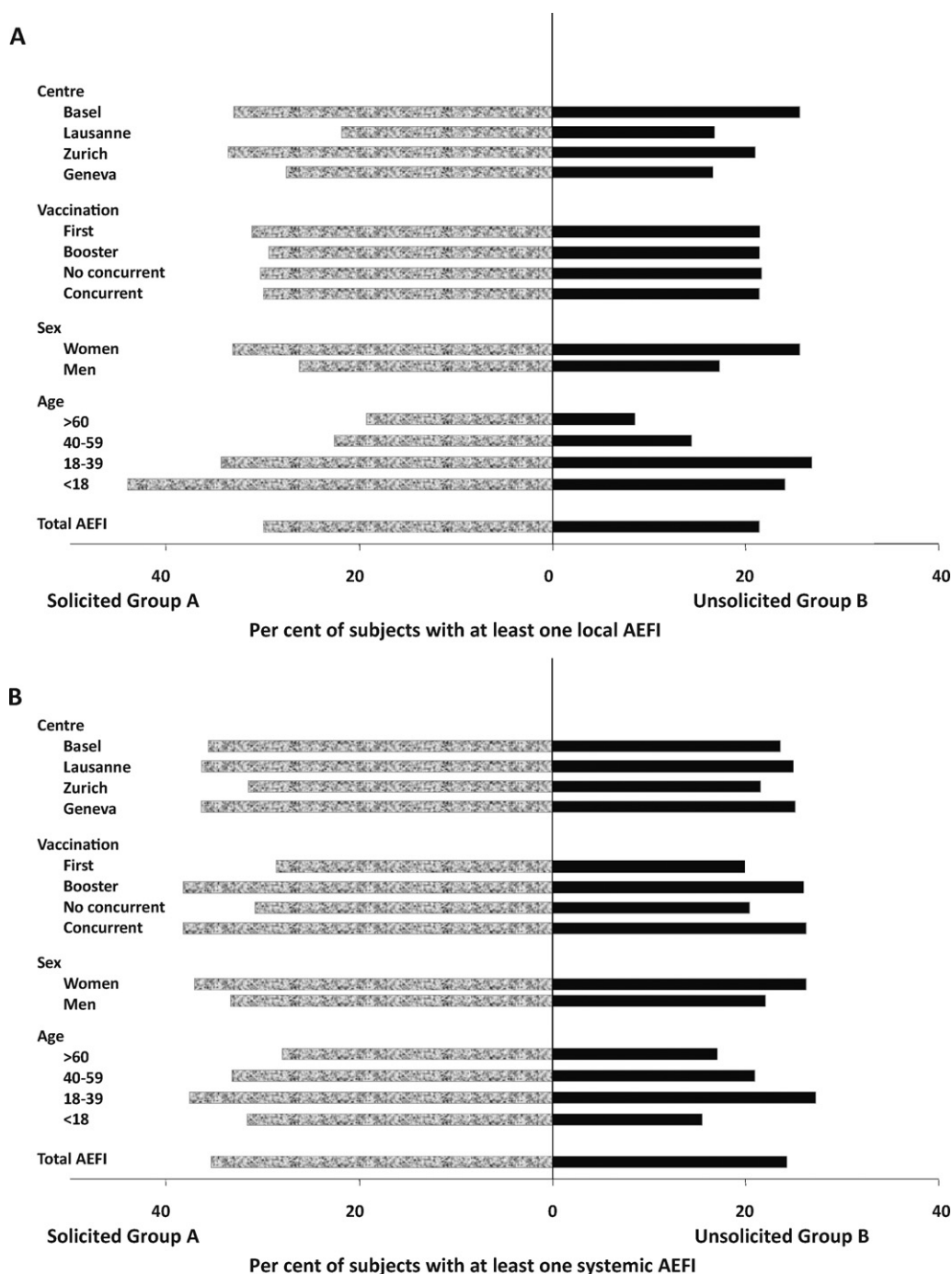


Fig. 3. Factors influencing differences in reporting rates: distribution of (A) local and (B) systemic AE according to subject age and sex, and to the type of vaccination and study centre. The scale indicates percentage of subjects reporting at least one local AE. Granulated bars represent solicited AE Group A and black bars unsolicited AE Group B, respectively. All AE were reported by preferred terms.

as systemic, were significantly influenced by subjects' sex or age ($p < 0.05$).

3.5. Discussion

Two main conclusions can be drawn from this work. Firstly, the reporting rates of unsolicited AEs found for Epaxal® are substantially lower than the ones described in the SPC [16]. The tolerability profile was highly similar to that in the SPC only when vaccinees' responses were solicited. In contrast, markedly lower rates of AEs were reported with an unsolicited approach. Secondly, the results confirm the need for reporting and differentiating the AE collec-

tion and assessment methods to make the safety assessment more transparent. Post immunization reporting rates have been shown systematically to overestimate the risk of AEs [17]. Our results underscore the need to develop adequate methods to separate the background incidence of health events from the incidence observed after vaccination.

Although most of the current debate about drug and vaccine safety centres on the risk of under-reporting safety issues [3], over-reporting may have relevant negative consequences, too. The discrepancies between solicited and unsolicited rates show that methodological and reporting decisions may have a profound influence on how the tolerability of a medication is perceived.

Physician's product preference and patient awareness may become compromised when the basis for a safety profile listed in the SPC of a medication is unclear. An uninformed comparison of solicited and unsolicited safety reports may lead to erroneous conclusions and to the use of less well-tolerated options or to patients avoiding elective procedures altogether.

This is not the first time such conclusions have been reached [18], but it is striking how little the therapeutic area, vaccines or drugs, influences differences between solicited and unsolicited rates of AEs. Solicited rates of headache in the current study are extremely similar to studies with placebo [5] and antihypertensive medications [19]. Regardless of differences in study design, indications, patient populations and therapies, 10–15% of patients typically report headache when prompted. This phenomenon could be observed in our population at baseline: in Group A headache was reported by 10.0% of subjects compared with 0.9% in Group B. The differences at baseline were maintained post-vaccination i.e., 15.6% versus 4.6% of subjects in Groups A and B, respectively reported headache. These differences in rates of headache obtained through solicited and unsolicited questioning are in excellent agreement with the rates reported in other clinical and post-marketing studies with Epaxal®. Thus, two randomized controlled studies and two open-label studies using solicited questioning reported rates of headache of up to 21% [11,13,14,20]. In contrast, rates of unsolicited headache were only 1% in a study using unsolicited recording in 413 travellers [15].

The strength of this study is the large number of travellers included and the very high return rates of questionnaires, which should reduce the risk of bias. A weakness is the vagueness inherent in the use of unsolicited reporting, which puts classification at risk of becoming somewhat arbitrary. The process of reconciliation of unsolicited terms (mapped with SOC based on MedDRA) with SPC terms on the questionnaire has not been independently validated in a prospective study. Since this data was collected in 1999–2000 substantial effort has gone into standardizing the reporting of AEs caused by vaccines [4], and thus, the methodology might deviate slightly from the one that would have been employed if the study were undertaken today. However, while the study-specific conclusions were relevant to conditions at the time the study was conducted, the consistency of the findings between this and the other Epaxal® studies indicates that the conclusions are still applicable to the current practices.

Regardless of the methods used, the data show that the studied vaccine was very well tolerated in this population of healthy travellers. Most of the factors that influenced the rates of AE were similar to those found in other studies. For local and systemic AE, increasing age correlated with fewer AE, a finding that has been seen before with HAV vaccinations including Epaxal® [11,21] and which may be explained by a lower immune response in elderly. Women reported more AE, which is also in line with what has been found in other studies on this vaccine [13,15] and in safety evaluations in general [22]. This could be explained by the fact that immunity is sexually dimorphic in animals and humans [23], and women exhibit a greater response to a variety of vaccines, including HAV (reviewed in Ref. [24]). The sex differences were not observed for systemic AE when subjects were solicited. Higher rates of systemic AE correlated with the type of vaccination (primary or booster) and with the presence or absence of concurrent vaccine(s). Other studies have found lower rates of systemic AEs following booster doses with Epaxal® [12,14]. The higher rates of systemic AEs in our study may have been due to concurrent vaccines in the booster group. Approximately 70% of travellers in this group received a concurrent vaccination, which has been shown in other studies to be associated with higher rates of AE [25,26].

Rates of local AE, both self-reported and solicited, varied significantly between study centres, but rates of systemic AE were similar

at all centres. As there were no significant differences between the study populations at the respective centres, differences in administration technique, counselling, etc. might have been responsible for this result, although any explanation remains speculative.

4. Conclusion

The pronounced differences in rates of AE obtained using solicited versus unsolicited AE collection methods highlight the need for a differentiated approach in reporting and assessing vaccine safety information in order to separate the background incidence of adverse health effects from the adverse incidences observed after vaccination.

It is most advisable to list in publications both solicited and unsolicited reporting rates when data are available. Furthermore, studies should disclose which AE collection method was used, with the appropriate caveats noted.

In conclusion, the reported results and the experience with the present study lead us to make the following proposals to make the safety assessment of new and licensed medicinal products more transparent:

1. There is a need for data comparability pre- and post licensure for a given product as well as across products. This can be achieved by reporting and differentiating the AE collection and assessment methods.
2. Phase IV studies are important due to their more comprehensive and precise safety information. Such studies should be considered as part of the SPC updates.
3. There is a need for observed versus expected analysis taking into account background rates.

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