Pharmacovigilance of Malaria Intermittent Preventive Treatment in Infants Coupled With Routine Immunizations in 6 African Countries

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Background. Intermittent preventive treatment in infants (IPTi) is a new malaria control strategy coupled with the delivery of routine immunizations recommended by the World Health Organization since 2009 for countries with moderate to high endemicity. To evaluate its safety profile and identify potential new adverse events (AEs) following simultaneous administration of sulfadoxine-pyrimethamine (SP-IPTi) with immunizations, we measured AE incidence and evaluated spontaneous AE reporting.

Methods. A cohort event monitoring study was conducted on 24,000 infants in 2 countries after administration of SP-IPTi during routine immunizations. Additional pharmacovigilance training and supervision were conducted to stimulate AE passive reporting in 6 African countries.

Results. No serious AEs were found by active follow-up, representing 95% probability that the rate does not exceed 1 per 8000. No serious AEs were found by retrospective review of hospital registers. The rate of moderate AEs probably linked to immunization and/or SP-IPTi was 1.8 per 1000 doses (95% confidence interval, 1.50–2.00). Spontaneous reporting of AEs remained <1% of cases collected by active follow-up.

Conclusions. Simultaneous administration of SP-IPTi and immunizations is a safe strategy for implementation with a low risk of serious AEs to infants. Strategies toward strengthening spontaneous reporting in Africa should include not only the provider but also beneficiaries or their caregivers.

Sulfadoxine-pyrimethamine (SP), a sulfonamide used for intermittent preventive treatment for malaria in pregnant women (IPTp), effectively improves maternal health, pregnancy outcomes, and newborn birth weight [1] and reduces neonatal mortality [2]. Recently, SP has been shown to reduce clinical malaria by 30.3%, anemia by 21%, and hospitalizations associated with malaria parasitemia by 38% when used in intermittent preventive treatment in infants (IPTi) administered concomitantly with routine immunizations at 10 weeks, 14 weeks, and 9 months of age [3] by the Expanded Programme on Immunisation (EPI).

Sulfadoxine-pyrimethamine is used for IPTi due to several advantages over other antimalarials, including good efficacy (long half-life and prophylactic effect [3]) and programmatic advantages (long shelf life, low cost [4], single-dose administration, and no interaction with immunizations [5]). A good understanding of its safety profile is essential because IPTi is offered in prophylaxis to presumptively healthy children and substantial adverse events (AEs) could impact immunization coverage and weaken communities’ trust in...
prophylactic interventions. However, the safety profile of SP administration to infants has not been thoroughly studied.

Children-specific AEs may differ from reports usually based on adult studies [6–9]. Pediatric AE studies are sparse [10, 11], and even more so in Africa [12, 13]. Additionally, in regions where human immunodeficiency virus (HIV) and malaria are endemic, many drugs are given to children without safety profile documentation. Progressively more drugs are being introduced and scaled up in Africa without postmarket monitoring [14, 15].

Sulfonamides are frequently implicated in Stevens-Johnson syndrome (SJS), a rare but life-threatening emergency characterized by widespread epidermal loss with mucous membrane involvement [16] that is managed in burn units by supportive therapy with fluid and electrolyte replacement as no specific treatment exists [17]. This syndrome has been reported after SP administration as antimalarial prophylaxis for adult Western travelers at rates ranging from 0.01 to 20.4 per 100 000 exposures [18–21]. What triggers SJS is unknown; the literature suggests that it may be influenced by coadministration with chloroquine [22], ethnic differences in susceptibility [23], genetic predisposition [24, 25], and drug metabolism [26]. Studies involving both children and adults suggest that another risk factor is age, because SJS is considerably less frequent in children [9, 27, 28]. One study in Malawi showed 5 times lower risk of SJS in children <15 years (0.3 per 100 000 exposures) compared with adults (1.7 per 100 000 exposures) [27].

High incidence of SJS was reported after administration of weekly high dosage (2 g) of sulfonamides, mostly occurring after the second dose [9, 29] and after repeated doses (mean, 3.4 doses) [21]. Repeated weekly SP administration resulted in a 40-fold higher risk of AEs compared with single-dose treatments [18]. Because the sulfadoxine portion of SP has a half-life of 200 hours (8.3 days) [30], the drug cannot be fully eliminated between weekly exposures. In IPTi low doses of sulfonamides (250 or 125 mg of SP) are given to infants at intervals of at least 1 month. An increased risk of SJS may be associated with the cumulative effect of high doses of sulfonamides; however, sensitization due to previous sulfonamides exposure is also possible. In malaria-, pneumonia-, and HIV-endemic areas, exposure to other sulfonamides (such as co-trimoxazole) is common, and previous drug sensitization cannot be excluded.

The temporal relationship between drug intake and the onset of SJS symptoms is also unclear. Most reactions occur after the first week but may appear earlier in previously sensitized individuals or up to 3 months after intake [9, 21, 31, 32]. The highest risk appears to be in the first 4 weeks [26].

The incidence of serious AEs due to SP is also uncertain. Studies of SJS due to sulfonamides showed an incidence of 1.5 per 10 000 and a mortality rate of 2 per 100 000 in Mozambique [33]. In Morocco the mortality rate was 1 per 10 000 [29], and in South Africa the incidence of SJS was 3 per 480 with no deaths due to SP or SP-artsunate intake [34, 35]. Although the incidence and mortality rates reported in these studies were higher than those reported for American and European travelers [20–22, 36], the dosage of sulfadoxine used was also much higher in Africa (2–2.5 g) compared with that administered to Western travelers (0.5 g), suggesting an increased risk association with high dosage. Indeed, recent reports on lower dosages of SP (0.5 g) in Africa indicate a much lower SJS incidence (1.2 per 100 000) [27].

In 2009 IPTi was recommended by the World Health Organization (WHO) Global Malaria Programme [37] and endorsed by the EPI and the United Nations Children’s Fund (UNICEF) [38] for implementation coupled with routine immunizations in African regions with moderate to high malaria burden. The lack of pharmacovigilance data on SP-IPTi in Africa and/or in children was a major bottleneck in the policy process.

We report here the results of a large study in 6 selected African countries where IPTi was implemented to evaluate its safety profile in order to identify potential new AEs that may arise from the coupling of SP with immunizations and/or a possible increased risk of serious AEs in infants taking SP-IPTi. We also evaluated the capacity of training and supervision in strengthening the countries’ passive pharmacovigilance systems. To our knowledge, this is the first extensive SP safety survey conducted in Africa and one of the very few active surveillance studies of any medicine given to large numbers of children in Africa.

METHODS

Cohort Event Monitoring Study

Cohort event monitoring (CEM) consisted of a prospective observation study of infants treated with SP-IPTi actively followed up at home with standard questionnaires to capture all possible events without assessing causality. The study, which did not include a preimmunization questionnaire typical of CEM, took place in 2007–2008 during the first year of IPTi pilot implementation in 2 districts in Ghana’s Upper East region and 3 districts in Madagascar’s Central East region where IPTi had been implemented for 6 and 9 months, respectively, and lasted 8 and 7 months, respectively. In these regions malaria incidence in infants was 1% [39] and 0.56%, respectively [40]; HIV prevalence in the 15- to 49-year age group was 1.8% and 0.2% [41], respectively; and third dose of diphtheria-tetanus-pertussis (DTP3) coverage was 94% and 81.9% [42], respectively.

We aimed at reaching a minimum sample of 10 000 doses of SP-IPTi followed per country for detection of relatively uncommon events at 1 per 3000 [43]. During administration of routine immunizations, trained nurses explained to caregivers the purpose of the study and the possibility of AEs to vaccines and/or SP. Contact information was obtained from parents that enrolled. No formal written consent was required as this study was part of a Ministry of Health (MOH) implementation
research with formal consent from national ethical committees. However, parents’ verbal agreement was requested to allow investigators to conduct home visits.

In IPTi pilot districts, infants visiting the health centers for immunizations between 10 and 16 weeks of age were given their second and third doses of DTP vaccine (DTP2 and DTP3), as well as hepatitis B (HepB) and oral poliovirus vaccine (OPV). At 56 weeks, infants were given measles vaccination. In Ghana, Haemophilus influenzae type b (Hib) vaccine was also given with DTP, and yellow fever vaccine was given with measles vaccine. In addition to standard vaccinations, one-half SP tablet (250 mg sulfadoxine, 12.5 mg pyrimethamine) was offered to infants weighing >5 kg and one-quarter tablet to those weighing <5 kg, and this information was recorded in the child’s health card and facility registries. Due to the lack of an SP pediatric liquid formulation, the tablets were crushed and mixed with expressed breast milk or clean water to produce a drinkable solution. Infants who vomited were given a second dose after 30 minutes of rest; they were excluded from administration if they vomited again. There were no age restrictions for receiving SP-IPTi. As long as the child was eligible for DTP2, DTP3, or measles immunization, he/she also received IPTi. The nomenclature used was IPTi followed by the number 1, 2, or 3 indicating the time of immunization (not the number of IPTi doses received); IPTi1 was administered with DTP2, IPTi2 with DTP3, and IPTi3 with measles immunization.

Parents were given a pictorial AE diary card to record events occurring after SP administration. Trained volunteers visited infants and their caregivers in their homes 7–10 days after the clinic visit, and caregivers were asked about events, including fever, diarrhea, rash, persistent crying, swelling, injection site abscess, coughing, or restlessness that might have occurred after immunization or SP administration. Case definitions were established for fever (temperature >38°C), diarrhea (≥3 loose stools/day), rashes, persistent crying (>3 hours), crying (<3 hours), swelling, and injection site reactions. The visits at 10 days allowed the detection of potential AEs occurring soon after the SP–immunizations coadministration, including identification of potential SJS prodromic signs [26] or early cases [25], and supported the management of potential moderate or serious AEs. Information was collected without attempting to assign causality, reviewed by health workers at the health facility, and entered into a common database. Vaccines, SP dosage, beneficiary’s description, and AE details (time of onset, duration, and treatment) were recorded on the AE card. Parents were also advised on how to identify and report AEs possibly occurring in the following weeks after the home visits and instructed to go immediately with the AE diary card (a new card that was stapled to the child’s health card during the home visit) to the health center, which would provide them with free treatment. Cards were collected by health workers at the next health clinic visit, and any events reported by parents were added to the database. Hospital registers were retrospectively reviewed for any skin disorders in all infants hospitalized in the study areas during the first 2 years of IPTi program administration, independently of their IPTi status. Events that resulted in hospital visits were immediately followed up by a medical doctor and reported to the local health authorities and national pharmacovigilance authorities. Multidisciplinary causality assessment committees at country level examined reported cases to classify the likelihood that immunization or SP was the cause (certain, probable, possible, unlikely, or unclassifiable) and to grade severity (mild, moderate, severe, or serious) using WHO guidelines [44] (Table 1). Ad hoc expertise was sought when necessary.

Data were entered into a database specifically designed for the study and cleaned by 2 independent data managers for statistical analysis. Analysis was performed with SPSS software version 16.0 (IBM SPSS) using the Student t test and the Pearson χ² P values.

Passive Reporting AE Study

The passive follow-up study consisted of evaluating the capacity of the classical methods of training and supervision to boost the spontaneous/passive pharmacovigilance systems in the 20 districts of the 6 countries (Benin, Ghana, Madagascar, Malawi, Mali, and Senegal) where IPTi was being offered to 270 000 infants annually. After a brief situational analysis, we concluded that most pharmacovigilance systems were either very weak or nonexistent. Thus, AE reporting cards were issued and distributed to all health centers, 3318 health workers received a 1-day training in general pharmacovigilance and specifically on how to recognize and manage SJS, and AE reporting was included in the IPTi/EPI monthly supervision visits. All spontaneously reported AE cases were fully investigated by the corresponding district medical doctor. Severity classification and evaluation of possible links with SP/immunizations were performed a posteriori by each country’s causality assessment committee. To evaluate the efficiency of training and supervision of providers in boosting the pharmacovigilance spontaneous reporting, we calculated the frequency of AEs reported spontaneously by the end of the first year and compared it with the AEs reported by active follow-up. The passive surveillance results covered a period of 1 year on variable dates between 2007 and 2009 depending on the countries.

RESULTS

Cohort Event Monitoring Study

A cohort of 23 998 infants (10 096 in Ghana and 13 902 in Madagascar) receiving a total of 28 564 SP doses was actively followed up for AEs occurring during the 10 days following IPTi/immunizations administration. Similar numbers of male (52%) and female (48%) infants were observed. The median age
for IPTi/immunizations uptake was 12, 17, and 41 weeks for IPTi1, 2, and 3, respectively, with wide ranges and interquartile rates (Table 2). We followed 10 844 IPTi1 doses, 10 047 IPTi2 doses, and 7673 IPTi3 doses. Sixty-seven infants were followed actively for all 3 SP-IPTi doses, 4432 infants for 2 doses, and 19,499 infants for 1 dose. Due to field conditions and associated logistical difficulties related to accessing populations in remote areas, including frequent population movements prior to visits, only half of the eligible children were successfully followed. After elimination of incomplete records, the rate of successfully followed eligible children was 47.5% (47% in Ghana and 48% in Madagascar).

A total of 2909 AEs were reported during the 10-day period post-immunizations, representing an incidence rate of 101.8 AEs per 1000 SP doses administered (95% confidence interval [CI], 100.0–103.7) (Table 3). There were neither serious AEs (SAEs) nor severe (grade 3) AEs reported. All events reported took place during the 10 days following immunizations. Although mothers were encouraged to report all events that could have taken place after the home visits, no further reporting was received. Most AEs (94%) were classified as mild (grade 1); only 6% were classified as moderate (grade 2). The total rate of moderate AEs was 6.2 per 1000 doses (95% CI, 5.7–6.6). Significantly more AEs were reported in Madagascar (155 per 1000 doses; 95% CI, 151.0–159.0) than in Ghana (29.2 per 1000 doses; 95% CI, 26.8–31.6), both overall and for each of the most common events. However, the proportion of mild and moderate AEs was similar in both sites. Interestingly, fever, crying, vomiting, coughing, itching, nausea, stomach pain, nervousness, and stuffy nose were symptoms classified by both countries’ causality assessment committees as mild AEs, whereas diarrhea, skin rashes, injection site reaction, refusal to breastfeed, and convulsions were classified as moderate. It was not possible to confirm the few cases that could have been classified as persistent crying (using the Brighton Collaboration definition for crying for >3 hours) and accurately differentiate them from crying for <3 hours; thus, all crying episodes were grouped and classified as mild AE following the WHO guidelines (Table 1).

The incidence of AEs per 1000 doses observed was 49.2 (95% CI, 47.9–50.5), 36.8 (95% CI, 35.6–37.9), and 15.9 (95% CI, 15.1–16.6) for IPTi1, 2, and 3, respectively (Table 4). Overall, the incidence of AEs decreased from IPTi1 to IPTi2 and IPTi3. In Madagascar, where presumably all the infants who were followed after intake of IPTi3 had also taken the previous 2 doses of IPTi (IPTi2 and IPTi3)—because IPTi administration started 9 months before the pharmacovigilance follow-up study and covered 97% of all immunized children—there was also no increase in the frequency of AEs after the third IPTi dose (Table 4). The frequency of AEs decreased with age (Figure 1), with most events occurring at around 12 weeks (60%), followed by 17 weeks (17%) and 41 weeks

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**Table 1. Summary of the Definitions Used by the World Health Organization to Classify Adverse Events by Causality and Grading**

<table>
<thead>
<tr>
<th>Causality Categories</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain</td>
<td>Clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of drugs (dechallenge) should be clinically plausibile. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary</td>
</tr>
<tr>
<td>Probable</td>
<td>Event or laboratory test abnormality with reasonable time relationship to drug intake; unlikely to be attributed to disease or other drugs; response to withdrawal clinically plausible; no rechallenge needed</td>
</tr>
<tr>
<td>Possible</td>
<td>Event or laboratory test abnormality with reasonable time relationship to drug intake; could also be explained by disease or other drugs; response to withdrawal lacking or unclear</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Event or laboratory test abnormality with a time to drug intake that makes a relationship improbable (but not impossible); diseases or other drugs provide plausible explanations</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>A report suggesting an adverse reaction that cannot be judged because of insufficient or contradictory information; report cannot be supplemented or verified</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Grading Categories</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (grade 1)</td>
<td>An event that is easily tolerated by study participant, causing minimal discomfort and not interfering with everyday activities</td>
</tr>
<tr>
<td>Moderate (grade 2)</td>
<td>An event that is sufficiently discomforting to interfere with everyday activities</td>
</tr>
<tr>
<td>Severe (grade 3)</td>
<td>An event that prevents normal everyday activities</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>Any untoward medical occurrence that results in death, is life-threatening, or requires hospitalization or prolongation of existing hospitalization</td>
</tr>
</tbody>
</table>

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**Table 2. Age of Infants Receiving Intermittent Preventive Treatment**

<table>
<thead>
<tr>
<th>Age</th>
<th>Average</th>
<th>SD</th>
<th>IQR</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPTi1/DTP2</td>
<td>11.33</td>
<td>6.51</td>
<td>11–15</td>
<td>12</td>
</tr>
<tr>
<td>IPTi2/DTP3</td>
<td>16.38</td>
<td>7.63</td>
<td>15–21</td>
<td>17</td>
</tr>
<tr>
<td>IPTi3/measles</td>
<td>38.20</td>
<td>11.80</td>
<td>39–44</td>
<td>41</td>
</tr>
</tbody>
</table>

Age is reported in weeks. Abbreviations: DTP, diphtheria-tetanus-pertussis vaccine; IPTi, intermittent preventive treatment in infants; IQR, interquartile range; SD, standard deviation.
which corresponds to when children received IPTi1, 2, and 3, respectively. Since infants received the same package of immunizations (DTP, Hib, Hep, OPV) at IPTi1 and at IPTi2, the frequency of AEs is probably negatively associated with age.

The most common events observed were fever (54.0 per 1000 doses; 95% CI, 52.6–55.4) followed by crying (31.2 per 1000 doses; 95% CI, 30.1–32.3), vomiting (9.2 per 1000 doses; 95% CI, 8.6–9.8), diarrhea (3.2 per 1000 doses; 95% CI, 2.9–3.6), and skin rashes (2.5 per 1000 doses; 95% CI, 2.2–2.8) (Figure 1). All other events (coughing, injection reactions, itching, nausea, refusal to breastfeed, convulsions, and nervousness) were rare (<1 per 1000 doses). More than 1 symptom per dose administered was reported in 532 children (2.2%), more frequently after the first (1.0%) and second (0.8%) IPTi administration compared with the third (0.3%) administration.

Most events (59.8 per 1000; 95% CI, 58.4–61.2) were classified by the causality assessment committee as possibly linked to immunizations or IPTi, whereas approximately 9.4 per 1000 (95% CI, 8.8–10.0) were unlikely linked, and 7.9 per 1000 (95% CI, 7.3–8.4) were probably linked; for the remainder (24.8 per 1000; 95% CI, 23.8–25.7), causality could not be assessed (Figure 2).

Potential risk factors, such as infant’s gender, age, immunization type, time of IPTi administration, and number of doses received, were analyzed for the probability of the 5 most frequent events to occur (Table 5). All observed events were less frequent among children aged 41 weeks than among younger children, as well as after IPTi3/measles compared with other time points, although in most cases the differences were not statistically significant. Fever and crying were significantly less common after IPTi3 than after IPTi1 (odds ratios [ORs], 0.66 and 0.48, respectively).

Since we could not determine how many of the children lost to follow-up could have been hospitalized, we conducted a retrospective review of all study sites’ hospitals registers, including secondary and tertiary care facilities with beds, for the first 2 years of IPTi implementation. We found no inpatient cases of children with SJS during 2 years of administration when 365 361 SP doses were given.

### Adverse Events Reported Passively

Only 12 AEs, consisting mainly of skin reactions (8 cases), were reported passively (or spontaneously) from 217 000 SP doses administered in 6 countries (Table 6). No SJS cases were reported spontaneously. All cases resolved satisfactorily without hospitalization except 1 severe dermatological skin reaction in a 2.5-month-old albino male who developed a facial exfoliate dermatitis a few hours after uptake of IPTi1/DTP2. The child was hospitalized and discharged free of symptoms on the fifth day. He was excluded from further IPTi administration. The patient subsequently developed another similar exfoliate dermatitis after taking traditional herbal medicines. This case was reviewed by 2 independent international experts on SJS and was considered an SAE unlikely linked to IPTi. No cases of mild AEs were reported spontaneously. Only 12 cases of

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### Table 3. Incidence of Adverse Events per 1000 Sulfadoxine-Pyrimethamine Doses

<table>
<thead>
<tr>
<th>Adverse Event Grade</th>
<th>Total Ghana</th>
<th>Madagascar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.  Per 1000</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mild</td>
<td>2733</td>
<td>95.7</td>
</tr>
<tr>
<td>Moderate</td>
<td>176</td>
<td>6.2</td>
</tr>
<tr>
<td>Severe/Serious</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>2909</td>
<td>101.8</td>
</tr>
<tr>
<td>Total doses administered</td>
<td>28564</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

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### Table 4. Distribution of Adverse Events by Intermittent Preventive Treatment in Infants Time Points

<table>
<thead>
<tr>
<th>IPTi/DTP2</th>
<th>Total Ghana</th>
<th>Madagascar</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.  Per 1000</td>
<td>95% CI</td>
<td>No.  Per 1000</td>
</tr>
<tr>
<td>IPTi1/DTP2</td>
<td>1405</td>
<td>49.2</td>
</tr>
<tr>
<td>IPTi2/DTP3</td>
<td>1051</td>
<td>36.8</td>
</tr>
<tr>
<td>IPTi3/Measles</td>
<td>453</td>
<td>15.9</td>
</tr>
<tr>
<td>Total</td>
<td>2909</td>
<td>101.8</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DTP, diphtheria-tetanus-pertussis vaccine; IPTi, intermittent preventive treatment in infants.
moderate or severe cases of AEs were reported passively, representing 0.8% of all moderate cases observed by active follow-up (12 per 176).

Together, the results from the active and passive follow-up studies indicate that there were no cases of severe or SAEs possibly linked to SP-IPTi.

DISCUSSION

This study is to our knowledge the largest pharmacovigilance active follow-up study conducted in African children, and the largest study conducted on a prophylactic malaria drug. Reporting AEs regardless of type, severity, or causality judgment allows collection of a larger number of events, estimation of AE rates, and risk measurement. Typically CEM studies aim at observing 10 000 drug exposures to permit identification of rates of 1 AE per 3000 cases. This study included around 30 000 doses, permitting detection of approximately 1 AE per 10 000 exposures. After excluding incomplete records, the cohort was 28 503 SP-IPTi doses given to almost 24 000 infants. The rate of moderate AEs probably linked to immunization and/or SP-IPTi was low (1.8 per 1000). No severe AEs or SAEs were reported, indicating that SP-IPTi has a risk of SAEs of 1 per 8000 doses (95% upper confidence limit). However, because a study weakness was the limited number of participants successfully followed and with complete records to be included in the analysis (47.5%), it is possible that infants with SAEs could have been lost to follow-up. Thus, a retrospective review of 2 years of hospital registers in the IPTi pilot implementing districts was conducted, revealing no cases of SJS hospitalizations in children. No cases of SAEs attributable to SP-IPTi were found by passive surveillance in 217 000 doses administered in 6 countries. Taken together, these results suggest that coadministration of SP-IPTi with routine vaccinations has a safe profile.

A significantly higher proportion of AEs were reported in Madagascar compared with Ghana for the 5 most common events (fever, crying, vomiting, diarrhea, and skin rashes). No endemic disease or epidemic could explain this difference. In both sites, events were reported by parents to personnel specifically trained in collecting the AE cards and reviewed in the facilities by trained health staff. However, the pharmacovigilance trainees collecting cards in Madagascar were predominantly volunteers (169 vs 30 in Ghana) rather than health staff (124 vs 310 in Ghana), suggesting that health staff applied more stringent definitions of AEs than volunteers.

No differences were found between the overall frequency of AEs and infants’ gender. Analysis of individual events revealed slightly lower risk among older children compared with younger children, but this was only statistically significant for fever and crying.

Causality assessment does not eliminate uncertainty [45]. In the present study, assignment of AE causality to SP-IPTi is complex because SP is given concomitantly with EPI vaccines. This study would have benefited from a concomitant CEM study in districts where IPTi was not being implemented. This could not be done due to the ethical consent geographic limitation to work within the IPTi implementation areas.

All events reported in this study (except diarrhea) are also commonly found after EPI immunizations alone, as reported in Western children [46] and in 1 study in Ghana [47]. Fever, reported here at a rate of 54 per 1000, is commonly observed at rates of 1 in 2 after DTP immunizations, 1–6 in 100 after HepB, and 1 in 9 after measles vaccination in Western settings [46]. Vomiting, crying, erythema, redness, and skin rashes are also reported at similar rates following DTP, HepB, and measles immunizations. Skin rashes, more commonly reported in Western settings after measles at a rate of 1 in 10 [48], show here 1.4 higher odds of occurring after IPTi3/measles than after IPTi1/DTP. Crying was 3-fold more common in our study.

Figure 1. Distribution of adverse events by infant’s age. For each symptom indicated, the incidence of reported adverse events per 1000 doses of sulfadoxine-pyrimethamine is shown.

Figure 2. Distribution of adverse events by their causality and severity. For each causality category indicated, the severity distribution is shown for adverse events per 1000 doses of sulfadoxine-pyrimethamine.
after IPTi immunizations (31 per 1000) than reported in the literature from developed countries regarding children after immunizations (10 per 1000) \[46\], possibly due to differences in parental perception between Western and African caregivers, the difficulty of monitoring crying time in the study settings (see Methods section), the extra stress resulting from the ingestion of the SP-IPTi solution, or a combination of these factors.

Diarrhea was the only AE observed that is not commonly reported after EPI immunizations or after SP. The incidence of diarrhea observed (3.2 per 1000 doses; 95% CI, 2.9–3.6) could be due to the water used to dissolve the SP tablets, which might not have been boiled as recommended when implementation became routine. When possible, health workers in Madagascar dissolved the tablets in mothers’ expressed breast milk, which could explain why diarrhea was less frequent in children <6 months. However, the most recent baseline incidence of diarrhea in children aged <5 years was higher in these countries (Ghana 15.4% [49], Madagascar 13.5% [50]) than that observed after 1 week of IPTi (3.2%). The incidence was higher in children, regardless of IPTi administration, and thus cannot be attributed to the intervention. This difference is possibly due to the length of the observation period (2 weeks in the household surveys, 1 week for IPTi), and the methods used (presence of diarrhea is specifically asked in the household surveys, and not specifically named in the IPTi collection of AEs). Seasonality having an effect is unlikely because surveys overlapped: in Ghana the baseline survey was conducted between August and October and the IPTi active follow-up was conducted between May and December, and in Madagascar the baseline survey was conducted between November and March and the active follow-up study was done between December and June.

The small number of children followed for all 3 IPTi doses and the absence of information on the uptake of other sulfonamides in addition to SP-IPTi were obvious study limitations. Additional studies evaluating the possible increased risk of SAEs due to multiple sulfamethoxazole exposures are needed. To that end, an ongoing study on high HIV prevalence settings in urban Malawi following 15 283 children, including 620 receiving all 3 IPTi doses, found very similar results, including no cases of SJS (authors’ unpublished data).

The results indicate that, although it is impossible to determine precisely which AEs are due specifically to the immunizations.

### Table 6. Summary of Adverse Events Reported Spontaneously

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Country</th>
<th>Grade</th>
<th>Causality Assessment</th>
<th>IPTi Time Point</th>
<th>Concomitant Immunization</th>
<th>Type of AE</th>
<th>Age (Weeks)</th>
<th>Duration (Days)</th>
<th>Sex</th>
<th>Time of Event (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benin</td>
<td>Moderate</td>
<td>Unlikely</td>
<td>1st</td>
<td>DTP, Hib, Yellow fever, Measles</td>
<td>Pneumonia</td>
<td>51</td>
<td>3</td>
<td>F</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Benin</td>
<td>Moderate</td>
<td>Unlikely</td>
<td>1st</td>
<td>DTP2, Hib, Hep, OPV</td>
<td>Skin reaction</td>
<td>9</td>
<td>3</td>
<td>F</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Ghana</td>
<td>Moderate</td>
<td>Possible</td>
<td>1st</td>
<td>DTP2</td>
<td>Dermatitis</td>
<td>9</td>
<td>3</td>
<td>M</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Ghana</td>
<td>Moderate</td>
<td>Probable</td>
<td>2nd</td>
<td>DTP3</td>
<td>Skin reaction</td>
<td>16</td>
<td>3</td>
<td>M</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Ghana</td>
<td>SAE</td>
<td>Unlikely</td>
<td>1st</td>
<td>DTP2</td>
<td>Exfoliative dermatitis</td>
<td>10</td>
<td>5</td>
<td>M</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ghana</td>
<td>Moderate</td>
<td>Possible</td>
<td>1st</td>
<td>Measles</td>
<td>Enteritis</td>
<td>36</td>
<td>4</td>
<td>F</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Ghana</td>
<td>Moderate</td>
<td>Possible</td>
<td>1st</td>
<td>Measles</td>
<td>Malaria/enteritis</td>
<td>37</td>
<td>3</td>
<td>F</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Ghana</td>
<td>Moderate</td>
<td>Possible</td>
<td>1st</td>
<td>DTP2</td>
<td>Diarrhea</td>
<td>9</td>
<td>3</td>
<td>M</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Mali</td>
<td>Moderate</td>
<td>Probable</td>
<td>2nd</td>
<td>Measles, Yellow fever</td>
<td>Pruritis</td>
<td>47</td>
<td>3</td>
<td>M</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Mali</td>
<td>Moderate</td>
<td>Possible</td>
<td>2nd</td>
<td>DTP3, Hep</td>
<td>Dermatitis</td>
<td>14</td>
<td>4</td>
<td>F</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>Senegal</td>
<td>Moderate</td>
<td>Possible</td>
<td>1st</td>
<td>Penta2, Polio2, Measles, Yellow fever</td>
<td>Generalized itching and hypochromic macula</td>
<td>38</td>
<td>90</td>
<td>F</td>
<td>23</td>
</tr>
<tr>
<td>12</td>
<td>Senegal</td>
<td>Moderate</td>
<td>Possible</td>
<td>2nd</td>
<td>Penta1, Polio2, Measles, Yellow fever</td>
<td>Generalized itching and hypochromic macula</td>
<td>45</td>
<td>90</td>
<td>M</td>
<td>12</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; DTP, diphtheria-tetanus-pertussis vaccine; F, female; Hep, hepatitis A vaccine; Hib, Haemophilus influenzae type b vaccine; IPTi, intermittent preventive treatment in infants; M, male; OPV, oral poliovirus vaccine; SAE, severe adverse event.
or to SP, there was no increase in frequency or type of AEs due to the addition of SP over those previously reported for EPI immunizations, except for diarrhea and excessive crying. Although spontaneous reporting of AEs in the African context suffers from considerable underreporting, there were no passive reports of SJS linked to IPTi in the large sample where IPTi was pilot implemented. Together, the results from the active and passive follow-up studies indicate that IPTi is a relatively safe intervention.

Passive reporting of AEs always underestimates true risk. For example, in Ghana the spontaneous total number of reports sent to the Food and Drugs Board was 123 in 2007 and 107 in 2008 (author’s unpublished data). However, the low levels of reporting achieved here indicate that the strengthening of African pharmacovigilance systems should not be limited to the training and supervision of providers only. Interventions to sensitize the population, especially those targeted at inducing health behavior changes, should be developed, evaluated, and if suitable, added to the current efforts to strengthen pharmacovigilance systems. Such studies are in progress.

**CONCLUSIONS**

SP-IPTi is an efficient malaria control intervention with an acceptable safety profile for implementation concomitantly with existing immunization programs. Because in scale-up mode the number of infants receiving SP-IPTi will ultimately increase to millions, the possibility of severe AEs occurring will also be higher. For these rare cases to be identified and managed, countries’ pharmacovigilance systems need to be improved. The potential contribution of IPTi to the already elevated incidence of diarrhea calls for an urgent pediatric SP formulation in liquid form.

**Notes**

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**References**


