

## Consortium Safety Panel (CSP) Report – April 2009

All unpublished data should not be used without prior contact with the Consortium. Please contact Dr. Andrea Egan, Coordinator, Intermittent Preventive Treatment of malaria in infants (IPTi) Consortium, Barcelona Centre for International Health Research (CRESIB) Hospital Clinic, University de Barcelona, Rossello 132, 4-2, 08036 Barcelona, Spain Tel - Direct line: +34 93 454 8203; Fax: +34 93 227 9853; Email: [aegan@clinic.ub.es](mailto:aegan@clinic.ub.es)

### Pooled analysis of IPTi-SP trials

Six trials on Intermittent Preventive Treatment of malaria in infants (IPTi) with Sulphadoxine-Pyrimethamine (SP) are included in this analysis. The CSP did not attempt to pool data statistically by causality assessment, but rather presents information in a series of tables on the number of deaths, serious adverse events (SAE) non-fatal hospitalisations, and SAE dermatological reactions by causality.

### Trials included

Ifakara, Tanzania – gave IPTi at 2, 3 and 9 months of age and followed up to 24 months of age  
Navrongo, Ghana – gave IPTi at 2, 3, 9 and 12 months of age and followed up to 24 months of age  
Manhiça, Mozambique – gave IPTi at 3, 4 and 9 months of age and followed up to 24 months of age  
Kumasi, Ghana – gave IPTi at 3, 9 and 15 months of age and followed up to 24 months of age  
Tamale, Ghana – gave IPTi at 3, 9 and 15 months of age and followed up to 24 months of age  
Lambaréné, Gabon – gave IPTi at 3, 9 and 15 months of age and will follow up to 30 months of age

### Methods

Passive clinical surveillance was used to assess safety and efficacy in all trials. In addition, active detection of malaria and anaemia was carried out monthly in Lambaréné and Kumasi, and every 3 months in Tamale; in Lambaréné a blood sample was taken only if the child was febrile while in Kumasi and Tamale the sample was taken regardless of the presence of symptoms. In Lambaréné, safety was also reviewed 1 week after each dose; a blood sample was taken if the child was febrile. In Manhiça, safety assessment was enhanced through home visits 1 week after each dose, through registration of dermatological complaints of children attending a health facility and through blood tests 1 month after the second IPTi dose. In Navrongo, 20% of infants were visited within 4 weeks of IPTi administration to assess side-effects.

Standard WHO definitions were used for adverse events (AEs) and for the grading of severity. In all trials except Kumasi, a SAE was a hospitalisation or death. In Kumasi a life threatening event or enduring disability were also considered an SAE (in the other trials a life threatening event would be hospitalized). Assessment of causality was made by the on-site Principal Investigator (PI) and/or physician. Causality was assessed on symptoms known to be related to SP except in the Kumasi trial where all AE/SAEs occurring within 8 weeks of IPTi administrations were considered possibly related to the study drug. SAEs that occurred more than 3 months after the last dose of IPTi were considered very unlikely to be related to IPTi and excluded from these analyses.

The number of deaths, non-fatal hospitalisations, dermatological SAEs, total sample size and person-time at risk were extracted by PIs or statisticians and reviewed by the CSP. A meta-analysis was conducted on the risk of mortality using Review Manager or StatsDirect software (Review Manager Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). For the mortality outcome, the numerator was the number of deaths, and denominator the number of infants who received at least 1 dose of IPTi. (Section A - up until 3 months after the last dose, or 12 months of age, whichever was earlier. Section B - up to 3 months after the last dose).

For the trial that was cluster randomised, the RR and standard error (SE) of the RR were estimated using a robust cluster method. The cluster adjusted SE was identical to the unadjusted SE for mortality. Heterogeneity between trials was assessed by visually inspecting forest plots of the effects and 95% CI for each site, carrying out a chi-squared test for heterogeneity (statistical significance at 10% level), and calculating the  $I^2$  statistic (which quantifies the amount of heterogeneity over and above that expected due to chance alone on a scale from 0% to 100%).

## Section A: Analysis up to 12 months of age (or 3 months after the last dose, whichever is earlier)

Analysis is for all infants that received at least one dose of IPTi and includes all safety data up to 12 months of age, or until 3 months after the last dose of IPTi was received, whichever was earlier. This involves approximately 10,000 doses of IPTi-SP given to approximately 4,000 infants.

Only doses given within 12 months of age are included in this analysis (Navrongo gave a 4th dose at 12 months of age, Tamale, Lambarene and Kumasi gave the 3rd dose at 15 months of age – analysis of these doses, given outside of the EPI schedule, are not included in this section of the analysis – but are included in the analysis of up to 3 months after the last dose given - in Section B).

### Results

#### Deaths – figure 1 and table 1

There was moderate statistical heterogeneity in the relative risk of death between trials ( $I^2 = 30.7\%$ ). Heterogeneity was greatly reduced ( $I^2 = 4.9\%$ ) in a sensitivity analysis removing the Ifakara trial (the first trial which was carried out, data not shown). A fixed effect meta-analysis was used to pool data. There was no statistically significant difference in the risk of death for infants who received SP compared with placebo across the 6 trials (54 in the SP group versus 51 in the placebo group, rate ratio = 1.06, 95% CI 0.73; 1.55).

One death, in the SP group in Kumasi, was classified as possibly due to IPTi as it occurred 19 days after an IPTi dose. At the visit following administration of the second dose of IPTi at 9 months of age, the infant had slide-proven malaria and received amodiaquine, iron and folic acid. Two weeks later the infant became very weak, was hospitalised, transfused for severe anaemia and received penicillin, artesunate, paracetamol, iron and folic acid. The infant was discharged 6 days later in apparently satisfactory condition but died the next night at home. The most probable cause of death was sepsis with complications of recent malaria and severe anaemia.

#### Non-fatal hospitalisations - table 1

In Ifakara, Navrongo and Manhiça, there were no hospitalisations related to IPTi. The number of hospitalisations possibly related to IPTi in both the placebo and SP group in the other 3 trials is shown in table 1; there were hospitalisations in the placebo and SP group classified as possibly related to IPTi (assigned while the trials were blinded). In Kumasi, 3 hospitalisations in the SP group and 2 in the placebo group were not assessable due to missing hospital files.

There were 3 hospitalisations in Kumasi possibly related to IPTi:

- 1 hospitalisation in the SP group – died (this is the death described above)
- 2 hospitalisations in the placebo group – both recovered

Placebo infant 1 - was admitted 3 weeks after IPTi-1 (3 months of age) with fever, convulsions, tachypnoea, diarrhoea and vomiting. Received anti-malaria treatment (no slide available), paracetamol, cotrimoxazol, penicillin and folic acid but was in good shape when seen 2 weeks later. As the SAE was within 3 weeks of receiving IPTi, the SAE was rated as possibly related to IPTi.

Placebo infant 2 - was admitted 5 days after IPTi-1 (3 months of age) with a non-specific allergic reaction. In hospital the child received cortisone, promethazine and a penicillin injection. As the SAE was within 5 days of receiving IPTi, the SAE was rated as possibly related to IPTi.

There were 2 hospitalisations in Tamale possibly related to IPTi:

- 1 hospitalisation in the SP group – recovered
- SP infant - was admitted 11 days after IPTi-2 (at 9 months of age) for severe anaemia.
  - 1 hospitalisation in the placebo group – recovered

Placebo infant - was admitted on the day of IPTi-2 (at 9 months of age) for convulsions.

There were 4 hospitalisations in Lambaréné possibly related to IPTi:

- 2 hospitalisations in the SP group – both recovered
  - 2 hospitalisations in the placebo group – both recovered
- SP infant 1 - was admitted 14 days after IPTi-2 (9 months of age) due to vomiting.
- SP infant 2 - was admitted 27 days after IPTi-2 (9 months of age) due to strong drop in haemoglobin, an interaction with study drug in children with certain erythrocyte polymorphisms was postulated.
- Placebo infant 1 - was admitted 9 days after IPTi-2 (9 months of age) because of loss of appetite.
- Placebo infant 2 - was admitted 28 days after IPTi-1 (3 months of age) due to vomiting.

### Dermatological SAEs – table 1

There were no IPTi-SP associated dermatological SAEs in the first year of life. In the Kumasi trial, 1 infant in the placebo group had a dermatological SAE classified as possibly related to IPTi as it occurred within 3 weeks after administration of IPTi. At the time of the second IPTi dose at 9 months of age, the infant had malaria and received artesunate-amodiaquine (in addition to the IPTi) but was not hospitalised. The infant developed bullous skin lesions 3 weeks later.

Another infant in the placebo group was diagnosed with Stevens Johnson Syndrome (SJS) and died at the age of 5 months due to multiple organ failure, 2 months after the first dose of IPTi-placebo. The infant was HIV-positive and had been started on agents known to be associated with SJS (anti-tuberculosis drugs [INH, RIF, PZA, and ETB] and cotrimoxazole) 5 days before the onset of dermatological symptoms. The child had not been admitted to hospital.

### **Conclusions**

The results presented here do not raise any major safety concerns when SP is used for IPTi. Furthermore, the recorded risks of IPTi-SP are far outweighed by the benefits.

- The total number of deaths in the SP treated group and in the controls is not statistically different. There was one death in the six trials (in the Kumasi trial) which included over 8,000 infants that was possibly attributable to IPTi-SP. This was an infant that had slide-proven malaria at the time of the second dose of IPTi-SP at 9 months of age.
- The Kumasi, Tamale and Lambaréné trials noted some hospitalisations that could be attributable to IPTi, these occurred in both the SP and placebo groups making it difficult to firmly assign causality linking IPTi-SP administration with these hospitalisations.
- The main adverse reactions of concern are dermatological, especially SJS. In the analysis up to 12 months of age, therefore doses that would be delivered alongside the EPI, there were no dermatological SAE considered related to IPTi-SP. There were less dermatological SAEs in the SP recipients (3) compared to the placebo recipients (13).

## Section B: Analysis up to 3 months after the actual last dose received

Analysis is for all infants that received at least one dose of IPTi and includes all safety data up until 3 months after the actual last dose of IPTi was received. This analysis includes doses given in the second year of life, given outside of the EPI schedule i.e. Navrongo gave a 4th dose at 12 months of age, Tamale, Lambarene and Kumasi gave the 3rd dose at 15 months of age. In this analysis approximately 12,000 doses of IPTi-SP were given to approximately 4,000 infants.

### Results

#### Deaths – figure 2 and table 2

There was little statistical heterogeneity in the risk of death ( $I^2=23.1\%$ ), so fixed effect meta-analysis was used to pool data for this outcome measure. There was no statistically significant difference in the risk of death for infants who received SP compared with placebo across the 6 trials (63 in the SP group versus 65 in the placebo group, rate ratio =0.97, 95% CI 0.69 to 1.37).

One death, in the SP group in Kumasi, 3 weeks after the second dose at 9 months of age, was considered possibly due to IPTi (see section A and table 1).

There was one death in the Kumasi trial in the placebo group possibly related to IPTi as the death occurred 35 days after the third dose of IPTi at 15 months of age. The probable cause of death was malaria, anaemia and dehydration.

#### Non-fatal hospitalisations - table 2

There was one additional hospitalisation in Kumasi possibly related to IPTi (see Section A, for the details of the other 3). The child was admitted 1 month after receiving the third dose of IPTi-SP (at 15 months of age). The diagnosis was clinical malaria (not confirmed by slide); the child had fever, cough and convulsions. The child received anti-malarial treatment, paracetamol, cotrimoxazol, metronidazol, diazepam and amoxicillin in hospital and was healthy when seen 2 days later. As the SAE was within 1 month of receiving IPTi, the SAE was rated as possibly related to IPTi.

There were two additional hospitalisations in Tamale possibly related to IPTi (see Section A, for the details of the other 2), both in the SP group. One child was admitted 4 days after IPTi-3 (at 15 months of age) due to inability to walk, there is no information about treatment or date of discharge. The other child was admitted 5 days after the IPTi-3 (at 15 months of age) due to fever, diarrhoea, vomiting, the diagnosis was enteritis with dehydration, there is no information about treatment or date of discharge.

There was one additional hospitalisation in Lambaréné possibly related to IPTi (see Section A, for the details of the other 4). The child was admitted 36 days after receiving the third dose of IPTi-placebo (at 15 months of age) due to a strong drop in the haemoglobin, an interaction with study drug in children with certain erythrocyte polymorphisms was postulated, and a probable relationship to IPTi was rated.

#### Dermatological SAEs – table 2

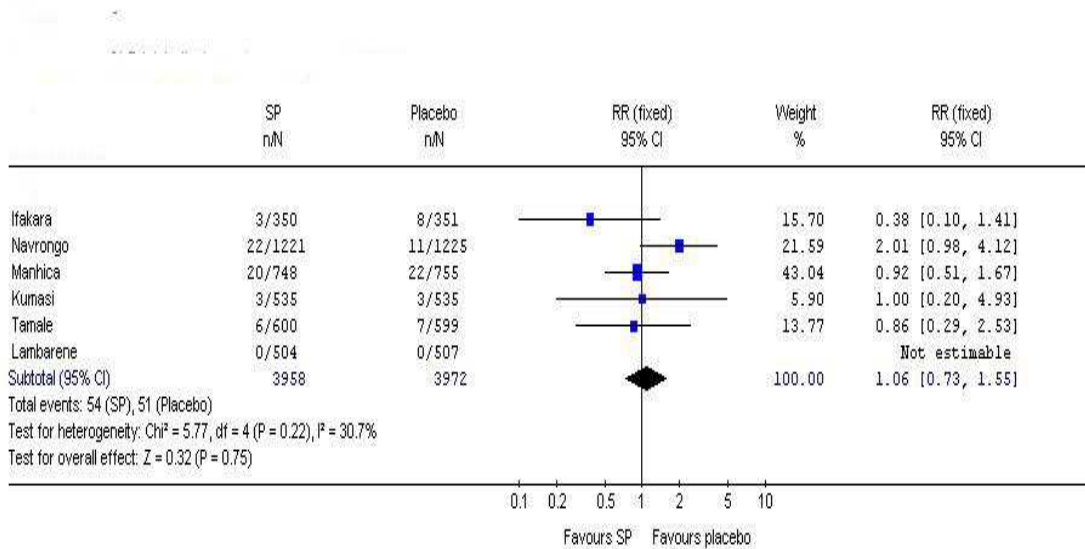
In the first year of life there was one dermatological SAE classified as possibly related to IPTi – this occurred in a placebo recipient in the Kumasi trial. There were 2 reported possible cases of SJS in children from the same site, after they received a third dose of IPTi-SP at 15 months of age. These cases recovered without hospitalisation and presented to the study team in the convalescent phase (when the diagnosis was confirmed). The study team erred on the side of caution and reported suspected SJS. After review of the existing information, reports and a photo of 1 of the cases, the CSP considered these 2 cases unlikely to be SJS. See report of the additional follow-up of the dermatological SAEs in the Kumasi trial.

## Conclusions

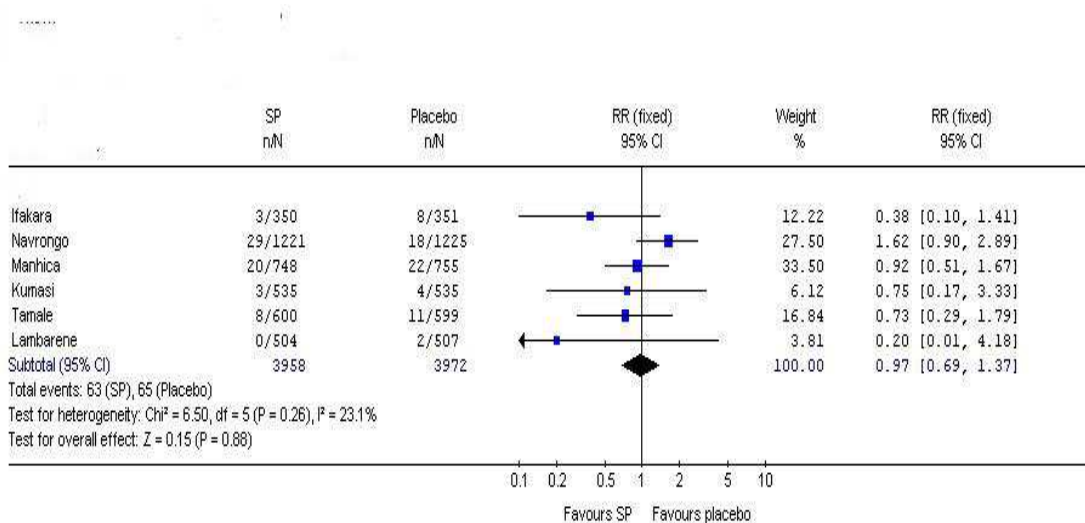
The results presented here do not raise any major safety concerns when SP is used for IPTi. Furthermore, the recorded risks of IPTi-SP are far outweighed by the benefits.

- The total number of deaths in the SP treated group and in the controls is was not statistically different. There was one death in the six trials (in the Kumasi trial) which included over 8,000 infants that was possibly attributable to IPTi-SP. This was an infant that had slide-proven malaria at the time of the second dose of IPTi-SP at 9 months of age, and had received artesunate-amodiaquine therapy, iron and folic acid. There was a death the Kumasi trial in the placebo group at the third dose of IPTi at 15 months of age possibly attributable to IPTi - making it difficult to firmly assign causality of deaths to IPTi-SP administration.
- The Kumasi, Tamale and Lambaréné trials noted some hospitalisations that could be attributable to IPTi, these occurred in both the SP and placebo groups making it difficult to firmly assign causality linking IPTi-SP administration with these hospitalisations.
- The main adverse reactions of concern are dermatological, especially SJS. There were no cases of SJS, or other SAE dermatological reactions related to treatment, in 5 of the 6 studies. In the Kumasi trial there were 3 dermatological SAEs diagnosed as related to IPTi; 2 in the SP group (both suspected SJS, both after the 3<sup>rd</sup> dose at 15 months of age), and one in the placebo group (after the 2<sup>nd</sup> dose at 9 months of age). The CSP call into question the diagnosis of the 2 SJS and a report is available on the dermatological SAE cases in the Kumasi trial. There were less dermatological SAEs in the SP recipients (6) compared to the placebo recipients (14).

**Figure 1 - Risk of death, by treatment group - Analysis up to 12 months of age (or 3 months after the last dose, whichever is earlier)**



**Figure 2 - Risk of death, by treatment group - Analysis up to 3 months after the last dose**



**Actual number of doses given up to 12 months of age:**

**Ifakara:**

SP IPTi-1 (350); IPTi-2 (330); IPTi-3 (272) = Total 952 doses  
Placebo IPTi-1 (351); IPTi-2 (340); IPTi-3 (268) = Total 959 doses

**Navrongo:**

SP IPTi-1 (1221); IPTi-2 (1198); IPTi-3 (1134) = Total 3553 doses  
Placebo IPTi-1 (1225); IPTi-2 (1205); IPTi-3 (1135) = Total 3565 doses

**Manhiça:**

SP IPTi-1 (748); IPTi-2 (703); IPTi-3 (643) = Total 2094 doses  
Placebo IPTi-1 (755); IPTi-2 (695); IPTi-3 (626) = Total 2076 doses

**Kumasi:**

SP IPTi-1 (535); IPTi-2 (505) = Total 1040 doses  
Placebo IPTi-1 (535); IPTi-2 (513) = Total 1048 doses

**Tamale:**

SP IPTi-1 (600); IPTi-2 (570) = Total 1170 doses  
Placebo IPTi-1 (599); IPTi-2 (575) = Total 1174 doses

**Lambaréné:**

SP IPTi-1 (504); IPTi-2 (426) = Total 930 doses  
Placebo IPTi-1 (507); IPTi-2 (430) = Total 937 doses

**Total doses for the 6 trials:**

SP 9,739 doses  
Placebo 9,759 doses

**Actual number of doses given (includes doses in 2<sup>nd</sup> year of life)**

**Ifakara:**

SP IPTi-1 (350); IPTi-2 (330); IPTi-3 (272) = Total 952 doses  
Placebo IPTi-1 (351); IPTi-2 (340); IPTi-3 (268) = Total 959 doses

**Navrongo:**

SP IPTi-1 (1221); IPTi-2 (1198); IPTi-3 (1134); IPTi-4 (1032) = Total 4548 doses  
Placebo IPTi-1 (1225); IPTi-2 (1205); IPTi-3 (1135); IPTi-4 (983) = Total 4585 doses

**Manhica:**

SP IPTi-1 (748); IPTi-2 (703); IPTi-3 (643) = Total 2094 doses  
Placebo IPTi-1 (755); IPTi-2 (695); IPTi-3 (626) = Total 2076 doses

**Kumasi:**

SP IPTi-1 (535); IPTi-2 (505); IPTi-3 (476) = Total 1516 doses  
Placebo IPTi-1 (535); IPTi-2 (513); IPTi-3 (477) = Total 1525 doses

**Tamale:**

SP IPTi-1 (600); IPTi-2 (570); IPTi-3 (532) = Total 1702 doses  
Placebo IPTi-1 (599); IPTi-2 (575); IPTi-3 (536) = Total 1710 doses

**Lambarene:**

SP IPTi-1 (504); IPTi-2 (426); IPTi-3 (346) = Total 1276 doses  
Placebo IPTi-1 (507); IPTi-2 (430); IPTi-3 (327) = Total 1264 doses

**Total doses for the 6 trials:**

SP 12,088 doses  
Placebo 12,119 doses

## Section C: Report on the dermatological Serious Adverse Events (SAEs) reported in the Kumasi trial of intermittent preventive treatment of malaria in infants (IPTi) with sulfadoxine-pyrimethamine (SP)

In the Kumasi trial 4 dermatological SAEs were reported; 2 in the SP group (in both cases causality was classified as "most likely" Stevens Johnson Syndrome, SJS), and 2 in the placebo group (1 rated as "most likely" SJS). The 2 dermatological SAEs in the SP group occurred after the third dose of IPTi at 15 months of age. No children were seen on the day of onset of symptoms.

**Child 1: SP group. Potential SJS 12 days after IPT-3** (age 17 months). The child received artesunate, amodiaquine and paracetamol as well as IPTi as the child had fever (38.7°C) and the IPTi study drug was blinded. The hospital record mentioned bullous skin lesions. The SAE was in a reasonable time after treatment and causality was rated by the study doctor as "most likely" related to IPTi. Symptomatic treatment was continued and the child recovered at home without any sequelae. (ID A0001)

29.10.02 Birth  
13.01.03 Recruitment  
26.03.04 IPTi-3  
10.04.04 SAE reported (3 days after on-set on symptoms)  
30.04.04 Active case detection visit 13 - unblinded (20 days after the SAE reported)

**Child 2: SP group. Potential SJS with mucosa involvement 2 days after the IPTi-3** (healthy when received IPTi-3, age 15 months and 2 days). Went to hospital and received treatment (Flucloxacillin, Metronidazol, Paracetamol, Multivitamins and Chloroquine). The hospital record mentioned bullous skin lesions. Four weeks later the study team saw the child. The study drug was unblinded. Rated the case "most likely" related to IPTi, continued symptomatic treatment and the child recovered at home without any sequelae. (ID K0283, picture available)

16.12.02 Birth  
21.03.03 Recruitment  
19.03.04 IPTi-3  
21.03.04 SAE reported  
23.04.04 Active case detection visit 11 – unblinded (four weeks after the SAE reported -photo taken)

**Child 3: Placebo group. Dermatological SAE ("blister lesions") 23 days after administration of IPTi-2** (age 9 months). The child received artesunate and amodiaquine as well as IPTi as the child had malaria and the IPTi study drug was blinded. Because the infant developed bullous skin lesions 23 days after IPTi it was rated as "most likely" related to IPTi. The child recovered at home without any sequelae. (ID K0278)

11.12.02 Birth  
21.03.03 Recruitment  
19.09.03 IPTi-2 (placebo)  
12.10.03 SAE reported (hospital visit)  
17.10.03 Active case detection visit 6 – unblinded (5 days after the SAE reported)

**Child 4: Placebo group. Diagnosed with SJS and died at the age of 5 months due to multiple organ failure, 2 months after the first dose of IPTi.** The infant was HIV-positive and had been started on agents known to be associated with SJS (anti-tuberculosis drugs [INH, RIF, PZA, and ETB] and cotrimoxazole) 5 days before the onset of dermatological symptoms. The child had not been admitted to hospital. The death was not considered related to IPTi as it occurred 2 months after IPTi.

The two suspected IPTi-SP SJS cases recovered without hospitalisation and the skin eruptions were seen by the study team in the convalescent phase (20 to 30 days after the SAE was reported). The study team erred on the side of caution and reported the SAEs as suspected SJS according to the study protocol. After reviewing this information plus a photo of one of the cases, the Consortium Safety Panel (CSP) considered these two cases unlikely to be SJS. IPTi data, including the safety analysis, were reviewed by a panel of experts convened by the US Institute of Medicine (IOM); they concluded that it is highly unlikely that these were SJS as SJS is a severe disorder requiring intensive care and is associated with a high case-fatality rate, with an unhospitalised case of SJS in an African rural setting unlikely to recover (Institute of Medicine, Assessment of the role of intermittent preventive treatment for malaria in infants, letter report, Washington DC, USA, The National Academies Press, 2008).

The photograph available of one of the suspected cases of SJS (child 2, ID K0283) was shared with Dr. Jean-Claude Roujeau (Department of Dermatology, Hôpital Henri-Mondor, Assistance Publique-Hôpitaux de Paris, Créteil, France), an expert in dermatological drug reactions. Dr. Jean-Claude Roujeau concluded that

“the picture does not suggest SJS: no mucous membrane lesions, minor skin lesions that could be as well impetigo. I could only accept a diagnosis of SJS as "not impossible" if the photograph had been taken very late (at least two weeks after the onset of reaction). Past erythema multiforme is also an option but again we do not see enough to say more than possible. Old erythema multiforme possible. Impetigo possible. SJS unlikely.”

The Kumasi study team were able to locate the three surviving children and using protocols supplied by Prof. Munir Pirmohamed (NHS Chair of Pharmacogenetics, MRC Centre for Drug Safety Sciences, Department of Pharmacology, The University of Liverpool, UK) took blood samples and shipped them to Hamburg. A person from the Hamburg/Kumasi team then took the blood samples to Prof. Pirmohamed's laboratory to conduct T cell proliferation assays to test for hypersensitivity to sulphadoxine. There was a concern about the viability of the cells, which was only 40%. The cells were incubated with sulphadoxine or a non-specific mitogen (PHA) for 7 days. The results of the assay are below:

Sulphadoxine mg/ml	Child 1 - SP group (A0001)				Child 2 - SP group (K0283)				Child 3 - Placebo group (K0278)			
	1	2	3	Mean	1	2	3	Mean	1	2	3	Mean
<b>0</b>	524	281	254	<b>353</b>	565	463	685	<b>571</b>	603	292	439	<b>445</b>
<b>50</b>	634	266	438	<b>446</b>	343	311	406	<b>353</b>	2677	672	488	<b>1279</b>
<b>100</b>	647	266	235	<b>383</b>	247	247	330	<b>275</b>	507	293	293	<b>364</b>
<b>250</b>	349	137	262	<b>249</b>	100	56	87	<b>81</b>	81	25	56	<b>54</b>
<b>500</b>	156	79	62	<b>99</b>	91	29	56	<b>59</b>	44	31	68	<b>48</b>
<b>1000</b>	118	31	75	<b>75</b>	50	62	62	<b>58</b>	50	62	62	<b>58</b>
<b>PHA</b>	100	37	106	<b>81</b>	1159	1620	442	<b>1074</b>	6320	5452	6797	<b>6190</b>

The cells from child 1 did not respond to PHA indicating the cells were not healthy. The other two children had negative results with sulphadoxine i.e. they did not have T cells that were reacting towards sulphadoxine. However, it is important to remember that these tests are not absolutely predictive, and therefore the children could still be allergic despite a negative T cell proliferation assay. Since the laboratory in Liverpool hadn't ever tested sulphadoxine before so sensitivity and specificity values could not be provided.

**Conclusions:** The two main questions that need to be answered are as follows:

1. Was the reaction suffered by the children SJS? From the photograph provided (of child 2), the clinical data, the fact that the children recovered without any hospitalization, and the comments from the dermatological expert (on child 2), it seems very unlikely that the children ever developed SJS.
2. Was this reaction, irrespective of morphology, due to SP? Although the timing in child 1 would be consistent with a SP reaction, the clinical features are not very clear, and no photograph is available. In addition, the child's cells did not arrive in a healthy state, and thus the lymphocyte transformation test (LTT) was unhelpful. Thus, a reaction to SP cannot be completely excluded in child 1 although this was highly unlikely to be SJS. In child 2, the timing is unusual (reaction developing after 2 days) for a reaction to SP. Taken together with a negative LTT, it seems unlikely that the child suffered a reaction to SP.

Thus, in summary, it is highly unlikely that the children suffered SJS from the use IPTi, but in child 1 the possibility of a reaction to SP cannot be completely excluded.

**Annex - CSP members:**

**Sir Alasdair Breckenridge** (Chairman)

Chairman of the UK Department of Health's Medicines and Healthcare Products Regulatory Agency (MHRA), United Kingdom

**Professor Peter Winstanley**

Director of the Wellcome Trust Tropical Centre, University of Liverpool, United Kingdom

**Dr Esperanza Sevene**

Secretariat of the National Ethics Committee of the Mozambican Ministry of Health, Pharmacology Department of Eduardo Mondlane University, Faculty of Medicine, P.O. BOX 257, Maputo, Mozambique

**Professor Zul Premji**

Professor of Infectious Diseases, Department of Parasitology/Medical Entomology, School of Public Health and Social Sciences, Muhimbili University College of Health Sciences, Box 65011, Dar es Salaam, Tanzania

**Dr Julia Critchley**

Senior Lecturer in Epidemiology, Institute of Health and Society, Advancing Research in Chronic Disease Epidemiology (ARCHEPI) programme, Leech Building, School of Population and Health Sciences, University of Newcastle, Newcastle upon Tyne NE2 4HH, United Kingdom

**Dr Rachida Soulaymani-Bencheikh**

Director of the Centre Anti-poisons et de Pharmacovigilance du Maroc, Madinat Al irfane Agdal BP 66 71, Agdal, 11400 Rabat, Morocco

**Dr Alexander Dodoo**

Senior Research Fellow and Acting Director of the Centre for Tropical Clinical Pharmacology & Therapeutics, University of Ghana Medical School, Korle-Bu Teaching Hospital, Korle-Bu, Accra, Ghana

**Table 1: Total deaths, non-fatal hospitalisations and dermatological SAEs, by causality, up to 12 months of age, or 3 months after the last dose received, whichever is earlier**

Trial	IPTi		Placebo	
<b>Total deaths/Total infants (Possibly related to treatment)</b>	<b>54/3958</b>	<b>(1)</b>	<b>51/3972</b>	<b>(0)</b>
Ifakara	3/350	(0)	8/351	(0)
Navrongo*	22/1221	(0)	11/1225	(0)
Manhica	20/748	(0)	22/755	(0)
Kumasi	3/535	(1)	3/535	(0)
Tamale	6/600	(0)	7/599	(0)
Lambaréné	0/504	(0)	0/507	(0)
<b>Total non-fatal hospitalizations/PYAR (Possibly related to treatment)</b>	<b>676</b>	<b>(4)</b>	<b>860</b>	<b>(5)</b>
Ifakara	106 / 247.7	(0)	151 / 250.5	(0)
Navrongo*	248 / 874.4	(0)	309 / 867.4	(0)
Manhica	227 / 494.6	(0)	279 / 487.1	(0)
Kumasi**	46 / 385.5	(1)	52 / 389.1	(2)
Tamale	23 / 401.9	(1)	52 / 401.3	(1)
Lambaréné	26 / 327.0	(2)	17 / 330.0	(2)
<b>Total dermatological SAEs/PYAR (Possibly related to treatment)</b>	<b>3</b>	<b>(0)</b>	<b>13</b>	<b>(1)</b>
Ifakara	0 / 247.7	(0)	0 / 250.5	(0)
Navrongo*	Not available		Not available	
Manhica	2 / 494.6	(0)	7 / 487.1	(0)
Kumasi	0 / 385.5	(0)	2 / 398.1	(1)
Tamale	0 / 401.9	(0)	2 / 401.3	(0)
Lambaréné	1 / 327.0	(0)	2 / 330	(0)

SAE = Serious adverse event

PYAR = person-years at risk

\* Navrongo - no deaths, hospitalizations or dermatological SAEs were considered related to treatment, but no more details are available

\*\* Kumasi - 3 hospitalizations in the SP group and 2 in the placebo group were not assessable to work out causality

**Table 2: Total deaths, non-fatal hospitalisations and dermatological SAEs, by causality, up to 3 months after the last dose received**

Trial	IPTi		Placebo	
<b>Total deaths/Total infants (Possibly related to treatment)</b>	<b>63/3958</b>	<b>(1)</b>	<b>65/3972</b>	<b>(1)</b>
Ifakara	3/350	(0)	8/351	(0)
Navrongo*	29/1221	(0)	18/1225	(0)
Manhica	20/748	(0)	22/755	(0)
Kumasi	3/535	(1)	4/535	(1)
Tamale	8/600	(0)	11/599	(0)
Lambaréné	0/504	(0)	2/507	(0)
<b>Total non-fatal hospitalizations/PYAR (Possibly related to treatment)</b>	<b>860</b>	<b>(7)</b>	<b>1056</b>	<b>(6)</b>
Ifakara	115 / 254.1	(0)	161 / 256.7	(0)
Navrongo*	351 / 1210.3	(0)	419 / 1202.9	(0)
Manhica	237 / 515.6	(0)	289 / 508.4	(0)
Kumasi**	80 / 616.8	(2)	85 / 618.4	(2)
Tamale	41 / 808.8	(3)	66 / 811.1	(1)
Lambaréné	36 / 473.6	(2)	36 / 456.1	(3)
<b>Total dermatological SAEs/PYAR (Possibly related to treatment)</b>	<b>6</b>	<b>(2)</b>	<b>14</b>	<b>(1)</b>
Ifakara	1 / 254.5	(0)	1 / 256.7	(0)
Navrongo*	Not available		Not available	
Manhica	2 / 515.6	(0)	7 / 508.4	(0)
Kumasi	2 / 618.6	(2)	2 / 618.4	(1)
Tamale	0 / 808.8	(0)	2 / 811.1	(0)
Lambaréné	1 / 473.6	(0)	2 / 456.1	(0)

SAE = Serious adverse event

PYAR = person-years at risk

\* Navrongo - no deaths, hospitalizations or dermatological SAEs were considered related to treatment, but no more details are available

\*\* Kumasi - 4 hospitalizations in the SP group and 3 in the placebo group were not assessable to work out causality