Safety of sulfadoxine/pyrimethamine for intermittent preventive treatment of malaria in infants: evidence from large-scale operational research in southern Tanzania

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ABSTRACT

Intermittent preventive treatment with sulfadoxine/pyrimethamine (SP) is recommended for malaria prevention in infants (IPTi-SP). Serious adverse events, including Stevens–Johnson syndrome (SJS), have been reported following exposure to SP, but few infant-specific data exist. The safety of IPTi-SP was evaluated as part of a pilot implementation programme in southern Tanzania using three methods: spontaneous adverse event reporting to capture suspected adverse drug reactions (ADR); a census survey documenting rash-related hospital admissions among children <2 years of age; and verbal autopsies (VA) completed for rash-related deaths in 2–11-month=olds. Approximately 82 000 IPTi-SP doses were administered to approximately 29 000 children. In total, 119 suspected ADRs were reported, 13 in children aged <2 years, only 1 of whom had received IPTi-SP. The census involved 243 612 households. Only one rash-related admission was reported amongst 1292 children aged 2–11 months, but this child had no history of exposure to SP. Moreover, 30 of 699 deaths in 2–11-month-olds were said to have been associated with a skin rash. The rates of rash-associated death were 0.6/1000 person-years at risk (PYAR) and 1.17/1000 PYAR in intervention and comparison areas, respectively ($P = 0.79$). VAs did not suggest SJS or any other ADR. We conclude that IPTi-SP is associated with a very low incidence of severe skin reactions.

Introduction

Disease and death due to *Plasmodium falciparum* infection continues to plague large swathes of sub-Saharan Africa. Despite evidence of recent improvements in the malaria situation in some settings,[1,2] it is likely that novel tools for malaria control will continue to be needed for decades to come. Intermittent preventive treatment for malaria in infants (IPTi) is a promising new intervention consisting of the administration of a treatment dose of sulfadoxine/pyrimethamine (SP) at the time of routine vaccinations in the first year of life.[3] A pooled analysis[4] of six randomised controlled trials (RCT) of IPTi using SP (IPTi-SP)[5–10] suggested that the intervention can reduce the incidence of clinical malaria in the first year of life by 30%. If such an effect can be achieved by delivering an available and affordable antimalarial treatment at the time of routine contacts with the health system, IPTi-SP may become a useful component of antimalarial strategies in some settings.

SP was licensed in 1974 and there is extensive experience of its use, including in young children. However, some concern exists over its safety when given as a preventive intervention because of the possibility of severe reactions, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), associated with the sulfadoxine component.[11] These concerns were initially raised in data from European and North American travellers taking SP weekly for prevention *of P. falciparum* malaria.[12,13] Fatality rates of 30–35% for TEN and 5–15% for SJS were highly influenced by the timing of diagnosis and access to appropriate treatment facilities, such as burns and Intensive Care Units.[14] Although the association between sulphonamides and SJS/TEN has been well established, fewer cases of SJS or TEN have been linked to SP.[12,13] A rate of serious adverse events to SP of 1.2/100 000 was reported using a spontaneous event reporting system in Malawi.[15] The occurrence of an adverse event has been shown to depend on the pattern of drug intake, drug dose and the number of doses taken.[15] A study on the regular use of long-acting sulphonamides for meningitis prophylaxis showed that 80% of SJS cases occurred between the second and fifth doses of weekly intake, with no cases reported when the drug was used only once.[16] The relationship between drug intake and the onset of symptoms and signs suggestive of an adverse reaction is not well understood. SJS and TEN can occur within 3 months of drug intake, although the highest risk appears to be during the first 3 or 4 weeks.[17,18] Other risk factors for developing SJS include age (less common in children <15 years than in adults), HIV status (more common in HIV-positive than in HIV-negative individuals)[19,20] and genetic factors.[17]

In southern Tanzania, an operational research programme developed and implemented a programme to evaluate the effectiveness and safety of IPTi-SP in an area with a total population of approximately 900 000 people. In the context of this programme, we implemented a consolidated, spontaneous, adverse event reporting system. After 2 years of IPTi-SP implementation, a census was conducted and information was gathered on the causes of death of young children as well as the reasons for admission of a representative subset of children living in the area. Here we report on the safety of IPTi-SP as documented in southern Tanzania.

Methods

2.1. Study area and intermittent preventive treatment for malaria in infants (IPTi) strategy

The project was carried out in five remote rural districts of the Lindi and Mtwara regions near the Mozambican border in southern Tanzania. The area, which covers approximately 20 000 km[2], is described in more detail elsewhere.[21] The first-line treatment for malaria was SP, which was widely used up to and after the introduction of artemether/lumefantrine into the study area in December 2006. Each district is split into 3–10 divisions (the fourth administrative level) and the study area comprised 24 divisions in total. One-half of these divisions initiated IPTi implementation in April 2005, as described in detail elsewhere.[22,23] In brief, a strategy for deployment of IPTi was developed in conjunction with stakeholders at national, regional and district levels. IPTi was deployed as part of the routine health system in 12 divisions commencing in March 2005. A single dose of SP was given at 2, 3 and 9 months of age when children presented to vaccination clinics for routine doses of the diphtheria, tetanus, pertussis and hepatitis B vaccine (DTP-Hb), given at 1, 2 and 3 months of age, and measles vaccine (given at 9 months). Tablets of 500 mg sulfadoxine and 25 mg pyrimethamine were donated by Hoffman-La Roche (Basel, Switzerland). Children weighing ?5 kg were given half a tablet and those weighing <5 kg were given a quarter of a tablet. Doses were administered after crushing and dissolving tablets in a small amount of clean water on a spoon.

Following evidence of the safety and benefits of IPTi generated by this project in 2006,[24] and after further discussion with national stakeholders, implementation was extended to the comparison areas in March 2008. Coverage surveys were conducted in 2006[24] and 2007. The total number of doses of IPTi-SP delivered between April 2005 and December 2008 was estimated by applying the 2007 coverage estimates to the number infants in the study area. Two estimates were generated: (a) based on the number of doses recorded on the child's health card; and (b) based on doses of IPTi reported by the mother. The true number of doses is likely to fall between these two estimates. To provide a conservative evaluation of the safety of IPTi-SP, the number of doses used as the denominator was the more conservative figure, based on health card information.

2.2. Spontaneous reporting of suspected adverse drug reactions (ADR)

A spontaneous reporting system was implemented in conjunction with the national regulatory agency, the Tanzanian Food and Drug Authority (TFDA). A standard reporting form was agreed and a series of workshops were conducted to train clinicians at the district level as well as front-line health workers in peripheral dispensaries, health centres and referral facilities. Case scenarios and test questions were included in the training sessions: a folder was provided containing graphic images of severe dermatological reactions, a copy of the training materials and reporting forms. This folder also contained contact telephone numbers of the project's safety monitor, whose job it was to follow-up relevant suspected ADRs. Clinicians were encouraged to complete the form in duplicate if they suspected an ADR to any drug in any age group. One copy of the form was sent

to the designated safety co-ordinator on the district health team who would telephone the project's safety co-ordinator if the reporter had not already done so. Suspected ADRs were then followed-up according to a prioritised response system, which ensured that any reaction in a child <2 years of age was followed-up at home by the project safety monitor within 72 h of notification. A re-assessment form was completed at these home visits to capture more detailed clinical information by a specially trained clinician. Quarterly visits to health facilities were made by the project safety monitor to maintain awareness of the system and to check for any missed reports. The system was fully operational from March 2005 and this paper documents reports received up to December 2008.

2.3. Rash-related hospital admissions in children <2 years of age

A census survey was conducted in the project area between July and November 2007. Mothers of children <2 years of age were identified and asked if they were willing to be visited by a child health interview team. A representative subsample of those willing to participate was visited within 4 weeks of the initial survey. In each division, eight clusters of young children were identified, with each cluster being a subvillage. The number of clusters per ward (the fifth administrative level) was determined with probability proportional to size. A simple random sample of clusters was selected and all children aged <2 years were identified and their mothers were approached for written informed consent for interview. Responses to questions about the child's health, vaccination and IPTi status and any admissions, including those associated with a rash, were directly entered into personal digital assistants (PDA), as described previously.[25] These data were used to estimate the coverage of IPTi during 2007, powered to detect a coverage of 50% to within five percentage points, as well as the incidence of hospital admission with a rash as part of the safety evaluation.

2.4. Rash-related deaths in children aged 2–11 months

All households in the project area were visited during the course of the census and birth history interviews were carried out with all women aged 13–45 years, as described previously.[21] Consenting mothers of any child who died aged 2–11 months were asked a series of questions to explore the possibility that the child had died because of a rash. If this was the case, consent was sought for a specialised follow-up team to visit the mother and to conduct a verbal autopsy (VA) using the standard INDEPTH post-mortem questionnaire.[26] This approach was expected to identify and follow-up any death potentially due to a skin rash in a 2–11-month-old and reported by a woman consenting to a birth history. The VA team consisted of four Clinical Officers who were trained as VA interviewers by a senior physician experienced in VA diagnosis coding. The training lasted 2 weeks and consisted of detailed questionnaire review, case studies and a 3-day pilot survey. Work lists were produced from the cleaned census data, which had been collected using PDAs,[25] and provided to the VA interviewers within 4 weeks of the original household visit. The flow of VA questionnaires and job lists between the data unit and field was managed by the VA team supervisor whose responsibility it was to conduct quality control checks. These included re-visits to randomly selected households and to

all households where it had not been possible to complete a VA. Completed VAs were reviewed by the supervisor before being sent to two experienced VA coders. The cause of death was coded independently using the *WHO International Classification of Diseases* (ICD-10) classification and codes were compared using a computer program. Where there was diagnostic disagreement, a third coder gave a further independent opinion. Diagnoses were considered definitive if two matching ICD-10 diagnoses were obtained.

2.5. Data management and analysis

Data were transferred from PDAs to Microsoft Access databases (Microsoft Corp., Redmond, WA, USA) using Pendragon Software (Pendragon Software Corp., Buffalo Grove, IL, USA). Analysis was conducted in Stata version 8 (Stata Corp., College Station, TX, USA) according to a pre-defined analytical plan. Proportions of hospital admissions are presented as well as incidence rates of death with skin rash. Statistical testing was based on the *t*-test using a summary measure of the data from each of the 12 intervention and 12 comparison divisions, adjusting for the clustered nature of the data.[27]

Results

3.1. Doses of intermittent preventive treatment for malaria in infants with sulfadoxine/pyrimethamine (IPTi-SP)

The coverage of three documented doses of IPTi during the 2007 survey was 48% (371/769; 95% CI 42–55%) and the coverage of two or more doses was 55% (426/769; 95% CI 49–61%). There were 11 523 children aged 12–23 months in the intervention area in 2007 and 13 444 children in the same age group in comparison areas. Roll-out of IPTi-SP to comparison areas was completed by 20 March 2008. Applying the coverage estimates to the population data and considering the timing of implementation in the different areas suggests that 3645 children received two doses of IPTi-SP each and 24 997 children received three doses. Hence, a total of approximately 82 280 doses of IPTi-SP were received by approximately 28 642 children.

3.2. Spontaneous adverse drug reactions

A total of 119 spontaneous ADR reports were received from intervention and comparison areas between March 2005 and December 2008. Only 13 of these concerned children <2 years of age. A single report was received about a child who had previously received IPTi-SP. He was 7 months old and presented on 6 March 2006 with a 2-day history of rash, 8 days after a reported half tablet of SP given as treatment. The child had received doses of IPTi-SP on 19 December 2005 and 31 January 2006. At re-assessment the child was well, with a resolving macular rash over his upper chest and back. Nikolsky's sign was positive, with blisters forming on lateral pressure, however there were no lesions in the mouth, nose, eyes or perianally. Four weeks later the child was well with some persisting discolouration of skin lesions. As the child had continued to behave as

normal, this was considered a Grade 1 adverse event, probably associated with SP. This was the only adverse reaction reported after a total of approximately 82 280 doses of IPTi-SP in an estimated 28 642 children. The spontaneous ADR reporting system captured two cases of SJS in people aged >15 years.

3.3. Rash-related hospital admissions and deaths

The census team identified 243 612 households. The head of the household was present in 93.5% of households ($N = 227\ 789$), of which 99.2% (225 980) agreed to participate in the survey. A total of 213 207 women of child-bearing age were registered, of whom 92.1% (196 302) were available and consented to be interviewed about their birth history. Mothers of a representative sample of 2780 children <2 years of age were interviewed between July and November 2007. Admissions reported among 1292 children aged 2–11 months are summarised in Table 1; no differences were seen between intervention and comparison areas. Only one admission was said to be due to a skin rash and this child had no history of exposure to SP.

Amongst the 699 children who died aged 2–11 months, 30 were said to have died with a skin rash (Table 1). The overall incidence rate of death associated with a rash in intervention areas was 0.59/1000 person-years and this did not differ from that in comparison divisions (Table 1). Of the 30 deaths associated with a rash, two mothers could not be found for a VA and two declined a VA; thus, 26 mothers were interviewed. For three of the VAs, no definitive diagnosis was reached by the VA coders and hence definitive diagnoses were available for 23 deaths. However, none of the VA diagnoses included SJS and none of the deaths was thought likely to be due to an ADR by any clinician.

Discussion

This report presents information on the safety of IPTi-SP as evaluated in the context of an operational research programme in southern Tanzania. The evaluation was initiated when SP was widely used as first-line treatment for malaria and may have been expected to increase the risk of adverse events associated with IPTi-SP. However, a consolidated adverse event reporting system identified only one Grade 1 adverse event in over 82 000 doses of IPTi-SP amongst approximately 29 000 children. Spontaneous reporting systems are known for their serious inadequacies, in particular the marked under-reporting associated with this approach. The project's safety monitor visited each health facility every 3 months to maintain awareness of the reporting system and to encourage the reporting of suspected adverse events. The system successfully identified two cases of SJS in older people, unrelated to IPTi, and we consider it likely to have identified children presenting to health facilities with SJS. Nevertheless, it is probable that these data under-report less severe, especially non-dermatological, adverse events due to IPTi-SP.

The household census involved every household in the entire project area. A representative subsample was asked about admissions associated with a rash in

children. Only one such admission was reported and this was not associated with prior use of SP. We were surprised in this analysis not to find a reduced rate of admissions in children living in areas where IPTi was delivered. This contrasts with the findings of the pooled analysis of the efficacy of IPTi-SP in which a 23% reduction in the rate of all-cause admission was documented in children receiving IPTi-SP.[4] However, in contrast to our project area in southern Tanzania, children involved in the placebo-controlled trials all lived within easy reach of hospitals and therefore may have been more likely to seek hospital care and to be admitted in the event of illness.

A systematic approach was adopted to identify children living in the project area who had died with a rash. The rate of death with a rash was not increased in intervention areas compared with comparison areas. Furthermore, the VAs reassured us that none of the deaths that were followed-up were likely to be a result of an ADR, in particular SJS.

The estimated number of doses of IPTi-SP is likely to be an underestimate as it is based on coverage estimates derived from doses recorded on children's health cards; it is likely that some doses went unrecorded. Coverage estimates based on mothers' reports of IPTi-SP doses suggest that 125 503 doses were administered to 42 702 children. We consider the lower estimates presented in the results to be more robust and recognise that these generate relatively conservative estimates of the safety of IPTi-SP. The low coverage estimate has implications for the interpretation of the absolute proportions of admissions and incidence of death associated with a rash, which are presented for the intervention group as a whole and not specifically the subgroup of patients who received IPTi-SP. It is possible that a higher intervention coverage might increase the frequency of these endpoints. It was not possible to document IPTi doses reliably in children who had died, as child health cards are rarely retained in such circumstances. However, even if the coverage had been complete, it is very unlikely that this would produce a significantly greater risk of death in infants receiving IPTi-SP than in those who did not. Assessment of the safety of an intervention is fraught with difficulties in any setting. Spontaneous adverse event reporting systems require clinicians to consider the possibility of an ADR and to be sufficiently motivated to complete a report form. The low frequencies of serious ADRs necessitate operating on a large scale and depending heavily on existing staff with competing priorities. Despite specific training that focused on the identification and reporting of ADRs, it is very likely that more subtle adverse events arising from IPTi-SP were not captured by this system. In this regard, it is reassuring that the results are consistent with those of the pooled analysis of RCTs of IPTi-SP that found a reduction in the incidence of serious adverse events, including severe dermatological events, in IPTi-recipients.[4]

An alternative accepted approach to capturing adverse events is cohort event monitoring in which a large number of individuals (typically 10 000) are followed-up at a limited number of time points after treatment to estimate the frequency of anticipated adverse events. Our evaluation was in the context of an operational research study that included an assessment of the acceptability of IPTi-SP; large-scale active follow-up of study participants for safety outcomes may well have interfered with our ability to assess acceptability in close to 'real-life' conditions. A novel approach to the generation of safety

signals is the use of self-controlled case series analysis.[28] This method compares the incidence of signs, symptoms, abnormal laboratory values or diagnoses in periods before and after administration of an intervention in individuals who are reliably identified at each contact with the health system. This approach has the advantage of not requiring a clinician to consider the possibility of an adverse event and to fill in a form, and can generate signals of adverse reactions not previously recognised as associated with the intervention, occurring a considerable time after the intervention or arising after multiple doses of the treatment. The method has been used to generate safety signals in several developed countries[29–32] but so far has not been evaluated in the tropics.

Data are now available from six RCTs of IPTi-SP. Pooled analysis of these RCTs showed a reduction in the risk of serious adverse events in IPTi recipients, with fewer serious dermatological events in IPTi versus control arms and no events considered related to IPTi.[4] The information presented here from southern Tanzania as well as that generated in the context of pilot implementation of IPTi-SP by UNICEF in a further six African countries offers further reassurance.[33] The evidence suggests that the incidence of severe dermatological or other reactions following IPTi-SP is very low. At the same time, IPTi-SP has been shown to reduce by 30% the incidence of clinical malaria, which causes hundreds of thousands of deaths per year.[34]

registered on clinical trials.gov (NCT00152204). Ethical approval for this study was obtained from the Ifakara Health Institute Institutional Review Board (Ifakara, Tanzania), the National Tanzanian Medical Research Co-coordinating Committee, and the Research and Ethical Review Committees of the Swiss Tropical Institute (Basel, Switzerland) and the London School of Hygiene and Tropical Medicine (London, UK). In the census survey and verbal autopsy study, written consent of principal care-givers was sought. Confidentiality of all study participants was assured.

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Table 1

Rates of admission and death in young children in the intermittent preventive treatment of malaria in infants (IPTi) project area

	Intervention areas a	Comparison areas	P-value b
Proportion of children aged 2-11 months admitted to hospital since birth	43/566 (8%)	46/726 (6%)	0.46
Proportion of children aged 2-11 months admitted to hospital with a rash	1/566	0/726	
Proportion of children aged 2-11 months admitted to hospital with a rash after SP	0/566	0/726	
Proportion of children aged 2-23 months admitted to hospital with a rash	1/1334 (0.1%, 95% CI 0-0.4%)	0/1688 (0.0%, 95% CI 0-0.2%)	
Children aged 2-11 months said to have died with a rash	9/15 168.7 PYAR (0.59/1000 PYAR; 95% CI 0.3-1.1)	21/17 885.1 PYAR (1.17/1000 PYAR; 95% CI 0.73-1.79)	0.79

SP: sulfadoxine/pyrimethamine; PYAR: person years at risk.

a Note that the frequencies of these endpoints are based on the entire intervention group and not specifically the subgroup of patients who received IPTi using SP (IPTi-SP).

b *P*-value based on *t*-test comparing proportions in intervention versus control divisions, accounting for the clustered nature of the data.