



Risk of sudden unexplained death after use of dihydroartemisinin–piperaquine for malaria: a systematic review and Bayesian meta-analysis

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Summary

Background Dihydroartemisinin–piperaquine is an effective and well tolerated artemisinin-based combination therapy that has been assessed extensively for the prevention and treatment of malaria. Piperaquine, similar to several structurally related antimalarials currently used, can prolong cardiac ventricular repolarisation duration and the electrocardiographic QT interval, leading to concerns about its proarrhythmic potential. We aimed to assess the risk of potentially lethal iatrogenic ventricular arrhythmias in individuals receiving dihydroartemisinin–piperaquine.

Methods We did a systematic review and Bayesian meta-analysis. We searched clinical bibliographic databases (last on May 24, 2017) for studies of dihydroartemisinin–piperaquine in human beings. Further unpublished studies were identified with the WHO Evidence Review Group on the Cardiotoxicity of Antimalarials. We searched for articles containing “dihydroartemisinin–piperaquine” as title, abstract, or subject heading keywords, with synonyms and variant spellings as additional search terms. We excluded animal studies, but did not apply limits on language or publication date. Eligible studies were prospective, randomised, controlled trials or cohort studies in which individuals received at least one 3-day treatment course of dihydroartemisinin–piperaquine for mass drug administration, preventive therapy, or case management of uncomplicated malaria, with follow-up over at least 3 days. At least two independent reviewers screened titles, abstracts, and full texts, agreed study eligibility, and extracted information about study and participant characteristics, adverse event surveillance methodology, dihydroartemisinin–piperaquine exposures, loss-to-follow up, and any deaths after dihydroartemisinin–piperaquine treatment into a standardised database. The risk of sudden unexplained death after dihydroartemisinin–piperaquine with 95% credible intervals (CI) generated by Bayesian meta-analysis was compared with the baseline rate of sudden cardiac death.

Findings Our search identified 94 eligible primary studies including data for 197 867 individuals who had received dihydroartemisinin–piperaquine: 154 505 in mass drug administration programmes; 15 188 in 14 studies of repeated courses in preventive therapies and case management of uncomplicated malaria; and 28 174 as single-course treatments of uncomplicated malaria in 76 case-management studies. There was one potentially drug-related sudden unexplained death: a healthy woman aged 16 in Mozambique who developed heart palpitations several hours after the second dose of dihydroartemisinin–piperaquine and collapsed and died on the way to hospital (no autopsy or ECG was done). The median pooled risk estimate of sudden unexplained death after dihydroartemisinin–piperaquine was 1 in 757 950 (95% CI 1 in 285 449 to 1 in 209 114). This risk estimate was not higher than the baseline rate of sudden cardiac death (0·7–11·9 per 100 000 person-years or 1 in 1714 280 to 1 in 100 835 over a 30-day risk period). The risk of bias was low in most studies and unclear in a few.

Interpretation Dihydroartemisinin–piperaquine was associated with a low risk of sudden unexplained death that was not higher than the baseline rate of sudden cardiac death. Concerns about repolarisation-related cardiotoxicity need not limit its current use for the prevention and treatment of malaria.

Funding Wellcome Trust, UK Medical Research Council, WHO, Bill & Melinda Gates Foundation, and University of Oxford.

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Introduction

Malaria is the most important parasitic infection of human beings. Despite advances in its prevention, control, and elimination in the past 15 years, progress

is now feared to have stalled,¹ and optimal application of available tools is more vital than ever. Antimalarial medicines reduce malaria-related morbidity and mortality, and are the cornerstone of malaria control and

Lancet Infect Dis 2018

Published Online

June 7, 2018

[http://dx.doi.org/10.1016/S1473-3099\(18\)30297-4](http://dx.doi.org/10.1016/S1473-3099(18)30297-4)

See Online/Comment

[http://dx.doi.org/10.1016/S1473-3099\(18\)30360-8](http://dx.doi.org/10.1016/S1473-3099(18)30360-8)

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Research in context

Evidence before this study

Dihydroartemisinin–piperaquine is an effective and well tolerated artemisinin-based combination antimalarial therapy. Its 20-day to 30-day terminal elimination half-life provides a long post-treatment prophylactic effect that makes it a candidate for intermittent preventive therapy and mass drug administration. However, piperaquine has been associated with dose-dependent prolongation of cardiac ventricular repolarisation duration and the electrocardiographic (ECG) QT interval, leading to concerns about its potential to cause lethal ventricular tachyarrhythmias.

With little access to ECG monitoring for arrhythmia detection and post-mortem examination for cause-of-death ascertainment in malaria-endemic regions, as well as the rarity of drug-induced ventricular tachyarrhythmias in general, data about the risk of sudden unexplained death potentially associated with drug-induced repolarisation-related tachyarrhythmia after dihydroartemisinin–piperaquine are scarce. We did a systematic review and Bayesian meta-analysis to quantify the risk of sudden unexplained death after dihydroartemisinin–piperaquine compared with the baseline global rate of sudden cardiac death.

We did a systematic search of the scientific literature (last search done on May 24, 2017) using the databases MEDLINE, Embase, Web of Science, CINAHL, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Global Health, WHO Global Health Library, and the WWARN Clinical Trials of Uncomplicated Malaria Publication Library. We searched for articles containing

“dihydroartemisinin–piperaquine” as title, abstract, or subject heading keywords, with synonyms and variant spellings as additional search terms. We excluded animal studies, but did not apply limits on language or publication date. Studies were eligible for inclusion if they were prospective, randomised, controlled trials or cohort studies administering in at least one arm or group a minimum of one full 3-day treatment course of dihydroartemisinin–piperaquine, with or without single low-dose primaquine, for mass drug administration, preventive therapy, or case management of uncomplicated malaria, with active follow-up over at least the first 3 days from drug initiation. Further unpublished or ongoing studies were identified as part of the WHO Evidence Review Group on the Cardiotoxicity of Antimalarials.

Added value of this study

This study is the most comprehensive attempt to synthesise the entirety of clinical evidence pertaining to risk of death after use of dihydroartemisinin–piperaquine to prevent or cure malaria. Dihydroartemisinin–piperaquine was associated with a low risk of sudden unexplained death, which was not higher than the baseline rate of sudden cardiac death.

Implications of all the available evidence

Dihydroartemisinin–piperaquine has a potentially valuable role in malaria control and elimination. It is associated with a low risk of sudden unexplained death, which is not higher than the baseline rate of sudden cardiac death. Concerns about repolarisation-related cardiotoxicity of dihydroartemisinin–piperaquine need not limit its current use for the prevention and treatment of malaria.

elimination. Antimalarials are deployed on a vast scale, with more than 500 million treatments distributed annually,¹ and 2·2 billion courses of artemisinin-based combination therapies (ACTs)—the gold standard oral treatment—delivered between 2005 and 2015.²

In malaria-endemic regions, oral antimalarials are used for the treatment of clinical malaria, for intermittent preventive therapy in high-risk subgroups such as pregnant women and young children, and sometimes in the form of mass drug administration to the entire population in a geographical area either for rapid malaria control or for elimination. All involve administration of full treatment courses of antimalarial medicines.

The ACT dihydroartemisinin–piperaquine is an attractive choice for all these indications. Dihydroartemisinin–piperaquine has proved highly efficacious and safe in the treatment of uncomplicated malaria^{3,4} and in repeated dosing⁵ including in healthy individuals receiving intermittent preventive therapy. Dihydroartemisinin–piperaquine is considered an ideal candidate for mass drug administration because it is well tolerated and has a long post-treatment prophylactic

effect. Piperaquine, a bisquinoline, has a terminal elimination half-life of 20–30 days⁶ and prevents patent reinfection for a month or more. Studies in the Greater Mekong subregion^{7–9} and early evidence from a large-scale pilot programme in Zambia¹⁰ confirm that mass drug administration with dihydroartemisinin–piperaquine has good tolerability and promising benefits in the short term. Before it was combined with dihydroartemisinin in the current ACT formulation, piperaquine was used extensively as monotherapy. 140 million piperaquine treatments were consumed in China for individual and mass treatments between 1978 and 1992 until piperaquine resistance prompted a change in treatment policy.¹¹

No adverse cardiovascular effects have been reported from this extensive early experience but the potential of piperaquine to produce repolarisation-related cardiotoxicity—manifested as prolongation of the electrocardiographic (ECG) QT interval—has received renewed interest. Dose-dependent QT interval prolongation occurred in healthy volunteers in a phase 1 thorough QT¹² assessment of the dihydroartemisinin–piperaquine formulation approved by the European Medicines

Agency (EMA)¹³ in 2011. Since then, dihydroartemisinin–piperaquine has become the most intensively studied antimalarial in relation to repolarisation-related cardiotoxicity. Particular attention has been paid to the effects of the highest plasma piperaquine concentrations, which usually occur 4–6 h after the third and final daily dose of dihydroartemisinin–piperaquine in a 3-day treatment course. Piperaquine has qualitatively similar cardiac effects to other antimalarials in the quinoline class in widespread use, notably chloroquine, amodiaquine, and quinine. These antimalarials were introduced more than 50 years ago, when the potential risks of drug-induced repolarisation-related cardiotoxicity were not known.¹⁴

Prolongation of the QT interval is a sensitive but not specific indicator of increased risk of torsade de pointes, a polymorphic ventricular tachyarrhythmia that, if sustained, can degenerate in some cases into ventricular fibrillation and cause sudden cardiac death. However, the relationship between QT interval prolongation and torsade de pointes is not straightforward. Drugs that cause QT interval prolongation are inconsistently associated with life-threatening tachyarrhythmias¹⁵ and only a small proportion of patients with QT interval prolongation develop these very rare arrhythmic complications. The incidence of drug-induced torsade de pointes and life-threatening ventricular arrhythmias has been reported as between 3.2 and 13 per million person-years in the general population in active surveillance studies done in Europe.^{16–18} There are few comparable data available from tropical areas.

Quantifying the risk of sudden unexplained death resulting from drug-induced repolarisation-related tachyarrhythmia is an important but challenging part of antimalarial cardiotoxicity risk assessment. In malaria-endemic regions, there is little access to electrocardiographic monitoring for arrhythmia detection and post-mortem examination for ascertainment of cause of death. The rarity of this adverse drug reaction necessitates a synthesis of all available clinical evidence. To address this, we assessed the risk of sudden unexplained death in individuals treated with dihydroartemisinin–piperaquine for mass drug administration, preventive therapy, and case management.

Methods

Search strategy and selection criteria

We did a systematic review and meta-analysis of the published evidence. We systematically searched the scientific literature on Sept 20, 2016 (updated on May 24, 2017) for clinical studies of dihydroartemisinin–piperaquine in human beings (appendix). We searched the bibliographic databases MEDLINE, Embase, Web of Science, CINAHL, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Global Health, WHO Global Health Library, and the WWARN Clinical Trials of Uncomplicated Malaria Publication

Library. Further unpublished or ongoing studies were identified as part of the Evidence Review Group on the Cardiotoxicity of Antimalarials convened by WHO.¹⁹ We searched for articles containing “dihydroartemisinin–piperaquine” as title, abstract, or subject heading keywords, with synonyms and variant spellings as additional search terms. We excluded animal studies, but did not apply limits on language or publication date.

Studies were eligible for inclusion if they were prospective randomised controlled trials or cohort studies administering, in at least one arm or group, a minimum of one full 3-day treatment course of dihydroartemisinin–piperaquine, with or without single low-dose primaquine,²⁰ for mass drug administration, preventive therapy, or case management of uncomplicated malaria, with active follow-up over at least the first 3 days from drug initiation when piperaquine concentrations and risk of drug-induced cardiotoxicity are highest. No ages or age groups were excluded from eligibility; however, malaria-endemic regions have young populations with median ages in the teens to early 20s. Secondary analyses of the studies identified from systematic reviews of dihydroartemisinin–piperaquine treatment were also included. Both published and unpublished studies were eligible for inclusion if sufficient information was available for interpretation.

Data extraction

At least two independent reviewers (out of XHSC, LJM, and YNW) screened titles, abstracts, and full texts, and agreed study eligibility. They also extracted information about study and participant characteristics, adverse event surveillance methodologies, dihydroartemisinin–piperaquine exposures, loss to follow-up, and any deaths after dihydroartemisinin–piperaquine treatment for inclusion in a standardised database (appendix). The number of individuals exposed to dihydroartemisinin–piperaquine in each study was obtained from the as-treated (where available) or intention-to-treat populations. In studies with repeated rounds of drug administration, if it was unclear whether the same individuals were included in all rounds of treatment, then the number of individuals was extracted from the first round of dosing only. Data from primary and secondary analyses of studies were checked for consistency. Where required, trial registry records or investigators were consulted for further information. We sought information about individual deaths identified.

Data analysis

Initial results of data extraction were reviewed at the WHO Evidence Review Group meeting on the Cardiotoxicity of Antimalarials in Geneva, Switzerland, Oct 13–14, 2016. The panel was comprised of experts in cardiology or cardiac electrophysiology, pharmacovigilance, clinical pharmacology, and clinical malariology. Authors or investigators of primary and

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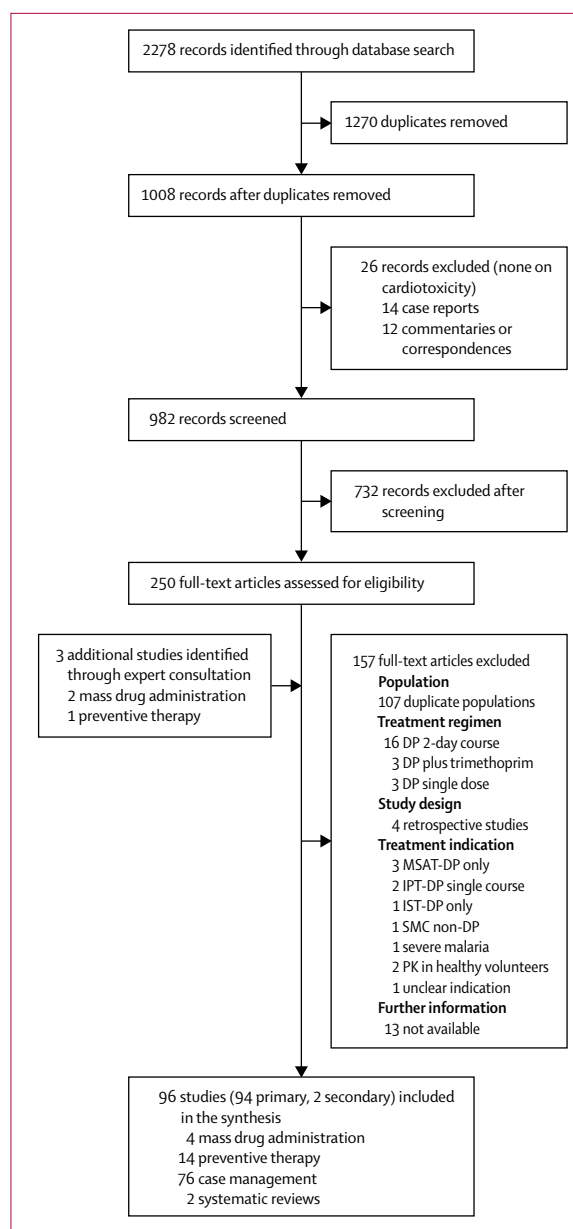


Figure 1: Study selection

DP=dihydroartemisinin-piperaquine. MSAT=mass screen and treat.
IPT=intermittent preventive therapy. IST=intermittent screen and treat.
SMC=seasonal malaria chemoprevention. PK=pharmacokinetic.

secondary analyses contributing more than 2500 individuals to this study attended as participants of the Evidence Review Group or designated appropriate expert representatives.¹⁹

The choice of the number of individuals rather than the number of courses or doses as the main denominator of exposure reflected expert advice that in the absence of acute illness, individual cardiotoxicity risk is unlikely to change substantially during the period of repeated dosing in mass drug administration and preventive

therapies. The 30-day window from initiation of dihydroartemisinin-piperaquine was agreed to be the risk period for drug-induced adverse events, because the terminal elimination half-life of piperaquine is between 20 and 30 days; after this time, the concentration of piperaquine in the blood is low.¹⁹

We selected a Bayesian approach to meta-analysis for its advantages in synthesising diverse types of evidence, such as expert opinion and surveillance data, in a formal, consistent, and coherent process while accounting for uncertainty at different levels. This allows for the generation of more realistic pooled estimates, especially when data are sparse. The use of informative clinical priors, in which existing knowledge is incorporated in the form of prior probability distributions, is an important feature of this approach. Bayesian methods also allow direct probability statements about the parameter being estimated and provide better characterisation of very low event counts in meta-analyses, whereas frequentist methods perform poorly.²¹

On the basis of the numerator agreed at the meeting, the absolute risk of sudden unexplained death after dihydroartemisinin-piperaquine was estimated as follows: each included study was treated as a unit, within which each individual was considered to be an independent trial with success probability equal to the absolute risk of sudden unexplained death after dihydroartemisinin-piperaquine (ie, modelling the likelihood as jointly independent binomial processes). A complete pooling intercept-only model parameterised by the log-odds of the absolute risk was used to generate a posterior probability distribution of the absolute risk of sudden unexplained death after dihydroartemisinin-piperaquine, and this was used to generate 95% credible intervals. We used a weakly informative prior with a normal distribution, confined to the probability scale using an inverse logit link function, centred on the estimated risk of drug-induced torsade de pointes of non-cardiovascular drugs with QT-prolonging potential provided from expert opinion (1 in 1000 000 exposures).¹⁵ For comparison, 95% CIs using frequentist methods were also calculated (appendix).

In recognition of the young populations of malaria-endemic regions, and that most individuals who have received dihydroartemisinin-piperaquine in clinical studies did so as part of mass drug administration programmes with participant age structures similar to that of the general population, the posterior probability distribution of the risk of sudden unexplained death after dihydroartemisinin-piperaquine and its 95% credible interval were compared with reported global surveillance rates of sudden cardiac death in the population aged younger than 35 years (0.7–11.9 per 100 000 person-years scaled to 30-day risks; appendix p 3).^{22–24} Risk of bias of individual studies at the outcome level was assessed using the PROTECT checklist for systematic reviews of drug adverse events.²⁵

Publication bias was minimised through inclusion of data from large unpublished studies, as well as the incorporation of estimates from the non-malaria literature as clinical priors as part of the Bayesian meta-analysis. All statistical analyses and data visualisation were done with R (version 3.4.3),²⁶ with the meta-analysis done using the RStanArm²⁷ package (version 2.13.1) for Bayesian applied regression modelling.

Role of the funding source

The WHO Global Malaria Programme coordinated the WHO Evidence Review Group on the Cardiotoxicity of Antimalarials and related meetings. All funders otherwise had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our search identified 94 eligible primary studies including data for 197 867 individuals who had received 501 156 courses of dihydroartemisinin–piperaquine (figure 1). 154 505 individuals received dihydroartemisinin–piperaquine in four mass drug administration programmes, 15 188 in 14 studies of repeated courses in preventive therapies and case management of uncomplicated malaria, and 28 174 as single courses in 76 case management studies.

14 case reports and 12 correspondences or editorial articles were excluded, but none of these were related to cardiotoxicity. 13 full-text records were excluded because further information was not available; these were conference abstracts from 2012 onwards of recently completed or ongoing studies for which corresponding journal articles could not be found and finalised results were not yet available from the investigators.

All primary studies included in the systematic reviews of dihydroartemisinin–piperaquine for case management of uncomplicated falciparum malaria⁴ and repeated dosing for prevention and treatment of malaria⁵ were included in the synthesis (table 1). 68 (72%) of the 94 studies were individually randomised or cluster-randomised controlled trials. 59 (63%) were published after EMA approval for Eurartesim in 2011. Almost all studies were done in Africa, southeast Asia, or the western Pacific region (table 1). 88 (99%) of 89 studies for which data on age were available, comprising 196 138 (99%) of all 197 867 individuals who received dihydroartemisinin–piperaquine, had a participant mean or median age of 35 years or younger.

A tenth of studies focused on pregnant women in their second and third trimesters (table 1). These were four studies of dihydroartemisinin–piperaquine for intermittent preventive therapy in pregnancy^{28–30} and five studies on malaria in pregnancy.^{31–35} The four mass drug

administration programmes all excluded women in the first trimester of pregnancy at enrolment.

Only 12 of the 94 studies specifically excluded risk factors for torsade de pointes.^{36–45} Almost all studies had directly observed therapy of dihydroartemisinin–piperaquine for at least the first dose of each treatment course (table 1).

Apart from one large, mass drug administration programme involving 103 963 individuals⁴⁰ and one cohort

	Studies	Exposed individuals	Deaths	Deaths within 30 days
Total number	94	197 867	61	31
Indication for study				
Mass drug administration	4	154 505	30	11
Preventive therapies and repeated treatment	14	15 188	16	6
Seasonal malaria chemoprevention	7	12 367	11	5
Intermittent preventive treatment in pregnancy	4	1491	0	0
Repeated treatment	2	562	4	1
Occupational prophylaxis	1	768	1	0
Case management	76	28 174	15	14
<i>Plasmodium falciparum</i> mono-infection	57	25 217	13	12
<i>P falciparum</i> mixed infection	9	1864	2	2
<i>Plasmodium vivax</i> mono-infection	9	1063	0	0
Other (<i>P falciparum</i> , <i>P vivax</i> , <i>Plasmodium ovale</i> , or <i>Plasmodium malariae</i>)	1	30	0	0
Year of publication				
2004–11	35	9490	11	7
2012–17	59	188 377	50	24
WHO region				
Africa	42	173 583	26	16
Southeast Asia	26	9162	6	6
Eastern Mediterranean	3	455	0	0
Western Pacific	19	3281	1	0
Americas	1	252	0	0
Southeast Asia and Western Pacific	2	10 554	28	9
Africa, Southeast Asia and Western Pacific	1	580	0	0
Study type				
Randomised controlled trial	68	141 890	53	23
Cohort	26	55 977	8	8
Mean or median age group (years)				
0 to ≤5	21	6971	15	8
>5 to ≤15	14	23 505	10	8
>15 to ≤35	53	165 662	35	15
>35	2	915	1	0
Not reported	4	814	0	0
Pregnant patients included				
Yes: study of pregnant women in second and third trimesters of pregnancy	9	2840	0	0
Yes: study of general population excluding women in first trimester of pregnancy	4	154 505	30	11
No	81	40 522	31	20
Torsade de pointes risk factors excluded				
Yes	12	22 547	9	8
No	82	175 320	52	23

(Table 1 continues on next page)

	Studies	Exposed individuals	Deaths	Deaths within 30 days
(Continued from previous page)				
Directly observed therapy				
Yes: at least the first dose of medication per treatment course	89	197 397	59	29
Yes: all doses of medication per treatment course	79	80 519	48	20
No: drug intake documented by parents	2	145	2	2
Not reported	3	325	0	0
Duration of follow-up (days)				
3	2	104 371	1	1
28	14	12 537	7	7
42	39	9332	4	3
56	6	41 322	1	1
63	12	3712	3	3
84	1	217	0	0
85–181	8	4399	8	4
182–365	8	11 893	4	1
>365	4	10 084	33	11
Brand of dihydroartemisinin–piperaquine				
Duo-cotecxin	64	24 055	22	10
Eurartesim	19	162 552	11	11
D-ARTEPP	2	602	0	0
Arterakine	1	164	0	0
Mixture (Eurartesim, D-ARTEPP, or Arterakine)	1	9785	28	9
Not reported	7	709	0	0
Used in combination with primaquine				
Yes: single-dose gametocytocide in mass drug administration	2	13 097	25	6
Yes: single-dose gametocytocide in case management of uncomplicated <i>P. falciparum</i> infection	6	1015	1	1
Yes: radical cure in <i>P. vivax</i> infection	6	487	0	0
No: primaquine use not documented	80	183 268	35	24
Studies examined individuals exposed to dihydroartemisinin–piperaquine and all-cause mortality after dihydroartemisinin–piperaquine administration.				
Table 1: Characteristics of included studies				

study of malaria in pregnancy³⁵ with active follow-up over 3 days, all 92 other studies, which enrolled 93 496 (47%) of 197 867 individuals who received dihydroartemisinin–piperaquine, had follow-up for at least 28 days, covering the duration of one terminal elimination half-life of piperaquine (figure 2).

Information about food intake was available from only three studies, in which a small amount of fat (6.4 mg or 8.5 mg) was co-administered with dihydroartemisinin–piperaquine in at least one study arm; this was reported in all three studies to not affect piperaquine exposure. These were two studies of dihydroartemisinin–piperaquine in case management of uncomplicated falciparum malaria,^{46,47} and one study of dihydro-artemisinin–piperaquine for occupational prophylaxis.⁴⁸ Although 64 (68%) of the 94 studies used Duo-cotecxin, Eurartesim was administered to 167 384 (85%) of 197 867 individuals

who were part of 20 studies (including the study that used a mixture of brands). Other studies for which information about brand of dihydroartemisinin–piperaquine was available used D-ARTEPP and Arterakine. All four of these formulations contain either 320 mg or 160 mg of piperaquine phosphate per tablet. Dihydroartemisinin–piperaquine was used in combination with primaquine in 14 studies: for case management of uncomplicated falciparum malaria in southeast Asia^{38,42,49–52} and as radical cure for vivax malaria.^{39,41,43,53–55}

31 deaths occurred within 30 days of dihydro-artemisinin–piperaquine administration, and a further 30 deaths occurred beyond one terminal elimination half-life of piperaquine (figure 2). Information on the number of deaths and all dihydroartemisinin–piperaquine exposures are in table 2. Only one of these deaths was thought to be consistent with sudden cardiac death and considered possibly causally related to drug exposure by experts at the WHO Evidence Review Group. This was the sudden death of an otherwise healthy 16-year-old female in Mozambique with no past medical or other medication history, who collapsed and died on the way to hospital after stating that she had heart palpitations several hours after the second dose of her first course of dihydroartemisinin–piperaquine in mass drug administration. According to her stepmother, the girl had self-administered her second dose about 20 min after eating rice, cooked salad, and bread. Both her malaria rapid diagnostic test and pregnancy test done at enrolment the day before were negative. No autopsy or ECG was done for this individual.¹⁹

All other deaths had alternative explanations (figure 3). In keeping with the main causes of death in low-income and middle-income countries, communicable diseases including malaria, sepsis, pneumonia, and diarrhoea accounted for most of the deaths overall, as well as for most of the deaths in children aged 0–5 years and 5–15 years. 13 (87%) of 15 deaths in the case management group were attributed to infections. Trauma or accidents were the next most frequent causes of death and were the dominant causes of death in young adults aged 15–35 years. Unexplained drownings and sudden deaths of drivers of vehicles could result from arrhythmias. Three deaths resulted from road traffic accidents: in two cases the individuals were passengers or pedestrians; the third death occurred 459 days after treatment, long after the terminal elimination half-life of piperaquine. Similarly, four of the five drownings occurred towards the end or beyond one termination elimination half-life of piperaquine. The one case of drowning within 1 week of dihydroartemisinin–piperaquine administration was of a 32-year-old man with both a personal and family history of poorly controlled epilepsy, who drowned while washing in a river after the first dose of his second course of dihydroartemisinin–piperaquine with primaquine in mass drug administration. He had not received the

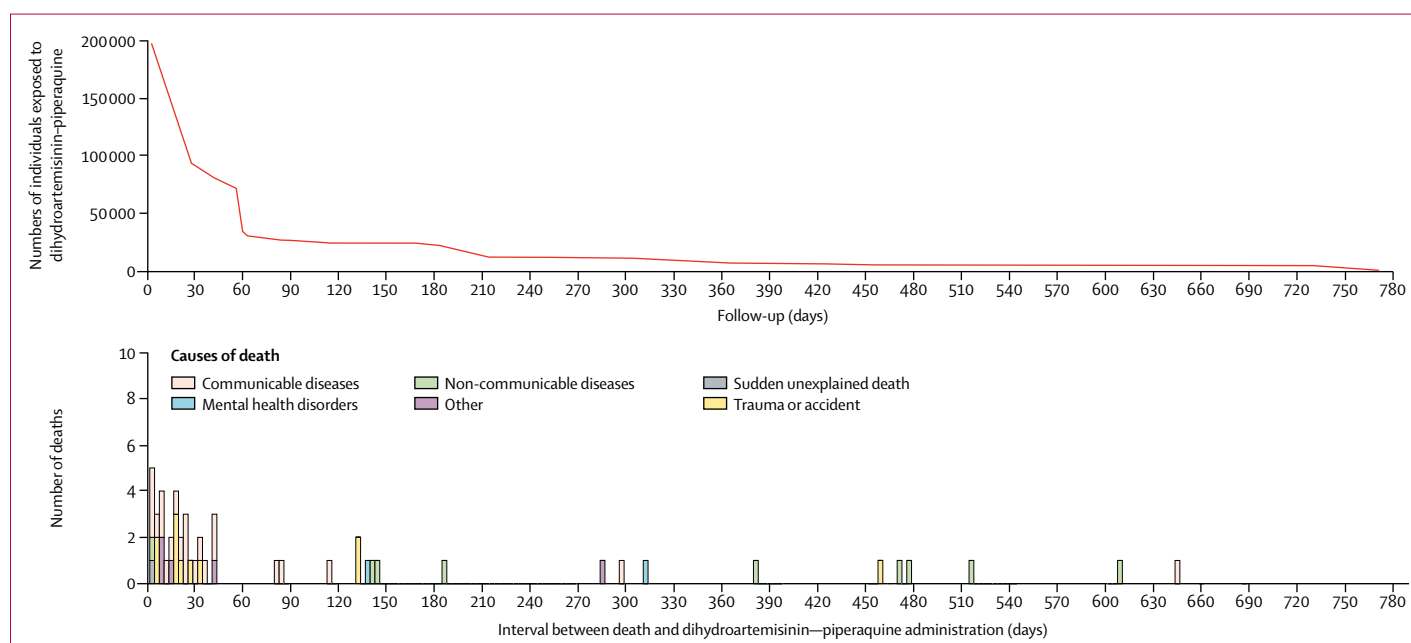


Figure 2: Number of individuals exposed to, and deaths after, dihydroartemisinin-piperaquine

	Individuals	Courses	Doses	Deaths	Deaths within 30 days	Sudden unexplained deaths
Mass drug administration	154 505	432 001*	1 189 029	30	11	1
Preventive therapies and case management repeated courses	15 188	40 981*	122 943*	16	6	0
Case management single courses	28 174	28 174*	84 522*	15	14	0
Total	197 867	501 156	1 396 494	61	31	1

*Derived from another denominator.

Table 2: Exposures to, and deaths after, dihydroartemisinin-piperaquine

full course of dihydroartemisinin-piperaquine because his wife had witnessed him drinking a large quantity of alcohol. His death was considered unrelated to dihydroartemisinin-piperaquine. Non-communicable diseases were the most common causes of death occurring more than 30 days after dihydroartemisinin-piperaquine administration in adults older than 35 years.

There were no deaths after dihydroartemisinin-piperaquine among the 2840 women who received it as part of studies of the antimalarial in pregnancy, nor among the 1063 individuals who were treated with dihydroartemisinin-piperaquine and primaquine for *Plasmodium vivax* mono-infections. Other than the death identified by the Evidence Review Group as possibly causally related to dihydroartemisinin-piperaquine, the only other death reported by investigators as being probably causally related to the drug was of a 2-year-old boy who choked on his first dose of dihydroartemisinin-piperaquine in mass drug administration and whose cause of death was confirmed by autopsy. His death was attributed directly to upper airway obstruction, and not to

cardiac causes. In keeping with death being a well defined outcome with established reporting mechanisms⁵⁶ occurring at a low rate, the risk of bias was low in most studies and unclear in a small minority (appendix).

All 94 primary studies were included in the meta-analysis of the risk of sudden unexplained death after dihydroartemisinin-piperaquine (appendix). The mass of the posterior probability distribution function of the risk of sudden unexplained death after dihydro-artemisinin-piperaquine was concentrated very close to 0 with a median pooled risk estimate of 1 in 757950 (95% credible interval 1 in 2854490 to 1 in 209114). Because almost all of the posterior probability distribution of the risk of sudden unexplained death after dihydroartemisinin-piperaquine lay within or below the reference range of baseline 30-day risk of sudden cardiac death in the young (0.7–11.9 per 100 000 person-years or 1 in 1714280 to 1 in 100835), the estimated risk of sudden unexplained death after dihydroartemisinin-piperaquine was no higher than the baseline rate of sudden cardiac death (appendix). Frequentist 95% CIs were unsatisfactory with negative

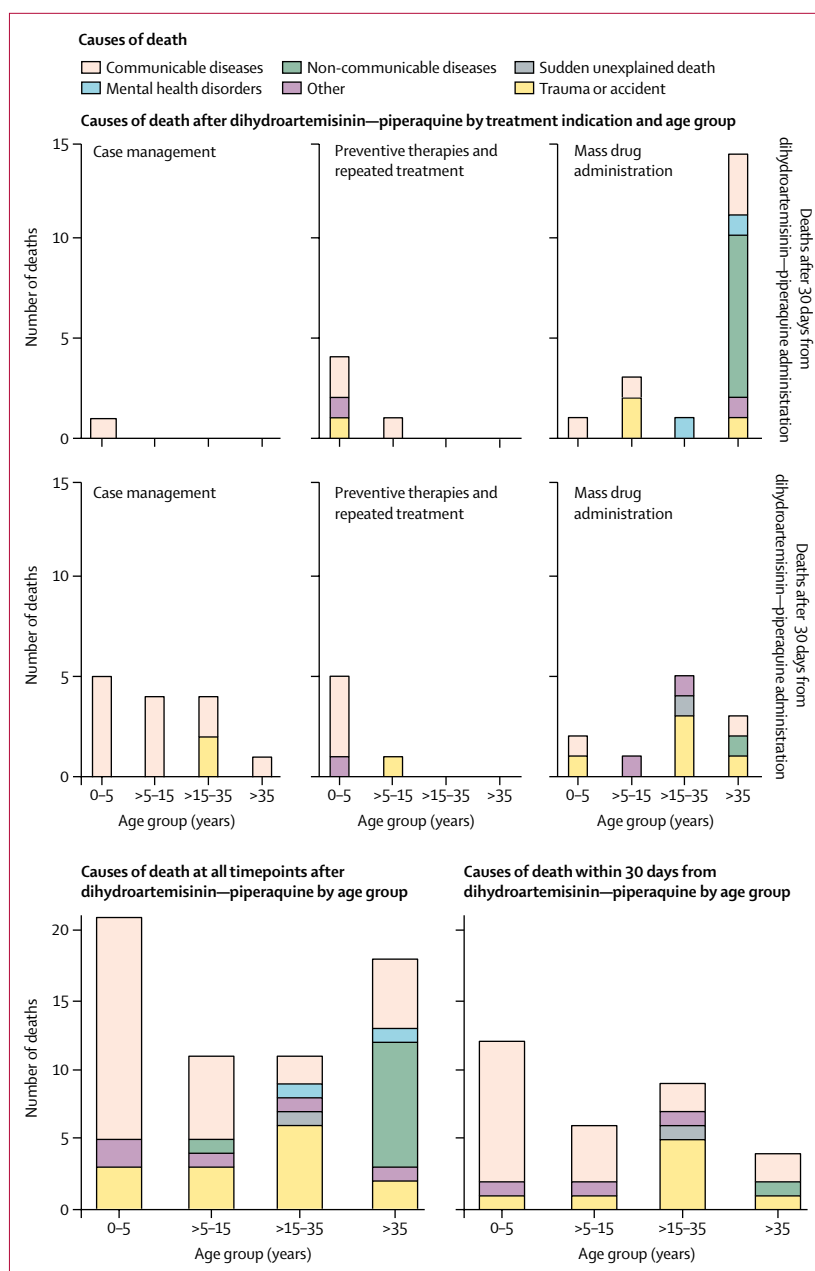


Figure 3: Causes of death after dihydroartemisinin-piperazine
Data presented by age group and treatment indication.

lower bounds (appendix). Further sensitivity analyses are in the appendix.

Discussion

This study is the most comprehensive attempt to consider the entirety of clinical evidence pertaining to risk of death after use of dihydroartemisinin-piperazine in the standard 3-day treatment course to prevent or cure malaria. Our analysis included clinical studies for which there was confirmed follow-up over the 3 days from drug initiation—ie, the window spanning the highest risk of

drug-induced repolarisation-related cardiotoxicity when piperazine concentrations are at their peak. It added to previous reviews of case management⁴ and preventive therapy⁵ with dihydroartemisinin-piperazine by including data from cohort studies and large pilot programmes of mass drug administration as well as incorporating risk estimates of drug-induced repolarisation-related cardiotoxicity from surveillance studies and experience with other non-cardiovascular drugs with QT-prolonging potential. However, a meaningful comparison with other antimalarial drugs was not possible because of the low quality of safety data reported in mass drug administration studies of other antimalarials,⁵⁷ which reflected passive reporting from routine pharmacovigilance systems. Without national or international prescription databases in malaria-endemic regions, it might be difficult to obtain more robust estimates.

This study showed that sudden unexplained death potentially caused by repolarisation-related tachyarrhythmia after treatment with dihydroartemisinin-piperazine is very rare. Only one possible sudden cardiac death associated with dihydroartemisinin-piperazine was reported among nearly 200 000 individuals with directly observed treatment and close follow-up, despite 87% of studies—including all four mass drug administration programmes—comprising 89% of individuals, not specifically excluding torsade de pointes risk factors. Synthesising these findings with previous information from expert advice through Bayesian meta-analysis suggested this risk is even lower. Additionally, since our search was concluded, dihydroartemisinin-piperazine has been reported to have been administered safely to 40 611 children as seasonal malaria chemoprevention in a refugee camp with reinforced surveillance in Uganda.⁵⁸

Although sudden cardiac death might be precipitated by torsade de pointes, life-threatening tachyarrhythmia leading to sudden cardiac death is the final common pathway of a wide range of cardiac conditions. Furthermore, sudden unexplained death can result from non-cardiac causes. These are all generally impossible to exclude with certainty, particularly in tropical settings where resources for post-mortem examinations and genetic testing are scarce. For this meta-analysis, nearly all the included studies had a participant mean or median age of 35 years or younger. Although information from tropical areas is scarce, the overall incidence rate of sudden cardiac death (ie, sudden death from any cardiac cause) is estimated to be less than 1 to 11.9 per 100 000 person-years in the population younger than 35 years.^{22–24} The incidence of sudden cardiac death in young people is one to two orders of magnitude lower than that in older adults²² and in infants younger than 1 year (which is around 96 per 100 000 person-years when deaths attributed to the sudden infant death syndrome are included).⁵⁹ There is insufficient clinical or statistical evidence to suggest

that this one case of sudden unexplained death represented a higher-than-expected rate of sudden cardiac death in our study population.

The main limitation of our study was the potential for under-reporting of deaths such as those undetected after loss to follow-up. However, our figures are unlikely to be a substantial underestimate because the data were from well conducted studies and deaths are serious adverse events that study investigators are obligated to report under Good Clinical Practice guidelines.⁵⁶ Furthermore, sudden deaths are notable events in the communities within which these studies were done, and have the potential to undermine confidence in the malaria treatment programme if they do occur. There was no evidence of such concerns, particularly from the four large-scale mass drug administration programmes. A previous meta-analysis⁵ also showed that repeated dosing of dihydroartemisinin–piperaquine was not associated with an increased risk of loss to follow-up relative to comparator antimalarials.

No further sudden unexplained deaths, sudden cardiac deaths, or cases of torsade de pointes were identified from searches of the WHO and drug manufacturer pharmacovigilance databases despite distribution of millions of doses of dihydroartemisinin–piperaquine⁵⁹ (at least 2·8 million doses of Eurartesim and 5·4 million doses of generic formulations). In view of the substantial attention given to this potential adverse drug reaction since the drug was registered, the absence of further deaths potentially attributable to cardiotoxicity despite widespread use is reassuring for prescribers and malaria-control programmes. This safety record contrasts starkly with the history of the structurally related antimalarial halofantrine, which has been associated with more than 30 sudden cardiac deaths and documented cases of torsade de pointes with progression to life-threatening ventricular tachyarrhythmias.^{19,60}

In view of the low rate of sudden unexplained deaths, it was not possible to determine from this study whether there was a difference in the risk of repolarisation-related cardiotoxicity between patients with uncomplicated malaria and healthy individuals in mass drug administration programmes or intermittent preventive therapy. Nor was there sufficient information to assess this risk in vulnerable subgroups such as pregnant women and infants, or to assess any differential risk after co-administration of dihydroartemisinin–piperaquine with fat. A large amount of coadministered fat has been found to increase piperazine concentrations significantly,^{61,62} whereas a small amount of fat in normal meals does not.^{46–48} Our study did not suggest there should be any change to recommendations to avoid high-fat meals with dihydroartemisinin–piperaquine to minimise the risk of repolarisation-related cardiotoxicity.⁶³

Dihydroartemisinin–piperaquine in a 3-day treatment course was associated with a low risk of sudden unexplained death, which was not higher than the baseline rate for

sudden cardiac death in the population aged younger than 35 years. Although monitoring for adverse drug effects should continue to be strengthened, such as through health and demographic surveillance system record linkage, cohort event monitoring, and targeted spontaneous reporting,⁶⁴ concerns about repolarisation-related cardiac safety need not limit use of dihydroartemisinin–piperaquine for the prevention and treatment of malaria.

Contributions

XHSC was the technical resource person and rapporteur and NJW and JB were co-chairs of the WHO Evidence Review Group of the Cardiotoxicity of Antimalarials. XHSC and NJW designed this study with input from all coauthors. XHSC, LJM, and YNW undertook the systematic review. XHSC, JYT, YNW did the analyses. XHSC wrote the first draft of the article. All authors reviewed all versions of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

This work was supported by the Wellcome Trust [106698/Z/14/Z], the Medical Research Council of the United Kingdom [MR/N013468/1], the World Health Organization Global Malaria Programme, the Bill & Melinda Gates Foundation [OPP1132628], and the Jill and Herbert Hunt Travelling Scholarship of the University of Oxford. We are grateful to all investigators and participants of the studies included in this analysis and Nia Roberts of the Bodleian Libraries (University of Oxford, UK) for assistance with the literature search. We thank Rukhsana Ahmed, Pedro Aide, Elizabeth Ashley, Matthew Coldiron, Arjen Dondorp, Grant Dorsey, James Heaton, Feiko ter Kuile, Mayfong Mayxay, John Miller, Nguyen Thuy-Nhien, Francois Nosten, Thomas Peto, Koukeo Phommason, Ric Price, Francisco Saute, Lorenz von Seidlein, Frank Smithuis, Sarah Staedke, Rick Steketee, Joel Tarning, Si Thura, Tran Tinh Hien, Rupam Tripura, Kyaw Myo Tun, and Charles Woodrow for additional information. We are also grateful to Karen Barnes, Albertino Damesceno, Milou-Daniel Drici, Nilima Kshirsagar, Eugène van Puijenbroek, and Kevin Marsh for illuminating discussions, and Nicholas Day for his support.

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