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Supplementary webappendix

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SUPPLEMENTARY APPENDIX

Risk of Sudden Unexplained Death after Use of Dihydroartemisinin-Piperaquine for Malaria: A Systematic Review and Bayesian Meta-analysis

Xin Hui S Chan, Yan Naung Win, Laura J Mawer, Jireh Y Tan, Josep Brugada & Nicholas J White

Search Strategy

An electronic literature search was conducted of the following clinical bibliographic databases for journal articles and conference abstracts: MEDLINE, EMBASE, Web of Science, CINAHL, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstract of Reviews of Effects, Global Health, the WHO Global Health Library, and the WWARN Clinical Trials of Uncomplicated Malaria Publication Library. We searched for "dihydroartemisinin-piperaquine" as title, abstract, and subject heading keywords, using synonyms and variant spellings as additional search terms. We excluded animal studies, but did not apply language or publication date limits. All references were imported into EndNote, de-deduplicated, and screened against eligibility criteria.

E.g. Medline search on 24 May 2017

# ▲	Searches
1	((dihydroartemisinin adj2 piperaquine) or dihydroartemisinin?piperaquine or dhappq or dha-ppq).mp.
2	((Artekin or Eurartesim or Diphos or Timequin or Duocotecxin or Malacur) and (malaria* or antimalaria* or anti-malaria* or plasmodium*)).mp.
3	1 or 2
4	exp animals/ not humans.sh.
5	3 not 4

Data Extraction

Additional Methods

The following information was extracted from study reports and trial database records, and where necessary, requested from study investigators:

1) Study and participant characteristics: study year of publication, study location, study design, treatment indication, inclusion and exclusion criteria, participant mean or median age with standard deviation or interquartile range
2) Drug dosing: regimen including dosing tables and DHA-PPQ brand name, frequency of courses if repeated, directly observed therapy/adherence checks
3) Pharmacovigilance: adverse event monitoring system, any other follow-up, number lost to follow-up after DHA-PPQ and comparators (if any) with reasons
4) Exposures: number of individuals treated with DHA-PPQ and comparators (if any), number of courses of DHA-PPQ administered with adherence figures if available
5) Adverse events: deaths after DHA-PPQ and comparators (if any), any other cardiac

If a death was identified, the following information about the deceased subject was sought from investigators:

1) Demographics: age and gender
2) Medical history: syncope or non-fatal cardiac arrest, other comorbidities, comedications
3) Family history: syncope, sudden cardiac death
4) Drug dosing: dose round, dose number, dose date, dose time
5) Death: death date, death time, autopsy report
6) Further investigator input: assessment of relatedness to drug, serious adverse event report

Additional Results

Further information about deaths from publications, trial documentation, and investigator contact is summarised in Table S1.

Table S1: Additional Characteristics of Deaths Identified after Dihydroartemisinin-Piperaquine

Characteristics of All Deaths	**Deaths at any Timepoint (out of 61)**	**Deaths within 30 Days (out of 31)**
Age	60	30
Gender	59	30
Time of death relative to dosing	56	31
Assessment of relationship to DHA-PPQ	50	23
Data Safety Monitoring Board oversight (+ Safety Monitor only)	50 (+ 4)	25 (+ 3)
Characteristics of Specific Deaths only	**Deaths at any Timepoint (out of 61)**	**Deaths within 30 Days (out of 31)**
Comorbidities	9	6
Comedications (including alcohol)	2	2
History of fits, syncope, or cardiac arrest (personal and/or family)	1	1
Source of Additional Information	**Deaths at any Timepoint (out of 61)**	**Deaths within 30 Days (out of 31)**
Investigator contact	60	30
Serious adverse event report	16	8
Autopsy report	1	1

DHA-PPQ = dihydroartemisinin-piperaquine

Characteristics expected to be present for all deaths were well-reported in general. Data Safety Monitoring Board oversight was confirmed in all except six studies of which three had a Safety Monitor. In keeping with the populations of malaria-endemic regions being young with often limited access to healthcare for prior diagnoses, information about comorbidities and comedications preceding study entry was limited.

Data Analysis

Standardisation of Rates of Sudden Cardiac Death and Drug-induced Torsade de Pointes from the Literature

Table S2: Standardisation of Population Rates from the Literature to 30-Day Risks for Analysis

Reference	Type of Estimate	Reported Risk/Rate	Scaled 30-day Risk*
Sarganas 2014[1]	Drug-induced TdP in the general population	3.2 in 1,000,000 person-years	1 in 3,750,000 subjects
Molokhia 2008[2]	Drug-induced TdP in the general population	10.9 in 1,000,000 person-years	1 in 1,100,912 subjects
Darpo 2001[3]	Drug-induced TdP in the general population	13.3 in 1,000,000 person-years	1 in 902,250 subjects
Roden 2016[4]	Drug-induced TdP after non-cardiovascular drugs	1 in 1,000,000 exposures	1 in 1,000,000 subjects
Ackerman 2016[5]	SCD in the young (<35 years) [lower bound of 18 studies from Europe, North America, and East Asia]	7 in 1,000,000 person-years	1 in 1,714,280 subjects
Ackerman 2016[5]	SCD in the young (<35 years) [upper bound of 18 studies from Europe, North America, and East Asia]	101 in 1,000,000 person-years	1 in 118,806 subjects
Bagnall 2016[6]	SCD in the young (<35 years) [Australasia – Australia and New Zealand]	13 in 1,000,000 person-years	1 in 923,071 subjects
Bonny 2017[7]	SCD in the young (<35 years) [Sub-Saharan Africa – Cameroon]	119 in 1,000,000 person-years	1 in 100,835 subjects

TdP = torsade de pointes, SCD = sudden cardiac death. *Incidence rates reported in person-years were scaled to monthly 30-day risks with an actuarial approximation using the following formula: $P_{month} = 1 - [(1 - P_{year})^{(1/12)}]$

Model Details, Results, and Sensitivity Analyses

Modelling the Likelihood

The overall likelihood was modelled as jointly independent binomial processes in view of these characteristics of the data:

1) The outcome of interest being binary, with each individual receiving the drug being an independent trial which resulted in one of two outcomes, either sudden unexplained death (SUD) or no SUD within one terminal elimination half-life of DHA-PPQ
2) The number of individual subjects receiving DHA-PPQ within each study, i.e. the number of trials within each unit of repeated trials, being fixed
3) Each study being conducted independently of all other studies, i.e. independence across units

Of related distributions, such as the Poisson, the binomial distribution was thought to be most appropriate for this dataset in consideration of the above characteristics of the data.

Estimating the Parameter of Interest

A complete pooling intercept-only model, i.e. a fixed-effects model assuming the true risk of SUD after DHA-PPQ was the same in all studies, was used to estimate the risk of SUD after DHA-PPQ. As the regression software we used utilises a sampling algorithm for parameter estimation, the extremely low event count in the data precluded the use of a partial pooling hierarchical generalised linear model with covariate levels.

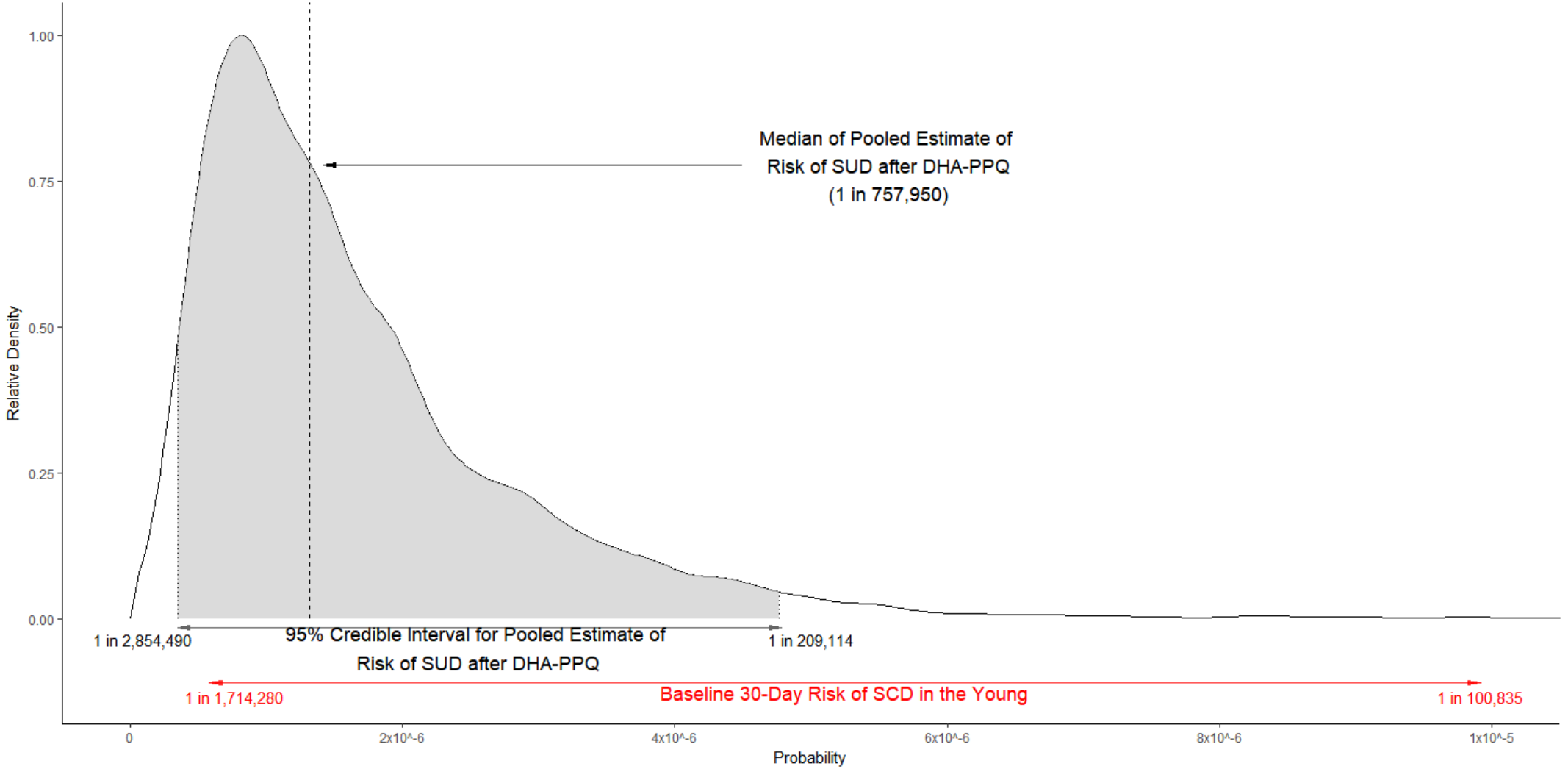
Computation of the Posterior Distribution and Posterior Predictive Check

Posterior distributions were estimated using Markov chain Monte Carlo with a Hamiltonian proposal. Convergence of the Hamiltonian algorithm was done by running four independent chains and computing the Gelman-Rubin statistic which was below the threshold of tolerance (1.01). Visual posterior predictive checks were satisfactory.

Results of the Meta-analysis

The results of the meta-analysis are summarised graphically in Figure S1.

Figure S1: Posterior Probability Distribution of Risk of Sudden Unexplained Death after Dihydroartemisinin-Piperaquine with 95% Credible Interval Compared with Baseline 30-Day Risk of Sudden Cardiac Death in the Young

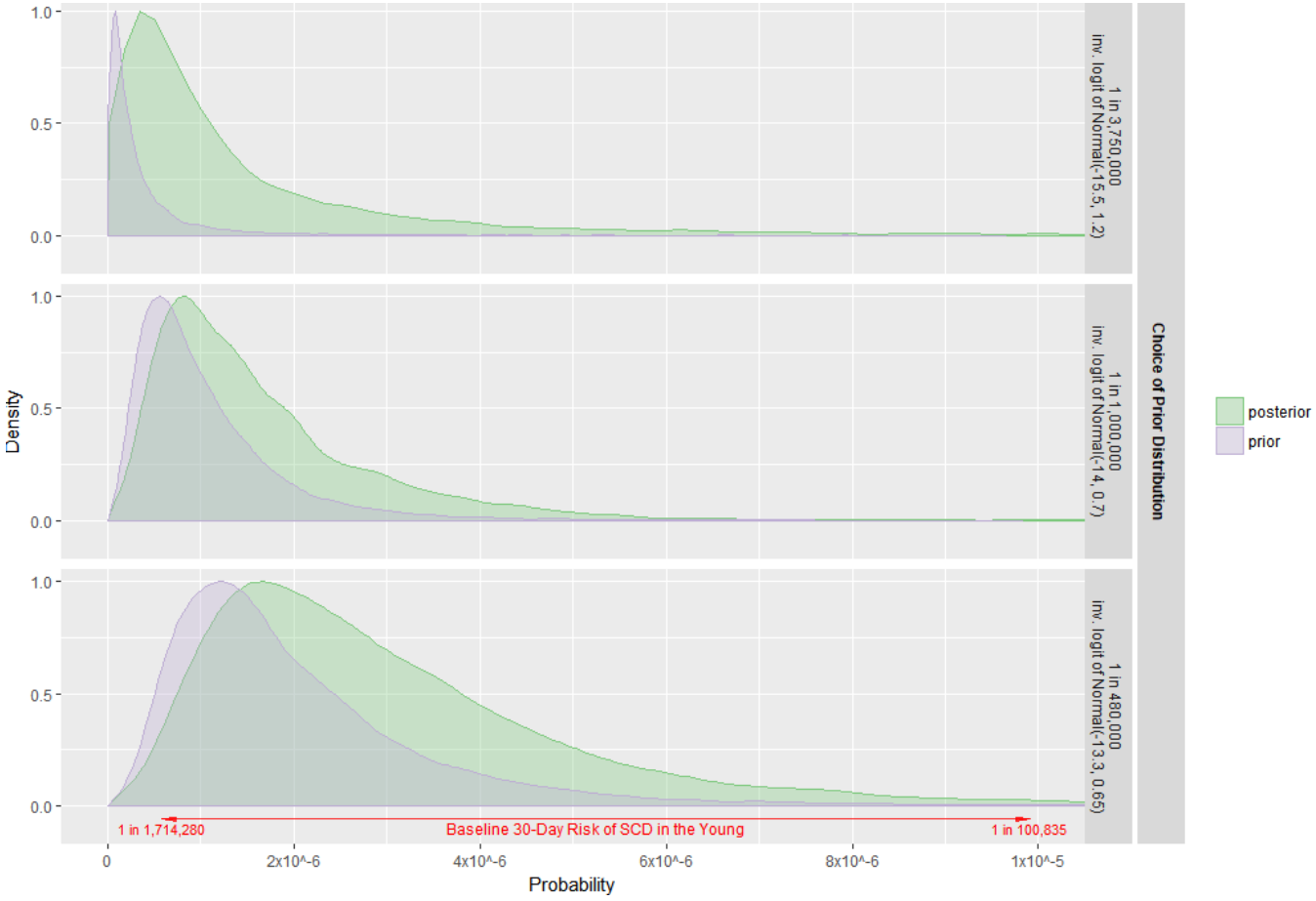


SUD = sudden unexplained death, SCD = sudden cardiac death, DHA-PPQ = dihydroartemisinin-piperaquine. The curve represents the posterior probability distribution function of the true value of the risk of SUD after DHA-PPQ. The probability the true value of the risk of SUD after DHA-PPQ lies between any two values *a* and *b* on the x-axis is the integral from *a* to *b*, i.e. the mass of the distribution.

Sensitivity Analyses – Priors

Sensitivity analyses were conducted using weakly informative alternative priors centred on probabilities about half an order of magnitude higher and lower than the prior used for the main model in keeping with the observed risks of this type of adverse event in the literature[1-4] (also listed in Table S2).

Figure S2: Prior and Posterior Probability Distributions of the Risk of Sudden Unexplained Death after Dihydroartemisinin-Piperaquine under Different Priors



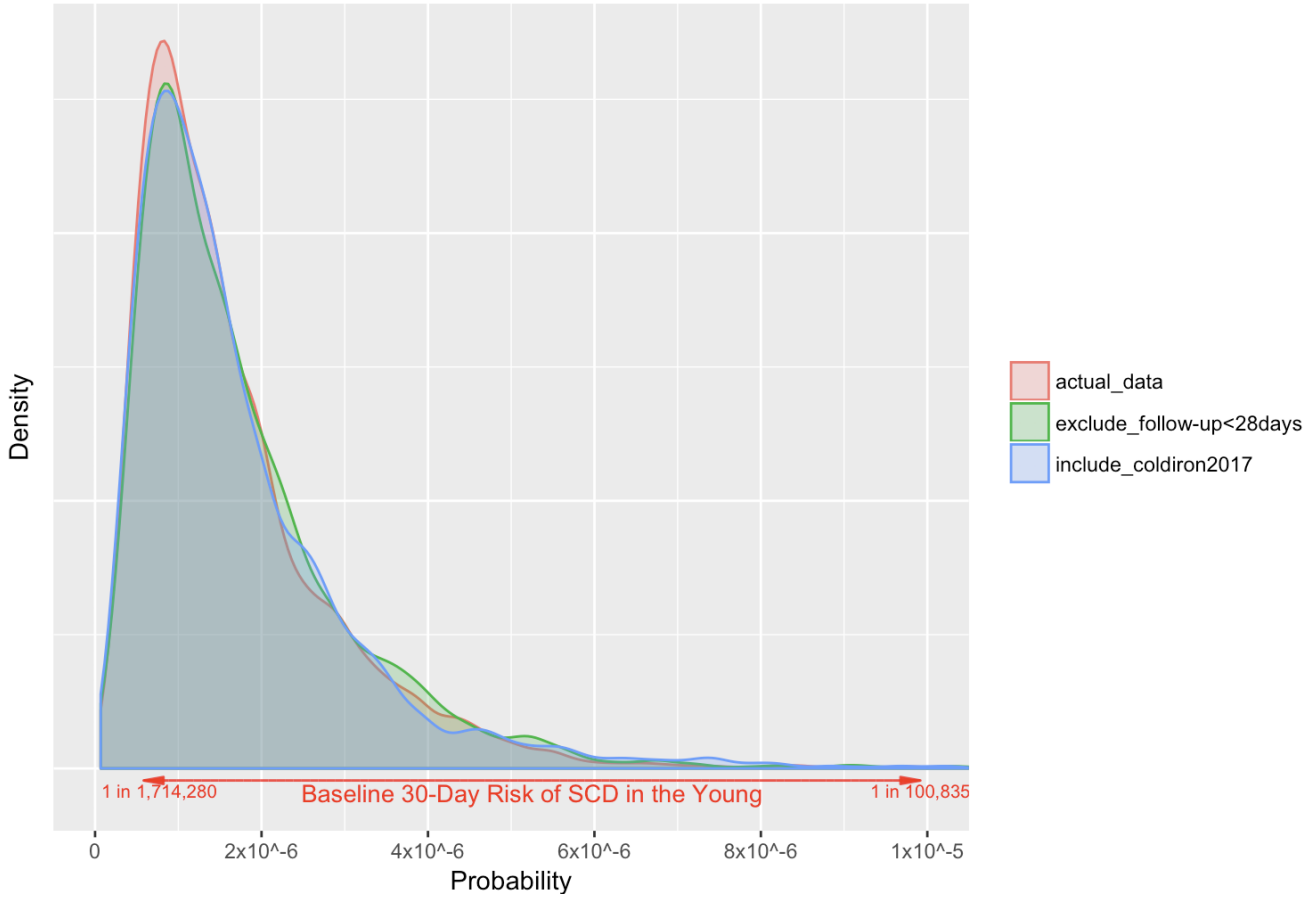
SCD = sudden cardiac death

From Figure S2, we can see that while the posterior probability mass shifted slightly with the use of each different prior, all of the posterior probability masses remained very close to zero and the vast majority of all the posterior probability masses remained within or below the boundaries of the reference range of baseline 30-day risk of SCD in the young. The conclusion that the risk of SUD after DHA-PPQ is extremely low and not higher than the baseline rate of SCD in the young appears to be robust for this range of priors.

Sensitivity Analyses – Quality of Follow-up

We also performed sensitivity analyses to consider the effects of adding or removing studies with different levels of follow-up (Figure S3). We excluded the studies which had <28 days of follow-up: these were two studies with follow-up time of 3 days (n = 104,371). In a separate sensitivity analysis, we added data from a large intermittent preventive therapy study (n = 40,166) published in 2017 by Coldiron and colleagues.[8] We did not include this study in the main meta-analysis according to our inclusion criteria as it had no active surveillance for adverse events. However, the authors state it is unlikely deaths would have been missed as the study was conducted with reinforced passive surveillance in the contained setting of a refugee camp.

Figure S3: Posterior Probability Distributions of the Risk of Sudden Unexplained Death after Dihydroartemisinin-Piperaquine with Addition and Removal of Studies with Different Quality of Follow-up



The posterior probability distributions did not change discernibly with the addition of the Coldiron 2017 study or the exclusion of studies with follow-up of <28 days. The conclusion that the risk of SUD after DHA-PPQ is extremely low and not higher than the baseline rate of SCD in the young appears to be robust to these changes to included studies.

The Frequentist Approach Performs Unsatisfactorily

From the very low baseline risks obtained from Table S2, we would expect frequentist confidence interval estimation to perform poorly with our data.

We used the recommended asymptotic and Agresti-Coull methods for large sample sizes[9] to estimate a 95% confidence interval for the one SUD we found among 197,867 subjects who received DHA-PPQ. With the very low event rate, frequentist 95% confidence interval estimates for the absolute risk of sudden unexplained death indeed exhibited unsatisfactory properties with negative lower bounds (Table S3).

Table S3: Frequentist 95% Confidence Intervals for the Risk of Sudden Unexplained Death after DHA-PPQ

Method	x	n	Mean	Lower bound of 95% CI	Upper bound of 95% CI
Asymptotic	1	197,867	0.000005053900	-0.00000485153680	0.00001495934
Agresti-Coull	1	197,867	0.000005053900	-0.00000216733337	0.00003168891

Since we are estimating a proportion between zero and one, the 95% confidence intervals in Table S4 allocate belief to impossible values, and the coverage of these intervals may be well below 95%. Although some corrections may enforce strictly non-negative confidence intervals, they may not guarantee the appropriate coverage[9], so would be deemed unsatisfactory for use in this case.

Risk of Bias Assessment of Individual Studies

	Study design and objectives	Bias in selection of subjects and constitution of study groups	Bias due to withdrawal or loss to follow up (attrition)	Information bias regarding the drug safety outcome	Other information bias	Statistical methods to control confounding	Statistical methods excluding methods to control confounding	Conflict of interest	SUMMARY RISK OF BIAS
Randomised Controlled Trials									
4ABC 2011[10]									
Adam 2010[11]									
Agarwal 2013[12]									
Annerberg 2011[13]									
Ashley 2004[14]									
Ashley 2005[15]									
Ashley 2014[16]									
Awab 2010[17]									
Awab 2016[18]									
Bassat 2009[19]									
Borrmann 2011[20]									
Dicko 2016[21]									
Grande 2007[22]									
Hasugian 2007[23]									
Hien 2012[24]									
Janssens 2007[25]									
Kamya 2007[26]									

Karema 2006[27]									
Karunajeewa 2008[28]									
Krudsood 2007[29]									
Lon 2014[30]									
Mayxay 2006[31]									
Mens 2008[32]									
Moore 2014[33]									
Nelwan 2015[34]									
Nji 2015[35]									
Ogutu 2014[36]									
Okebe 2016[37]									
Onyamboko 2014[38]									
Pasaribu 2013[39]									
Phyo 2011[40]									
PregACT 2016[41]									
Ratcliff 2007[42]									
Sawa 2013[43]									
Smithuis 2006[44]									
Smithuis 2010[45]									
Sowumni 2016[46]									
Spring 2015[47]									
Sutanto 2013[48]									

Sutanto 2013a[49]									
Sylla 2013[50]									
Tangpukdee 2005[51]									
Thanh 2009[52]									
Thuan 2016[53]									
Tijtra 2012[54]									
Tran 2004[55]									
Ursing 2016[56]									
Valecha 2010[57]									
Wang 2008[58]									
Whegang 2010[59]									
Yavo 2011[60]									
Yeka 2008[61]									
Zongo 2007[62]									
Bigira 2014[63]									
Bojang 2010[64]									
Cisse 2009[65]									
Desai 2015[66]									
Kakuru 2016[67]									
Kamya 2014[68]									
Lwin 2012[69]									
Nankabirwa 2014[70]									

Natureeba 2017[71]									
Wanzira 2014[72]									
Zongo 2015[73]									
START-IPT[74]									
STOPMIP-ID									
MACEPA[75]									
TME									
Cohort									
Adam 2012[76]									
Amaratunga 2016[77]									
Baiden 2015[78]									
Chu 2017[79]									
Irawati 2007[80]									
Kakar 2016[81]									
Kheng 2015[82]									
Leang 2013[83]									
Leang 2015[84]									
Lidia 2015[85]									
Liu 2015[86]									
Mohamed 2017[87]									
Myint 2017[88]									
Plucinski 2015[89]									
Plucinski 2017[90]									

Rijken 2008[91]									
Rijken 2011[92]									
Sow 2016[93]									
Thanh 2017[94]									
Thriemer 2014[95]									
Tun 2016[96]									
Wang 2015[97]									
Zongo 2014[98]									
Poespoprodjo 2014[99]									
MALTEM									
BMEP									
Systematic Reviews & Meta-analyses									
Gutman 2017[100]									
Zani 2014[101]									

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