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Combining individual patient data and aggregate data in mixed treatment comparison meta-analysis: Individual patient data may be beneficial if only for a subset of trials

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Background
Individual patient data (IPD) meta-analysis is the gold standard. Aggregate data (AD) and IPD can be combined using conventional pairwise meta-analysis when IPD cannot be obtained for all relevant studies. We extend the methodology to combine IPD and AD in a mixed treatment comparison (MTC) meta-analysis.
Methods
The proposed random-effects MTC models combine IPD and AD for a dichotomous outcome. We study the benefits of acquiring IPD for a subset of trials when assessing the underlying consistency assumption by including treatment-by-covariate interactions in the model. We describe three different model specifications that make increasingly stronger assumptions regarding the interactions. We illustrate the methodology through application to real data sets to compare drugs for treating malaria by using the outcome unadjusted treatment success at day 28. We compare results from AD alone, IPD alone and all data.
Results
When IPD contributed (i.e. either using IPD alone or combining IPD and AD), the chains converged, and we identified statistically significant regression coefficients for the interactions. Using IPD alone, we were able to compare only three of the six treatments of interest. When models were fitted to AD, the treatment effects and regression coefficients for the interactions were far more imprecise, and the chains did not converge.
Conclusions
The models combining IPD and AD encapsulated all available evidence. When exploring interactions, it can be beneficial to obtain IPD for a subset of trials and to combine IPD with additional AD. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: mixed treatment comparison; multiple treatments meta-analysis; network meta-analysis; similarity; consistency; individual patient data

1. Introduction

Meta-analysis can use individual patient data (IPD), supplied by trial investigators, and/or aggregate data (AD), usually extracted from published trial reports. In brief, IPD are raw data collected in each trial and contribute an outcome and treatment allocation for each patient of each trial, whereas AD include either a statistical summary of patient outcomes for each trial as a whole (e.g. odds ratio and its standard error) or a summary statistic for each treatment group of each trial (e.g. event rates of each trial).

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Acquiring IPD improves the quality of the meta-analysis in a multitude of ways [1, 2]. For instance, a consistent analytic technique can be implemented across trials, thus avoiding problems concerning missing or inconsistently reported results in the trial reports. For conventional pairwise meta-analysis, major benefits have been established regarding the exploration of interactions by using IPD rather than AD [3–7]. A patient-specific covariate (e.g. age) is available for each patient when using IPD, whereas a trial-specific covariate (e.g. average age) is obtainable for each trial when AD are collected. When using study-level summaries of patient-level covariates, a large number of trials are required to detect interactions, and ecological bias could be introduced [3–7]. Using IPD is the more powerful option when patients within the same trial differ with respect to their covariate values, especially when covariate distributions are similar across trials [3].

Although an IPD meta-analysis is the gold standard, patient-level data may be unavailable for some studies [5]. Therefore, occasions arise when IPD are accessible for a subset of trials and AD are available for the remaining trials. Several articles have described approaches to combine IPD and AD in pairwise meta-analysis. A systematic review found that the following methods were applied in published reviews: reducing IPD to AD and then combining the newly reduced AD with the existing AD; analysis of partially reconstructed IPD; combining IPD and AD in a multilevel model; and 'Bayesian hierarchical related regression' [1, 2]. Riley *et al.* [8] and Sutton *et al.* [9] also presented methods to combine IPD and AD by using pairwise meta-analysis while investigating interactions. Such methods are important because they exploit the benefits of IPD while synthesising evidence from all studies.

However, methods to combine IPD and AD in mixed treatment comparison (MTC) meta-analysis have not been described; yet it is likely to be even more of an issue in this setting. When the relative effect of numerous treatments is of interest (e.g. A, B, C and D), a single MTC model can be used to estimate the relative effects for all treatment pairings (e.g. B versus A, C versus A, D versus A, C versus B, D versus B and D versus C) by using a combination of direct evidence and indirect evidence. Such models can be applied when the treatments form a connected network, such that each treatment (e.g. A) has been directly compared with one or more of the other treatments (e.g. B, C and D) in trials [10]. Extension of the methodology to MTCs would be particularly valuable because evidence is synthesised across numerous comparisons and therefore is more likely to have IPD missing for some trials or comparisons.

Furthermore, the inclusion of potential treatment effect-modifying covariates in MTC models is a suitable method to assess the underlying consistency assumption [11–18]. The assumption is satisfied if the so-called consistency equations hold [19–22]. For instance, for a network of three treatments A, B and C, one consistency equation must hold: $d_{BC} = d_{AC} - d_{AB}$, where d_{BC}, d_{AC} and d_{AB} denote the treatment effect of C relative to B, C relative to A, and B relative to A, respectively. In other words, the consistency assumption holds when for each treatment comparison the true treatment effect is similar across all trials. If one, or more, true treatment effect is modified by a particular covariate and the included trials differ with respect to the covariate, the assumption would be invalidated. By including interactions, the existence of treatment effect-modifying covariates can be studied to assess the validity of the assumption.

This article introduces an MTC approach to combine IPD and AD for a dichotomous outcome. In Section 2, we propose the models. In Section 3, we summarise data sets that are used to illustrate the methodology, explain the technicalities of applying the models and provide the results from the applications. In Section 4, we discuss the models.

2. Methods

The approach involves entering IPD from one set of trials and AD from a second set of trials into a single model to allow both data sets to contribute to the estimation of the model parameters. Dias *et al.* [11] describe such models as shared parameter models. In this article, AD are taken to be event rates (i.e. the number of patients with the event and the total number patients in each treatment group of each trial) and a trial-level summary of the covariates of patients. IPD consist of an outcome, treatment allocation and covariate value for each patient. The model will initially be presented without interactions, then extended to include interactions and to explore within-trial and across-trial interactions.

2.1. Notation

Suppose that there are two sets of trials: IPD are available for the first set of trials, whereas AD are obtained for the second trial set. Denote j to be the trial where $j = 1, \ldots, NS_{\text{IPD}}, \ldots, (NS_{\text{IPD}} + NS_{\text{AD}})$,

where NS_{IPD} is the number of independent IPD trials and NS_{AD} is the number of independent AD trials. Denote k to be the treatment where $k \in \{A, B, C, D\}$ and A is a referent treatment [23]. The notation can be extended to accommodate any number of treatments.

Let d_{XY} denote the treatment effect of treatment Y relative to treatment X. Under an MTC framework, the treatment effects relative to A (e.g. d_{AB}, d_{AC} and d_{AD}) are denoted as basic parameters and are estimated by the model. The remaining treatment effects (e.g. d_{BC}, d_{BD} and d_{CD}) are functional parameters, which are linear combinations of the basic parameters (e.g. $d_{BC} = d_{AC} - d_{AB}$; $d_{BD} = d_{AD} - d_{AB}$; and $d_{CD} = d_{AD} - d_{AC}$) [23].

For IPD trials (i.e. $j = 1, \ldots, NS_{\text{IPD}}$), assume that the outcomes of patients, y_{ijk}, are independent and distributed as $y_{ijk} \sim \text{Bernoulli}(p_{ijk})$, where p_{ijk} is the probability of an event for the ith patient in the jth trial on treatment k. For AD trials (i.e. $j = (NS_{\text{IPD}+1}), \ldots, (NS_{\text{IPD}} + NS_{\text{AD}})$), assume that the number of events on treatment k, r_{jk}, is independent and distributed as $r_{jk} \sim \text{binomial}(p_{jk}, n_{jk})$, where p_{jk} is the probability of an event on treatment k in trial j and n_{jk} is the number of patients on treatment k in trial j.

All models assume random effects; that is, for each treatment comparison, there is no single underlying treatment effect but that different trials are estimating unique treatment effects that are realisations from a normal distribution. Also, the models assume the same between-trial variance for each comparison of k versus b. Lastly, the models assume that each trial compares two treatments b and k, where $b, k \in \{A, B, C, D\}$ and k is after b alphabetically. In this article, $k > b$ indicates that k is after b in the alphabet.

Each model has three parts. Part 1 models IPD for the first trial set, part 2 models AD for the second trial set, and part 3 models trial-specific treatment effects, allowing all trials to contribute to the estimation of the treatment effect and between-trial variance. Sutton *et al.* [16] describe a similar structure for pairwise meta-analysis.

2.2. *Mixed treatment comparison model without interactions (model 1)*

The first part of the model is for IPD trials:

$$\text{logit}(p_{ijk}) = \begin{cases} \mu_{jb} & \text{if } k = b, b \in \{A, B, C\} \\ \mu_{jb} + \delta_{jbk} & \text{if } k > b \end{cases},$$

where $j = (1, \ldots, NS_{\text{IPD}})$, the log odds of an event on treatment b in the jth IPD trial is given by μ_{jb}, and δ_{jbk} represents the log odds ratio of k versus b in the jth trial.

The second part of the model is for AD trials:

$$\text{logit}(p_{jk}) = \begin{cases} \lambda_{jb} & \text{if } k = b, b \in \{A, B, C\} \\ \lambda_{jb} + \delta_{jbk} & \text{if } k > b \end{cases},$$

where $i = ((NS_{\text{IPD}} + 1), \ldots, (NS_{\text{IPD}} + NS_{\text{AD}}))$ and the log odds of an event on treatment b in the jth AD trial is given by λ_{jb}.

The third part of the model is

$$\delta_{jbk} \sim N\left(d_{bk}, \tau^2\right),$$

where $j = (1, \ldots, (NS_{\text{IPD}} + NS_{\text{AD}}))$ and the trial-specific treatment effects, δ_{jbk}, are realisations from a normal distribution with mean d_{bk} and variance τ^2. We estimate the log odds ratio, d_{bk}, and the between-trial variance, τ^2, by using data from all trials. By writing the functional parameters in terms of basic parameters (i.e. setting $d_{bk} = d_{Ak} - d_{Ab}$), $\delta_{jbk} \sim N(d_{bk}, \tau^2)$ is replaced by $\delta_{jbk} \sim N(d_{Ak} - d_{Ab}, \tau^2)$, where $d_{AA} = 0$.

2.3. *Mixed treatment comparison models with treatment-by-covariate interactions*

To include interactions, suppose that β_{XY} is the regression coefficient for the interaction of treatment Y relative to treatment X. The regression coefficients corresponding to the basic parameters (e.g. β_{AB}, β_{AC} and β_{AD}) are estimated by the model and are used to estimate the remaining coefficients (e.g. $\beta_{BC} = \beta_{AC} - \beta_{AB}$; $\beta_{BD} = \beta_{AD} - \beta_{AB}$; and $\beta_{CD} = \beta_{AD} - \beta_{AC}$).

We will describe three different model specifications that make increasingly stronger assumptions regarding the interactions [10]. The first specification assumes that the regression coefficients corresponding to the basic parameters (e.g. β_{AB}, β_{AC} and β_{AD}) are independent, that is, different and

unrelated to each other. The second specification assumes that the regression coefficients are exchangeable with each other, that is, the coefficients are different but related, and the magnitude of the coefficients cannot be predicted. The third specification assumes that the regression coefficients are identical.

In the models, x_{ijk} is a patient-level covariate for the ith patient in the jth trial on treatment k available for patients in IPD trials, and z_j is the mean covariate value for the jth trial. The regression coefficient β_{bk} represents the difference in log odds ratio for k versus b per unit increase in the covariate x_{ijk} or z_j. Both IPD and AD contribute to the estimation of β_{bk}.

2.3.1. Independent treatment-by-covariate interactions (model 2). Assuming independent interaction, the first part of the model is for IPD trials:

$$\text{logit}(p_{ijk}) = \begin{cases} \mu_{jb} + \beta_{0jb}x_{ijk} & \text{if } k = b, b \in \{A, B, C\} \\ \mu_{jb} + \beta_{0jb}x_{ijk} + \delta_{jbk} + \beta_{bk}x_{ijk} & \text{if } k > b \end{cases},$$

where $j = (1, \ldots, NS_{\text{IPD}})$ and β_{0jb} is a trial-specific regression parameter that represents the difference in the log odds of an event on treatment b per unit increase in the covariate x_{ijk}. The functional parameters can be rewritten in terms of the basic parameters (i.e. by setting $\beta_{bk} = \beta_{Ak} - \beta_{Ab}$) as follows:

$$\text{logit}(p_{ijk}) = \begin{cases} \mu_{jb} + \beta_{0jb}x_{ijk} & \text{if } k = b, b \in \{A, B, C\} \\ \mu_{jb} + \beta_{0jb}x_{ijk} + \delta_{jbk} + (\beta_{Ak} - \beta_{Ab})x_{ijk} & \text{if } k > b \end{cases},$$

where $\beta_{AA} = 0$.

The second part of the model is for AD trials:

$$\text{logit}(p_{jk}) = \begin{cases} \lambda_{jb} & \text{if } k = b, b \in \{A, B, C\} \\ \lambda_{jb} + \delta_{jbk} + \beta_{bk}z_j & \text{if } k > b \end{cases}.$$

This part of the model can be rewritten by setting $\beta_{bk} = \beta_{Ak} - \beta_{Ab}$:

$$\text{logit}(p_{jk}) = \begin{cases} \lambda_{jb} & \text{if } k = b, b \in \{A, B, C\} \\ \lambda_{jb} + \delta_{jbk} + (\beta_{Ak} - \beta_{Ab})z_j & \text{if } k > b \end{cases},$$

where $j = ((NS_{\text{IPD}} + 1), \ldots, (NS_{\text{IPD}} + NS_{\text{AD}}))$ and $\beta_{AA} = 0$.

The third part of the model is the same as for the model without interactions (model 1). In models with interactions, d_{bk} represents the mean log odds ratio of k versus b when the covariate values are zero ($x_{ijk} = z_j = 0$).

2.3.2. Exchangeable treatment-by-covariate interactions (model 3). Assuming exchangeable interactions, the model specification is identical to model 2 but with a distribution placed on the regression coefficient $\beta_{Ak} \sim N\left(m_B, \tau_B^2\right)$, where m_B is the mean and τ_B^2 is the variance.

2.3.3. Common treatment-by-covariate interactions (model 4). With common interactions, the first part of the model is for IPD trials:

$$\text{logit}(p_{ijk}) = \begin{cases} \mu_{jb} + \beta_{0jb}x_{ijk} & \text{if } k = b, b \in \{A, B, C\} \\ \mu_{jb} + \beta_{0jb}x_{ijk} + \delta_{jbk} & \text{if } k > b \text{ and } b \neq A \\ \mu_{jb} + \beta_{0jb}x_{ijk} + \delta_{jbk} + \beta x_{ijk} & \text{if } k > b \text{ and } b = A \end{cases},$$

where $j = (1, \ldots, NS_{\text{IPD}})$ and β represents the difference in the log odds ratio per unit increase in the covariate. We include no interaction term for each comparison of k versus b when $b \neq A$ because the common regression coefficient cancels out (i.e. $\beta_{bk} = \beta_{Ak} - \beta_{Ab} = \beta - \beta = 0$); but we include an interaction term for each comparison of k versus A because $\beta_{AA} = 0$ (i.e. $\beta_{bk} = \beta_{Ak} - \beta_{AA} = \beta$) [19].

The second part of the model is for AD trials:

$$\text{logit}(p_{jk}) = \begin{cases} \lambda_{jb} & \text{if } k = b, b \in \{A, B, C\} \\ \lambda_{jb} + \delta_{jbk} & \text{if } k > b \text{ and } b \neq A \\ \lambda_{jb} + \delta_{jbk} + \beta z_j & \text{if } k > b \text{ and } b = A \end{cases},$$

where $j = ((NS_{\text{IPD}} + 1), \ldots, (NS_{\text{IPD}} + NS_{\text{AD}}))$.

The third part of the model is the same as for previous models.

2.4. Exploring within-trial and across-trial treatment-by-covariate interactions by using individual patient data mixed treatment comparison models

Models 2–4 assume that within-trial and across-trial interactions are identical [19]. However, the two types of interactions may not be equivalent. Across-trial interactions are prone to ecological biases and confounding, whereas within-trial interactions are not influenced [9, 24]. Furthermore, the two types of interactions may differ owing to the covariate distributions. If the study-specific covariate values vary across trials but the patient-level covariates within each trial are alike, then across-trial interactions may be detected, whereas no within-trial interactions are found. Conversely, if the covariate values of patients within the same trial differ but study-level summaries of the covariate are similar across trials, then within-trial interactions may be detected, whereas across-trial interactions are not apparent.

It is possible to explore how the across-trial and within-trial interactions compare by fitting models that separate the two types of interaction, as described by Riley *et al.* [9] and Riley and Steyerberg [24]. If the two types of interaction are similar, then inferences can be drawn from models that assume that within-trial and across-trial interactions are identical. However, if the within-trial and across-trial interactions differ, then ecological bias or confounding may be at play, and therefore, the results from such models may be biased because across-trial interactions contribute to the parameter estimates. In such cases, a meta-analyst may base inferences on the within-trial interactions estimated by models that separate the two types of interaction. Here, we develop the MTC models to allow exploration of across-trial and within-trial interactions. The models assume that the within-trial interaction is common across all trials.

2.4.1. Independent treatment-by-covariate interactions (model 5). Suppose that β^w_{bk} represents the difference in the log odds ratio per unit increase in the covariate x_{ij} for k versus b and that β^a_{bk} represents the difference in the log odds ratio per unit increase in the covariate mean z_j for k versus b. Independent interactions can be included by setting $\beta^w_{bk} = \beta^w_{Ak} - \beta^w_{Ab}$ and $\beta^a_{bk} = \beta^a_{Ak} - \beta^a_{Ab}$. The first part of the model is for IPD trials:

$$\text{logit}(p_{ijk}) = \begin{cases} \mu_{jb} + \beta_{0jb} x_{ijk} & \text{if } k = b, b \in \{A, B, C\} \\ \mu_{jb} + \beta_{0jb} x_{ijk} + \delta_{jbk} + \left(\beta^w_{Ak} - \beta^w_{Ab}\right)\left(x_{ijk} - z_j\right) + \left(\beta^a_{Ak} - \beta^a_{Ab}\right) z_j & \text{if } k > b \end{cases},$$

where $j = (1, \ldots, NS_{\text{IPD}})$, $\beta^w_{AA} = 0$ and $\beta^a_{AA} = 0$; z_j is the mean of the patient-level covariate values of the jth IPD trial; and β_{0jb} is a trial-specific regression parameter that represents the difference in the log odds of an event on treatment b per unit increase in the covariate x_{ijk}.

The second part of the model is for AD trials:

$$\text{logit}(p_{jk}) = \begin{cases} \lambda_{jb} & \text{if } k = b, b \in \{A, B, C\} \\ \lambda_{jb} + \delta_{jbk} + \left(\beta^a_{Ak} - \beta^a_{Ab}\right) z_j & \text{if } k > b \end{cases},$$

where $j = ((NS_{\text{IPD}} + 1), \ldots, (NS_{\text{IPD}} + NS_{\text{AD}}))$, $\beta^a_{AA} = 0$, and z_j is the mean covariate value of the jth AD trial.

The third part of the model is as defined for previous models.

2.4.2. Exchangeable treatment-by-covariate interactions (model 6). With exchangeable interactions, the model specification is identical to model 5 but with a distribution placed on the within-trial regression coefficient $\beta^w_{Ak} \sim N\left(m^w_B, \left(\tau^w_B\right)^2\right)$, where m^w_B is the mean and $\left(\tau^w_B\right)^2$ is the variance, and on the across-trial regression coefficient $\beta^a_{Ak} \sim N\left(m^a_B, \left(\tau^a_B\right)^2\right)$, where m^a_B is the mean and $\left(\tau^a_B\right)^2$ is the variance.

2.4.3. Common treatment-by-covariate interactions (model 7). Including common interactions, the first part of the model is for IPD trials:

$$\text{logit}(p_{ijk}) = \begin{cases} \mu_{jb} + \beta_{0jb} x_{ijk} & \text{if } k = b, b \in \{A, B, C\} \\ \mu_{jb} + \beta_{0jb} x_{ijk} + \delta_{jbk} & \text{if } k > b \text{ and } b \neq A \\ \mu_{jb} + \beta_{0jb} x_{ijk} + \delta_{jbk} + \beta^w (x_{ijk} - z_j) + \beta^a z_j & \text{if } k > b \text{ and } b = A \end{cases},$$

where $j = (1, \ldots, NS_{\text{IPD}})$, β^w represents the difference in the log odds ratio per unit increase in the covariate x_{ijk}, and β^a represents the difference in the log odds ratio per unit increase in the covariate mean z_j.

The second part of the model is for AD trials:

$$\text{logit}(p_{jk}) = \begin{cases} \lambda_{jb} & \text{if } k = b, b \in \{A, B, C\} \\ \lambda_{jb} + \delta_{jbk} & \text{if } k > b \text{ and } b \neq A \\ \lambda_{jb} + \delta_{jbk} + \beta^a z_j & \text{if } k > b \text{ and } b = A \end{cases},$$

where $j = ((NS_{\text{IPD}} + 1), \ldots, (NS_{\text{IPD}} + NS_{\text{AD}}))$.

The third part of the model is the same as for the previous models.

2.5. *Models including multi-arm trials*

When a trial compared more than two treatments, for example, A, C and D, the trial-specific treatment effects δ_{jAC}, δ_{jAD} and δ_{jCD} are correlated [9, 24]. The specified models would treat multi-arm trials as two-arm trials with a common treatment b and therefore would not take account of the correlation. The models can be adapted to accommodate the correlation by allowing the trial-specific treatment effects to follow a multivariate normal distribution [11, 14, 15, 19].

3. Application: Artemisinin-based combinations for treating uncomplicated malaria

In this section, we illustrate the models by using IPD from a multicentre trial and AD from similar trials comparing artemisinin-based combination therapies (ACTs) for treating malaria.

3.1. *The data sets*

3.1.1. Aggregate data set (Cochrane review). We extracted AD of randomised controlled trials from a Cochrane review [11, 12, 14, 15, 19, 21, 23, 25–32]. The aim of the review was to compare ACTs with other ACTs and non-ACTs for treating uncomplicated *Plasmodium falciparum* malaria in adults or children. The specific drugs included were dihydroartemisinin plus piperaquine (DHAPQ), artesunate plus mefloquine (AS+MQ), artemether–lumefantrine (AL), amodiaquine plus artesunate (AQ+AS), artesunate plus sulfadoxine–pyrimethamine (AS+SP) and amodiaquine plus sulfadoxine–pyrimethamine (AQ+SP). A primary outcome was unadjusted treatment success at day 28. The review's analyses were stratified by location, because malaria transmission rates and drug resistance vary spatially. In this article, we used AD from trials carried out in Africa.

We consider here the effect of one potential treatment effect-modifying covariate, patient age. The justification is that in endemic areas older patients are more likely to achieve treatment success because they have greater protective immunity. We extracted average age from each trial report [33], that is, mean age when it was reported, otherwise, median age. Age was found to be approximately normally distributed, and therefore, the median is a reasonable approximation of the mean.

In total, 29 African trials measured unadjusted treatment success at day 28 [34–62]. Table I displays the AD (i.e. event rates and covariate information). The trials compared two or more of the following six treatments: AL, AQ+AS, AQ+SP, AS+MQ, AS+SP and DHAPQ (Figure 1). There were 15 possible treatment comparisons, of which 12 comparisons were supported by direct evidence (Figure 1). Supplementary Table 1[‡] displays trial characteristics.

3.1.2. Individual patient data set (4ABC trial). Individual patient data from a randomised trial (4ABC trial) carried out in 11 sites across seven African countries were made available [34–62]. The trial's primary objective was to compare four ACTs for treating uncomplicated *P. falciparum* malaria in children. Each site compared up to three of four ACTs: AQ+AS, DHAPQ, AL or chlorproguanil–dapsone plus artesunate (CD+A) (Table II). A primary outcome was unadjusted treatment success at day 28. The randomisation sequence was stratified by site. The treatments allocated at each site were

[‡]*Supporting information may be found in the online version of this article.*

Table I. Aggregate data from the Cochrane review.

Trial	ACT (number of patients that achieved treatment success/number of patients)						Total number of patients that achieved treatment success/total number of patients	Average age (years)
	DHAPQ	AQ+AS	AL	AS+MQ	AQ+SP	AS+SP		
Karema 2004	226/250	206/251	—	—	189/255	—	621/756	2.91
Mens 2007	67/67	—	66/67	—	—	—	133/134	4.67
Zongo 2007	168/172	—	142/178	—	160/171	—	470/521	4.03
Adjei 2006	—	102/107	97/103	—	—	—	199/210	5.60
Bukirwa 2005	—	68/201	100/202	—	—	—	168/403	1.96
Falade 2005	—	56/61	59/62	—	—	—	115/123	4.70
Guthmann 2004	—	60/64	59/61	—	—	—	119/125	2.13
Kobbe 2007	—	81/96	80/103	—	—	—	161/199	2.62
Koram 2003	—	38/51	39/47	—	—	—	77/98	2.63
Martensson 2003	—	149/206	183/197	—	—	—	332/403	2.47
Owusu-Agyei 2006	—	129/151	110/152	—	—	—	239/303	3.10
Faye 2003	—	340/349	147/147	142/144	154/156	—	783/796	13.75
Dorsey 2006	—	98/105	95/100	—	80/105	—	273/310	6.20
Mutabingwa 2004	—	279/472	382/485	—	181/463	—	842/1420	1.89
Van der Broek 2004	—	66/97	87/100	—	—	64/85	217/282	2.23
Menard 2006	—	64/76	—	—	75/79	—	139/155	0.33
Staedke 2003	—	111/130	—	—	105/129	—	216/259	4.25
Yeka 2004	—	356/706	—	—	386/701	—	742/1407	2.01
Kayentao 2006	—	73/131	—	—	127/130	118/130	318/391	3.00
Bonnet 2004	—	101/107	—	—	—	97/106	198/213	2.43
Djimde 2004	—	191/235	—	—	—	222/232	413/467	3.45
Guthmann 2003	—	78/84	—	—	—	81/84	159/168	2.47
Hamour 2003	—	51/80	—	—	—	52/79	103/159	2.54
Swarthout 2004	—	69/83	—	—	—	53/81	122/164	1.98
Sagara 2005b	—	—	155/231	183/230	—	—	338/461	7.25
Fanello 2004	—	—	210/246	—	158/247	—	368/493	2.85
Zongo 2005	—	—	208/245	—	222/233	—	430/478	4.50
Bousema 2004	—	—	72/75	—	—	131/160	203/235	3.27
Mukhtar 2005	—	—	72/80	—	—	65/77	137/157	18.17
Total number of patients that achieved treatment success/total number of patients	461/489	2766/3843	2363/2881	325/374	1837/2669	883/1034	8635/11290	—

ACT, artemisinin-based combination therapy; AL, artemether–lumefantrine; AQ+AS, amodiaquine plus artesunate; AQ+SP, amodiaquine plus sulfadoxine–pyrimethamine; AS+MQ, artesunate plus mefloquine; AS+SP, artesunate plus sulfadoxine–pyrimethamine; DHAPQ, dihydroartemisinin plus piperaquine.

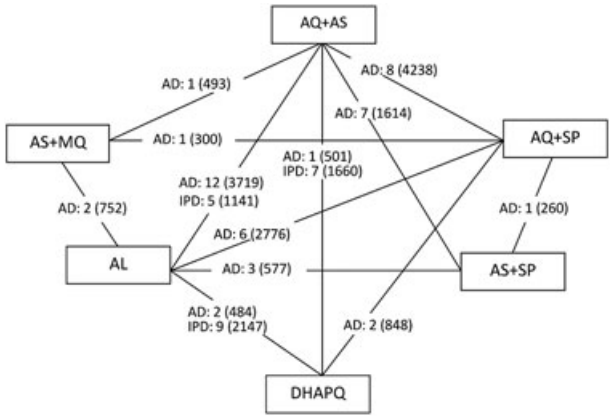

Figure 1. Network diagram of artemisinin-based combination therapies for AD (Cochrane review) and IPD (4ABC trial). The number of sites (number of patients) is displayed. AD, aggregate data; AL, artemether–lumefantrine; AQ+AS, amodiaquine plus artesunate; AQ+SP, amodiaquine plus sulfadoxine–pyrimethamine; AS+MQ, artesunate plus mefloquine; AS+SP, artesunate plus sulfadoxine–pyrimethamine; DHAPQ, dihydroartemisinin plus piperaquine; IPD, individual patient data.

Table II. Summary of individual patient data from the 4ABC trial.

Site	ACT (number of patients that achieved treatment success/number of patients)			Total number of patients that achieved treatment success/ total number of patients	Mean age (years)
	DHAPQ	AQ+AS	AL		
Manhica	164/174	140/173	—	304/347	2.84
Mbarara	135/144	119/145	—	254/289	2.47
Nanoro	173/200	180/264	109/272	462/736	2.25
Gabon	61/62	62/71	65/70	188/203	2.84
Afokang	66/70	78/83	82/85	226/238	2.95
Pamol	60/64	70/74	71/78	201/216	2.68
Ndola	67/67	63/69	63/75	193/211	2.45
Rukara	68/70	—	64/71	132/141	2.97
Jinja	187/195	—	182/196	369/391	2.42
Tororo	162/214	—	119/207	281/421	2.06
Mashesha	72/76	—	74/75	146/151	2.89
Total number of patients that achieved treatment success/total number of patients	1215/1336	712/879	829/1129	2756/3344	—

ACT, artemisinin-based combination therapy; AL, artemether–lumefantrine; AQ+AS, amodiaquine plus artesunate; DHAPQ, dihydroartemisinin plus piperaquine.

chosen by considering the local first line treatments, antimalarial resistance and malaria endemicity. Therefore, meta-analysis was applied to provide a pooled estimate of treatment efficacy across all sites [63].

In this article, we excluded patients treated with CD+A in order to be consistent with the review. Table II displays a summary of IPD (i.e. event rates and covariate information). The 11 sites each compared two or three of the following treatments: AQ+AS, DHAPQ and AL (Figure 1). All three possible pairwise comparisons were supported by direct evidence (Figure 1).

3.2. Implementation

We applied models 1–7 by using the R2WinBUGS package in R (R Foundation for Statistical Computing, Vienna, Austria) and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) [63]. In addition, we applied AD models with and without interactions to the data from the Cochrane review

and fitted IPD models with and without interactions to the 4ABC trial's data [64–66]. We assumed the between-trial/site variances to be equal across treatment comparisons (i.e. $\tau^2_{bk} = \tau^2$) and took into account the correlation between trial/site-specific treatment effects from the same multi-arm trial/site. We chose diffuse normal prior distributions for μ_{jb}, λ_{jb}, d_{Ak}, β_{Ak}, β_{0jb}, m_B, β, β^w_{Ak}, β^a_{Ak}, m^w_B, m^a_B, β^w and β^a, that is, normal(0, 100 000). We selected a uniform prior distribution for the between-trial/site standard deviation, that is, $\tau \sim$ uniform(0, 10), and for the standard deviations of the exchangeable regression coefficients, τ_B, τ^w_B and τ^a_B, that is, uniform(0, 2). For each model, we ran three Markov chain Monte Carlo chains with different initial values for 300 000 iterations, of which the first 100 000 were discarded, giving an overall sample of 600 000. Every 10th iteration in the overall sample was retained to estimate parameters. We assessed convergence of the chains by Gelman Rubin convergence methods and by inspecting plots of the draws.

We compared models by evaluating the statistical significance of the regression coefficients for interactions and by monitoring the reduction in the between-trial/site variance following the inclusion of interactions in the model. We did not use the deviance information criterion to compare models with and without interactions because it was anticipated that the random-effects model without interactions would fit any data reasonably well and that including an interaction would not substantially improve the model fit [19].

We chose the referent treatment to be DHAPQ to be consistent with the analysis plan of the trial. Odds ratios and rankings for children aged 1 year and those aged 5 years were presented because describing the difference between these age groups is the most interesting clinically. For patients aged 1 year, we estimated the probability that each drug was best by ranking the treatment effects corresponding to the basic parameters (i.e. $d_{AB} + \beta_{AB}$, $d_{AC} + \beta_{AC}$ and $d_{AD} + \beta_{AD}$) at each iteration of the chain and by counting the number of iterations for which each drug was ranked first. Similarly, for patients aged 5 years, we ranked the treatment effects (i.e. $d_{AB} + 5\beta_{AB}$, $d_{AC} + 5\beta_{AC}$ and $d_{AD} + 5\beta_{AD}$) at each iteration.

3.3. Results

3.3.1. Combining individual patient data (4ABC trial) and aggregate data (Cochrane review). For each model (models 1–4), the diagnostics suggest convergence of the chains. The number of data points (i.e. 3410) by far exceeds the number of parameters (i.e. 57–62), and therefore, the models are not over-specified (Table III).

With independent interactions (model 2), the regression coefficient for the interaction for AQ+AS versus DHAPQ is statistically significant; with exchangeable interactions (model 3), the regression coefficient for each comparison is statistically significant; and with common interactions (model 4), the common regression coefficient is statistically significant (Table III). The estimate of the between-trial variance increases from 1.04 without interactions (model 1) to 1.16 with independent interactions (model 2), 1.09 with exchangeable interactions (model 3) and 1.07 with common interactions (model 4) (Figure 2).

When no interactions are included (model 1), we found DHAPQ to be significantly more efficacious as compared with AQ+AS (odds ratio, 0.26; 95% credibility interval (CrI), (0.13, 0.51)), AL (odds ratio, 0.40; 95% CrI, (0.21, 0.76)), AQ+SP (odds ratio, 0.33; 95% CrI, (0.14, 0.76)) and AS+SP (odds ratio, 0.28; 95% CrI, (0.11, 0.73))); DHAPQ is more efficacious than AS+MQ (odds ratio, 0.52; 95% CrI, (0.09, 2.92)) although the result is not statistically significant. With interactions (models 2–4), for patients aged 1 year, DHAPQ is more efficacious than AQ+AS, AL, AQ+SP and AS+SP, but only the odds ratio for AQ+AS versus DHAPQ is statistically significant (Figure 2). The CrIs for the odds ratios of AS+MQ versus DHAPQ are wide for patients aged 1 year, but the odds ratio favours AS+MQ using independent interactions (model 2) but favours DHAPQ in the models with exchangeable or common interactions (models 3 and 4) (Figure 2). For patients aged 5 years, DHAPQ is significantly more efficacious than AQ+AS, AL, AQ+SP and AS+SP (Figure 2). Again, the CrIs for the odds ratios of AS+MQ versus DHAPQ are wide, but the odds ratio favours DHAPQ.

Without interactions (model 1), DHAPQ has the highest probability of being the best drug (i.e. 77% certainty), followed by AS+MQ with 22% certainty; the remaining drugs are equally ranked at 0%. With independent interactions (model 2), for patients aged 1 year, AS+MQ has the highest probability of being the best drug, followed by DHAPQ. For patients aged 5 years, DHAPQ has the highest probability, followed by AS+MQ. Under exchangeable or common interactions (models 3 and 4), for children of

Table III. Results of MTC models including treatment-by-age interactions, combining IPD (4ABC trial) and AD (Cochrane review), for unadjusted treatment success.

Description		No interactions (model 1)	Independent interactions (model 2)	Exchangeable interactions (model 3)	Common interactions (model 4)
Number of data points		3410	3410	3410	3410
Number of model parameters[1]		57	62	59	58
Log odds ratios (uncentred)[2]	AQ+AS versus DHAPQ	−1.33 (−2.01, −0.67)	−0.61 (−1.57, 0.33)	−0.67 (−1.57, 0.22)	−0.68 (−1.55, 0.20)
	AL versus DHAPQ	−0.92 (−1.59, −0.27)	−0.33 (−1.26, 0.58)	−0.30 (−1.17, 0.58)	−0.27 (−1.15, 0.61)
	AS+MQ versus DHAPQ	−0.66 (−2.37, 1.06)	1.82 (−4.05, 7.68)	0.09 (−2.14, 2.69)	0.00 (−1.82, 1.83)
	AQ+SP versus DHAPQ	−1.12 (−1.95, −0.29)	−0.25 (−1.60, 1.11)	−0.41 (−1.50, 0.71)	−0.43 (−1.45, 0.59)
	AS+SP versus DHAPQ	−1.27 (−2.24, −0.32)	−0.64 (−2.00, 0.72)	−0.60 (−1.80, 0.57)	−0.61 (−1.74, 0.50)
Log odds ratios (centred)[3]	AQ+AS versus DHAPQ	−1.33 (−2.01, −0.67)	−1.57 (−2.30, −0.84)	−1.55 (−2.28, −0.85)	−1.55 (−2.26, −0.85)
	AL versus DHAPQ	−0.92 (−1.59, −0.27)	−1.13 (−1.85, −0.42)	−1.14 (−1.85, −0.45)	−1.14 (−1.84, −0.46)
	AS+MQ versus DHAPQ	−0.66 (−2.37, 1.06)	0.30 (−3.74, 4.41)	−0.80 (−2.74, 1.30)	−0.88 (−2.61, 0.88)
	AQ+SP versus DHAPQ	−1.12 (−1.95, −0.29)	−1.30 (−2.20, −0.41)	−1.30 (−2.18, −0.44)	−1.31 (−2.18, −0.46)
	AS+SP versus DHAPQ	−1.27 (−2.24, −0.32)	−1.47 (−2.50, −0.44)	−1.47 (−2.49, −0.48)	−0.62 (−2.41, 1.20)
Regression coefficients for interactions	AQ+AS versus DHAPQ	—	−0.28 (−0.52, −0.03)*	−0.26 (−0.48, −0.04)*	−0.26 (−0.48, −0.04)*
	AL versus DHAPQ	—	−0.23 (−0.47, 0.00)	−0.24 (−0.47, −0.03)*	−0.26 (−0.48, −0.04)*
	AS+MQ versus DHAPQ	—	−0.44 (−1.03, 0.16)	−0.26 (−0.55, −0.01)*	−0.26 (−0.48, −0.04)*
	AQ+SP versus DHAPQ	—	−0.31 (−0.63, 0.01)	−0.26 (−0.51, −0.03)*	−0.26 (−0.48, −0.04)*
	AS+SP versus DHAPQ	—	−0.24 (−0.53, 0.04)	−0.25 (−0.49, −0.02)*	−0.26 (−0.48, −0.04)*
Mean for distribution of regression coefficients		—	—	−0.26 (−0.50, −0.03)	—
Variance for distribution of regression coefficients		—	—	0.00 (0.00, 0.06)	—
Between-trial variance[4]		1.04 (0.63, 1.79)	1.16 (0.70, 2.03)	1.09 (0.66, 1.88)	1.07 (0.65, 1.84)

Posterior median (95% credibility interval, i.e. 2.5th and 97.5th percentiles of the posterior distribution) is presented. AD, aggregate data; AL, artemether–lumefantrine; AQ+AS, amodiaquine plus artesunate; AQ+SP, amodiaquine plus sulfadoxine–pyrimethamine; AS+MQ, artesunate plus mefloquine; AS+SP, artesunate plus sulfadoxine–pyrimethamine; DHAPQ, dihydroartemisinin plus piperaquine; IPD, individual patient data.

*Statistically significant regression coefficient (i.e. zero excluded from the credibility interval) or between-trial variance decreases after including the interaction.

[1]Model parameters include 11 log odds for treatment $b(\mu_{jb})$; 29 log odds for treatment $b(\lambda_{jb})$; 11 differences in the log odds for treatment b per unit increase in the covariate (β_{0jb}); 5 log odds ratios (d_{Ak}); 1 between-trial variance (τ^2); 5 regression coefficients for treatment-by-age interactions (β_{Ak}) for the model with independent interactions; the overall mean (m_B) and variance (τ_B^2) for the model with exchangeable interactions; and the common regression coefficient (β) for the model with common interactions.

[2]For models including interactions, the log odds ratio at age zero is presented.

[3]For models including interactions, the log odds ratio at the mean age is presented (i.e. 3.42 years).

[4]The between-trial variance is the variance between trials/sites.

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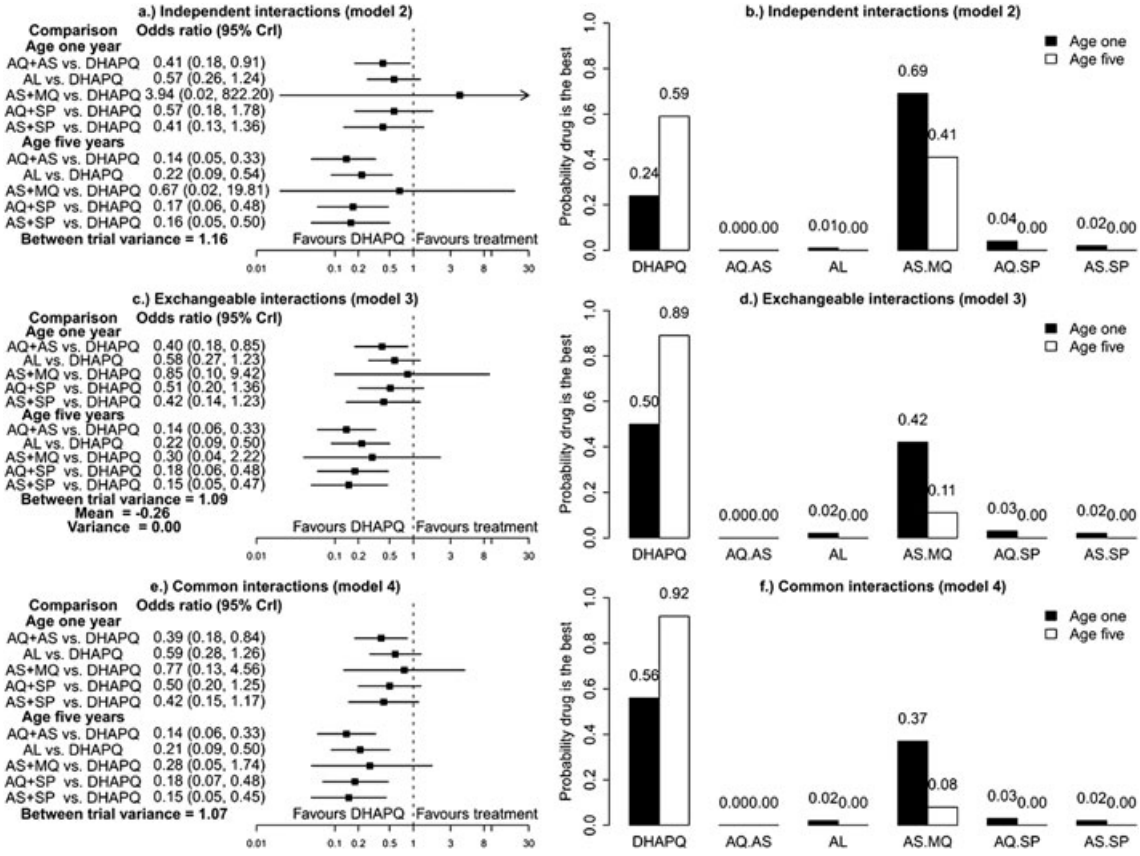

Figure 2. Odds ratios and the probability that each drug is the best from mixed treatment comparison models including treatment-by-age interactions, combining individual patient data (4ABC trial) and aggregate data (Cochrane review), for unadjusted treatment success. Posterior median (95% credibility interval (CrI), i.e. 2.5th and 97.5th percentiles of the posterior distribution) is presented. 'Mean' and 'variance' are the mean and variance of the distribution of the regression coefficients for the interactions. The between-trial variance is the variance between trials/sites. AL, artemether–lumefantrine; AQ+AS, amodiaquine plus artesunate; AQ+SP, amodiaquine plus sulfadoxine–pyrimethamine; AS+MQ, artesunate plus mefloquine; AS+SP, artesunate plus sulfadoxine–pyrimethamine; DHAPQ, dihydroartemisinin plus piperaquine.

any age, DHAPQ has the highest probability of being the best drug, followed by AS+MQ. The other drugs have much lower probabilities of being the best drug (Figure 2).

3.3.1.1. Exploring within-site and across-trial treatment-by-age interactions. When investigating across-trial and within-site interactions, the chains for the log odds ratios and regression coefficients for the across-trial interactions do not converge (models 5–7). The covariate distributions within sites and across trials is the likely cause of the nonconvergence. The trace plot for the within-site variance for the exchangeable regression coefficients reveals that the prior distribution is influential (model 6).

The results produced are unreliable but are presented to illustrate methodology that could be applied to other data sets (Table IV). No across-trial interactions are statistically significant. With independent or exchangeable interactions (models 5 and 6), the within-site regression coefficient for the interaction for AL versus DHAPQ is statistically significant. With common interactions (model 7), the common within-site regression coefficient is statistically significant. The Bayesian p-values indicate that there are no differences between the within-site and across-trial regression coefficients. The estimate of the between-trial variance is higher than that of the model with independent interactions (model 5) (i.e. 1.24 rather than 1.16), with exchangeable interactions (model 6) (i.e. 1.13 rather than 1.09) and with common interactions (model 7) (i.e. 1.09 rather than 1.07).

3.3.2. Aggregate data set (Cochrane review). With the use of AD alone, without interactions, convergence of the chains is achieved. However, interactions are included; the trace plots show nonconvergence

Table IV. Results of investigation of across-trial and within-site treatment-by-age interactions by using MTC models for unadjusted treatment success combining IPD (4ABC trial) and AD (Cochrane review).

Description		Independent interactions (model 5)	Exchangeable interactions (model 6)	Common interactions (model 7)
Number of data points		3410	3410	3410
Number of model parameters[1]		64	61	59
Log odds ratios (uncentred)[2]	AQ+AS versus DHAPQ	−0.36 (−3.97, 3.96)	−0.57 (−3.57, 2.90)	−0.96 (−4.16, 2.26)
	AL versus DHAPQ	−0.51 (−4.14, 3.70)	−0.26 (−3.28, 3.17)	−0.55 (−3.75, 2.66)
	AS+MQ versus DHAPQ	3.04 (−3.93, 11.01)	0.27 (−3.56, 4.90)	−0.29 (−3.89, 3.33)
	AQ+SP versus DHAPQ	−0.03 (−3.88, 4.47)	−0.31 (−3.47, 3.30)	−0.72 (−4.03, 2.60)
	AS+SP versus DHAPQ	−0.72 (−4.48, 3.59)	−0.54 (−3.67, 2.99)	−0.89 (−4.18, 2.42)
Within-site regression coefficients for interactions	AQ+AS versus DHAPQ	−0.24 (−0.51, 0.03)	−0.24 (−0.50, 0.01)	−0.26 (−0.49, −0.04)*
	AL versus DHAPQ	−0.27 (−0.52, −0.03)*	−0.27 (−0.51, −0.03)*	−0.26 (−0.49, −0.04)*
Across-trial regression coefficients for interactions[3]	AQ+AS versus DHAPQ	−0.36 (−1.91, 0.92)	−0.29 (−1.53, 0.76)	−0.15 (−1.29, 0.97)
	AL versus DHAPQ	−0.18 (−1.69, 1.11)	−0.26 (−1.49, 0.79)	−0.15 (−1.29, 0.97)
	AS+MQ versus DHAPQ	−0.58 (−2.25, 0.81)	−0.30 (−1.55, 0.78)	−0.15 (−1.29, 0.97)
	AQ+SP versus DHAPQ	−0.37 (−1.92, 0.95)	−0.29 (−1.54, 0.77)	−0.15 (−1.29, 0.97)
	AS+SP versus DHAPQ	−0.20 (−1.72, 1.10)	−0.27 (−1.50, 0.79)	−0.15 (−1.29, 0.97)
Bayesian p-value (difference between within-site and across-trial regression coefficients)[4]	AQ+AS versus DHAPQ	0.88	0.94	0.86
	AL versus DHAPQ	0.90	1.00	0.86
	AS+MQ versus DHAPQ	0.42	0.60	0.86
	AQ+SP versus DHAPQ	0.62	0.60	0.86
	AS+SP versus DHAPQ	0.80	0.64	0.86
Mean for distribution of within-site regression coefficients		—	−0.26 (−1.43, 0.92)	—
Variance for distribution of within-site regression coefficients		—	0.08 (0.00, 3.32)	—
Mean for distribution of across-trial regression coefficients		—	−0.28 (−1.52, 0.78)	—
Variance for distribution of across-trial regression coefficients		—	0.00 (0.00, 0.12)	—
Between-trial variance[5]		1.24 (0.74, 2.19)	1.13 (0.68, 1.95)	1.09 (0.66, 1.88)

The results are invalid because chains did not converge. Posterior median (95% credibility interval (CrI), i.e. 2.5th and 97.5th percentiles of the posterior distribution) is presented. AD, aggregate data; AL, artemether–lumefantrine; AQ+AS, amodiaquine plus artesunate; AQ+SP, amodiaquine plus sulfadoxine–pyrimethamine; AS+MQ, artesunate plus mefloquine; AS+SP, artesunate plus sulfadoxine–pyrimethamine; DHAPQ, dihydroartemisinin plus piperaquine; IPD, individual patient data.

*Statistically significant regression coefficient (i.e. zero excluded from the CrI) or between-trial variance decreases after including the interaction.

[1]Model parameters include 11 log odds for treatment b (μ_{jb}); 29 log odds for treatment b (λ_{jb}); 11 differences in the log odds of treatment b per unit increase in the covariate (β_{ojb}); 5 log odds ratios (d_{Ak}); 1 between-trial variance (τ^2); 7 regression coefficients for treatment-by-age interactions ($\beta^a_{Ak}, \beta^w_{Ak}$) for the model with independent interactions; 2 overall means (m^a_B, m^w_B) and 2 variances ($(\tau^a_B)^2, (\tau^w_B)^2$) for the model with exchangeable interactions; and 2 common regression coefficients (β^a, β^w) for the model with common interactions.

[2]For models including interactions, the log odds ratio at age zero is presented.

[3]Across-trial interactions refer to the interactions across the trials of the Cochrane review and across the sites of the 4ABC trial.

[4]For each treatment pairing, a Bayesian p-value was estimated by calculating the difference (i.e. diff) between the within-site and across-trial regression coefficients, at each iteration of the chain, and counting the number of iterations for which diff ≥ 0. It was then possible to calculate the probability (i.e. prob) that the within-site regression coefficient exceeded the across-trial coefficient, by dividing the number of counted iterations by the total number of iterations of the chain. Lastly, assuming that the posterior distribution of the differences (i.e. diff) was symmetric and unimodal, the p-value was obtained by $p = 2 \times \text{minimum}(\text{prob}, 1 - \text{prob})$ [11, 12, 68]. Results were considered to be significantly different when $p \leq 0.1$.

[5]The between-trial variance is the variance between trials/sites.

for the log odds ratios and the regression coefficients for the interactions. The lack of direct evidence for the comparisons corresponding to the basic parameters (i.e. AQ+AS versus DHAPQ (one trial), AL versus DHAPQ (two trials), AS+MQ versus DHAPQ (no studies), AQ+SP versus DHAPQ (two trials) and AS+SP versus DHAPQ (no trials)) is the probable cause of the nonconvergence. Consequently, samples are not drawn from the true posterior distributions of the parameters.

Although it is inadvisable to make recommendations concerning efficacy, we present the results to demonstrate the imprecision of the estimates. No regression coefficients for the interactions are statistically significant (Supplementary Table 2). With interactions, the between-trial variance increases, and therefore, no variability is explained by mean age (Supplementary Figures 1 and 2). Results are extremely imprecise for children aged 1 year (Supplementary Figure 2). Rankings alter depending on mean age (Supplementary Figure 3).

3.3.3. Individual patient data set (4ABC trial). With the use of IPD, the chains converged. The trace plot for the variance for the exchangeable regression coefficients indicates that the results are influenced by the vague prior distribution. Only two regression coefficients are exchangeable, and therefore, data are limited.

With exchangeable interactions, the regression coefficient for the interaction for AL versus DHAPQ is statistically significant, and with common interactions, the common regression coefficient is statistically significant (Supplementary Table 2). The estimate of the between-site variance increases after including interactions (Supplementary Figures 1 and 2). The between-site variances are smaller than for AD because each site adhered to the same protocol.

Without interactions, DHAPQ is significantly more efficacious than AQ+AS and AL (Supplementary Figure 1), whereas with interactions, DHAPQ is more efficacious than AQ+AS and AL. However, the results only reach statistical significance for patients aged 5 years (Supplementary Figure 2). The best drug is DHAPQ (Supplementary Figures 1 and 3).

3.3.3.1. Exploring within-site and across-site treatment-by-age interactions. When investigating across-site and within-site interactions, the chains for the log odds ratios and regression coefficients for the across-site interactions do not converge. The log odds ratio (i.e. treatment effect when covariate values are zero) and the across-site regression coefficient (representing the change in the treatment effect with each unit increase in the mean covariate value) cannot be estimated distinctly almost certainly because the mean ages are very similar across sites. The results from these models are invalid.

4. Discussion

This article introduced MTC models to combine IPD and AD for a dichotomous outcome. We illustrated the methodology through application to real data sets. To gain a greater understanding of the data, we also applied MTC models to AD and IPD in turn. When IPD contributed (i.e. either using IPD alone or combining IPD and AD), we detected statistically significant interactions. The CrIs for the results were much narrower than those obtained using AD alone. Precision is required when determining whether interactions exist, because when CrIs are wide, it is impossible to distinguish whether interactions exist. Therefore, all available data are needed to detect whether interactions exist. Using IPD alone, we were able to compare only three of the six treatments of interest. Using AD alone, results showed that the chains did not converge, and we identified no significant interactions. In each case, the variance increased following the inclusion of interactions, indicating that age did not explain the between-trial variability. This suggests the need to investigate other covariates to ascertain whether the consistency assumption is reasonable. When applying models that separated across-site and within-site interactions, convergence was not achieved in this instance.

The distribution of the covariates within and across studies should be considered to establish if the data permit investigation of interactions and to avoid extrapolation. As five regression coefficients for the interactions were estimated by the models with independent or exchangeable interactions (i.e. corresponding to AQ+AS versus DHAPQ, AL versus DHAPQ, AS+MQ versus DHAPQ, AQ+SP versus DHAPQ, and AS+SP versus DHAPQ), the covariate distributions of studies providing evidence for each of the five comparisons should be considered. Patients with ages ranging from 0.5 to 5 years contributed to the estimation of regression coefficients for AQ+AS versus DHAPQ and for AL versus DHAPQ; therefore, extrapolation was not an issue, and parameters were accurately estimated. However, for AS+MQ versus DHAPQ, AQ+SP versus DHAPQ, and AS+SP versus DHAPQ, there was very

limited direct evidence contributing to the model parameters; therefore, estimation was reliant on indirect evidence and, in models 3 and 6, on the assumption of exchangeable interactions. Also, the mean ages of the contributing trials may not have spanned ages 1 to 5 years, and therefore, the results presented in this article for patients aged 1 year and those aged 5 years may be invalid.

We described three model specifications including interactions, that is, models including independent, exchangeable or common interactions [67]. Independent interactions are the most desirable, provided that data are not limited. Data limitation issues would arise, for example, if for one or more comparisons there is a low number of contributing trials or if covariate values were alike. Exchangeable interactions are useful when data are limited because strength is borrowed across comparisons. However, when the number of treatments is low and vague prior distributions are used, models including independent interactions will be similar to those with exchangeable interactions. Common interactions will rarely be appropriate and make the most stringent assumption. In the presented example, including exchangeable interactions seemed most appropriate because strength was borrowed across the five comparisons to improve the precision of the results for AS+MQ versus DHAPQ as compared with those from the model with independent interactions.

In this instance, combining IPD with AD dramatically improved the precision of the results, such that the extra effort to obtain IPD was worthwhile. IPD were from 3344 children at 11 sites, whereas AD included 29 trials and 11 290 patients; therefore, IPD contributed 30% of patients to the combined data set. It would be interesting to compare the proposed approach with AD meta-analysis of all studies, while varying the number of studies that contribute IPD, to establish whether equally dramatic improvements are observed.

Here, we introduced models for a dichotomous outcome; however, the model specification could easily be tailored to allow application to other types of outcomes, such as continuous outcomes. In this article, models combined IPD and event rates along with study-level covariates. The model specification and WinBUGS code was further extended to allow trial-specific estimates of log odds ratios, standard errors and study-level covariates to be combined, in addition to IPD and event rates. We did not present such models in this article because event rates were available for all relevant trials.

The models assumed random effects but can easily be simplified to assume fixed effects; that is, for each treatment comparison, there is a single underlying treatment effect. We applied fixed-effect models but did not present the results because heterogeneity existed. Here, we assumed the same between-trial variance for each treatment comparison, which may not be reasonable. Lu and Ades [19] showed that the consistency equations also constrain the variance parameters. Models that allow the between-trial variability for each treatment comparison to differ could be applied, but this would entail specifying informative prior distributions for the variance parameters [68]. Furthermore, to explore the influence of the prior distributions on the conclusions, the models could be refitted using different vague, or informative, prior distributions for model parameters.

In conclusion, when exploring interactions in MTCs, it can be beneficial to obtain IPD, if only for a subset of trials, and to combine IPD with any additional AD. However, within-trial and across-trial interactions should be studied to detect differences. If the across-trial and within-trial interactions differ, then inferences should be drawn from the within-trial interactions alone because across-trial interactions may be affected by ecological biases.

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Contributions of authors

Sarah Donegan proposed the idea, carried out the analysis and wrote the first draft of the manuscript. Catrin Tudur Smith provided oversight and contributed to writing the manuscript. Umberto D'Alessandro and Paul Garner provided helpful discussions regarding clinical aspects. All authors provided comments on the manuscript.

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