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Comparative benefit of malaria chemoprophylaxis modelled in United Kingdom travellers☆

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Summary *Background:* Chemoprophylaxis against falciparum malaria is recommended for travellers from non-endemic countries to malarious destinations, but debate continues on benefit, especially with regard to mefloquine. Quantification of benefit for travellers from the United Kingdom (UK) was modelled to assist clinical and public health decision making.
Methods: The model was constructed utilising: World Tourism Organization data showing total number of arrivals from the UK in countries with moderate or high malaria risk; data from a retrospective UK Clinical Practice Research Datalink (CPRD) drug utilisation study; additional information on chemoprophylaxis, case fatality and tolerability were derived from the travel medicine literature. Chemoprophylaxis with the following agents was considered: atovaquone-proguanil (AP), chloroquine with and without proguanil (C ± P), doxycycline (Dx), mefloquine (Mq). The model was validated for the most recent year with temporally matched datasets for UK travel destinations and imported malaria (2007) against UK Health Protection Agency data on imported malaria.
Results: The median (mean) duration of chemoprophylaxis for each agent in weeks (CPRD) was: AP 3.3 (3.5), C ± P 9 (12.1), Dx 8 (10.3), Mq 9 (12.3): the maximum duration of use of all regimens was 52 weeks. The model correctly predicted falciparum malaria deaths and gave a robust estimate of total cases – model: 5 deaths from 1118 cases; UK Health Protection Agency: 5 deaths from 1153 cases. The number needed to take chemoprophylaxis (NNP) to

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prevent a case of malaria considered against the 'background' reported incidence in non-users of chemoprophylaxis deemed in need of chemoprophylaxis was: C ± P 272, Dx 269, Mq 260, AP 252; the NNP to prevent a UK traveller malaria death was: C ± P 62613, Dx 61923, Mq 59973, AP 58059; increasing the 'background' rate by 50% yielded NNPs of: C ± P 176, Dx 175, Mq 171, AP 168. The impact of substituting atovaquone-proguanil for all mefloquine usage resulted in a 2.3% decrease in estimated infections. The number of travellers experiencing moderate adverse events (AE) or those requiring medical attention or drug withdrawal per case prevented is as follows: C ± P 170, Mq 146, Dx 114, AP 103.

Conclusions: The model correctly predicted the number of malaria deaths, providing a robust and reliable estimate of the number of imported malaria cases in the UK, and giving a measure of benefit derived from chemoprophylaxis use against the likely adverse events generated. Overall numbers needed to prevent a malaria infection are comparable among the four options and are sensitive to changes in the background infection rates. Only a limited impact on the number of infections can be expected if Mq is substituted by AP.

1. Introduction

Falciparum malaria is a progressive and potentially lethal disease in patients who do not possess some degree of pre-existing immunity to *Plasmodium falciparum*, the causative parasite; such immunity is usually acquired through having grown up in, and having continued to reside in, a malaria endemic region [1]. Thus, most travellers from developed countries will be at elevated risk of serious and potentially fatal illness should they visit a malaria endemic region. Emigrants from malarious regions settled in non-malarious countries lose protective immunity over time, and hence are at increased risk of clinical malaria should they visit malarious destinations, typically upon making a return visit to their countries of origin. Settled immigrants do however retain some residual semi-immunity and are less likely to die from malaria than non-immune travellers [2]. Anti-malarial chemoprophylaxis is accordingly recommended for travellers from malaria free countries who visit malarious regions, to prevent development of acute malaria and its complications, including severe disease and death [3].

All medication is associated with the risk of developing adverse events (AEs), and these risks are quite well characterised for the antimalarial chemoprophylactic agents in current use: mefloquine, atovaquone-proguanil, doxycycline, chloroquine with and without proguanil [4], however, to enable a more complete assessment of the benefit-risk ratio for antimalarial chemoprophylaxis, quantification of benefit would be helpful. To this end we have modelled the benefits of chemoprophylaxis for travellers from the United Kingdom visiting moderate and high-risk malarious destinations. As travellers to low-risk malaria destinations are often recommended stand-by emergency medication rather than chemoprophylaxis, we excluded such destinations from our datasets [5].

2. Materials and methods

The model attempts to track the flow of travellers from the United Kingdom to moderate and high-risk malaria destinations in calendar year 2007, the latest year for which complete data sets for all model variables were available, and to assess the benefit conferred by the use of chemoprophylaxis. The data sources utilised to populate the model are detailed below.

The numbers of travellers at travel related risk of malaria exposure were obtained from the United Nations World Tourism Organization (UNWTO) dataset, "Data on Outbound Tourism (2012)" [6]. Destination countries were then cross referenced to country risk category from the US CDC malaria risk tables [7]. For the purposes of this model, countries on the CDC list were reclassified by a malariologist as high, low, or no risk destinations for malaria. In the case of countries such as South Africa, which are mostly malaria free, but which do contain only localised high risk malarious regions, the risk for the whole country was set to 'no risk' in order to not overinflate "high risk" exposure.

To ascertain the number of UK travellers who sought advice and were assessed by health care professional prior to departure, numbers were obtained from those reported in a survey of departing passengers conducted in 2003 at Heathrow Airport, London, UK, and from the results of a field study of UK travellers [8,9].

The allocation of travellers to each of the four chemoprophylactic drug groups, mefloquine, atovaquone-proguanil, doxycycline, chloroquine and proguanil was determined from the results of a separate study by Blöchliger et al. of prescribing patterns in UK general practice, conducted using the UK Community Practice Research Database (formerly known as the UK General Practice Research Database) [10]. The split between agents, derived from the absolute number of travellers prescribed each chemoprophylactic agent is as follows: mefloquine 15.3%, atovaquone-proguanil 65.6%, doxycycline 14%, and chloroquine with and without proguanil 5.1%.

Malaria infection and death rates in UK travellers for the calendar year 2007 were obtained from published UK Health Protection Agency data [11]. The number of reported cases of malaria occurring in UK users of each chemoprophylactic agent was based upon the analysis of