Journal of Tropical Diseases

Rahman, J Trop Dis 2019, 7:3
DOI: 10.4172/2329-891X.1000311

Commentary Open Access

Intermittent Preventive Treatment (IPTc) for Seasonal Malaria Transmission-An Opinion

AAM Shazzadur Rahman*

Department of Medicine, North East Medical College Hospital, Sylhet, Bangladesh

***Corresponding author:** AAM Shazzadur Rahman, Department of Medicine, North East Medical College Hospital, Sylhet, Bangladesh, Tel: +8801796589891; E-mail: dr.aam_rahman@yahoo.co.uk

Received date: January 24, 2019; **Accepted date:** April 08, 2019; **Published date:** April 15, 2019

Abstract

The World Health Organization (WHO) currently recommends seasonal malaria Chemoprevention (SMC) against falciparum malaria, which is "effective, cost-effective, safe, and feasible for the prevention of malaria among children less than five years of age in areas with highly seasonal malaria transmission". Due to tropical monsoon (rainy season followed by dry season), hilly forests with the river, Bangladesh is an ideal setting for seasonal malaria transmission, especially in Chittagong Hill Tract (CHT) districts. Intermittent Preventive Treatment in children (IPTc) has been successfully implemented in West African countries that prevent three-quarter of all clinical malaria episodes. Bangladesh has a similar context in terms of climate, malaria species, and structure of the health system are similar to these African countries. So, IPTc can be applicable in Bangladesh along with the National Malaria Control Program (NMCP). But need to secure consistent funding ensure good management of drugs supply, storage, and delivery.

Keywords: Malaria; Seasonal malaria transmission; Intermittent chemoprevention

List of Abbreviations IPTc: Intermittent Preventive Treatment in children; WHO: World Health Organization; SMC: Seasonal Malaria Chemoprevention; CHT: Chittagong Hill Tracks; GOB: Government of Bangladesh; HPNSDP: Health, Population and Nutrition Sector Development Program; MoH: Ministry of Health; NMCP: National Malaria Control Program; GFTAM: Global Fund to Fight AIDS, Tuberculosis, and Malaria; IRS: Indoor Residual Spraying; IVM: Integrated Vector Management; ITN: Insecticide Treated Net; LLIN: Long-lasting Insecticidal Net; NGO: Non-Governmental Organization; UNICEF: United Nations Children's Funds; RCT: Randomised Controlled Trial; CI: Confidence Interval; RR: Relative Risk

Introduction

Although achieving significant progress, Malaria remains a major public health issue among the 13 (out of 64) endemic districts, located in the Eastern and Northeastern part of Bangladesh, bordering mostly with India and partly with Myanmar. The disease has different transmission potentials (high, moderate and low). The overall prevalence of malaria in these 13 endemic districts is 3.1% to 3.97% [1]. Approximately 14 million people are at high risk in these districts [2]. The highest endemic region was identified in three Chittagong Hill Tract (CHT) districts (Rangamati, Khagrachari, and Bandarban) with the prevalence of malaria is more than 10% [2]. About 80% of the total cases of malaria have been reported in these CHT districts in 2013 [3]. The reasons for high endemicity are that these areas have perennial and seasonal transmission throughout the year due to a geographical location in the hilly, forested and the foothills, lake, tropical monsoon, and global climate changes provide excellent habitat for malaria vectors.

Populations at all age groups are affected by malaria; however adult males are more likely to be affected because of occupations, moving around and behavior. Children under five years and pregnant women are biologically at higher risk and they are most vulnerable to develop severe malaria due to the low level of immunity. Priority should be given for intervention among these groups, particularly in high transmission areas like CHT districts in Bangladesh. More than 90% of malaria cases occur due to *P. falciparum* and remaining mostly caused by *P. vivax* of these areas.

National Malaria Control Program (NMCP) in Bangladesh has been developed with the aim of achieving 'Zero indigenous transmission' and 'Zero deaths' by 2020, ensuring equitable and universal accesses to effective preventive and curative services to all 'at risk population' through rigorous efforts from the government, NGOs, private sectors and the community, by adapting malaria strategic plan (2008-2014; and 2015-2020). GoB-HPNSDP, GFATM and WHO mainly fund NMCP. Though Bangladesh has been achieved a significant reduction in malaria cases, these three CHT districts along with Chittagong and Cox's Bazar districts need intensified malaria control intervention in order to achieve 2020 malaria elimination target. The decrease of malaria burden in the CHT districts, definitely a major challenge.

At present, NMCP operates two interventions towards malaria control by home management (ITNs and LLINs) and vector control (IRS, LRS, and IVM). Intermittent preventive treatment (IPTc) could be used in CHT districts (seasonal transmission) along with ITNs, thus reducing malaria transmission synergistically as well as prevent death from malaria."IPTc, defined as a full curative dose of an antimalarial alone or in combination given to children monthly or every two months during the malaria transmission season" [4,5].

Summary of Results

Based on Meremikwu et al. [4] this Cochrane review aimed to summarize the effects (benefits and harms) of IPTc to reduce seasonal transmission of malaria. This review included-seven trials including six individual-randomized controlled trials and one cluster-randomized

controlled trial, enrolling 12,589 participants among them six trials were restricted to children under five years of age.

The benefits of using IPTC

- It prevents three-quarters of all clinical malaria episodes (RR 0.26; 95% CI 0.17 to 0.38; 9321 participants, six trials, high-quality evidence) [4]
- It prevents three-quarters of severe malaria episodes (RR 0.27; 95% CI 0.10 to 0.76; 5964 participants, two trials, high-quality evidence) [4]
- IPTc probably produces a small reduction in all-cause mortality consistent with the effect on severe malaria (RR 0.66; 5% CI 0.31 to 1.39; moderate-quality evidence) [4]
- IPTc probably lowers the risk of moderately severe anemia (RR 0.71; 95% CI 0.52 to 0.98; 8805 participants; five trials, moderate quality evidence) [4]

The harms of using IPTc

- Serious drug-related adverse effects probably rare, with none reported in the six trials (9533 participants, moderate quality evidence) [4]
- Amodiaquine plus sulphadoxine-pyrimethamine effective but causes increase vomiting (RR 2.78; 95% CI 2.31 to 3.35; two trials, high-quality evidence) [4]

The quality of evidence of this review was assessed using the GRADE approach in which we can be confident that the estimates of effect are judgmental and accurate. "The level of 'quality' is judged on a 4-point scale; evidence from RCTs is initially graded as high and downgraded by one, two or three levels after full consideration of risk of bias (any limitation of the study design), the directness (applicability), inconsistency (variation in results between studies), precision of the results and the possibility of publication bias" [4].

In this Cochrane review, showed that IPTc reduces both clinical malaria and severe malaria episodes by approximately 75%, is reflected to be high-quality evidence, which means we can be confident that these estimates of effect are correct and further research is very unlikely to change our confidence in the estimates of effect.

Assessment of reliability (also can be found on Annex 1: AMSTAR Tool)

This systematic review has designed the research question and set of inclusion criteria prior to conducting the review. A comprehensive search was conducted for this Cochrane review using Cochrane library database (July 2011), MEDLINE (1966 to July 2011), EMBASE (1974 to July 2011), LILACS (1982 to July 2011). The authors also searched metaRegister of a Controlled Trial (mRCT) and unpublished and ongoing trials [6]. Two authors independently screened the results of the searched literature, and independently assessed the eligibility of inclusion criteria; two authors independently extracted data from the included trials using data extraction form 4. Any disagreement was resolved by discussion. A list of inclusion and exclusion of studies were provided with the reasons. Publication bias was assessed with the use of a funnel plot. Heterogeneity was assessed with the forest plot to see any overlapping CIs; the authors also applied Chi-square test with a 10% level of statistical significance and an I-squire statistic value greater than 40% to indicate a moderate level of heterogeneity [7]. Subgroup analysis and Sensitivity analysis were also conducted in this Cochrane review. The quality of evidence of this Cochrane review was assessed using GRADE criteria.

This Cochrane review showed IPTc given to the children less than six years of age in the seasonal malaria transmission area, prevents approximately 75% of clinical and severe malaria (high-quality evidence), it means we can be confident that this result is accurate and further research is not likely to be required in similar settings.

Assessment of Applicability (details can be found on Annex 2: SUPPORT tool 9)

All seven studies in this Cochrane review were conducted in West African countries and where *Plasmodium falciparum* is the main agent to cause malaria and highly seasonal transmission [8]. This review recommended that the result could be applicable to a similar context. Bangladesh is an ideal context. Other South East Asian (SEA) countries like Myanmar, India, Thailand, Cambodia have similar climate and health infrastructure [9], IPTc can be applicable to these SEA countries but resistant vectors will be a concern [10,11]. More studies may be needed for this issue.

More than 90% of malaria cases in 13 endemic districts in Bangladesh caused by *P. falciparum*. Bangladesh has tropical monsoon where heavy rain followed by the dry season, amplified seasonal malaria transmission. In terms of climate, malaria species and socioeconomic condition of the population are similar in both settings.

Bangladesh has a dominant public health care system along with private sectors and NGO's play an important contribution to the health system. Health system arrangement in Bangladesh is nearly similar to West African settings. NMCP in Bangladesh funded by Global Fund (GFATM), WHO and GOB-HPNSDP has already implemented two interventions-home management by providing ITNs and LLINs; vector control by introducing IRS and IVM. A reasonable amount of staffs and resources already in place, so IPTc can be incorporated with existing malaria control programs. The available budget will be a concern, and the government and other sectors need better collaboration. Good management of drugs supply, storage and delivery are essential. Donors and other stakeholders continue their interest to achieve the 2020 goal ('zero indigenous transmission and zero death') of NMCP in Bangladesh. IPTc can work synergistically with other programs to prevent seasonal malaria transmission in children under six years of age.

Discussion and Conclusion

IPTc is very effective in reducing the transmission of seasonal malaria in children. Bangladesh has a similar context in terms of climate, malaria species, and structures of the health system are similar to these African countries where the studies were conducted. Nevertheless, these studies were done under a controlled environment where trained staff and active community involvement were present. In Bangladesh, a reasonable amount of staffs and resources already in place, so IPTc can be incorporated with existing malaria control programs in Bangladesh. The available budget will be a concern, and the government and other sectors need better collaboration.

Declaration

Ethics approval

This is an 'opinion' from a review analysis and no identifiable human subjects were involved in the research, therefore ethical approval was not sought and informed consent was not applicable.

Availability of data and materials

Annex 1 and Annex 2 are attached to this paper as separate files.

Consent for Publication

Not applicable

Funding

This article did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interest

Author has no conflict of interest to declare.

Author's Contribution

AR has done all of the work of this paper

Acknowledgment

I thank Professor Paul Garner (Managing editor, Cochrane Infectious Diseases Group, UK), Dr. David Sinclair and Dr. Ivor Langley, Liverpool School of Tropical Medicine, who reviewed and assessed this work.

References

1. Haque U, Ahmed SM, Hossain S, Huda M, Hossain A, et al. (2009) Malaria prevalence in endemic districts of Bangladesh. PLoS ONE 4: e6737.
2. Haque U, Overgaard HJ, Clements ACA, Norris DE, Islam N, et al. (2014) Malaria burden and control in Bangladesh and prospects for elimination: An epidemiological and economic assessment. Lancet Global Health 2: e98-e105.
3. Malaria National Strategic Plan (2020) National Malaria Control Program (NMCP), Bangladesh.
4. Meremikwu MM, Donegan S, Sinclair D, Esu E, Oringanje C (2012) Intermittent preventive treatment for children living in areas with seasonal transmission. Cochrane Database Sys Rev CD003756.
5. WHO Policy Recommendation (2012) Seasonal malaria chemoprevention (SMC) for Plasmodium falciparum malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa: World Health Organization.
6. Shea B, Grimshaw J, Wells G, Boers M, Andersson N, et al. (2007) Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 7: 10.
7. Higgings JP, Altman DG, Gotzsce PC, et al. (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343: d5928.
8. Lavis JN, Oxman AD, Souza NM, Lewin S, Gruen RL, et al. (2009) SUPPORT Tools for evidence-informed health Policymaking (STP) 9: Assessing the applicability of the findings of a systematic review. Health Res Policy Syst 7: S9.
9. Behrens RH, Bisoffi Z, Björkman A, Gascon J, Hatz CF, et al. (2006) Malaria prophylaxis policy for travellers from Europe to the Indian Sub-Continent. Malaria J 5: 1-7.
10. WHO (2012) World malaria report. Non serial publication. World Health Organization, pp: 260.
11. Behrens RH, Carroll B, Hellgren U, Visser LG, Siikamaki H, et al. (2010) The incidence of malaria in travellers to South-East Asia: Is local malaria transmission a useful risk indicator? Malaria J 9: 266.

Annex 1:

The AMSTAR Tool for appraising systematic reviews

1. Was an ‘a priori’ design provided?

The research question and inclusion criteria should be established before the conduct of the review.

☐ Yes
☐ No
☐ Can’t answer
☐ Not applicable

2. Was there duplicate study selection and data extraction?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

☐ Yes
☐ No
☐ Can’t answer
☐ Not applicable

3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

☐ Yes
☐ No
☐ Can’t answer
☐ Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

☐ Yes
☐ No
☐ Can’t answer
☐ Not applicable

5. Was a list of studies (included and excluded) provided?

A list of included and excluded studies should be provided.

☐ Yes
☐ No
☐ Can’t answer
☐ Not applicable

6. Were the characteristics of the included studies provided?

In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age; race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

7. Was the scientific quality of the included studies assessed and documented?

'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

11. Was the conflict of interest stated?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

For information on the AMSTAR tool see: Shea B, Grimshaw J, Wells G, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology. 2007;7(1):10.

Annex 2:

Assessment of the local applicability of the systematic review (SUPPORT tool 9)

Review reference: *Meremikwu MM, Donegan S, Sinclair D, Esu E, Oringanje C. (2012), Intermittent preventive treatment for children living in areas with seasonal transmission. Cochrane Database of Systematic Reviews, Issue 2. Art No.: CD003756. DOI: 10.1002/14651858.CD003756.pub4.*

1. Were the studies included in this systematic review conducted in settings similar to your country, or were the findings consistent across settings and time periods?

YES

All seven studies in this systematic review were conducted in west African countries, having topical and sub topical climate similar to Bangladesh. Over 90% of malaria cases in 13 endemic Districts of Bangladesh caused by plasmodium falciparum, which also predominant in African setting. Bangladesh also has topical monsoon, which provoked seasonal transmission of malaria; pre-school children and pregnant women are at higher biological risk. These studies included children less than six years of age. I think in terms of climate, malaria species and socioeconomic condition of the population are similar in both settings.

2. Are there important differences in on-the-ground realities and constraints in your chosen country that might substantially alter the feasibility and acceptability of the option?

NO

In the context of Bangladesh, three CHT districts among 13 high endemic districts are bordering with India and Myanmar, cross-country migration between populations is common leading to increase new cases. National Malaria Control Program (NMCP) in Bangladesh currently implemented home management of malaria control by providing ITNs and LLINs; and vector control by introducing IRS, LRS and IVM. The country achieved a significant progress towards malaria control though these 3 endemic (CHT) districts remain vulnerable. IPTc could be effective in CHT districts by reducing seasonal transmission and preventing new cases caused by migration.

According to WHO, IPTc should be used as 'Seasonal Malaria Chemoprevention' and it shows significant health benefits among children less than five years old [1]. "IPTc, defined as a full curative dose of an antimalarial alone or in combination given to children monthly or every two months during the malaria transmission season" [2].

The advantage of IPTc is that can be delivered through malaria clinics, run by NMCP. Adequate funds for the IPTc program need to be secured. The continuous integrated efforts from GFATM, GOB-HPNSDP and WHO towards funding make NMCP successful in terms of achieving malaria control in Bangladesh. Alongside, active participation of Government, NGO's, Private sectors and community already in place. So feasibility and acceptability should not be a problem.

3. Are there important differences in health system arrangements that may mean this option could not work in the same way?

NO

Bangladesh has dominant public health care system along with private sectors and NGO's. Integrated effort from NMCP and its partners funded mainly by Global fund (GFATM) and WHO; Bangladesh achieved substantial progress in decreasing malaria incidence. NMCP in Bangladesh has developed with the aim of achieving 'Zero indigenous transmission' and 'Zero death' by 2020.

Dedicated NMCP's field staffs are working rigorously in the community- distributing ITN's, LLIN's and also regular spraying of IRS in the endemic areas. NMCP has a good reporting system, so all the new malaria cases are being reported promptly.

Health system arrangements in Bangladesh are more or less Similar to the health systems in West African countries. Sufficient budget will be a major concern and also government and other sectors need to be collaborated, in terms of implementing IPTc.

4. Are there important differences in the baseline conditions that might yield different absolute effects even if the relative effectiveness was the same?

Yes

The overall prevalence of malaria in Bangladesh was 3.97 [4] and also found incidence of malaria was 2.1 cases /1000 population in 2012 [5]. In terms of disease prevalence and incidence, this Cochrane review data for relative reduction is the most suitable to apply in Bangladesh for malaria prevention.

Outcome	Assumed risk	Corresponding risk	Relative effect (95%CI)
	Control	IPTc	
Malaria incidence	2.1 per 1000	0.55 per 1000 (0.35 to 0.79)	RR 0.26 (0.17 to 0.38)
Parasite prevalence	3.97 per 1000	1.07 per 1000 (0.39 to 3.01)	RR 0.27 (0.1 to 0.76)

Approximately 14 million people are at risk of developing malaria in 13 endemic districts in Bangladesh [5]. The table below shows that the absolute number of reduction of malaria cases and the rate of reduction when IPTc is used

Malaria incidence	29,400 incidence of malaria if IPTc is not used	7700, incidence of malaria if IPTc is used	21,700 absolute number reduction
Parasite prevalence	55,580 parasite prevalence if IPTc is not used	14,980 incidence of malaria if IPTc is used	40,400 absolute number reduction

5. What insights can be drawn about options, implementation, and monitoring and evaluation?

IPTc is very effective in reducing transmission of seasonal malaria in children. Bangladesh has similar context in terms of climate, malaria species, and structure of the health system are similar to these African countries where the studies were conducted. Nevertheless, these studies were done under controlled environment where trained staff and active community involvement were present. In Bangladesh, a reasonable amount of staffs and resources already in place, so IPTc can be incorporated with existing malaria control programs. Available budget will be a concern, and the government and other sectors need better collaboration.

For further information on the SUPPORT tool used for this assessment see: Lavis JN, Oxman AD, Souza NM, Lewin S, Gruen RL, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP) 9: Assessing the applicability of the findings of a systematic review. Health Res Policy Syst 2009, 7 Suppl 1:S9