STRATEGIES TO DECREASE RELAPSES IN *P. VIVAX* CASES

Background Document for Session 6

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1 BACKGROUND

Relapses are one of the main challenges in the elimination of *P. vivax* malaria in the Americas. One of the barriers has been lack of adherence to treatment in patients given that the treatment regimen recommended by WHO includes primaquine (0.25 mg/kg body weight) to be given over 14 days. Some tropical strains of the parasite, particularly those located in East Asia and Oceania countries are tolerant to primaquine and require a higher dose (0.5 mg/kg body weight for 14 days). In order to improve adherence, some countries of the Region use a shortened scheme which includes primaquine (0.5 mg / kg body weight) given over 7 days. This shortened scheme has been based on the fact that the total primaquine dose of 3.5 mg/kg body weight is the key factor to avoid relapses in the strains prevalent in the Americas.[1] In meta-analyses performed, no significant difference in relapse rates has been found in the two schemes in the Americas, although the evidence base is not-strong.[2]

In studies conducted in the Americas using a total dose of 3.5mg/kg/body weight, a median un-weighted recurrence rate of 9.74% (IQR: 3.51% - 18.47%) was observed among the 14 different studies performed up to the year 2010.[3-12] Among the studies conducted between 2000 and 2015, the un-weighted recurrence was in median of 12.28% (IQR: 6.76%-18.47%) of the exposed participants.[5-14] No published studies have been found that may have evaluated the treatment schedule of PQ 0.5mg/kg body weight for 14 days in the Americas.

Furthermore, Brazil reports that for every 100 new cases of *P. vivax* and mixed infections in the years 2013-2015, around 18 cases were recurrences/relapses of *P. vivax.* This reported recurrence rate is however much lower in Colombia (11% in 2015) and Honduras (5% in 2015-2016). On the other hand data from Venezuela demonstrates recurrence rate as high as 28.9% in *P. vivax* and mixed infections in 2016 in the state of Bolivar. Other countries have not had relapse cases in the past 3 years, or do not have surveillance systems sensitive enough to detect recurrences and relapses.

A majority of these recurrences, when considered relapses, are usually ascribed to be due to non-adherence to the complete treatment scheme. Studies in South America have demonstrated varied rates of non-adherence to primaquine therapy. Even with the primaquine treatment scheme shortened to 7 days, the adherence did not exceed 62.2% in the Amazon region of Peru.[15] However, in Brazil this has been consistently higher than 75% in multiple studies conducted in recent years. [16-18] In either case, it indicates that around ≥25% of cases of all *P. vivax* cases could be actual relapses given the non-adherence to the complete treatment scheme.

Nonetheless, not all relapses may be due to non-adherence to treatment. Even in controlled clinical trials, the median un-weighted relapse rate is quite high at 12%. This may be because of tolerant strains circulating in the Region and which require a total dose greater than 3.5 mg / kg body weight. Resistance to primaquine could also be a possible reason. However, even if resistance to primaquine is detected, there is no second line of therapy for *P. vivax* hypnozoites.

The risk of adverse events and patient tolerance in G6PD normal patients at higher doses also limits increasing daily doses and decreasing the number of total days of treatment still further.

2 Strategies to be considered:

2.1 Strategies that can be implemented with available evidence

1. Graphic instructions to improve adherence.
2. Improved prescription.
3. Change of treatment schedule from 0.25 mg/kg for 14 days to 0.5 mg/kg for 7 days. (low G6PDd prevalence areas with exceptional situations were adherence to 14 days is seriously affected)
4. Semi-supervised treatment strategies and completion of treatment in non-adherent patients.
5. Strictly supervised treatment.
6. Promote use of PQ always with food to decrease possible side effects.
7. Monitoring with parasitological tests of control monthly up to 6 months.
8. Local surveillance systems capable of detecting possible recurrences of infection at the time of notification in burden reduction areas.
9. Investigation of cases to identify relapses in elimination areas.

2.2 Strategies that require operational research

10. Cost-effectiveness of strictly supervised vs. semi-supervised treatment with primaquine.
11. Increase in adherence to treatment when shortening of schemes from 14 to 7 days. (low G6PDd prevalence areas with exceptional situations were adherence to 14 days is seriously affected)

2.3 Innovative strategies requiring review of policies, evidence or consultative processes

12. **Retreatment of cases of P. vivax (like China "spring treatment").**

For further development by PAHO

13. Increase of PQ dose to 0.5 mg/kg for 14 day and use of PQ doses at 0.5mg/kg for 14 days in case of recurrences / relapses.
14. First-line treatment with a medication with a longer half-life than that of chloroquine: ACT
15. Promote use of PQ even when taking alcohol, especially in populations like miners.
16. Introduction of Tafenoquina

3 References

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