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Reducing *P. vivax* relapses for malaria control and elimination in the Americas

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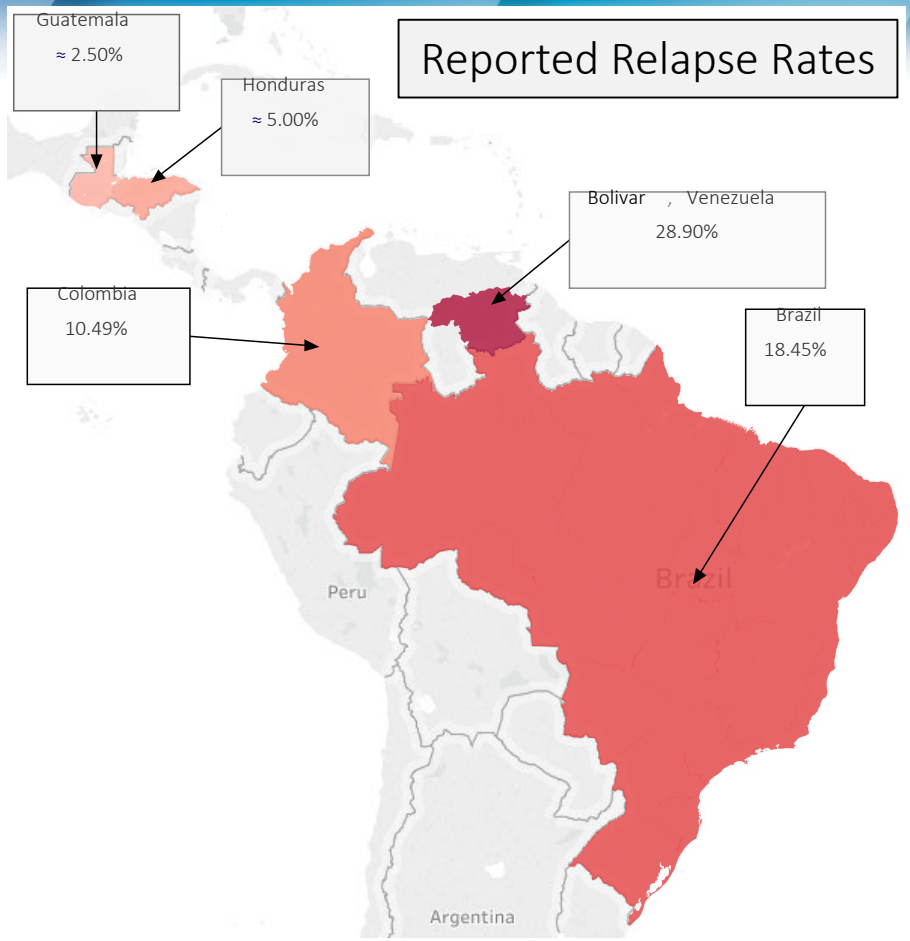
Background (1)

- Relapses in *P. vivax* are considered to be the main challenge to elimination
- 0.25 mg/kg body weight over 14 days – current recommended treatment scheme with primaquine
- 0.5 mg/kg body weight over 7 days used in some countries
  - Based on the rationale that “total dose” of 3.5mg/kg is more important
- Meta-analyses have not found significant difference between relapse rates between the two schemes
  - However, evidence base is not strong and more studies are required

Background (2)

- Efficacy of primaquine (3.5mg/kg body weight) in the Americas
  - 9.74% (IQR: 3.51% - 18.47%) median un-weighted recurrence rate in 14 studies up to 2010
  - 12.28% (IQR: 6.76%-18.47%) median un-weighted recurrence rate in studies conducted between 2000-2015
- No studies conducted for PQ 0.5mg/kg body weight for 14 days in the Americas



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Background (3)

- Adherence rates with PQ given for 7 days
  - 62.2% in Peru (1 study)
  - 65.9% in Ecuador (1 study)
  - >75% in Brazil (3 studies)

- Controlled trials show relapse rate >10%
- ≥25% of cases not adherent with shortened dosage
- Relapse higher in areas with higher transmission
- Primaquine only anti-hypnozoite treatment currently available

Adherence rates with PQ given for 7 days vs 14 days (Grey literature)

Country	Location	Year	Adherence	
			7 days	14 days
*Ecuador	Esmeraldas	2004	80.0%	46.9%
*Ecuador	Milagro	2004	87.8%	27.8%
*Venezuela	Tumeremo	2004	88.2%	84.3%
*Venezuela	Atures	2004	66.7%	68.3%
*Colombia	Tierralta	2004		13.2%
Ecuador	Huaquillas	2004		74.6%
Brazil	Braganca-Augusto	2005	95.7%	
Brazil	Colniza	2005	93.0%	
Colombia	Apartado	2005		83.6%
Ecuador	Varios	2005	60.4%	
**Colombia	Tumaco	2009	0%	
**Colombia	Pizarro	2009		33%

*No standardized protocol
**Sample size very small (<10)

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Strategies (1)
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.*
4. Semi-supervised treatment strategies and completion of treatment in non-adherent patients.
5. Strictly supervised treatment.

*low G6PDd prevalence areas and where adherence to 14 days is low

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Strategies (2)
That can be implemented with available evidence

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.

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Strategies (3)
That require operational research

1. Cost-effectiveness of strictly supervised vs. semi-supervised treatment with primaquine.

2. Increase in adherence to treatment when shortening of schemes from 14 to 7 days by country.*

*low G6PDd prevalence areas and where adherence to 14 days is low

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Strategies (4)

That require review of policies, evidence or consultative process

1. **Retreatment of cases of *P. vivax* (China's "spring treatment").**

For further development by PAHO

2. Increase of PQ dose to 0.5 mg/kg for 14 day.
3. Use of PQ doses at 0.5mg/kg for 14 days in case of recurrences / relapses.
4. First-line treatment with a medication with a longer half-life than that of chloroquine: ACT.
5. Promote use of PQ even when taking alcohol, especially in populations like miners.
6. Introduction of Tafenoquine.

*low G6PDd prevalence areas and where adherence to 14 days is low

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RETREATMENT OF CASES OF *P. VIVAX*

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Retreatment (1)
Hypothesis and Evidence base

- Relapses in tropical strains occur at very frequent and short intervals
- Those with *P. vivax* can harbour hypnozoites even after treatment – various reasons
- Second treatment before the first relapse would decrease early relapses – especially in tropical strains
- Potential to decrease transmission intensity and possible elimination

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Retreatment (2)
Hypothesis and Evidence base

- Evidence from studies conducted in China (circa 1960s)

Table 1: Dose Regimens by Group Type

Group type	Group number	Experimental protocol	Dose for one regimen (adults, mg)				Double regimen (Days between regimens)
			Primaquine (base value)			Chloroquine (base value)	
			Daily dosage	# days medicated	Total amount		
Experimental group	1	135mg Primaquine double regimen	22.5	6	135	600	15
	2	112.5mg Primaquine double regimen	22.5	5	112.5	600	15
	3	90mg Primaquine double regimen	30	3	90	600	15
Control group	4	135mg Primaquine single regimen	22.5	8	180	600	-
	5	135mg Primaquine single regimen	30	3	90	600	-
	6	600 mg Chloroquine double regimen	-	-	-	600	20

Table 2: Results- Relapse Rates by month by therapy regimens

Group type	Group number	Number of cases	Relapse rate after taking medication by month (%, cumulative)					
			1	2	3	4	5	6
Experimental group	1	137	0	0	0	0	2.2	2.2
	2	125	0	0	0	0	1.6	3.2
	3	126	0	0.8	1.6	4	5.6	10.3
Control group	4	153	0.7	2	3.3	6.5	8.5	11.8
	5	68	0	1.5	4.4	13.2	25	32.4
	6	136	1.5	11.8	25	39.7	52.9	66.2

Retreatment (3)
Hypothesis and Evidence base

- Evidence from studies conducted in China (circa 1960s)

Table 3: Number of malaria cases by month in XXX county, China in 3 years

Year	Number people surveyed	Number people falling ill	Illness rate (%)	Number people falling ill by month											
				Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
1959	974	425	43.6	0	1	2	10	38	69	176	105	21	3	0	0
1960	974	600	61.6	0	3	6	21	54	103	266	112	21	5	4	5
1961	1029	219	21.3	8	21	27	25	25	18	34	27	21	6	7	-

Table 4: Results from blood surveys conducted before and after retreatment with antimalarials

Age group	Early May (before antimalarials)			Early August			Early October		
	Number tested	Number Positive	%	Number tested	Number Positive	%	Number tested	Number Positive	%
0-14	155	76	49	143	64	44.7	142	73	51.4
15 years and up	154	25	16.2	168	18	10.7	193	26	13.5
All ages	309	101	32.7	311	82	16.4	335	99	29.5

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Retreatment (4)
Proposed strategy

- All *P. vivax* cases (with exceptions) after 45 days of diagnosis
  - Asymptomatic – treated as *P. vivax* case irrespective of compliance in previous episode
  - Symptomatic – tested with microscopy
    - Positive – treated as per diagnosis
    - Negative – considered as asymptomatic and treated as *P. vivax* case
- Alternative: treatment after 60 days
- G6PD and adverse reactions: only those previously treated with PQ and no adverse reactions will be retreated

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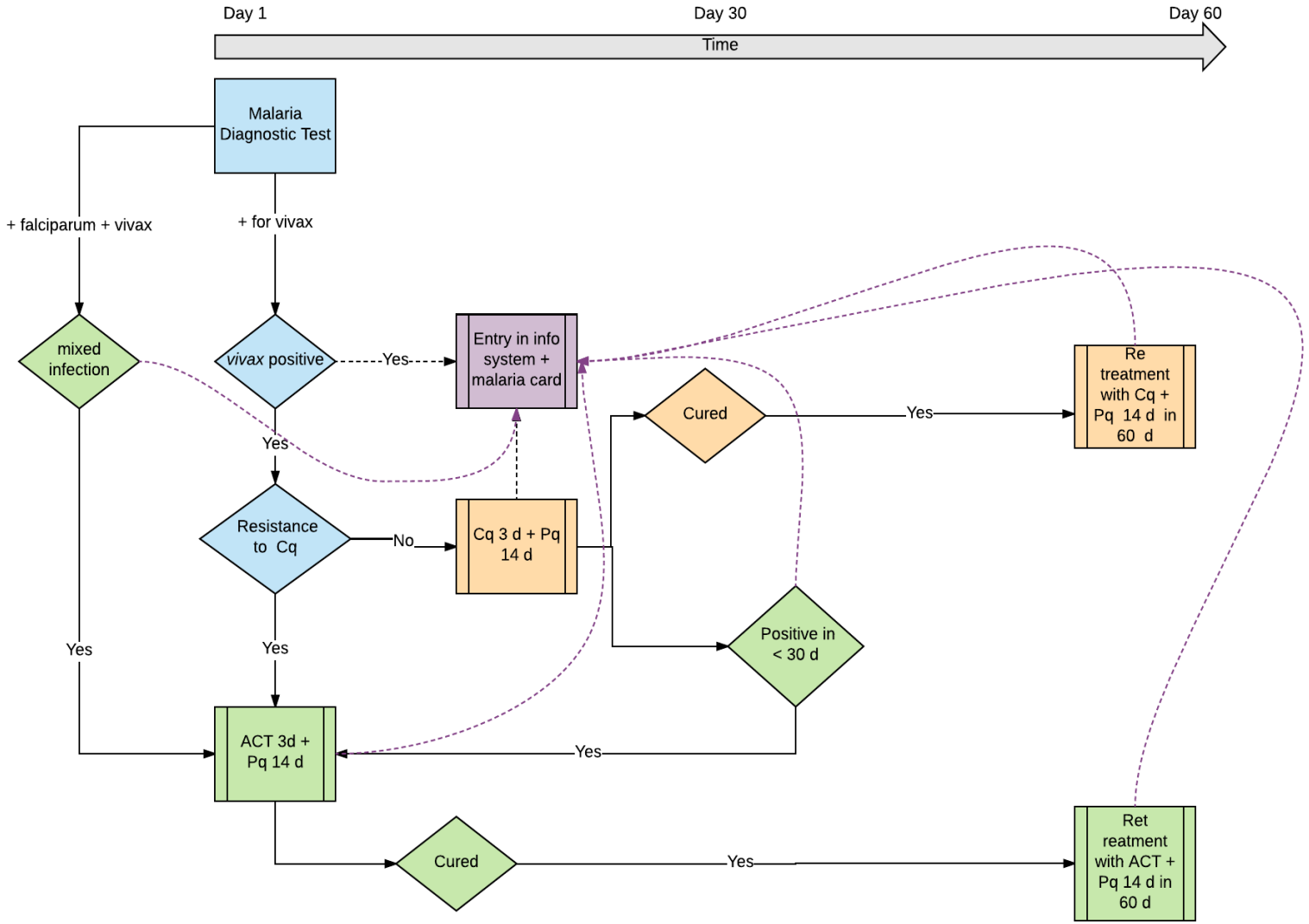
Retreatment (5)
Proposed strategy



Retreatment (6)
Cost Benefit Analysis

Factors in favour

- Individual benefits: less incapacity, anemia in children, suffering among others
- Collective benefits: Reduce transmissions
- Collateral benefits: would sensitize the heath system about importance of relapses
- Improves the tracking of patients, cluster of cases and hot spots with *P. vivax* malaria
- Complements other elements of a comprehensive strategy for *P. vivax*
- Easily adapted to seasonal and work related malaria in *P. vivax*

Factors against

- Operational issues: more effort to find patients, consumption of resources and working hours
- Ethical concerns related to treatment of people that don't need it
- The expectation that there will be a second treatment may reduce adherence to the first course of treatment.
- Adherence problem can also be an issue on the second course of treatment.
- More risk of adverse effects that with only one course of treatment.
- Minor side effects during the first course of treatment may not be noticed or reported by the patient who will be exposed to a second course.

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Questions and Discussion Points

1. Does the TAG consider that PAHO should promote retreatment as one innovative intervention to reduce relapses?

2. If so, specific comments regarding the retreatment scheme and strategy

3. Recommendations and comments about road map to the implementation of retreatment

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Thank you

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