Pharmacological modelling of malaria drug treatment and evaluation of drug efficacy trials

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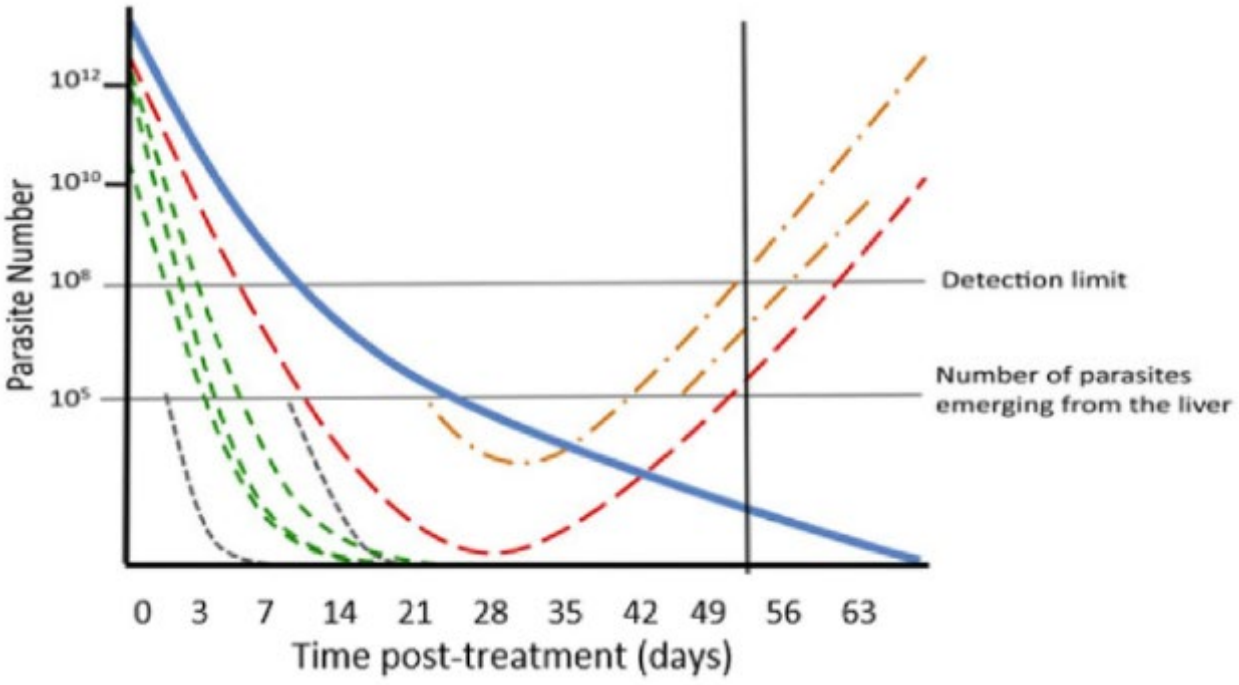
Talk structure

1. The method
2. The problem
3. The solution (?)
4. The implications

Note: I am only going to talk about falciparum malaria

1. Method: mechanistic pharmacokinetic/ pharmacodynamic modelling (mPK/PD)

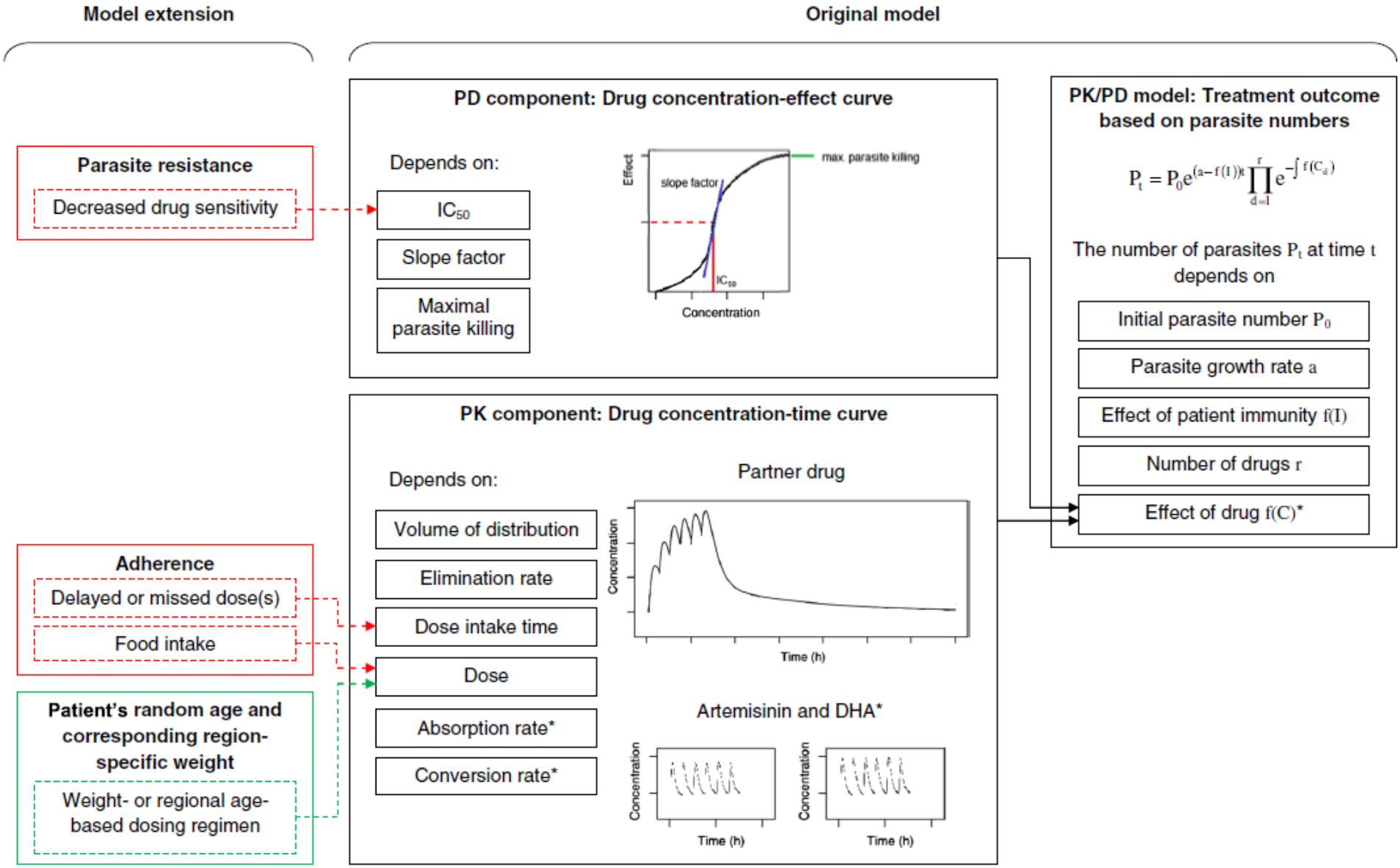


Hill equation

$$f(C) = \frac{V \cdot C^n}{C^n + K^n}$$

f(C) is drug killing function
C is the drug concentration
V is the maximal parasite-killing
K is the IC50 concentration i.e. at which 50% of the maximal killing rate occurs
n is the slope of the dose-response curve.

Blue line is drug concentration
This is converted into parasite killing through the Hill equation
Therapeutic outcome is a simple race: does the body eliminate the drug before the drug eliminates the infection



From: Hodel, E., et al. (2014). "Optimizing the programmatic deployment of the anti-malarials artemether-lumefantrine and dihydroartemisinin-piperaquine using pharmacological modelling." *Malaria Journal* 13(1): 138.

The modelling has been applied to different questions e.g.

Jaki, T., et al. (2013). "Analysing malaria drug trials on a per-individual or per-clone basis: a comparison of methods." *Statistics in Medicine* 32(17): 3020-3038.

Hodel, E., et al. (2014). "Optimizing the programmatic deployment of the anti-malarials artemether-lumefantrine and dihydroartemisinin-piperaquine using pharmacological modelling." *Malaria Journal* 13(1): 138.

Kay, K. and I. M. Hastings (2015). "Measuring windows of selection for anti-malarial drug treatments." *Malaria Journal* 14(1): 1-10.

Jones, S., et al. (2019). "Optimal treatments for severe malaria and the threat posed by artemisinin resistance." *Journal of Infectious Diseases* 219: 1243-1253.

2. The problem: antimalarial drugs have long half lives, so….

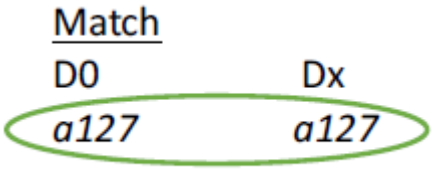
When a patient enrolled in a malaria drug trial comes back with recurrent malaria after, say, 3 weeks is that malaria a drug failure or a new infection?

One solution is “molecular correction” i.e. genotype the infections at treatment and if a patient returns during follow up:

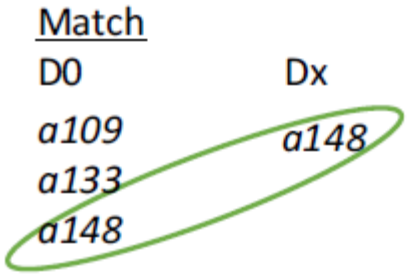
- If the genetic profiles “match”, then s/he has a drug failure
- If the profiles differ, then s/he has a new infection

Example of genotyping at one locus: D0 is sample taken at treatment, Dx is when patient returns

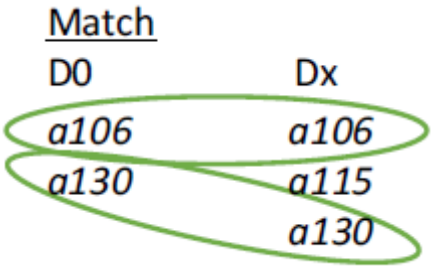
Patient #1:
Single clone in DO
Single clone in Dx samples



Patient #2:
Three clones in DO
one clone in Dx samples



Patient #3:
Two clone in DO
Three clone in Dx samples



Etc, etc, etc

So what defines a “Drug failure”

- **WHO recommend genotyping 3 hypervariable genes (msp1, msp2, glurp)**
- **At each locus: A “match” occurs if one (or more) allele(s) detected in both treatment and recurrent blood samples [the allele potentially comes from a clone that failed treatment].**
- **<u>If</u> a match occurs at all three loci than the malaria is classed as a drug failure. <u>Else</u> it is a new infection**
- **[Logic is fine provided genotyping is perfect]**

World Health Organization, Malaria for Medicines Venture. 2008. Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations. World Health Organization, Geneva, Switzerland.

BUT genotyping is extremely imperfect

- **Genotyping WHO markers miss clones present at <25% of the total biomass**
- **Genetic signal varies from day to day (presumably due to sequestration) with only around 50% of alleles found on consecutive days.**
- ***Ever since the 2007 WHO meeting, researchers have been worrying about how this lack of perfection affects accuracy of molecular correction.***
- ***Its not a question of whether the WHO method is inaccurate: it's a question of how inaccurate***

3. The solution?? Modelling!

Already have

- **Drug mPK/PD simulations for current first line antimalarials**

Combine with

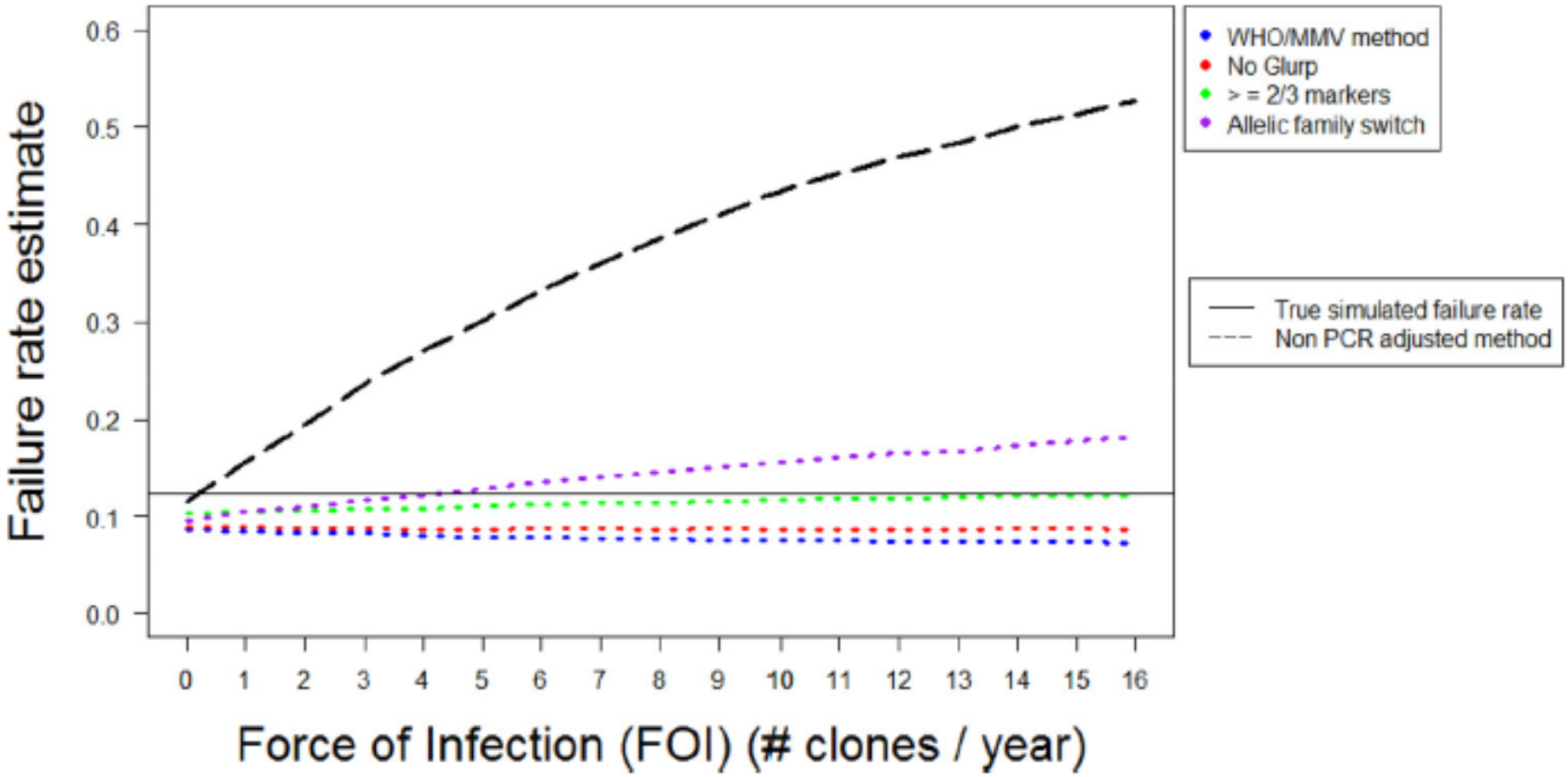
- **Genotyping methodologies and limitations**
- **Trial follow-up and analyses**
- **Local malaria epidemiology, in particular rate of acquisition of new infections**

Simulate clinical trials, blood genotyping and analysis.

Validated against field/clinical data

Key result: Current WHO method misses around half drug failures (many plots like the one below)

Analysis of simulated trial data for DHA-PPQ with a follow-up period of 42 days.



But our simulations suggest:

Can get accurate results by

- **Using a >2/3 algorithm with the WHO genotyping**
- **Bayesian analysis of microsatellites (CDC markers)**
- **Using deep-sequenced amplicons**

Jones, S., et al. (2019). "Improving methods for analysing anti-malarial drug efficacy trials: molecular correction based on length-polymorphic markers *msp-1, msp-2 and glurp." Antimicrobial Agents & Chemotherapy 63.*

Jones, S., M.Pluckinski et al. (2020). "A Computer Modelling Approach To Evaluate the Accuracy of Microsatellite Markers for Classification of Recurrent Infections during Routine Monitoring of Antimalarial Drug Efficacy." *Antimicrobial Agents and Chemotherapy* 64(4): e01517-01519.

Jones, S., et al. (2021). "Should deep-sequenced amplicons become the new gold-standard for analysing malaria drug clinical trials?" *Antimicrobial Agents Chemotherapy* 65(10): e00437-00421.

Simulations are consistent with field data

- **Then 2/3 algorithm gives roughly double the failure rate compared to the WHO methodology.**

- **In the few cases where the WHO method, the ≥2/3 method and deep sequenced amplicons were applied to same data set, the latter two were consistent and both reported roughly double failure rate compared to WHO method.**

(See Hastings, I. M. and I. Felger (2022). "WHO antimalarial trial guidelines: good science, bad news?" Trends in Parasitology 38(11): 933-941.)

4. The implications

- **Drug resistance is spreading through Africa***
- **WHO mandate change in first line antimalarial when failure rate exceeds 10%**
- **Current WHO-approved surveillance methods are poor at detecting drug failures and estimated failure rate should reasonably be doubled**

***Example of places where trials show ACT efficacy <90%:**

- **2013 Angola AL<90%**
- **2015 Angola AL<90%**
- **2016-2017 Kenya AL<90%**
- **2017-2018 Burkina Faso AL<90%, DP<90% (2 sites each)**
- **2017-2018 DRC AL<90%, DP<90%**
- **2018-2019 Uganda AL<90%**
- **2019 Angola AL<90%**
- **2021 Angola AL<90% (*Still unpublished)**
- **2022 Tanzania AL<90% (*Still unpublished)**

We have been in this situation before with Chloroquine: policy decision making is typically slow to respond

LSTM

VIEWPOINT

Viewpoint

WHO, the Global Fund, and medical malpractice in malaria treatment

Amir Attaran, Karen I Barnes, Christopher Curtis, Umberto d'Alessandro, Caterina I Fanello, Mary R Galinski, Gilbert Kokwaro, Sornchai Looareesuwan, Michael Makanga, Theonest K Mutabingwa, Ambrose Talisuna, Jean François Trape, William M Watkins

These links between drug resistance, treatment failure, and finally death are not controversial. WHO concurs that chloroquine resistance is a "very likely" reason why childhood malaria deaths in Africa are increasing, and that chloroquine "has become useless in most malaria-endemic areas".[2,9] WHO further agrees that resistance to

(Lancet 2004 Vol. 363 pp 237-240)

We have been in this situation before: care-givers generally do not recognise the problem

Most antimalarials given presumptively to treat (undiagnosed) fevers.

BUT

- **Most childhood fevers (~67% even in moderate/high transmission areas) are not due to malaria and self-resolve.**
- **Even if resistance if high the most infections may still be cured (e.g. if resistance is 20% then 80% of infections are cleared)**
- **The small proportion that do fail treatment likely recur weeks after treatment and are not recognised**

"the most insidious consequence of presumptive treatment may be that perceived drug efficacy remains high even for a drug that is failing badly, leading to its continued use and a lack of consumer pressure to change treatment policies"

Hastings, I. M., E. L. Korenromp and P. B. Bloland (2007). "The anatomy of a malaria disaster: drug policy choice and mortality in African children." *Lancet Infectious Diseases* 7(11): 739-748.

Conclusions

- **Mechanistic Pk/PD modelling allows us to infer malaria parasite dynamics that cannot be directly observed.**
- **We can combine this modelling with technical details of genotyping used in molecular correction to evaluate how well malaria drug trials perform in practice.**
- **Current WHO-recommended method in areas of moderate to high transmission (i.e. in presence of new infections) probably miss around half of drug failures in trials.**
- **It will almost certainly fall on the academic community to try and implement improved methodologies to drive drug policy changes**

Acknowledgments

Sam Jones (now at Medicines for Malaria Venture (MMV))

Katherine Kay (Now at Metrum Research Group, Connecticut, USA)

Eva Maria Hodel (Now at University of Berne)

Ingrid Felger (Swiss TPH)

Mateusz Plucinski (CDC)

Eric Halsey (CDC)

Funding: Medical Research Council, B&MGF, Swiss TPH

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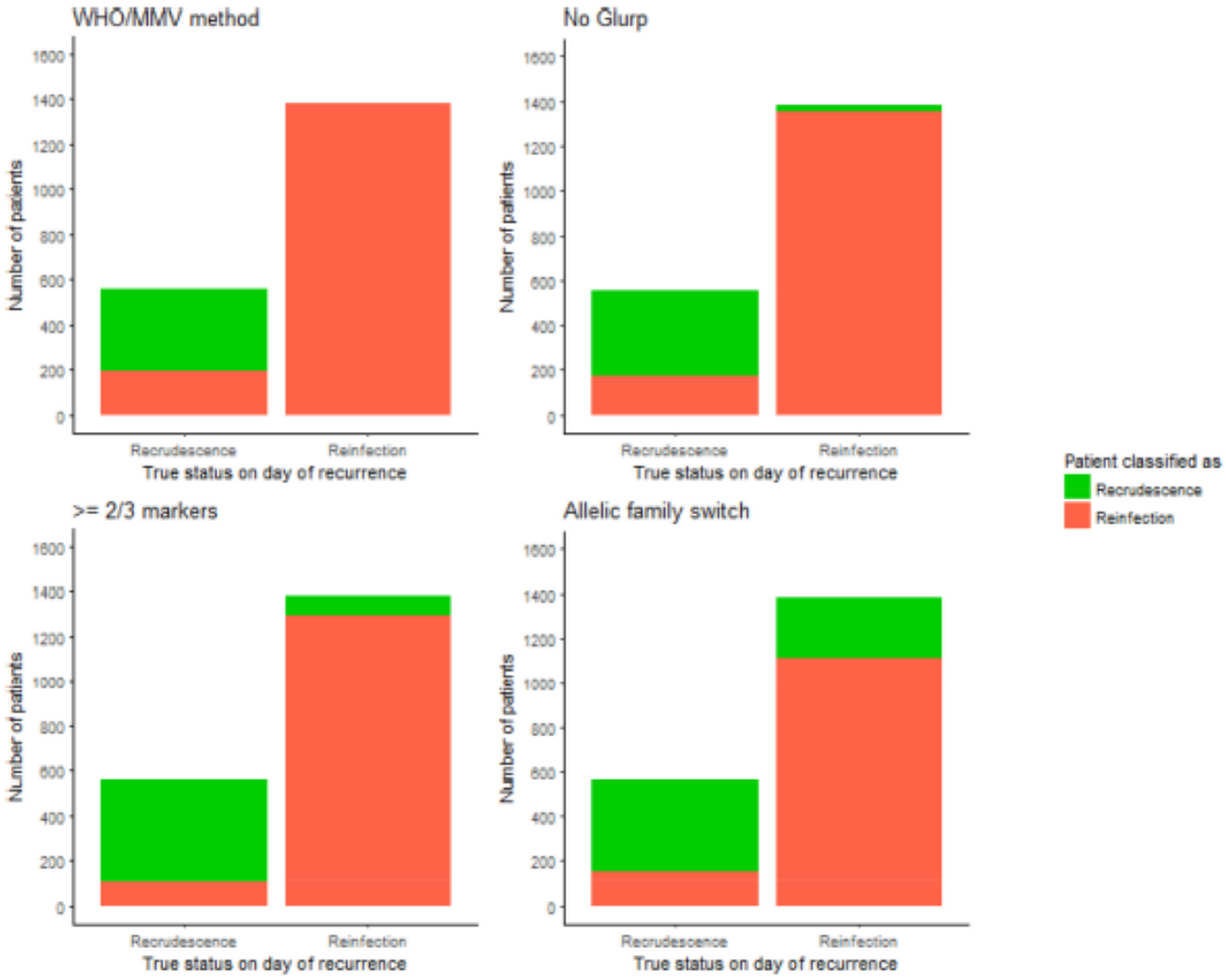

Reserve slide #2