Malaria Molecular Surveillance Study Design Workshop

Module 6: Designing a study for multiple end-points

What do we mean by multiple end-points?

We are often interested in designing our study to test more than one outcome

In MMS, our sequencing panels often capture genetic information on ***many molecular markers***

E.g. *pfhrp2* gene deletions + drug resistance markers

How do we design and power our study?

Prevalence estimation: drug resistance mutations

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Sample size* = **32 samples**

**We can use DRpower* `get_sample_size_presence()`

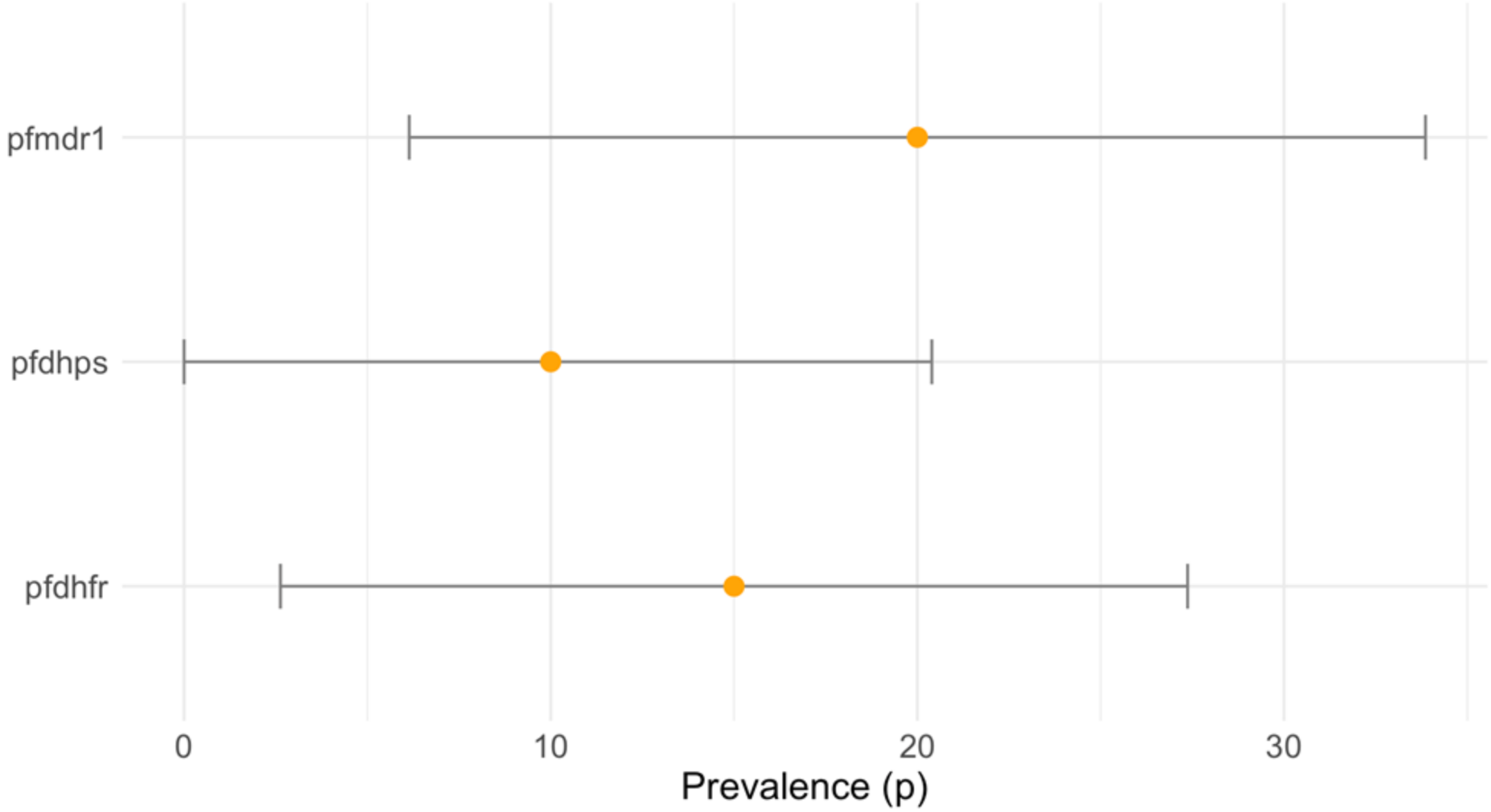
Prevalence estimation: drug resistance mutations

We have now collected data from our 32 samples, but we also want to estimate the prevalence of other drug resistance markers.

Based on expert knowledge, we suspect many of these markers are at high prevalence.

Drug resistance marker	Assumed prevalence (p)
pfdhps	0.10 (10%)
pfdhfr	0.15 (15%)
pfmdr1	0.2 (20%)

High margin of error (CIs)



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   - This will ensure that you have sufficient power and sample size over all end-points!

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3. You don't have to be powered to detect everything!
   - It's OK if some things are estimated with low power or precision (eg secondary end-points). They can still act as pilot data to guide future studies.

Going back to our worked example

We design our study to have **two primary end-points**:

1. Detect rare *pfk13* variant mutations (assuming 5% prevalence)
2. Estimate prevalence of *pfdhps* mutation (assuming 10% prevalence)

What steps do we need to take?

Power analysis for both end-points

Calculate minimum sample size required for both end-points (80% power)

- Detection of *pfk13* mutation (assumed prevalence 5%)

  Sample size = **32 samples**

- Estimation of *pfdhps* mutation prevalence (assumed prevalence 10%)

  Sample size* = **139 samples**

  **We can use DRpower* `get_sample_size_margin()`

Which sample size do you choose?

Choose the largest sample size!

We choose 139 as our target sample size (to estimate prevalence of *pfmdr1*) but we are now over-powered for detection of *pfk13* rare mutations

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We are now powered to detect a prevalence of **2% rather than 5%**
… and 75% powered to detect a **1% prevalence**!

Choose the largest sample size!

We choose 139 as our target sample size (to estimate prevalence of *pfmdr1*) but we are now over-powered for detection of *pfk13* rare mutations

Let's revisit our analysis now….

We are now powered to detect a prevalence of **2% rather than 5%**
… and 75% powered to detect a **1% prevalence**!

There is interplay between the different power analyses for our various primary endpoints. As always, we are looking to strike a balance between what is feasible and what provides the most useful information

Summary

- Studies with multiple end-points are common and it is important to specify our primary end-points *before* conducting our study

- We power for our primary end-points and always select the largest sample size

- We always need to balance power vs feasibility of target sample sizes (eg we don't have to be powered to detect *everything* - pilot data is still useful!)

Module 6 activity

Format: Scenario-based role-play

- Work in groups. Each person given a specific role
- Together, you will design a multi-cluster study for multiple end-points
- You will need to trade off design choices – there is no one right answer!
- Present you design back to the group

Workshop materials

https://mrc-ide.github.io/MMS-SD_workshop/