Comparative modelling of dengue vaccine impact

WHO modelling working group

Overview

- Groups and models contributing
- Model fit to trial data
- Predicted health impacts of vaccination
- Health-economic outputs
- Conclusions

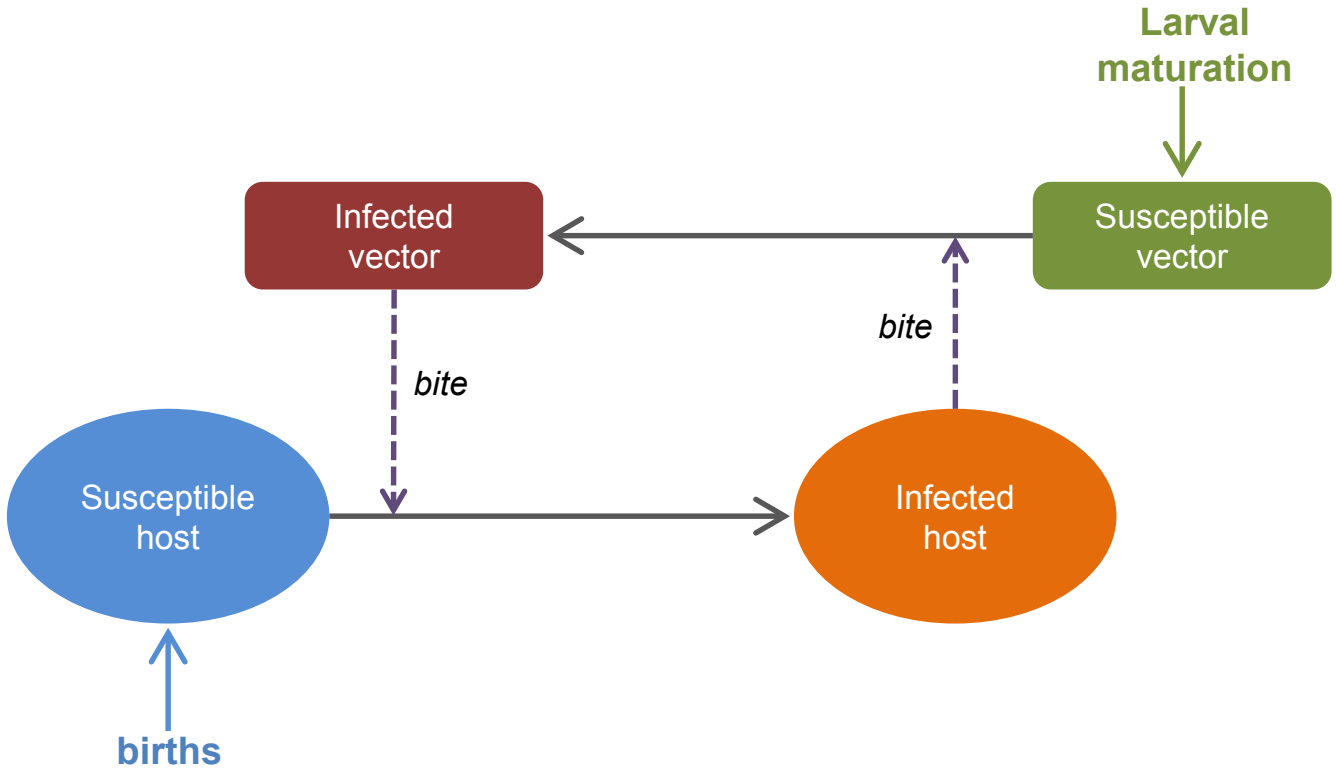
Groups and models

Groups & models

Group	Model type	Fitted to trial	Vectors	Trans ∝ symptoms	Demography
Sanofi Pasteur	Deterministic non-spatial	Yes (both, pre LTFU)	Yes	Yes	Brazil
Johns Hopkins + Univ Florida	Deterministic non-spatial	Yes (both)	Yes	Yes	Brazil
Imperial College London	Deterministic non-spatial	Yes (both)	Yes	Yes	Brazil
Duke Univ	Deterministic non-spatial	Calibrated	No	No	Brazil
Univ Florida	Stochastic spatial	No	Yes	Yes	Mexico
Univ Western Australia	Stochastic spatial	No	Yes	No	Thailand
Notre Dame Univ	Stochastic spatial	No	Yes	Yes	Peru
Exeter+Oxford Univs	Stochastic spatial	Yes (CYD14)	Yes	No	Generic (65 y mean lifespan)

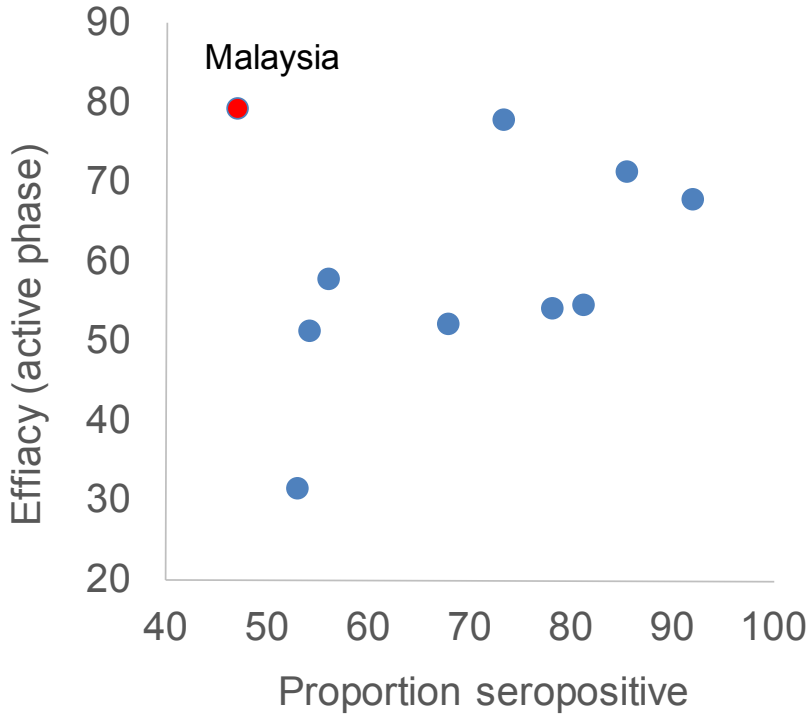
Common features

- 4 serotypes – homologous and heterologous immunity
- Vectors (all but 1 model)
- Stratified by host age
- Include immunity, disease, seasonality
- Standardised outputs for this exercise



Seropositivity and efficacy

- Loose (but significant) correlation between active phase efficacy and proportion seropositive by country across CYD14 and CYD15
- Malaysia an outlier in active phase – but not in hospital phase



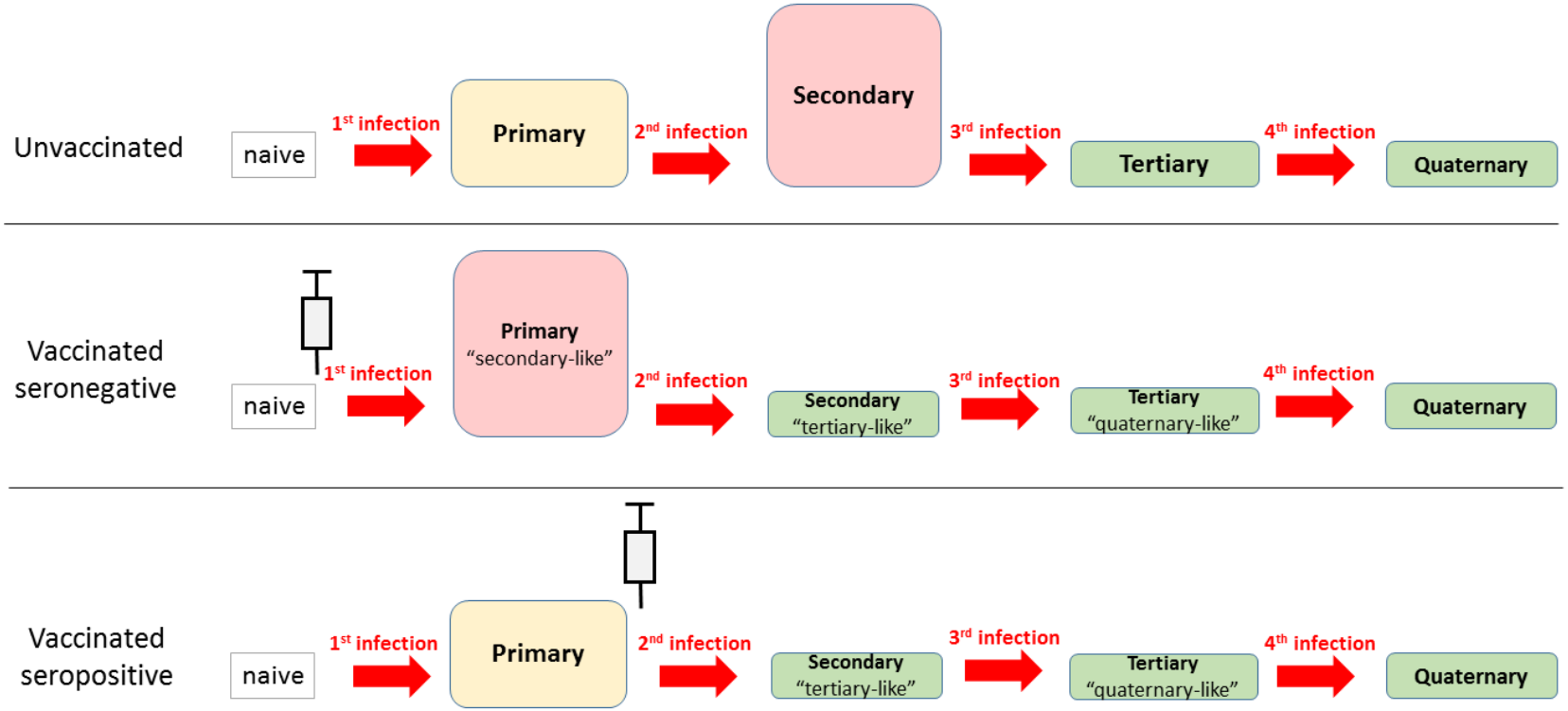
Comparing hospitalisation in active and hospital phases

Incl Y4 data

	Active phase Relative Risk	Y3 Hospital phase Relative Risk	Y4 Hospital phase Relative Risk	Fold increase
CYD15 (9-16) [Latin America]	0.21 (18 & 43 cases)	0.53 (16 & 15 cases)	0.43 (6 & 7 cases)	2.5
CYD14 (9-14) [SE Asia]	0.17 (10 & 30 cases)	0.57 (8 & 7 cases)	0.73 (19 & 13 cases)	3.4
CYD14 (2-8) [SE Asia]	0.44 (30 & 34 cases)	1.58 (19 & 6 cases)	1.19 (38 & 16 cases)	3.6

- Relative risk of hospitalisation increased ~3 fold in both <9s and >9s in both CYD 14 and 15, comparing Y1+Y2 with Y3
- Y4 data broadly consistent with Y3 – slight indication of reduced relative risk in 2-5s, increased in 9-11s (esp in CYD14)
- Cumulative relative risk of hospitalisation for Y1-4 now >1 for 2-5s, <1 for all other age groups

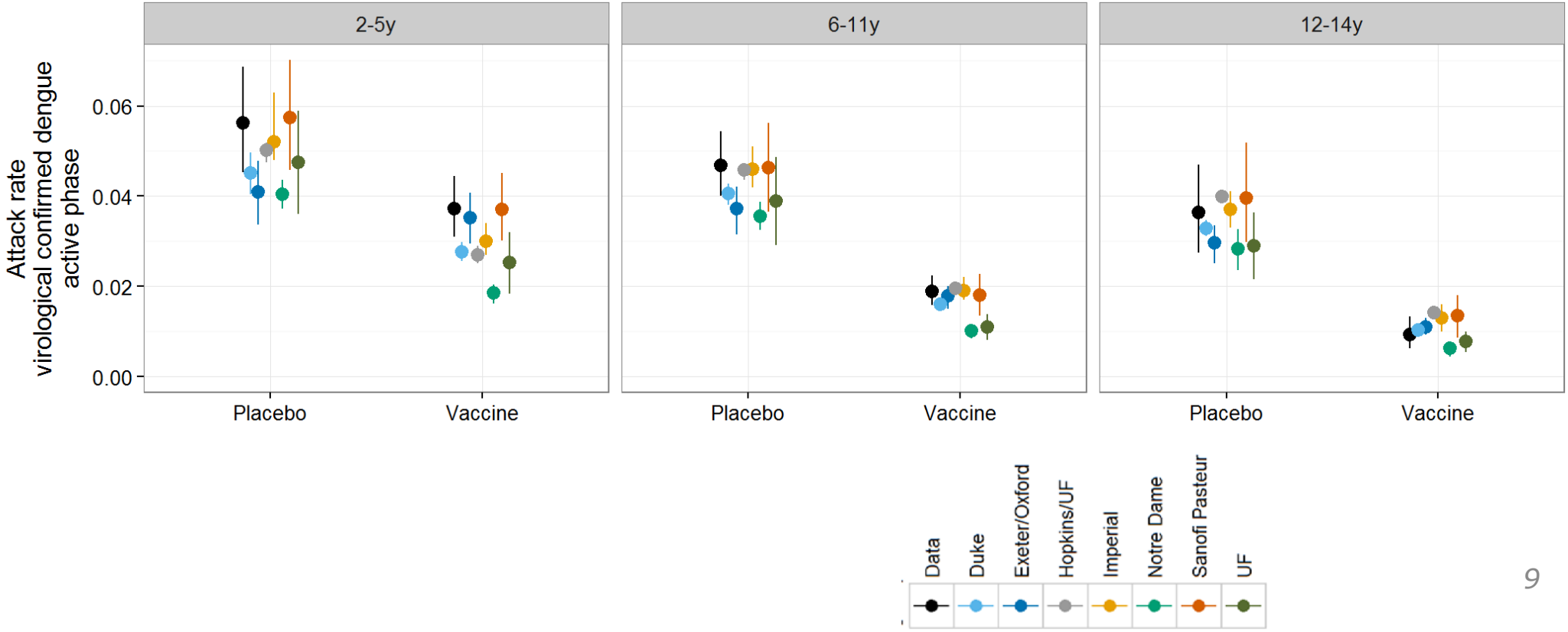
Vaccine mode of action



- Vaccination primes the immune system similarly to infection:
  1. Temporary high degree of cross-immunity in at least seronegative recipients
  2. Seronegative recipients have secondary-like infection once cross-immunity wanes
  3. Seropositive recipients have tertiary-like infection once cross-immunity wane

CYD14 fit: active phase attack rates

- Sanofi, Imperial, Hopkins, Duke & Exeter models fitted to or calibrated against phase 3 trial data for Y1-3 (other models used similar parameters)
- Y4 data not available when models fitted
- Models fitted to data do better than others, but all adequately reproduce trends



CYD14 fit: hospital phase attack rates

- No model fully reproduces 2-5 relative risk, but 6 out of 8 show RR>1
- Sanofi, UF models give 2-5y RR <1

Model calibration predates Y4 data – RR>1 in CYD14 6-11 age group not currently predicted by any model

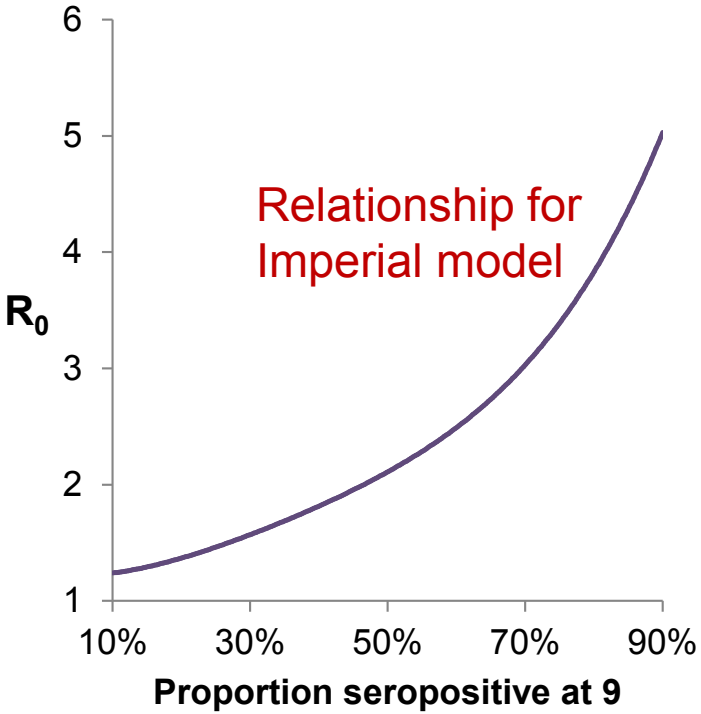
Health impact of vaccine

Vaccination policies modelled

- **Reference** scenario: routine vaccination of 9 year olds
  - Assume 80% coverage by default, but also consider 50%
  - Examine alternative ages of vaccination between 10 and 18
  - Also examine additional effect of one-off catch-up campaign - 80% of 10-17 year olds when vaccine is first introduced
- Assume all vaccine recipients receive 3 courses

‘Endemicity’ and transmission intensity

- Dependence of efficacy on serostatus means that vaccination impact varies with the proportion of recipients who are seropositive
- So we examine impact in settings with 10%, 30%, 50%, 70% or 90% of 9 year olds being seropositive on average
- Proxy for dengue transmission intensity (R_0)

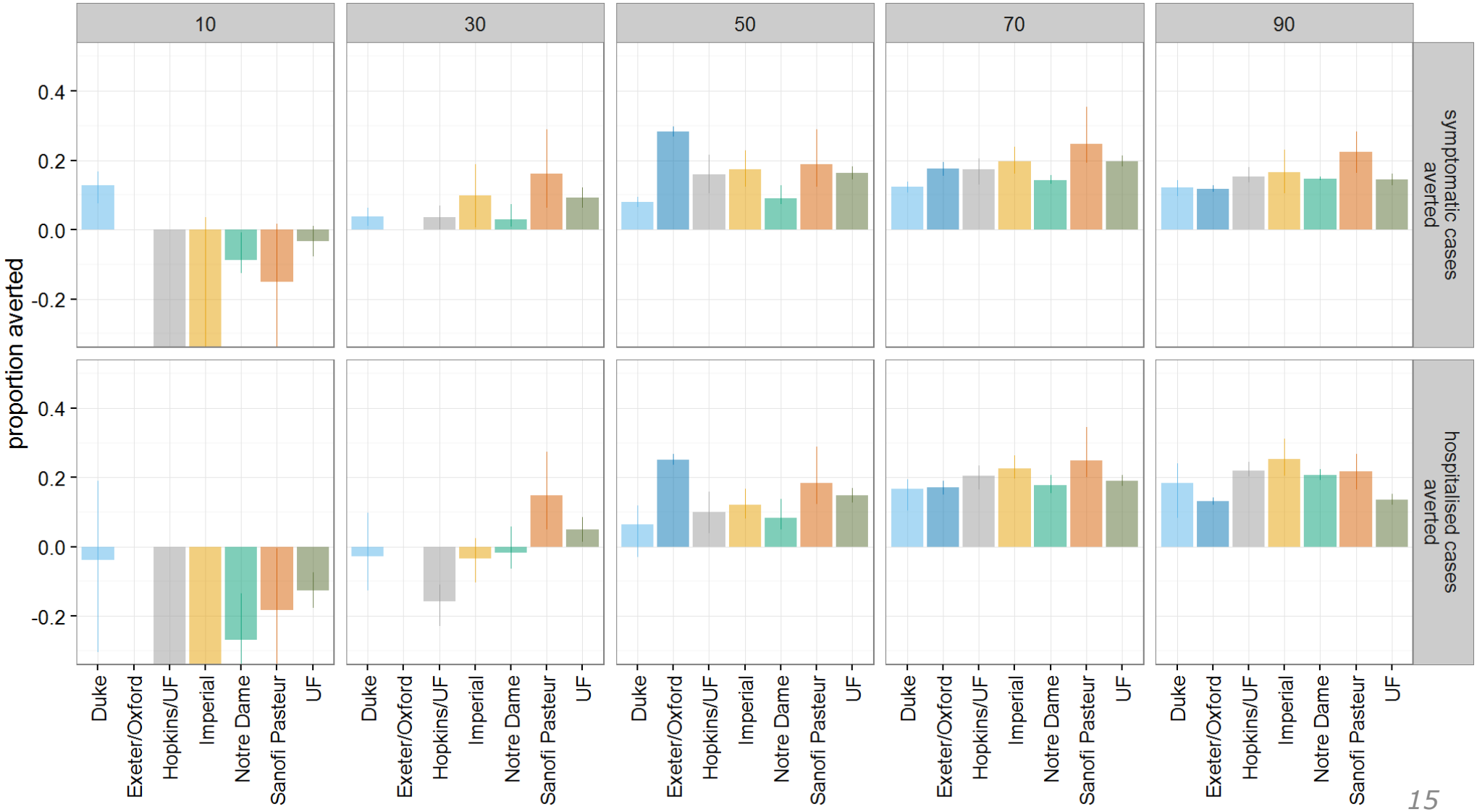


Health impact outputs

- **Symptomatic cases** – models matched to active phase trial data, so output represents all cases, not just those seeking healthcare
- **Hospitalised dengue** – impact predictions use rates similar to SE Asia/CYD14 rather than lower rates seen in CYD15/Latin America
- **Deaths** – models assume between 0.04% and 0.08% CFR (~0.5% of hospitalised cases)
- Output population impact over 30 years

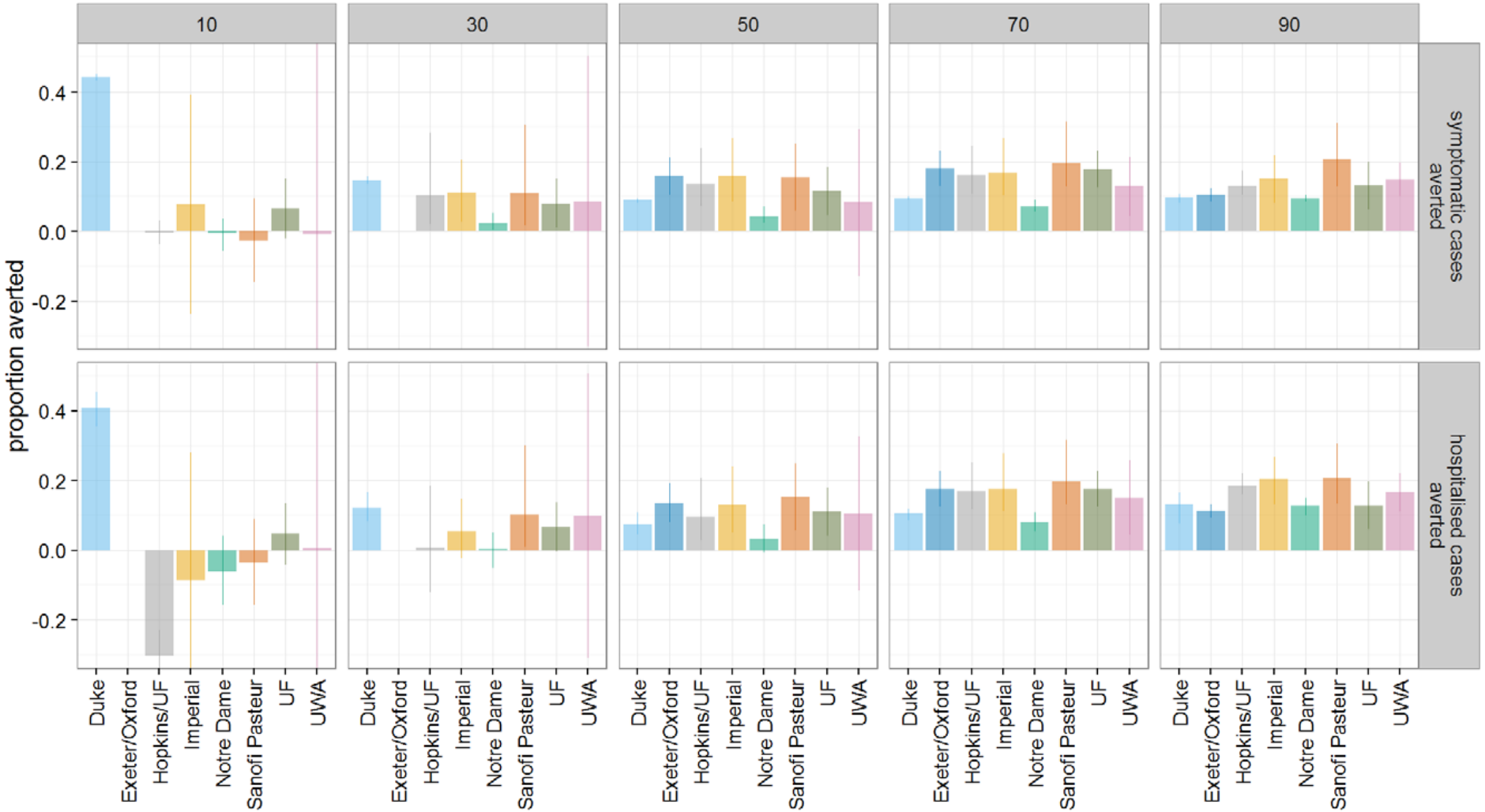
Reference scenario results: Proportion averted

Routine vaccination of 9 year olds, 80% coverage – results over 30 years



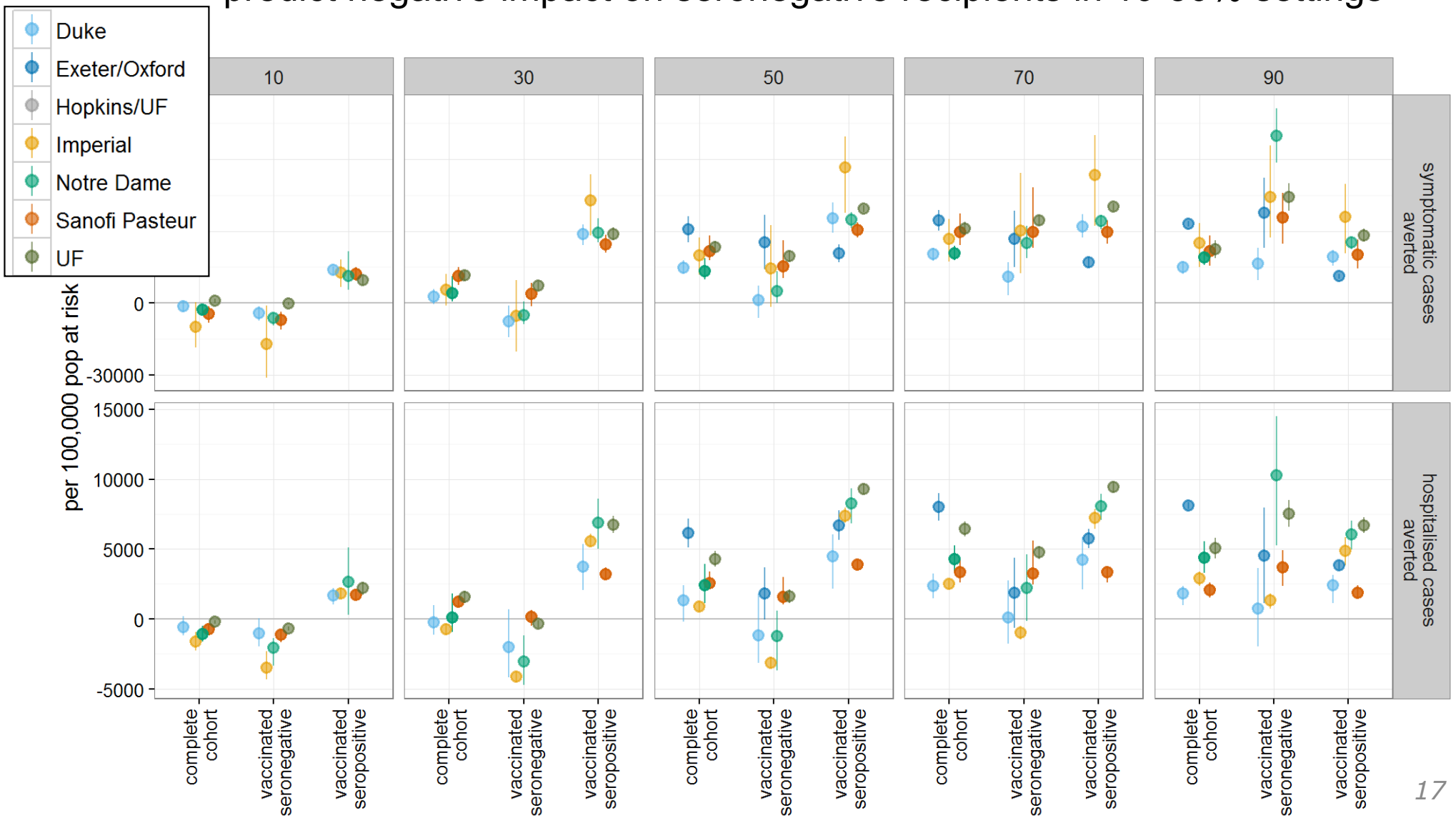
Reference scenario results: proportion averted – 10 year horizon

- Vaccination introduction perturbs transmission dynamics for ~10 years, after which impacts are fairly constant (limited indirect effects overall)
- In low transmission settings, vaccination can have a short-term benefit, but impacts become negative after 10 years



Impact by serostatus at vaccination (over 30 years)

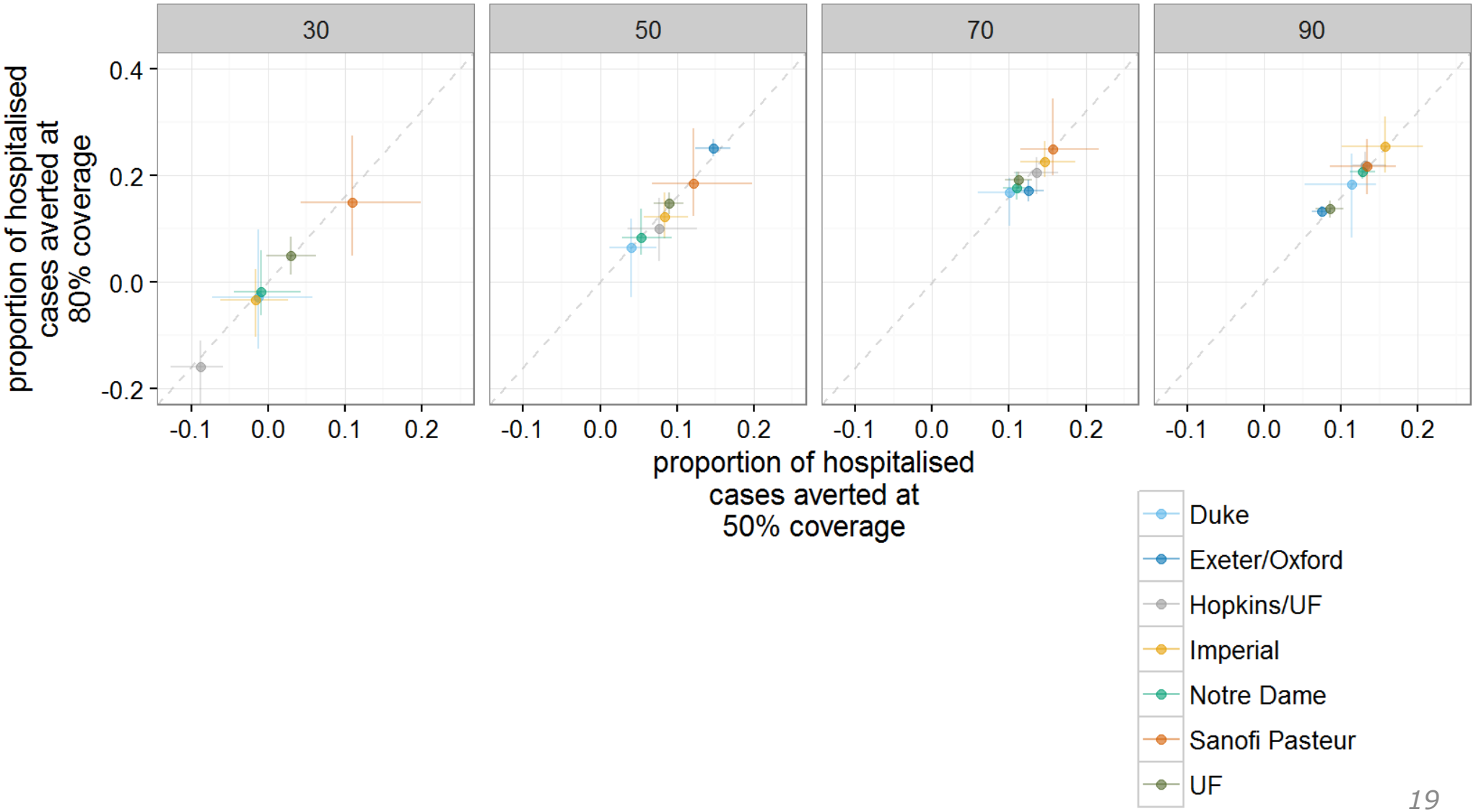
Models which reproduce 2-5y RR>1 in CYD hospital phase tend to predict negative impact on seronegative recipients in 10-50% settings



Key sensitivities

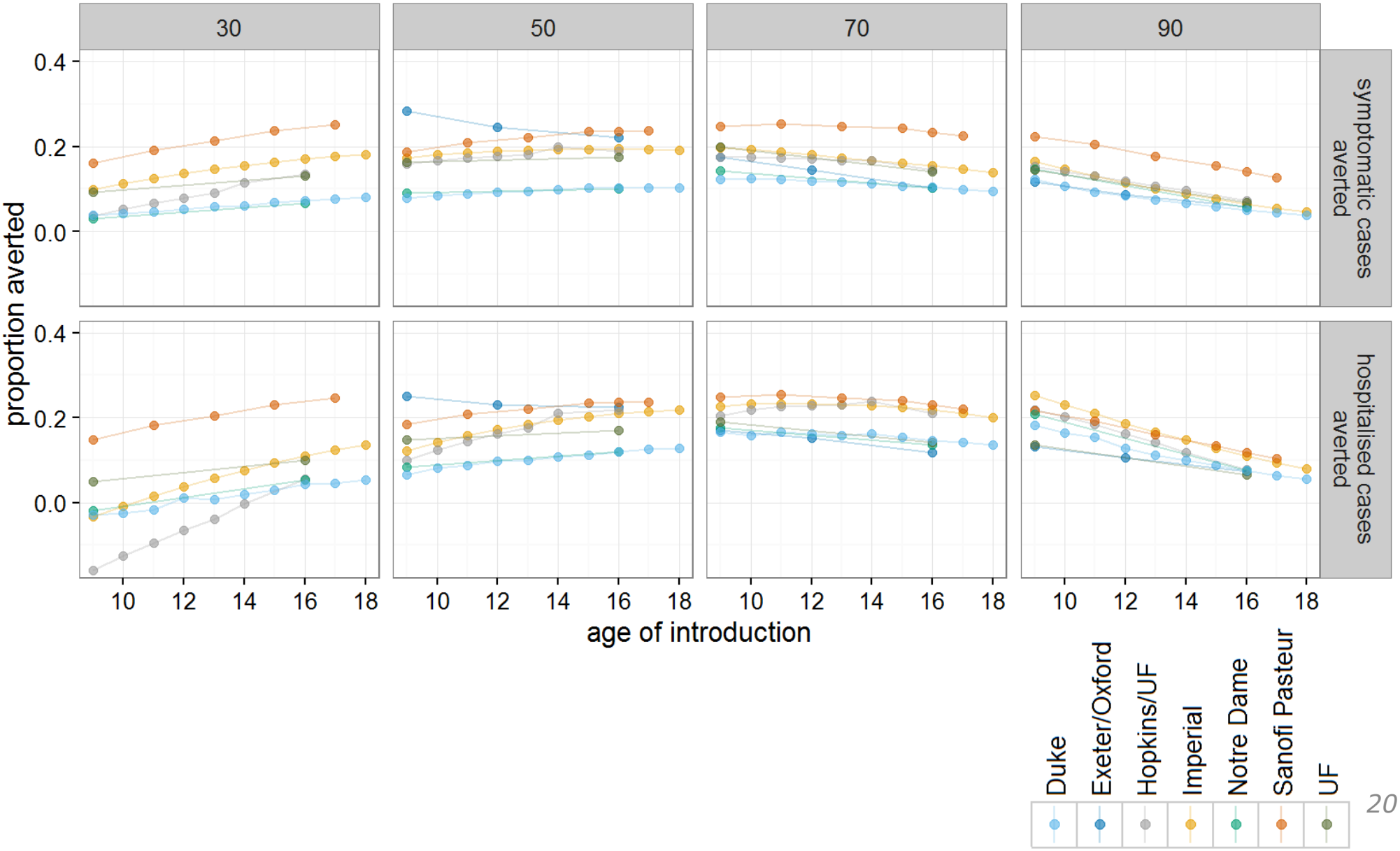
Effect of coverage level

Compare 50% and 80% coverage – impacts scale almost linearly



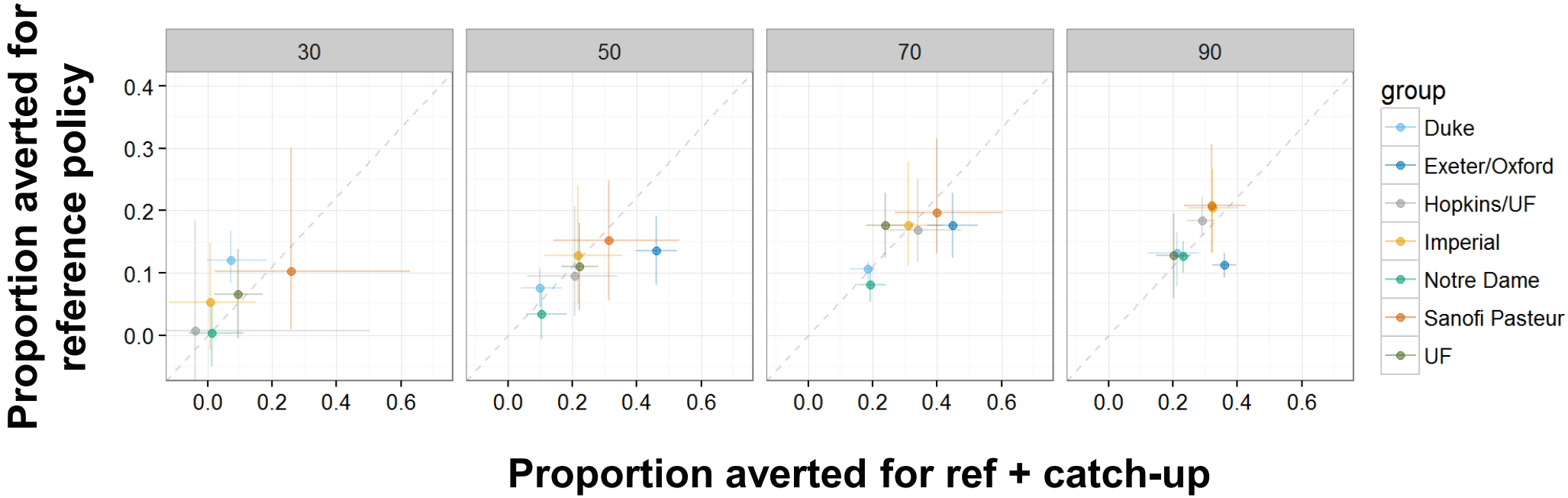
Varying age of routine vaccination

Impacts positive for all models by 14 years in 30% setting



Impact of catch-up campaign

- One-off 80% coverage of 10-17 year olds
- Impact over 10 years shown - largest in 50% & 70% settings
- Catch-up prevents a similar number of DENV hospitalisations per dose of vaccine delivered as routine vaccination



Health-economic outputs

Threshold cost per vaccinated person

- Use because ICER not suited to context where health benefits can be negative
- Defined as the maximum that could be paid (for procurement and delivery) to fully vaccinate someone before vaccination stops being cost-effective

Threshold cost per course of vaccine =

Incremental cost savings as a result of vaccination

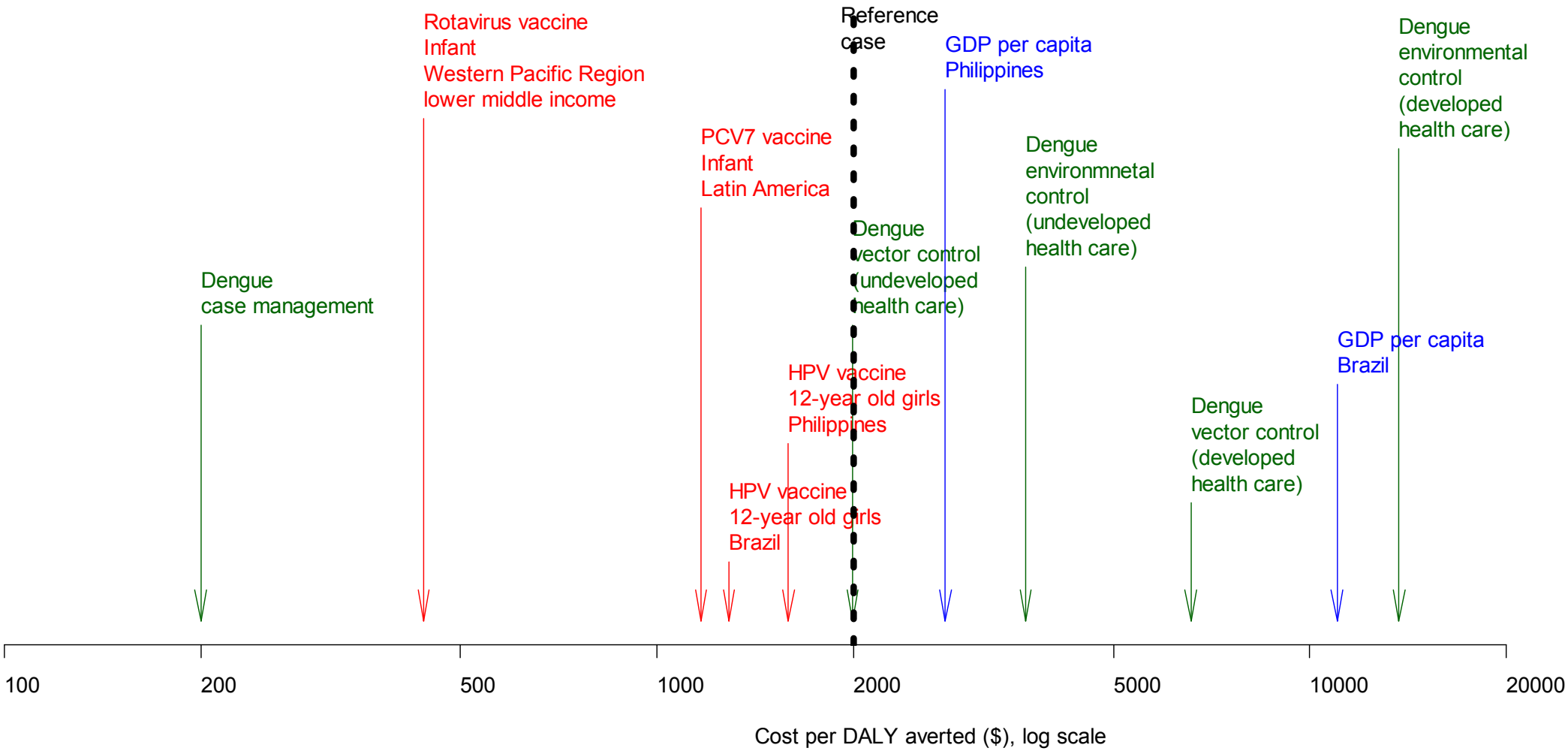
+

Incremental DALYs averted as a result of vaccination

×

Threshold cost per DALY

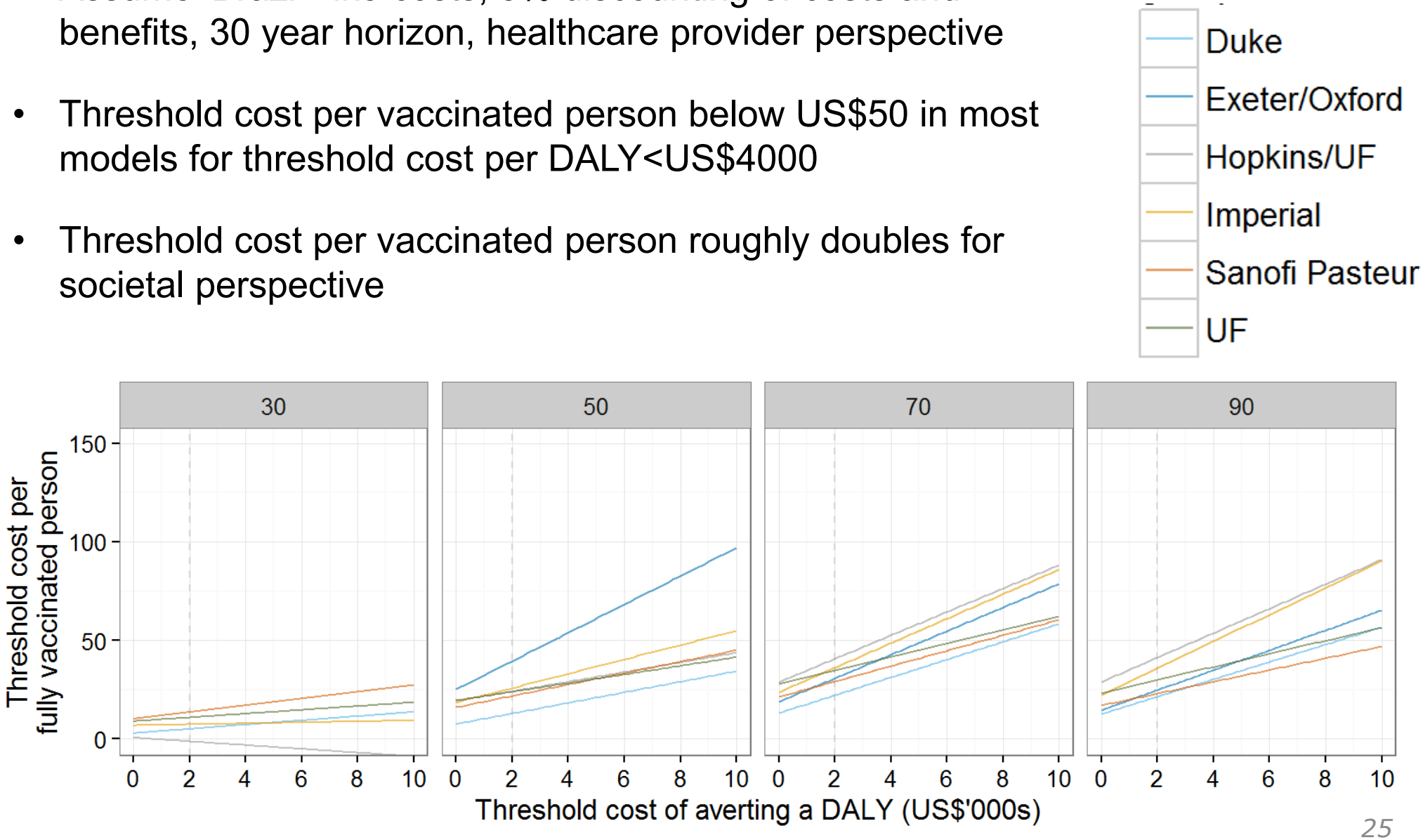
Example threshold costs per DALY



HPV: Jit et al. Lancet Global Health 2014; 2:e406, PCV: Sinha et al. Rev Panam Salud Publica 2008; 24:304, Rotavirus: Rheingans et al. JID 2009; 200:S16-27, Dengue: Shepard and Halstead. Dengue. In: *Disease Control Priorities in Developing Countries* (1993).

Routine vaccination of 9 year olds

- Assume ‘Brazil’-like costs, 3% discounting of costs and benefits, 30 year horizon, healthcare provider perspective
- Threshold cost per vaccinated person below US$50 in most models for threshold cost per DALY<US$4000
- Threshold cost per vaccinated person roughly doubles for societal perspective



Conclusions

Conclusions

- Predicted impact of vaccination programs:
  - Routine immunisation of 9+ year olds at 80% coverage predicted to reduce dengue disease by 10-30% long-term in moderate-to-high transmission settings
  - Impact scales linearly with coverage
  - Adding 80% coverage catch-up in 10-17 year olds might achieve overall ~30-40% reduction in dengue hospitalisations over 10 years
- Key heterogeneity: variation of efficacy with serostatus:
  - Target age for vaccination should be tuned to setting - 9 years only optimal for highest transmission setting
  - 11-14 year olds a good compromise in moderate to high transmission settings
  - Vaccine unlikely to be beneficial in low transmission settings
  - Vaccination *may* increase the risk of hospitalised dengue in substantial subset of recipients (*i.e.* seronegatives) in low-to-moderate transmission settings
- In most settings and for most models, the total cost of fully vaccinating one person cannot exceed $50 for the vaccine to remain cost-effective
- Moderate and heterogeneous efficacy requires careful communication (to policy-makers, populations,)

Caveats

- Y4 data not included – predicted impacts may be less when models fitted to Y1-4 due to increasing relative risk in older age groups
- Efficacy may vary by serotype:
  - Seen in trial endpoints, but this may reflect differing propensity between serotypes to cause disease in primary vs secondary infection
  - Impossible to model accurately without access to more finely stratified phase 3 trial data
  - Such variation unlikely to pose risks of negative outcomes
- Efficacy may vary by age:
  - Seen in trial endpoints, but can largely be explained by assuming only serostatus-dependent efficacy
  - But can't rule out an additional causal effect of age
- These and other uncertainties may affect long term impact:
  - Need long-term follow-up
  - Early vaccination programmes/phase 4 trials need careful monitoring