WHO Strategic Advisory Group of Experts on Immunization (SAGE), Geneva, 8-10 Oct 2019

Measles-rubella eradication investment case

Matt Ferrari[1] and Mark Jit[2,3,4]
on behalf of the measles-rubella eradication investment case consortium
[1]Department of Biology, Penn State University
[2]London School of Hygiene & Tropical Medicine
[3]Modelling and Economics Unit, Public Health England
[4]School of Public Health, University of Hong Kong

We have no conflicts of interest to declare.

Background

- August 2018: SAGE measles-rubella working group and IVIR-AC reviewed current measles-rubella eradication modelling efforts and recommended that a new group be commissioned to provide further evidence to inform SAGE.
- March 2019: Vaccine Impact Modelling Consortium (VIMC) modellers commissioned to provide modelling work.
- May 2019: Vaccine coverage scenarios provided to modellers from work done by CDC and others.
- July 2019: Modelling work reviewed by SAGE measles-rubella working group and revised.
- September 2019: Modelling work reviewed by IVIR-AC and revised.

MR elimination modelling consortium

VACCINE IMPACT MODELLING CONSORTIUM

- Measles – DynaMICE (LSHTM)[1]
- Measles – Ferrari (PSU)[2]
- Rubella – Vynnycky (PHE)[3]
- Rubella – Winter/Truelove (JHU)[4]

Subnational model
McCarthy (IDM)[5]

→ Disease impact
Likelihood of elimination threshold

Vaccine costs
Cost of illness

→ Cost-effectiveness
Budget impact

[1]Verguet S et al. Controlling measles using supplemental immunization activities: a mathematical model to inform optimal policy. Vaccine. 2015 Mar 3;33(10):1291-6.

[2]Eilertson KE et al. Estimation and prediction for a mechanistic model of measles transmission using particle filtering and maximum likelihood estimation. Statistics in medicine. 2019 Sep 20;38(21):4146-58.

[3]Vynnycky E et al. The impact of Measles-Rubella vaccination on the morbidity and mortality from Congenital Rubella Syndrome in 92 countries. Human vaccines & immunotherapeutics. 2019 Feb 1;15(2):309-16.

[4]Metcalf CJ et al. Impact of birth rate, seasonality and transmission rate on minimum levels of coverage needed for rubella vaccination. Epidemiology & Infection. 2012 Dec;140(12):2290-301. Metcalf CJ et al. Structured models of infectious disease: inference with discrete data. Theoretical population biology. 2012 Dec 1;82(4):275-82.

[5]Zimmermann M et al. Optimization of frequency and targeting of measles supplemental immunization activities in Nigeria: A cost-effectiveness analysis. Vaccine. 2019 Aug 27.

Models

Model	Disease	Structure	Seasonality	Maternal immunity	Mixing	CFR	Vaccine efficacy	Case importation
DynaMICE	Measles	Dynamic deterministic MSIRV	Yes	Yes	Age-dependent, POLYMOD Great Britain	Country-specific	Dose 1: 84% @ 9mo / 93% @ 12mo Dose 2: 99%	No
PSU	Measles	Semi-mechanistic stochastic MSIR fitted to observed cases with Kalman filter	No	Yes	Not applicable	Country-specific	Dose 1: 85% @ 9mo / 93% @ 12 mo Dose 2: 99% SIA: 99%	Random variation in annual attack rate
IDM	Measles	Agent-based stochastic SEIR for each district of NGA	Yes	Yes		2.1%		Constant rate.
PHE	Rubella	Dynamic continuous MSIRV	No	Yes	WAIFW by age (<13yrs, ≥13 yrs) (POLYMOD)	30% (95% range 10-50%)	All doses 95%	Yes
JHU	Rubella	Dynamic discrete MSIRV	Yes	Yes	Country-specific WAIFW by age (Prem et al 2017)	Not country-specific	RCV1: age-specific efficacy per Boulianne et al (1995), saturating at 97% RCV2: 97%	Yes

Coverage scenarios

	Base case	Continuing trends	Constant improvement	Intensified investment
MCV1	Maintain at base year coverage.	Natural log fit to historical coverage.	1%/yr up to 95% (Gavi) or 90% (other).	4.4% compound rate up to 99% (unless reach 95% by 2016).
MCV2	Maintain at base year coverage. No new introductions after 2017.	Introductions based on current commitments. Projected MCV2 coverage.	Introduction in 2020. Start 10% below MCV1. 1%/yr up to 95% (Gavi) or 90% (other).	Introduction in 2018-2024. Projected MCV2 coverage.
RCV	No new introductions after 2017.	Introductions based on current commitments.	Introduction in 2020.	Introduction in 2018-2024.
SIA	When susceptibles = 100% of birth cohort ("rule of thumb").	When susceptibles = 100% of birth cohort ("rule of thumb"). Stop after 90% MCV1/2, RCV introduction, 2 years of susceptibles < birth cohort.	Every 3 years. Stop after MCV2 > 90%.	When susceptibles = 75% of birth cohort. Stop after 90% MCV1/2, RCV introduction, 2 years of susceptibles < birth cohort.

Only the results for Base Case and Intensified Investment will be presented as these illustrate the key issues involved.

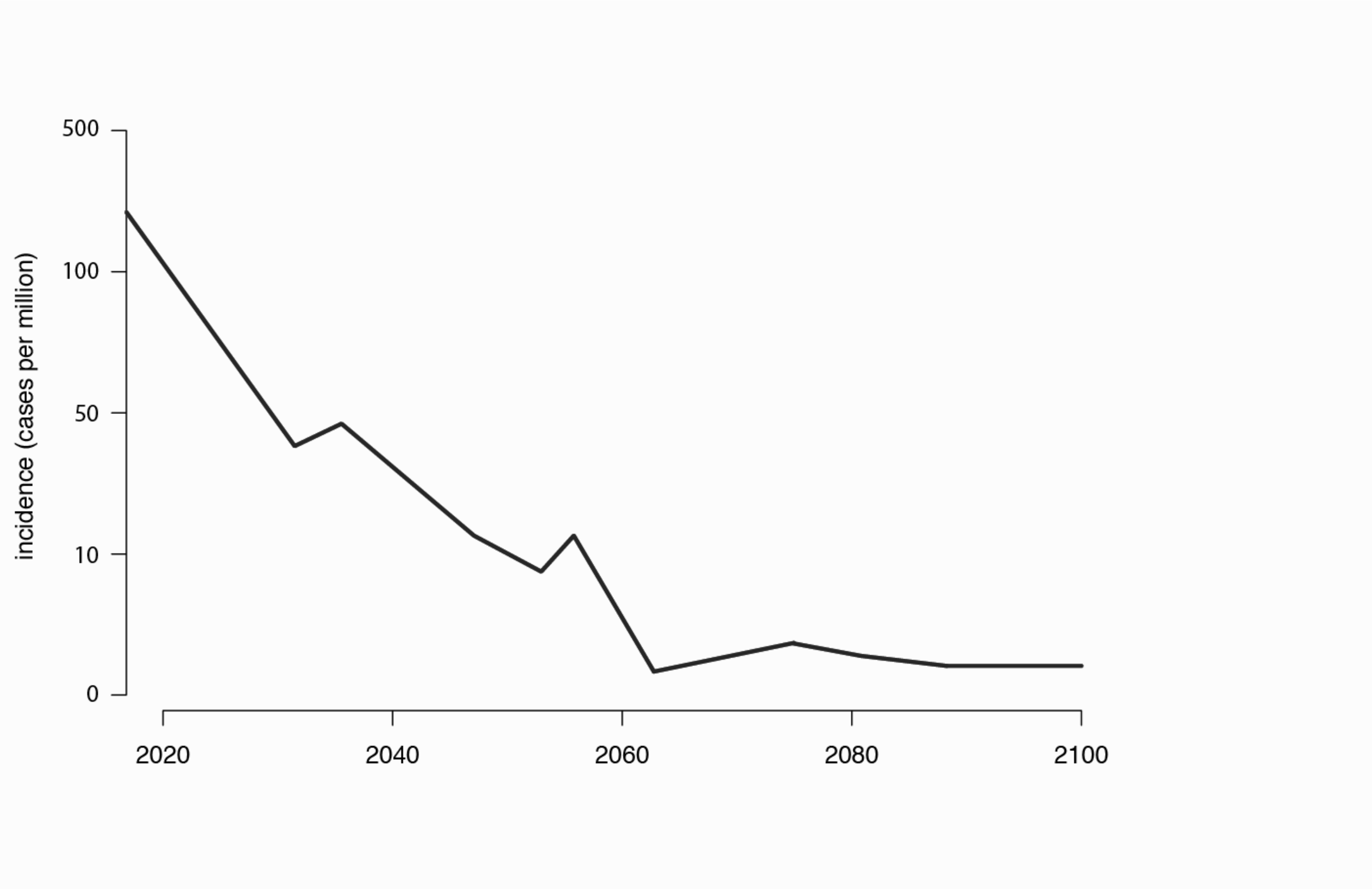
“Elimination” threshold

- Elimination threshold: 5 per 1,000,000 true (not reported) cases
- Represents measles/rubella incidence low enough to produce transmission interruption at national levels.
- Caveats
  - Models were not designed to model actual elimination as they do not explicitly model factors important at very low incidence such as localised outbreaks, outbreak response, PIRIs, political and other crises, enhanced surveillance etc.
  - Models are designed to show the likelihood of elimination under different levels of investment, rather than to inform programmatic choices or to capture all possible strategies for measles eradication.
  - Doses are assumed to be given uniformly across the entire population (apart from the IDM model).
  - Cross-border transmission between countries is not modelled (except as a constant probability of reintroduction in some models).

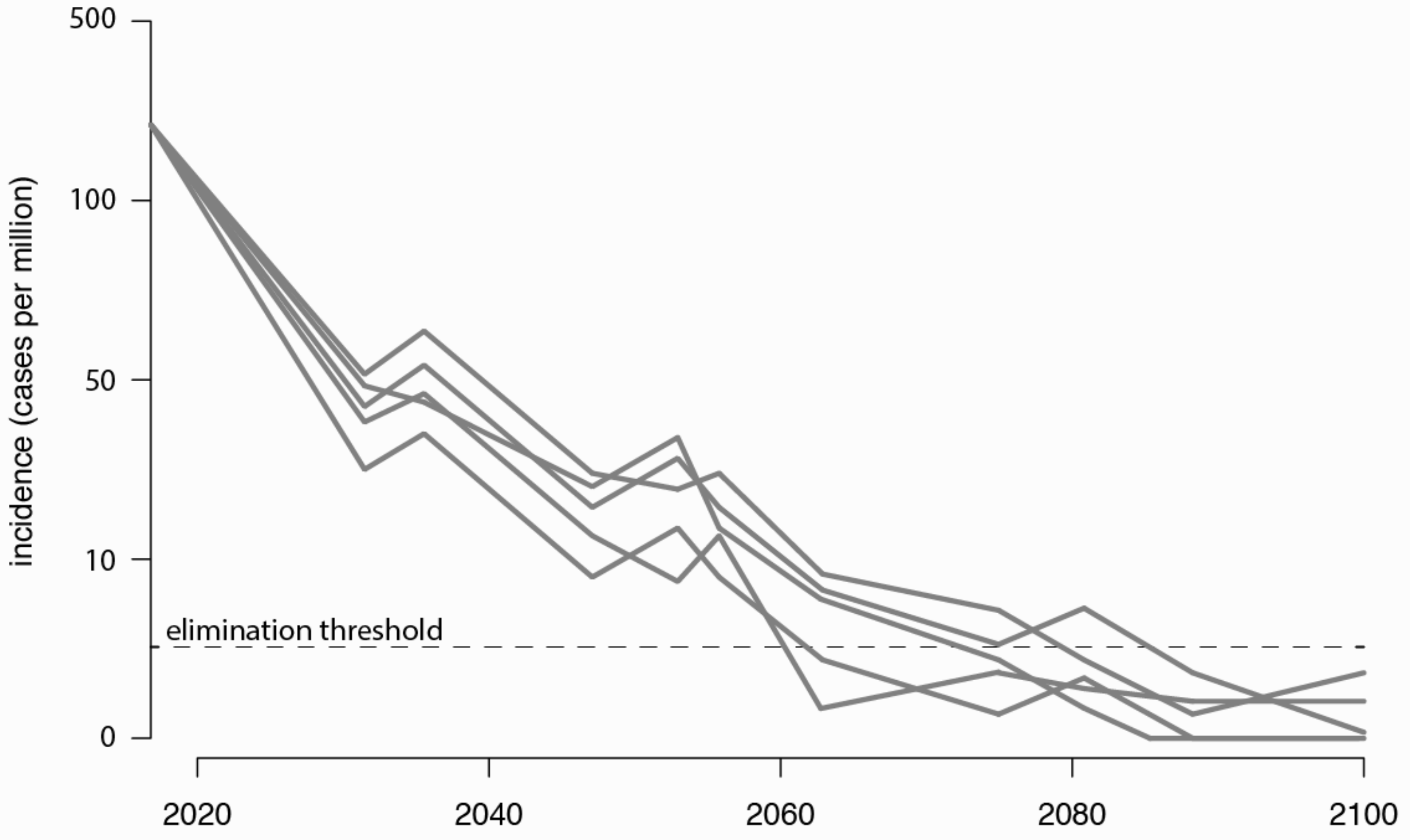
Things to look out for

- ❑ Elimination is more likely for rubella than measles
- ❑ Among countries that achieve incidence threshold, there may be significant variation in timing
- ❑ A fraction of stochastic runs may achieve a given threshold, even if the mean of all runs does not
- Mean may achieve threshold, but upper bounds may not
- Indicator of the likelihood of elimination

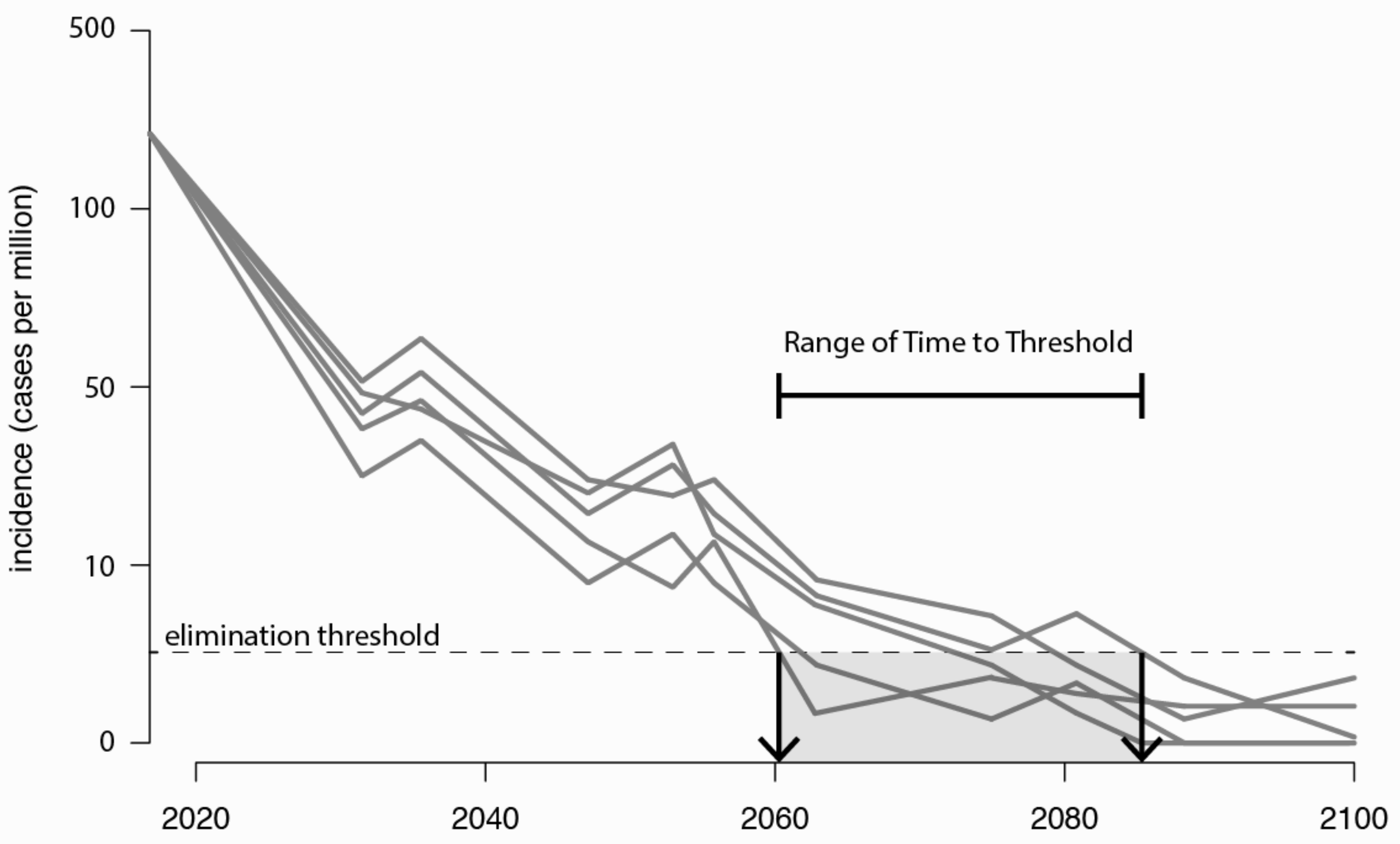
Consider 1 simulation run: 1 country, 1 scenario



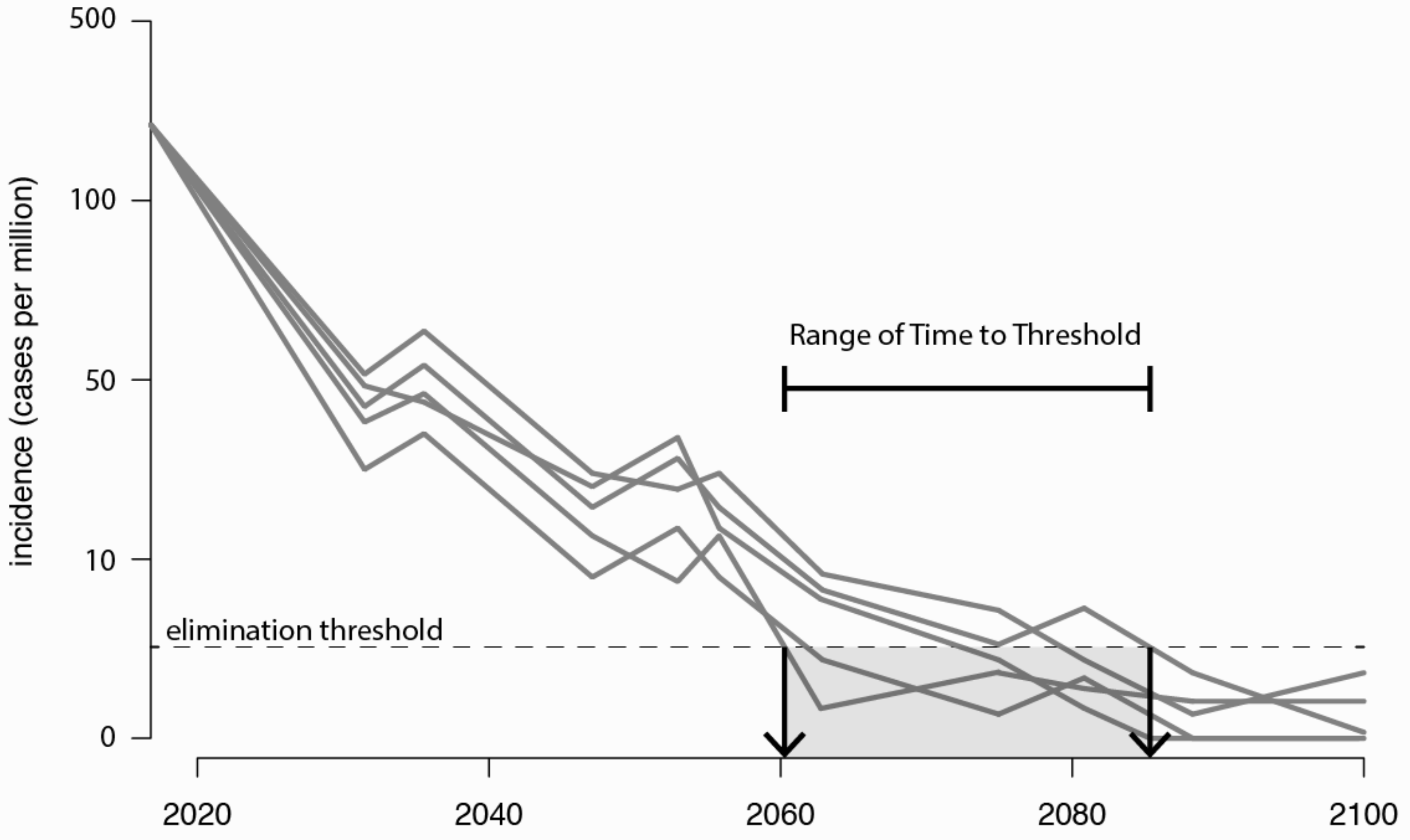
For a given elimination threshold

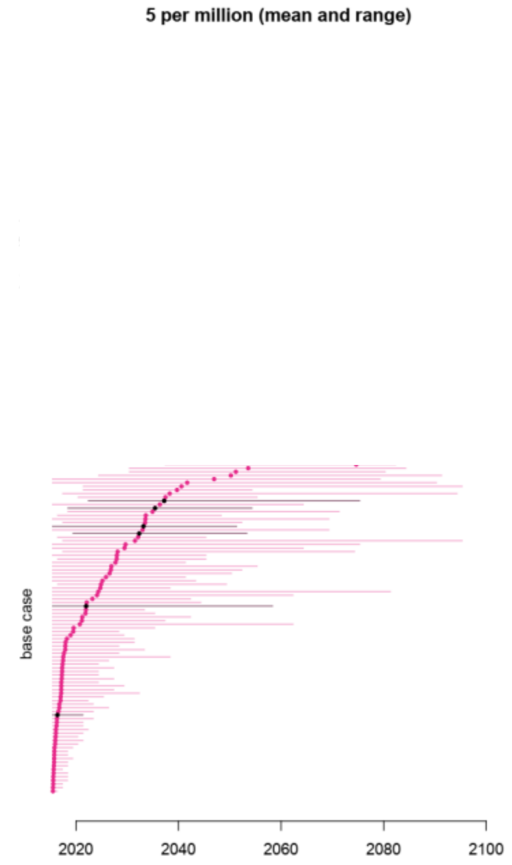


We can summarize the distribution of time until the threshold is reached



Compare for All Countries and Scenarios





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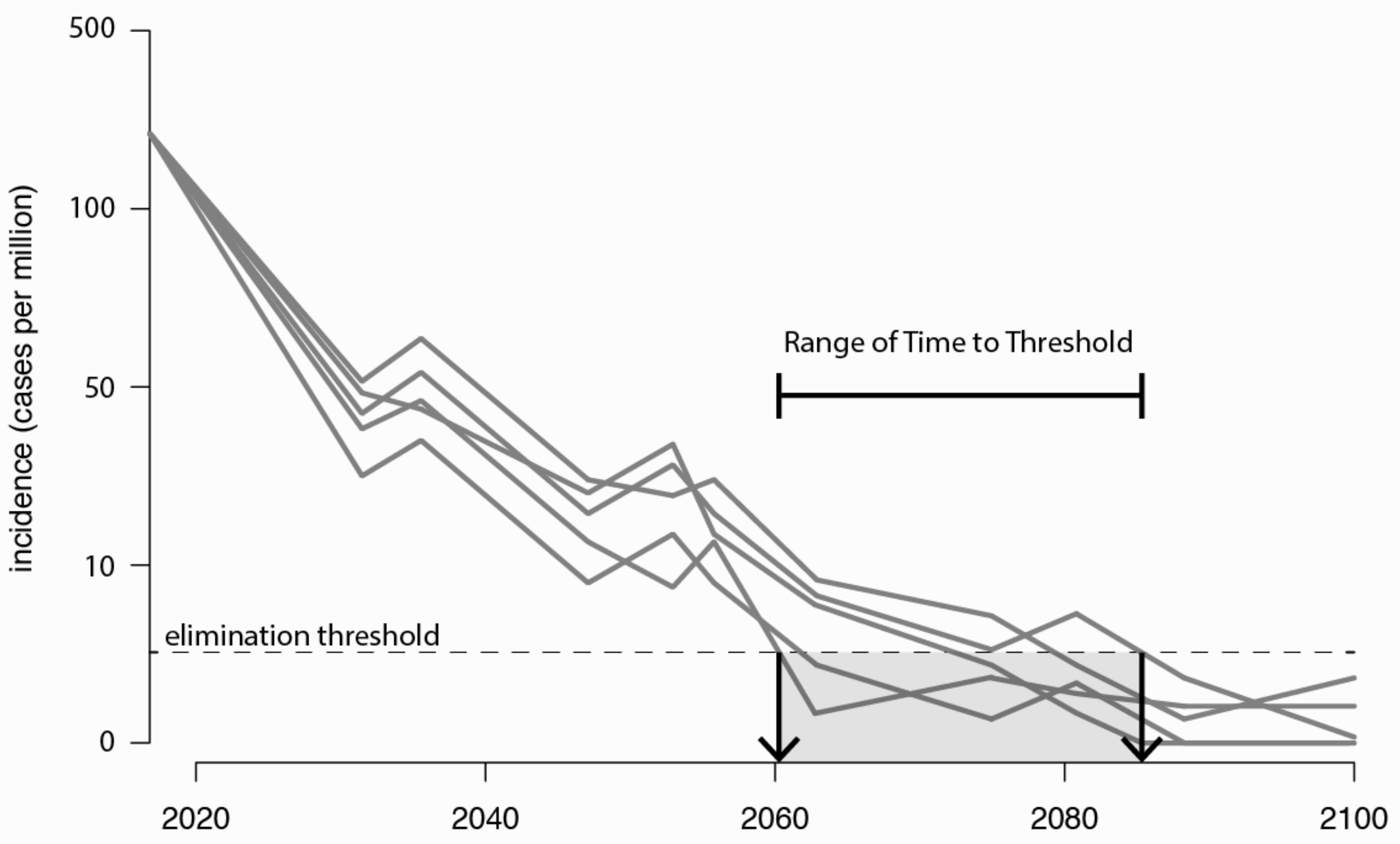
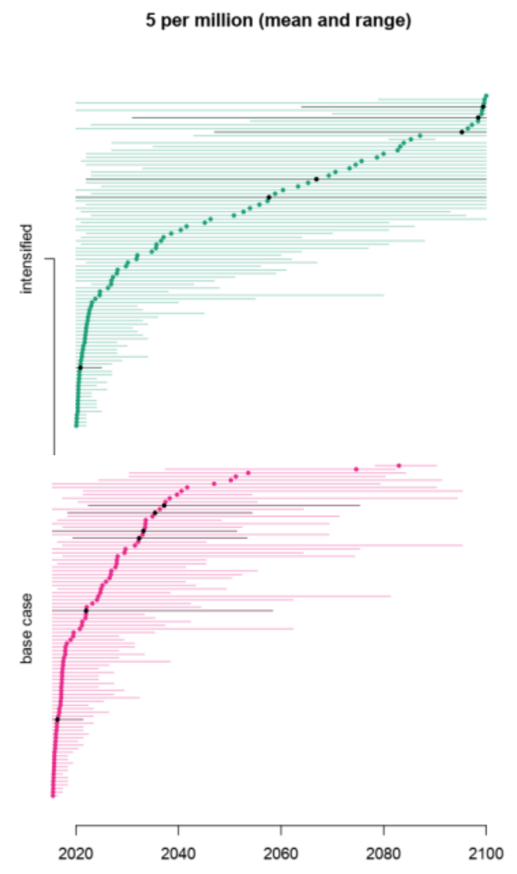
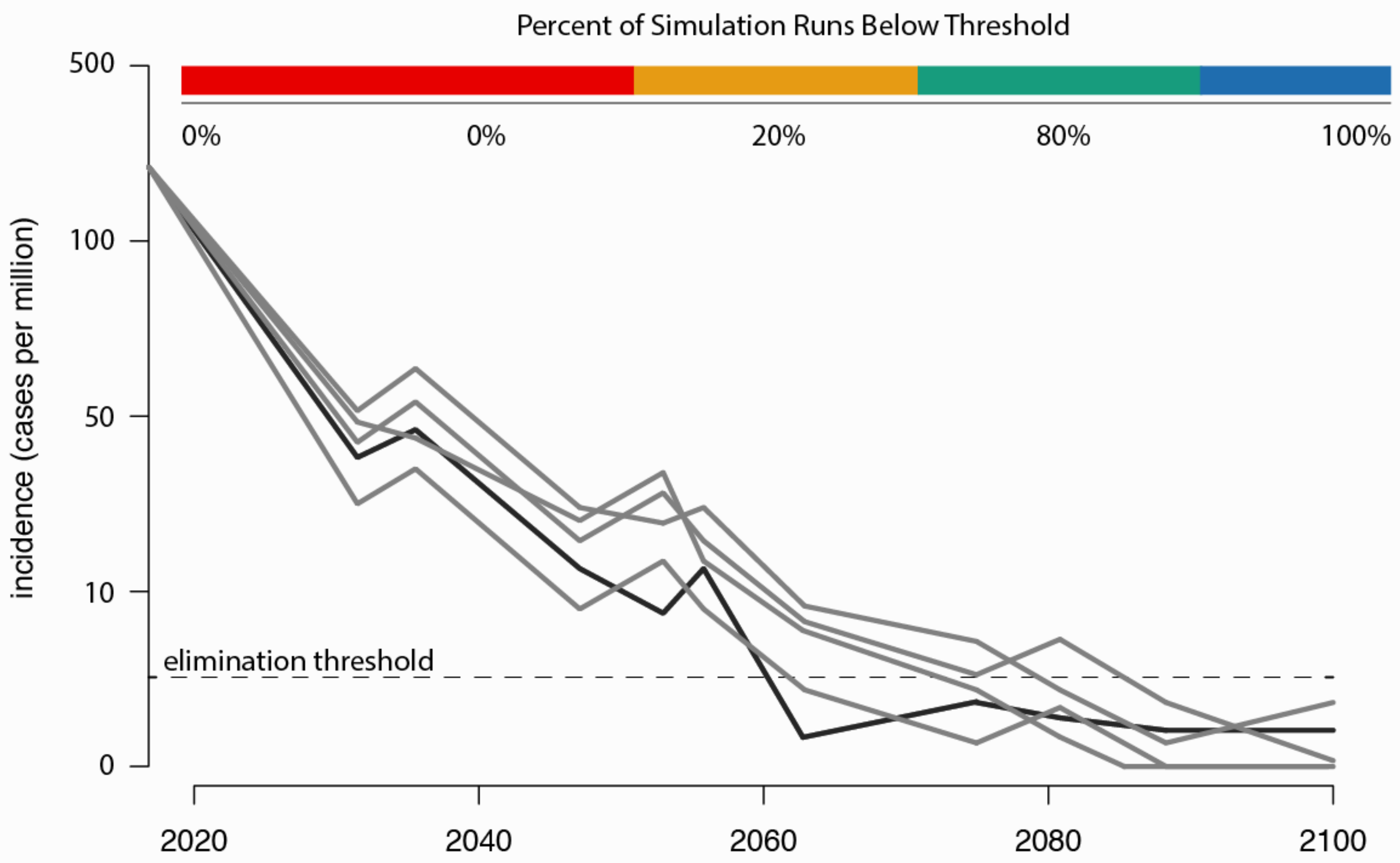




Percent of runs below threshold at each time



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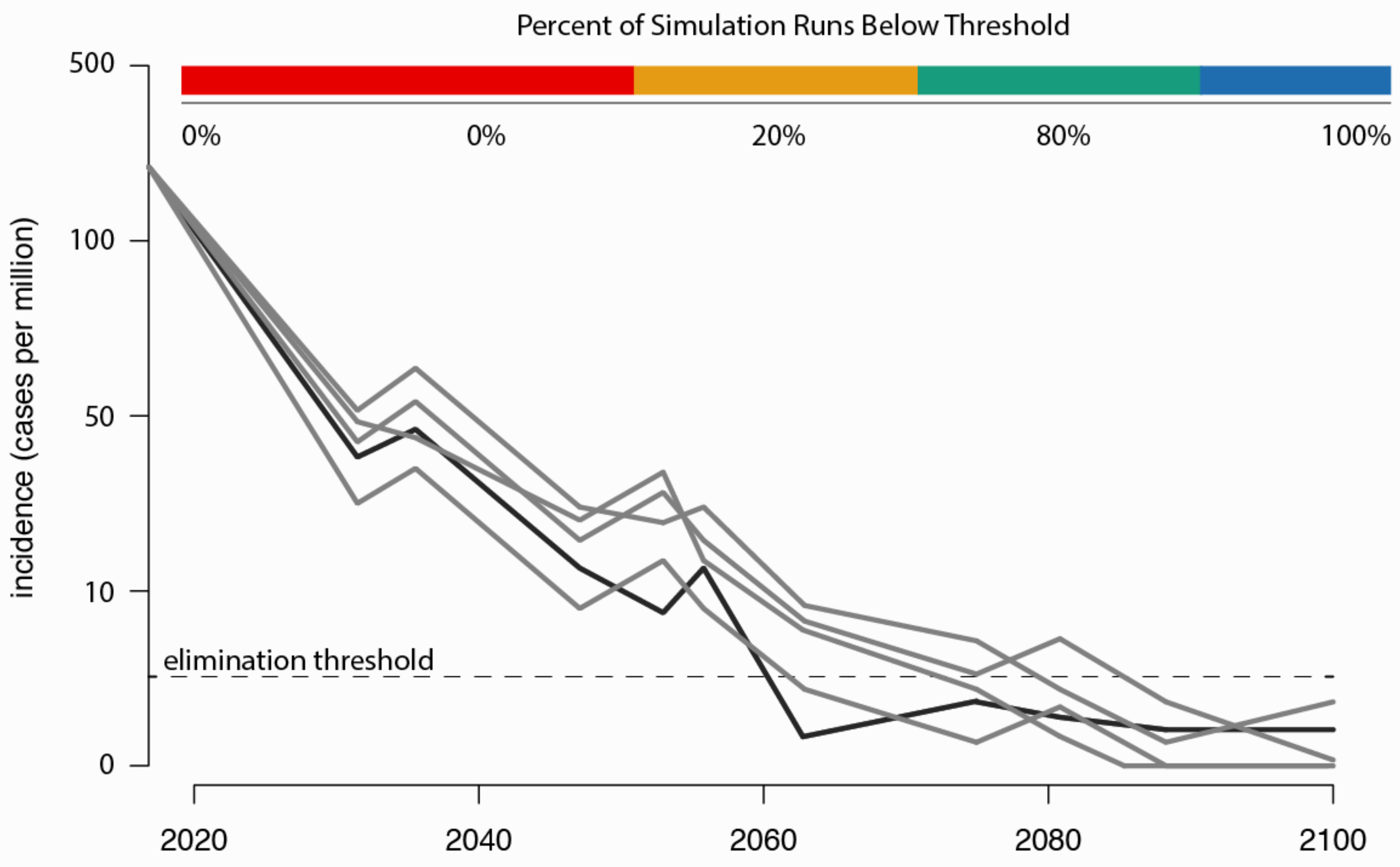
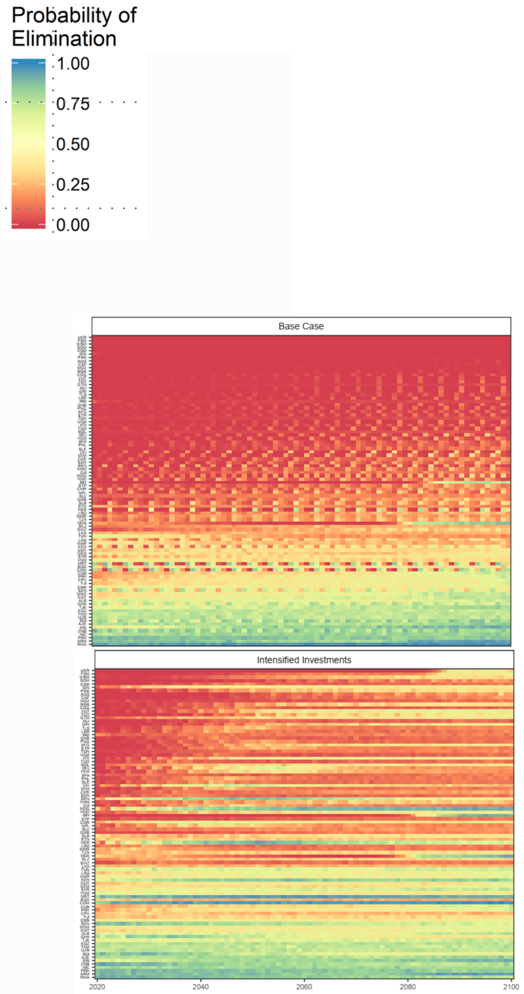
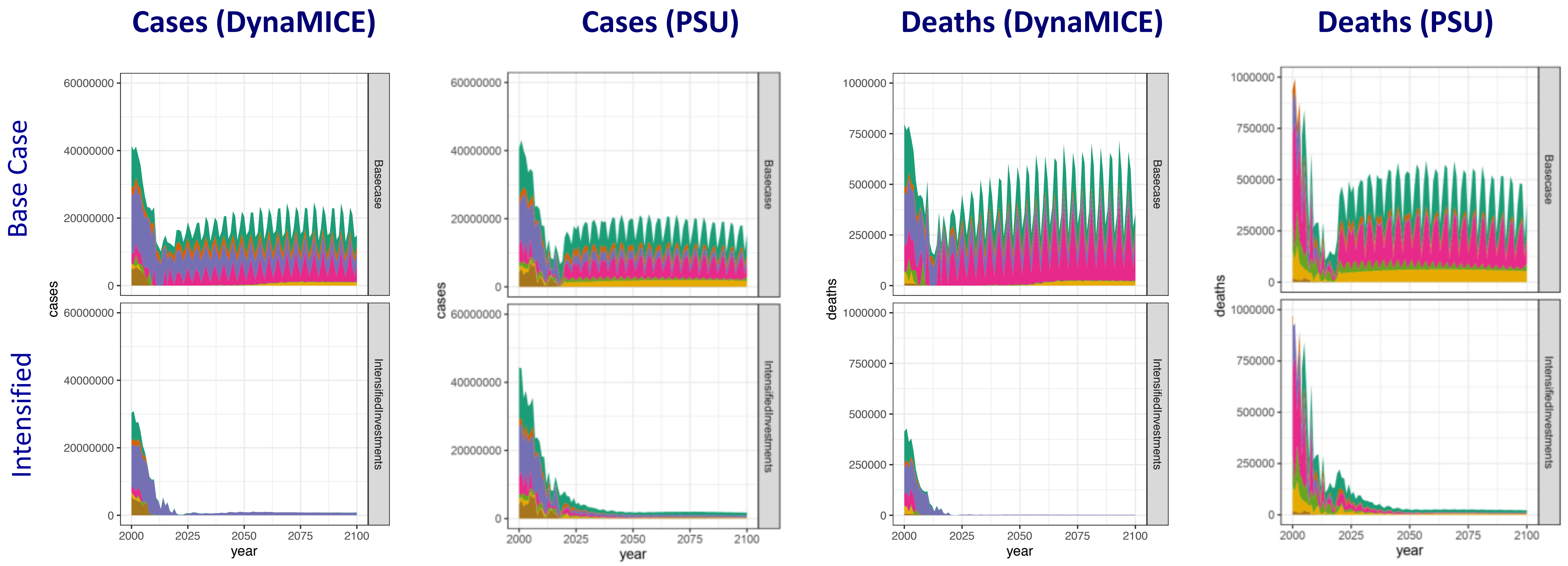




Results: Epidemiological Models

MEASLES

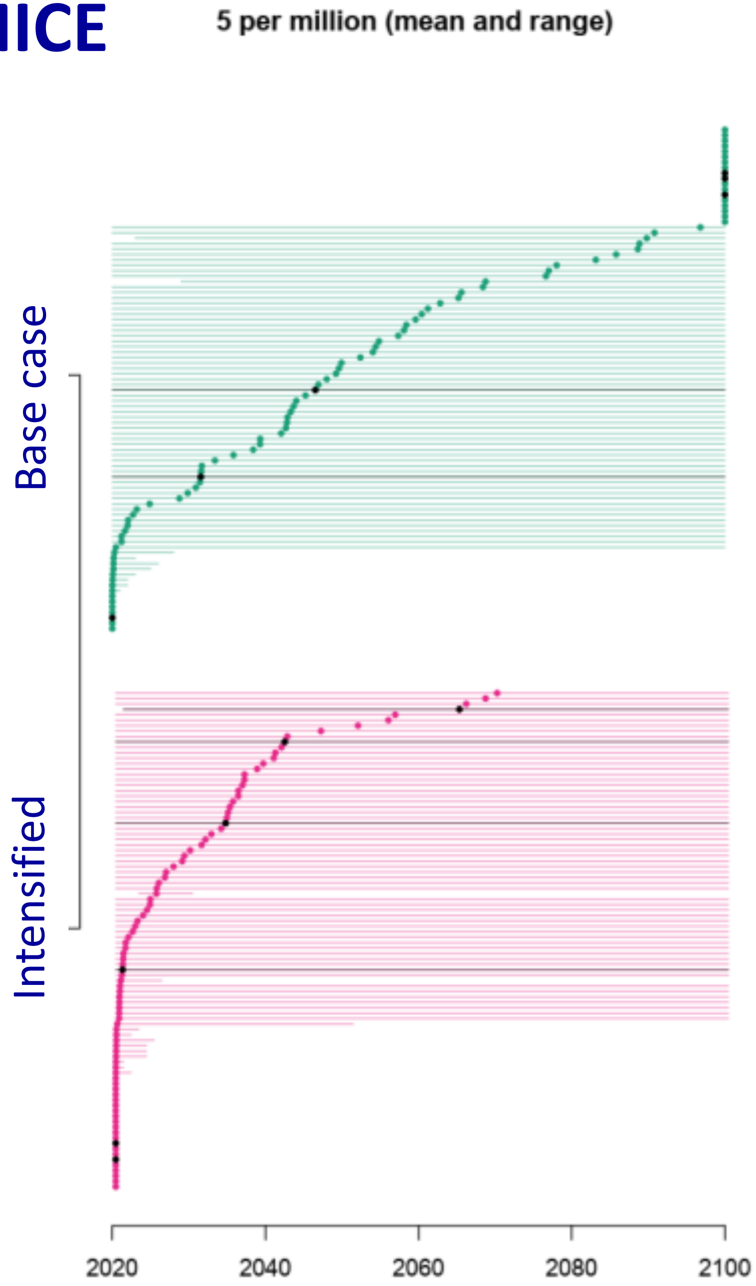
Measles cases and deaths (median of 200 stochastic runs)



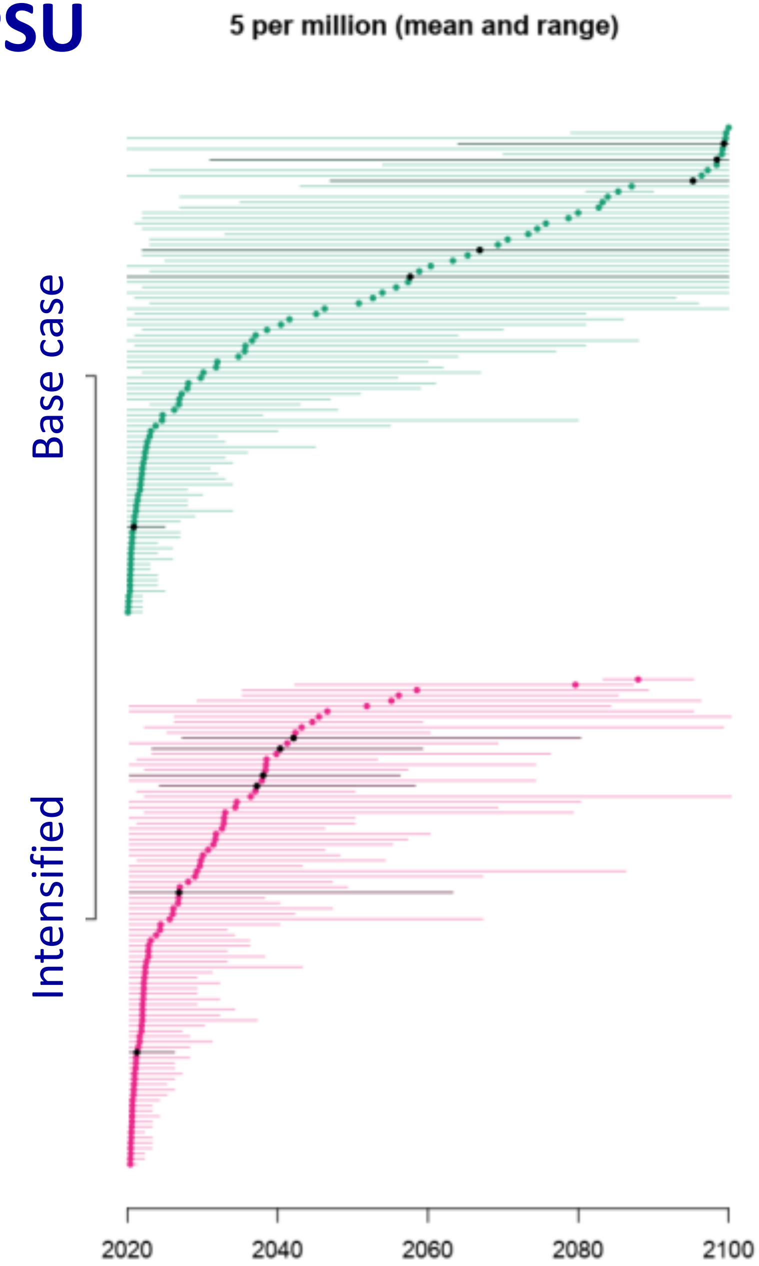
For both the DynaMICE and the PSU models, the intensified investment scenario is predicted to achieve dramatic reductions in the burden of disease and mortality by the year 2050

Measles time to reach threshold

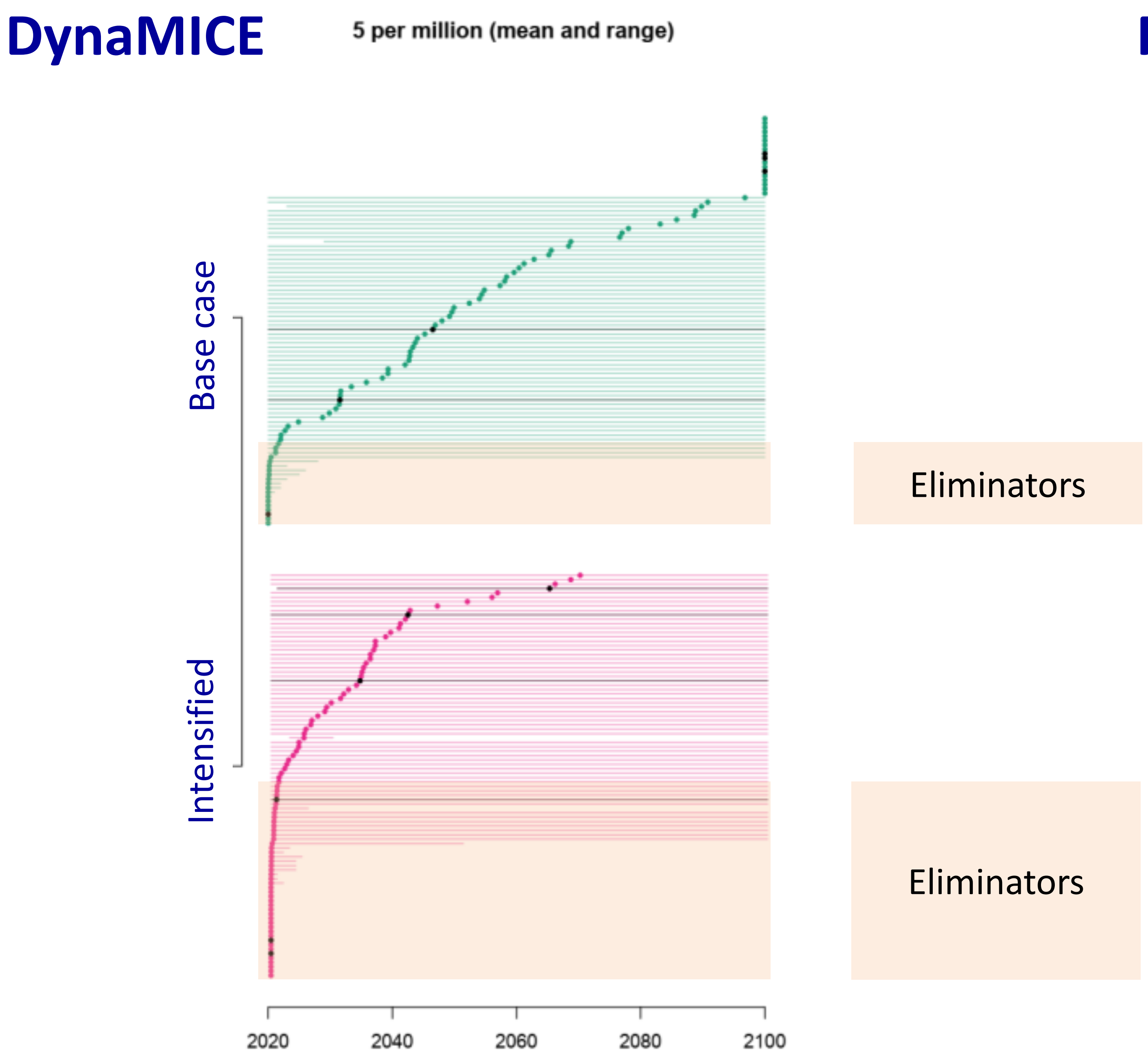
DynaMICE

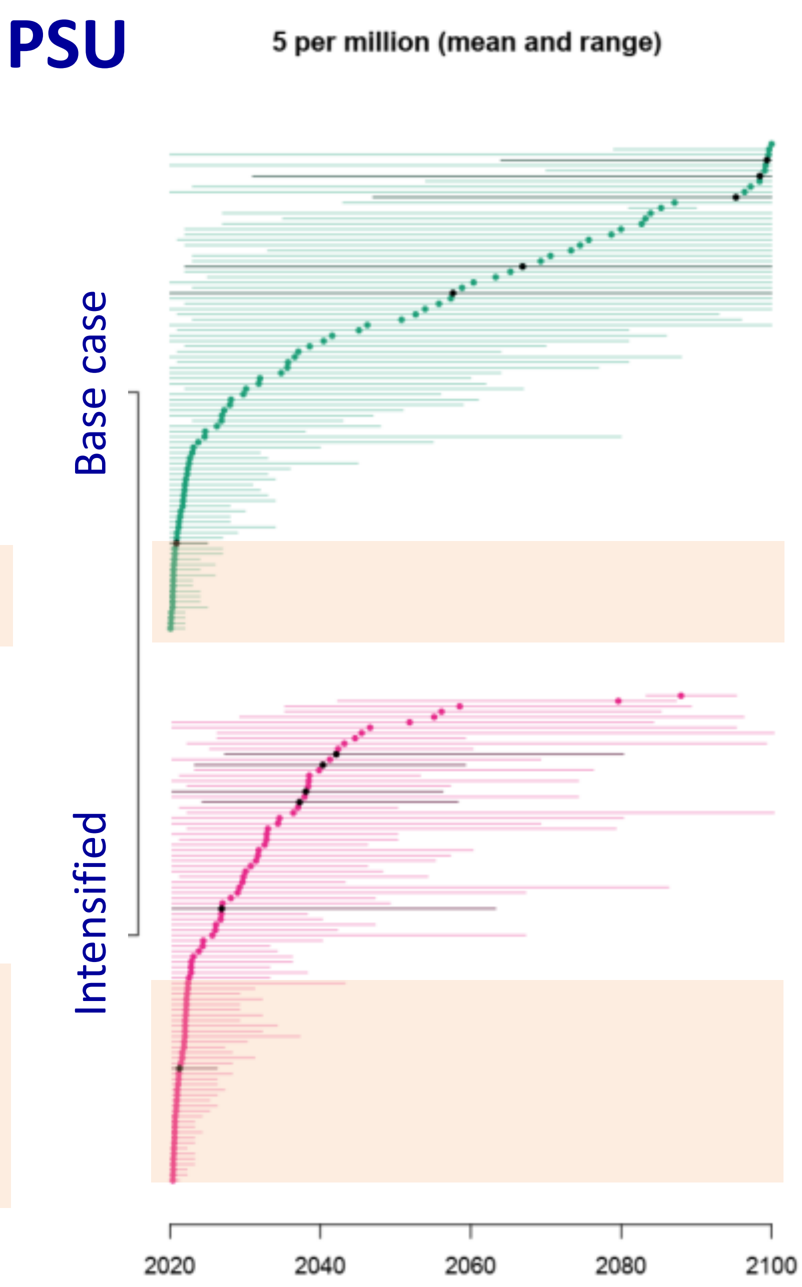


PSU

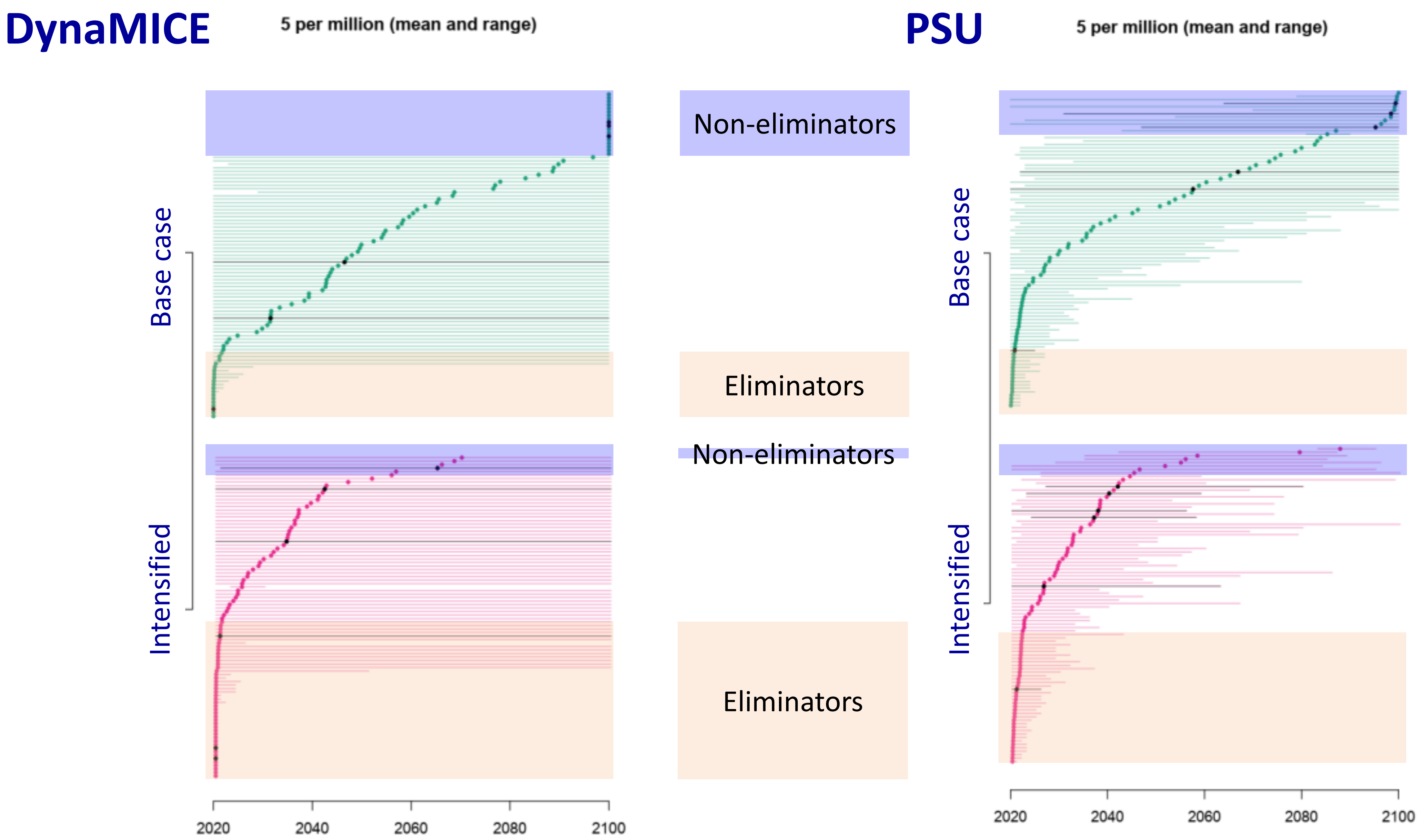


Measles: Time to Reach Threshold





Measles: Time to Reach Threshold



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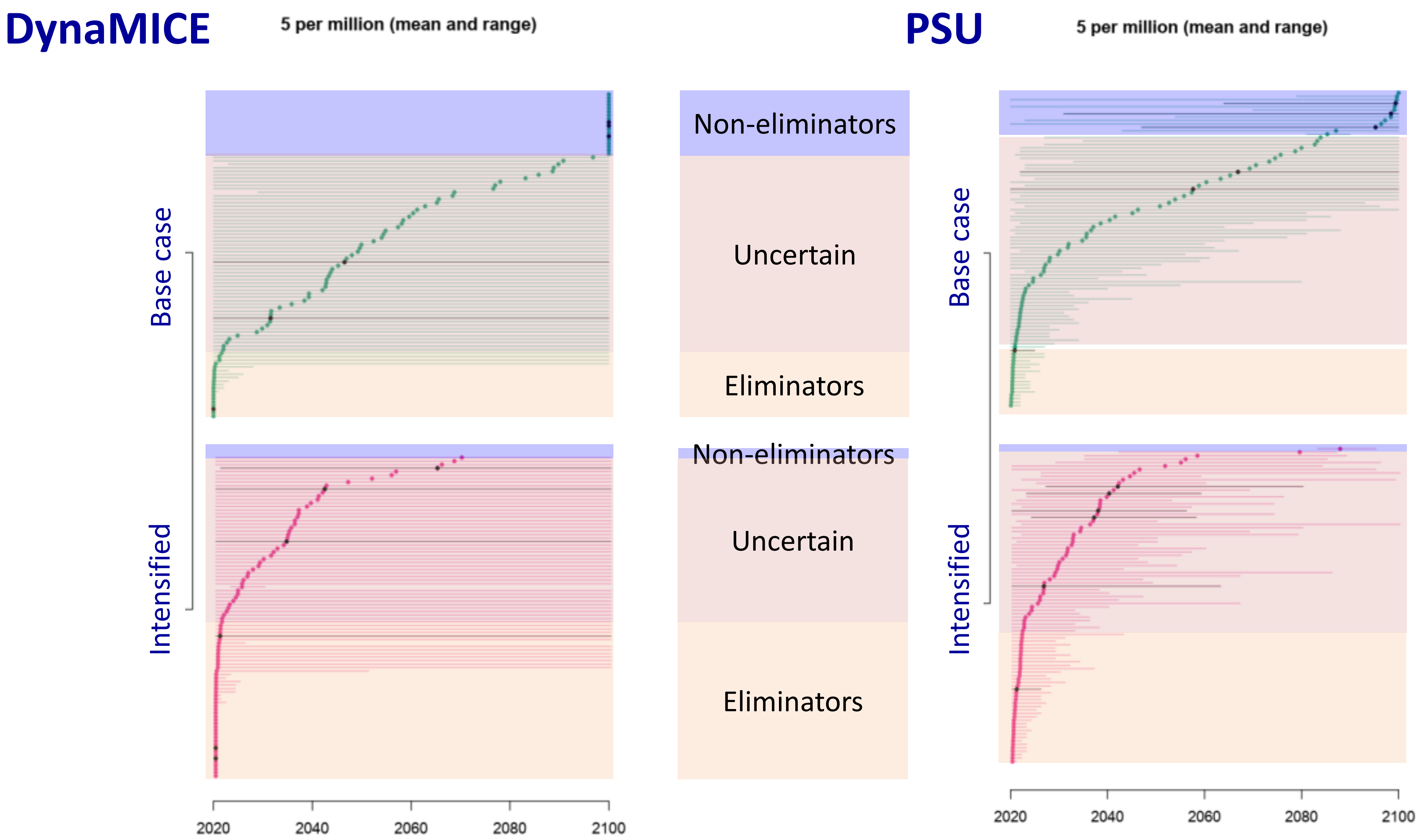
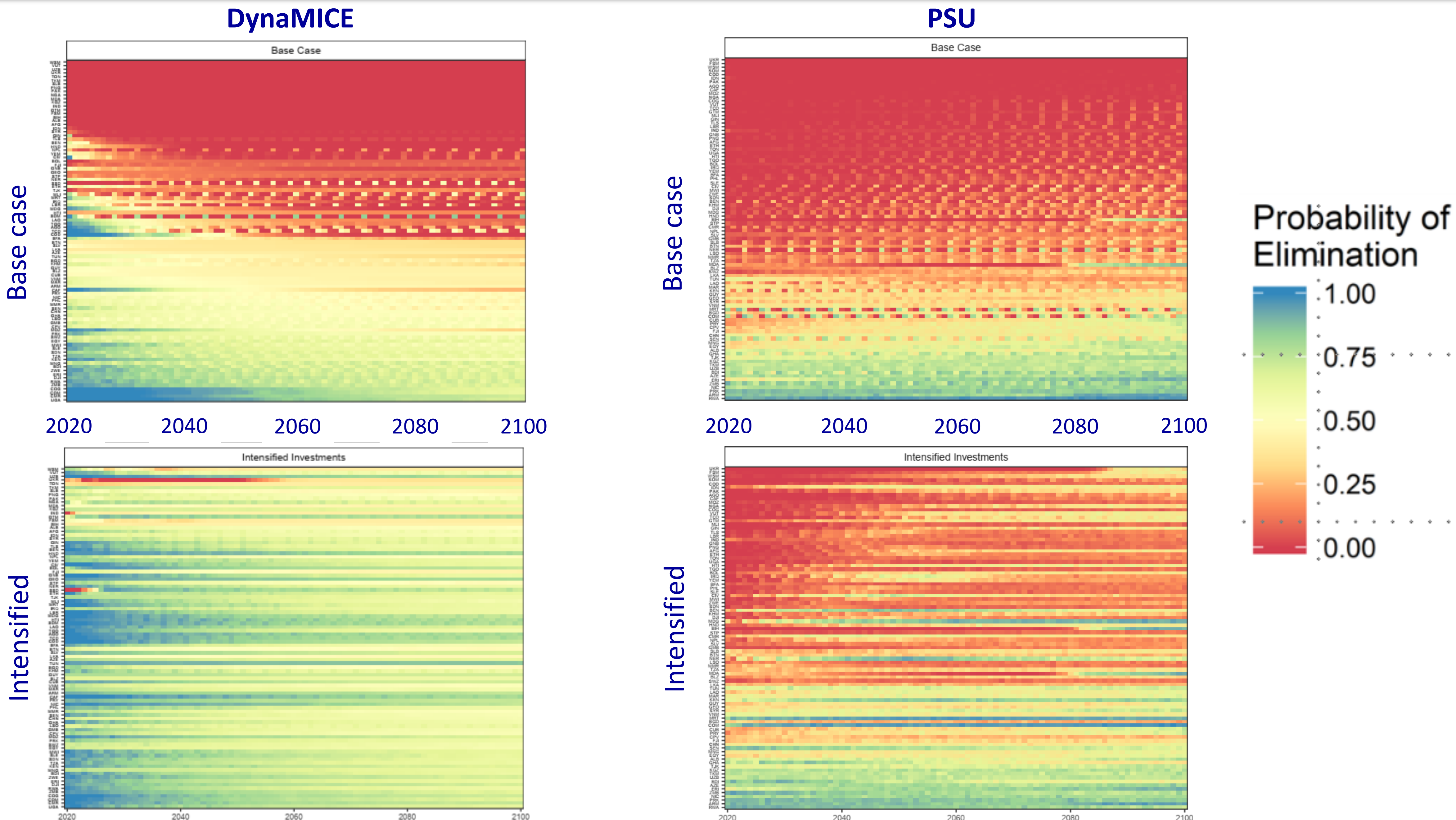


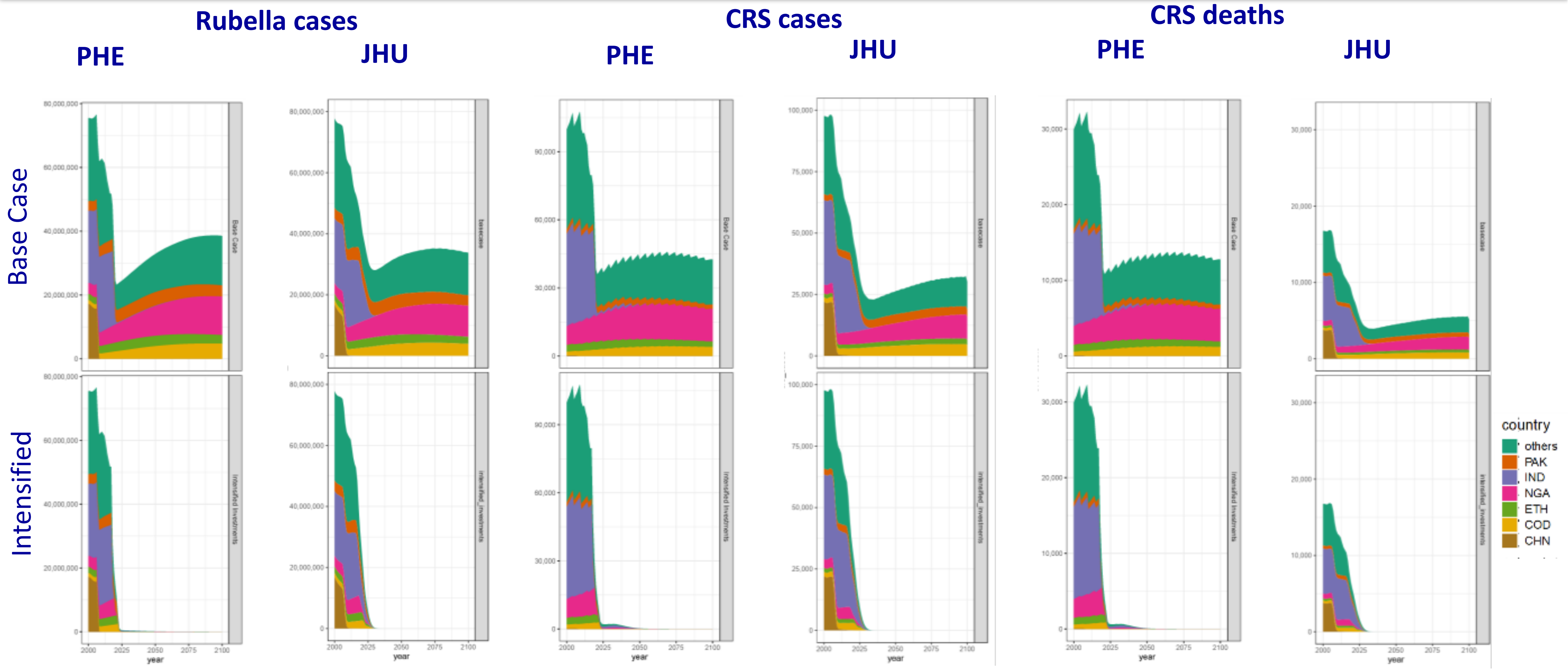
Measles probability of threshold (% of stochastic runs < 5 per 1,000,000)



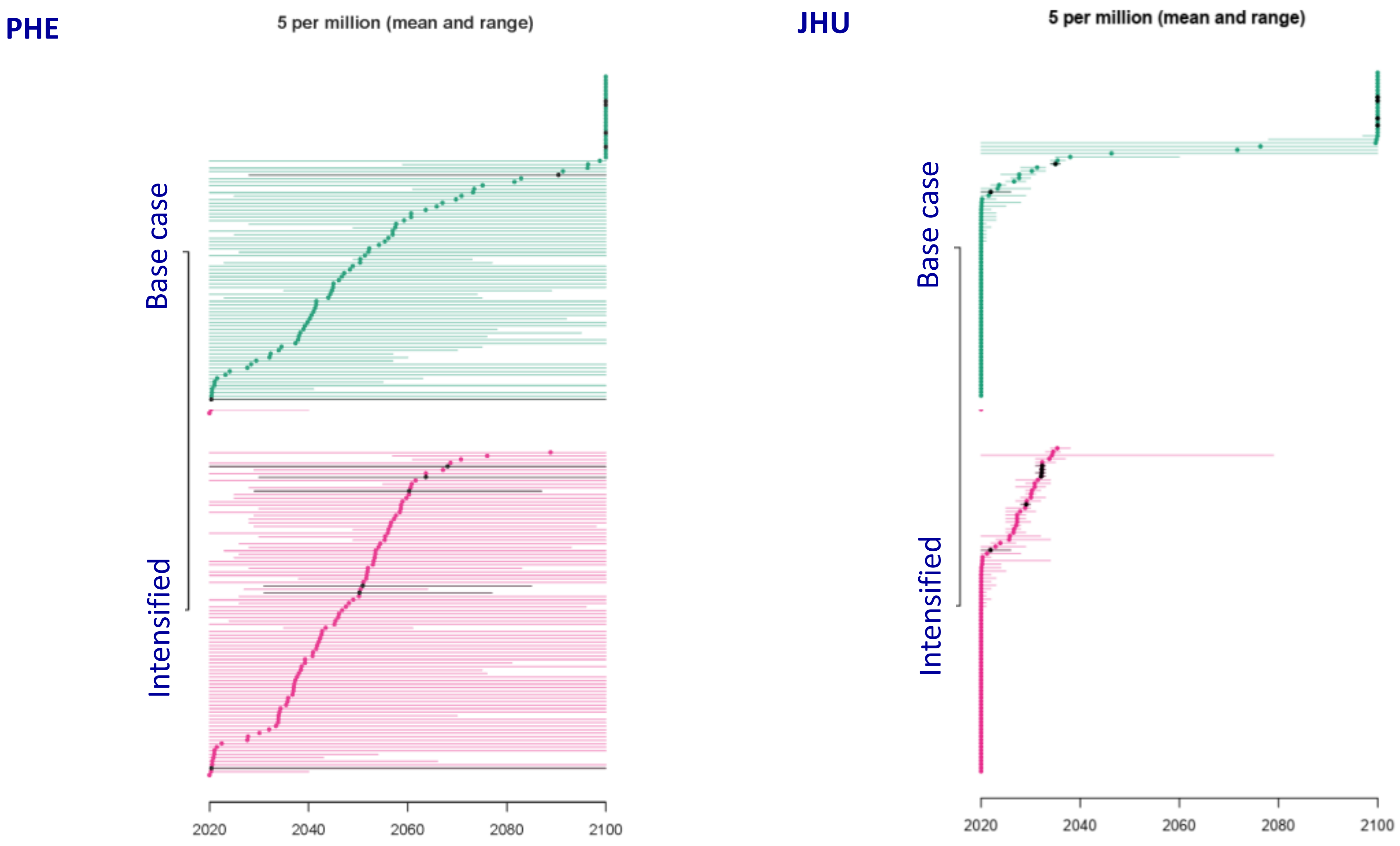
Results: Epidemiological Models

RUBELLA

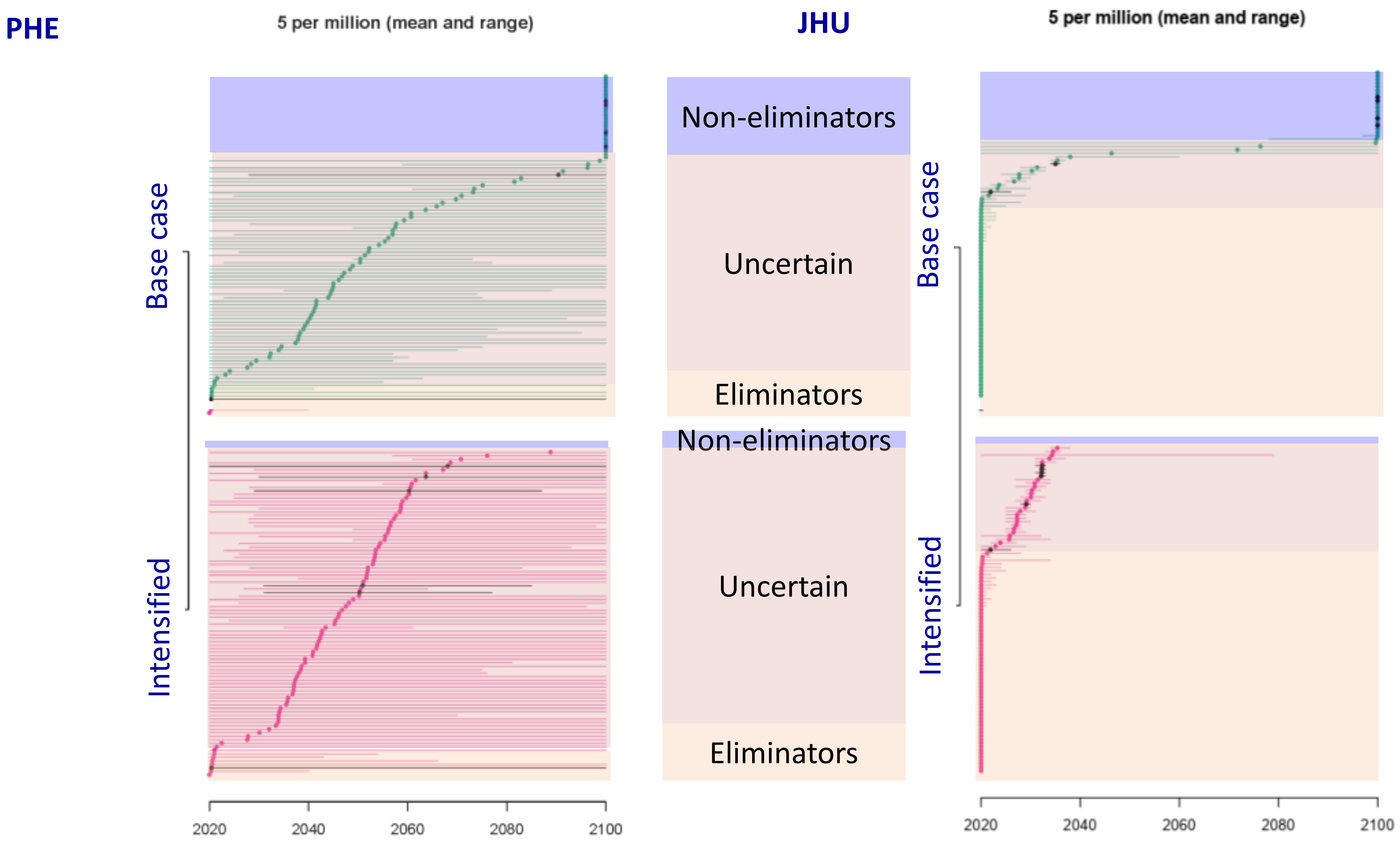
Rubella cases, CRS cases and deaths (median of 200 stochastic runs)



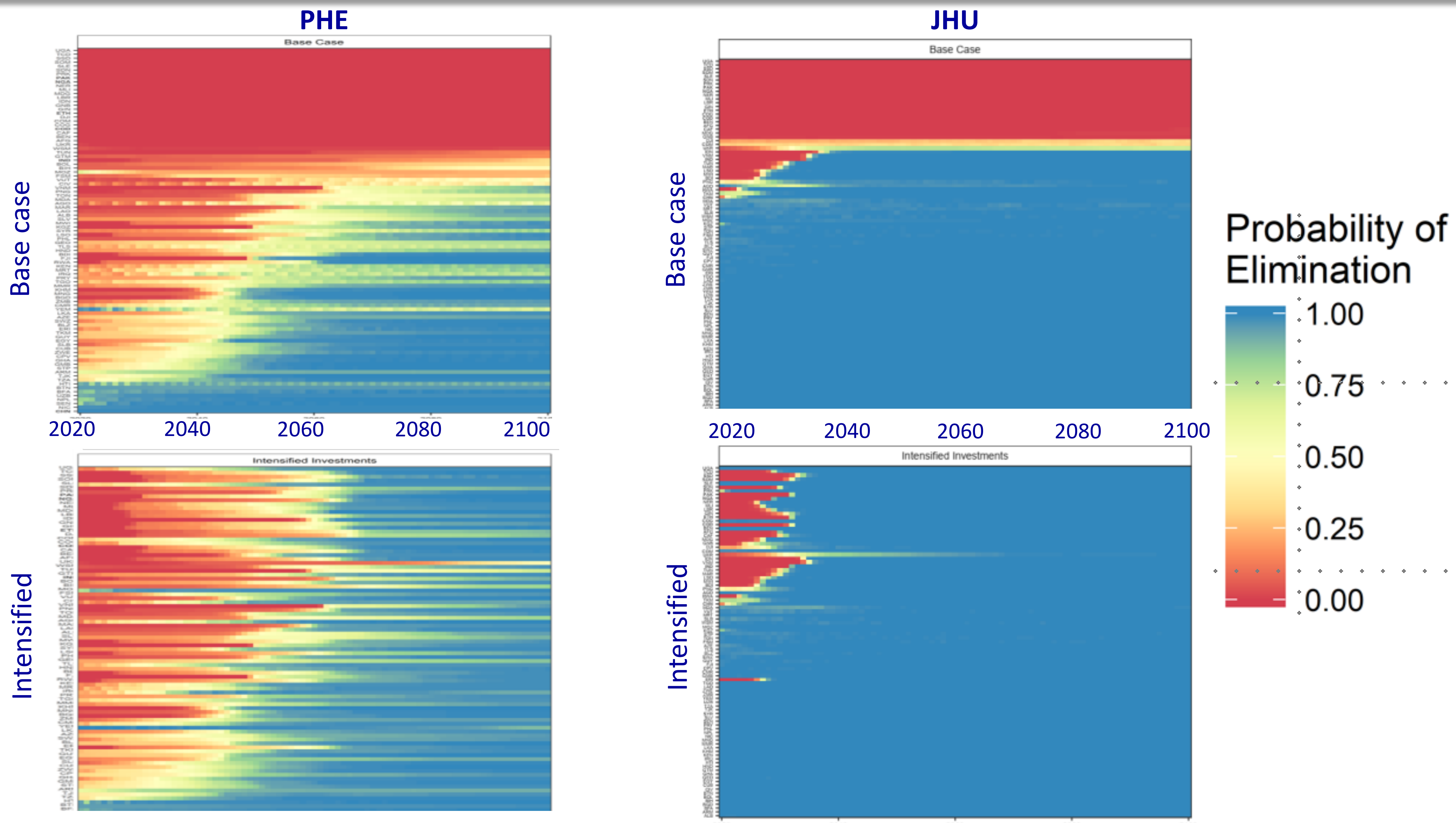
Rubella time to reach threshold



Rubella time to reach threshold



Rubella probability of elimination (% of stochastic runs < 5 per 1,000,000)



Summary of findings

Broad qualitative consensus in patterns between 3 measles models and 2 rubella models, but divergence in country quantitative details.

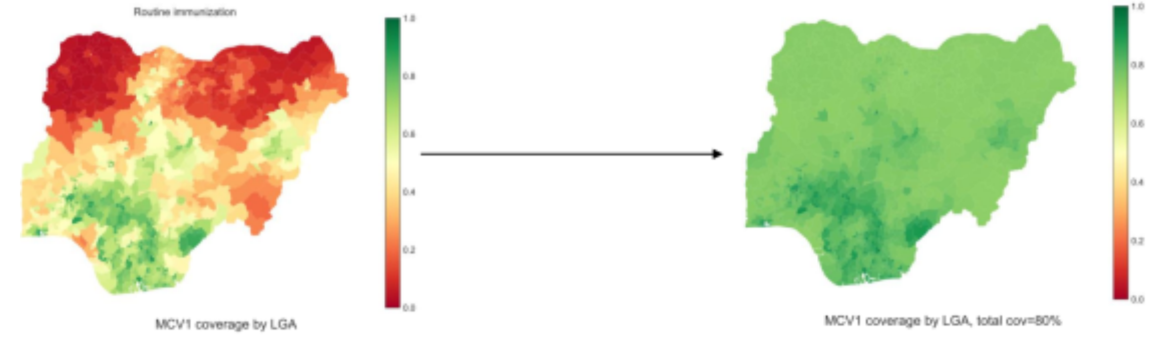
	Measles	Rubella
Eliminators	Most countries are likely to reach measles elimination threshold (< 5 per 1,000,000) under the intensified investments scenario.	All countries introducing RCV may eliminate rubella (< 5 per million) under the three improved scenarios, including some in the base case scenario.
Non-eliminators	Some countries are not likely to reach threshold under the **currently modelled** scenarios partly due to cessation of SIAs). All countries eliminate measles in some runs under the intensified investment scenario.	A few countries have a lower probability of elimination (0.5 - 0.75) over time across scenarios, specifically in the PHE model.
Uncertain	Many countries will eliminate measles in some simulations/models and not in others.	Some countries will have delayed or sporadic elimination before elimination can be maintained, and may be at risk of transient rubella/CRS outbreaks.

Results: Sub-National Model

MEASLES

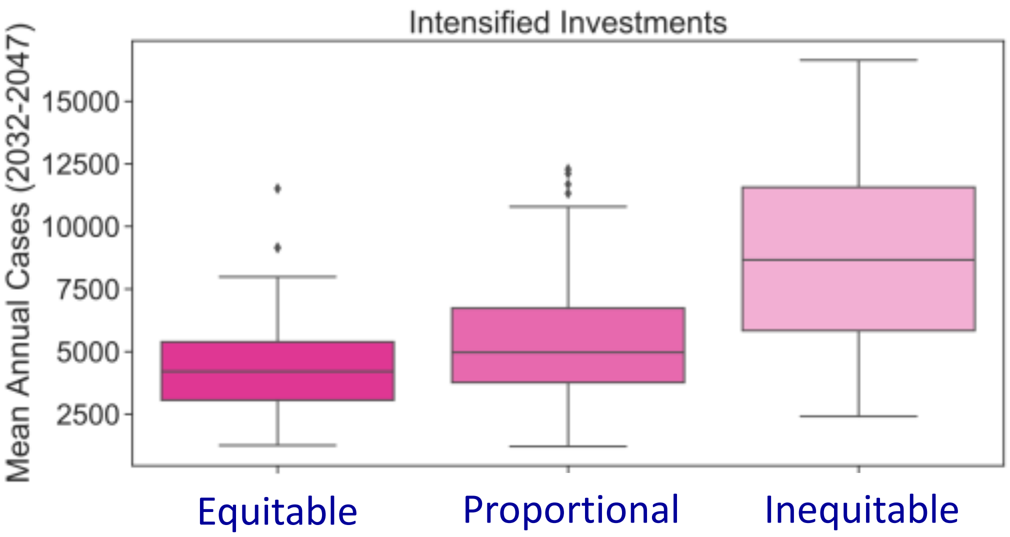
Subnational modelling: Nigeria (IDM)

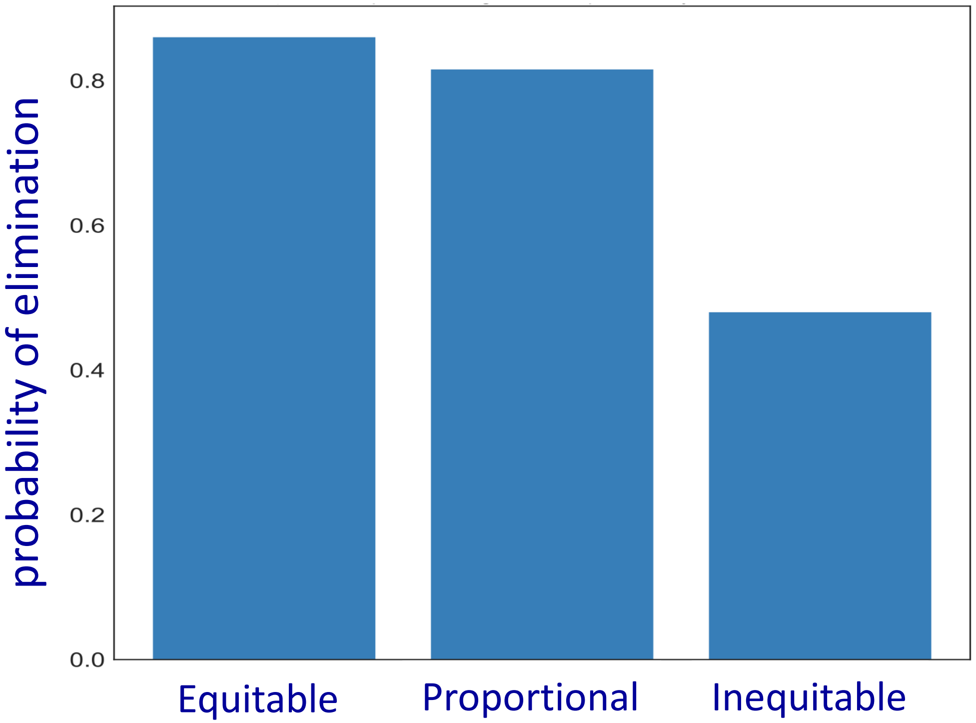
Equitable improvement



Proportionate improvement

Inequitable improvement

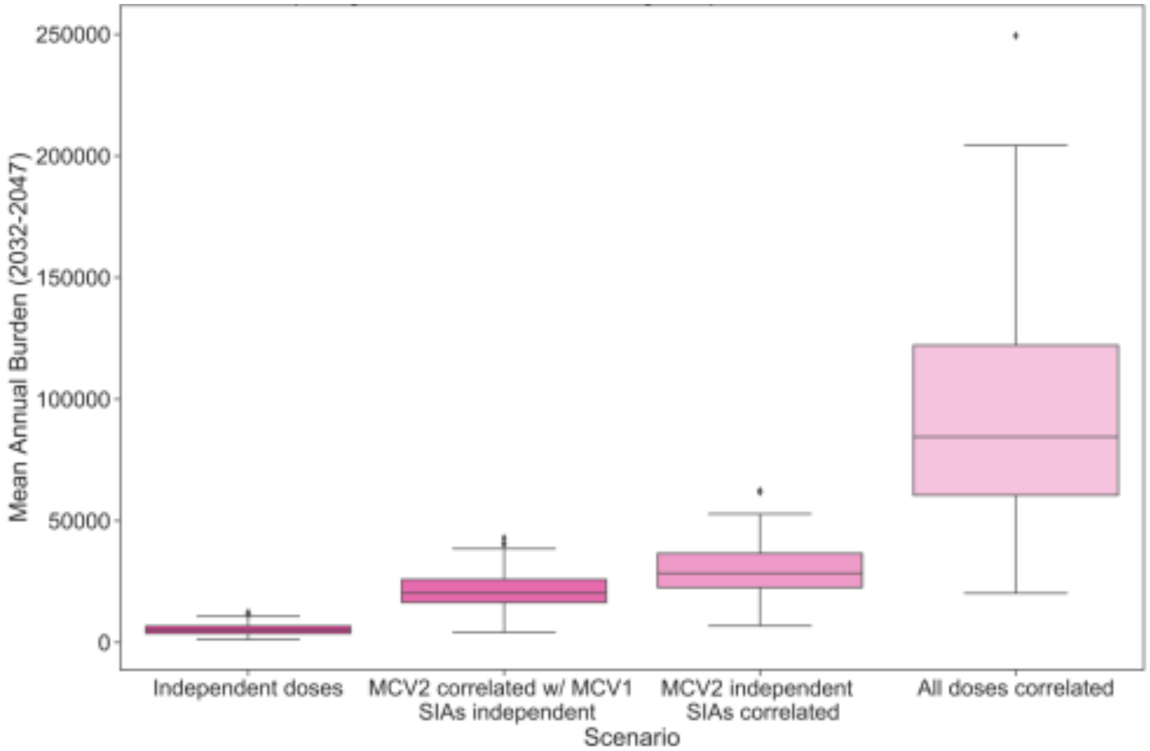




Subnational modelling: Nigeria (IDM)

- ❑ IDM (subnational) model gives qualitatively similar results to the other (national only) measles models.
- ❑ However, this relies on optimistic assumptions about equity of measles coverage (now and in the future).
- ❑ Inequitable distribution of coverage increases burden and reduces probability of elimination

Nigeria Measles Burden: Intensified Scenario



Results: Economic Analysis

MEASLES AND RUBELLA

Economic analysis: key assumptions

Parameter	Value	Source
Cost of routine vaccine dose	Measles: \$1.71-\$2.97 Rubella: \$0.33-\$1.13 (extra)	Immunization Costing Action Network (ICAN) cost catalogue[1]
Cost of SIA dose	Measles: \$0.99-\$2.50 Rubella: \$0.39 (extra)	Levin et al. 2011 Gandhi et al. 2014
Cost of surveillance per dose	\$0.10-\$0.50	Erondu et al. 2019
Cost of increasing coverage	\$1.81-\$3.10 (<60%) to \$2.75-\$4.14 (>90%)	Reanalysis of data from Ozawa et al. 2018

Other key assumptions: Health care provider perspective, 3% discounting for costs (0% for DALYs), time horizon of 30 years (2018-2047)

Total economic costs of vaccination

Vaccine	Scenario	Undiscounted costs ($bn)	Discounted costs ($bn)
Measles	Base case	15.8	10.4
Measles	Intensified Investment	22.5	14.7
Rubella	Base case	4.6	3.0
Rubella	Intensified Investment	6.7	4.4

These do not include additional costs as countries approach elimination eg. enhanced surveillance, outbreak response as these activities are also not included in the modelling. Data on treatment costs, particularly for CRS, are limited.

Economic evaluation: other outcomes

- Intensified investment is cost-effective and may even be cost-saving in most countries compared to base case.

- Effects on health systems may be both positive and negative (Hanvoravongchai et al. 2011).

Implications for MR elimination

- Rubella is likely to be eliminated in most/all countries that introduce RCV.
- Global measles eradication appears unlikely under the coverage scenarios given, but elimination in most countries is likely under several scenarios. Hence alternative strategies to those being modelled may be needed to achieve eradication e.g. strategies to reach 0-dose children.
- Improved coverage scenarios will be cost-effective and will lead to large (orders of magnitude) reductions in measles/rubella incidence and mortality despite increases in population size, so outcomes short of eradication may still be valuable.
- Countries differ in their likelihood of measles elimination so resources could be directed at the countries facing the greatest challenges.
- Some countries may need to maintain frequent SIAs until MCV1/2 coverage exceeds 95%.
- Equity of coverage (spatial, accessibility) will improve the likelihood of eradication.

Contributors

- Measles-rubella modelling: Mark Jit, Petra Klepac (LSHTM), Matt Ferrari (PSU), Emilia Vynnycky, Timos Papadopoulos (PHE), Amy Winter, Shaun Truelove, Justin Lessler, Jess Metcalf (JHU)

- Coordinating centre: Colleen Burgess (Ramboll)

- Economic evaluation: Ann Levin (Levin Morgan)

- Coverage scenarios: Susan Reef, Jennifer Knapp, Lidia Kayembe (CDC)

- Comments/input from:
  - SAGE measles-rubella working group
  - IVIR-AC
  - WHO Secretariat: Stephanie Shendale, Katrina Kretsinger, Raymond Hutubessy, Alya Dabbagh

Review by WHO working groups

MEASLES AND RUBELLA

Recommendations from IVIR-AC (September 2019)

- Immediate recommendations (already implemented)
  - Focus on Base Case and Intensified Investment scenario only since intermediate scenarios still fall short of elimination.
  - Focus on total cost rather than cost-effectiveness since all scenarios are cost-effective.
  - Minor changes to graphs, etc.

- Recommendations for future work
  - The uncertainty in both epidemiological and economic parameters should be taken into account

  - When presenting to decision makers it is important to talk about budget implications and affordability of measles and rubella eradication

Recommendations by SAGE Measles Rubella Working Group and by IVIR-AC: Potential future work

- What would it take to reach eradication?
  - Explore scenarios where all countries eliminate both measles and rubella with high probability
  - Retrofit models to PAHO situation for validation
  - Use epidemiological definition of elimination: “interruption of sustained transmission”
  - Look more closely at some of the big/challenging countries – what would it take to get these countries over the line?
  - Include outbreaks, cross-border dynamics and interconnected countries

- What are the country characteristics that determine probability and time to elimination?

- What kind of investments are needed to achieve eradication?
  - Explore cost for a “go big, go fast” strategy
  - Look at health systems requirements, not just the financial outlay

- What are the costs of inaction?
  - Explore a “negative trends” scenario capturing what would happen if the world continues to backslide, with no new investments