Modelling to inform rubella vaccine introduction: latest vaccination coverage threshold from modelling work

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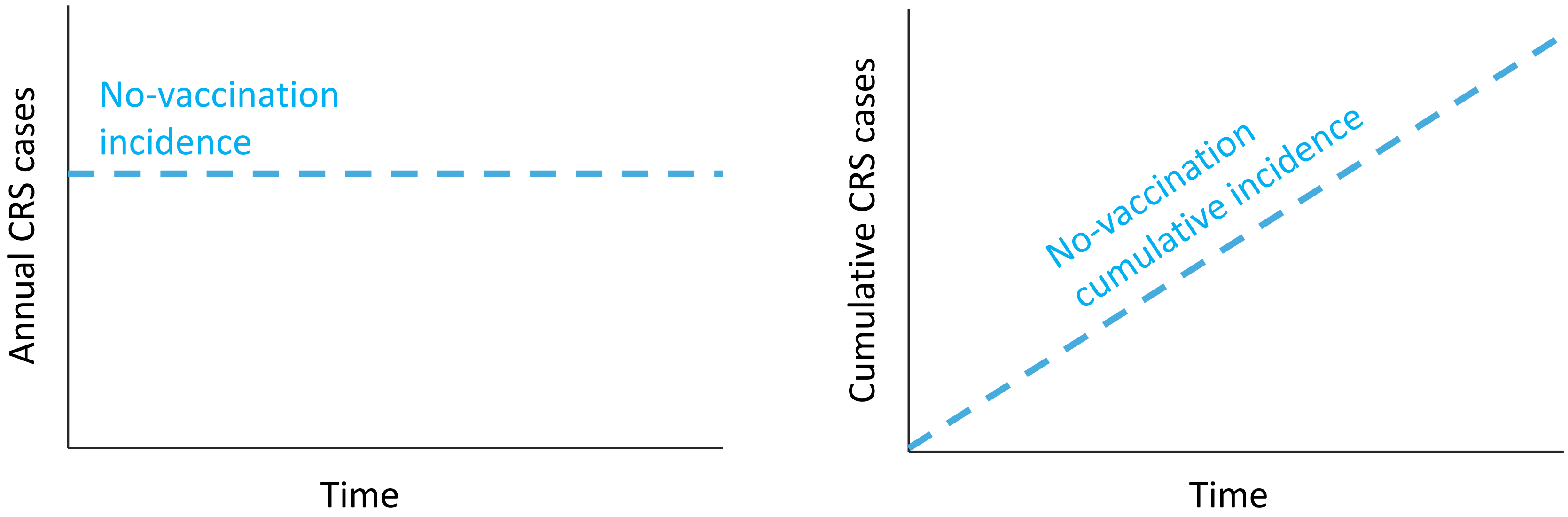
Introduction and Motivation

The Paradoxical Effect

- A “paradoxical effect” for rubella occurs when low-to-intermediate RCV coverage leads to a rebound in CRS burden that exceeds no-vaccination levels.
    - Effect has support both theoretically and empirically



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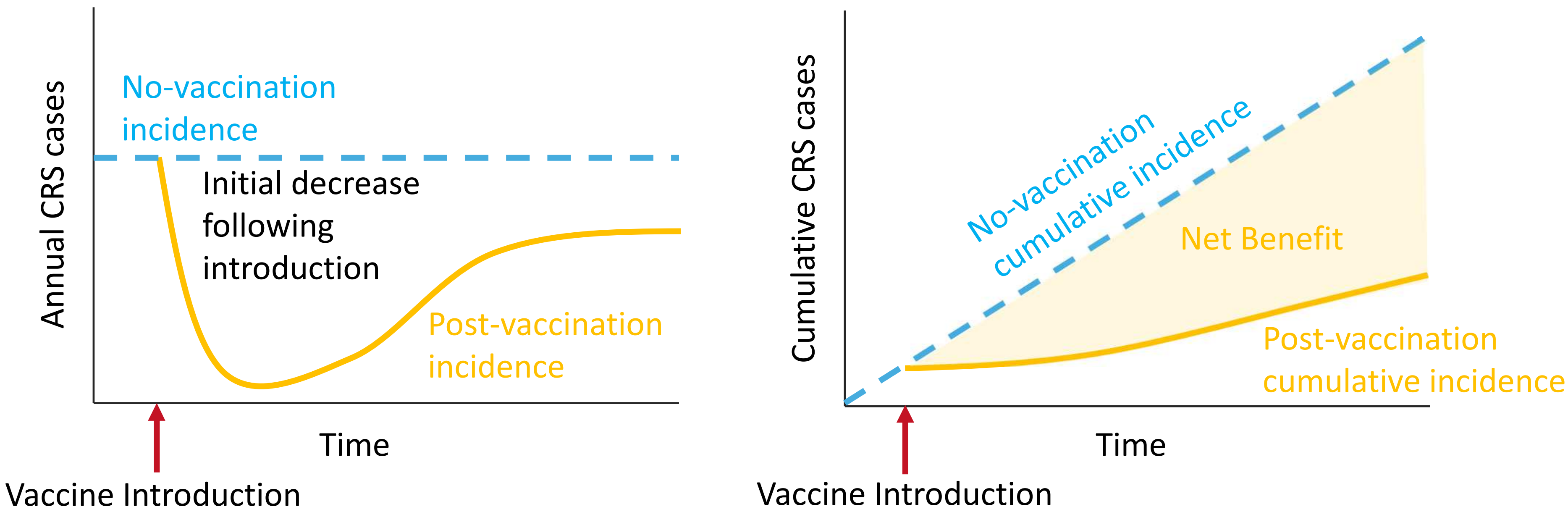

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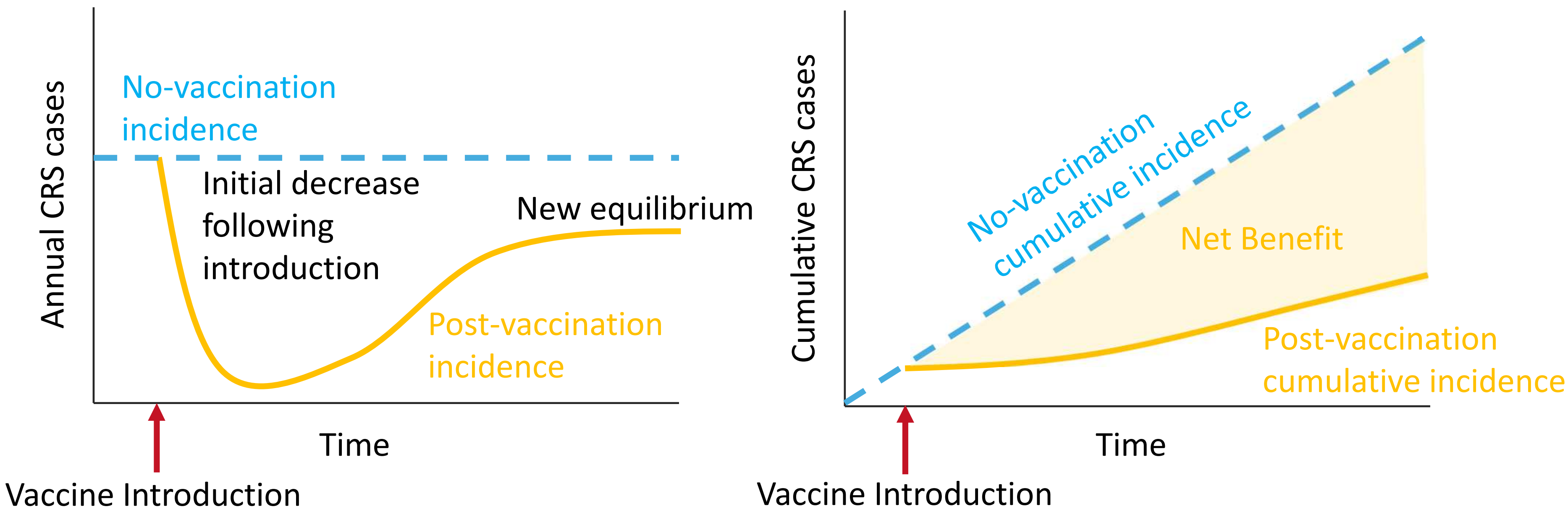

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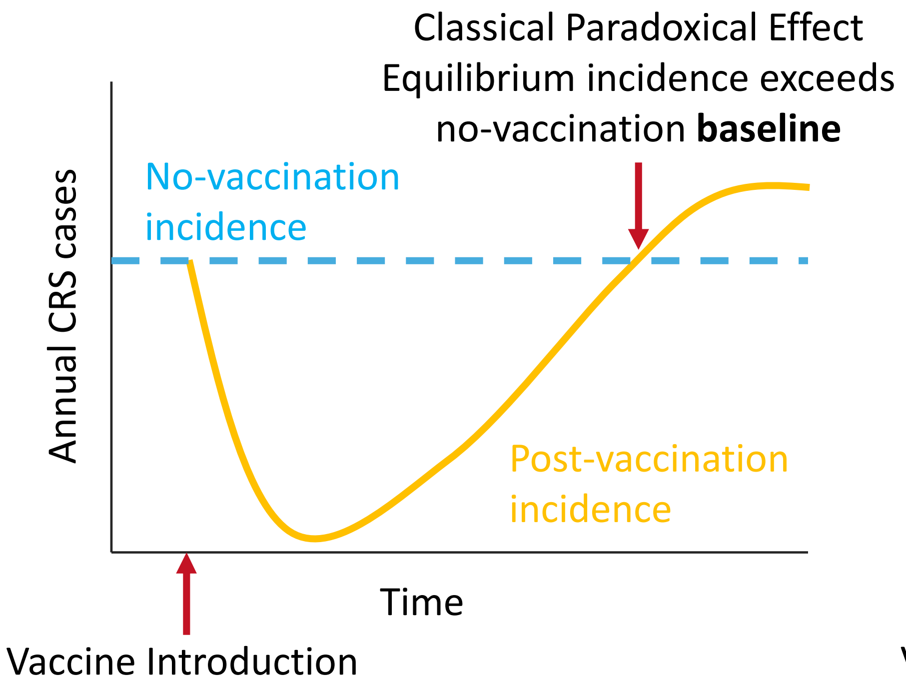

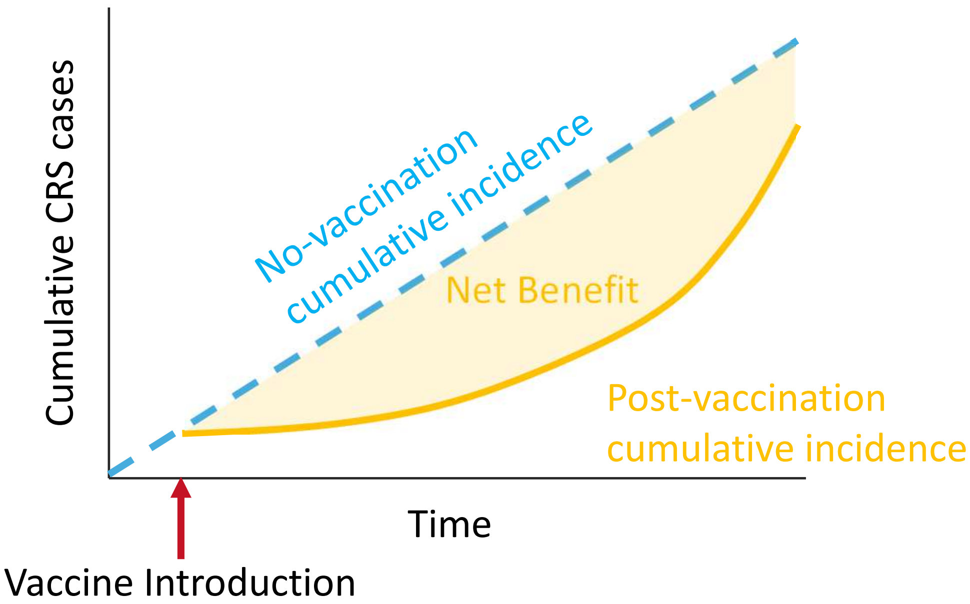

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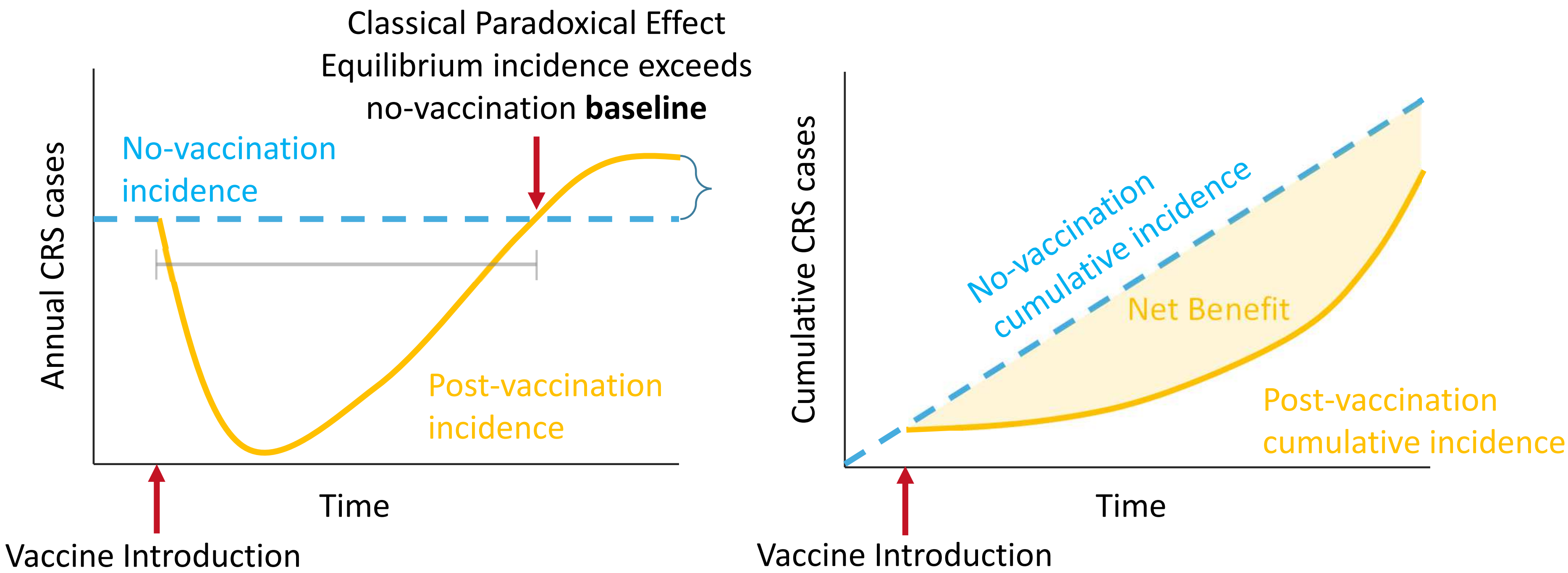

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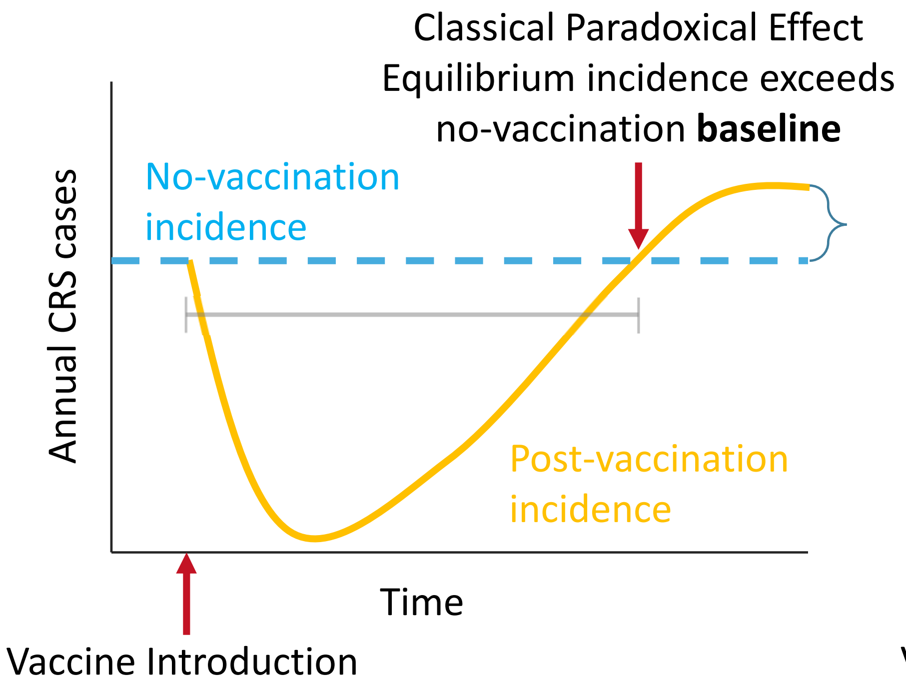

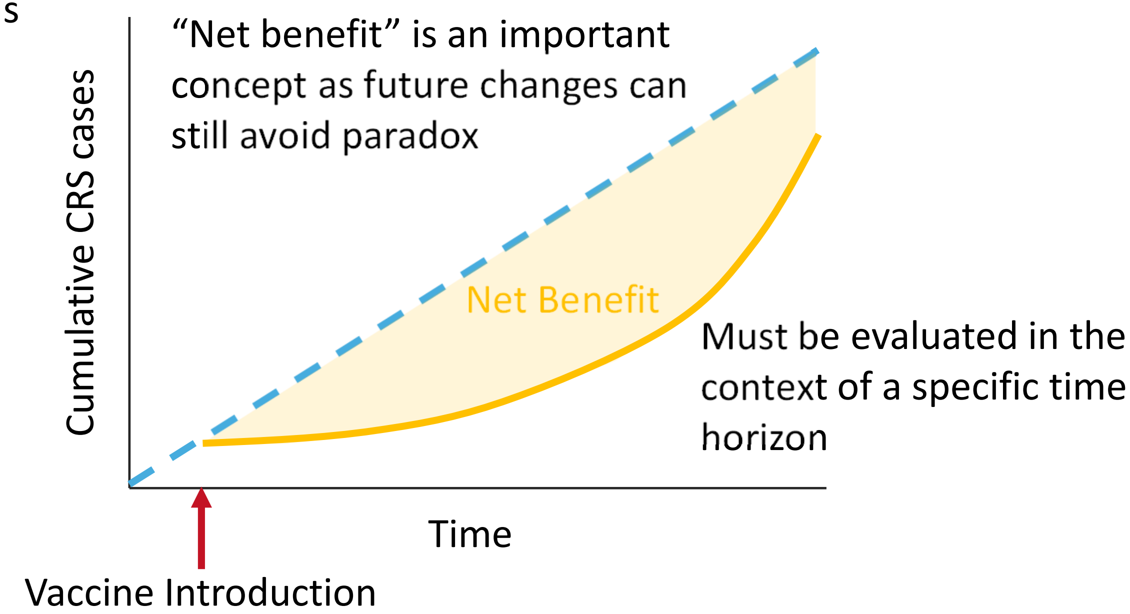

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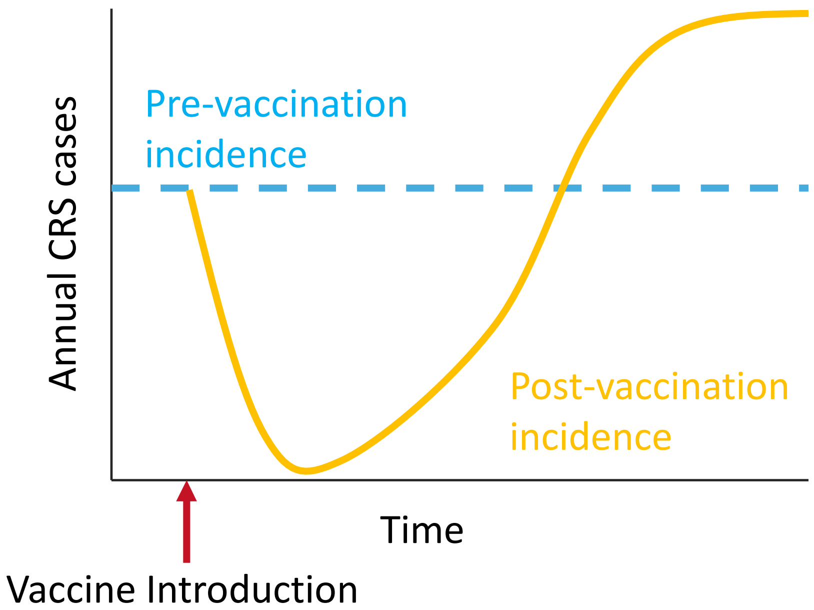

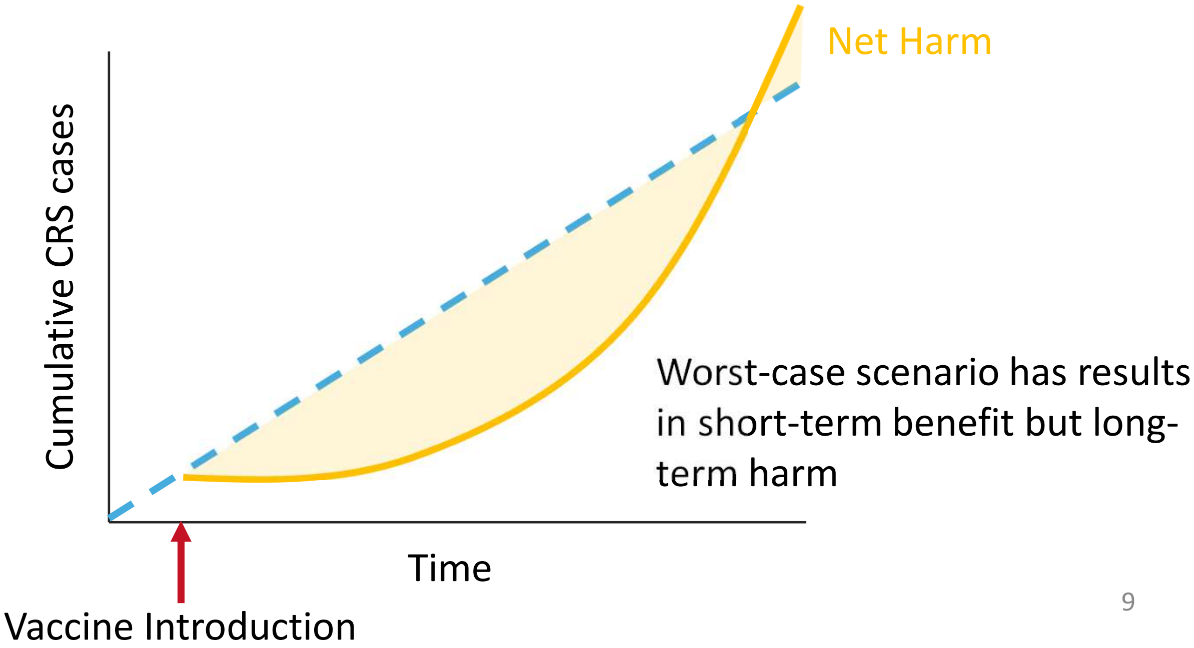

The Paradoxical Effect

- A "paradoxical effect" for rubella occurs when low-to-intermediate RCV coverage leads to a rebound in CRS burden that exceeds no-vaccination levels.
  - Effect has support both theoretically and empirically
  - Actual coverage threshold depends on context (**R_0 and demographics**)

- History of understanding and programmatic impact:
  - Theory was developed in settings where CRS was rare
  - Theory for **long-term** impact was first described in early 80s

Knox 1981 – Mathematical characterization of 'paradoxical effect' of rubella vaccine introduction. Shows that, following an initial transient period of low rubella and CRS incidence, CRS incidence can increase above pre-vaccine levels even while rubella incidence remains low, IF childhood vaccination is below a critical threshold

Anderson and May 1983 – Example using England. Estimation of critical vaccination coverage at 55%

1980 1990 2000 2010 2020 2030

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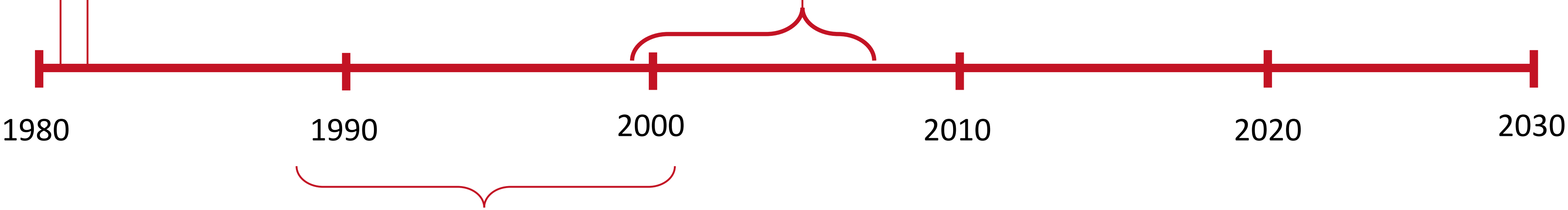

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WER 2000: All countries undertaking rubella elimination should ensure that women of childbearing age are immune and that routine coverage in children is sustained >80%

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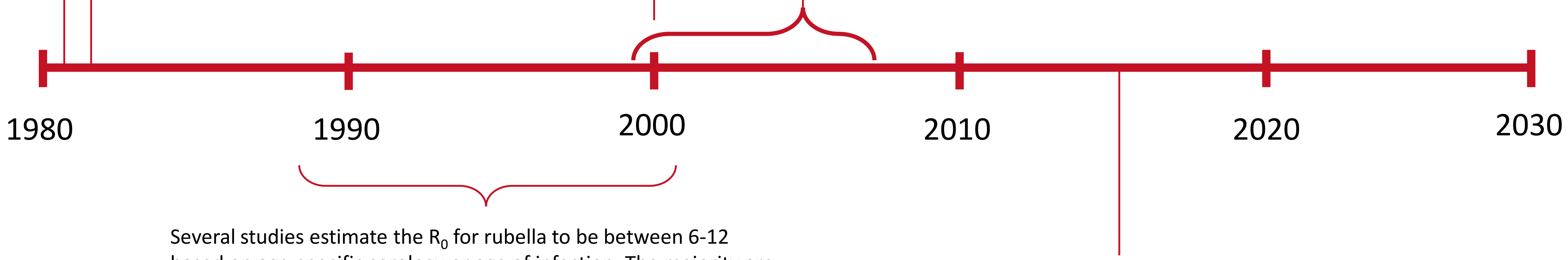

WER 2011: To avoid the potential of an increased risk of CRS, countries should achieve and maintain immunization coverage of 80% or greater with at least 1 dose of an RCV delivered through routine services or regular SIAs, or both

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Lessler & Metcalf 2013 – Illustrate lower risk with campaigns in addition to RI

WER 2020: Countries that have not yet introduced RCV into their immunization programmes should do so if they can achieve a coverage level of 80% or greater, through either routine immunization or campaigns

Papadopoulos and Vynnycky 2022 - review of R_0 estimates

1980 1990 2000 2010 2020 2030

Why This Work Now?

Goal of these collected modelling activities is to update the understanding of the risks and consequences of RCV introduction with **contemporary epidemiological data** and **programmatic activities**

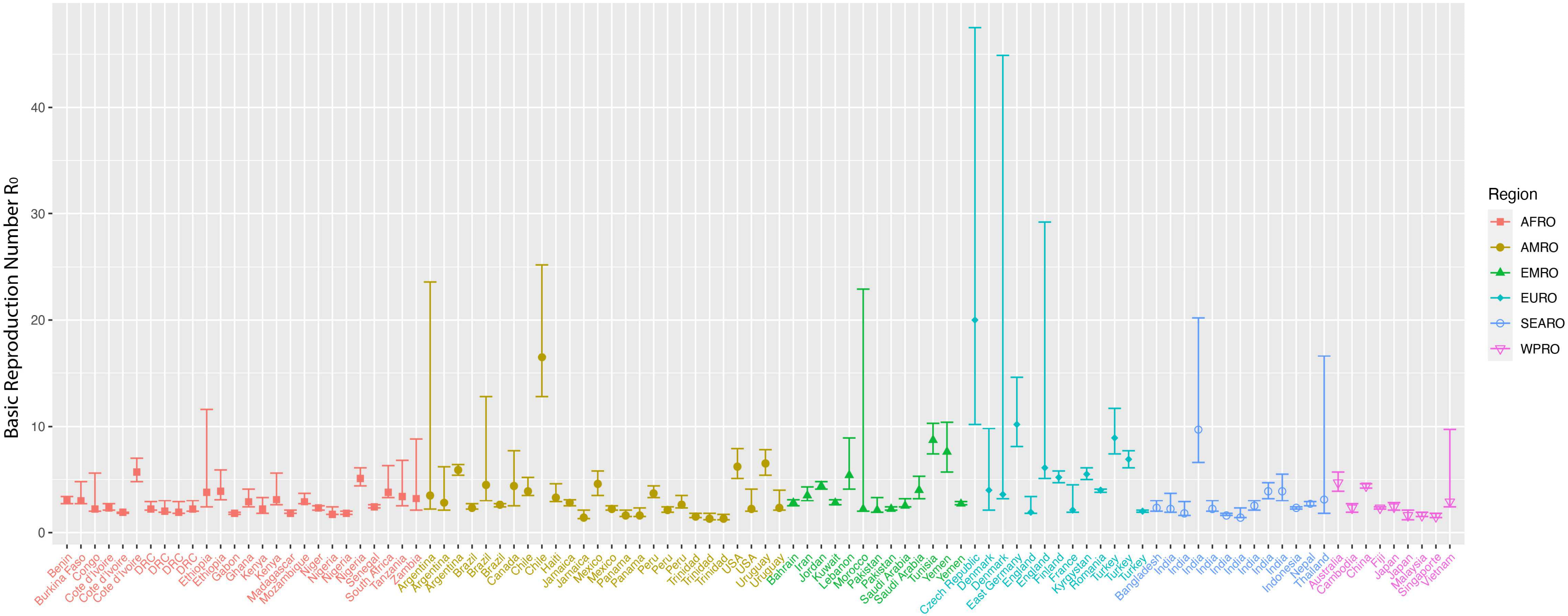
Provide a critical evaluation of the current guidance as a barrier to CRS control and rubella elimination

New Insights from Modeling Activities

1. Current CRS burden is significant and avoidable
2. R_0 for rubella in countries yet to introduce RCV is lower than previous assumptions, even at a sub-national level
3. Expected birth rate declines and aging populations will increase CRS rate in the absence of vaccination
4. RI is currently sufficient to prevent paradoxical effect in most countries. RI plus campaigns prevent paradoxical effect in all countries.

Rubella transmission and demography

Review of R0 estimates



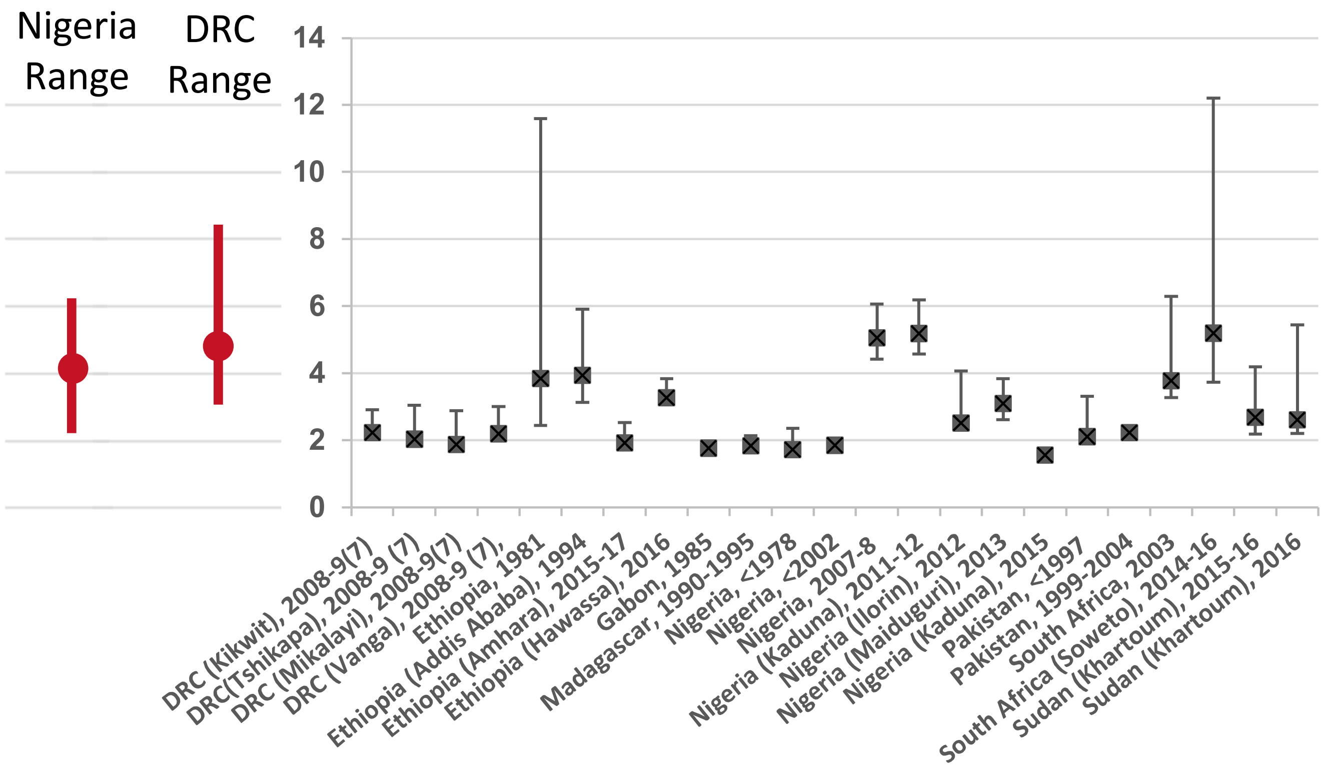
Papadopoulos and Vynnycky 2022

Focus on 19 countries

Updated from *PLoS Comp Bio* 2022; 18(3): e1008858
with data in *Int J Infect Dis* 2023; 137: 149-156

The range of subnational R_0 estimates from Nigeria and DRC are consistent with the distribution of national-level estimates from Papadopoulos and Vynnycky (from serology).

No indication that subnational hotspots are outside the range of national-level estimates.



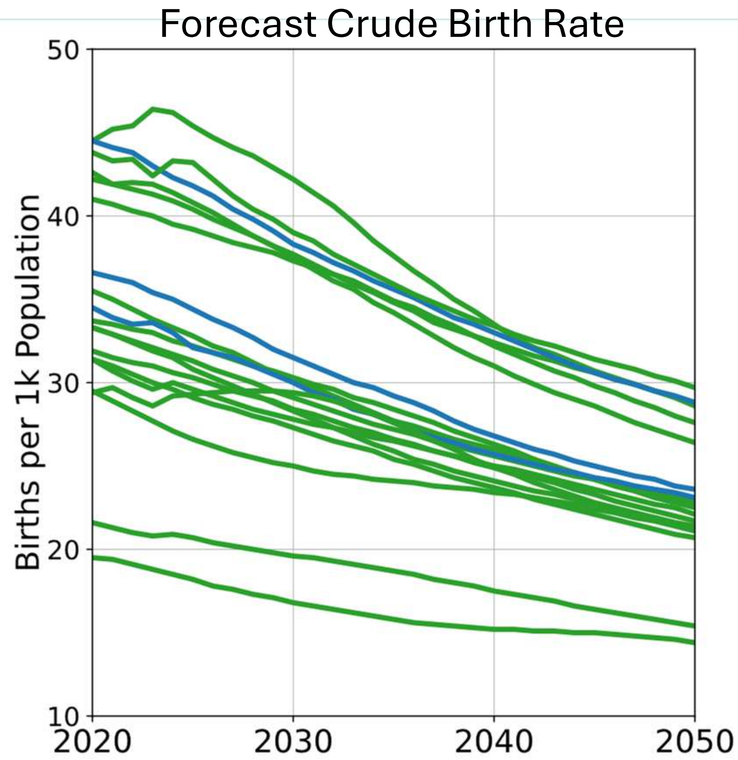
- These confirm the magnitude of the subnational estimates.
- They suggest the risk of paradoxical effect is low.

Projections assuming no vaccination

Birth rates are expected to decline in both the AFRO and EMRO regions over the coming decades.

When birth rates decline:

- Adults become a larger fraction of the overall population.
- Average transmission rates decrease, because adults have fewer contacts than children.

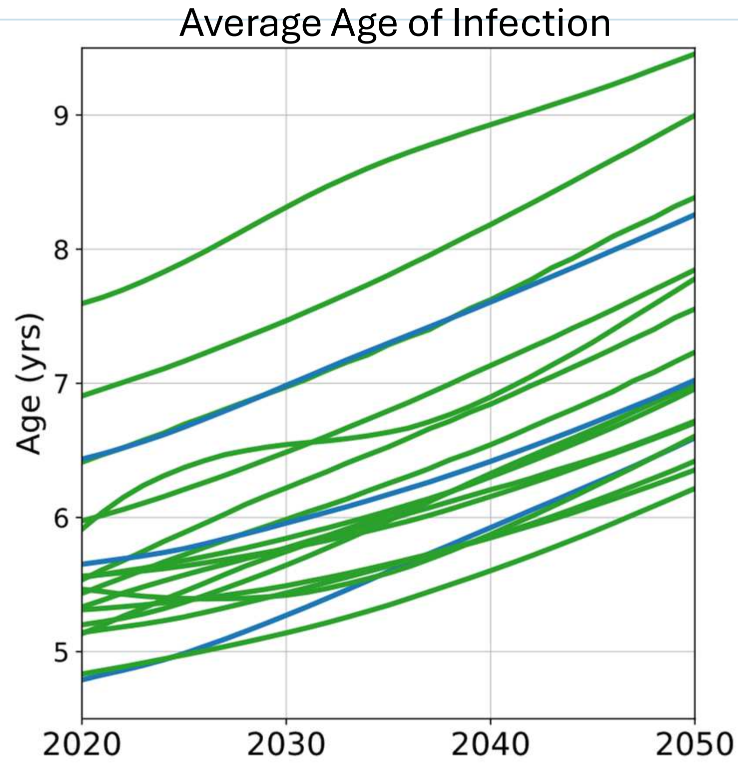


Projections for all 19 countries
UN WPP 2024 Revision

Projections assuming no vaccination

Birth rates are expected to decline in both the AFRO and EMRO regions over the coming decades.

Lower transmission rates mean a decreased force of infection, leading to greater average ages of infection and greater susceptibility later in life.



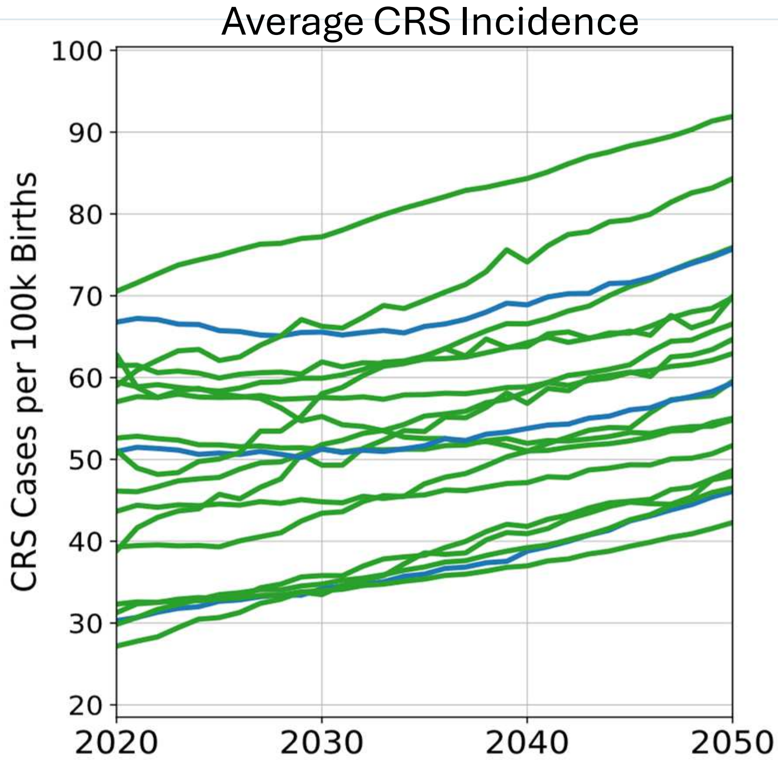
Projections for all 19 countries
UGA model: No Vaccination

Projections assuming no vaccination

Birth rates are expected to decline in both the AFRO and EMRO regions over the coming decades.

Greater susceptibility in older age groups increases the expected rate of CRS in the absence of vaccination.

Each 10% decline in crude birth rate leads to an increase of around 10% in the rate of CRS.



Projections for all 19 countries
UGA model: No Vaccination

Rubella Epidemiology and Demographic Change

Contemporary estimates of rubella transmission rate indicate that 80% criterion is conservative. This holds for subnational analyses of two largest countries among those yet to introduce.

Projected changes in birth rates are expected to lead to increase in CRS rate per 100K births in the absence of vaccination leading to opportunity cost of delayed introduction.

Introduction Scenario Modelling

National Scale Analysis

- National-scale analysis of 19 countries yet to introduce RCV as of start of 2024
- Goal
  - to evaluate future risk of CRS under realistic scenarios of future demographic change
  - and realistic introduction and SIA scenarios consistent with contemporary standard
    - Evaluated multiple scenarios that reflect optimistic to pessimistic assumptions
- All scenarios run using two independent models (UGA and UKHSA)
  - Methods have been reviewed by IVIR-AC and previously presented to SAGE

Simulation Scenarios

	Routine Immunization
1	Mean of WUENIC coverage from 2018-2019
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	

Simulation Scenarios

Campaigns	
Target	Coverage
Wide age range	90%
	80%
Narrow age range	70%
	60%

	Routine Immunization	Introductory Campaign
1	Mean of WUENIC coverage from 2018-2019	≤ 14y 90% coverage
2		≤ 14y 80% coverage
3		≤ 14y 70% coverage
4		≤ 14y 60% coverage
5		≤ 14y 90% coverage
6		≤ 14y 80% coverage
7		≤ 14y 70% coverage
8		≤ 14y 60% coverage
9		≤ 4y 90% coverage
10		≤ 4y 80% coverage
11		≤ 4y 70% coverage
12		≤ 4y 60% coverage
13		≤ 14y 90% coverage
14		≤ 14y 80% coverage
15		≤ 14y 70% coverage
16		≤ 14y 60% coverage
17		None

Simulation Scenarios

Campaigns	
Target	Coverage
Wide age range	90%
	80%
Narrow age range	70%
	60%

Post-introduction continued campaigns are assumed to be conducted every 4 years

	Routine Immunization	Introductory Campaign	Continued Campaigns
1	Mean of WUENIC coverage from 2018-2019	≤ 14y 90% coverage	≤ 4y 90% coverage
2		≤ 14y 80% coverage	≤ 4y 90% coverage
3		≤ 14y 70% coverage	≤ 4y 90% coverage
4		≤ 14y 60% coverage	≤ 4y 90% coverage
5		≤ 14y 90% coverage	≤ 4y 60% coverage
6		≤ 14y 80% coverage	≤ 4y 60% coverage
7		≤ 14y 70% coverage	≤ 4y 60% coverage
8		≤ 14y 60% coverage	≤ 4y 60% coverage
9		≤ 4y 90% coverage	≤ 4y 90% coverage
10		≤ 4y 80% coverage	≤ 4y 80% coverage
11		≤ 4y 70% coverage	≤ 4y 70% coverage
12		≤ 4y 60% coverage	≤ 4y 60% coverage
13		≤ 14y 90% coverage	None
14		≤ 14y 80% coverage	None
15		≤ 14y 70% coverage	None
16		≤ 14y 60% coverage	None
17		None	None

Simulation Scenarios

Campaigns	
Target	Coverage
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Recommended Schedule
Good Coverage

	Routine Immunization	Introductory Campaign	Continued Campaigns
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5		≤ 14y 90% coverage	≤ 4y 60% coverage
6		≤ 14y 80% coverage	≤ 4y 60% coverage
7		≤ 14y 70% coverage	≤ 4y 60% coverage
8		≤ 14y 60% coverage	≤ 4y 60% coverage
9		≤ 4y 90% coverage	≤ 4y 90% coverage
10		≤ 4y 80% coverage	≤ 4y 80% coverage
11		≤ 4y 70% coverage	≤ 4y 70% coverage
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16		≤ 14y 60% coverage	None
17		None	None

Simulation Scenarios

Campaigns	
Target	Coverage
Wide age range	90%
	80%
Narrow age range	70%
	60%

Recommended Schedule
Good Coverage

Recommended Schedule
Poor Coverage

	Routine Immunization	Introductory Campaign	Continued Campaigns
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16		≤ 14y 60% coverage	None
17		None	None

Simulation Scenarios

Campaigns	
Target	Coverage
Wide age range	90%
	80%
Narrow age range	70%
	60%

Narrow Campaigns only (scenarios 9–12)

	Routine Immunization	Introductory Campaign	Continued Campaigns
1	Mean of WUENIC coverage from 2018-2019	≤ 14y 90% coverage	≤ 4y 90% coverage
2		≤ 14y 80% coverage	≤ 4y 90% coverage
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Simulation Scenarios

Campaigns	
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13		≤ 14y 90% coverage	None
14		≤ 14y 80% coverage	None
15		≤ 14y 70% coverage	None
16		≤ 14y 60% coverage	None
17		None	None

Introductory wide age Campaigns only (scenarios 13–16)

Simulation Scenarios

Campaigns	
Target	Coverage
Wide age range	90%
	80%
Narrow age range	70%
	60%

	Routine Immunization	Introductory Campaign	Continued Campaigns
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12		≤ 4y 60% coverage	≤ 4y 60% coverage
13		≤ 14y 90% coverage	None
14		≤ 14y 80% coverage	None
15		≤ 14y 70% coverage	None
16		≤ 14y 60% coverage	None
17 (Routine Only, No campaigns)		None	None

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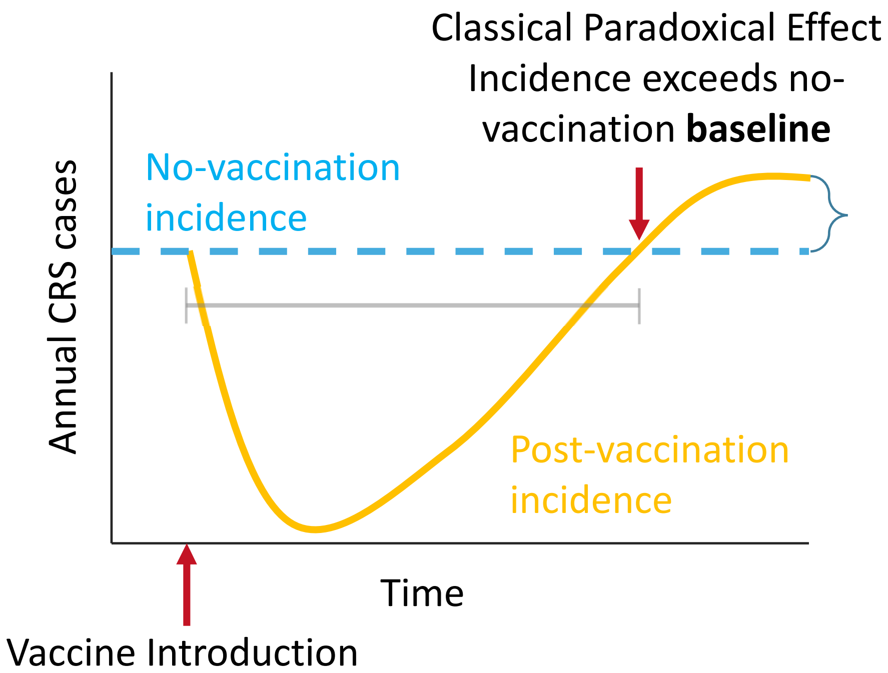
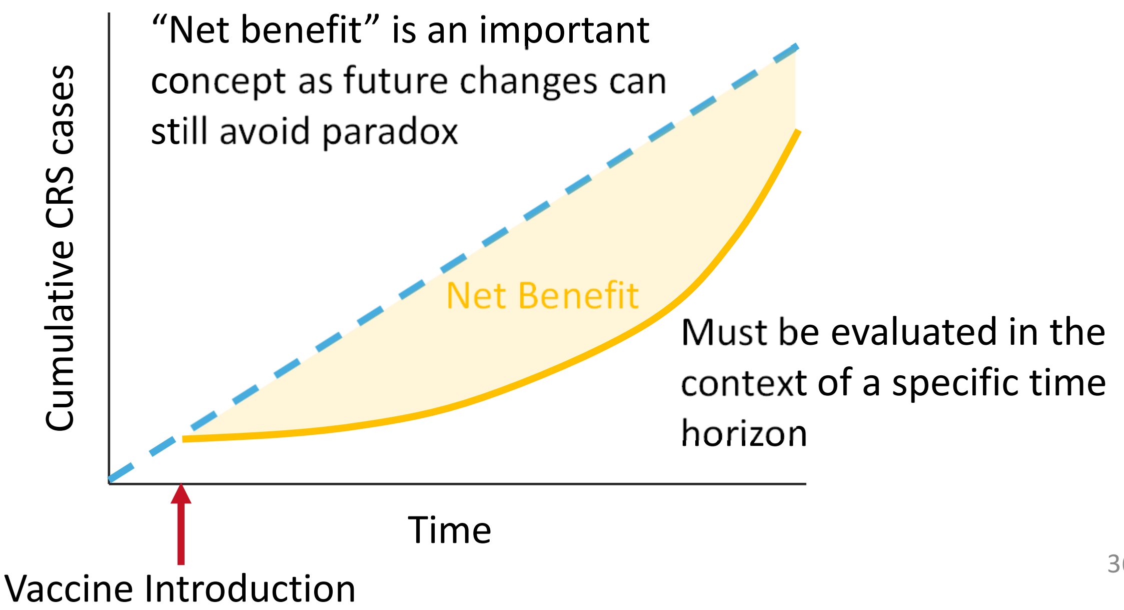




Net Benefit of CRS Reduction Over 30 Years Compared to No-Vaccination Baseline

Scenarios organized as in previous slides; ordered from best to least

SCENARIO			AFG	
RI	Intro	Continued	UGA	UKHSA
WUENIC	90%	90%	96	96
WUENIC	80%	90%	96	96
WUENIC	70%	90%	96	95
WUENIC	60%	90%	96	95
WUENIC	90%	60%	95	96
WUENIC	80%	60%	95	95
WUENIC	70%	60%	94	95
WUENIC	60%	60%	94	94
WUENIC	90%	90%	95	94
WUENIC	80%	80%	95	94
WUENIC	70%	70%	94	93
WUENIC	60%	60%	91	91
WUENIC	90%		66	86
WUENIC	80%		65	83
WUENIC	70%		62	79
WUENIC	60%		59	76
WUENIC			48	57

Value in each cell is the net benefit (% reduction of CRS cases) in each scenario compared to the no-vaccination baseline over the 30 year simulation. Color scale is darker for **SMALLER** reduction.

Campaigns	
Target	Coverage
Wide age range	90%
	80%
Narrow age range	70%
	60%

Results from each model are presented in columns.
Left is UGA, Right is UKHSA

Net Benefit of CRS Reduction Over 30 Years Compared to No-Vaccination Baseline

	SCENARIO		AFG		CAF		COD		DJI		ETH		GAB		GIN		GNB		GNQ		LBR		MDG		MLI		NER		NGA		SDN		SOM		SSD		TCD		ZAF	
RI	Intro	Continued	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA
WUENIC	90%	90%	96	96	89	96	97	97	98	96	97	96	98	97	91	96	98	97	68	97	97	96	97	96	97	97	97	97	70	96	97	96	67	97	77	96	71	96	96	96
	80%	90%	96	96	89	96	97	97	98	96	96	95	98	97	90	95	98	96	67	96	97	96	97	96	96	96	97	97	70	96	97	96	67	96	77	96	71	96	96	95
	70%	90%	96	95	88	95	96	97	98	96	96	94	98	97	90	95	98	95	68	96	97	95	97	96	96	96	97	96	70	96	97	95	67	96	77	95	71	95	96	94
	60%	90%	96	95	87	94	96	96	98	96	96	93	98	97	89	94	98	94	68	95	97	94	97	96	96	95	97	96	70	95	97	95	67	95	77	94	70	95	96	94
	90%	60%	95	96	73	95	94	97	98	96	94	95	95	97	83	95	98	97	68	97	97	96	97	96	95	96	97	97	70	96	97	96	67	94	77	96	67	96	96	95
	80%	60%	95	95	72	94	93	97	98	96	93	94	94	97	83	94	98	96	67	95	97	96	97	96	95	96	97	97	70	95	97	96	67	93	77	95	67	95	96	95
	70%	60%	94	95	71	93	92	96	98	96	92	92	93	97	82	93	98	95	68	94	96	95	96	96	94	95	96	96	70	95	97	95	67	92	77	94	67	94	96	94
	60%	60%	94	94	68	92	91	96	98	96	91	91	93	97	81	92	98	94	68	93	96	94	96	96	93	94	96	95	70	95	97	95	67	90	77	93	67	92	96	93
	90%	90%	95	94	84	92	95	96	97	96	95	90	98	96	84	91	97	92	61	91	97	91	96	96	94	92	96	93	63	94	96	93	59	95	72	91	63	92	90	91
	80%	80%	95	94	84	91	94	96	97	94	94	89	97	96	84	91	97	91	61	91	96	91	96	95	94	92	96	93	63	94	96	93	59	94	72	91	63	92	89	90
	70%	70%	94	93	74	89	91	95	97	93	92	88	94	96	82	89	97	91	60	90	96	90	95	95	92	92	95	93	63	93	96	92	59	92	72	90	63	90	88	88
	60%	60%	91	91	60	85	87	95	97	92	86	84	89	95	73	85	96	90	61	87	94	89	94	95	88	90	94	92	63	91	95	92	59	84	72	88	59	87	87	88
	90%		66	86	23	68	53	96	98	96	53	79	51	96	29	73	90	95	18	79	77	91	85	96	58	92	84	96	10	85	97	96	13	58	40	87	13	70	95	92
	80%		65	83	22	63	48	95	98	95	48	74	46	96	29	68	88	93	18	75	74	90	83	96	57	90	82	95	10	82	97	96	13	51	40	84	13	65	95	90
	70%		62	79	19	58	44	94	98	93	43	69	42	96	28	63	86	91	17	70	71	87	81	95	53	88	79	94	10	80	97	95	13	44	40	81	13	59	95	88
	60%		59	76	14	52	39	94	98	92	39	64	37	95	24	58	85	90	18	66	68	85	80	95	49	86	77	93	10	76	96	94	13	37	40	78	12	54	93	86
			48	57	1	26	28	84	91	77	26	42	25	89	11	32	74	75	9	41	56	69	67	89	37	70	68	84	1	56	89	89	3	11	33	58	1	29	77	71

Value in each cell is the net benefit (% reduction of CRS cases) in each scenario compared to the no-vaccination baseline over the 30 year simulation. Color scale is darker for **SMALLER** reduction.

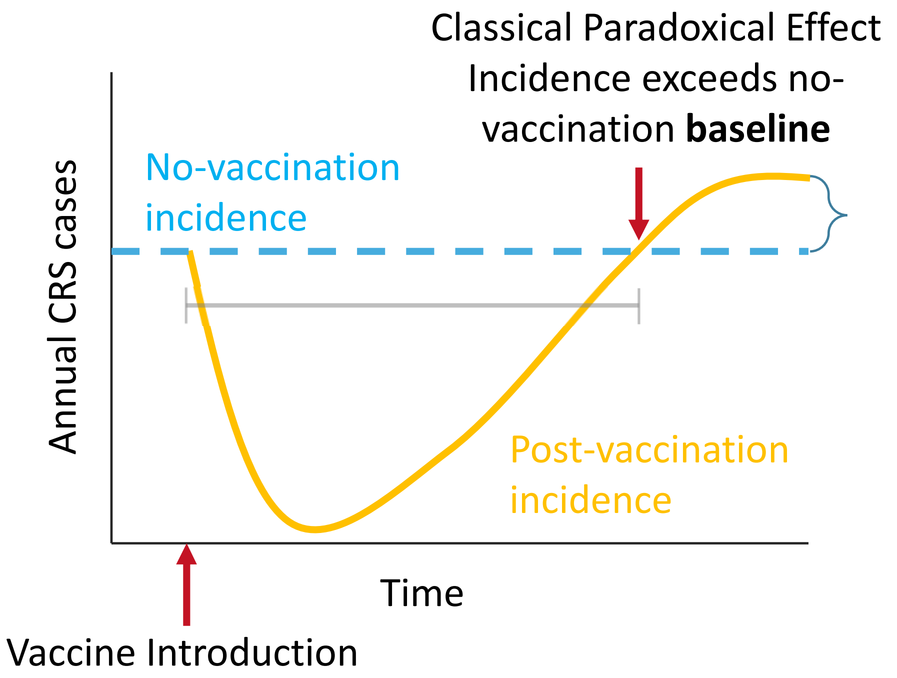
Net Benefit of CRS Reduction Over 30 Years Compared to No-Vaccination Baseline

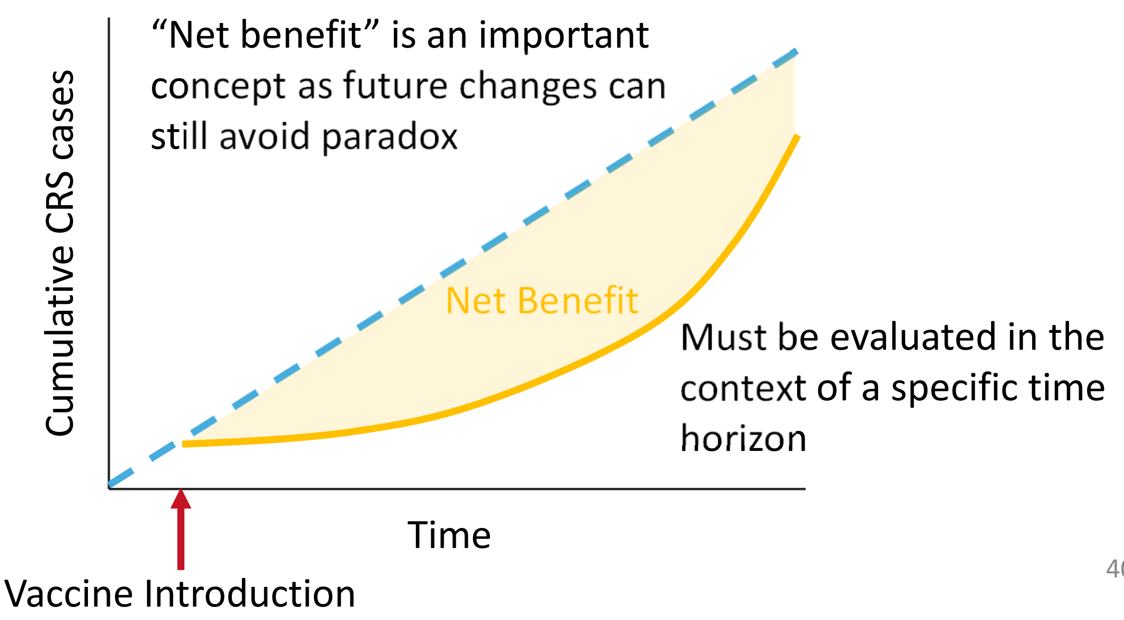
SCENARIO			AFG		CAF		COD		DJI		ETH		GAB		GIN		GNB		GNQ		LBR		MDG		MLI		NER		NGA		SDN		SOM		SSD		TCD		ZAF	
RI	Intro	Continued	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA	UGA	UKHSA
WUENIC	90%	90%	96	96	89	96	97	97	98	96	97	96	98	97	91	96	98	97	68	97	97	96	97	96	97	97	97	97	70	96	97	96	67	97	77	96	71	96	96	96
	80%	90%	96	96	89	96	97	97	98	96	96	95	98	97	90	95	98	96	67	96	97	96	97	96	96	96	97	97	70	96	97	96	67	96	77	96	71	96	96	95
	70%	90%	96	95	88	95	96	97	98	96	96	94	98	97	90	95	98	95	68	96	97	95	97	96	96	96	97	96	70	96	97	95	67	96	77	95	71	95	96	94
	60%	90%	96	95	87	94	96	96	98	96	96	93	98	97	89	94	98	94	68	95	97	94	97	96	96	95	97	96	70	95	97	95	67	95	77	94	70	95	96	94
	90%	60%	95	96	73	95	94	97	98	96	94	95	95	97	83	95	98	97	68	97	97	96	97	96	95	96	97	97	70	96	97	96	67	94	77	96	67	96	96	95
	80%	60%	95	95	72	94	93	97	98	96	93	94	94	97	83	94	98	96	67	95	97	96	97	96	95	96	97	97	70	95	97	96	67	93	77	95	67	95	96	95
	70%	60%	94	95	71	93	92	96	98	96	92	92	93	97	82	93	98	95	68	94	96	95	96	96	94	95	96	96	70	95	97	95	67	92	77	94	67	94	96	94
	60%	60%	94	94	68	92	91	96	98	96	91	91	93	97	81	92	98	94	68	93	96	94	96	96	93	94	96	95	70	95	97	95	67	90	77	93	67	92	96	93
	90%	90%	95	94	84	92	95	96	97	96	95	90	98	96	84	91	97	92	61	91	97	91	96	96	94	92	96	93	63	94	96	93	59	95	72	91	63	92	90	91
	80%	80%	95	94	84	91	94	96	97	94	94	89	97	96	84	91	97	91	61	91	96	91	96	95	94	92	96	93	63	94	96	93	59	94	72	91	63	92	89	90
	70%	70%	94	93	74	89	91	95	97	93	92	88	94	96	82	89	97	91	60	90	96	90	95	95	92	92	95	93	63	93	96	92	59	92	72	90	63	90	88	88
	60%	60%	91	91	60	85	87	95	97	92	86	84	89	95	73	85	96	90	61	87	94	89	94	95	88	90	94	92	63	91	95	92	59	84	72	88	59	87	87	88
	90%		66	86	23	68	53	96	98	96	53	79	51	96	29	73	90	95	18	79	77	91	85	96	58	92	84	96	10	85	97	96	13	58	40	87	13	70	95	92
	80%		65	83	22	63	48	95	98	95	48	74	46	96	29	68	88	93	18	75	74	90	83	96	57	90	82	95	10	82	97	96	13	51	40	84	13	65	95	90
	70%		62	79	19	58	44	94	98	93	43	69	42	96	28	63	86	91	17	70	71	87	81	95	53	88	79	94	10	80	97	95	13	44	40	81	13	59	95	88
	60%		59	76	14	52	39	94	98	92	39	64	37	95	24	58	85	90	18	66	68	85	80	95	49	86	77	93	10	76	96	94	13	37	40	78	12	54	93	86
			48	57	1	26	28	84	91	77	26	42	25	89	11	32	74	75	9	41	56	69	67	89	37	70	68	84	1	56	89	89	3	11	33	58	1	29	77	71

All scenarios in **both models** predict **positive net benefit over 30 years in all countries**

The Paradoxical Effect

- A "paradoxical effect" for rubella occurs when low-to-intermediate RCV coverage leads to a rebound in CRS burden that exceeds no-vaccination levels.
  - Effect has support both theoretically and empirically





Summary of Results: Recommended Scenario

SCENARIO			Country																		
RI	Intro	continued	SOM	CAF	GNQ	NGA	TCD	GIN	AFG	COD	DJI	ETH	GAB	GNB	LBR	MDG	MLI	NER	SDN	SSD	ZAF
WUENIC	90%	90%																			
	80%	90%																			
	70%	90%																			
	60%	90%																			

Neither model exceeds baseline

One model exceeds baseline

Both models exceed baseline

This set of tables indicates whether the no-vaccine baseline is **EVER** exceeded **IN A SINGLE YEAR**.

Campaigns

Target	Coverage
Wide age range	90%
	80%
Narrow age range	70%
	60%

The recommended introduction strategy – wide age-range catch-up and follow-up campaigns consistent with measles control activities – **never exceeds no-vaccine baseline for all 19 countries modeled**

Summary of Results: Recommended Scenario

SCENARIO			Country																		
RI	Intro	continued	SOM	CAF	GNQ	NGA	TCD	GIN	AFG	COD	DJI	ETH	GAB	GNB	LBR	MDG	MLI	NER	SDN	SSD	ZAF
WUENIC	90%	90%																			
	80%	90%																			
	70%	90%																			
	60%	90%																			
	90%	60%																			
	80%	60%																			
	70%	60%																			
	60%	60%																			

Neither model exceeds baseline

One model exceeds baseline

Both models exceed baseline

This also holds if follow-ups are only 60% coverage

Summary of Results: Recommended Scenario

	SCENARIO		Country																		
RI	Intro	continued	SOM	CAF	GNQ	NGA	TCD	GIN	AFG	COD	DJI	ETH	GAB	GNB	LBR	MDG	MLI	NER	SDN	SSD	ZAF
WUENIC	90%	90%																			
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	70%	90%																			
	60%	90%																			
	90%	60%																			
	80%	60%																			
	70%	60%																			
	60%	60%																			
	90%	90%																			
	80%	80%																			
	70%	70%																			
	60%	60%																			

Neither model exceeds baseline

One model exceeds baseline

Both models exceed baseline

And holds if there is no wide-age range campaign for all follow-up coverages greater than 60%

Summary of Results: Recommended Scenario

	SCENARIO		Country																		
RI	Intro	continued	SOM	CAF	GNQ	NGA	TCD	GIN	AFG	COD	DJI	ETH	GAB	GNB	LBR	MDG	MLI	NER	SDN	SSD	ZAF
WUENIC	90%	90%																			
	80%	90%																			
	70%	90%																			
	60%	90%																			
	90%	60%																			
	80%	60%																			
	70%	60%																			
	60%	60%																			
	90%	90%																			
	80%	80%																			
	70%	70%																			
	60%	60%																			
	90%		20/30	20	17	18	18														
	80%		20/28	14	17	18	19														
	70%		19/27	18	17	18	19														
	60%		18/26	18	17	18	18														

Numbers indicate the years until annual CRS incidence exceeds pre-vaccine baseline

- Neither model exceeds baseline
- One model exceeds baseline
- Both models exceed baseline

Without sustained follow-up campaigns, some countries may see an **increase in annual CRS incidence above the no-vaccine baseline** after 14 or more years following introduction, even with a high-quality catch-up campaign.

Summary of Results: Recommended Scenario

SCENARIO			Country																		
RI	Intro	continued	SOM	CAF	GNQ	NGA	TCD	GIN	AFG	COD	DJI	ETH	GAB	GNB	LBR	MDG	MLI	NER	SDN	SSD	ZAF
WUENIC	90%	90%																			
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	70%		19/27	18	17	18	19														
	60%		18/26	18	17	18	18														

- Neither model exceeds baseline
- One model exceeds baseline
- Both models exceed baseline

Without sustained follow-up campaigns, some countries may see an **increase in annual CRS incidence above the no-vaccine baseline** after 14 or more years following introduction, even with a high-quality catch-up campaign. But 14 countries would see no increase in CRS even without follow-up campaigns

Summary of Results: Recommended Scenario

	SCENARIO		Country																		
RI	Intro	continued	SOM	CAF	GNQ	NGA	TCD	GIN	AFG	COD	DJI	ETH	GAB	GNB	LBR	MDG	MLI	NER	SDN	SSD	ZAF
WUENIC	90%	90%																			
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	70%		19/27	18	17	18	19														
	60%		18/26	18	17	18	18														
			16/19	16	16	17	16	26													

- Neither model exceeds baseline
- One model exceeds baseline
- Both models exceed baseline

And 13 countries would see NOT increase in annual CRS above no-vaccine baseline with introduction via routine immunization only

Summary

New Insights from Modeling Activities

1. Current CRS burden is significant and avoidable

Model to model variability in estimates in the absence of vaccination, but all estimate thousands of cases per year under current conditions

Country	Model	Annual Burden	Lower Bound	Upper Bound
DRC	IDM	15,817	234	53,570
DRC	UGA	3,037	621	6,845
DRC	UKHSA	4,482	0	14,295
Nigeria	PSU	2,479	2,332	2,633
Nigeria	UGA	3,452	1,119	6,776
Nigeria	UKHSA	13,652	1	30,739

sub-national analyses

New Insights from Modeling Activities

1. Current CRS burden is significant and avoidable

All Models consistently predict reductions under introduction scenarios

90% CU + 90% FU **Ideal Scenario**

Country	Model	% reduction
DRC	IDM	99%
DRC	UGA	97%
DRC	UKHSA	97%
Nigeria	PSU	95%
Nigeria	UGA	70%
Nigeria	UKHSA	97%

All models (sub-national and national) predict no increase in CRS above no-vaccination baseline under this scenario

And no increase above no-vaccination baseline even if campaign coverage is as low as 60%

New Insights from Modeling Activities

1. Current CRS burden is significant and avoidable
2. R_0 for rubella in remaining countries is lower than previous assumptions, even at a sub-national level
3. Expected birth rate declines and aging populations will increase CRS risk in the absence of vaccination.

A decision to maintain the status quo will lead to an increase in CRS

4. All introduction scenarios lead to significant reductions in CRS over 10 to 15-year and net reductions over 30 years
5. RI is currently sufficient to prevent paradoxical effect in most countries. RI plus campaigns prevent paradoxical effect in all countries.

Thank you

VACCINE IMPACT MODELLING CONSORTIUM

Members: Measles and Rubella Partnership as a Working Group of the IA2030Task Team on Congenital Rubella Syndrome Prevention through Rubella Vaccine Introduction

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Gavi	• Marguerite Cornu, MA, MBA • Arunima Khanduri, MA, MscPH • Stephen Sosler, PhD, MPH
Institute for Disease Modelling (IDM)	• **Kurt Frey, ScD, MS**
Global Experts	• Susan Reef, MD
Pennsylvania State University	• Matthew Ferrari, PhD, MSc. • **Brian Lambert, MSc.**
Program Support Unit of the Measles and Rubella Partnership	• Lamine Barry • Clara Gaida, MPH, MPP • Andy Gill
UK Health Security Agency	• Emilia Vynnycky, PhD • **Timos Papadopoulos, PhD**
University of Georgia	• Amy Winter, PhD, MPH
WHO (World Health Organization)	• Natasha Crowcroft, MD (Cantab), MSc • Muhammad Farid, MD, MPH • Balcha Masresha, MD • Patrick O'Connor, MD • Richard Ray Luce Jr., MD

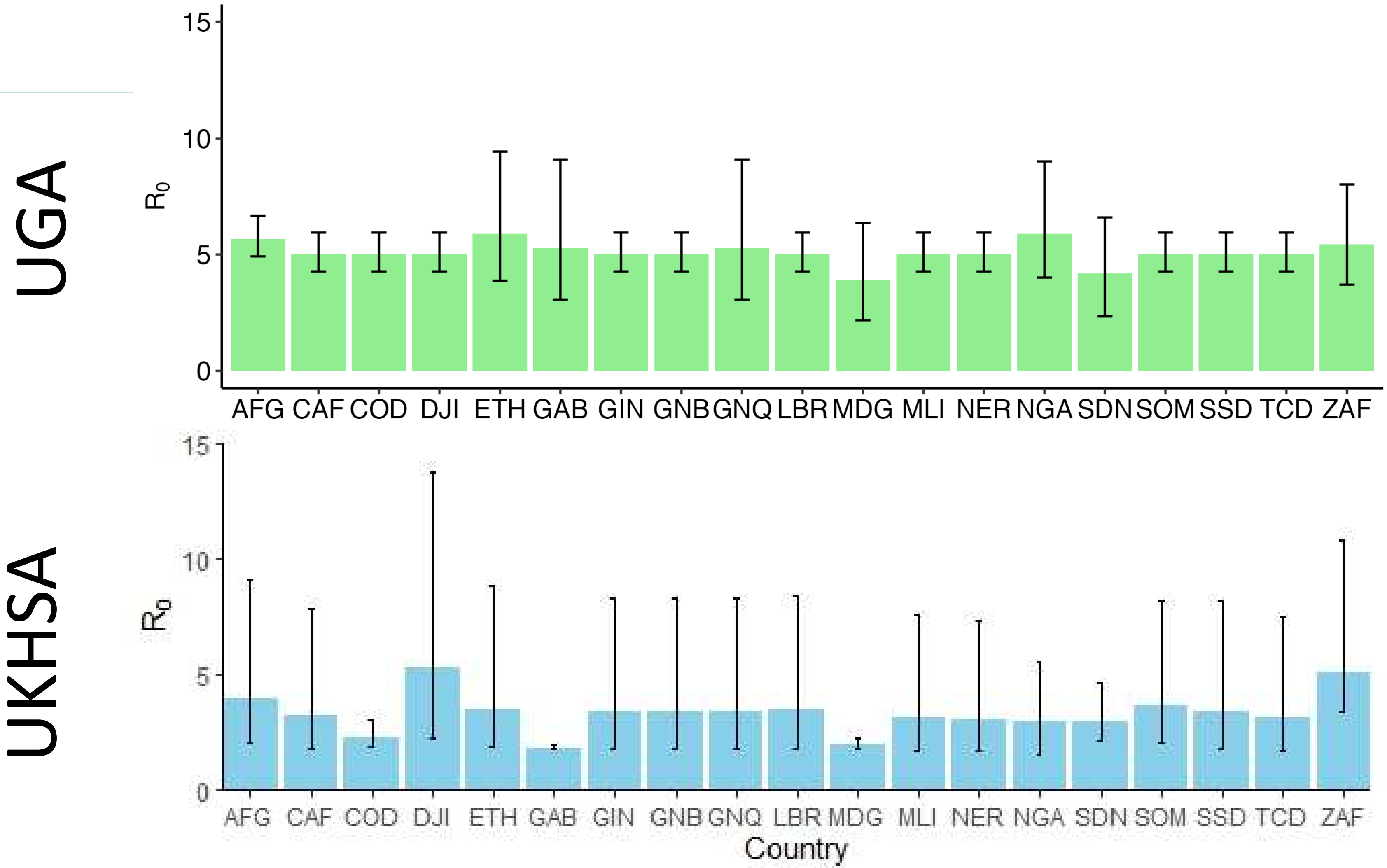
Back-up Slides for Questions

Model Comparison: More similar than different

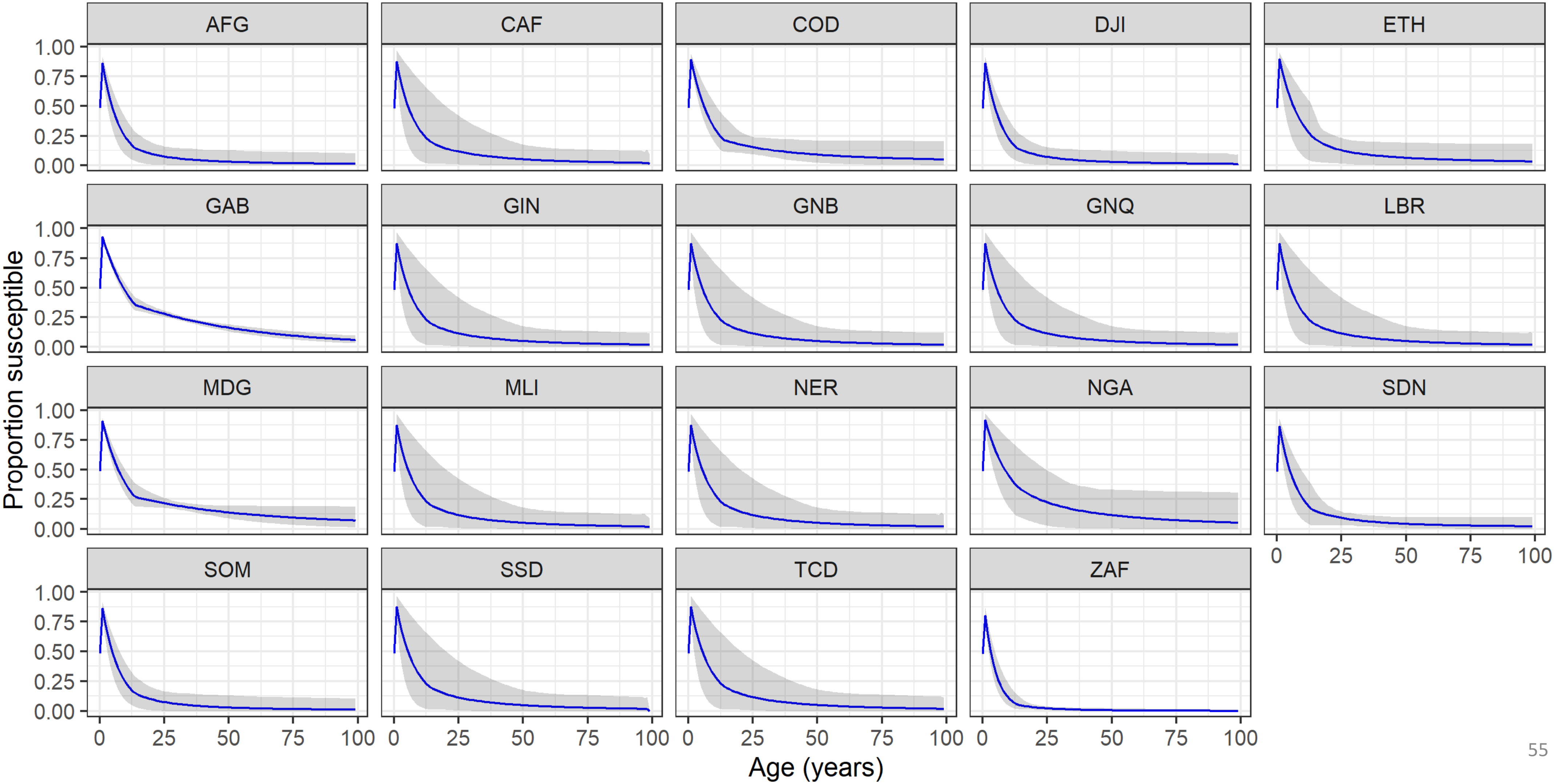
	UGA	UKHSA
Model Type	MSIRV transmission model, age-structured	MSEIRV transmission model, sex & age-structured
Inclusion criteria for IgG serological studies	Must have ≥4 age categories, with at least 2 <15yo and at least 2 ≥15yo	Must have ≥3 age categories, with at least 1 ≥15yo
Force of infection (FOI), age stratum	320 age groups 1 month btw 0-20y, 1 year btw 21-100 y	2 age groups 0-13 years old, 13-100 years old
Demography	Non-stable population allows changing birth and death rates per UN population projections	Stable population with fixed birth and death rates (but outputs scaled to UN population projections)
Demographic transitions	Every rubella generation	Every year (Schenzle approach)
Seasonality	Annual peak in transmission	No seasonality
Vaccination timing	Every rubella generation	Every year
Vaccine efficacy	Increases over 1st year of life to 97%	95% point estimate
Vaccine dose correlation	RCV1 and RCV2 dependent, RI and SIA independent	Where possible: 50% of those vaccinated previously are vaccinated in SIAs; 100% of those who have received RCV1 receive RCV2
Probability of CRS given infection in 1st 16 wks of pregnancy	0.65	
Infected introduction rate per 100,000 population annually	2.6 infected importations	5 infected importations
How stochasticity is incorporated into the model	Randomly drawn R0 for each simulation Demographic and epidemiological transitions in each time step are **random draws**	Randomly drawn parameters for each simulation: Pre-vaccination force of infection, risk of a child being born with CRS following the mother's infection with rubella; vaccine efficacy Demographic and epidemiological transitions in each timestep are **deterministic**

Vynnycky

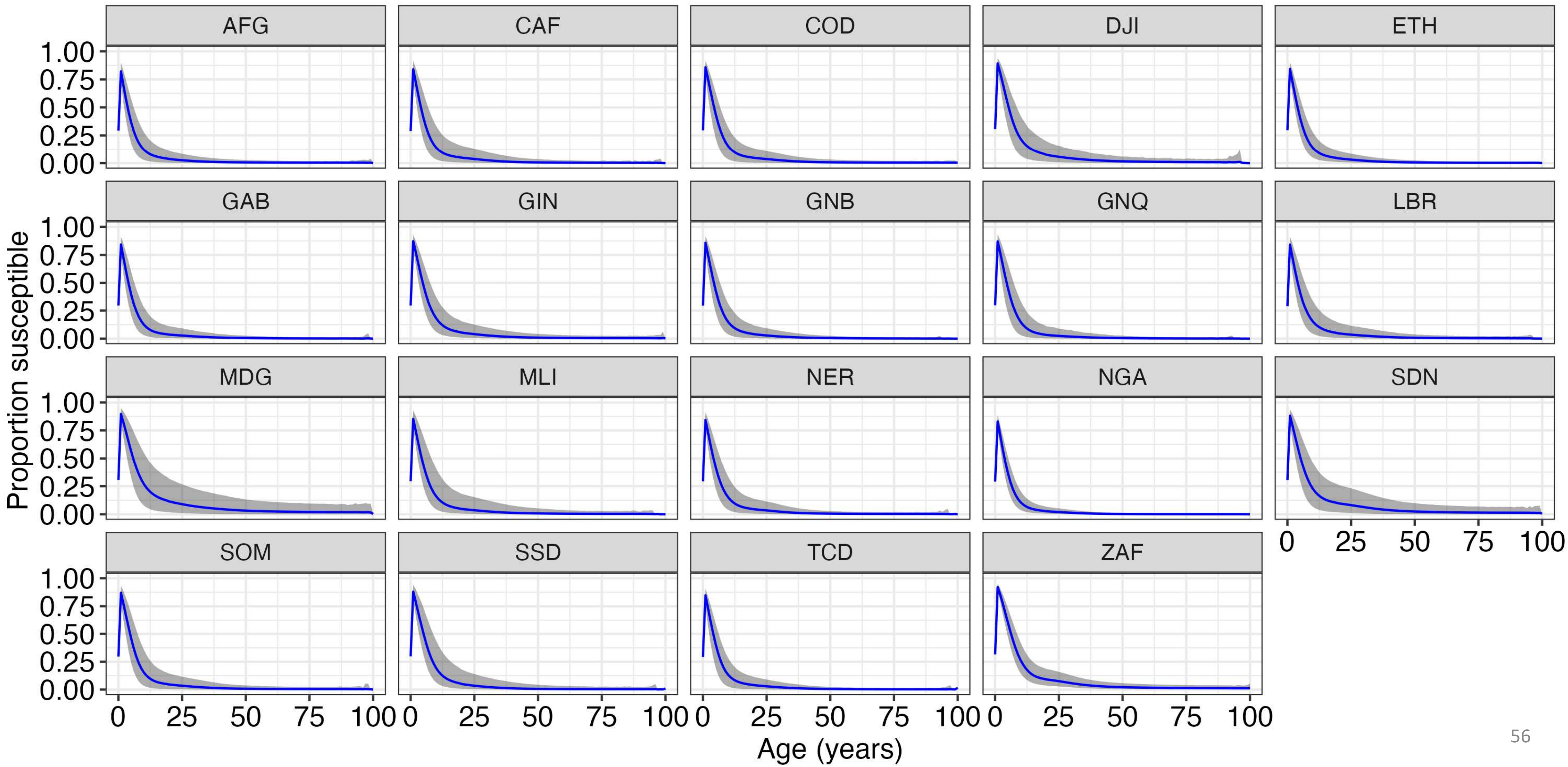
Assumed country-specific R0 values



Baseline age-specific proportion susceptible – UKHSA model

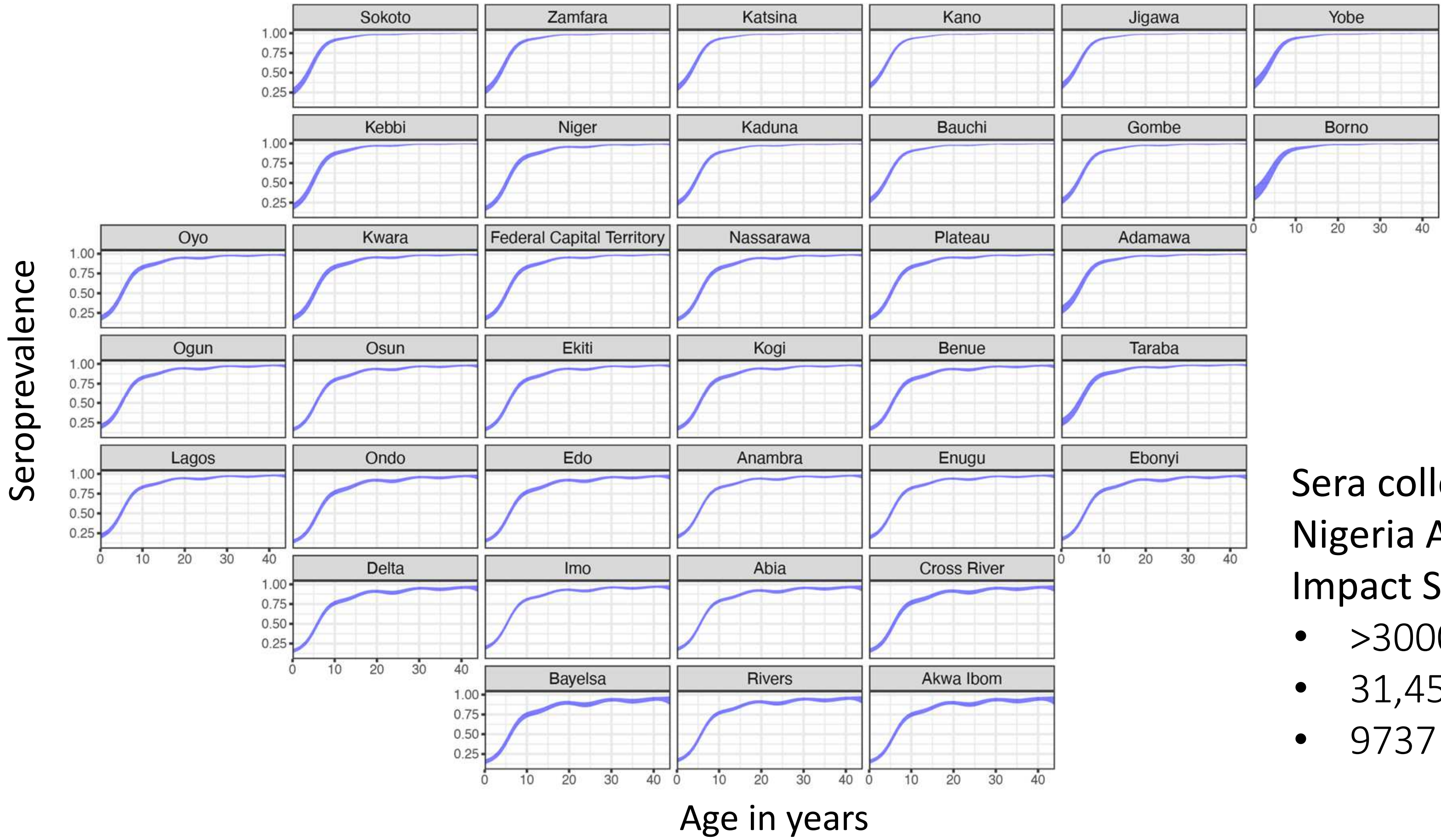


Baseline age-specific proportion susceptible – UGA model



https://www.sciencedirect.com/science/article/pii/S0264410X24005899

State Level Seroprevalence Nigeria

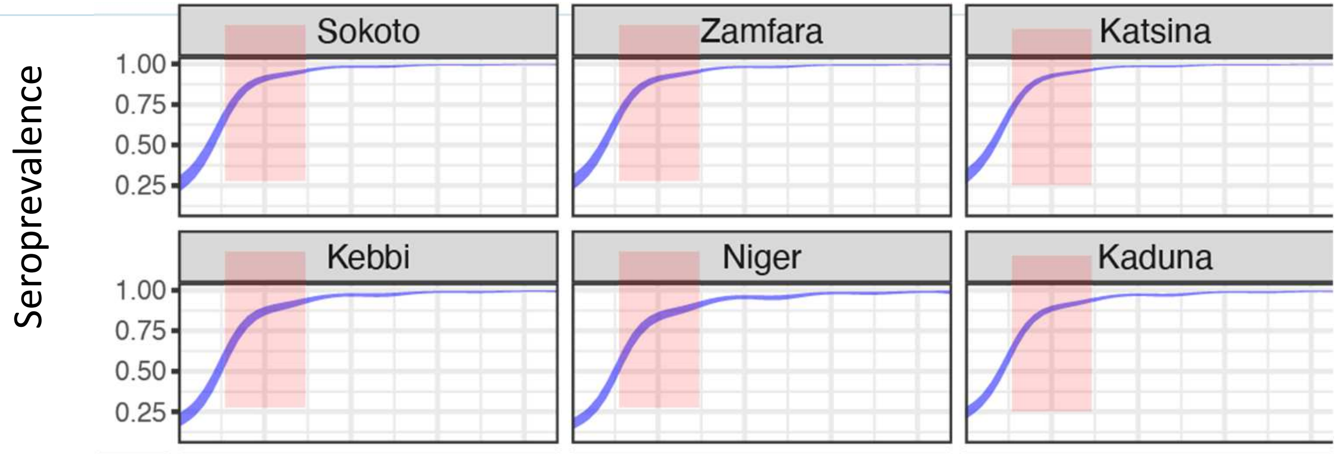


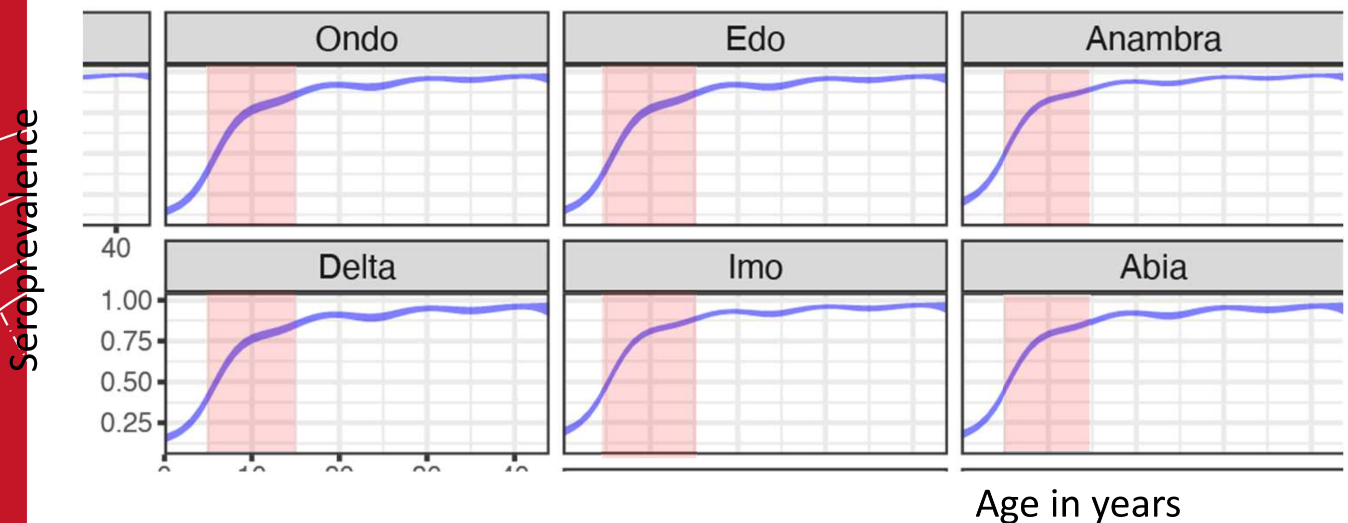
Sera collected from the 2018 Nigeria AIDS Indicator and Impact Survey (NAIIS)

- >3000 clusters
- 31,459 children under 15 y
- 9737 women 15-45y

https://www.sciencedirect.com/science/article/pii/S0264410X24005899

State Level Seroprevalence Nigeria





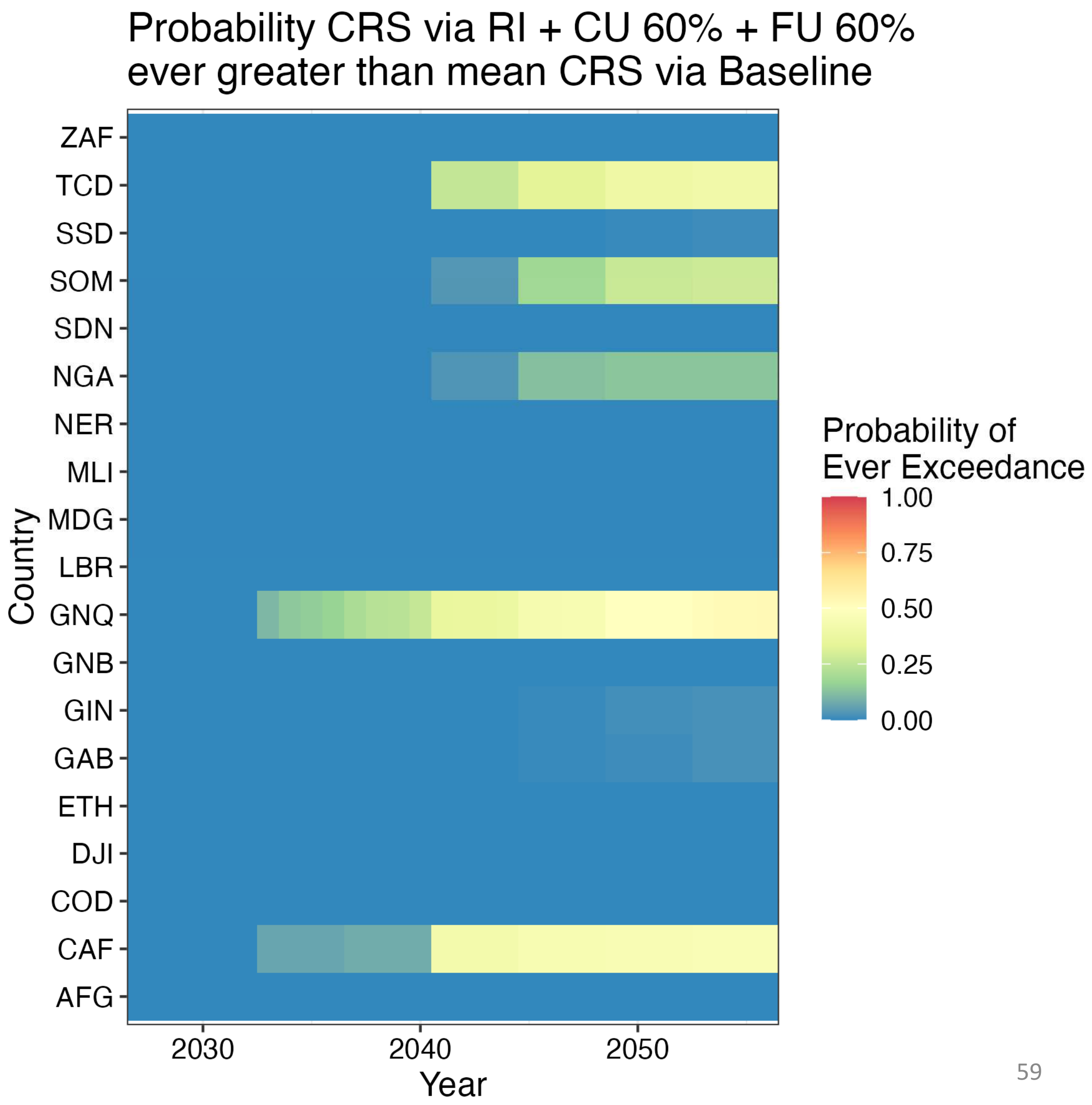
Sera collected from the 2018 Nigeria AIDS Indicator and Impact Survey (NAIIS)

- >3000 clusters
- 31,459 children under 15 y
- 9737 women 15-45y

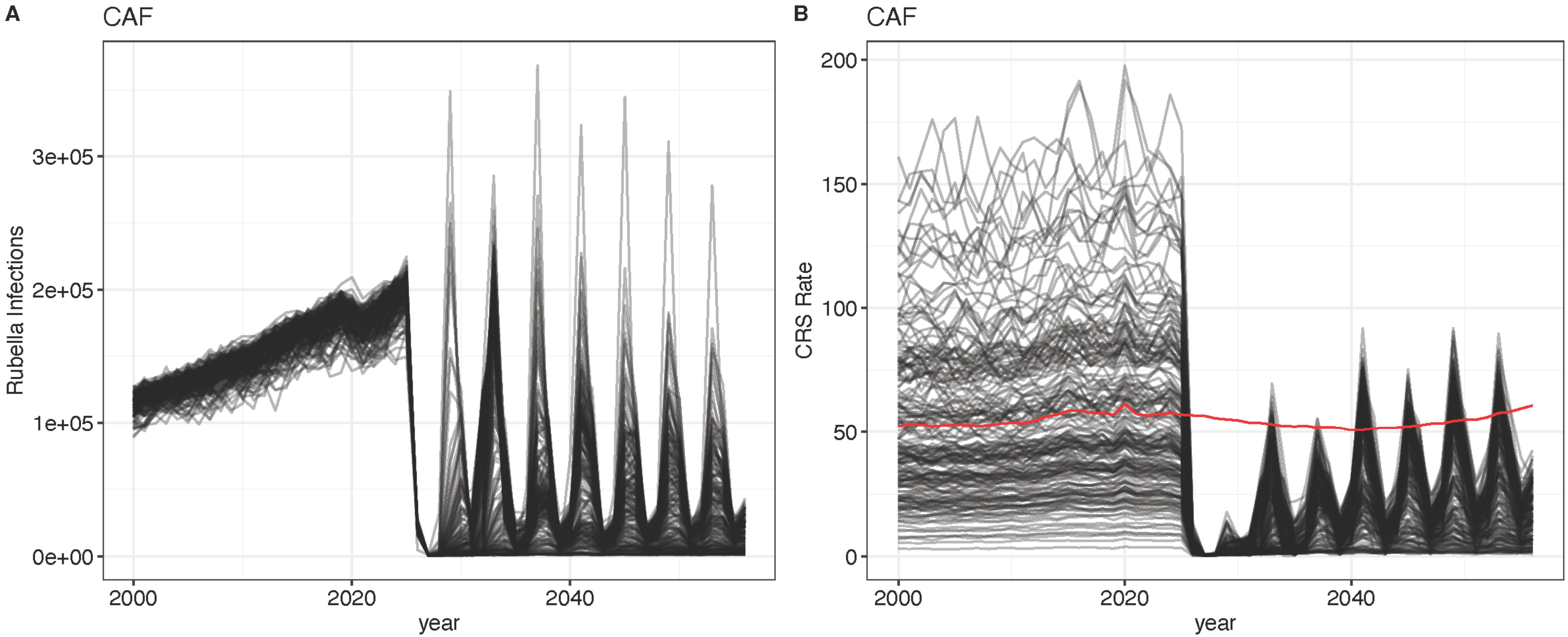
Incorporating Uncertainty

Proportion of 200 simulations per "RI + CU 60% + FU 60%" scenario in which yearly CRS rate ever exceeded yearly mean baseline CRS rate

per (more conservative) UGA model

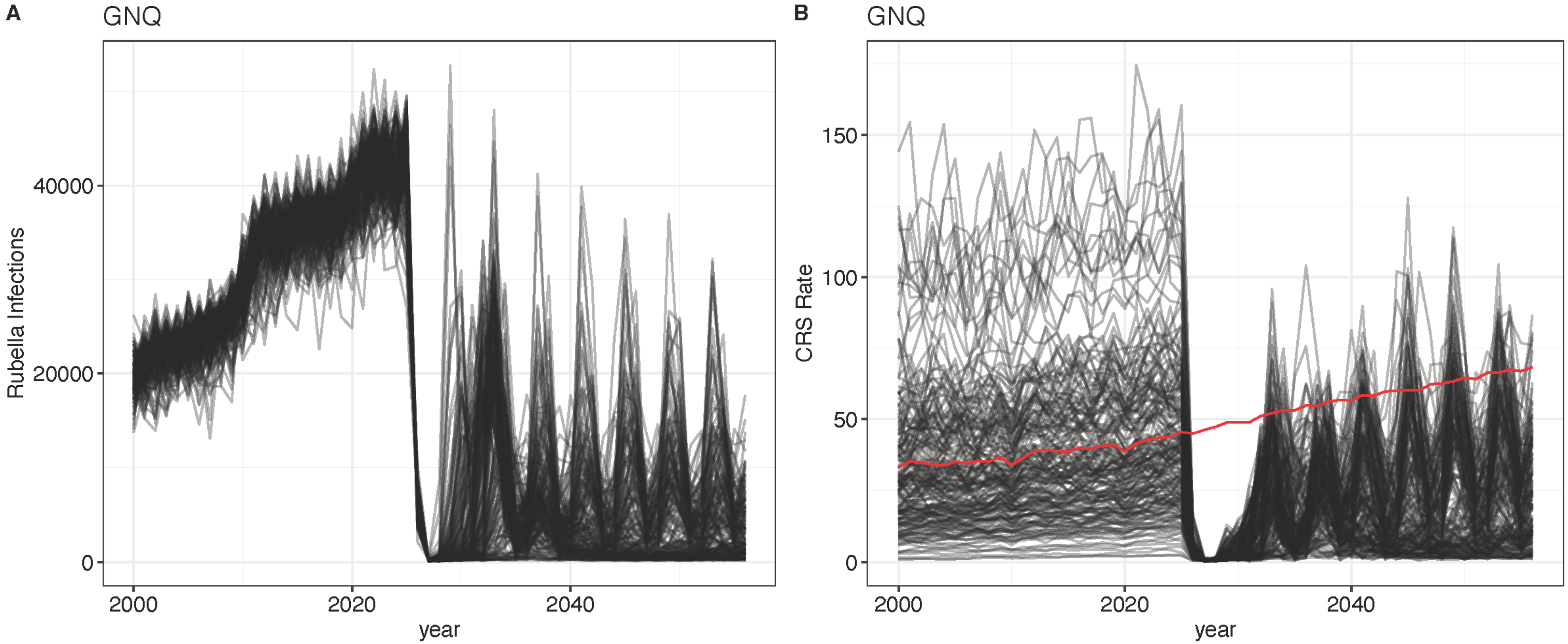


Deep Dive – "RI + CU 60% + FU 60%" scenario simulations for CAF



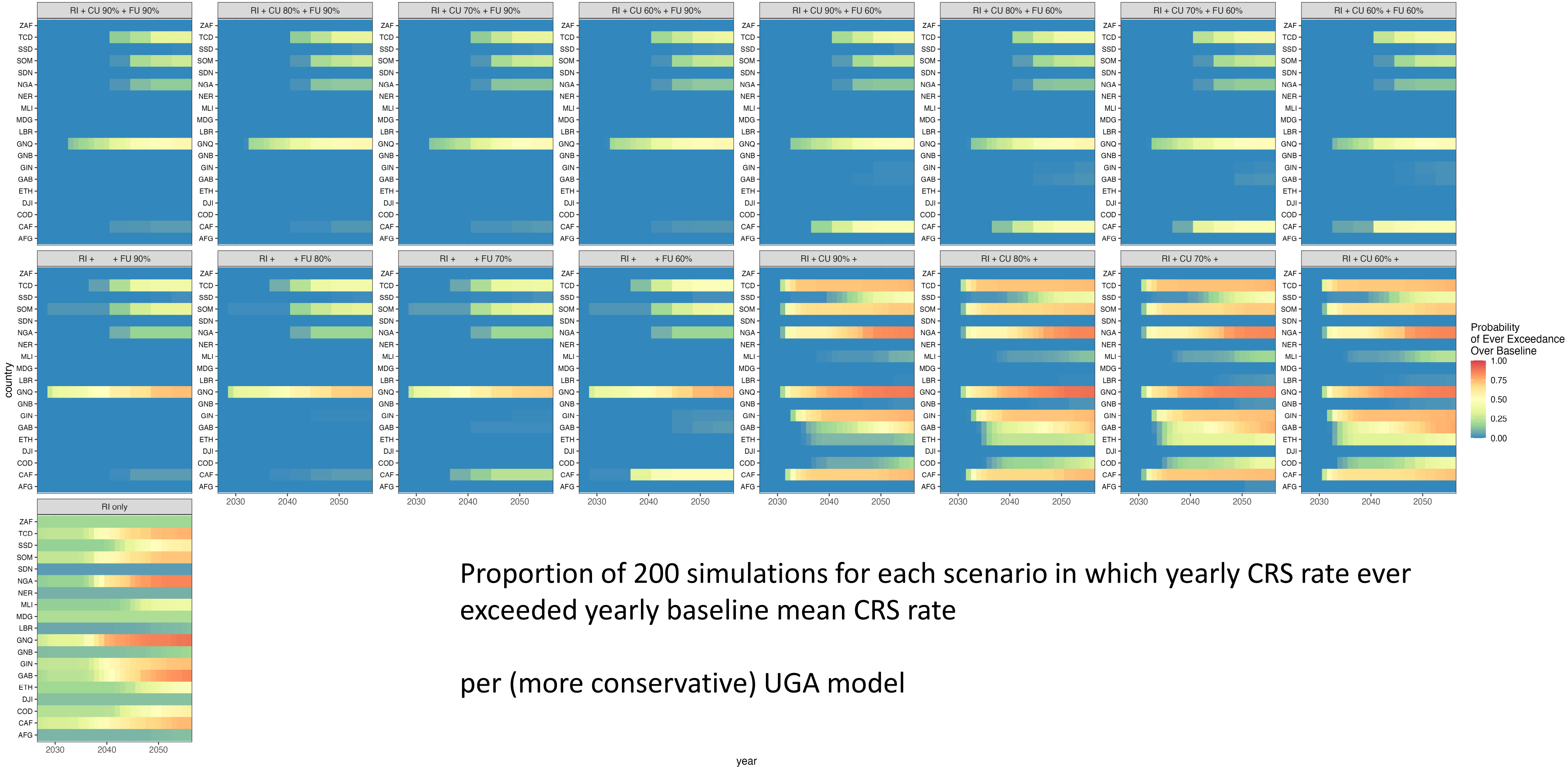
Red line is baseline mean CRS rate

Deep Dive – "RI + CU 60% + FU 60%" scenario simulations for GNQ



Red line is baseline mean CRS rate

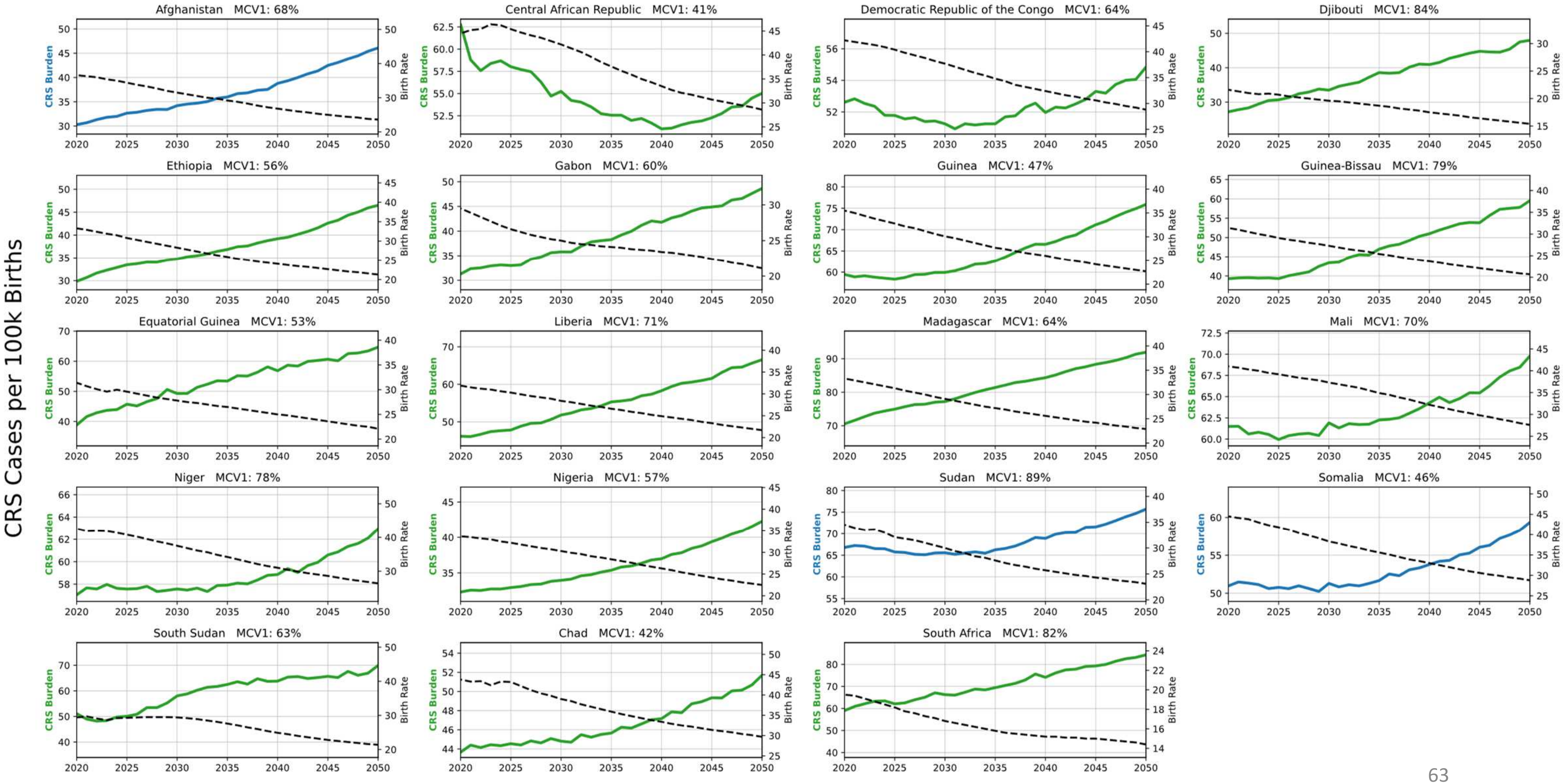
Incorporating Uncertainty



Proportion of 200 simulations for each scenario in which yearly CRS rate ever exceeded yearly baseline mean CRS rate

per (more conservative) UGA model

Contrasting CRS Burden and Birth Rate



Campaign definitions for Supplementary Immunization Activities (SIAs)

- **“Follow-up” campaign** refers to regular supplementary immunization activities designed to reach children **born since the previous campaign** to fill immunity gaps due to suboptimal routine immunization coverage. Usually for <5 years
- **“Catch-up” campaign** refers to a wide age-range campaign that is designed to ensure that older children **who would otherwise not be vaccinated through the routine schedule** have a chance to be immunized. For rubella vaccine introductions these are generally up to 15 years but can be wider if indicated.

Note that this is different from **individual** “catch up immunization” where children who are or were age-eligible for vaccination are given doses they missed.