Immunologic Response to Measles-Containing Vaccines (MCVs) and Yellow Fever (YF) Vaccines when Co-administered

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With input from the SAGE Measles & Rubella Working Group and invited YF experts

Presentation Objectives

- Review existing data on potential interference between MCVs and YF vaccines when co-administered
- Consider programmatic implications of administering these vaccines at separate visits
- Summarize conclusions and recommendations for SAGE

WHO Position Papers: Recommendations on co-administration of MCVs and YF vaccine

- Live vaccines should be co-administered or given at least 4 weeks apart; Rubella 2011 and Measles 2017

- Immunogenicity is usually unaffected when YF is co-administered with other vaccines; YF 2013
  - Based on literature review of 8 studies with measles & YF vaccines and 1 study with MMR & YF

- All 3 position papers have statement saying that interference may occur between MMR and YF vaccines if co-administered to young children based on results from 2011 study in Brazil

Use of MCVs and YF Vaccines Globally

- All countries administer MCVs through national immunization program
  - 167/194 countries use a rubella-containing combination vaccine
  - Remaining countries expected to eventually change from M to MR/MMR
- 35/40 YF-endemic countries provide YF vaccine through national immunization program
  - Remaining 5 expected to introduce YF vaccine
- AFRO Region: M/MR and YF co-administered at 9 months
- PAHO Region: Several countries co-administer MMR and YF vaccines at 12 months

Programmatic Perspective

- Rationale for co-administration of vaccines:
  - Provides protection at earliest possible age
  - Maximizes efficient use of healthcare resources
  - Prevents children from missing vaccine doses if they fail to return for subsequent visits
  - May also be used in outbreak settings to maximize efficient use of resources and optimize chance of children getting all needed vaccines

Methodology

- Identified published and unpublished studies evaluating co-administration of MCVs and YF vaccine
- Considered 2 aspects of interference:
  - Decreased seroconversion or response rates
  - Decreased magnitude of antibody response
- Used JRF and WUENIC data to evaluate programmatic considerations
- Findings and recommendations discussed with SAGE MR working group and invited YF experts on several occasions

Terminology used in presentation

- Co-administration:
  - Administration of two vaccines at same vaccination visit
- Sequential administration:
  - Two vaccines administered at separate vaccination visits
- Individual administration:
  - Only one vaccine is administered

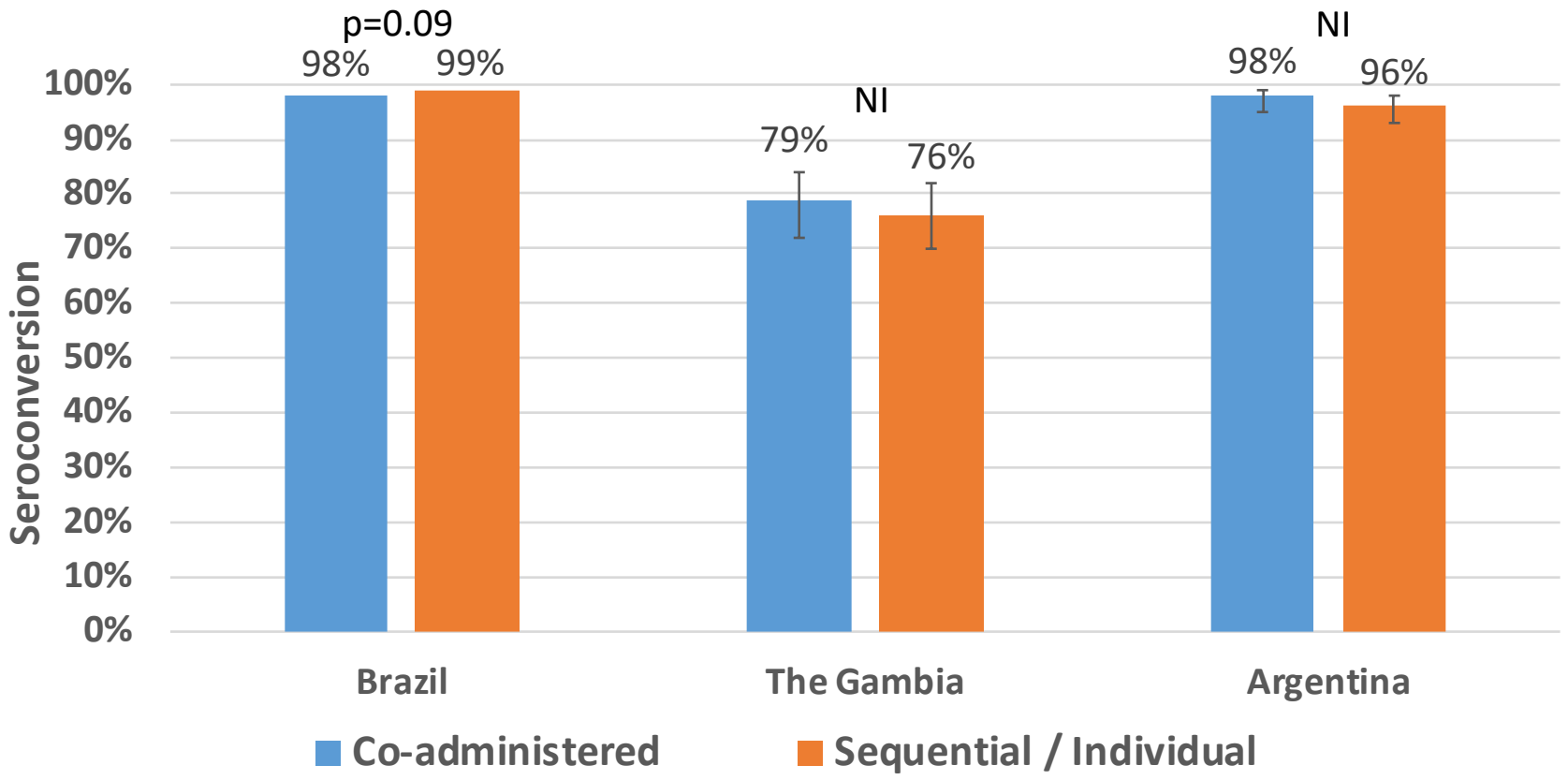
Review Findings

- Identified 3 RCTs and 1 observational study
  - Removed observational study from policy considerations and GRADE assessment due to study design and power limitations
- Used data from 2 published and 1 unpublished RCTs
  - Unpublished study completed Sept 2018
    - Data shared with working group
    - Will be submitted for publication late 2018

Study Design: Vaccination and Specimen Collection

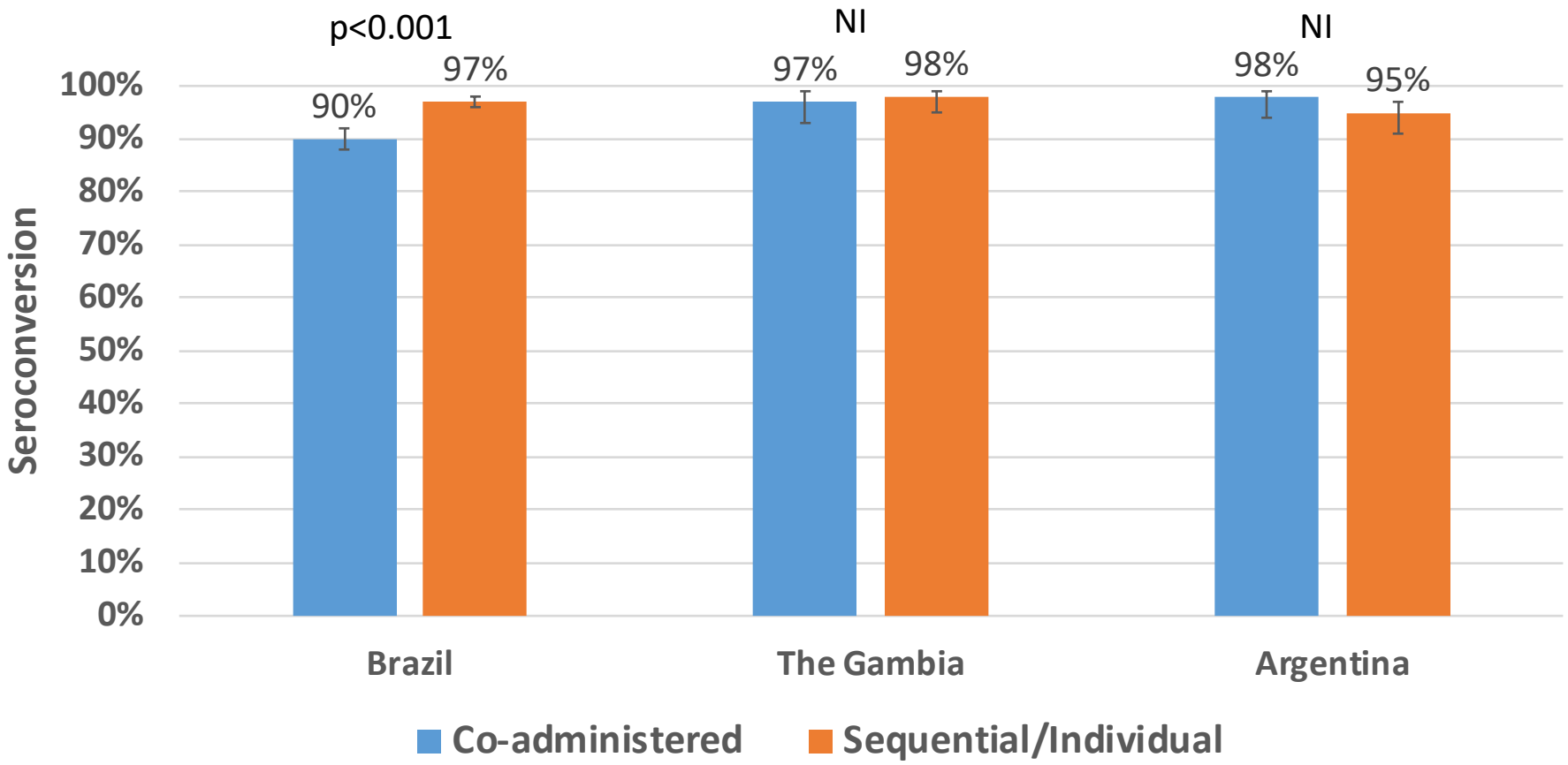
Study & Arm	Schedule for Vaccination and Specimen Collection		
	Day 0	**Day 28-30**	**Day 56-60**
Brazil (children 12 -23 months old)			
Co-administration (n=906)	MMR & YF	Specimen Collection	
Sequential (n=922)	MMR	YF	Specimen Collection
The Gambia (children 9-10 months old)			
Co-administration (n=188)	MR & YF	Specimen Collection	
Individual – MR (n=189)	MR	Specimen Collection	
Individual – YF (n=187)	YF	Specimen Collection	
Argentina (children 12-13 months old)			
Co-administration (n=244)	MMR & YF	Specimen Collection	
Individual – MMR (n=248)	MMR	Specimen Collection	
Individual – YF (n=245)	YF	Specimen Collection	

Results – Measles Seroconversion



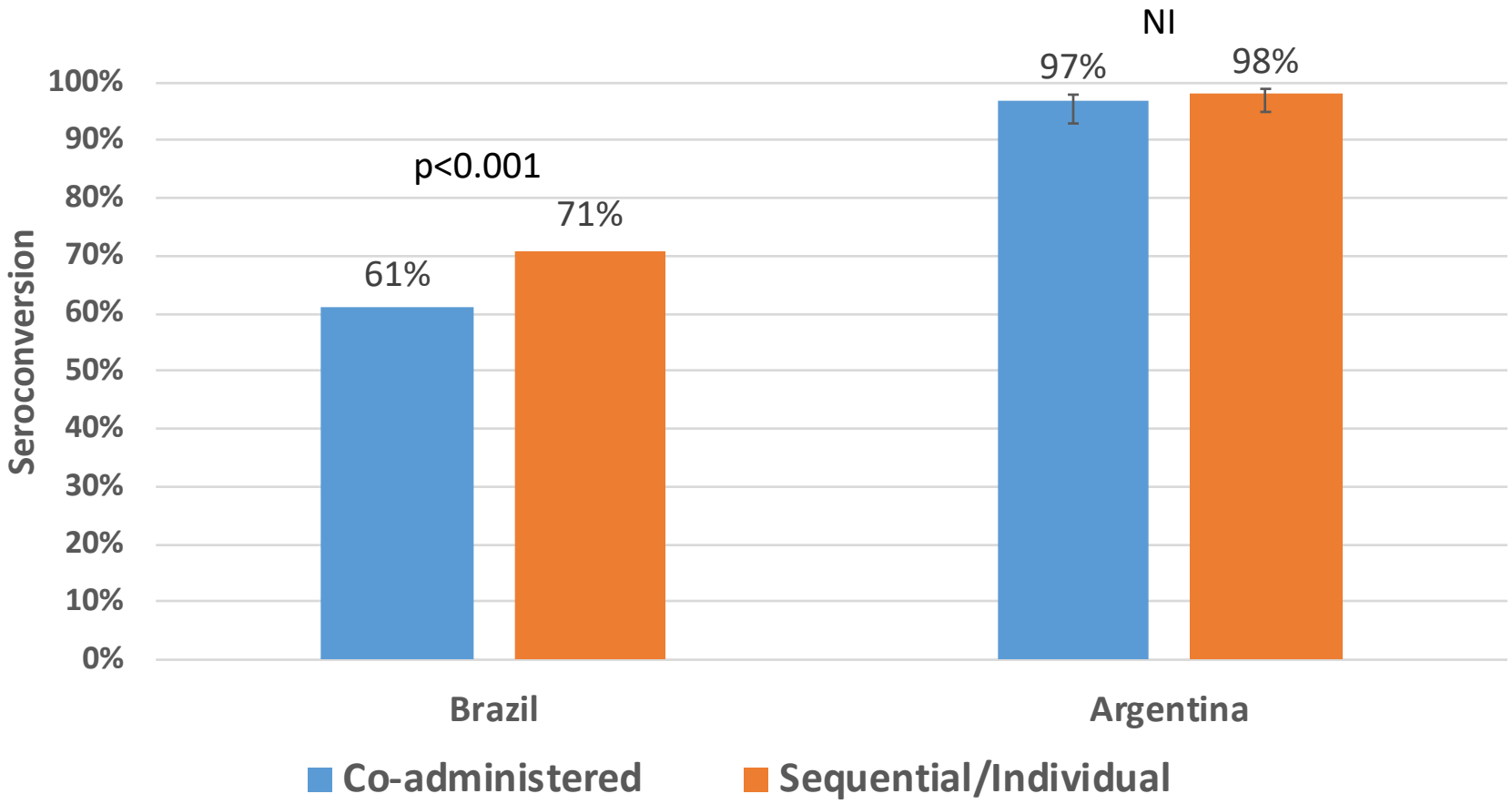
NI = non-inferior

Results – Rubella Seroconversion



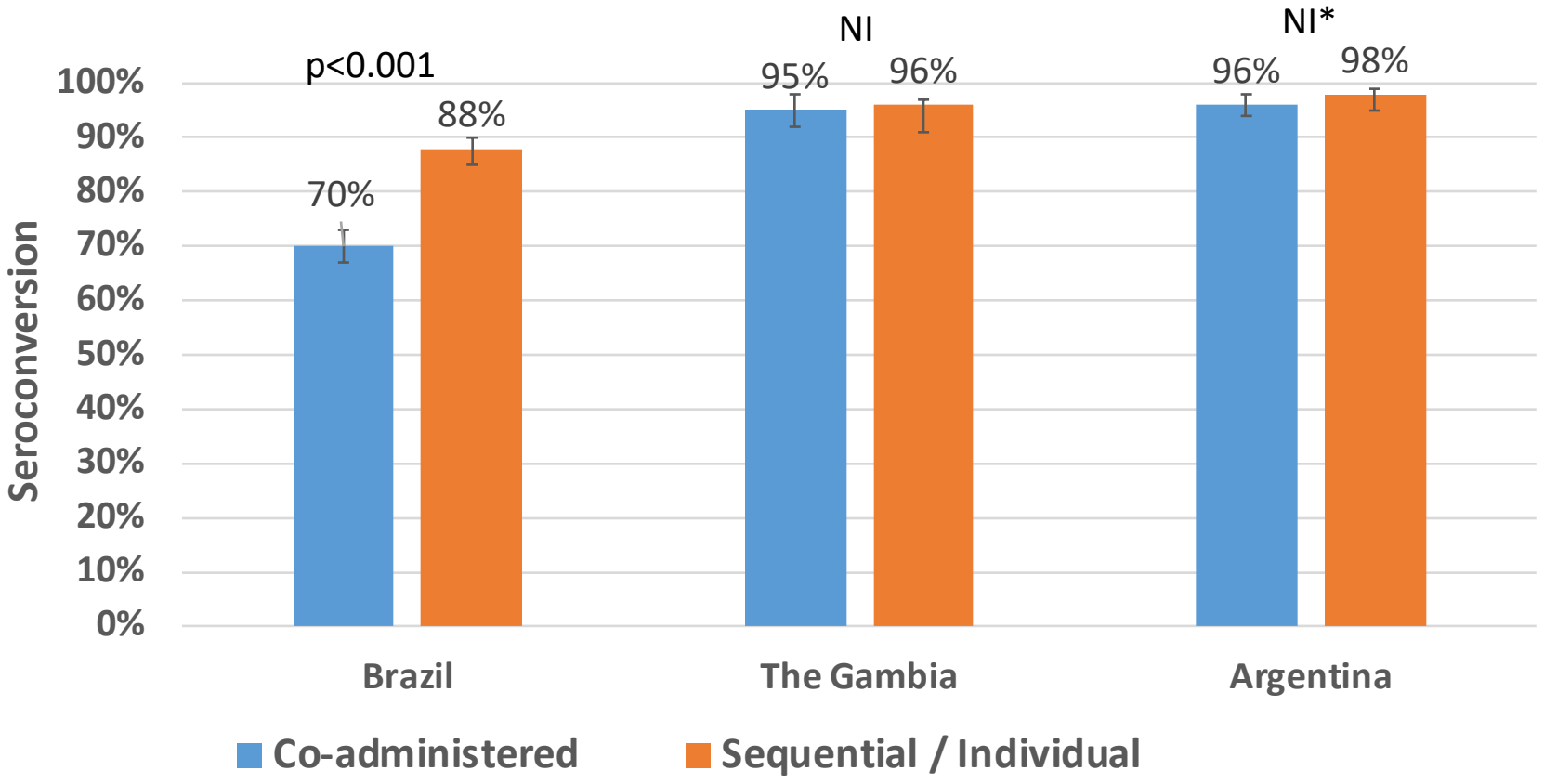
NI = non-inferior

Results – Mumps Seroconversion



NI = non-inferior

Results – YF Seroconversion



*NI in the intent-to-treat analysis; Inconclusive in the per protocol analysis but was underpowered due to smaller sample size ; NI = non-inferior

Results – Magnitude of Measles Antibody Concentrations

	Co-administration[1]	Sequential/ Individual Administration[1]	P-value / non-inferiority conclusion
Brazil (IU/mL)	3.4 (3.2 – 3.7)	3.2 (3.0 – 3.4)	Not stated
The Gambia (IU/mL)	270 (243 – 310)	250 (230 – 280)	NI
Argentina (mIU/mL)	1956 (1629 – 2348)	1561 (1245 – 1956)	0.17

[1]GMT (95% CI) for studies from Brazil and Argentina; Median (IQR) for study from The Gambia
NI = non-inferior

Results – Magnitude of Rubella Antibody Concentrations

	Co-administration[1]	Sequential/ Individual Administration[1]	P-value / non-inferiority conclusion
Brazil (IU/mL)	25 (23 – 27)	60 (56 – 64)	p<0.001
The Gambia (IU/mL)	27 (24 – 31)	31 (27 – 36)	NI not shown
Argentina (IU/mL)	32 (28 – 37)	39 (33 – 46)	p=0.0007

[1]GMT (95% CI) for studies from Brazil and Argentina; Median (IQR) for study from The Gambia;
NI = non-inferior

Results – Magnitude of Mumps Antibody Concentrations

	Co-administration[1]	Sequential/ Individual Administration[1]	P-value / non-inferiority conclusion
Brazil (IU/mL)	335 (314 – 358)	414 (388 – 442)	Not stated
Argentina (U/mL)	1745 (1390 – 2192)	2320 (1925 – 2795)	p=0.04

[1]GMT (95% CI); NI = non-inferior

Results – Magnitude of Yellow Fever Antibody Titers

	Co-administration[1]	Sequential/ Individual Administration[1]	P-value / non-inferiority conclusion
Brazil (GMT)	1064 (976 – 1161)	3385 (3105 – 3690)	p<0.001
The Gambia (GMT)	64 (64 – 91)	128 (91 – 128)	NI not shown
Argentina (GMT)	225 (181 – 279)	373 (308 – 452)	p<0.001

[1]GMT (95% CI) for studies from Brazil and Argentina; Median (IQR) for study from The Gambia ; NI = non-inferior

Summary of Study Findings

Seroconversion

- Measles: None of the studies showed interference
- Mumps, rubella, and YF:
  - Brazil study showed interference
  - Other studies showed no interference

Magnitude of antibody response

- Measles: None of the studies showed interference
- Mumps, rubella, and YF: all studies showed interference
  - Despite being significantly lower, titers/concentrations were robust in co-administration groups
  - Unknown whether lower titers/concentrations have clinical implications or affect long-term immunity

Discussion of Study Findings: Potential reasons for discordant results

- Differing intervals between MMR vaccination and sample collection in Brazil
- Different vaccines
  - Argentina and The Gambia: 17D-204 YF vaccine from 2 manufacturers
  - Brazil: 17DD and 17D-213 YF vaccines from Brazil
    - 17DD has higher potency than other pre-qualified vaccines
  - Some variation in MMR strains
- Variation in laboratory procedures and cut-points
- Different background rates of exposure to related viruses could have affected response to vaccines

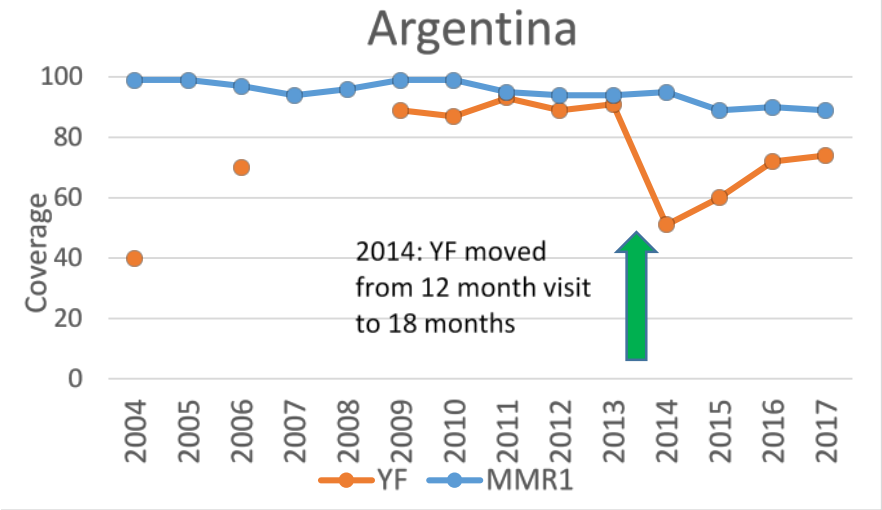
Results – Adverse Events Following Immunization (AEFIs)

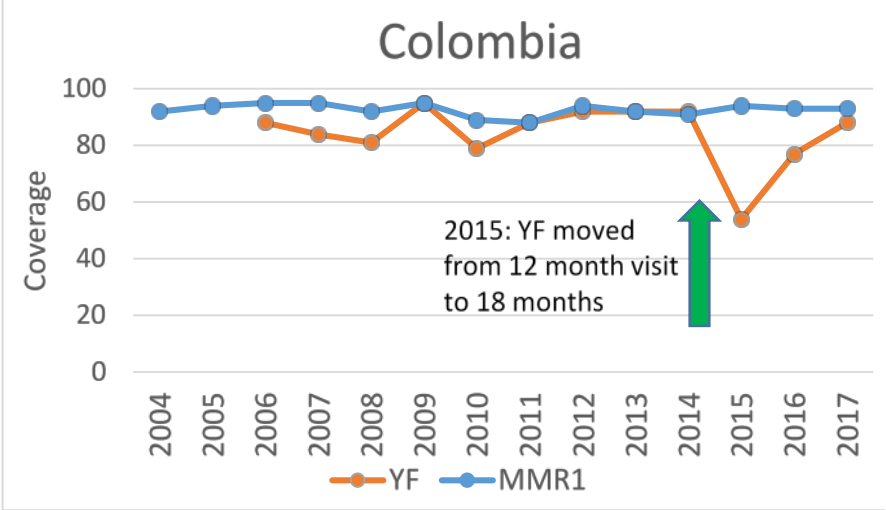
Study	Main AEFI findings
Brazil	• No serious AEFIs • Among mild/moderate AEFIs, greater proportion of children in co-administration group had fever (17% vs. 12%) and any sign/symptom (27% vs. 19%)
The Gambia	• Only 1 serious AEFI that was *possibly* related to individual YF vaccine • No significant differences in mild/moderate AEFIs between groups
Argentina	• No serious AEFIs • No significant differences in mild/moderate AEFIs between groups

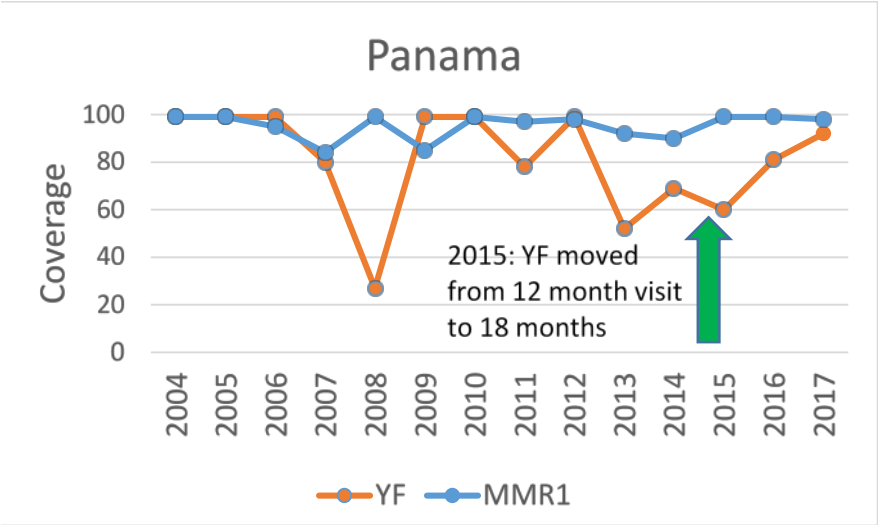
Programmatic Considerations

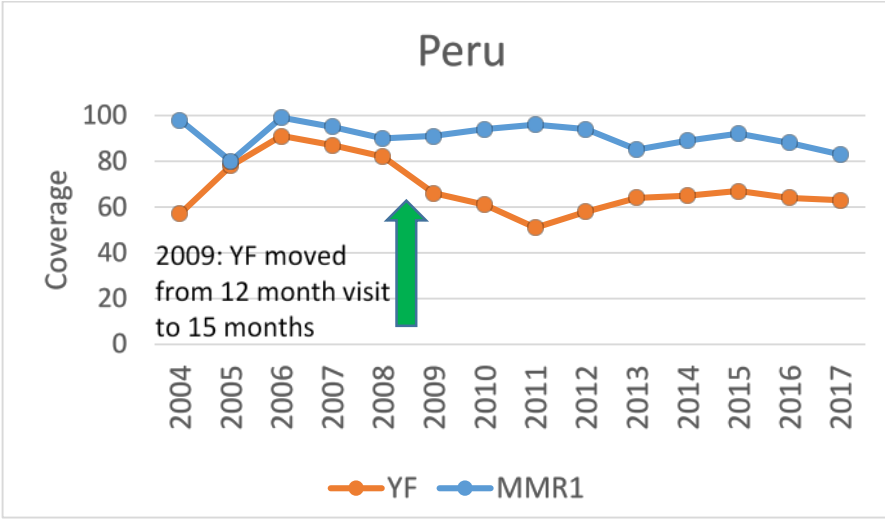
- To avoid any interference, vaccines would need to be administered at different visits
  - Delay one vaccine until after 9 or 12-month visit
  - Given measles and rubella elimination goals, YF would more likely be delayed
- WHO recommends 2 doses of MCV; most children have 2nd opportunity for vaccination
- WHO recommends 1 dose of YF; lower coverage could significantly impact population immunity

PAHO Experience: Impact of YF Vaccination Schedule on Coverage



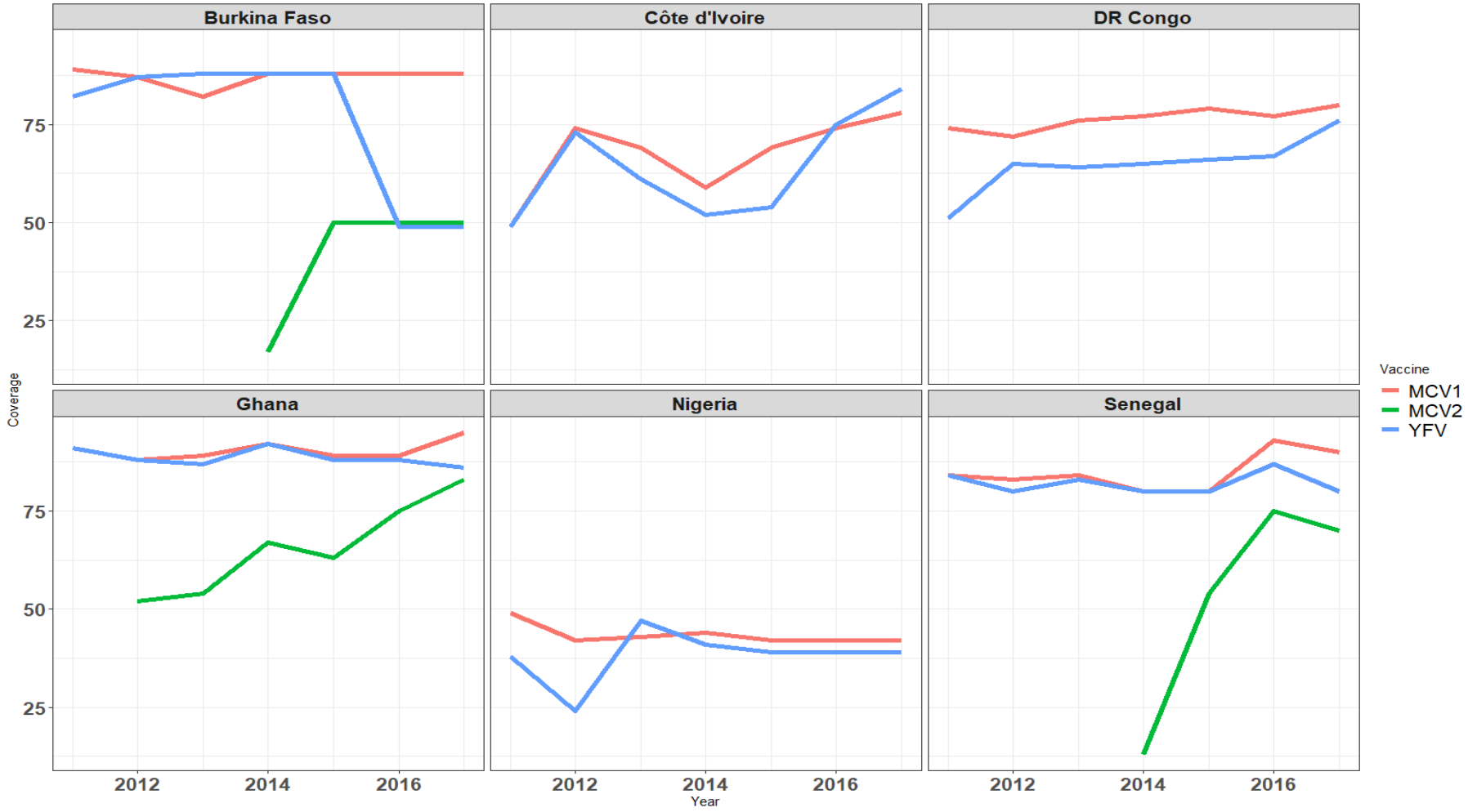






[1] MMR – measles, mumps, and rubella vaccine; MMR1 – first dose of MMR vaccine; YF – yellow fever vaccine; JFR – WHO-UNICEF joint reporting form

MCV1, MCV2, and YF Coverage – AFRO Experience



Country selection based on: (a) nationwide YF vaccination; (b) mixture of high, medium, low MCV1 coverage; (c) preference for populous countries. Additional countries shown in extra slide.

Study Conclusions

- No evidence of interference with measles seroconversion or magnitude of antibody response
- Inconsistent evidence regarding interference with rubella, mumps and YF seroconversion
- There is evidence of interference with magnitude of antibody response for rubella, mumps, and YF
  - However, titers were robust in all groups
  - Clinical implications and whether this affects long-term immunity are unknown

Programmatic Implications and Next Steps

- Programmatic implications likely have greater impact on population immunity than any potential reduction in immune response due to co-administration
- Additional research is needed on:
  - Clinical implications of lower titers/concentrations for rubella, mumps and YF
  - Impact of lower titers/concentrations on long-term immunity
  - Potential interference when different combinations of YF vaccines and MCVs are co-administered

Draft Recommendations

- WHO maintains its current guidance stating that MR/MMR and YF vaccines should be administered at the same visit or at least 4 weeks apart, according to the schedule that will maximize coverage for all antigens in the national immunization schedule [*removing all qualifications/precautions about co-administration]*
- Additional research is needed to determine if the lower titers or antibody concentrations observed following co-administration will impact long-term immunity and cause secondary vaccine failures

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THANK YOU!

Extra Slides

Study Design of RCTs: Analysis

Study	Type of analysis conducted and presentation of statistical results			
	Seroconversion	**Presentation of statistical results**	**Magnitude of antibody response**	**Presentation of statistical results**
Brazil	Comparison of proportions	p-value	Non-parametric comparison of distributions	p-value
The Gambia	Non-inferiority	Non-inferior (NI) / NI not shown	Non-inferiority	NI / NI not shown
Argentina	Non-inferiority	NI / NI not shown	Non-parametric comparison of distributions	p-value

NI = non-inferior

Vaccine strains in each study

Study	Measles	Mumps	Rubella	Yellow Fever
Brazil	-Moraten -Schwartz	-Jeryl Lynn -RIT 4385*	-RA 27/3	-17D-213 (Brazil) -17DD (Brazil)
The Gambia	-Edmonston-Zagreb	N/A	-RA 27/3	-17D-204 (Senegal)
France	-Enders' Edmonston -Schwartz	-RIT 4385* -Jeryl Lynn	-RA 27/3	-17D-204 (France)
Argentina	-Schwartz -Edmonston	-Urabe AM-9 -Jeryl Lynn	-RA 27/3	-17D-204 (France)† -17DD (Brazil)

* Derived from Jeryl Lynn strain
† ~98% of participants received 17D-204

Assays and cut-offs in each study

Study	Measles		Mumps		Rubella		Yellow Fever	
	Assay	Cut-off	Assay	Cut-off	Assay	Cut-off	Assay	Cut-off
Brazil	PRNT50	Not stated	ELISA (Siemens)	≥231 U/mL	ELISA (Siemens)	Non-reactive: <4.0; Inconclusive: 4.0 – 6.5; Reactive: >6.5 IU/mL	PRNT50	>2.7 $\log_{10}$ mIU/mL
The Gambia	ELISA (Siemens)	≥150 IU/mL	N/A	N/A	ELISA (Siemens)	≥4 IU/mL	PRNT50	Positive ≥ 8
France	ELISA (Siemens)	Per manufacturer	ELISA (Siemens)	≥230 U/mL	ELISA (Siemens)	Non-reactive: <8; Inconclusive: 8 – 11; Reactive: >11 IU/mL	PRNT80	Positive ≥ 10
Argentina	ELISA (Siemens)	≥150 mIU/mL	ELISA (Siemens)	≥231 U/mL	ELISA (Siemens)	≥4 IU/mL	PRNT50	Positive ≥ 10

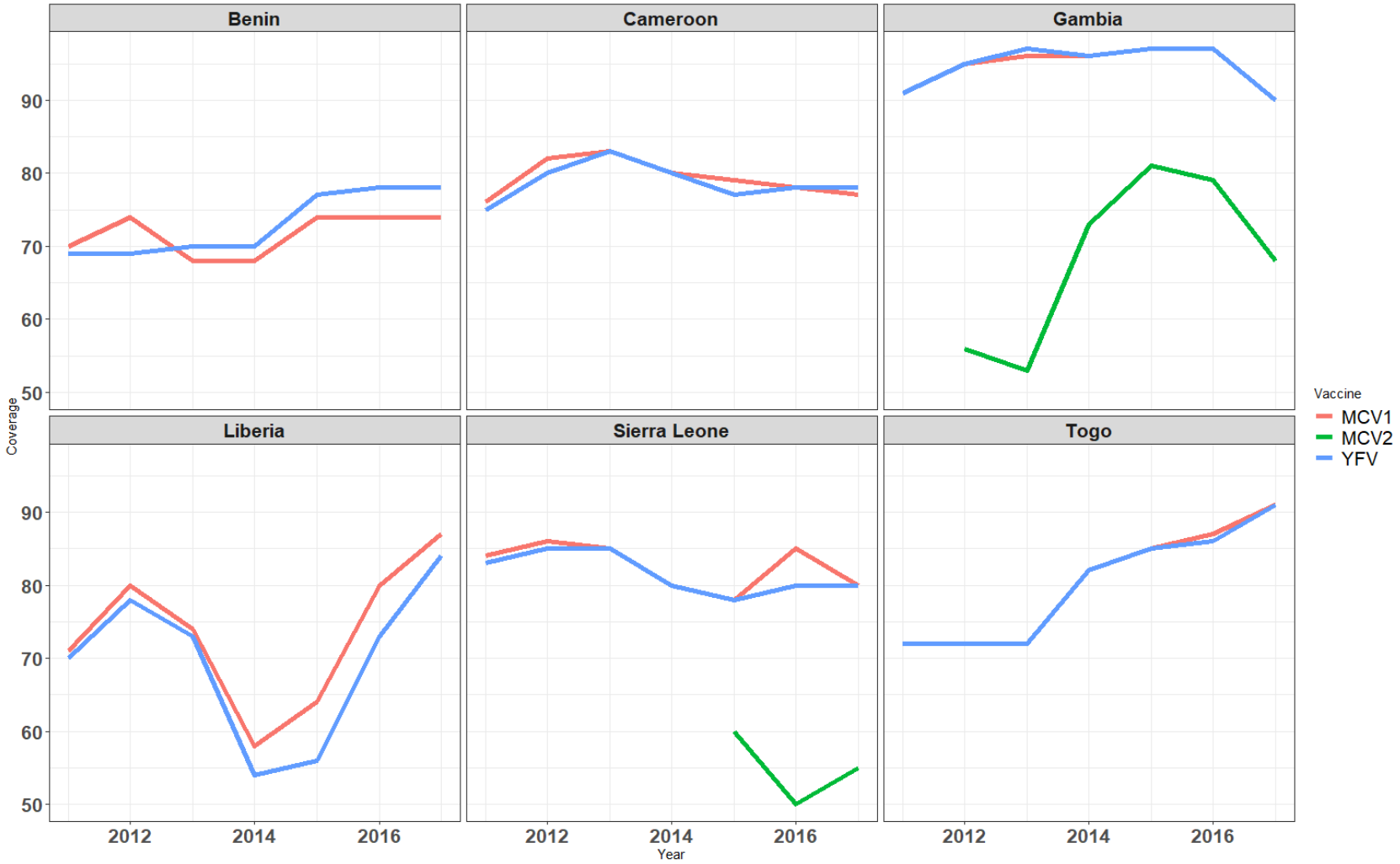
Summary of Results – Seroconversion

Study	Interference with seroconversion?			
	Measles	**Rubella**	**Mumps**	**Yellow Fever**
Brazil	No interference	Interference	Interference	Interference
The Gambia	No interference	No interference	N / A	No interference
Argentina	No interference	No interference	No interference	No interference

Summary of Results – Magnitude of Antibody Response

Study	Interference with the magnitude of antibody titers/concentrations?			
	Measles	**Rubella**	**Mumps**	**Yellow Fever**
Brazil	No interference	Interference	Interference	Interference
The Gambia	No interference	Interference	N / A	Interference
Argentina	No interference	Interference	Interference	Interference

MCV1, MCV2, and YF Coverage – AFRO Experience



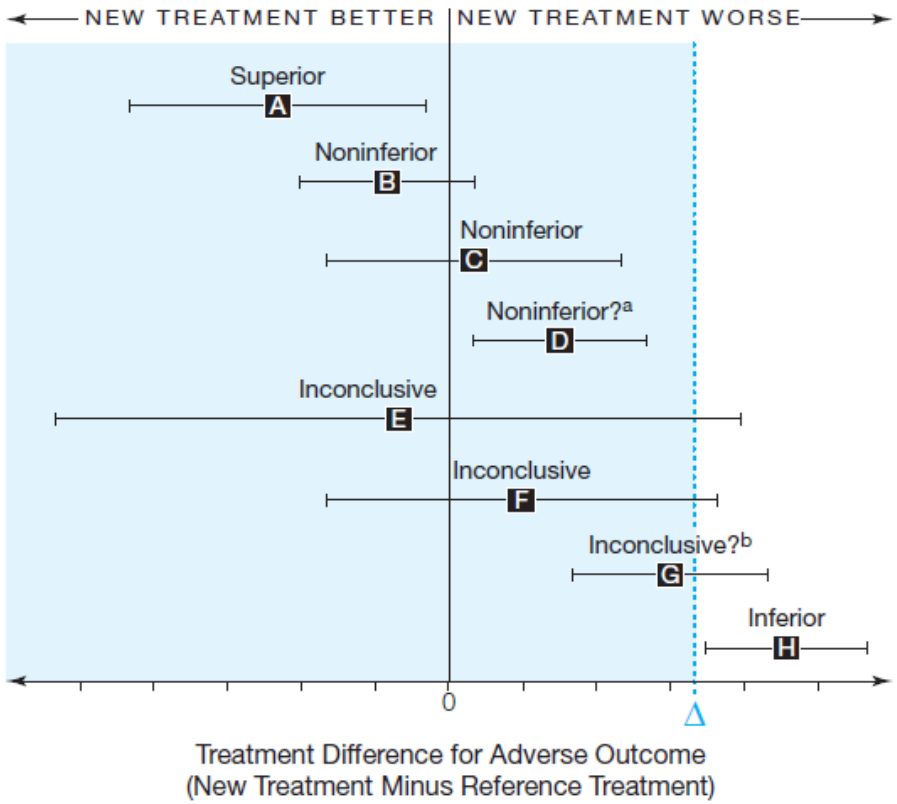
Country selection based on: (a) nationwide YF vaccination; (b) mixture of high, medium, low MCV1 coverage; (c) lower populous countries than in main presentation slide.

GRADE Assessment

Outcome	Conclusion	Strength of Evidence
Seroconversion – measles	No interference	High
Seroconversion – rubella	No interference	Limited
Seroconversion – mumps	No interference	Limited
Seroconversion – YF	No interference	Limited
Magnitude of response – measles	No interference	High
Magnitude of response – rubella	Interference	Moderate
Magnitude of response – mumps	Interference	Moderate
Magnitude of response – YF	Interference	High

Interpretation of Non-Inferiority Study Results

Figure 1. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials



Error bars indicate 2-sided 95% CIs. The blue dashed line at x=Δ indicates the noninferiority margin; the blue tinted region to the left of x=Δ indicates the zone of inferiority. A, If the CI lies wholly to the left of zero, the new treatment is superior. B and C, If the CI lies to the left of Δ and includes zero, the new treatment is noninferior but not shown to be superior. D, If the CI lies wholly to the left of Δ and wholly to the right of zero, the new treatment is noninferior in the sense already defined but also inferior in the sense that a null treatment difference is excluded. This puzzling circumstance is rare, because it requires a very large sample size. It also can result from a noninferiority margin that is too wide. E and F, If the CI includes Δ and zero, the difference is nonsignificant but the result regarding noninferiority is inconclusive. G, If the CI includes Δ and is wholly to the right of zero, the difference is statistically significant but the result is inconclusive regarding possible inferiority of magnitude Δ or worse. H, If the CI is wholly above Δ, the new treatment is inferior.
[a]This CI indicates noninferiority in the sense that it does not include Δ, but the new treatment is significantly worse than the standard. Such a result is unlikely because it would require a very large sample size.
[b]This CI is inconclusive in that it is still plausible that the true treatment difference is less than Δ, but the new treatment is significantly worse than the standard. Adapted from Piaggio et al.[6]

Piaggo et al., "Reporting of Noninferiority and Equivalence Randomized Trials. Extemsopm pf the CPMSPRT 2010 Statement" JAMA, 2012.