

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

## Key Findings

- 1- There is inconsistent evidence that co-administration of MR/MMR and YF vaccines interferes with rubella, mumps and YF seroconversion. There is no evidence from any studies that co-administration of MR/MMR and YF vaccines interfere with measles seroconversion.
- 2- There is evidence of interference with the magnitude of antibody response against rubella, mumps, and YF when MR/MMR and YF vaccines are co-administered; however, titers were robust (well above the cut-off points for seroconversion) in all groups. The clinical implications of this and whether it has any effect on long-term immunity are not known. There is no evidence of interference with the magnitude of antibody response against measles when MR/MMR and YF vaccines are co-administered.
- 3- The programmatic implications of delaying one of these vaccines to a later vaccination visit instead of co-administering them would likely have a far greater impact on population immunity than any potential reduction in the immune response due to co-administration.
- 4- Additional research is needed in several areas.

## Introduction

In line with regional measles elimination goals, all countries administer MCVs through their childhood vaccination programs. Most countries (167/194 countries and territories) also provide rubella vaccine, administered in a combination vaccine with measles vaccine (MR) or with measles and mumps vaccines (MMR). Of the 40 countries worldwide that are categorized as high risk for YF, either nationwide or within subnational areas, 13/13 in South America and 22/27 in Africa administer YF vaccine through their national immunization programs. The remaining 5 countries in Africa are expected to introduce YF vaccine in the next few years; in addition, YF vaccination is also used for outbreak control through campaigns. Countries in the World Health Organization (WHO) African region (AFR) typically administer YF vaccine along with measles or MR vaccine to children at 9 months of age; all countries that currently administer measles vaccine will eventually transition to MR vaccine. In countries in the region of the Pan American Health Organization (PAHO), YF vaccine has traditionally been co-administered at 12 months of age with MMR vaccine, though there are a few exceptions.

MCVs and YF vaccines are live attenuated vaccines and the WHO position papers on rubella and measles vaccines both state that live vaccines should be administered at the same time or at least 4 weeks apart.[1, 2] However, the rubella position paper from 2011 also states that “interference may occur between MMR and YF vaccines if they are simultaneously administered to young children.” This

was based on the findings of one study that found lower seroconversion rates against rubella, mumps, and YF (but not measles) when MMR and YF vaccines were co-administered compared to being administered 30 days apart to children aged 12-23 months in Brazil [3]. Because of this, the rubella position paper also states that “it may be prudent for routine immunization programmes to avoid simultaneously administering YF vaccine and MMR to children aged < 2 years.” In 2013, the SAGE YF working group conducted a literature review on co-administration of YF and other vaccines, including eight studies that evaluated co-administration of YF and MCVs. None of the seven studies that evaluated co-administration with measles-only and YF vaccines showed evidence of interference. The previously-mentioned study from Brazil was the only study evaluating co-administration of YF vaccine and a combination measles vaccine.[4] They concluded in the 2013 YF position paper that “Immunogenicity is usually unaffected when YF vaccine is co-administered with other vaccines” but then reference the study in Brazil as a “notable exception”. Based on the available data, they further stated “there is insufficient evidence to change current recommendations and SAGE recommended that additional studies should be undertaken...”[5] Since the publication of the Brazil study in 2011, there have been three additional studies that evaluated potential interference between MCVs and YF vaccine when they are co-administered as compared to sequential administration (MCV and YF vaccines separated by  $\geq 28$  days with follow-up serum samples taken  $\geq 28$  days after the 2<sup>nd</sup> vaccine was received) or individually (receipt of one vaccine with follow-up sample collected  $\geq 28$  days later, prior to receiving the second vaccine). In this background paper, we review the evidence from the previously-mentioned Brazil study and these three additional studies.

From a programmatic perspective, co-administration of vaccines provides protection at the earliest possible age, maximizes efficient use of healthcare resources, and prevents children from potentially missing the vaccine dose should they not return for a later vaccination visit.[6] Hence the risk of interference needs to be weighed against the risk of non-vaccination should administration of one of the vaccines be delayed to a later, scheduled vaccination visit (e.g. 15 or 18-month visits). In this paper, we present programmatic data to show the potential impact on vaccination coverage if MR/MMR or YF vaccine were to be provided at a 15 or 18-month vaccination visit instead of the 9 or 12-month visit.

## **Methodology**

We reviewed four studies evaluating co-administration of MCVs and YF vaccines. Three studies are published in peer-reviewed journals [3, 7, 8] and one is unpublished. The unpublished data was shared with the SAGE Measles-Rubella (MR) working group in September, 2018 and will be submitted for publication later this year. We also used data from the WHO-UNICEF Joint Reporting Form (JRF) and WHO-UNICEF estimates of immunization coverage (WUENIC) to look at programmatic implications.

When evaluating potential interference, we considered two aspects of interference:

- (1) Decreased seroconversion or response rates, as evidence by developing a detectable titer or having a titer increase by a defined amount.

(2) Decreased magnitude of antibody response, as evidence by lower antibody concentrations/titers

All four study designs were reviewed by the SAGE MR working group in July 2018 and results were further reviewed in September. At the September meeting, programmatic data were also reviewed and proposed recommendations were discussed with the MR working group members and invited YF subject matter experts. All working group members and several YF subject matter experts have had the opportunity to provide critical feedback to draft versions of this document, including the recommendations.

## **Existing Evidence**

### *Study Findings*

The methodologies of the four studies that evaluated the immune response of MCVs and YF vaccines when given together, individually, or separated by approximately one month are outlined in Table 1. The studies varied some in the specific vaccines administered and laboratory procedures used to assess immune response (Table 2). Three of these studies were randomized clinical trials (RCTs) and one was an observational study. Of note, the RCT from Brazil had differing time gaps between MMR vaccination and follow-up sample collection for their sequential and co-administration groups; samples were collected 30 days post-vaccination for the co-administration group and 60 days post-vaccination for the sequential group. Additionally, the results from the observational study in France were given much less weight by the working group when formulating recommendations due to the study's observational design and power limitations.

None of the studies showed decreased seroconversion against measles when the vaccines were co-administered compared to when the vaccines are administered individually or sequentially. The studies in The Gambia and Argentina did not find decreased seroconversion for any of the other antigens (mumps, rubella, YF) (Table 3). However, the study from Brazil did find interference in seroconversion to mumps, rubella and YF when MMR and YF vaccines were co-administered compared to being administered 30 days apart. The study from France also observed interference for YF, however their sample size calculations show that they were significantly underpowered to do the non-inferiority test that they performed making the findings difficult to interpret.

All of the studies, except the study from France which had limited power, show interference in the magnitude of antibody response with lower antibody concentrations/titers against all antigens except measles in the co-administration group compared to the individual or sequential groups (Table 4). However, it should be noted that the geometric mean titers (GMTs) for both the co-administration and individual/sequential groups are robust in all studies. Furthermore, while significantly lower titers were observed in the children that had the vaccines co-administered, the clinical implications of these differences and their impact on long-term immunity, in particular secondary vaccine failures, is

unknown. More research is needed to better understand whether lower antibodies concentrations/titers following vaccination are associated with different kinetics or rates of antibody decline.

### *Discussion of study findings*

The results of the three RCTs were concordant for demonstrating interference as measured by a decrease in antibody concentrations/titers when the vaccines are co-administered. For interference measured by a decrease in seroconversion, the RCTs from Argentina and The Gambia showed no interference, while the Brazilian results showed interference for mumps, rubella and YF. The results from the French study were more difficult to interpret and were given much less weight by the working group due to the study's limitations.

Several hypotheses were discussed to explain the differing results for interference with seroconversion observed between the study from Brazil and the studies from Gambia and Argentina. The differing time gap between vaccination and sample collection may have contributed to the lower seroconversion for mumps and rubella observed in the Brazilian study, but this time gap did not exist for the YF results, yet differing titers were observed. Other hypotheses for the apparent difference is use of different vaccines; the Brazil study used 17DD and 17D-213 YF vaccines while the studies from The Gambia and Argentina used 17D-204 YF vaccine (manufactured in Senegal or France, respectively). This difference in children's immunologic response to different strains of YF vaccines has been noted by others.[9] The 17DD vaccine has on average a higher potency than other prequalified 17D vaccines [10] and its higher potency might have resulted in greater interference. Another possibility is the difference in laboratory tests and cut-off points used to classify people as seropositive or seronegative. While the studies in Brazil, The Gambia, and Argentina used the same testing procedure for YF (plaque reduction neutralization test with a cut-off of 50%, PRNT50), they used different criteria for classifying seropositive results (Table 2). For rubella testing, all RCTs used Siemens ELISA kits, but it is unclear how the Brazil study classified indeterminate results. Furthermore, during the working group discussions, laboratory experts commented that it would not be unusual to have slightly varying results from different laboratories, even when using the same test kits. Finally, it is possible that there were different background rates of exposure to related viruses (e.g., flaviviruses) in the different study populations and this affected the children's immunologic response to the vaccines.

### *Programmatic Considerations*

To avoid any potential interference on the immunologic response to MCVs and YF vaccine, the two vaccines would need to be administered at different vaccination visits, typically with one of them delayed to a visit after the standard visit for MR/MMR and YF vaccines at 9- or 12-months of age. To assess the potential programmatic impact of delaying one dose, we examined vaccine coverage rates for MMR and YF in the 4 countries in the PAHO region that have moved YF vaccination from the 12-month vaccination visit (where it was co-administered with MMR) to either the 15 or 18-month visit. In each case, there was a substantial drop in coverage in the year the change was implemented (Figure

1). In Panama and Colombia, following the initial decrease in YF vaccine coverage, there has been a steady increase so the gap is almost closed. In Argentina and Peru, a coverage gap of approximately 20% has persisted after the change in the schedule that moved YF vaccine to a separate visit from MMR. In the AFRO region, all countries that provide YF through their national immunization program co-administer YF with M/MMR at the 9-month vaccination visit and no changes have been made, hence similar case examples do not exist. However, coverage for YF, even when co-administered with MCV1 at the 9-month visit, is often lower than MCV1 (Figure 2). More significantly, second year of life vaccination programs are much less developed in the AFRO region than in the PAHO region. A few countries with stronger immunization programs (and without significant gaps between MCV1 and YF coverage) have introduced MCV2 during the second year of life, typically at a 15 or 18-month visit. In these countries, a significant coverage gap between MCV1 and MCV2 still exists several years after MCV2 introduction (Figure 2). These data suggest that delaying one of these vaccines to a visit during the second year of life may have an even stronger negative impact on coverage in the AFRO region than it did in the PAHO region.

Additional programmatic issues to consider are that there are measles and rubella elimination goals. Hence there is rationale not to delay MCV1 administration. However, WHO recommends two doses of MCV and thus most children receive a second dose either through MCV2 in routine immunization or through supplemental immunization activities. WHO recommends only one dose of YF vaccine; hence decreased coverage with YF vaccine could have significant impacts on population-level immunity to YF.

### **Conclusions and Recommendations:**

Given the evidence just discussed, the working group concluded that:

- 1- There is inconsistent evidence that co-administration of MR/MMR and YF vaccines interferes with rubella, mumps and YF seroconversion. Two of three RCTs did not show a decrease (i.e., non-inferior) in seroconversion when MMR and YF vaccines were co-administered while one showed decreased seroconversion against rubella, mumps and YF when these vaccines were co-administered. There is no evidence from any studies that co-administration of MR/MMR and YF vaccines interferes with measles seroconversion.
- 2- There is evidence of interference with the magnitude of antibody response against rubella, mumps, and YF when MR/MMR and YF vaccines are co-administered; however, titers were robust in all groups. This was demonstrated in all three RCTs that examined this. The clinical implications of this and whether it has any effect on long-term immunity are not known. There is no evidence of interference with the magnitude of antibody response against measles when MR/MMR are and YF vaccines are co-administered.
- 3- The programmatic implications of delaying one of these vaccines to a later vaccination visit instead of co-administering them are substantial and would likely have a far greater impact on population immunity than any potential reduction in the immune response due to co-administration.

- 4- Additional research is needed in several areas: 1) better understand whether there are any clinical implications from the reduction in the magnitude of the antibody response for rubella, mumps and YF immunity; 2) determine if the lower titers or antibody concentrations observed following co-administration of MR/MMR and YF vaccine will impact long-term immunity; and 3) further examine the potential interference when different combinations of available YF and measles-containing vaccines (e.g., 17DD, 17D-204, MMR, and MR from different manufacturers) are co-administered.

Given these conclusions, the working group recommends the following:

**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 of MR/MMR and YF vaccine will impact long-term immunity and cause secondary vaccine failures.**

## REFERENCES

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**Table 1: Study Design and Statistical Comparison**

Study Reference [Location]	Target population	Study Design*	Sample size*	Statistical Comparison - Seroconversion	Statistical Comparison – Antibody titers /concentrations	Comments
Nascimento Silva et al., 2011 [3] [Brazil]	12-23-month old children	RCT: Children randomized to receive MMR & YF at same visit (co-administration) or MMR followed by YF 30 days later (sequential). Samples collected at baseline and 30 days after the last vaccination.	906 in co-administration group; 922 in sequential group	Difference in proportions seroconverting	Non-parametric test of difference in antibody concentrations / titers	Time gap between MMR vaccination and sample collection differed between groups: in sequential group, sample collection was 60 days post-vaccination; in co-administration group it was 30 days post vaccination
Clarke et al., 2016 [7] [The Gambia]	9-10 month old children	RCT: Children randomized to receive MR (individual), YF (individual), or MR & YF (co-administration) Samples collected at baseline and 30 days post-vaccination.	189 in individual MR group; 187 in individual YF group; 188 in co-administration group	Non-inferiority test with 10% margin	Non-inferiority test with 1/3 log <sub>2</sub> titer / concentration	
Unpublished, 2018 [Argentina]	12-month old children	RCT: Children randomized to receive MMR (individual), YF (individual), or MMR & YF (co-administration) Samples collected at baseline and 30 days post-vaccination	248 in individual MMR group; 245 in individual YF group; 244 in co-administration group	Non-inferiority tests with 5% margin	Non-parametric test of difference in antibody concentrations / titers	
Goujon et al., 2017 [8] [France]	Children aged 6-24 months at time of YF vaccination	Observational: Children identified through YF vaccination record; grouped according to timing of prior M/MMR vaccine: Control 1: M/MMR & YF less than 24 hours apart (co-administration) Control 2: M/MMR & YF ≥ 28 days apart (sequential). Follow-up samples collected 6-12 months post YF vaccination	50 in co-administration group; 19 in sequential group	Non-inferiority test with 10% margin		Observational design; no baseline samples; did not reach sample size needed, hence they were underpowered for the planned statistical testing

\*Definitions of selected terminology:

Co-administration: Received MR/MMR and YF at the same vaccination visit (or within 24 hours in Goujon et al. study)

Sequential: Received MMR and YF sequentially (MMR followed by YF at least 28 days later) with sample collected after both vaccinations received

Individual: Received either MR/MMR or YF individually with follow-up sample collected prior to receipt of the second vaccine

**Table 2: Vaccine Strains and Laboratory procedures**

Study Reference [Locations]	Vaccine strains				Laboratory methodology and cut-off criteria							
	Measles	Mumps	Rubella	Yellow fever	Measles test	Measles cut-off	Mumps test	Mumps cut-off	Rubella test	Rubella cut-off	Yellow fever test	Yellow fever cut-off
Nascimento Silva et al., 2011 [3] [Brazil]	-Moraten, -Schwartz	Jeryl Lynn -RIT 4385*	RA 27/3	-17D-213 (Brazil) -17DD (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 <sub>10</sub> mIU/mL
Clarke et al., 2016 [7] [The Gambia]	Edmonston-Zagreb	N/A	RA 27/3	17D-204 (Senegal)	ELISA (Siemens)	≥150 IU/mL	N/A		ELISA (Siemens)	≥4 IU/mL	PRNT50	Positive ≥ 8
Unpublished, 2018 [Argentina]	-Schwartz, -Edmonston	-Urabe AM-9 -Jeryl Lynn	RA 27/3	-17D-204 (France) <sup>†</sup> -17DD (Brazil)	ELISA (Siemens)	Per manufacturer	ELISA (Siemens)	≥231 U/mL	ELISA (Siemens)	≥4 IU/mL	PRNT50	Positive ≥ 10
Goujon et al., 2017 [8] [France]	-Enders' Edmonston, -Schwartz	-RIT 4385* -Jeryl Lynn	RA 27/3	-17D-204 (France)	ELISA (Siemens)	≥150 mIU/mL	ELISA (Siemens)	≥231 U/mL	ELISA (Siemens)	Non-reactive: <8; Inconclusive: 8 – 11; Reactive: >11 IU/mL	PRNT80	Positive ≥ 10

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

**Table 3: Seroconversion: Co-administration compared to individual or sequential administration of measles-containing vaccines and yellow fever vaccine**

Study Reference [Location]	Measles (%)	Mumps (%)	Rubella (%)	Yellow Fever (%)
Nascimento Silva et al., 2011 [3] [Brazil]	Co-admin: 98.2* Sequen: 99.2 p=0.090	Co-admin: 61.1* Sequen: 70.8 P<0.001	<u>Per protocol cohort</u> Co-admin: 90.2 (88.0-92.2) Sequen: 97.2 (95.8 – 98.2) P<0.001 <u>Intent to Treat Cohort</u> Co-admin: 86.2 (83.8-89.0) Sequen: 94.4 (92.6 – 95.6) P<0.001	<u>Per protocol cohort</u> Co-admin: 69.7 66.4-72.8) Sequen: 87.7 (85.3 – 89.8) P<0.001 <u>Intent to Treat Cohort</u> Co-admin: 66.5 (63.3-69.6) Sequen: 82.8 (80.2 – 85.2) P<0.001
Clarke et al., 2016 [7] [The Gambia]	Co-admin: 78.9 (72.4 – 84.2) Individ: 76.9 (70.3 – 82.4) Co-admin was non-inferior	N/A	Co-admin: 96.8 (92.8 – 98.6) Individ: 98.2 (94.9 – 99.4) Co-admin was non-inferior	Co-admin: 94.9 (90.6 – 97.3) Individ: 96.0 (92.0 – 98.1) Co-admin was non-inferior
Unpublished, 2018 [Argentina]	<u>Per protocol cohort</u> Co-admin: 98.0 (95.0 – 99.2) Individ: 96.4 (93.0 – 98.1) Co-admin was non-inferior <u>Intent to Treat Cohort</u> Co-admin: 97.9 (95.3 – 99.1) Individ: 96.3 (93.1 – 98.1) Co-admin was non-inferior	<u>Per protocol cohort</u> Co-admin: 96.6 (93.1 – 98.3) Individ: 98.2 (95.4 – 99.3) Co-admin was non-inferior <u>Intent to Treat Cohort</u> Co-admin: 96.7 (93.6 – 98.3) Individ: 97.9 (95.3 – 99.1) Co-admin was non-inferior	<u>Per protocol cohort</u> Co-admin: 97.5 (94.3 – 98.9) Individ: 94.5 (90.6 – 96.8) Co-admin was non-inferior <u>Intent to Treat Cohort</u> Co-admin: 97.9 (95.2 – 99.1) Individ: 94.6 (91.0 – 96.8) Co-admin was non-inferior	<u>Per protocol cohort</u> Co-admin: 96.1 (92.5 – 98.0) Individ: 98.1 (95.1 – 99.2) Inconclusive result <sup>#</sup> <u>Intent to Treat Cohort</u> Co-admin: 96.3 (93.1 – 98.1) Individ: 97.5 (94.7 – 98.9) Co-admin was non-inferior
Goujon et al., 2017 [8] [France]	Co-admin: 92 <sup>&amp;</sup> Sequential: 95 P-value not stated	Co-admin: 86 Sequential: 95 P-value not stated	Co-admin: 94 Sequential: 100 P-value not stated	Co-admin: 92 Sequential: 100 Non-inferiority not shown

Co-admin: Received MR/MMR and YF co-administered

Sequen: Received MMR and YF sequentially (MMR followed by YF at least 28 days later) with sample collected after both vaccinations received

Individ: Received either MR/MMR or YF individually with follow-up sample collected prior to receipt of the second vaccine

\*Paper focused on rubella and yellow fever results; less data presented for measles and mumps

<sup>#</sup>Per protocol cohort had 20-30 children per group fewer than the intent to treat cohort and was underpowered for a non-inferiority analysis with 5% margin

<sup>&</sup>Results from the Goujon et al. study are seropositivity rather than seroconversion as there were no baseline samples

**Table 4: Antibody titers / concentrations: Co-administration compared to individual or sequential administration of measles-containing vaccines and yellow fever vaccine**

Study Reference [Location]	Measles	Mumps	Rubella	Yellow Fever
Nascimento Silva et al., 2011 [3] [Brazil]	<u>GMTs (95% CI) in IU/mL</u> Co-admin: 3.44 (3.20 – 3.70)* Sequen: 3.19 (3.00 – 3.39) P-value not stated	<u>GMTs (95% CI) in mIU/mL</u> Co-admin: 335.5 (314.4 – 358.0)* Sequen: 414.1 (388.0 – 442.1) P-value not stated	<u>GMTs (95% CI) in IU/mL</u> <u>Per protocol cohort</u> Co-admin: 24.9 (23.3 – 26.6) Sequen: 59.9 (56.3 – 63.7) P<0.001 <u>Intent to Treat Cohort</u> Co-admin: 24.8 (23.2 – 26.5) Sequen: 60.1 (56.5 – 63.9) P<0.001	<u>GMTs (95% CI)</u> <u>Per protocol cohort</u> Co-admin: 1064.6 (976 – 1161.2) Sequen: 3385.2 (3105.2 – 3690.4) P<0.001 <u>Intent to Treat Cohort</u> Co-admin: 1060.2 (1015.1 – 114.6) Sequen: 3381.3 (3236.8- 3683.7) P<0.001
Clarke et al., 2016 [7] [The Gambia]	<u>Median (95% CI) in IU/mL</u> Co-admin: 270 (243 – 310) Individ: 250 (230 – 280) Co-admin was non-inferior	N/A	<u>Median (95% CI) in IU/mL</u> Co-admin: 27 (24 – 31) Individ: 31 (27- 36) Non-inferiority not shown / inconclusive	<u>GMTs (95% CI)</u> Co-admin: 64 (64 -491) Individ: 128 (91- 128) Non-inferiority not shown
Unpublished, 2018 [Argentina]	<u>GMTs (95% CI) in mIU/mL</u> <u>Per protocol cohort</u> Co-admin: 1956 (1629 – 2348) Individ: 1561 (124 – 1956) P=0.17 <u>Intent to Treat Cohort</u> Co-admin: 2024 (1705 – 2402) Individ: 1631 (1317 – 2021) p=0.16	<u>GMTs (95% CI) in U/mL</u> <u>Per protocol cohort</u> Co-admin: 1745 (1390 – 2192) Individ: 2320 (1925 – 2795) P=0.04 <u>Intent to Treat Cohort</u> Co-admin: 1806 (1470 – 2220) Individ: 2252 (1876 – 2703) P=0.08	<u>GMTs (95% CI) in IU/mL</u> <u>Per protocol cohort</u> Co-admin: 32.2 (28 – 37.1) Individ: 39.4 (33.5 – 46.4) P=0.0007 <u>Intent to Treat Cohort</u> Co-admin: 35.8 (31.5 – 40.7) Individ: 40.8 ( 34.9 – 47.5) P=0.005	<u>GMTs (95% CI)</u> <u>Per protocol cohort</u> Co-admin: 225 (181 – 279) Individ: 373 (308 – 452) P<0.001 <u>Intent to Treat Cohort</u> Co-admin: 219 (181 – 265) Individ: 340 (283 – 408) P<0.001
Goujon et al., 2017 [8] [France]	<u>GMTs (95% CI) in mIU/mL</u> Co-admin: 2872 (2013 – 4094) Sequential: 4076 (2377 – 6988) P> 0.05	Not reported	<u>GMTs (95% CI) in IU/mL</u> Co-admin: 97 (71 – 133) Sequential: 111 (79 – 156) P>0.05	<u>N (%) with stated titer</u> Co-admin: Sequential: <5: 0 <5: 4 (8) 10: 0 10: 1 (2) 20: 3 (16) 20: 4 (8) 40: 4 (21) 40: 15 (30) ≥80: 12 (63) ≥80: 26 (52) P-value not reported

Co-admin: Received MR/MMR and YF co-administered

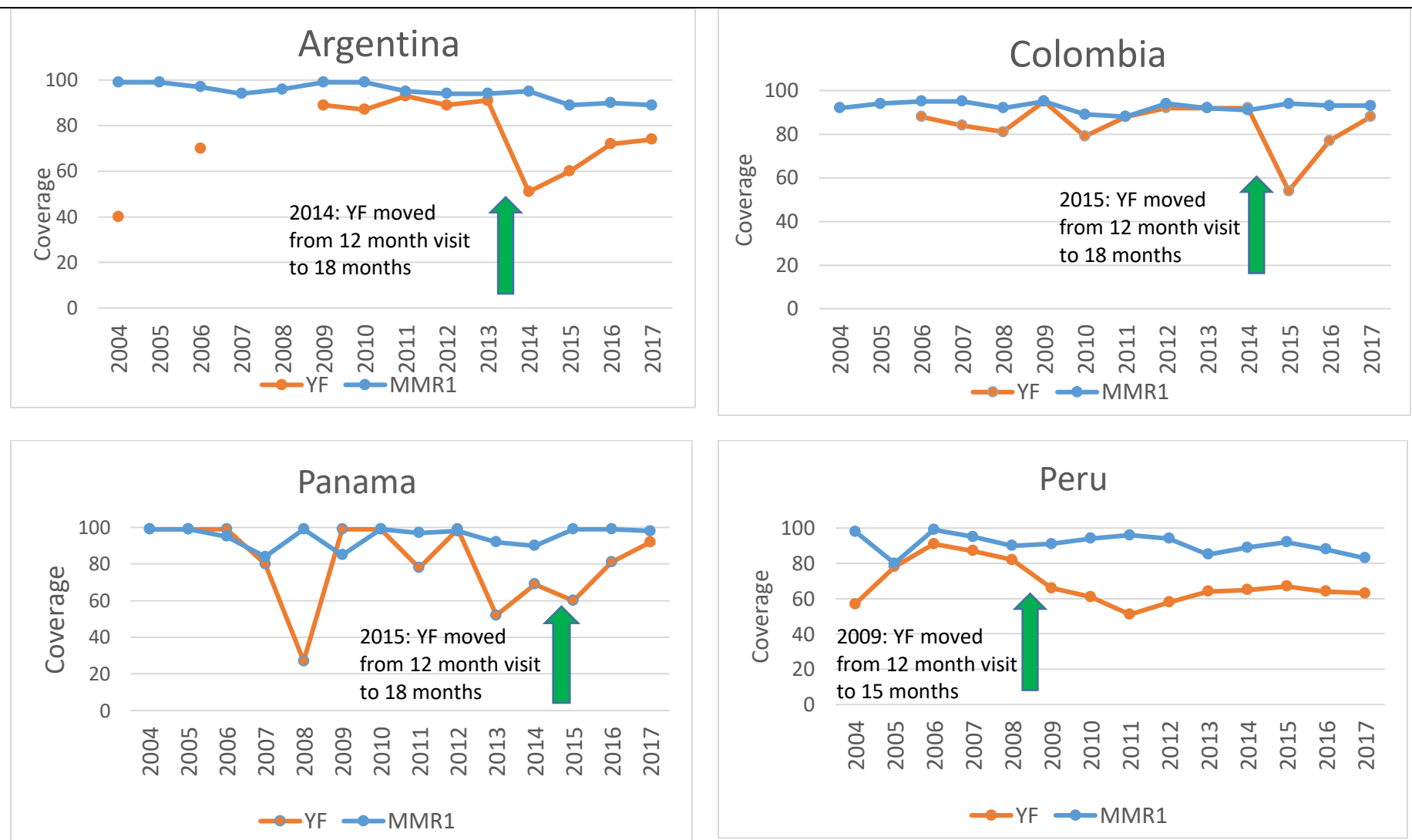
Sequen: Received MMR an YF sequentially (MMR followed by YF at least 28 days later) with sample collected after both vaccinations complete

Individ: Received either MR/MMR or YF individually (follow-up sample collection was prior to receipt of the second vaccine)

\*Paper focused on rubella and yellow fever results; data presented for measles and mumps is minimal

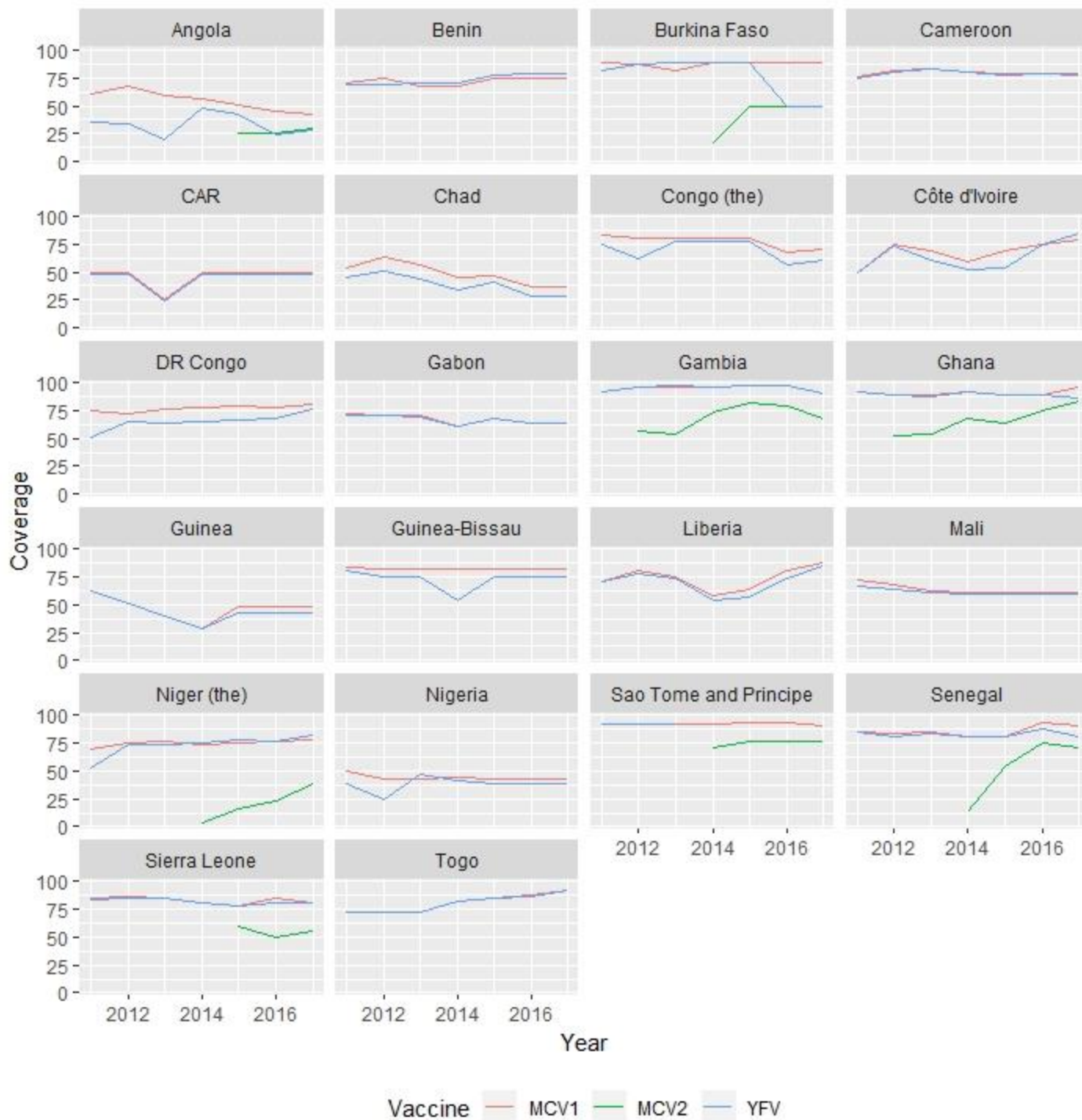
#Per protocol cohort had 20-30 children per group fewer than the intent to treat cohort and was underpowered for a non-inferiority analysis with 5% margin

**Figure 1: MMR1 and YF coverage in the 4 PAHO countries that initially co-administered YF with MMR at the 12 month vaccination visit and then moved YF to the 15 or 18 month vaccination visit (JRF data)\***



\* MMR – measles, mumps, and rubella vaccine; MMR1 – first dose of MMR vaccine; YF – yellow fever vaccine; JRF – WHO-UNICEF joint reporting form

**Figure 2: MCV1, MCV2, and YF in YF-endemic countries\* in the AFRO region: 2010 - 2017 (WUENIC data)**



\*Includes all countries in AFRO region that have  $\geq 2$  years of YF WUENIC estimates. All available MCV2 WUENIC data for these countries is included. Abbreviations: CAR=Central African Republic; DR Congo=Democratic Republic of Congo; MCV – measles-containing vaccines. Note: MCV1 – first dose of MCV; MCV2 – second dose of MCV.