Refinements to the vaccination strategies for measles and rubella control and elimination

SAGE October 2015

Peter Figueroa
On behalf of the MR working group

Policy Questions?

1. Under what epidemiological circumstances is it recommended to give a zero dose of MCV to infants <9 months of age?

2. How can existing data from vaccination and surveillance be used to determine the target age range for a measles or MR SIA needed to prevent an outbreak or stop transmission?

Current Recommendations for age of administration of MCV1

- Measles position paper (2009)
  - Where risk of measles mortality among infants remains high, MCV1 should be administered at 9 months of age.
  - In countries with low risk of measles infection among infants, MCV1 can be administered at 12 months
- Rubella position paper (2011)
  - In most countries: age of administration follows the schedule for measles – first dose at 9 months or 12–15 months and a second dose at 15–18 months or 4–6 years.
- Mumps position paper (2007)
  - First dose of mumps vaccine should be given at 12–18 months.
  - Countries planning to add mumps vaccine should first reduce measles transmission to low levels to enable them to increase the age of MCV1 to 12 months.

Policy Gaps

- Need to standardize global recommendations on use of MCVs (M, MR, MMR) among infants <9m

- Gaps in 2009 measles position paper:

  No recommendation for an early dose (MCV0)

  – during outbreaks

  – for international travellers

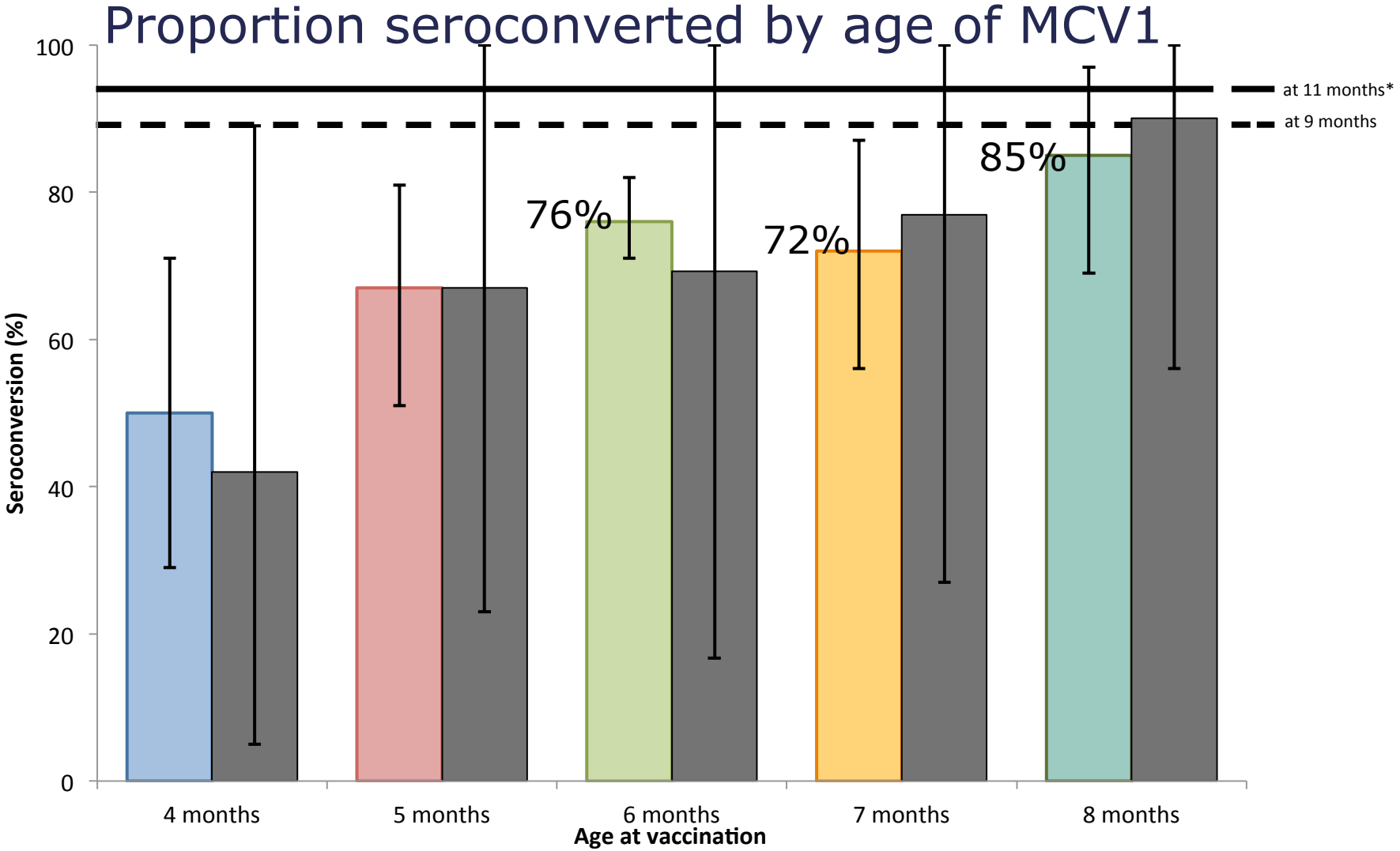
  No guidance on use of combined vaccines among infants (MR at <9 m or MMR <12m)

Approach to address the question

Under what epidemiological circumstances is it recommended to give a zero dose of MCV to infants <9 months of age?

Sub-questions	Approach
What is the potential for prevention of measles in infants <9 month-olds?	Analysis of recent outbreaks using case-based measles surveillance data reported to global level, 2010-2014 (J. Nicholson, CDC/Atlanta)
Are MCVs (M, MR, MMR) immunogenic, effective and safe when given at <9m?	Systematic review of literature on use of MCVs <9 months of age (Dr Susan Hahne et al RIVM)
Is blunting of the antibody response a real concern?	Systematic review of literature (RIVM) and further analysis by Dr Bill Moss, JHU)
How big a difference is there between vaccine-induced vs. natural immunity in mothers and does this lead to earlier susceptibility in infants?	Literature review by CDC (Dr Sharapov for MCV and Dr Grant for RCV)
What are the practical implications of giving MCV at <9 months of age?	Programme perspective from WHO secretariat and CDC Atlanta

Humoral immunity

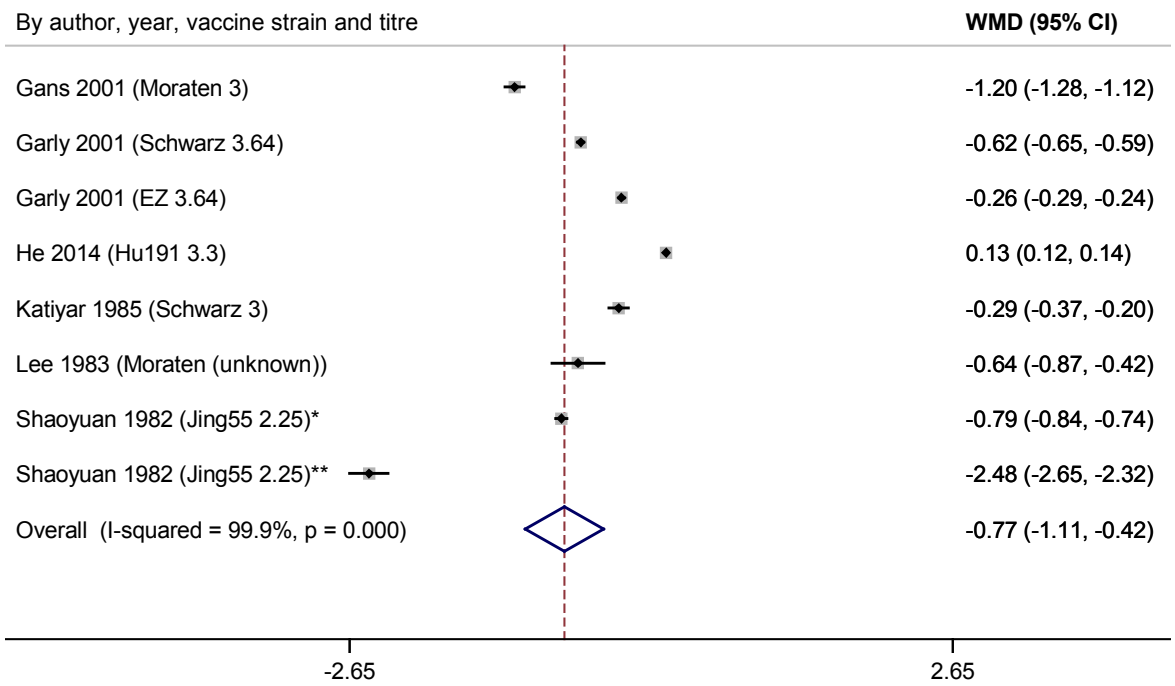


Coloured blocks are from Hahne et al review; grey blocks represent data from Moss & Scott 2009

* From Moss & Scott, 2009

Humoral immunity GMTs <9 vs ≥9 months

Within-study comparisons



Log scale: exponentiated weighted mean difference (WMD) = GMT ratio

Applied to **248 mIU/ml** (GMT for MCV1<9 months)

Estimated GMT for MCV1 ≥9 months **536 mIU/ml** (95% CI 377-753 mIU/ml)

Avidity index (AI)

- Only one study reported an Avidity Index after MCV1 <9 months of age (Nair 2007)
- AI after MCV1 at 6 months was significantly lower than at 9 and 12 months
- AI at 9 months was lower than at 12 months

Conclusions humoral/cellular immunity

- Limitations:
  - Variety of definitions used for sero-conversion and sero-positive
  - Laboratory tests not standardised between labs
  - Only plaque reduction neutralization test (PRNT) is somewhat comparable
  - Many studies presented results grouped by age
- Increase in proportion seroconverted with age (4-8 months)
  - Dependent on vaccine strain and presence of maternal antibodies (data not shown)
- Lower GMTs after MCV at <9 months vs MCV at ≥9 months
- Avidity index was significantly lower after MCV at 6 months vs. 9 months or 12 months
- Duration of immunity
  - Limited number of studies with comparison <9 and ≥9 months at MCV1
- Cellular immunity
  - Not lower when MCV1 <9 months (very limited data)

Effectiveness

Vaccine effectiveness for MCV1 <9 versus ≥9 months

Within-study comparisons

Author and year	Age at MCV1	N (measles cases vaccinated and unvaccinated)	Vaccine Efficacy	95% CI
Hull 1983	6-8	49	37	-71-76
	>9	57	89	79-94
John 2009	6-8	63	24	-27-55
	>8	21	62	-8-87
Judelsohn 1980	≤ 9	5	61	-145-94
	>9	22	89	79-94
Kaninda 1998	6-8	1168	87	81-91
	>9	1075	95	93-95
Shasby 1977	<9	12	-6	-162-57
	9-11	44	59	18-80
Simba 1995	6-8	(case-control)	73	11-92
	>9	(case-control)	84	61-93

Estimated VE difference: **18% higher** VE for MCV1 ≥9 months compared to MCV1<9 months

Conclusions: vaccine effectiveness

- Few eligible studies (n=8 found for VE of MCV<9 months)
  - Large variation in follow-up time
- VE for MCV1 <9 months **72%** (95% CI 53-91%)
  - Reference VE for 9-11 months: **77%** (IQR 62-91%) (Uzicanin, 2011)

    ≥12 months: **92%** (IQR 86-96%) (Uzicanin, 2011)
- Within study comparisons **18% higher** VE for MCV1 ≥9 months compared to MCV1<9 months (n=6)
- Only one estimate for VE against measles hospitalisation and death
  - MCV1 (Edmonston-Zagreb) at 4.5 months (Martins, 2008 & 2014)
  - Both VEs 100%, wide CIs, very short follow-up time

Blunting

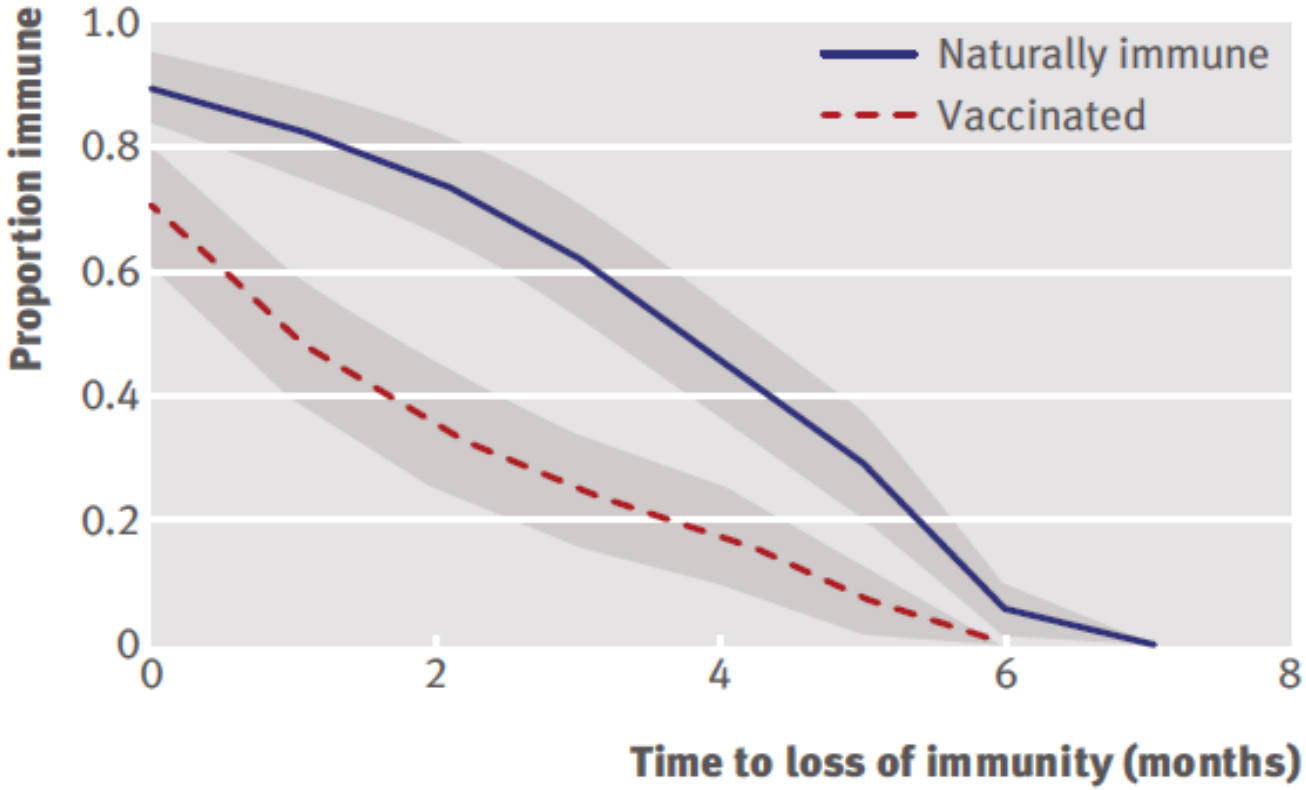
Conclusions

- Limited number of studies available
  - especially for avidity, cellular immunity and Vaccine Efficacy
- Limited evidence for blunting found
  - for GMT and avidity
  - not for proportion seropositive, VE and T cell immunity
- Possible causes
  - inadequate priming and/or tolerance

Conclusions

- MCV1 at <9 months: 3% more fever than ≥9 months.
  - Rash and diarrhea also increased (not significant)
- Observation can be confounded by other causes of rash, fever etc which are more frequent in younger children: inadequate study designs
- Meta-regression did not find age (or strain, titre) to be determinants
- Severe AEFIs: 4 studies reported on this
  - 0 in 2,042 infants with MCV1 <9months (limited sample size)

Proportion of infants of vaccinated women and naturally immune women still immune as a function of time to loss of immunity *



The median time to loss of immunity:

Infants of naturally infected mothers	3.78 months
Infants of vaccinated mothers	0.97 months

Shaded area is 95% confidence interval

**Source: Leuridan, E., et al., Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. BMJ, 2010. 340: p. c1626.*

Under what epidemiological circumstances is it recommended to give a zero dose of MCV to infants <9 months of age?

1. What is the potential for prevention of measles <9 m?
2. Are MCVs immunogenic, effective and safe when given at <9m?
3. Is blunting a real concern?
4. How big a difference is there between vaccine-induced vs. natural immunity in mothers and does this lead to earlier susceptibility in infants?
5. What are the practical implications of giving MCV at <9 months of age?

1. 13% of cases occur before the recommended age for MCV1
2. Yes, but less immunogenic, less effective, probably equally safe
3. Blunting of the immune response does occur but is unlikely to affect VE after the 2nd dose
4. Infants of vaccinated mothers become susceptible 2-3 months earlier than infants of naturally immune mothers
5. Increased cost due to an additional dose; may require an additional visit; potential for confusion with recording of doses

Recommendations - 1

- SAGE recommends that infants from 6 months of age receive a dose of measles containing vaccine in the following epidemiological circumstances:
  - During a measles outbreak as part of intensified service delivery;
  - During SIAs (i.e., mass vaccination campaigns) in settings where risk of measles among infants remains high
  - for internally displaced populations and refugees, and populations in conflict zones;
  - for individual children at high risk of contracting measles (exposed or at high risk of exposure to measles)
  - for infants travelling to countries experiencing extensive measles transmission
  - for infants known to be HIV positive

Recommendations - 2

- MCV administered more than a month prior to the recommended age of MCV1 should be considered a “zero dose” (MCV0) rather than the first dose. Because:
  - immunogenicity and effectiveness are lower than for doses administered at a later age
  - concern about the long term effectiveness of an early two dose schedule,
- Children who receive an early dose of MCV (i.e., MCV0) should then receive subsequent measles containing vaccines at the recommended ages according to the national schedule.

Recommendations - 3

- Available evidence on safety and immunogenicity of rubella and mumps-containing vaccines support their use from 6 months of age.
- Countries using MR or MMR in their national schedule should use the combined vaccine rather than measles-only formulations in children <1 year
- SAGE recognizes that this is an off-label recommendation; governments should not restrict the use of the vaccine in this age group for this reason only.
- Manufacturers should consider obtaining licensure to use MCV from 6 months of age.

Research priorities

Clinical and epidemiological studies

- head-to-head vaccine strain comparisons of MCV1 <9 months
- vaccine effectiveness studies
- cellular immunity and avidity after MCV1 <9 months
- blunting of response to MCV-2 after MCV1 <9 months
  (esp. avidity, VE and cellular immunity)
- review of severity of disease in children with vaccine failures after MCV1 <9 months of age
- safety: larger number of observations needed

Modeling studies

- Cost and impact on population immunity of different schedules (1 vs. 2 vs.3 doses)

M, MR SIA Target Age Range
Why is this an issue?

- Measles
  - Classic paradigm is wide age-range "catch-up" SIA, followed in countries with low-moderate (<90%) MCV1 coverage by regular "follow-up" SIAs targeting children <5y
  - Medium and low-performing countries using this approach have had large outbreaks with increasing proportion of cases >5y
  - Gavi focuses on preventing measles deaths and questions need to target >5y

- Rubella not introduced in 54 countries
  - Rubella susceptibility may be high in women of childbearing age
  - Need algorithm to guide these countries on need to target >15y
  - Need to find donors other than Gavi to fund >15y target age range

Current Global Recommendations

Measles position paper:

- Follow-up SIAs nationwide every 2–4 years and target children aged 9–59 months
- Monitor vaccination coverage data and conduct an SIAs before the number of susceptible children of pre-school age reaches the size of the birth cohort

Rubella position paper:

Elimination of Rubella and CRS:

- Use MR or MMR vaccine in a campaign targeting <15 years, followed by MR or MMR in the routine programme
- Countries may accelerate progress towards elimination by conducting wide age range campaigns targeting both adult males and females.

Current Global Recommendations

SAGE recommendations, Nov 2013:

- Countries integrate their surveillance, demographic, survey and (if available) seroprevalence data together with vaccination coverage information, history of MCV and RCV use, and local knowledge to determine the age distribution of susceptibility and hence the target age range of measles and MR SIAs
- Additional information to consider in relation to MR SIAs is rubella immunity among women of child-bearing age, the epidemiology of rubella and CRS, age-specific fertility rates, and the age of mothers of CRS-affected infants.

Policy Questions

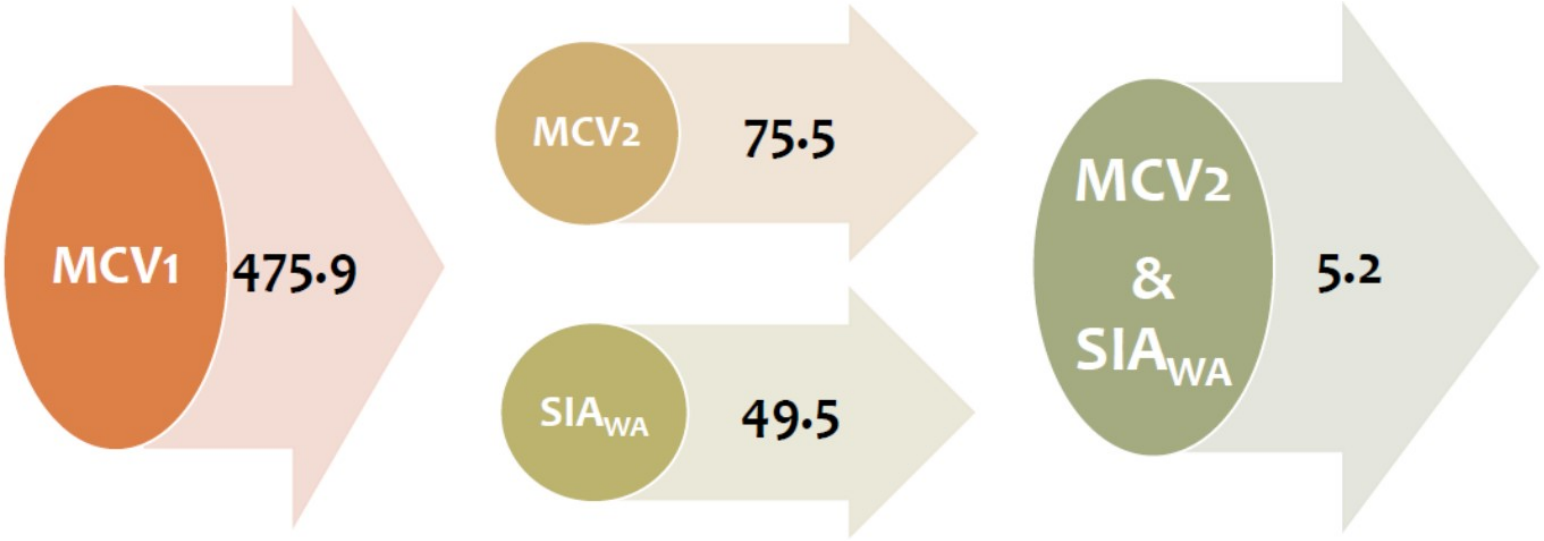
- How can existing data from vaccination and surveillance be used to determine the target age range for a measles or MR SIA needed to prevent an outbreak or stop transmission?

Approach to address the question

Sub-questions	Approach
What is the impact of different SIA strategies on measles incidence?	Multi country analysis using annual routine and SIA coverage, and measles incidence data (Dr Jennifer Knapp, CDC/Atlanta)
What SIA target age range is needed to maintain herd immunity?	Mathematical modeling on conditions needed to maintain elimination (Dr Matt Ferrari, Penn State University)
How well does a taxonomic approach assess the choice of SIA target age range?	Mathematical modeling (Drs Matthew Graham and Justin Lessler, Johns Hopkins Bloomberg School of Public Health)
How well does an algorithm for the target age for SIAs for rubella introduction perform against historical country data?	Analysis of country experience (Dr Susan Reef, CDC, SAGE WG member)

Results – multi-country analysis

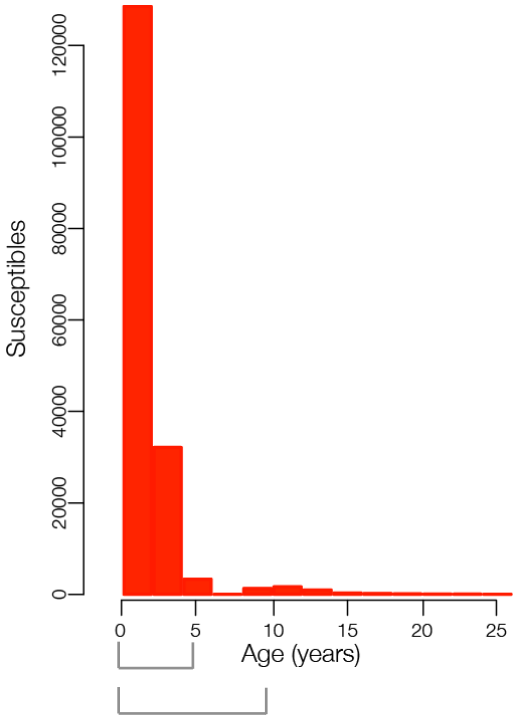
- Starting with 1 dose in routine, adding a second dose (through routine or SIAs) and then adding both SIAs and MCV2 in routine, each decreased median measles incidence 10-fold:

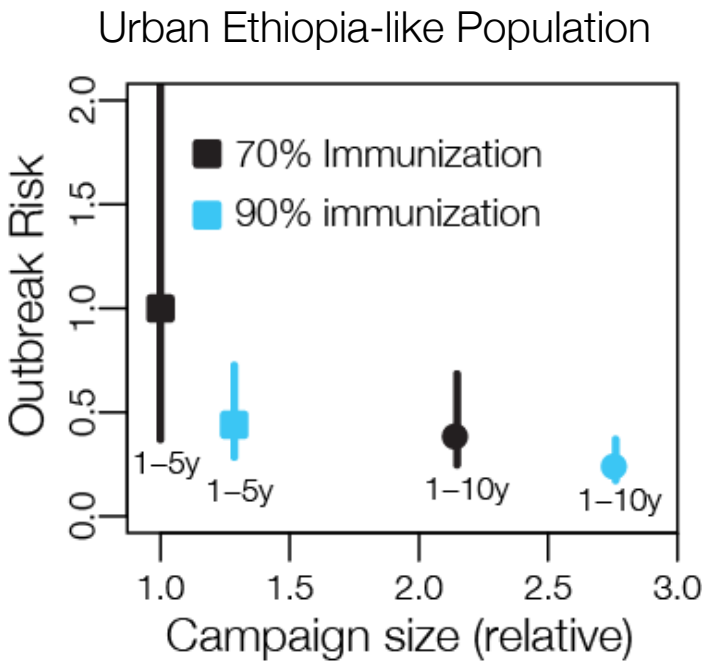


Median global incidence per million population by vaccination strategy, 1985-20014

Results: SIAs to Maintain Herd Immunity

- In a setting like urban Ethiopia, where most susceptibility is in children <5y
  - Narrower age range SIAs (<5y) with higher quality (reach 90% of previously-susceptible children) are equally effective as wider age range SIAs (<10y) with moderate quality (reaching 70% of previously-susceptible children)
  - Wider target age range campaigns require more doses per coverage level



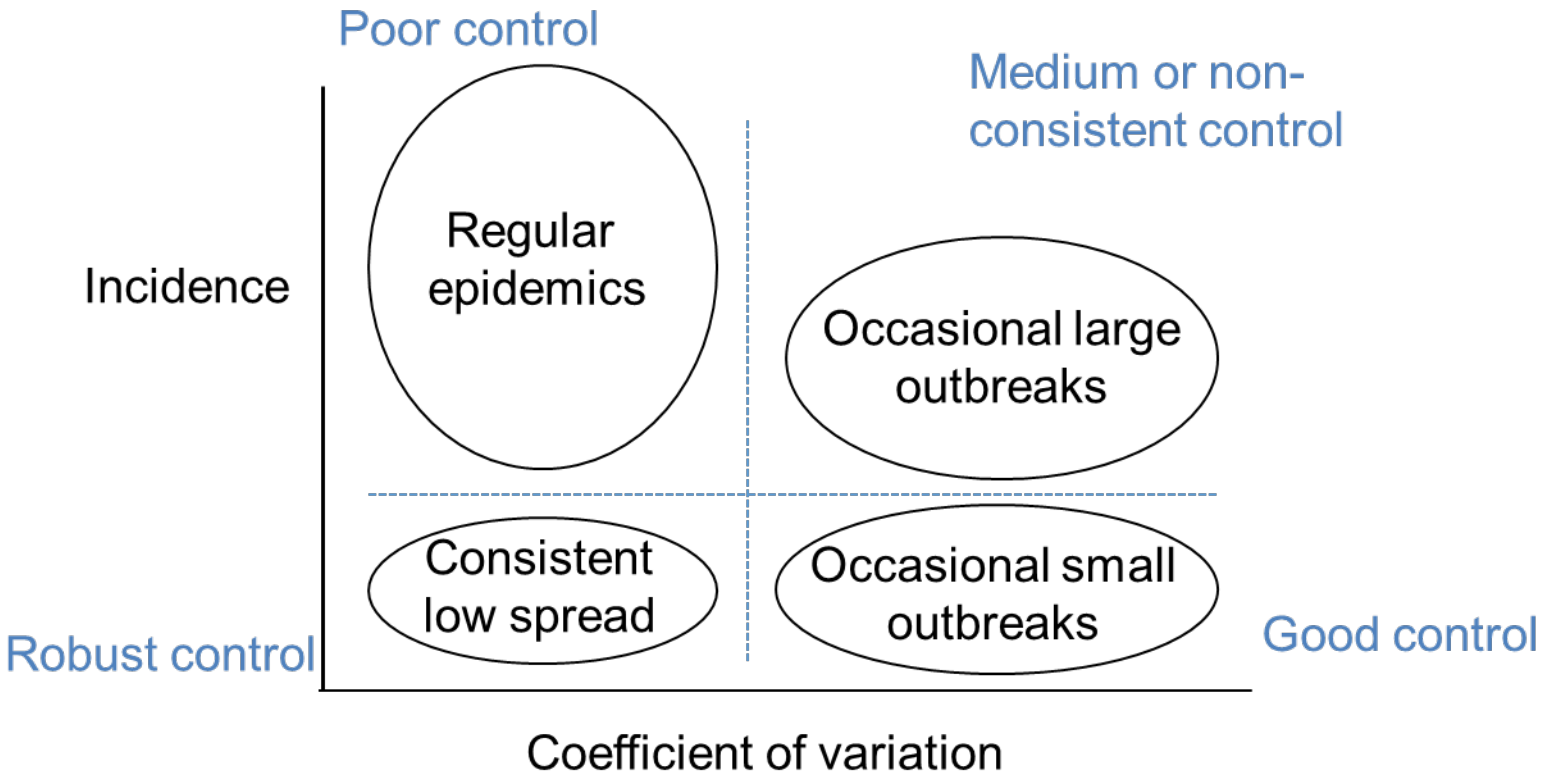


Conclusions

Maintaining herd immunity:

- When susceptibility is mostly in <5y, follow-up SIAs targeting children < 5y can maintain herd immunity when they reach high coverage in unvaccinated children in SIAs
- Where high quality <5y follow-up SIAs are difficult to achieve, targeting children <10y can achieve similar effect
- Repeated follow-up SIAs targeting children <15y have little marginal impact on outbreak risk

Taxonomic Approach



Conclusions – taxonomy approach

- Looking only at the current or past age distribution of cases (current approach) may not be as effective as basing SIA target age ranges on predicted age group likely to have immunity gaps in the future
  - Using the current approach, SIAs have targeted only younger ages as they experience the highest incidence
  - May be missing pockets of susceptibility in older age groups.
  - Current approach did not predict the large multi-country outbreak in 2009-2011 affecting children >5 years of age.
- As countries move to higher coefficient of variation, they are more likely to have susceptibility in older ages.

Comparison of outcome of simplified rubella algorithm

Rationale for algorithm

- To simplify how to determine the appropriate age range for a Rubella containing SIA

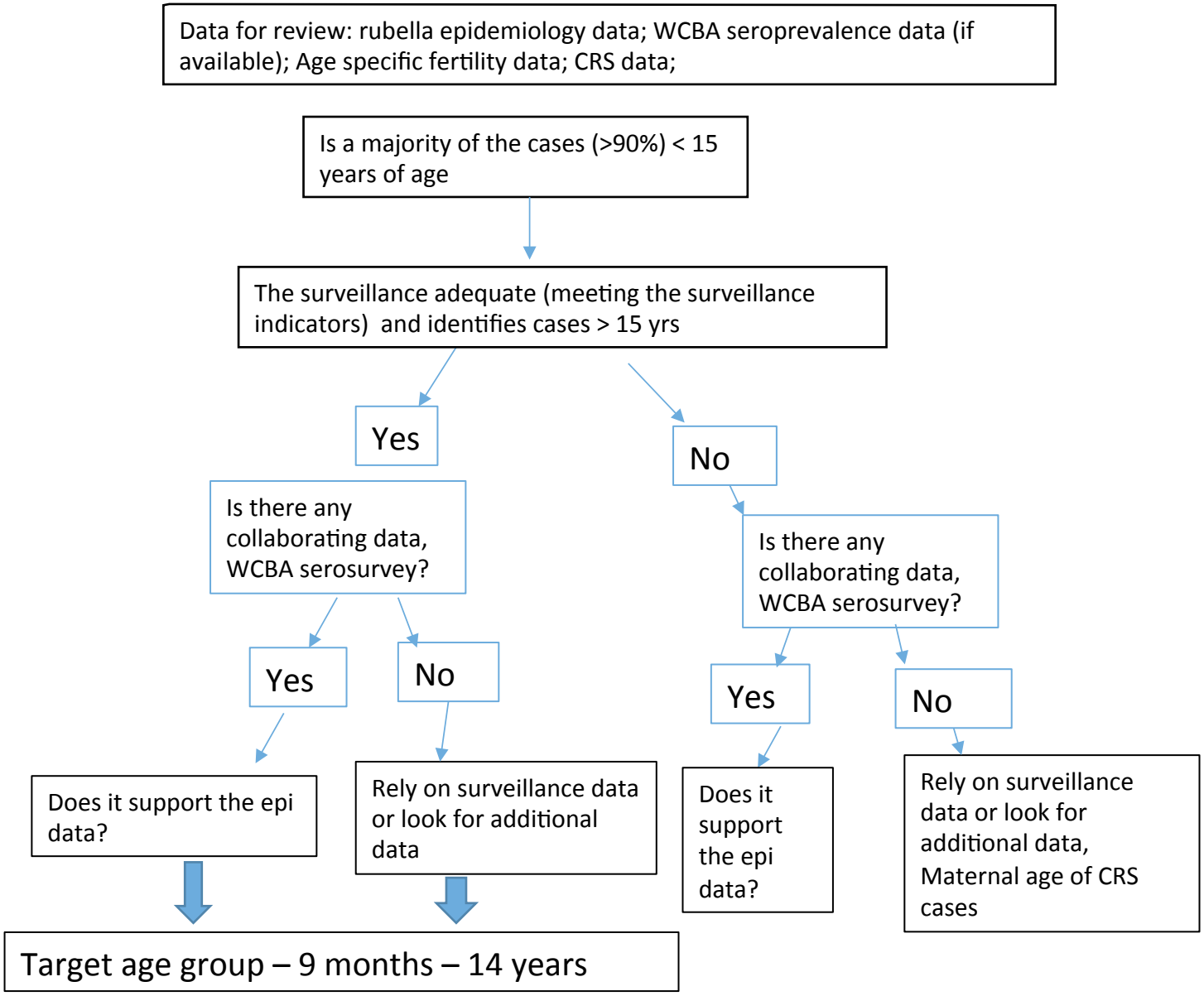
Important questions:

- When introducing RCV: what criteria would require targeting >15y?
- In the presence of outbreaks, what criteria would be used to determine the target age group?

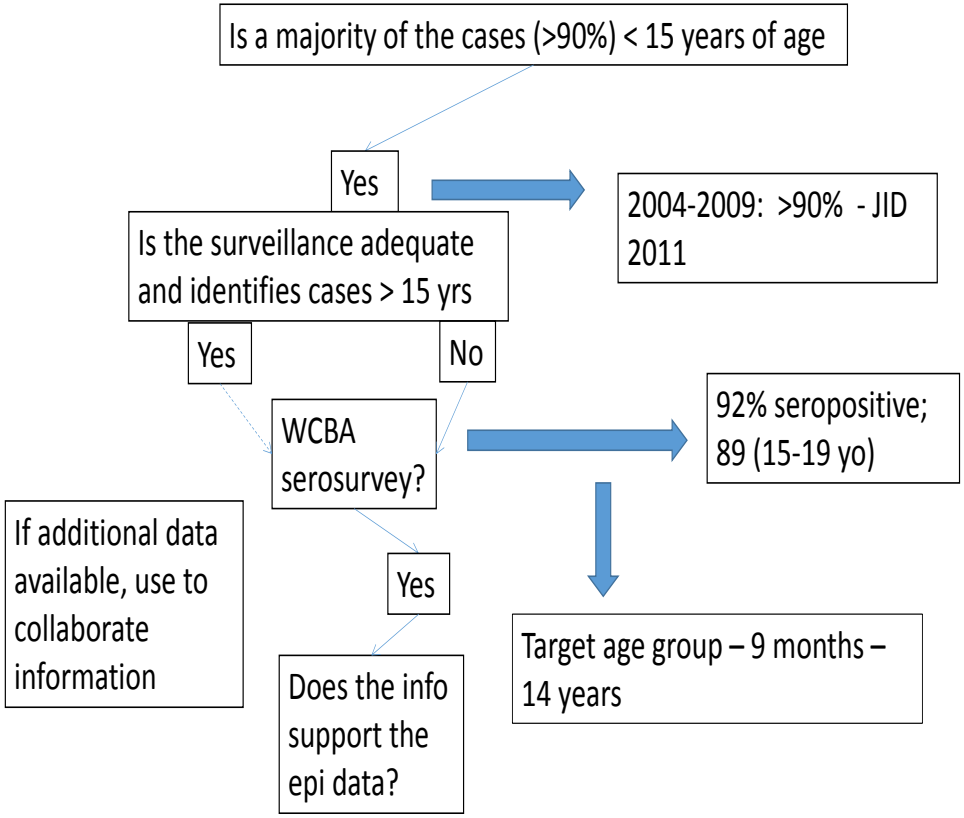
An algorithm developed to guide programs

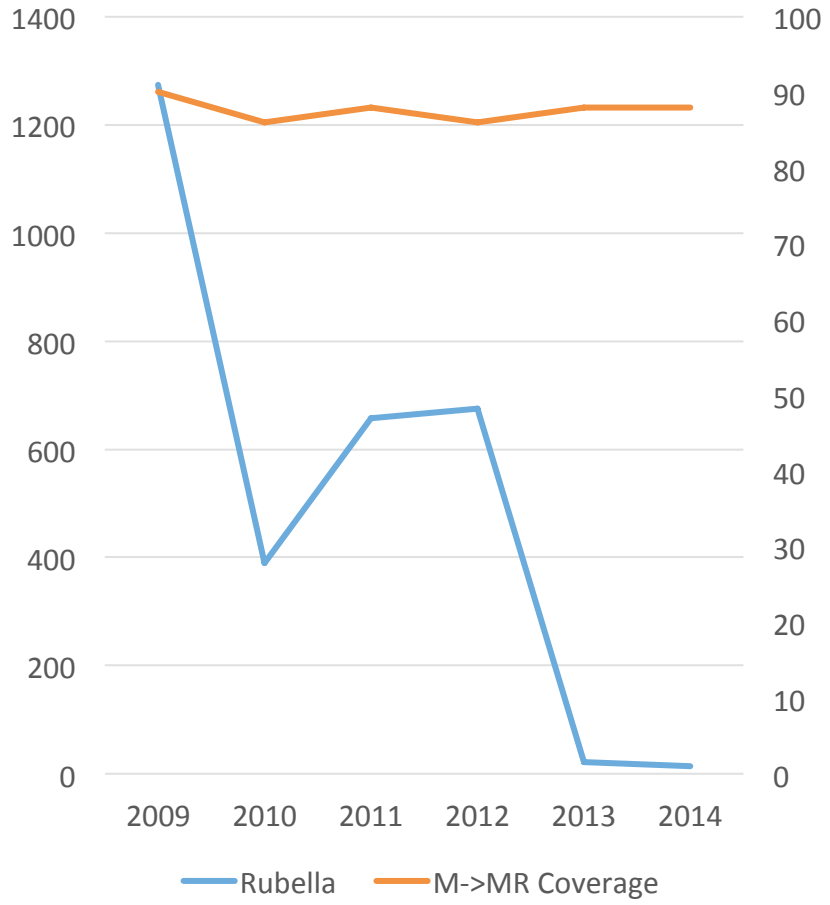
- Immunity in WCBA >=80%, the initial MR catch-up SIA does *not* need to target >15y
- Immunity in WCBA <80% the catch-up SIA probably *should* target men and women >15y

Algorithm to assess need to target >15 years in rubella introduction SIA



Nepal – algorithm and outcome





Conclusion – rubella algorithm

- Simplified algorithm can be used by countries to determine their appropriate age range for introduction of rubella-containing vaccine
- 80% immunity among women of child bearing age appears to be a reasonable cut-off for determining the age range as <15 years
- Validation of algorithm
  - Monitoring countries that based strategies on the 2011 position paper
  - Use dynamic disease models to validate algorithm recommendations
- Algorithm for measles also needed
- Need an integrated algorithm for measles and rubella

Next steps for work on M, MR SIA Target Age Range

- Multi-country analysis of the impact of SIA strategies and the comparison of surveillance and susceptibility data are still at an early stage.
- Mathematical modeling shows some interesting early results
  - Narrower target age range effective when high (≥90%) proportion of susceptibles immunized
  - Wider target age range equally effective when SIAs can reach <90% of susceptibles, but less efficient
- Taxonomy using adjusted incidence and coefficient of variation of incidence looks promising to help predict when significant susceptibility exists in older age groups.
- In selected countries an algorithm to guide inclusion of older age groups in introductory MR SIAs appears to result in very low rubella incidence.
  - Additional examples and modelling needed to confirm applicability of the algorithm and adjust its parameters.
  - Need a similar algorithm for inclusion of older (>5y) age groups in measles SIAs and to have an integrated measles-rubella approach.

Summary

1. Under what epidemiological circumstances is it recommended to give a zero dose of MCV to infants <9 months of age?

   For decision: 3 draft recommendations

2. How can existing data from vaccination and surveillance be used to determine the target age range for a measles or MR SIA needed to prevent an outbreak or stop transmission?

   For discussion: approach being taken and next steps