

# Measles in infants less than 6 months of age and effectiveness and safety of vaccination.

Dr. N.S.Crowcroft on behalf of the SAGE Measles and Rubella working group  
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SAGE, 19<sup>th</sup> October 2017

# Background (1)

- Countries are experiencing measles outbreaks with high incidence in children < 6 months of age.
- A systematic literature review of effects and safety of measles vaccination < 9 months of age was conducted in 2015.
- SAGE (October 2015) recommended that infants from 6 months of age receive a dose of MCV in the following circumstances:
  - during a measles outbreak as part of intensified service delivery;
  - during SIAs in settings where the risk of measles among infants remains high (e.g. in endemic countries experiencing regular outbreaks);
  - for internally displaced populations and refugees, and populations in conflict zones;
  - for individual children at high risk of contracting measles
  - for infants travelling to countries experiencing measles outbreaks;
  - for infants known to be HIV-exposed.

## Background (2)

- MCV administered at 6 months of age should be considered a supplementary dose and recorded on the child's vaccination record as "MCV0".
- This policy guidance protects infants from 6 months.
- Question remains on how to protect infants < 6 months.
- Two approaches to this question:
  - Analysis of the epidemiology of measles in infants < 6m.
  - Systematic review of vaccine immunogenicity, effectiveness and safety when given to infants < 6 months.

# **Epidemiology of Measles in Infants Younger Than 6 Months: Analysis of Surveillance Data 2011-2016**

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## Research Questions

- What is the burden of measles epidemiology among infants <6 months old?
- What epidemiological circumstances and country situations are associated with a significant proportion of children <6 months old affected?

# Analytic Methods

1. Epidemiologic analysis: assess the scale of measles epidemiology among infants <6 months 2011-2016
  - Descriptive analysis of infant cases and the country contexts
    - Absolute numbers of cases
    - As a proportion of all measles cases
    - Age-specific incidence
2. Comparative study: bivariate and multivariate regression analyses

- Evaluate associations between country/programmatic characteristics and measles cases among infants <6 months

Dependent Variable	Regression Model
proportion <6 months (continuous)	beta
high vs. low proportion <6 months	logistic
age-specific incidence (continuous)	Poisson

- Independent variables: region, income classification, MCV1 and MCV2 coverage and programmatic characteristics, SIAs, population density, birth rate, total incidence

# Inclusion & Exclusion Criteria

## Inclusion criteria:

Countries with case-based measles surveillance data available for 2011-2016 (2014-2016 for SEAR) at WHO-HQ (n = 149)

## Exclusions:

### Excluded:

- <30 confirmed cases reported in case-based data (n=32 countries excluded)
- Countries that only report ages in years (n=36)
  - Most EUR countries (n=30 countries excluded; except for Armenia, Azerbaijan, Belarus, Georgia, Israel, Russia, Tajikistan, Turkey, and Uzbekistan)
  - All remaining SEAR countries except India (n=6 countries excluded)
- Hong Kong not a MS so WUENIC estimates and population data not available (n=1)

## Countries included in epidemiologic analysis (n = 80)

- All regions represented, except only 1 country in SEAR and only 9 countries in

### Excluded for regression models:

- India (cases reported in case-based data not representative of all cases)

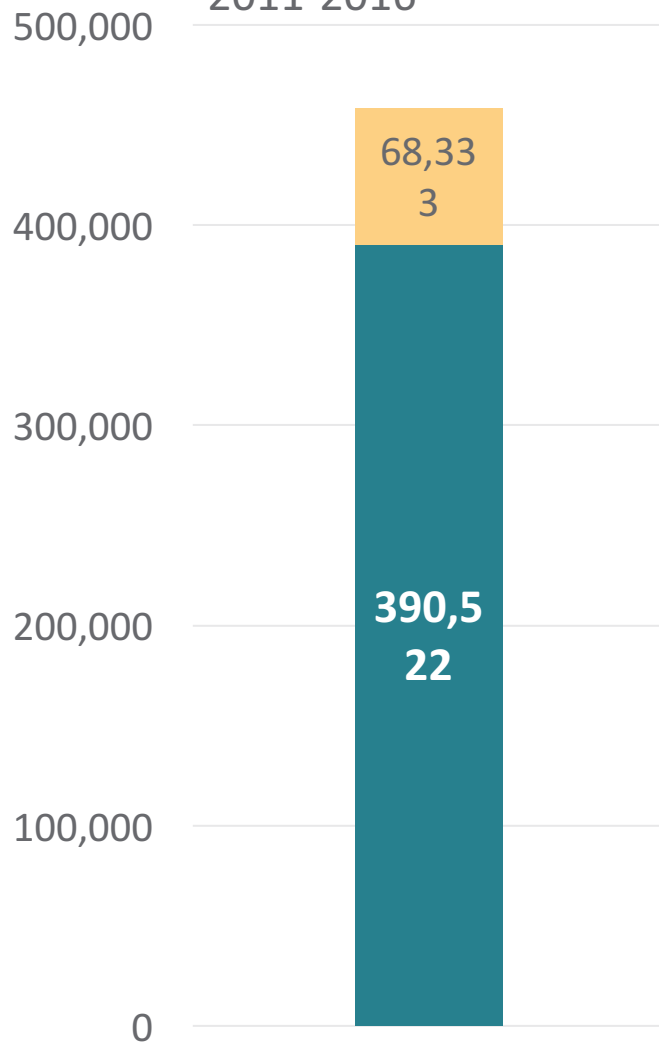
# Limitations

- A lot of data excluded because of incomplete age data
  - Whole countries: 30 EUR countries, 6 SEAR countries + India for regression models
  - Including countries with recent large outbreaks – Romania
- Ecologic analysis – aggregate data only allowed for analysis of 6 years grouped together, using the unit of observation as the country (not individual cases)
- Small sample size (n=79 countries)
- Questionable quality of some of the data, and no way to measure and control for poor quality (e.g., quality of coverage data, variable surveillance sensitivity)
- Associational, not causal

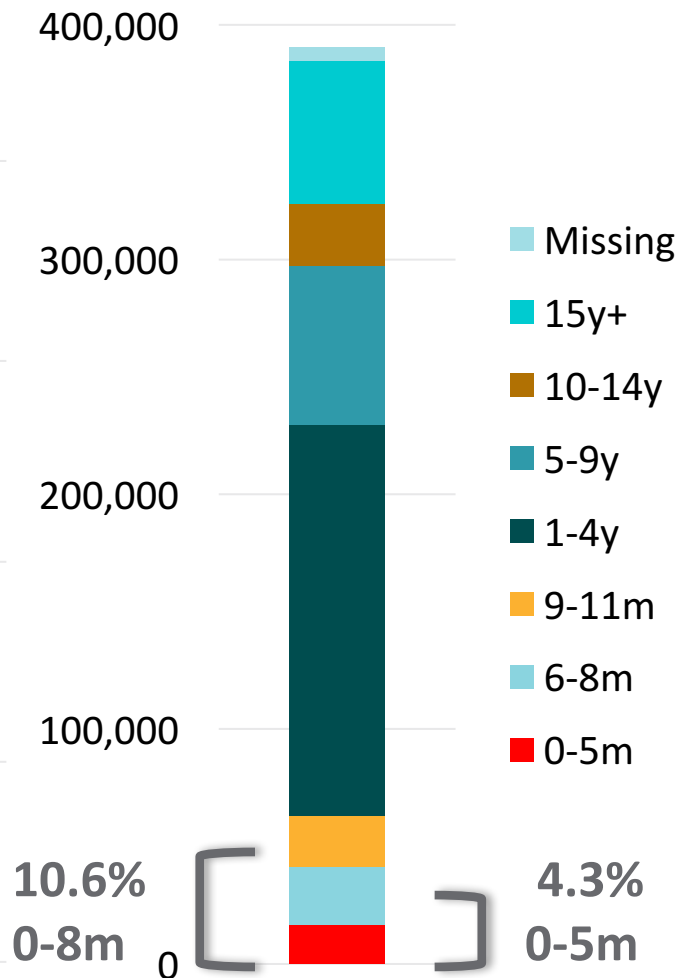


# Confirmed Measles Cases, 2011-2016

Measles cases, all ages,  
2011-2016



Measles cases, by age,  
2011-2016 (n=390,522)

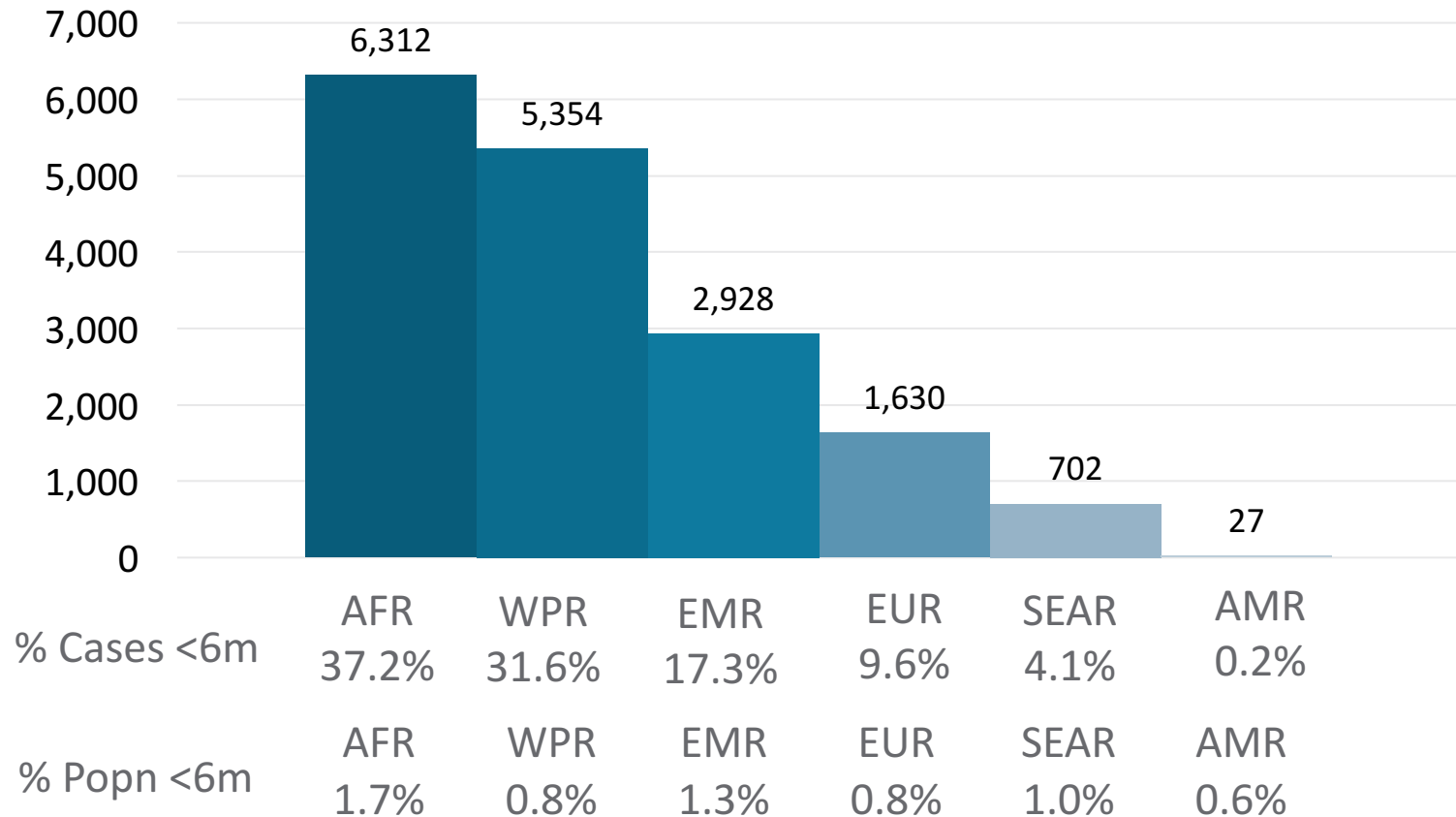


- 390,522 confirmed\* measles cases of all ages, 2011-2016
- 68,333 cases excluded in EUR/SEAR countries
- 16,953 (4.3%) <6m

\*laboratory-confirmed and epi-linked; 30 EUR and 10 SEAR countries not included.

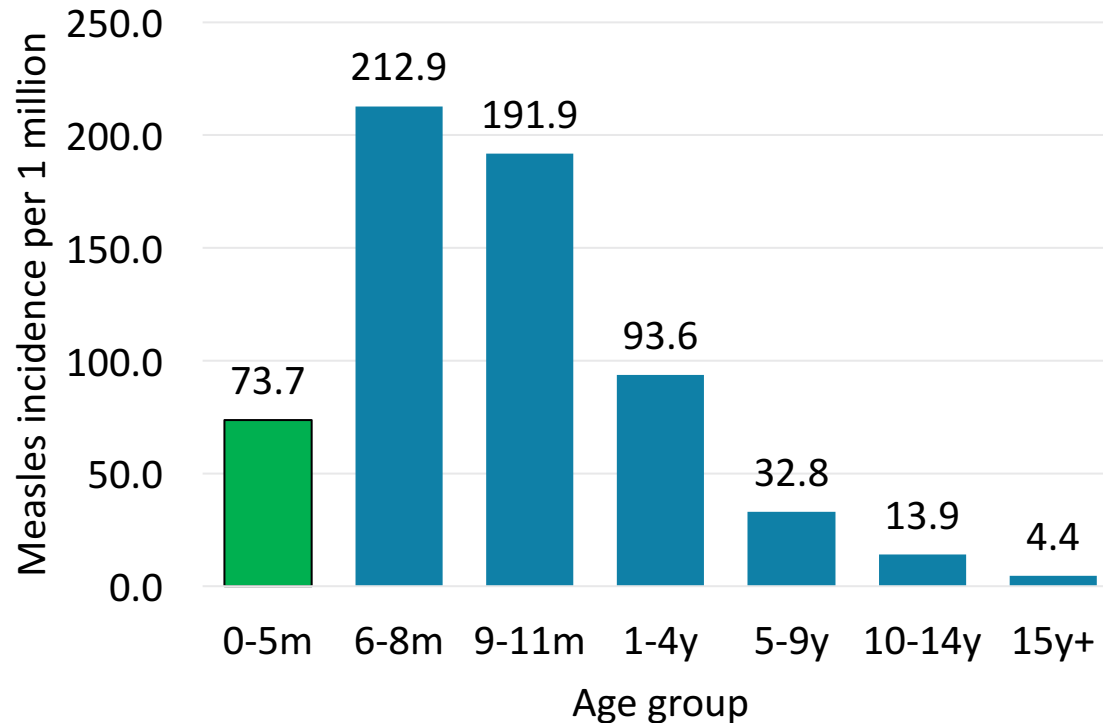
# Cases <6 Months by Region

16,953 (4.3%) Measles cases <6 months, by region, 2011-2016\*



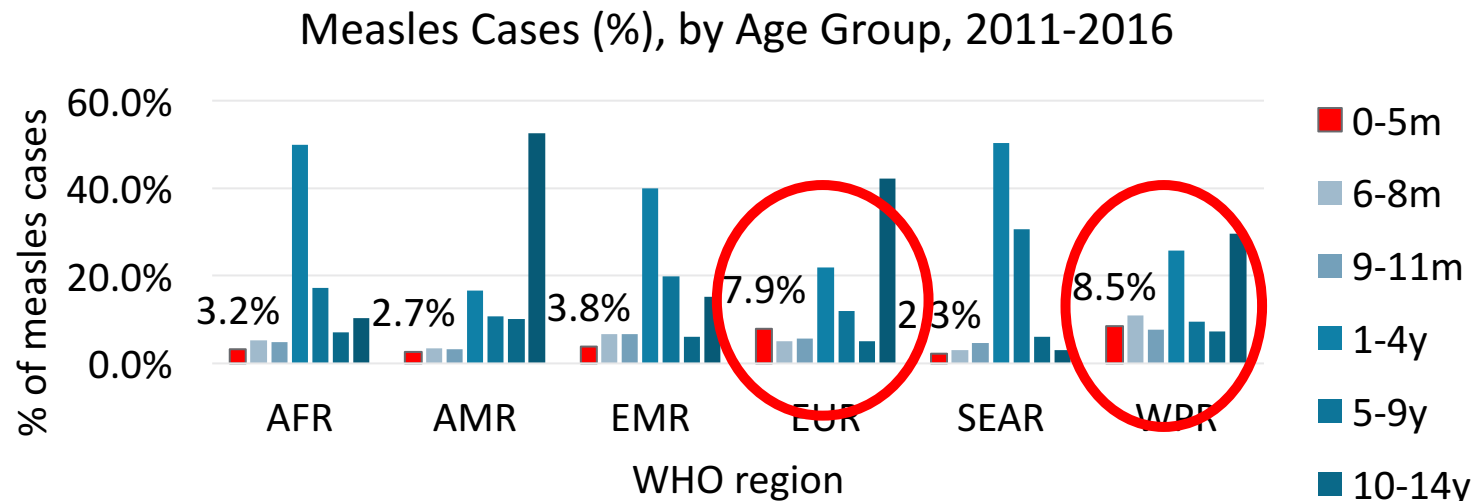
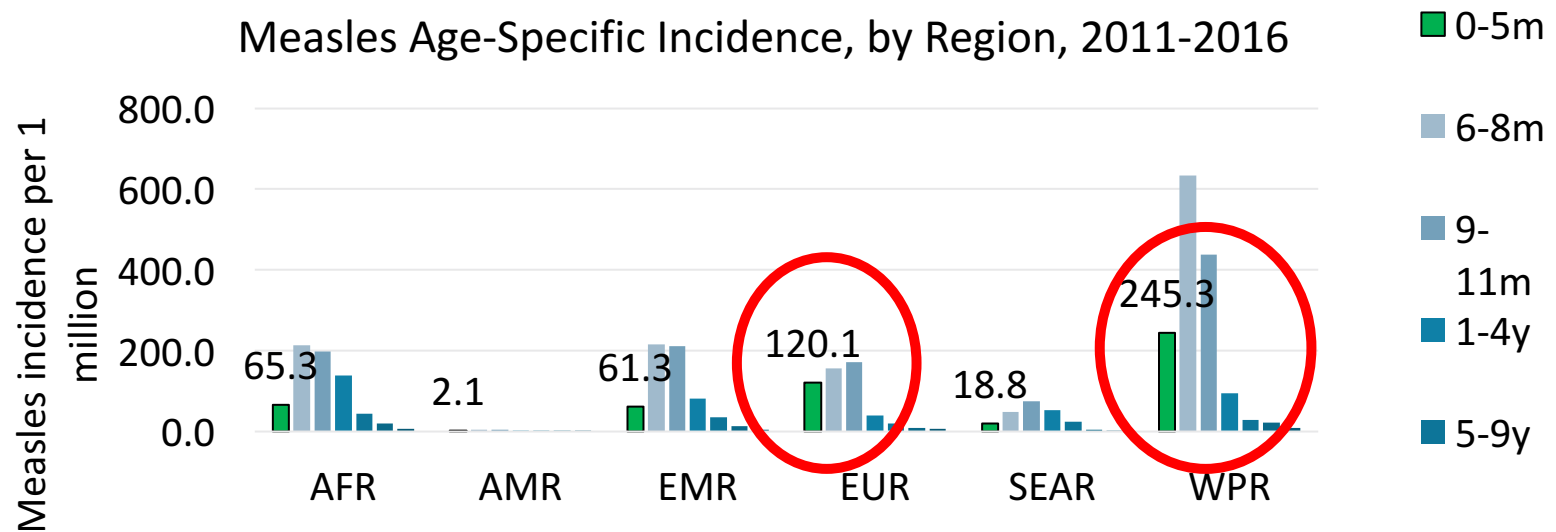
Majority of cases <6 months in AFR (37%) and WPR (32%) countries  
SEAR and EUR under-represented because of missing age data

# Measles Age-Specific Incidence, by age group, 2011-2016



- Cases <6 months comprised 4.3% of all cases
- Incidence in this age group: 73.7 per million
- Higher than incidences for 5-9y, 10-14y, and  $\geq 15y$
- Incidence falls after 9 months

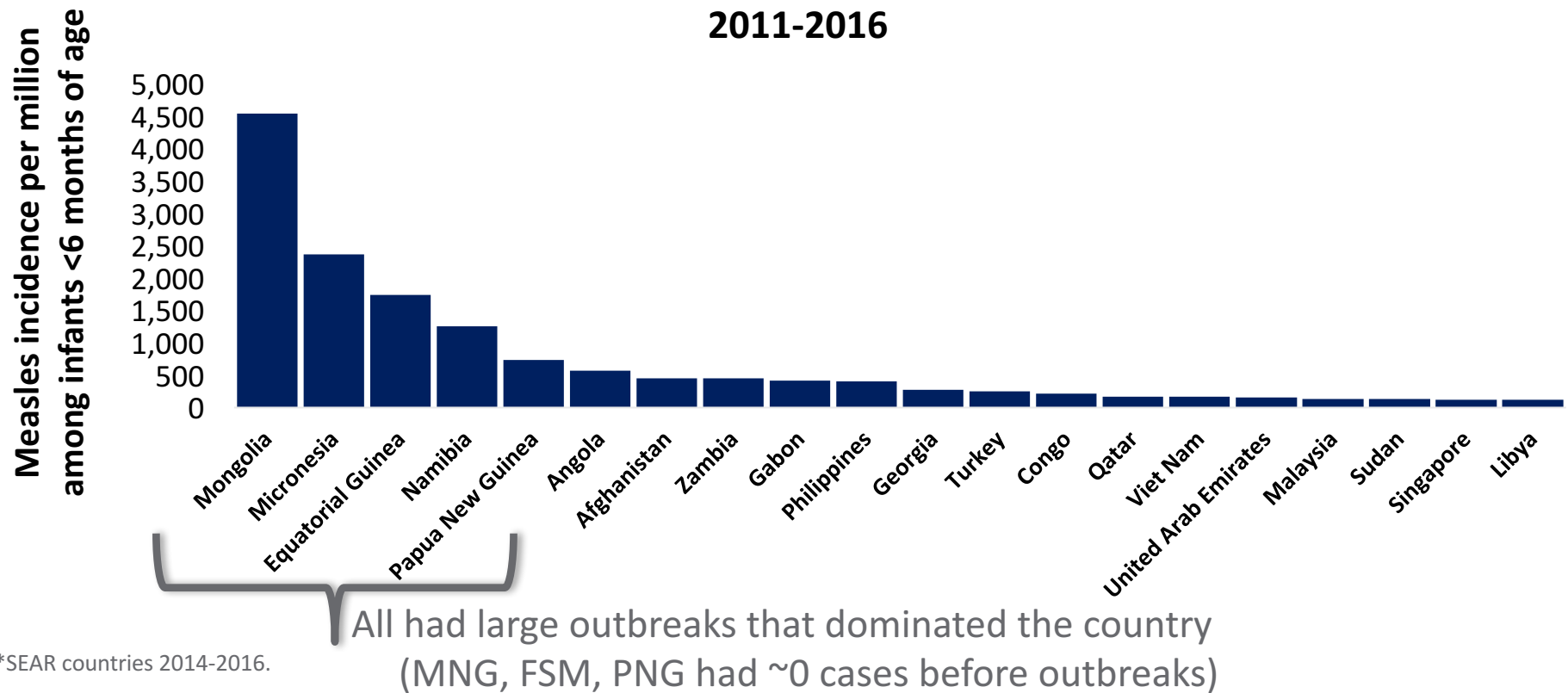
# Comparing 2 different measures: Age-specific incidence and proportion (%) of cases by age



Note that EUR and WPR have **both** highest incidence and % 12

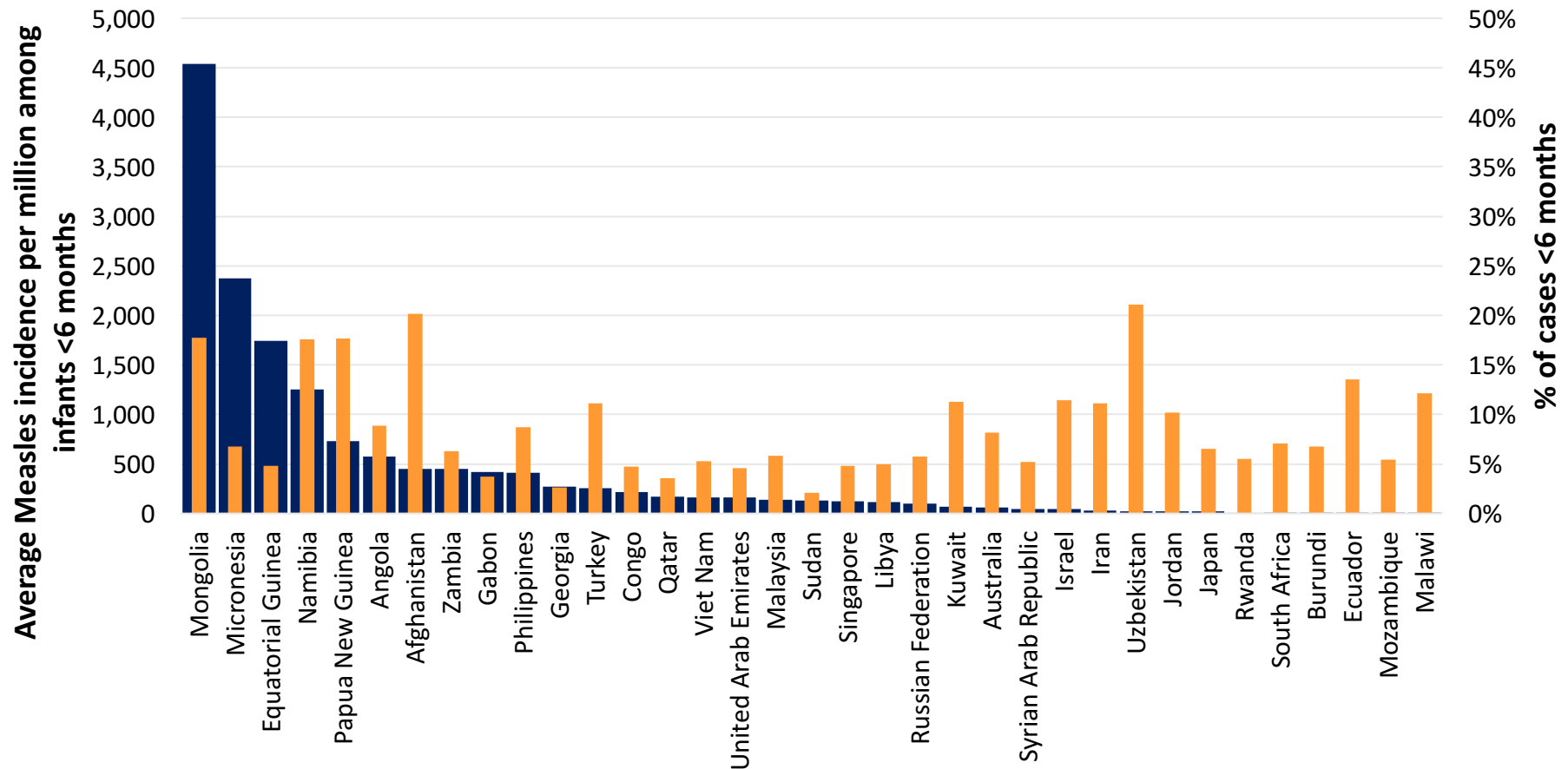
# Countries with Highest Age-Specific Incidence for Infants <6 Months

Measles incidence per million among infants <6 months, top countries, 2011-2016



\*SEAR countries 2014-2016.

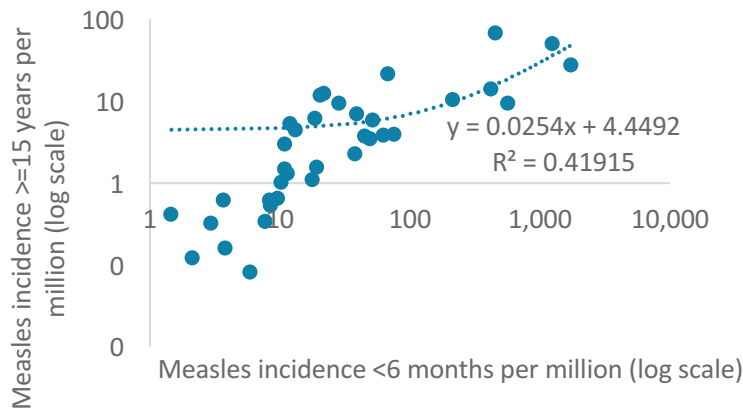
# Measles incidence per million (blue) and proportion of cases (orange) among infants <6 months of age, top countries, 2011-2016



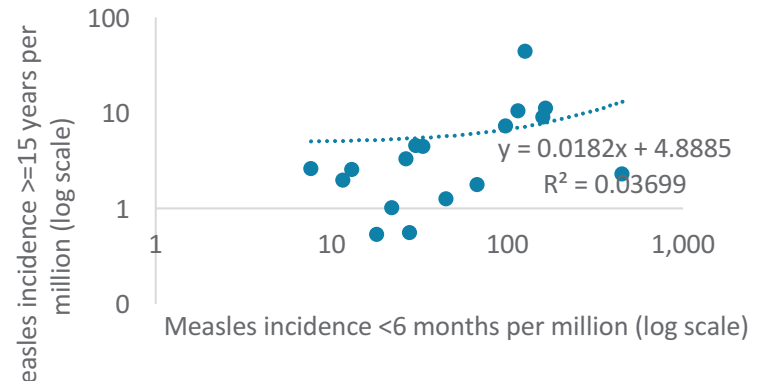
- Countries with the highest incidences of measles in infants <6 months *do not necessarily* have the highest proportions of cases among infants <6 months, but many do
- Driven by high overall incidence years, outbreaks

# Correlation Between Incidence <6 Months and Incidence >15 Years, Stratified by Region

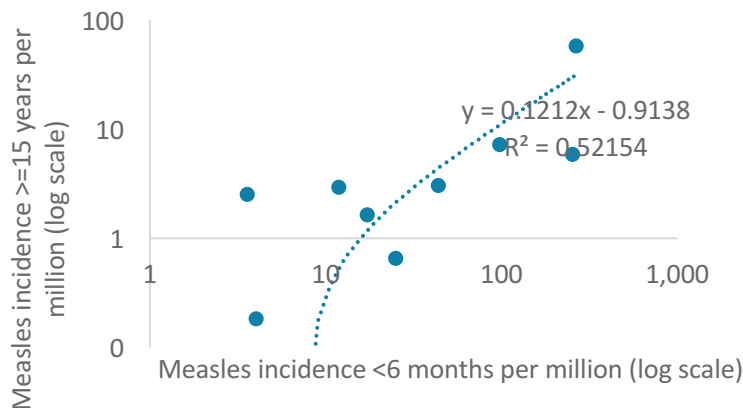
Correlation between incidence <6 months and incidence >15 years, **African region**



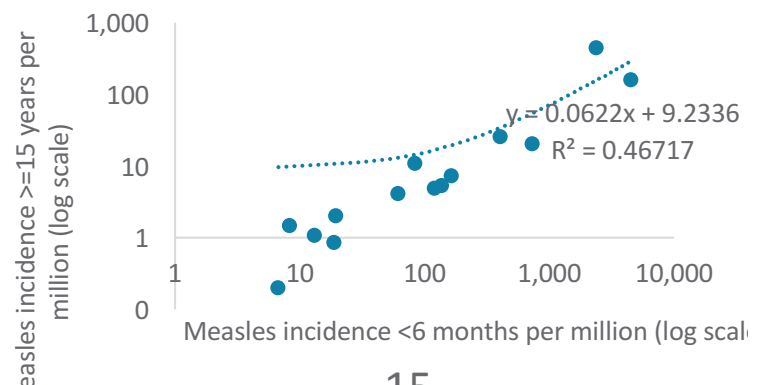
Correlation between incidence <6 months and incidence >15 years, **Eastern Mediterranean region**



Correlation between incidence <6 months and incidence >15 years, **European region**



Correlation between incidence <6 months and incidence >15 years, **Western Pacific region**



# Summary of epidemiological analysis

- During 2011-2016, almost 17,000 confirmed measles cases reported among infants <6 months
  - Underestimate since 30 EUR and 6 SEAR countries not included, includes lab-confirmed and epi-linked cases only
  - Majority of cases were in AFR and WPR countries
  - Highest age-specific incidence <6 months in WPR and EUR
- Half of countries had at least 3.6% of their cases among infants <6 months (compared to median 1.4% of the population is <6 months) → disproportionately affected
- WPR and EUR highest proportion of cases aged <6 months AND aged 15+ years
- Incidence increases with age corresponding to declining maternally derived immunity, and declines after 9 month MCV1



# **MCV1 below 6 months of age Benefits and Risks**

Laura Nic Lochlainn and Susan Hahné

**RIVM - Centre for Infectious Disease Control  
The Netherlands**

# Review questions

- Is the effect of MCV1 given to children <6 months of age equal or less than when administered at 6-8 months of age?
  - Immunogenicity
  - Duration of immunity
  - Efficacy/effectiveness
- Does a dose of MCV1 administered <6 months of age blunt the immune response to a subsequent dose of measles vaccine?
- Is the safety profile for infants vaccinated with MCV1 at <6 months of age comparable with infants vaccinated with MCV1 at 6-8 months of age?

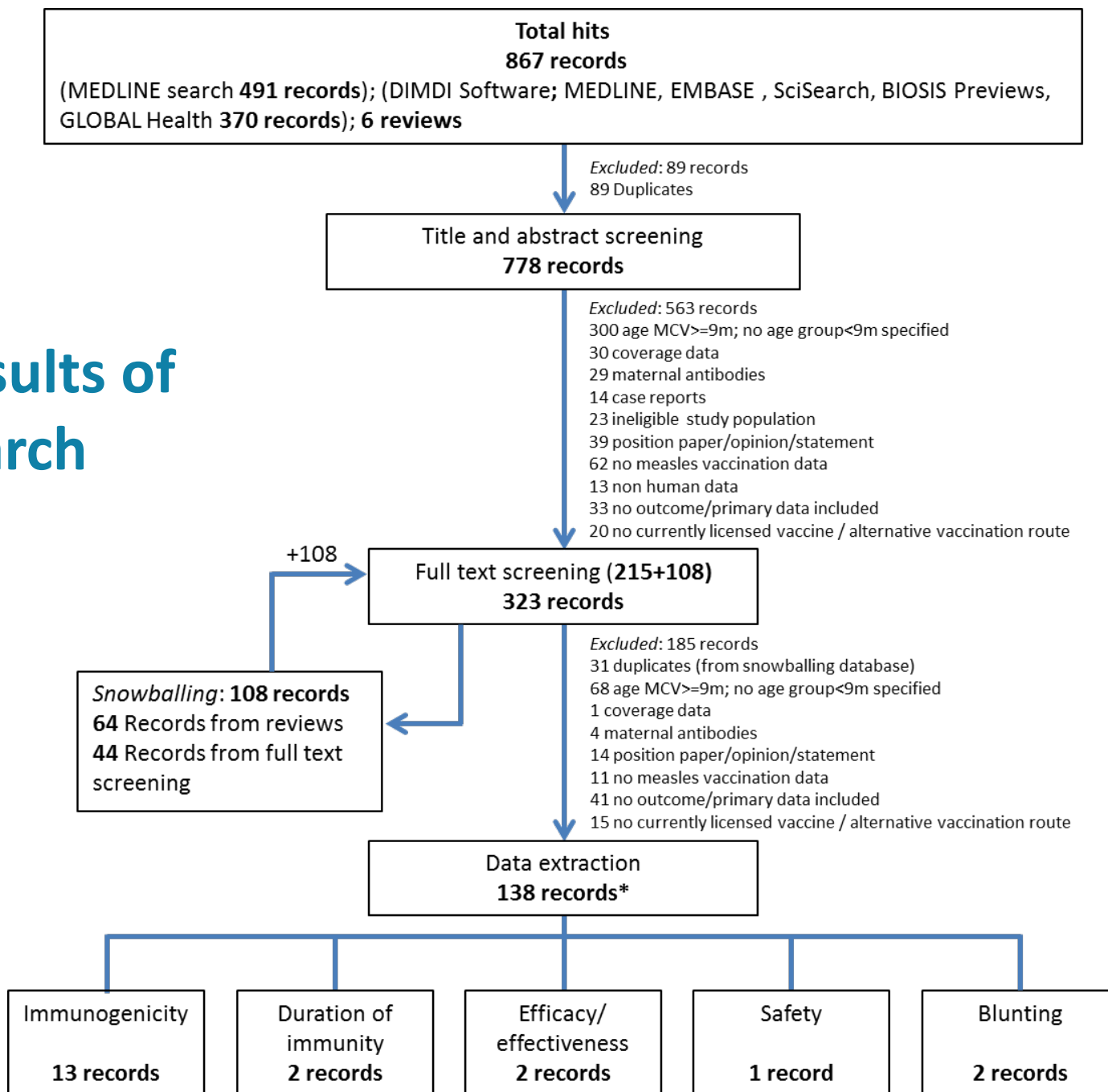
# Methods: Analyses

- Meta-analyses
  - Random effects meta analyses of continuous outcomes, proportions and within-study comparisons, resulting in forest plots, pooled estimates and heterogeneity indicator I<sup>2</sup> statistic.
  - Vaccine strains analyzed as subgroups.
- Meta-regression
  - Random effects meta-regression to explore whether age at MCV1, vaccine strain and titer, continent, type of test, or decade of study explained heterogeneity between studies.

# Methods: Search

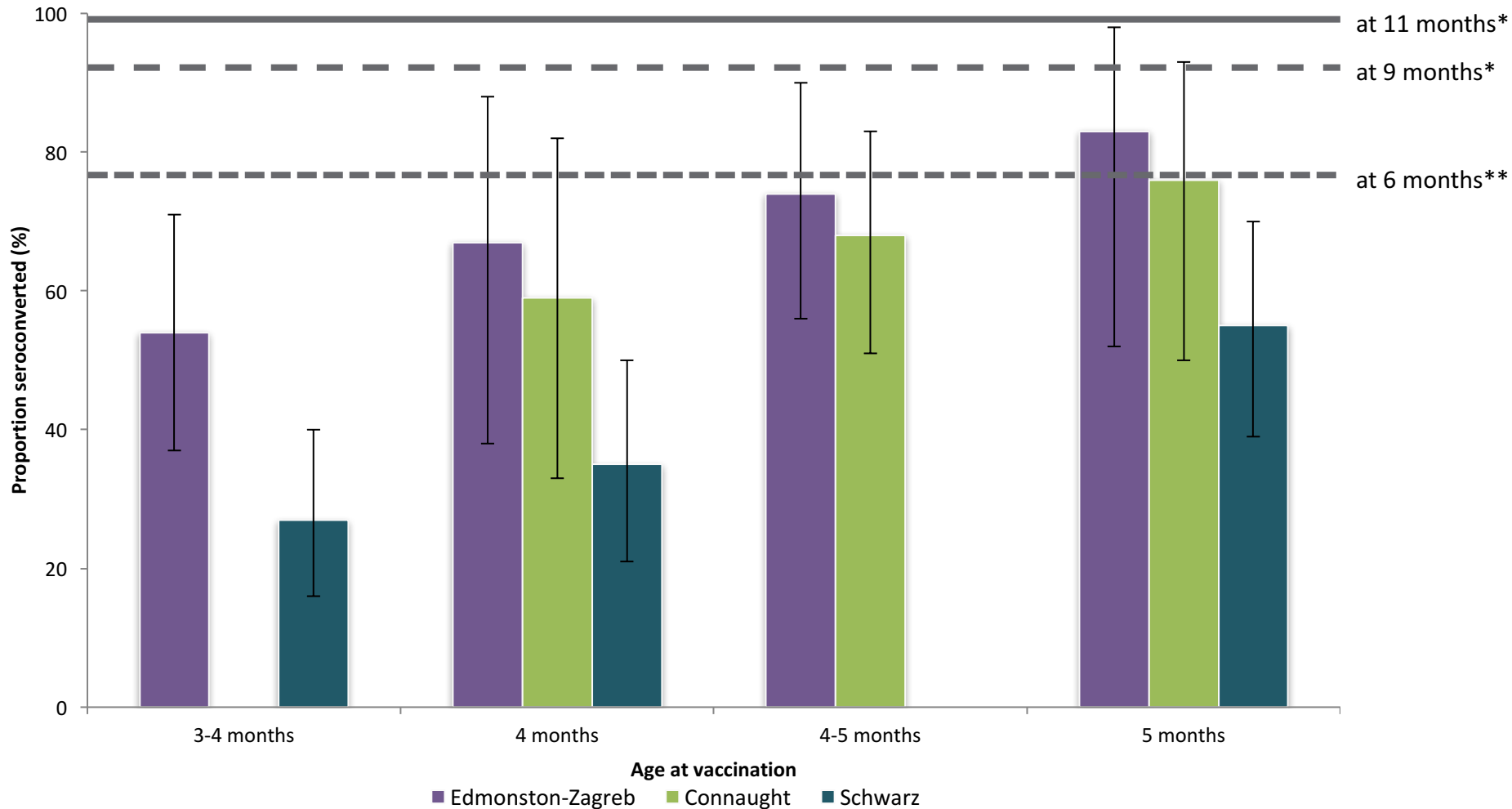
- Dates of search
  - Initial search carried out 01-06-2015 for any articles published in relevant databases
  - Updated search carried out on 13-04-2017 for articles published after 01-01-2015 in relevant databases
- Sources
  - Embase.com (MEDLINE + EMBASE); Scopus; ProQuest (SciSearch, Global Health, BIOSIS Previews); Google scholar; WHO: WHOLIS and IRIS
  - Key reviews: Cutts et al, 1995; Markowitz, 1990; Moss & Scott, 2009; Nic Lochlainn et al, 2015

## Results of search



# Humoral immunity in <6 months

Proportion seroconverted by age of MCV1 and strain

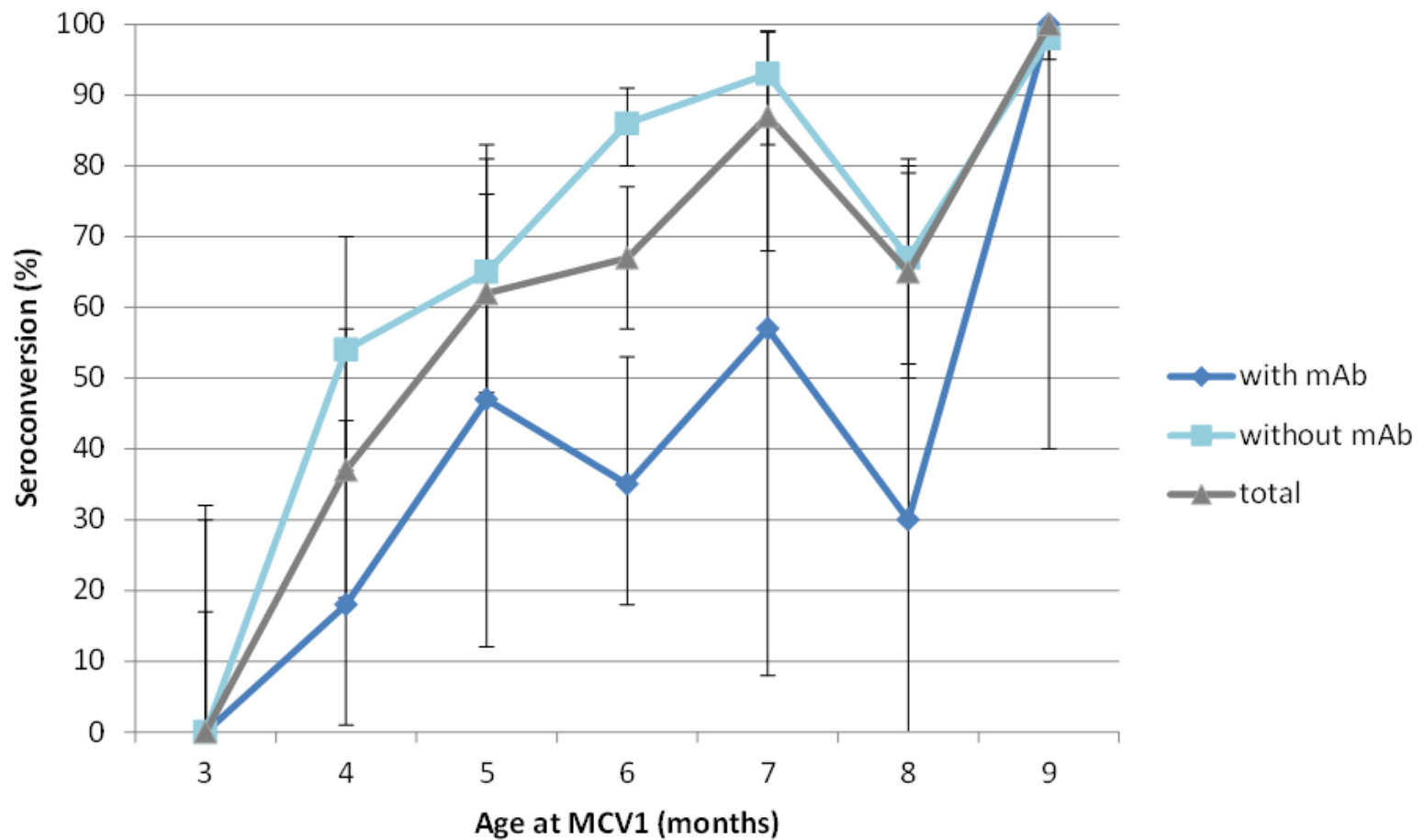


\*Moss & Scott, 2009  
\*\*Nic Lochlainn et al, 2015

# Humoral/cellular immunity

- Increase in proportion seroconverted with age (4-5 months)
  - Dependent on strain
- Duration of immunity (2 studies)
  - Limited number of studies with comparison  $<6$  and  $\geq 6$  months at MCV1
- Cellular immunity
  - Not lower when MCV1  $<6$  months
  - Very limited data (one study)

# Maternal antibodies



Results based on PRNT, HIA and ELISA



## Effectiveness

- Few eligible studies (n=2) with small sample sizes
- VE estimate for MCV1 at 9-11 months: 77% (IQR 62-91%) (Uzicanin et al, 2011)
- VE estimate MCV1 at 6-8 months 61% (95%CI 28-95%) (Nic Lochlainn et al, 2015)

## Blunting

- Limited evidence (2 studies) found high seropositivity (97-98%) although GMTs were lower following MCV1<6 months of age.

# Safety

- Limited number of studies reporting safety (n=2)
- No adverse events following MCV1 below 6 months among 1128 infants
- Observation can be confounded by other causes of rash, fever which are more frequent in younger children: inadequate study designs
- No studies reporting serious adverse events following immunization

## Conclusions of literature review

- Humoral immunogenicity dependent on age of MCV1
  - Increase in proportion seroconverted with age
  - Also dependent on presence of maternal antibodies and vaccine strain (Edmonston-Zagreb strain highest)
- Cellular immunity, vaccine effectiveness and blunting
  - Limited evidence available

## SAGE WG recommendations

- Data from the systematic review is insufficient to recommend vaccination under 6 months of age
- Immunizing infants <6 months would not be a primary strategy as it is not as effective as protecting through herd immunity achieved by high coverage in older age groups
- The current policy statement on vaccination of infants from 6 months is already broad and inclusive
- No need to expand the current recommendations

# Research gaps

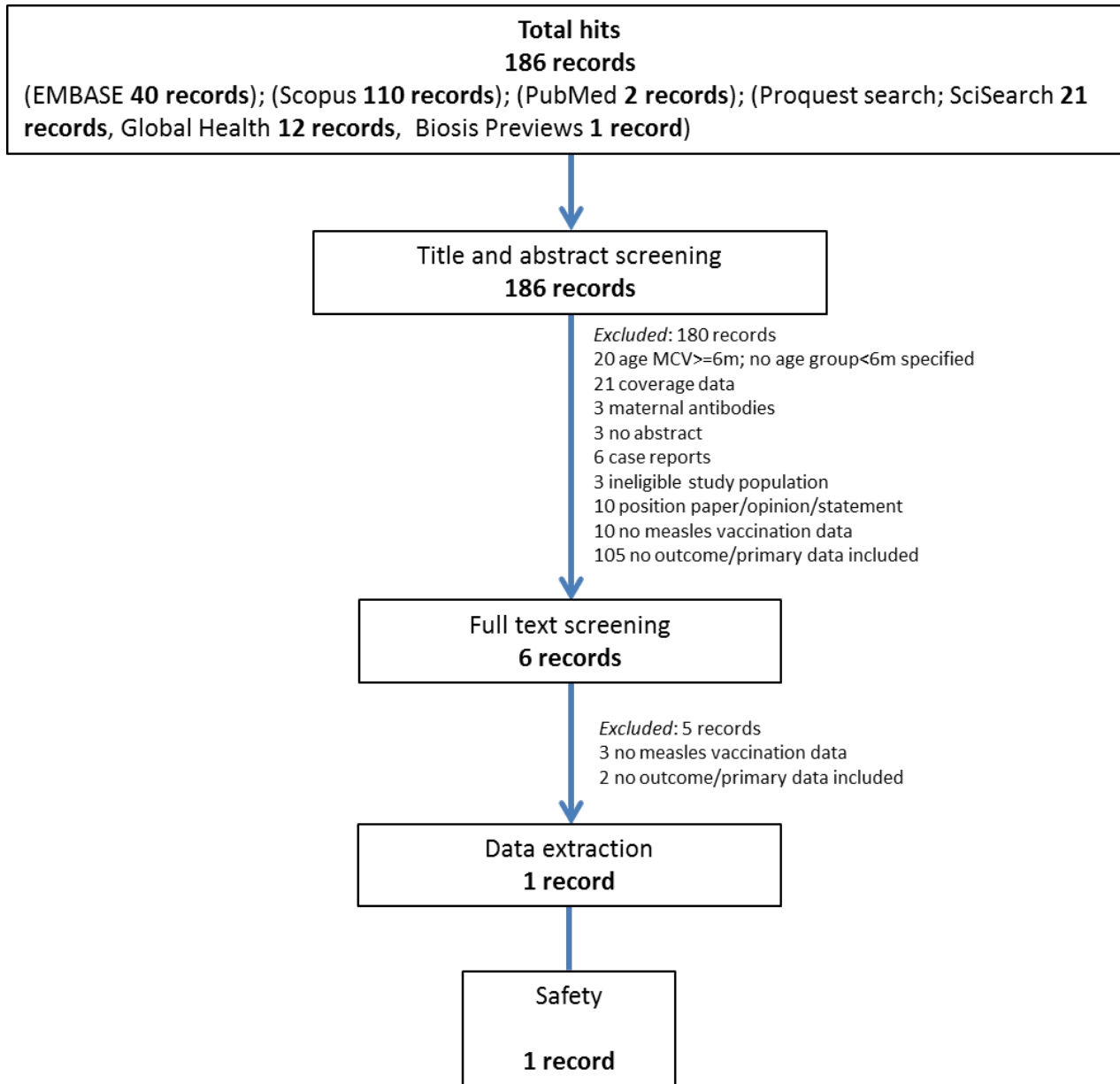
- There is a need to:
  - Address the substantial information gap on transmission sources, disease burden and role of factors such as blunting and maternal immunity in infants under 6 months
  - Better understand the transmission drivers (e.g. young adults or parents) to enable more effective targeting
  - Identify ways to improve data quality and tools to be able to interpret data according to data quality, completeness of surveillance and other contextual factors at country and region levels
  - Conduct clinical trials in infants <6 months to improve the evidence concerning effectiveness, safety and long term effects on the effectiveness of subsequent MCV doses (i.e. MCV1 and MCV2)

## **SAGE Measles and Rubella Working Group**

- Members: Narendra Arora, Natasha Crowcroft, David Durrheim, Ilesh Jani, Jalila Jawad, Mark Jit, Bill Moss, Walter Orenstein, Susan Reef, Helen Rees, Nikki Turner (Chair).
- WHO: Alya Dabbagh, Minal Patel, Katrina Kretsinger, Thomas Cherian.

# Extra Slides

# Updated search results





# Data Sources

- Case-based data available at WHO-HQ for year of onset 2011-2016
  - Except SEAR is 2014-2016
  - Age-specific incidence is 6-year average, except SEARO is 3 years
  - Percentage of cases <6 months, calculated using denominator cases with known age (cases missing age are excluded from denominator)
- Population: UNDP estimates for year 2015 (revision 2015)
- Income classification: World Bank country classification (2011)
- Vaccine coverage: WUENIC, 5-year average (2007-2011)
- Vaccination schedule: as reported in 2016 JRF submission
- Vaccination introduction: WHO spreadsheet
- SIA information: WHO spreadsheet
- Population density: persons per km<sup>2</sup>; UNDP estimates for year 2011
- Birth rate: per 1,000 population; UNDP estimates for years 2010-2015