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, 19th 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

Jennifer L. Kriss, PhD, MPH
CDC/Global Immunization Division
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

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Regression Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>proportion &lt;6 months (continuous)</td>
<td>beta</td>
</tr>
<tr>
<td>high vs. low proportion &lt;6 months</td>
<td>logistic</td>
</tr>
<tr>
<td>age-specific incidence (continuous)</td>
<td>Poisson</td>
</tr>
</tbody>
</table>

• 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:
- <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)

*SEAR: India; EUR: Armenia, Azerbaijan, Belarus, Georgia, Israel, Russian Federation, Tajikistan, Turkey, Uzbekistan.
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

- 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*

<table>
<thead>
<tr>
<th>Region</th>
<th>% Cases &lt;6m</th>
<th>% Popn &lt;6m</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td>37.2%</td>
<td>1.7%</td>
</tr>
<tr>
<td>WPR</td>
<td>31.6%</td>
<td>0.8%</td>
</tr>
<tr>
<td>EMR</td>
<td>17.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>EUR</td>
<td>9.6%</td>
<td>0.8%</td>
</tr>
<tr>
<td>SEAR</td>
<td>4.1%</td>
<td>1.0%</td>
</tr>
<tr>
<td>AMR</td>
<td>0.2%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

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 >15y
- Incidence falls after 9 months
Comparing 2 different measures: Age-specific incidence and proportion (%) of cases by age

Measles Age-Specific Incidence, by Region, 2011-2016

Note that EUR and WPR have both highest incidence and %
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.

All had large outbreaks that dominated the country (MNG, FSM, PNG had ~0 cases before outbreaks)
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**

\[ y = 0.0254x + 4.4492 \]

\[ R^2 = 0.41915 \]

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

\[ y = 0.0182x + 4.8885 \]

\[ R^2 = 0.03699 \]

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

\[ y = 0.1212x - 0.9138 \]

\[ R^2 = 0.52154 \]

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

\[ y = 0.0622x + 9.2336 \]

\[ R^2 = 0.46717 \]
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 I2 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

Total hits
867 records
(MEDLINE search 491 records); (DIMDI Software; MEDLINE, EMBASE, SciSearch, BIOSIS Previews, GLOBAL Health 370 records); 6 reviews

Excluded: 89 records
89 Duplicates

Title and abstract screening
778 records

Excluded: 563 records
300 age MCV>=9m; no age group<9m specified
30 coverage data
29 maternal antibodies
14 case reports
23 ineligible study population
39 position paper/opinion/statement
62 no measles vaccination data
13 non human data
33 no outcome/primary data included
20 no currently licensed vaccine / alternative vaccination route

Full text screening (215+108)
323 records

Excluded: 185 records
31 duplicates (from snowballing database)
68 age MCV>=9m; no age group<9m specified
1 coverage data
4 maternal antibodies
14 position paper/opinion/statement
11 no measles vaccination data
41 no outcome/primary data included
15 no currently licensed vaccine / alternative vaccination route

Snowballing: 108 records
64 Records from reviews
44 Records from full text screening

Data extraction
138 records*

Immunogenicity
13 records

Duration of immunity
2 records

Efficacy/effectiveness
2 records

Safety
1 record

Blunting
2 records
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 ≥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

Total hits
186 records
(EMBASE 40 records); (Scopus 110 records); (PubMed 2 records); (Proquest search; SciSearch 21 records, Global Health 12 records, Biosis Previews 1 record)

Title and abstract screening
186 records

Excluded: 180 records
20 age MCV>6m; no age group<6m specified
21 coverage data
3 maternal antibodies
3 no abstract
6 case reports
3 ineligible study population
10 position paper/opinion/statement
10 no measles vaccination data
105 no outcome/primary data included

Full text screening
6 records

Excluded: 5 records
3 no measles vaccination data
2 no outcome/primary data included

Data extraction
1 record

Safety
1 record
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 km2; UNDP estimates for year 2011

• Birth rate: per 1,000 population; UNDP estimates for years 2010-2015