CONTROLLED DIRECT EFFECT OF MEASLES VACCINATION ON MARKERS OF INFECTIOUS DISEASE AMONG CHILDREN 9-59 MONTHS OF AGE IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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OVERVIEW

- Measles in DRC
- Prolonged association of measles with acute episodes of fever, cough, and diarrhea
- Decrease in serologic tetanus antibody
- Beneficial nonspecific effects of measles vaccination
MEASLES IN DRC

- **DRC overall** reported measles vaccination coverage was **79% in 2015** (MMWR, 2017; 66(17))

- Coverage by province varies from **53%** (Katanga) to **89%** (Kinshasa) (DHS 2013-2014)

- **23%** of DRC children under 5 years are **acutely malnourished** (wasted) and **43%** are **chronically malnourished** (stunted) (2013-2014 DHS)
“Immune amnesia” (de Vries et al., 2012; Mina et al., 2015)
- Proposed mechanism: depletion of memory lymphocytes following measles infection
- Non-measles mortality rates in the pre-measles vaccine era were compared with rates of the vaccine era
  - Wealthy countries
- DRC
  - Host immune function is crucially important
    - Limited health care services
    - Poor nutrition
    - High levels of infectious disease
Association of measles disease history with acute episode of fever (n = 6340), cough (n = 6339), diarrhea (n = 6340), and fever + cough + diarrhea (n = 6338) in the two weeks prior to interview among children 9-59 months of age.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fever</th>
<th>Cough</th>
<th>Diarrhea</th>
<th>Fever + Cough + Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>1.49 (1.14, 1.96)</td>
<td>1.46 (1.13, 1.89)</td>
<td>1.29 (0.96, 1.73)</td>
<td>1.80 (1.16, 2.78)</td>
</tr>
<tr>
<td>Measles-vaccinated</td>
<td>0.84 (0.70, 1.01)</td>
<td>0.96 (0.78, 1.17)</td>
<td></td>
<td>0.68 (0.55, 0.85)</td>
</tr>
</tbody>
</table>

Selected covariates

a Controlling for the following covariates: measles vaccination, rural versus urban residence, province, wealth index, wealth index*residence interaction, sex, malaria positive status, age, birth order, chronic malnutrition (according to NCHS/CDC/WHO international references standard for height/age SD).

b 339 observations reporting fever, cough, and diarrhea within the previous two weeks.
Association of measles disease history with tetanus antibody levels among previously vaccinated children 6-59 months of age.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR and 95% CI(^1)</th>
<th>Adjusted OR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>2.99 (1.45, 6.00)</td>
<td>2.66 (1.29, 5.49)</td>
</tr>
</tbody>
</table>

\(^1\) Controlling for the following covariates: rural versus urban residence, wealth index, sex, age, birth order, chronic malnutrition (according to NCHS/CDC/WHO international references standard for height/age SD).

- Children with history of measles had 2.7 times the odds of having a tetanus antibody level below the median than children with no history of measles, controlling for covariates.
Previous measles infection was associated with increased odds of fever and cough outcomes

- Fever + cough + diarrhea: possible dose-response association

Measles vaccination: protective association against diarrhea and fever + cough + diarrhea

- May suggest beneficial nonspecific effects

Measles may have a long-term impact on levels of pre-existing, vaccine-induced immunity to tetanus
NONSPECIFIC EFFECTS (NSE) OF MEASLES VACCINE

- NSEs affect resistance to infectious diseases other than the targeted disease (Benn et al., 2013)
  - Proposed mechanisms include
    - Enhanced innate immune response
    - T cell cross-reactivity

- NSEs can be “indirect” or “direct” (Mina et al., 2017)
  - “Indirect”
    - Preventing negative effects that would have occurred with measles infection
  - “Direct” NSEs
    - Benefit the immune system independent of measles prevention
METHODS

- RCT versus observational data

- Quantify impact in populations at-risk for measles and eligible for vaccination

- Assess impact of measles vaccination on acute fever, cough, or diarrhea episodes using causal mediation analysis via g-computation
  - Independent of prevention of measles infection
**C1:** Age, Sex, Residence, Wealth index, Number of children < 5, Conflict

**C2:** Age, Sex, Residence, Number of children < 5, Conflict, BCG, DTP, Malaria status

**C1**
- Age
- Sex
- Residence
- Wealth index
- Number of children < 5
- Conflict

**C2**
- Age
- Sex
- Residence
- Number of children < 5
- Conflict
- BCG
- DTP
- Malaria status

**Vaccination (exposure)**

**Measles**

**Measles (mediator)**

**Vaccination \* Measles**

**Vaccination \* Measles** (interaction)

**Child health status**
The Demographic and Health Survey (DHS) 2013-2014 is designed to provide data for monitoring the population and health situation in DRC

- Maternal and child health: testing for HIV, anemia, malaria, and serology for vaccine preventable diseases
- Stage 1: Stratified sample of geographic clusters (n = 540)
- Stage 2: Household selection (n = 9,000)
- 18,827 women ages 15-49 from all households and 8,656 men ages 15-59 from 50% of selected households were interviewed
  - Dried blood spots (DBS), were collected for children 6 to 59 months in households selected for the men’s questionnaire
    - 8,420 children were eligible for antibody testing
### METHODS

<table>
<thead>
<tr>
<th>Description</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date on card:</td>
<td>16%</td>
</tr>
<tr>
<td>Child has a date recorded for the vaccination</td>
<td></td>
</tr>
<tr>
<td>Maternal report:</td>
<td>79%</td>
</tr>
<tr>
<td>Respondent reported that the child had received the vaccination although the health card was not seen or did not exist, or the vaccination was not recorded on the health card, but was reported by the mother</td>
<td></td>
</tr>
<tr>
<td>Vaccination marked on card:</td>
<td>3%</td>
</tr>
<tr>
<td>Vaccination card clearly marked to indicate that the vaccination was given, but no date was recorded on the health card for the vaccination</td>
<td></td>
</tr>
</tbody>
</table>
# METHODS

## Inclusion criteria

Children **9-59 months of age** eligible for participation in the **serosurvey** (households selected for the men’s questionnaire)

## Variables collected/defined

**Past measles infection**: positive maternal report and serology (20 mIU/mL)

**Measles vaccination**: binary
- Limited to report via dated card
- **Date** of measles disease

**Marker of infectious disease**: fever, cough, or diarrhea occurring within the **past two weeks, reported by the mother**

2,350 children meeting inclusion criteria and reporting all covariates of interest

## Respondent

**Mother**
- Displacement due to conflict
- Malnutrition
- **Bacillus Calmette–Guérin (BCG) vaccine**
- **Diphtheria-Tetanus-Pertussis vaccination (any dose, any report)**

## Covariates

- Wealth index
- Rural versus urban residence
- Age
- Sex
- Birth order
- Geographic location
# Vaccination status by basic demographics (weighted) among children 9-59 months.

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>Vaccinated</th>
<th>%</th>
<th>Unvaccinated</th>
<th>%</th>
<th>p-value$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-11</td>
<td>264</td>
<td>53</td>
<td>20</td>
<td>211</td>
<td>80</td>
<td>0.0006</td>
</tr>
<tr>
<td>12-23</td>
<td>730</td>
<td>230</td>
<td>32</td>
<td>500</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>24-35</td>
<td>554</td>
<td>219</td>
<td>40</td>
<td>335</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>36-47</td>
<td>415</td>
<td>111</td>
<td>27</td>
<td>304</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>48-59</td>
<td>431</td>
<td>141</td>
<td>33</td>
<td>290</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td><strong>Measles$^2$</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>222</td>
<td>35</td>
<td>16</td>
<td>188</td>
<td>85</td>
<td>0.0003</td>
</tr>
<tr>
<td>-</td>
<td>2348</td>
<td>711</td>
<td>30</td>
<td>1415</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1165</td>
<td>362</td>
<td>31</td>
<td>803</td>
<td>69</td>
<td>0.7585</td>
</tr>
<tr>
<td>Female</td>
<td>1229</td>
<td>392</td>
<td>32</td>
<td>837</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td><strong>Residence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>714</td>
<td>345</td>
<td>48</td>
<td>369</td>
<td>52</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Rural</td>
<td>1681</td>
<td>410</td>
<td>24</td>
<td>1271</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td><strong>Severe stunting$^2$</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>582</td>
<td>152</td>
<td>26</td>
<td>430</td>
<td>74</td>
<td>0.0215</td>
</tr>
<tr>
<td>No</td>
<td>1813</td>
<td>602</td>
<td>33</td>
<td>1211</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td><strong>Total observations</strong></td>
<td>2395</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$Wald chi-square testing for independence of the row and column variables.

$^2$23 children (unweighted) missing measles report data.

$^3$Severe stunting as defined by the NCHS/CDC/WHO international references standard for height/age SD.
RESULTS FOR FEVER

- **Stochastic controlled direct effect (CDE),** RR: 0.84, 95% CI: 0.74, 0.94
  - When measles prevalence is 10%, the risk of acute fever episode among vaccinated children is **16% lower** than unvaccinated children.

- **Index CDE,** RR: 0.59, 95% CI: 0.39, 0.90
  - If every child had measles, vv would **reduce risk of acute fever episode by 41%**.

- **Reference CDE,** RR: 0.86, 95% CI: 0.76, 0.99
  - If every child was measles-free, **vaccination would reduce risk of acute fever episode by 14%**.
RESULTS FOR COUGH AND DIARRHEA

- **Index CDE for cough**, RR: 0.63, 95% CI: 0.41, 0.97
  - If every child had measles, vaccination would **reduce risk of acute cough episode by 37%**.

- **Index CDE for diarrhea**, RR: 0.17, 95% CI: 0.06, 0.48
  - If every child had measles, vaccination would **reduce risk of acute diarrhea episode by 83%**.

*Vaccination showed no statistically significant decrease in risk of severe stunting*
CONCLUSIONS

- This study supports the hypothesis that measles vaccination exerts direct beneficial NSEs
  - Greatest reductions occurred with the index CDE estimates (fever and diarrhea)
- Previous work suggests
  - Improvements in mortality following vaccination likely due to indirect NSEs in high-incidence regions
- Direct nonspecific effects will increase in importance with decreasing measles incidence
- These results suggest
  - Direct NSEs → larger reduction of risk among populations with high measles incidence versus low
  - Beneficial effects more impactful among children experiencing prolonged immune suppression due to measles
CONCLUSIONS

**Strengths:**
- To the authors’ knowledge, first study to quantify impact of NSEs on child health outcomes in a population eligible for vaccination and susceptible to measles
- **Dates available** for vaccination and measles variables

**Limitations:**
- Potential *misclassification* of measles and fever/cough/diarrhea outcomes
- Potential *underestimate* of acute fever/cough/diarrhea due to *cross-sectional* nature of survey
These results highlight the importance of **improving measles vaccination coverage and immunity**…

- Reaching the most **difficult to reach** with vaccinations
- Determining **reasons for failure** to mount an immune response
- Recognizing the potential **long-term consequences** of measles disease

…and potential consequences of **measles vaccination** on **host immunity**

- Measles vaccination appears to exert beneficial **nonspecific effects** in high-incidence areas
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QUESTIONS?