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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DISCLAIMER

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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)

PROLONGED IMMUNOMODULATION FOLLOWING MEASLES

- **"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.

	Fever	Cough	Diarrhea	Fever + Cough + Diarrhea
Variable	**OR and 95% CI[ab]**	**OR and 95% CI**	**OR and 95% CI**	**OR and 95% CI**
Measles	**1.49 (1.14, 1.96)**	**1.46 (1.13, 1.89)**	1.29 (0.96, 1.73)	**1.80 (1.16, 2.78)**
Selected covariates				
Measles-vaccinated	0.84 (0.70, 1.01)	0.96 (0.78, 1.17)	**0.68 (0.55, 0.85)**	**0.53 (0.38, 0.73)**

[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.

Variable	Unadjusted OR and 95% CI[1]	Adjusted OR and 95% CI
Measles	2.99 (1.45, 6.00)	2.66 (1.29, 5.49)

[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

SUMMARY

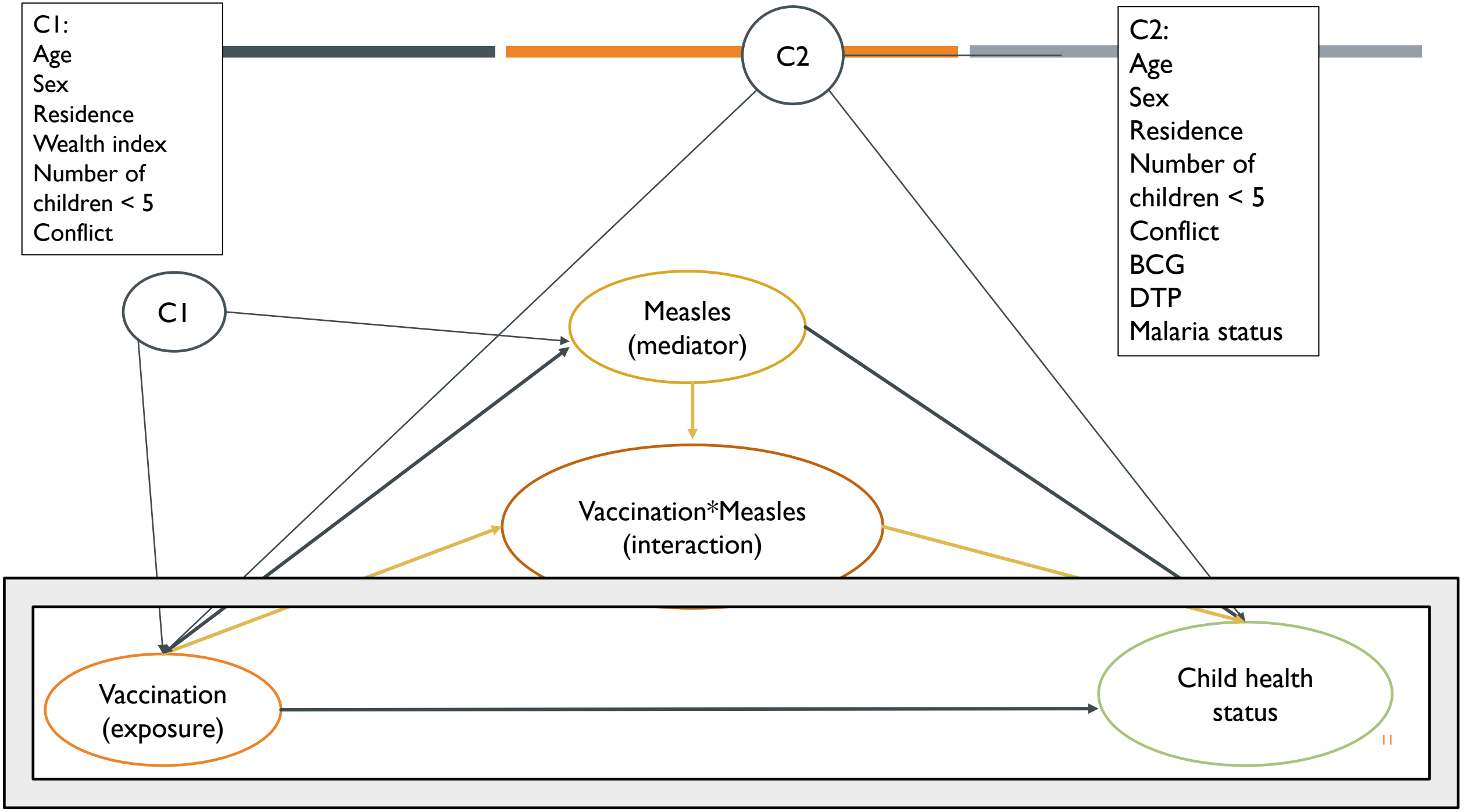
- Previous measles infection was associated with **increased odds of fever and cough** outcomes
  - Fever + cough + diarrhea: possible **dose-response association**
- Measles **vaccination:** protective association against diarrhea and fever + cough + diarrhea
  - May suggest **beneficial nonspecific 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

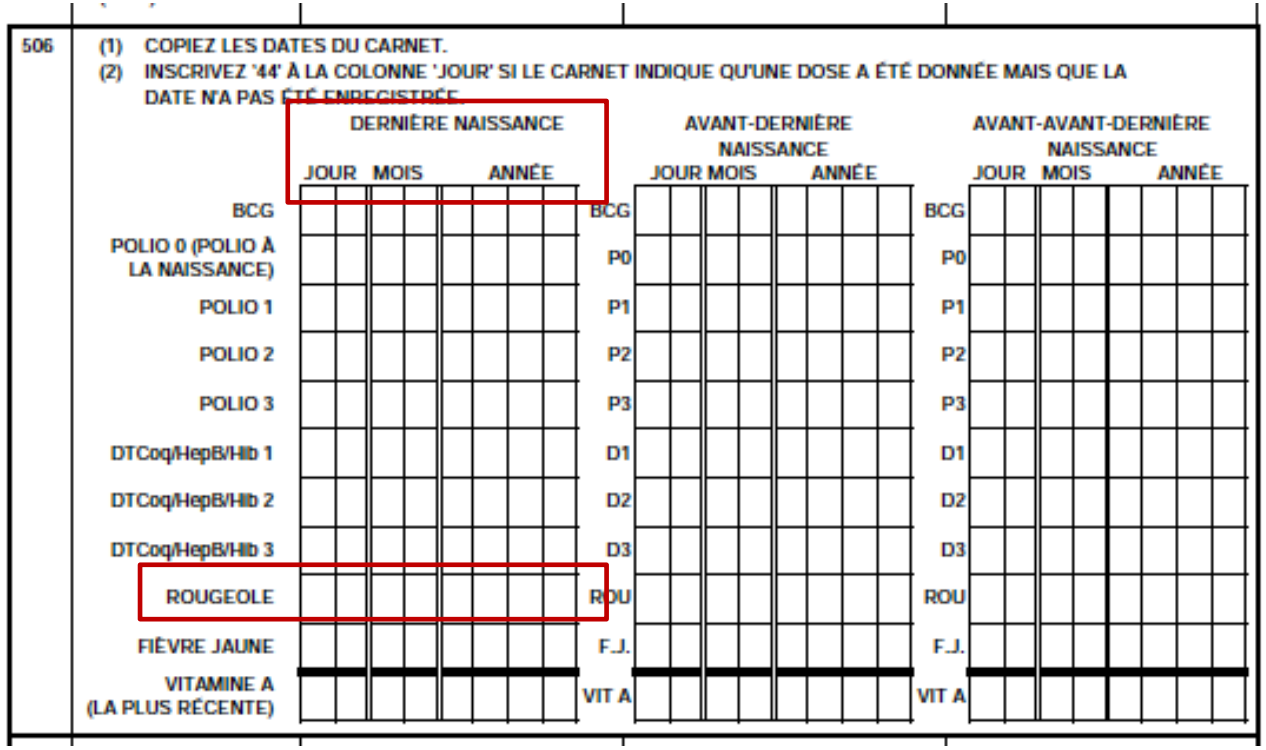

C1:
Age
Sex
Residence
Wealth index
Number of children < 5
Conflict
C2
C2:
Age
Sex
Residence
Number of children < 5
Conflict
BCG
DTP
Malaria status
C1
Measles (mediator)
Vaccination*Measles (interaction)
Vaccination (exposure)
Child health status

DATA SOURCE

- 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

Date on card: 16%	Child has a date recorded for the vaccination
Maternal report: 79%	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
Vaccination marked on card: 3%	Vaccination card clearly marked to indicate that the vaccination was given, but no date was recorded on the health card for the vaccination


506 (1) COPIEZ LES DATES DU CARNET.
(2) INSCRIVEZ '44' À LA COLONNE 'JOUR' SI LE CARNET INDIQUE QU'UNE DOSE A ÉTÉ DONNÉE MAIS QUE LA DATE N'A PAS ÉTÉ ENREGISTRÉE.

	DERNIÈRE NAISSANCE JOUR MOIS ANNÉE		AVANT-DERNIÈRE NAISSANCE JOUR MOIS ANNÉE		AVANT-AVANT-DERNIÈRE NAISSANCE JOUR MOIS ANNÉE	
BCG		BCG		BCG		BCG
POLIO 0 (POLIO À LA NAISSANCE)		P0		P0		P0
POLIO 1		P1		P1		P1
POLIO 2		P2		P2		P2
POLIO 3		P3		P3		P3
DTCoq/HepB/Hib 1		D1		D1		D1
DTCoq/HepB/Hib 2		D2		D2		D2
DTCoq/HepB/Hib 3		D3		D3		D3
ROUGEOLE		ROU		ROU		ROU
FIÈVRE JAUNE		F.J.		F.J.		F.J.
VITAMINE A (LA PLUS RÉCENTE)		VIT A		VIT A		VIT A

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**
Covariates	• wealth index • rural versus urban residence • Age • Sex • Birth order • geographic location • Displacement due to conflict • malnutrition • **Bacillus Calmette–Guérin (BCG) vaccine** • **Diphtheria-Tetanus-Pertussis vaccination (any dose, any report)**

Vaccination status by basic demographics (weighted) among children 9-59 months.

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

[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, vx 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

PUBLIC HEALTH IMPLICATIONS

- 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?