MY DISSERTATION PROCESS
&
EFFECTIVENESS OF ROTAVIRUS VACCINES IN LOW-INCOME SETTINGS

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OUTLINE FOR TODAY

- What do you want out of your PhD?
- My dissertation
  - Background
  - Aim 1
  - Aim 2
  - Aim 3
- How did I get here?

WHAT I (THOUGHT) I WANTED IN A PHD

Skills/Experience

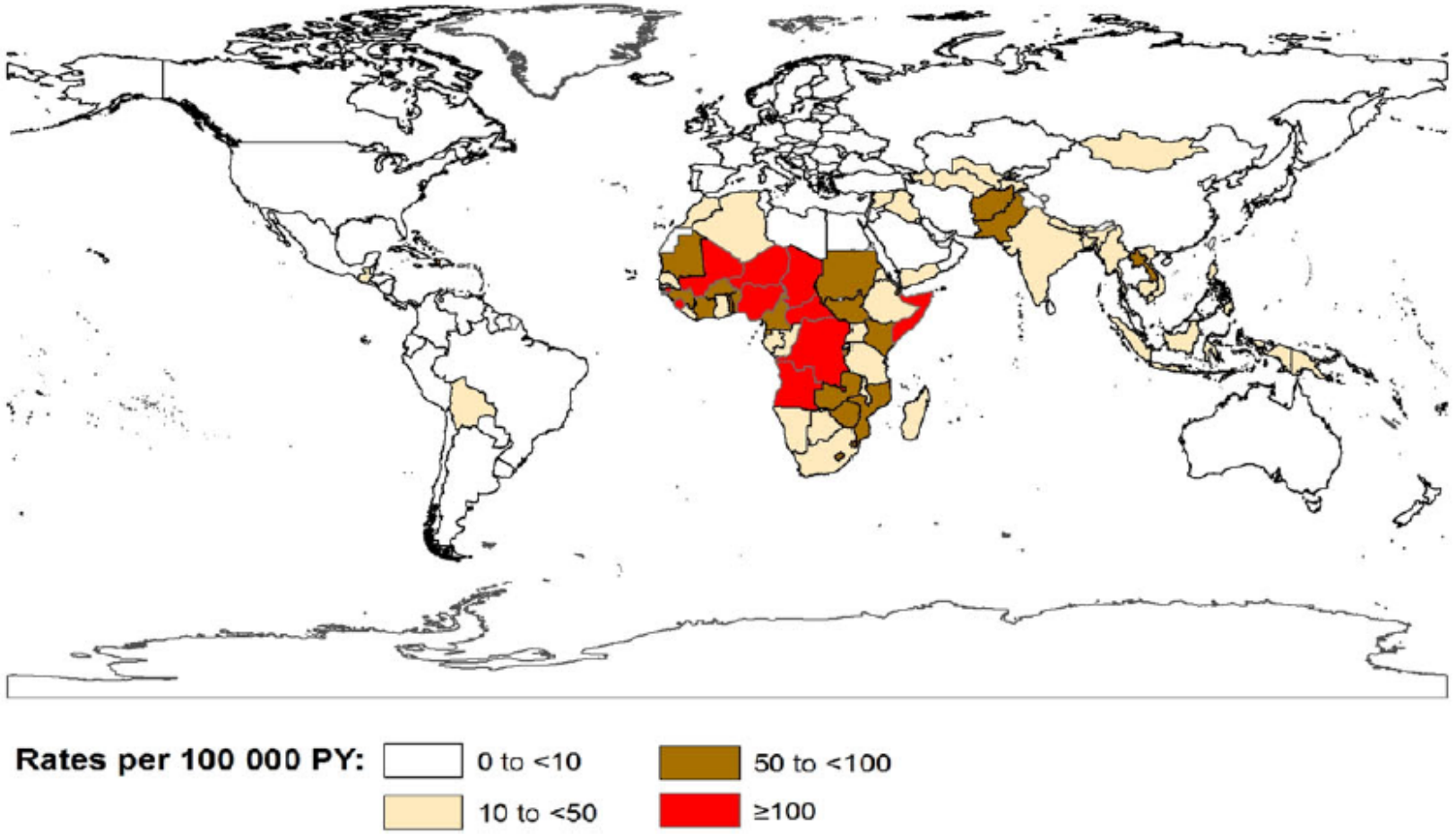
- International fieldwork
- Study management
- Advanced epidemiologic methods
- Grant writing

Research Areas

- International Health
- Infectious Diseases (non-HIV)
- Vaccines
- Clinical trials

Good/Present/Helpful Mentors
Work-life Balance

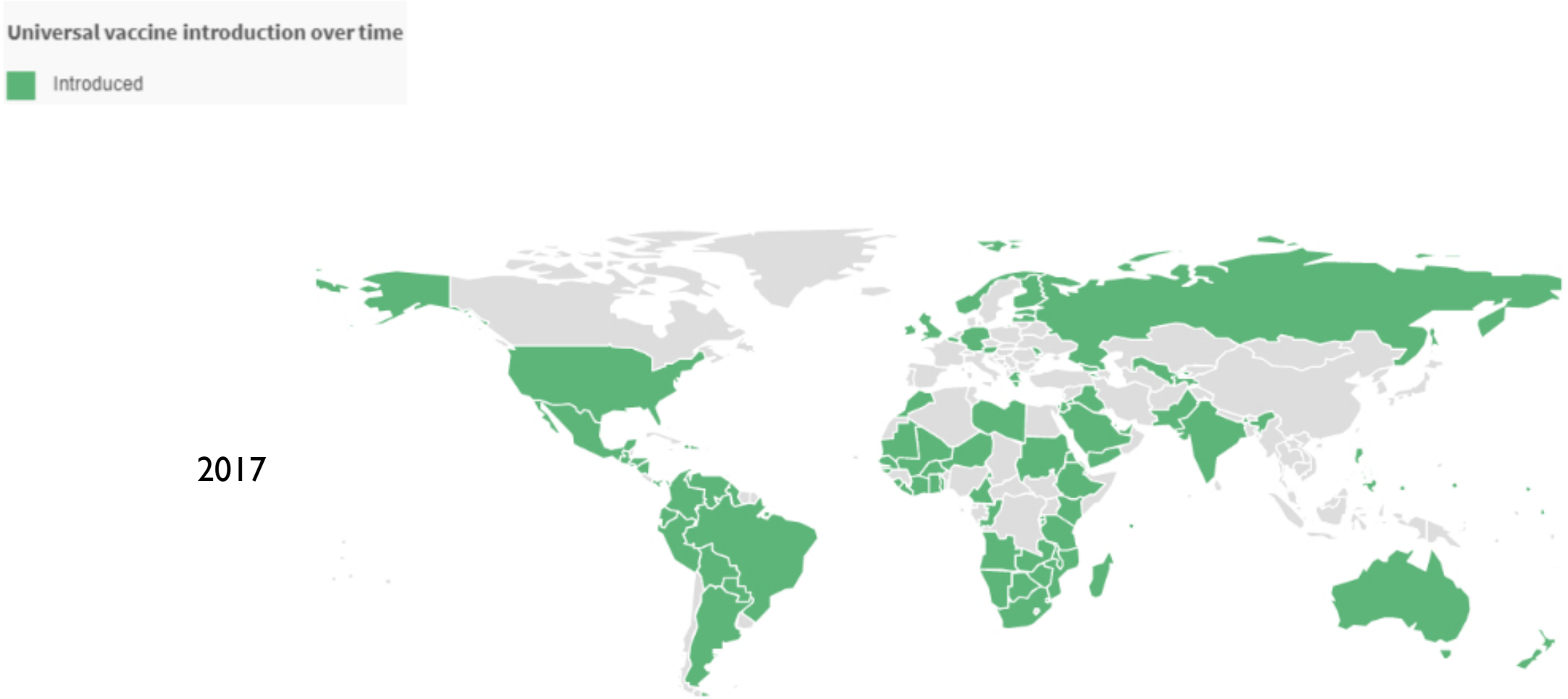
ROTAVIRUS BURDEN



Tate 2016 CID

Figure 4. Number of rotavirus deaths (*A*) and rates of rotavirus mortality (*B*) among children <5 years of age, by country, 2013. Abbreviation: PY, person-years.

RV - Universal vaccine introduction over time



VIEW-hub

Source: IVAC, accessed February 7, 2018. Exported from www.VIEW-hub.org.

WHERE I AM TODAY…THE NON-TRADITIONAL DISSERTATION

Aim 1: To evaluate the test-negative design to measure rotavirus vaccine effectiveness in low-income settings.

- *Approach:* RCTs for two rotavirus vaccines in sub-Saharan Africa and Asia will be analyzed as test-negative case-control studies. Vaccine effectiveness estimates will be compared to the original RCT efficacy estimates.

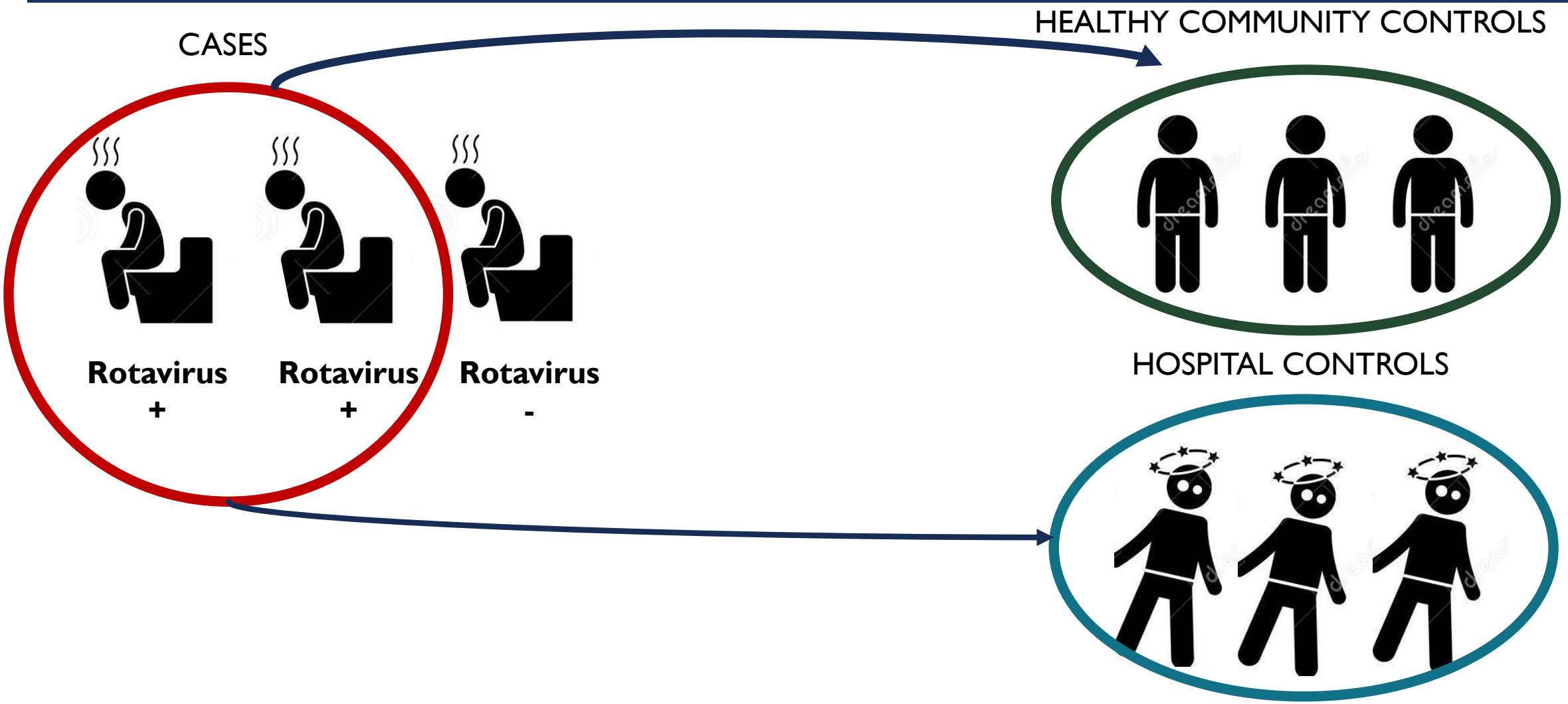
Aim 2: To estimate the relative reduction of all-cause and rotavirus-specific diarrhea incidence after rotavirus vaccine introduction in Matlab, Bangladesh in children <5 years old.

- *Approach*: Routine diarrheal surveillance over a 14 year period in Matlab, Bangladesh will be used to estimate incidence rates over time. Interrupted time-series analyses will compare incidence rates before and after rotavirus vaccine introduction.

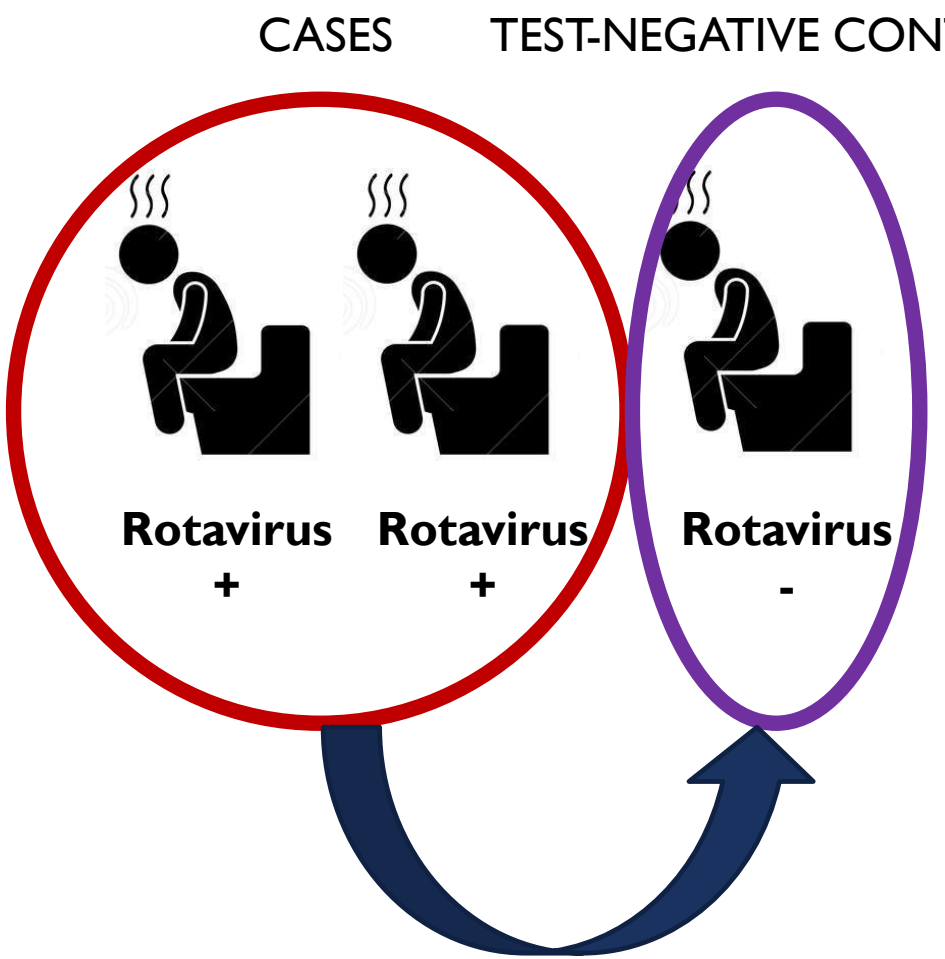
Aim 3: To test the association between genetic mutations in histo-blood group antigens (HBGAs) and rotavirus diarrhea (vaccine failure) among children with a full course of rotavirus vaccinations in The Gambia, Mali and Kenya.

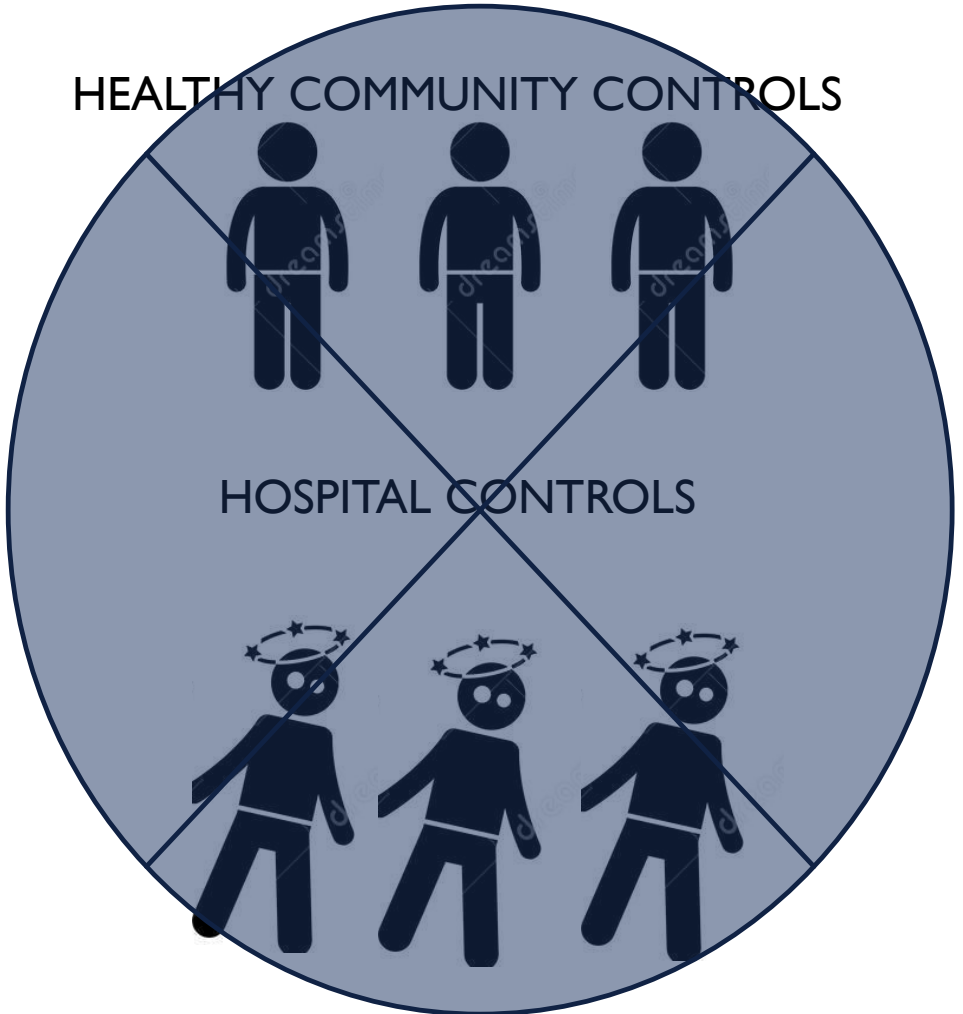
- *Approach:* The Vaccine Impact on Diarrhea in Africa (VIDA) study is an ongoing case-control study to estimate the effectiveness of rotavirus vaccine introduction. Saliva collection will be incorporated into the ongoing study to assess relevant genetic mutations.

ESTIMATING VACCINE EFFECTIVENESS USING CASE-CONTROL STUDIES



ESTIMATING VACCINE EFFECTIVENESS USING THE TEST-NEGATIVE DESIGN



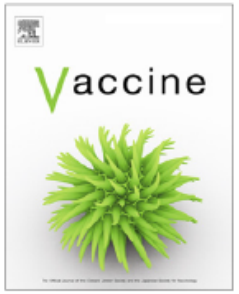


RESULTS: VE-TND AND VE-RCT ESTIMATES (95% CI)

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Rotavirus vaccine effectiveness in low-income settings: An evaluation of the test-negative design

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*rotavi

WHERE I AM TODAY…THE NON-TRADITIONAL DISSERTATION

Aim 1: To test the validity of the test-negative case-control design to measure rotavirus vaccine effectiveness in low-income settings.

- *Approach:* RCTs for two rotavirus vaccines in sub-Saharan Africa and Asia will be analyzed as test-negative case-control studies. Vaccine effectiveness estimates will be compared to the original RCT efficacy estimates.

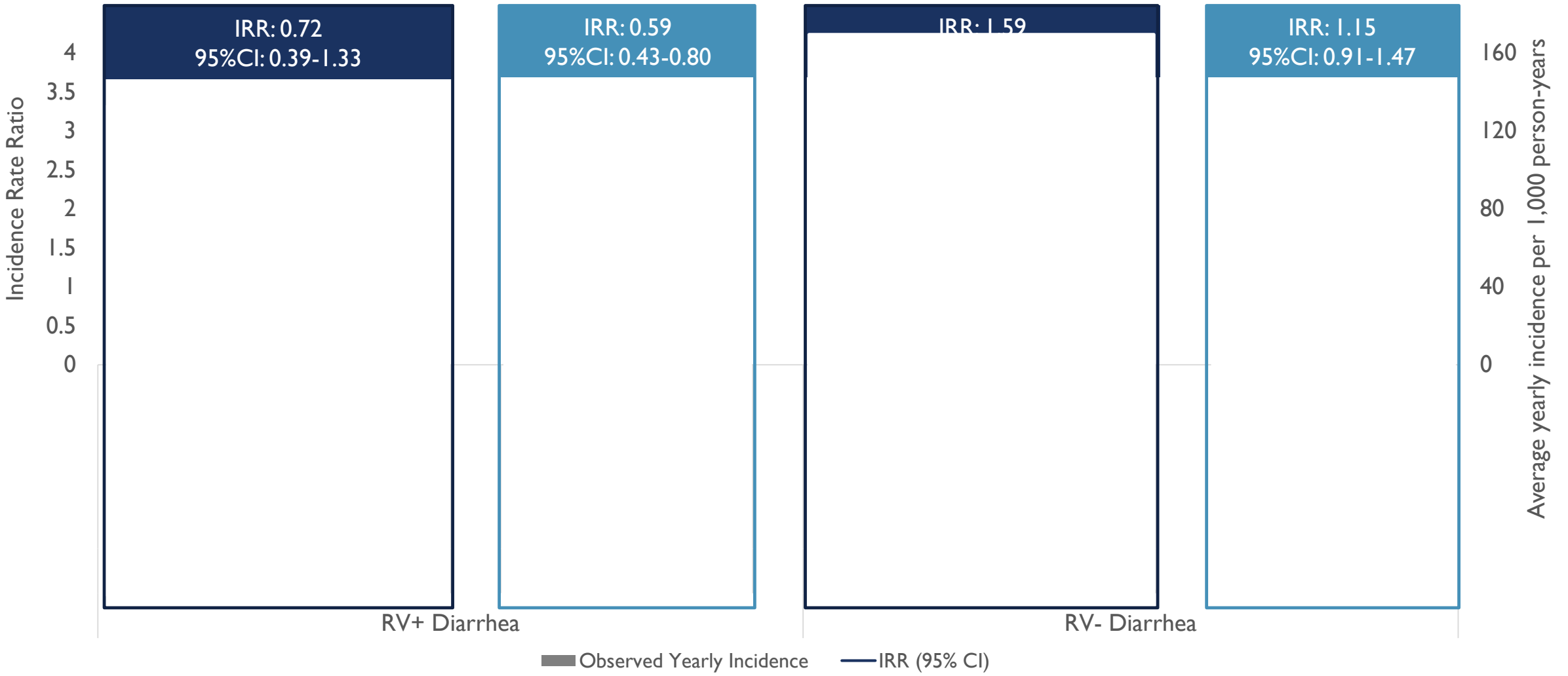
Aim 2: To estimate the population impact of rotavirus vaccine introduction in rural Matlab, Bangladesh.

- *Approach*: Routine diarrheal surveillance over a 16 year period in Matlab, Bangladesh will be used to estimate incidence rates over time. Interrupted time-series analyses will compare incidence rates before and after rotavirus vaccine introduction.

Aim 3: To test the association between genetic mutations in histo-blood group antigens (HBGAs) and rotavirus diarrhea (vaccine failure) among children with a full course of rotavirus vaccinations in The Gambia, Mali and Kenya.

- *Approach:* The Vaccine Impact on Diarrhea in Africa (VIDA) study is an ongoing case-control study to estimate the effectiveness of rotavirus vaccine introduction. Saliva collection will be incorporated into the ongoing study to assess relevant genetic mutations.

ISA VILLAGES, 0-<12 MONTHS OF AGE



WHERE I AM TODAY…THE NON-TRADITIONAL DISSERTATION

Aim 1: To test the validity of the test-negative case-control design to measure rotavirus vaccine effectiveness in low-income settings.

- *Approach:* RCTs for two rotavirus vaccines in sub-Saharan Africa and Asia will be analyzed as test-negative case-control studies. Vaccine effectiveness estimates will be compared to the original RCT efficacy estimates.

Aim 2: To estimate the relative reduction of all-cause and rotavirus-specific diarrhea incidence after rotavirus vaccine introduction in Matlab, Bangladesh in children <5 years old.

- *Approach:* Routine diarrheal surveillance over a 14 year period in Matlab, Bangladesh will be used to estimate incidence rates over time. Interrupted time-series analyses will compare incidence rates before and after rotavirus vaccine introduction.

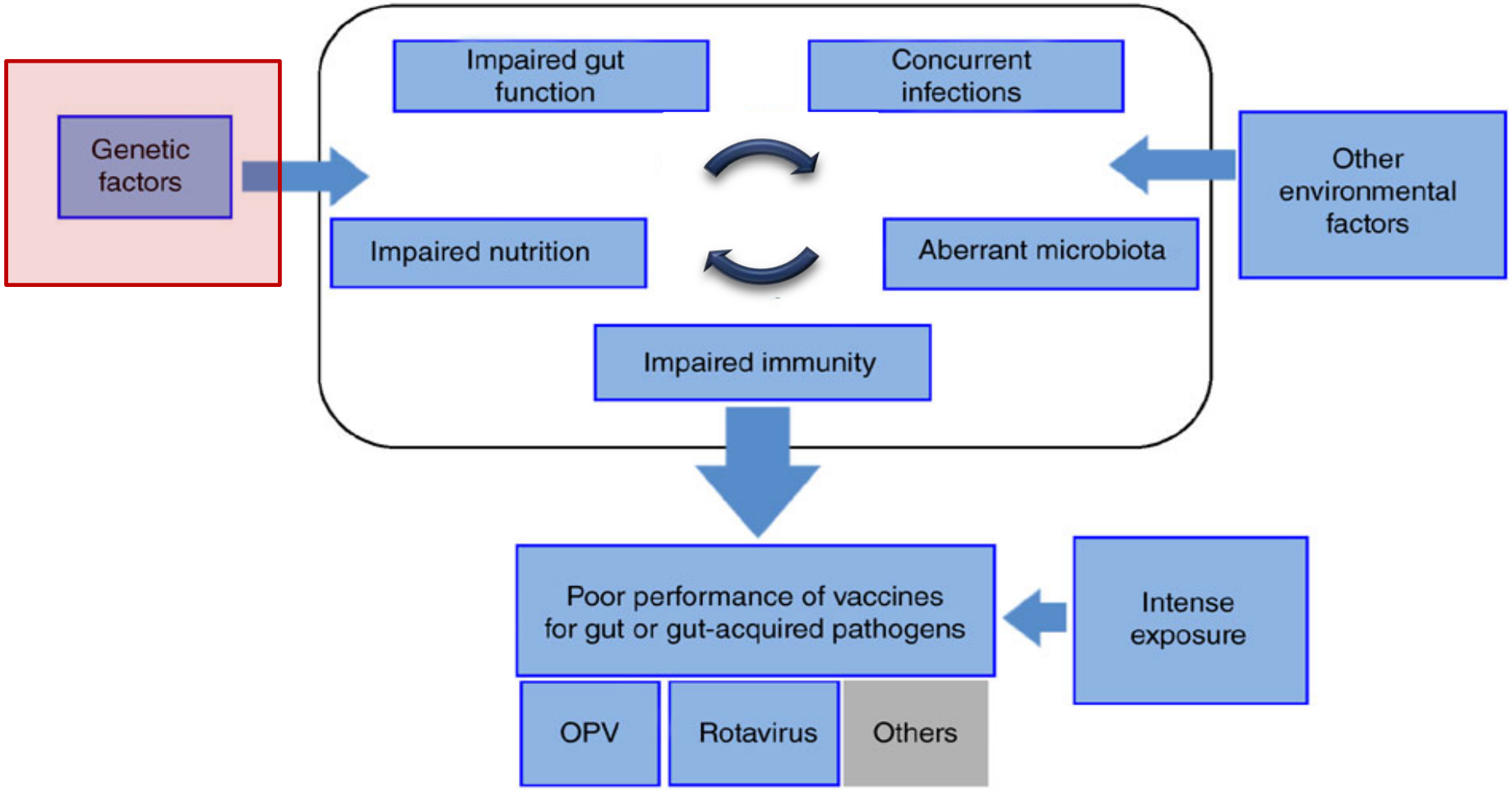
Aim 3: To assess host genetic determinants of rotavirus vaccine failure among children with a full course of rotavirus vaccinations in The Gambia, Mali and Kenya.

- *Approach:* The Vaccine Impact on Diarrhea in Africa (VIDA) study is an ongoing case-control study to estimate the effectiveness of rotavirus vaccine introduction. Saliva collection will be incorporated into the ongoing study to assess relevant genetic mutations.

VACCINE IMPACT ON DIARRHEA IN AFRICA (VIDA) STUDY

Case-control study of the etiology, and adverse clinical consequences of moderate-to-severe diarrhea (MSD); data from the case-control study will also be used to measure rotavirus vaccine impact and effectiveness

FACTORS AFFECTING ORAL ROTAVIRUS VACCINE PERFORMANCE



Serazin *Nat. Immunol.* (2010)

VACCINE IMPACT ON DIARRHEA IN AFRICA (VIDA) STUDY

UNIVERSITY OF MARYLAND

1. To assess the impact of rotavirus vaccine introduction on the
   A. Etiology of moderate to severe diarrhea (MSD)
   B. Adverse clinical consequences of MSD (liner growth, persistent diarrhea, mortality)
   C. Overall incidence of moderate to severe diarrhea
2. Rotavirus vaccine effectiveness using a case-control study (healthy community controls and test-negative controls)

Vaccine Impact on Diarrhea (VIDA) Case-Control Study

Moderate-to-severe diarrhea cases

0-12 months, 12-24 months, 24-59 months

Identified at sentinel health center

Age, Sex, Community/Nearby, Time

Matched healthy community controls

0-12 months, 12-24 months, 24-59 months

Randomly selected from DSS and recruited at home

Data collection:

Clinical characteristics (cases)

Demographics

Stool sample (Enteropathogen)

Anthropometric measures

Vaccination history (card/admin center)

Saliva collection

60 day follow-up

Data collection:

Clinical history within follow-up period

Anthropometric measures

Survival/Verbal Autopsy

Saliva collection (as needed)

60 day follow-up

DUAL TIMELINES:
SCHOOL REQUIREMENTS AND RESEARCH

YEAR 1 – 2013/2014

Timeline	Funding	Courses	School Requirements	Dissertation/Research	Aim 1	Aim 2	Aim 3
Q1	Top Scholar Award	EPI512, BIOSTAT517		Ideas on dengue vaccines in Mexico	Dengue Vaccine Project in Mexico		
Q2	Top Scholar Award	EPI513, BIOSTAT518, GH Research Methods		Dengue Vaccine Literature Review	Dengue Vaccine Project in Mexico		
Q3	Top Scholar Award	Exposure Measurement, Pharmacoepi		Dengue Vaccine Literature Review	~~Dengue Vaccine Project in Mexico~~		
				Meeting with faculty			
				Meeting with PATH**	?????		
Summer	Hourly RA	SISMID	Preliminary Exam	3 month research project in Uganda			

YEAR 2 – 2014/2015

Timeline	Funding	Courses	School Requirements	Dissertation/Research	Aim 1	Aim 2	Aim 3
Q1	RA	BIOSTAT356, EPI554, Doctoral Dissertation Seminar		Meeting with faculty/PATH investigators	Development of methods/statistical analysis plan		
Q2	PATH RA	BIOSTAT357, R Course, Doctoral Dissertation Seminar	Presentation at doctoral dissertation seminar (short proposal)--with only Aim 1!	Phone calls with University of Maryland (VIDA study)	Development of methods/statistical analysis plan		
Q3	PATH RA	Advanced Epi, Grant Writing		Phone calls with University of Maryland (VIDA study)	Analysis		
Summer	PATH RA			Vaccines in Enteric Diseases Conference (attendance)	Analysis	Develop methods	Proposal for VIDA - genetic determinants of rotavirus vaccine failure, request for Gates funding

YEAR 3 – 2015/2016

Timeline	Funding	Courses	School Requirements	Dissertation/Research	Aim 1	Aim 2	Aim 3
Q1	PATH RA	F31 weekly meeting		Writing and submitting F31 proposal	Analysis (additional data requested)	Development of methods	Gates Foundation - Funding awarded! Writing protocols, choosing appropriate laboratory assays and saliva collection instruments
Q2	RA		Submit Short Proposal, Write Long Proposal		Analysis		Travel to the Gambia for VIDA investigators meeting, saliva collection training
Q3	RA		General Exam - written and oral		Writing		
Summer	Hourly				Writing/Co-author Edits	Travel to Bangladesh	Travel to Kenya, Mali (saliva collection training)

YEAR 4 & YEAR 5 – 2016/2017/2018

Timeline	Funding	Courses	School Requirements	Dissertation/Research	Aim 1	Aim 2	Aim 3
Q1	F31, EPI512 TA			Present Aim 1 oral Abstract at ASTMH	Paper submitted	Waiting on data…	Travel to Mali Continued study management
Q2	F31, EPI513 TA			Looking at jobs/post-docs	Paper accepted	Data Arrive! Analysis begins	Continued study management
Q3	F31		Plan for dissertation defense	Looking at jobs/post-docs	Oral presentation at ASTMH	Analysis/Writing	Continued study management
Summer	F31			Looking at jobs/post-docs, putting together dissertation		Writing	Preliminary Analysis/Writing/ Travel to Kenya
Q1-Q3	F31… Consulting		Dissertation Defense	Putting together dissertation and defense presentation		Paper Submitted/ Poster ASTMH	Preliminary Analysis/ Writing

Thank you!
Questions?

University of Washington
Betz Halloran
Ali Rowhani-Rahbar
Jai Lingappa

University of Maryland
Karen Kotloff and VIDA Team
Kathleen Neuzil
Samba Sow (Mali-UMB)
Jahangir Hossain (MRC-Gambia)
Richard Omore (Kenya-CDC)

PATH
J. Chris Victor

ICDDR,B
K. Zaman

Bill & Melinda Gates Foundation
Rotavirus and VIDA Grants

NIH/NIAID MERIT R37 AI032042

NIH/NIAID 1F31AI126629-01