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

MARCH 3, 2017

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LAURENMS@UW.EDU
OUTLINE FOR TODAY

- What do you want to get 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
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.
81 countries have introduced rotavirus vaccines into their national immunization programs.
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

Cases:
- Rotavirus +
- Rotavirus +
- Rotavirus -

Healthy Community Controls:

Hospital Controls:
ESTIMATING VACCINE EFFECTIVENESS USING THE TEST-NEGATIVE DESIGN

CASES

TEST-NEGATIVE CONTROLS

Rotavirus + Rotavirus + Rotavirus -

HEALTHY COMMUNITY CONTROLS

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

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\textsuperscript{c} Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Seattle, WA, United States
\textsuperscript{d} Center for Inference and Dynamics of Infectious Diseases, Seattle, WA, United States
\textsuperscript{e} Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD, United States
\textsuperscript{f} Center for Vaccine Innovation and Access, PATH, Seattle, WA, United States

*rotavii
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 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.
AIM 2 RESULTS ONGOING

Rotavirus Incidence, Matlab Bangladesh

Incidence per 1,000
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.


- **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

Sites in Africa:
• Basse, The Gambia
• Bamako, Mali
• Siaya County, Kenya

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

- Genetic factors
- Impaired gut function
- Concurrent infections
- Impaired nutrition
- Aberrant microbiota
- Impaired immunity

Other environmental factors

Poor performance of vaccines for gut or gut-acquired pathogens
- OPV
- Rotavirus
- Others

Intense exposure

**Study Overview**

1. **Survey health centers for diarrhea cases**
   - CRF 02: Case Registration log

2. **Enroll CASES (8-9 cases every 2 weeks per age group 0-11 mo., 12-23 mo., 24-58 mo.)**
   - Follow CASES until they are discharged from clinic or hospital
     - Determine eligibility
     - CRF 03: Case eligibility
     - Interview caretaker
     - CRF 04A: Case enrollment, non-medical
     - Record medical information
     - CRF 04B: Case enrollment, medical
     - Measure height, weight, mid-upper arm circumference
     - CRF 04B: Case enrollment, medical
     - Collect a stool sample & send to lab
     - CRF 12A: Saliva collection form

3. **VIDA plus: all other MSD cases**
   - CRF 9 (eligibility)
   - CRF 4A, 4B
   - CRF 11: Stool collection

4. **CRF 12A: Saliva collection**
   - CRF 12B: Saliva collection; as needed, collected at a convenient time

5. **Enroll CONTROL, matched to case**
   - Determine eligibility
   - CRF 06: Control eligibility
   - Interview caretaker
   - CRF 07: Control enrollment
   - Measure height, weight, mid-upper arm circumference
   - CRF 07: Control enrollment
   - Collect a stool sample & send to lab
   - CRF 12A: Saliva collection form

6. **VIDA plus: 3 controls per case**
   - CRF 6 (control eligibility)
   - CRF 7 (control enrollment)

7. **Parent completes memory aid describing the child’s stools for 14 days**

8. **If child dies during enrollment encounter**
   - CRF 10: Health Center Information

9. **60-day follow-up visit at child’s home**
   - Interview caretaker, record required observations
   - CRF 05: 60 day follow-up questionnaire for cases & controls
   - Measure height, weight, mid-upper arm circumference
   - CRF 05: 60 day follow-up questionnaire for cases & controls
   - Review and collect memory aid
   - CRF 12B: Saliva collection form, as needed

10. **If child death is reported at 60 day follow-up visit**
    - Inform demographic surveillance team
      - Verbal autopsy CRF

11. **Yellow box indicates health center based activities**
12. **Blue box indicates community-based activities**
HOW DID I GET HERE?
<table>
<thead>
<tr>
<th>Timeline</th>
<th>Funding</th>
<th>Courses</th>
<th>School Requirements</th>
<th>Dissertation/Research</th>
<th>Aim 1</th>
<th>Aim 2</th>
<th>Aim 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Top Scholar Award</td>
<td>EPI512, BIOSTAT517</td>
<td></td>
<td>Ideas on dengue vaccines in Mexico</td>
<td>Dengue Vaccine Project in Mexico</td>
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<tr>
<td>Q2</td>
<td>Top Scholar Award</td>
<td>EPI513, BIOSTAT518, GH Research Methods</td>
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<td>Dengue Vaccine Literature Review</td>
<td>Dengue Vaccine Project in Mexico</td>
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<tr>
<td>Q3</td>
<td>Top Scholar Award</td>
<td>Exposure Measurement, Pharmacoepi</td>
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<td>Dengue Vaccine Literature Review</td>
<td>Dengue Vaccine Project in Mexico</td>
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<td>Meeting with faculty</td>
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<td></td>
<td></td>
<td>Meeting with PATH**</td>
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<tr>
<td>Summer</td>
<td>Hourly RA</td>
<td>SISMID</td>
<td>Preliminary Exam</td>
<td>3 month research project in Uganda</td>
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<td>???????</td>
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## YEAR 2 – 2014/2015

<table>
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<tr>
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<tbody>
<tr>
<td>Q1</td>
<td>RA</td>
<td>BIOSTAT356, EPI554, Doctoral Dissertation Seminar</td>
<td>Meeting with faculty/PATH investigators</td>
<td>Development of methods/statistical analysis plan</td>
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<tr>
<td>Q2</td>
<td>PATH RA</td>
<td>BIOSTAT357, R Course, Doctoral Dissertation Seminar</td>
<td>Presentation at doctoral dissertation seminar (short proposal)--with only Aim 1!</td>
<td>Phone calls with University of Maryland (VIDA study)</td>
<td>Development of methods/statistical analysis plan</td>
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<tr>
<td>Q3</td>
<td>PATH RA</td>
<td>Advanced Epi, Grant Writing</td>
<td>Phone calls with University of Maryland (VIDA study)</td>
<td>Analysis</td>
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<tr>
<td>Summer</td>
<td>PATH RA</td>
<td></td>
<td>Vaccines in Enteric Diseases Conference (attendance)</td>
<td>Analysis</td>
<td>Develop methods</td>
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<td>Proposal for VIDA - genetic determinants of rotavirus vaccine failure, request for Gates funding</td>
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## YEAR 3 – 2015/2016

<table>
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<th>Aim 2</th>
<th>Aim 3</th>
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</thead>
<tbody>
<tr>
<td>Q1</td>
<td>PATH RA</td>
<td>F31 weekly meeting</td>
<td>Writing and submitting F31 proposal</td>
<td>Analysis (additional data requested)</td>
<td>Development of methods</td>
<td>Gates Foundation - Funding awarded!</td>
<td>Writing protocols, choosing appropriate laboratory assays and saliva collection instruments</td>
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<tr>
<td>Q2</td>
<td>RA</td>
<td>Submit Short Proposal, Write Long Proposal</td>
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<td>Analysis</td>
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<td>Travel to the Gambia for VIDA investigators meeting, saliva collection training</td>
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<tr>
<td>Q3</td>
<td>RA</td>
<td>General Exam - written and oral</td>
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<td>Writing</td>
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<tr>
<td>Summer</td>
<td>Hourly</td>
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<td>Writing/Co-author Edits</td>
<td>Travel to Bangladesh</td>
<td>Travel to Kenya, Mali (saliva collection training)</td>
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### YEAR 4 & YEAR 5 – 2016/2017

<table>
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<tr>
<th>Timeline</th>
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<th>Aim 3</th>
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</thead>
<tbody>
<tr>
<td>Q1</td>
<td>F31, EPI512 TA</td>
<td></td>
<td></td>
<td>Present Aim 1 oral Abstract at ASTMH</td>
<td>Paper submitted</td>
<td>Waiting on data…</td>
<td>Travel to Mali</td>
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<td></td>
<td>Continued study management</td>
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<tr>
<td>Q2</td>
<td>F31, EPI513 TA</td>
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<td></td>
<td>Looking at jobs/post-docs</td>
<td>Paper accepted</td>
<td>Data Arrive! Analysis begins</td>
<td>Continued study management</td>
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<tr>
<td>Q3</td>
<td>F31</td>
<td></td>
<td></td>
<td>Plan for dissertation defense</td>
<td>Looking at jobs/post-docs</td>
<td>Analysis/Writing</td>
<td>Continued study management</td>
</tr>
<tr>
<td>Summer</td>
<td>F31</td>
<td></td>
<td></td>
<td>Looking at jobs/post-docs, putting together dissertation</td>
<td></td>
<td>Writing</td>
<td>Preliminary Analysis/Writing</td>
</tr>
<tr>
<td>Q1</td>
<td>F31</td>
<td></td>
<td></td>
<td>Dissertation Defense (!?)</td>
<td>Putting together dissertation and dissertation defense presentation</td>
<td>Writing, submit paper</td>
<td>Preliminary Analysis, Writing</td>
</tr>
</tbody>
</table>
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
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