Rickettsial Pathogen
Research Coordination Network

Singapore • 6-8 March 2018



Meeting Final Report

HANDLING INSTRUCTIONS

- The title of this document is *The Final Report of the Research Coordination Network on Rickettsial Pathogens (RCN-RP) Meeting – Singapore 2018*.
- The information gathered in this Final Report should be safeguarded, handled, transmitted, and stored in accordance with appropriate security directives. Reproduction of this document, in whole or in part, without prior approval is prohibited.
- **DISTRIBUTION STATEMENT A**: Approved for public release; distribution unlimited.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The Rickettsial Pathogens Research Coordination Network (RCN) met during the week of 6-8 March 2018 in Singapore. This meeting served as a follow-up to its kick-off meeting in Baltimore, Maryland in November 2017, where the group-chartered research objectives. Members of RCN developed an agenda to meet the following objectives:

- Convene multi-disciplinary researchers, health implementers, policy makers and funding authorities to identify and prioritize *Rickettsia* research needs and gaps
- Characterize the distribution and prevalence of Rickettsial pathogens, to include vectors and reservoir host in Southeast Asia to better understand and address the human and animal health burden using statistical analysis and other best practices for assessing the global burden of other neglected infectious diseases
- Employ, monitor, and evaluate the consistent use of "gold standard" diagnostics and community accepted case definitions to determine if better standards are needed for detection in lab and clinical settings
- Increase awareness for *Rickettsia* amongst at-risk populations, clinicians, laboratory staff, national decision makers for better prevention, detection, and response

A complete agenda from the meeting in addition to a list of its participants may be found in Annex B and in Annex A, respectively.

The meeting kicked off with welcome remarks from Dr. Martha Stokes, Defense Threat Reduction Agency (DTRA) Chemical Biological Engagement Program (CBEP) Southeast Asia (SEA) Science Lead, who facilitated a review of the network objectives, set the guidelines for the meeting, and discussed CBEP's role in the RCN. Following the welcome remarks, RCN members reviewed their current research or agency funding on *Rickettsia* pathogens before breaking out into focus areas. Participants began developing their strategic maps that outlined what their focus area should achieve, how success will be measured, risks and needs, and listed activities and projects to accelerate short and long-term objectives.

Ultimately, meeting organizers and facilitators agreed that the meeting achieved its objectives. Working within their focus group areas they were able to develop an ambitious year-long strategy and characterize associated challenges and risks to achieving their goals. The group agreed on the importance of its momentum to develop supportive structures for communication and outreach both internally and externally to firmly establish itself as a unique global network of multi-disciplined researchers who aim to answer complex questions at the nexus of One Health.

The meeting's success is evident in the responses from the participants. The participants were given an opportunity to provide feedback via an anonymous survey shortly after the conclusion of meeting. Unanimously the group agreed that the meeting was productive and outlined a path forward for the Rickettsial Pathogen RCN. All members noted that their contributions were beneficial and there is consensus about taking steps to moving forward with research and publications. The RCN meeting was seen as a success for participants and there was an overwhelming willingness to continue to meet end goals of the RCN. The survey was sent to all participants via email and a summary of the responses can be found in the participant feedback section.

BACKGROUND

There is a long tradition of international cooperation in scientific research. Scientific networks can be instrumental to bridge cultural boundaries, build trust, and address the global threat of emerging infectious diseases. Current trends in scientific research funding, specifically competition for ever-decreasing research budgets, necessitate international collaborations focused around specific and prioritized research questions.

DTRA CBEP is sponsoring a disease surveillance Research Coordination Network to mitigate the threat of rickettsial pathogens of security concern in Southeast Asia. This network aims to identify and connect interdisciplinary expertise, convening an agile group to adapt to a wide spectrum of arising challenges and threats. The CBEP mission limits its funding to research for pathogens of security concern that are listed on the U.S. Select Agent List; however, in the case of rickettsial agents, national and international policy makers require better characterization and understanding of the full scope of geographical distribution, for the entire genus of *Rickettsia*, to produce better diagnostics and standards of practice. To this end, the Rickettsial Pathogen RCN focuses on all rickettsial and related rickettsial pathogens with a heavy emphasis on *Rickettsia typhi, Rickettsia prowazekii*, Rickettsia rickettsii, Orientia tsutsugamushi,* and *Coxiella burnetii**. (*Indicates a US Department of Health and Human Services and Department of Agriculture Select Agent. https://www.selectagents.gov/selectagentsandtoxinslist.html)

Rickettsial pathogens are under-recognized with wide distribution across Southeast Asia and are considered some of the most surreptitious emerging and re-emerging diseases. While not on the WHO list of neglected tropical diseases, they account for the second most frequently reported infections for non-malarial febrile illnesses among residents in the region (dengue rates as the first). Rickettsial infections are difficult to treat and if left untreated can have fatality rates as high as 30-45 percent.

MISSION AND VISION

The Rickettsial Pathogens RCN aims to leverage existing networks and communities of practice within Southeast Asia; its goal is to enable better disease recognition and reporting in clinical and laboratory settings. The RCN approach, which has been modeled on similar CBEP-sponsored activities for melioidosis and bat-borne pathogens, integrates subject matter experts, mid-level professionals, and novices across a horizontal span of expertise (e.g., clinicians, diagnosticians, statisticians, ecologists, and others) to meet One Health challenges.

CBEP plans to facilitate a series of discussions and workshops, to identify current research, discuss critical needs for the community, and prioritize gaps and needs. CBEP will assist the RCN with developing short and long-term work plans to meet identified requirements. Other U.S. government agencies and non-governmental entities with an invested interest in the output of the network are invited to observe and advise on the Rickettsial Pathogens RCN sustainment goals.

NETWORK OBJECTIVES

The following are overarching goals for the Rickettsial Pathogens RCN:

- Convene multi-disciplinary researchers, health implementers, policy makers and funding authorities to identify and prioritize *Rickettsia* research needs and gaps
- Characterize the distribution and prevalence of rickettsial pathogens and their vectors in Southeast Asia to better understand and address the human and animal health burden using statistical analysis and other best practices for assessing the global burden of other neglected infectious diseases
- Employ, monitor, and evaluate the consistent use of "gold standard" diagnostics and community accepted case definitions to determine if better standards are needed for detection in lab and clinical settings
- Increase awareness for *Rickettsia* amongst at-risk populations, clinicians, laboratory staff, national decision makers for better prevention, detection, and response

END STATE GOALS

The end state goals of the Rickettsial Pathogens RCN were decided upon during the November 2017 and March 2018 Rickettsial Disease RCN meetings and aim to improve:

- Characterization of geographic distribution of rickettsial pathogens and their vectors, to include vectors and reservoir host in Southeast Asia
- Understanding of pathogen diversity and the full spectrum of its epidemiology in Southeast Asia and beyond
- Technology for diagnostics of *Rickettsia* pathogens
- Technology and standard operating procedures, access to accurate and affordable diagnostics and countermeasures
- Standard operating procedures for Immunofluorescent Antibody Assay
- Improved treatment of rickettsias
- Interest in *Rickettsia* research
- National surveillance

OUTCOMES FROM RESEARCH FOCUS AREAS BREAKOUT SESSIONS

OPENING COMMENTS

Opening remarks from Dr. Martha Stokes, DTRA CBEP SEA Science Lead, gave an introduction into CBEP's mission and its approach for research-based networks. Dr. Stokes outlined CBEP's program goals to aid in building national and regional research capacity while emphasizing priorities in sustainability and defining global disease prevalence and burden. She highlighted the desire for the RCN to help in facilitating better detection and diagnostics for these diseases in SEA. By building horizontal networks the RCN can integrate research and align with the goals of CBEP. Additionally, Dr. Stokes reviewed the Department of Defense's historical interest in Rickettsial pathogens and the global distribution of Rickettsial pathogens. Please refer to Annex C for Dr. Stokes' presentation slides.

RICKETTSIAS IN SOUTHEAST ASIA

Dr. Paul Newton of Lao-Mahidol Oxford Tropical Medicine Research Unit provided the large group an overview of the burden of Rickettsial Pathogens in Southeast Asia. Dr. Newton stressed the importance of these diseases as they are the major cause of undiagnosed fever in SEA. He emphasized the need for innovation, mapping of pathogens, geographically focused diagnostic tests, and multi-site research. While reviewing the major rickettsial pathogens, Dr. Newton discussed the inadequacies in diagnostics and how the RCN could work to shape the future research in SEA. Please refer to Annex C for Dr. Newton's presentation slides.

CURRENT RESEARCH IN RICKETTSIAL DISEASES

Prior to the RCN meeting, participants were asked to fill in a quad chart on their current research on Rickettsial pathogens. Each agency or representing member filled out one quad chart on their project(s) using the following criteria: (1) Technical Description and Project; (2) Approach; (3) Milestones, Schedule, and Status; and (4) Impact. Each of the below presenters gave a short overview of current projects, work, and future initiatives in their field. Quad charts and summaries can be found in Annex D.

The following organizations were represented in these presentations:

- Duke-National University of Singapore, Dr. Ian Mendenhall
- Australian Rickettsial Research Laboratory, Dr. John Stenos
- Rare and Imported Pathogens Laboratory, National Infections Services, Dr. Jackie Duggan
- Christian Medical College, Vellore, India, Dr. George Varghese
- Mahidol-Oxford Tropical Medicine Research Unit, Dr. Matthew Robinson
- University of Malaysia, Tropical Infectious Disease Research and Education Center, Dr. Sazaly Bakar
- Armed Forces Research Institute of Medical Science, Royal-Thai Army, COL Jariyanart Gaywee, Ph.D.
- Armed Forces Research Institute of Medical Science, LTC Matthew Wegner DVM
- Navy Medical Research Center- Asia, LCDR Jeffrey Hertz, Ph.D.
- Navy Medical Research Center, Dr. Al Richards
- Uniformed Services University, Dr. Stephen Dumler
- Communicable Disease Centre – National Centre for Infectious Diseases, Dr. Yazid Abdad
- Center for Disease Control and Prevention, Division of Vector-Borne Diseases, Dr. Cecilia Kato

CURRENT FUNDING IN RICKETTSIAL DISEASES

Prior to the RCN meeting, participants were asked to fill in a quad chart on their current funding opportunities on rickettsial pathogens. Each agency or representing member filled out one quad chart on their project(s) using the following criteria: (1) Organization description; (2) Funding Announcement Types; (3) Funding Timeline; and (4) Points of Contact. Each presenter gave a short overview of funding mechanisms and timelines for these announcements. Funding quad charts from the following presenters can be found in Annex D.

- Defense Threat Reduction Agency, Cooperative Biological Engagement Program, Dr. Martha Stokes

- Defense Threat Reduction Agency, Research and Development Chemical and Biological Technologies, Dr. Diane Dutt
- Global Emerging Infections Surveillance, Dr. Brett Forshey

MEETING FORMAT AND AGENDA

MEETING FORMAT

The goals of this Rickettsial Pathogens RCN meeting were:

(1) Define focus areas, resource needs, and outreach plans;
(2) Build strategy maps to identify, prioritize, and address RCN research gaps and needs; and
(3) Discuss short-term and long-term processes to collect and collate applications to the network

These objectives were set to provide a target for participants to think about success from the beginning. General meeting instructions emphasized the importance of working collaboratively, but to also think about general limitations that have inhibited research goals. Emphasis was added that these objectives should be owned by the entire group.

Additionally, the participants worked to finalize the Terms of Reference. The participants collectively edited the Terms of Reference which will be sent to the group for final concurrence.

AGENDA

The meeting agenda was designed to create awareness of current research and funding on rickettsial pathogens along with two breakout sessions to guide focus areas through a single strategy map. The first day included a morning session on CBEP's mission and current research and funding along with a large group review of the focus area research areas. Participants then moved into their research focus areas to identify objectives, create metrics, and highlight challenges. The first day ended with groups compiling their information for presentations the next morning. The second day began with breakout groups sharing the group's findings, followed by the second breakout group to identify initiatives to meet each group's objectives. These initiatives were shared the afternoon of the second day. The third day was to review steps forward, next meeting dates, and review the Terms of Reference. The full breakout of the agenda can be found in Annex B.

LESSONS LEARNED

Based on participant feedback and observations from event planners, participants agree that future meetings should be held to continue the progress of the RCN to its end goals. In future meetings, the RCN participants would like to bring in more participants from various backgrounds. Suggestions for future meeting participants included: involvement of locals, representatives from organizations within countries who need assistance, and various researchers. In addition, members asked for meeting objectives, end goals, and an agenda to be provided well ahead of the meeting.

RESEARCH FOCUS AREA

Prior to breakouts, a whole group discussion outlined and defined the research focus areas. Below are the focuses of each group along with the research members for each group.

FOCUS AREA 1: REGIONAL RISKS AND BURDEN

Epidemiological studies of the disease have not fully captured the prevalence and variance of rickettsioses throughout Southeast Asia. The focus should be on the following:

- Conducting consolidated studies across the region
- Define at risk locations and populations
- Research regional burdens and economic impact of infections

FOCUS AREA 1 RESEARCH MEMBERS

- Dr. Paul Newton
- Dr. Sazaly Bakar
- Dr. Kartika Saraswati
- Dr. Le Thi Hoi
- Dr. Nguyen Vu Trung
- LCDR Jeffrey Hertz, Ph.D.
- MAJ Elizabeth Wanja, Ph.D.
- MAJ Silas Davidson, Ph.D.
- Dr. Ian Mendenhall
- Dr. Piyada Chanroensinphon
- COL Jariyanart Gaywee
- Dr. Brett Forshey

FOCUS AREA 2: DETECTION AND DIAGNOSIS

The most commonly used tests to diagnose *Rickettsia* infections lack sensitivity and specificity and are not particularly useful for acute diagnosis in an endemic setting; however, they are commonly employed because they are the cheapest and quickest option for low-resourced settings. The focus should be on the following:

- Survey available diagnostics
- Test and evaluate current diagnostics
- Survey national case definitions for rickettsial pathogens

FOCUS AREA 2 RESEARCH MEMBERS

- Dr. Cecilia Kato
- Dr. George Varghese

- Dr. Matthew Robinson
- Dr. Jackie Duggan
- Dr. Stuart Blacksell
- COL Wuttikon Rodkvamtook, Ph.D.
- Dr. Yazid Abdad
- Dr. John Stenos

FOCUS AREA 3: PATHOGENICITY AND IMMUNE RESPONSE, TREATMENT, AND PREVENTION

Clinical recognition is a challenge due to vast variability and non-specific presentation of symptoms for rickettsial infections. The focus should be on the following:

- Research human susceptibility
- Research current and new treatments
- Research host-pathogen interaction
- Research pathogen diversity for vaccine development

FOCUS GROUP 3 RESEARCH MEMBERS

- Dr. Nick Day
- Dr. Steve Dumler
- Dr. Tri Wangrangsimaku
- LTC Matthew Wegner, DVM
- Dr. Stephen Graves
- Dr. Al Richards

OUTCOMES FROM RESEARCH FOCUS AREA BREAKOUT SESSIONS

BRIEF-OUT FROM FOCUS AREA BREAKOUT SESSIONS

Working within their focus areas, each develop multi-year objectives, measurements for success, and identified overall challenges to success. In the table below, the group's multi-year objectives are each outlined along with measure for success. Finally, the groups identified key initiatives with associated timelines and challenges for future work. The below table reflects a summary of the key findings from the breakout groups. For the original focus area out-briefs please reference Annex C.

Focus Area 1: Regional Risks and Burden – Session 1

Objectives	Metrics	Challenges
Obj. 1: Develop a surveillance and data sharing network in SEA Obj. 2: Better understand epidemiological factors Obj. 3: Establish standards, protocols, and associated training	• Increased understanding of threats for partner nation policy and decision makers • Increased awareness amongst health care professionals • Increased publications on *Rickettsia* topics • Increased identification of new species • Increased awareness amongst diagnosticians	• Seeking national policy-maker/decision-maker buy-in • Identifying vertebrate and arthropods • Ensuring funding/prioritization challenges align with RCN goals • Geographical obstructions to sample collection • Building awareness amongst POC health professionals • Building awareness amongst at risk populations Conducting research in BSL3 • Sharing data amongst • researchers/transparency • Ensuring sustainability

Focus Area 1: Regional Risks and Burden – Session 2

Initiatives	Timeline
1. Establish baseline understanding of existing capabilities, knowledge, resources 2. Establish a web-based network 3. Establish minimum human and vector case data collection and sharing protocols 4. Conduct Outreach/ Next Planning Meeting	1. 36 Months 2. 8 months 3. 12-18 Months 4. Immediately

Focus Area 2: Detection and Diagnostics – Session 1		
Objectives	**Metrics**	**Challenges**
Obj. 1: Sample Preparation Obj. 2: Sample Banking Obj. 3: Sample Testing Obj. 4: Assessment of Assays	• Standard operative procedures • Mechanism for informing others of positive material • Methods of Sharing clinical and vector samples, peptides and antigens, and nucleic acid preps • Standards and positive controls • Equipment calibration and standardization • Training and proficiency	• Validation of sample types/ tissue types • Honest broker as a Biobank Cross-border shipment Cost per test • Testing platforms (existing vs. novel, point of care vs. laboratory, simplex vs. multiplex, ELISA or IFA or PCR or Other IgM vs IgG • PCR Based Country variation Patient populations Understanding different national standards for reporting • Sustainment in resources in limited settings • Preparation of antigen “in house” • Data/Reporting/Publication

Focus Area 2: Detection and Diagnostics – Session 2	
Objectives	**Metrics**
1. Multiplex PCR Test 2. Constructed analytical samples 3. Serology Assays to Mirror PCR (IgM/IgG) 4. Constructed Analytical Samples 5. Alternative Assays	1. 3 to 6 months 2. 6 to 12 months 3. 6 to 12 months 4. 6 to 12 months 5. 6 to 12 months

Focus Area 3: Pathogenicity and Immune Response, Treatment, and Prevention – Session 1		
Objectives	**Metrics**	**Challenges**

Obj. 1: Clinical Treatment Trials for Scrub Typhus Obj. 2: Adjunctive treatment for Scrub Typhus Obj. 3: Develop Vaccines for Scrub Typhus Obj. 4: Develop Vaccines for Q Fever Obj. 5: Clinical Treatment Trials for Murine Typhus Obj. 6: Burden of other *Rickettsia* Pathogens	• Trial outcomes and publishing results • Developing and initiate trials involving adjunctive therapies (e.g., Steroids) • Gather available data • Develop immune correlates of protection • Efficacy in mouse/NHP/human challenge model • Development of highly effective, easy use vaccine for general rural populations and military • Trial outcome and publishing results	• Funding to maintain output • Policy change • Difficulties in areas with entrenched practices • Primate models: problematic/testing different isolates • Human models: ethical and issues with persistence requires clarification • Prevalence in other areas • Lack of information •

Focus Area 3: Pathogenicity and Immune Response, Treatment, and Prevention – Session 2	
Initiatives	**Timeline**
1. In-depth review of gaps in treatment and prevention of Rickettsial diseases 2. ST Treatment Trials 3. Review use of chloramphenicol and other antibiotic treatments 4. Review adjunctive treatments 5. Develop immune correlates, assess persistence and evaluate vaccine candidates for Scrub Typhus 6. Develop immune correlates, animal and human trials, and evaluate vaccine candidates for Q Fever 7. Treatment for Murine Typhus	1. SUT: 1 year 2. START: end of 2019, INTREST: starting in summer 2018 18 Months 3. 2 years 4. IFN-gamma, flow cytometry, humoral (1yr), 5. gene transcription profiling (1-2yrs), Follow up/Extension of current studies and obtain funding for additional analysis (3 to 4 years) 2 - 3 years 6. 3 - 4 years 7.

The following Action Items were recorded and compiled by the organizational and administrative support staff of CBEP for the Rickettsial Pathogens RCN. The following working groups were organized by focus areas. The heavy emphasis on focus area 1 is due to the need to set the parameters for burden and understanding of rickettsial pathogens. However, members from all three focus areas are represented in the responsible agents. Organizational support members will be in touch before meetings with responsible agents to check status of working groups and provide communication support.

ACTION	RESPONSIBLE AGENTS
Focus Area 1: Working Group 1 will establish protocols for field sampling	Hertz, Davidson, Bakar, Mendenhall, Serge Moran **Organization Support:** Leahy
Focus Area 1: Working Group 2 will transition melioidosis website and integrate other website data	Stokes, Day, Richards **Organization Support:** Hudson
Focus Area 1: Working Group 3 will set literature review (existing knowledge, gaps, and resources) foci and bounds	Saraswati, Day, Varghese, and Dumler **Organization Support:** Becker
Focus Area 2: Working Group 4 will survey existing molecular and serological tests and survey available reagents and SOPs	Kato, Richards, Duggan, Robinson, Blacksell, Stenos, and Abdad **Organization Support:** Leahy

An after-event survey was sent to the participants to collect information on their progress and overall thoughts on the progress of the RCN. Members were asked to answer the following questions:

1. What did you like about the meeting?
2. Do you think the objectives for the 6- 8 March Rickettsial RCN meeting were achieved? Please explain your answer.
3. What do you wish we did differently?
4. What does success of this network look like to you, for your field of study? 5. Additional comments.

All participants agreed the objectives of the Rickettsial Pathogen RCN were met during the 6-8 March meeting and the meeting facilitated the introduction of relevant researchers. The RCN meeting helped participants to prioritize research on rickettsial pathogens and identify gaps in knowledge. In addition, the RCN successfully set goals, finalized objectives for the RCN, and created an action list for next

steps. Participants agreed that success of this RCN will be evident when there is an increased awareness of rickettsial pathogens, increased number of studies or deliverables from the RCN, innovative tools and diagnostics, support to all aspects of clinical and research levels of studies, increased funding for research, and vector identification. Suggestions for future meeting participants included: involvement of locals, representatives from organizations within countries who need assistance, and various researchers. In addition, members asked for meeting objectives, end goals, and an agenda to be provided well ahead of the meeting. Overall, participants commented positively on the RCN meeting and were pleased with the mix of educational and research backgrounds and hope to continue to foster the communication between group members to sustain the RCN.

The following participants attended or were invited to attend:

STEERING COMMITTEE MEETING INVITEES, DID ATTEND		
Abdad	Yazid	Communicable Disease Centre, Singapore
Bakar	Sazaly	University of Malaysia, Tropical Infectious Disease Research and Education Centre
Blacksell	Stuart	Mahidol-Oxford Tropical Medical Research Unit
Chanroensinphon	Piyada	Armed Forces Research Institute of Medical Science
Day	Nick	Mahidol-Oxford Tropical Medical Research Unit
Davidson	Silas	Armed Forces Research Institute of Medical Science
Duggan	Jackie	Rare and Imported Pathogens Laboratory National Infections Sevices
Dumler	Stephen	Uniformed Services University of Health Sciences
Forshey	Brett	Global Emerging Infections Surveillance
Gaywee	Jariyanart	Armed Forces Research Institute of Medical Science – Royal Thai Army
Graves	Stephen	Australian Rickettsial Reference Laboratory
Hertz	Jeffrey	Navy Medical Research Center - Asia
Hoi	Le Thi	National Hospital for Tropical Diseases, Vietnam
Kato	Cecilia	CDC, Division of Vector-borne Diseases
Mendenhall	Ian	Duke-National University of Singapore
Newton	Paul	Lao-Oxford-Mahosot Hospital-Wellcome Research Unit
Richards	Al	Naval Medical Research Center
Robinson	Matthew	Lao-Oxford-Mahosot Hospital-Wellcome Research Unit
Rodkvamtook	Wuttikon	Armed Forces Research Institute of Medical Science – Royal Thai Army
Saraswati	Kartika	Lao-Oxford-Mahosot Hospital-Wellcome Research Unit

Stenos	John	Australian Rickettsial Reference Laboratory
Trung	Nguyen Vu	National Hospital for Tropical Diseases, Vietnam
Varghese	George	Christian Medical College in Vellore, India
Wangrangsimakul	Tri	Mahidol-Oxford Tropical Medicine Research Unit
Wanja	Elizabeth	Armed Forces Research Institute of Medical Science
Wegner	Matthew	Armed Forces Research Institute of Medical Science
Stokes	Marty	DTRA CBEP
Tuttle	Emerson	DTRA CBEP
Dutt	Diane	DTRA RD-CB
Becker	Stephen	A&AS
Leahy	Katie	GSE
Hudson	Megan	GSE

ANNEX B – MEETING AGENDA

The following agenda was set for the meeting. The majority of discussions focused on the administration, organization, and focus of the network.

Day 1 – 6 March 2018

Time	To pic
0830 – 0850	Welcome, Agenda Review, and Introduction to Networks Dr. Martha Stokes, CBEP
0850 – 0900	Housekeeping and Admin Ms. Katie Leahy, GSE
0900 – 0930	Introductions and Icebreaker All
0930 – 1000	Rickettsia in Southeast Asia Dr. Paul Newton, Lao-Oxford- Mahosot Hospital-Wellcome Resea
1000 – 1030	Current Research and Interests (Researcher and Funder Quad C Facilitated by Ms. Megan Hudson, GSE
1030 – 1100	Tea Break
1100 – 1130	Current Research and Interests (Researcher and Funder Quad C Facilitated by Ms. Megan Hudson, GSE
1130 – 1200	Introduction to Strategic Mapping Ms. Katie Leahy, GSE
1200 – 1330	Lunch Break
1330 – 1500	Breakout Group Session 1 All Work through strategic mapping template for session 1 (objective Instructions are in your folders
1500 – 1530	Tea Break
1530 – 1600	Breakout Group Session 1 All Translate discussion materials onto slides Instructions are in your folders

1600 – 1630	Review for Day 2 Ms. Katie Leahy, GSE

Day 2 – 7 March 2018

Time	To pic
0900 – 1000	Session 1 Group Discussion 5 minutes / group Followed by 10 minutes Q&A / group
1000 – 1015	CBEP Review Dr. Marty Stokes
1015 – 1200	Breakout Group Session 2 All Work through strategic mapping template for session 2 (initiatives, timel outreach)
1200 – 1330	Lunch
1330 – 1400	Breakout Group Session 2 All Translate discussion materials onto slides
1400 – 1445	Session 2 Group Discussion 5 minutes / group Followed by 10 minutes Q&A / group
1445 – 1515	Tea Break
1515 – 1600	Terms of Reference Discussion Draft is in your folders Please review in-time for this discussion and be ready to provide opinio

Day 3 – 8 March 2018

Time	To pic
0900 – 1100	Event Hotwash and Next Steps Questions to think about: 1. Who and what disciplines are we missing? 2. What events do we want to put on the calendar for the nex 3. How will we map and record progress (e.g., defining regio regional disease burden)
1100 – 1130	Tea Break

DR. MARTHA STOKES, CBEP AND RESEARCH COORDINATION NETWORKS, 6 MARCH 2018

CBEP AND RESEARCH COORDINATION NETWORKS

Dr. Martha Stokes, CBEP

0830 – 0900

UNCLASSIFIED

CBEP Science Research Program

- The CBEP science research program builds national and regional research capacity and rooted in:
- Biosurveillance
- Biosafety and Biosecurity
- Collaborative Research • Priorities for the program:
- Sustainability
- Defining global disease prevalence and burden of underreported and underdiagnosed pathogens *
- Compliance with other international guidelines, regimes, and norms, e.g., BWC, IHR, GHSA

UNCLASSIFIED
UNCLASSIFIED

CBEP in Southeast Asia

- Region has unique challenges and opportunities
- Geography (e.g., shared borders)
- Changing demographics and land-use (e.g., anthropogenic effects on land-use)
- Transborder movement of people and animals (e.g., undocumented migrant workers and unregistered asylum seekers)
- Existing networks and communities of practice (e.g., sub-regional disease surveillance)
- Emerging infectious disease (e.g., Nipah, SARS, ???)
- CBEP works with individuals and organizations to enable better disease recognition and reporting in a safe and secure settings at the clinical and laboratory levels
- CBEP serves as an integrator in the region, building horizontal frameworks by convening or enhancing existing efforts

** Must also be on the U.S. Select Agent List or a pathogen that requires differential diagnosis to rule out an intentional or accidental threat*

Why Do We Use Research-Based Networks?

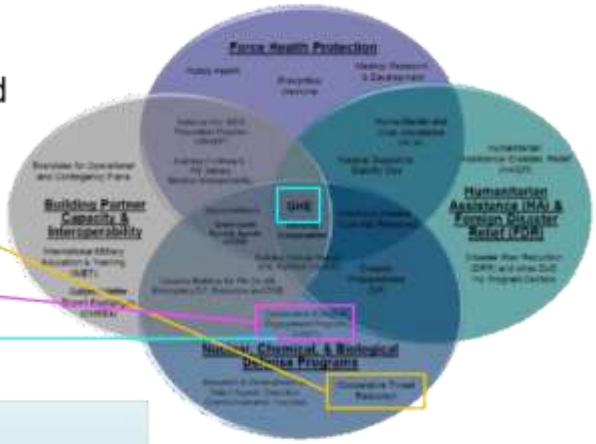
- CBEP uses the term Research Coordination Network* as a coordination mechanism to gather multidiscipline investors to:
- Share information, data, samples and protocols
- Develop community standards and best research practices
- Leverage funding opportunities
- Coordinate research activities, training events, workshops
- Advance science and education initiatives in the region
- Foster long-term relationships with partner governments
- Bridge geographic, disciplinary and cultural boundaries
- RCNs are part of the program's Threat Reduction Networks

Foundation **Note: Term in 2000 was established by the U.S. National Science*

UNCLASSIFIED

CBEP's Relationship to U.S. DoD

- DoD focuses on reducing health security threats to U.S. forces abroad and citizens at home
- Cooperative Threat Reduction, and CBEP are part of a broader suite of health security tools that make up DoD "Global Health Engagement"



SOURCES: 2017 National Security Strategy and DoD Instruction 2000.30 Global Health Engagement Activities (July 2017)

UNCLASSIFIED

UNCLASSIFIED

Q: Why is DoD Interested in Rickettsial Pathogens?

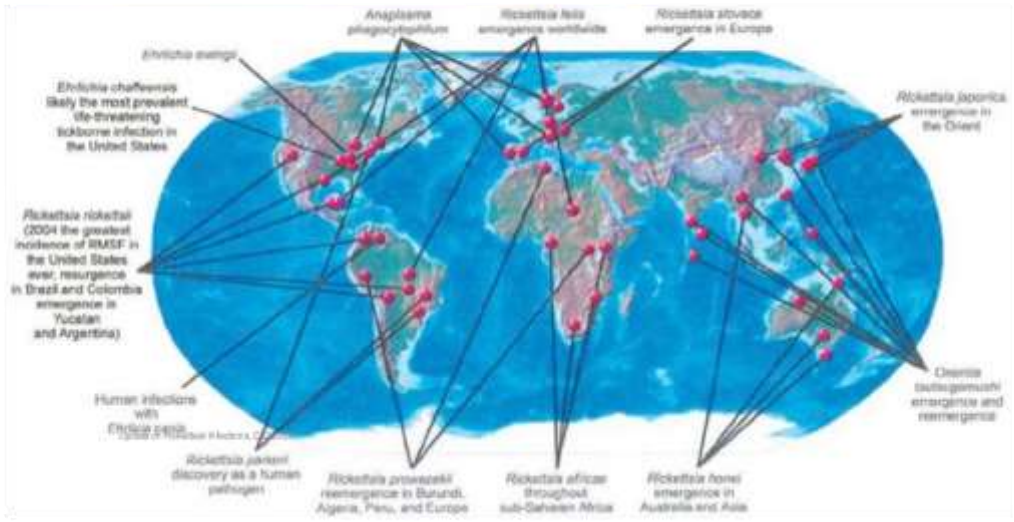
- Several rickettsial disease have potential impacts on military missions
  - Outbreaks remain common in temperate and tropical regions particularly in Southeast Asia, Japan, Korea, and Afghanistan
  - Increased troop presence to these areas increase the disease threat
- Newly emerging strains of scrub typhus rickettsia in Asia-Pacific regions present an increased threat en to troop health
- Increasingly important for joint efforts to develop standards of practice for surveillance, diagnostics and treatment of rickettsial pathogens
- Biological characteristics of rickettsial pathogens could lead to potential use as bioterrorism agent

SOURCES: Bavaro, M.F., et al., "History of U.S. Military Contributions to the study of Rickettsial Diseases." Military Medicine 170 (2005): 49-60

UNCLASSIFIED

UNCLASSIFIED

Global distribution of rickettsias



SOURCE: Lecture presented at Pediatric ID, Viral Diseases Branch in Walter Reed Army Institute of Research, Dr. Richard Ruck. February 2014.

UNCLASSIFIED

UNCLASSIFIED

Network Objectives *

- Convene multi-disciplinary researchers, health implementers, policy makers and funding authorities to identify and prioritize rickettsia research needs and gaps

- Characterize the distribution and prevalence of rickettsial diseases in Southeast Asia to better understand and address the human health burden using statistical analysis and other best practices for assessing the global burden of other neglected infectious diseases
- Employ, monitor, and evaluate the consistent use of “gold standard” diagnostics and community accepted case definitions to determine if better standards are needed for detection in lab and clinical settings
- Increase awareness for rickettsia amongst at-risk populations, clinicians, laboratory staff, national decision makers for better prevention, detection, and

response

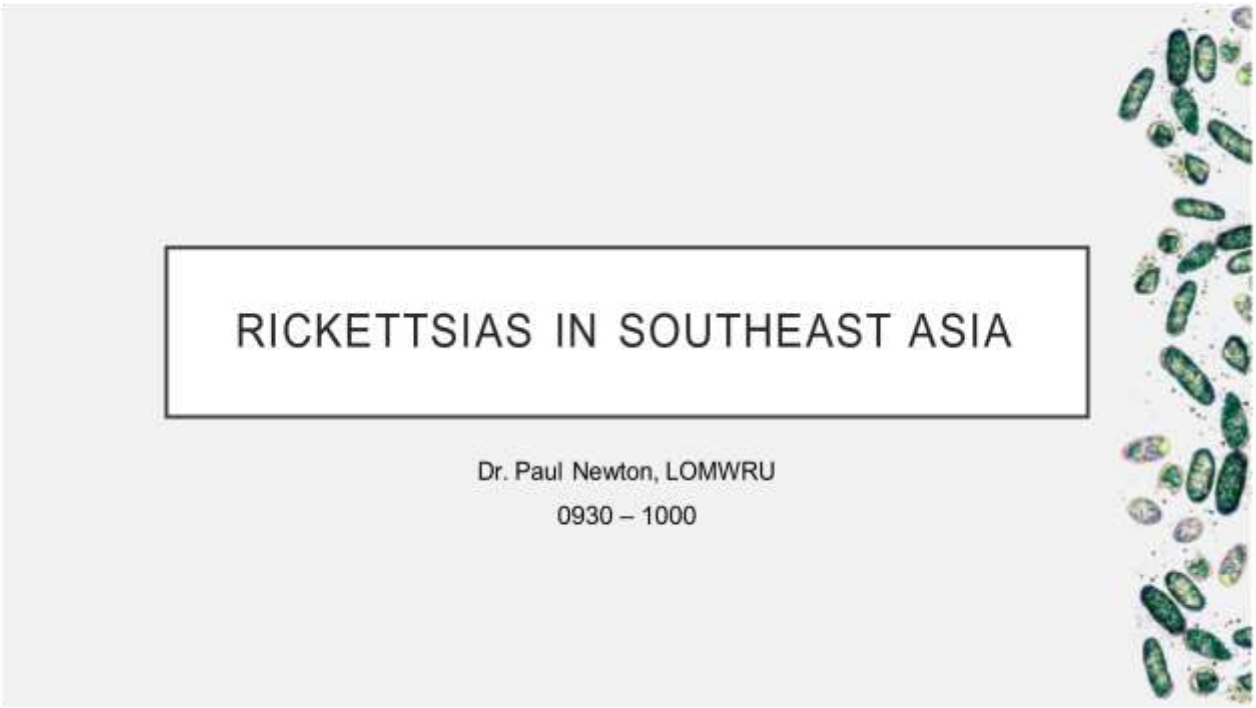
November meeting in Baltimore

* ***Note:*** *the text on this slide was discussed and modified during the 9*

Expected Network End States *

- Improved characterization of geographic distribution in SEA
- Improved understanding of pathogen diversity and the full spectrum of its epidemiology in SEA (and beyond)
- Improved technology for diagnostics
- Improved technology and SOPs, access to accurate and affordable diagnostics and countermeasures
- Better SOP for IFA
- Improved global interest in rickettsia research
- National surveillance / data collection data from Thailand feeding estimates across the region

* ***Note:*** *the text on this slide was discussed and modified during the 9 November meeting in Baltimore*



Rickettsial Diseases in SE Asia

Overview

MORU Tropical Health Network

- Provide overview of the current findings and knowledge gaps in SEA

- Discuss gaps in mapping the disease and surveillance
- Discuss inadequacies in diagnostics
- Shape the problem in SEA and provide context to the meeting

Rickettsial Diseases

All – headache, fever & myalgia
Severe disease – CNS, lungs & liver

Spotted Fever Group

Typhus Group:
Rickettsia typhi (Rt) *&*
R. prowazekii (Rp)

Orientia tsutsugamushi

mites vectors & reservoirs. Not just in 'scrub'.

Eschar & rash in variable %. New evidence for *Orientia* spp. in Chile and Dubai.

Data suggests responds to tetracyclines (T), chloramphenicol (C) & azithromycin. Intrinsic resistance to fluoroquinolones Resistance to T & C in northern Thailand?

Scrub typhus. Trombiculid

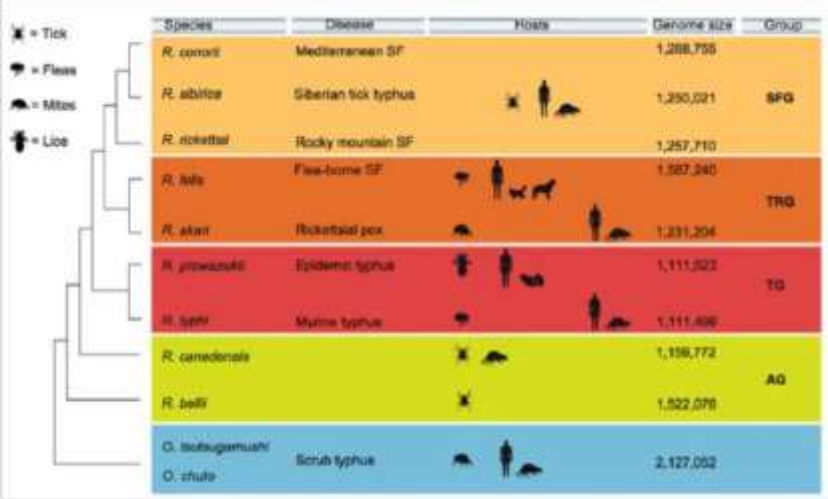
South Asia, SE and NE Asia, northern Australia.

Cannot enter host cell nuclei. Rt – probably global – murine/endemic typhus. Flea faeces. Rp – focal, global - epidemic typhus. Body lice. No eschar. Rash in variable %. Rp -Brill-Zinsser disease.
Rp has caused many millions of deaths, recent jail outbreaks. Rt an under-recognized cause of fever.

Tetracyclines & chloramphenicol - conventional. Probably not fluoroquinolones. Not azithromycin–other macrolides ?

Multiple species, expanding list. Can enter host cell nuclei. Mostly tick borne. *R. felis* flea borne and *R. akari* mite borne. Includes Rocky Mountain Spotted Fever (*R. rickettsii*), African Tick Bite Fever (*R. africae*), Mediterranean/Indian/Israel i Spotted Fever (*R. conorii*). Eschar in tick & mite borne SFG, in variable %.
Variable % rash. Many as 'unspotted spotted fever'

Few data. Tetracyclines the conventional choice



Summary of genetic groups of *Rickettsia* and *Orientia* spp.

Fuxelius et al. The genomic and metabolic diversity of *Rickettsia*. Res Microbiol 2007;158:745-53

Why are they and a network important ?

- Major causes of undiagnosed but treatable fever in rural Asia
- But few accessible diagnostic tools – innovation needed !
- Need for platforms for joined up mapping in space and time of rickettsial pathogens in vectors, humans and non-human vertebrates to inform risk analysis
- Need for multicenter diagnostic evaluations informing consensus protocols across Asia
- Need for multicenter clinical trials to inform, rapidly, optimal therapy across Asia
- Relatively little clinical awareness and research for their probable disease burden

Causes non-malarial, haemoculture negative fever in rural Asia ?

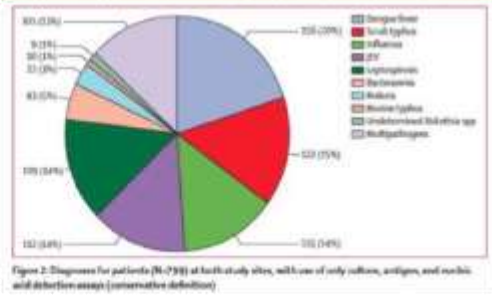

Etiology of Acute, Non-Malaria, Febrile Illnesses in Jayapura, Northeastern Papua, Indonesia

In Vientiane, hospitalised patients, blood culture negative

▪Doxycycline responsive illnesses▪ 39 %

Scrub typhus	16%
Leptospirosis	10%
Dengue	10%
Murine typhus	10%
Spotted fever	3%


Clinical and Epidemiological Characteristics of Scrub Typhus and Murine Typhus among Hospitalized Patients with Acute Undifferentiated Fever in Northern Vietnam



Murine or Endemic Typhus

Flea-borne rickettsiosis caused by *R. typhi*

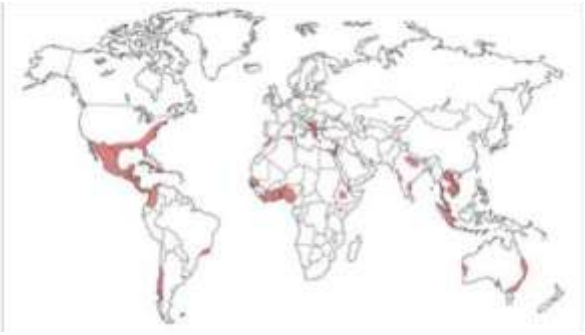
Oriental rat flea *Xenopsylla cheopis* is the principal vector and rodents, mainly *Rattus norvegicus* and *R. rattus*, act as reservoirs

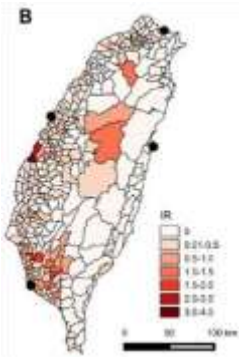
Infection via flea faeces self-inoculation of skin

Recent evidence for involvement of dog ticks *Rhipicephalus sanguineus*

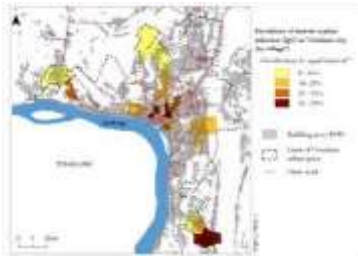
Can cause severe disease, CNS, interstitial pneumonitis,

cholecystitis….
Little awareness
Diagnostics rarely available



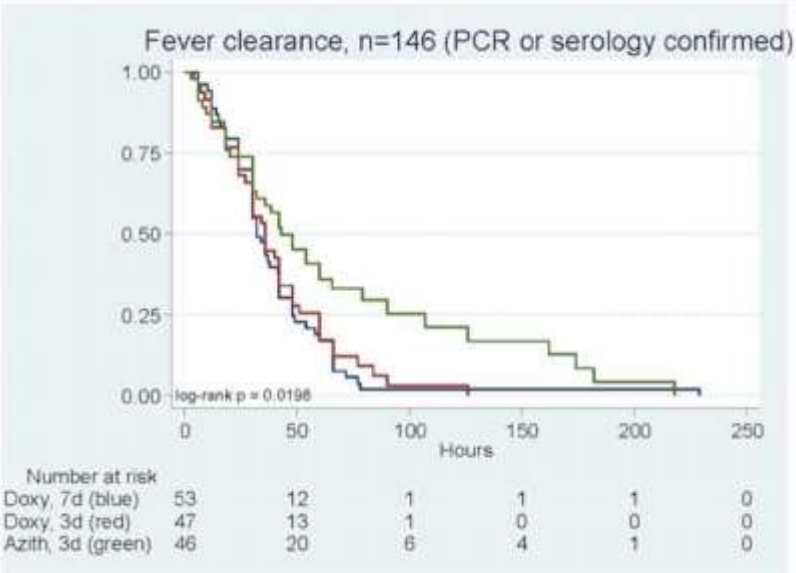


*No objective global mapping systems _ evidence that is associated with markets and seaports



*PCR available but low bacterial load
* One slow RDT available
* No objective evidence on serological cut-offs and how they may vary by geography

Kaplan-Meier plot of fever clearance for patients with PCR confirmed murine typhus only (N=49, Log-rank test P=0.007)



Epidemic Typhus

- *R. prowazekii*

- Terrible epidemics associated with war
- Louse-borne via louse faeces, aerosols & by skin auto-inoculation, following scratching
- Not transmitted vertically in lice and humans are the major reservoir
- No recent reports from SE Asia

Tokyo 1914

Closest to SE Asia and most recent,

Yunnan 1950s

Pune, India 1989 but using CF

? In Asian body lice

? At high altitude – eastern Himalaya ?

Meningoencephalitis, tinnitus, deafness, and altered consciousness ranging from mild confusion through agitated delirium and coma

Rash, diarrhoea, pulmonary involvement, myocarditis, splenomegaly and conjunctivitis may also occur.

Recent epidemics in central African prisons

In outbreaks 200mg doxycycline stat and louse control – boil clothing

Recrudescence of epidemic typhus unrelated to louse infestation = Brill–Zinsser disease. Case report suggest that azithromycin may not be efficacious

Sporadic cases through contact with flying squirrels in USA

Squirrels elsewhere?

Spotted Fever Group

- Large and expanding number of rickettsial species, transmitted by ticks - > 26 species

- Tick distribution the ecological key
- Often with eschar
- Commonly ‘unspotted’ spotted fever • Many species – more each year. In Asia e.g.
  - *R. japonica*
  - *R. conori*
  - *R. honei*
  - *R. tamurae*

Tick surveillance to map which ticks are where and what pathogens thay contain – to inform human surveillance

Serology for SFG complicated and uncertain – consensus protocols ? Decreasing

number of tick morphological taxonomists

PCR and MALDI-TOF tick identification, combined with pathogen detection

Splitters and lumpers…..

Molecular and MALDI-TOF identification of ticks and tick-associated bacteria in Mali

Adama Zan Diarra[1,2], Lionel Almeras[1,3], Maureen Laroche[1], Jean-Michel Berenger[1], Abdoulaye K. Koné[2], Zakaria Bocoum[2], Abdoulaye Dabo[2], Ogobara Doumbo[2], Didier Raoult[1], Philippe Parola[1]*

Transitional group rickettsiae

R. australis, *R. akari* and emerging group of *R. felis* and *R. felis*-like rickettsiae (transmitted by ticks, mites, fleas…*Anopheles* ….

Rickettsialpox - a vesicular skin eruption, caused by *R. akari*, transmitted by

Liponyssoides sanguineus, a mite that lives on house mice…no records from Asia ?

Scrub Typhus

- Scrub typhus. Trombiculid mites vectors &

- Described in Japan in the 1800s –
- South Asia, SE and NE Asia, northern
- New evidence for *Orientia* spp. in Chile and Dubai……Africa ?

http://www.vectormap.org/Project_ScrubTyphus.htm

Multiple ecological uncertainties

- What determines chigger distribution?
- What determines mite islands and do they occur

- How do they change through time?
- The ecology of the chigger-rodent interaction?
- How important are birds – for dispersal ?
- Do chiggers only bite once in the wild?
- Are other vectors important – leeches?
- How do arboreal squirrels get infected?

Prevention

- Risk stratification by time and space
- Vaccine
- Optimal miticides
- Engagement with those at risk

reservoirs. Not just in 'scrub' tsutsugamushi, river fever, Chiba…..

Australia. Eschar & rash in variable %

in the different habitats scrub typhus can be contracted within? e.g. beach and gardens?

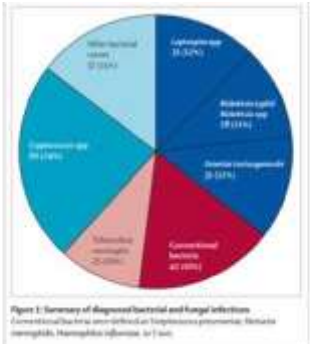
- Median series untreated mortality 6%
  (range 0-70%)
- Mortality higher with age and varied by location
- Increased mortality in patients with myocarditis, delirium, pneumonitis, haemorrhage but not with presence of eschar or meningitis

SCRUB TYPHUS IN ASSAM AND BURMA

A Clinical Study of 616 Cases

JOHN J. SAYEN, Capt., M.C., HAROLD S. POND, Capt., M.C., JAMES S. FORRESTER, Lt. Col., M.C., and FRANCIS C. WOOD, Col., M.C.

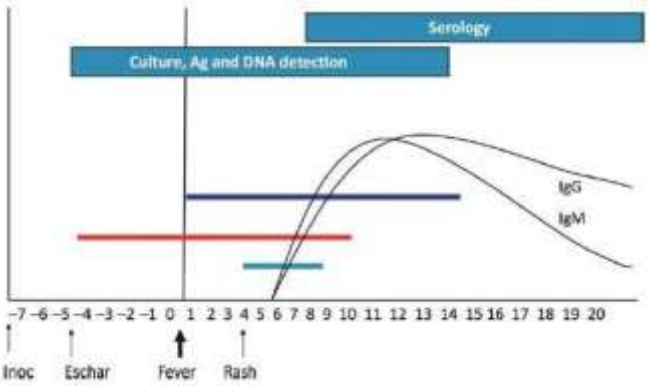
(3) *Summary:* Meningoencephalitis was found in all scrub typhus cases at necropsy. There was reason to think that the central nervous system was involved at least slightly in almost all patients. The meningeal involvement did not always produce clinical signs and even when these occurred they indicated a severe, but not necessarily a grave, illness. Confusion, tremor and myoclonia were common. Delirium occurred frequently in the dangerous group. Malignant restlessness or convulsions were among the most ominous signs of the disease, and coma was usually followed by exitus.



- Serology
  - Immunofluorescence assays - Relatively low sensitivity & specificity of antibody assays on admission sera. Poor intra- and inter-observer IFA agreement – cut-offs not evidence based

Laboratory diagnosis

- Australian RRL EQA
- ELISA – progress as screening tools
- Molecular assays –PCR & LAMP from buffy coat and eschars. Relatively low sensitivity of PCR assays – low bacterial load
- Portable, inexpensive PCR machines becoming available. LAMP assays
- Culture – BLS3

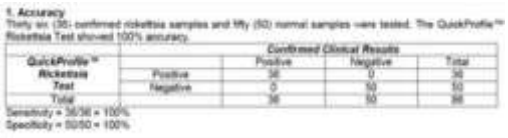


Clinical and diagnostic timeline

Richards AL. Worldwide detection and identification of new and old rickettsiae and rickettsial diseases. FEMS Immunol Med Microbiol 2012;64:107-110

Rickettsial diagnosis in rural Asia

- Rapid diagnostic tests (RDTs) – available for scrub typhus – slowly increasing evidence base for accuracy
- Some commonly sold in Asia have no evidence of their diagnostic accuracy
- Therefore, use both serology and molecular diagnosis ?
- Could there be specific antigens? cf dengue NS1 and recent work



1. Accuracy

Thirty six (36) confirmed rickettsia samples and fifty (50) normal samples were tested. The QuickProfile™ Rickettsia Test showed 100% accuracy.

		Confirmed Clinical Results		
QuickProfile™ Rickettsia Test		Positive	Negative	Total
	Positive	36	0	36
	Negative	0	50	50
	Total	36	50	86

Sensitivity = 36/36 = 100%
Specificity = 50/50 = 100%

Disease sleuths unmask deadly encephalitis culprit

on *B. burgdorferi*

EXPERT REVIEWS

Treatment of *Rickettsia* spp. infections: a review

Elisabeth Botelho-Nevers, Cristina Socolovschi, Didier Raoult and Philippe Parola*

Trans R Soc Trop Med Hyg 2017; **111**: 336–344
doi:10.1093/trstmh/trx066 Advance Access publication 15 December 2017

Drug treatment of scrub typhus: a systematic review and meta-analysis of controlled clinical trials

Ian Wee[a], Adeline Lo[b] and Chaturaka Rodrigo[c,*]

Treatment

- Few trials for scrub typhus, none for murine typhus. Problem of 'relapse' definition
- Oral doxycycline usually used for uncomplicated disease – but for 1 or 7 days ? 2mg/kg twice a day after a loading dose of 4mg/kg ?
- Chloramphenicol, telithromycin, roxithromycin, rifampicin and azithromycin ….but murine typhus
- Scrub typhus intrinsically resistant to flouroquinolones
- Genetic diversity of scrub typhus and geographical variability in mortality suggests that one Rx may not be appropriate over range of scrub typhus
- Severe typhus – no clinical trial data from Asia


Scrub typhus infections poorly responsive to antibiotics in northern Thailand

Resistance ?

- 1996 - on third day of oral doxycycline treatment, fever had cleared in all seven patients from Thai/Burma border, but in only five of the 12 (40%) from N Thailand ($p<0{\cdot}01$). Median fever clearance time in N Thailand (80 h; range 15–190) was significantly longer than Thai/Burma border (30 h; range 4–58; $p<0{\cdot}005$)
- Doxycycline & chloramphenicol prevented death in mice infected by Chiangrai strains of *O. tsutsugamushi* less often than after infection by the prototype strain ($p<0{\cdot}05$). Only one of three N Thai strains tested in cell culture was fully susceptible to doxycycline
- *O. tsutsugamushi* is intrinsically resistant to fluoroquinolones – virtue of their *gyr* genes

Needs revisiting across all rickettsial pathogens with interlinked:

- Clinical trials with standardized consensus FCT, treatment failure and relapse definitions
- MIC monitoring with standardized consensus protocols & dashboards
- Genomic analysis of markers of antimicrobial susceptibility

Neorickettsia sennetsu

1999 – described from Laos for first time – second report globally since the 1960s in Japan

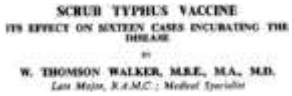
PCR for *N. sennetsu* positive in one fish and four patient sbut high background seroprevalence in Laos

Other *Neorickettsia* spp. in Cambodian fish

Important in societies eating raw/fermented fish

Many key questions remain

- The comparative ecology of diverse rickettsial pathogens, risk and risk mitigation – needs multiple skill sets
- Vector control
- What is the burden of disease – where, when and why?
- How to facilitate simple, accurate, accessible, rapid, affordable diagnosis in rural Asia
- Is severe disease associated with host or pathogen factors or both ? How to treat severe disease?
- Should antibiotic treatment vary by geography ? How many days of doxycycline ?
- Where is antibiotic resistance and why ?
- Vaccines ?


SCRUB TYPHUS VACCINE

ITS EFFECT ON SIXTEEN CASES INCUBATING THE DISEASE

BY

W. THOMSON WALKER, M.R.E., M.A., M.D.

Late Major, R.A.M.C.; Medical Specialist

Ode to Rickettsiae[1]

Veranja Liyanapathirana

Oh! dear Rickettsiae.

Why did you become such a difficult bug?

You and your cousin (once removed) *Orientia*,

So tiny: yet so powerful

I cannot grow you, because you need special care.

My poor home can not offer a cocoon for you to grow

My poor home has no safety nets to contain you.

You are an illusion to me.

I see you in the darkened room, indirectly as a bright green star,

Illuminated on the glassy shrines.

I try to look for you, for your DNA

You still manage to evade me.

Some day my dear, some day,

I will build a house, with walls so strong,

So I can grow you and nurture you within.

Some day my dear, some day soon,

I will find a little DNA, amplify and see.

Till then, let us meet, in the darkened room, you dressed in your finest green.

Brightly illuminated like the Milky Way.

Dr Liyanapathirana is a lecturer in the Department of Microbiology, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka. Her research interests include rickettsial infections and molecular microbiology.

Address for correspondence: Veranja Liyanapathirana, Department of Microbiology, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka. email: veranjal@yahoo.com

Thank you

DR. MARTHA STOKES, CBEP REVIEW, 7 MARCH 2018

CBEP REVIEW

Day 1 Review and Comment

1000 – 1015

RESEARCH COORDINATION NEXT STEPS

- CBEP serves as an integrator in the region, convening or enhancing existing efforts

- We can assist with:
  - Partnerships between institutions (e.g., twinning, training exchanges)
  - Training support (e.g., diagnostic protocols and SOPs, multi-sectoral coordination)
  - Awareness-building amongst practitioners, stakeholders, and decision-makers
  - Convening experts, communities of practice, and other networks (formal and informal) into an objectives-based research network with tangible goals and outcomes

RCNS: TRANSLATING DATA INTO ACTION

RCNS: TRANSLATING DATA INTO ACTION

MELIOIDOSIS RCN

MULTIDISCIPLINARY SCIENCE RESEARCH
Research Coordination Network
SOUTHEAST ASIA WORKSHOP • 23 - 25 FEBRUARY 2016

- Convened international experts, organizations and U.S. funding entities in One Health Research
- Mapped areas of research across the region to determine overlaps, needs, and priorities
- Set timelines, objectives, and short and long-term implementation plans
- Adopted terms of reference for RCN

- BIGGEST OUTCOMES??
  - Need for policy maker awareness
  - Better characterization of the disease in under-reporting areas (**Cambodia** and Lao)

CAMBODIA Training Event for Awareness of Melioidosis (C-TEAM) Objectives

- Build national awareness of disease burden through increased knowledge amongst policy makers, clinicians, laboratory technicians, and other relevant stakeholders in One Health (human, animal, and environmental)
- Improve the capabilities of clinicians and lab staff to safely identify, treat, and report cases
- Enhance mutual understanding of the roles and responsibilities of clinicians and laboratory staffs for better communication, and ultimately improved identification of melioidosis
- Inform decision makers of needs and gaps for prevention, detection, diagnosis, treatment, surveillance, and reporting

KEY OUTCOMES

- Very Positive Event
  - Highly engaged participants in clinical and lab training; participation from 6 out of 14 provincial diagnostic labs
  - Communication exercise enabled first-time interactions between the doctors and lab staff from the same hospital
  - Demonstrated improvement since 2010 initial awareness event
  - International expert participation and recognition
- Tangible Outcomes
  - C-TEAM gathered a community of practice and established a country-wide network; with volunteer leadership from outside Siem Reap
  - Several hospitals committed to setting up formal MOUs to accept and process animal samples
  - Draft clinical guidelines and lab SOPs were validated by National Ministry of Health
  - The Ministry of Health, Ministry of Environment, and Ministry of Agriculture, Fisheries, and Forestry declared melioidosis to be a One Health issue for the country
  - Country Representatives from the World Health Organization and Food and Agriculture Organization of the UN were in attendance and committed to advocating the outcomes of the event to their regional offices

NEXT STEPS FOR MELIOIDOSIS

- Transition C-TEAM from CBEP Regional Science to Cambodia Country Team
  - Follow-up training assessment (FEB 2018 and MAY 2018)
  - C-TEAM II (TBD) using "Champions" from C-TEAM I
  - Establish technical working group (first step for informal lab referral network)
- SEA RCN for Melioidosis Activities
  - Draft letter with C-TEAM outcomes to international organization Country Teams
    - From International Experts
    - On RCN letterhead
    - Key themes
      - "Suspect that Cambodia has the highest incident rate in Southeast Asia"
      - "In 2016 there were 800 culture confirmed cases and 200 deaths"
      - "Increase in national diagnostic capacity since 2010, but only a quarter of the labs are performing routine culture tests"
  - L-TEAM (Late-fall 2018), Onward to Lao!
  - RCN Publishing and Grant Writing Workshop (Late-fall 2018)

Melioidosis website link

INSTRUCTION AND MEETING FORMAT SLIDES 6-8 MARCH 2018

INTRODUCTION TO STRATEGIC MAPPING

Ms. Katie Leahy, GSE

1130 – 1200

TODAY'S MEETING OBJECTIVES

- Define focus area objectives, challenges and needs, and outreach plans; and
- Build strategy maps to identify, prioritize, and address rickettsia research gaps and needs; and
- Discuss processes to collect and collate data on rickettsia pathogens in SEA
- Discuss short- and long-term schedule of activities and projects

GENERAL MEETING INSTRUCTIONS

- What do we want to achieve?
  - **Think about the end at the beginning**; what are the indicators of success (Short-term? Long-term?)
  - What are the objectives for each working group?
  - What are the interdependencies with other working groups?
  - Think about your working group scope of research now; where do you want to be?
- What are the challenges to success?
  - What are the 'BIG QUESTIONS' within your working group?
  - What is limiting you and your community from achieving your research goals?
  - What is a common misunderstanding of your research community?

NETWORK OBJECTIVES *

- Convene multi-disciplinary researchers, health implementers, policy makers and funding authorities to identify and prioritize *rickettsia* research needs and gaps
- Characterize the distribution and prevalence of rickettsial diseases in Southeast Asia to better understand and address the human health burden using statistical analysis and other best practices for assessing the global burden of other neglected infectious diseases
- Employ, monitor, and evaluate the consistent use of "gold standard" diagnostics and community accepted case definitions to determine if better standards are needed for detection in lab and clinical settings
- Increase awareness for *rickettsia* amongst at-risk populations, clinicians, laboratory staff, national decision makers for better prevention, detection, and response

** **Note:** the text on this slide was discussed and modified during the 9 November meeting in Baltimore*

NETWORK OBJECTIVES *

- Convene multi-disciplinary researchers, health implementers, policy makers and funding authorities to identify and prioritize *rickettsia* research needs and gaps
- Characterize the distribution and prevalence of rickettsial diseases in Southeast Asia to better understand and address the human health burden using statistical analysis and other best practices for assessing the global burden of other neglected infectious diseases
- Employ, monitor, and evaluate the consistent use of "gold standard" diagnostics and community accepted case definitions to determine if better standards are needed for detection in lab and clinical settings
- Increase awareness for *rickettsia* amongst at-risk populations, clinicians, laboratory staff, national decision makers for better prevention, detection, and response

** **Note:** the text on this slide was discussed and modified during the 9 November meeting in Baltimore*

RESEARCH NEEDS *

- Define regional risk and burden
  - Conduct a consolidated study across the region (sero-prevalance, vector competence / distribution, niche modeling and mapping for ecological factors, and compare data with syndromic surveillance studies)
  - Define at-risk locations, populations
  - Research regional burden and economic impact of human and animal infections
- Perform routine diagnostics
  - Survey available diagnostics; test and evaluate POC assays
  - Survey national case definitions for rickettsial pathogens
- Define pathogenicity and immune response
  - Research human susceptibility
  - Research pathogen diversity for vaccine development
  - Research antimicrobial resistance
  - Research host-pathogen interaction

** **Note:** the text on this slide was discussed and modified during the 9 November meeting in Baltimore*

WORKING GROUPS

- **Group 1:** better define and characterize the regional risk and burden
- **Group 2:** identify and employ better methods for lab diagnostics and clinical recognition
- **Group 3:** better understand pathogenicity and immune response

INSTRUCTIONS FOR BREAK-OUT SESSIONS

(1) You will be asked to self-nominate yourself into a group (we would like to keep the groups even)

(2) You will have an opportunity to comment on other group's output during brief-out sessions

(3) Each group will choose a rapporteur (recorder / presenter) who will facilitate discussion and present the group's output

(4) Please pay attention to expertise that may be wanted or lacking within your group; consider this absence as a first step for outreach

Session 1

OBJECTIVES	METRICS	CHALLENGES
What are the objectives for each focus area?	How will you measure success for each focus area?	What are the challenges, needs, and risks for each objective?

Session 2

INITIATIVES / ACTIONS	TIMELINE	RESPONSIBLITY
What are some initiatives, activities, projects, and events that you could plan to support the objectives	What is the short and long-term timeline for your work (3-5 months, 1-year, 18 months)	Who is responsible for each step; what external outreach do you need to perform to seek other support?

BREAKOUT GROUP DISTRIBUTION

GROUP 1 PREVENT
(1) Regional risk and burden
(2) Policy, awareness building and outreach

GROUP 2 DETECT
(1) Diagnostic tools, methods, and protocols
(2) Clinical recognition

GROUP 3 RESPONSE
(1) Pathogenicity
(2) Immune response
(3) Treatment therapies

IMMEDIATE NEXT STEPS – THIS YEAR

- Establish working groups
  - Working group (Hertz, Davidson, Bakar, Mendenhall, and Serge Moran) to establish protocols for field sampling
  - Working group to transition melioidosis website (Stokes, Day, and Richards) and integrate other website data
  - Working group (Kato, Richards, Duggan, Robinson, Blacksell, and Stenos) to (1) survey existing molecular and serological tests and (2) survey available reagents and SOPs
  - Working group (Tika, Day, Varghese, and Dummler) to set literature review (existing knowledge, gaps, and resources) foci and bounds
- Conduct concurrent working group meetings following Wellcome Trust / Oxford Meeting 28-29 May in Bangkok (30 May – 1 June)
- RCN meeting concurrent with ASTMH Oct 2018 (working groups report-out); next steps

ANNEX D – FUNDING AND RESEARCH QUAD CHARTS

DUKE-NATIONAL UNIVERSITY OF SINGAPORE

Dr. Ian Mendenhall reviewed a project to develop predictive bat and small mammal distribution models. The models will be used to predict the presence or absence of ectoparasites and bacteria/viruses. Sampling small mammals and bats, samples are collected and screened for Rickettsia, Bartonella, Ehrlichia, and Anaplasma. The project is currently in its third of five years with over 10,000 total samples. The study will generate predictive maps that can help aid in surveillance efforts in humans and reservoirs.

TECHNICAL DESCRIPTION AND PROJECT	**APPROACH**
This project is to develop predictive bat and small mammal distribution models in addition to predicting the presence or absence of ectoparasites and bacteria/viruses.We will test these animals using PCR/qPCR and serological tests.We are also collecting blood from humans across the country who catch, trade and butcher rats and bats. In addition, we are working with Matt Kasper at NMRC to screen sera samples from staff who spent time in Cambodia. • To determine the epidemiological and evolutionary dynamics of small mammal-borne and bat-borne viruses and bacteria with zoonotic potential • To investigate the extent of transmission of small mammal-borne and bat-borne parasites to humans • To develop spatio-temporal models for the prediction of risk of	• We are sampling small mammals and bats using a randomly stratified approach by habitat type across the entire country.The majority of animals are catch and release, though voucher specimens are being collected to confirm identification and tissues are collected. • Samples are being screened for Rickettsia, Bartonella, Ehrlichia, and Anaplasma (in addition to several virus families).We are also using NGS to complement this screening. • Using occupancy modeling we can incorporate imperfect detection to account for missing species present at sampled sites.With the host and parasite data, we will make predictive maps that will inform future surveillance.
MILESTONES, SCHEDULE, AND STATUS	**IMPACT**
• We are in year 3 of this 5 year project. • Over 1,120 animals sampled (37 species of bats and 17 species of small mammals) with over 10,000 total samples. • Collected 149 human blood samples collected for screening.We anticipate and additional 18 months of sampling. • Laboratory training will be held at the National Animal Health and Production Research Institute in Phnom Penh. Next generation sequencing will be performed at NAMRU-2. • We have a proposal to validate these models in Laos to determine their suitability of the tool across the region.	Zoonotic disease surveillance can be resource intensive and may yield few results. Our goal is to generate predictive maps that illustrate the presence/absence/abundance of vertebrate reservoirs and their community of parasites.This can guide future surveillance efforts in humans and reservoirs. • Establish standardized screening at National Animal Health and Production Research Institute • Conduct training courses on field surveillance, laboratory screening of animal samples, PCR and primer design, bioinformatics analysis, bat acoustic data analysis, bat identification, ecological survey design, the use of GIS in parasite surveillance

AUSTRALIAN RICKETTSIAL RESEARCH LABORATORY

Dr. John Stenos and Dr. Stephen Graves summarized the ARRL's opportunities to investigate and determine the rickettsial burned in countries in the Asia Pacific region. Through epidemiological studies, research, and education ARRL could help lessen the burden of rickettsial diseases.

TECHNICAL PROJECT AND DESCRIPTION	**APPROACH**
To determine the rickettsial burden in countries in the Asia Pacific region. This will involve the investigation of disease burden on the population and the identification of potential vector and animal reservoirs. Is Q fever a problem and will it be included in this study?	<u>Epidemiological Studies</u> Seroepidemiological studies need to be performed to establish the extent of the rickettsial problem. <u>Research</u> Field work to collect samples for laboratory evaluation Use of molecular techniques to establish vector and animal reservoirs. <u>Education</u> Medical practitioner education. Establishing local expertise with rickettsial diagnostics.

MILESTONES, SCHEDULE, AND STATUS	IMPACT
Disease prevalence established via seroepidemiological studies which can be performed at a reference laboratory (eg. ARRL). Once specimens are delivered, results are returned within a few weeks (Dependent on specimen numbers). Our laboratory is ready to deploy its expertise within a few days of request. If there is a rickettsial burden field work (with local help) can be undertaken and samples collected from potential vectors and their animal hosts. The analysis of these samples can be undertaken at a reference laboratory. Once the overall rickettsial picture has been established, education of health professionals and training of local laboratories can be undertaken. The ARRL would be willing to help with this aspect.	Ultimately, if we are able to lessen the rickettsial disease burden in the population via education so the appropriate treatment can be implemented and provide local laboratories with rickettsial diagnostics and expertise the ARRL will have achieved its objectives.

RARE AND IMPORTED PATHOGENS LABORATORY, NATIONAL INFECTIONS SERVICES

Dr. Jackie Duggan reviewed an on-going activity aiming to introduce new and improved assays into clinical service delivery within the next five years. The goal is to improve diagnostics available and surveillance and to inform intervention strategies and public health awareness. It was noted that RIPL has limited funding for assay development.

TECHNICAL PROJECT AND DESCRIPTION	APPROACH
a) PCR and serology for diagnosis of Rickettsia spp. ○ Lack of specificity ○ Serology – cross-reactivity ○ Single source commercial assay availability b) Differentiation and speciation by serology c) Clinical evaluation – access to samples d) Improved diagnostics – sensitivity and specificity e) Improved interventions and epidemiology f) Larger scale clinical trials/studies	**1. What can be done to address the challenges** **a) NGS approaches to identify better genomic targets for PCR development – surveillance** **b) Multiplex PCR and array cards** **c) Diagnostic panels based on geographical regions** **d) Better serology assay development – multiplex serology** **e) Proteomics, protein arrays and AI** **2. What are the key steps along the way** **a)** Funding programmes **b)** Collaborative work and partnerships **3. What tools and technologies are needed to address the challenges?** **a)** Engage with industry and health organisations (WHO,FIND)
MILESTONES, SCHEDULE, AND STATUS • **Timeline for Delivery** On-going activity by aiming to introduce new, improved assays into clinical service delivery within 5 years. • **Overview of project status** Partnership and collaborations Funding opportunities and application	**IMPACT** a) Improved diagnostics available Improved access to new diagnostic technologies b) Improved surveillance c) Inform intervention strategies d) Inform public health awareness

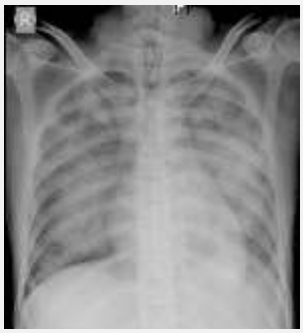
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

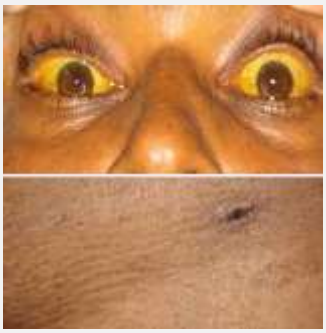
Dr. George Varghese introduced the Intravenous Treatment for Scrub Typhus (INTEREST) Trials to determine the best IV treatment for severe scrub typhus. The trial hopes to assess a reduction in mortality and improvement of complications. While the study is just beginning in June 2018, it has a three-year timeline with hopes to improve patient outcomes.

RICKETTSIAL RESEARCH IN INDIA: AN INCREDIBLE JOURNEY

Dr. George M.Varghese MD, DNB, DTMH, FRCP, FIDSA

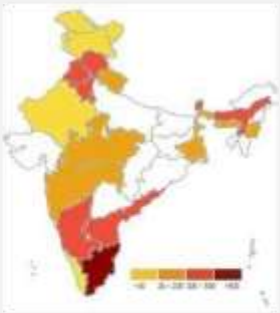
Christian Medical College,Vellore, India





SCRUB TYPHUS: A MAJOR PUBLIC

- More than 1 billion people at risk in SE Asia, the 'tsutsugamushi triangle'
- Estimated 1 million cases per year resulting in 150000 deaths per year
- Re-emergence documented in >25 states in India
- Multi-organ dysfunction in a third
- **Major gaps:**
  - Grossly under recognized: burden and pattern of disease unknown
  - Severe disease case fatality >20%
  - Lack of a point of care test



Watt G etal. Curr Opin Infect Dis. 2003

Varghese GM et al. Int J Infect Dis 2013

MAKING AN IMPACT

Genotyping *O. tsutsugamushi*	Optimal treatment for severe scrub typhus	Point of care diagnostics	Epidemiological understanding
• From 3 regions of India • Laying foundation for diagnostics and vaccines • *Varghese GM et al. Emerg Infect Dis. 2015*	• Improved clinical outcomes • Network in SEA • INTREST trial • 1509 patients • 8 centers in India, Thailand, Laos	• Peptide based POCs • Improved lateral flow tests • Network with Bhutan, Srilanka	• Risk factors and seasonality • Increasing seroprevalance • Current community seroprevalance of 30%

INtravenous TREatment for Scrub Typhus (INTREST) Trial

Funded by: Wellcome Trust DBT Alliance

Goal	To determine best IV treatment for severe scrub typhus by assessing reduction in mortality and improvement of complications
Study population	Adult patients with severe Scrub Typhus
Intervention & control	IV Azithromycin + Placebo IV Doxycycline + Placebo IV Doxycycline + Azithromycin
Outcome	• **Primary**: Composite endpoint of mortality at 28 days or persisting complications on day 7 or persisting fever at day 5 • **Secondary**: In-hospital mortality, Fever defervescence duration, duration of ventilation, ICU stay & hospitalization, adverse effects
Other objectives	• Analyze the pharmacokinetics and pharmacodynamics of azithromycin & doxycycline and optimizing dosing parameters • Bacterial isolation and characterization including WGS
Study Sites	1. CMC, Vellore 2. JIPMER, Pondicherry 3. KMC, Manipal 4. PGI, Chandigarh 5. IGMC, Shimla 6. PGIMS, Rohtak 7. Phrachanukroh hospital, Chiangrai, Thailand 8. Mahosot Hospital, Vientiane, Lao PD

RESEARCH QUAD CHART

Technical Description

1. Treatment challenges
- Optimal treatment in severe scrub typhus
- Role of steroids

2. Diagnostic challenges
- Diagnostics including POC tests

3. Epidemiological Challenges
- Improved understanding of the epidemiology

Milestone	Schedule	Status
Patient recruitment for INTREST Trial	June (Timeline : 3 years)	• Ready for recruitment in Indian sites • Funding for the SEA countries including Thailand & Laos
Characterization of organism incl. WGS	3-5 years	• Needs additional funding
POC tests Peptide screening	3 years	To be implemented Need funding
Case detection-spatial epidemiology & mapping	2-3 years	Need funding

Approach

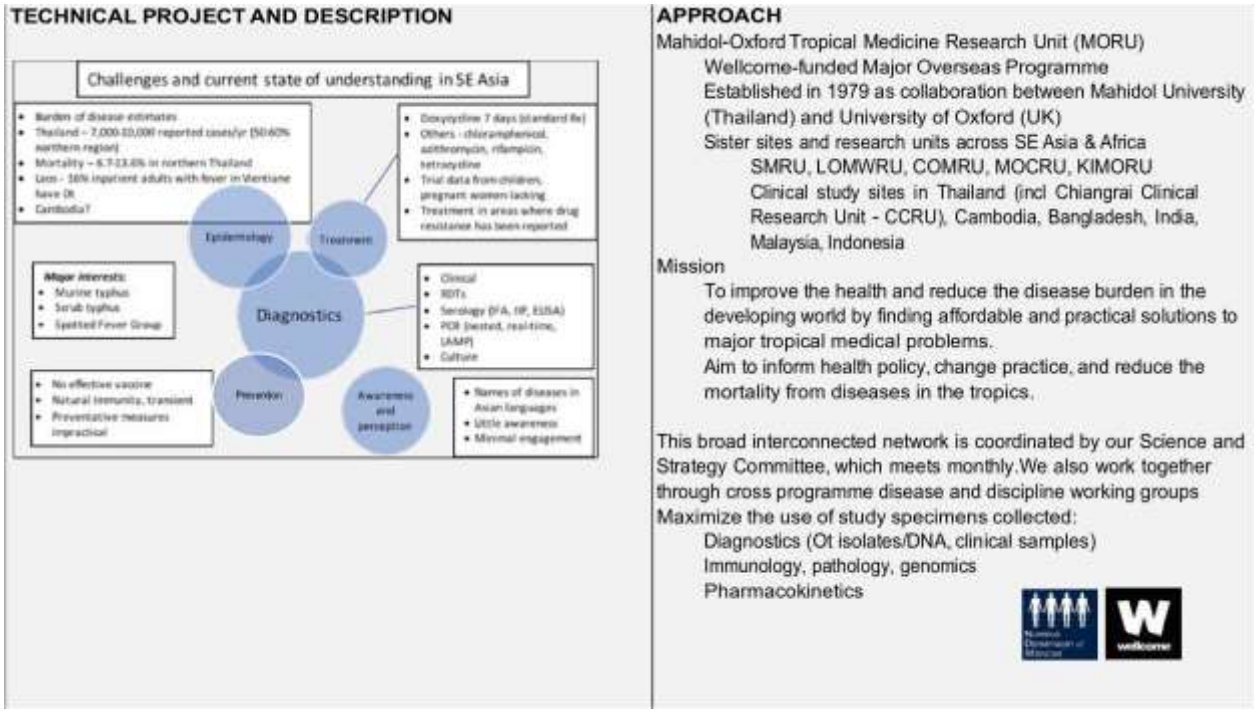
- **INTREST trial**
  -Network of SEA countries
  -Further characterization of organism for drug targets, vaccines etc.
  -Other clinical questions like role of steroids
- **POC test** – peptide based/ recombinant antigen based lateral flow test
  - Peptide screening for vaccine candidates
- **Dynamic spatial epidemiology and mapping**

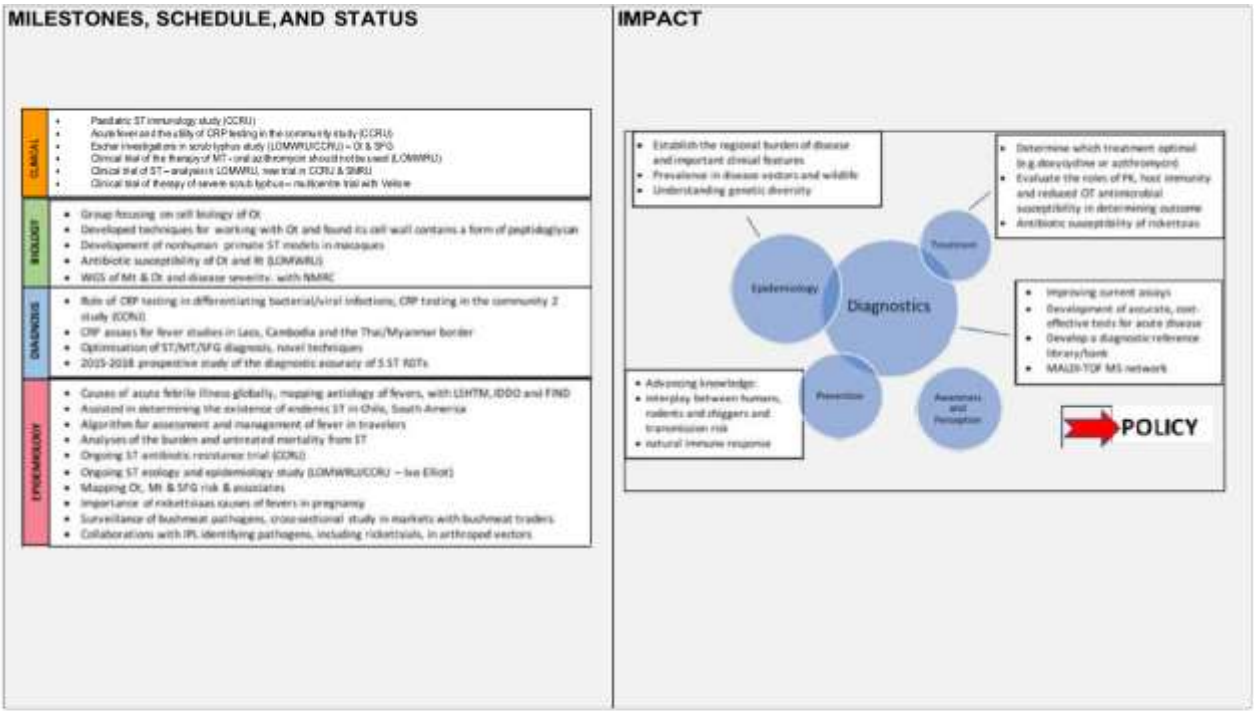
Impact

- **Improved patient outcomes and reduction in mortality**
- **Wide deployment of POCs across the country resulting in early diagnosis and better outcome**
- **Real-time epidemiology and hot-spot mapping for public health interventions**
- **Peptide based vaccines**

MAHIDOL-OXFORD TROPICAL MEDICINE RESEARCH UNIT

Dr. Matthew Robinson, Dr. Nick Day, Dr. Paul Newton, Dr. Stuart Blacksell, Dr. Tri Wangrangsimakul, and Dr. Kartika Saraswati presented on MORU's mission to improve the health and reduce the disease burden in the developing world by finding affordable and practical solutions to tropical medical problems. The aim of MORU is to inform health policy and change practice while reducing the mortality from diseases in the tropics.





UNIVERSITY OF MALAYSIA, TROPICAL INFECTIOUS DISEASE RESEARCH AND EDUCATION CENTER

Dr. Sazaly Bakar reviewed the current status of *Rickettsia* pathogens in Malaysia and the challenges associated with low awareness of these diseases among populations most at risk. Developing new and effective research and diagnostic tools and improving surveillance of rickettsial infections can improve the baseline exposure data and identify new findings on causative rickettsial agents.

TECHNICAL PROJECT AND DESCRIPTION	**APPROACH**
Current status in Malaysia: • Rickettsial infections are in general under-recognized. • Diagnostic tools are not available. Patients with PUO not tested for rickettsial infections, exposure history not consulted to see if they are at risk. • Baseline exposure among potential population-at-risks (ie animal handlers, pet owners, vets, eco-tourists, travelers, urban slum dwellers etc) not known • Potentially novel Rickettsia (and others like Coxiella, Ehrlichia etc) are being detected molecularly from animals, ectoparasites and small number (2) of human patients with febrile illnesses* • No isolates however, are recovered so far for further characterization or used for further research **Challenges:** • Low awareness among potential population-at-risks and health care providers (ie medical doctors) • Lack of effective diagnostics and research tools • Isolation is costly, technically difficult and requires BSL3	**What can be done to address the challenges?** • Develop new and effective research and diagnostic tools • Improve surveillance of rickettsial infections among patients with PUO and population-at-risks **Key steps (proposed research to be undertaken):** • Systematic detection of rickettsial infections among patients with PUO and from population-at-risks: Identify patients that matches the clinical presentations or exposure history (ie to fleas/ticks/animals) for testing of rickettsial infections ○ **Expertise needed for patient identification and diagnosis (among Rickettsia RCN?)** • Isolation of rickettsial agents for use in developing suitable diagnostic tools - to be done in collaboration with research partners. • Assess seroprevalence in healthy potential population-at-risks to determine the baseline exposure **Tools and technologies required:** • Facilities for rickettsia work – BSL2/3 (available in TIDREC, UM) • Reagents: tick cell lines and detection tools

MILESTONES, SCHEDULE, AND STATUS	IMPACT
Quick overview of current projects in TIDREC, UM • **Currently no funding for actual research in rickettsial infections** • In collaboration with with NMRC (Prof Richard Allens) for seroprevalence study using archived healthy human samples from at risk population in the rural communities • Establish Tick Cell Biobank (2018-2020): Asia Outpost in TIDREC, UM together with University of Liverpool, UK • Provide established tick cell lines as research tools • Establish novel tick cell lines from Asian-specific tick species as research tools • Potential collaborations • 2018-2020: Funding for linkages and expertise transfer in using tick cell lines for research in rickettsial agents - with UoL	Determine seroprevalence in population-at-risks to determine the baseline exposure **Impact: Generate baseline exposure data to determine how widespread is the infections and which population is at risk, to enable design of disease prevention strategies targeted to that population** Systematic detection of rickettsial infections among patients with PUO from population-at-risks **Impact: New findings on the causative rickettsial agent causing infections, which is useful for improving disease management (ie managing antibiotics administration to prevent rampant use)** Tick Cell Biobank: Asia Outpost and expertise transfer from UoL **Impact: Novel rickettsial isolates reflecting the rickettsial species found in this region for use in future research** • **For development of new diagnostic tools to be used in clinical setting** • **Further characterization of the novel rickettsial agents**

ARMED FORCES RESEARCH INSTITUTE OF MEDICAL SCIENCE, ROYAL-THAI ARMY

COL Jariyanart Gaywee, Ph.D. and COL Wuttikon Rodkvamtook, Ph.D. presented on the molecular epidemiology of Rickettsiosis spreading in Thailand. Their approach is to develop molecular tools for detection and characterization of pathogenic *Rickettsiae*, analyze the detected *Rickettsia* species using GIS technology, and use digital media to make research finding available to the public. While the main objectives of this study are complete the study will continue over the next two years.

TECHNICAL PROJECT AND DESCRIPTION	APPROACH
Molecular Epidemiology of Rickettsiosis Spreading in Thailand Objectives: To identify rickettsial species and related bacterial pathogens causing diseases in Thailand and regional countries. To study transmission cycle of each rickettsial species. To generate risk maps for rickettsiosis and arthropod vectors. To establish disease prevention and control program.	1. Develop molecular tools for detection and characterization of pathogenic rickettsiae and related bacterial pathogens. 2. Analysis of detected rickettsia species with geographical information using GIS technology. 3. Using digital media to allow research findings available for public (eg:Web-based Application).
MILESTONES, SCHEDULE, AND STATUS	**IMPACT**
Milestone: All 4 objectives are complete, continue study to cover more areas. Schedule: Complete in 2 years Status: Ongoing	Research findings are epidemiology information of rickettsial agents and their transmission cycle of bacteria that crucial for establishing an effective disease protection and control. Active disease prevention program is highly impact on patient reduction and economic issues for save cost of health care.

ARMED FORCES RESEARCH INSTITUTE OF MEDICAL SCIENCE

LTC Matthew Wegner DVM, MAJ Silas Davidson Ph.D., MAJ Elizabeth Wanja Ph.D., and Dr. Piyada Chanroensinphon reviewed several ongoing studies on: (1) surveillance for *Rickettsia* diseases in vectors, animals, and human samples, (2) identification of vectors and advance characterization of pathogens, (3) evaluate control methods for arthropod vectors, (4) understanding vector transmission of pathogens, (5) host immune response, and (6) protective immunity for vaccine development. These studies have led to multiple collaborations and increased surveillance.

TECHNICAL PROJECT AND DESCRIPTION	APPROACH
Primary Objectives: 1. Surveillance for Rickettsial diseases in vectors, animals, and human samples. 2. Identification of vectors and advanced characterization of pathogens. 3. Evaluation of control methods for the arthropod vectors. 4. Conduct studies to better understand vector transmission of pathogens. 5. Study host immune response to *Rickettsia* infection. 6. Study key protective immunity for vaccine development. **Challenges:** 1. Vector identification is difficult due to lack of taxonomic keys and reference material from this region. 2. Need for better diagnostic tools. 3. Current lack of vaccines and proven challenge model. 4. ABSL-3 maintenance.	1. Maintain chigger colonies • 3 uninfected lines and 11 *O.t.* infected lines (ABSL-3) • Possible tick and flea colonies in the future 2. Vector identification • Morphological ID leading to barcoding (mites, ticks. fleas) • Pictorial key for ticks of Thailand being developed 3. Control measures for the vector • Insecticide treated clothing, traps and baits for rodents 4. Well-trained and fully equipped veterinary pathology section • Characterization of effector and memory T-cell response in rhesus scrub typhus model 5. Development of scrub typhus vaccine challenge model using infected chiggers and NHPs. • AFRIMS has only AAALAC accredited NHP facility in Thailand 6. Development of broad spectrum scrub
MILESTONES, SCHEDULE, AND STATUS	**IMPACT**
1. Conduct regular rodent trappings in endemic areas (twice/month). 2. Ongoing studies to evaluate pathogen presence and seroprevalence from animal and human samples in Thailand, Bhutan, Nepal, and Kenya. 3. Starting project to characterize proteins in chigger saliva (possible vaccine candidate). 4. Completed characterization of the rhesus macaque (*Macaca mulatta*) scrub typhus model: susceptibility to intradermal challenge with the human pathogen *Orientia tsutsugamushi* Karp strain. (with MORU) 5. Completed study on the disease course and immune response in rhesus monkeys by increasing doses of intradermal injection of *O. tsutsugamushi*. (with MORU) 6. Completed an immunopathological study of scrub typhus in rhesus macaque by intradermal inoculation. (with MORU)	1. WHO collaborating center for scrub typhus; provided outbreak response support to the Maldives, Nepal, Bhutan. 2. Have assisted the Royal Thai Army with scrub typhus surveillance at military installations in Thailand. 3. Provided surveillance during multi-national Cobra Gold military training exercise. 4. Recently identified new records for several *Rickettsia* spp. and other bacterial pathogens from the countries where we have surveillance projects (publications in progress). 5. Successfully develop rhesus macaque scrub typhus model (with MORU)

NAVY MEDICAL RESEARCH CENTER- ASIA

LCDR Jeffrey Hertz, Ph.D. reviewed the underlying challenges and current state of understanding of rickettsial pathogens. By addressing challenges, creating joint protocols, training and reachback AFRIMS continues to develop baseline *Rickettsia* surveillance. Current projects include multiple sites in Cambodia and Laos that have ectoparasite febrile surveillance.

TECHNICAL PROJECT AND DESCRIPTION	APPROACH
1. Underlying Challenges a. Bandwidth (vector, diagnostics) i. Culture isolation ii. Vector identification/distributions b. Sample movement **2. Current State of Understanding** a. Rickettsia not well understood in host nations i. Late diagnosis, if any b. DoD network (GEIS) c. N2 smart, agile surveillance i. Human > Vector ii. Clear hotspots, but true burden or attack rates unknown; Vector correlation very limited	**1. What can be done to address the challenges?** a. Relationships and agreements b. Build capacity: sustained platforms, training **2. What are the key steps along the way?** a. Joint protocols (e.g. NMRC) b. Training/SMEE, including hands-on c. Reach back (AFRIMS, NMRC, WRBU, other) **3. What tools and technologies are needed to address the challenges**? a. Web-based, sharing platform (SOPs, protocols, expert contacts, etc) b. Bioinformatics, & NGS at some locations c. Vector identification keys/tools

MILESTONES, SCHEDULE, AND STATUS	IMPACT
1. Provide timeline for delivery a. Continue to baseline rickettsia surveillance **2. Quick overview on project status** a. Cambodia i. Ectoparasite surveillance (GEIS) • 6 sites: ticks, fleas, some mites ii. Febrile surveillance (GEIS) • 16 sites b. Laos (LOMWRU/IPL) i. Ectoparasite surveillance (GEIS) • 4 sites: primarily ticks ii. Febrile surveillance (GEIS) • 4 sites	1. Ultimately, N2 has a responsibility to the Pacific Command a. Communicate risk b. Prevent exposure c. Rapidly diagnose illness d. Guide proper treatment 1. N2 requires network to fill bandwidth gaps to allow us to rapidly pull information, expertise, or technical support not readily available internally. 1. N2 would like to move towards a 'smarter' surveillance system. a. Strategic lattice versus random dots b. Synergistically coordinated

NAVY MEDICAL RESEARCH CENTER

Dr. Al Richards explained the objectives and work of the Rickettsial Diseases Research Lab at NMRC. Their main objectives are to develop diagnostic assays and vaccine candidates and to conduct surveillance for rickettsial diseases through developing, producing, and providing serologic and molecular assays and reagents, standard operating procedures (SOPs), and training. With 15 years of experience and work with collaborators from 6 continents, NMRC hopes to reach its main objectives.

UNIFORMED SERVICES UNIVERSITY

Dr. Stephen Dumler presented a project to show that a substantial proportion of non-malarial, non-dengue acute febrile illness in Malaysia is undiagnosed rickettsial infections. By using serum, whole blood, buffy coat, and eschar specimens from patients enrolled USU is demonstrating the occurrence of rickettsial infections and defining species or strains in Malaysia. The study will have direct implications for diagnosis and treatment along with public health and policies in the region.

Rickettsial Infections in Malaysia

NIAID 7R03AI111300-03

PI: Megan E. Reller, MD, PhD , co-PI John S. Dumler, M.D. **Org: Duke University,** Uniformed Services University **Award Amount:** 50,000 USD

TECHNICAL DESCRIPTION AND OBJECTIVES

1. Underlying Challenges

- Non-malarial acute febrile illness (AFI) causes greater morbidity and mortality world-wide than malaria, but this burden is underappreciated, owing to overlapping clinical presentations and limited access to confirmatory diagnostic tests. ○ studies suggest rickettsial infections may be the most common cause of AFI in some regions of Southeast Asia. ○ confirming rickettsioses is particularly difficult because of endothelial cell infection, therefore, are poorly-cultivable and low level clinical bacteremia.
  - ○ Broad-spectrum antimicrobial agents used empirically for AFI, such as penicillins and cephalosporins, are ineffective against rickettsiae.
  - ○ Effective preventive vaccines are not available.

2. Current State of Understanding

- Scrub typhus was recognized in Malaysia in 1912 and murine typhus is endemic in surrounding countries, but only 52 cases of acute rickettsiosis were reported by the Malaysian Ministry of Health between 2009 and 2015.
- Contemporary studies and serosurveys confirm 2 to 9% of blood donors and 12 to 44% of febrile patients presenting to hospital have anti-rickettsial antibodies.

3. Hypothesis

- A substantial proportion of the non-malaria, non-dengue AFI in Sabah, Malaysia and surrounding regions results from undiagnosed rickettsial infections.

APPROACH

Specific Aims. Use serum, whole blood, buffy coat, and eschar specimens from patients enrolled prospectively with AFI to identify and characterize unsuspected rickettsial infections.

- demonstrate occurrence and describe the epidemiology of rickettsial infections in Sabah, Malaysia.
- define species or strain substructure of spotted fever and typhus group rickettsioses and scrub typhus in Sabah, Malaysia.

1. **What can be done to address the challenges?** Careful prospective clinical/epidemiologic studies using reproducible enrollment criteria and reference standard tests where not yet applied (e.g. across Malaysia).
2. **What are the key steps along the way?** PIs knowledgeable about rickettsiology – both laboratory and clinical aspects using rigorous study design. Partnerships with local PIs.
3. **What tools and technologies are needed to address the challenges?** Improved nucleic acid detection tests: RNA targets, high blood volume, buffy coat, etc.; Improved recombinant or peptide-based serology for high-throughput and POC testing, supported by rigorous clinical validation and interpretation.

Timeline for Delivery and Overview on Progress

1. Clinical study December 2013 through 15th July 2015
2. Clinical study results:
   - 557 patients met eligibility criteria; 444 consented to enrollment; 184 returned for convalescent follow-up (median days 13; IQR 12-14).
   - Of 124 with convalescent sera, 102 had acute sera available; an additional 147 patients provided acute serum only.
   - Acute-phase whole blood or buffy coat was available for 255 patients.
3. IFA (IgG, IgM; *Orientia tsutsugamushi*, SFGR, and *R. typhi*) testing completed March 2017; PCR testing completed March 2017.
4. Data analysis complete October 2017
5. Abstracts presented at ESCCAR (Marseille FR, June 2017) and ASTMH (Baltimore, MD USA, Nov. 2017)
6. Manuscript in preparation
7. Followup detailed study of rickettsioses in Sabah and Peninsular Malaysia in preparation.
   - Local clinical and research partners needed for Peninsular Malaysia studies

Define quantitative impact of project

Sabah Malaysia study

- 31 of 123 subjects (25%; 95%CI 18-34) had acute rickettsial infections confirmed by IFA ○ 19 OT, 7 SFGR, 3 TGR, 1 OT/SFGR, and 1 OT/TGR
- PCR identified an additional 6 patients with confirmed rickettsioses (1 OT, 2 MT, 3 SFGR)
- 65/269 (24%; 95%CI 19-30) patients had seroprevalent infections: 47 OT, 13 SFGR, and 11 TGR

Impact on Malaysia and Southeast Asia

- lack of capacity for routine testing underlies under-reporting
- large discrepancy in adjusted incidence rate (15/100,000) compared to national and state notifications.
- Under-reporting impacts on the clinical awareness of the causes of non-malarial AFI
- Direct implications for the correct initiation of appropriate empirical treatment and public healthy and policies, consistent with regional observations.

COMMUNICABLE DISEASE CENTRE – NATIONAL CENTRE FOR INFECTIOUS DISEASES

Dr. Yazid Abdad gave an overview of Singapore's CDC transition to the NCID. NCID will be a new and purposefully designed building for both during an outbreak and during peacetime. In addition, NCID will have a full-suite research clinic, research ward, research offices, and an ID research laboratory. The new building will house a biorepository for infectious disease clinical samples and pathogen isolates.

CDC TO NCID

Past Outbreaks in Singapore – A Centralised Management Model

1907	1960s	2000s	2018
1907 Smallpox, plague 1938 Typhoid 1945-46 Polio outbreak 1957 Asian Flu 1958 Polio 1959 Smallpox	1961 Diphtheria 1963 Cholera 1964 Typhoid 1999 Nipah Outbreak	2003 SARS 2005 Worst dengue epidemic 2008 Chikungunya 2009 H1N1 2013 Worst dengue epidemic 2016 ZIKA **H7N9** **EBOLA** **MERS CoV**	
1907 Isolation camp 1920 Middleton Hospital	1985 Merged with TTSH 1992 Dept ID formed	**2012 IIDE formed**	National Centre for Infectious Diseases (NCID)

NCID – A PURPOSEFULLY DESIGNED BUILDING

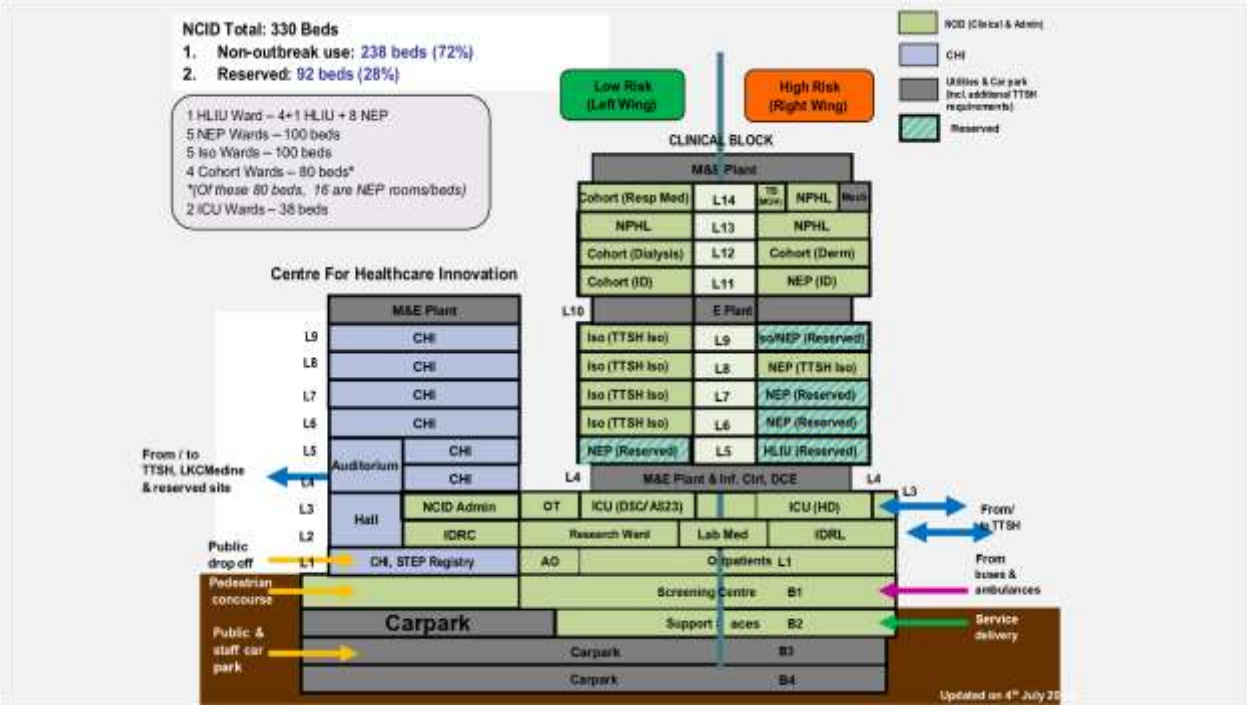
During an Outbreak

- ü Centralised national outbreak management
- ü Designated outbreak centre & isolation facility
- ü Capability for Complete Lockdown

During Peacetime

- ü Surveillance and Housing of National Public Health Functions
- ü Outpatient and inpatient services for general infectious diseases (e.g. HIV, TB, etc.)
- ü Augment hospital's isolation capacity
- ü Surge capacity for infectious and mass casualty
- ü Training/ planning for outbreaks

Tan Tock Seng Hospital



RESEARCH CAPABILITIES AT NCID

Research Ward

ID Research Laboratory

- BSL2
- Biorepository

Full-suite Research Clinic

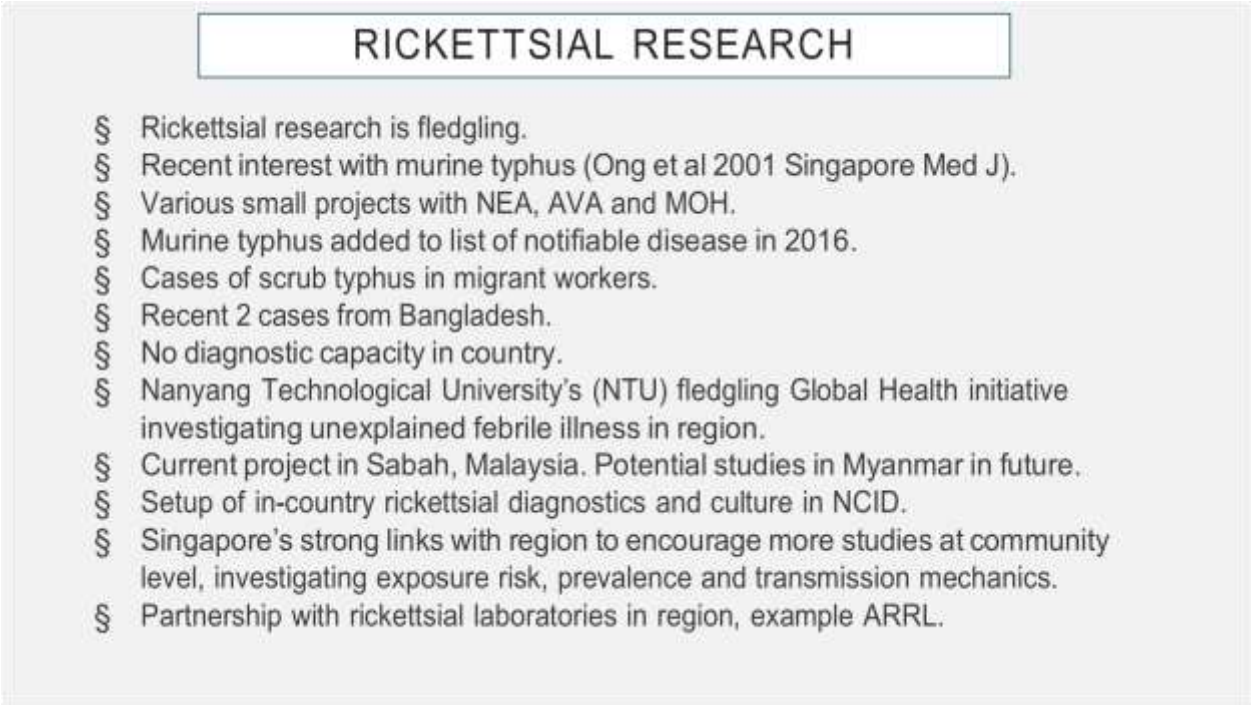
- Drug preparation room
- Sample processing lab

Research Office

- Holds 80-pax

BIOREPOSITORY

§ IDRL tasked with setup of PathogenHub/Biorepository for infectious disease clinical samples and pathogen isolates to be done in 2 phases.
§ Phase 1 – Bacterial Isolates as proof of concept
§ Phase 2a – Viral Isolates
§ Phase 2b – Clinical samples positive for infectious diseases (Pending Governance Paper Approval)
§ Act as custodians for all isolates and clinical samples stored at NCID
§ Characterize isolates and samples
§ Coordinating body for all isolates and samples stored in public laboratories and allocated for national use



CENTER FOR DISEASE CONTROL AND PREVENTION, DIVISION OF VECTOR-BORNE DISEASES

Dr. Cecilia Kato presented on the CDC's work with developing highly sensitive *Rickettsia* species molecular assays and Orientia molecular assays. By developing these specific diagnostic tools, a clearer picture of the true *Rickettsia* disease burden will come to light. Developing these highly sensitive assays will provide the ability for timely laboratory diagnosis of rickettsial diseases and more accurate surveillance data.

1.

Underlying Challenges

a. Limited sensitivity and specificity of current acute diagnostic methods for *Rickettsia* and *Orientia*.
b. Limited understanding of the utility and limitations of molecular detection methods for acute stage diagnosis.

1. **Current State of Understanding**

a. Optimal methods for acute Rickettsial disease diagnosis needs to be identified.
b. The understanding of the usefulness and limitations for the new technologies need to be established.
c. Sensitive and specific diagnostic tools will help provide a clearer picture of the true burden of disease.

1. **What can be done to address the challenges?**
   a. New highly sensitive real-time PCR and point-of-care diagnostic methods under development need to be tested and optimized using patient samples for more accurate and useful methodologies.
2. **What are the key steps along the way**
   a. Further the development of highly sensitive and specific detection methods.
   b. Further the validation and optimization of these diagnostic methods with use with patient samples.
   c. Support capacity for diagnosis in counties.
3. **What tools and technologies are needed to address the challenges?**
   a. Validated and optimized assays.
   b. Clinical laboratory and point-of-care devices needed

MILESTONES, SCHEDULE, AND STATUS

1. **Quick overview on project status**
   a. Highly sensitive *Rickettsia* species molecular assay issued provisional patent February 2018. Analytical validation complete, further optimization and clinical validation in progress. Application to point-of-care methods and devices currently in development. Collaborations for validation are being developed.
   b. Highly sensitive *Orientia tsutsugamushi* molecular assay developed and undergoing analytical validation.
2. **Timeline**
   a. Validations and optimizations for real-time PCR to be completed 2019.
   b. Initial testing of acute surveillance samples and comparison of standard molecular techniques to be completed 2019.
   c. Optimized protocols developed 2019.
   d. Point-of care method validation 2019.

IMPACT

1. The validation and optimization of highly sensitive and specific assays for acute diagnosis of Rickettsial diseases will provide the following.
   a. Ability to provide timely laboratory diagnosis of Rickettsial diseases.
   b. More accurate surveillance data and burden estimates.

1. The development, validation, and optimization of point-of-care methods will provide the following.
   a. Fast accurate diagnosis
      i. Surveillance in rural areas ii.
      More effective patient care

FUNDING QUAD CHARTS

DEFENSE THREAT REDUCTION AGENCY, COOPERATIVE BIOLOGICAL ENGAGEMENT PROGRAM

ORGANIZATION'S DESCRIPTION

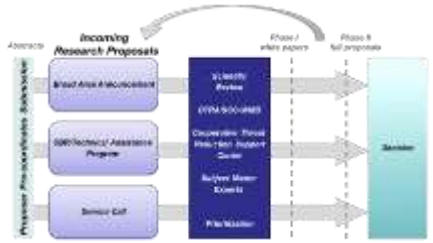
1. Defense Threat Reduction Agency (DTRA), Cooperative Threat Reduction (CTR), Cooperative Biological Engagement Program (CBEP)
2. Mission: Reduce the threat posed by pathogens of security concern
3. Research Foci: International research collaborations at nexus between threat reduction and public/animals health. Conducted in a safe and responsible manner, that inform and enhance disease surveillance and health security.

FUNDING ANNOUNCEMENT TYPES

1. BAA
   a. Academia, industry, non-governmental organizations, foreign government labs
   b. Grants (typically 3-5 year projects)
2. Service Call
   a. US Government only (including national labs)

Interagency Agreements and Military Interdepartmental Purchase Requests (typically 3-5 year

FUNDING TIMELINE



POINTS OF CONTACT

1. Dr. Martha Stokes (CBEP Regional Science Manager, SEA)
2. Dr. Emerson Tuttle (CBEP Regional Science Manager, SEA)

DEFENSE THREAT REDUCTION AGENCY, RESEARCH AND DEVELOPMENT CHEMICAL AND BIOLOGICAL TECHNOLOGIES

ORGANIZATION'S DESCRIPTION	FUNDING ANNOUNCEMENT TYPES
1. DTRA RD-CBAA: Defense Threat Reduction Agency (DTRA), Research & Development (R&D), Chemical and Biological Technologies (CB), Medical Diagnostics Branch **2. Mission:** Finding and fostering Science and Technology that informs rapid and efficient consequence management, to include endemic and emerging disease **3. Research Foci:** Development of *In vitro* diagnostics (IVDs) against high threat biological, chemical and toxin agents	**Chem-Bio Defense Program BAA** Who can submit: Academia, industry, non-gov't organizations, foreign gov't labs Type of research: Fundamental & Applied Frequency of Calls: Once a year Acquisition Vehicle: Contract **Chem-Bio Defense Program Service Call** Who can submit: US Government only (including national labs) Type of research: Fundamental & Applied Frequency of Calls: Once a Year Acquisition Vehicle: Contract
FUNDING ANNOUCEMENT TYPES cont.	**POINTS OF CONTACT**
Other Transactional Authority (OTA) Who can submit: Non-traditional performers Type of research: Applied Frequency of Calls:Year Round Acquisition Vehicle: Contract **DTRA Fundamental & Basic BAAs** Who can submit: Academia, industry, non-gov't organizations, foreign gov't labs Type of research: Fundamental & Basic Frequency of Calls:Year Round (Fundamental),Twice a Year (Basic) Acquisition Vehicle: Grant **DTRA SBIRs and STTRs** Who can submit: Small businesses Type of research: Basic - Applied Frequency of Calls: Once a Year Acquisition Vehicle: Grant or Contract	Dr. Diane Dutt (Medical Diagnostics Science & Technology Manager) 

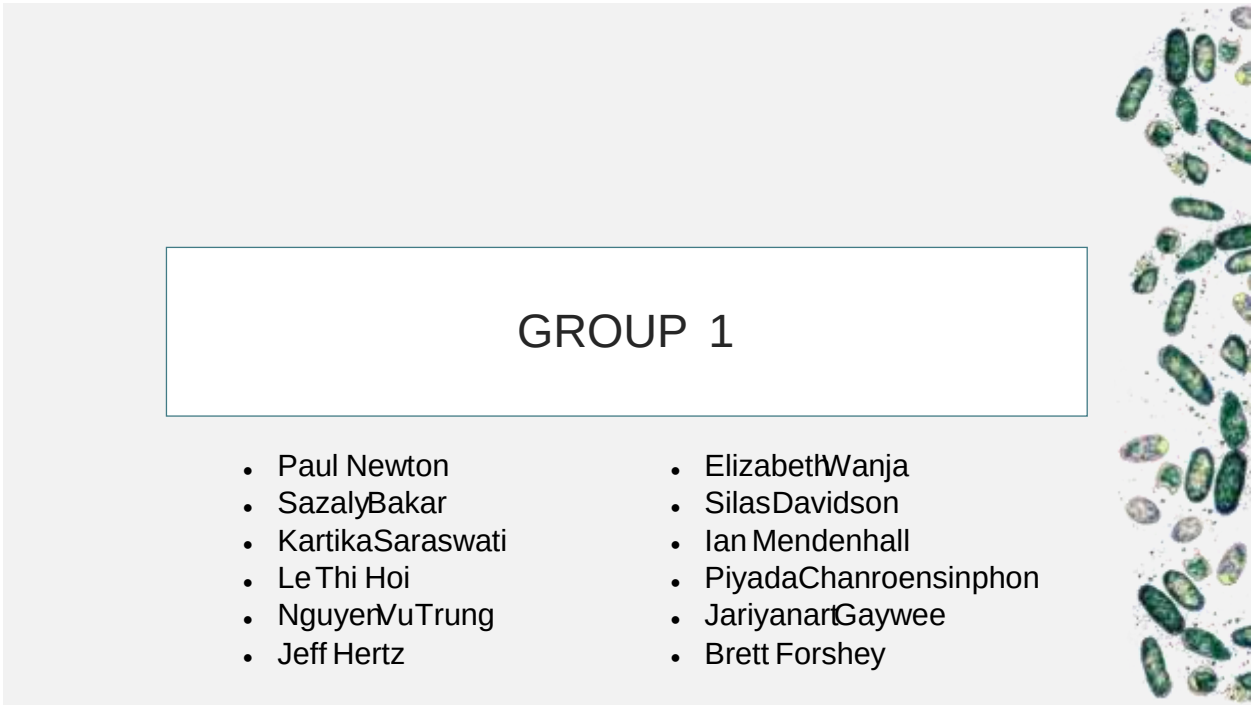
GLOBAL EMERGING INFECTIONS SURVEILLANCE

ORGANIZATION'S DESCRIPTION	FUNDING ANNOUNCEMENT TYPES
1. Defense Health Agency, Public Health Division, Armed Forces Health Surveillance Branch (AFHSB), **Global Emerging Infections Surveillance** (GEIS) 2. Mission: **Inform force health protection decision making** and enhance global health security by preventing, detecting, and responding to infectious disease threats through **supporting Geographic Combatant Command** priorities and strengthening surveillance, outbreak response, collaboration, and coordination of the global DoD laboratory network. 3. Research Foci: Surveillance for militarily-relevant emerging infectious diseases (which includes *Rickettsia* and *Rickettsia*-like organisms	1. Request for Proposals a. Primarily DoD organizations b. Limited funding to other USG organizations (e.g. NASA, FDA) c. Non-USG organizations partner with DoD organizations on surveillance projects d. DHP Operations and Maintenance funds (1 year money)
FUNDING TIMELINE	**POINTS OF CONTACT**
• RFP release in late April/early May • Proposals due in late June • Funding decisions made in late September/early October • Funding release contingent on availability of funds to DHA	1. GEIS Chief: CDR Franca Jones (franca.r.jones.mil@mail.mil) 2. LTC Michael Boivin (michael.r.boivin2.mil@mail.mil) 3. Dr. Brett Forshey (brett.m.forshey.ctr@mail.mil) See also: https://health.mil/Military-Health-Topics/Health-Readiness/Armed-Forces-Health-Surveillance-Branch/Global-Emerging-Infections-Surveillance-and-Response

ANNEX E – BRIEF-OUT SLIDES

Each group was provided 10 minutes at the end of the day to present their strategic mapping work; below are the final slides that were presented.

DAY 1 BRIEF-OUT



GROUP OBJECTIVES

Develop a surveillance and data sharing network in SEA

- Better understand vector and parasite competence and distribution (temporal and spatial distribution and abundance)
- Better understand host specificity and distribution
- Conduct regular and consistent information sharing
- Build morphological and molecular vector repository
- Identify novel and divergent strains
- Communicate economic impact

Better understand epidemiological factors

- Determine at-risk human and animal populations
- Identify ecological factors
- Identify anthropogenic factors
- Work with partner nations to build consistent awareness amongst health care providers
- Support retrospective studies using existing sample sets (e.g., malaria, influenza)

Establish standards, protocols, and associated training

- Develop a standard case definition
- Establish SOPs and protocols (surveillance, identification, prevention, and control)
- Establish SEA training center (and curriculum
- Establish Centers of Excellence for confirmation, further testing and characterization, and expertise
- Establish standards for information collection and sharing
- Develop testing kits (human and animal)
- Ensure labs are equipped with proper materials (antigens, reagents, etc.)

GROUP METRICS

Increased understanding of threats for partner nation policy- and decision-makers (for better prevention and control initiatives)

- Memorandums of Agreements and/or Understand in-place to allow sample sharing, data sharing, etc.
- Rickettsia are incorporated into national strategies for priority pathogens that enables training and certification

Increased awareness amongst health care professionals

- Standard case definition is established and used
- POC facilities use standardized data collection for follow-up care and reporting

Increase in publications on rickettsia topics

- Based on retrospective data analysis
- Rooted in collaboration (multi-discipline, multi-institution projects)

Increased identification of new species

Increased awareness amongst diagnosticians

- SOPs and protocols are part of routine
- Labs are equipped with proper materials
- Inter-institutional partnerships to share resources, samples, testing

CHALLENGES

- Seeking national policy-maker / decision-maker buy-in (training, data collection and sharing, regulatory frameworks (sample protocols)) to overcome potential obstructions
- Identifying vertebrate and arthropods
- Ensuring funding / prioritization challenges (organization, country) align with RCN goals
- Geographical obstructions to sample collection (e.g., road access, safe areas)
- Building awareness amongst POC health professionals
- Building awareness amongst at-risk populations
- Conducting research in BSL3 (access, proficiency, and certification)
- Sharing data amongst researchers / transparency – race to publish
- Ensuring sustainability

GROUP 2

- Cecilia Kato
- George Varghese
- Matt Robinson
- Jackie Duggan
- Stuart Blacksell
- Wuttikon Rodkvamtook
- Yazid Abdad
- John Stenos

OBJECTIVES	METRICS	CHALLENGES
Mission Statement: There currently exists a frustration in the rickettsial disease community. Current clinical assays are old, display a low sensitivity, and are often ambiguous and difficult to interpret. Clinical diagnosis is an “art form”, not standardized or objective; lab to lab variation may be common. What is needed is one or more tests which are quick, cheap, and accurate. Assays should be validated against pathogen prevalence, region, and population composition.		
		• Validation of sample types/tissue types
Sample Preparation	• Standard Operating Procedures (SOPs)	

Sample Banking	• Mechanism for informing others of positive materials • Methods of sharing: Ÿ clinical & vector samples Ÿ peptides/antigen Ÿ nucleic acid preps	• Honest broker as a Biobank • Cross border shipment • can be a problem • Need to try to test in place 
Sample Testing	• Standards and Positive Controls • Standard Operating Procedures (SOPs) • Equipment calibration/standardization • Training and proficiency	• Cost per test • Testing Platform(s): • Existing vs. Novel • Point of care vs. Laboratory • Singleplex vs. Multiplex • ELISA or IFA or PCR or Other
Assessment of Assays	• Standard Operating Procedures (SOPs)	• IgM vs. IgG (serology) • PCR based • Country variation (which work well where?) • Patient population (e.g. pediatric vs. adult)
Logistical issues		• Understand different national standards for reporting • Sustainment in resource limited settings • Preparation of antigen “in house” • Data/Reporting/Publication

GROUP 3

- Nick Day
- Steve Dumler
- Tri Wangrangsimaku
- Matt Wegner
- Stephen Graves
- Al Richards

OBJECTI	METRIC	CHALLENGES
What are the objectives fo	How will you measure succ area?	What are the challenges, needs, and risks for each objective?
Clinical Treatment Trials for Scrub Typhus Adjunctive treatment for Scrub Typhus	Trial outcome and publishing results Develop and initiate trials involving adjunctive therapy (e.g. steroids) Gather available data	Funding to maintain output Policy change Difficulties in areas with entrenched practices

Develop vaccines for S - Develop vaccine can	Develop immune protection Eff mouse/NHP/human ch	 • Primate models: problematic/testing different isolates • Human models: ethical and issues with persistence requires clarification 
Develop vaccines for Q Fever	Development of highly effective, easy use vaccine for general rural population and military	• Prevalence in other areas
Clinical Treatment Trials for Murine Typhus	Trial outcome and publishing results	Lack of information
Burden of other Rickettsia pathogens		

GROUP 1

- Paul Newton
- Sazaly Bakar
- Kartika Saraswati
- Le Thi Hoi
- Nguyen Vu Trung
- Jeff Hertz
- Elizabeth Wanja
- Silas Davidson
- Ian Mendenhall
- Piyada Chanroensinphon
- Jariyanart Gaywee
- Brett Forshey

PROJECT PLAN

Project 1: ESTABLISH A BASELINE UNDERSTANDING OF EXISTING CAPABILTIES, KNOWLEDGE, RESOURCES

Total Timeline: (once funded) 36 months

- Conduct a series of group and species-specific literature reviews (where, who, topics); this is an opportunity to track what has worked and gaps in research; consider evidence mapping – other deep-dive alternatives (once funded, 18 months)
  - Establish working group (with multi-national and pathogen-specific interests representation)
  - Conduct a meeting to establish literature review foci and bounds
- Conduct a series of national surveys amongst human and animal health providers (follow-on, 12 months)
- Conduct a series of national surveys amongst diagnosticians (follow-on, 12 months)
- Conduct a survey of national human and animal health lab capacity for rickettsia pathogen diagnosis and surveillance (NOTE: based on WHO SARA facility readiness guidelines) across the region (follow-on, 12 months)
- Conduct a survey of database capabilities for GIS, disease surveillance, ( )
- Based on the surveys:
  - Maintain a list common gaps and challenges to allocate resources (human and material), build tailored training plans, etc.
  - Establish a list of regional experts, centers of excellence (e.g., for bio banking, training, NGS, reference, etc.), training centers

PROJECT PLAN

Project 2: ESTABLISH A WEB-BASED NETWORK
Timeline: (once funded) live website within 8 months

- Map with GIS (spatial and temporal)
  - Overlays: vector distribution, host distribution, human distribution
  - Look into Vector Map
- SOPs and protocols
  - Diagnostic practices
  - Surveillance practices
  - Clinical guidelines
  - Sampling collection
  - Biosafety and biosecurity
- Relevant publications
- Outreach (practitioners and general public (infographics)
- Pictorial identification keys (like what WBRU does with mosquitos)
- Subject matter experts, Centers of Excellence, reference facilities with links (skills, locations, and capabilities)
  - Show who are active members / contributors to the network
- Other relevant networks and websites (WRBU, AFRIMS-RTA, CERO-Path, Infectious Diseases Data Observatory (beyond malaria), Meliodosis.Info)
- Upcoming events and funding calls
- Tables
  - Confirmed cases
  - Deaths
  - On-going outbreaks (links to Pro-Med)
  - Develop a data extraction and curation protocol
- Request for supplies (antigens and reagents)
- Blog, communication, and/or chat tool ("Rick-chat")

PROJECT PLAN

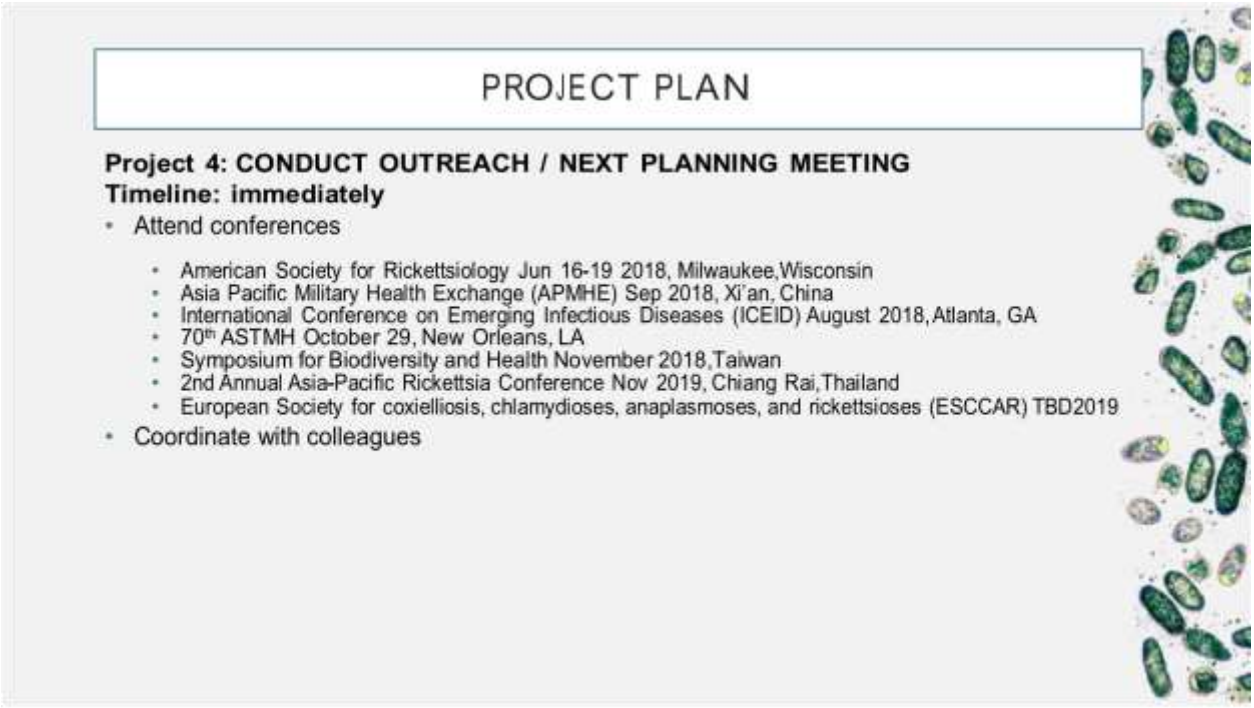
Project 3: ESTABLISH MINIMUM HUMAN AND VECTOR CASE DATA COLLECTION AND SHARING PROTOCOLS
Timeline: (once funded) 12-18 months

1. ESTABLISH MINIMUM HUMAN CASE DATA COLLECTION AND SHARING (MODELED ON AFRIMS-RTA)

- Collector name
- Collecting institution
- Species
- Detected pathogen
- Date of collection
- Location
  - Patient address
  - Location of infection

2. ESTABLISH MINIMUM VECTOR AND HOST DATA COLLECTION AND SHARING (MODELED ON WRBU, CDC, and AFRIMS-RTA)

- GIS Data (get a GIS person - NASA guy)
  - Rodent collection sites
  - Ectoparasites collection sites
  - Pathogens in the rodents or ectoparasites
  - Ecology
  - Temporal filter



INITIATIVES/ACTIONS	TIMELINE	RESPONSIBILITY
Mission Statement: Ideally, we would want to develop and validate one or more assays which detect both pathogen DNA and anti-pathogen immune response, with an objective readout		ill quantitatively identify e sample (whole blood), be able to .

Multiplex PCR Test: • Anaplasma • Coxiella • Erlichea • Rickettsia • Orientia	3 to 6 months	Jerawan (maybe) Cecilia
• Borrellia • Bartonella • Leptospira		 Matt
Constructed Analytical Samples • Spiked sample with known organism (cfu) • Whole blood	6 to 12 months	
Serology Assays to Mirror PCR (IgM/IgG)	6 to 12 months	Stuart Blacksell
Constructed Analytical Samples: • Non-human primate serum • 2-3 animals, blood daily • No select agents for new organisms • possilbe if killed • Could also be retested using Multiplex PCR	6 to 12 months Or more, for shipping outside Thailand CITES	AFRIMS (Matt Wagner, our hero)
Alternative Assays:		

GROUP 3

- Nick Day
- Steve Dumler
- Tri Wangrangsimaku
- Matt Wegner
- Stephen Graves
- Al Richards

INITIATIVES / ACTIONS	TIMELINE	RESPONSIBLITY
What are some initiatives, activities, projects, and events that you could plan to support the objectives	What is the short and long-term timeline for your work (3-5 months, 1-year, 18 months)	Who is responsible for each step; what external outreach do you need to perform to seek other support?
Treatment: • In-depth review of gaps in treatment and prevention of rickettsial diseases • ST Treatment trials • Ensure funding adequate, seek alternative funding streams to complete studies • Review use of chloramphenicol and other antibiotic treatments for rickettsial diseases • Adjunctive Treatments: cation chelators, steroids	1. SUT: 1 year 2. START: end of 2019 3. INTREST: starting in summer 2018 (India), seek funding and EC approvals for CR/LOMWRU, end of 2018 18 Months 2 years Steroids – gather data, propose new RCT for ST	1. Paul Newton 2. Al ,Tri, DHP 3. George, Nick, Paul, and Tri Tri (mainly for ST) Steve D. Tri

Vaccines: Scrub Typhus: 1. Develop immune correlates 2. Persistence 3. Evaluate vaccine candidates Q Fever: Vaccine Candidates Animal/human trials Immune correlates of protection	Scrub Typhus: 1. IFN-gamma, flow cytometry, humoral (1yr), gene transcription profiling (1-2yrs) 2. Follow up/Extension of current studies and obtain funding for additional analysis (3 to 4 years) Q Fever: 2-3 years (pre-clinical)	Scrub Typhus: 1. Tri, Nick, Susie Dunachie, Daniel Paris, Steve D., David Walker 2. Nick,Tri Q fever: Steve G.
Treatment for Murine Typhus Funding Challenges Antibiotic treatment options Potential sites for multi-centre trial (Laos, Nepal, Myanmar, Vietnam, Indonesia)	Seek funding (DHP,WT), propose and initiate RCT, 3-4 years	Nick and Paul