Ebola Research Project: Final Report
Dr. Adam Levine, Reshma Roshania, Michaela Mallow

Background

When International Medical Corps first launched its Ebola response in Liberia in the summer of 2014, very little was known about optimal prevention, treatment, or management strategies for Ebola Virus Disease (EVD). Despite more than two dozen prior outbreaks over the past four decades, little empiric evidence existed at the time to help guide our response operations. Even now, after more than 28,000 infections and 11,000 deaths in Sierra Leone, Liberia and Guinea, little operational research has been published that could lead to direct and significant improvements in our response to a future outbreak.

Starting from September 2014, International Medical Corps opened five Ebola Treatment Units (ETUs), which cumulatively cared for over 2,500 patients, and dozens of Screening and Referral Units (SRUs), which cared for thousands more. Over 25,000 patient charts containing epidemiologic, clinical, psychosocial and operational data were collected by International Medical Corps during the course of its Ebola response. International Medical Corps recognized that these data could be used to answer a variety of questions about the best methods for diagnosing EVD, predicting mortality and optimizing clinical and psychosocial care in the context of an EVD outbreak.

In May 2015, International Medical Corps established the Ebola Research Team. The goal of the team was to collect, aggregate, standardize, analyze and disseminate these data and the results from any analyses for the benefit of the entire humanitarian community. In addition, the team partnered with external investigators to research new drugs and devices that can aid in the future management of EVD. Finally, we are partnered with local Ministries of Health (MOH), the World Health Organization (WHO) and several other humanitarian partners to share data and knowledge in the hopes of improving the response to future epidemics.

Internal Research Activities

Merged IMC EVD Database

The Ebola Research Team (Adam Levine, Reshma Roshania, and Michaela Mallow) and Ebola Research Project IT Team (Nadezda Sekularac, Saikrishna Madhireddy, Mehmet Tumer, Melody Xie, and Benedict Adjogah) worked together to develop a unified database. After merging many databases and variables, we've pulled data from all five ETUs into a single unified database, which now houses all International Medical Corps data collected during the Ebola Response, including epidemiologic, clinical, laboratory, and psychosocial data. The database is relational in structure and includes ten separate tables encompassing patient demographic, triage, rounding, treatment, laboratory, psychosocial, outcome, and follow up data. The final relational database was completed in March 2016. Figure 1 demonstrates the high-level schematic of the structure for this combined database.

Figure 1: International Medical Corps Unified Database Structure
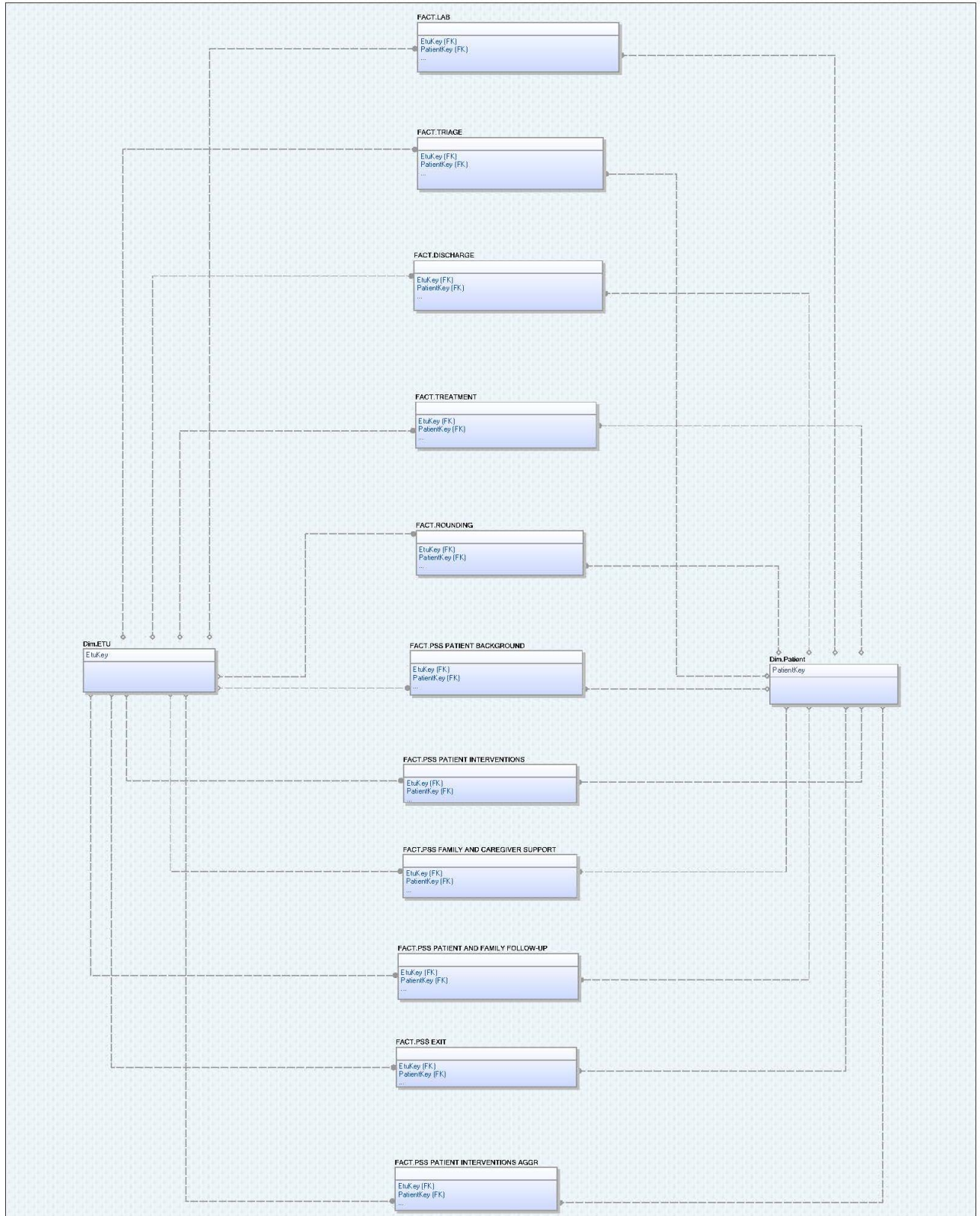
Data Quality

In November 2015, we used lot quality assurance sampling (LQAS), a random sampling methodology, to assess the quality of the data entered from original patient charts into the ETU-specific databases. A random sample of 19 patient ID numbers from 2 substrata, EVD-positive (EVD+) and EVD-negative (EVD-), were selected from each ETU (except Margibi, where 19 total patient ID numbers were randomly selected because only 5 EVD+ patients were admitted) for this data quality audit.

Due to a high number of discrepancies found among triage, rounding, and treatment patient charts and data entered in the unified database, we reentered these data using scanned files of original patient charts. Triage data were reentered for all admitted patients; daily rounding and treatment data were reentered only for EVD+ patients, to prioritize limited resources. We took the following steps to ensure minimal errors during data reentry: (1) using data validation settings in Excel reentry documents, (2) using a codebook to ensure that patient data from various types of patient charts were standardized, (3) conducting additional audits by data entry research assistants, and (4) discussing data entry concerns with the principal investigator.

Once data reentry was complete, we conducted another data quality audit using LQAS. From each ETU, we selected 19 patient IDs from 2 substrata, EVD+ and EVD- (except in Margibi). We then compared data on scans of EVD+ and EVD- triage, EVD+ rounding, and EVD+ treatment in patient charts with data in the unified database. Each discrepancy was recorded as an error. The number of errors per patient chart was divided by the total number of data points for the specific patient, which depended on the patient's length of stay. The total percentage of errors was then calculated. With the results from this audit, we concluded that approximately 99% of the data in IMC's unified database were consistent with information from scans of patient charts. Table 1 summarizes the results of the LQAS.

Table 1: Results from Audit by Table

Table	Percent of data entered correctly
Patient	99.52%
Triage	99.39%
Rounding	98.14%
Treatment	99.06%
Discharge	99.80%
OVERALL	98.8%

Data Storage

Data, including all scanned patient charts from all five ETUs and database tables, are stored on an International Medical Corps network drive as well as ShareFile with access restricted to prime team users.

Analyses

Analyses of the International Medical Corps EVD database began in January 2016 and were led in three ways:
1. By International Medical Corps EVD Research Team and Research Review Committee (RRC) staff
2. By physicians who responded to the Ebola crisis with International Medical Corps in close coordination with our EVD Research Team
3. By external organizations (e.g. Broad Institute at Harvard)

All parties involved have signed an agreement detailing data sharing and confidentiality measures and the requirements of acknowledging International Medical Corps in any manuscript or presentation. In addition, we have provided data on a case by case basis to external researchers conducting their own projects.

Appendix 1 includes a summary of research projects completed and ongoing.

Dissemination

<u>Manuscripts</u>

Based on analyses of the International Medical Corps EVD database, several manuscripts were drafted and submitted for publication. Below is a list of all drafted manuscripts (as of June 2017).

Published

- "Ebola Virus Disease in Pregnancy: A Retrospective Cohort Study of Patients Managed at Five Ebola Treatment Units in West Africa"
  Published in March 2017 in *Clinical Infectious Diseases*
- "Baseline characteristics and survival of patients infected with Malaria and Ebola Virus in Ebola Treatment Centers in Sierra Leone"
  Published in March 2017 *The Lancet Infectious Diseases*
- "Characteristics and Outcomes of Pediatric Patients with Ebola Virus Disease Admitted to Treatment Units in Liberia and Sierra Leone: A Retrospective Cohort Study"
  Published in October 2016 in *Clinical Infectious Diseases* ***Authors Choice Award
- "A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection"
  Published in October 2016 in *The New England Journal of Medicine*
- "Successful Implementation of a Multicountry Clinical Surveillance and Data Collection System for Ebola Virus Disease in West Africa: Findings and Lessons Learned"
  Published in September 2016 in *Global Health: Science and Practice*
- "Validation of a portable, deployable system for continuous vital sign monitoring using a multiparametric wearable sensor and personalised analytics in an Ebola treatment center"
  Published in July 2016 in *The BMJ*
- "Derivation and internal validation of the Ebola prediction score for risk stratification of patients with suspected Ebola virus disease"
  Published in September 2015 in *Annals of Emergency Medicine*
- "A Liberian Health Care Worker with Fever"
  Published in January 2015 in *The New England Journal of Medicine*

Accepted for Publication

–   "The Natural History of Ebola Virus Disease among Patients Managed in Five Ebola Treatment Units in West Africa"
    Accepted to *PLOS NTD* June 2017, awaiting publication
–   "Integrating Psychosocial Support at Ebola Treatment Units in Sierra Leone and Liberia"
    Accepted to *Intervention: Journal of Mental Health and Psychosocial Support in Conflict Affected Areas* May 2017, awaiting publication

Submitted for Publication

–   "Prognostic models for Ebola virus disease derived from data collected at five treatment units in Sierra Leone and Liberia: performance and external validation"
    Submitted to *PLOS Medicine* January 2017, awaiting response
–   "Water, Sanitation, and Hygiene (WASH) Operations in an ETU setting"
    Submitted to *Journal of Humanitarian Logistics and Supply Chain Management* November 2016, awaiting response

Appendix 2 includes abstracts for each manuscript.

ASTMH 2016 Annual Meeting

The Ebola Research Team submitted seven abstracts to the American Society of Tropical Medicine and Hygiene (ASTMH) and each was accepted for presentation. The team traveled to Atlanta, Georgia to present at the annual meeting in November 2016. See the list of presentations below:
1. Descriptive Summary of EVD Clinical Response
2. EVD Natural History
3. EVD and Malaria Symptoms
4. EVD and Malaria Outcomes
5. EVD in Pregnancy
6. EVD in Children
7. Ebola Prediction Score Validation

International Medical Corps Research Symposium

The Ebola Research Team worked together with Mary Pack and Serge Duss to plan an International Medical Corps Research Symposium held in in Washington DC on October 19, 2016. The event highlighted various methods of research used by key actors in the health and humanitarian sectors to mitigate and eventually stem the spread of Ebola. Panelists from International Medical Corps, National Institutes of Health, and Global Communities shared their contributions to methods for diagnosis, clinical, and psychological care in the context of EVD, as well as implications for future outbreaks of infectious diseases. They also discussed the challenges of conducting research in the midst of an emergency. The event was moderated by an individual from USAID's Bureau for Global Health.

Other Events

Dr. Adam Levine has attended and presented at several events on Ebola virus disease over the past couple of years. See below:

1. World Health Organization Ebola Science Committee Meeting. "Learning from Ebola: Towards an Evidence-Based Humanitarian Response." Montreux, Switzerland, 2015
2. World Health Organization Meeting on Clinical Aspects of Ebola Virus Disease. "Systematic Data Collection and Data Sharing." Rome, Italy, 2015
3. World Health Organization Ebola Research and Development Summit. "Panel Discussion: Establishing and using networks/platforms for collaborations for effective R&D responses in times of need." Geneva, Switzerland, 2015
4. Society for Clinical Trials Annual Meeting. "Panel Discussion: Courage, Controversy, and Clinical Trials: Lessons from the Ebola Epidemic." Montreal, Canada, 2016
5. The National Academies of Science, Engineering, and Medicine. "Panel: Experiences and Challenges Faced in Disaster Research." Washington, DC, 2016
6. Future of Outbreak Response Symposium. "Lessons from Ebola: Towards an Evidence-Based Humanitarian Response." Broad Institute, Cambridge, Massachusetts, 2016
7. Member, World Health Organization Guideline Development Group on Acute Supportive Care of Patients with Ebola Virus Disease in Resource Limited Settings, London, UK August 2016
8. World Health Organization. "Evidence for Innovative Personal Protective Equipment (PPE)." Geneva, Switzerland, October 2016

External Research Activities

Ebola Data Sharing Platform

Led by International Medical Corps, Médecins Sans Frontières, the University of Oxford, the Welcome Trust, the West African Task Force for the Control of Emerging and Re-Emerging Infectious Diseases, and the West African Health Organization, the Ebola Data Sharing Platform wishes to become the repository of all data related to Ebola as well as to foster a culture in which data sharing is the expected norm, conducted in the public interest and interests of the individuals and communities from which the data originates. Several humanitarian organizations involved in the West Africa Ebola outbreak, including International Medical Corps, have submitted their data to the platform, and several more have committed to submitting their data in the near future. The platform has begun to take these data to build their technical systems. Ethics systems are also being built. By the end of 2017, structures will be in place for researchers to apply for access to data to analyze and at to the existing evidence base.

Figure 2 illustrates the Ebola Data Sharing Platform Governance Structure, which is made up of four groups:

1. The **Steering Committee** defines the platform's research agenda based on input from other platform stakeholders, contributors, and the WHO. Steering Committee nominated members will work to engage EVD-affected communities in platform policy definition, and support the security of long term funding for platform activities. The Steering Committee develops, and regularly reviews and evolves, the Terms and Conditions of Data Access, as well as appoints the Data Access Committee. The Steering Committee will meet bi-annually to discuss and review platform policy, strategy and

outputs. Committee members will take an active role in promoting the impact and sustainability of the platform through stimulation of funding and participation from relevant stakeholders. International Medical Corps has been named as one of just two NGO members of the Steering Committee, alongside representatives from the three Ebola affected countries, WHO, Oxford, and the Welcome Trust.

2. The **Data Access Committee (DAC)** is responsible for evaluating proposals for data access and determining whether data requests are consistent with the Terms and Conditions of Data Access, and that the requests do not pose undue risk to the individuals, communities or organizations to which they relate. This includes evaluation of risk of loss of privacy and assurance that appropriate protections of confidentiality and ethics review are in place.

3. The **Secretariat** will manage the administration of both of the above Committees. The Secretariat will be based at the Infectious Diseases Data Observatory, University of Oxford, where the platform will be hosted. Platform hosting involves responsibility for platform technical architecture, data curation, data security, data management and transfer, budget administration, and platform website development and management. The Secretariat will support the development and execution of platform proposals, policy and approvals.

4. A **Stakeholder Advisory Group (SAG)** is in place to advise on the design and implementation of platform policy, and to support the objectives of the platform through stimulation of Stakeholder participation. All individuals and organizations involved in Ebola data or outbreak response are welcome to engage with this group through active participation. Regular meetings of the SAG have been held since mid-2015 via teleconference to discuss the design and development of platform governance and objectives.

Figure 2: Ebola Data Sharing Platform Governance Structure
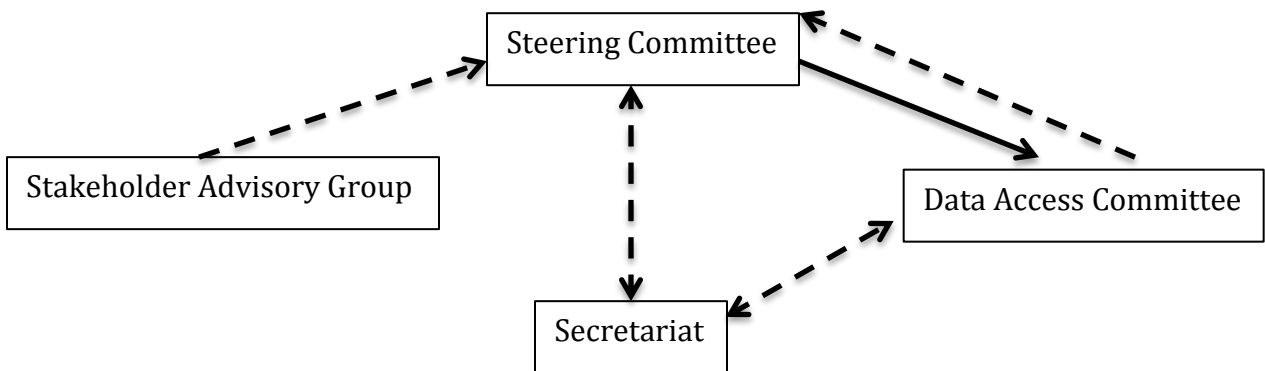
Next Steps Forward

As the end of the internally funded Ebola Research Project came nearer, the Ebola Research Team sought out external funding in order to continue the work done over the past couple of years.

1. **Awarded:** National Institutes of Health (NIH) grant
   Prime: Brown University; Sub: International Medical Corps
   IRB approval received from lifespan; May apply for IRB in Sierra Leone.

This research will focus on assessing the supportive care measures that may work to reduce mortality and morbidity in patients with EVD including intravenous fluids, micronutrient supplements and antimicrobials, specifically antibiotics.

2. **Upcoming opportunity:** Department of Defense (DOD), Defense Threat Reduction Agency and The Henry Jackson Foundation for Military Medicine
This research will focus on the natural history of EVD including: how it causes death, which patients are most at risk for EVD, and which patients who are diagnosed with EVD are most at risk of dying from it.

Conclusion

Significant work has been done in the two years since the initial development of our Ebola Research Team. We have digitized and merged together all of International Medical Corps' EVD data. We have established collaborations with a number of outside research institutions and created a framework for reviewing and approving future research. We have submitted twelve manuscripts to journals for publication; 10 have already been accepted and/or published by renowned journals including *The BMJ, New England Journal of Medicine, Lancet Infectious Diseases,* and more. In addition, we continue to be an active participant in the larger EVD Data Sharing Platform. With secured funding from the NIH and a funding opportunity in the pipeline with the DOD, more results will surely be added to the growing evidence base to influence future response to EVD and other infectious disease outbreaks for years to come.

Appendix 1: International Medical Corps EVD Research Agenda

Research Project	Summary
Descriptive Summary of EVD Clinical Response	Provides an overall summary of patient characteristics and outcomes as well as data collection methods utilized at IMC-supported facilities in West Africa
EVD Natural History	Describes the evolution of clinical symptoms and biomarkers in patients with EVD over the course of their illness and their associations with patient outcomes
EVD and Malaria	Analyzes the variable states of EVD and malarial infection in patients presenting to ETUs and the differences in clinical symptoms and impact on EVD mortality
EVD in Pregnancy	Analyzes EVD natural history and outcomes in pregnant women
EVD in Children	Analyzes EVD natural history and outcomes in children
MHPSS in an ETU Setting	Describes mental health-related patient characteristics and psychosocial interventions used
WASH Operations in an ETU Setting	Analyzes data on WASH operations to better understand needs for water, chlorine, personal protective equipment, and other supplies in the operation of an Ebola Treatment Unit
Genetic Sequencing	Analyzes the linkage of Ebola viral sequence data to clinical and outcome data, to investigate the variation in clinical presentation, transmissibility and host outcome associated with each of the different viral lineages
Geographic Information Systems (GIS) Analysis	Analyzes the impact of patient origin and location of illness on presentation and outcomes in order to identify local patterns in EVD spread
Making Ebola Prognosis Models Actionable	Develops a prognostic model for EVD outcomes using baseline patient data that can be incorporated into an app for use by frontline providers
Ebola Prediction Score Derivation	Develops a clinical prediction model that can help clinicians stratify patients by risk patients with suspected Ebola Virus Disease in the context of an Ebola epidemic
EVD Prediction Score Validation	Utilizes data from Sierra Leone and Guinea to validate the International Medical Corps Ebola Prediction Score for screening of patients
STAMP2	Tests the feasibility of the MultiSense patch, which allows for real-time, remote monitoring of patient vital signs, in an ETU setting.
ZMAPP	Clinical trial assesses several important outcomes, including clinical course, laboratory test results and mortality in patients receiving standard EVD care or standard EVD care plus an infusion of ZMapp

Appendix 2: Abstracts

Published

"Ebola Virus Disease in Pregnancy: A Retrospective Cohort Study of Patients Managed at Five Ebola Treatment Units in West Africa"
Published in March 2017 in *Clinical Infectious Diseases*

Background: Reliable data are lacking on pregnancy outcomes during Ebola virus disease (EVD) epidemics. We aimed to characterize symptoms and outcomes among pregnant women admitted to Ebola treatment units (ETUs) with suspected and confirmed EVD to better inform obstetric management.
Methods: We analyzed a retrospective cohort of reproductive-aged women presenting to 5 West African ETUs from September 2014 to September 2015. We compared clinical symptoms, risk of EVD diagnosis, and mortality between pregnant and nonpregnant women.
Results: Of 729 reproductive-aged women admitted to study ETUs, 44 (6%) reported pregnancy. Thirteen of 44 pregnant women (30%) tested EVD positive; 6 of 13 (46%) died. Pregnant women were less likely than nonpregnant women to report anorexia, asthenia, diarrhea, fever, myalgias/arthralgias, nausea, or vomiting (P < .05) at admission. Pregnant women with suspected EVD had the same risk, however, of laboratory-confirmed EVD (30% vs 24%, P = .38). While pregnant women with confirmed EVD had similar Ebola viral loads on presentation to nonpregnant women, as measured by initial cycle threshold (26.4 vs 23.2, P = .16), they were less likely to have myalgias/arthralgias (P< .001) and vomiting (P = .02). Both all-cause mortality (14% vs 19%, P = .39) and EVD-specific mortality (46% vs 54%, P = .60) were not significantly different between pregnant and nonpregnant women. Two neonates born live in the ETU died within 8 days.
Conclusions: We find no evidence to support a difference in the risk of death between pregnant women with suspected or confirmed EVD compared to nonpregnant women. Limited data suggest poor fetal and neonatal outcomes in EVD-affected pregnancies.

"Baseline characteristics and survival of patients infected with Malaria and Ebola Virus in Ebola Treatment Centers in Sierra Leone"
Published in March 2017 *The Lancet Infectious Diseases*

Background: The 2014–15 Ebola virus disease (EVD) epidemic strained health systems in west Africa already overburdened with other diseases, including malaria. Because EVD and malaria can be difficult to distinguish clinically, and rapid testing was not available in many Ebola Treatment Units (ETUs), guidelines recommended empirical malaria treatment. Little is known, however, about the prevalence and characteristics of patients entering an ETU who were infected with malaria parasites, either alone or concurrently with Ebola virus.
Methods: Data for sociodemographics, disease characteristics, and mortality were analysed for patients with suspected EVD admitted to three ETUs in Sierra Leone using a retrospective cohort design. Testing for Ebola virus was done by real-time PCR and for malaria by a rapid diagnostic test. Characteristics of patients were compared and survival analyses were done to evaluate the effect of infection status on mortality.
Findings: Between Dec 1, 2014, and Oct 15, 2015, 1524 cases were treated at the three ETUs for suspected EVD, of whom 1368 (90%) had diagnostic data for malaria and EVD. Median age of patients was 29 years (IQR 20–44) and 715 (52%) were men. 1114 patients were EVD negative,

of whom 365 (33%) tested positive for malaria. Of 254 EVD positive patients, 53 (21%) also tested positive for malaria. Mortality risk was highest in patients diagnosed with both EVD and malaria (35 [66%] of 53 died) and patients diagnosed with EVD alone (105 [52%] of 201 died). Compared with patients presenting to ETUs without malaria or EVD, mortality was increased in the malaria positive and EVD positive group (adjusted hazard ratio 9·36, 95% CI 6·18–14·18, p<0·0001), and the malaria negative and EVD positive group (5·97, 4·44–8·02, p<0·0001), but reduced in the malaria positive and EVD negative group (0·37, 0·20–1·23, p=0·0010). Interpretation: Malaria parasite co-infection was common in patients presenting to ETUs and conferred an increased mortality risk in patients infected with Ebola virus, supporting empirical malaria treatment in ETUs. The high mortality among patients without EVD or malaria suggests expanded testing and treatment might improve care in future EVD epidemics.

"Characteristics and Outcomes of Pediatric Patients with Ebola Virus Disease Admitted to Treatment Units in Liberia and Sierra Leone: A Retrospective Cohort Study"
Published in October 2016 in *Clinical Infectious Diseases* ***Authors Choice Award

Background: The clinical and virologic characteristics of Ebola virus disease (EVD) in children have not been thoroughly documented.
Methods: Consecutive children aged <18 years with real-time polymerase chain reaction (RT-PCR)–confirmed EVD were enrolled retrospectively in 5 Ebola treatment units in Liberia and Sierra Leone in 2014/2015. Data collection and medical management were based on standardized International Medical Corps protocols. We performed descriptive statistics, multivariate logistic regression, and Kaplan-Meier survival analyses.
Results: Of 122 children enrolled, the median age was 7 years and one-third were aged <5 years. The female-to-male ratio was 1.3. The most common clinical features at triage and during hospitalization were fever, weakness, anorexia, and diarrhea, although 21% of patients were initially afebrile and 6 patients remained afebrile. Bleeding was rare at presentation (5%) and manifested subsequently in fewer than 50%. The overall case fatality rate was 57%. Factors associated with death in bivariate analyses were age <5 years, bleeding at any time during hospitalization, and high viral load. After adjustment with logistic regression modeling, the odds of death were 14.8-fold higher if patients were aged <5 years, 5-fold higher if the patient had any evidence of bleeding, and 5.2-fold higher if EVD RT-PCR cycle threshold value was ≤20. Plasmodium parasitemia had no impact on EVD outcomes.
Conclusions: Age <5 years, bleeding, and high viral loads were poor prognostic indicators of children with EVD. Research to understand mechanisms of these risk factors and the impact of dehydration and electrolyte imbalance will improve health outcomes.

"A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection"
Published in October 2016 in *The New England Journal of Medicine*

Background: Data from studies in nonhuman primates suggest that the triple monoclonal antibody cocktail ZMapp is a promising immune-based treatment for Ebola virus disease (EVD).
Methods: Beginning in March 2015, we conducted a randomized, controlled trial of ZMapp plus the current standard of care as compared with the current standard of care alone in patients with EVD that was diagnosed in West Africa by polymerase-chain-reaction (PCR) assay. Eligible patients of any age were randomly assigned in a 1:1 ratio to receive either the current standard of care or the current standard of care plus three intravenous infusions of ZMapp (50 mg per kilogram of body weight, administered every third day). Patients were stratified according to

baseline PCR cycle-threshold value for the virus (≤22 vs. >22) and country of enrollment. Oral favipiravir was part of the current standard of care in Guinea. The primary end point was mortality at 28 days.

Results: A total of 72 patients were enrolled at sites in Liberia, Sierra Leone, Guinea, and the United States. Of the 71 patients who could be evaluated, 21 died, representing an overall case fatality rate of 30%. Death occurred in 13 of 35 patients (37%) who received the current standard of care alone and in 8 of 36 patients (22%) who received the current standard of care plus ZMapp. The observed posterior probability that ZMapp plus the current standard of care was superior to the current standard of care alone was 91.2%, falling short of the prespecified threshold of 97.5%. Frequentist analyses yielded similar results (absolute difference in mortality with ZMapp, −15 percentage points; 95% confidence interval, −36 to 7). Baseline viral load was strongly predictive of both mortality and duration of hospitalization in all age groups.

Conclusions: In this randomized, controlled trial of a putative therapeutic agent for EVD, although the estimated effect of ZMapp appeared to be beneficial, the result did not meet the prespecified statistical threshold for efficacy. (Funded by the National Institute of Allergy and Infectious Diseases and others; PREVAIL II ClinicalTrials.gov number, NCT02363322.)

"Successful Implementation of a Multicountry Clinical Surveillance and Data Collection System for Ebola Virus Disease in West Africa: Findings and Lessons Learned"
Published in September 2016 in *Global Health: Science and Practice*

Background: The 2014 outbreak of Ebola virus disease (EVD) in West Africa was the largest ever recorded. Starting in September 2014, International Medical Corps (IMC) managed 5 Ebola treatment units (ETUs) in Liberia and Sierra Leone, which cumulatively cared for about 2,500 patients. We conducted a retrospective cohort study of patient data collected at the 5 ETUs over 1 year of operations.

Methods: To collect clinical and epidemiological data from the patient care areas, each chart was either manually copied across the fence between the high-risk zone and low-risk zone, imaged across the fence, or imaged in the high-risk zone. Each ETU's data were entered into a separate electronic database, and these were later combined into a single relational database. Lot quality assurance sampling was used to ensure data quality, with reentry of data with high error rates from imaged records.

Results: The IMC database contains records on 2,768 patient presentations, including 2,351 patient admissions with full follow-up data. Of the patients admitted, 470 (20.0%) tested positive for EVD, with an overall case fatality ratio (CFR) of 57.0% for EVD-positive patients and 8.1% for EVD-negative patients. Although more men were admitted than women (53.4% vs. 46.6%), a larger proportion of women were diagnosed EVD positive (25.6% vs. 15.2%). Diarrhea, red eyes, contact with an ill person, and funeral attendance were significantly more common in patients with EVD than in those with other diagnoses. Among EVD-positive patients, age was a significant predictor of mortality: the highest CFRs were among children under 5 (89.1%) and adults over 55 (71.4%).

Discussion: While several prior reports have documented the experiences of individual ETUs, this study is the first to present data from multiple ETUs across 2 countries run by the same organization with similar clinical protocols. Our experience demonstrates that even in austere settings under difficult conditions, it is possible for humanitarian organizations to collect high-quality clinical and epidemiologic data during a major infectious disease outbreak.

"Validation of a portable, deployable system for continuous vital sign monitoring using a multiparametric wearable sensor and personalised analytics in an Ebola treatment center"
Published in July 2016 in *The BMJ*

Background: The recent Ebola epidemic in West Africa strained existing healthcare systems well beyond their capacities due to the extreme volume and severity of illness of the patients. The implementation of innovative digital technologies within available care centres could potentially improve patient care as well as healthcare worker safety and effectiveness.
Methods: We developed a Modular Wireless Patient Monitoring System (MWPMS) and conducted a proof of concept study in an Ebola treatment centre (ETC) in Makeni, Sierra Leone. The system was built around a wireless, multiparametric 'band-aid' patch sensor for continuous vital sign monitoring and transmission, plus sophisticated data analytics. Results were used to develop personalised analytics to support automated alerting of early changes in patient status.
Results: During the 3-week study period, all eligible patients (n=26) admitted to the ETC were enrolled in the study, generating a total of 1838 hours of continuous vital sign data (mean of 67.8 hours/patient), including heart rate, heart rate variability, activity, respiratory rate, pulse transit time (inversely related to blood pressure), uncalibrated skin temperature and posture. All patients tolerated the patch sensor without problems. Manually determined and automated vital signs were well correlated. Algorithm-generated Multivariate Change Index, pulse transit time and arrhythmia burden demonstrated encouraging preliminary findings of important physiological changes, as did ECG waveform changes.
Conclusions: In this proof of concept study, we were able to demonstrate that a portable, deployable system for continuous vital sign monitoring via a wireless, wearable sensor supported by a sophisticated, personalised analytics platform can provide high-acuity monitoring with a continuous, objective measure of physiological status of all patients that is achievable in virtually any healthcare setting, anywhere in the world.

"Derivation and internal validation of the Ebola prediction score for risk stratification of patients with suspected Ebola virus disease"
Published in September 2015 in *Annals of Emergency Medicine*

Study Objective: The current outbreak of Ebola virus disease in West Africa is the largest on record and has overwhelmed the capacity of local health systems and the international community to provide sufficient isolation and treatment of all suspected cases. The goal of this study is to develop a clinical prediction model that can help clinicians risk-stratify patients with suspected Ebola virus disease in the context of such an epidemic.
Methods: A retrospective analysis was performed of patient data collected during routine clinical care at the Bong County Ebola Treatment Unit in Liberia during its first 16 weeks of operation. The predictive power of 14 clinical and epidemiologic variables was measured against the primary outcome of laboratory-confirmed Ebola virus disease, using logistic regression to develop a final prediction model. Bootstrap sampling was used to assess the internal validity of the model and estimate its performance in a simulated validation cohort.
Results: Ebola virus disease testing results were available for 382 (97%) of 395 patients admitted to the Ebola treatment unit during the study period. A total of 160 patients (42%) tested positive for Ebola virus disease. Logistic regression analysis identified 6 variables independently predictive of laboratory-confirmed Ebola virus disease, including sick contact, diarrhea, loss of appetite, muscle pains, difficulty swallowing, and absence of abdominal pain. The Ebola

Prediction Score, constructed with these 6 variables, had an area under the receiver operator characteristic curve of 0.75 (95% confidence interval 0.70 to 0.80) for the prediction of laboratory-confirmed Ebola virus disease. Patients with higher Ebola Prediction Scores had higher likelihoods of laboratory-confirmed Ebola virus disease.

Conclusion: The Ebola Prediction Score can be used by clinicians as an adjunct to current Ebola virus disease case definitions to risk-stratify patients with suspected Ebola virus disease. Clinicians can use this new tool for the purpose of cohorting patients within the suspected-disease ward of an Ebola treatment unit or community-based isolation center to prevent nosocomial infection or as a triage tool when patient numbers overwhelm available capacity. Given the inherent limitations of clinical prediction models, however, a low-cost, point-of-care test that can rapidly and definitively exclude Ebola virus disease in patients should be a research priority.

"A Liberian Health Care Worker with Fever"
Published in January 2015 in *The New England Journal of Medicine*

This is an interactive case. Each interactive case presents an evolving patient history and a series of questions and exercises designed to test your diagnostic and therapeutic skills. You will receive immediate feedback on your answers and treatment choices, along with the opportunity to compare your final score with those of your peers. Video, animation, and interactive content allow you to learn more about mechanisms, diagnostic tests, and treatments.

Accepted for Publication

"The Natural History of Ebola Virus Disease among Patients Managed in Five Ebola Treatment Units in West Africa"
Accepted to *PLOS NTD* June 2017, awaiting publication

Background: Previous studies of Ebola Virus Disease (EVD) have focused on clinical symptoms and Ebola virus (EBOV) cycle threshold (CT) values recorded at patient triage. Our study explores EVD symptoms and EBOV CT values from onset of illness to recovery or death in a diverse population of patients.

Methodology/Principal Findings: We analyzed clinical care data from EBOV positive patients admitted to five Ebola treatment units in West Africa from 2014–2015. Prevalence of clinical signs/symptoms and CT values were explored using descriptive statistics. Logistic regression was used to examine their association with mortality. Survival was analyzed using Kaplan-Meier estimators from symptom onset date to death. During the first week of illness, dyspnea (OR=2·44, 95% CI: 1·07–5·85) and tachycardia (OR=10·22, 95% CI: 2·20–56·71) were associated with higher odds of mortality. Dyspnea (OR=2·33, 95% CI: 1·210–4·581), bleeding (OR=2·51, 95% CI: 1·219–5·337), and diarrhoea (OR=2·79, 95% CI: 1·171–6·970) at any point during the illness course were associated with higher odds of mortality. Higher initial (OR=0·85, 95% CI: 0·81–0·89) and mean (OR=0·60, 95% CI: 0·53–0·66) CT values were associated with lower odds of mortality. CT values reached their nadir after 3–5 days of illness and then rose in both survivors and non-survivors until recovery or death.

Conclusions/Significance: Our study demonstrates the population prevalence of clinical signs/symptoms and EBOV CT values over time in a large, diverse cohort of patients with EVD, as well as associations between symptoms/EBOV CT values and mortality. These findings have implications on surveillance, operational planning, and clinical care for future EVD outbreaks.

"Integrating Psychosocial Support at Ebola Treatment Units in Sierra Leone and Liberia"
Accepted to *Intervention: Journal of Mental Health and Psychosocial Support in Conflict Affected Areas* May 2017, awaiting publication

The Ebola virus disease (EVD) epidemic killed almost 12,000 people across Sierra Leone, Liberia and Guinea, causing significant psychological distress and suffering. This paper describes International Medical Corps' innovative and comprehensive model for integrating mental health and psychosocial support (MHPSS) considerations and activities into Ebola treatment units (ETUs) across Sierra Leone and Liberia. This includes staff capacity building as well as psychosocial considerations and activities to address needs and challenges at the ETUs. This model was aimed at reducing patient and family distress and promoting healthy behaviors and recovery. We also include data describing mental health related symptoms reported by our ETU patients, as well as psychosocial support interventions utilised. We discuss recommendations and lessons learned and conclude that in line with global guidelines, MHPSS considerations and activities should be integral to all aspects of EVD care.

Submitted for Publication

"Water, Sanitation, and Hygiene (WASH) Operations in an ETU setting"
Submitted to *PLOS One* May 2017, awaiting response

Purpose: The 2014 outbreak of Ebola virus disease (EVD) in West Africa was the largest in history. International Medical Corps (IMC) operated five Ebola treatment units (ETUs) in Sierra Leone and Liberia. This paper explores how future infectious disease outbreak facilities in resource-limited settings can be planned, organized, and managed by analyzing data collected on water, sanitation, and hygiene (WASH) and infection prevention control (IPC) protocols. Design/methodology/approach: WASH/IPC activity data were routinely recorded on paper forms or white boards and were later merged into a database. We conducted a retrospective cohort study by analyzing WASH/IPC data collected at two IMC-run ETUs between December 2014 and December 2015.
Findings: The IMC WASH/IPC database contains data from two ETUs in Sierra Leone over 369 days. Our results highlight parameters key to designing and maintaining an ETU. High concentration chlorine solution usage was highly correlated with both patient occupancy and high-risk zone staff entries; low concentration chlorine usage was less well explained by these measures. There is high demand for laundering and disinfecting of personal protective equipment (PPE) on a daily basis and approximately 1 (0-4) piece of PPE is damaged each day. Research limitations/implications: Lack of standardization in the type and format of data collected at ETUs made constructing the WASH//IPC database difficult. The severe logistical constraints of data collection in a highly contagious setting may have led to recall bias. Originality/value: This paper will inform the planning, organizing, and managing of ETUs in future Ebola or other infectious disease outbreaks.

"Prognostic models for Ebola virus disease derived from data collected at five treatment units in Sierra Leone and Liberia: performance and external validation"f
Submitted to *PLOS Medicine* January 2017, awaiting response

Background: The 2014-2016 Ebola Virus Disease (EVD) outbreak highlighted the need for rigorous, rapid, and field-deployable tools to enable case management. We previously introduced an

approach for EVD prognosis prediction, using models that can be implemented in the field and updated in light of new data. Here we enhance and validate our methods with the largest published EVD dataset to date. We also present a proof-of-concept medical app that summarizes patient information and offers tailored treatment options using an interactive visualization for quick interpretation and decision-making.

Methods and Findings: We derived prognosis prediction models for EVD using data from 470 patients admitted to five Ebola treatment units (ETUs) operated by International Medical Corps (IMC) in Liberia and Sierra Leone. We fitted logistic regression models, handled missing data by multiple imputation, and conducted internal validation with bootstrap sampling. We also validated our models with independent datasets from two treatment centers in Sierra Leone comprising 106 patients at Kenema Government Hospital and 158 patients at the GOAL-Mathaska ETU in Port Loko district. We corroborated earlier reports on the importance of viral load and age as mortality predictors and identified jaundice and bleeding to be features with highest predictive value at presentation. Additional clinical symptoms at presentation, although weakly correlated with outcome, help broaden sensitivity and refine discrimination. The app provides a visual representation of the predictive outcome as well as attributing dose-adjusted clinical protocols, prioritized to target the largest contributing factor to overall risk.

Conclusions: We derived high performance models of EVD prognosis prediction from the largest and most geographically diverse EVD patients available to date. The performance was maintained during external validations on two independent datasets representing different treatment settings and mortality rates, which suggests that the models could be generalized to new populations. This tool may better inform treatment choices in future EVD outbreaks and provides a template on which to validate further datasets for the development of novel clinical-decision support systems useful in both EVD and other emerging infectious diseases.