How might we make cholera diagnostics more resilient to the negative effects of antibiotics and lytic phages?

June 27, 2023

UF: Eric Jorge Nelson, Md Abu Sayeed MS, E. Cato, A. Vustepalli, E. Freeman, A. Creasy-Marrazzo
Collaborators: K. Islam, Md. I.UI. Khabir, Md. T. R. Bhuiyan, Y. Begum, D. Sack, A. Debes, K. B. Basso, **A. I. Khan, F. Qadri**

Funding: Wellcome Trust 215676/Z/19/Z, NIH R21TW010182, NIH R01AI123422 (D. Sack)
Disclosures: None

EMERGING PATHOGENS INSTITUTE
UNIVERSITY OF FLORIDA

Onset (cholera)	Triage	Diagnosis	Rehydration	Antimicrobials	Response*
Household	Hospital				Population

implementation/telemed J Peds. 2022 AJTMH. 2022 BMJ Open. 2021 NEJM. 2011 Lancet ID. 2009	informatics/eCDS Lancet DH. 2020* Soc Sci Med. 2020 PloS NTD. 2017*	informatics/AI** eLife 2023 JAMApeds. 2022 AJTMH. 2022 PloS NTD. 2022 microbiology I & I. 2022 JID. 2019	informatics/AI** eLife. 2023 PLoS NDT. 2016 AJTMH. 2021 TropMed Int H. 2016 PLoS NTD. 2021	informatics/AI** In J Infect Des. 2021 microbiology Mic. Genomics. 2022 JCM. 2020 PNAS. 2020 bioRxiv. 2023***	policy WHO GTFCC

* Triage software feeds data to public health officials

** AI/ML in collaboration with A. Levine (Brown) and D. Leung (Utah)

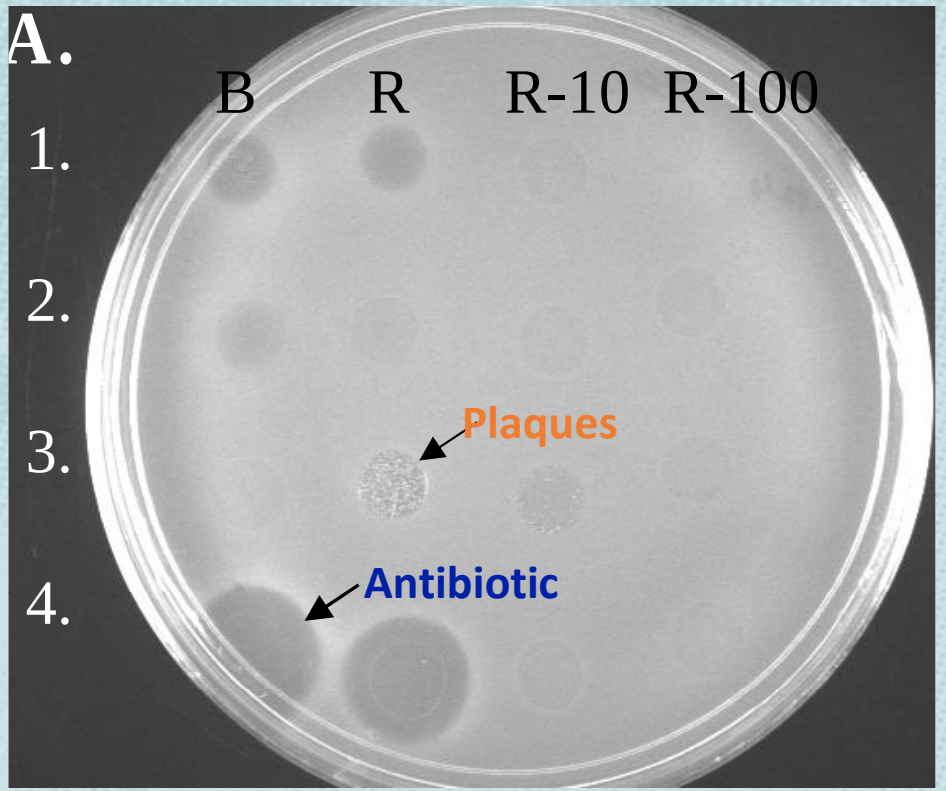
*** Madi et al. Under review. Phage as a biomarker of disease severity

Mindset for innovation

"The significant problems we face cannot be solved at the **same** level of thinking we were at when we [humanity] created them." Albert Einstein

We know that RDTS can have inconsistent results. Why?

Could antibiotic exposure be an explanation?

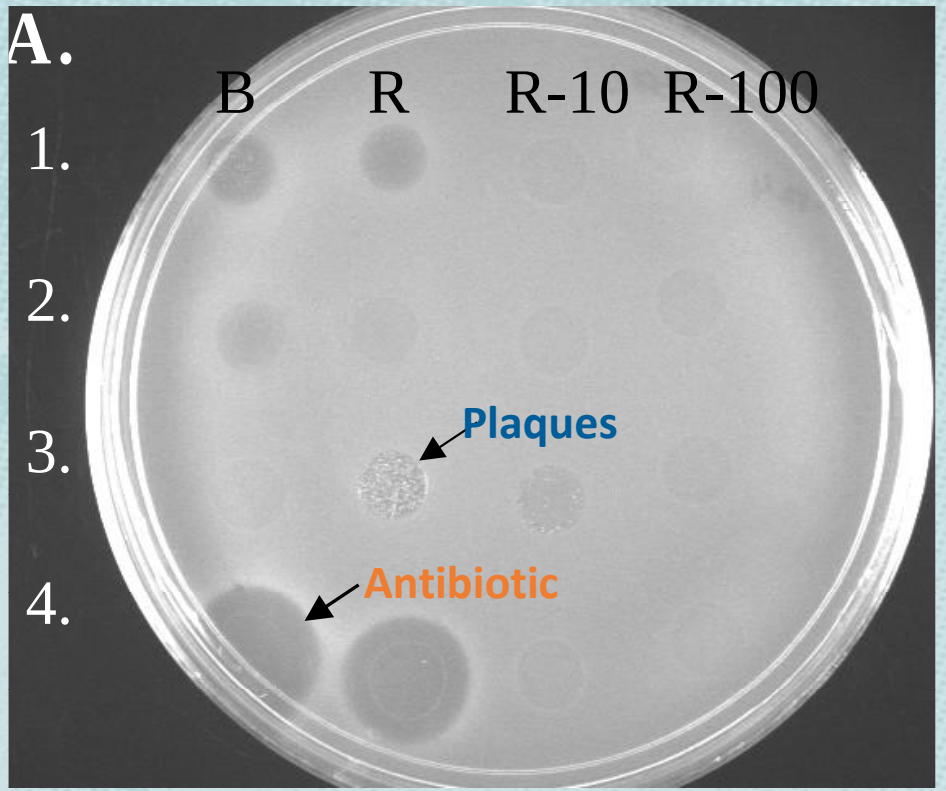


"Among diarrheal samples positive by nanoliter quantitative PCR (qPCR) *for V. cholerae*, the odds that an RDT was positive was reduced by more than **99%** when azithromycin was detected."

(2015 Single Site Study. JCM. Nelson and Khan et al. 2020)

We know that RDTS can have inconsistent results. Why?

Could lytic phage be an explanation?



"Among diarrheal samples positive by nanoliter quantitative PCR (qPCR) *for V. cholerae*, the odds that a RDT was positive was reduced by **89%** when lytic phages were detected."

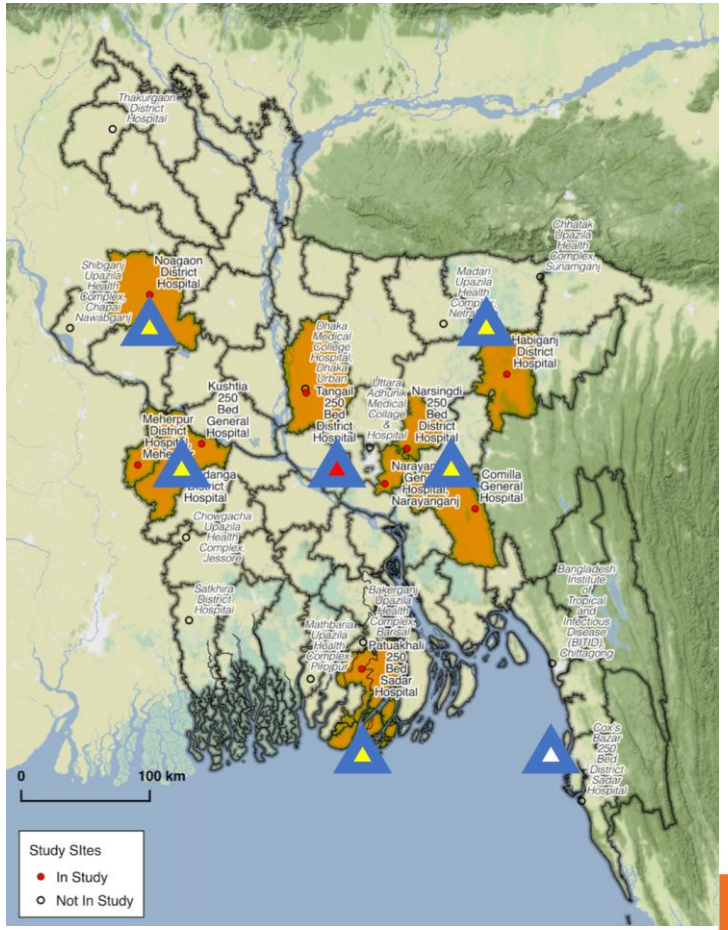
(2015 Single Site Study. JCM. Nelson and Khan et al. 2020)

Electronic decision support and diarrhoeal disease guideline adherence (mHDM): a cluster randomised controlled trial

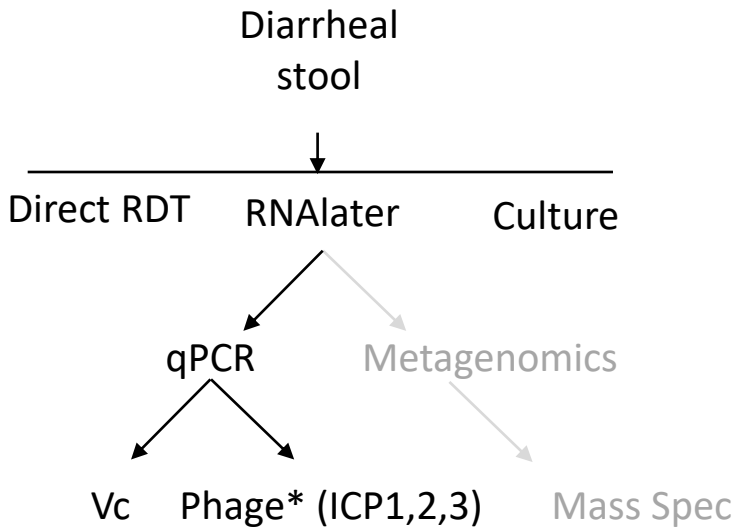
Ashraful I Khan, Jasmine A Mack, M Salimuzzaman, Mazharul I Zion,Hasnat Sujon, Robyn L Ball, Stace Maples, Md Mahbubur Rashid, Mohammod J Chisti, Shafiqul A Sarker, Debashish Biswas, Raduan Hossin, Kevin L Bardosh, Yasmin A Begum, Azimuddin Ahmed, Dane Pieri, Farhana Haque, Mahmudur Rahman, Adam C Levine, Firdausi Qadri, Meerjady S Flora, Matthew J Gurka, Eric J Nelson

Lancet DH. 2021

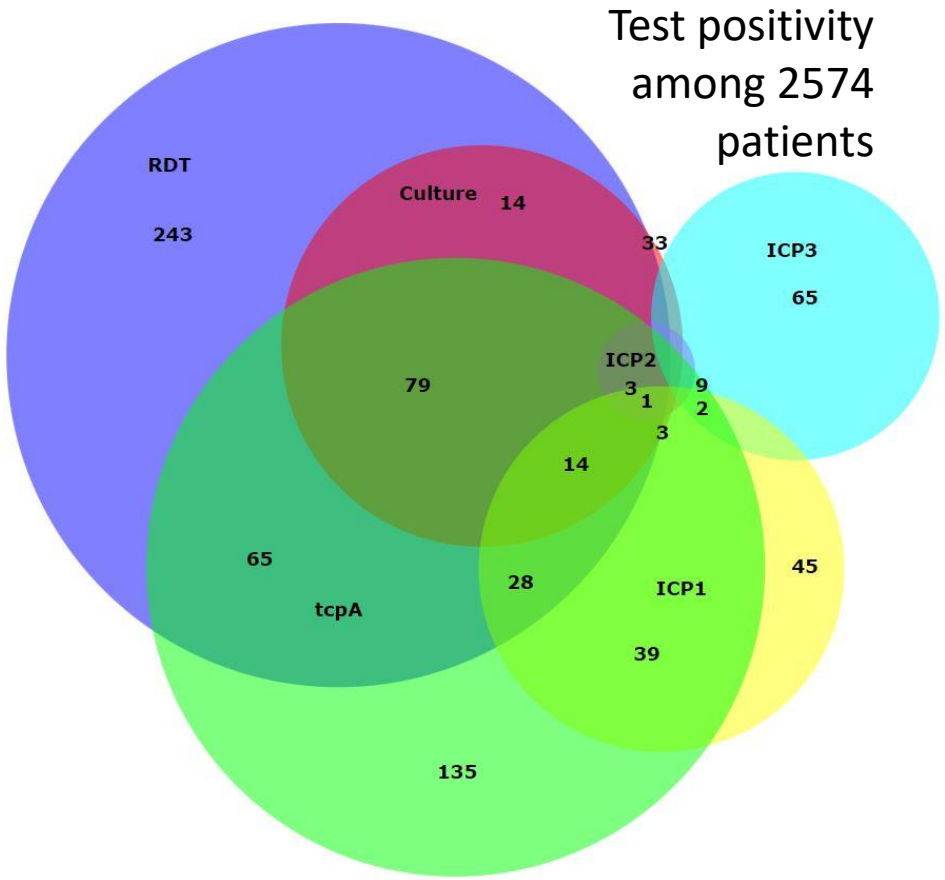
A.



B.



*ICP1 is in S. East Asian, the DRC (UF), S. Sudan (JHU), Kenya (JHU). ICP2 and ICP3 have not been detected in DRC, S. Sudan, Kenya.



Results (conventional mindset)

RDT with qPCR (*tcpA*) as reference standard*

Sensitivity: **48%** (44-53%)

Specificity: 85% (83-86%)

PPV**:** **42%** (38-47%)

NPV: 88% (86-89%)

Culture with qPCR (*tcpA*) as reference standard*

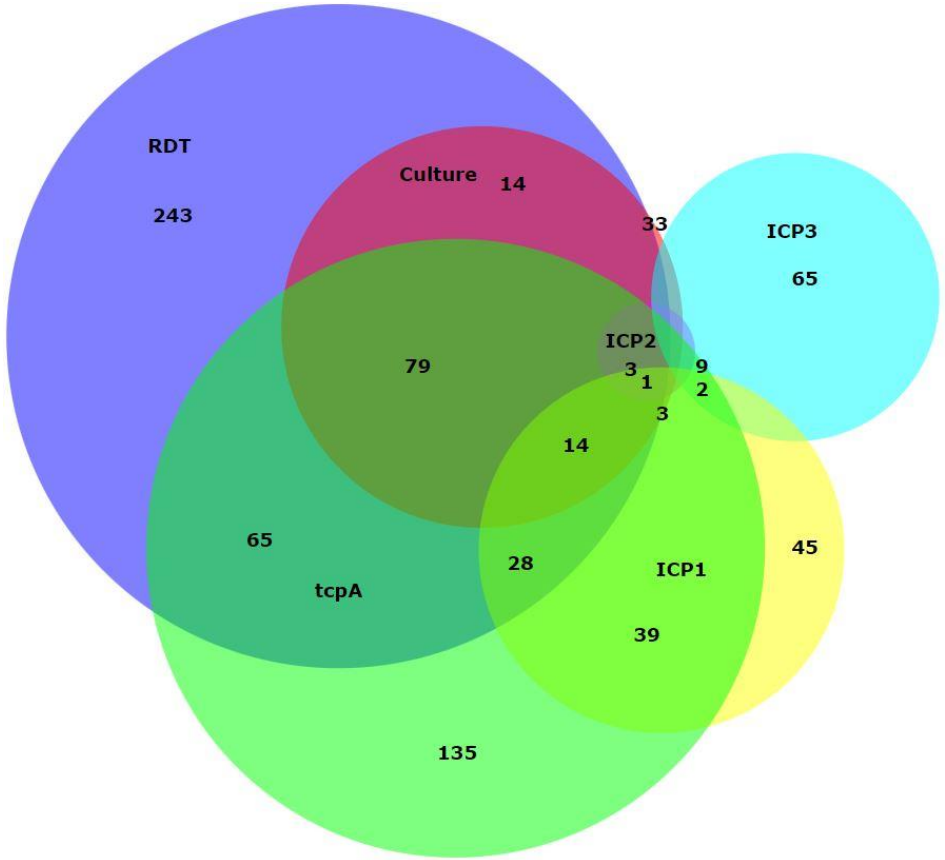
Sensitivity: **30%** (26-35%)

Specificity: 97% (96-98%)

PPV: 72% (64-78%)

NPV: 86% (84-87%)

*Analyses do not control for antibiotic exposure. Ct cutoffs at 28.



Take home points

- Antibiotics can reduce odds of RDT positivity by >90%
- Phage can reduce odds of RDT positivity by >80%
- We may be judging diagnostics with the wrong standard
- There is no one gold standard, requires an *in silico* gold standard

Next steps towards innovation

- When to use RDT? Need decision-support on when to use
- How to interpret RDT? Decision-support to predict true pos/neg
- Determine the biologic mechanisms by which diagnostics fail
- Develop diagnostics that include phage detection

Mindset for innovation

At GTFCC, **let's** explore how **might** we make cholera diagnostics that are more resilient to fit the needs/wants of stakeholders?

UF: Eric Jorge Nelson, Md Abu Sayeed MS, E. Cato, A. Vustepalli, E. Freeman, A. Creasy-Marrazzo
Collaborators: K. Islam, Md. I.UI. Khabir, Md. T. R. Bhuiyan, Y. Begum, D. Sack, A. Debes, K. B. Basso, **A. I. Khan, F. Qadri**
Funding: Wellcome Trust 215676/Z/19/Z (EJN), NIH R21TW010182 (EJN), NIH R01AI123422 (D. Sack)
Disclosures: None