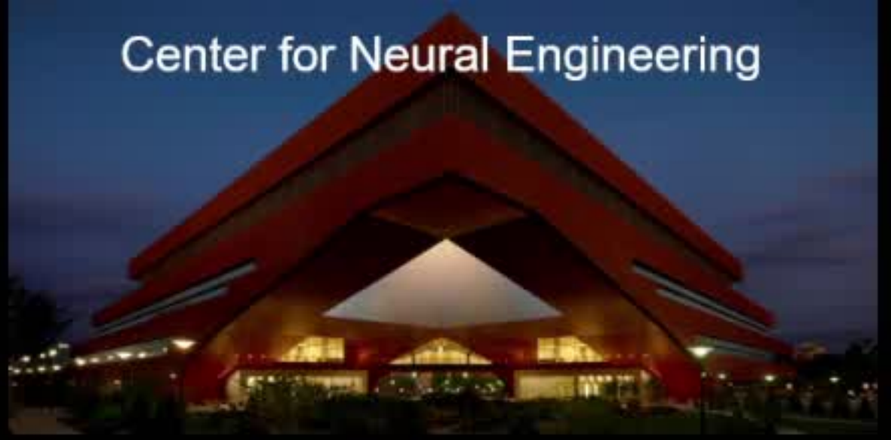


The Spatiotemporal Dynamics of African Infant Infections

Steven J. Schiff

Center for Neural Engineering
Center for Infectious Disease Dynamics
Departments of Neurosurgery,
Engineering Science and Mechanics,
and Physics
Penn State University

NIH Director's Pioneer Award (OD, NICHD, Fogarty, NINDS)
NIH Director's Transformative Award (OD, NIAID)
NIH NICHD/Fogarty (Phase III RCT #NCT01936272)
NIH NICHD/Fogarty, NIH NINDS HCRN, Netherlands NWO

The CURE Children's Hospital of Uganda has Treated > 10,000 cases of Hydrocephalus since 2001

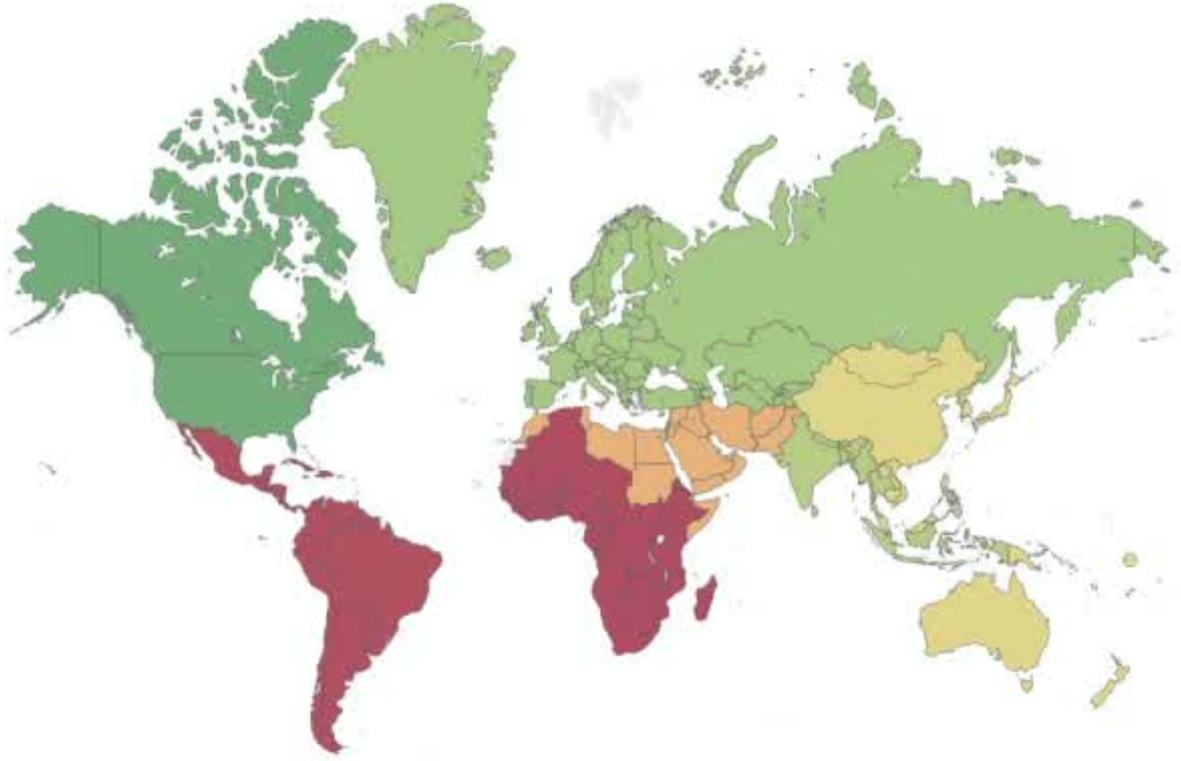
I missed 1 SIAM DS meeting since 1993

Because I visited …

The CURE Children's Hospital of Uganda has Treated > 10,000 cases of Hydrocephalus since 2001

Global Hydrocephalus

400,000 New Pediatric Cases Per Year



WHO Region	Crude Births, Annual (no.)	New Cases of PIH, Annual (no.)	Total Estimated New Cases of HC, Annual (no.)
AFR	36,376,124	108,440	180,733
AMR-US/Can	4,408,520	—	5,647
AMR-L	10,948,403	15,972	53,241
EMR	17,394,811	11,493	38,309
EUR	11,447,692	—	15,968
SEAR	37,525,360	16,073	53,578
WPR	24,320,979	10,874	36,247
Worldwide	142,421,888.51	162,852	383,724

96% in Developing World

Dewan et al, J Neurosurg Peds 2018

Optimizing Hydrocephalus Treatment

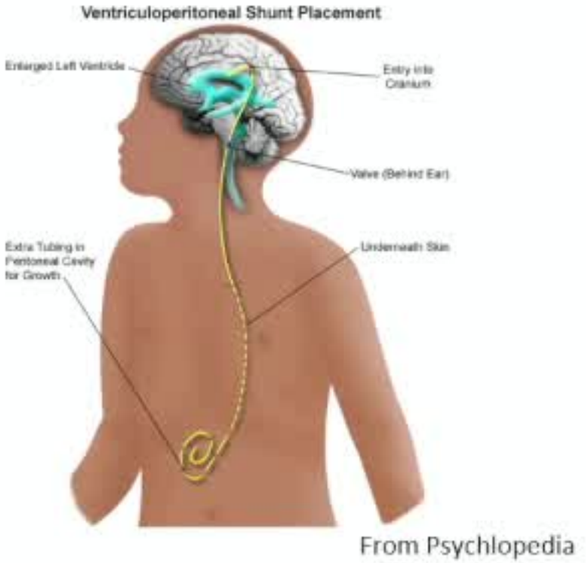
NICHD Randomized Clinical Trial in Africa

- 100 Infants: 51 Scope, 49 Shunt
- Primary Outcome: Bailey Scale Infant Development **Cognitive** Score

Scope

vs

Shunt

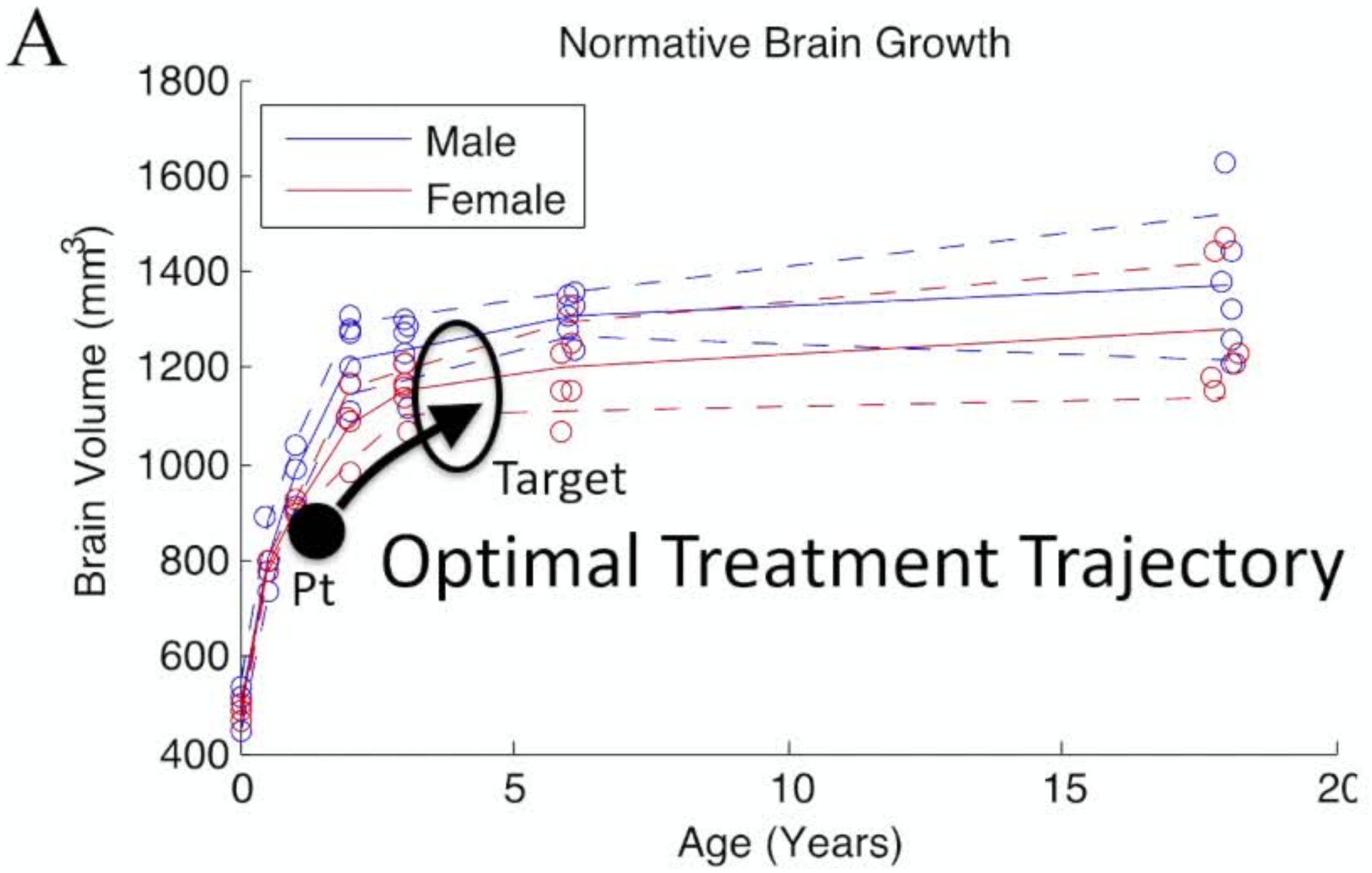


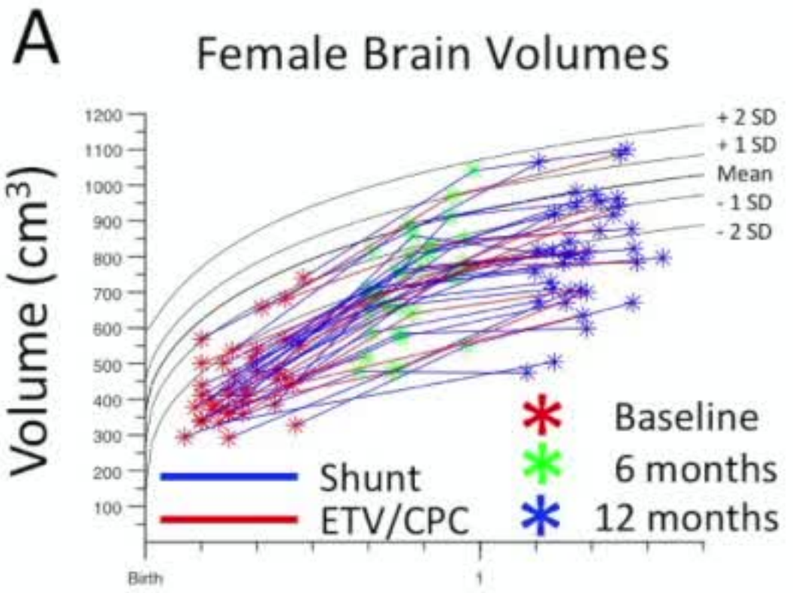
From Psychlopedia

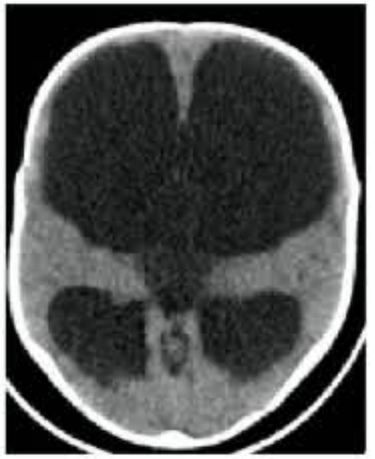
Kulkarni et al, New England Journal of Medicine 2017

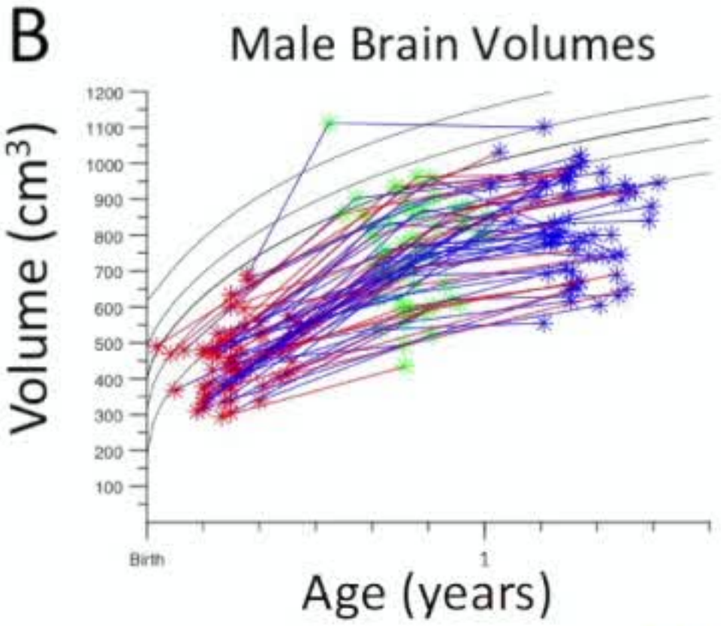
ClinicalTrials.gov number, NCT01936272

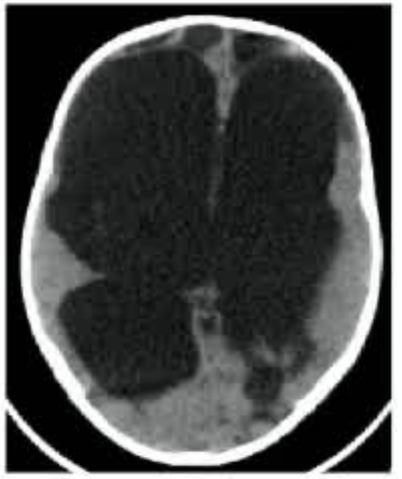
Towards Predictive Hydrocephalus Treatment









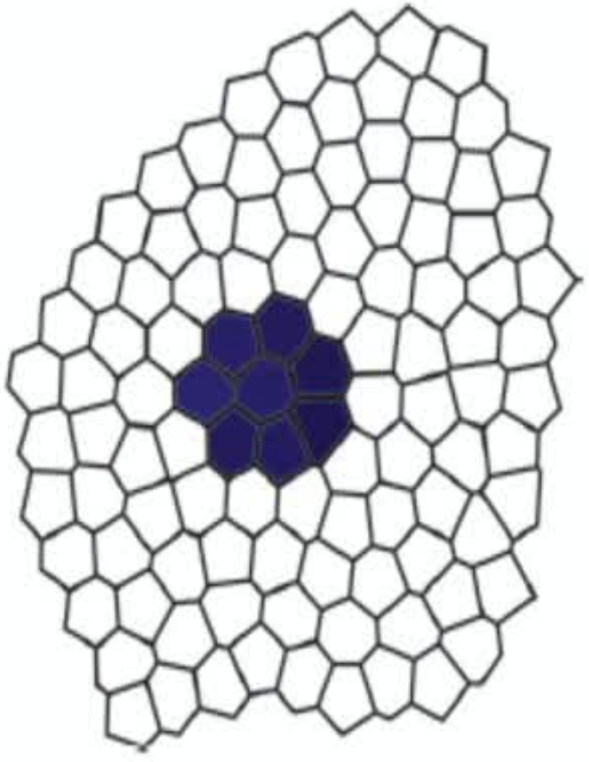


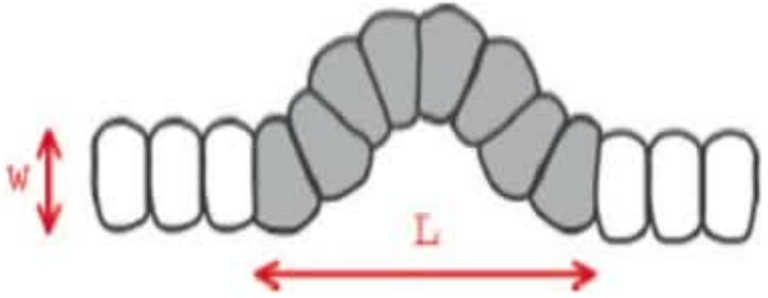
Kulkarni et al, NEJM 2017

Mechanical feedback as a possible regulator of tissue growth

Boris I. Shraiman†

PNAS 2005





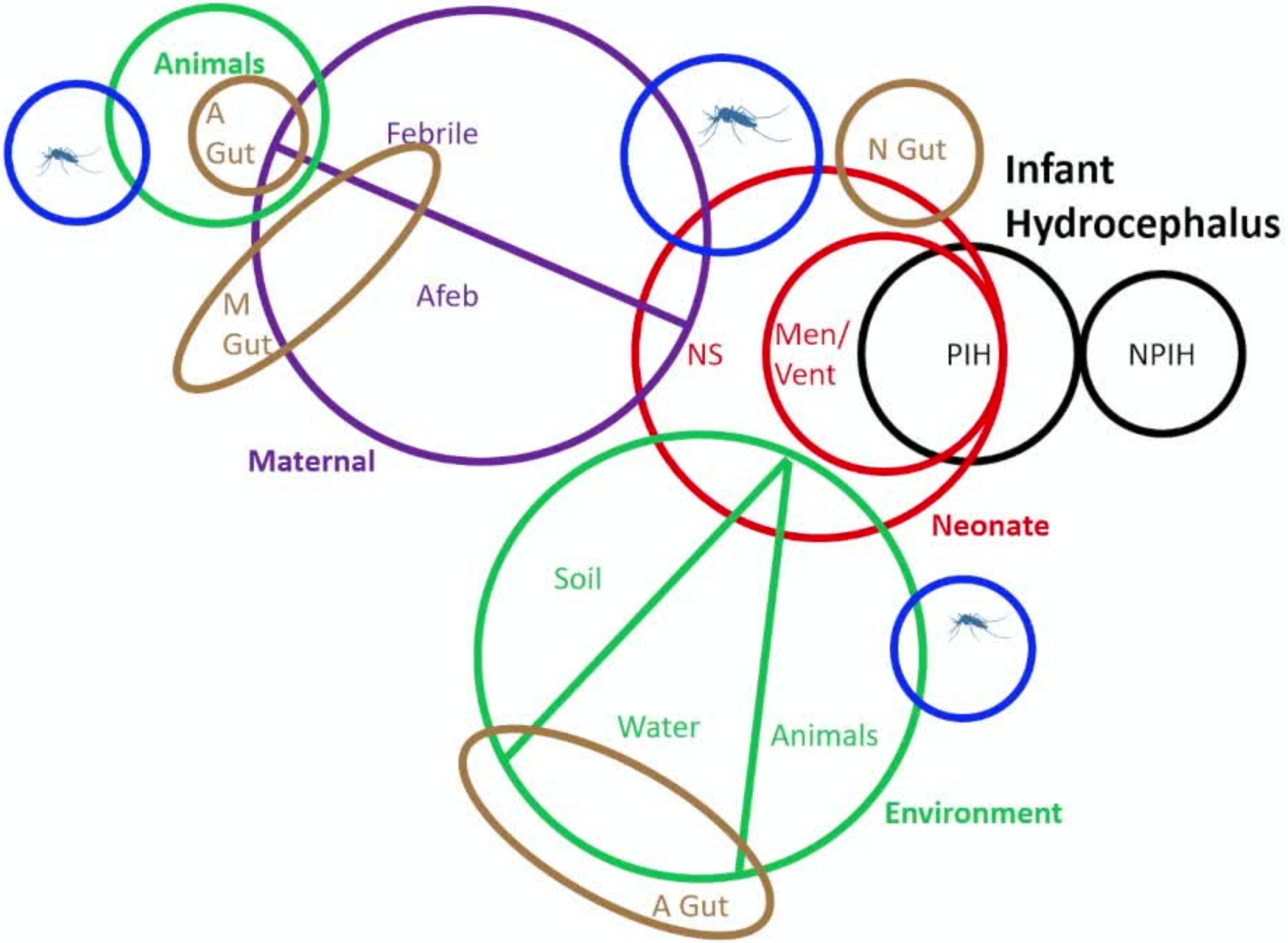
Postinfectious
Hydrocephalus

Postinfectious Hydrocephalus

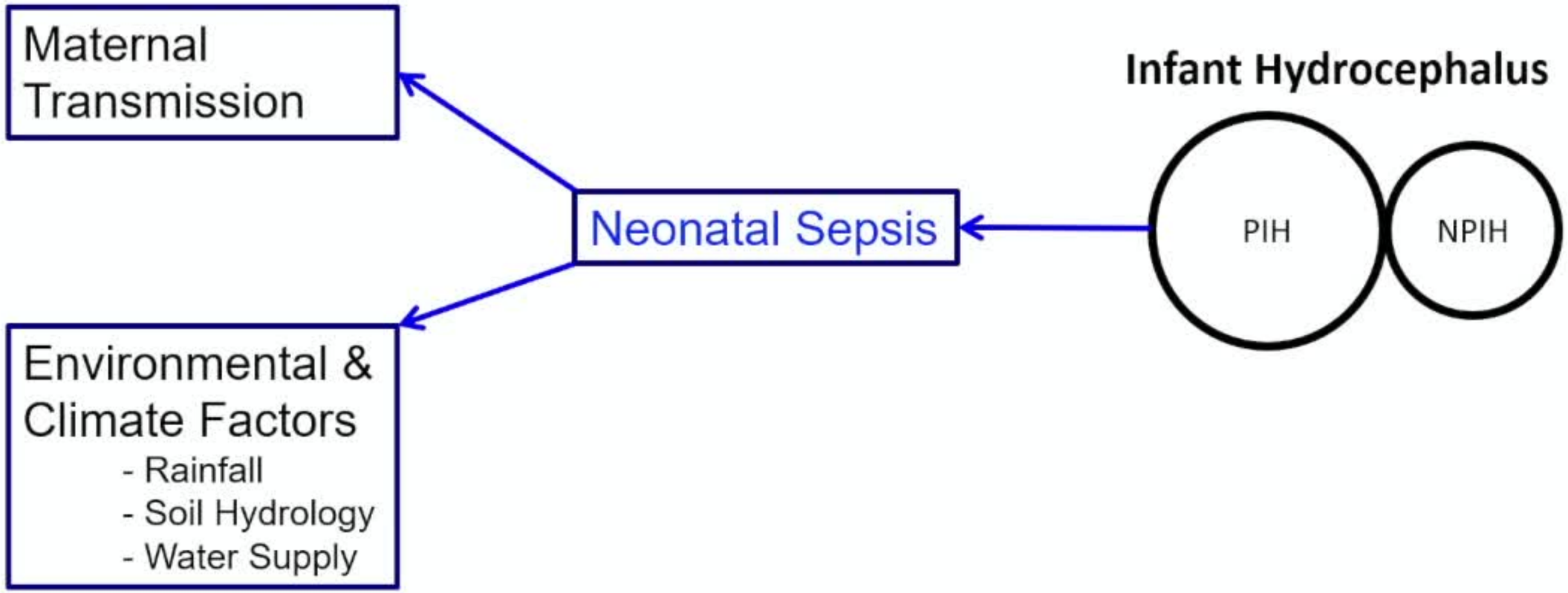
Neonatal Sepsis

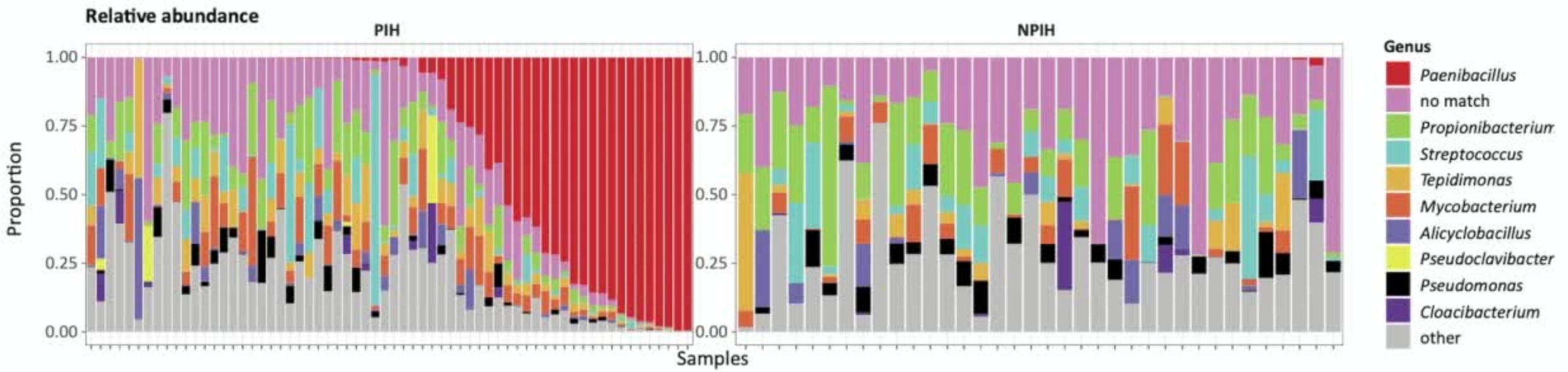
Neonatal Sepsis

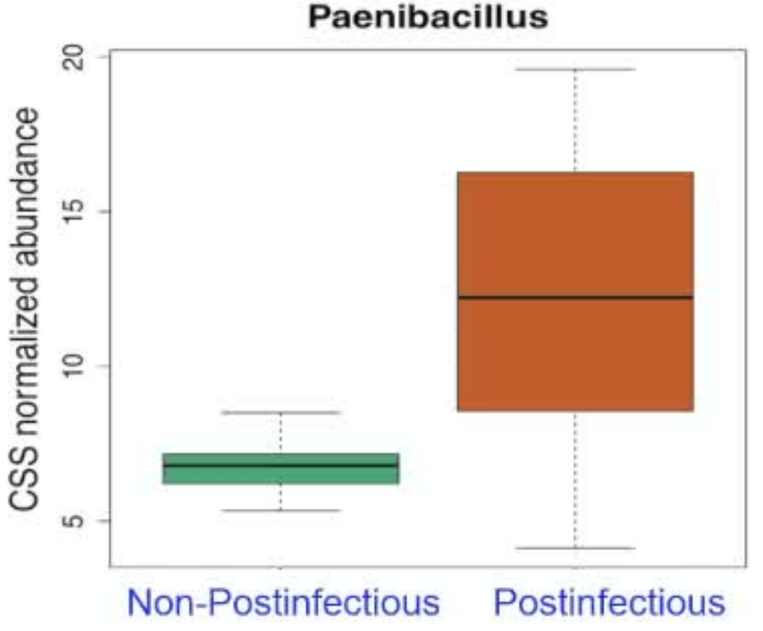
134 Million yearly births
>1 Million die of Sepsis
(> Malaria, > TB)


Animals
A
Gut
Febrile
N Gut
Infant
Hydrocephalus
M
Gut
Afeb
NS
Men/
Vent
PIH
NPIH
Maternal
Neonate
Soil
Water
Animals
Environment
A Gut

Let's Work Backwards …





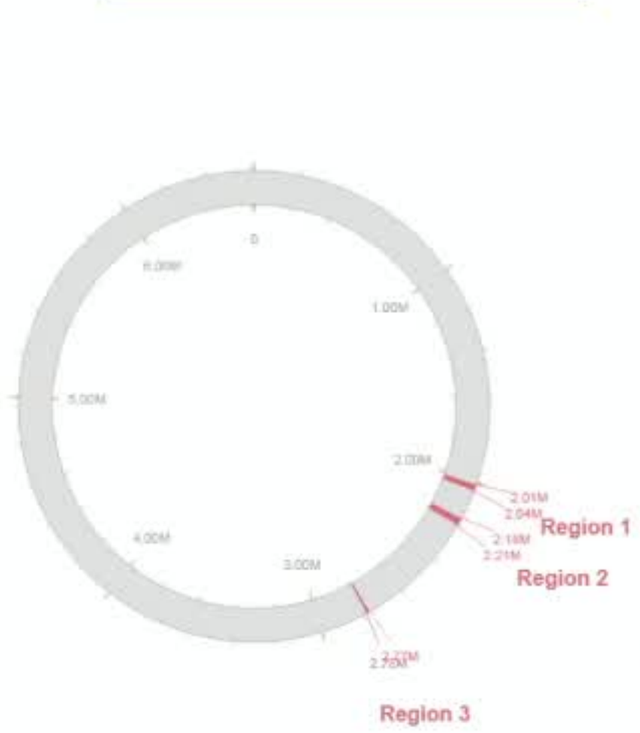


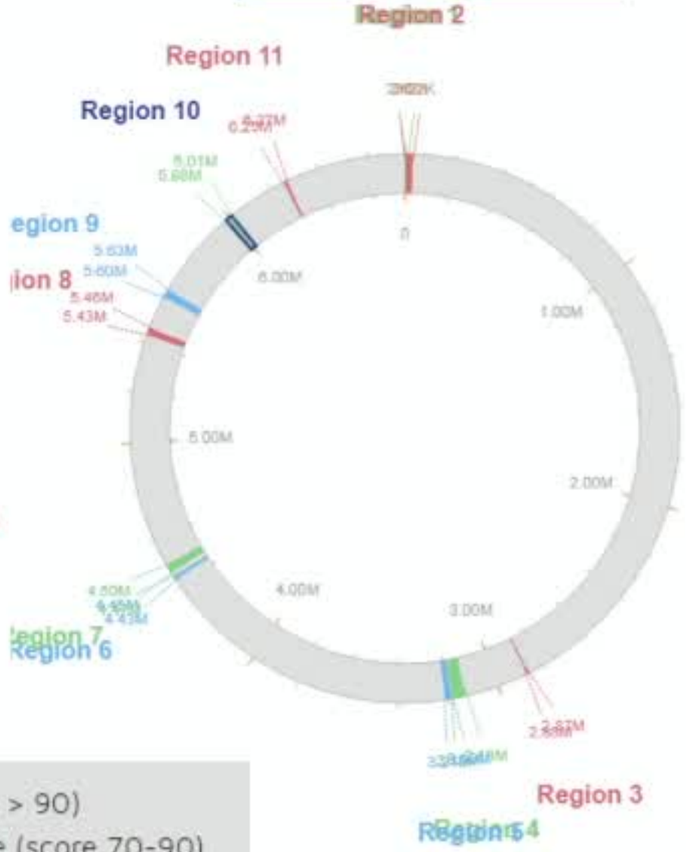
Paulson, Williams, Hehnly, Sinnar, Zhang, Ssentongo, Mbabazi,
Wijetunge, von Bredow, Mulondo, Mishra, Kiwanuka, et al, in preparation

Paenibacillus thiaminolyticus Mbale

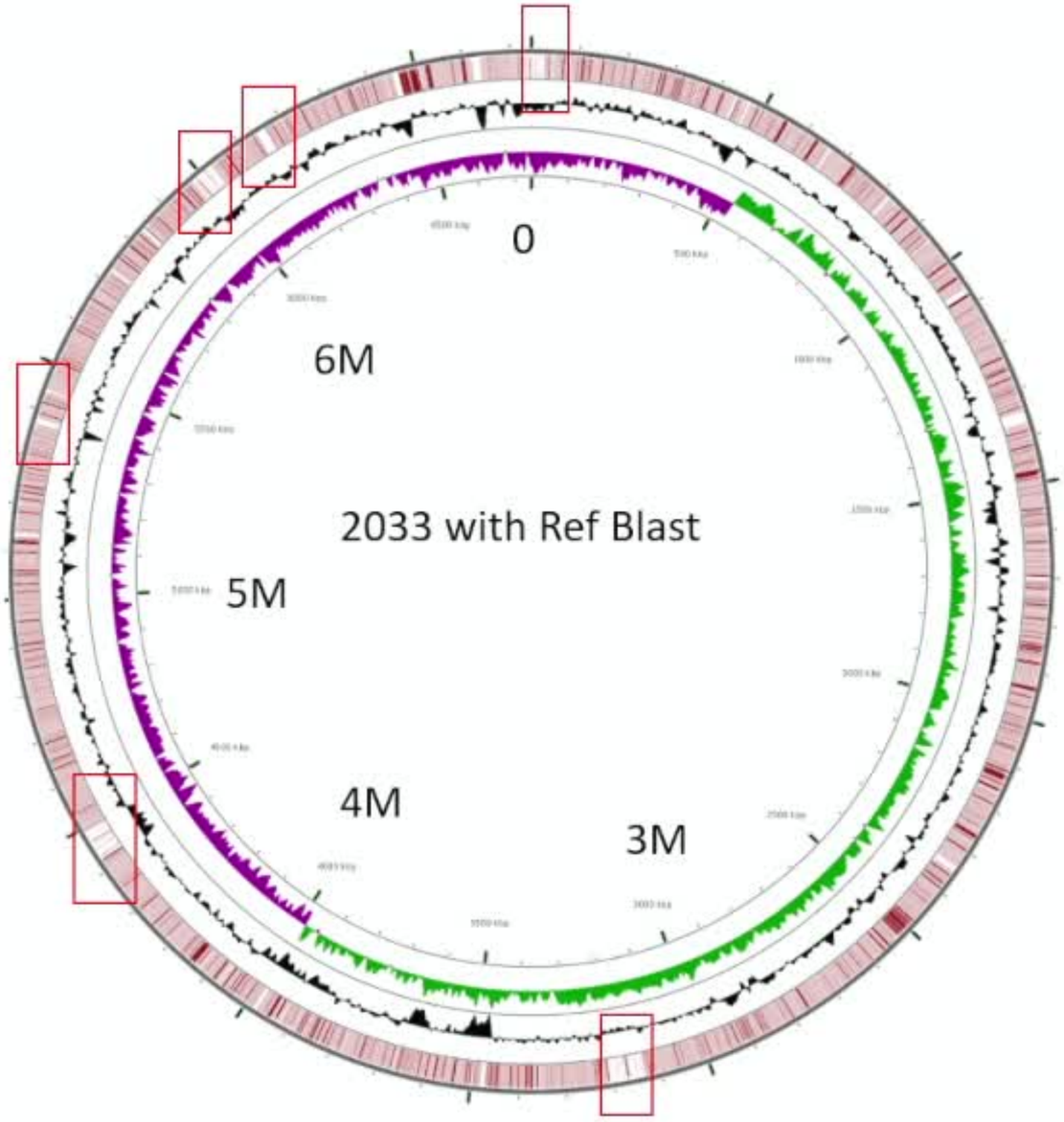
Reference: 6.6Mbp
6kb phage

2033: 6.9Mbp
280kb phage





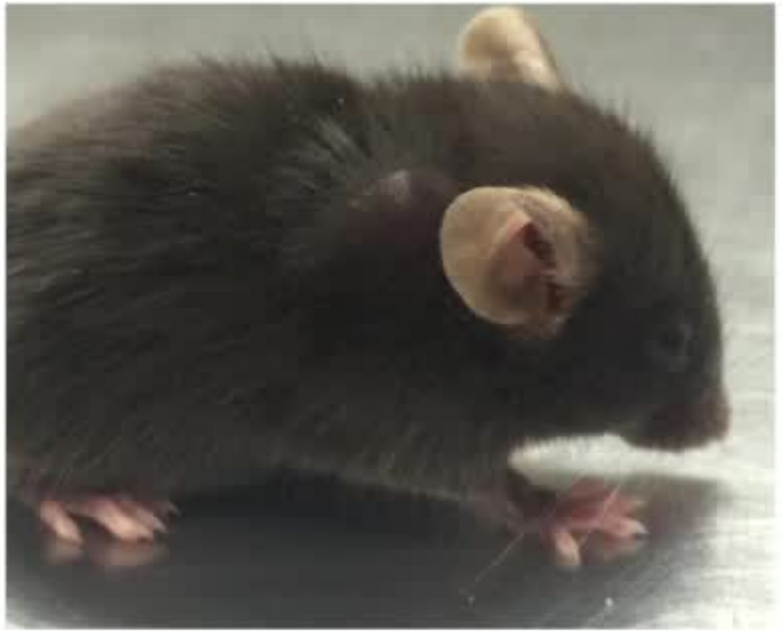
Intact (score > 90)
Questionable (score 70-90)
Incomplete (score < 70)



Paddy Ssentongo
Christine Hehnly

Reference Strain – 0% (0/10) lethal

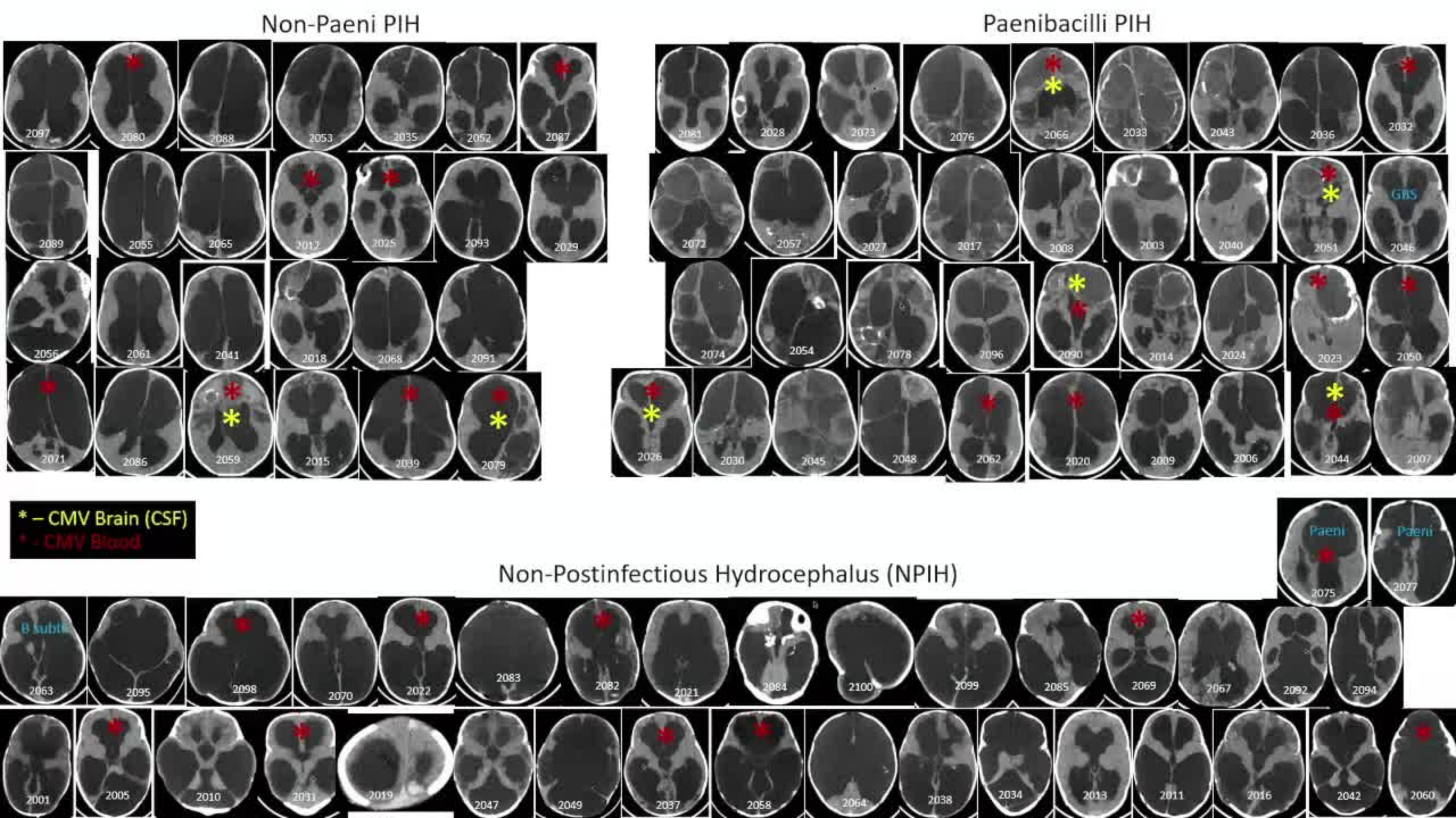
African Strain – 93% (15/16) lethal



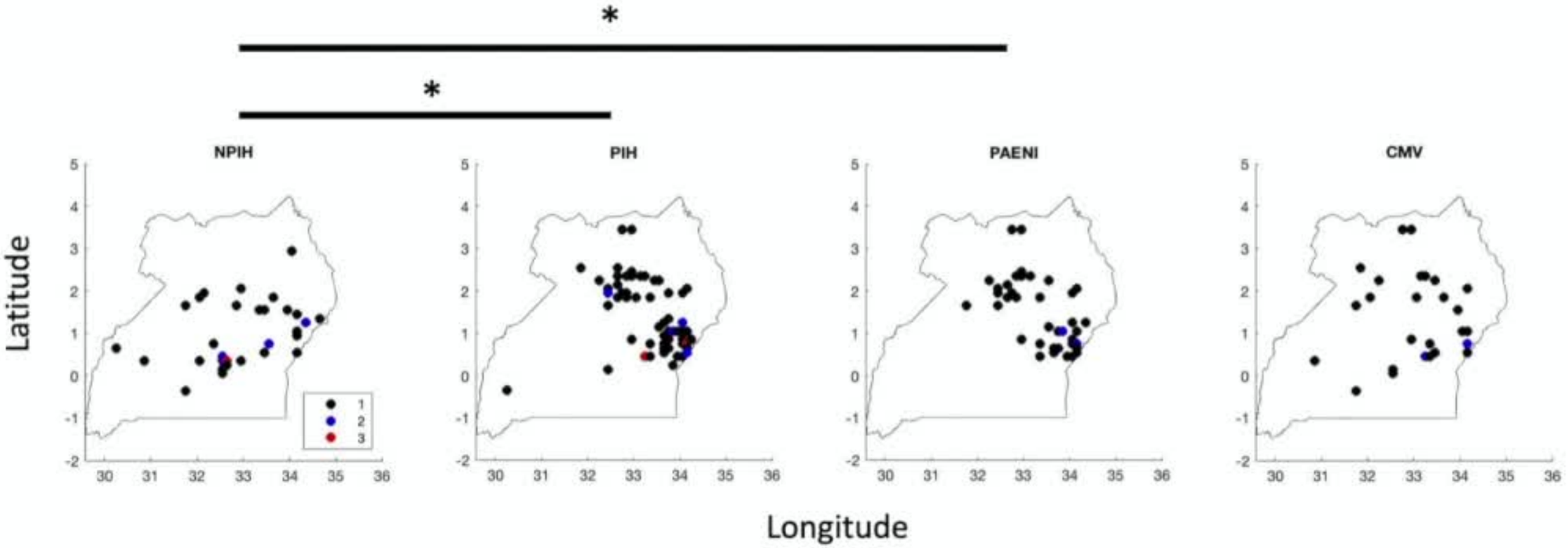
Is There a Viral Background?

Table 2: Viral Results

Viral Summary Results	VirCapSeq-VERT		PCR				RNA-Seq	
	PIH (64)	NPIH (36)	PIH (n)		NPIH (n)		PIH (64)	NPIH (36)
Viral reads	CSF		Blood	CSF	Blood	CSF	CSF	
Human Herpesvirus 5 (CMV)	8		18 (64)	8 (64)	9 (35)	0 (36)	4	0
Human Papillomavirus	8	8	0 (64)	0 (64)	0 (35)	0(36)		
Human Pegivirus / GBV-C	3	1						
Human Herpesvirus 6A	1							
Human Herpesvirus 6B	1	2						
Human Rotavirus	1	1						
Torque Teno Virus	2	1						
Human Parvovirus (B19/V9)	1			2 (64)		0 (36)		
Norovirus	1							
Merkel Cell Polyomavirus		1						
Circovirus		1						
No Viral Reads	43	21						


Non-Paeni PIH
Paenibacilli PIH
2097
2080
2088
2053
2035
2052
2087
2089
2055
2065
2012
2025
2093
2029
2056
2061
2041
2018
2068
2091
2071
2086
2059
2015
2039
2079
2081
2028
2073
2076
2066
2033
2043
2036
2032
2072
2057
2027
2017
2008
2003
2040
2051
GBS
2046
2074
2054
2078
2096
2090
2014
2024
2023
2050
2026
2030
2045
2048
2062
2020
2009
2006
2044
2007
* – CMV Brain (CSF)
* - CMV Blood
Non-Postinfectious Hydrocephalus (NPIH)
Paeni
Paeni
2075
2077
B subtil
2063
2095
2098
2070
2022
2083
2082
2021
2084
2100
2099
2085
2069
2067
2092
2094
2001
2005
2010
2031
2019
2047
2049
2037
2058
2064
2038
2034
2013
2011
2016
2042
2060

Classification based on Latitude and Longitude



Paulson, Williams, Hehnly, Sinnar, Zhang, Ssentongo, Mbabazi, Wijetunge, von Bredow, Mulondo, Mishra, Kiwanuka, et al, in preparation

So Now What?

- This testing is very expensive and slow
- None of this scales globally
- And at point of care need instant prediction
  - Organism Probabilities
  - Antibiotic Recommendations

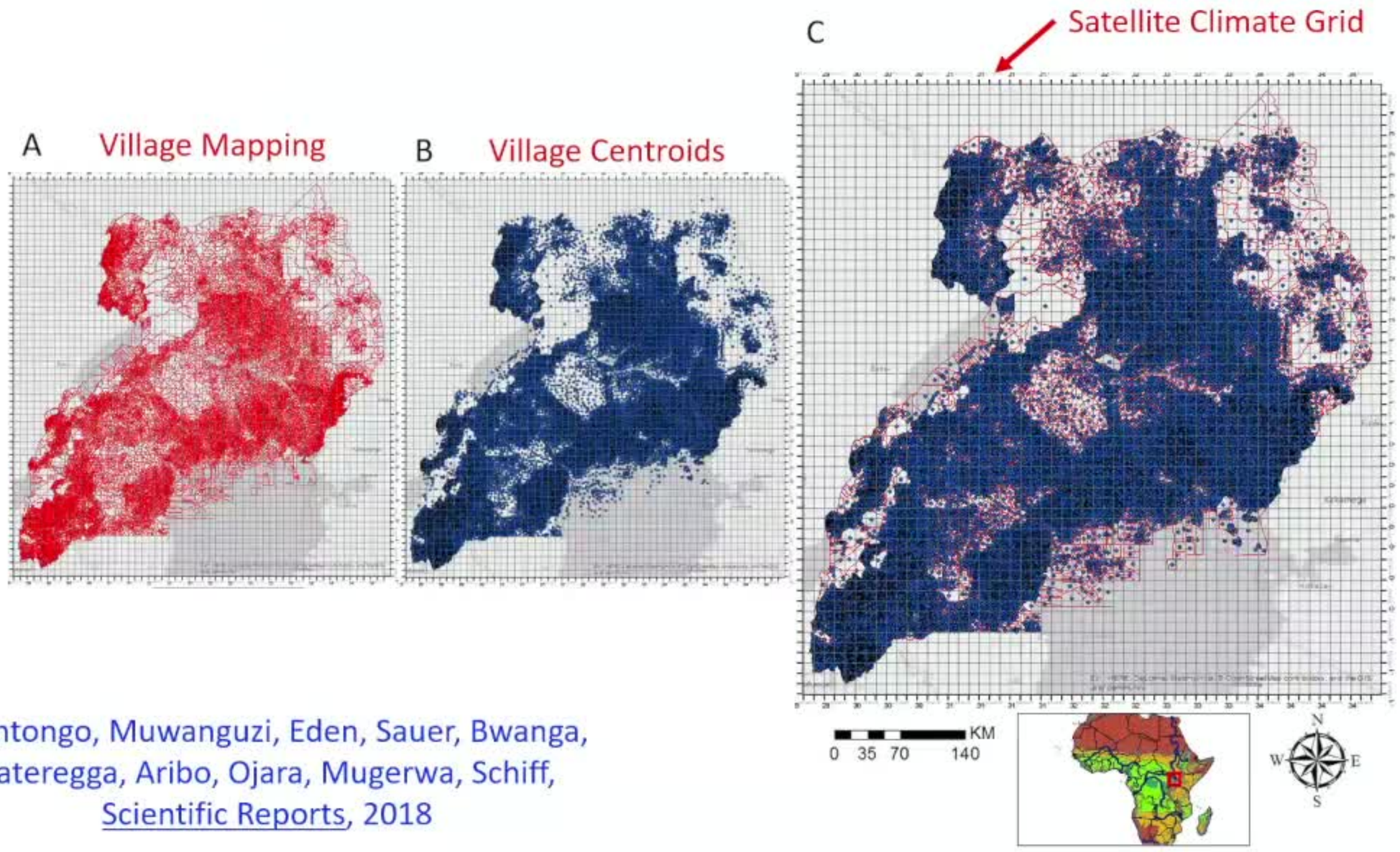
Let’s use the tools from SIAM DS …

P3H

Predictive Personalized Public Health: A Novel Paradigm to Treat Infectious Disease

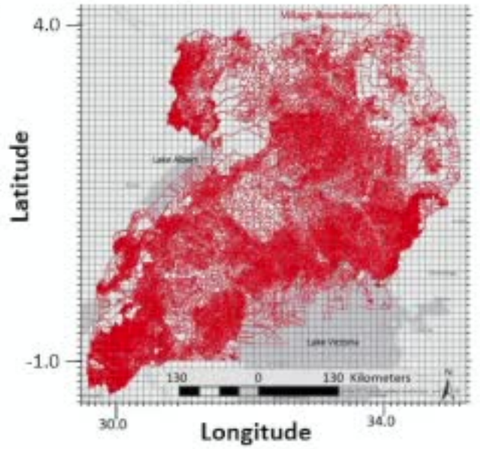
An Optimal Control Approach

Precision Fusing Village Location and Rainfall Data

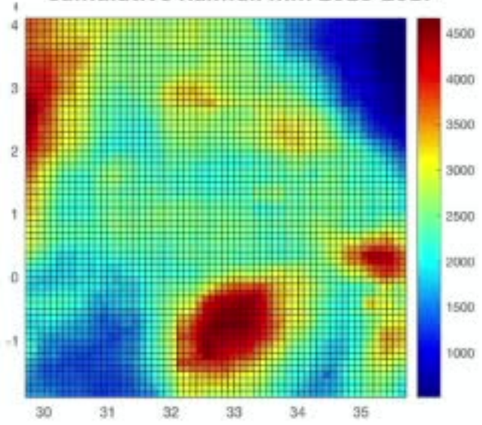


Ssentongo, Muwanguzi, Eden, Sauer, Bwanga, Kateregga, Aribo, Ojara, Mugerwa, Schiff, Scientific Reports, 2018

A

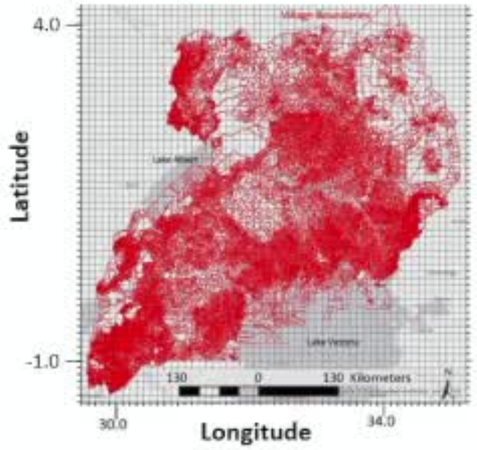


B

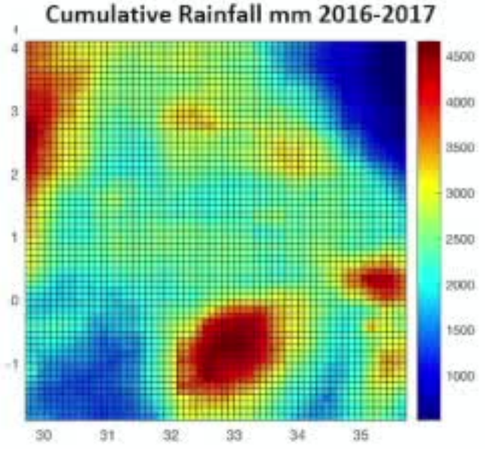


Sci Rep 2018

A

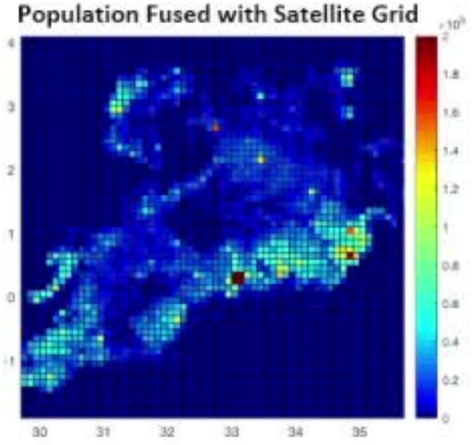


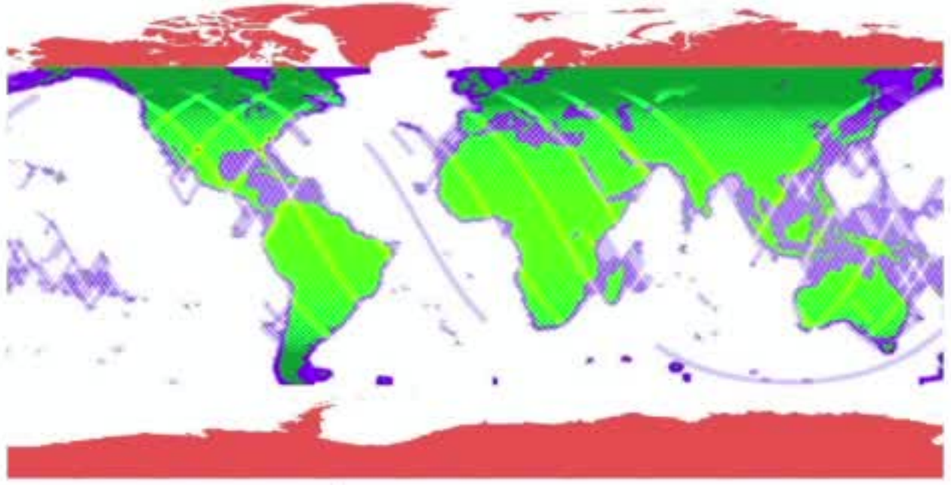
B

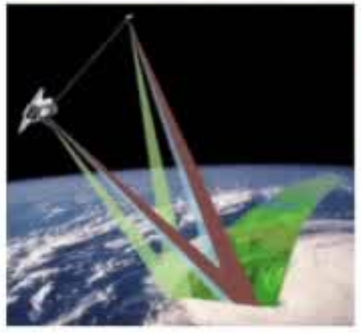


Sci Rep 2018

C

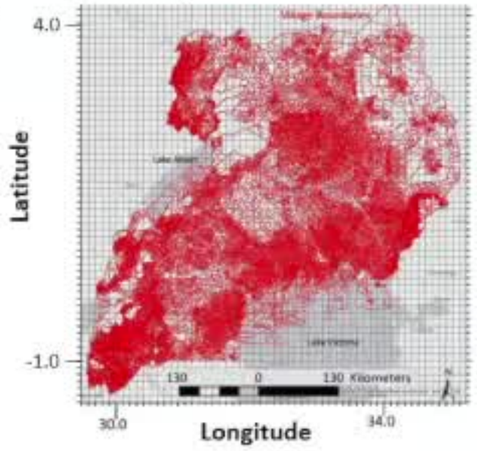






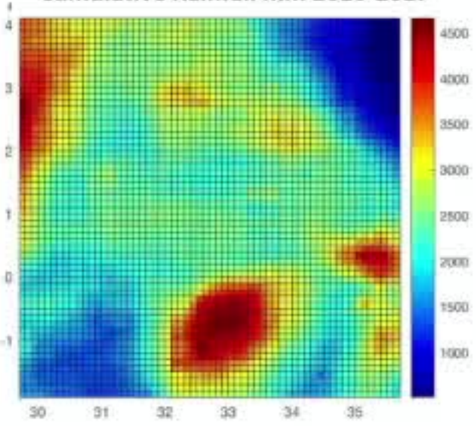
US Space Shuttle Radar Mapping

A



Sci Rep 2018

B



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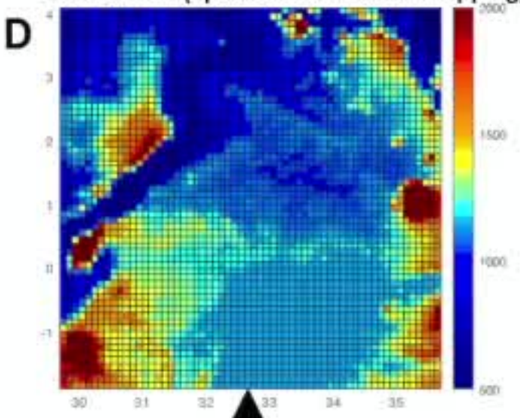
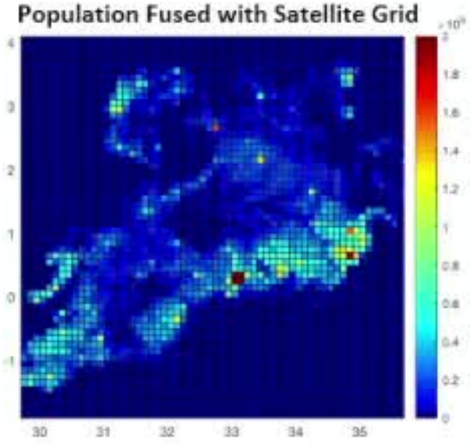
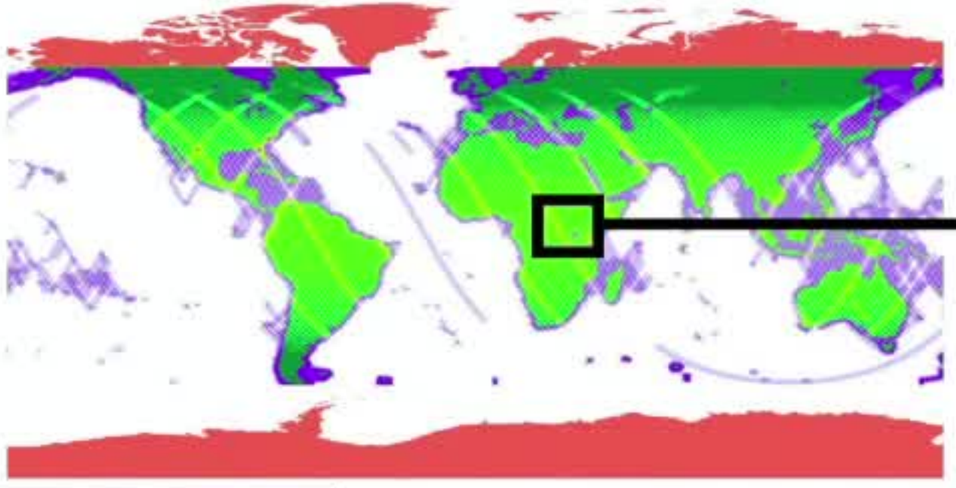
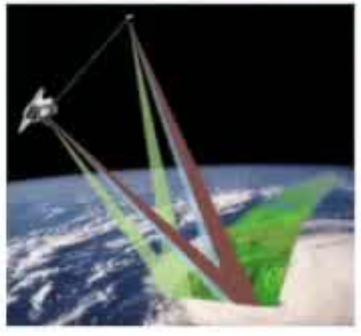


C

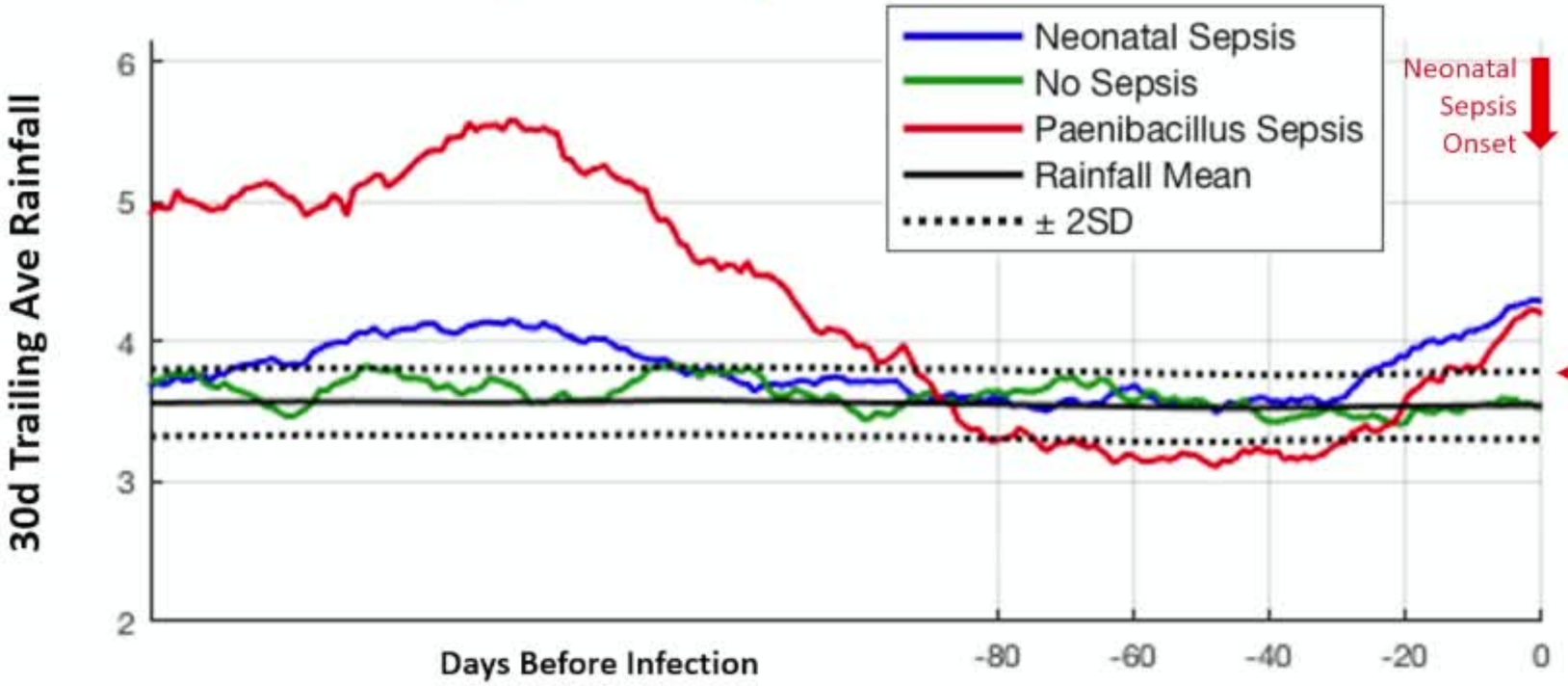






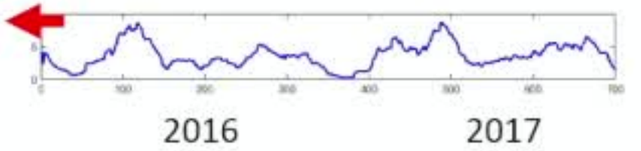
US Space Shuttle Radar Mapping

Neonatal Sepsis leading to PIH,

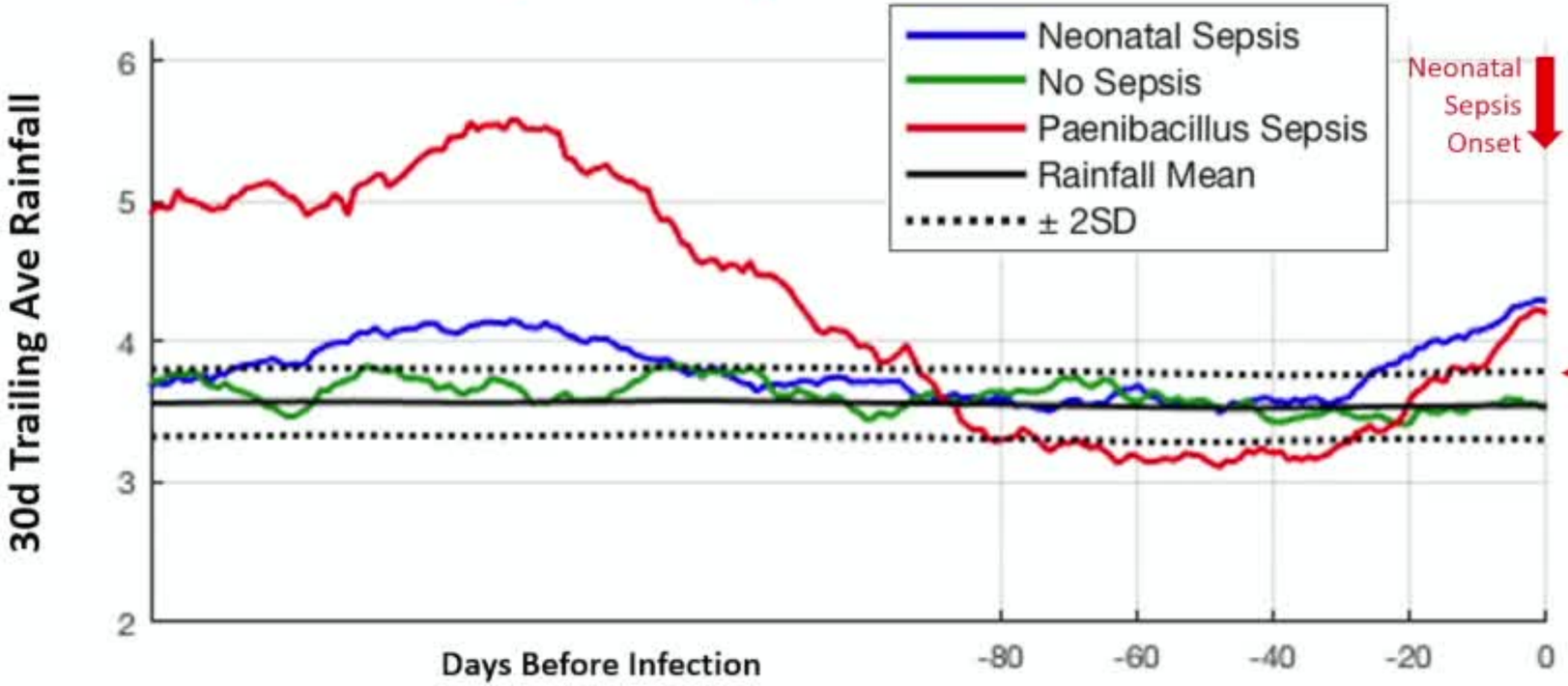


380 Cases

Controlled for Time ± 2SD

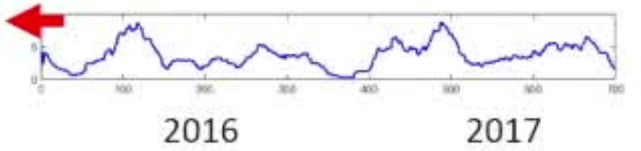


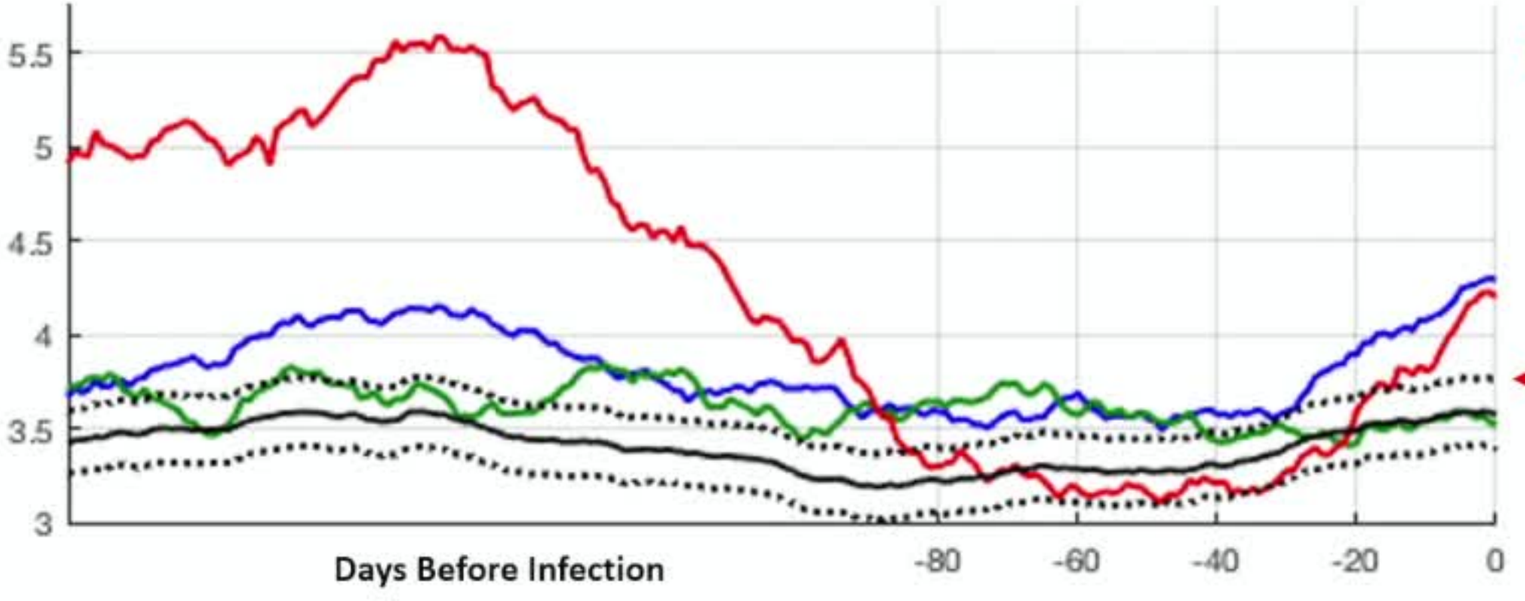
Neonatal Sepsis leading to PIH,



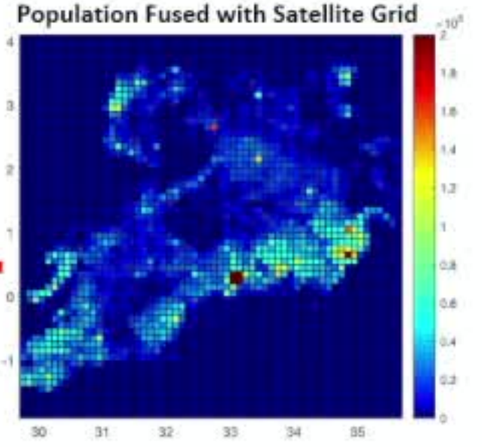
380 Cases

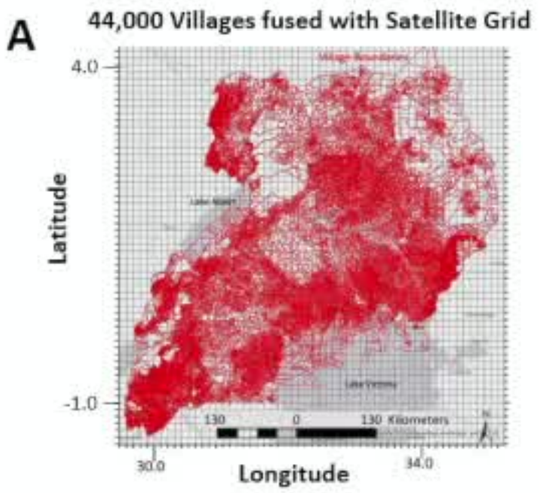
Controlled for Time ± 2SD

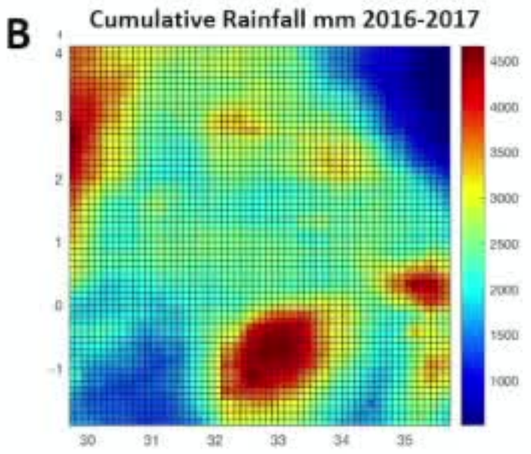


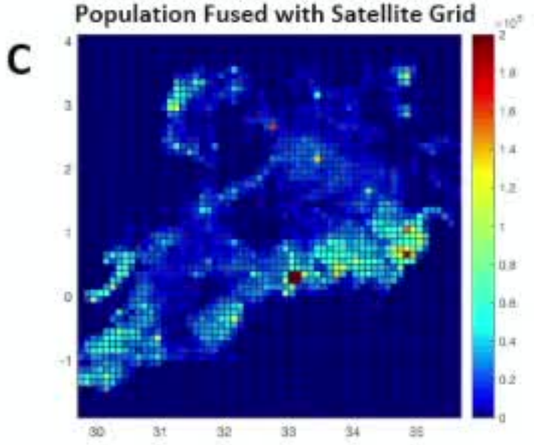


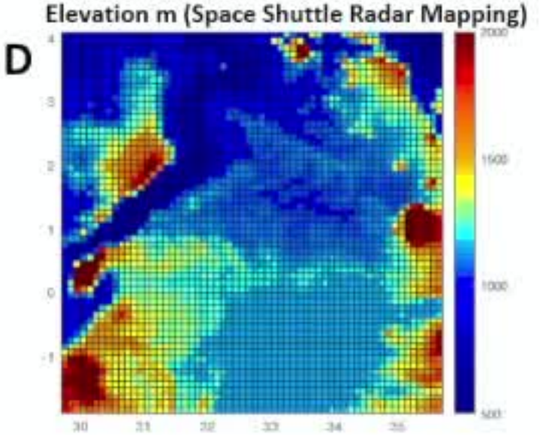
Controlled for Location ± 2SD



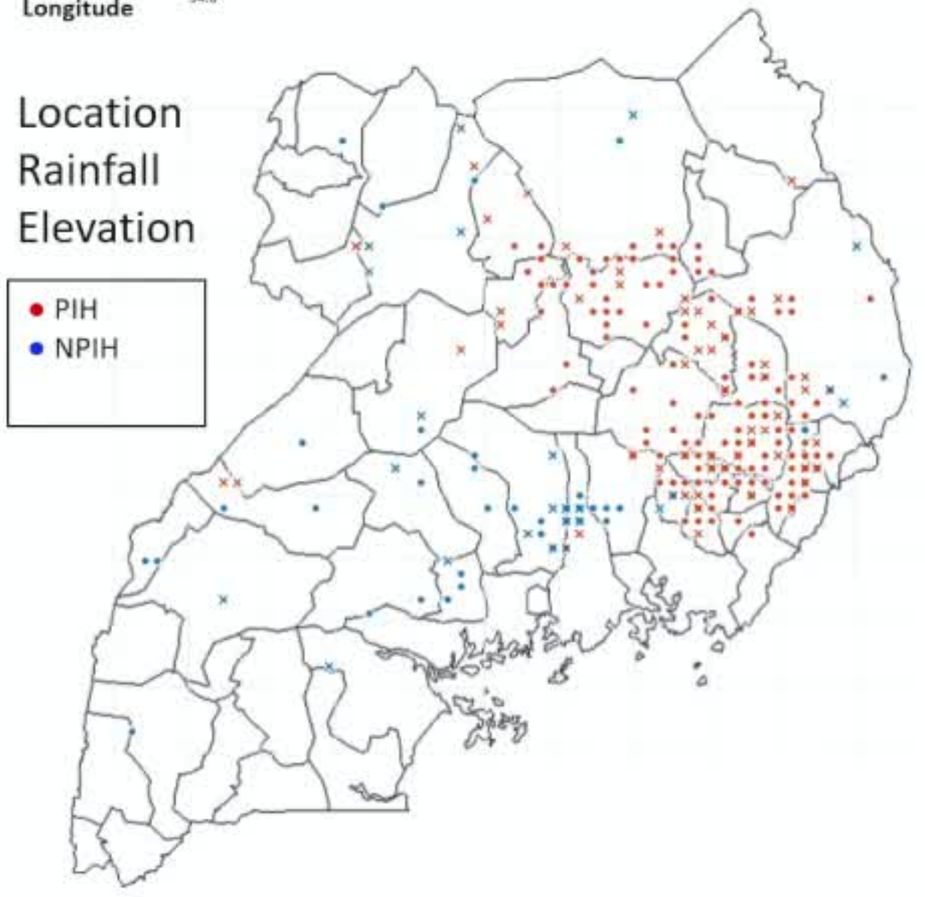


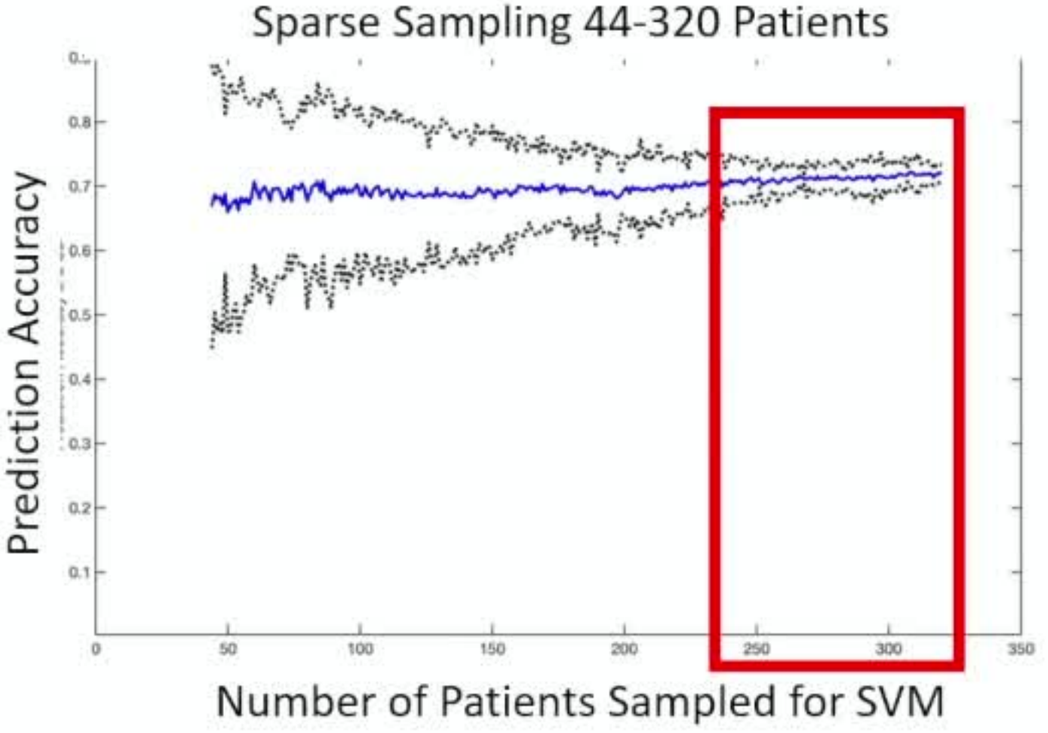






- Location
- Rainfall
- Elevation





P3H

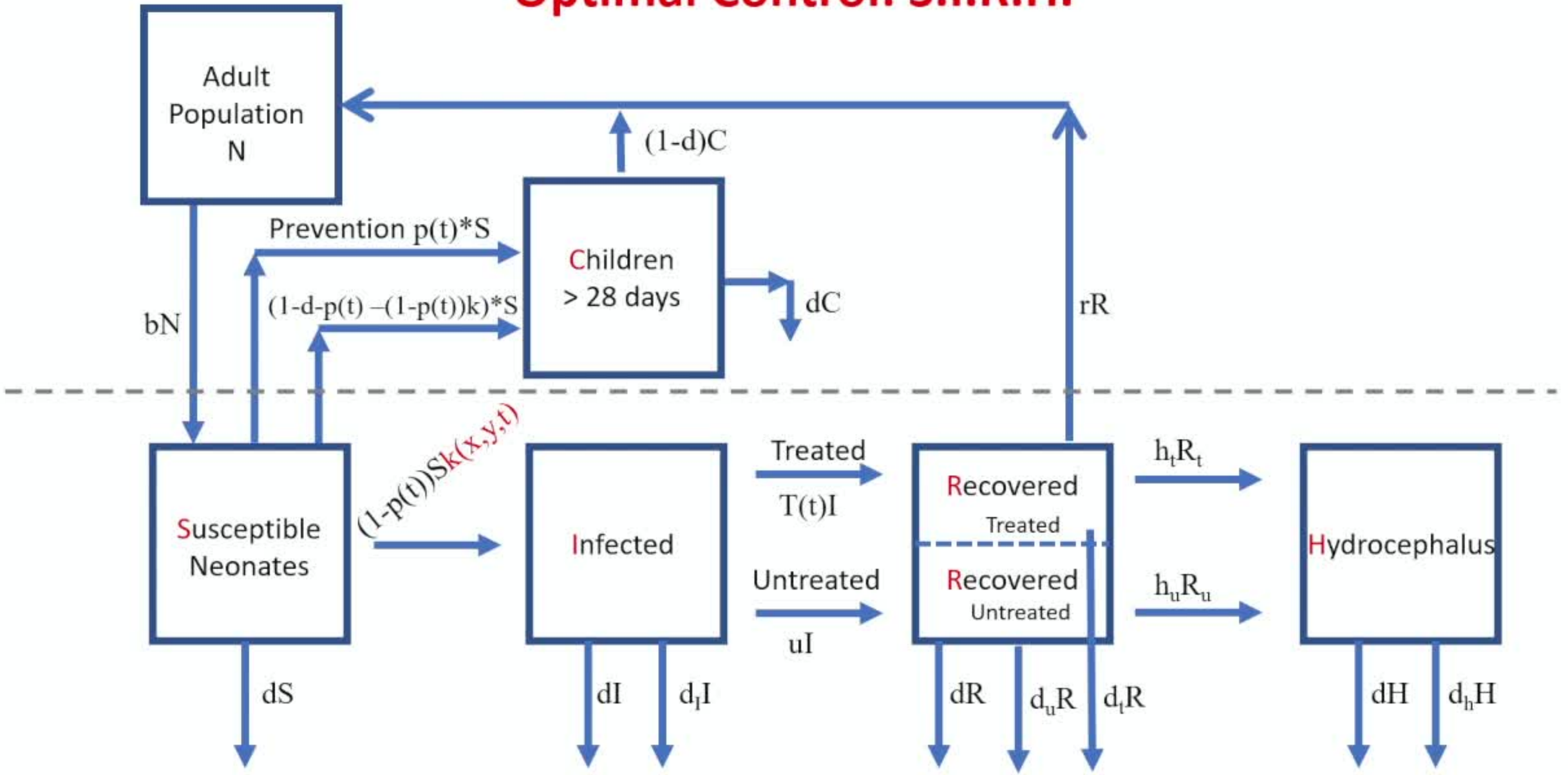
Two Questions at Point-of-Care:

1. When did the infant get sick?
2. What village are you from?

Use model to predict:

1. The most likely organisms
2. The best choices of available antimicrobials

Optimal Control: S.I.R.H.



Optimal Control: S.I.R.H.

With T. Berry and T. Sauer

$$S' = b - dS - (1 - p(t))Sk(x,y,t)$$

$$I' = (1 - p(t)Sk(x,y,t) - (d + d_I + u)I - T(t)I$$

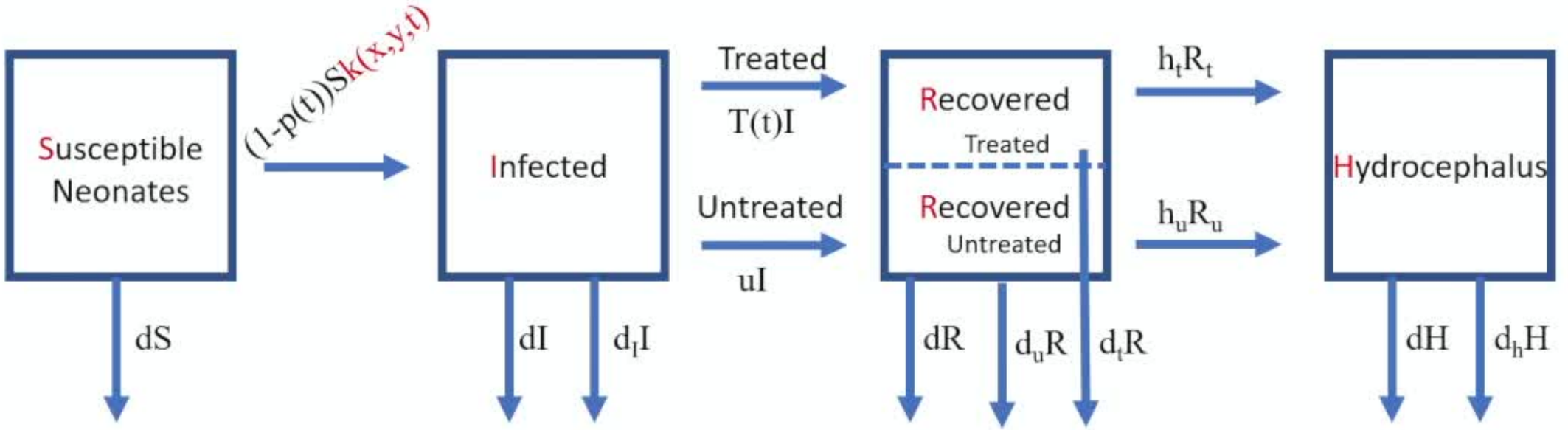
$$R_u' = uI - (d + d_u)R_u - h_u R_u$$

$$R_t' = T(t)I - (d + d_t)R_t - h_t R_t$$

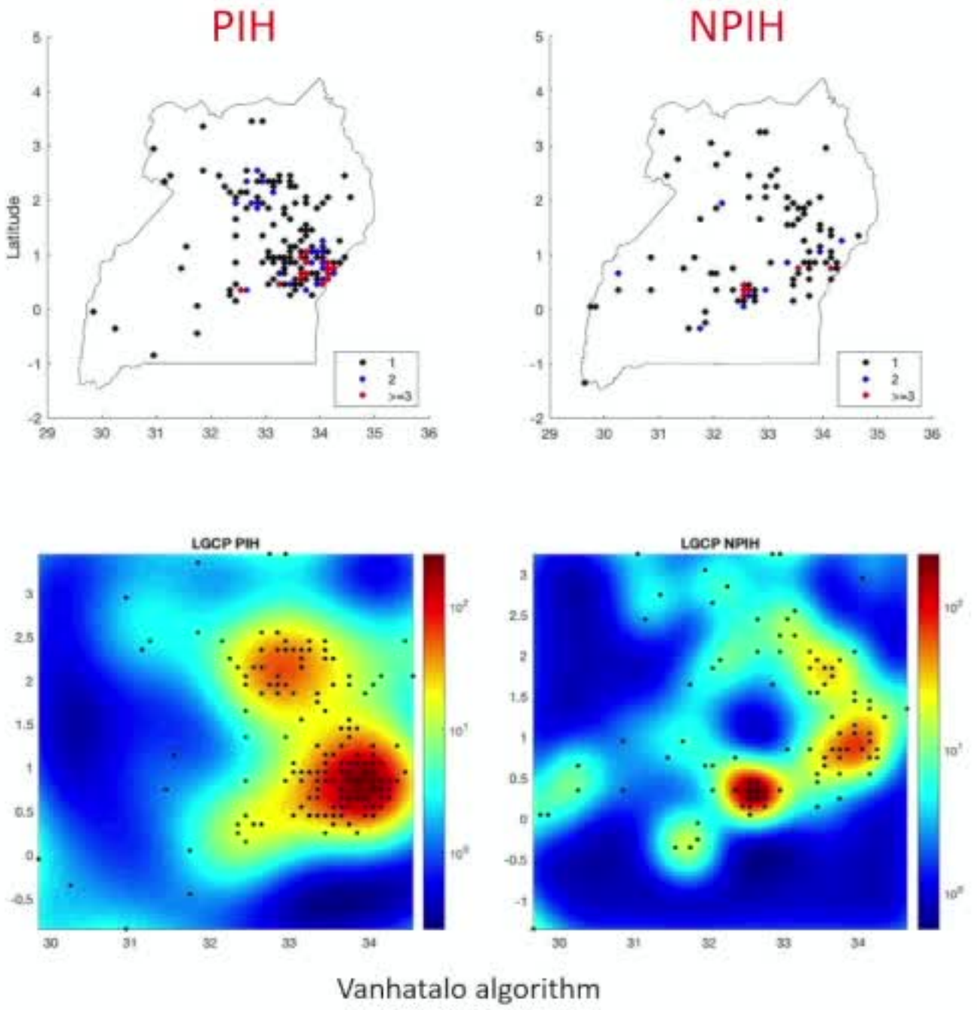
$$H' = h_t R_t + h_u R_u - (d + d_h)H$$

$$N' = S + I + R + H$$

$$R = R_u + R_g$$



Estimating and Predicting Risk: k(x,t)



Vanhatalo algorithm

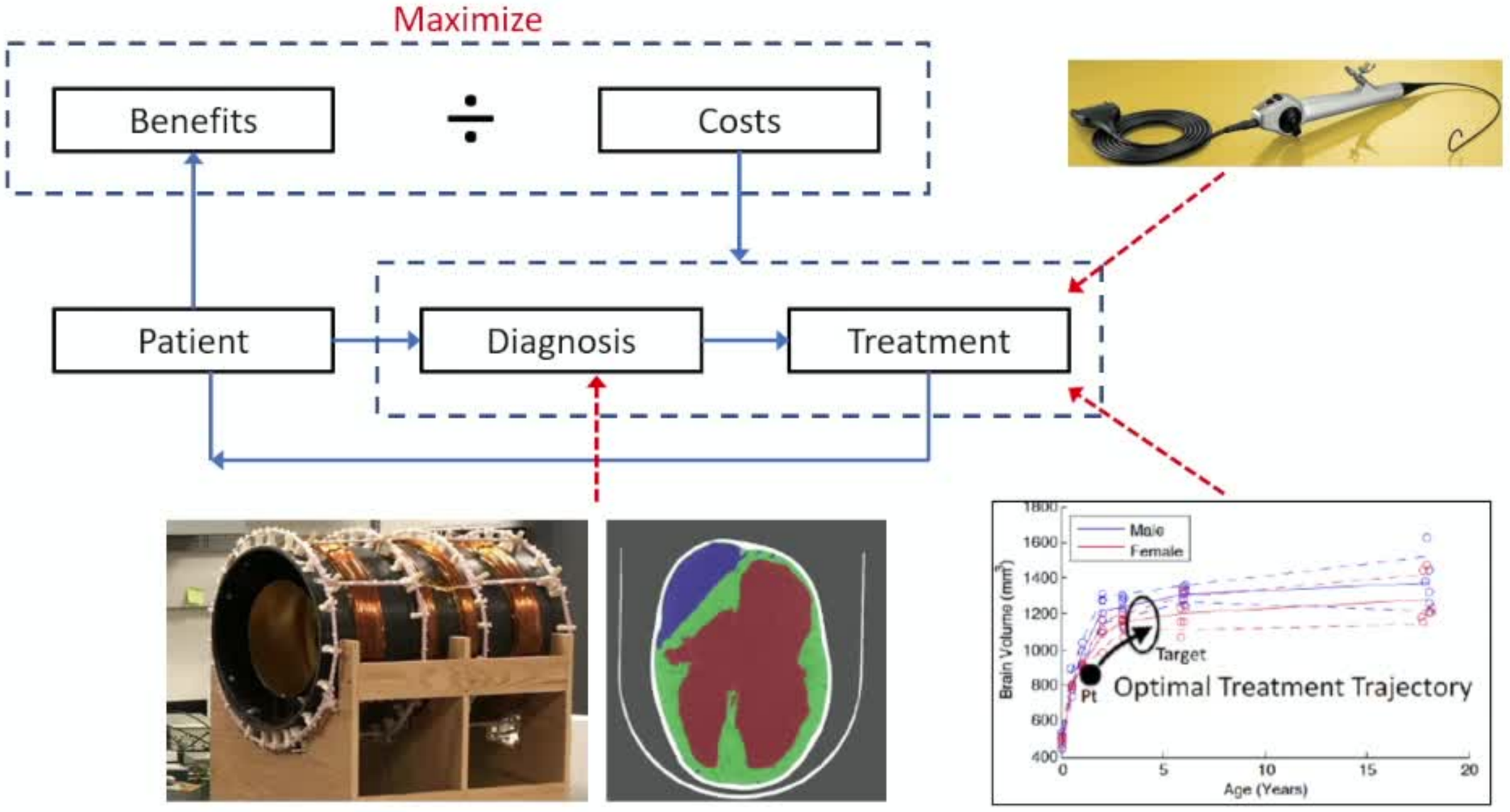
Log Gaussian Cox Process Estimation

$$\lambda(x) = \exp\left\{\alpha + \beta d(x) + S(x)\right\}$$

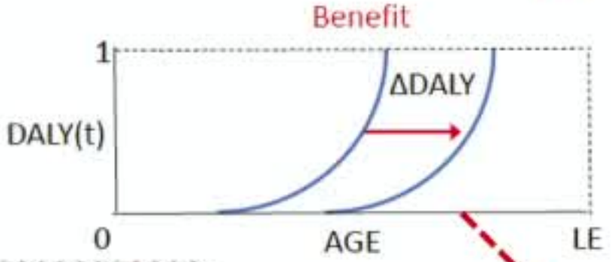
$$\mu_i = \int_{A_i} \lambda(x)\, dx$$

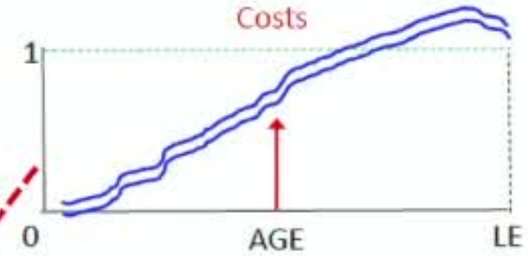
With X. Li, M. Haran, M. Ferrari

Sustainability is a Control Optimization Problem



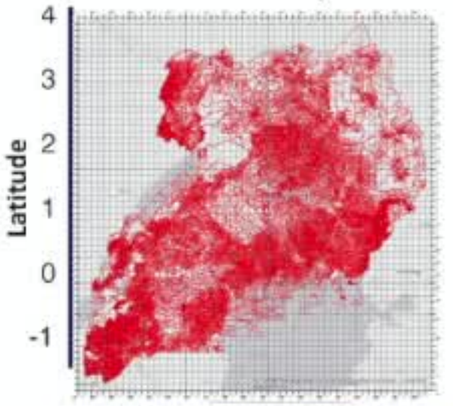
Sustainability is a Control Optimization Problem



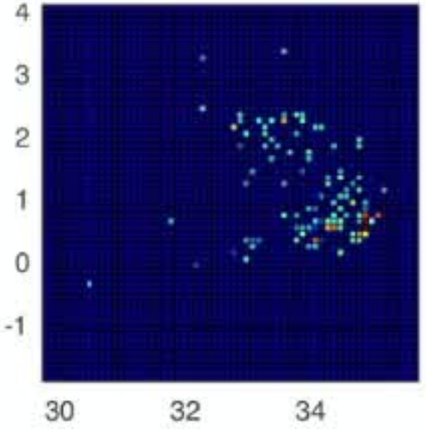


Maximize

Benefits ÷ Costs



X



Patient → Diagnosis → Treatment