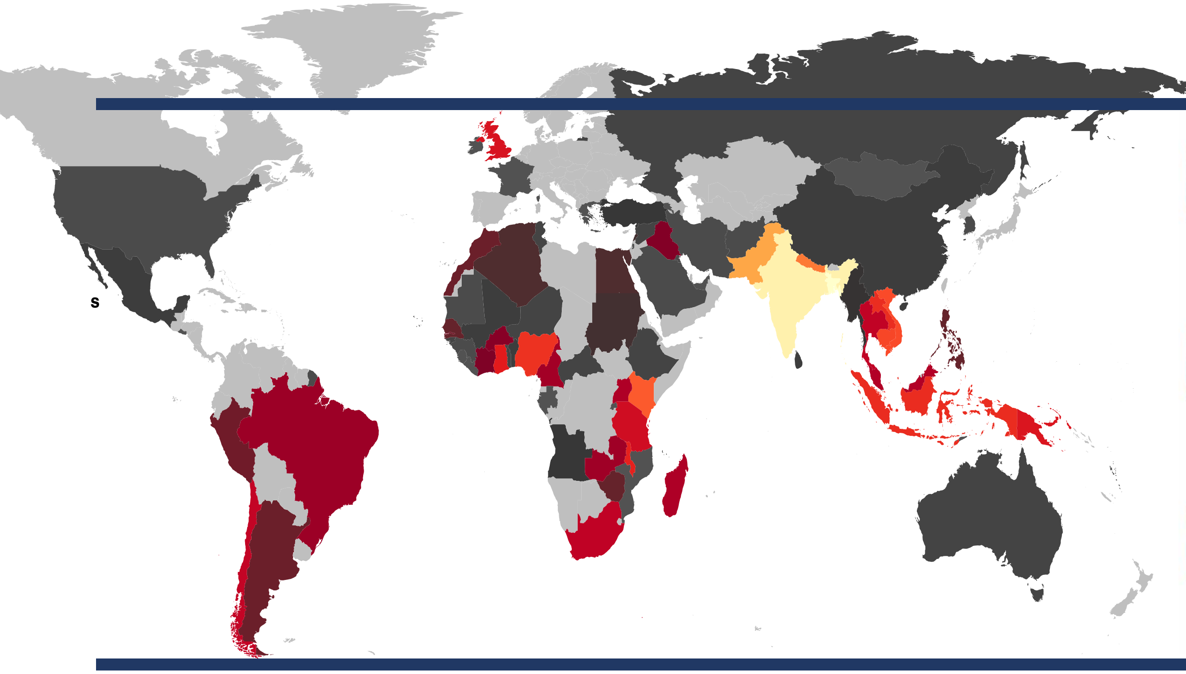
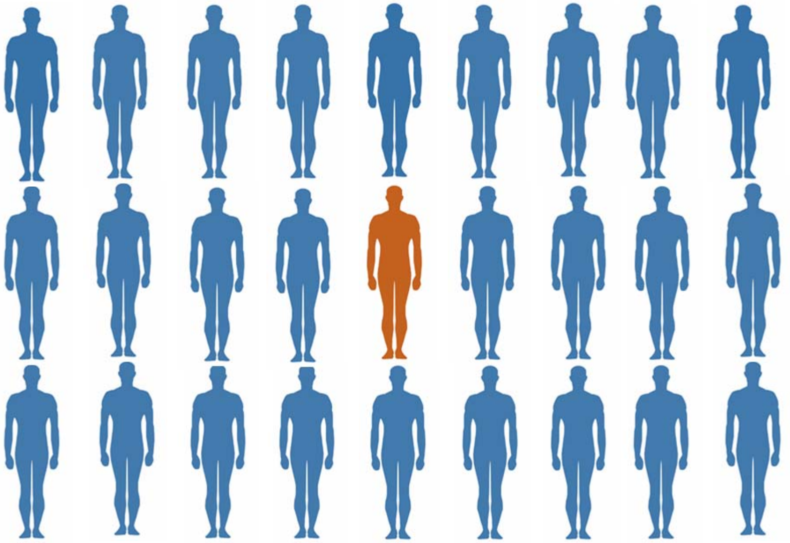
The role of genomics in typhoid control: sentinel traveler surveillance, in-host evolution, and transmission dynamics





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11th International Conference on Typhoid and Other Invasive Salmonelloses
Hanoi, Vietnam, March 2019

Acknowledgements

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Public Health England, UK

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Marie Chattaway

Satheesh Nair

Philip Ashton

Hassan Hartman

Joanne Freedman

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Christian Medical College, India

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St. Johns Medical College Hospital & St. Johns Research Institute, India

Savitha Nagaraj

STRATAA
STRATEGIC TYPHOID ALLIANCE
ACROSS AFRICA & ASIA

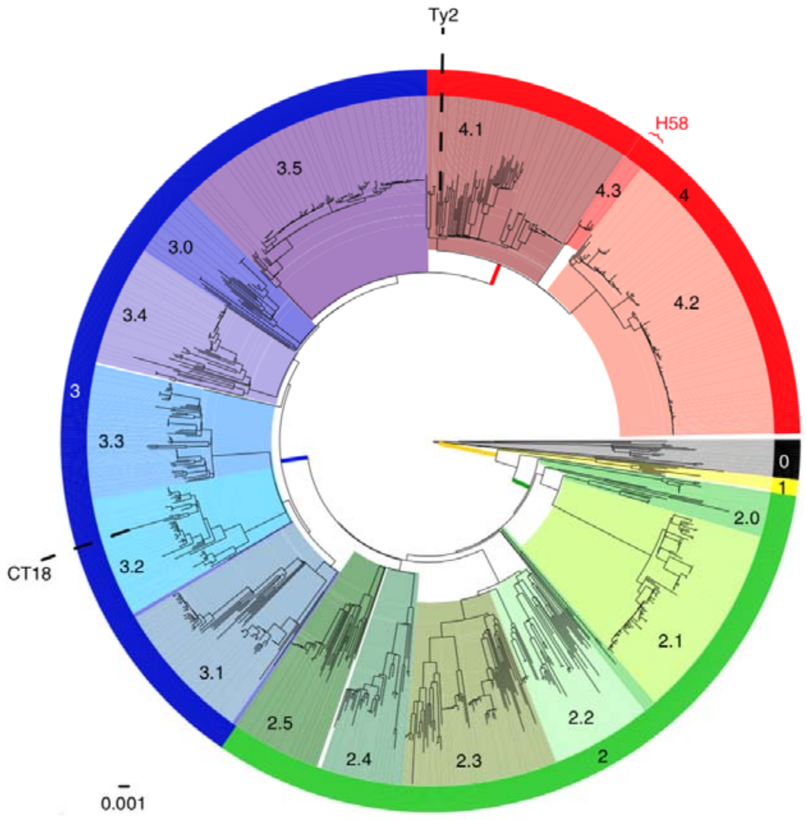
oxford vaccine group

wellcome trust
sanger
institute

wellcome trust

Global genomic framework of *S.* Typhi

- **Global framework of ~2000 *S.* Typhi**
  - Highly structured population
  - Strong geographical clustering
  - GenoTyphi tool: calls genotypes from genomes



Global population structure of *Salmonella* Typhi (49 subclades)

Source: Wong *et al.* 2016, Nat. Commun.

https://github.com/katholt/genotyphi

Global genomic framework of *S.* Typhi

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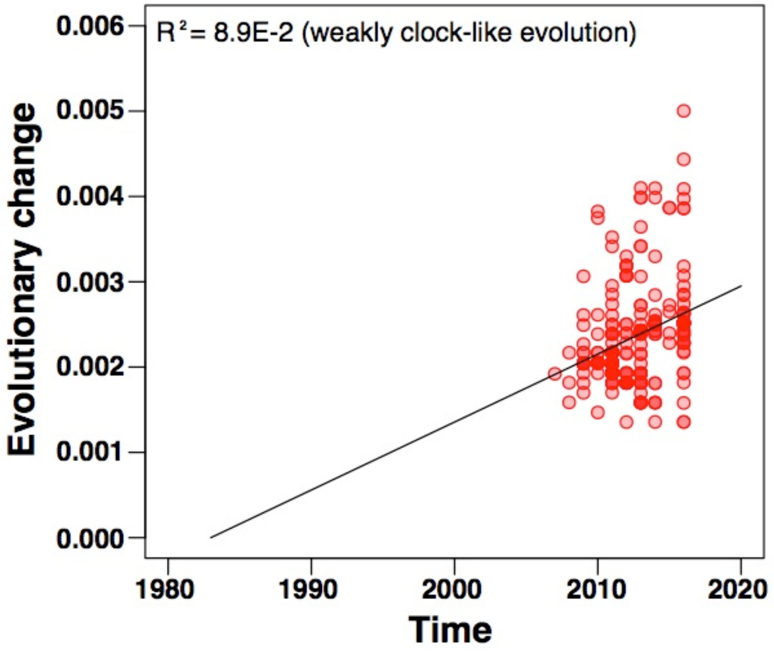

Weak temporal signal in Nepal H58 (4.3.1) Typhi

Source: Britto *et al.* 2018, PLoS NTDs
Wong *et al.* 2015, Nat. Genet.

Global genomic framework of *S.* Typhi

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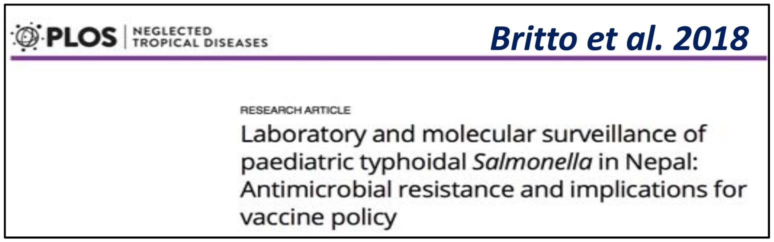
- **Global genomic framework provides context for local epidemiological studies**
  - AMR, circulating genotypes, transmission dynamics

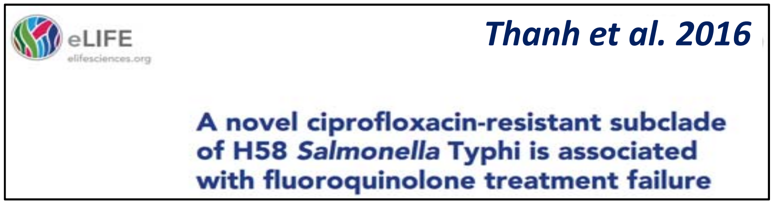


PLOS | NEGLECTED TROPICAL DISEASES

Britto et al. 2018

RESEARCH ARTICLE

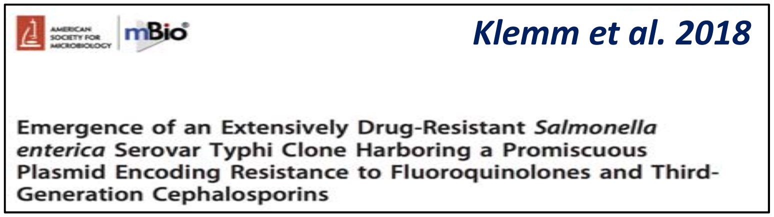
Laboratory and molecular surveillance of paediatric typhoidal *Salmonella* in Nepal: Antimicrobial resistance and implications for vaccine policy



eLIFE
elifesciences.org

Thanh et al. 2016

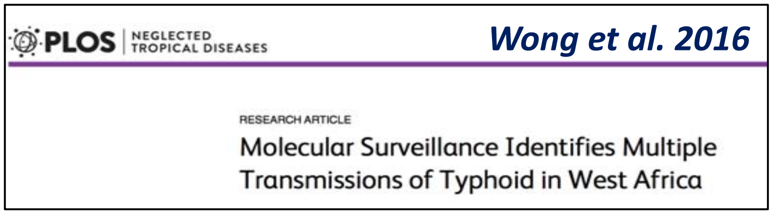
A novel ciprofloxacin-resistant subclade of H58 *Salmonella* Typhi is associated with fluoroquinolone treatment failure



AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

Klemm et al. 2018

Emergence of an Extensively Drug-Resistant *Salmonella enterica* Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins



PLOS | NEGLECTED TROPICAL DISEASES

Wong et al. 2016

RESEARCH ARTICLE

Molecular Surveillance Identifies Multiple Transmissions of Typhoid in West Africa

nature COMMUNICATIONS

Park et al. 2018

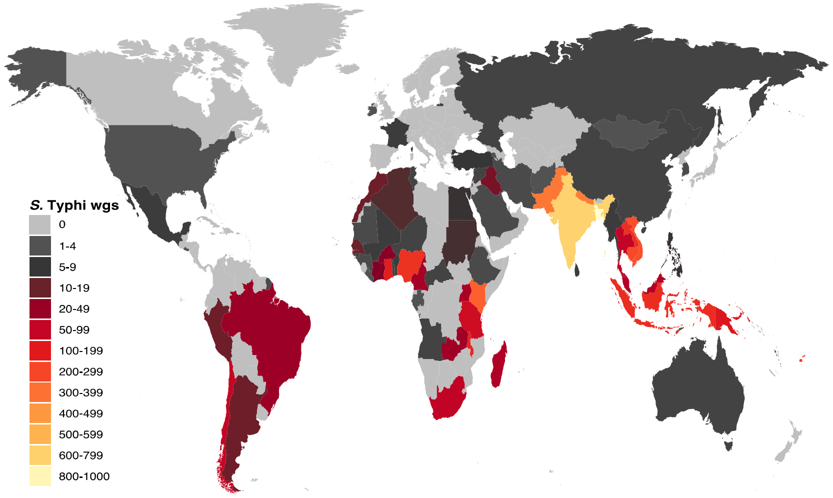
ARTICLE

DOI: 10.1038/s41467-018-07370-z OPEN

The phylogeography and incidence of multi-drug resistant typhoid fever in sub-Saharan Africa

Open questions in typhoid genomics

1. **Where are the gaps in typhoid WGS (whole genome sequencing) surveillance and can travel-associated typhoid cases help fill these?**



Location of travel for 533 *S.* Typhi WGS from Public Health England (PHE) from 2014-2017

Source: Ingle *et al.* 2019, bioRxiv

<u>Please see:</u> Poster 108 "*Salmonella* Genomics: A Revolution in Public Health Microbiology", Nair *et al.* PHE

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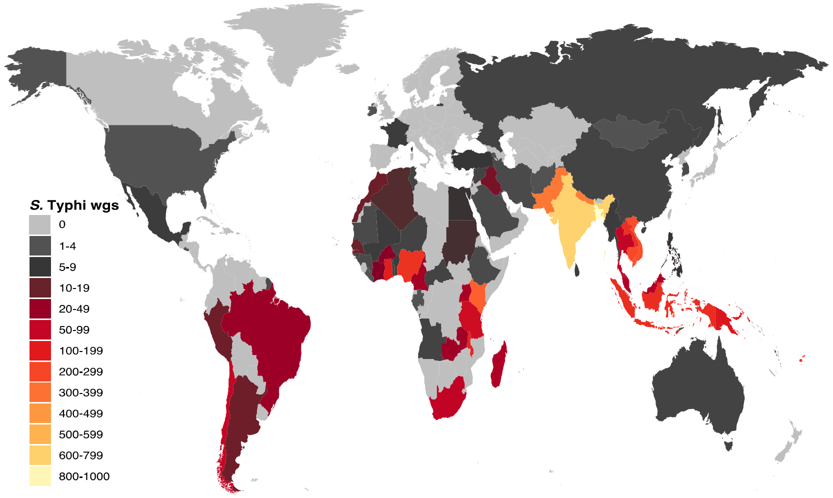

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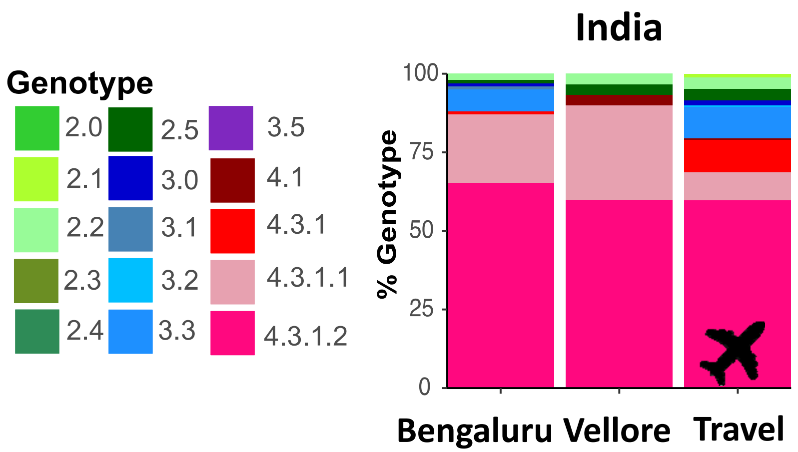
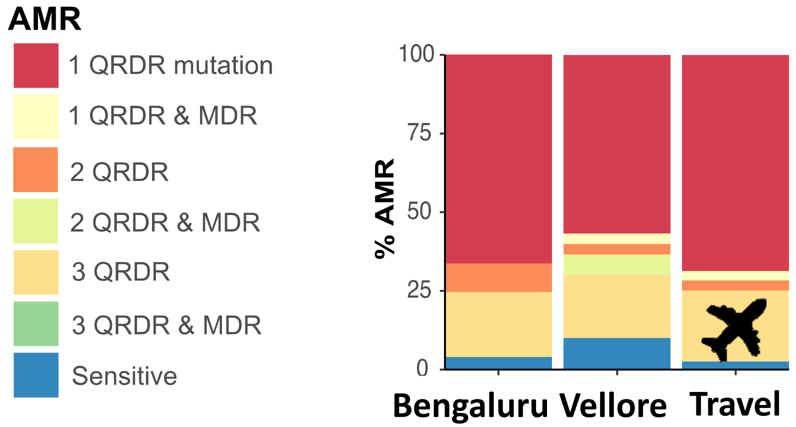
Travel-associated *S.* Typhi are useful sentinels for surveillance in endemic countries

Genotypes



AMR



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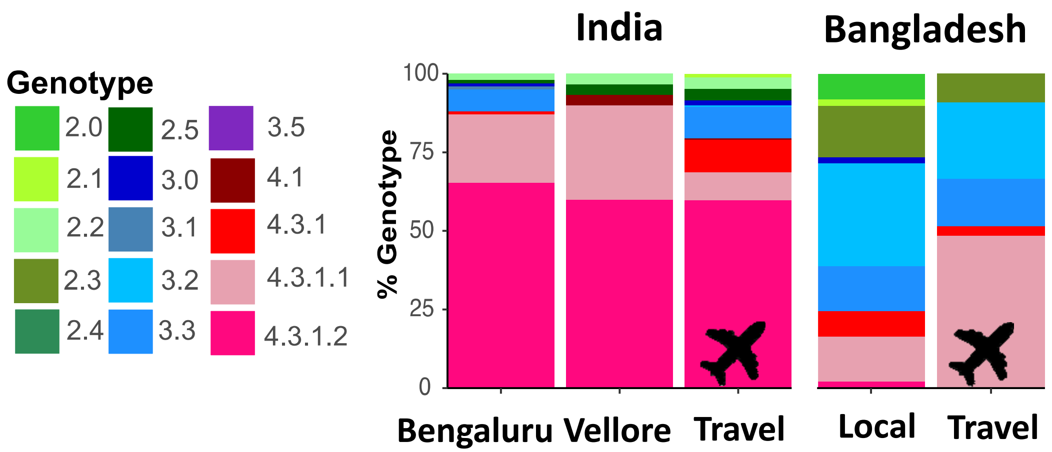

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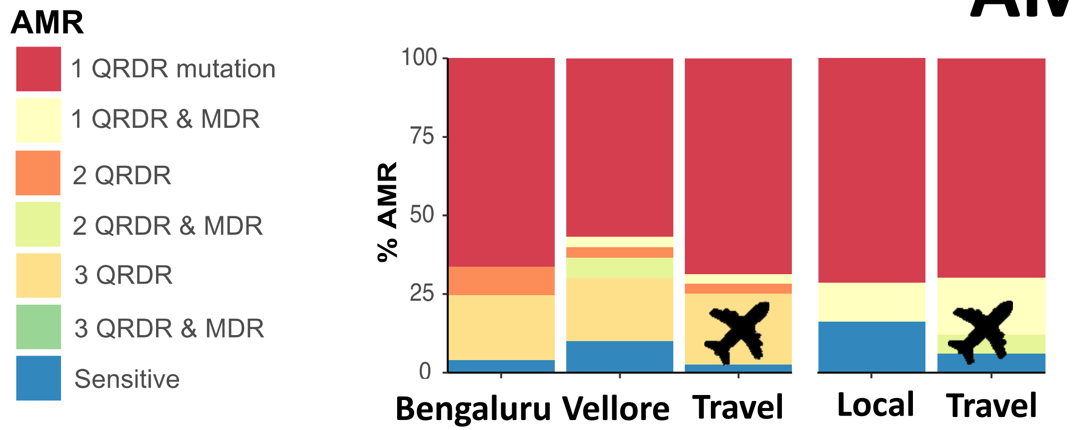

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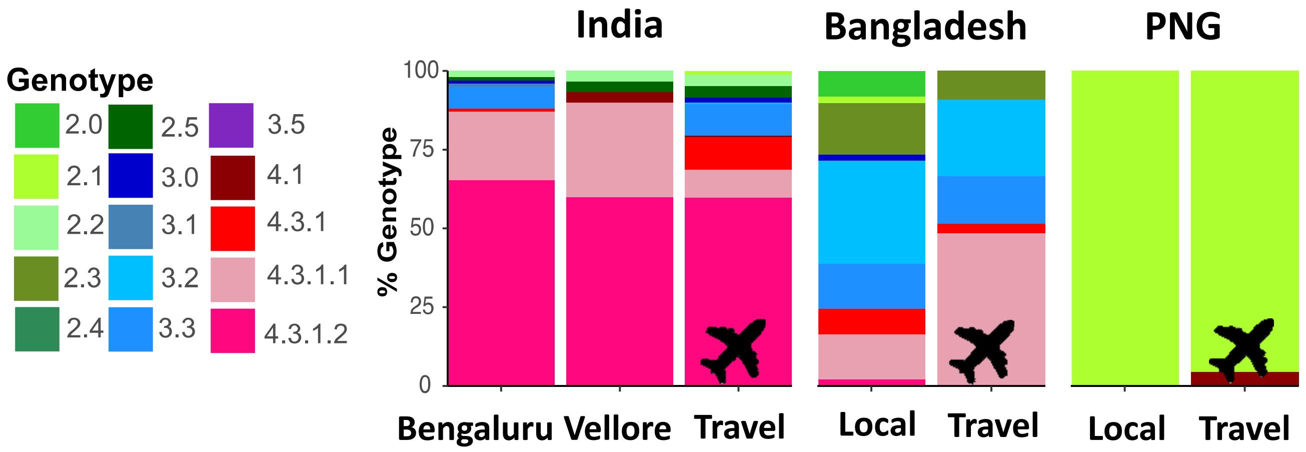

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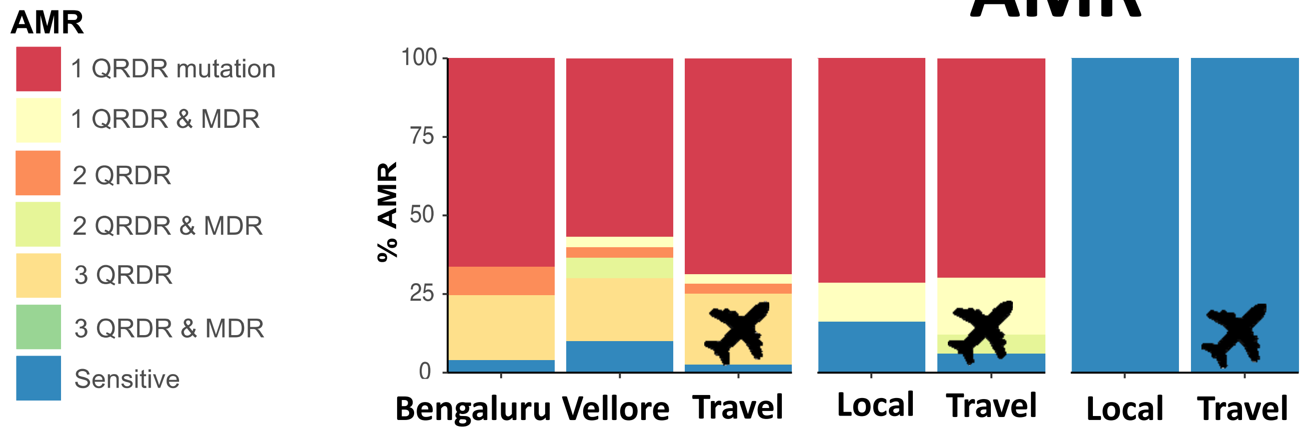

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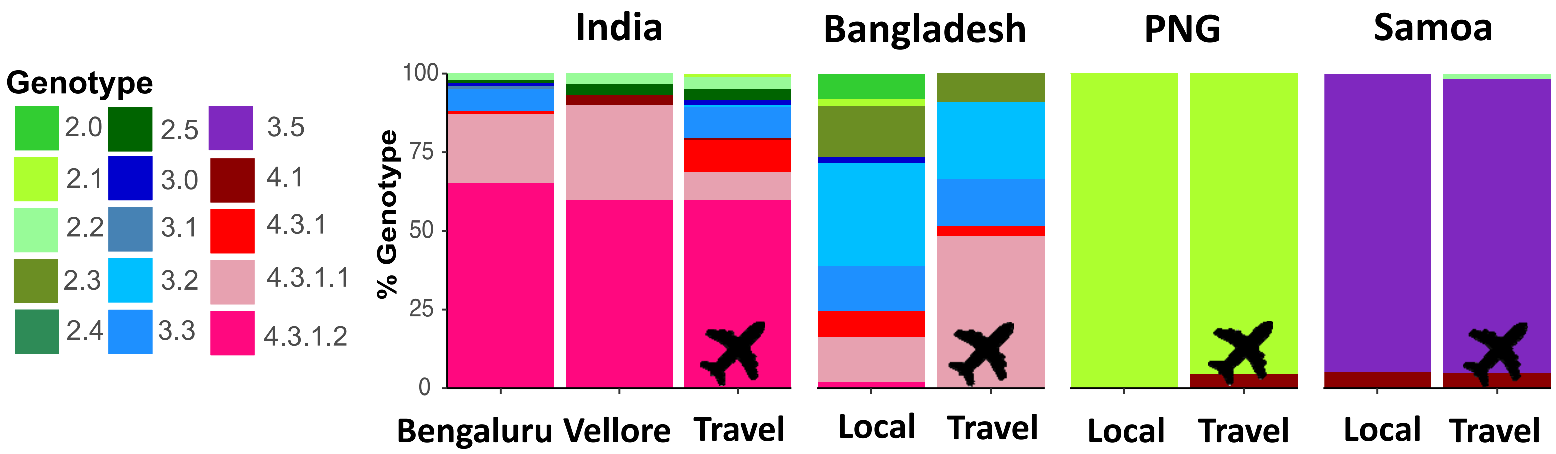
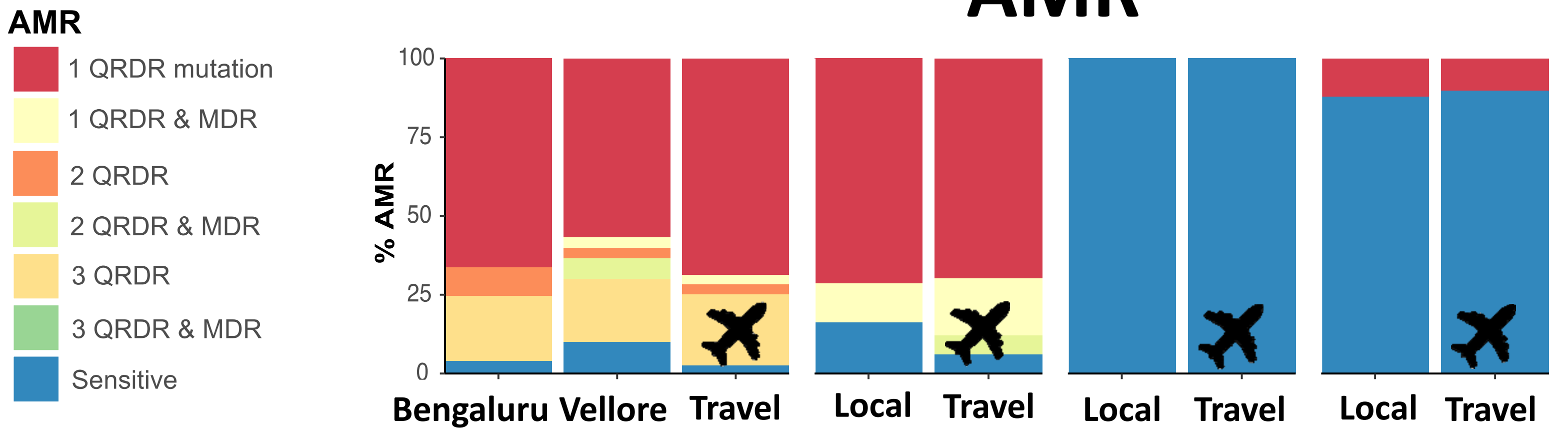


Pearson correlation
r = 0.94
R^2 = 0.88
$p=1.1\times10^{-15}$

AMR



Pearson correlation
r = 0.96
R^2 = 0.92
$p=2.22\times10^{-7}$

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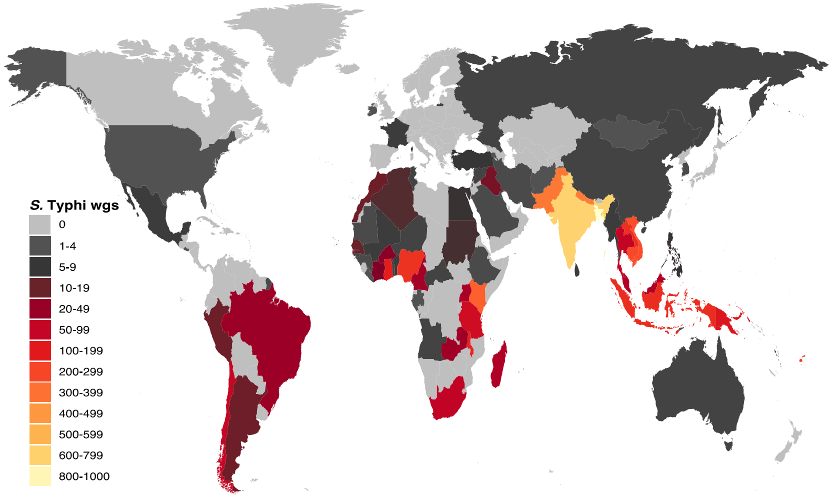

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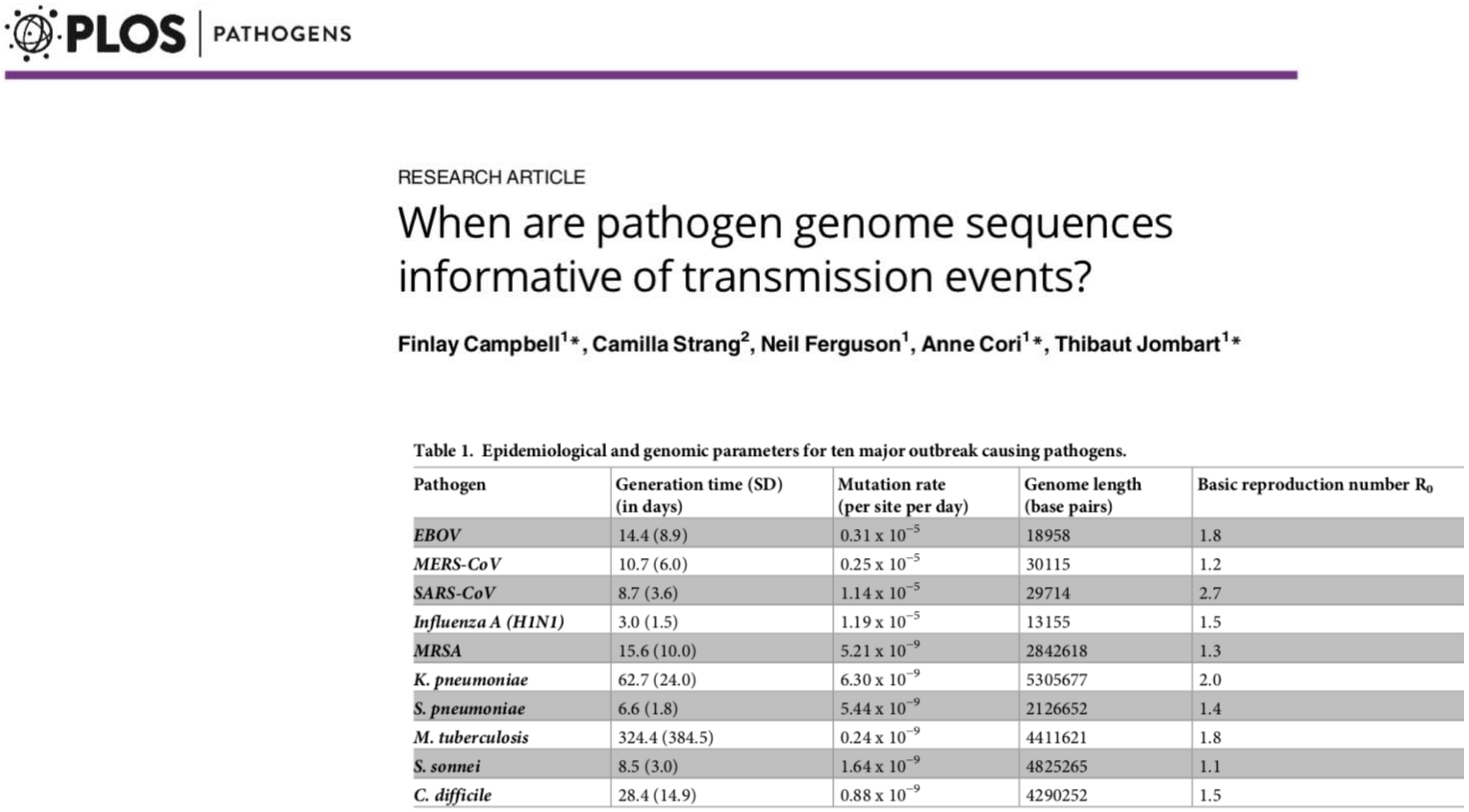
In vivo evolutionary rate & transmission



PLOS | PATHOGENS

RESEARCH ARTICLE

When are pathogen genome sequences informative of transmission events?

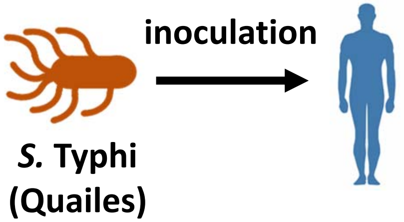
Finlay Campbell[1]*, Camilla Strang[2], Neil Ferguson[1], Anne Cori[1]*, Thibaut Jombart[1]*

Table 1. Epidemiological and genomic parameters for ten major outbreak causing pathogens.

Pathogen	Generation time (SD) (in days)	Mutation rate (per site per day)	Genome length (base pairs)	Basic reproduction number R_0
EBOV	14.4 (8.9)	0.31×10^{-5}	18958	1.8
MERS-CoV	10.7 (6.0)	0.25×10^{-5}	30115	1.2
SARS-CoV	8.7 (3.6)	1.14×10^{-5}	29714	2.7
Influenza A (H1N1)	3.0 (1.5)	1.19×10^{-5}	13155	1.5
MRSA	15.6 (10.0)	5.21×10^{-9}	2842618	1.3
K. pneumoniae	62.7 (24.0)	6.30×10^{-9}	5305677	2.0
S. pneumoniae	6.6 (1.8)	5.44×10^{-9}	2126652	1.4
M. tuberculosis	324.4 (384.5)	0.24×10^{-9}	4411621	1.8
S. sonnei	8.5 (3.0)	1.64×10^{-9}	4825265	1.1
C. difficile	28.4 (14.9)	0.88×10^{-9}	4290252	1.5

Human challenge model of infection

- **189 post challenge stool and blood cultures from 4 studies**
- **Compared WGS data from post-challenge strains to the inoculating (Quailes) strain**



n=38, TI. Observational: Challenge model development (Waddington *et al.* 2014); **n=88, TII.** Vaccine Randomized Control Trial: M01ZH09, Ty21a, placebo (Darton *et al.* 2016); **n=18 from VAST.** Vaccine Randomized Control Trial: Vi-TT, Vi-PS, placebo (Jin *et al.* 2017); **n=45, PATCH.** RCT: Re-challenge & Microbiome (Gibani *et al.* 2018)

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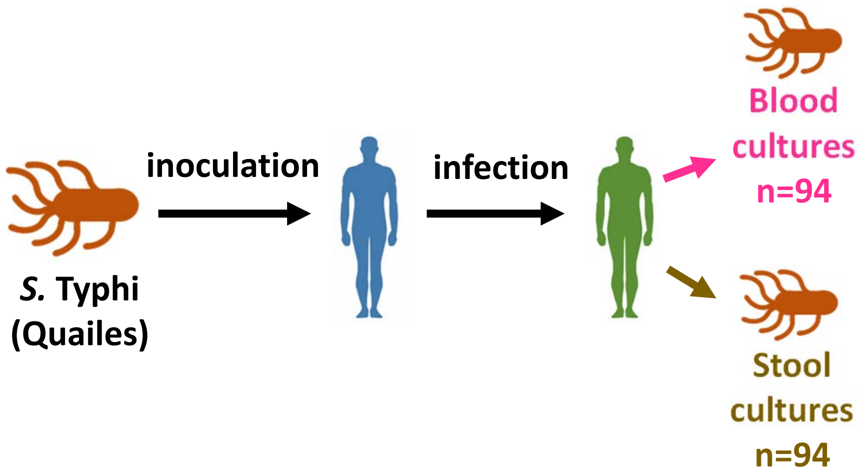

inoculation

infection

***S.* Typhi (Quailes)**

Blood cultures n=94

Stool cultures n=94

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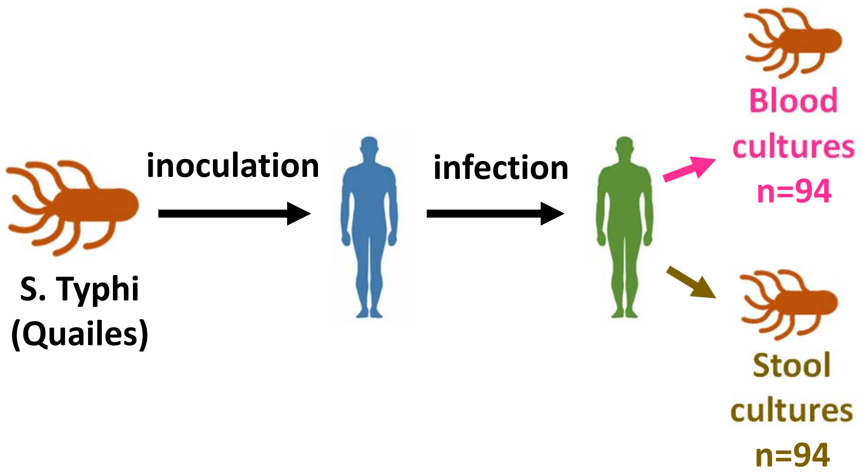

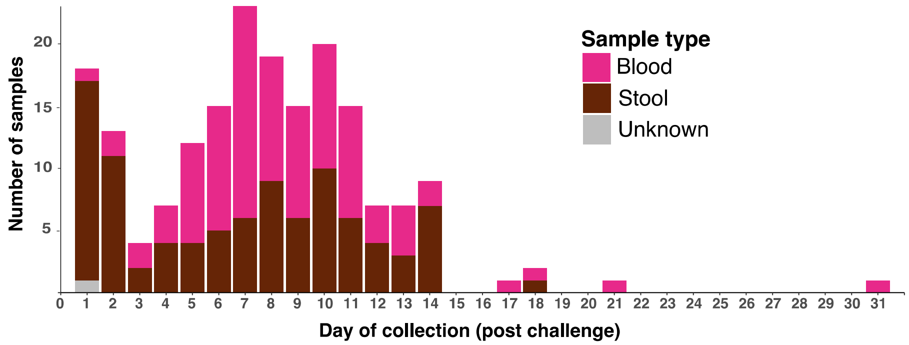

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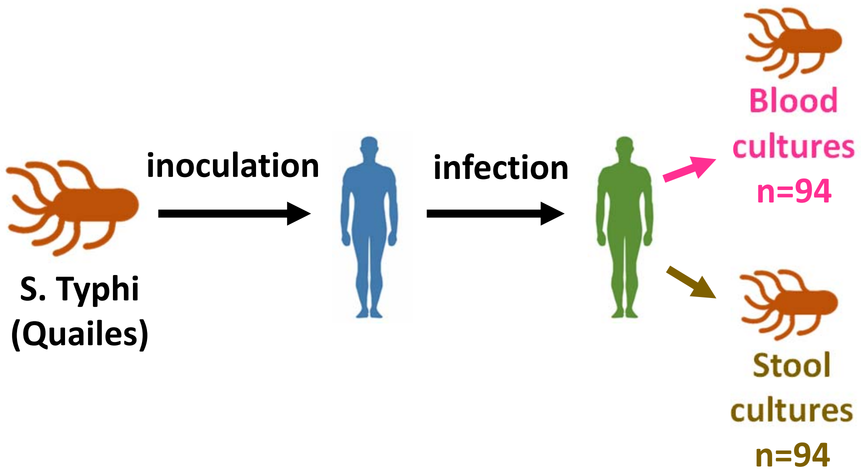

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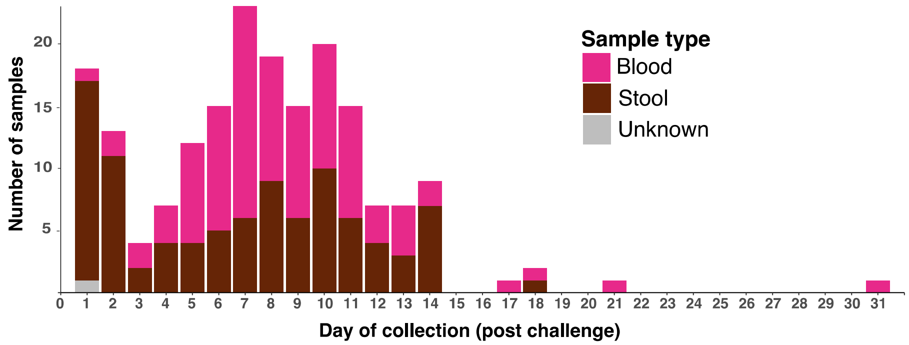

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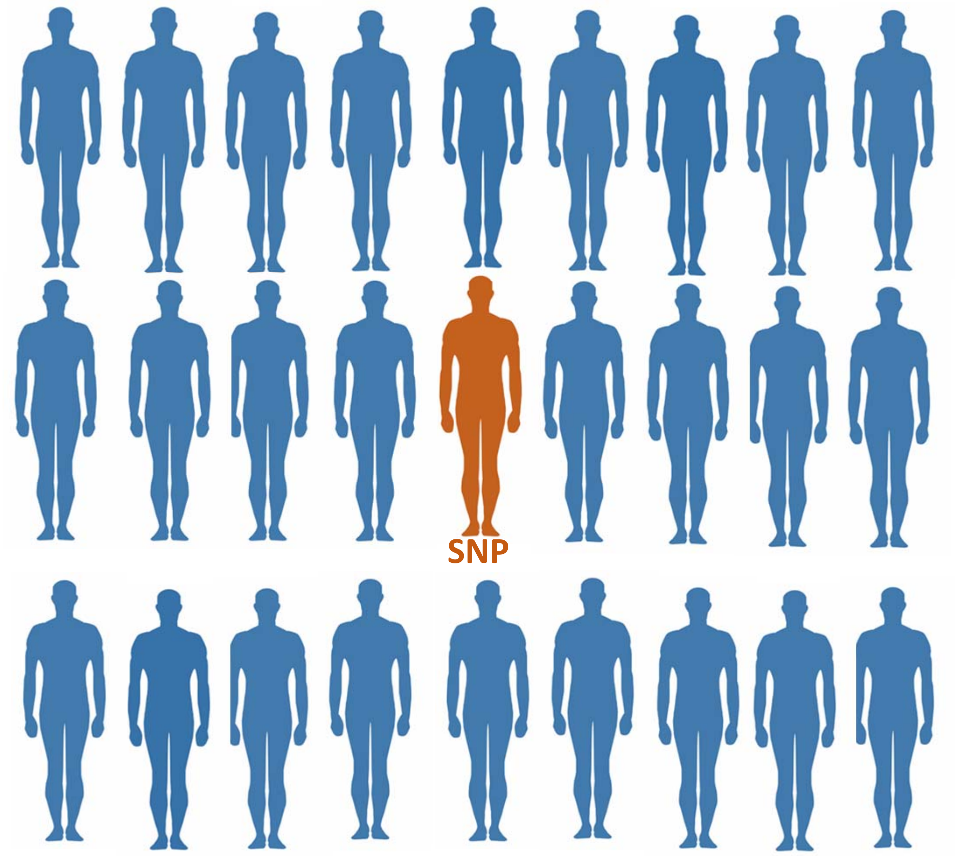

~1 in 27 samples harbored a single base change (SNP)

Individual transmission events

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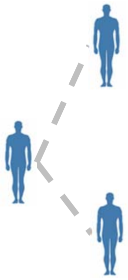

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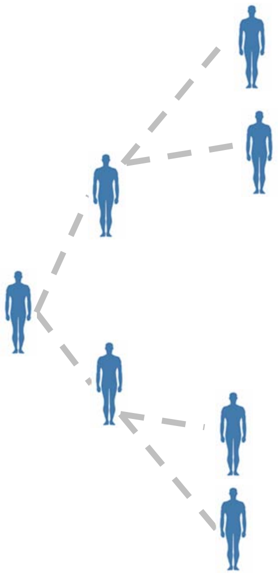

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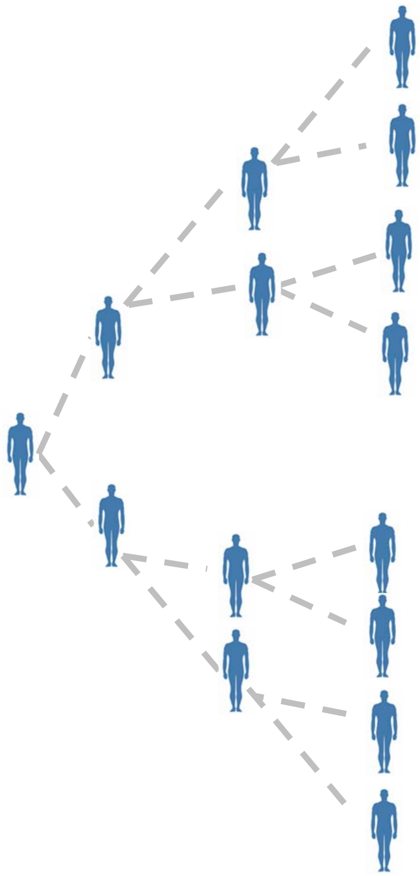

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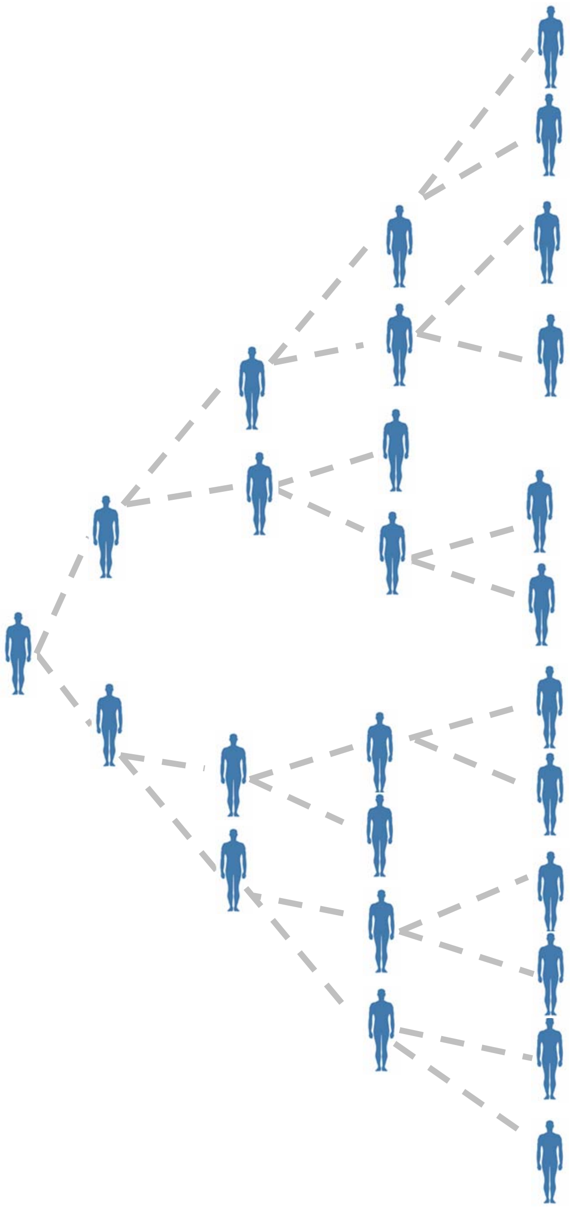

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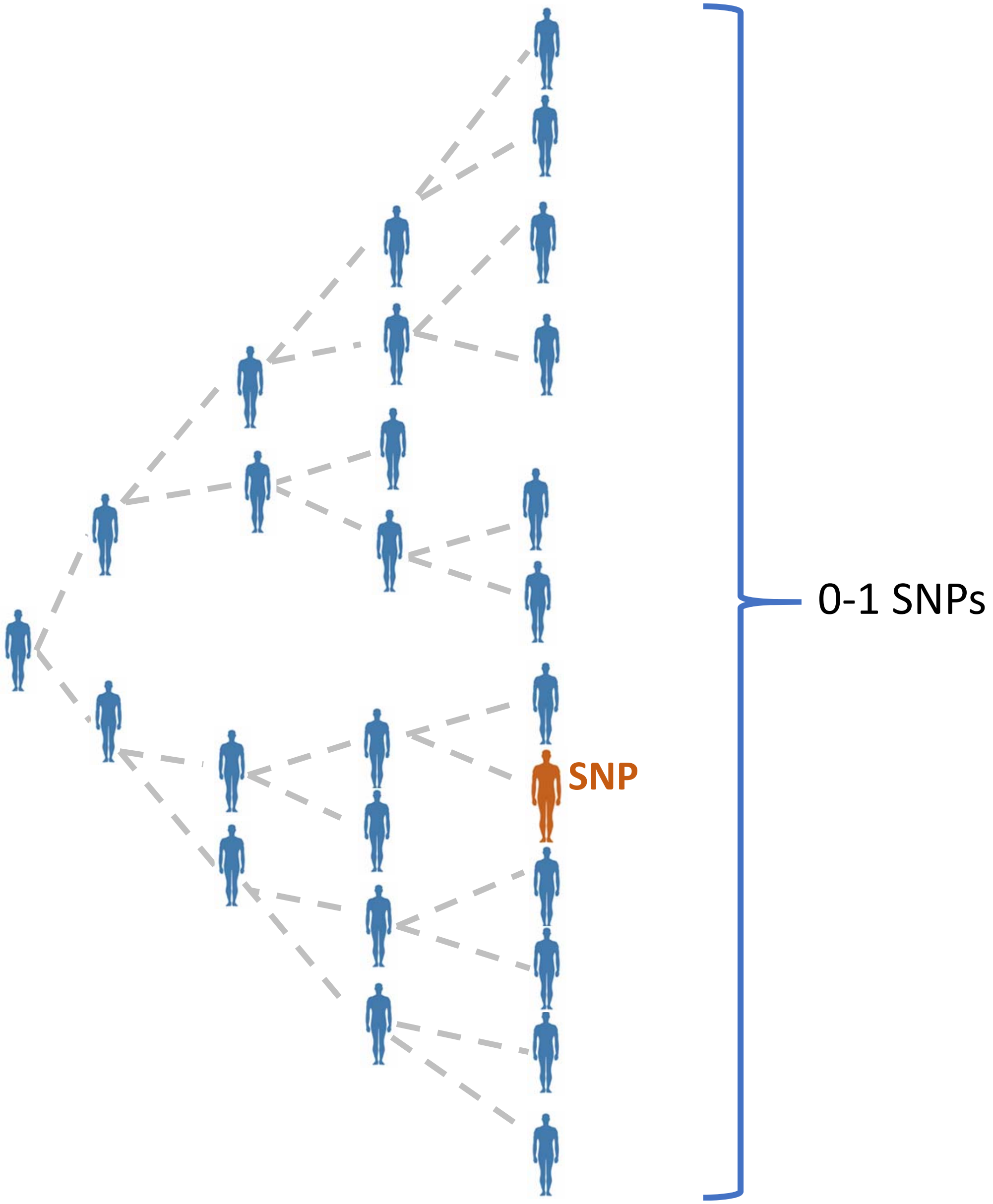

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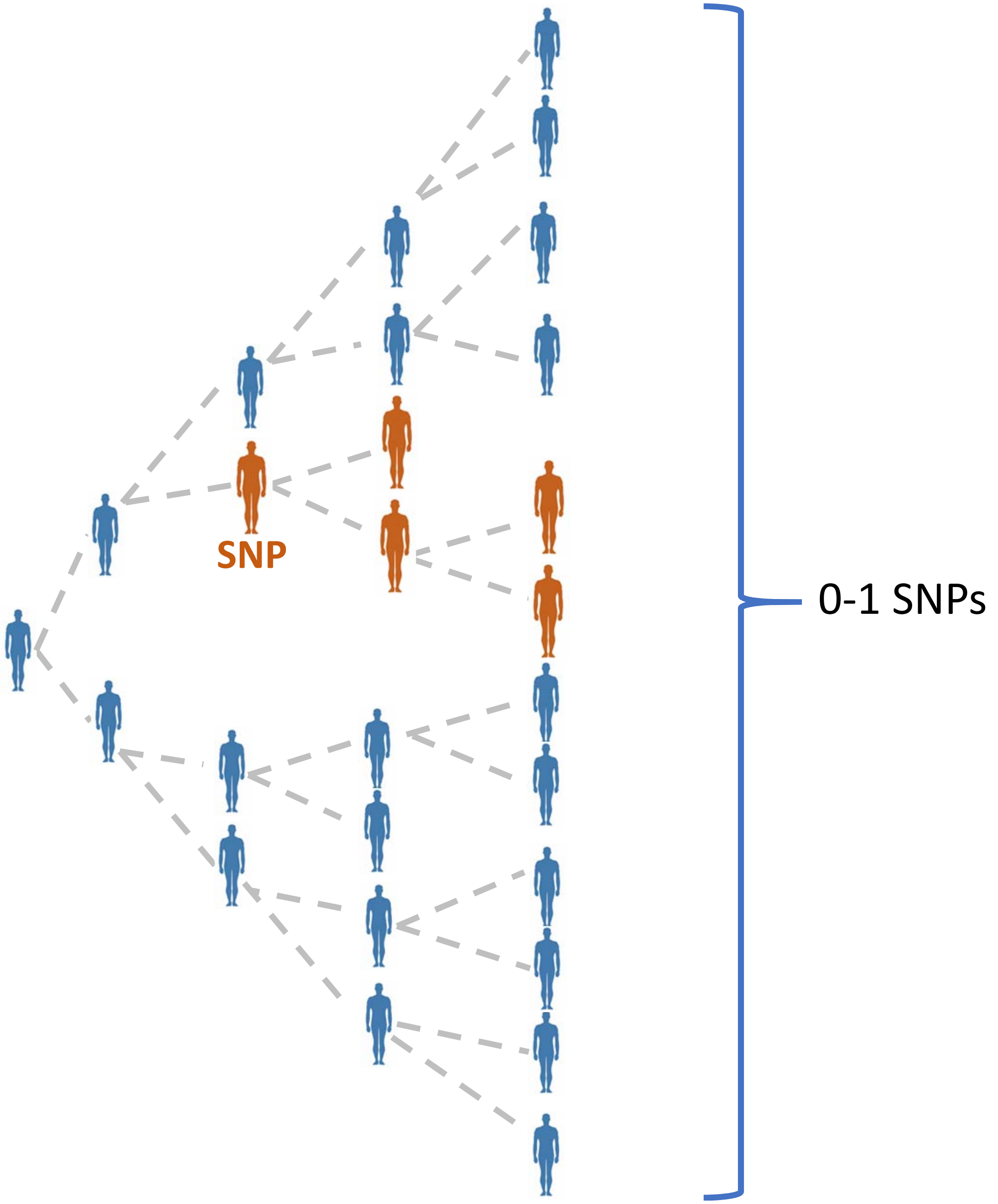
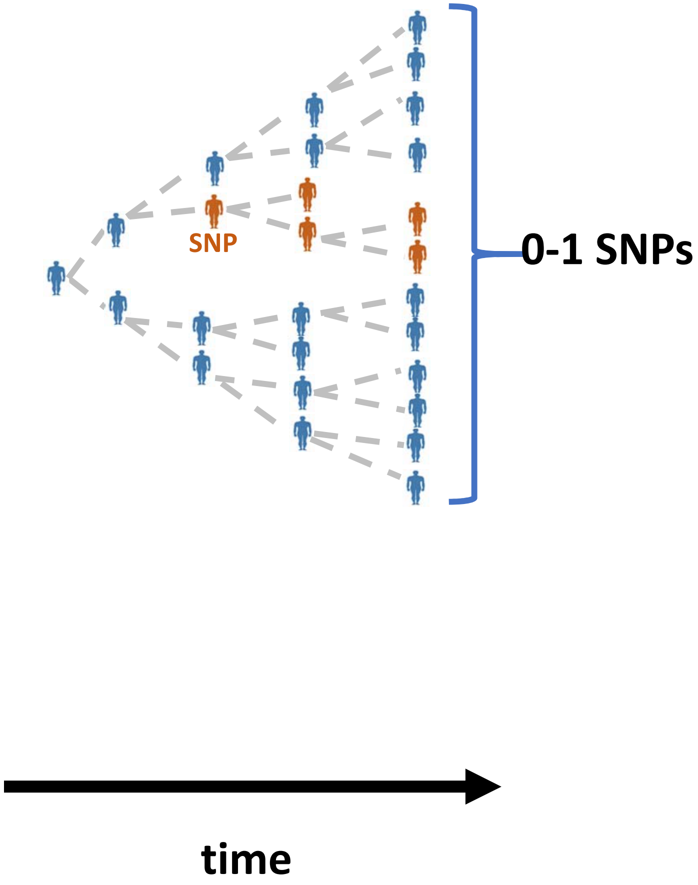


Transmission dynamics



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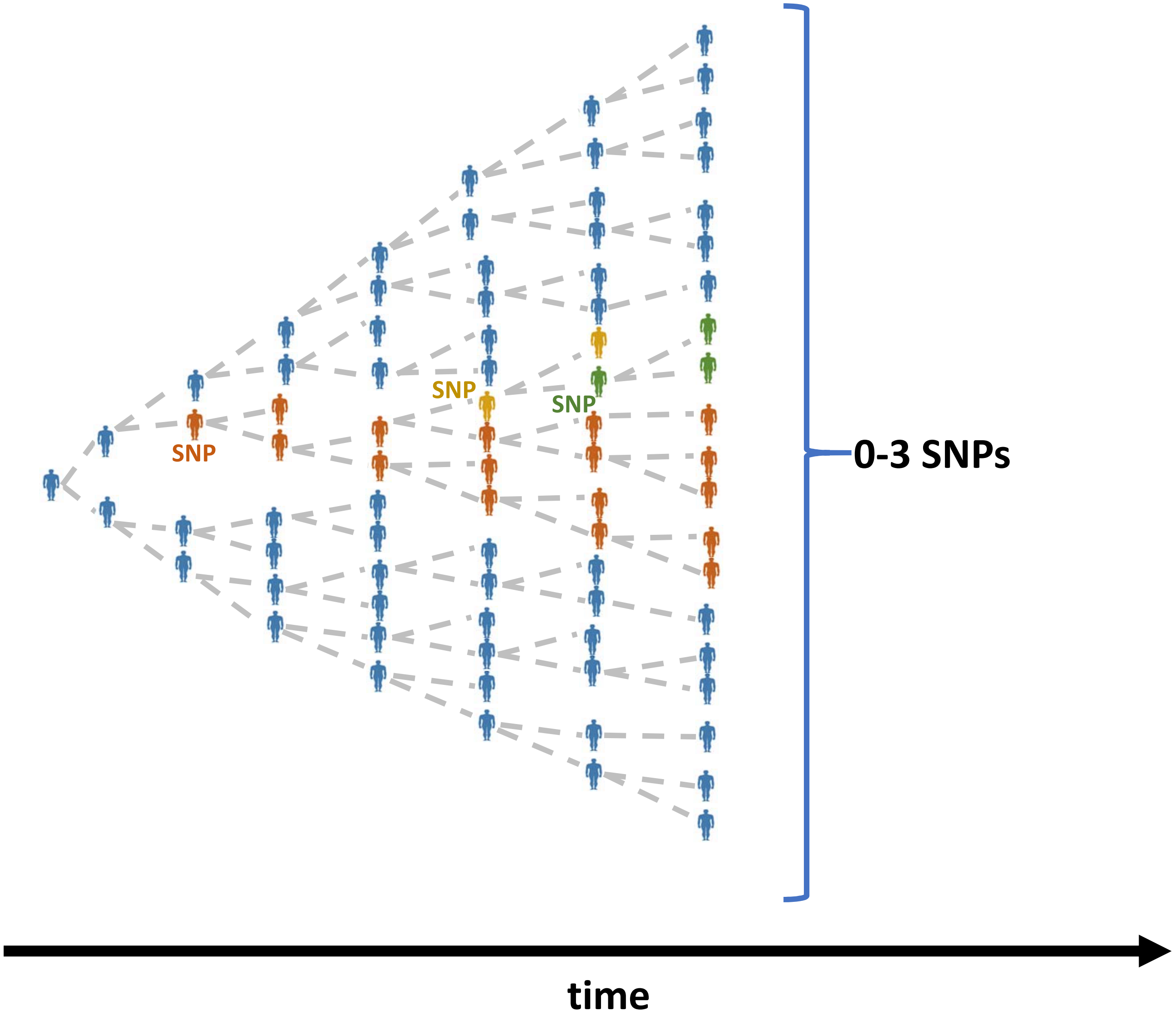
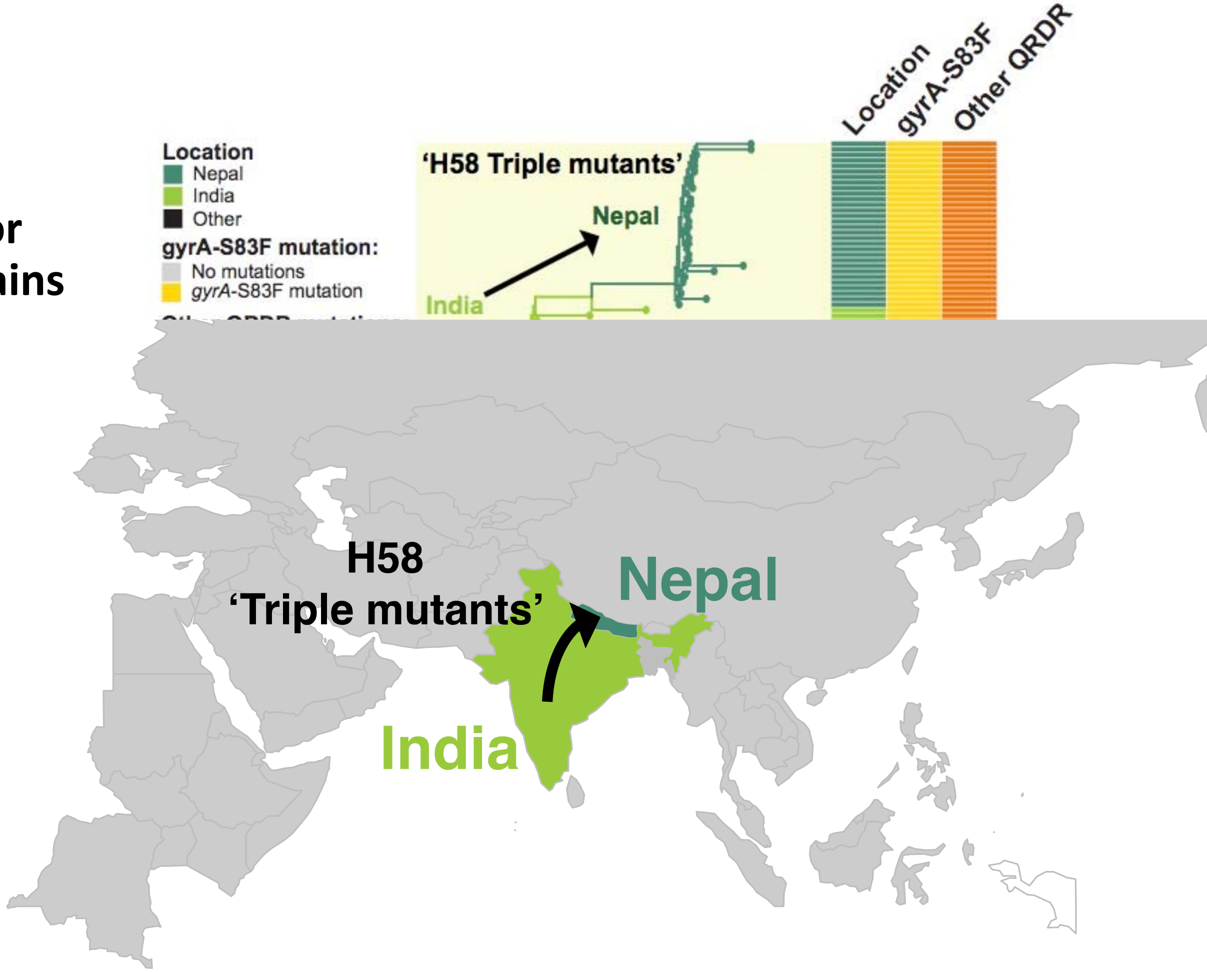


The role of WGS in *S.* Typhi in understanding transmission dynamics

- **Classify strains by genotype**
  - e.g. H58 (4.3.1)
- **Detect Multi-drug resistant (MDR) or Extensively drug resistant (XDR) strains**
  - Detection of AMR
  - Detection of mobil elements e.g. plas
- **Date AMR acquisition e**
- **Understand changes in structure & AMR over t**
- **Understand regional an transmission and circul**
- **Understanding age dist genotypes and other pa**
  - e.g. seasonal patte patterns



Conclusions

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2. However, WGS data are key in understanding **transmission dynamics**, AMR, regional and global strain circulation patterns, and resolving point source outbreaks in different endemic settings

Recommendations

1. For endemic countries which do not yet have formal WGS based surveillance programmes, return traveler WGS data routinely generated by public health laboratories (e.g. PHE) are suitable for **temporary sentinel surveillance**

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