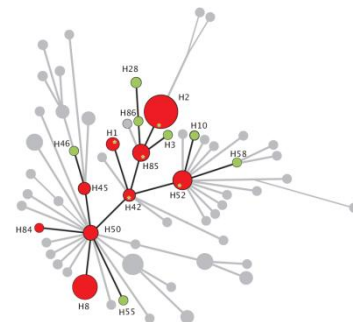
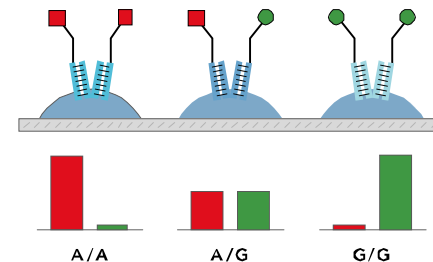
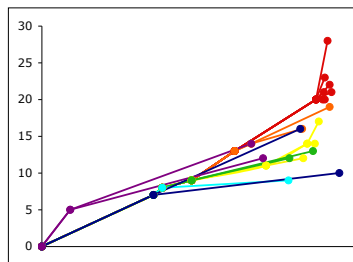
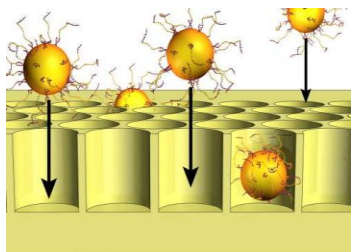




# How can genomics help us tackle typhoid?

Professor Gordon Dougan

Wellcome Trust Sanger Institute and  
Cambridge University



## **This presentation will focus on.....**

- **How genomic data can be used to track S. Typhi/Paratyphi**
- **How we have the ultimate typing tool giving details of isolate origin, virulence traits, resistance in a single sample**
- **Replacing all other typing techniques including phage typing, VNTR, PFGE etc.**
- **Why we should set up a global database**
- **How we could track Typhi locally**
- **How it can help control measures**

# Salmonella enterica is a broad and variable species but harbours conserved host adapted pathotypes



100,000 SNPs  
Horizontal islands

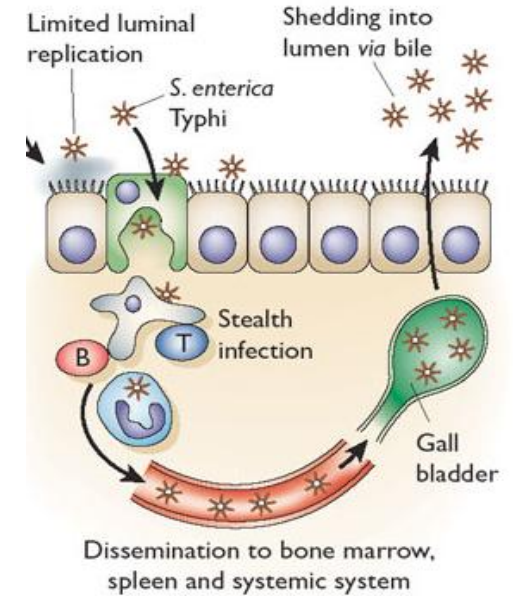
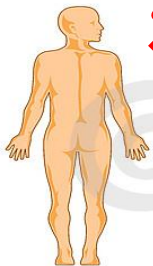
10000 SNPs

Typhimurium

Paratyphi A

Typhi

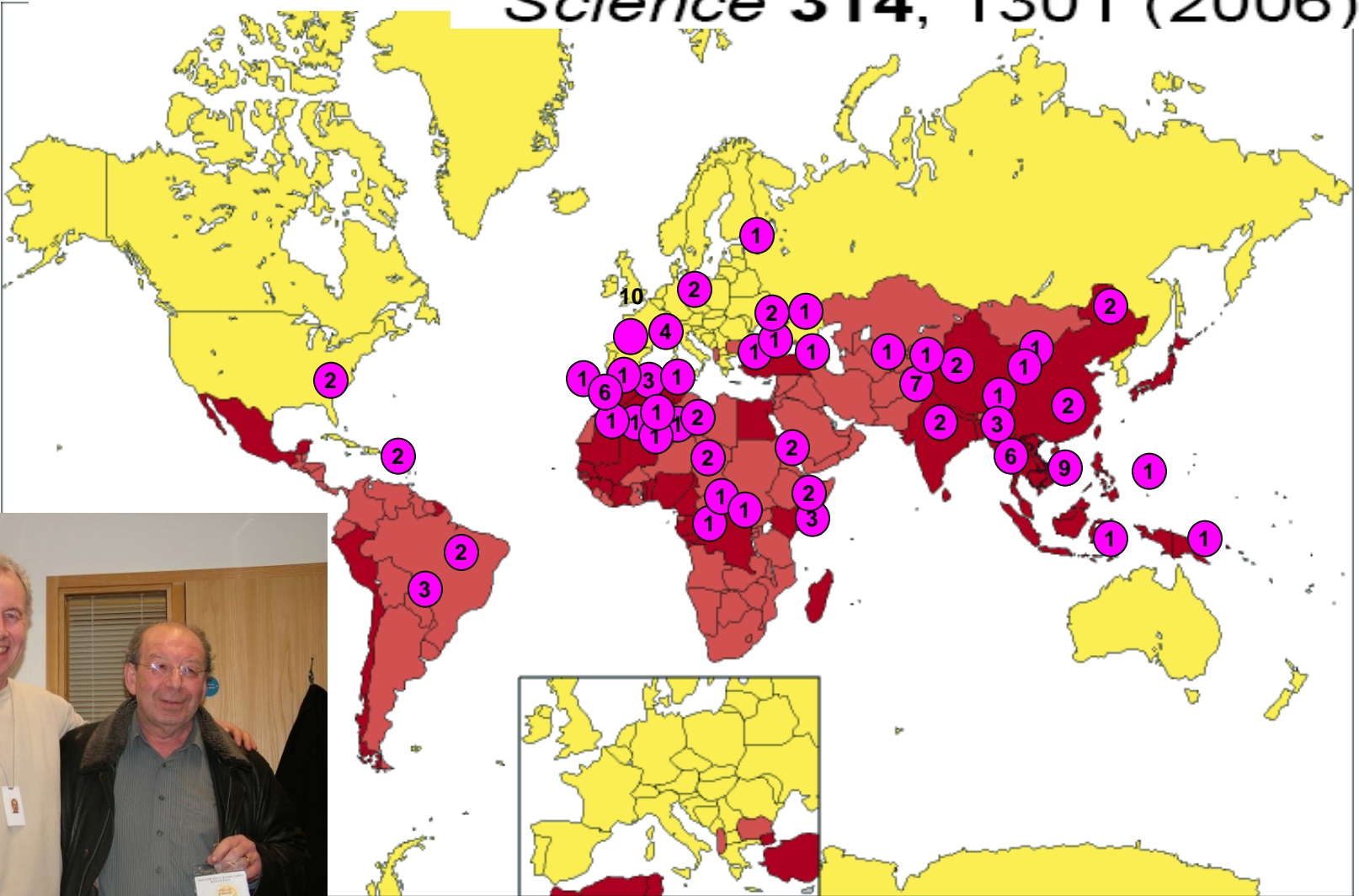
2000 SNPs



# Evolutionary History of *Salmonella* Typhi

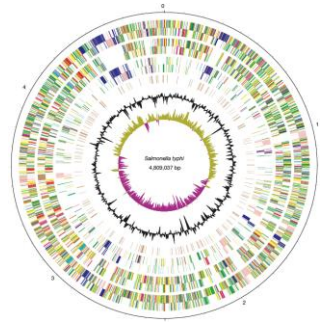
Philippe Roumagnac,<sup>1</sup> François-Xavier Weill,<sup>2</sup> Christiane Dolecek,<sup>3</sup> Stephen Baker,<sup>4</sup>  
Sylvain Brisse,<sup>2</sup> Nguyen Tran Chinh,<sup>5</sup> Thi Anh Hong Le,<sup>6</sup> Camilo J. Acosta,<sup>7\*</sup> Jeremy Farrar,<sup>3</sup>  
Gordon Dougan,<sup>4</sup> Mark Achtman<sup>1</sup>†

*Science* **314**, 1301 (2006)

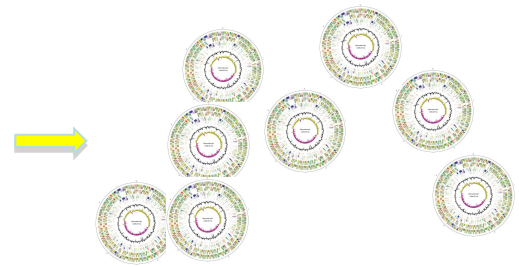


# Natural pathogen variation discovery its exploitation in typhoid

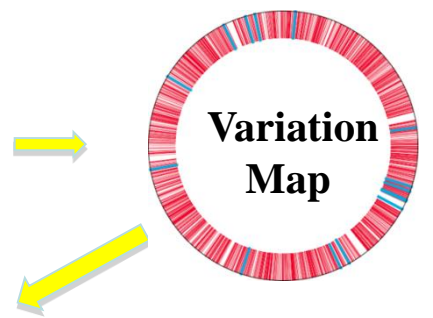
S. Typhi reference genome



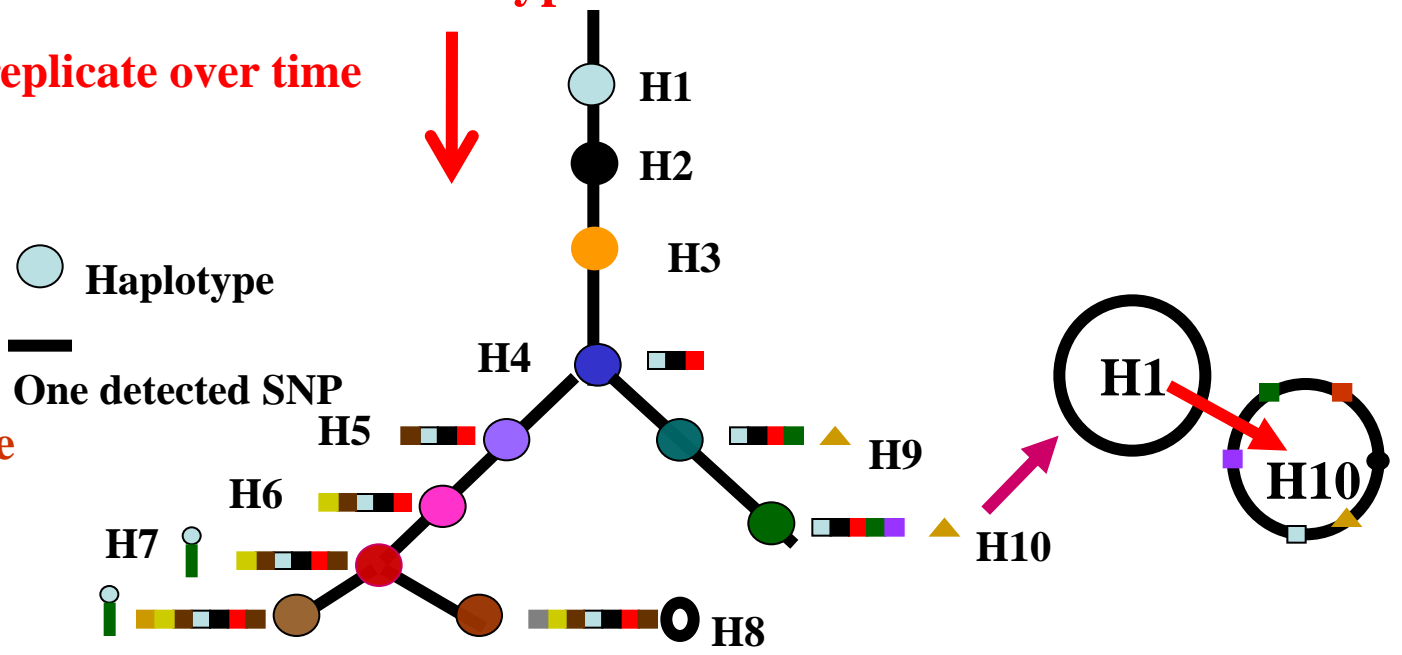
Whole genome sequence a Global or local collection



2,000 SNPs



Typhi replicate over time  
Typhi ancestor



Molecular Bar Code



# **What do DNA-based population studies tell us?**

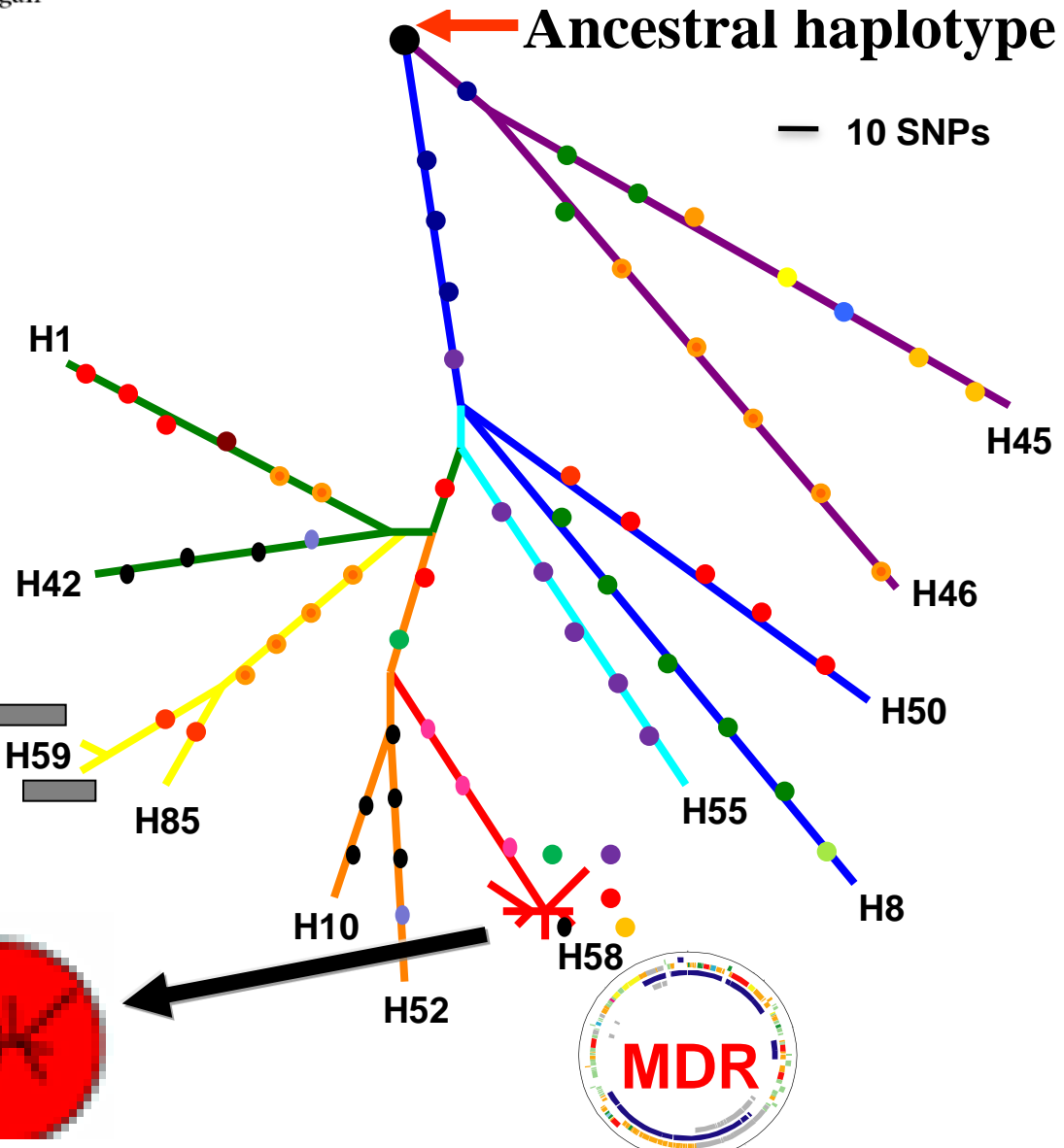
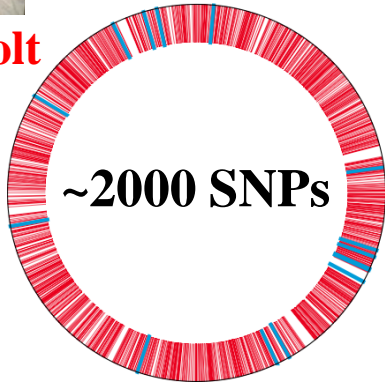
- **All S. Typhi isolates originate from the same bacteria that entered the human population once thousands of years ago**
- **We have a fully parsimonious phylogenetic tree with limited recombination**
- **‘All’ isolates can be distinguished and placed in an evolutionary context on the tree**
- **Lack of evidence of immune selection**
- **Predicts small population size with carriers key to evolution?**



# High-throughput sequencing provides insights into genome variation and evolution in *Salmonella* Typhi

Kathryn E Holt<sup>1</sup>, Julian Parkhill<sup>1</sup>, Camila J Mazzoni<sup>2,3</sup>, Philippe Roumagnac<sup>3,4</sup>, François-Xavier Weill<sup>5</sup>, Ian Goodhead<sup>1,8</sup>, Richard Rance<sup>1</sup>, Stephen Baker<sup>1,6</sup>, Duncan J Maskell<sup>7</sup>, John Wain<sup>1</sup>, Christiane Dolecek<sup>6</sup>, Mark Achtman<sup>2,3</sup> & Gordon Dougan<sup>1</sup>

**Kathryn Holt**

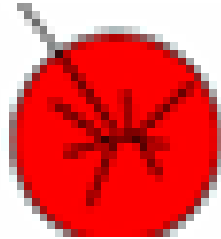
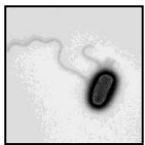


Nalidixic acid resistant

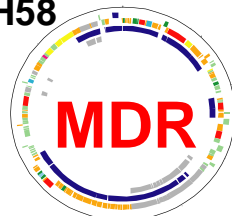


point mutations SNPs

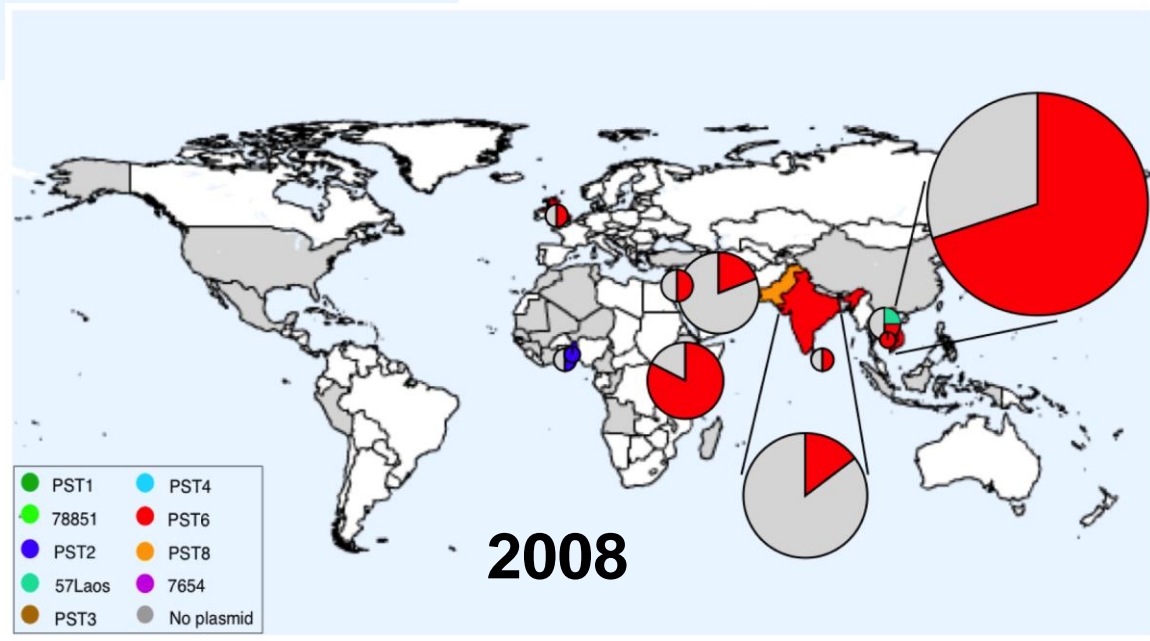
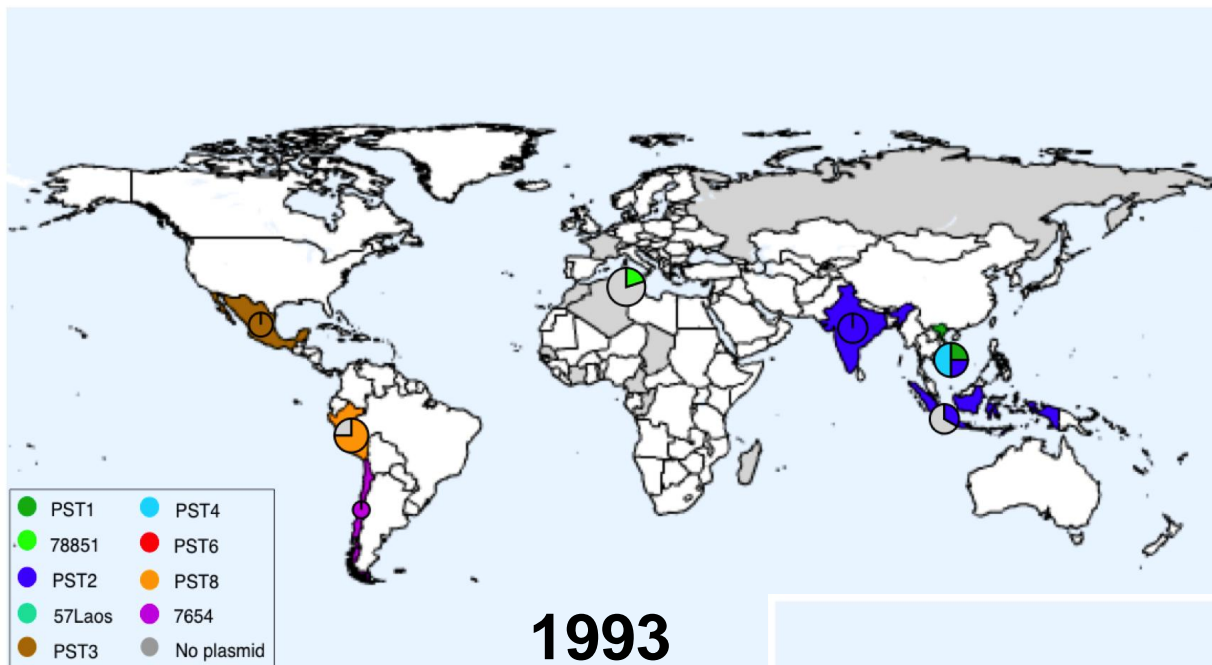
	NAS	GGC	GAT	TCC	GCA	GTG	TAT	GAC	ACC	ATC
Tyr83	GGC	GAT	TCC	GCA	GTG	TAT	GAC	ACC	ATC	
Phe83	GGC	GAT	<b>A</b>	GCA	GTG	TAT	GAC	ACC	ATC	
Pro83	GGC	GAT	<b>T</b>	GCA	GTG	TAT	GAC	ACC	ATC	
Gly87	GGC	GAT	<b>CCC</b>	GCA	GTG	TAT	GAC	ACC	ATC	
Asn87	GGC	GAT	TCC	GCA	GTG	TAT	<b>G</b>	ACC	ATC	
Tyr87	GGC	GAT	TCC	GCA	GTG	TAT	<b>AAC</b>	ACC	ATC	
	GGC	GAT	TCC	GCA	GTG	TAT	<b>TAC</b>	ACC	ATC	



**H58 is expanding!**

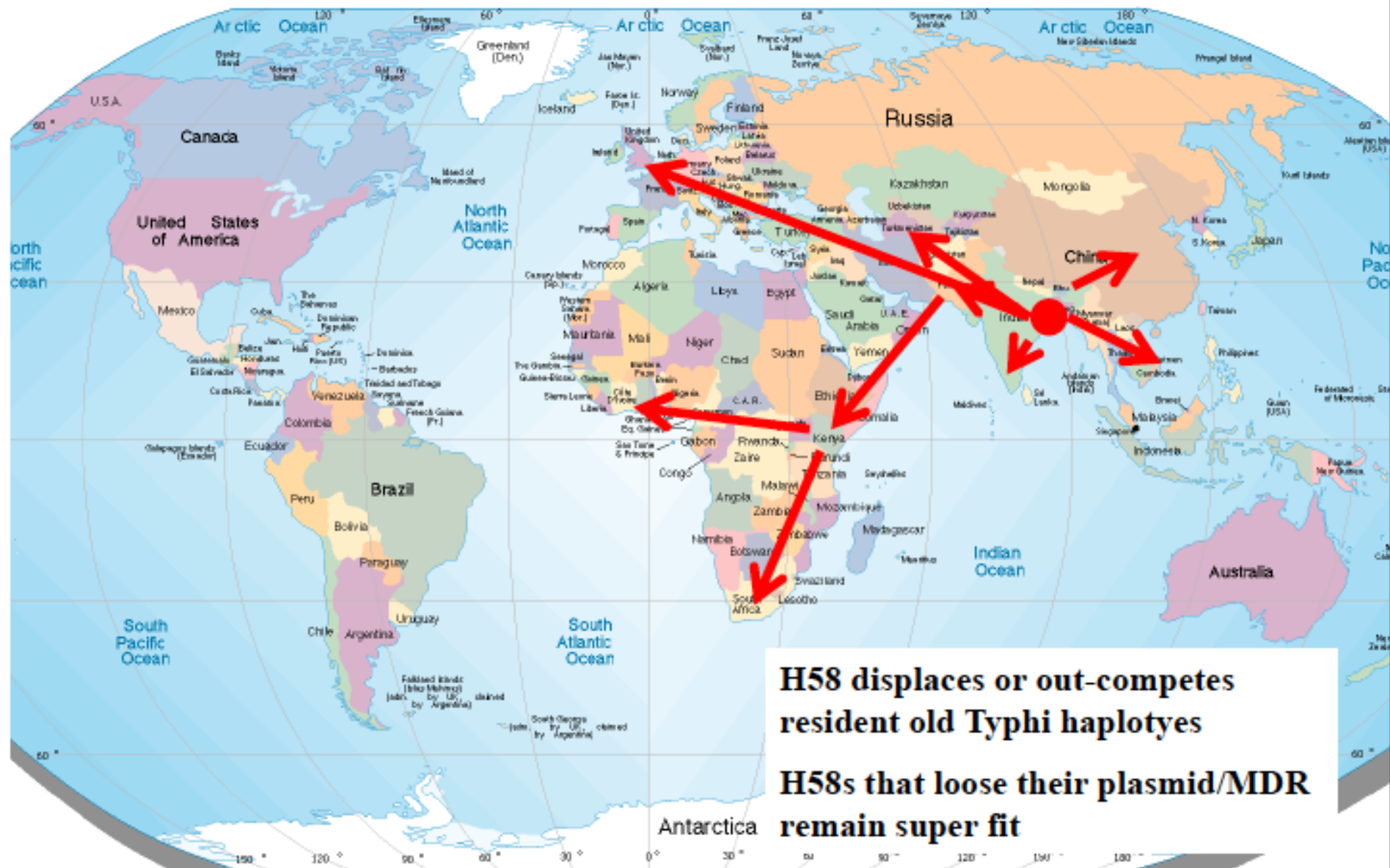


# The global expansion of *S. Typhi* H58 with multiple antibiotic resistance potential

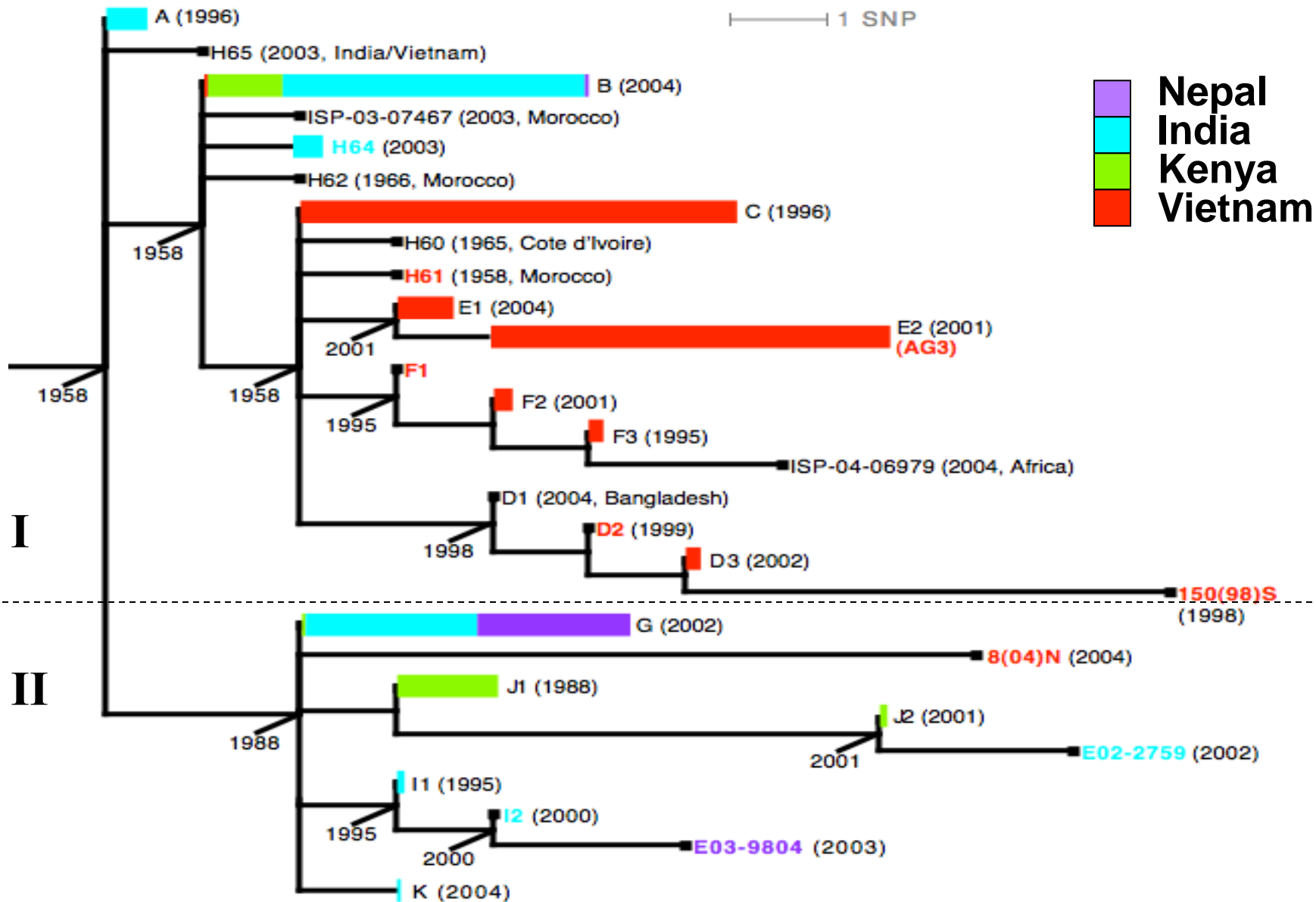


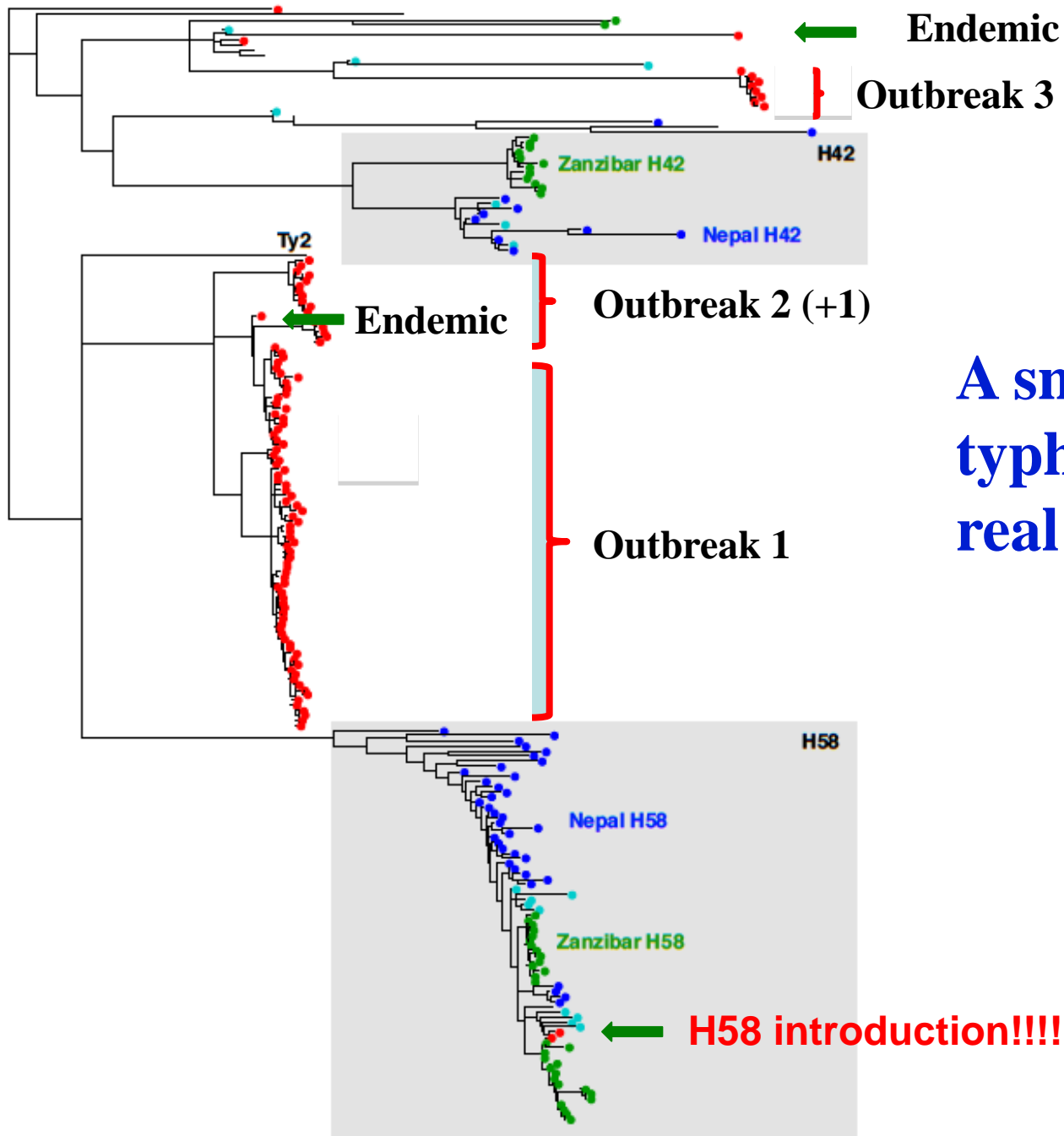


# The spread of the H58 multidrug resistant, IncH1 plasmid super haplotype of *S. Typhi* around the world



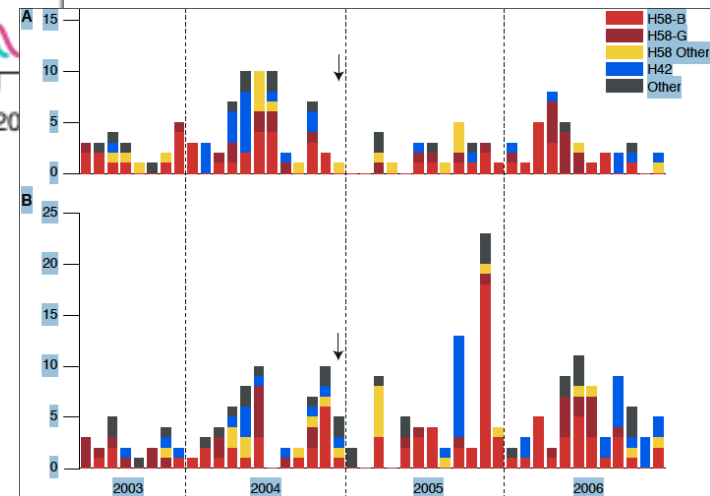
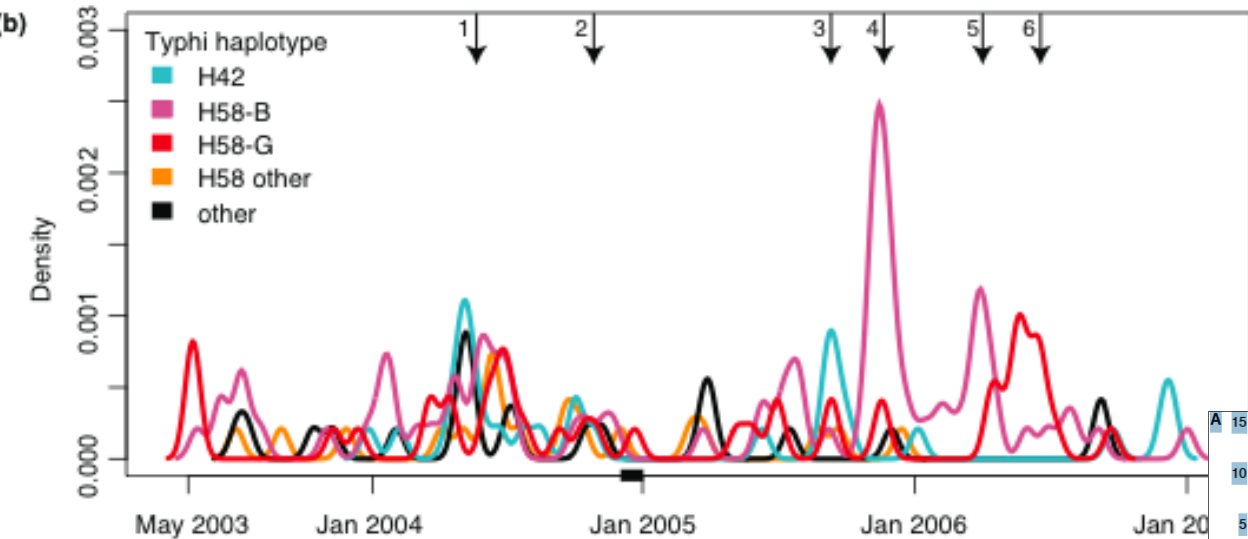
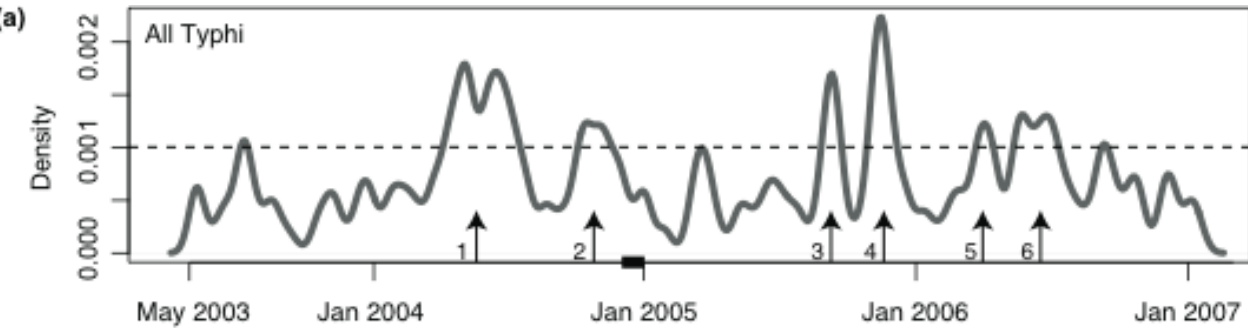
# S. Typhi H58 lineages in local regions around the globe





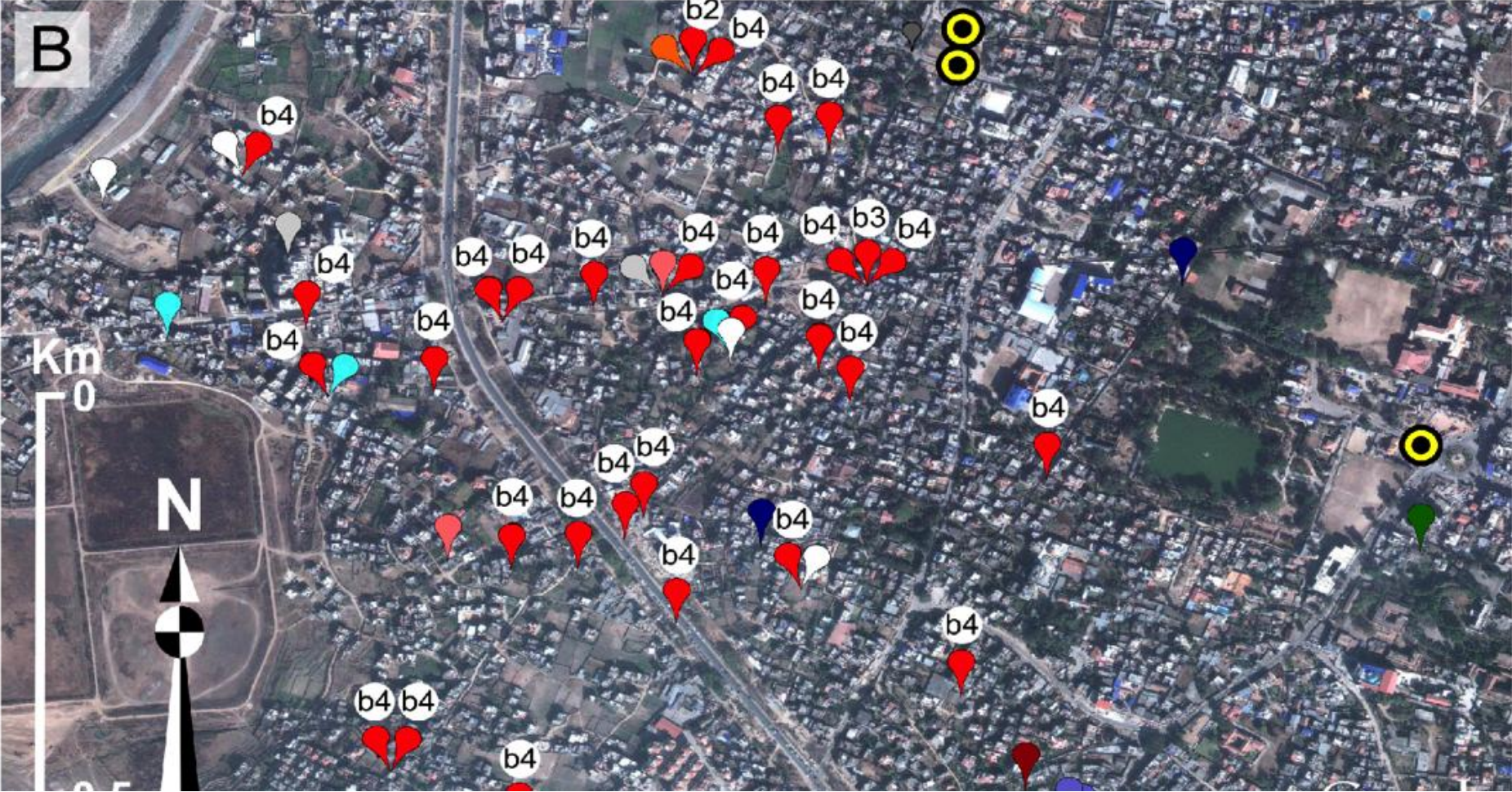
**A snapshot of a typhoid epidemic in real time**

# Incidence of typhoid and associated haplotypes in Kolkata, India



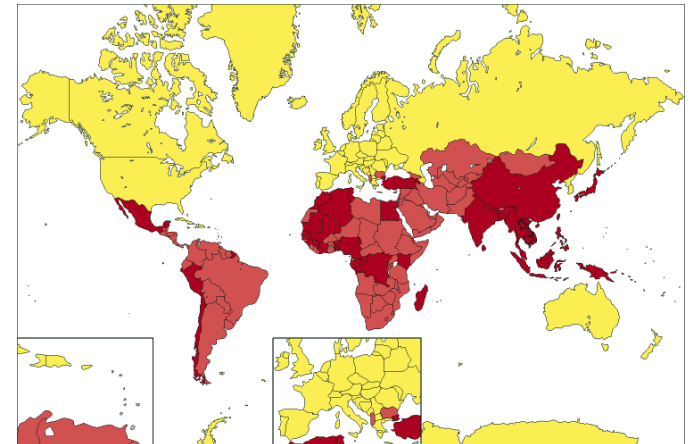


# Evidence for H58b4 outbreak in Kathmandu



# Proposal

- **We form an international consortium to map and genotype *S. Typhi*/*Paratyphi* across the world**
- **We create a central web site based on free software to coordinate this**
- **We design simple SNP-based assays for field testing**
- **We use this to advocate typhoid control**



# Acknowledgements

**Stephen Baker (Vietnam), Oxford)**

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**Mohammad Ali (IVI)**

**Leon Ochai (IVI)**

**Jeremy Farrar (Vietnam)**

**Abhilasha Karkey (Kathmandu)**

**Buddha Basnyat**

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**Shanta Dutta NICED, Kolkata**

