

Emergence of azithromycin resistance in typhoidal *Salmonella* in Dhaka, Bangladesh

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and Other Invasive Salmonellosis, Hanoi, Vietnam



GLOBAL HEALTH

‘We’re Out of Options’: Doctors Battle Drug-Resistant Typhoid Outbreak



April 13, 2018

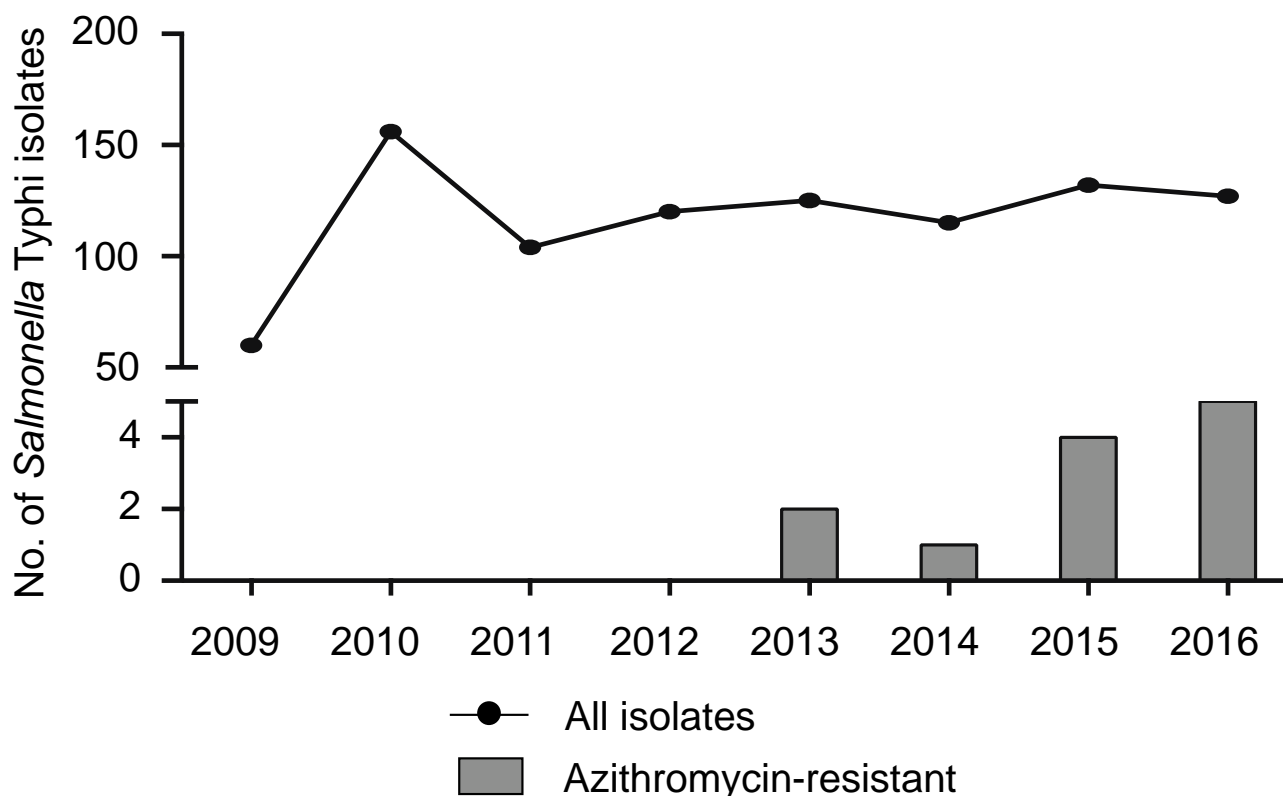
“It’s a global concern at this point,” said Dr. Eric Mintz, an epidemiologist at the Centers for Disease Control and Prevention. “Everything suggests this strain will survive well and spread easily — and acquiring resistance to azithromycin is only a matter of time.”

A baby believed to have typhoid fever in Pakistan in February. N



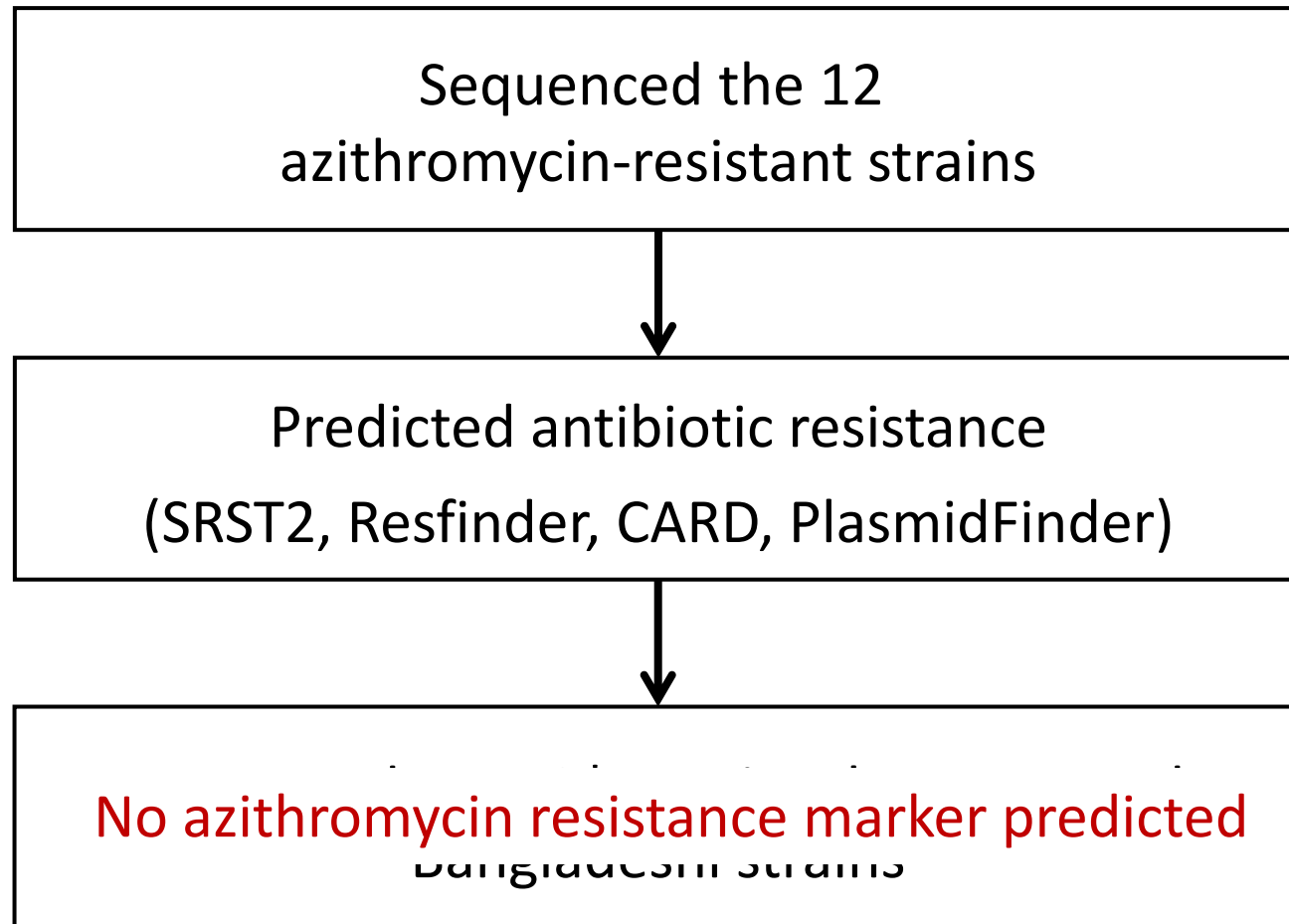
Emergence on azithromycin resistance in Dhaka, Bangladesh: 2009 - 2016

Between 2009 and 2016, **939 Typhi isolates*** were isolated and tested, **12 were azithromycin resistant**, emerging in 2013



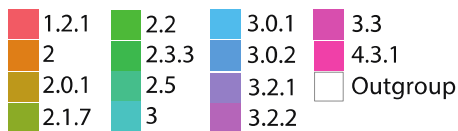
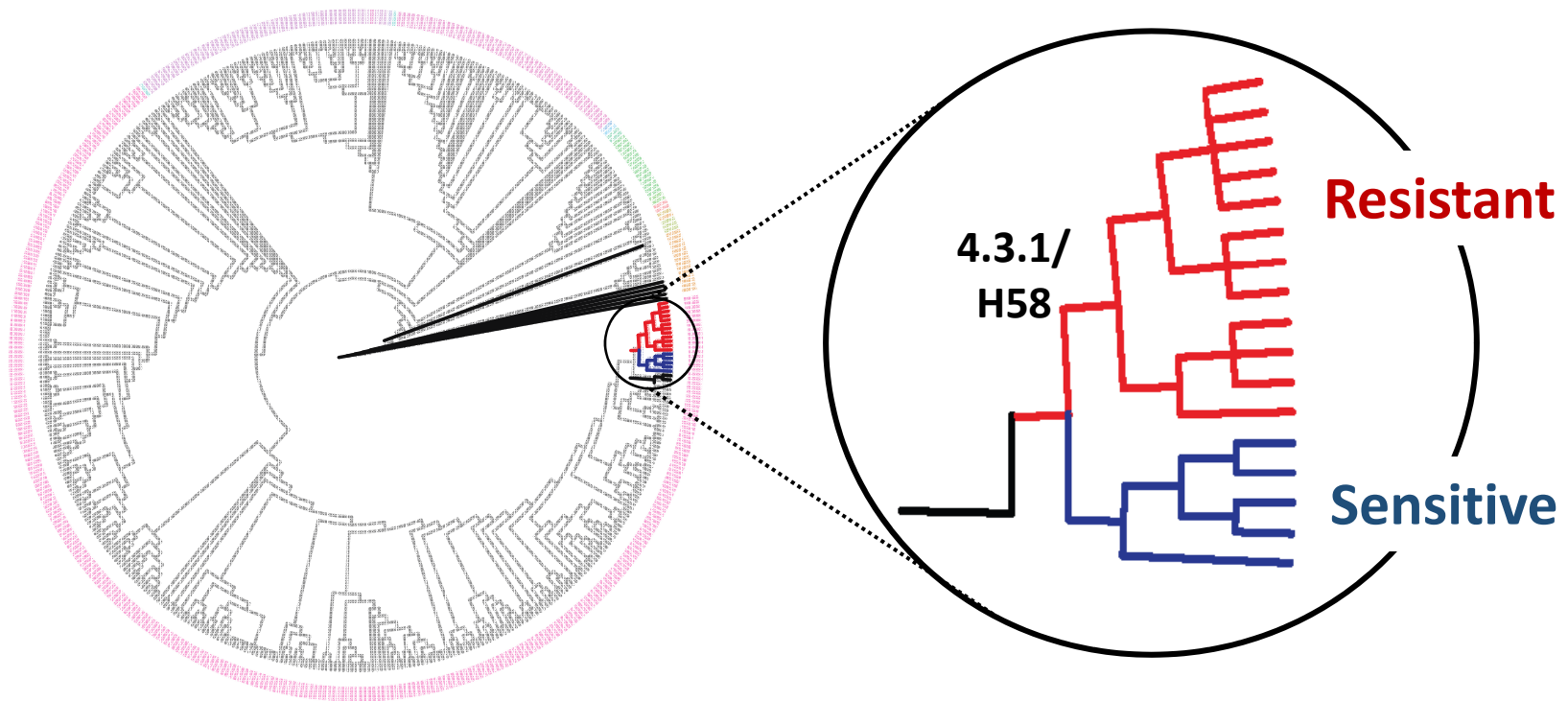
*From the IPD of Dhaka Shishu Hospital and Shishu Shasthya Foundation Hospital

What causes a Typhi strain to become azithromycin-resistant?

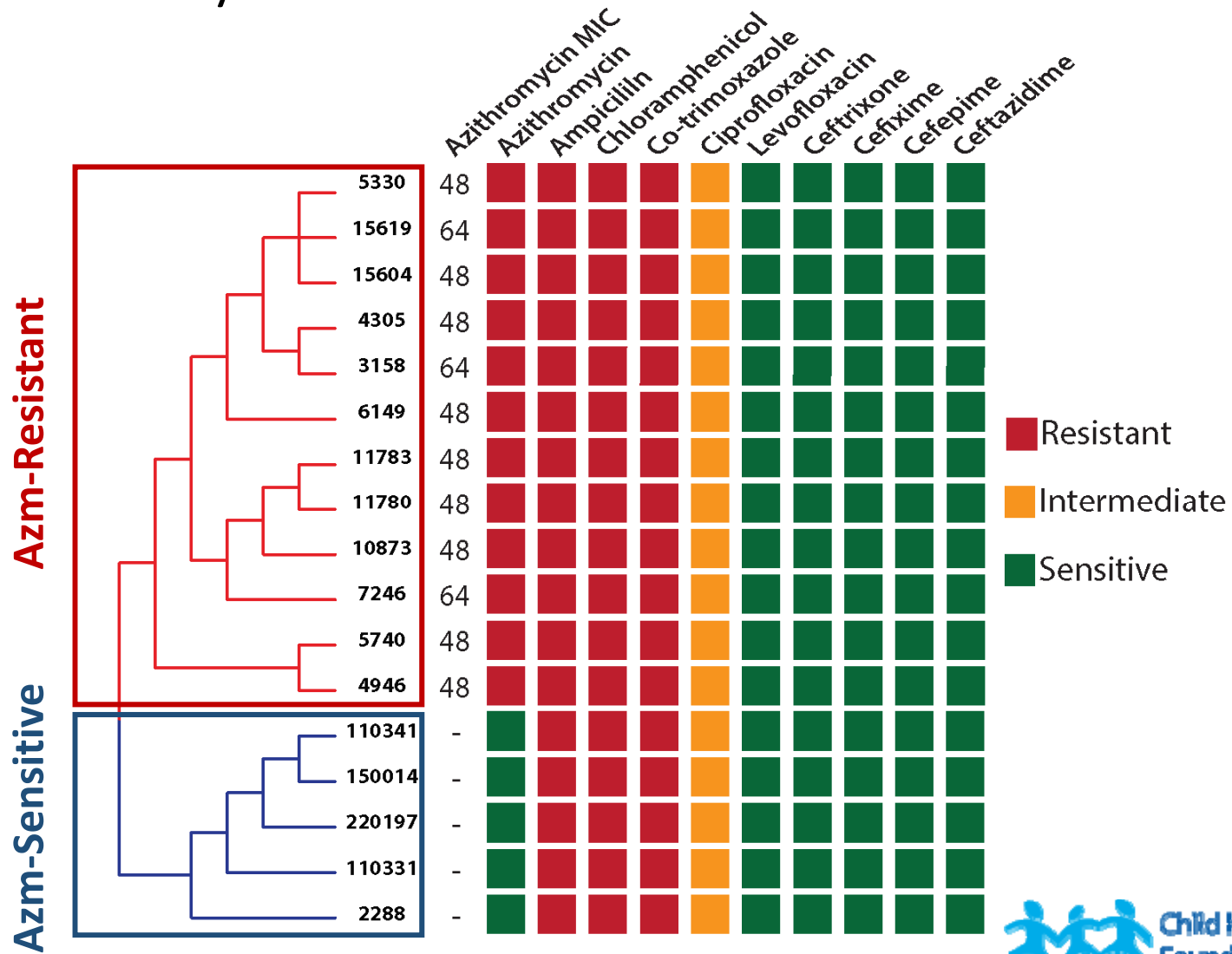


* Tanmoy et al, 2018, *mBio*

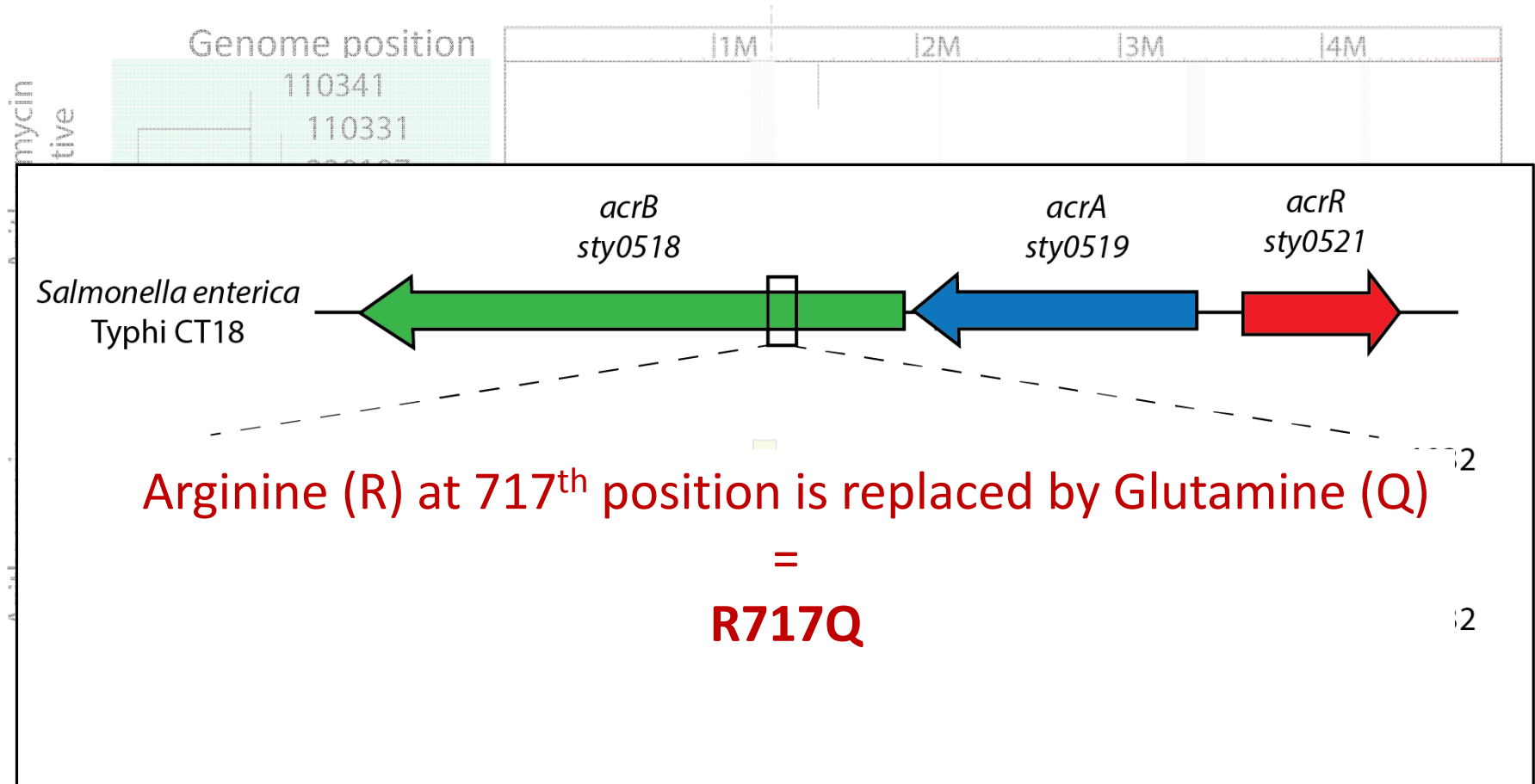
The azithromycin-resistant strains are closely related to each other



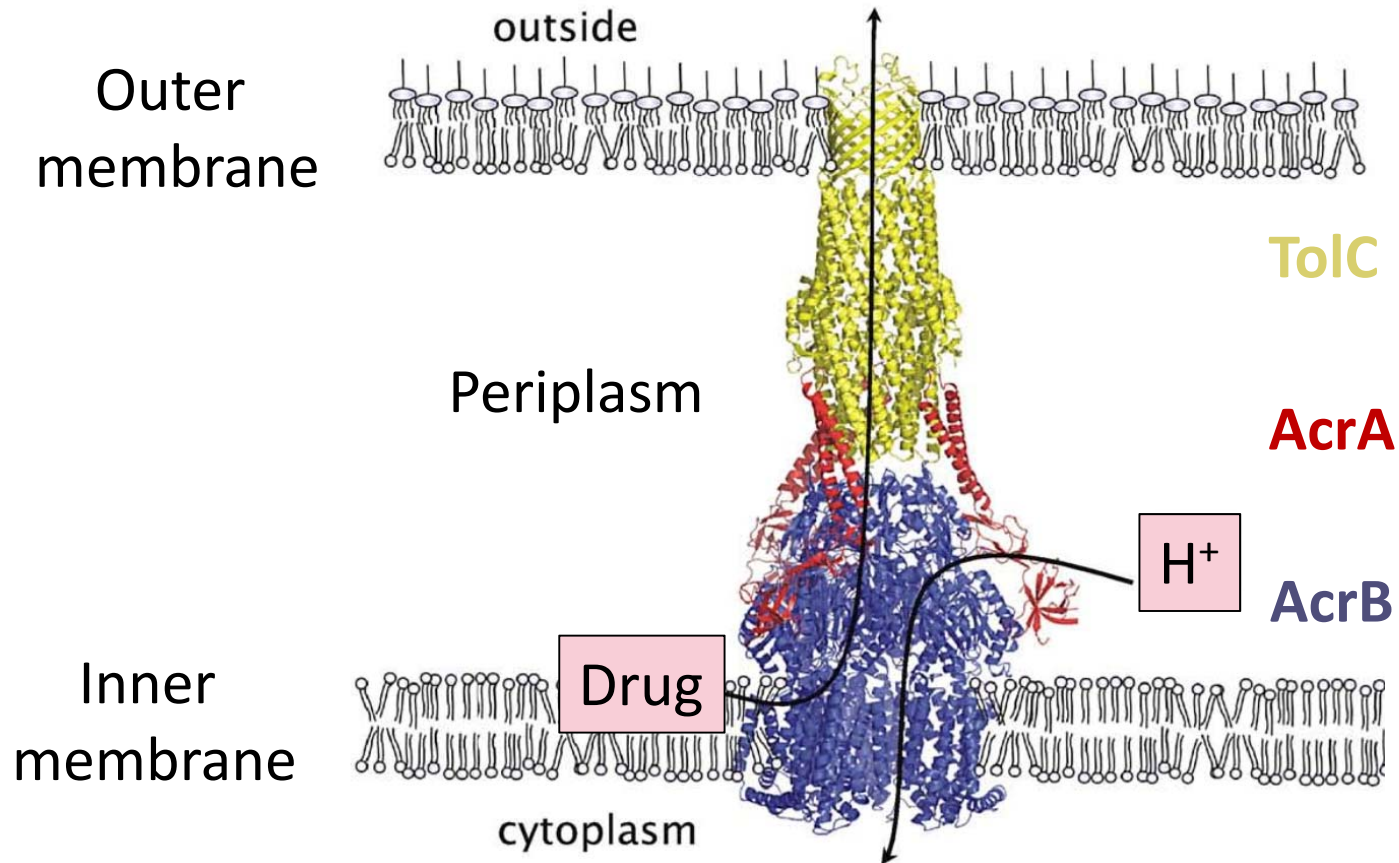
Antibiotic resistant patterns of azithromycin-resistant and sensitive strains



Whole genome SNP tree revealed 3 non-synonymous exclusive to resistance strains



AcrB-TolC drug efflux pump transports antibiotics out of bacterial cells



Adapted from Pos KM et al.
Biochimica et Biophysica Acta 2009

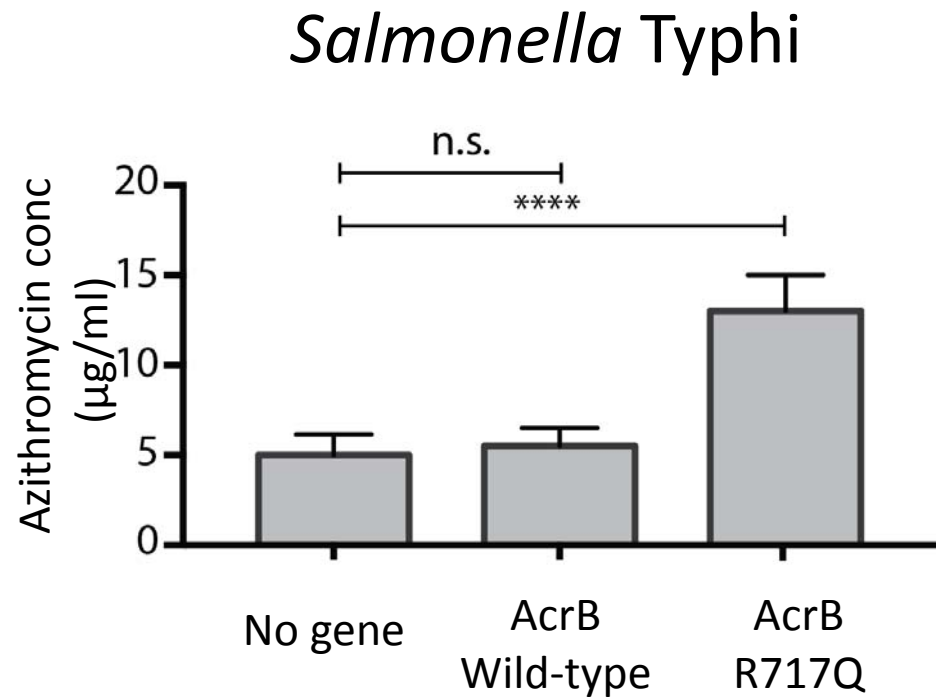
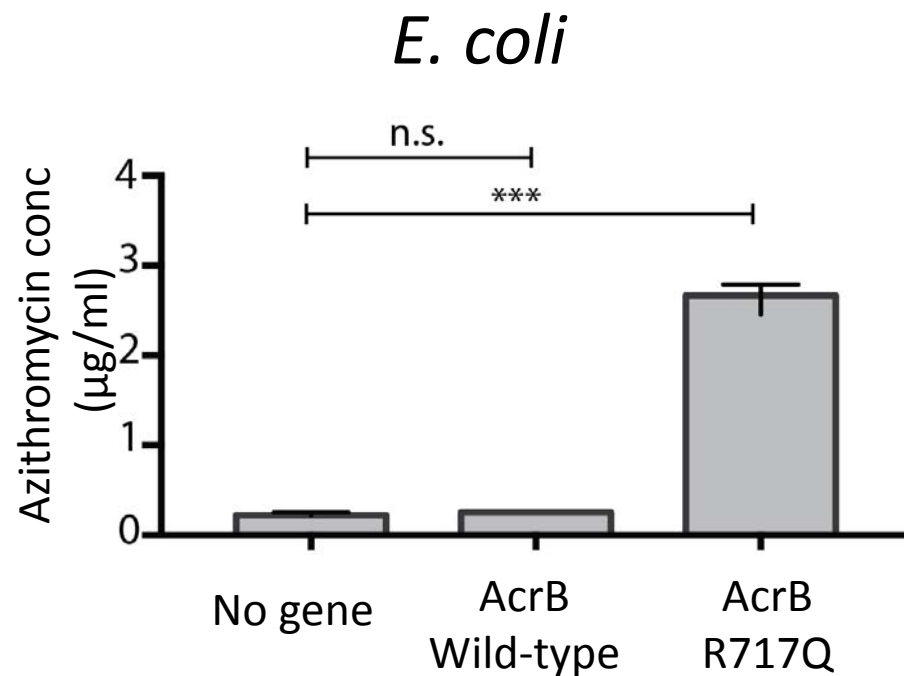
Hypothesis:

Mutation in AcrB R717 causes azithromycin-resistance.

What happens when we introduce these mutations into azithromycin-sensitive *E. coli* and Typhi strains?

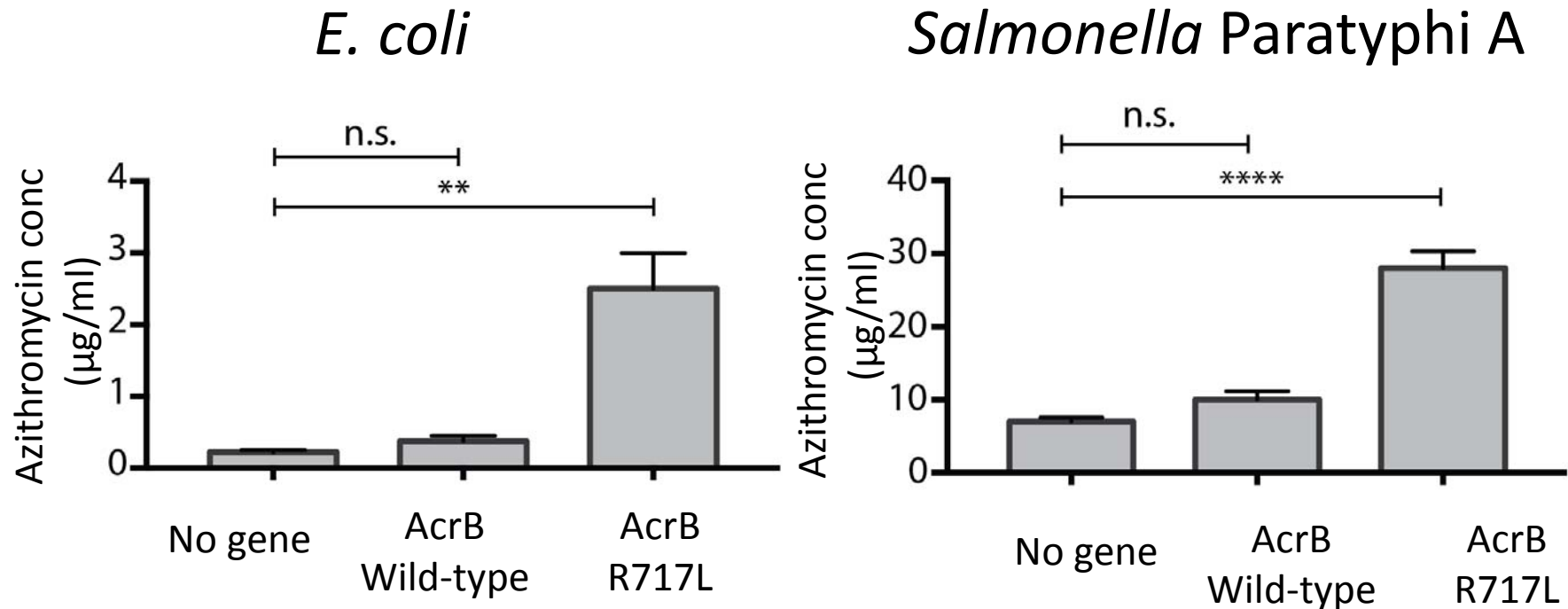


R717Q mutation makes azithromycin sensitive *E. coli* and Typhi strains resistant in the lab



Azithromycin resistant Paratyphi A strain also has a mutation at R717 which drives resistance

Between 2009 and 2016, **143 Paratyphi A isolates** were isolated and **1 was azithromycin resistant and it had R717L mutation.**



Immediate actions for antibiotic stewardship and interventions are imperative

- One point mutation can make a strain azithromycin resistant
 - The mutations leads to changes in a conserved arginine residue at position 717, which is present on the periplasmic drug entry cleft of AcrB
- With increase in azithromycin use, strains with R717 mutations may spread and lead to treatment failures.



Thank you.



Yogesh Hooda and Senjuti Saha made equal contributions.
We are thankful to Dr. Joseph Bondy-Denomy's lab for
hosting us in UCSF for a week to prove our hypothesis.



Coming to bioRxiv soon....



The mutation R717 is present on the periplasmic cleft of AcrB at the drug entry portal

