Molecular mechanisms of antimicrobial resistance and phylogenetic relationship of *Salmonella enterica* serovars from febrile patients in Yangon, Myanmar

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Myanmar
(Burma)
Yangon (Rangoon)

Background: enteric fever in Myanmar

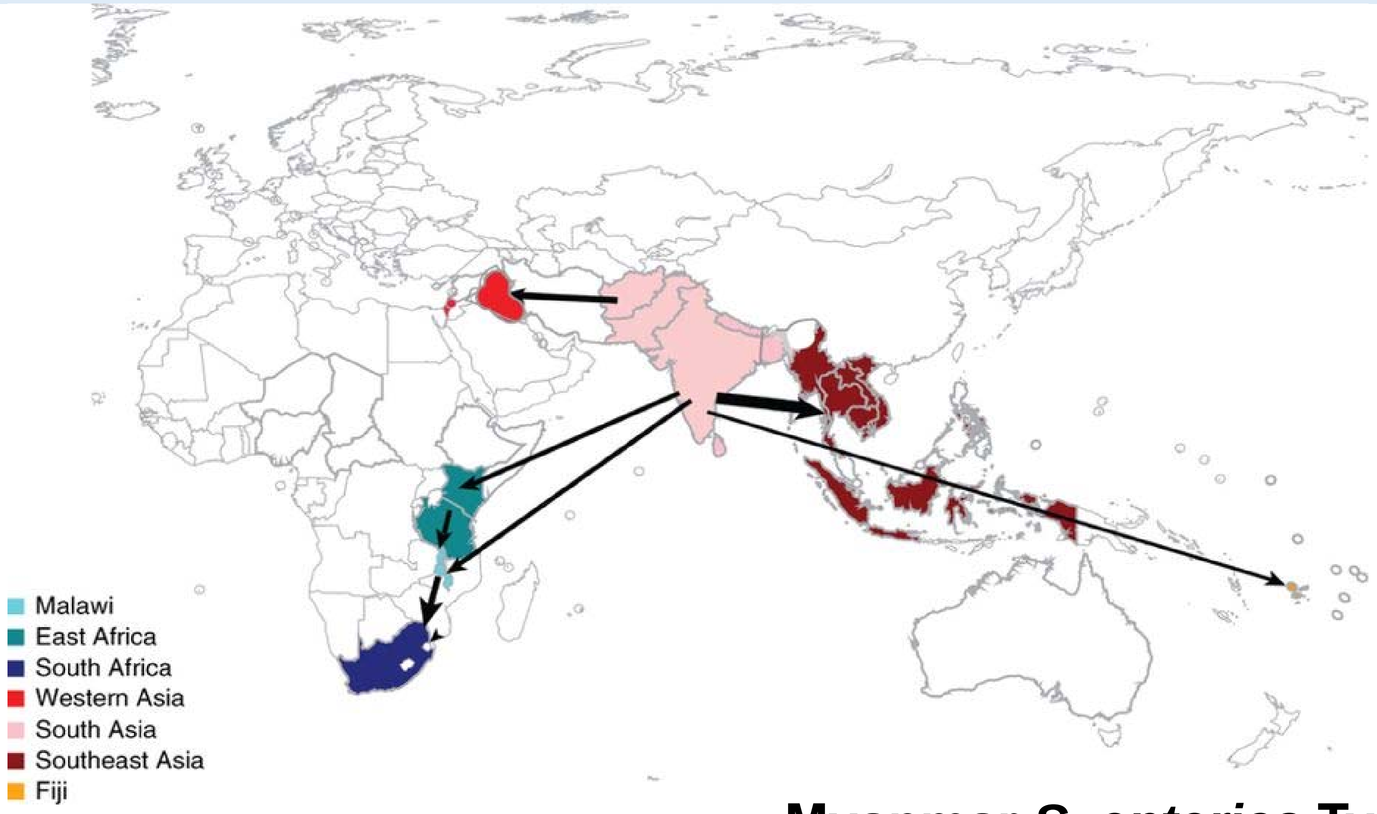
- **Endemic in Myanmar**
- **One of differential diagnoses of febrile illness >3 days**
- **Treatment trend**
  - **Chloramphenicol and/or ampicillin**
  - **Ciprofloxacin - began by the end of 1990s**
  - **Cephalosporins if unresponsive to ciprofloxacin**

Background: studies on *Salmonella* Typhi in Myanmar

Study year	Study place	Population	Antimicrobial resistance	Author
1996	Yangon	All ages	- Resistance to first line agents - No MDR	Htike, WW (Unpublished data)
1998-1999	Yangon	Paediatric (<12 years old)	- MDR	Shwe,TN et al
2000 *	Mandalay	All ages	- Resistance not found	Aye,TT et al
2012-2013	Mandalay	All ages	- MDR - nalidixic acid resistance (25%)	Thwe,SM et al
2014 ±	Yangon	Adolescent and adult (≥12 years old)	- No MDR - Ciprofloxacin resistance (50%)	Myat, TO et al

* Outbreak study;
± Retrospective study of gram-negative bloodstream isolates

Background: Global study of *Salmonella enterica* Typhi and traveller-associated Myanmar isolates



Myanmar *S. enterica* Typhi from travelers

- **subclade 4.3.1 (n=2)**
- **subclade 3.3.1 (n=2)**

Wong et al. *Nat. Genet.* 2015; 47: 632–639

Aims

- To isolate and identify *Salmonella enterica* serovars from blood cultures among febrile patients at two hospitals in Yangon
- To identify their AMR pattern and mechanisms of resistance
- To determine phylogenetic relatedness of *Salmonella enterica* serovars

Methods: participant enrolment

- **Study period:**
  - **5 October 2015 – 4 October 2016**

- **Study population:**
  - **adolescent and adult febrile patients ≥12 years old**

- **Study sites:**
  - **Yangon General Hospital (YGH)**
  - **A private Hospital**

Methods: laboratory evaluations

Yangon, Myanmar

Sample collection

Blood culture (BacT/ALERT)

Vitek2 automated system

- Isolate identification (ID)
- Antimicrobial susceptibility testing (AST)

Dunedin, New Zealand

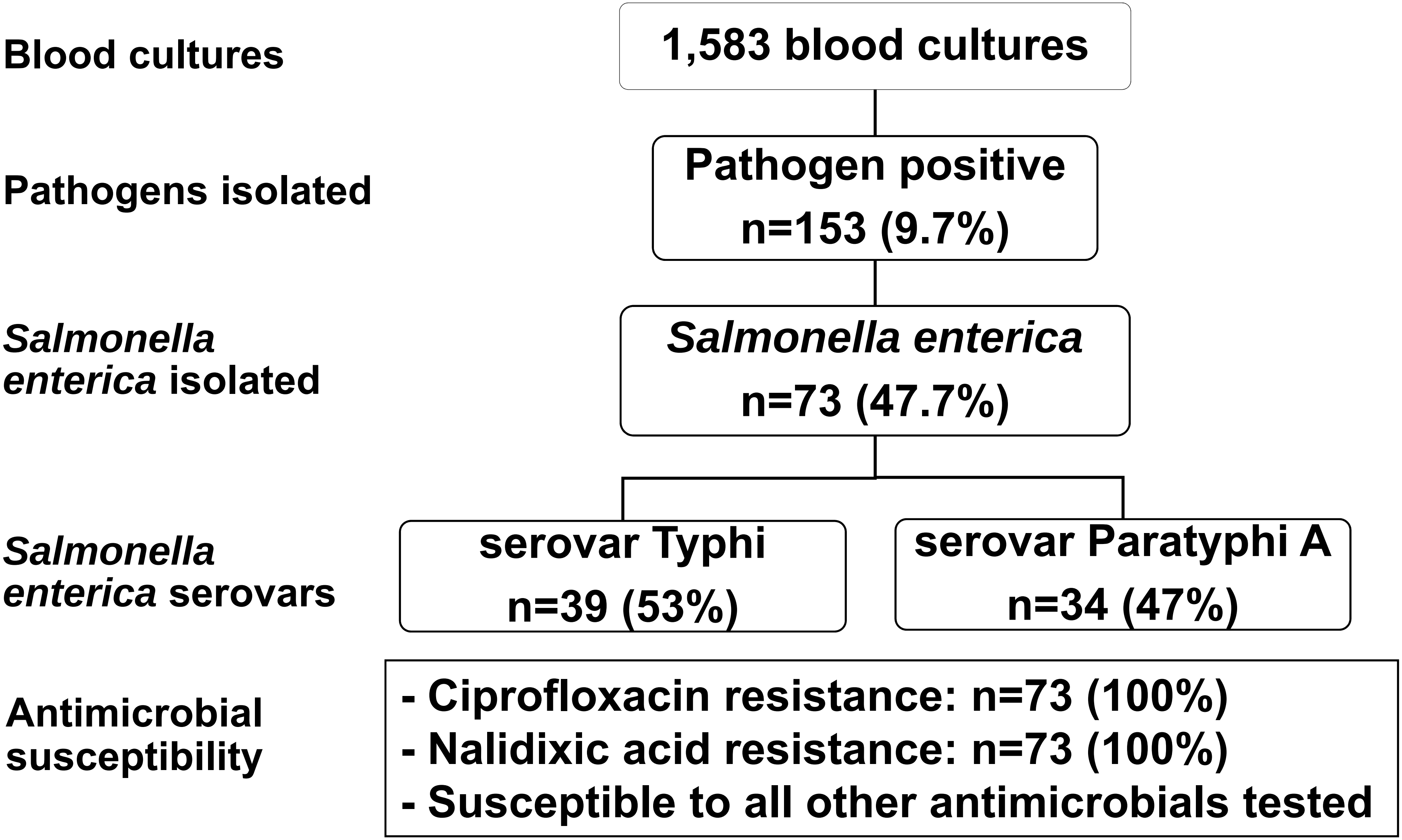
Confirmation of ID and AST

DNA extraction

Whole-genome sequencing (WGS)

- Serotype confirmation
- AMR mechanisms
- Phylogenetic analysis

Results: isolation, identification & antimicrobial susceptibility



Blood cultures

1,583 blood cultures

Pathogens isolated

Pathogen positive
n=153 (9.7%)

Salmonella enterica **isolated**

Salmonella enterica
n=73 (47.7%)

Salmonella enterica **serovars**

serovar Typhi
n=39 (53%)

serovar Paratyphi A
n=34 (47%)

Antimicrobial susceptibility

- **Ciprofloxacin resistance: n=73 (100%)**
- **Nalidixic acid resistance: n=73 (100%)**
- **Susceptible to all other antimicrobials tested**

Results: molecular mechanism of fluoroquinolone resistance

Minimum inhibitory concentrations vs. mutations among ciprofloxacin-resistant *Salmonella enterica* isolated from febrile patients in Yangon, Myanmar 2015 - 2016

Salmonella enterica serovar	Ciprofloxacin MIC (mg/L)	Isolates	Amino acid substitutions at QRDRs			
		no. (%)	*gyrA*	*gyrB*	*parC*	PMQR
S. enterica Typhi (n=39)	≥ 8.0	16 (41.0)	Ser83Phe Asp87Asn	ND	Ser80Ile	ND
	0.5 (or) 1.0	22 (56.4)	Ser83Phe	ND	ND	ND
	0.25	1 (2.6)	Ser83Phe	Ser464Phe	ND	ND
S. enterica Paratyphi A (n=34)	0.5 (or) 1.0	34 (100.0)	Ser83Phe	ND	Thr57Ser	ND

QRDR, quinolone-resistance determining region
PMQR, plasmid-mediated quinolone resistance

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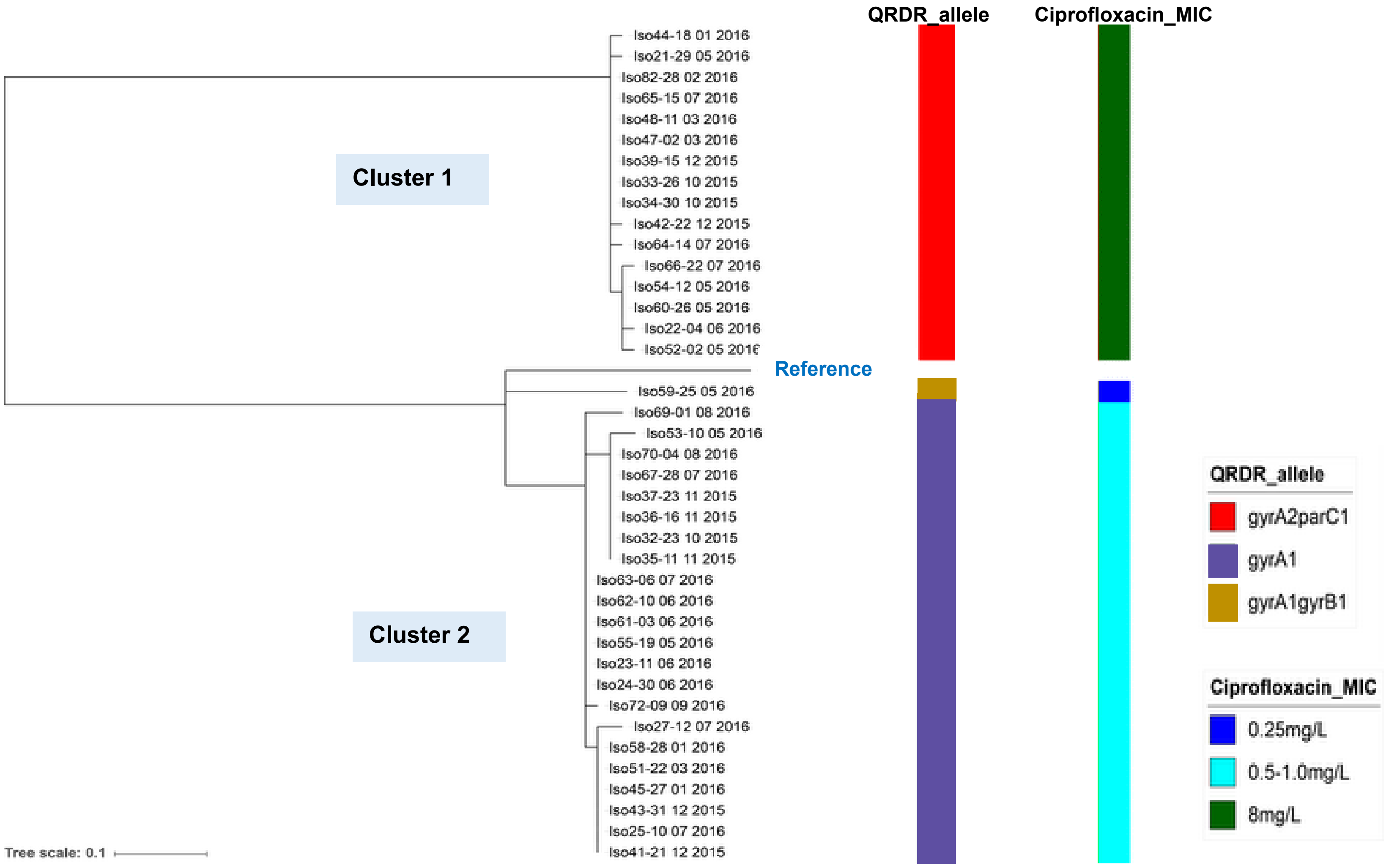
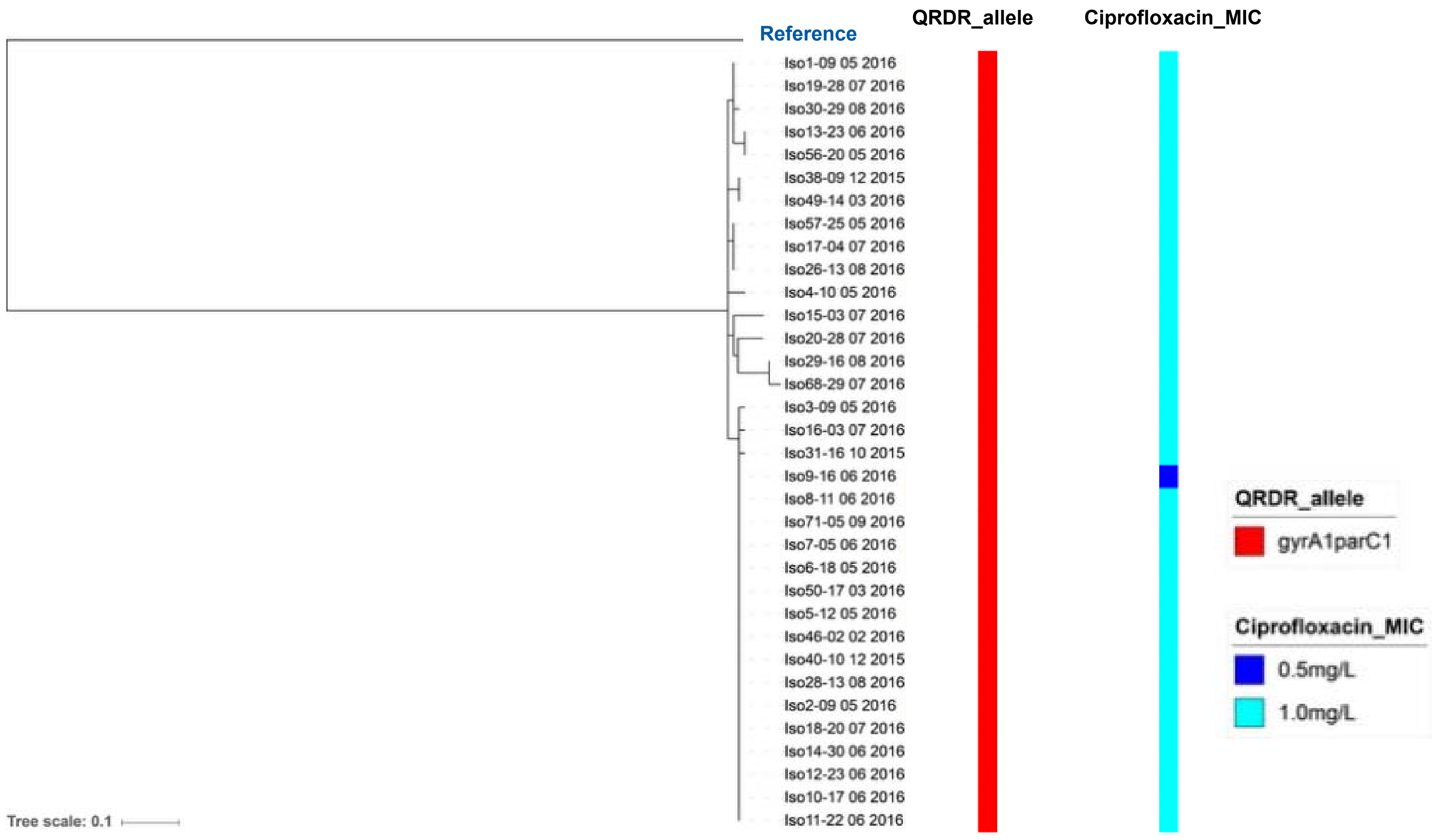
Results: phylogenetic analysis

Core SNP phylogeny of *Salmonella enterica* Typhi isolates from febrile patients in Yangon, Myanmar, 2015-2016



Core SNP phylogeny of *Salmonella enterica* Paratyphi A isolates from febrile patients in Yangon, Myanmar, 2015-2016



Phylogenetic analysis of *Salmonella enterica* ser. Typhi in the regional context

- **Analysed with:**
  - **previously sequenced isolates from neighbouring countries from South and South-East Asia regions**
  - **two Myanmar isolates with subclades 4.3.1**

- **Findings:**
  - **subclade 4.3.1 (H58): n=39 (100%)**
  - **Cluster 1 closely related to an *S. enterica* Typhi from India, 2012**
  - **Cluster 2 closely related to 2 traveler-associated Myanmar subclade 4.3.1 isolates from 2010 and 2011 and 2 MDR strains from India from 2012**

Conclusion

- Identified circulating strains of *Salmonella enterica,* 2015-2016
- Identified fluoroquinolone resistance in all
- Detected underlying genetic mechanism

- Forms the basis for future surveillance, epidemiological studies and research on enteric fever in Myanmar

- Highlights the need for continuous surveillance and typing

- Consideration for vaccine introduction if outbreak occur

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