Genomic and population epidemiology of the re-emerging *Shigella flexneri* 3a serotype in England, United Kingdom

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Background

Shigellosis is a gastrointestinal, sexually transmissible infection. It is caused by *Shigella* bacteria, commonly *Shigella sonnei* (*S. sonnei*) and *Shigella flexneri* (*S. flexneri*) in England. Its symptoms include fever and bloody diarrhoea. It is transmitted via the oral-faecal route: by food and sexual practices among men who have sex with men (MSM). Having declined after the 2009 – 2014 outbreak, *S. flexneri* 3a re-emerged in 2020 despite SARS-CoV-2 restrictions. Why did *S. flexneri* 3a re-emerge, and why instead of the other species and serotypes?

Genomic Epidemiology Questions

- Has *S. flexneri* 3a genetically changed to improve its survivability?

- Is there a change in the virulence determinants of *S. flexneri* 3a?

- Is there a change in the antimicrobial resistance of *S. flexneri* 3a?

Genomic Epidemiology Results
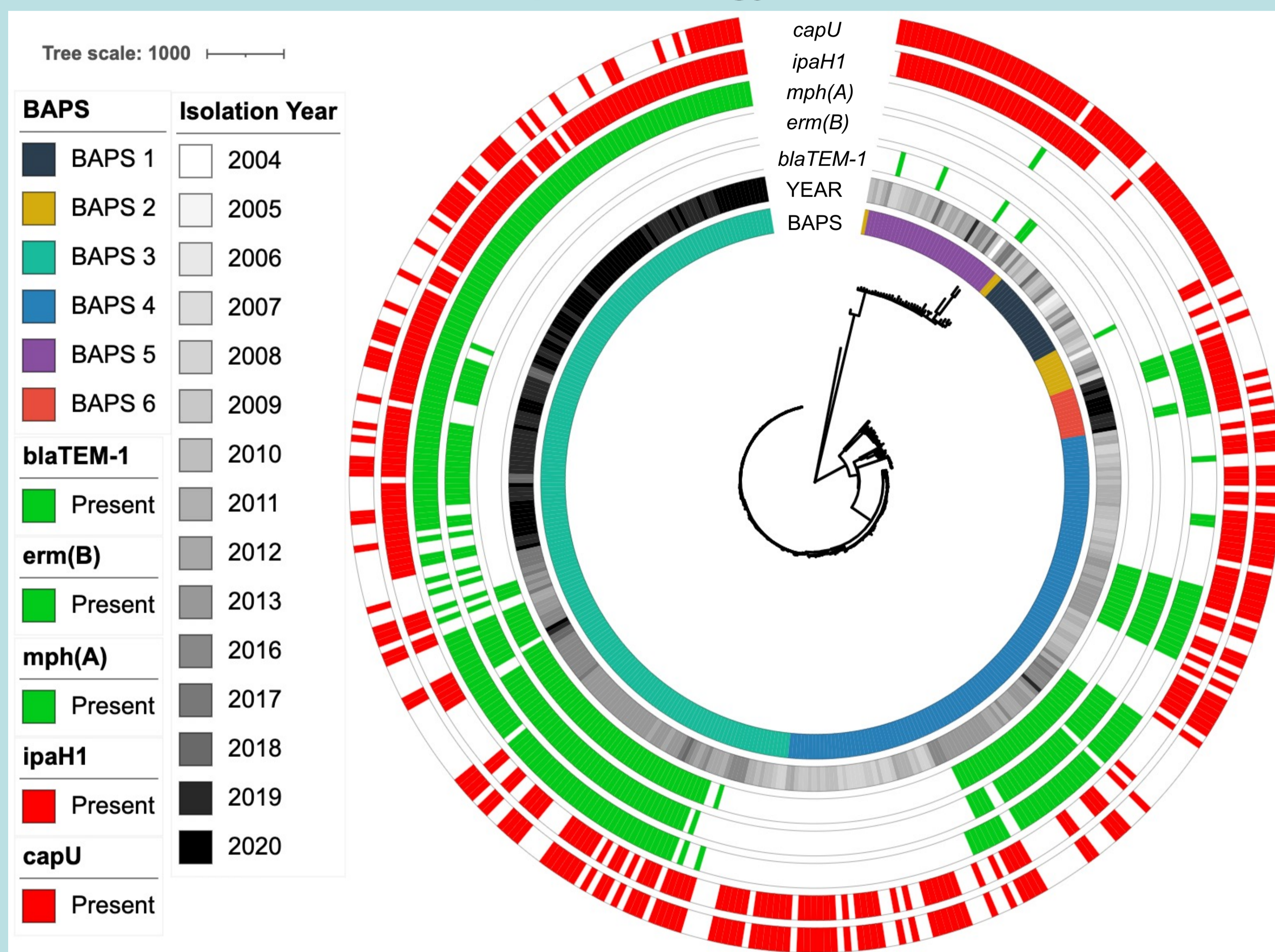
Figure 1. Phylogenetic tree (IQTree) visualised in iTOL showing the genomic characteristics of *Shigella flexneri* 3a samples between 2004 and 2020. AMR genes were identified with AMRFinderPlus. BAPS groups are clusters of isolates identified as being genomically by hierBAPS. Note the loss of *blaTEM-1* and *erm(B)* in more recent isolates, but retention of *mph(A)* and *ipaH1*. Note the interesting presence of the BAPS 6, 2019/2020 isolates.

Population Epidemiology Questions

- Has *S. flexneri* 3a re-emerged due to changes in travel?

- Has patient sexual and healthcare-seeking behaviours changed?

- Has the geographical and age distribution of shigellosis changed?

Population Epidemiology Results

Characteristic	2012-2013 n (%)	2019-2020 n (%)
Age		
16-34	95 (39.7)	54 (42.2)
35-64	136 (56.9)	67 (52.3)
65+	5 (2.1)	7 (5.5)
Unknown	3 (1.3)	0 (0.0)
Median age [IQR]	38.5 [30-46.5]	36 [29-45.5]
Region		
London	140 (58.6)	91 (71.1)
South East	36 (15.1)	20 (15.6)
North West	28 (11.7)	2 (1.6)
West Midlands	8 (3.4)	1 (0.8)
East of England	13 (5.4)	8 (6.3)
South West	6 (2.5)	4 (3.1)
Yorkshire & Humber	2 (0.8)	1 (0.8)
North East	4 (1.7)	1 (0.8)
East Midlands	2 (0.8)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)
Hospitalised		
Yes		18 (35.3)
No		33 (64.7)
Median nights in hospital [IQR]		2 [2-4]

Table 1. Summary of characteristics of the recent re-emergence of *S. flexneri* 3a cases among presumptive MSM and comparison to the original emergence, in England. Slightly younger median age, most isolates are still from patients in London. Hospitalisation data acquired from questionaries which were more likely to be received and completed by people already in hospital.

Combined Genomic & Population Epidemiology Results & Conclusions
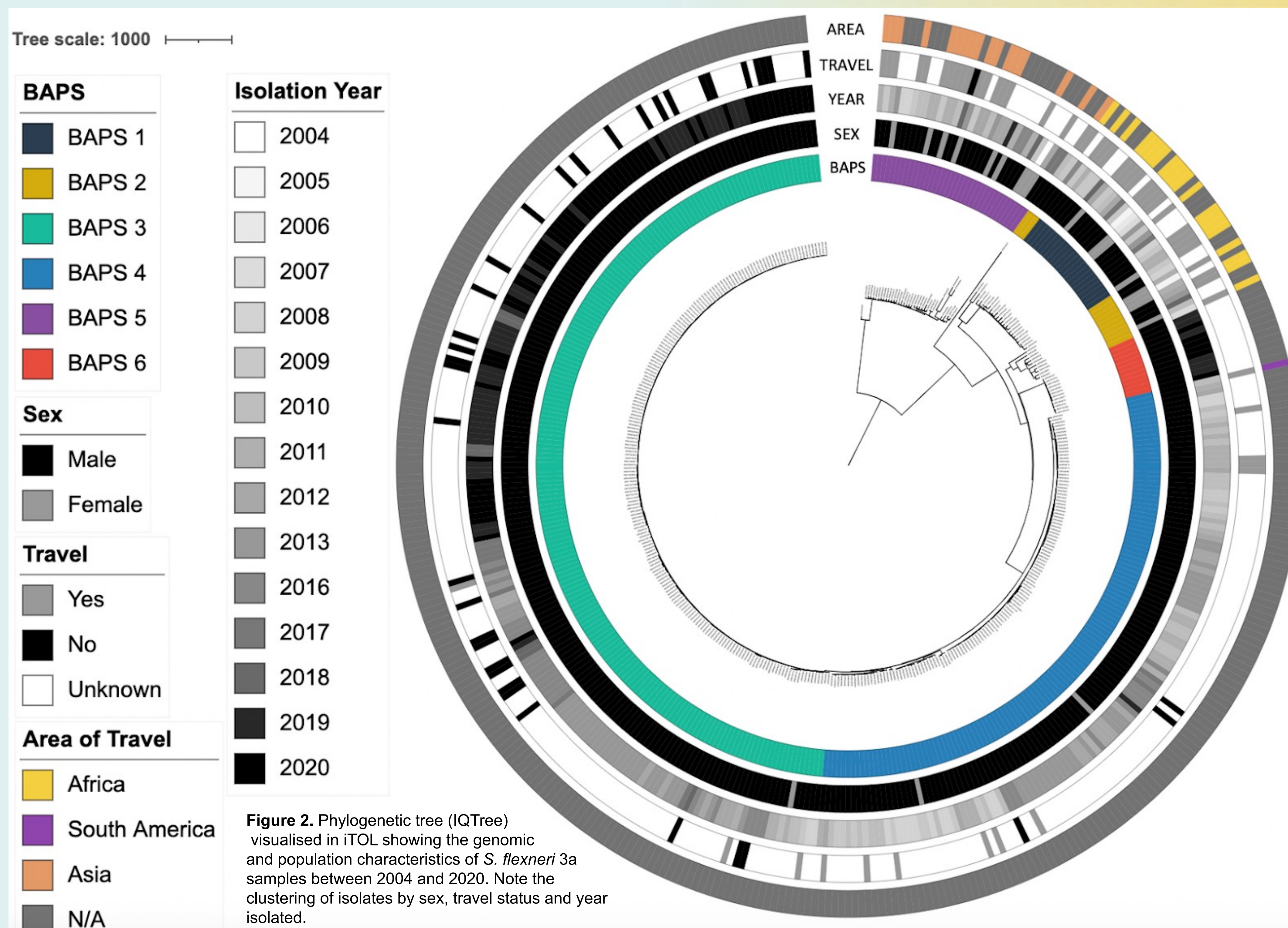
Figure 2. Phylogenetic tree (IQTree) visualised in iTOL showing the genomic and population characteristics of *S. flexneri* 3a samples between 2004 and 2020. Note the clustering of isolates by sex, travel status and year isolated.

- There is a distinct antimicrobial resistance (AMR) profile between pre-2015 isolates and post-2015 isolates.

- There is a distinct antimicrobial resistance (AMR) profile between travel associated and non-travel associated isolates.

- There has been a strong loss of *blaTEM-1*, moderate loss of *erm(B)* and a strong retention of *mph(A)*.

- There has been a recent strong retention of *ipaH1*. Could this contribute to pathogenicity and ability to invade?

- Minimum inhibitory concentrations (MICs) will be undertaken to investigate phenotypic associations with changes in the genotype.

References

Feldgarden M, Brover V, Gonzalez-Escalona N, Frye JG, Haendiges J, Haft DH, Hoffmann M, Pettengill JB, Prasad AB, Tillman GE, Tyson GH, Klimke W. AMRFinderPlus and the Reference Gene Catalog facilitate examination of the genomic links among antimicrobial resistance, stress response, and virulence. Sci Rep. 2021 Jun 16;11(1):12728. doi: 10.1038/s41598-021-91456-0. PMID: 34135355; PMCID: PMC8208984.

Minh, B., Schmidt, H., Chernomor, O., Schrempf, D., Woodhams, M., von Haeseler, A. and Lanfear, R., 2020. IQ-TREE 2: New Models and Efficient Methods for Phylogenetic Inference in the Genomic Era. *Molecular Biology and Evolution*, 37(5), pp.1530-1534.