The Dynamics of *bla*$_{\text{TEM}}$ Resistance Gene in *Salmonella* Typhi

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  - Flanking gene profiles
  - Association of the profiles with the data
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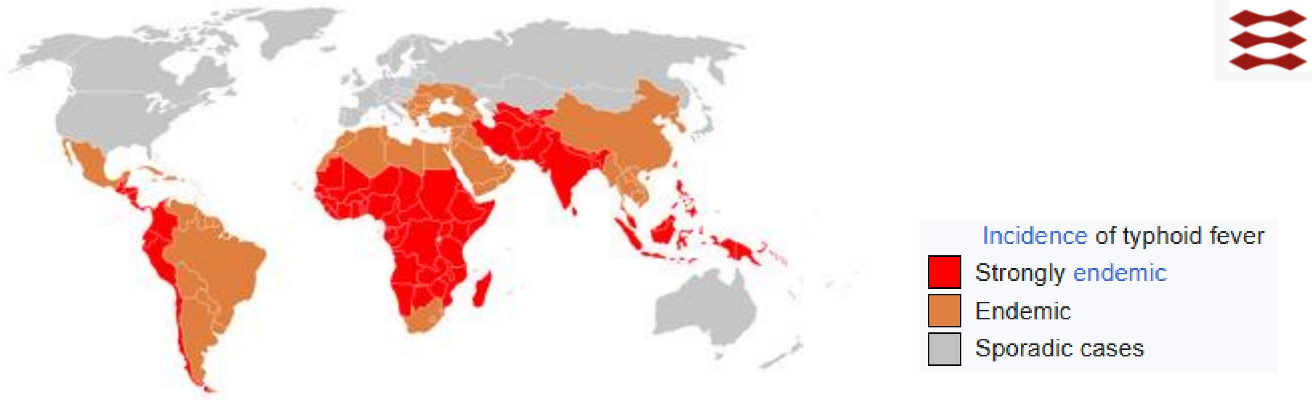
Introduction



- *S*. Typhi -> Typhoid
- 9 million people illness and 110,000 people death (WHO, 2019)
  - restricted infection in human
  - contaminated water and food
- more resistance -> more complicated treatment
- still a major worldwide public health concern
  - In USA, 80% of these cases are from travelers returning from an endemic region.
  - 1% to 5% of patients will become chronic carriers despite adequate antimicrobial therapy

Typhoid (who.int) https://www.ncbi.nlm.nih.gov/books/NBK519002/

Antibiotic resistance in *S.* Typhi

MDR / XDR / CipR

bla$_{\text{TEM}}$

(most common of beta-lactamase)

-201 variants

https://elifesciences.org/articles/85867

Objective

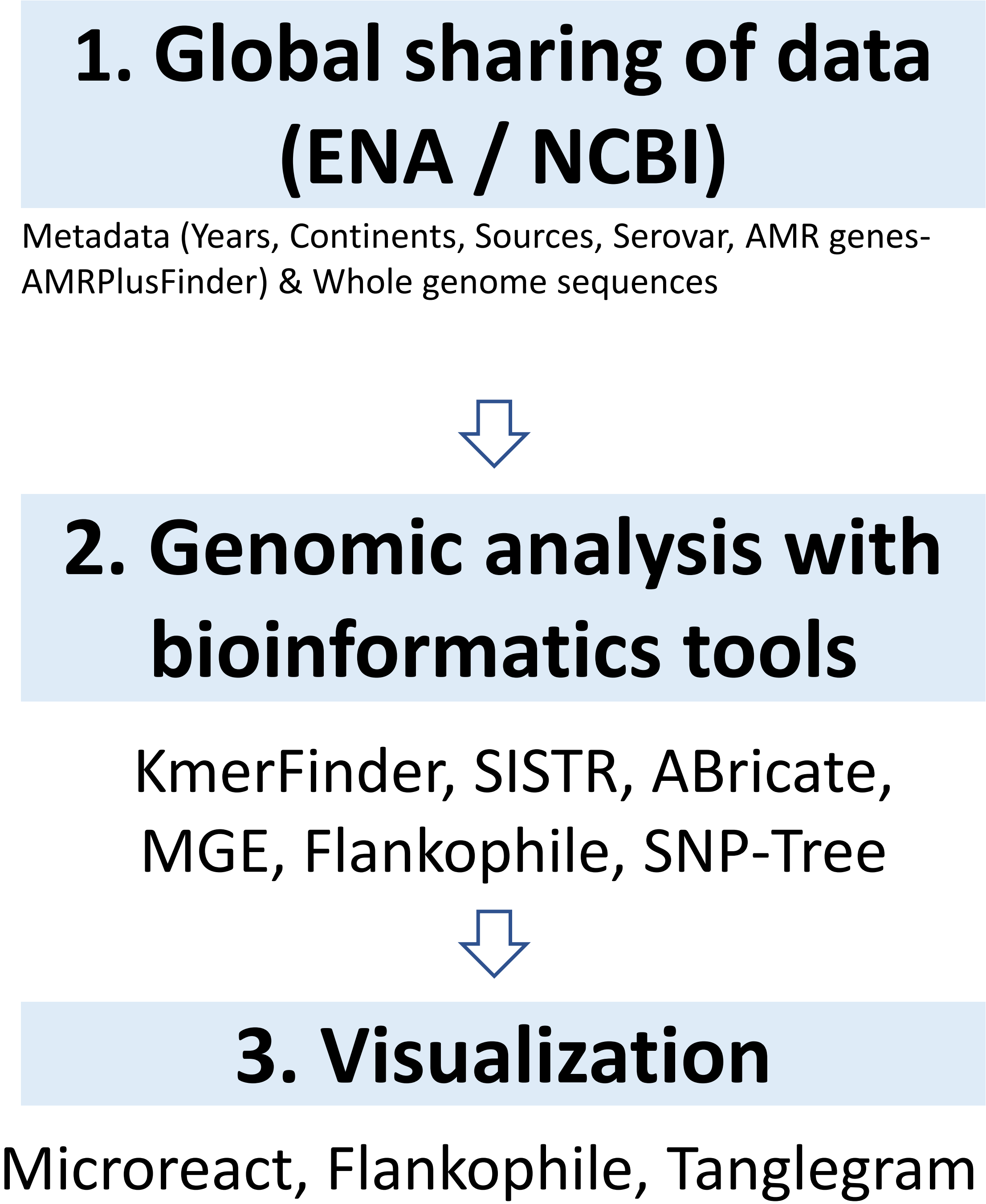
1) investigate dynamics of *bla*$_{\text{TEM}}$ gene in *S*. Typhi through flanking gene profiles

2) find association of the profiles with

    -sample metadata (year, country)

    -analyzed genomic data (genotype, ARGs and MGEs)

Methods



1. Global sharing of data (ENA / NCBI)

Metadata (Years, Continents, Sources, Serovar, AMR genes-AMRPlusFinder) & Whole genome sequences

⇩

2. Genomic analysis with bioinformatics tools

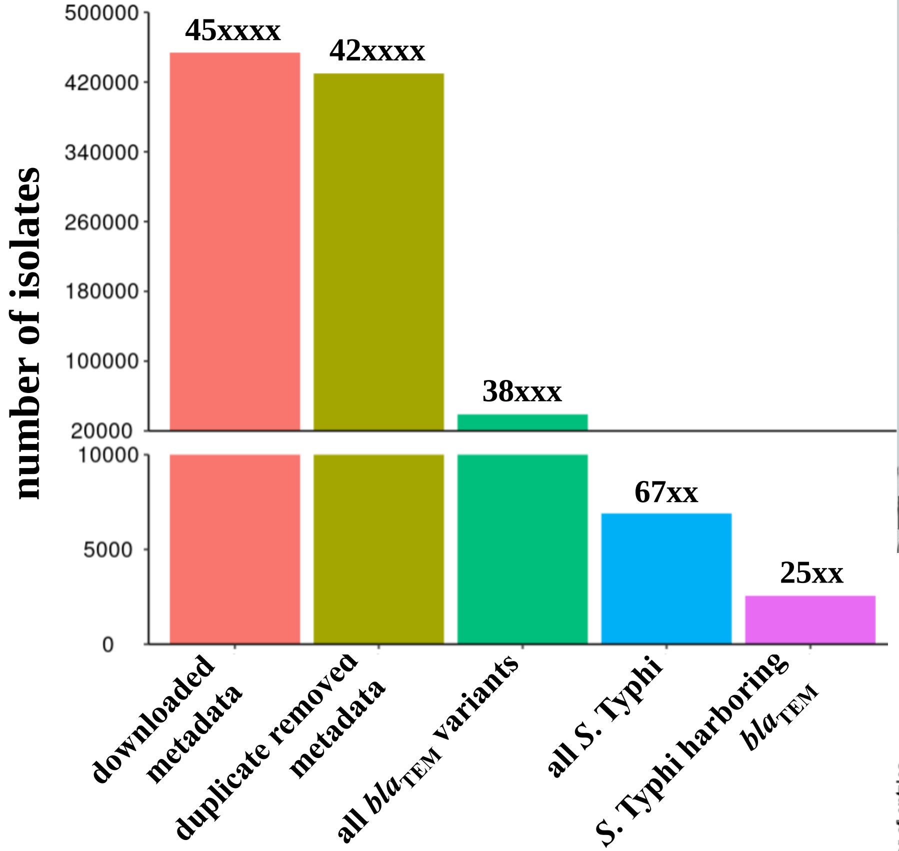
KmerFinder, SISTR, ABricate, MGE, Flankophile, SNP-Tree

⇩

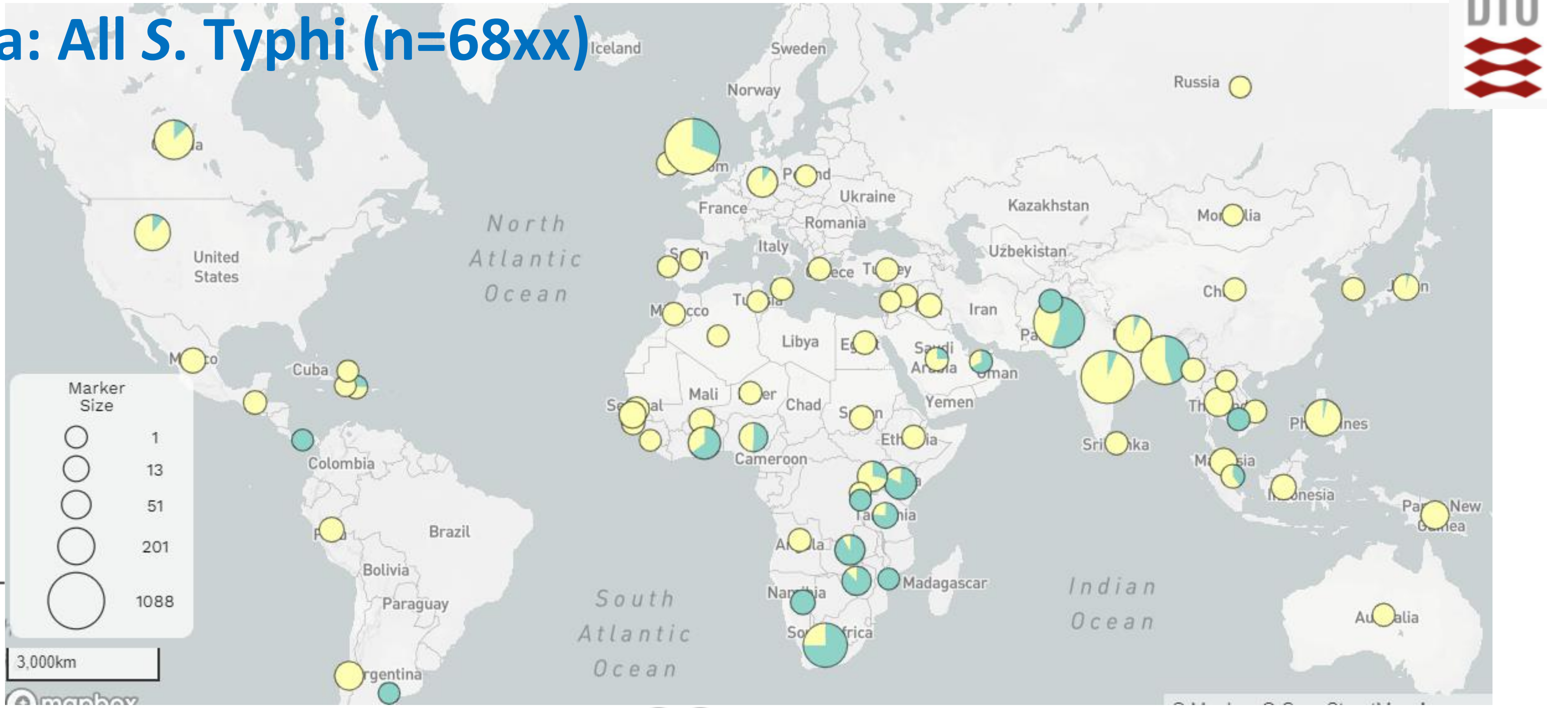
3. Visualization

Microreact, Flankophile, Tanglegram

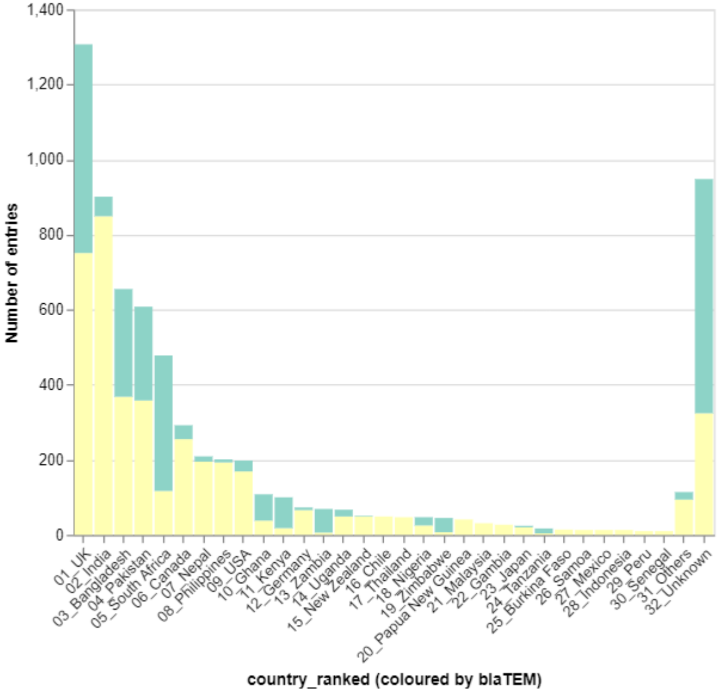
Overview of downloaded metadata: All *S*. Typhi (n=68xx)



selection of *Salmonella* Typhi harboring bla_{TEM} isolates



world map (colored by bla_{TEM})

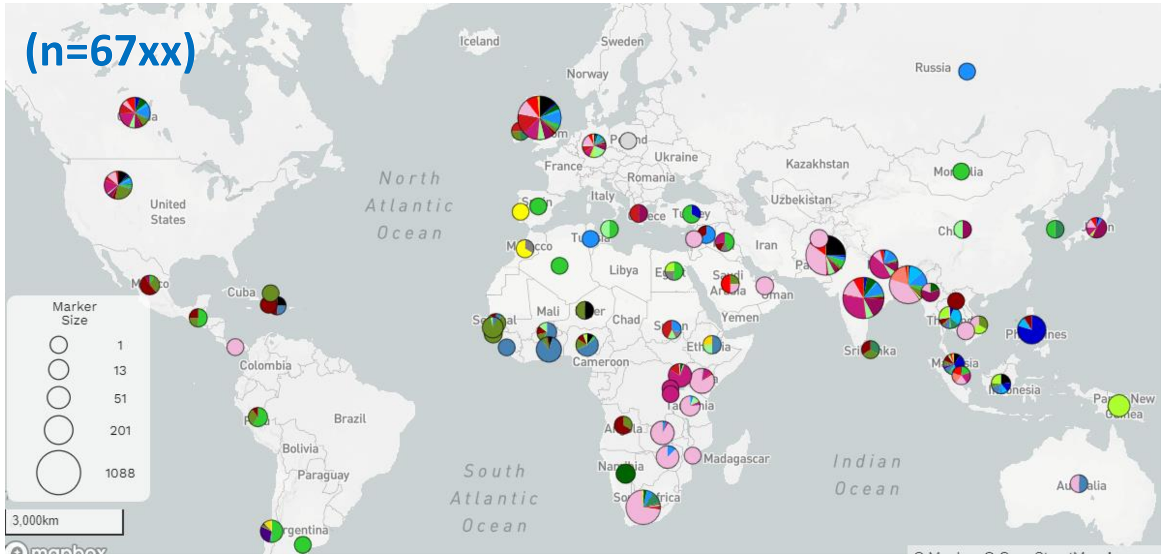


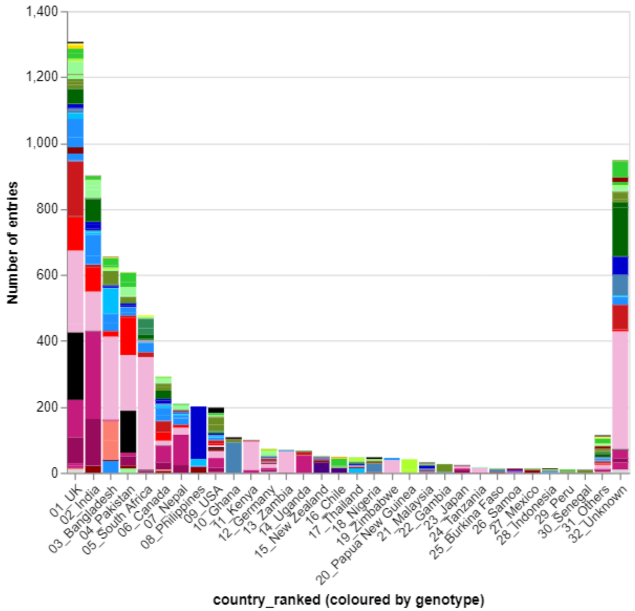
Legend : bla_{TEM} variant detection

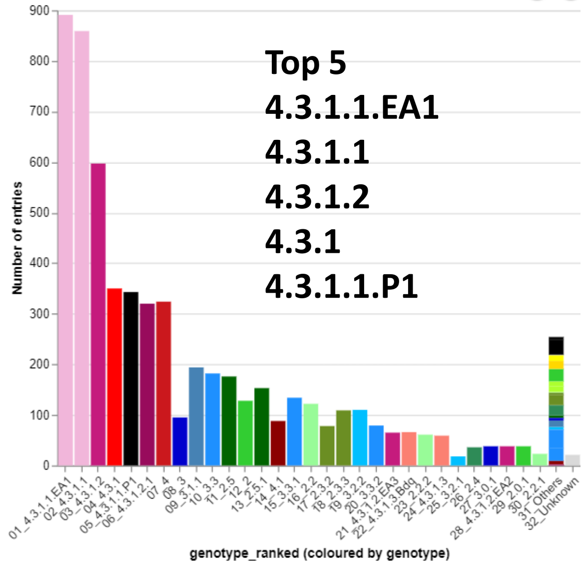
🟩 **Presence**

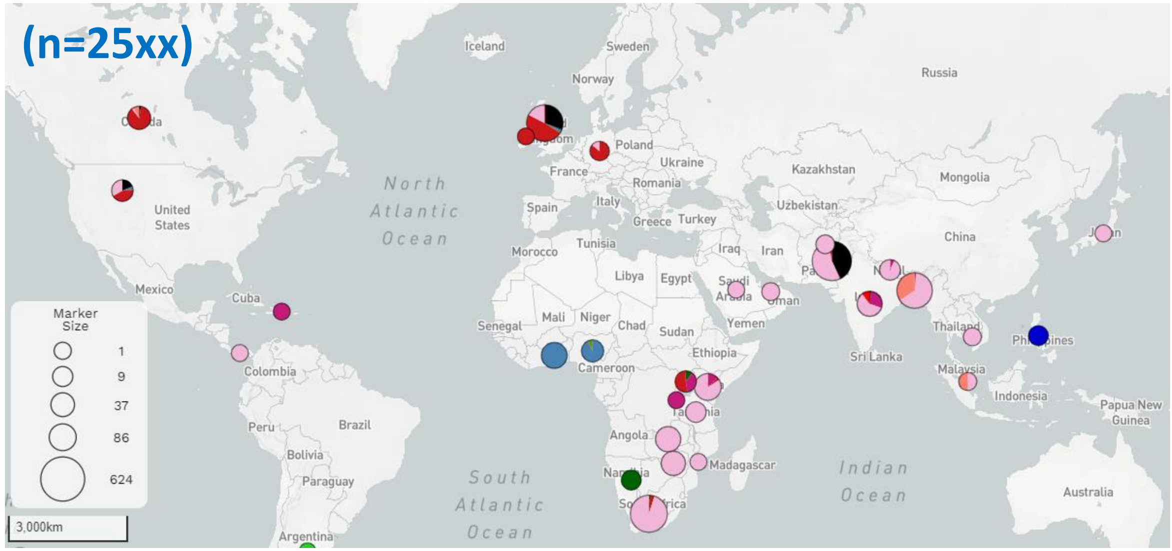
🟨 **Absence**

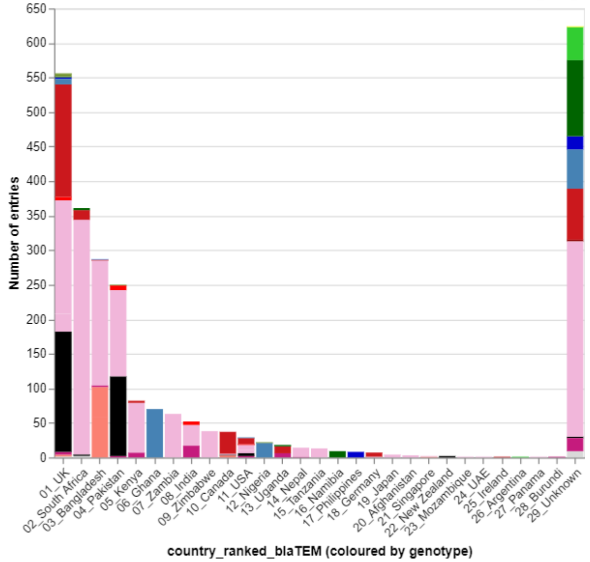
Overview of genotypes of *S*. Typhi [6870 vs 25xx]

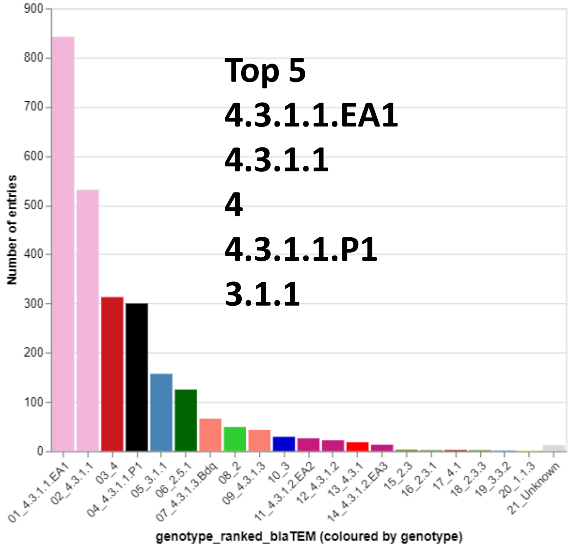

(n=67xx)



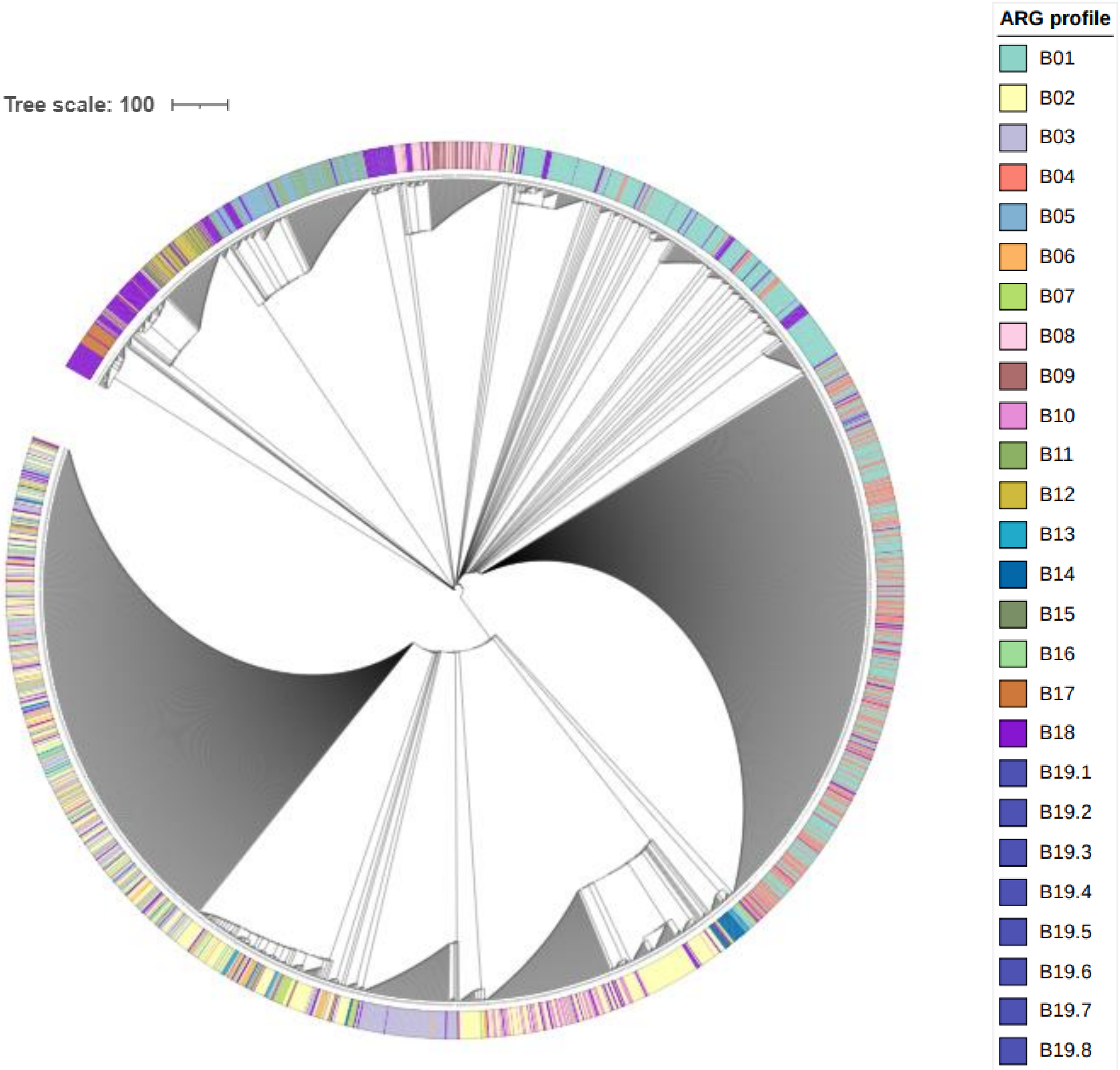

Top 5
4.3.1.1.EA1
4.3.1.1
4.3.1.2
4.3.1
4.3.1.1.P1


(n=25xx)




Top 5
4.3.1.1.EA1
4.3.1.1
4
4.3.1.1.P1
3.1.1

Overview of ARG profiles of *S*. Typhi harboring *bla*$_{\text{TEM}}$



B01__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA7*, *gyrA*[S83F], *sul1*, *sul2*

B02__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA7*, *sul1*, *sul2*

B03__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA7*, *sul1*, *sul2*, *tet*(B)

B04__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{CTX-M-15}}$, *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA7*, *gyrA*[S83F], *qnrS1*, *sul1*, *sul2*

B05__*bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA15*, *sul1*, *tet*(B)

B06__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA7*, *gyrA*[S83F], *sul1*, *sul2*, *tet*(B)

B07__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA7*, *gyrA*[S83Y], *sul1*, *sul2*

B08__*bla*$_{\text{TEM-1B}}$, *gyrA*[S83Y], *qnrS1*, *sul2*, *tet*(A)

B09__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA7*, *gyrA*[S83Y], *sul1*, *sul2*, *tet*(B)

B10__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA7*, *dfrA14*, *qnrS1*, *sul1*, *sul2*, *tet*(A)

B11__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *dfrA14*, *gyrA*[S83Y], *sul2*, *tet*(A)

B12__*bla*$_{\text{TEM-1B}}$, *dfrA7*, *gyrA*[S83F], *sul1*

B13__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *dfrA14*, *sul2*

B14__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA7*, *gyrB*[S464F], *sul1*, *sul2*, *tet*(B)

B15__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *dfrA7*, *gyrA*[S83F], *sul1*, *sul2*, *tet*(B)

B16__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA7*, *gyrA*[D87N], *sul1*, *sul2*

B17__*aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *catA2*, *dfrA7*, *mdsA*, *mdsB*, *sul1*, *sul2*, *tet*(A)

B18__Others: number of each profile < 12

B19.1__Others: *bla*$_{\text{TEM-135}}$

B19.2__Others: *bla*$_{\text{TEM-135}}$, *farB*, *norM*, *tet*(M)

B19.3__Others: *bla*$_{\text{TEM-35}}$, *erm(B)*, *gyrA*[S83Y], *mph*(A)

B19.4__Others: *bla*$_{\text{TEM-1A}}$, *gyrA*[S83F]

B19.5__Others: *bla*$_{\text{TEM-116}}$, *gyrA*[S83Y]

B19.6__Others: *aadA1*, *aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-104}}$, *catA1*, *dfrA1*, *dfrA15*, *sul1*, *sul2*

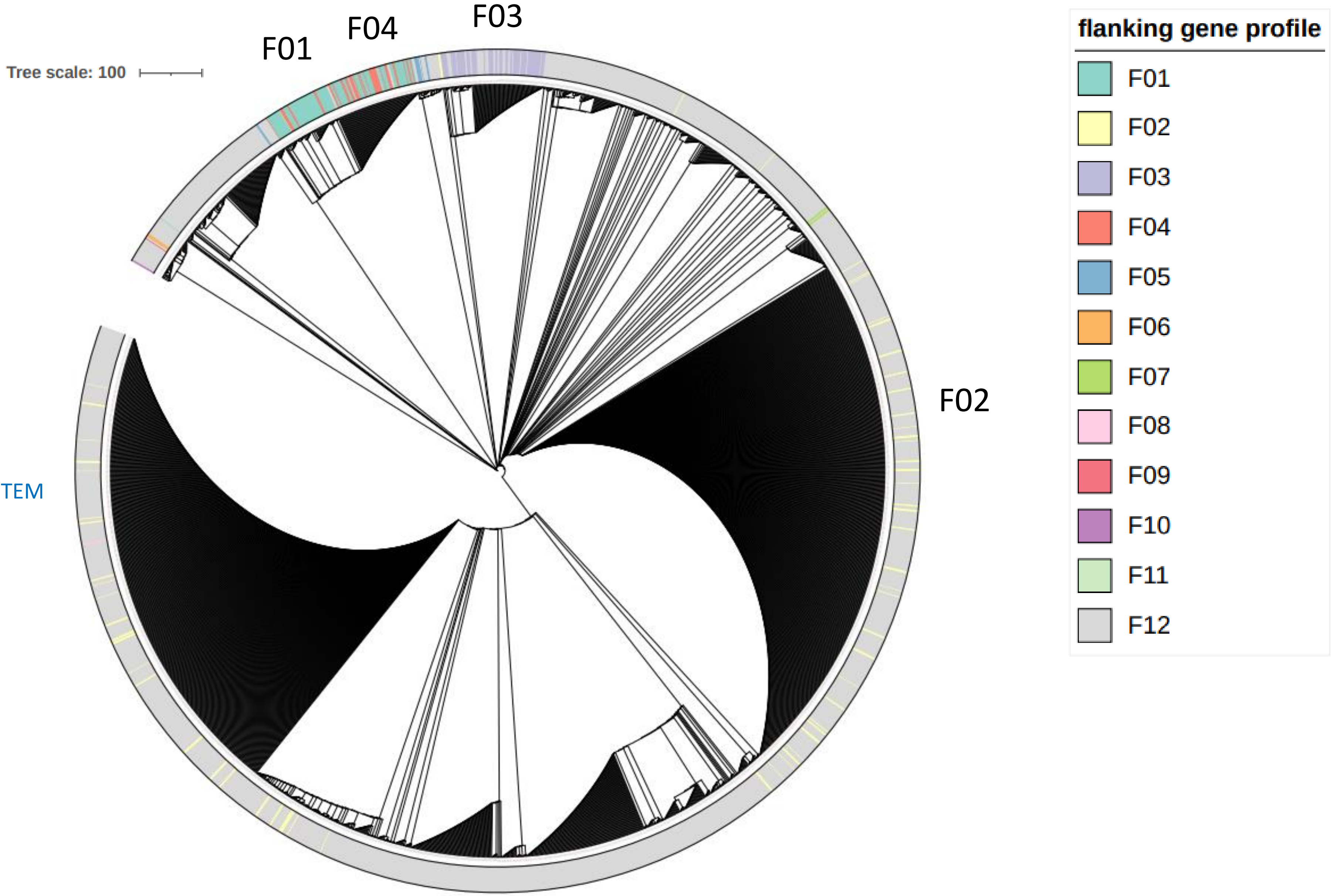
B19.7__Others: *bla*$_{\text{CTX-M-15}}$, *bla*$_{\text{TEM-35}}$, *gyrA*[S83F], *mph*(A), *qnrS1*

B19.8__Others: *bla*$_{\text{TEM-10}}$, *catA1*, *dfrA15*, *sul1*, *tet*(B)

Flanking gene profiles (F) showing in SNP Tree

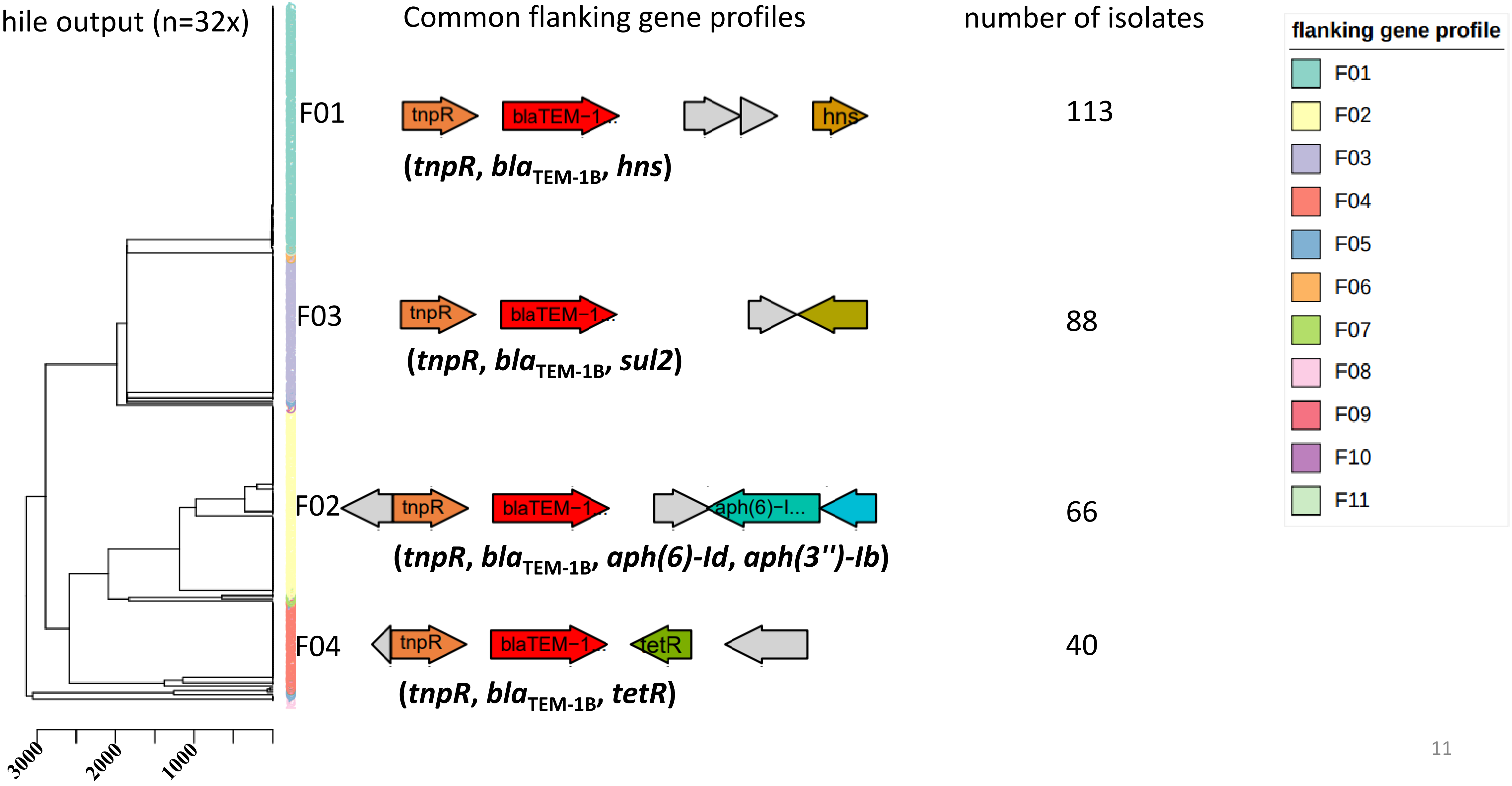
Flankophile output
- as flanking gene profiles
- 32x / 25xx (12.8%)
- 12 total profiles
- 4 common profiles

SNP Tree
- 25xx *S.* Typhi harboring *bla*$_{\text{TEM}}$



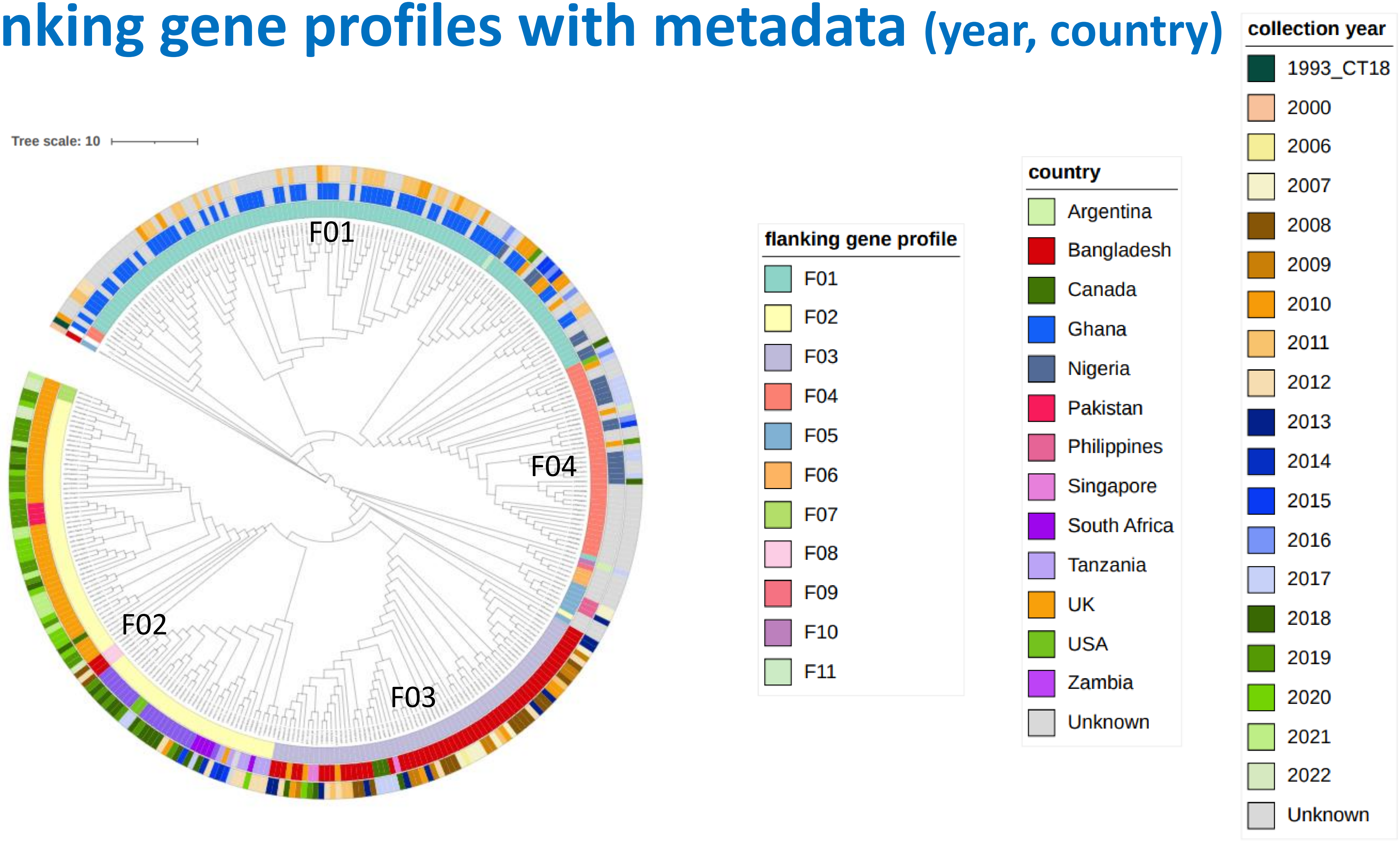
Common flanking gene profiles

Flank length upstreams and downstreams stting: “2000 bp“



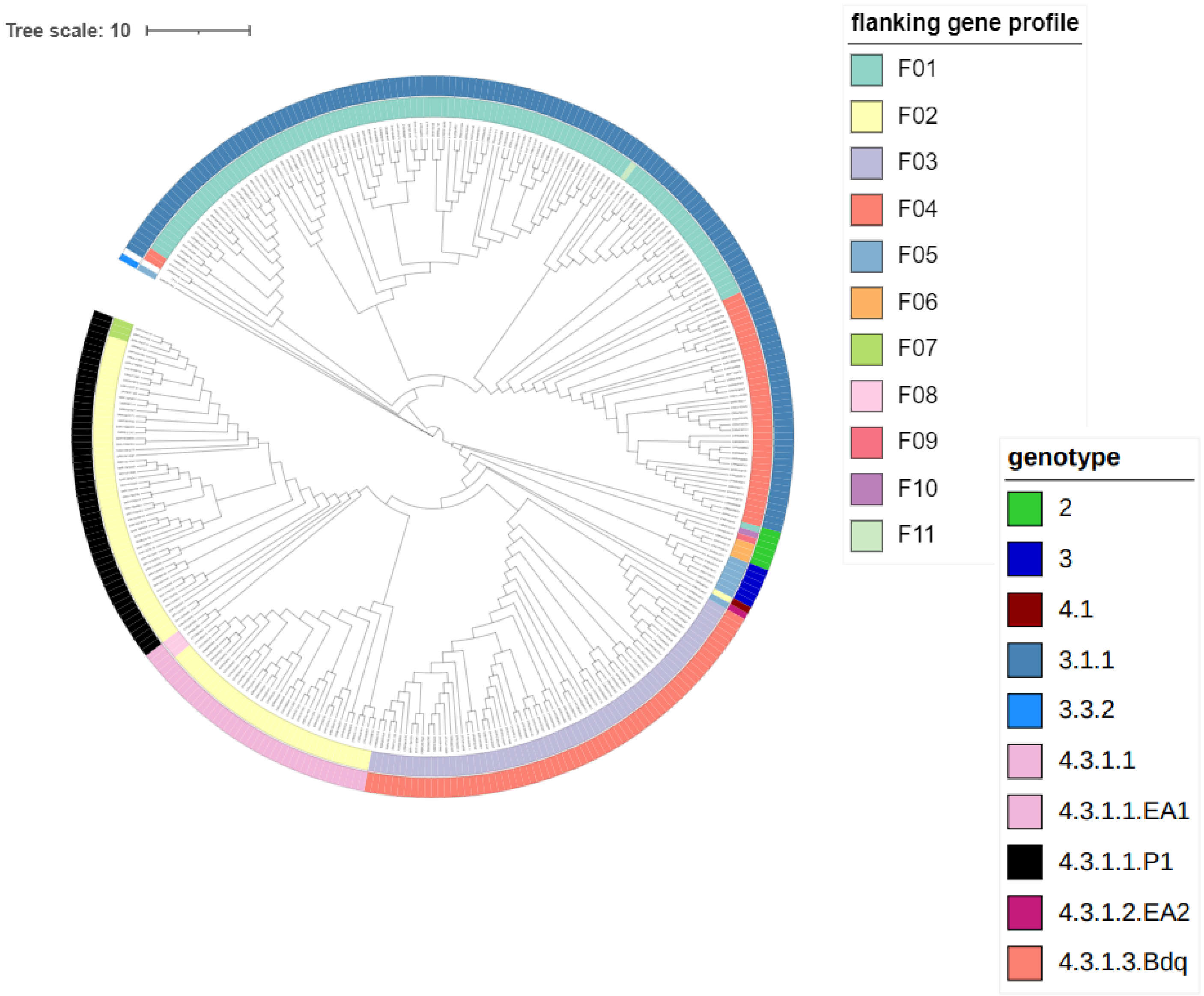
flankophile output (n=32x)	Common flanking gene profiles	number of isolates
F01	**(*tnpR*, *$bla_{\text{TEM-1B}}$*, *hns*)**	113
F03	**(*tnpR*, *$bla_{\text{TEM-1B}}$*, *sul2*)**	88
F02	**(*tnpR*, *$bla_{\text{TEM-1B}}$*, *aph(6)-Id*, *aph(3'')-Ib*)**	66
F04	**(*tnpR*, *$bla_{\text{TEM-1B}}$*, *tetR*)**	40

Flanking gene profiles with metadata (year, country)



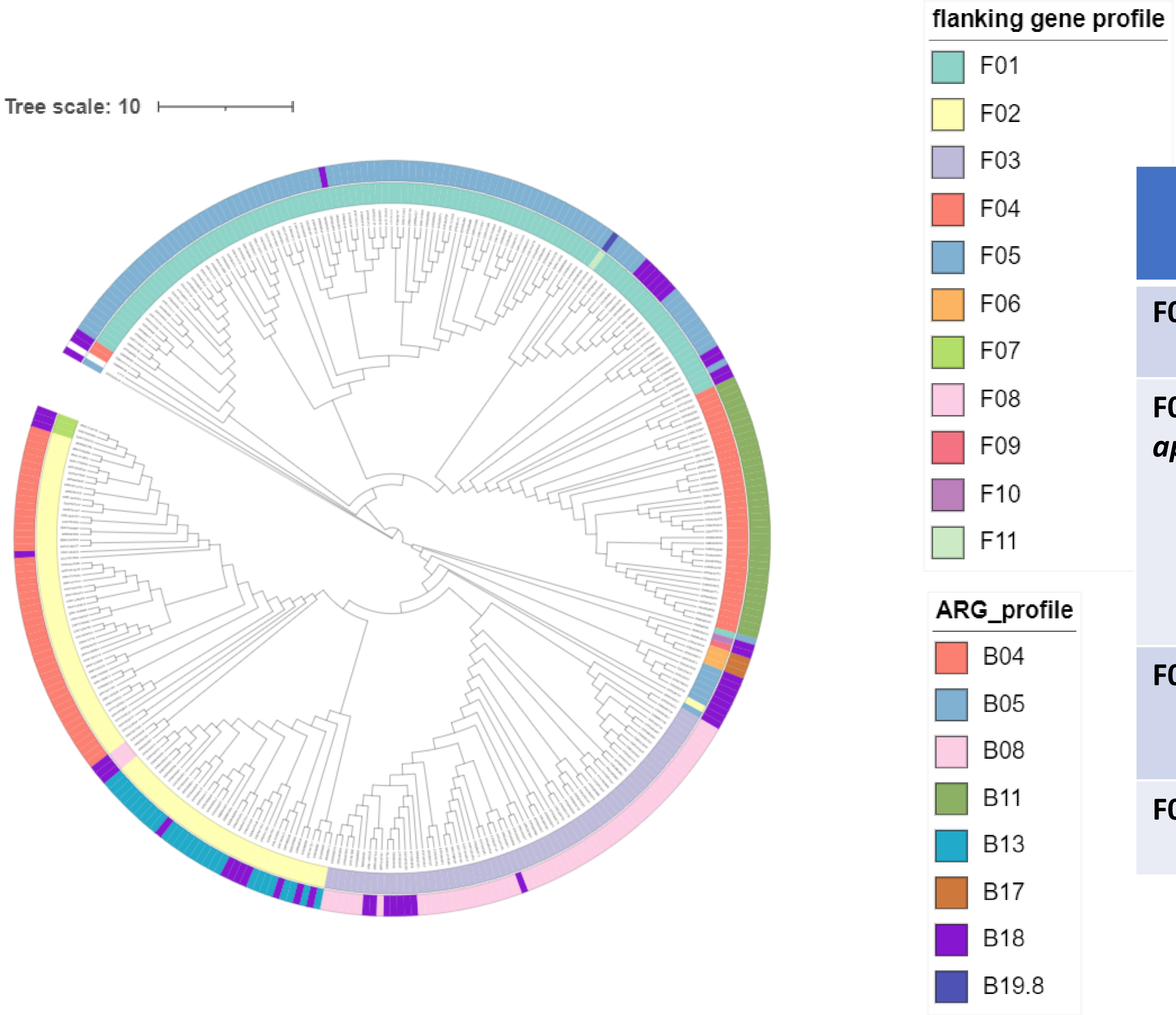
Timeline: F01&F03 - -> F04 - -> F02

Flanking gene profiles and genotypes



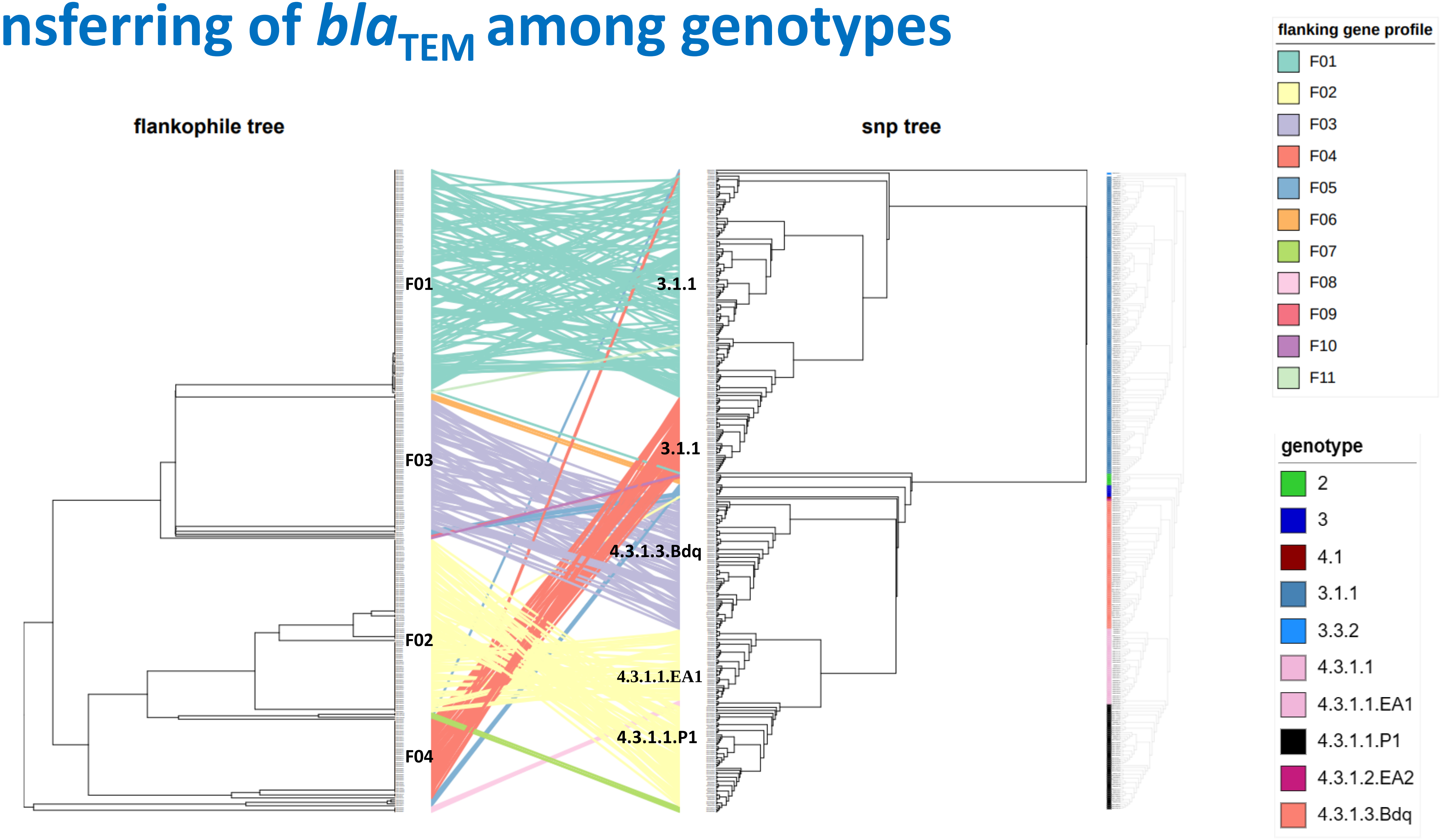
Flanking gene profiles	Main genotypes
F01__*tnpR*, *bla*$_{\text{TEM-1B}}$, *hns*	**3.1.1**
F02__*tnpR*, *bla*$_{\text{TEM-1B}}$, *aph(6)-Id*, *aph(3'')-Ib*	**4.3.1.1.EA1** **4.3.1.1.P1**
F03__*tnpR*, *bla*$_{\text{TEM-1B}}$, *sul2*	**4.3.1.3.Bdq**
F04__*tnpR*, *bla*$_{\text{TEM-1B}}$, *tetR*	**3.1.1**

Flanking gene profiles and ARG profiles



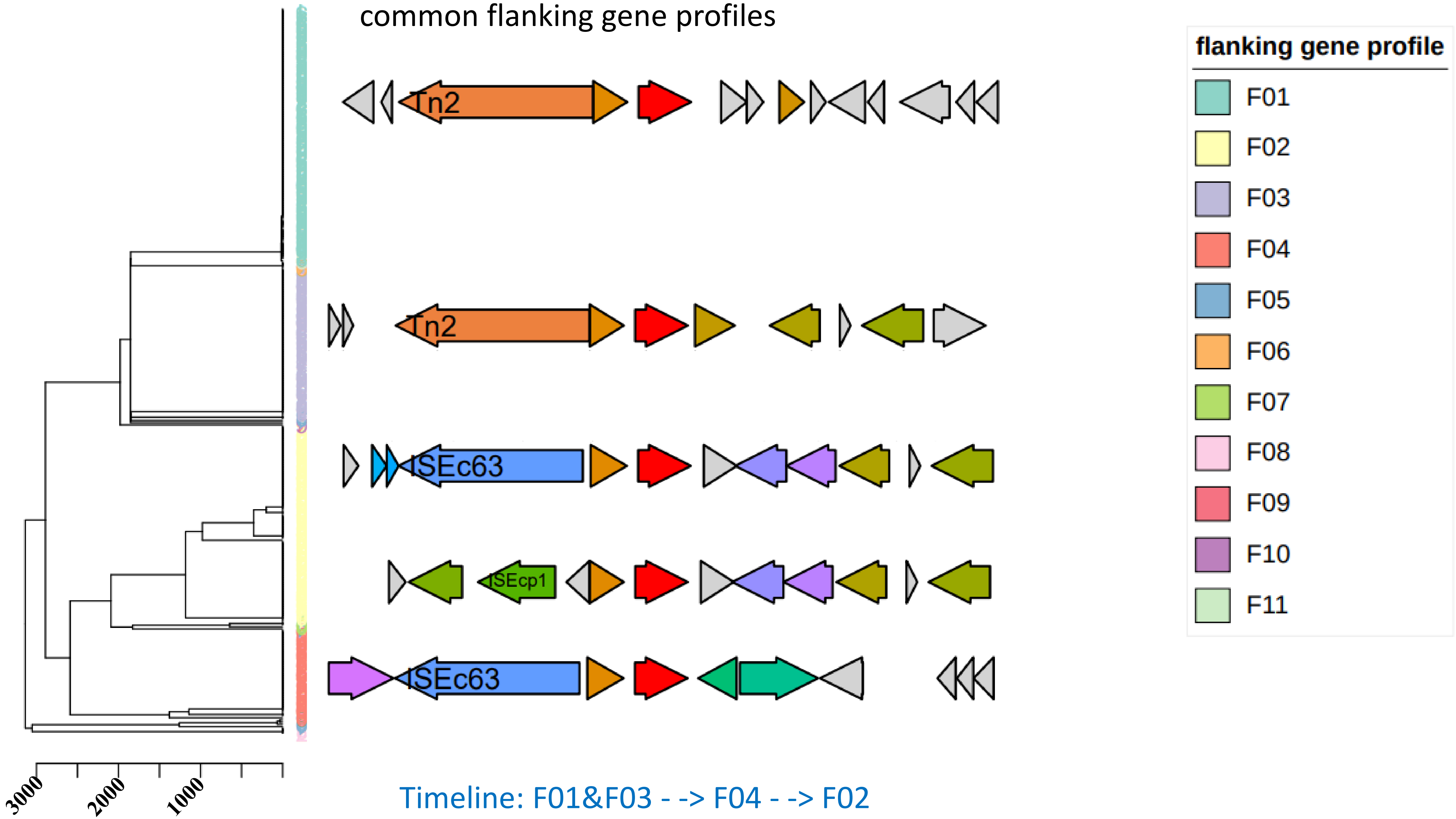
Flanking gene profiles	Main ARG profiles
F01__*tnpR*, *bla*$_{\text{TEM-1B}}$, *hns*	**B05: *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA15*, *sul1*, *tet*(B)**
F02__*tnpR*, *bla*$_{\text{TEM-1B}}$, *aph(6)-Id*, *aph(3'')-Ib*	**B04: *aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{CTX-M-15}}$, *bla*$_{\text{TEM-1B}}$, *catA1*, *dfrA7*, *gyrA*[S83F], *qnrS1*, *sul1*, *sul2*** **B13: *aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *dfrA14*, *sul2***
F03__*tnpR*, *bla*$_{\text{TEM-1B}}$, *sul2*	**B08: *bla*$_{\text{TEM-1B}}$, *gyrA*[S83Y], *qnrS1*, *sul2*, *tet*(A)**
F04__*tnpR*, *bla*$_{\text{TEM-1B}}$, *tetR*	**B11: *aph(3'')-Ib*, *aph(6)-Id*, *bla*$_{\text{TEM-1B}}$, *dfrA14*, *gyrA*[S83Y], *sul2*, *tet*(A)**

Transferring of *bla*$_{\text{TEM}}$ among genotypes



Flanking gene profiles and MGEs

Flank length upstreams and downstreams setting: “5000 bp“



Timeline: F01&F03 - -> F04 - -> F02

Limitation

- Data gaps between countries
- Flankophile output (12.8%) at 2000 upstream and downstream setting
    - 1881/2557 (74%) isolates are < 4861 bp contig length -> excluded

Conclusion

- F01 – F04 are one of the common profiles for transferring *bla*$_{\text{TEM-1B}}$.

- *bla*$_{\text{TEM}}$ transferring
  - in closer clusters (or genotype)

- Transferring associated with MGEs:
  - upstream MGEs: Tn2, ISEc63, ISEcp1,
  - downstream MGEs: ISVsa5, IS5075
  - *tnpR* encodes DNA invertase

Any Question?