# A global resource for genomic predictions of antimicrobial resistance and surveillance of *Salmonella* Typhi at Pathogenwatch

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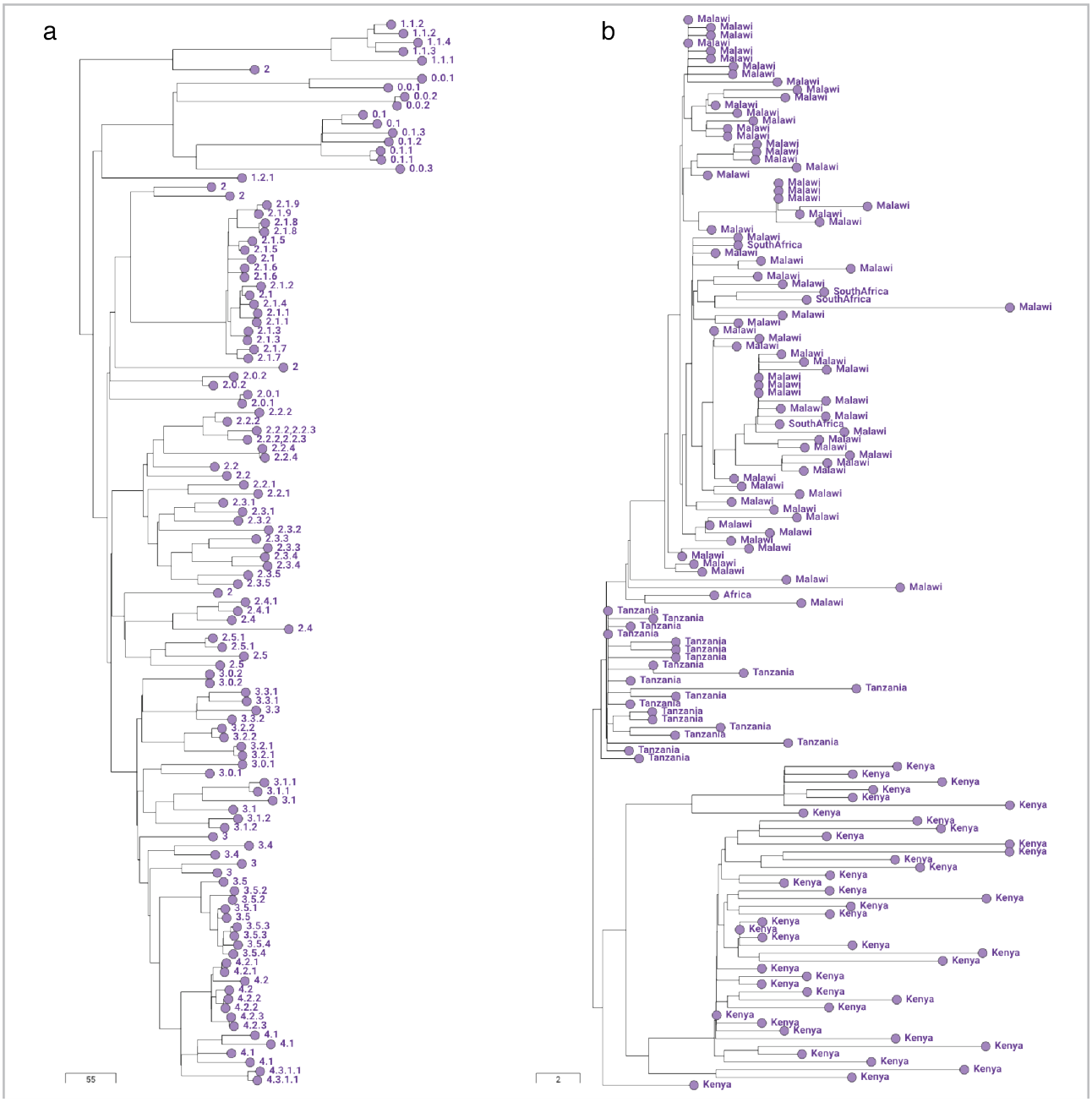
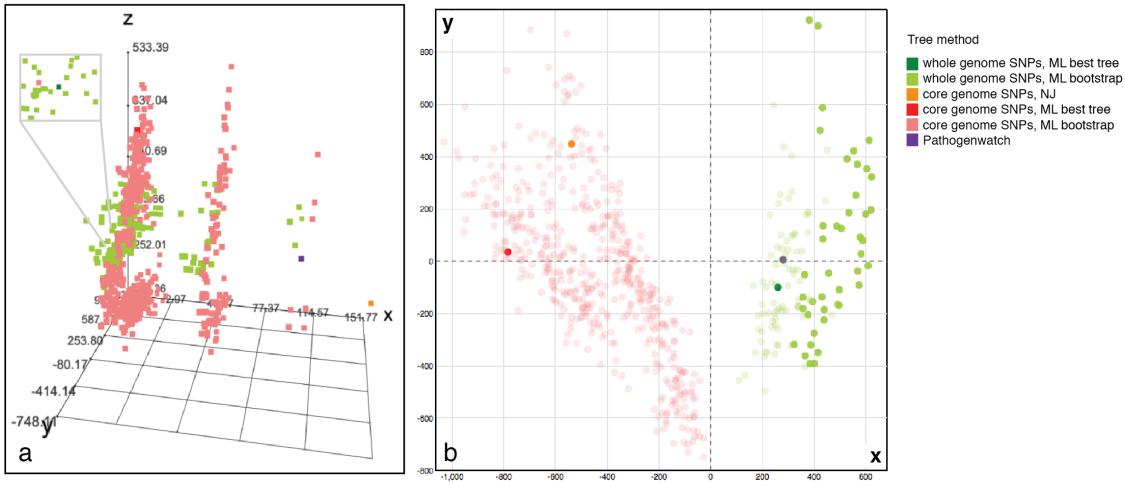
## Supplementary Information

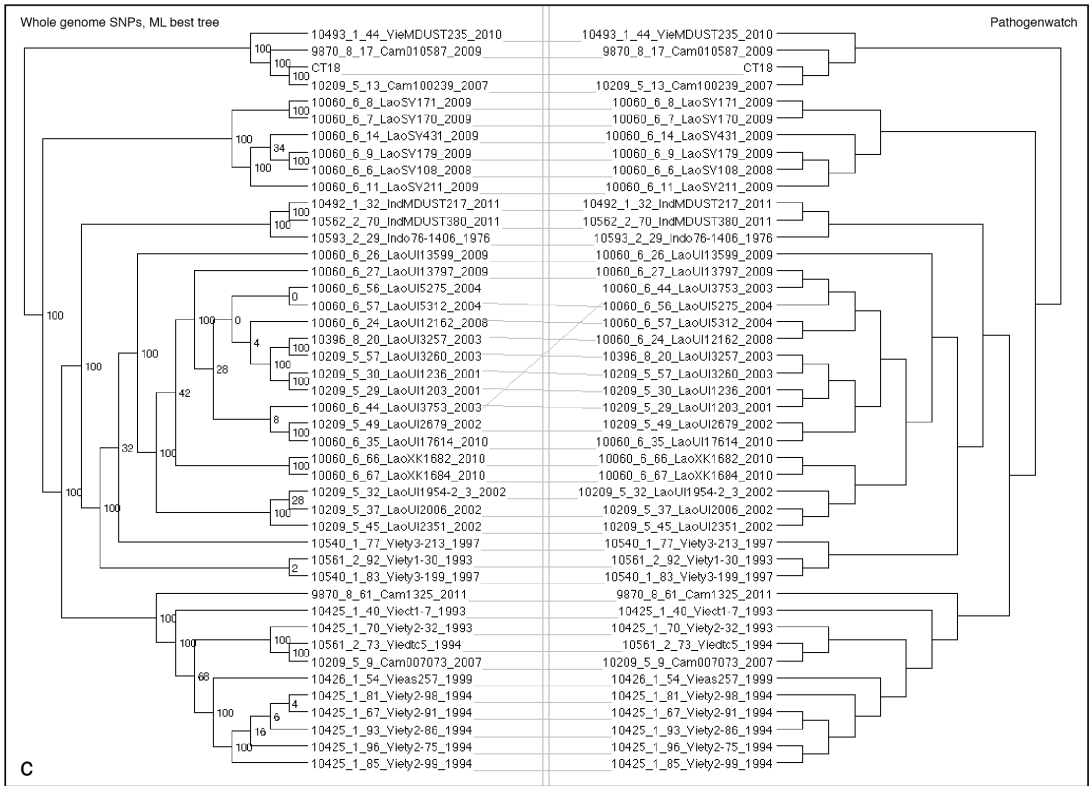
This file includes:



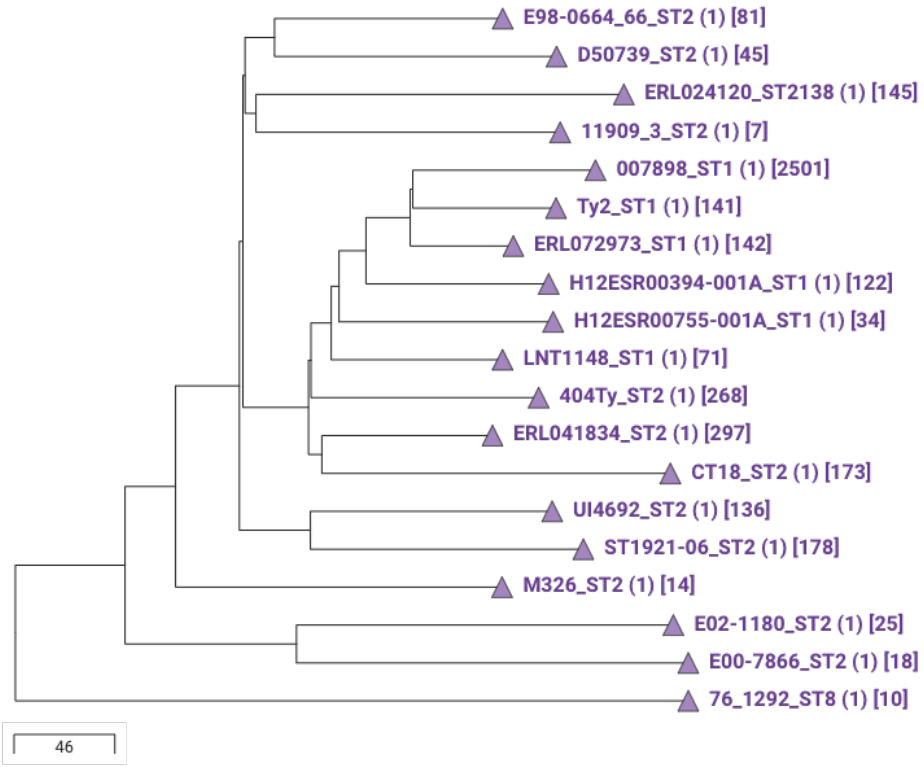

**Supplementary Figure 1. a** Pathogenwatch collection tree of 118 diverse *S.* Typhi genomes (dataset I) representing 62 genotypes (tree labels). **b** Pathogenwatch collection tree of 138 closely-related genomes from a clonal expansion within East Africa (dataset II). The tree nodes are labelled by country of isolation. The scale bars represent the number of SNP differences.



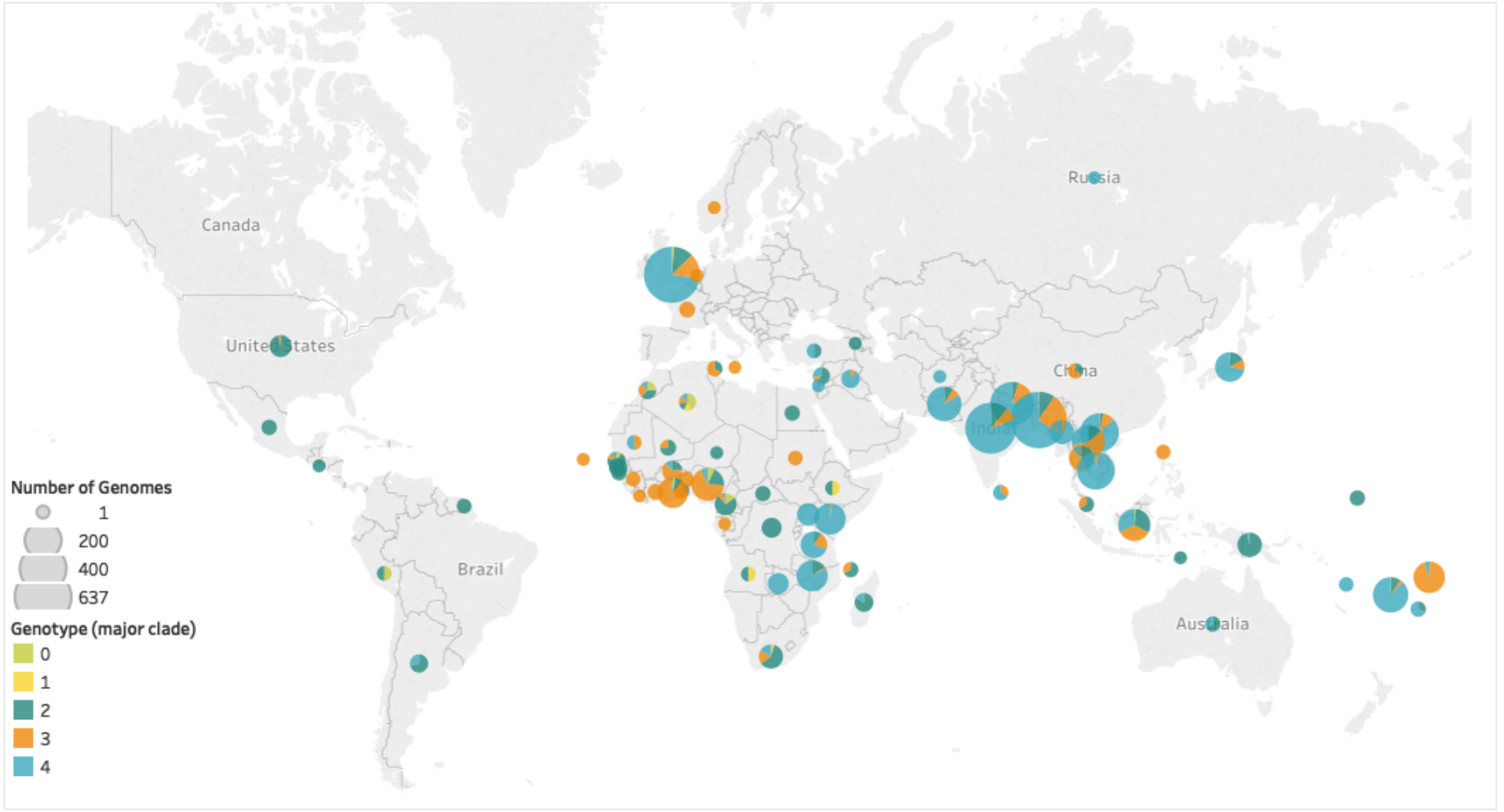

| | pathogenwatch | roary_raxml | roary_NJ | mapping_raxml |
|---|---|---|---|---|
| pathogenwatch | 0 | 1232.87 | 1103.917 | 261.7919 |
| roary_raxml | 126.8621 | 0 | 900.6298 | 1213.995 |
| roary_NJ | 67.09694 | 167.5112 | 0 | 1127.043 |
| mapping_raxml | 123.065 | 36.59235 | 167.544 | 0 |



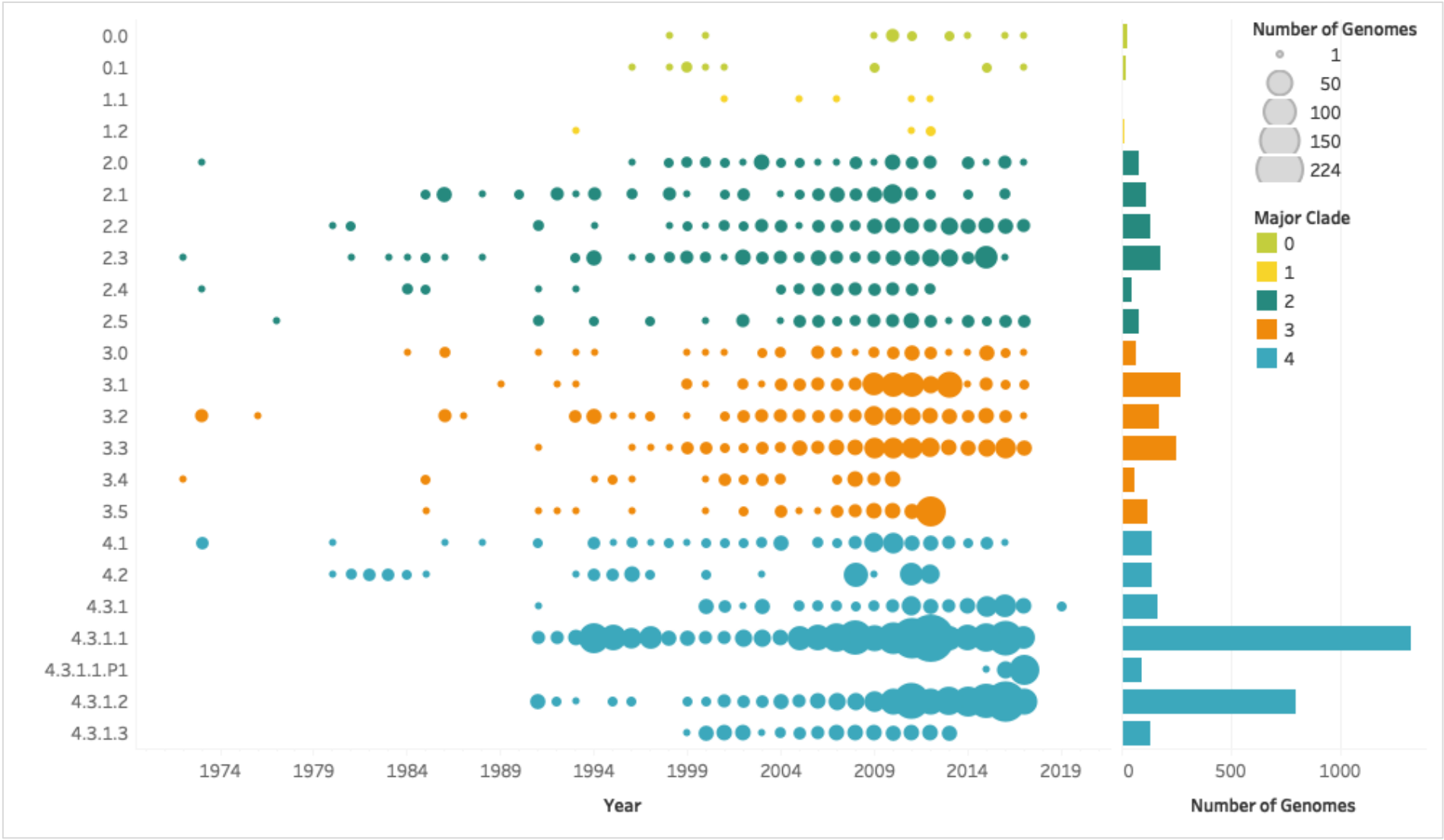

**Supplementary Figure 2. a** Three-dimensional multidimensional scaling (MDS) plot of pairwise tree distances from dataset I (118 genomes), and **b** Two-dimensional MDS plot of pairwise tree distances from dataset II (138 genomes), both generated with Treescape. Trees were generated with four methods: 1) Pathogenwatch (purple); 2) Maximum likelihood on 9112 SNPs identified on an alignment of 3996 concatenated core genes estimated with roary (best tree, red); 3) Neighbour joining on the same alignment in 2) (orange); and 4) Maximum likelihood on 8598 SNPs called on a CT18-guided alignment (best tree, green). Five hundred bootstrap replicates were computed for each of the methods 2 (pink) and 4 (lime green). The inset in **a** unveils the position of the best tree from method 4 (green). The matrix shows the pairwise distances between the trees from methods 1-4 for dataset I (below diagonal) and dataset II (above diagonal). **c** Tanglegram comparison of the Pathogenwatch tree of 43 genomes from subclade 3.2.1 (right) with the CT18-guided alignment tree from method 4 (left).



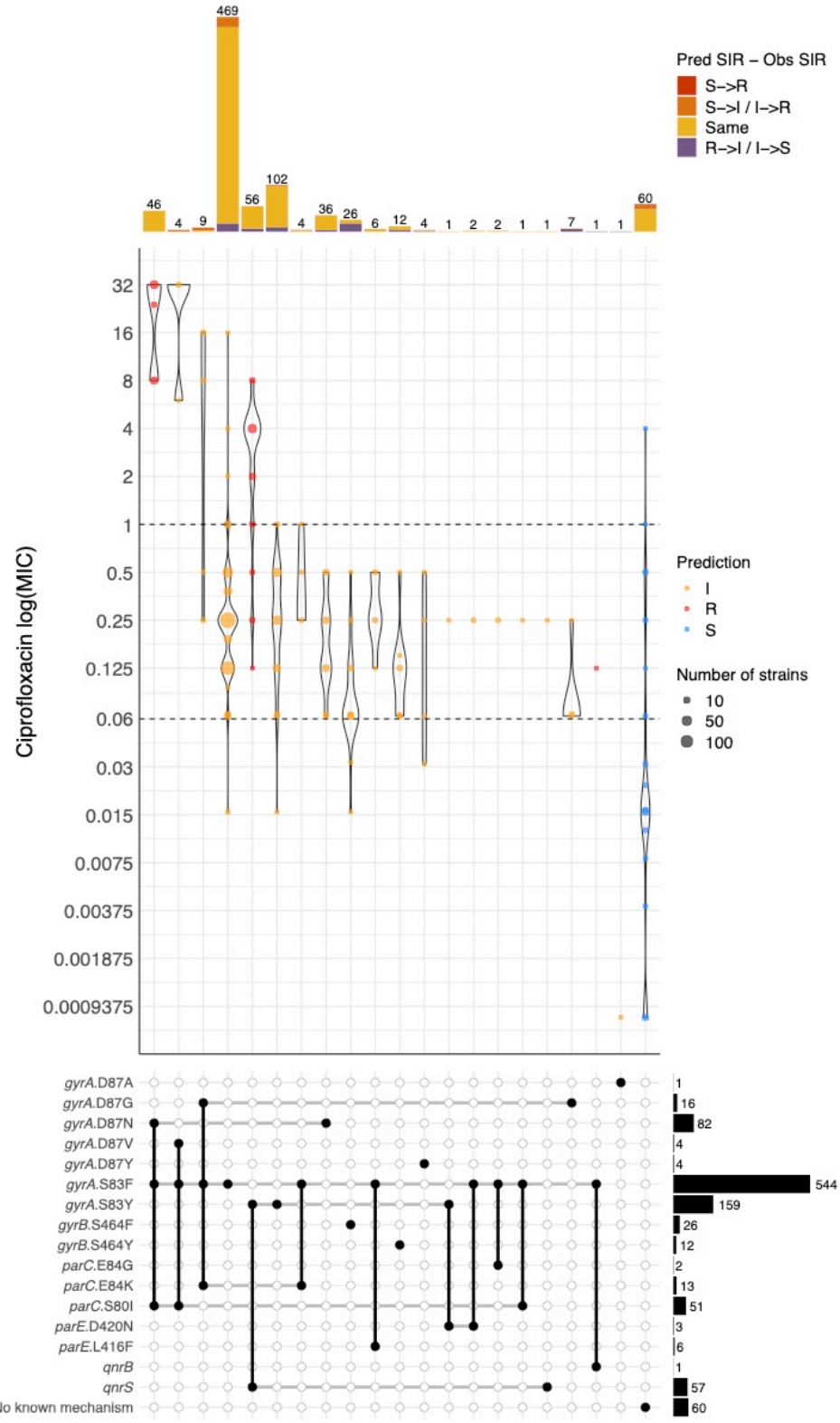

**Supplementary Figure 3.** The Typhi Pathogenwatch population Tree of 19 reference genomes, inferred from 2409 polymorphic sites found in 1639 of the 3916 core gene families. The numbers in parenthesis indicate the number of user genomes that have been sub-clustered with each reference in the tree. The numbers in brackets indicate the number of public genomes available on each subtree, which are also clustered with the user genomes.



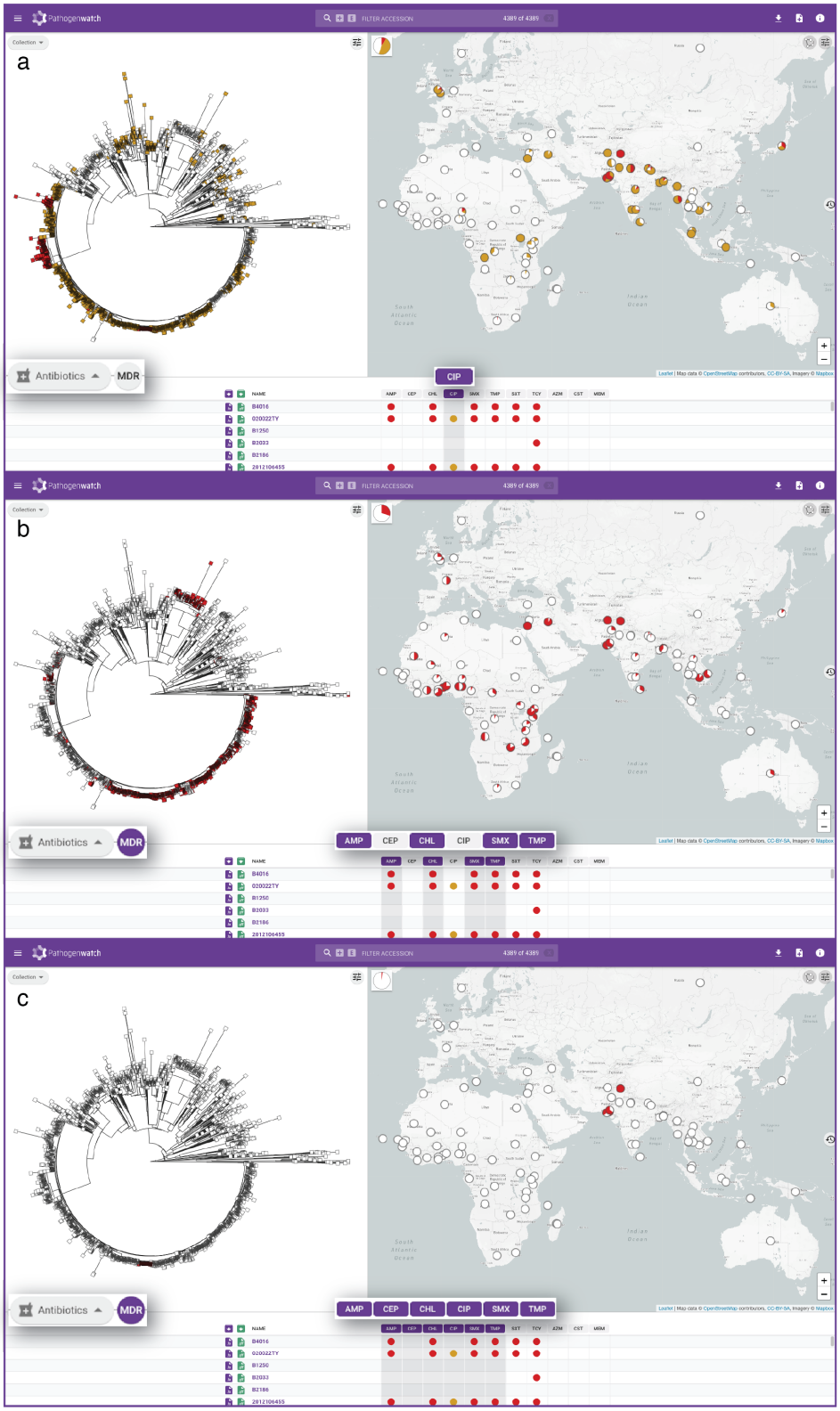

**Supplementary Figure 4.** Geographic distribution of public *S.* Typhi genomes available in Pathogenwatch. The size of the markers is proportional to the number of genomes in each country. The pie charts show the relative abundance of the four major clades per country. The visualization was created with Tableau Desktop v2018.3.



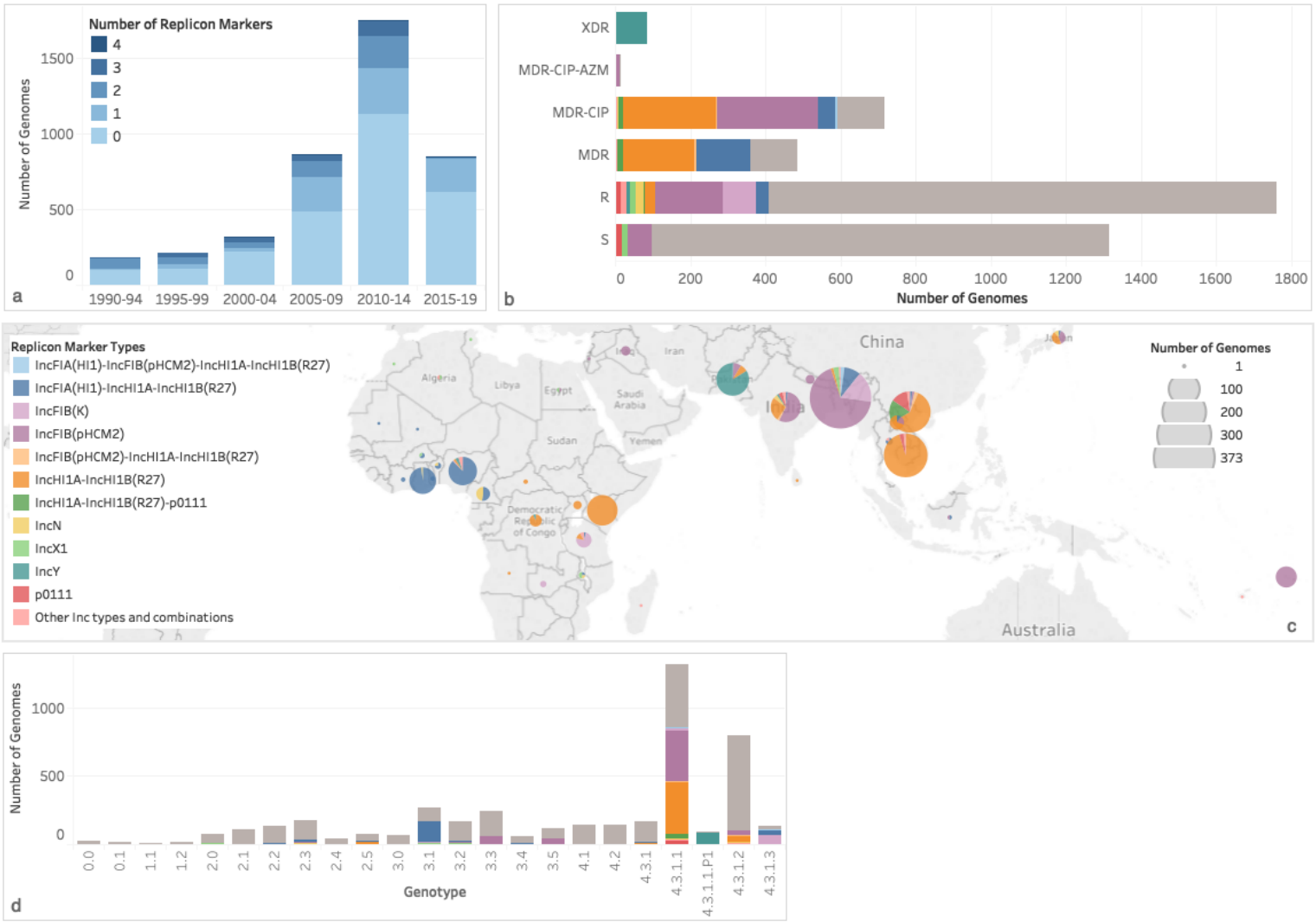

**Supplementary Figure 5.** Temporal distribution (left) and frequency (right) of the genotypes in the Typhi Pathogenwatch public collection of genomes. Genotypes were grouped by clade (e.g. 4.2) with the exception of 4.3, which was further discriminated into subclades. The markers on the timeline were coloured by the major clade they belong to, and their size is proportional to the number of genomes. The bar chart show the frequency of the genotypes, coloured by the major clade they belong to. Isolates collected before 1970 were excluded from the graphs. The visualization was created with Tableau Desktop v2018.3.



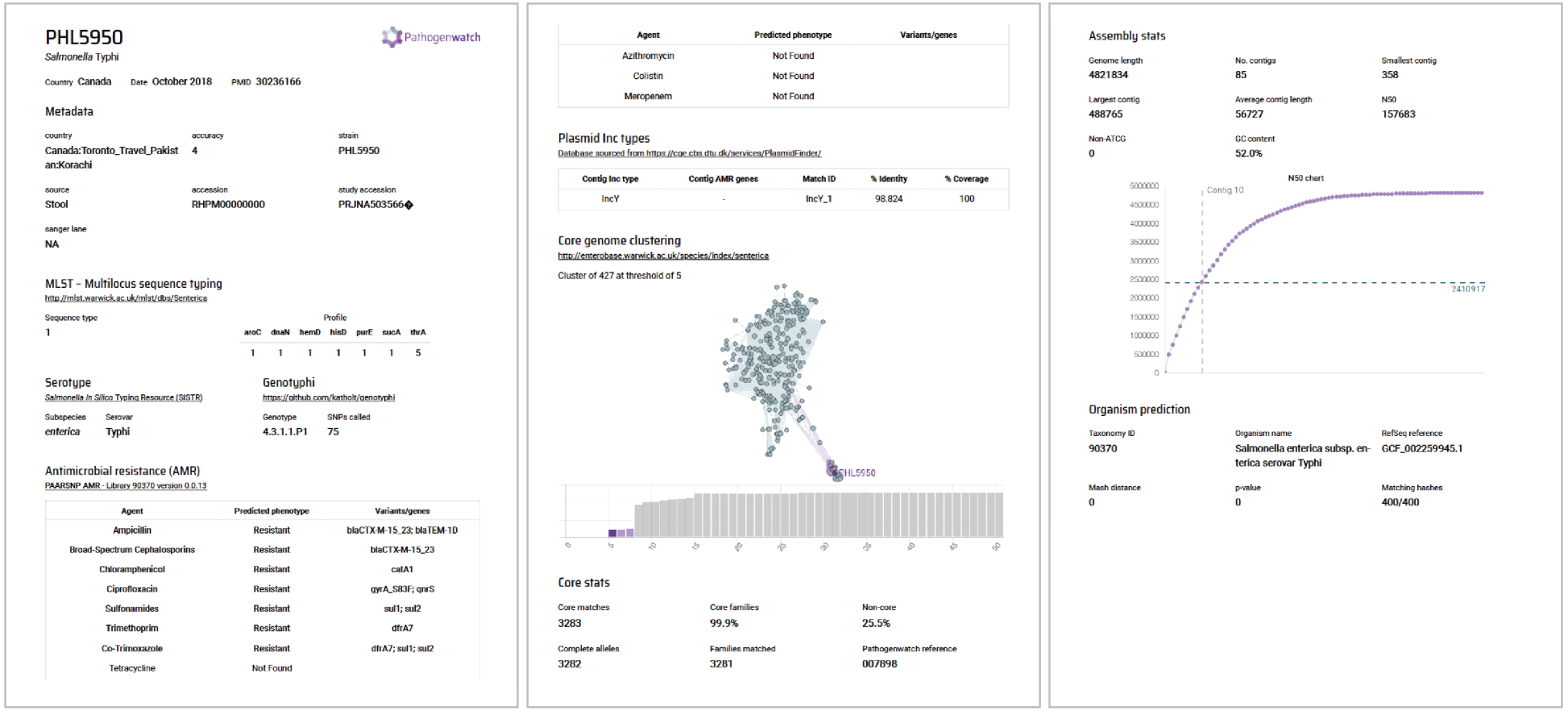

**Supplementary Figure 6.** Distribution of minimum inhibitory concentration (MIC) values (mg $L^{-1}$) for ciprofloxacin in a collection of 889 *S.* Typhi isolates with different combinations of genetic mechanisms that are known to confer resistance to this antibiotic. Dashed horizontal lines on the violin plots mark the CLSI clinical breakpoint for ciprofloxacin. Point colours inside violins represent the genotypic AMR prediction by Pathogenwatch on each combination of mechanisms. Bar plots on the top show the abundance of genomes with each combination of mechanisms. Bar colours represent the differences between the predicted and the observed SIR (e.g. red for a predicted susceptible mechanism when the observed phenotype is resistant). S = susceptible, I = intermediate, and R = resistant.




**Supplementary Figure 7.** Distribution of predicted (**a**) ciprofloxacin-resistant (CIP), (**b**) MDR (resistant to ampicillin, chloramphenicol, sulfamethoxazole, and trimethoprim), and (**c**) XDR (MDR with additional resistance to ciprofloxacin, and extended-spectrum cephalosporins) *S.* Typhi on the map and tree of 4389 genomes. Tree nodes are coloured red (resistant), yellow (intermediate), or white (no resistance determinants found). The map pie charts display the proportion of resistant/intermediate genomes at each location. The expandable pie chart at the top-left corner of the map view indicates the proportion of resistant/intermediate genomes for the entire set of 4389 genomes.




**Supplementary Figure 8.** Distribution of plasmid replicon marker types across the 4389 public genomes in Typhi Pathogenwatch. **a** Number of replicon markers per year interval. The genomes from isolates collected before 1990 were excluded. **b** Distribution of replicon marker types across the different predicted resistance profiles grouped as in Supplementary Figure 4. **c** Geographical distribution. **d** Distribution of replicon types across the different predicted genotypes. The visualization was created with Tableau Desktop v2018.3.




**Supplementary Figure 9.** Pathogenwatch genome report for assembly PHL595.

**Supplementary Table 1.** Collections of *S.* Typhi genomes included in Pathogenwatch at the time of writing. The availability of strain-level antimicrobial susceptibility testing (AST) data and of MIC values for ciprofloxacin is indicated.

| Collection name | PMID | No. of Genomes | Location | AST performed/ data used for concordance | CIP MIC data available | Reference |
|---|---|---|---|---|---|---|
| Ahmad et al. (2017) | 28254988 | 1 | Malaysia | yes / no | no | (1) |
| Ashton et al. (2016) | 27069781 | 513 | UK (Travel multi) | no | no | (2) |
| Baker et al. (2015) | 26411565 | 37 | NA | no | no | (3) |
| Britto et al. (2018) | 29684021 | 192 | Nepal | yes / yes | no | (4) |
| Britto et al. (2020) | 31665304 | 94 | India | yes / yes | no | (5) |
| Burnsed et al. (2018) | 30236166 | 30 | USA (Travel Marshall Islands) | yes / no | no | (6) |
| Djeghout et al. (2018) | 29616895 | 1 | Bangladesh | yes / yes | yes | (7) |
| Dyson et al. (2017) | 28060810 | 45 | Thailand | no | no | (8) |
| Gul et al. (2017) | 29051234 | 1 | Pakistan | yes / no | no | (9) |
| Hendriksen et al. (2015) | 25392358 | 22 | Zambia | yes / no | no | (10) |
| Hendriksen et al. (2015) | 25428145 | 2 | Netherlands and Norway (Travel Philippines) | yes / yes | yes | (11) |
| Hooda et al. (2019) | 31730615 | 12 | Bangladesh | yes / yes | no | (12) |
| Ingle et al. (2019) | 31513580 | 524 | UK (Travel multi) | yes (N=173) / yes | yes | (13) |
| Klemm et al. (2018) | 29463654 | 100 | Pakistan | yes / yes | no | (14) |
| Matono et al. (2017) | 29255729 | 93 | Japan (Travel multi) | yes / yes | no | (15) |
| Oo et al. (2019) | 31225619 | 39 | Myanmar | yes / yes | yes | (16) |
| Park et al. (2018) | 30504848 | 249 | Africa multi | no | no | (17) |
| Pham Thanh et al. (2016) | 26974227 | 78 | Nepal | yes / yes | yes | (18) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Phoba et al. (2017) | 29136410 | 1 | DR Congo | yes/no | no | (19) |
| Pragasam et al. (2020) | 32003431 | 194 | India | yes (N=30) / yes | no | (20) |
| Rodrigues et al. (2017) | 25961941 | 3 | India | yes / no | no | (21) |
| Sah et al. (2019) | 31872221 | 2 | India | yes / yes | yes | (22) |
| Tanmoy et al. (2018) | 32003431 | 536 | Bangladesh | yes / yes | yes | (23) |
| Wong et al. (2015) | 25961941 | 1822 | Multi | no | no | (24) |
| Wong et al. (2016) | 27703135 | 99 | Multi | no | no | (25) |
| Wong et al. (2016) | 27657909 | 128 | Nigeria | yes / no | no | (26) |

**Supplementary Table 2.** List of genetic AMR determinants in Typhi Pathogenwatch. Effect: R = Resistance, I = Intermediate resistance (decreased susceptibility). Genes and mutations in bold type have been demonstrated to have a role on AMR in *S.* Typhi, the remaining mechanisms are of emerging importance in Gram negative bacteria. Pathogenwatch Library 1: *S.* Typhi AMR (27), 2: ESBL (28), 3: Carbapenemases (29), 4: Colistin resistance (30)

| Antibiotic class | Antibiotic (abbreviation used in Pathogenwatch) | Genetic determinants of resistance | Effect | Pathogenwatch Library (References) |
|---|---|---|---|---|
| Phenicols | Chloramphenicol (CHL) | ***catA1*** | R | 1 (31) |
| | | ***cmlA*** | R | 1 (32) |
| Fluoroquinolones | Ciprofloxacin (CIP) | ***qnrS*, *qnrB***, *qnrA*, *qnrD* | I | 1 (33) |
| | | ***gyrA* S83F, S83Y, D87N, D87Y, D87A, D87G, D87V** | I | 1 (33, 34) |
| | | ***gyrB* S464F, S464Y, Q465R, Q465L** | I | 1 (33) |
| | | ***parC* S80I, E84G, E84K** | I | 1 (33) |
| | | ***parE* L416F, D420N** | I | 1 (33, 35, 36) |
| Sulfonamides | Sulfamethoxazole (SXM) | ***sul1*, *sul2*** | R | 1 (32) |
| Folate Pathway Inhibitors | Trimethoprim (TMP) | ***dfrA1*, *dfrA5*, *dfrA7*, *drfA14*, *dfrA15*, *dfrA17*, *dfrA18*** | R | 1 (32) |
| | Tetracycline (TCY) | ***tetA*(A), *tetA*(B), *tetA*(C), *tetA*(D)** | R | 1 (31) |
| Macrolides | Azithromycin (AZM) | *ermA*, *ermB*, *ermC* | R | 1 |
| | | *ereA*, *ereB* | R | 1 |
| | | *mefA* | R | 1 |
| | | *mphA*, *mphB* | R | 1 |
| | | *msrA*, *msrD* | R | 1 |
| | | ***acrB* R717Q** | R | 1 (12) |
| Penicillins | Ampicillin (AMP) | ***bla*$_{\text{TEM-1}}$** | R | 1 (31) |
| | | *bla*$_{\text{OXA-1}}$, *bla*$_{\text{OXA-7}}$ | R | 1 |
| | | Determinants of CEP and MEM | R | 2,3 |
| Cephalosporins | Extended-spectrum cephalosporins (CEP) | *bla*$_{\text{CMY-2}}$ | R | 1 |
| | | *ampC* | R | 1 |
| | | ***bla*$_{\text{CTX-M}}$** | R | 2 (37) |
| | | ***bla*$_{\text{SHV}}$** | R | 2 (38) |
| | | *bla*$_{\text{OXA-11}}$, *bla*$_{\text{OXA-15}}$ | R | 2 |
| | | *bla*$_{\text{TEM-10}}$, *bla*$_{\text{TEM-124}}$ | R | 2 |
| | | Determinants of MEM | R | 3 |
| Carbapenems | Meropenem (MEM) | *bla*$_{\text{AIM}}$ | R | 3 |
| | | *bla*$_{\text{BIC}}$ | R | 3 |
| | | *bla*$_{\text{DIM}}$ | R | 3 |
| | | *bla*$_{\text{GES}}$ | R | 3 |
| | | *bla*$_{\text{GIM}}$ | R | 3 |
| | | *bla*$_{\text{IMI}}$ | R | 3 |
| | | *bla*$_{\text{IMP}}$ | R | 3 |
| | | *bla*$_{\text{KPC}}$ | R | 3 |
| | | *bla*$_{\text{LMB}}$ | R | 3 |

| | | | | |
|---|---|---|---|---|
| | | *bla*$_{NDM}$ | R | 3 |
| | | *bla*$_{NMCA}$ | R | 3 |
| | | *bla*$_{OXA-48}$ like | R | 3 |
| | | *bla*$_{SIM}$ | R | 3 |
| | | *bla*$_{SPM}$ | R | 3 |
| | | *bla*$_{VIM}$ | R | 3 |
| Polymixins | Colistin (CST) | *mcr-12345678* | R | 4 |

**Supplementary Table 3.** Distribution of known fluoroquinolone (Flq) resistance determinants (genes and mutations) in the 4389 public genomes in Pathogenwatch, and the linked genomic prediction of ciprofloxacin resistance provided by in the Antibiotics table.

| No. of Genomes | No. of Flq resistance genes | No. of Flq resistance mutations | Flq resistance determinants identified in the genomes | Genomic prediction of ciprofloxacin resistance |
|---|---|---|---|---|
| 1939 | 0 | 0 | None | Susceptible |
| 1219 | 0 | 1 | *gyrA*_S83F | Intermediate |
| 421 | 0 | 1 | *gyrA*_S83Y | Intermediate |
| 80 | 0 | 1 | *gyrB*_S464F | Intermediate |
| 68 | 0 | 1 | *gyrA*_D87N | Intermediate |
| 26 | 0 | 1 | *gyrA*_D87G | Intermediate |
| 16 | 0 | 1 | *gyrB*_S464Y | Intermediate |
| 14 | 0 | 1 | *gyrA*_D87Y | Intermediate |
| 1 | 0 | 1 | *gyrA*_D87V | Intermediate |
| 1 | 0 | 1 | *gyrA*_D87A | Intermediate |
| 1 | 0 | 1 | *gyrB*_Q465L | Intermediate |
| 158 | 0 | 2 | *gyrA*_S83F,*parE*_D420N | Intermediate |
| 27 | 0 | 2 | *gyrA*_S83F,*parC*_E84G | Intermediate |
| 23 | 0 | 2 | *gyrA*_S83F,*parE*_L416F | Intermediate |
| 7 | 0 | 2 | *gyrA*_S83F,*parC*_E84K | Intermediate |
| 4 | 0 | 2 | *gyrA*_S83F,*parC*_S80I | Intermediate |
| 3 | 0 | 2 | *gyrA*_S83Y,*parE*_D420N | Intermediate |
| 1 | 0 | 2 | *gyrB*_S464F,*gyrB*_Q465L | Intermediate |
| 1 | 0 | 2 | *gyrA*_D87N,*gyrB*_Q465L | Intermediate |
| 192 | 0 | 3 | *gyrA*_S83F,*gyrA*_D87N,*parC*_S80I | Resistant |
| 9 | 0 | 3 | *gyrA*_S83F,*gyrA*_D87G,*parC*_E84K | Intermediate |
| 6 | 0 | 3 | *gyrA*_S83F,*gyrB*_Q465R,*parE*_D420N | Intermediate |
| 5 | 0 | 3 | *gyrA*_S83F,*gyrA*_D87V,*parC*_S80I | Intermediate |
| 2 | 0 | 3 | *gyrA*_S83F,*gyrA*_D87G,*parC*_S80I | Intermediate |
| 1 | 0 | 3 | *gyrA*_S83F,*gyrA*_D87N,*parC*_E84K | Intermediate |
| 1 | 0 | 3 | *gyrA*_S83Y,*gyrA*_D87G,*parC*_S80I | Intermediate |
| 1 | 0 | 3 | *gyrA*_S83F,*gyrA*_D87G,*parE*_D420N | Intermediate |
| 1 | 0 | 3 | *gyrA*_S83F,*gyrA*_D87G,*parC*_E84G | Intermediate |
| 3 | 1 | 0 | *qnrS* | Intermediate |
| 87 | 1 | 1 | *qnrS*,*gyrA*_S83F | Resistant |
| 64 | 1 | 1 | *qnrS*,*gyrA*_S83Y | Resistant |
| 2 | 1 | 1 | *qnrB*,*gyrA*_S83F | Resistant |
| 2 | 1 | 2 | *qnrB*,*gyrA*_S83F,*parC*_E84K | Resistant |
| 3 | 1 | 3 | *qnrB*,*gyrA*_S83F,*gyrA*_D87N,*parC*_S80I | Resistant |

**Supplementary Table 4.** Reference genomes used to compute the Pathogenwatch *S.* Typhi core genome library (N=26) and the population tree (N=19).

| Strain Name | Country | Collection Year | MLST ST | GenoTyphi genotype | Assembly Length | N50 | No. contigs | Non-ATCG | % GC Content | % Core Families | Accessions | Study Accession | PMID | Core Library | Population Tree Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| E02-1180 | India | 2002 | 2 | 0.0.3 | 4838914 | 4793071 | 4 | 0 | 52.1 | 100 | ERR581073, ERR581085 | PRJEB5919 | 25961941 | yes | yes |
| E00-7866 | Morocco | 2000 | 2 | 0.1 | 4831122 | 4797408 | 3 | 0 | 52.1 | 100 | ERR581072, ERR581087 | PRJEB5919 | 25961941 | yes | yes |
| 76-1292 | Democratic Republic of Congo | 1976 | 8 | 1.1.3 | 4934685 | 4780549 | 3 | 0 | 52.1 | 100 | ERR601541, ERR601549 | PRJEB5919 | 25961941 | yes | yes |
| M326 | Unknown | 1939 | 2 | 1.2.1 | 4775555 | 204340 | 47 | 8 | 52 | 100 | ERR279243 | PRJEB3255 | 26411565 | no | yes |
| 11909_3 | Mexico | 2011 | 2 | 2.0.2 | 4811824 | 4753305 | 4 | 0 | 52 | 100 | ERR584382, ERR584388 | PRJEB5919 | 25961941 | yes | yes |
| E98-3139 | Mexico | 1998 | 2 | 2.0.2 | 4675865 | 3003486 | 6 | 0 | 52.1 | 100 | ERR581098, ERR581108, ERR601543 | PRJEB5919 | 25961941 | yes | no |
| ERL024120 | Indonesia | 2002 | 2138 | 2.1.2 | 4811886 | 4811886 | 1 | 0 | 52.1 | 100 | ERR581076, ERR581091 | PRJEB5919 | 25961941 | yes | yes |
| M223 | Unknown | 1939 | 2 | 2.1.7 | 4849011 | 4806333 | 3 | 0 | 52.1 | 100 | ERR581077, ERR581088 | PRJEB5919 | 25961941 | yes | no |
| 80-2002 | Madagascar | 1980 | 2 | 2.2 | 5061131 | 4819925 | 4 | 0 | 52.1 | 100 | ERR601542, ERR601550 | PRJEB5919 | 25961941 | yes | no |
| ERL114000 | Nepal | 2011 | 2 | 2.2 | 4776059 | 4776059 | 1 | 0 | 52.1 | 100 | ERR581075, ERR581086 | PRJEB5919 | 25961941 | yes | no |
| UI4692 | Laos | 2004 | 2 | 2.2.2,2.2.3 | 4707798 | 185395 | 43 | 0 | 52.1 | 100 | ERR331348 | PRJEB3215 | 25961941 | no | yes |
| ERL103914 | South America | 2010 | 2 | 2.3.2 | 4789623 | 4789623 | 1 | 0 | 52.1 | 100 | ERR581074, ERR581092 | PRJEB5919 | 25961941 | yes | no |
| ST1921-06 | Argentina | 2006 | 2 | 2.3.3 | 4718006 | 204238 | 42 | 0 | 52.1 | 100 | ERR353335 | PRJEB3215 | 25961941 | no | yes |
| LNT1360 | Laos | 2010 | 2218 | 2.4 | 4794285 | 206322 | 40 | 2 | 52.1 | 100 | ERR326664 | PRJEB3215 | 25961941 | yes | no |
| D50739 | Malawi | 2009 | 2 | 2.4.1 | 4704071 | 206289 | 45 | 24 | 52.1 | 100 | ERR279161 | PRJEB3215 | 25961941 | yes | yes |
| E98-0664 | Kenya | 1998 | 2 | 2.5 | 4764488 | 4752533 | 3 | 0 | 52.1 | 100 | ERR601554, ERR601551 | PRJEB5919 | 25961941 | yes | yes |
| H12ESR00755-001A | Philippines | 2012 | 1 | 3 | 4814227 | 4802146 | 2 | 0 | 52.1 | 100 | ERR581080, ERR581089 | PRJEB5919 | 25961941 | yes | yes |
| Quailes | USA | 1958 | 2 | 3.1 | 4841927 | 4797293 | 4 | 0 | 52.1 | 100 | ERR634098, ERR634100, ERR654508 | PRJEB5919 | 25961941 | yes | no |
| 404Ty | Indonesia | 1983 | 2 | 3.1.2 | 4890679 | 4807711 | 6 | 0 | 52 | 100 | ERR581078, ERR581090 | PRJEB5919 | 25961941 | yes | yes |
| CT18 | Vietnam | 1993 | 2 | 3.2.1 | 5133713 | 4809037 | 3 | 0 | 51.9 | 100 | GCA_000195995.1 | PRJNA236 | 11677608 | yes | yes |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ERL041834 | India | 2004 | 2 | 3.3 | 4892436 | 4675147 | 5 | 0 | 52.1 | 100 | ERR581081, ERR581083 | PRJEB5919 | 25961941 | yes | yes |
| H12ESR04734-001A | India | 2012 | 2 | 3.3 | 4943859 | 4876386 | 5 | 0 | 52.1 | 100 | ERR581099, ERR581105 | PRJEB5919 | 25961941 | yes | no |
| 002168 | Cambodia | 2010 | 1 | 3.4 | 4764266 | 217780 | 42 | 2 | 52.1 | 100 | ERR360747 | PRJEB3215 | 25961941 | yes | no |
| LNT1148 | Laos | 2001 | 1 | 3.4 | 4743503 | 204320 | 46 | 2 | 52.1 | 100 | ERR340779 | PRJEB3215 | 25961941 | yes | yes |
| ERL024919 | Samoa | 2002 | 1 | 3.5.4 | 4805266 | 4784637 | 2 | 0 | 52.1 | 100 | ERR581094, ERR581102 | PRJEB5919 | 25961941 | yes | no |
| H12ESR00394-001A | Samoa | 2012 | 1 | 3.5.4 | 4808147 | 4808147 | 1 | 0 | 52.1 | 100 | ERR581095, ERR581103 | PRJEB5919 | 25961941 | yes | yes |
| Ty2 | Russia | 1916 | 1 | 4.1 | 4791961 | 4791961 | 1 | 11 | 52.1 | 100 | GCA_000007545.1 | PRJNA371 | 12644504 | yes | yes |
| ERL072973 | Fiji | 2007 | 1 | 4.2.2 | 4806043 | 4789877 | 2 | 0 | 52.1 | 100 | ERR581097, ERR581107 | PRJEB5919 | 25961941 | yes | yes |
| 007898 | Cambodia | 2010 | 1 | 4.3.1.1 | 4793925 | 4793925 | 1 | 0 | 52.1 | 100 | ERR752439, ERR752446 | PRJEB5919 | 25961941 | yes | yes |

## Supplementary References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