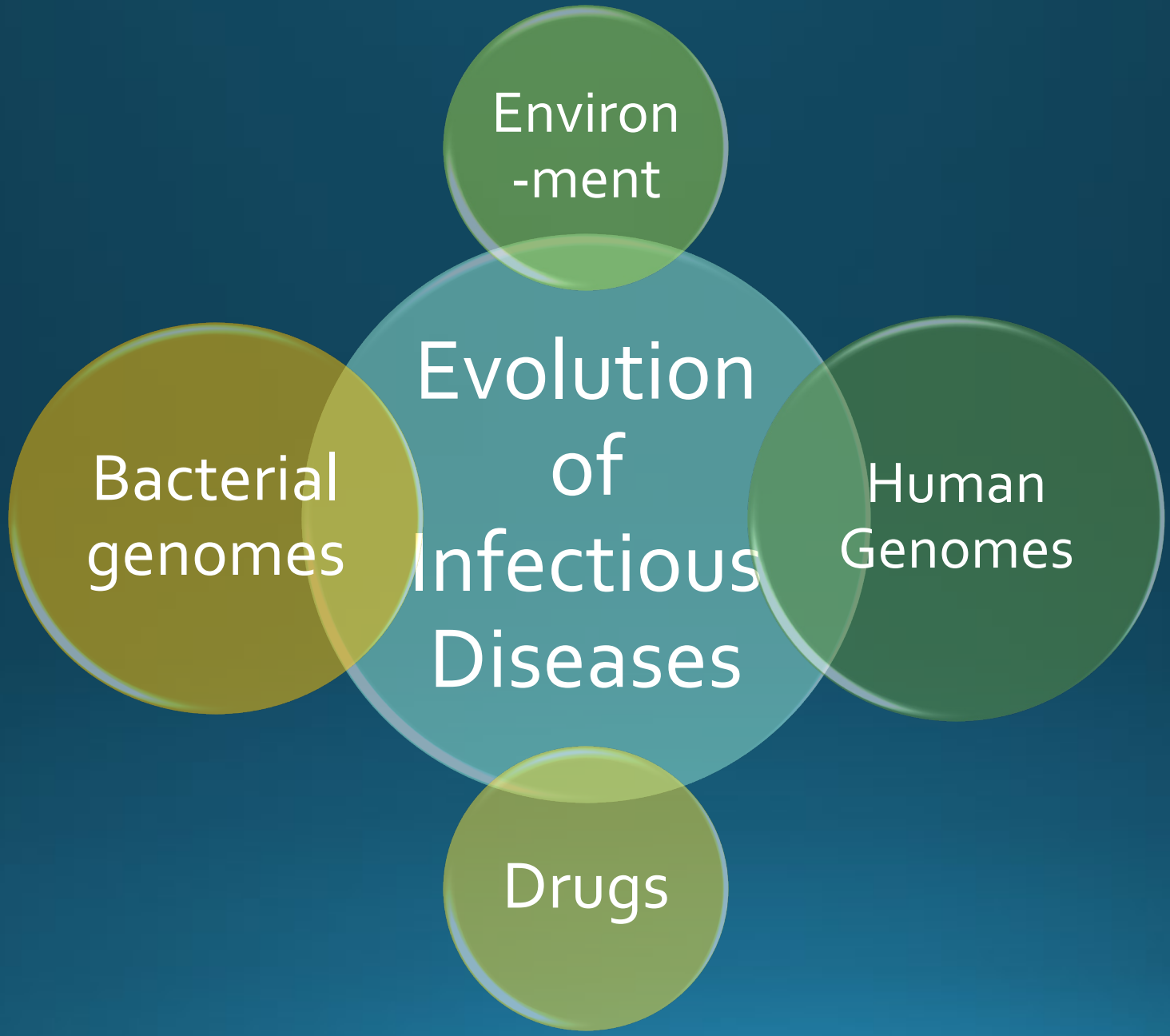
การประยุกต์ใช้เทคโนโลยีจีโนมิกส์ในโรคติดเชื้อ

โดย ศ.นพ.ประสิทธิ์ ผลิตผลการพิมพ์
หัวหน้าศูนย์วิจัยจีโนมจุลินทรีย์ ศาสตราจารย์เกียรติคุณ
นายแพทย์พรชัย มาตังคสมบัติ (CENMIG)
คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล

Prasit Palittapongarnpim, M.D.

Emeritus Professor Pornchai Matangkasombut Center for Microbial Genomics,
Department of Microbiology, Faculty of Science, Mahidol University

Uncovering Genomics Applications in Infection Diseases


Environ
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Bacterial
genomes
Evolution
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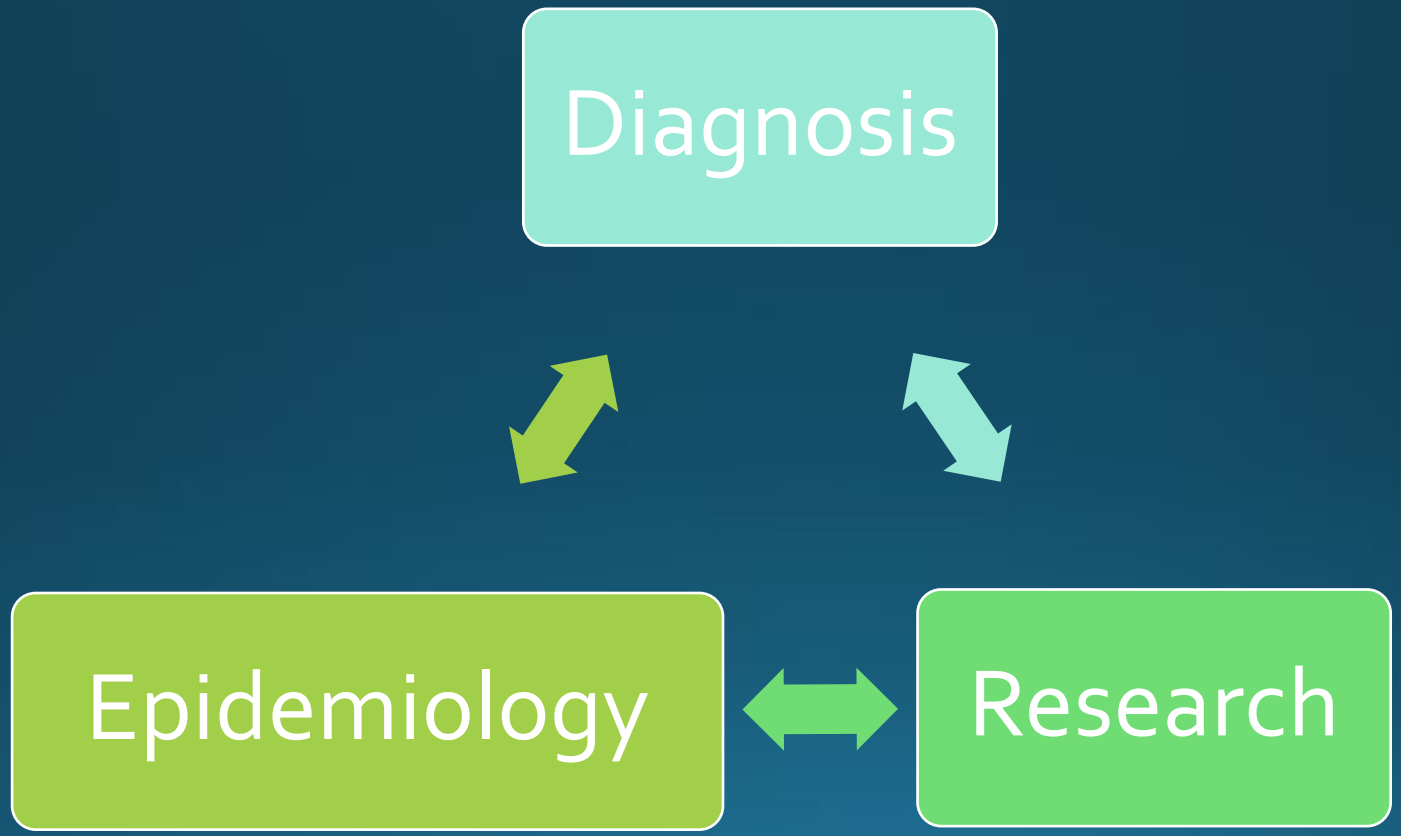
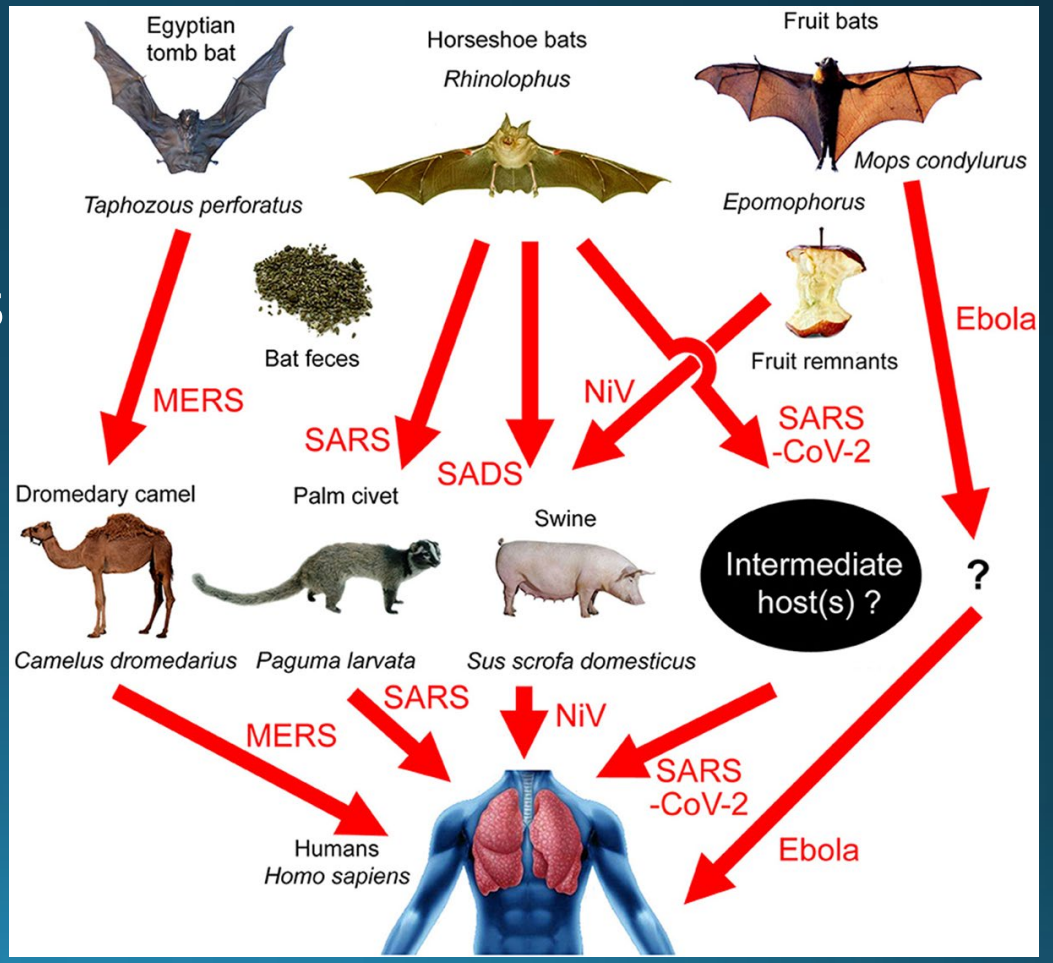
Infectious
Diseases
Human
Genomes
Drugs

Areas of Applications of WGS of Microbes

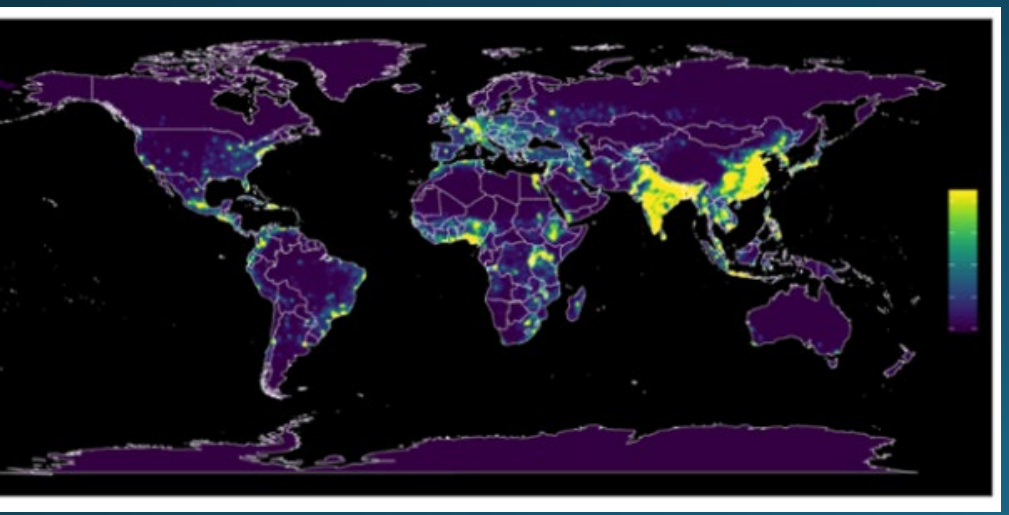


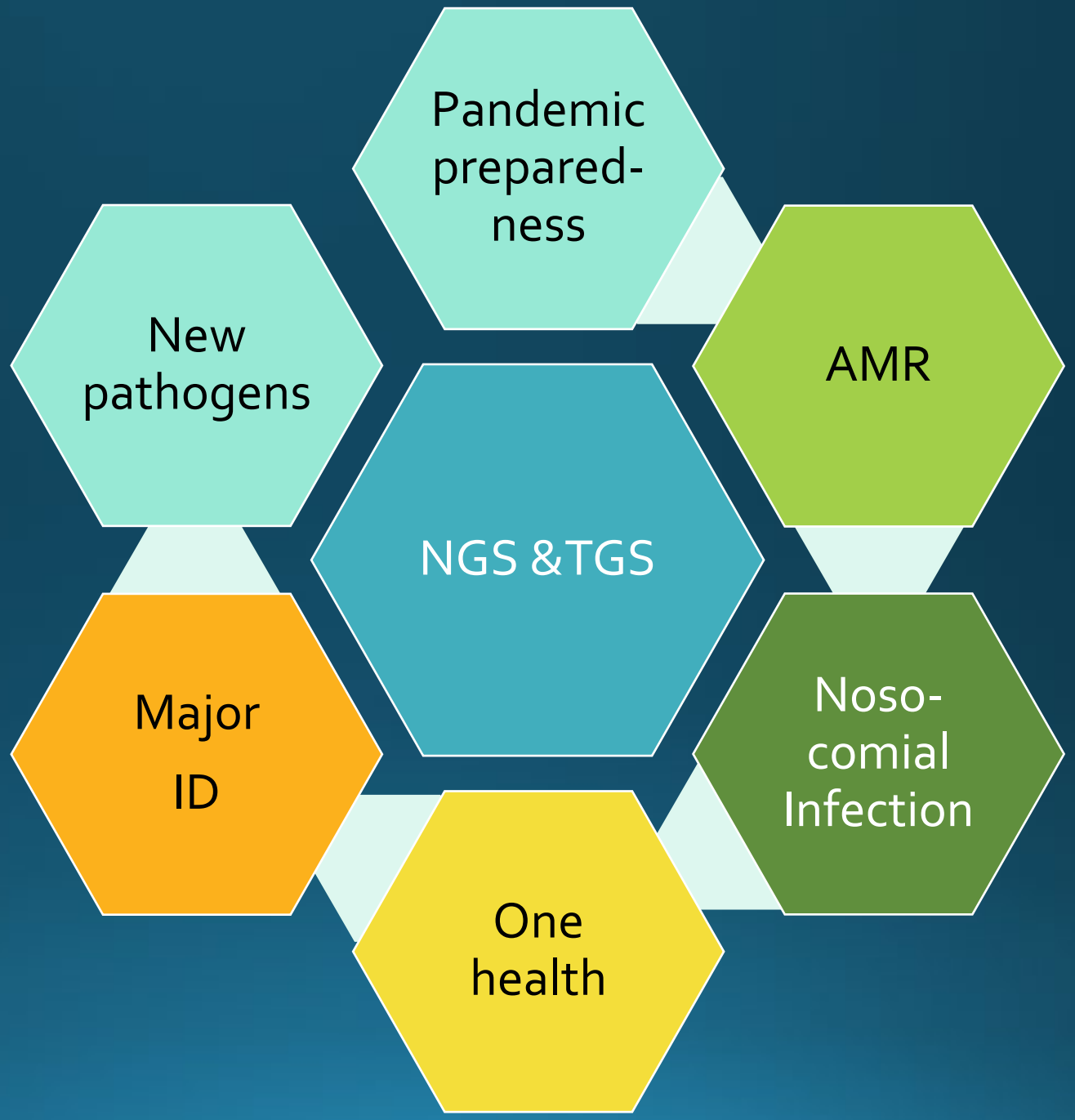
The Continuous Threat of Infectious Diseases

- New pathogens of pandemic potentials: Corona viruses (SARS, SARS CoV2, MERS), Influenza, Ebola, including AMR.
- Major ID remain to be solved-Hospital-acquired infections, TB, Dengue, sepsis
- New populations/new pathogens:
  - Aging population
  - Immunocompromised (cancer).

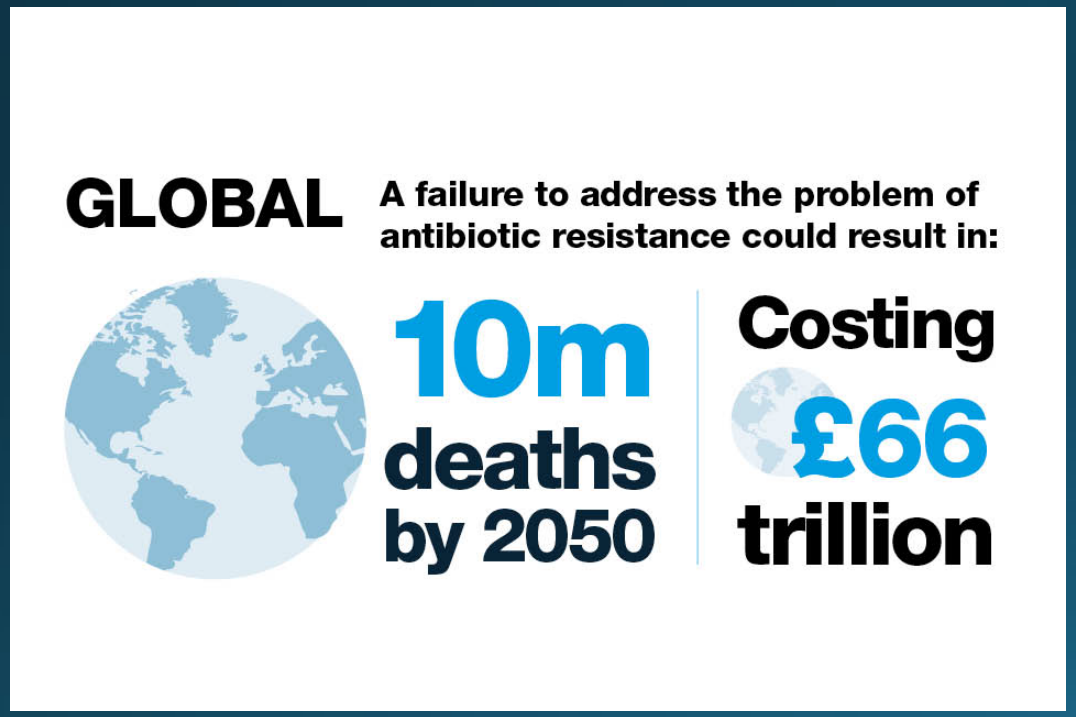


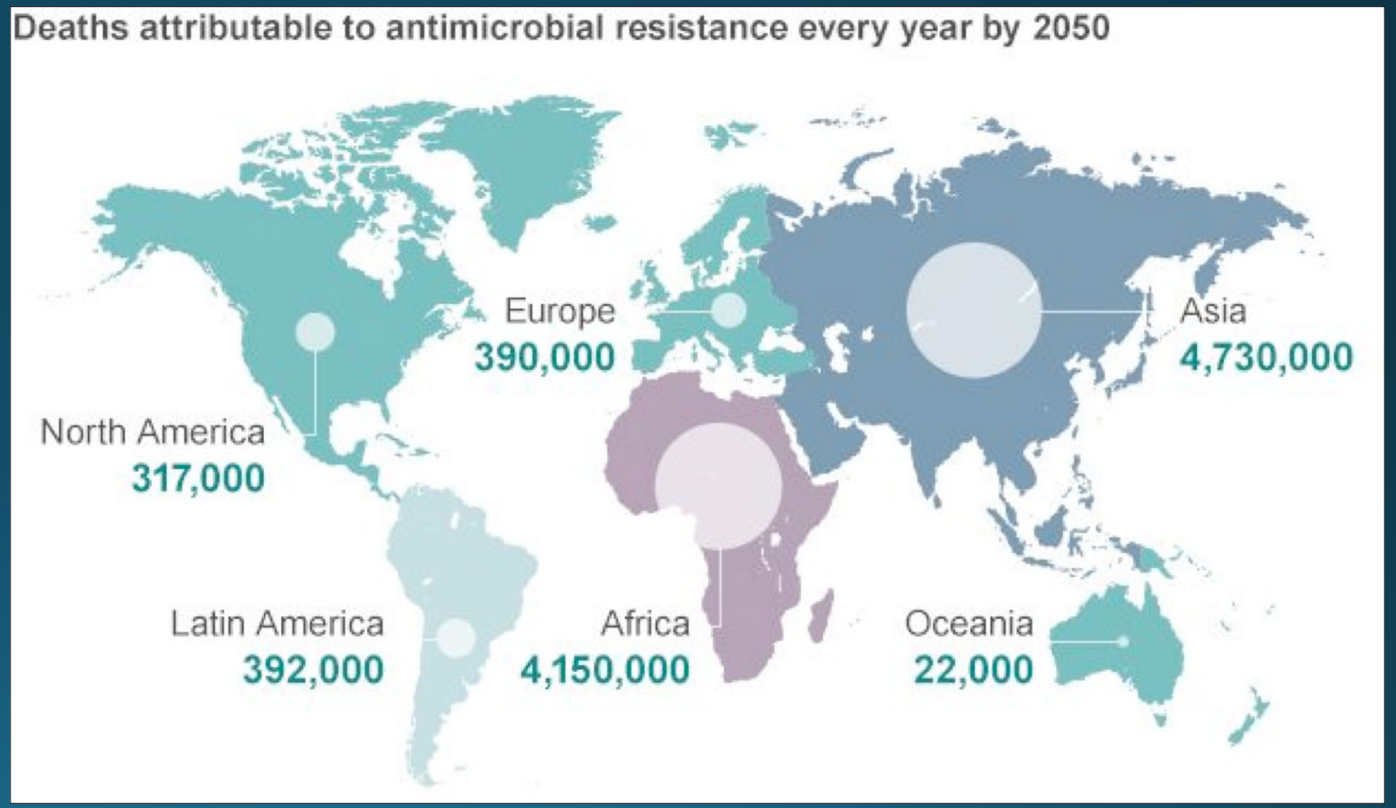
Types of Infectious Diseases benefited from WGS.





One health is essential for preventing the pandemic of AMR.

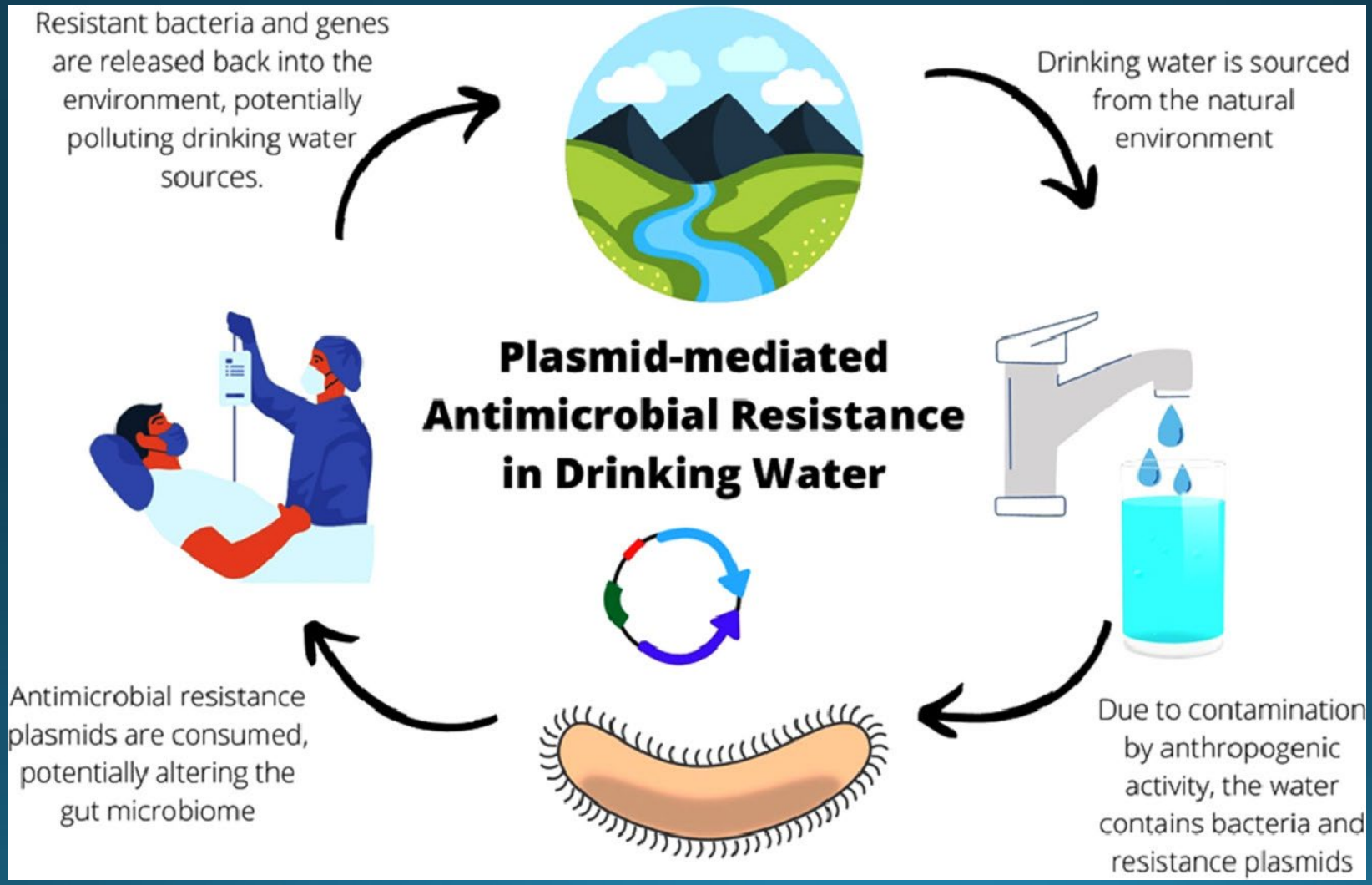




The number of deaths in 2020 is 700,000

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/image_data/file/47286/Health_Matters_AMR_960x6404.jpg

One health


Resistant bacteria and genes are released back into the environment, potentially polluting drinking water sources.
Drinking water is sourced from the natural environment
Plasmid-mediated Antimicrobial Resistance in Drinking Water
Antimicrobial resistance plasmids are consumed, potentially altering the gut microbiome
Due to contamination by anthropogenic activity, the water contains bacteria and resistance plasmids

The Use of Genomic Sequencing Technology in Controlling Infectious Diseases

①Mutations into the **pandemic** strain need to **occur only once** and can happen anywhere.
②However, the mutations **may be multiple steps**. If each step has a chance to establish, the final clone may rapidly expand. Then stopping the pandemic becomes impossible.
③So, detection of the potential pandemic strain needs to be done at the early step to mutations or early phase of clonal expansion .

- With current technology, the cost-effective way is by **genomic surveillance.**

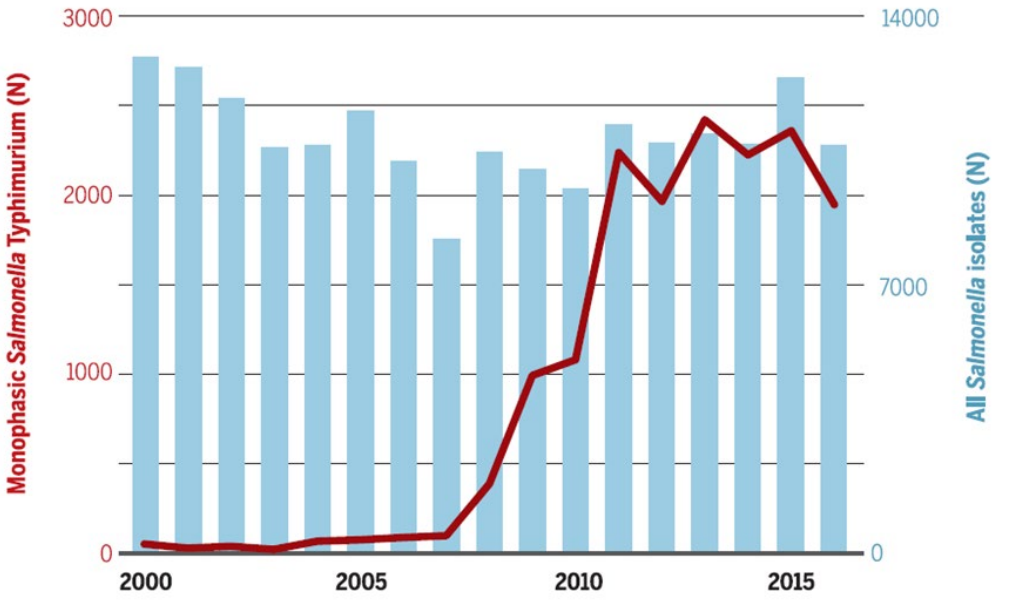


Fig. 3. The epidemic of monophasic *Salmonella* Typhimurium (1,4,[5],12:i:-). The graph shows the number of *Salmonella* isolates from human infections at the French National Reference Centre for *Salmonella* during 2000 to 2016. The blue bars depict the total number of *Salmonella* spp. isolated by year over the defined period; the red plot depicts the number of *Salmonella* Typhimurium (1,4,[5],12:i:-) isolated by year.

WGS is becoming an integral part of EID genomic surveillance.

Evolution of SARS CoV2 in Thailand based on 27000 sequences from Thailand +7000 similar sequences worldwide deposited in GISAID.

MICROBIAL GENOMICS

RESEARCH ARTICLE

Aiewsakun *et al.*, *Microbial Genomics* 2023;9:001170

DOI 10.1099/mgen.0.001170

MICROBIOLOGY SOCIETY

OPEN DATA OPEN ACCESS

Spatiotemporal evolution of SARS-CoV-2 in the Bangkok metropolitan region, Thailand, 2020–2022: implications for future outbreak preparedness

Pakorn Aiewsakun[1,2,*], Bharkbhoom Jamsai[1,2], Worakorn Phumiphanjarphak[1,2], Waritta Sawaengdee[3], Prasit Palittapongarnpim[1,2] and Surakameth Mahasirimongkol[3,*]

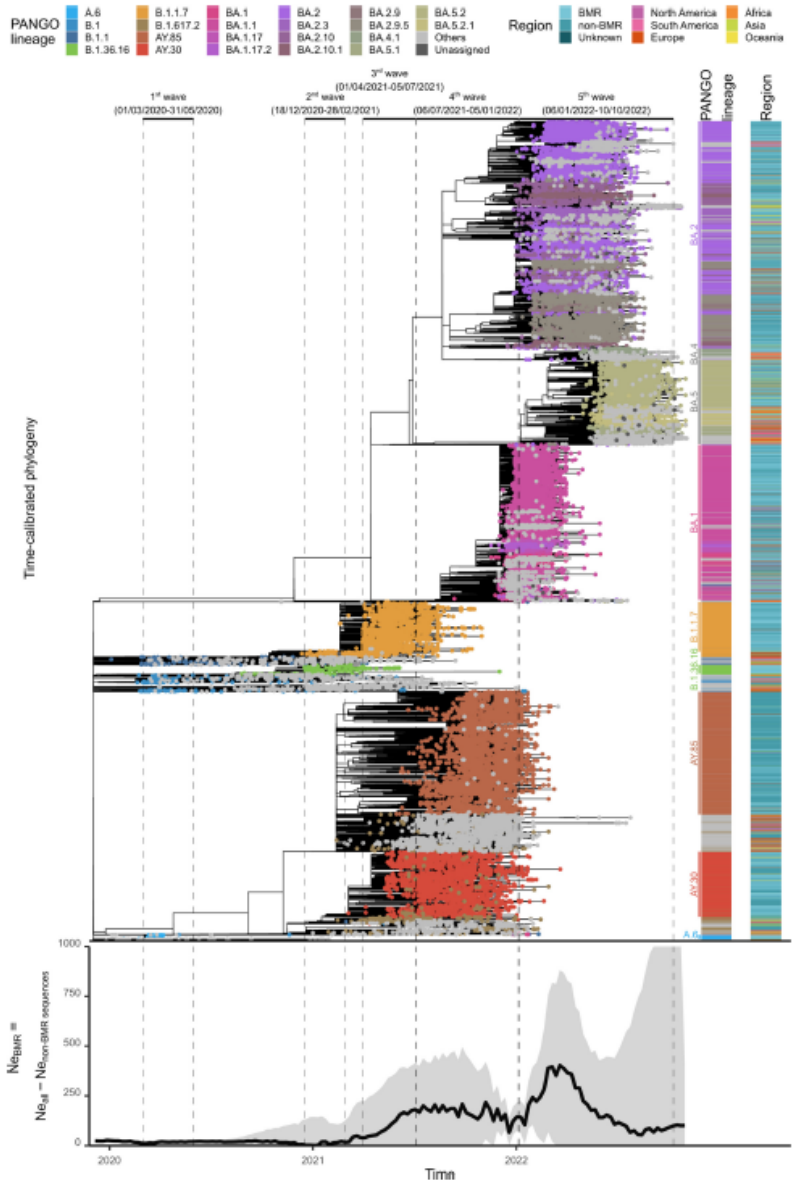
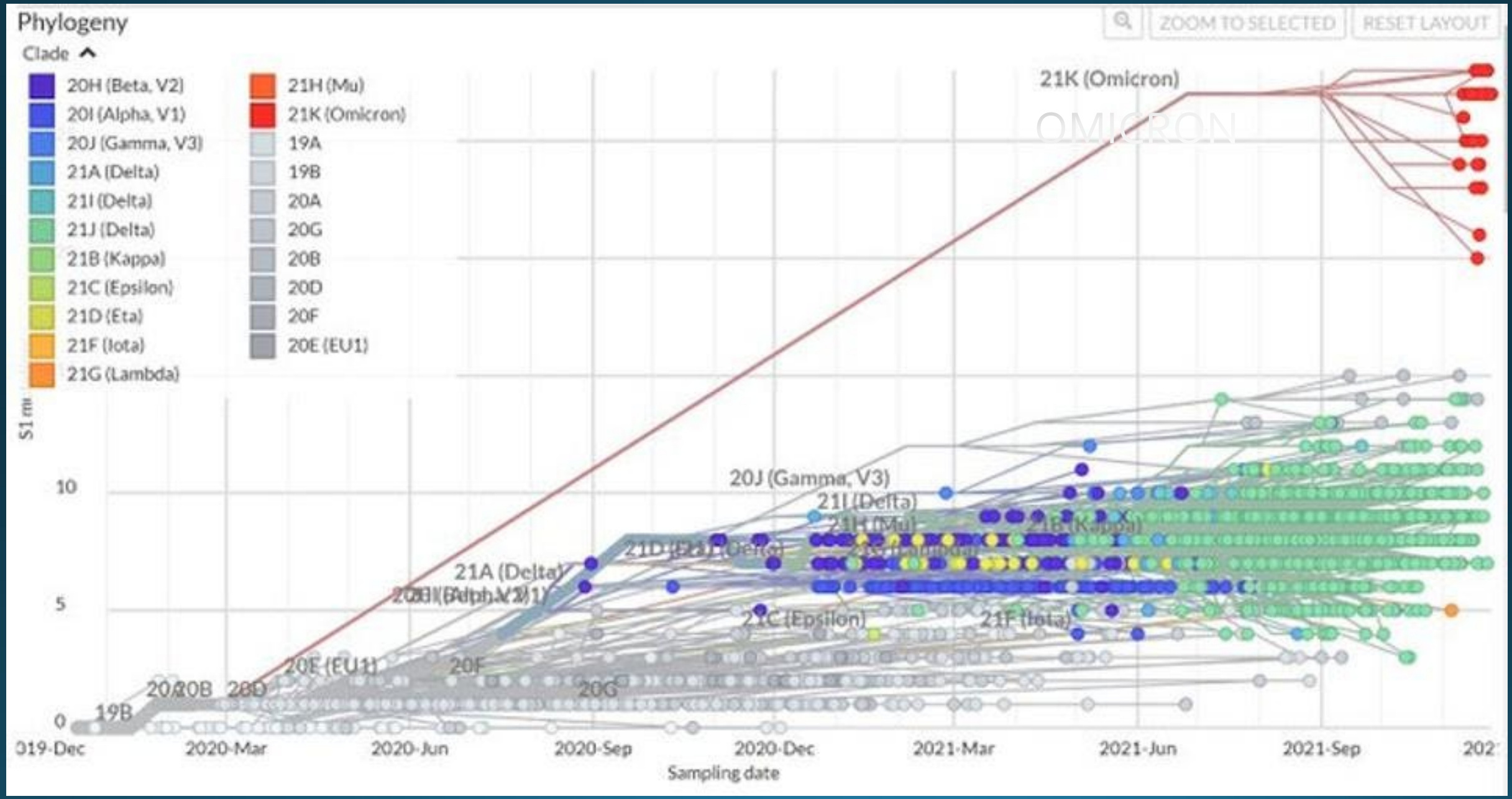
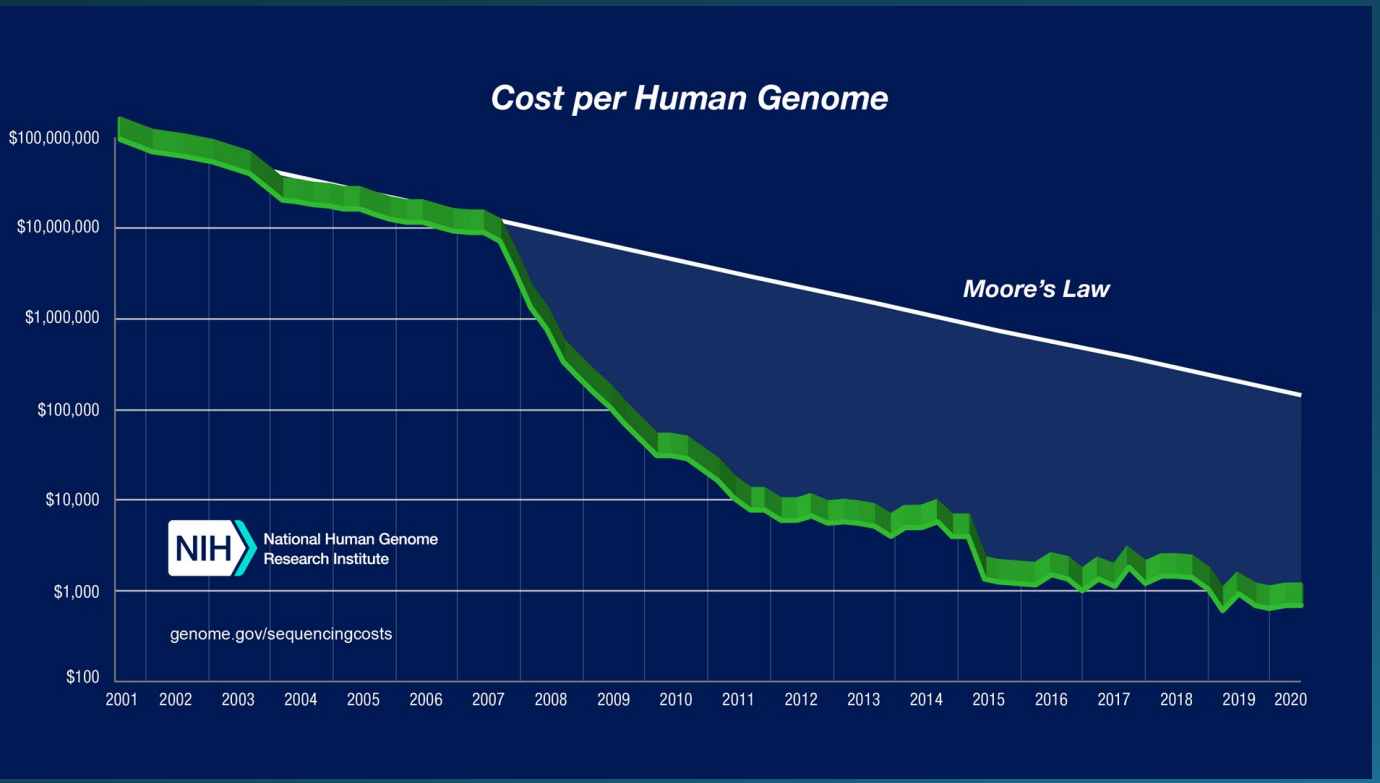


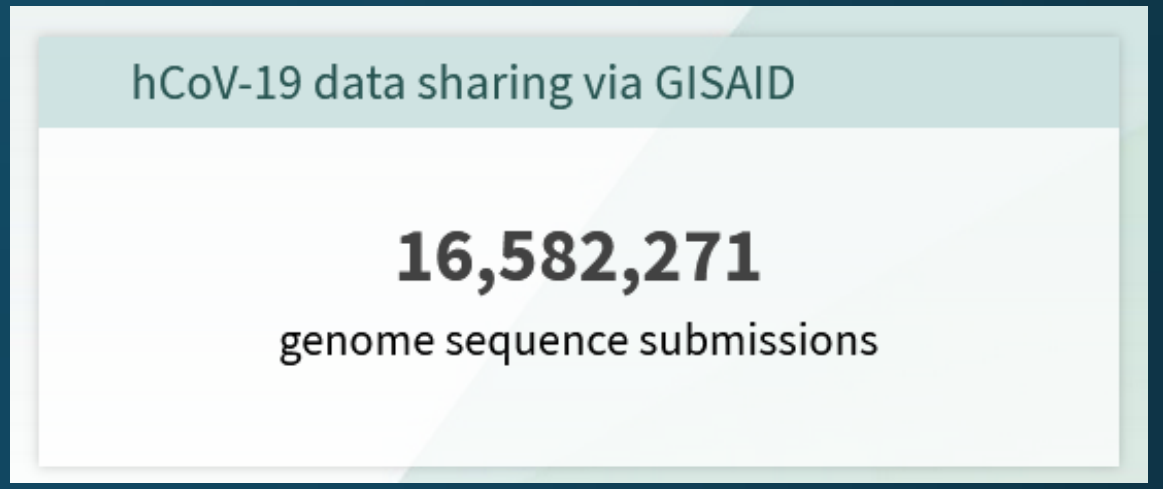
Fig. 3. Top: time-calibrated phylogeny of SARS-CoV-2 in the BMR (n=13005) against a backdrop of non-BMR sequences from Thailand (n=14720) and global reference sequences (n=7173), and (bottom) their effective population size (Ne) dynamic. Time frames of the five waves of COVID-19 in the country are indicated. The Ne dynamics of the viruses in the BMR was estimated by estimating the Ne dynamic of all viruses in the dataset and subtracting that of the viruses from outside the BMR. Solid black line indicates the median estimate and the grey shading area ind… highest probability density. The graph depicts Ne values between 0 and 1000 only.

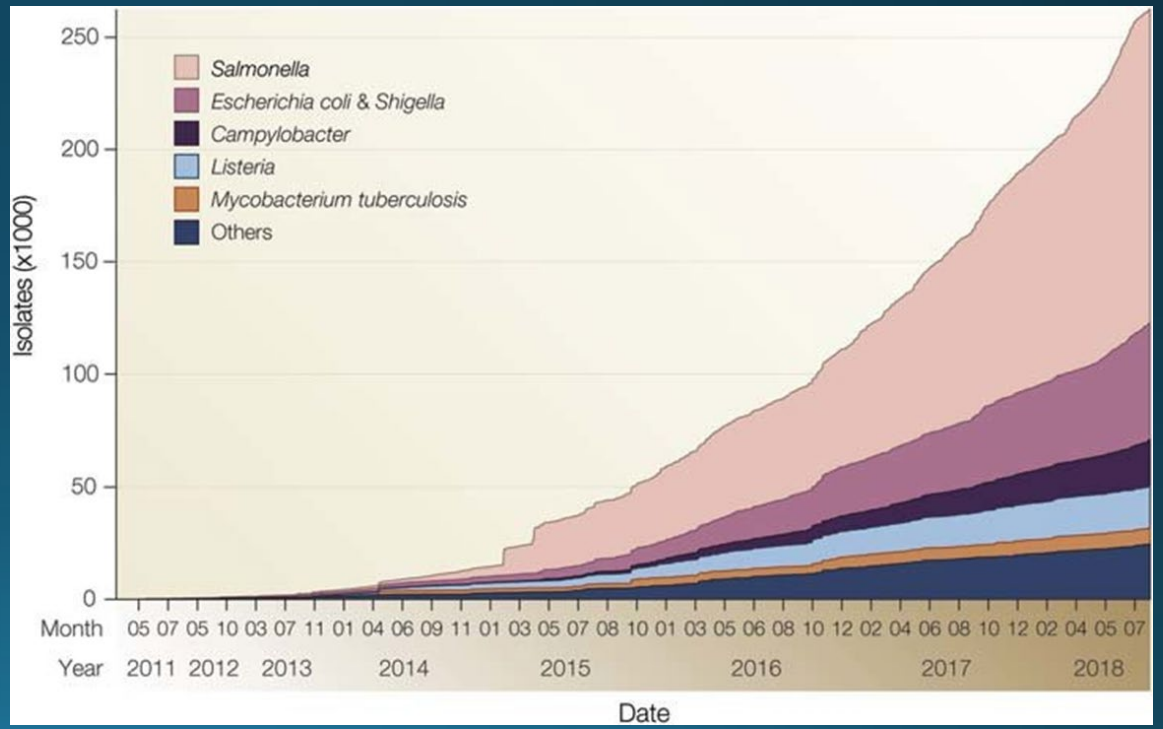
CENMIG


Phylogeny
ZOOM TO SELECTED
RESET LAYOUT
Clade
20H (Beta, V2)
20I (Alpha, V1)
20J (Gamma, V3)
21A (Delta)
21I (Delta)
21J (Delta)
21B (Kappa)
21C (Epsilon)
21D (Eta)
21F (Iota)
21G (Lambda)
21H (Mu)
21K (Omicron)
19A
19B
20A
20G
20B
20D
20F
20E (EU1)
21K (Omicron)
OMICRON
20J (Gamma, V3)
21I (Delta)
21H (Mu)
21B (Kappa)
21A (Delta)
21C (Epsilon)
21F (Iota)
20E (EU1)
20F
20G
20A/20B
20D
19B
10
5
0
019-Dec
2020-Mar
2020-Jun
2020-Sep
2020-Dec
2021-Mar
2021-Jun
2021-Sep
Sampling date

WGS data of several millions of microbes available in public databases are priceless resources for studying evolution of EID pathogens.







Diagnosis of Infectious Diseases by WGS

Metagenomic diagnosis

Drug r

Genotyping

Bacteria: amplification-sequencing of rRNA, rpoB, etc.

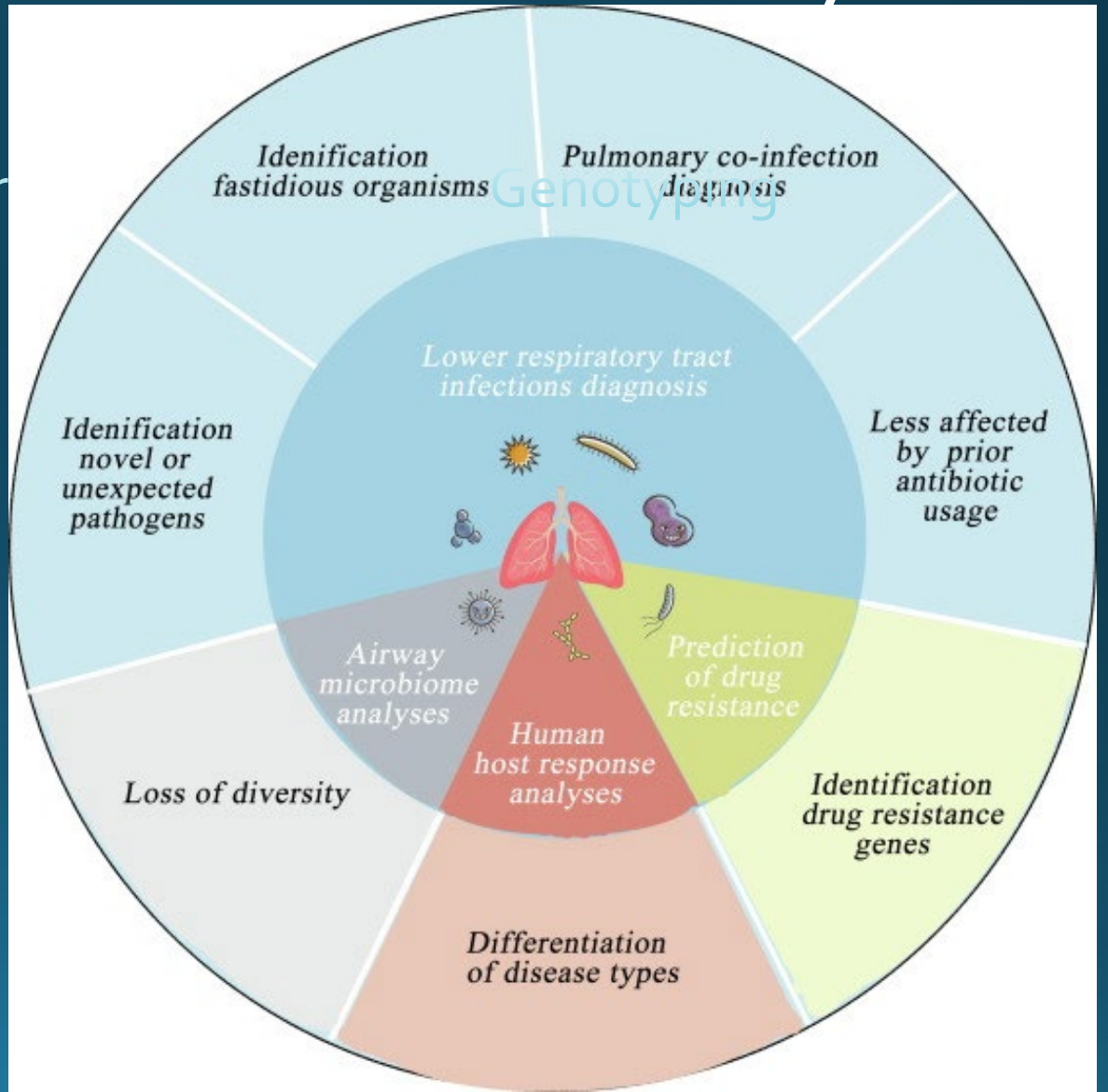
Eukaryotic pathogens

Viruses:

For

Clinical diagnosis

Sentinel sequencing of lower respiratory tract infections and CNS infections.



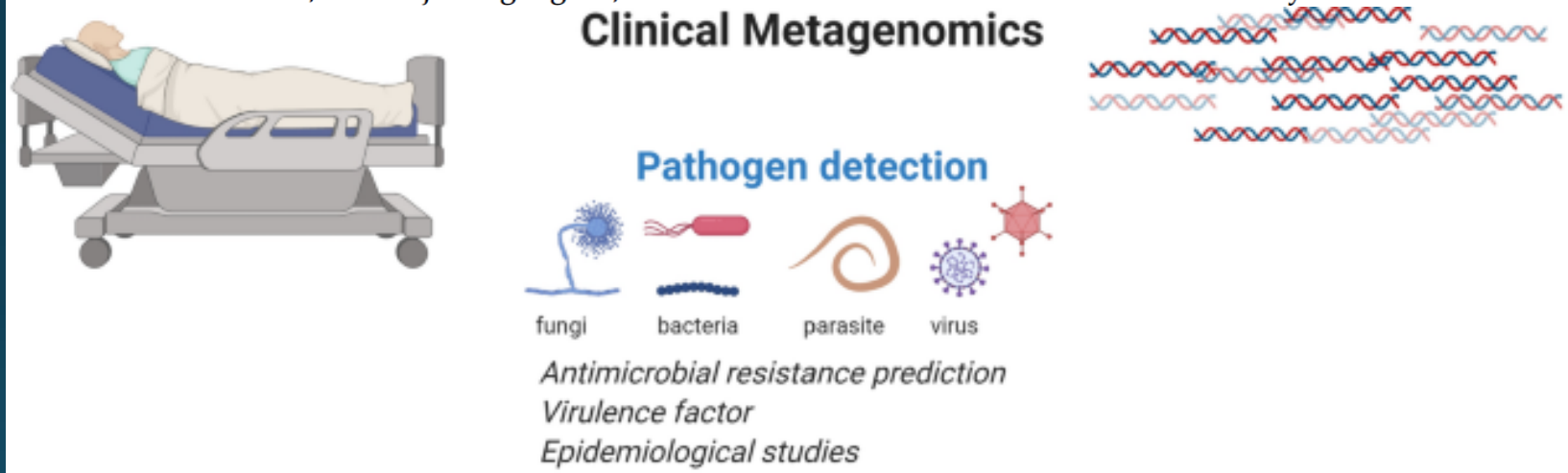
viruses

MDPI

Article

Target Enrichment Metagenomics Reveals Human Pegivirus-1 in Pediatric Hematopoietic Stem Cell Transplantation Recipients

Natali Ludowyke [1], Worakorn Phumiphanjarphak [1,2], Nopporn Apiwattanakul [3], Suwimon Manopwisedjaroen [1], Samart Pakakasama [3], Insee Sensorn [4], Ekawat Pasomsub [5], Wasun Chantratita [4], Suradej Hongeng [3], Pakorn Aiewsakun [1,2,*] and Arunee Thitithanyanont [1,2,*]



Diagnosis of Infectious Diseases by WGS

Metagenomic diagnosis

Bacteria: amplification-sequencing of rRNA, rpoB, etc.

Eukaryotic pathogens

Viruses:

Clinical diagnosis

Sentinel sequencing of lower respiratory tract infections and CAN infections.

Drug resistance

Providing comprehensive information on drug resistance.

Detecting both presence/absence of genes and resistance-conferring mutations

Time consuming-. may be overcome by targeted NGS

Not all genetic mechanisms of phenotypic resistance are well documented.

Genotyping

2018

The use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in *Mycobacterium tuberculosis* complex: technical guide

World Health Organization

FIND
Because diagnosis matters
WHO collaborating centre for the evaluation of new diagnostic technologies

Catalogue of mutations in *Mycobacterium tuberculosis* complex and their association with drug resistance

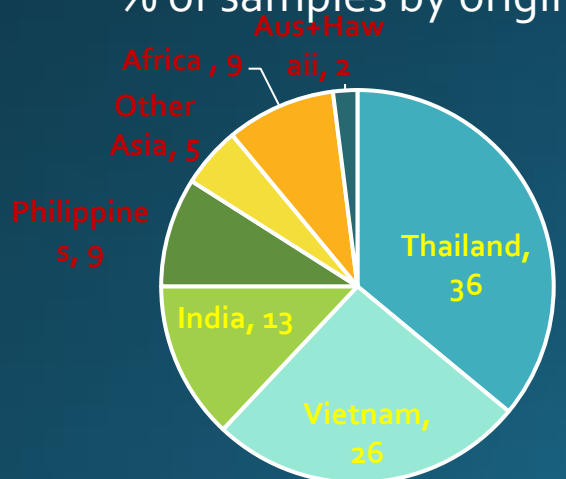
World Health Organization

Diagnosis of MTB resistance by WGS:

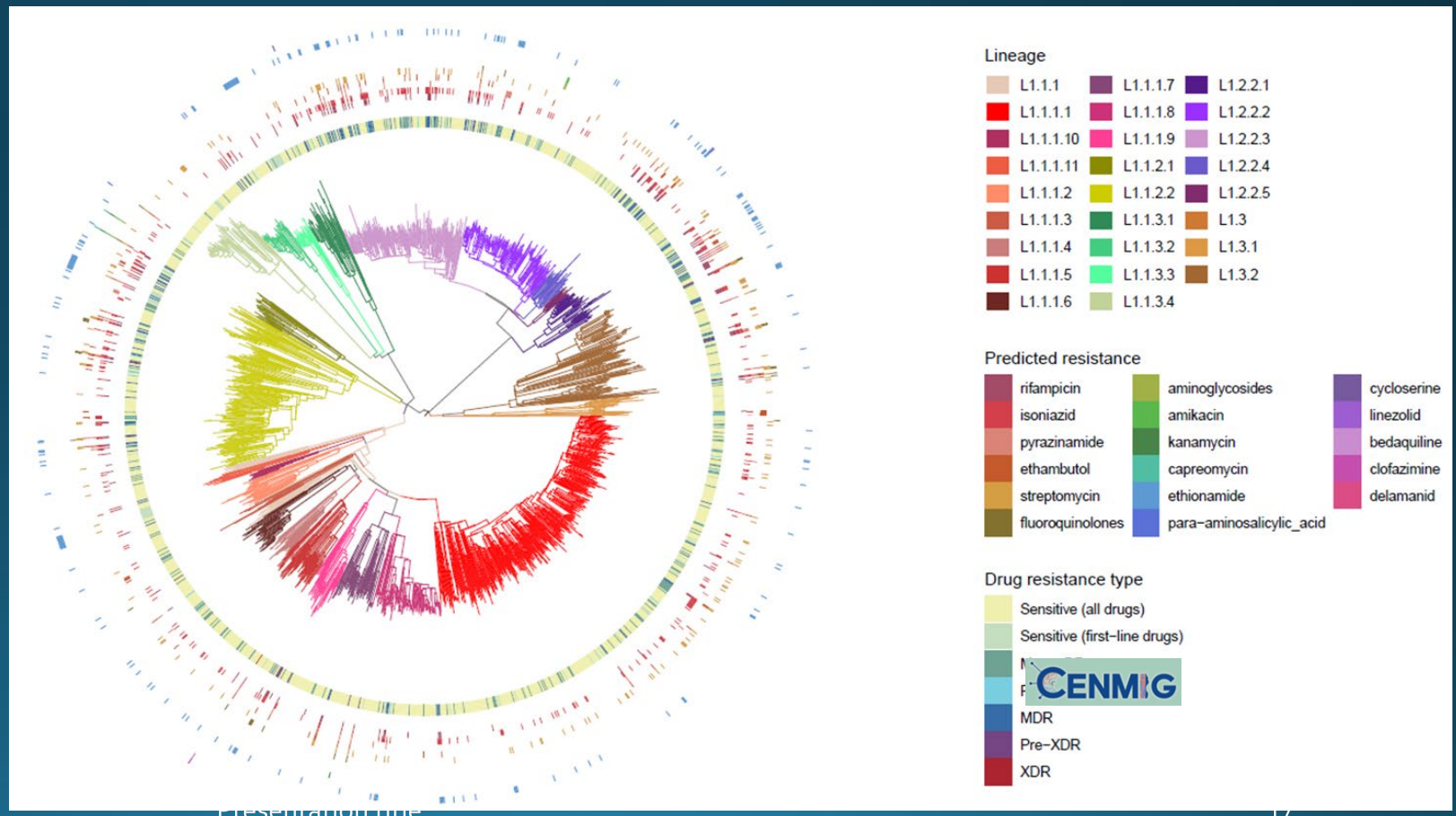
Identification of resistance to new drugs: bedaquiline, protanamid (Using the TB-profiler).

Identification of resistance in a very large number of samples.

% of samples by origins



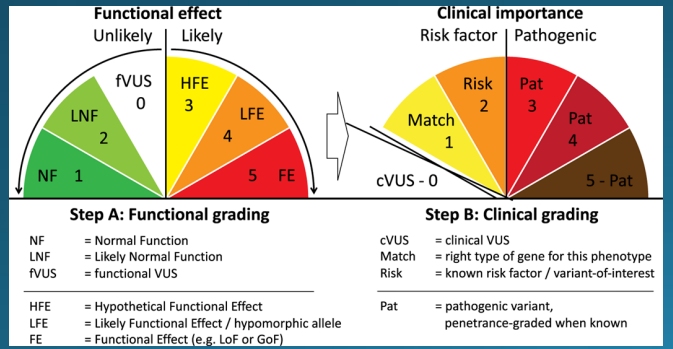
Profiles of resistance-conferring mutations in 1764 MTB-L1 isolates.



Diagnosis of AMR by WGS (by ResFinder, etc.)

Determining the presence of drug resistance genes

- The genes encode ATB degrading/modifying enzymes.
- **Many genes** are well-known, e.g., *bla*, *mcr*, *aac*, *ant*, *aph*, etc.
- Presence of genes do not guarantee that the genes are functional.



Identifying resistance-conferring mutations.

- The common mutations may not be exactly the same in every species.
- **Validation (diversity and accuracy) needs to be done for each species**. Most have not been done to the MTB scale yet.

Structural variations of ATB Resistance Genes (ARGs) require TGS. Locations of the genes suggest the ease of Transmission.

Plasmids

Rapid spreading across species.

Many ARGs can be transmitted together.

Mobile genetic elements

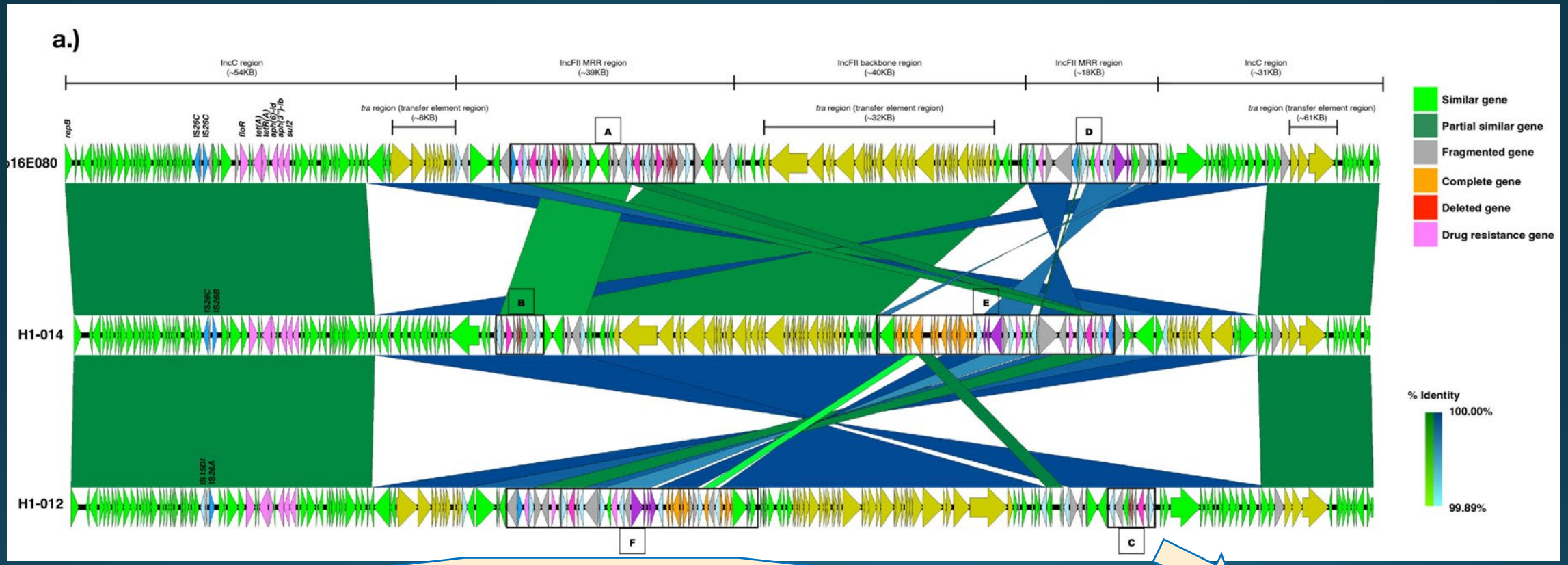
May be in plasmid or chromosome.

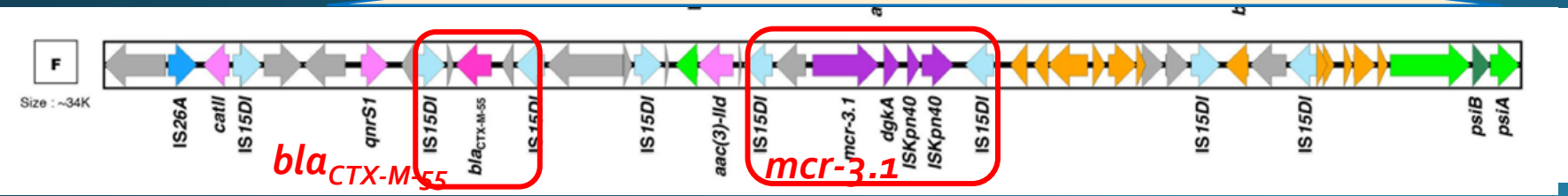
Facilitate transmission of ARG

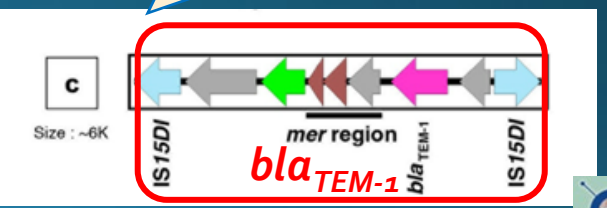
Chromosome

Spreading of needs expansion of the clones

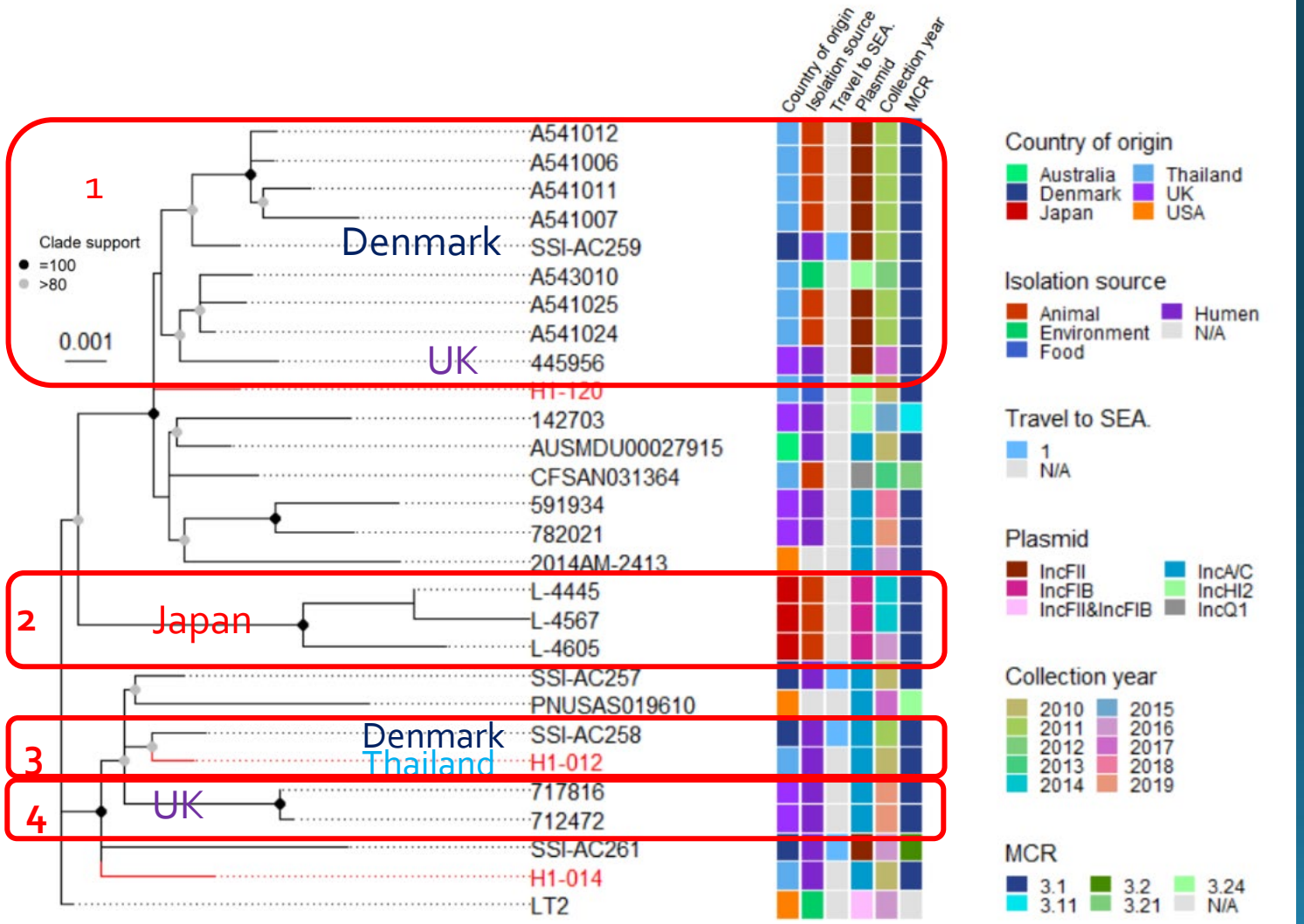
Gene (arrow) maps of IncA/C plasmids of 3 isolates of *Salmonella enterica* serovar 4,[5],12:i:-. ARGs are in pink. ***bla*$_{TEM-1}$, *bla*$_{CTX-M-55}$ and *mcr3.1*** are all co-located in Thai isolates. Defining structures of ARGs-containing segments facilitate tracing of transmission.







Core genome phylogenetic tree of 27 isolates of *S.* 4,[5],12:i:- (Monophasic *S.* Typhimurium). The **phylogenetic clades** correlated with chromosomal ***fljAB-hin* deletion** and **plasmid profiles**. Several groups are related by transmission.



PeerJ

Whole-genome characterisation of multidrug resistant monophasic variants of *Salmonella* Typhimurium from pig production in Thailand

Prapas Patchanee[1], Prawitchaya Tanamai[1], Phacharaporn Tadee[2], Matthew D. Hitchings[3], Jessica K. Calland[4], Samuel K. Sheppard[4,5], Dethaloun Meunsene[6], Ben Pascoe[4,5] and Pakpoom Tadee[1]

RAPID COMMUNICATIONS

Plasmid-borne colistin resistance gene *mcr-3* in *Salmonella* isolates from human infections, Denmark, 2009–17

E Litrup [1], K Kiil [1], AM Hammerum [1], L Roer [1], EM Nielsen [1], M Torpdahl [1]
1. Department of Bacteria, Parasites and Fungi, Statens Serum Institut, Copenhagen, Denmark
Correspondence: Eva Litrup (evl@ssi.dk)

scientific reports

Check for updates

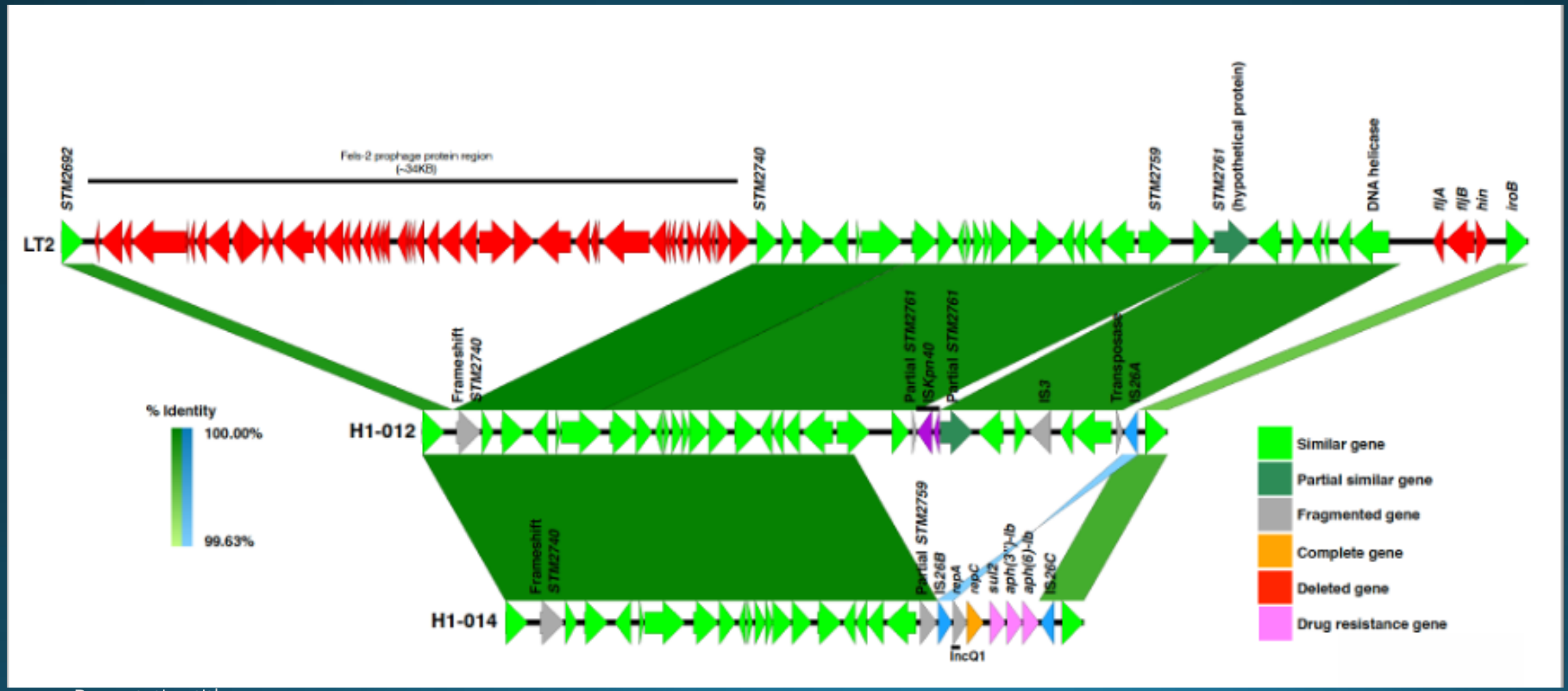
OPEN

Evidence of international transmission of mobile colistin resistant monophasic *Salmonella* Typhimurium ST34

Sirirak Supa-amornkul[1,2], Rattanaporn Intuy[2], Wuthiwat Ruangchai[2], Soraya Chaturongakul[2,3] & Prasit Palittapongarnpim[2,4]

CENMIG

Gene maps of the *fljAB-hin* region of two isolates of *S.* 4,[5],12:i:- (information from hybrid assembly)



In contrast, ARGs of *Salmonella* Kentucky are all in chromosome, many in SGI1-K. (Manuscript in revision for **Microbiology Spectrum**)

- *S. enterica* serovar Kentucky is a polyphyletic group, composed of several genotypes, including ST198, ST152, etc.
- It is commonly isolated from chicken, occasionally from human (not yet in Thailand).
- S. Kentucky ST198 is usually resistant to **fluoroquinolones**, due to mutations in *gyrA* and *parC*, and to **3rd gen cephalosporins**, making it in the priority list of WHO.
- Multiple ARGs are usually found in **Salmonella Genomic Island 1K (SGI1-K).**

Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella spp., fluoroquinolone-resistant

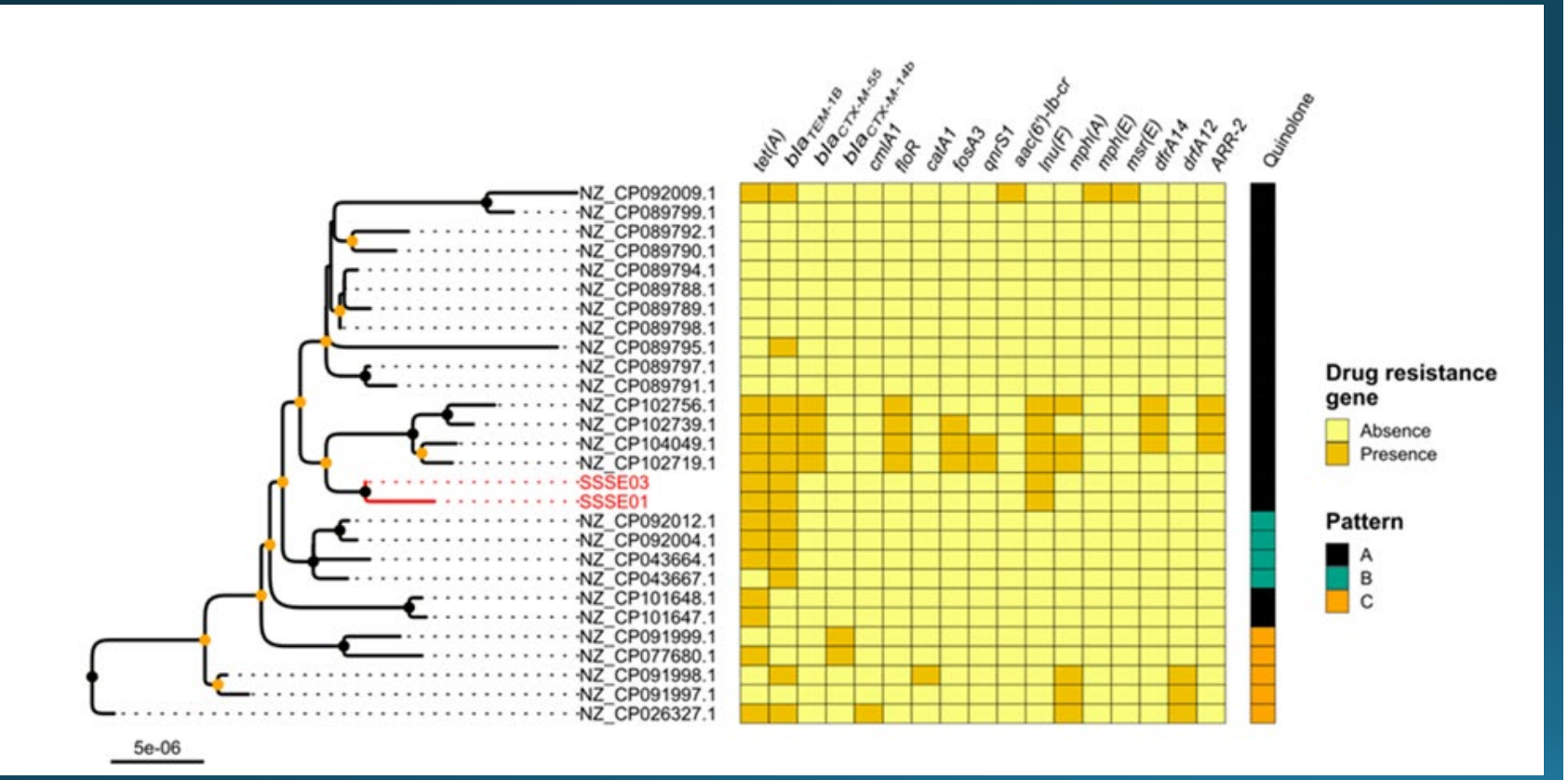
 # Mycobacteria (including *Mycobacterium tuberculosis*, the cause of human tuberculosis), was not subjected to review for inclusion in this prioritization exercise as it is already a globally established priority for which innovative new treatments are urgently needed.

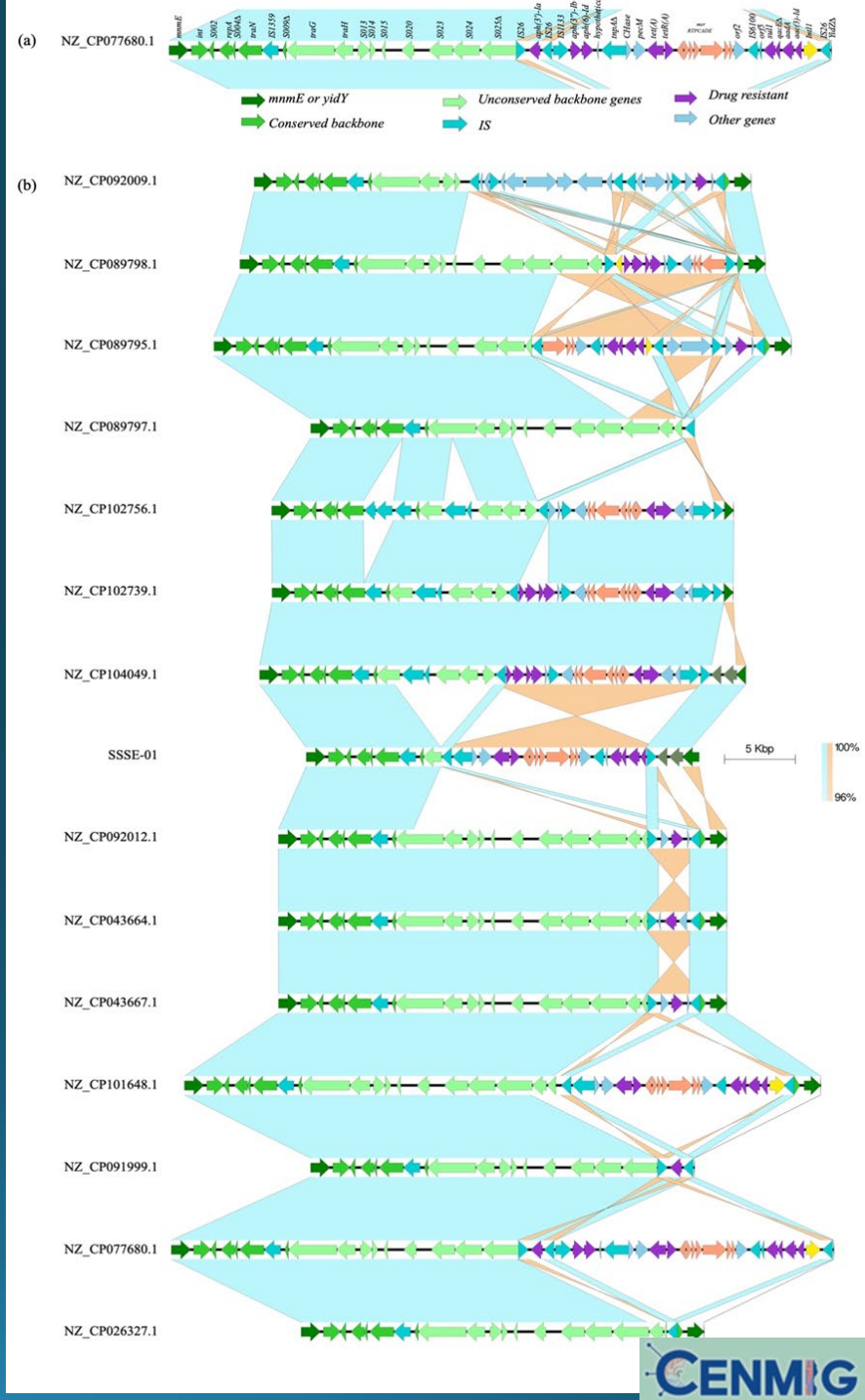
* Enterobacteriaceae include: *Klebsiella pneumonia*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., and *Providencia* spp, *Morganella* spp.

Sample Set:

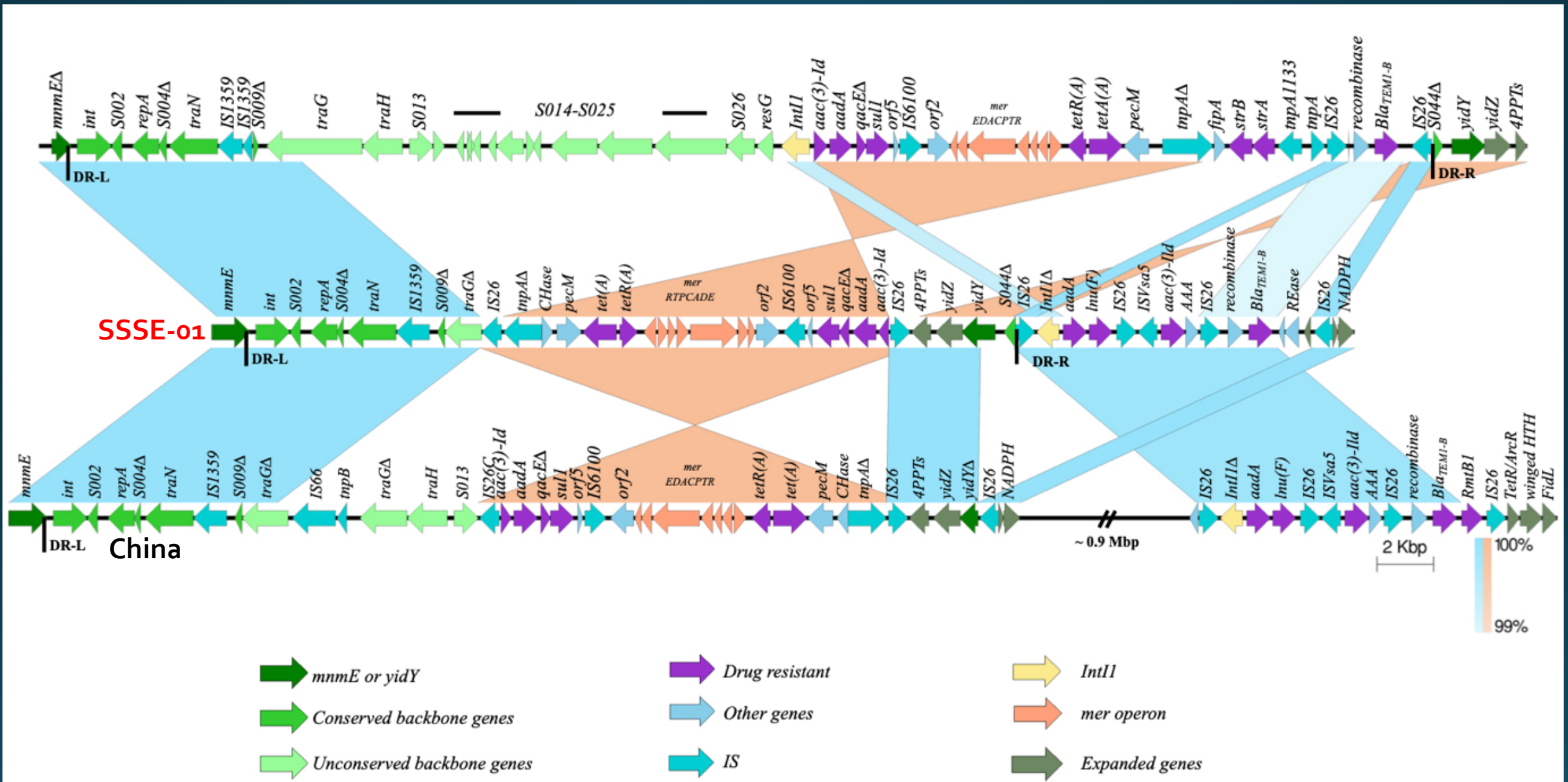
- 2 MDR *S.* Kentucky ST198 samples from chicken slaughter house in Mukdahan, subjected to both short read and nanopore sequencing. Complete genomes were composed of a circular chromosome and 3 small plasmids. The isolates contained several ARGs, all in chromosome.
- Complete genomes of 26 samples of *S.* Kentucky ST198 from NCBI
    - The origins of the other samples were Spain [10], Switzerland [6], Israel [2], USA [2], China [5], Canada [1] and Indonesia [2].

Gene maps of SGI1-K of 28 isolates of *S.* Kentucky indicate extensive variations.





SRC73 (AY463797.8)



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Sentinel sequencing of lower respiratory tract infections and CAN infections.

Drug resistance

Providing comprehensive information on drug resistance.

Detecting both presence/absence of genes and resistance-conferring mutations

Time consuming-. may be overcome by targeted NGS

Not all genetic mechanisms of phenotypic resistance are known.

Genotyping

Correlate with important phenotypes, e.g. drug resistance/sensitivity.

Molecular epidemiology

Tracing outbreaks/ transmission

Molecular Epidemiology: Pathogen genotypes, are usually associated with

Demography

- **Ages**
- **Geography**
- **Ethnicity**
- **Host genetics**

Clinical phenotypes

- **Drug resistance**
- **Transmission potential**
- Clinical presentations
- Treatment outcomes

ARTICLES
https://doi.org/10.1038/s41564-022-01130-y
nature microbiology

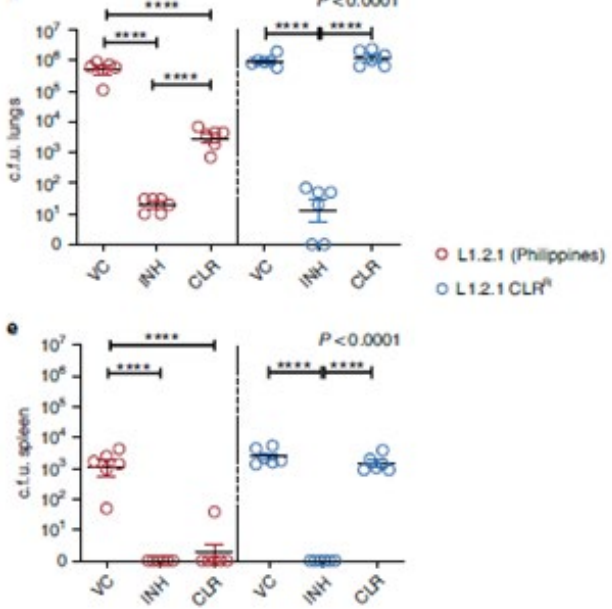
Check for updates

OPEN

CRISPRi chemical genetics and comparative genomics identify genes mediating drug potency in *Mycobacterium tuberculosis*

Shuqi Li[1,5], Nicholas C. Poulton[1,5], Jesseon S. Chang[1], Zachary A. Azadian[1], Michael A. DeJesus[1], Nadine Ruecker[2], Matthew D. Zimmerman[3], Kathryn A. Eckartt[1], Barbara Bosch[1], Curtis A. Engelhart[2], Daniel F. Sullivan[2], Martin Gengenbacher[3,4], Véronique A. Dartois[3,4], Dirk Schnappinger[2] and Jeremy M. Rock[1]✉

A frameshift mutation in ***whiB7*** resulted in inactivation of *whiB7*, making it sensitive to **clarithromycin**. The mutation is found in all isolates belonging to **L1.2.2 (EAI2)-16-20% of MTB in Thailand and 800,000 new cases/y.**



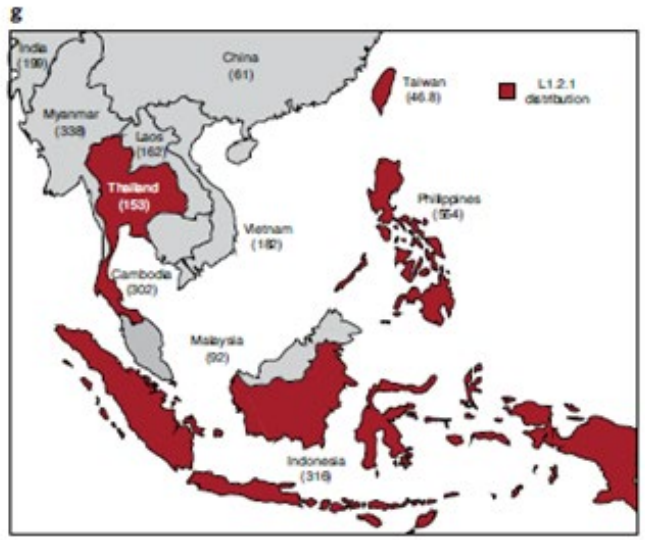


Fig. 6 | A loss-of-function mutation in *whiB7* renders an endemic Indo-Oceanic Mtb lineage hypersusceptible to macrolides. a, Diagram of Mtb *whiB7* with the eight most common *whiB7* variants observed in our clinical strain genome database. Pie chart depicts the observed frequencies of each variant. L, dominant lineage in which variant is observed. **b**, Sanger sequencing of *whiB7* from the indicated Mtb clinical strains and their country of origin. PTC, premature termination codon. The colour of each peak represents the base at the indicated position (black, G; green, A; red, T; blue, C). **c**, Dose-response curves (mean ± s.e.m., $n = 3$ biological replicates) were measured for a reference set of Mtb clinical and lab strains. **d**,**e**, Lung (**d**) and spleen (**e**) Mtb c.f.u. (mean ± s.e.m.) in BALB/c mice after 24 d of INH (25 mg kg^{-1}) or CLR (200 mg kg^{-1}) treatment. Statistical significance was assessed by one-way ANOVA followed by Tukey's post-hoc test. VC, vehicle control; CLR^R, clarithromycin-resistant (23S rRNA A2297G). Black line, median. $n = 6$ mice per group/condition. **f**, Phylogenetic tree of 178 Mtb clinical strains isolated during the 2012 nationwide drug resistance survey in the Philippines[10] (Source Data Fig. 6). The presence of the *whiB7* Glv64delG mutation and genotypically predicted drug-resistance status are shown as in Fig. 5f. **g**, Map showing L1.2.1

Journal of Global Antimicrobial Resistance 3 (2015) 262–266

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journal homepage: www.elsevier.com/locate/jgar

Genetic characterisation of a *whiB7* mutant of a *Mycobacterium tuberculosis* clinical strain

Saradee Warit[a], Saranya Phunpruch[b,c], Chaitas Jityam[b], Sarinya Jaitrong[a], Pamaree Billamas[a], Angkana Chaiprasert[d], Prasit Palittapongarnpim[a,e], Therdsak Prammananan[a,*]

scientific reports

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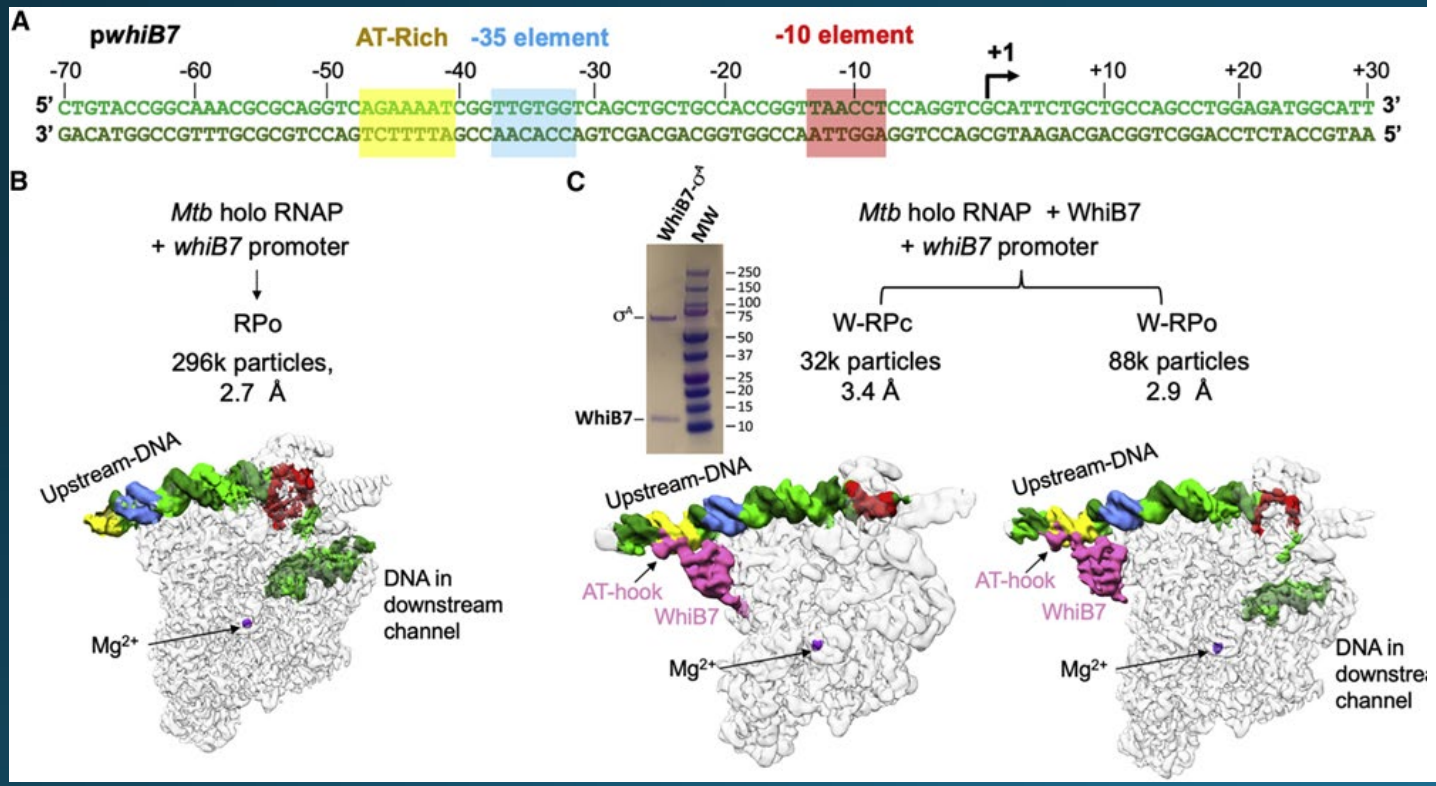
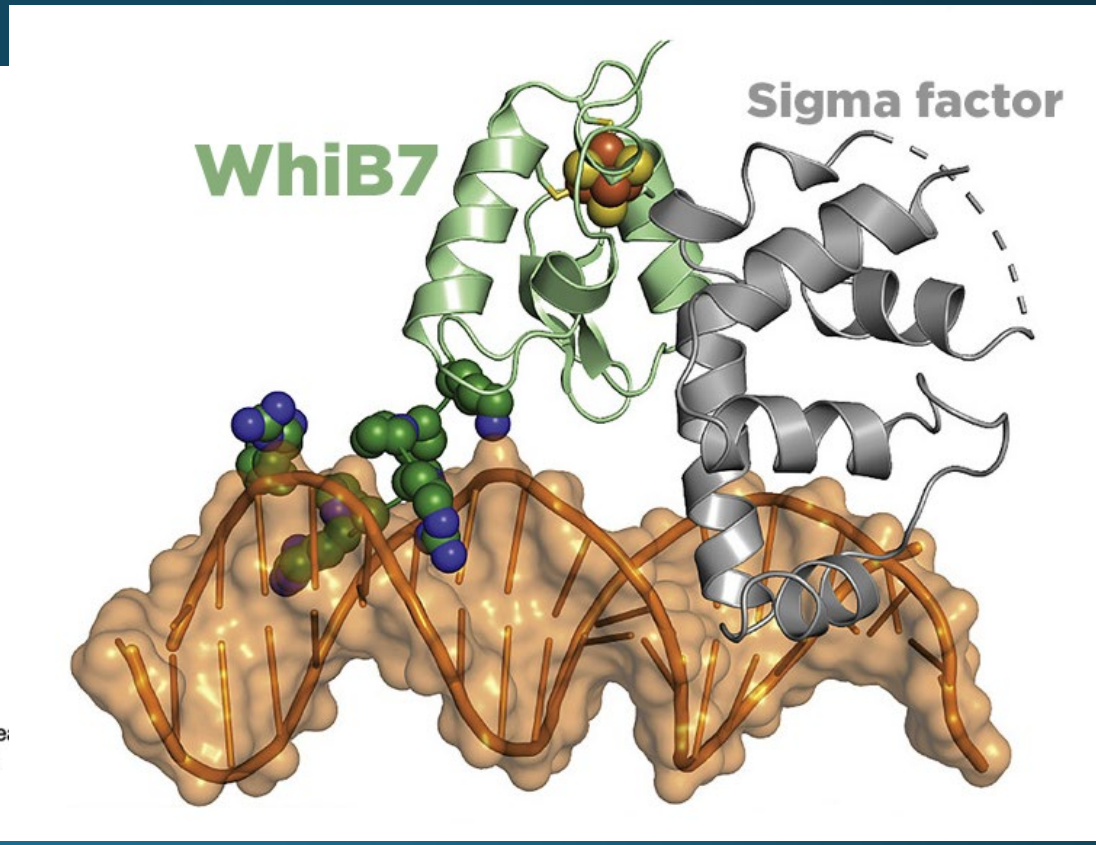
Analysis of *whiB7* in *Mycobacterium tuberculosis* reveals novel AT-hook deletion mutations

Olabisi Flora Davies-Bolorunduro[1,2,3], Bharkbhoom Jaemsai[2], Wuthiwat Ruangchai[1], Worakorn Phumiphanjarphak[2], Pakorn Aiewsakun[1,2] & Prasit Palittapongarnpim[1,2]✉

WhiB proteins of Actinobacteria.

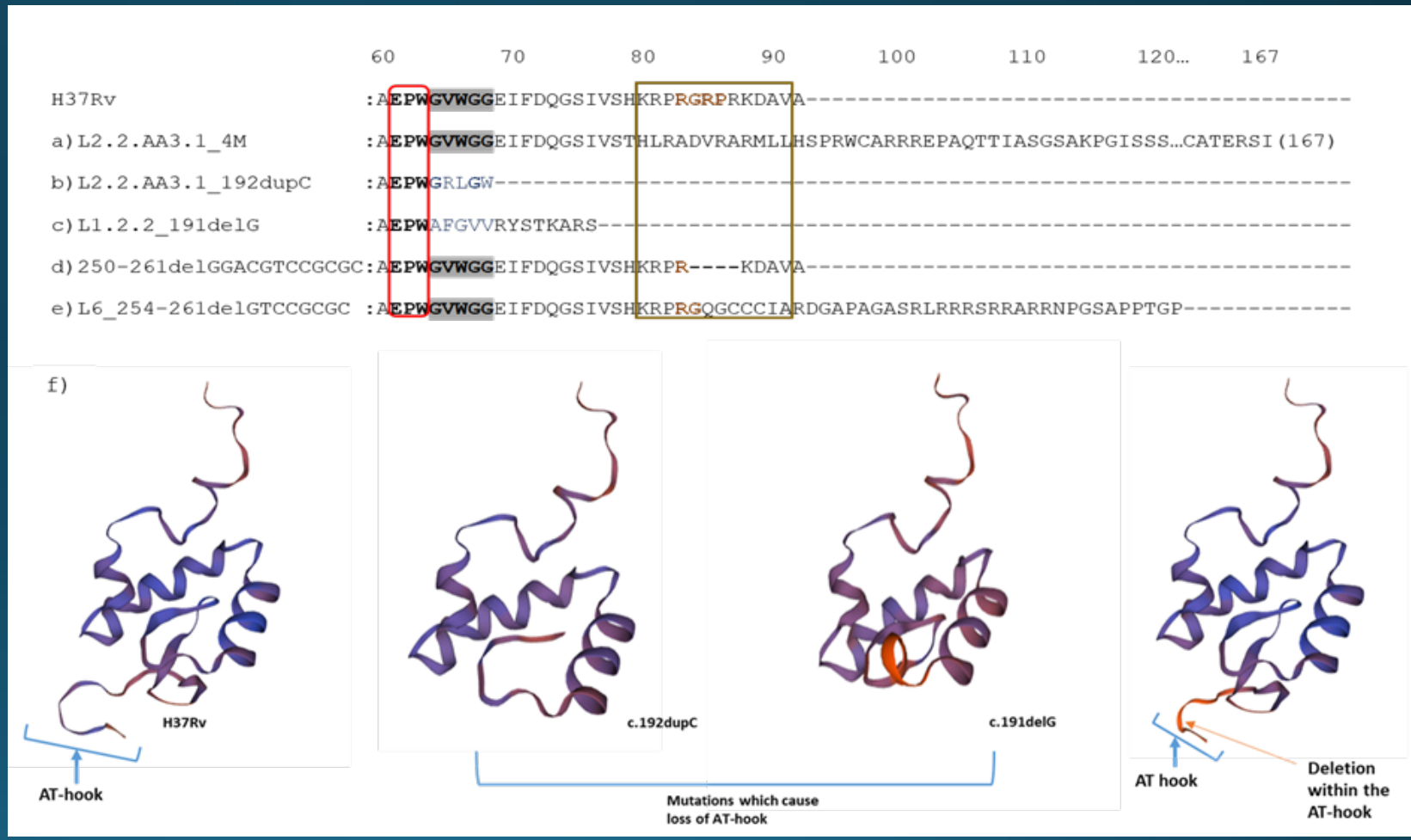




Analysis of *whiB7* in *MTB* reveals novel AT-hook deletion mutations

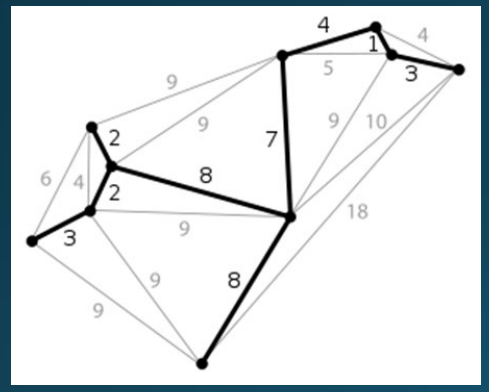
Olabisi Flora Davies-Bolorunduro, Bharkboom Jaemsai, Wuthiwat Ruangchai, Worakorn Phumiphanjarphak, P Aiewsakun[1], P Palittapongarnpim

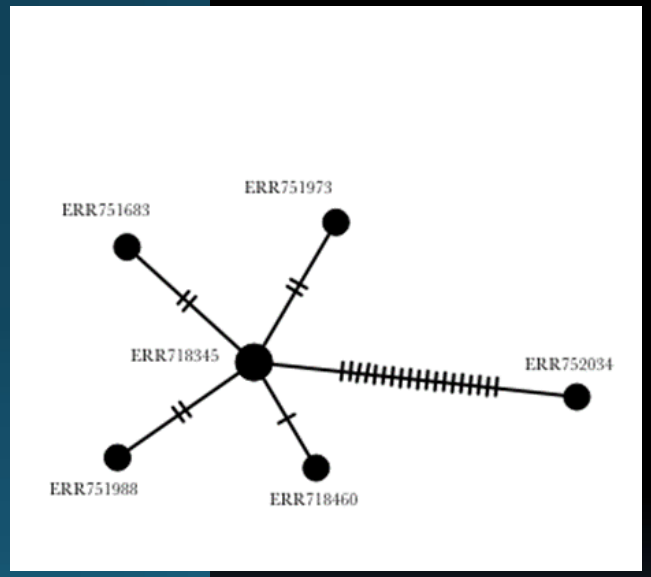
- 40500 WGS of global isolates including L1-L8.
- c.191delG specificity to L1.2.2 is confirmed.
- c.191delG results in the loss of β-turn structure and C-terminal AT hook.
- Other mutations causing loss of AT hook have been identified
  - 192dupG
  - 4 M mutations
  - Deletion of core amino acid of AT hook in 17 sublineages



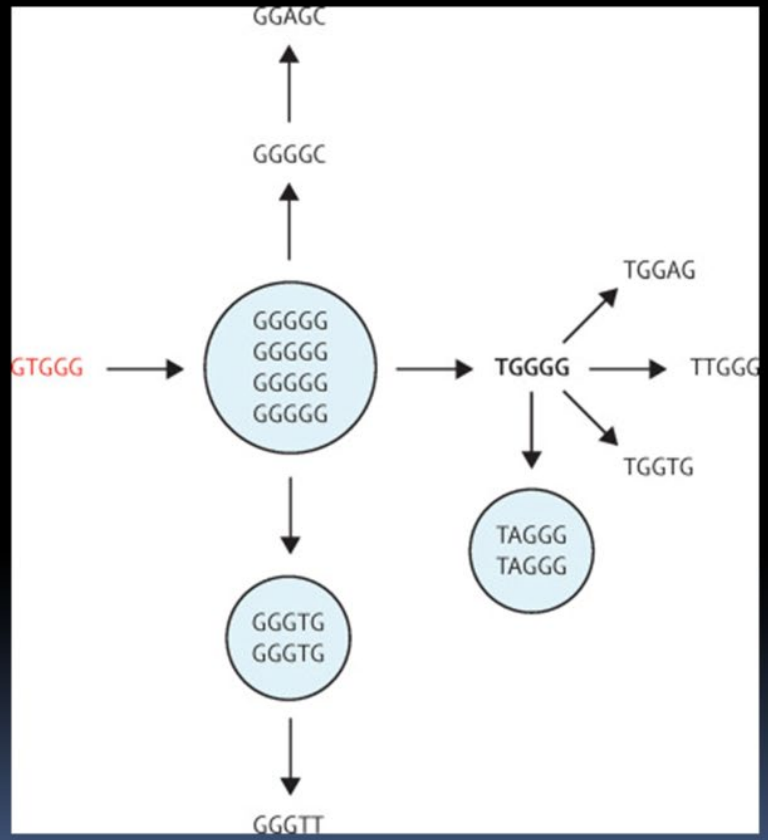
Genetic clustering of MTB samples (based of Pairwise SNV distances < X) suggests epidemiological linkage (recent transmission).

Minimal Spanning tree links isolates with edge<X by minimizing the numbers of required mutations to explain the set of samples.



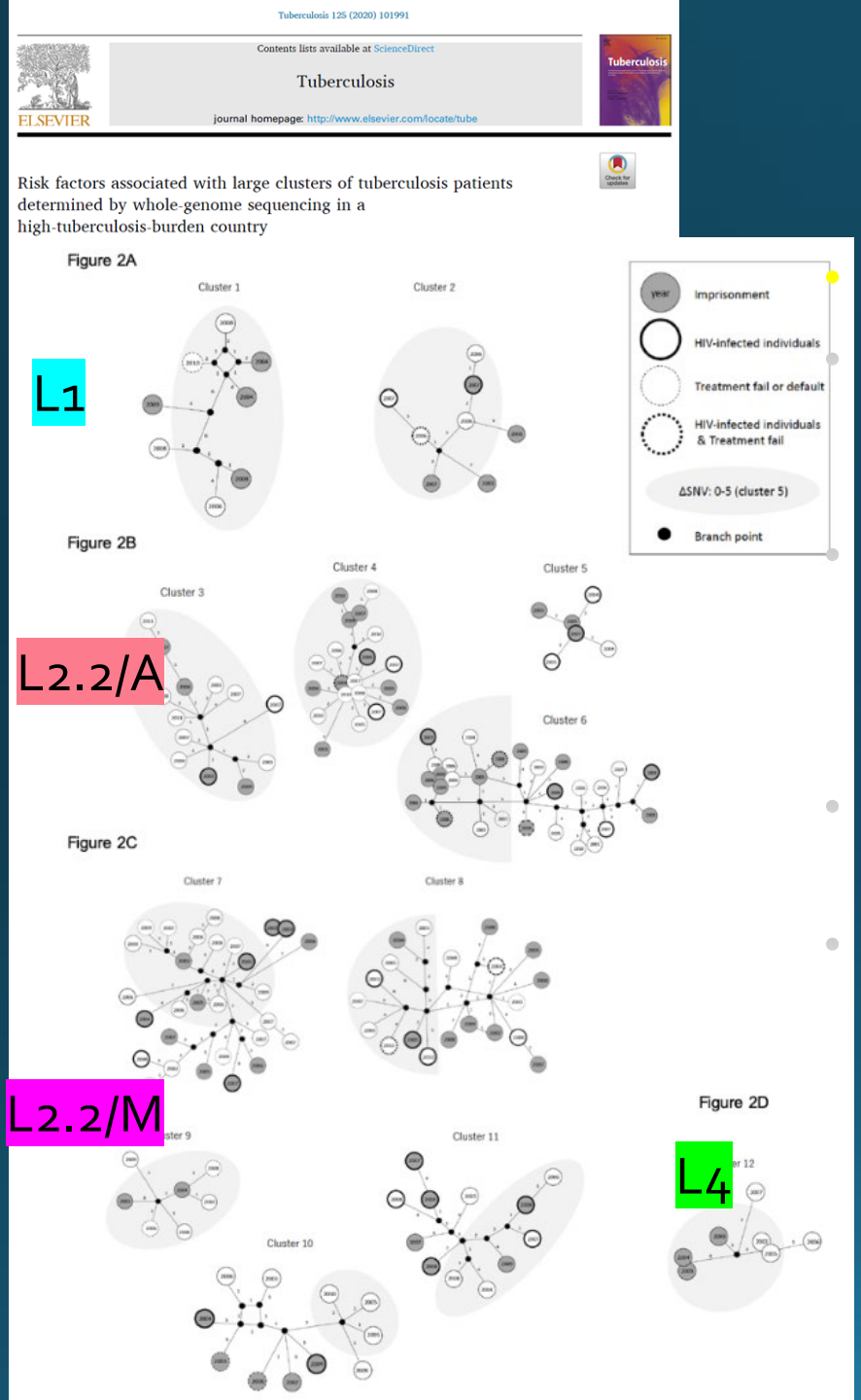


Howard E Takiff, Oscar Feo
Lancet Infect Dis Volume 15, Issue 9, 2015, 1077–1090
http://dx.doi.org/10.1016/S1473-3099(15)00071-7



Current SNV difference cutpoints

- 5 SNVs for outbreaks in low-burden areas.
- 12 SNVs for outbreak in high-burden areas- poor coverage of health care- missing linkage patients.
- 20 SNVs when only a small proportion of samples is sequenced- more missing link



Large genetic clusters of MTB in Chiangrai (cutoff= 12 SNVs) are mostly L2, both Ancestral and Modern

Sampling proportion -1146/6727 **(17%)**

431/1146 **(38%)** were **clustered** into 111 ones.

- L1 19% L2.2.(Anc) 57% L2.2.(Mod) 59% L4 32%

12 **(large) clusters** had >5 members**. About 30% of all Beijing cases belonged to large clusters.**

- L1 3% L2.2.(Anc) 27% L2.2.(Mod) 34 % L4 4%

Independent **Risk factors** for clustering: young age, HIV+, hill tribes, L2.2 (Beijing strains).

Independent **Risk factors** in Large clusters: **L2.2 (Beijing)**

- L2.2.Ancestral: **Imprisonment**
- L2.2.Modern: **Treatment Failure**

Risk for Prison-to-Community Tuberculosis Transmission, Thailand, 2017–2020

Reiko Miyahara, Pundharika Piboonsiri, Boonchai Chiyasirinroje, Worarat Imsanguan, Supalert Nedsuwan, Hideki Yanai, Katsushi Tokunaga, Prasit Palittapongarnpim, Megan Murray, Surakameth Mahasirimongkol

- Settings: Population based study in Chiangrai 2017-2020
- Pairwise SNV distances cutoff: 20
- Large genetic cluster: >10 patients

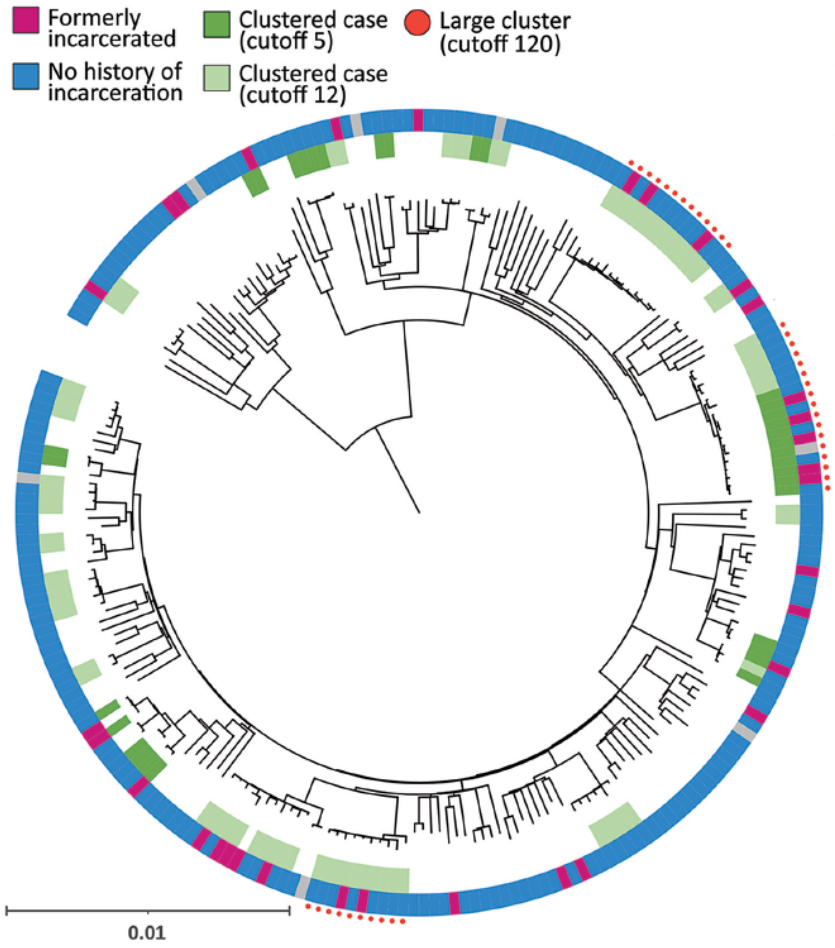


Figure 1. Phylogenetic tree of patients with pulmonary tuberculosis of *Mycobacterium tuberculosis* lineage in study of risk for prison-to-community tuberculosis transmission, Chiang Rai Province, Thailand, 2017–2020. Scale bar indicates 0.01 substitutions per site SNP, single-nucleotide polymorphism.

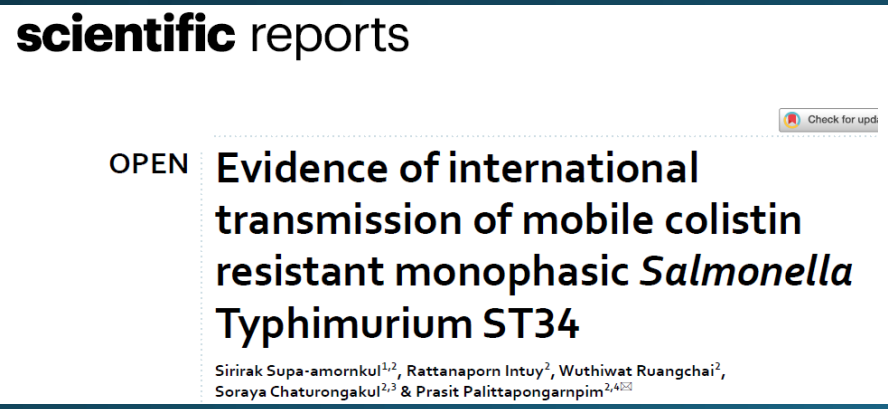
Pathogen Transmission Reports in Thailand

Reported

- MTB
- Salmonella
- MRSA

Expected

- Streptococcus agalactiae
- Acinetobacter baumanii and other nosocomial infections.



scientific reports

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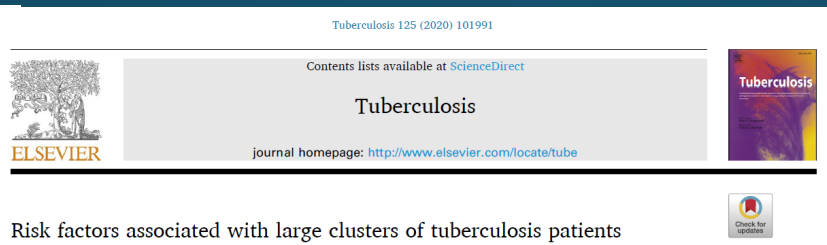
Evidence of international transmission of mobile colistin resistant monophasic *Salmonella* Typhimurium ST34

Sirirak Supa-amornkul[1,2], Rattanaporn Intuy[2], Wuthiwat Ruangchai[2], Soraya Chaturongakul[2,3] & Prasit Palittapongarnpim[2,4]✉



Tuberculosis 125 (2020) 101991

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Tuberculosis

journal homepage: http://www.elsevier.com/locate/tube

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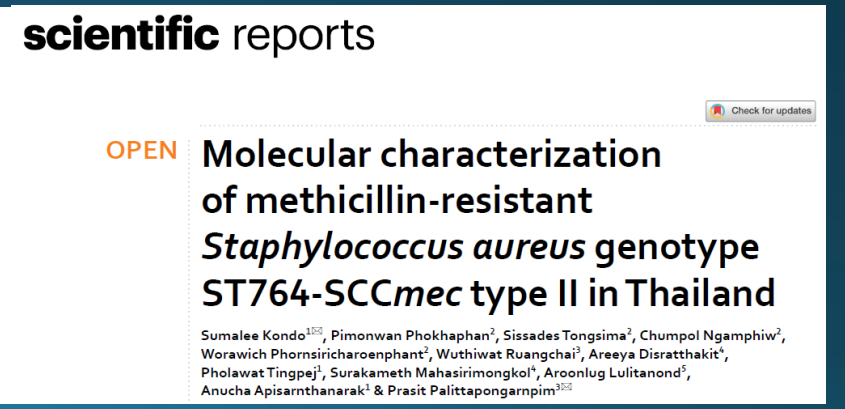
Risk factors associated with large clusters of tuberculosis patients determined by whole-genome sequencing in a high-tuberculosis-burden country

Reiko Miyahara[a,b], Nat Smittipat[c], Tada Juthayothin[c], Hideki Yanai[d], Areeya Disratthakit[e], Worarat Imsanguan[f], Daranee Intralawan[f], Supalert Nedsuwan[f], Boonchai Chaiyasirinroje[g], Surasit Bupachat[g], Katsushi Tokunaga[a,b], Surakameth Mahasirimongkol[e], Prasit Palittapongarnpim[c,h,*]



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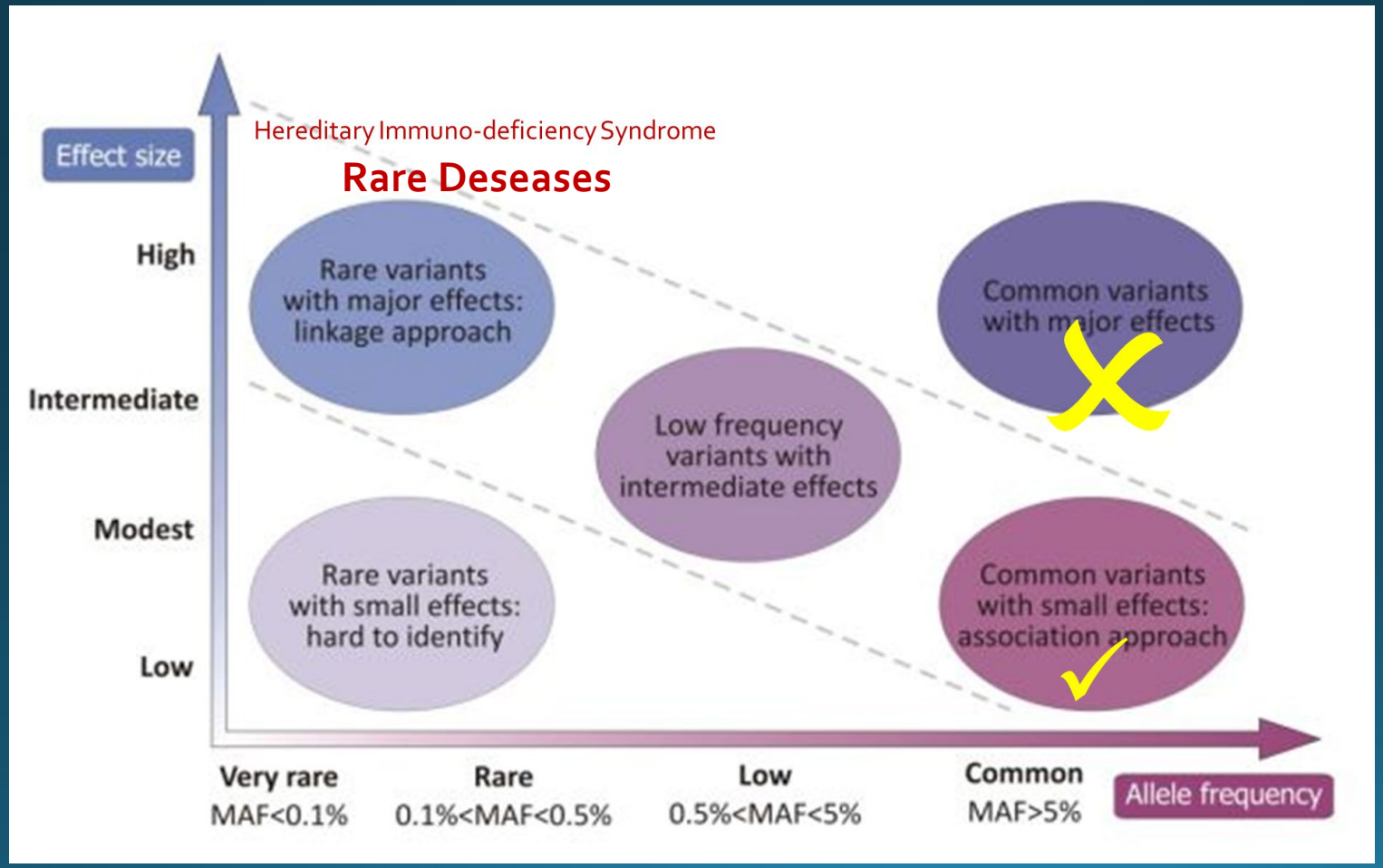
Molecular characterization of methicillin-resistant *Staphylococcus aureus* genotype ST764-SCC*mec* type II in Thailand

Sumalee Kondo[1]✉, Pimonwan Phokhaphan[2], Sissades Tongsima[2], Chumpol Ngamphiw[2], Worawich Phornsiricharoenphant[2], Wuthiwat Ruangchai[3], Areeya Disratthakit[4], Pholawat Tingpej[1], Surakameth Mahasirimongkol[4], Aroonlug Lulitanond[5], Anucha Apisarnthanarak[1] & Prasit Palittapongarnpim[3]✉

Each genetic factor related to susceptibility to ID almost always has a minor effect.



co-evolution

Co-evolution is frequently seen in pairs of species that **interact frequently or closely**.

A **change in the traits** of one species acts as a **selection pressure** on the other species.

Evolutionary Arms Race (Red Queen Hypothesis):
predator-prey & host-parasite

"Well, in our country," said Alice, still panting a little, "you'd generally get to somewhere else — if you run very fast for a long time, as we've been doing."

"A slow sort of country!" said the Queen. "Now here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"

— Lewis Carroll, *Alice through the Looking Glass*

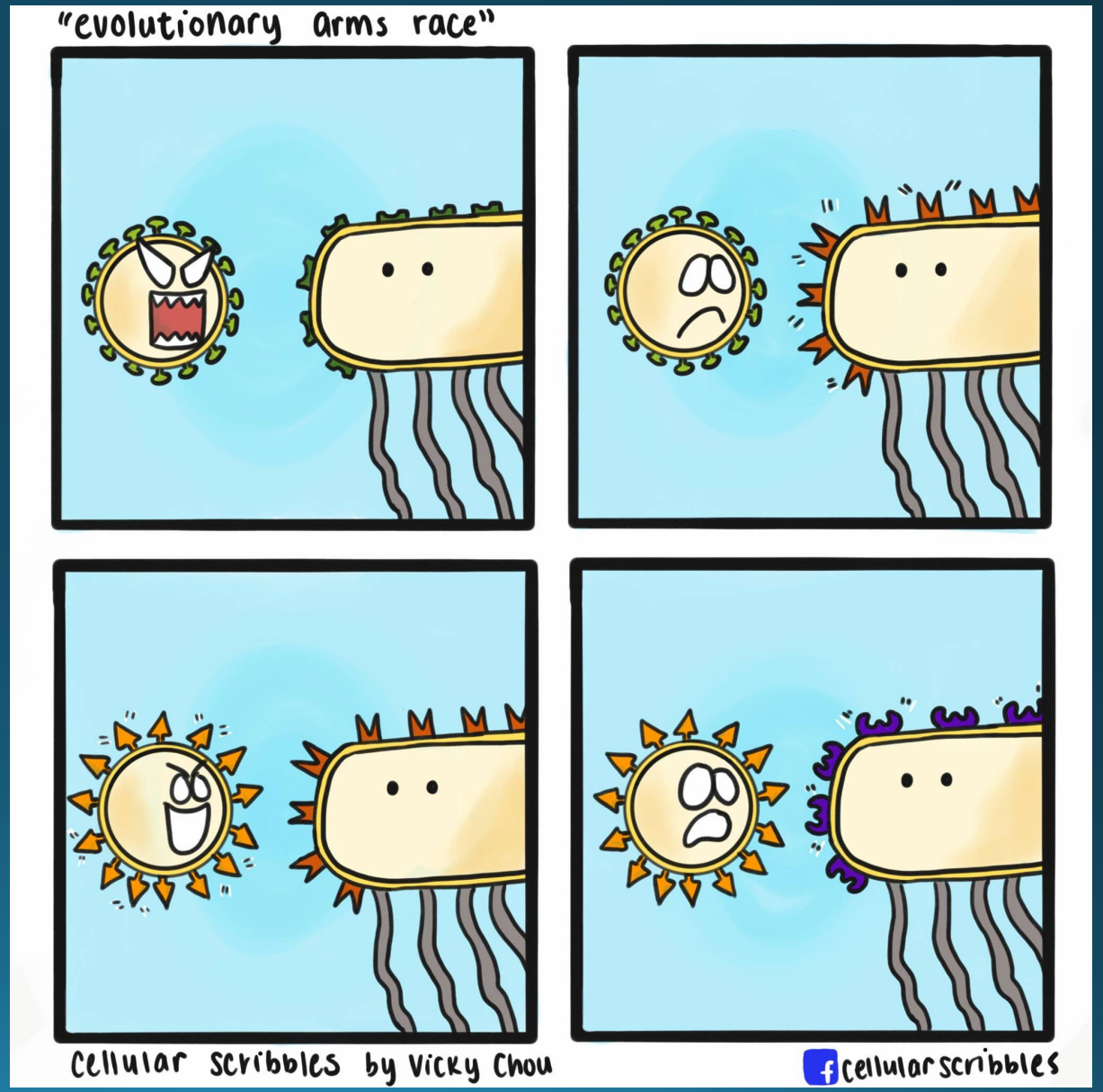
2. **Evolutionary arms race**- coevolution can occur in competitive relationships

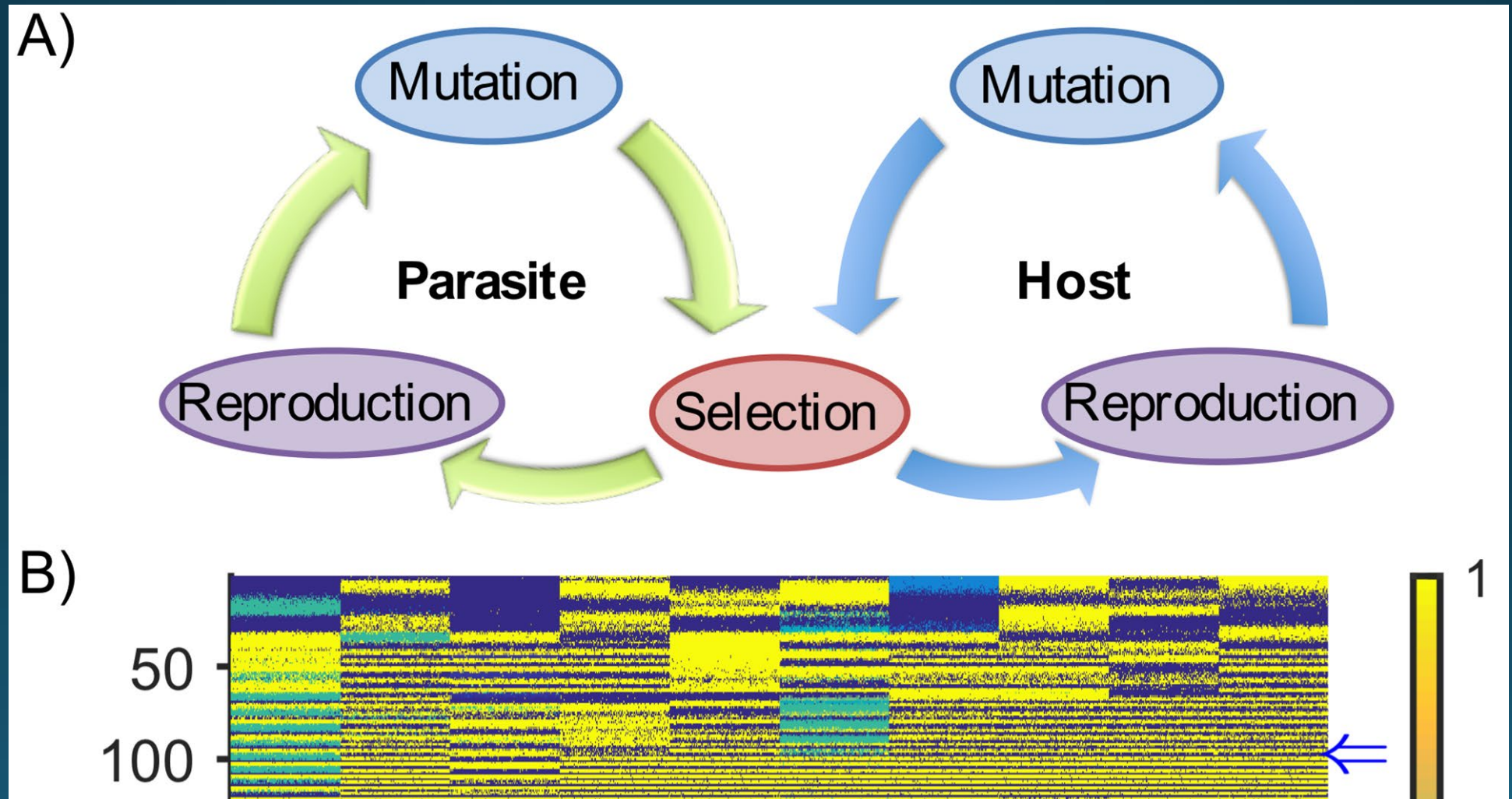
The crab is the natural predator of the snail.

Natural selection favors snails with thicker shells and spines.

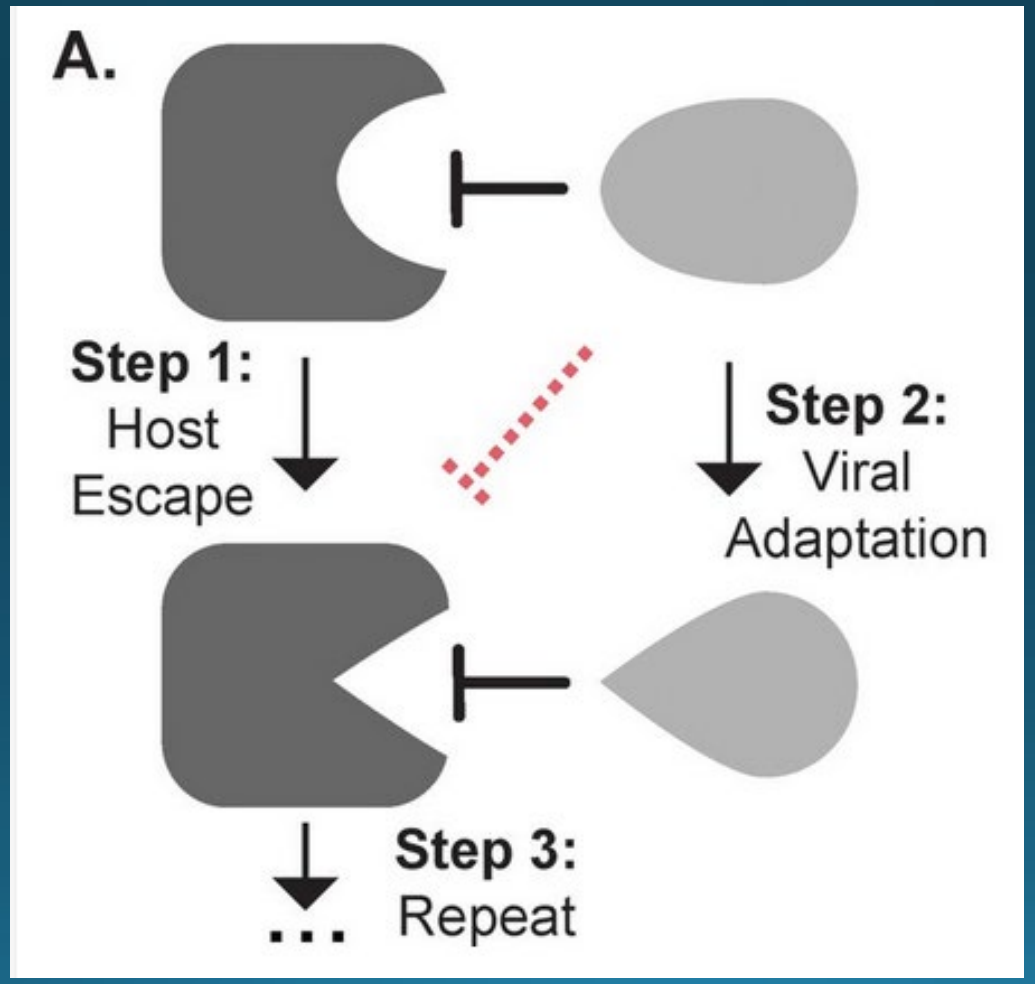
Through natural selection, crabs evolve more powerful claws that can pierce the snails' thick, spiny shells.

In response, natural selection favors snails with even thicker shells and spines.

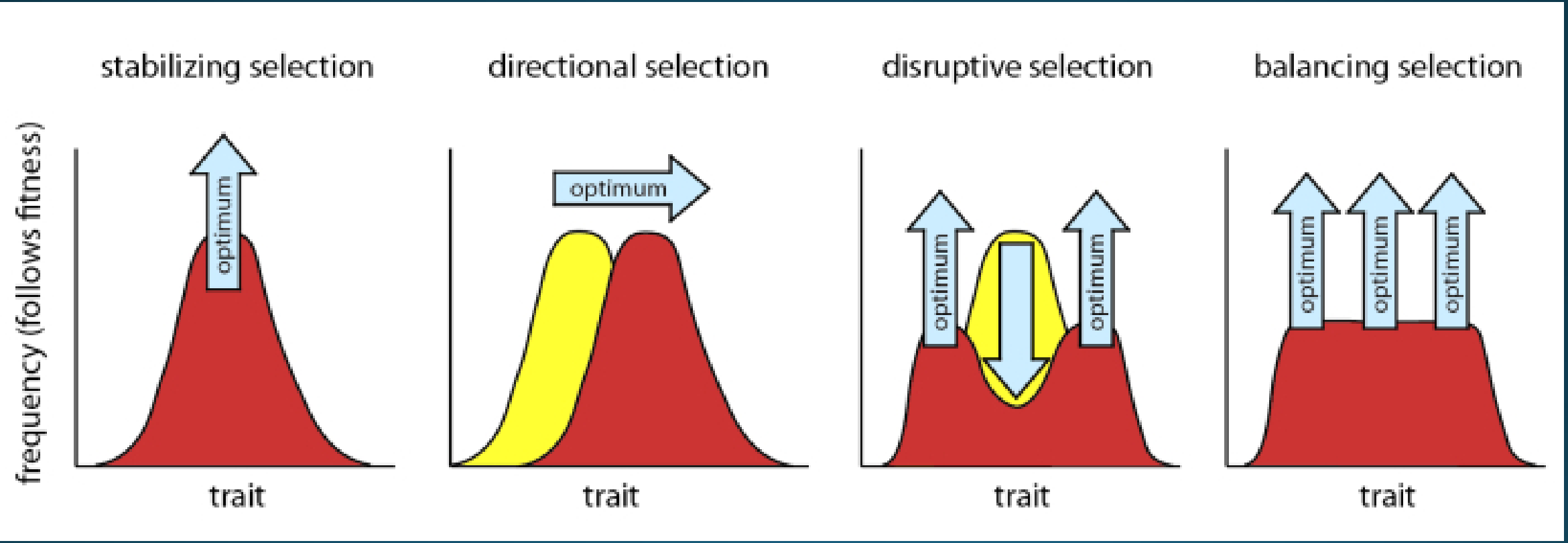



A)
Mutation
Mutation
Parasite
Host
Reproduction
Selection
Reproduction
B)
50
100
1

Evolutionary arm race at the molecular level may provide information for development of new effective vaccines.

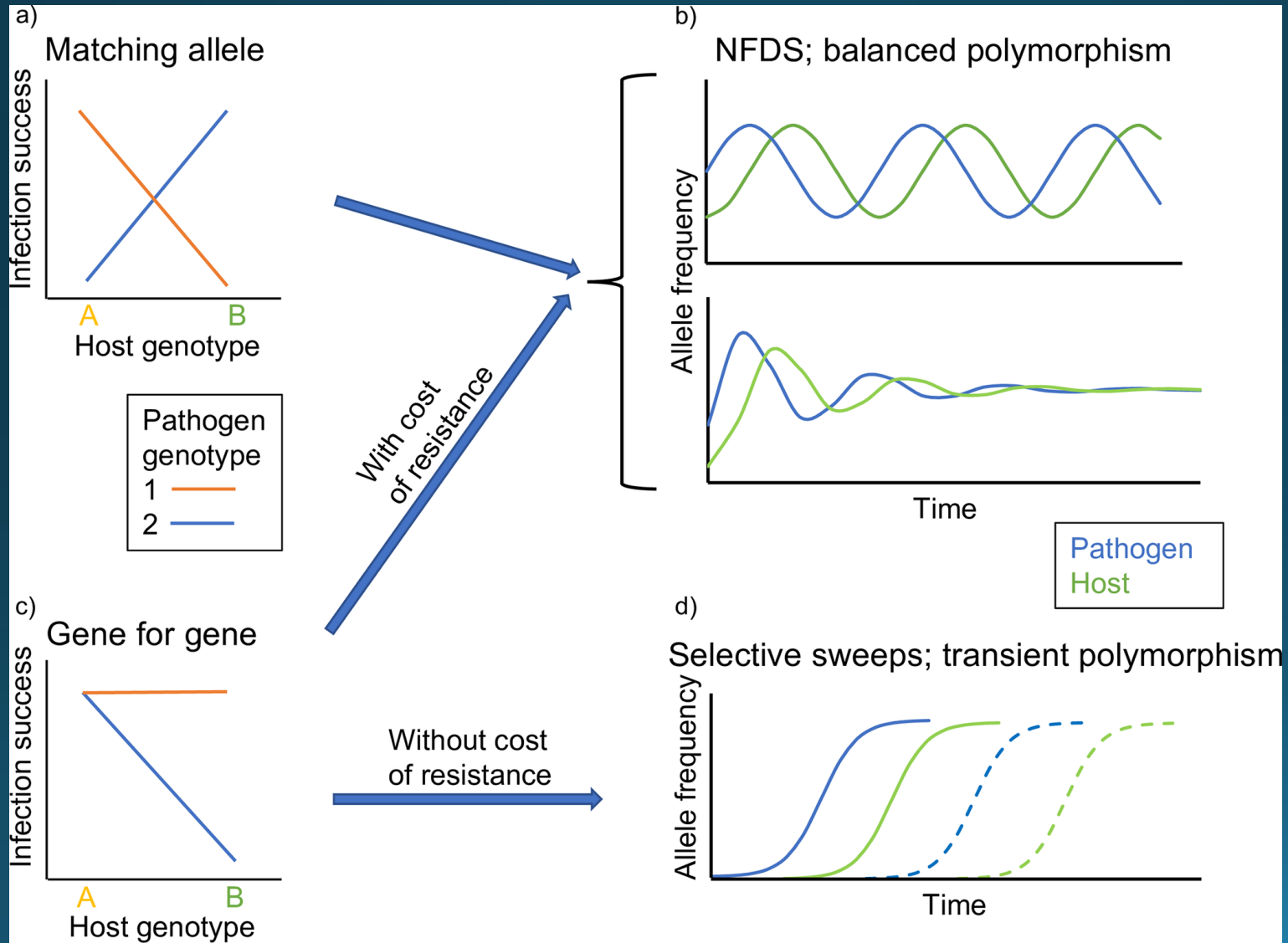


Co-evolution of diverse population of pathogens and hosts lead to balanced selection



The presence of multiple pathogen genotypes in a population may indicate co-evolution

A sign of co-evolution is the differential susceptibility to different genotypes of pathogen by different geotypes of hosts



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Article

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Genome-wide host-pathogen analyses reveal genetic interaction points in tuberculosis disease

Received: 16 August 2022

Accepted: 24 January 2023

Published online: 01 February 2023

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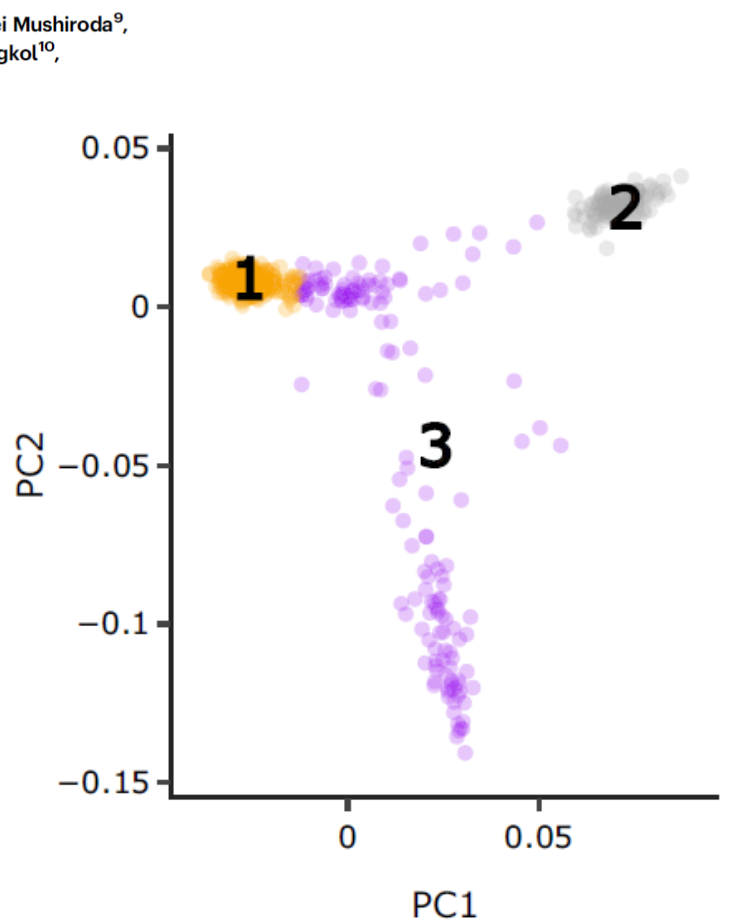
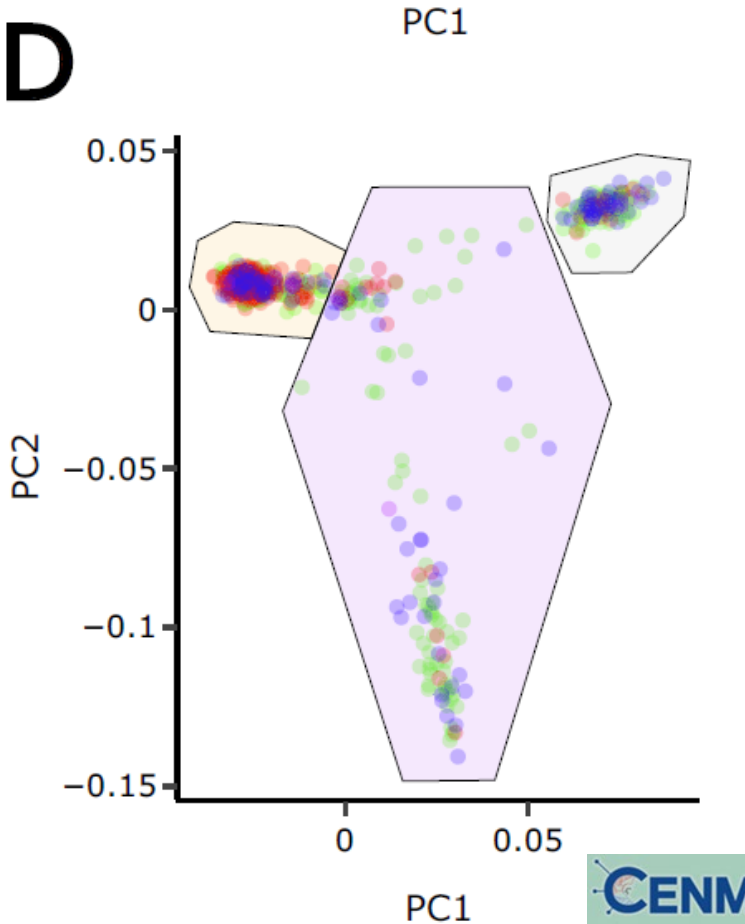
Jody Phelan[1], Paula Josefina Gomez-Gonzalez[1], Nuria Andreu[1], Yosuke Omae[2], Licht Toyo-Oka[2], Hideki Yanai[3], Reiko Miyahara[4], Supalert Nedsuwan[5], Paola Florez de Sessions[6], Susana Campino[1], Neneh Sallah[1], Julian Parkhill[7], Nat Smittipat[8], Prasit Palittapongarnpim[8], Taisei Mushiroda[9], Michiaki Kubo[9], Katsushi Tokunaga[2], Surakameth Mahasirimongkol[10], Martin L. Hibberd[1] & Taane G. Clark[1,11]

Pathogens x Human Genome-to-Genome Interactions

- Genetic markers for TB susceptibility are likely to vary by bacterial genotypes X human genetic groups.





Supplementary figure 5
A phylogenetic tree for the Thailand *M. tuberculosis* (n=714) with the top host genome-to-genome association hits (rs numbers) and associated nodes highlighted (black bands).

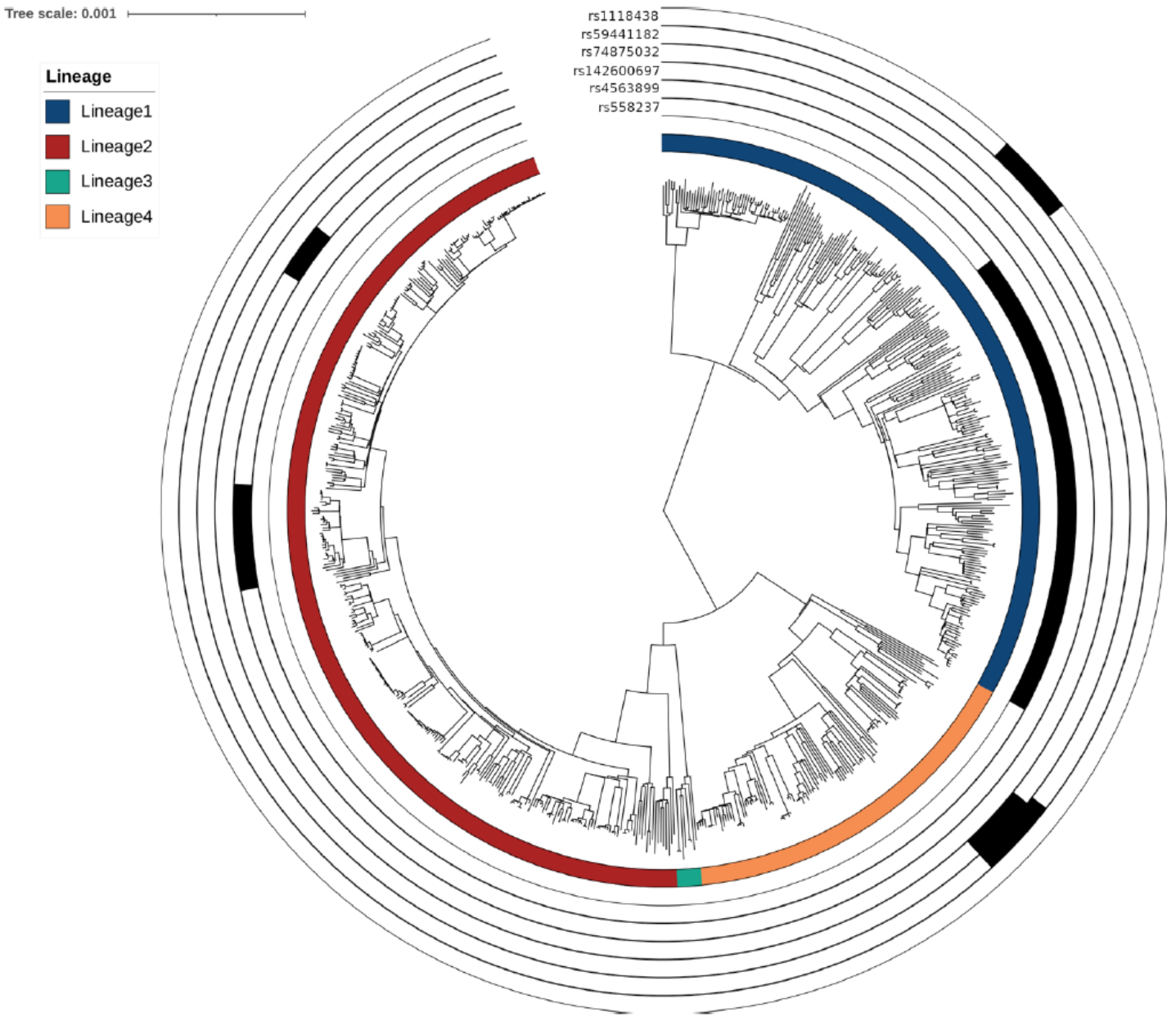


Table 1 | Genome-to-genome association results

Host Chr.	Host Region	No. SNPs[a]	SNP[b]	*P* value	Odds ratio	Host Locus	Host Locus Annotation	*Mtb* Clade lineage	Analysis[c]
5	10712199–10758562	18	rs267951	1.41×10^{-9}	40.52	DAP	Intronic	2.2.1	All
14	97134528–97150790	4	rs74875032	2.11×10^{-9}	21.47	Intergenic	–	4.4.2	All
1	17303792–17310019	5	rs529617685	8.57×10^{-9}	129.69	MFAP2	Intronic	2.2.1.1	Main
4	162602209–162620104	10	rs142600697	1.59×10^{-8}	42.49	FSTL5	Intronic	2.2.1	All
2	35360834–35367230	6	rs1118438	2.47×10^{-8}	22.78	Intergenic	–	1.1.3	All, Main
1	41067739–41074312	14	rs558237	2.86×10^{-8}	3.61	RIMS3	Downstream	1.1	All, Main
3	8308620–8310990	3	rs59441182	3.12×10^{-8}	19.79	Intergenic	–	4.4.2	All
8	19413249–19418028	3	rs4563899	4.84×10^{-8}	29.27	CSGALNACT	Intronic	2.2.1	All

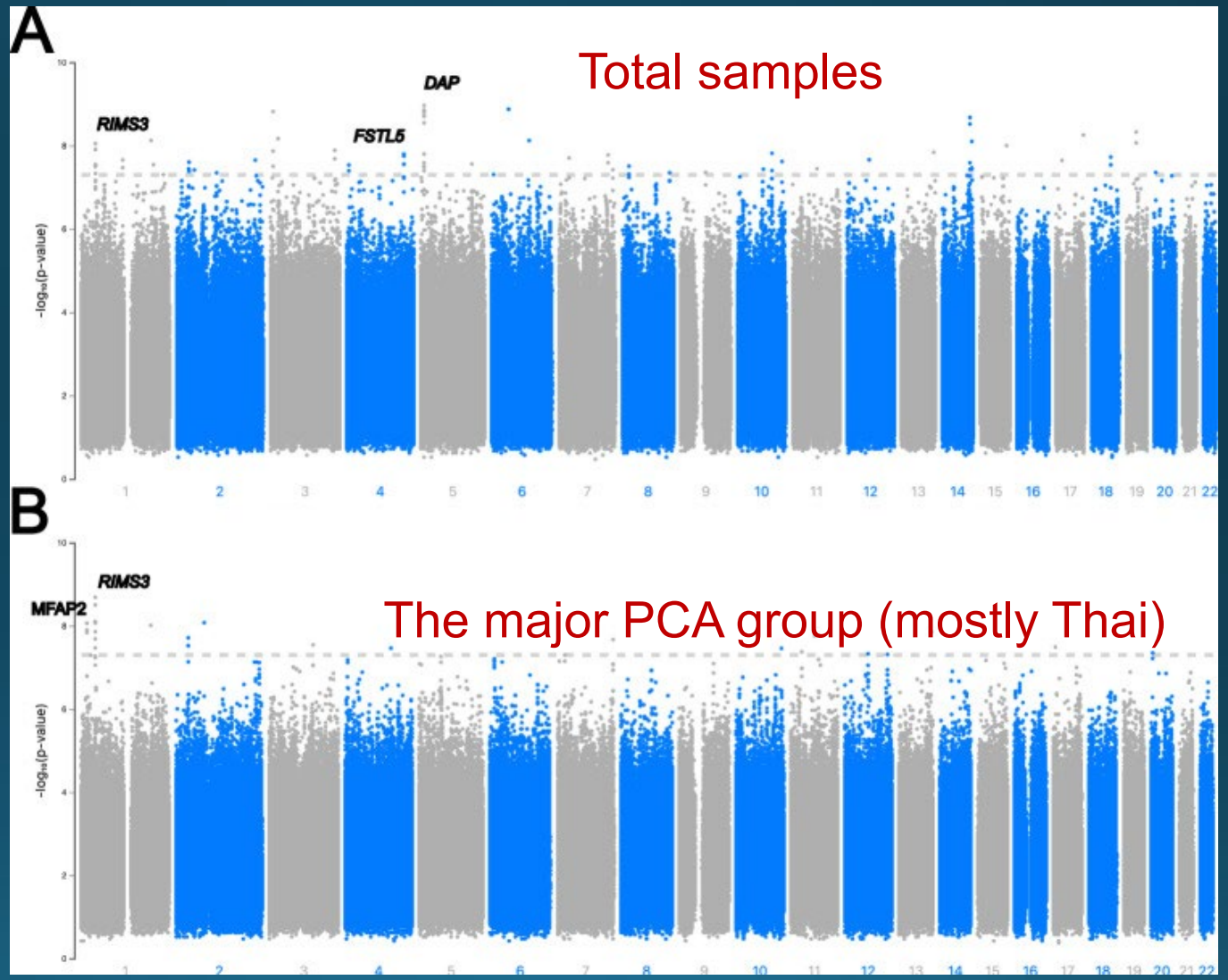
The minimum P-value per gene and the associated odds ratio and lineage of the *M. tuberculosis* variant (*Mtb*).

[a]Number of SNPs with $P < 5\times10^{-8}$;

[b]the SNP with the strongest association (minimum *P* value);

[c]Analyses were performed using all paired samples ($n = 714$) and the main cluster only ($n = 426$) as determined using the first two principal components (see Fig. 1C).

GWAS results also depends on human PCA groups.



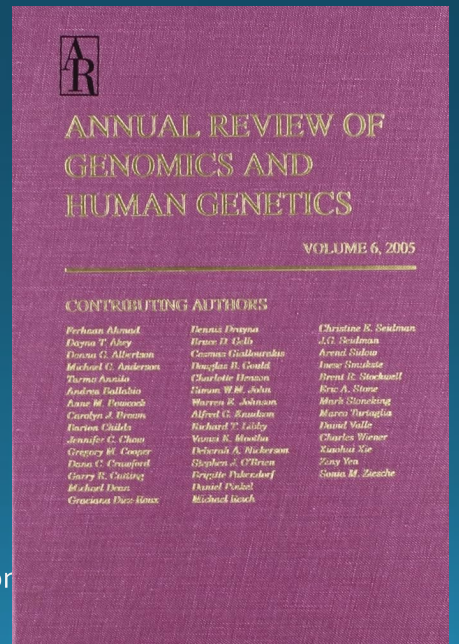
Ongoing Genome-to-Genome Interactions Projects

MTB x Human Genome-to-Genome Interactions Phase 2

- Samples: 2003-2020 (1293 patients)
- Human genotypes
  - Human PCA groups
  - Imputed SNPs from high-density SNP array results
  - Candidate genes
- Bacterial genotypes
  - WGS phylogeny based genotypes
- Phenotypes
  - Outcome of treatment
  - Pulmonary cavitation
  - Bacterial Genetic Clustering (Transmissibility)

Dengue Virus x Human Genome-to-Genome Interactions Phase I

- Other possible projects- needs good patient cohort and sample collection task forces.
  - Melioidosis



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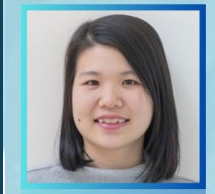

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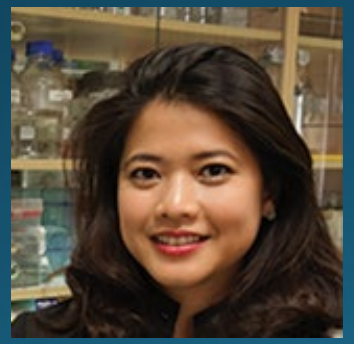

Congratulations to Assoc. Prof. Arunee Thitithanyanont for being selected as an honoree on the Asian Scientist 100 list!

Year 2021

ASIAN SCIENTIST 100

Arunee Thitithanyanont

Mahidol University
Thailand

Thitithanyanont received the L'Oréal Thailand COVID-19 Solidarity Prize in the field of life sciences for her research projects addressing the COVID-19 pandemic, including diagnostic methods, treatments and vaccines. In an early study of 217 recovered COVID-19 patients, Thitithanyanont and her team at the department of microbiology at Mahidol University were able to identify viral clearance as well as the pattern of antibody responses with SARS-CoV-2. This understanding of natural host defenses and antibody duration provides a foundation for further research into controlling the spread of the virus.

(Photo: Loop)



Faculty of Science
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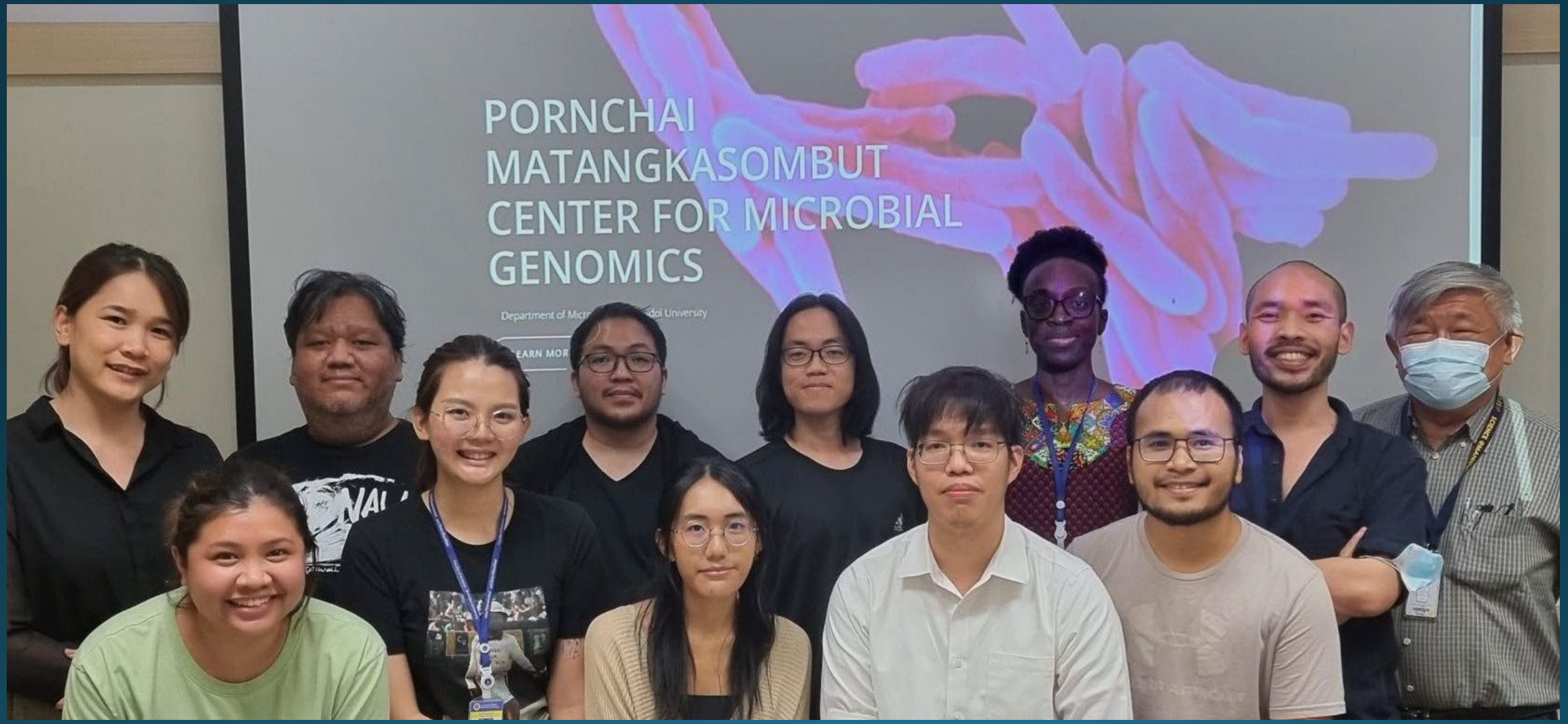
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