# Genomic epidemiology and lineage-specific risk stratification of *tet*(X4)-mediated tigecycline resistance along the pork production chain: A One Health perspective

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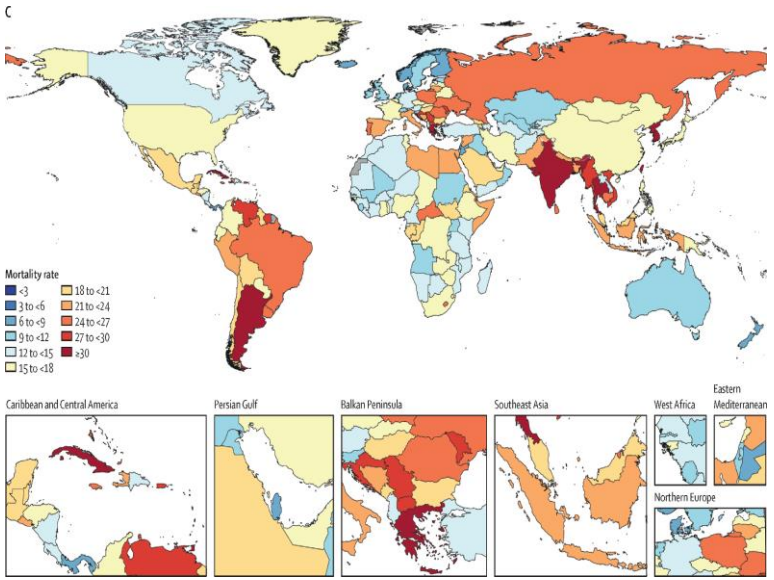
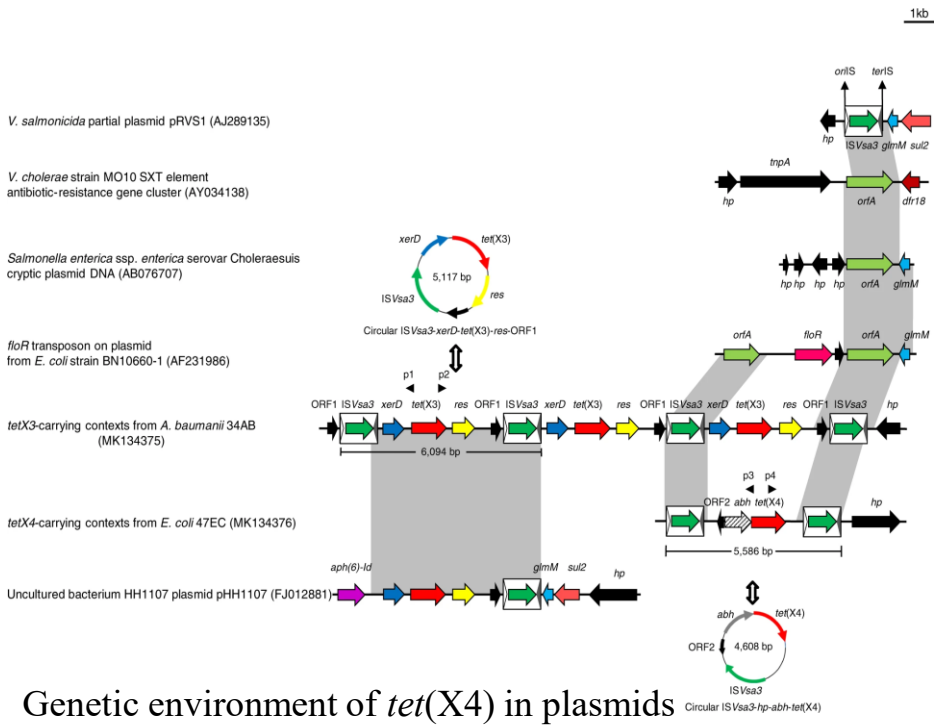
# Introduction

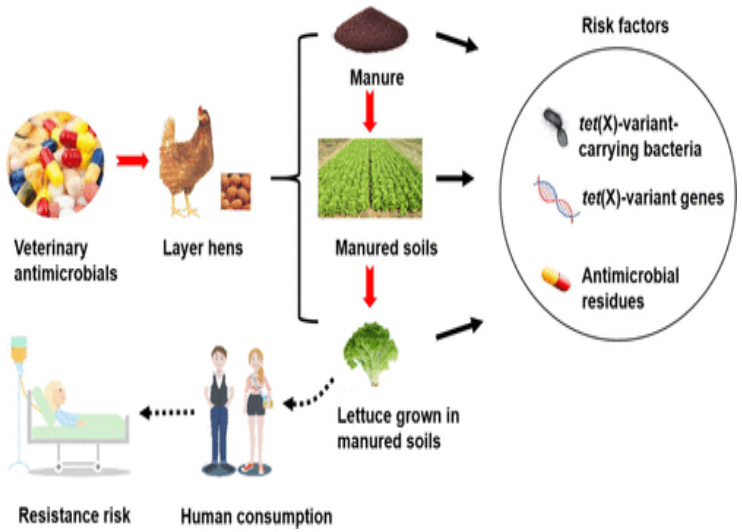
- Antimicrobial resistance is rising worldwide and already causes a major health burden;
- Tigecycline is a last-resort option for MDR Gram-negative bacteria infections, but its efficacy is increasingly compromised by rapid dissemination of plasmid-borne *tet*(X4);
- High-resolution and farm-to-table genomic data targeting *tet*(X4)-positive isolates along the pork production chain remain limited.




All-age mortality attributable to antimicrobial resistance in 2050



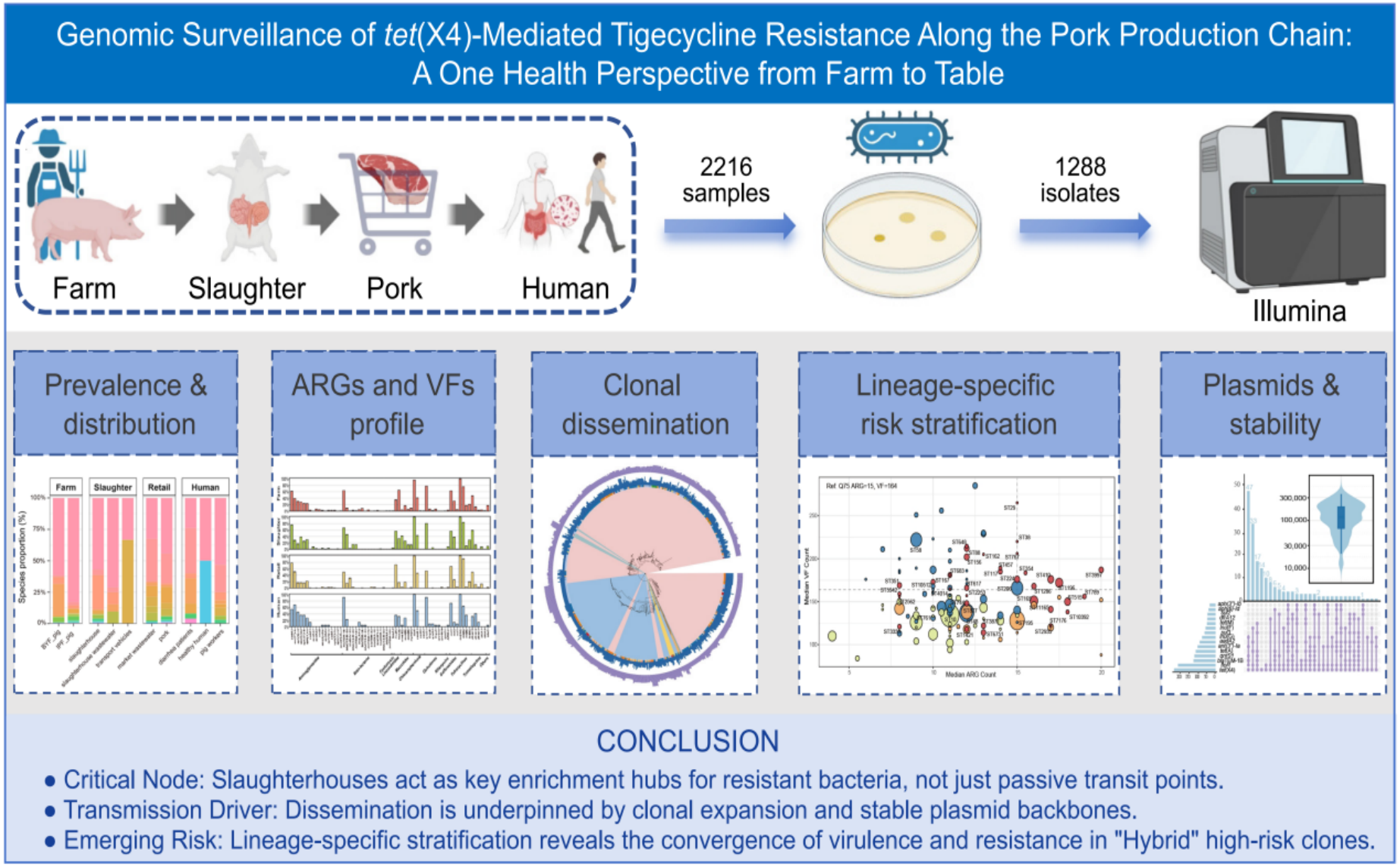

Genetic environment of *tet*(X4) in plasmids




Spread of *tet*(X) from layer farms to soil and lettuce

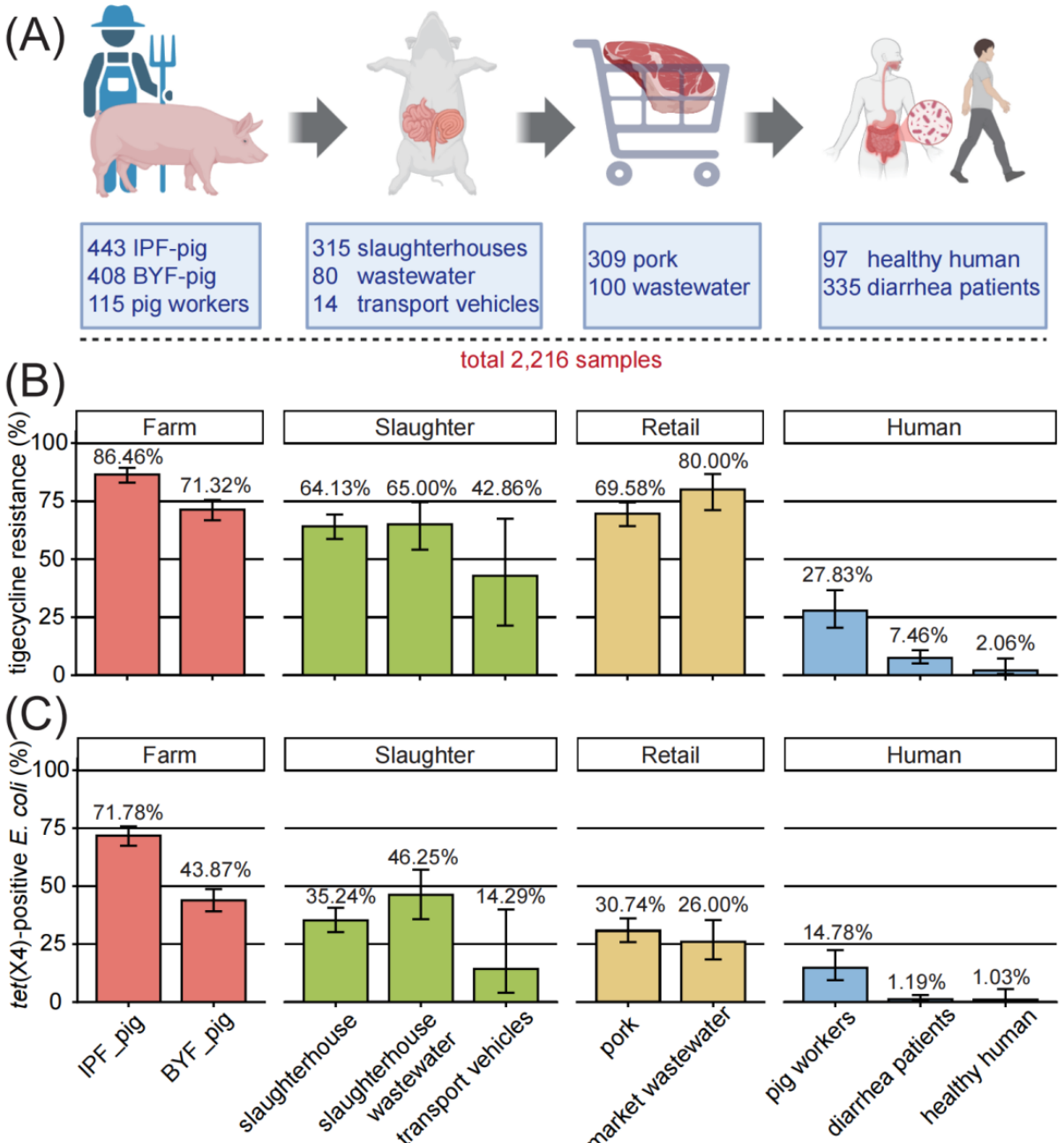

GBD Antimicrobial Resistance Collaborators. *The Lancet*. 2024.
He T *et al*. *Nature Microbiology*. 2019.
He T *et al*. *Environmental Science & Technology*. 2021.

# Highlights



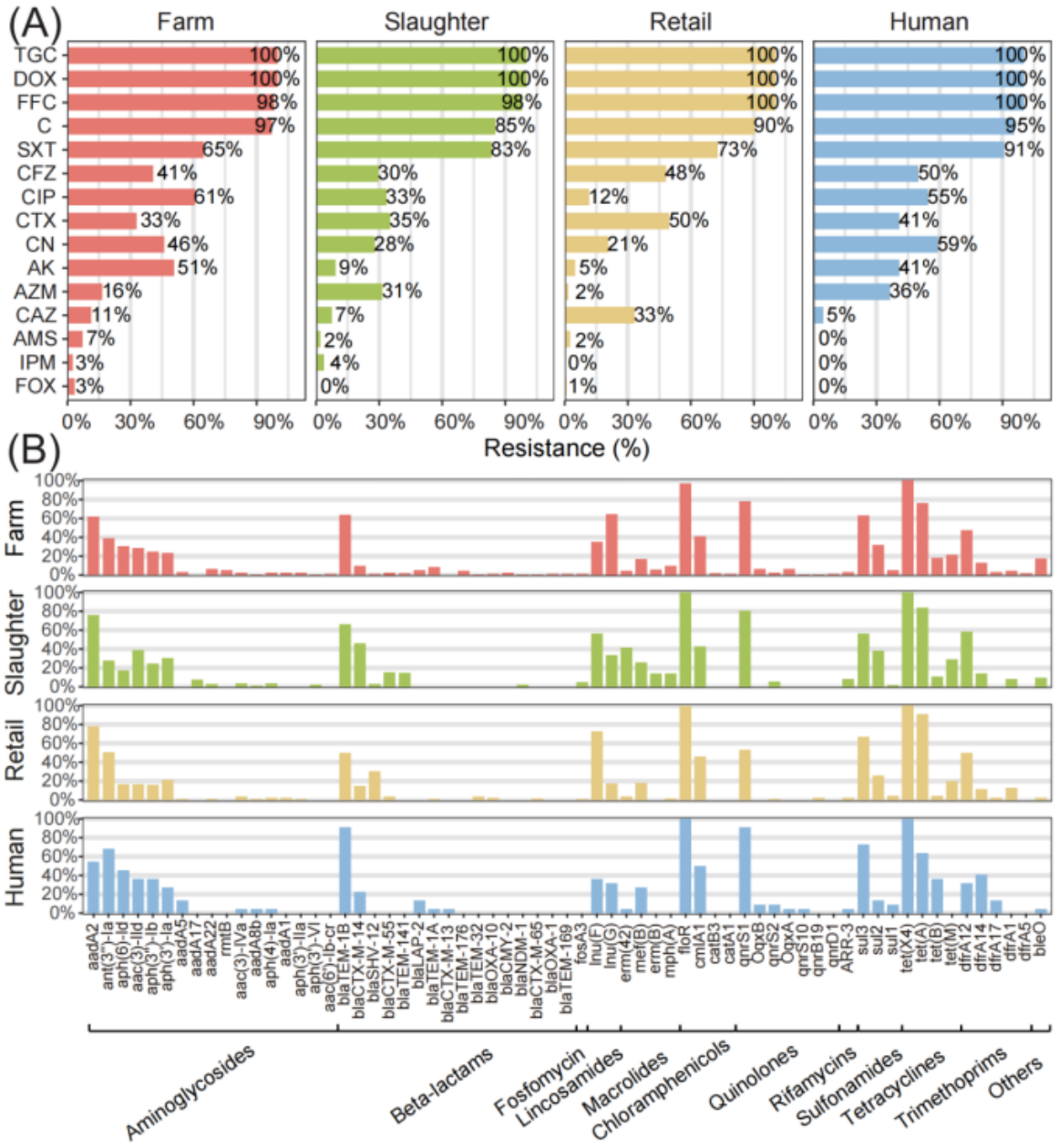

- Surveillance identifies slaughterhouses as key enrichment nodes in the spread of *tet*(X4)-positive *E. coli* along the pork chain;
- Lineage risk stratification reveals hybrid high-risk *E. coli* clones;
- Occupational exposure poses higher risks than general community contact;
- Conserved plasmid backbones drive *tet*(X4) persistence in food systems.

# Occurrence and burden of *tet*(X4)-positive *E. coli* along the pork production chain



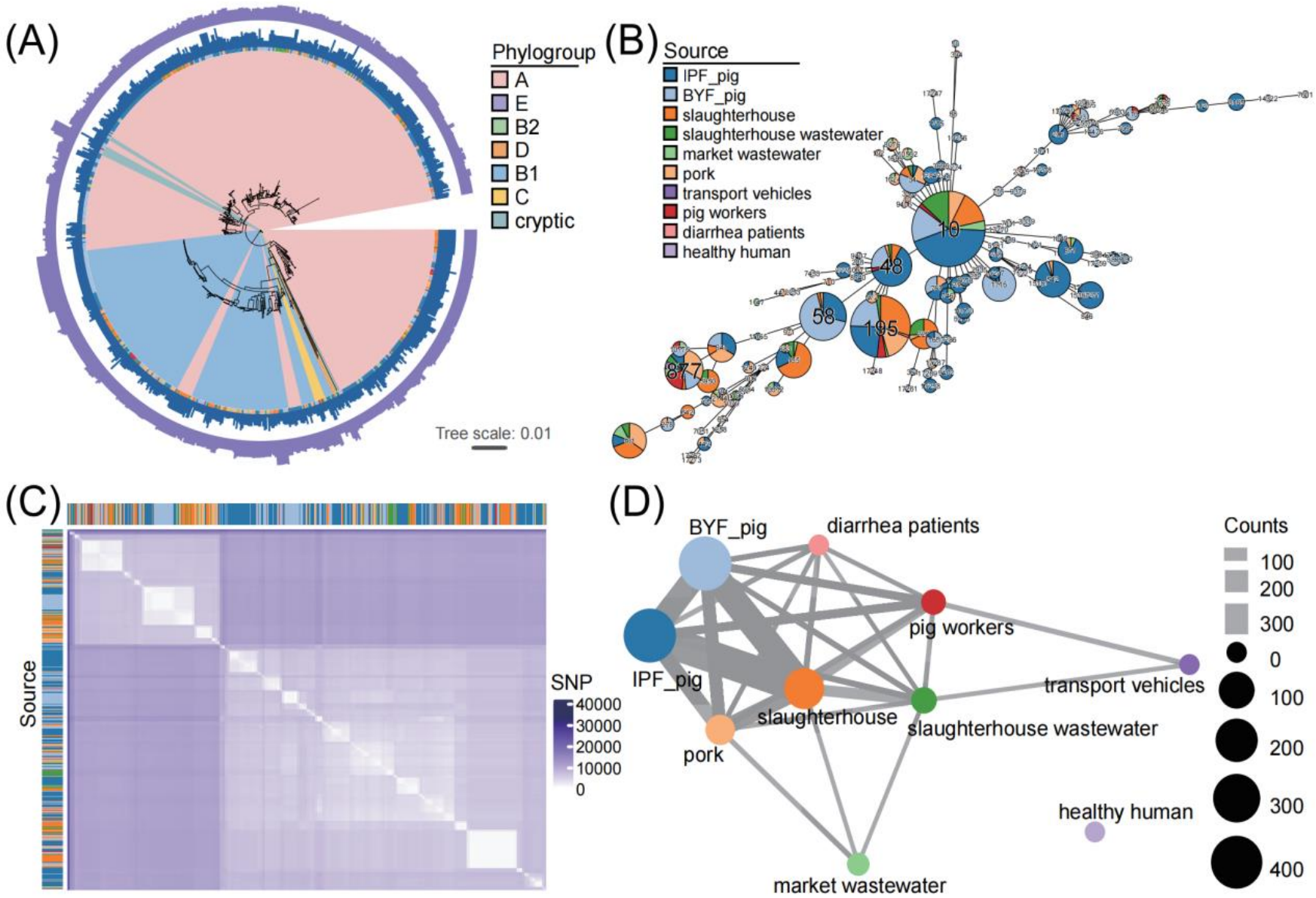

- Overall recovery rate under tigecycline-based selective enrichment was 58.12% across the pork chain;
- The isolate population was dominated by *E. coli*, and *tet*(X4) was the primary resistance gene;
- Farms and slaughterhouses showed the highest recovery rates of *tet*(X4)-positive *E. coli*;
- The *tet*(X4)-positive *E. coli* rate in pig farm workers (14.78%) was markedly higher than in the general population (diarrhea patients and healthy humans, 1.03%-1.19%).

# Antimicrobial resistance profile and virulence spectrum of *tet*(X4)-positive *E. coli*



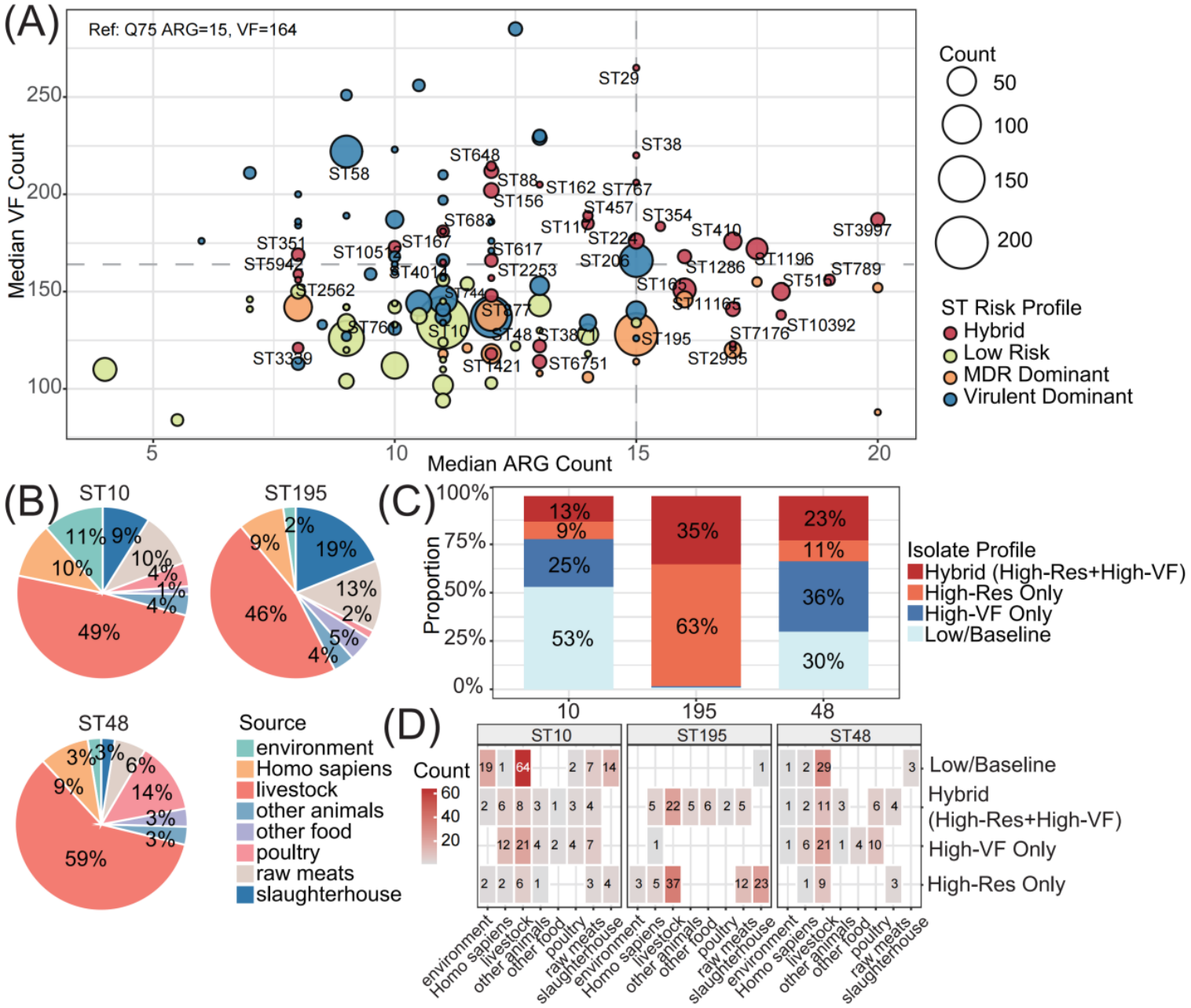

- Testing 15 agents in 9 classes showed an extremely high MDR rate (99.9%);
- A total of 212 ARGs were identified; farm isolates had the broadest resistome, while human isolates showed enrichment of PMQR and selected β-lactamase families;
- A total of 730 virulence genes were detected. ExPEC was the most common. UPEC and EPEC were present at low frequencies. NMEC was limited to non-human sources. STEC and ETEC were almost absent.
- *tet*(X4)-positive isolates were dominated by extraintestinal rather than classical diarrheagenic pathotypes.

# Clonal dissemination of *tet*(X4)-positive *E. coli* along the pork production chain



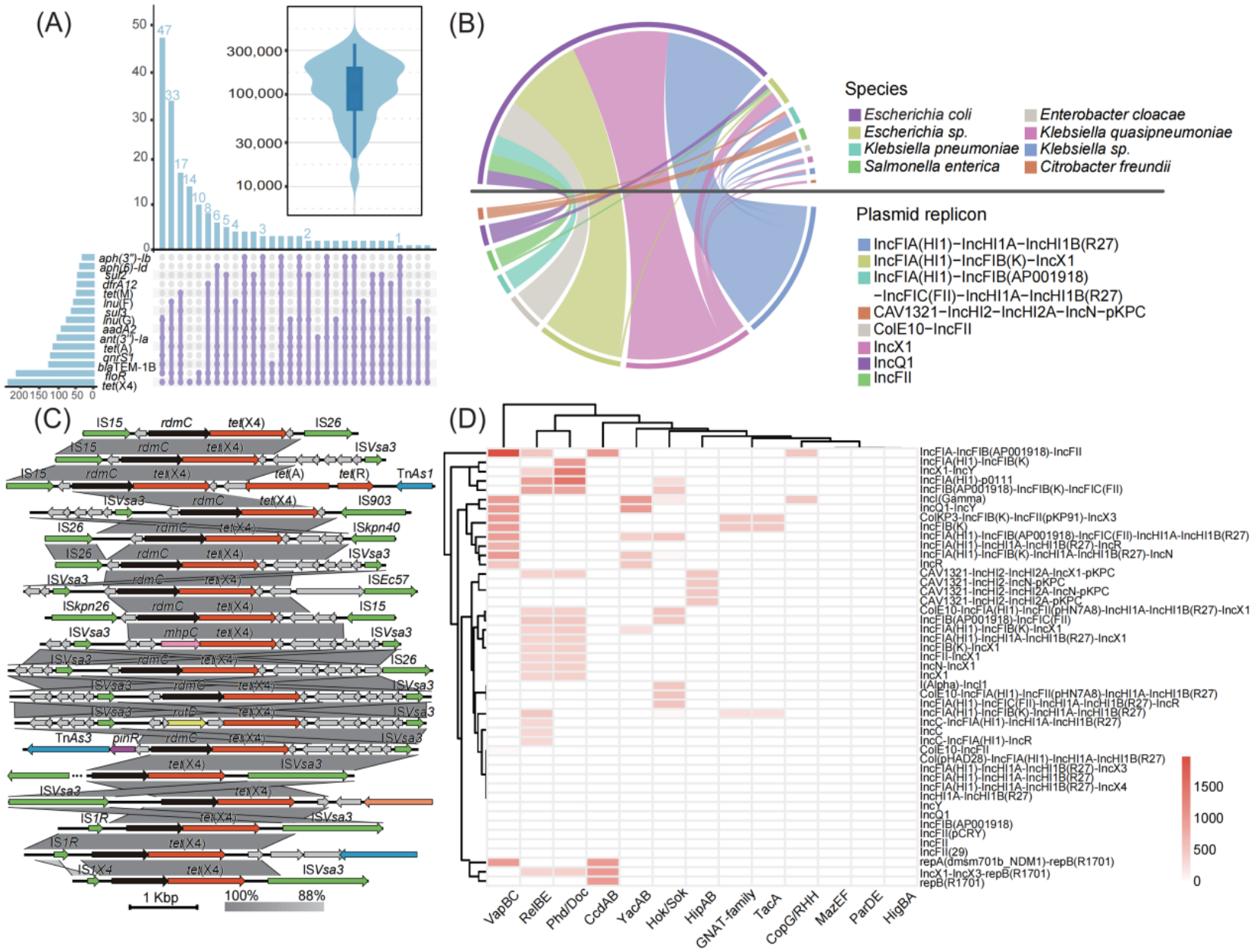

- WGS analysis of 790 *tet*(X4)-positive *E. coli* showed a population dominated by phylogroups A (70.0%) and B1 (27.2%);
- ST10 and ST195 were the main prevalent lineages and were widely detected in farms, slaughterhouses, pork, and wastewater, indicating multi-stage dissemination;
- Using a ≤ 10 core-genome SNP cutoff, 2,574 putative clonal transmission events were identified, with more between-source than within-source events;
- Clonal links were concentrated at the farm-slaughterhouse-retail interfaces, marking these nodes as key control points for *tet*(X4)-positive *E. coli* dissemination.

# Lineage-specific risk stratification of *tet*(X4)-positive *E. coli*




- Integrating data from NCBI, we constructed a global database of 1945 *tet*(X4)-positive *E. coli* isolates for lineage-level risk stratification analysis
- Based on ARG and VF burdens, isolates were classified as Low/Baseline, High-VF only, High-Res only, and Hybrid; Hybrid high-risk isolates accounted for 26.7%;
- Hybrid isolates showed convergence of resistance and virulence, mainly EPEC and EAEC, and were enriched for key determinants such as *mcr*, carbapenemases, and *tmexCD-toprJ*;
- Risk architecture was strongly lineage-specific: ST195 was resistance-dominant, ST48 was virulence-enriched, and Hybrid isolates spanned multiple ST backgrounds rather than a single epidemic clone.

# Plasmid backbones and stability mechanisms




- A total of 234 *tet*(X4)-carrying plasmids were retrieved from NCBI, covering 47 replicon types, with IncF/IncHI/IncX1 as the dominant backbones;
- *E. coli* was the key host for *tet*(X4)-positive plasmids, with pig-derived and China-origin plasmids accounting for large proportions;
- *tet*(X4)-positive plasmids frequently co-carried multiple ARGs, including last-resort resistance determinants such as *mcr* and *tmexCD3-toprJ3*;
- A conserved-flexible genetic structure centered on *rdmC-tet*(X4) and mediated by IS*Vsa3*/IS*1R*/IS*26*/IS*15*, together with TA-system "double-lock" maintenance, may promote plasmid stability and horizontal transfer.

# Conclusion

- This study systematically mapped *tet*(X4)-mediated tigecycline-resistant *E. coli* across pork production chain in China from a One Health perspective;
- Farms and slaughterhouses were key dissemination and enrichment nodes, with ST10 and ST195 showing clonal links across farm-slaughterhouse-retail interfaces;
- Lineage-specific risk stratification identified two routes: resistance-heavy commensals in processing nodes and resistance-virulence convergence in Hybrid lineages;
- *tet*(X4)-positive plasmids were driven by IncF/IncHI/IncX1 backbones, and maintains stable transmission through the conserved *rdmC-tet*(X4) genetic module and TA system, highlighting farms, slaughterhouses, wastewater, and workers as control priorities.

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