



# Azithromycin resistance in *Chlamydia trachomatis*

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# *Chlamydia trachomatis*

## About the Pathogen

- Obligate intracellular bacterium
- Most common cause of bacterial STI globally

## Diseases Caused

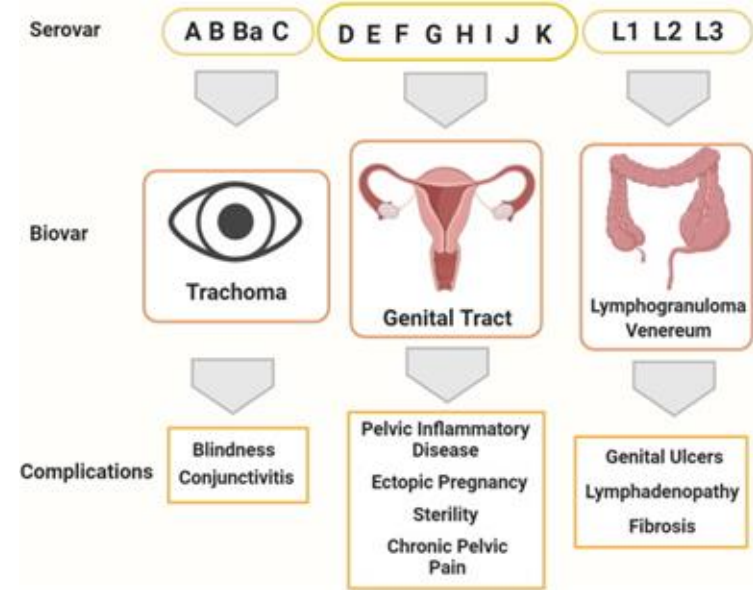
- urogenital and anorectal Infections
- Lymphogranuloma Venereum (LGV): invasive STI affecting lymph nodes
- Ocular Trachoma: leading infectious cause of blindness globally

## Treatment

- Antibiotics like Doxycycline and Azithromycin.
- Azithromycin used for Mass Drug administration Campaigns.

## Global Burden

- High in young adults (15–24 years) worldwide
- Ocular trachoma prevalent in Sub-Saharan Africa, Southeast Asia, Middle East
- >70% females and ~50% males are asymptomatic



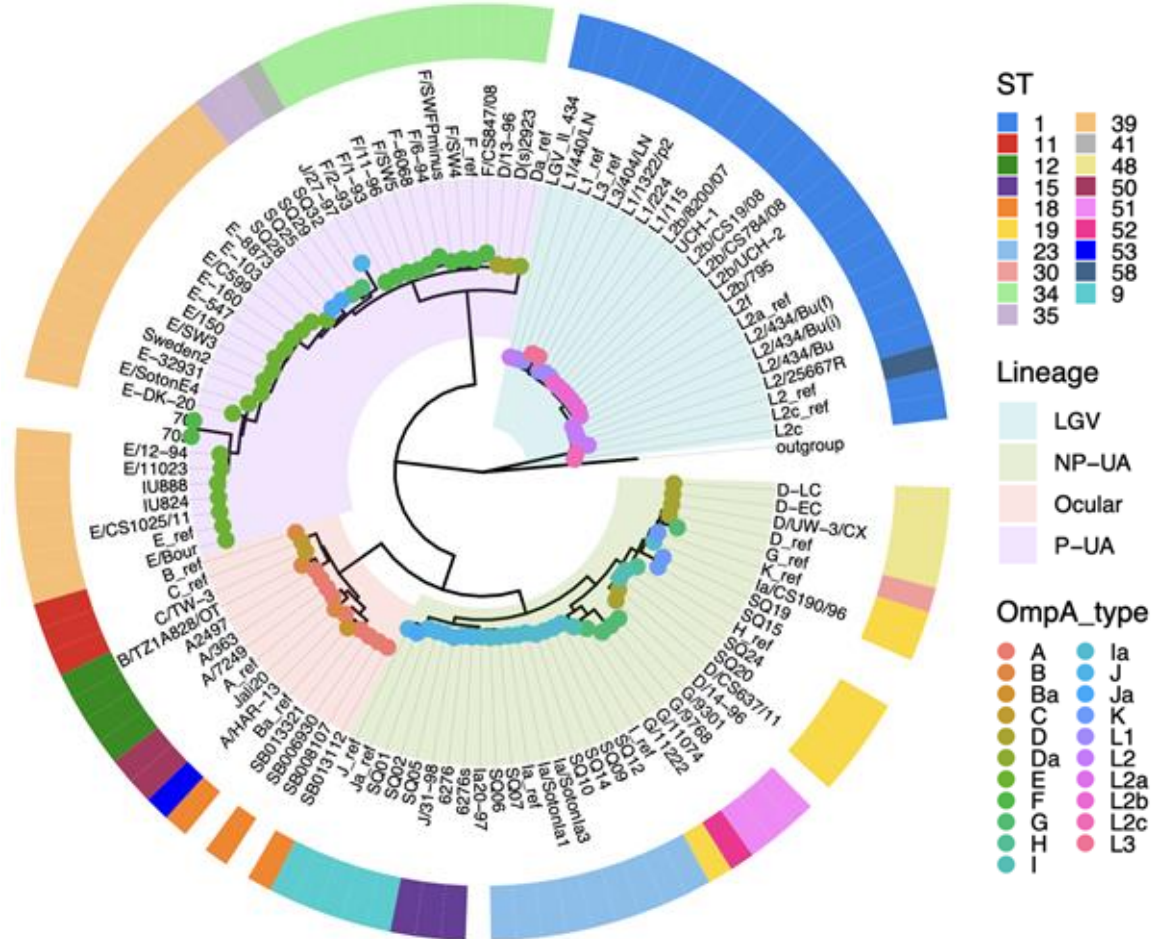
# Core-genome phylogeny divides the species into 4 distinct lineages

Tree clearly distinguishes the 4 **lineages** of CT associated with different infections:

- **LGV**: Lymphogranuloma Venereum
- **NP-UA**: Non-prevalent Urogenital and Anorectal infections
- **P-UA**: Prevalent Urogenital and Anorectal infections
- **Ocular**: ocular trachoma

*OmpA* genotype is marked at the nodes of the tree. Varies in the different lineages but clusters of *OmpA* type are distinct for LGV and Ocular lineages while there are some overlap in NP-UA and P-UA clusters.

MLST Sequence Types are marked at the outer ring of the tree. STs are distinct between the 4 lineages but not reliable since many genomes (even some ref genomes) are left unassigned.



# Recent studies highlight treatment failures indicating antibiotic resistance



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▶ [Sex Transm Dis](#). Author manuscript; available in PMC: 2017 Oct 1.

Published in final edited form as: [Sex Transm Dis](#). 2016 Oct;43(10):599–602. doi: [10.1097/OLQ.0000000000000489](https://doi.org/10.1097/OLQ.0000000000000489)

## Azithromycin treatment failure for *Chlamydia trachomatis* among heterosexual men with nongonococcal urethritis

[Patricia Kissinger](#), [Scott White](#), [Lisa E Manhart](#), [Jane Schwebke](#), [Stephanie N Taylor](#), [Leandro Mena](#), [Christine M Khosropour](#), [Larissa Wilcox](#), [Norine Schmidt](#), [David H Martin](#)

▶ [Int J Reprod Biomed](#). 2019 Sep 22;17(9):603–620. doi: [10.18502/ijrm.v17i9.5093](https://doi.org/10.18502/ijrm.v17i9.5093)

## Urogenital chlamydia trachomatis treatment failure with azithromycin: A meta-analysis

[Farnaz Mohammadzadeh](#)<sup>1</sup>, [Mahrokh Dolatian](#)<sup>1</sup>, [Masoumeh Jorjani](#)<sup>2</sup>, [Maryam Afrakhteh](#)<sup>3</sup>, [Hamid Alavi Majd](#)<sup>4</sup>, [Fatemeh Abdi](#)<sup>5</sup>, [Reza Pakzad](#)<sup>6,7</sup>

High treatment failure rate is better explained by resistance gene detection than by minimum inhibitory concentration in patients with urogenital *Chlamydia trachomatis* infection

[Lili Shao](#)<sup>a,1</sup>, [Cong You](#)<sup>a,1</sup>, [Junya Cao](#)<sup>a</sup>, [Yong Jiang](#)<sup>b</sup>, [Yuanjun Liu](#)<sup>a</sup>, [Quanzhong Liu](#)<sup>a</sup>

Review | [Open access](#) | Published: 03 September 2021

## An overview of genes and mutations associated with *Chlamydiae* species' resistance to antibiotics

[Ichrak Benamri](#), [Maryame Azzouzi](#), [Kholoud Sanak](#), [Ahmed Moussa](#) & [Fouzia Radouani](#)

[Annals of Clinical Microbiology and Antimicrobials](#) 20, Article number: 59 (2021) | [Cite this article](#)

8908 Accesses | 38 Citations | 17 Altmetric | [Metrics](#)

# AIM: Study azithromycin resistance in globally circulating CT strains

- Create a comprehensive dataset of high quality CT genomes
- Evaluate resistance by looking at associated genes and mutations

# Datasets and mutations

**AllTheBacteria**

All bacterial genomes assembled, available and searchable

AllTheBacteria is a large-scale, collaborative, open-access project that assembles, annotates, and catalogs millions of bacterial and archaeal genomes from public sequencing data.

2,440,377 assemblies in total (as of August 2024)



Designed to support the global microbiology community, it provides standardized, high-quality genomic data, with some key analyses and annotations run consistently across the whole data (e.g. gene annotation and AMR gene detection), and other targeted tools run on specific species.

NCBI : 87 high quality genomes

'AllTheBacteria' database (assembled SRA) : 1319

Ref genomes : 20

Sequence Data (Infected Patients): 288

**Total: 1714**

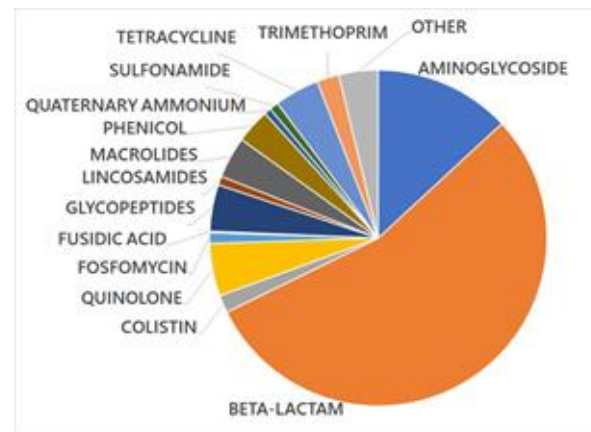
## Quality Filtration:

Selecting for high completeness (>97%) and low contamination (<5%)

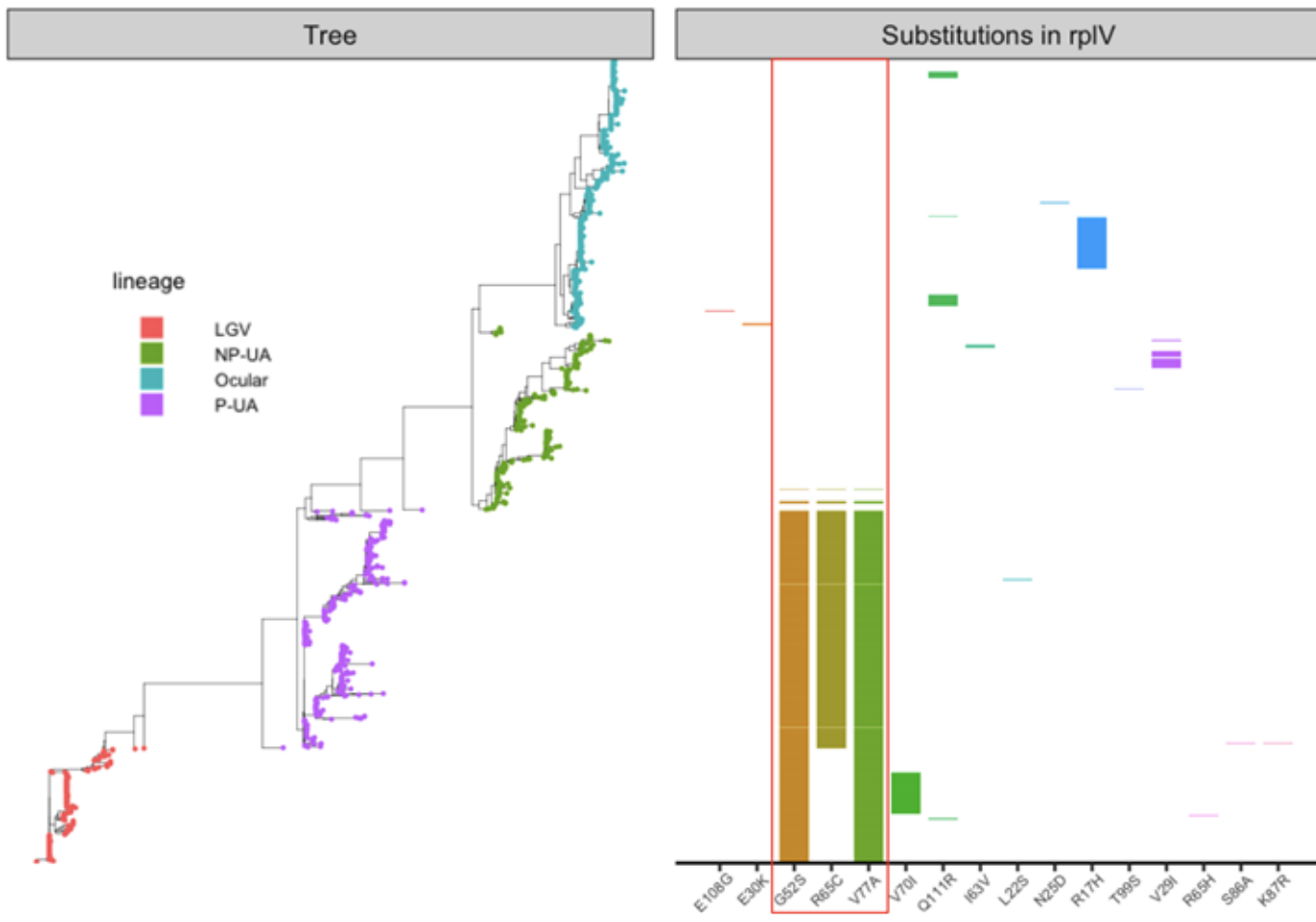
## Final Dataset:

**1349** high quality assembled genomes

- Mutations and substitutions from public databases like NCBI AMR database and CARD
- Literature survey
- Candidate genes: *23S rRNA*, *rpIV* and *rpID*



# Putative resistance mutations in *rpIV* gene are lineage specific



- Core phylogeny of 1349 genomes (left)

- total 16 mutations (x-axis)

- 3 mutations linked with AZ resistance highlighted in red box

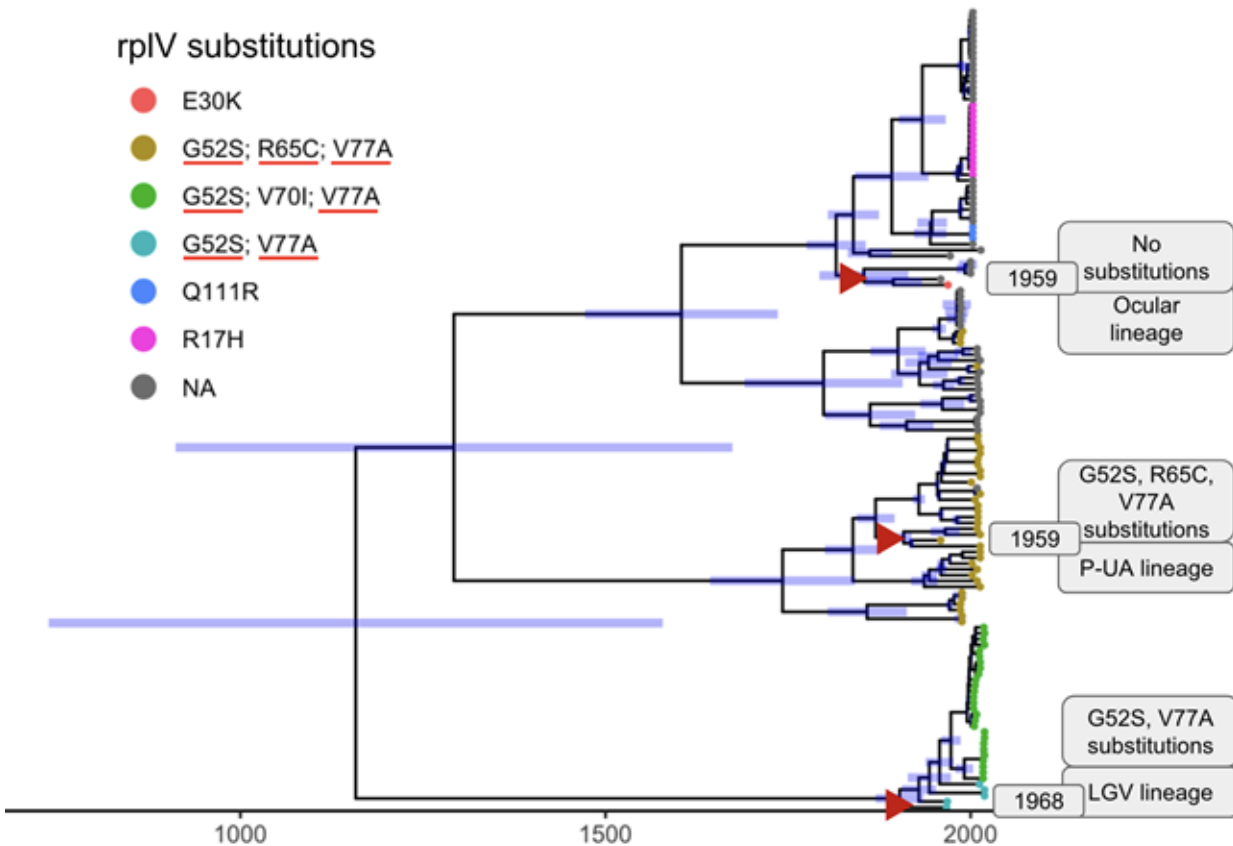
- **100%** of LGV genomes carry G52S and V77A

- **98.8%** of P-UA genomes carry G52S, V77A and R65C

# Time scaled analysis reveal these mutations developed before widespread use of AZ

rpIV substitutions

- E30K
- G52S; R65C; V77A
- G52S; V70I; V77A
- G52S; V77A
- Q111R
- R17H
- NA



Azithromycin was discovered in 1980 and approved for medical use in 1988.

3 Oldest isolates are:

- **1959** (Taiwan) ocular strain - no mutations
- **1959** (USA) P-UA strain - triple AZ mutation
- **1967** (USA) LGV strain - G52S+V77A mutation

# Putative resistance mutations in 23S rRNA were present in all genomes

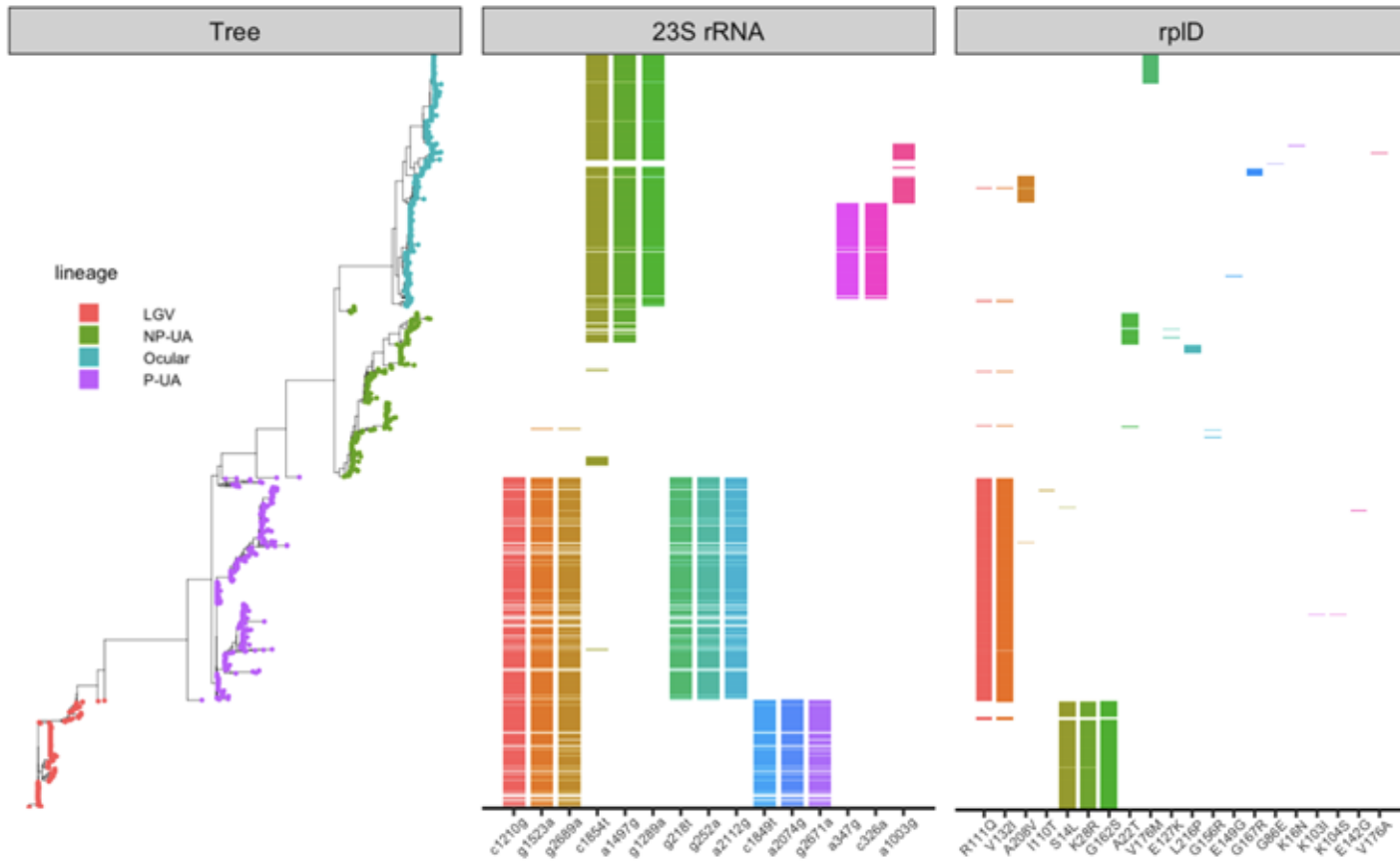
Allele	Reference species	CT-numerung	Detected
a2074c / a2074g / a2074t	<i>Campylobacter coli</i> , <i>Campylobacter jejuni</i>	a1879c / a1879g / a1879t	yes (a->g)
a2075g	<i>Campylobacter coli</i> , <i>Campylobacter jejuni</i>	a1880g	
a2059g	<i>Neisseria gonorrhoeae</i>	a2036g	yes
a2058g / a2058t	<i>Escherichia coli</i>	a2038g	
a2114g	<i>Streptococcus pneumoniae</i>	a2449g	
a2115g	<i>Streptococcus pneumoniae</i>	a2450g	
c2627a	<i>Campylobacter coli</i> , <i>Campylobacter jejuni</i>	c2592a	
c2611t	<i>Neisseria gonorrhoeae</i> , <i>Escherichia coli</i>	c2592t / c2592g	yes (c->t)
g2032t	<i>Escherichia coli</i>	g2012t	
c2630a / c2630g	<i>Streptococcus pneumoniae</i>	na*	
t2609c	<i>Escherichia coli</i>	t2590c	
t754a	<i>Escherichia coli</i>	t740a	yes (t->g)

- Mutations were found from NCBI AMR database and CARD.

- Genomes were **positive for 4 macrolide resistance mutations**

- These mutations were also found in **98%-99% of the isolates** in the dataset

# Patterns of Mutations in 23S rRNA and *rpID*



- 15 most frequent 23S mutations

- 20 total mutations in *rpID*

- Mutations were lineage-specific

# Conclusion

- Putative resistance **mutations predate clinical introduction** of azithromycin.
- **High lineage specificity** reflects neutral evolution rather than acquired resistance after azithromycin use.
- Azithromycin Treatment failures for *C. trachomatis*, *i.e* the **resistance phenotype may be multifactorial**, involving epistatic genetic mutations or physiological factors beyond the presence of known mutations. Treatment failures may also result from reinfection from an untreated partner, inadequate drug treatment, or noncompliance with medication.
- Resistance markers (listed in public databases) are non-transferable across species.
- Studies like these, help refine targets for designing efficient phenotypic validations for clinical relevance.

LINK to this published study: <https://doi.org/10.1128/aac.01708-25>

**Putative azithromycin resistance mutations in *Chlamydia trachomatis* are globally distributed but arose before azithromycin was discovered**

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