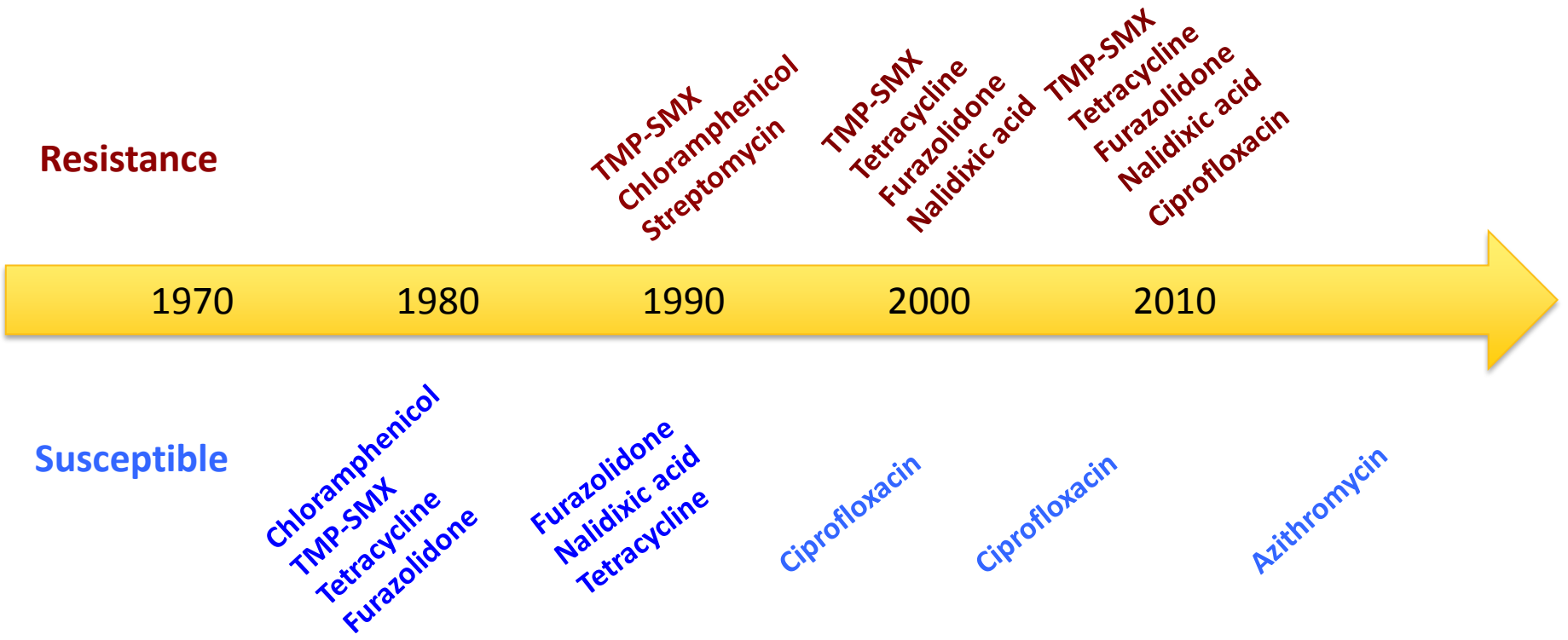
AMR in the Context of Cholera

Trends in antimicrobial resistance of *V. cholerae* O1/O139



Current recommendations of antibiotics

First line

Azithromycin: Adults: po 1g (500 mg x 2) single dose
Children: po 200 mg/kg single dose

Second line (not for children <5 years and pg women)

Ciprofloxacin: Adults po 1g (500 mg x 2) daily for 3 days
Children po 20 mg/kg daily for 3 days

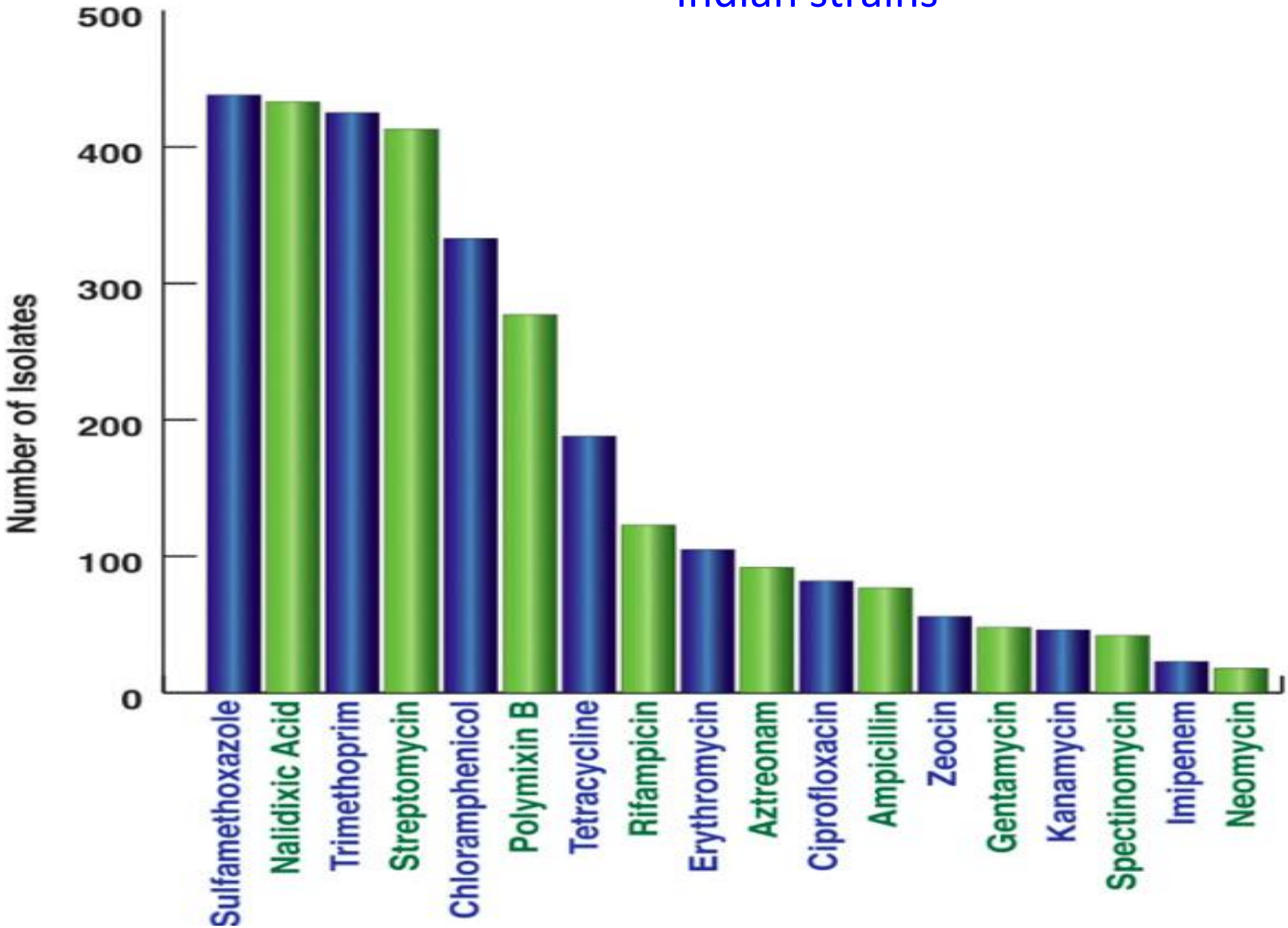
Third line

Doxycycline: 300 mg-single dose (not children of pg women)

***Erythromycin:** 6 hrs x 3 days , 2 yrs 125 mg; 2-8 years 250 mg;
>8 yrs 250-500 mg

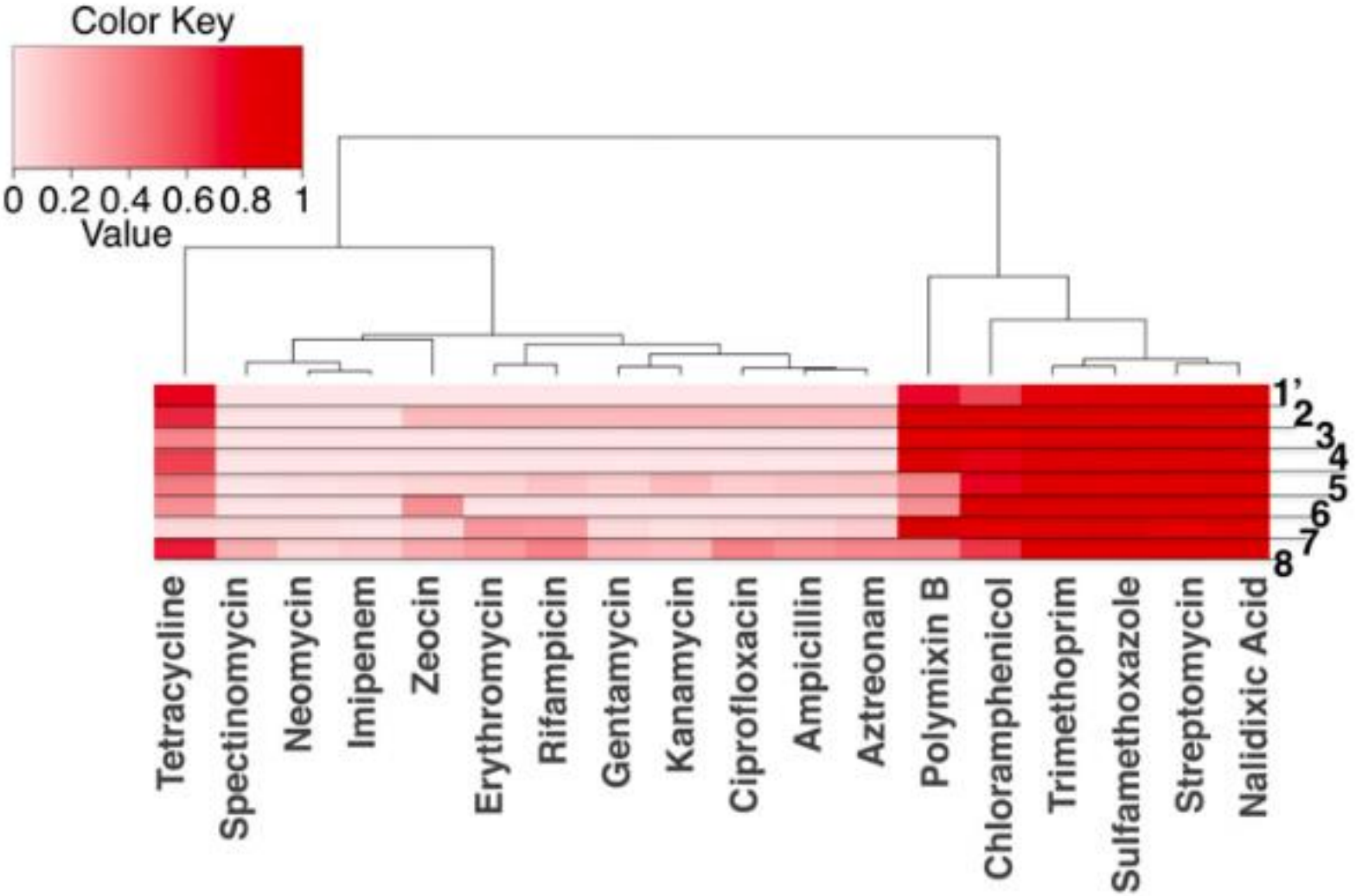
Pietroni. Vaccine 2019

Resistance profile of *V. cholerae* against different antibiotics Indian strains



Verma et al., Proc Nat Aca Sci. 2019; 116:6226-31

Year wise resistance pattern of *V. cholerae* O1 strains isolated during 2008-2015 Indian strains



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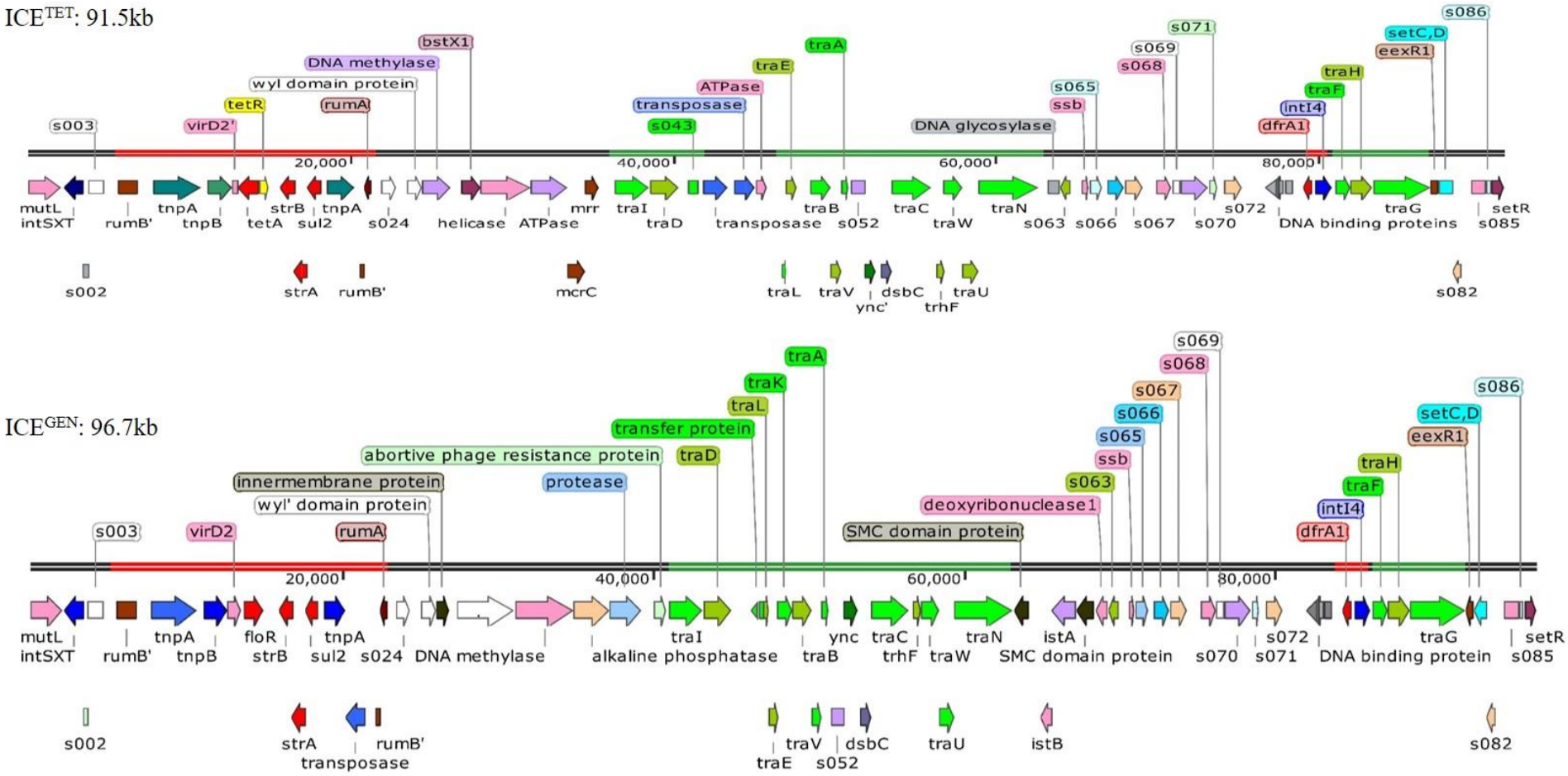
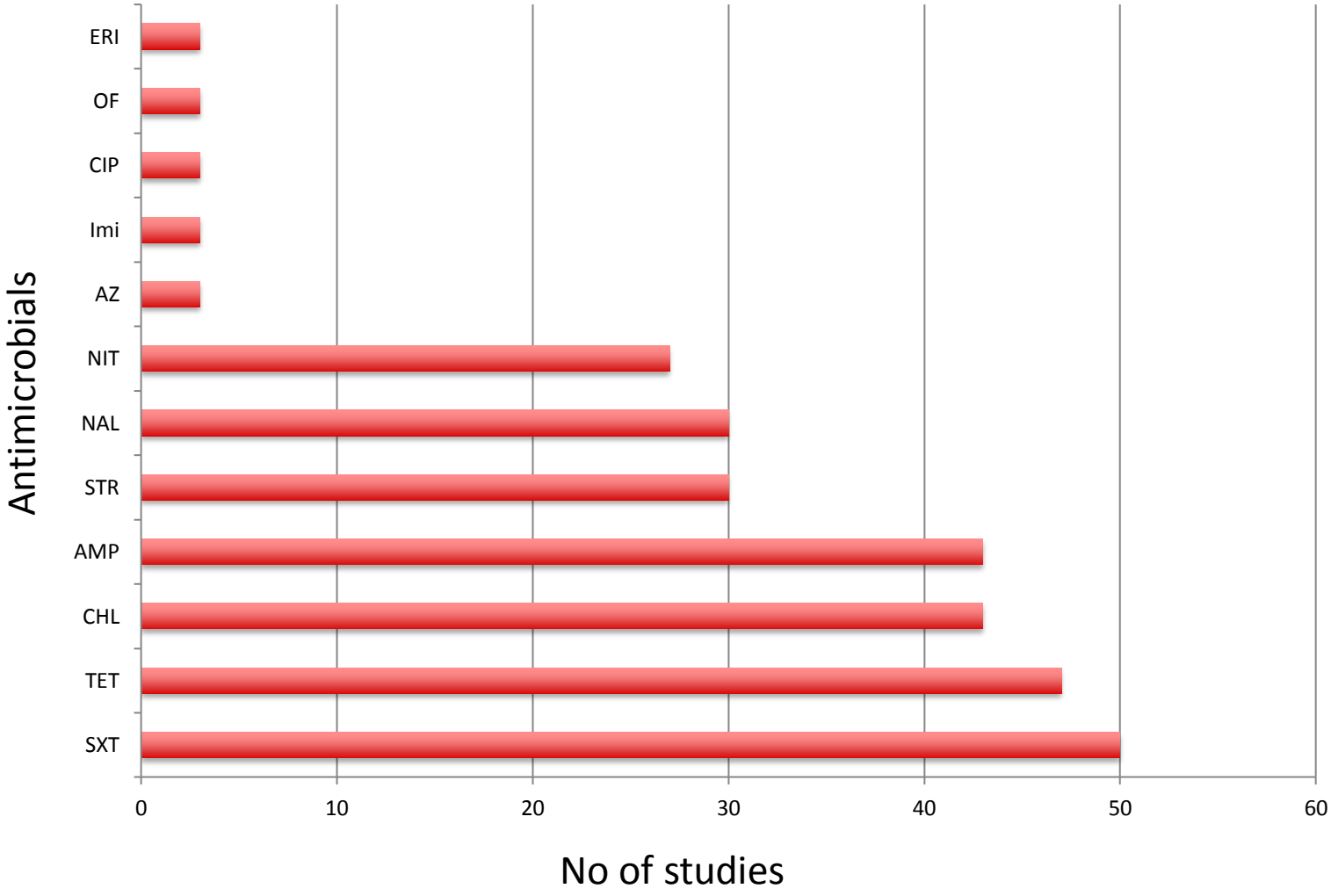
Verma et al., Proc Nat Aca Sci. 2019; 116:6226-31

Tetracycline gene carried by SXT element



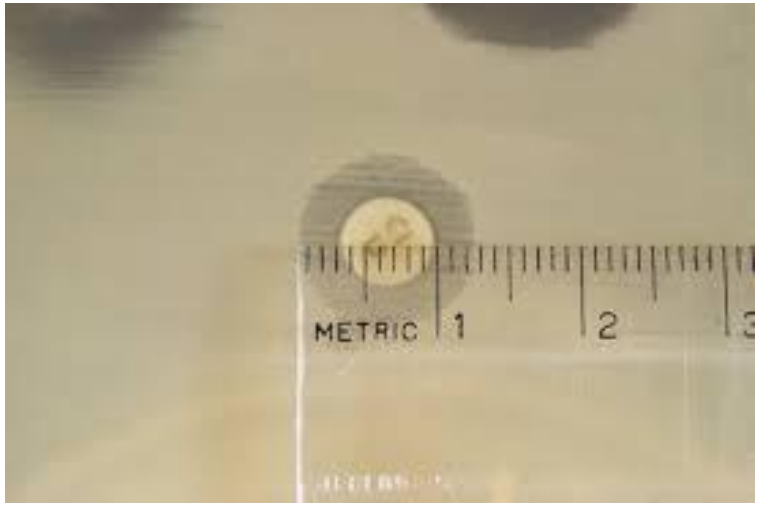
Sarkar et al., 2019

AMR of *Vibrio cholerae* from sub-Saharan Africa



Afr J Lab Med. 2018; 7(2): 778.

Antibiotic sensitivity test pictures



Antimicrobial susceptibility testing committees

CLINICAL AND LABORATORY STANDARDS INSTITUTE (Formerly NCCLS)

BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

CLSI (NCCLS)

✓ **CLINICAL BREAKPOINTS**

EUCAST

✓ **CLINICAL BREAKPOINTS**
✓ **EPIDEMIOLOGYCAL CUT-OFF**

Breakpoints are defined for **clinical purposes** (to treat patients) and not with the specific aim to detect resistance mechanisms

Epidemiological cut-off values can be used to **detect resistance mechanisms**


CLINICAL AND
LABORATORY
STANDARDS
INSTITUTE®
26th Edition
M100S
Performance Standards for Antimicrobial Susceptibility Testing

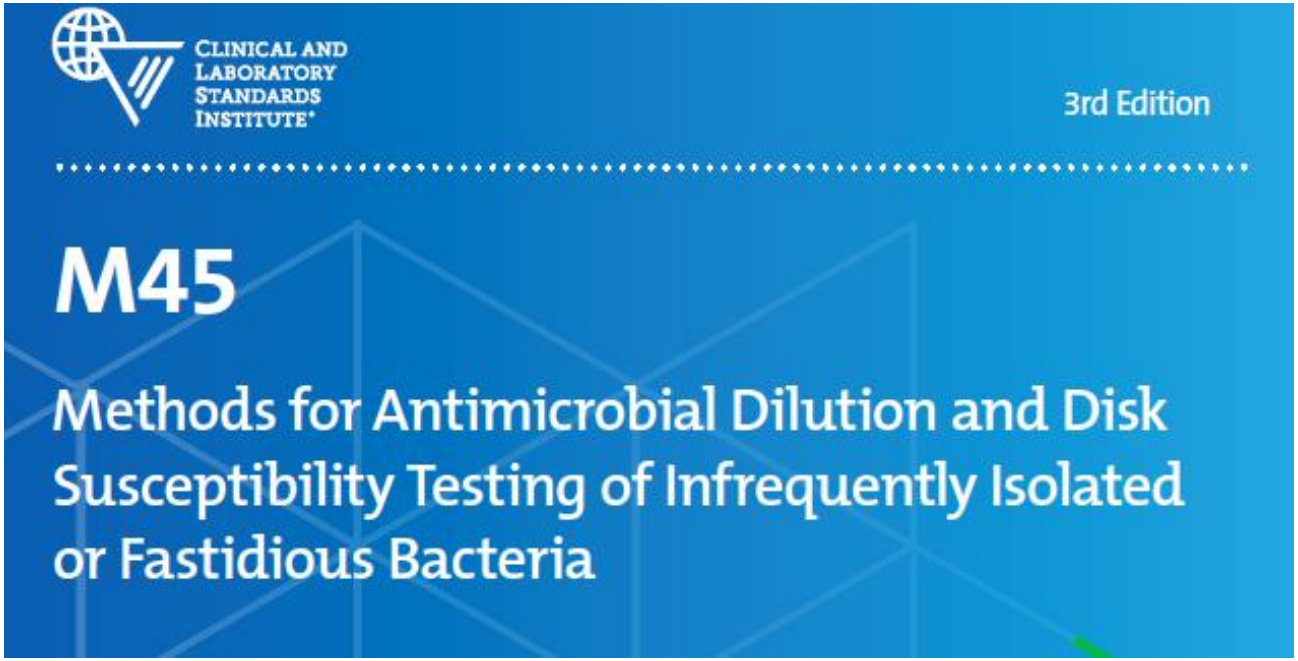

CLINICAL AND
LABORATORY
STANDARDS
INSTITUTE®
3rd Edition
M45
Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria

Table 20. (Continued)

Antimicrobial Class	Antimicrobial Agent	Disk Diffusion	Zone Diameter (mm) Interpretive Criteria			MIC (µg/mL) Interpretive Criteria			Comments
			S	I	R	S	I	R	
CEPHEMS (Continued)									**See comment (3).**
	Ceftazidime	30 µg	≥21	18–20	≤17	≤4	8	≥16	Breakpoints are based on a dosage regimen of 1 g every 8 h.
	Cefuroxime sodium (parenteral)	30 µg	≥18	15–17	≤14	≤8	16	≥32	Breakpoints are based on a dosage regimen of 1.5 g every 8 h.
CARBAPENEMS									**See comment (3).**
	Imipenem	10 µg	**≥23**	**20–22**	**≤19**	**≤1**	**2**	**≥4**	**Breakpoints are based on a dosage regimen of 500 mg every 6 h or 1 g every 8 h.**
	Meropenem	10 µg	**≥23**	**20–22**	**≤19**	**≤1**	**2**	**≥4**	**Breakpoints are based on a dosage regimen of 1 g every 8 h.**
MACROLIDES									
	Azithromycin	–	–	–	–	≤2	–	–	**(4) Due to limited clinical or *in vitro* MIC data for azithromycin and doxycycline, the utility of these interpretive criteria for *Vibrio* spp. other than *V. cholerae* is uncertain.**
AMINOGLYCOSIDES									See comment (3).
	Amikacin	30 µg	≥17	15–16	≤14	≤16	32	≥64	
	Gentamicin	10 µg	≥15	13–14	≤12	≤4	8	≥16	
TETRACYCLINES									(5) For *V. cholerae*, isolates susceptible to tetracycline are also susceptible to doxycycline.
	Doxycycline	–	–	–	–	≤4	8	≥16	**See comment (4).**
	Tetracycline	30 µg	≥15	12–14	≤11	≤4	8	≥16	
FLUOROQUINOLONES									**See comment (3).**
	Ciprofloxacin	5 µg	≥21	16–20	≤15	≤1	2	≥4	
	Levofloxacin	5 µg	≥17	14–16	≤13	≤2	4	≥8	
	Ofloxacin	5 µg	≥16	13–15	≤12	≤2	4	≥8	
FOLATE PATHWAY INHIBITORS									
	Sulfonamides	250 µg or 300 µg	≥17	13–16	≤12	≤256	–	≥512	(6) Sulfasoxazole can be used to represent any of the current available sulfonamide preparations. (7) For *V. cholerae* only.
	Trimethoprim-sulfamethoxazole	1.25/23.75 µg	≥16	11–15	≤10	≤2/38	–	≥4/76	

Rapid detection of antimicrobial resistance

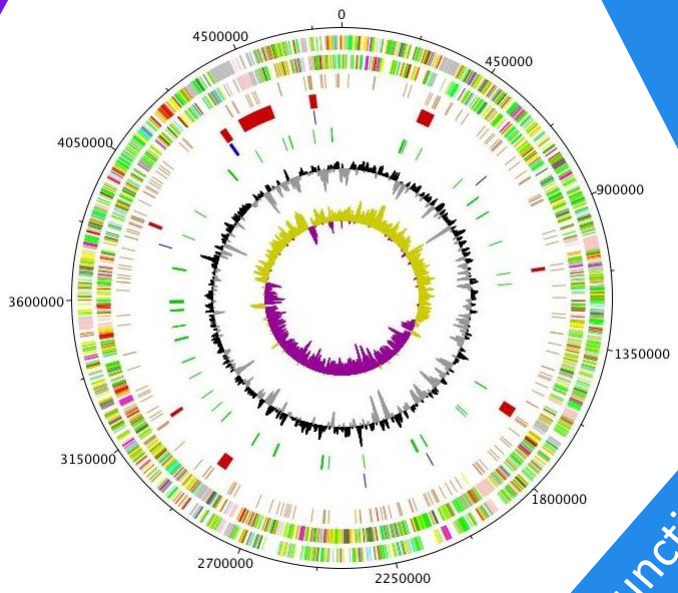
- MALDI-TOF MS mass spectral profiles and/or shifts within
- Real-time microscopy time lapse imaging
- Colorimetric and turbidity measurements (BD Phoenix)
- Transmittance of light due to turbidity (VITEK 2)
- Metabolic growth (MicroScan WalkAway)
- Identification and real-time imaging (PhenoTest BC)

Versatility of WGS

Identification of Species/virulence

Predicting/evolution of AMR

Genomic assisted cloning



Protein profiling

Functional analysis

Molecular epidemiology

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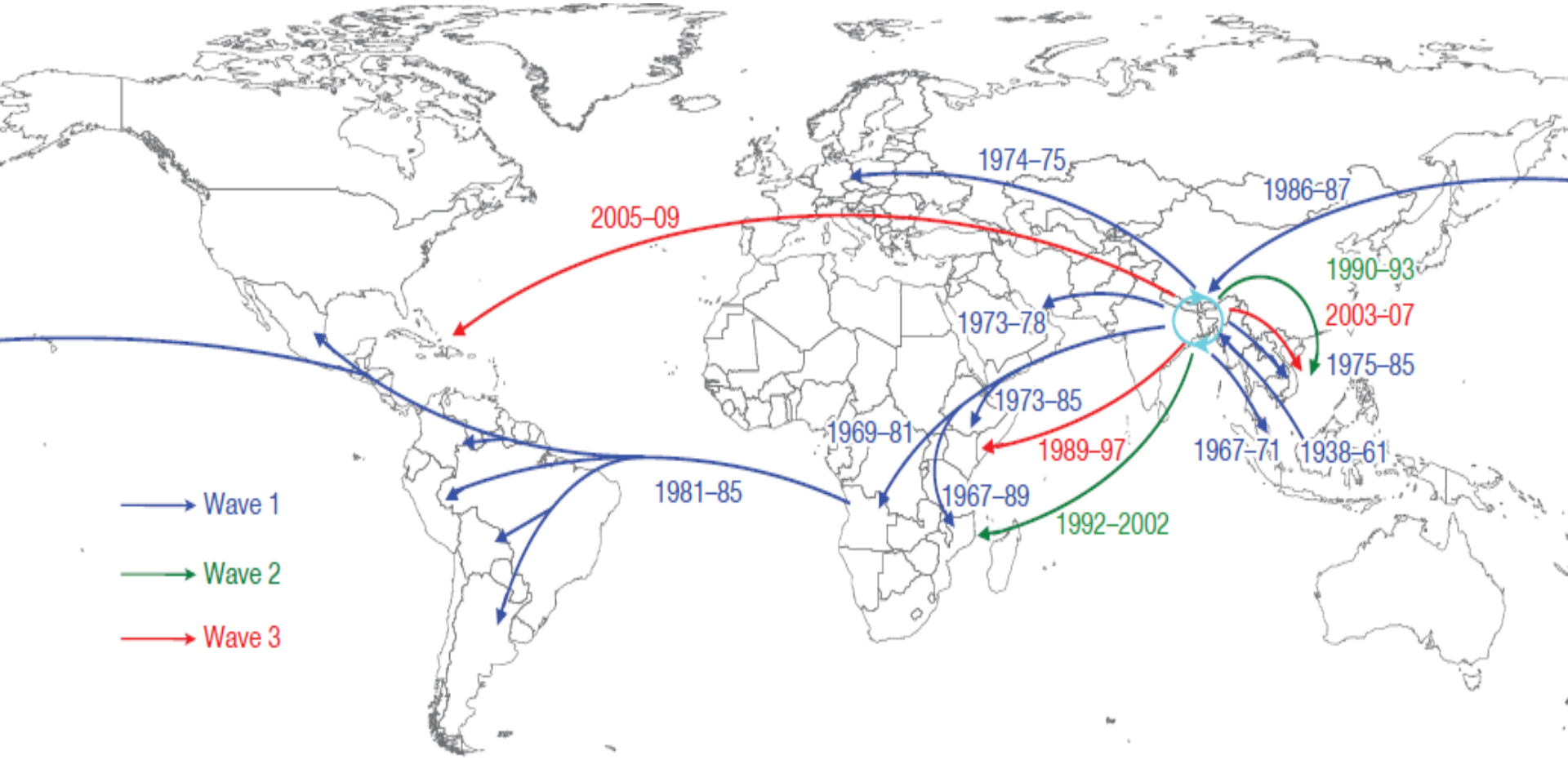
Transmission events of seventh pandemic cholera



28 African isolates studied but all but one from East Africa :

Angola 1989 (n=1); Djibouti 2007 (n=3); Kenya 2005-2007 (n=17); Mozambique 1991, 2005 (n=6); Tanzania 2009 (n=1).

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Mutreja *et al.,* Nature. 2011;477:462-65.

Cholera in Africa, 1970-2014

11 introductions to Africa

Guinea 1970 ←Middle East

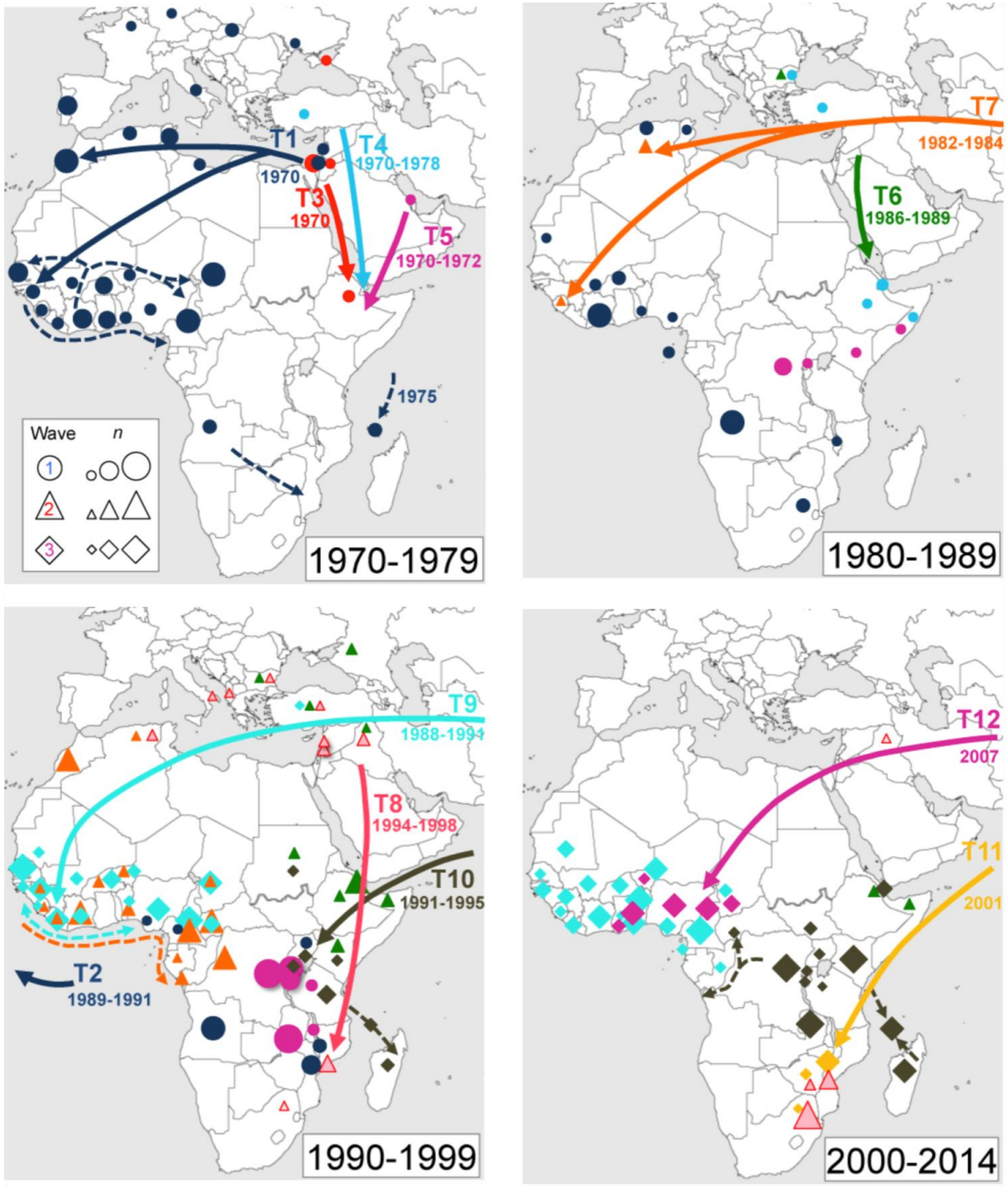
Angola 1971 ←West Africa

Five introductions to West Africa and six to East Africa

Middle East acting as a springboard during six introductions.

Followed by up to 28 years of regional circulation

Two separated and persistent foci (West Africa and the Great Lakes-Horn of Africa region). Rare exceptions.



Weill et al. Science. 2017;358:785-789.

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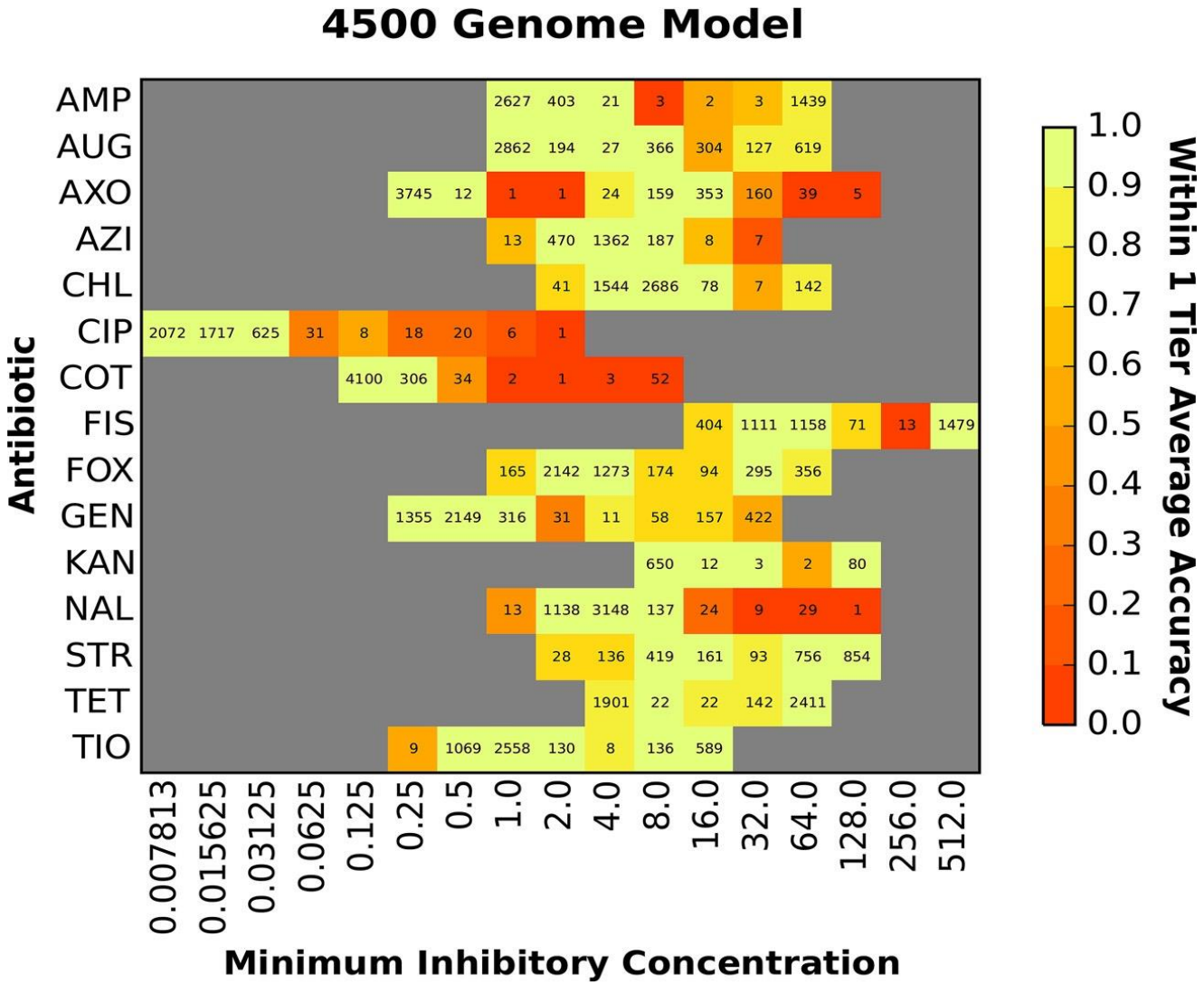
Prediction of MICs from the Whole Genome Data



Nguyen et al., JCM 2019

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Alternative measures to control AMR

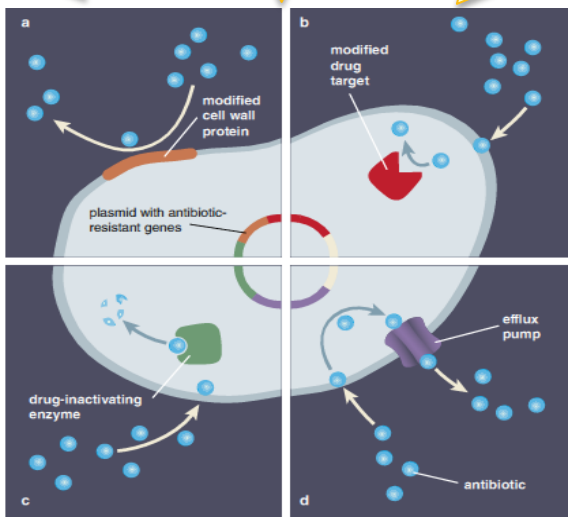
Nanotherapeutics

Anti-biofilm

Phage therapy

RNA-interference

Antibodies



Genome editing

Vaccines

Bacteriocins
Antimicrobial peptide

Essential oils

Resensitizing

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Focus areas
Development of NAP in line with GAP-AMR
AMR-related awareness-raising
National AMR surveillance
Rational use of antimicrobials and surveillance of use/sale (community)
IPC programme and AMS programme in health-care settings
Research and innovation
One Health engagement

GAP: Global Action Plan
IPC: infection prevention and control
NAP: national action plan

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WHO priority pathogens list for R&D of new antibiotics

Priority 1: CRITICAL

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae, carbapenem-resistant, ESBL-producing

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter spp., fluoroquinolone-resistant

Salmonellae, fluoroquinolone-resistant

Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella spp., fluoroquinolone-resistant

Actions and the Gaps

Prioritizing the antimicrobials (Critical/High/Medium) [oral/IV]

Clarity in identifying S/I/R

Setting a lab manual for AMR testing with cut-off values, std strains etc.,

Unified AMR screening with EQS

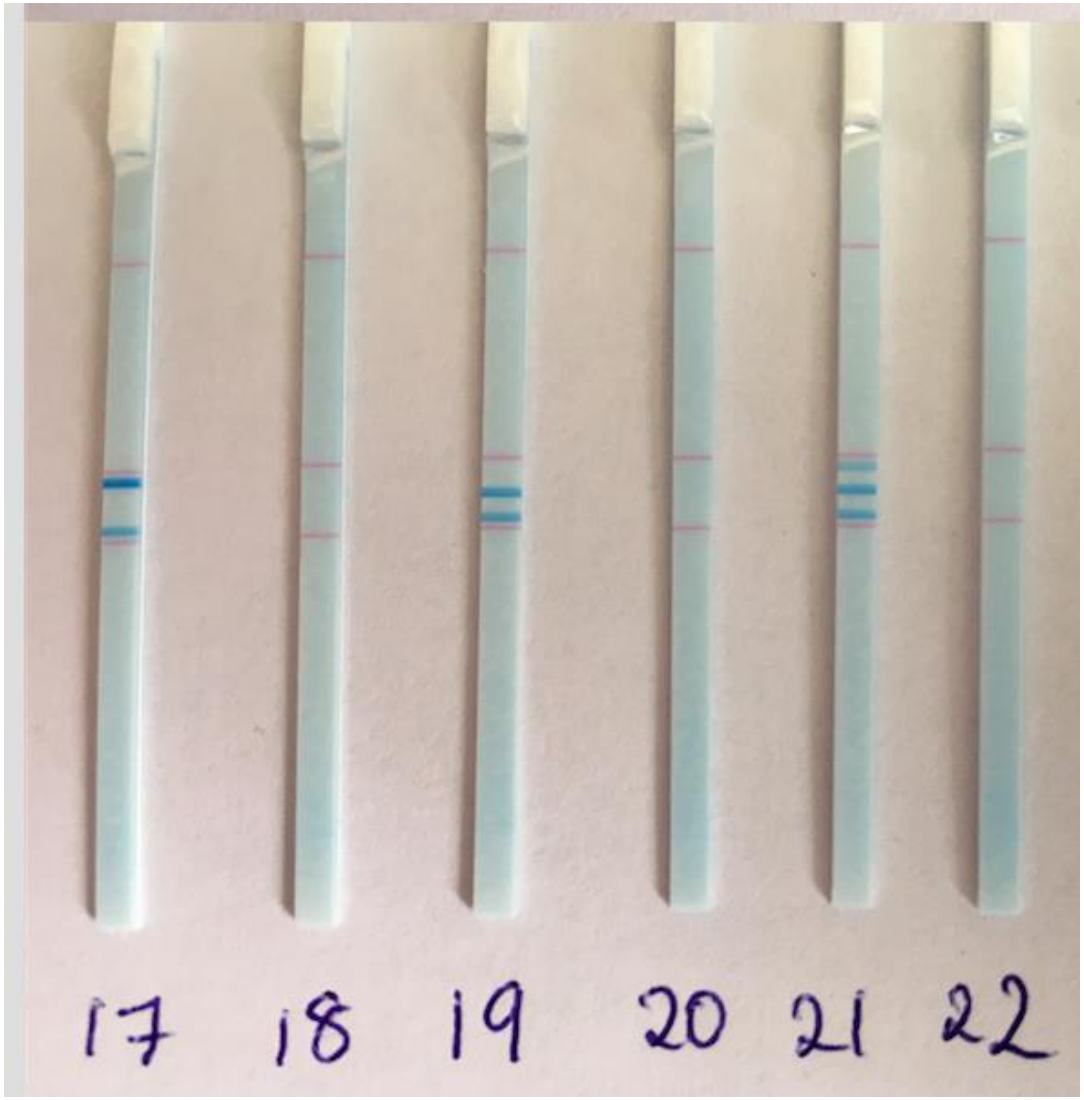
Development of rapid AMR testing

More research on “Knock-on” (indirect, or cumulative) effects include persister cell formation, alterations of the levels of virulence and pathogenicity during and after antibiotic treatment

Rapid detection of *V. cholerae* O1

Mini-PCR machine operated by smartphone

Oligochromatograph of PCR amplicons



17 ctx and VSP-1
19 ctx and O1
21 ctx + O1 + VSP-1
18, 20, 22 -ve Contorls

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2nd Meeting of the GTFCC in THSTI (2015)

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