Priority or minimum panel for testing – phenotypic vs genotypic, public health needs vs One Health

FWD AMR – RefLabCap Network meeting

26-27 April 2023, Therese Westrell and Cecilia Jernberg

Surveillance objectives for EU-level monitoring of AMR in *Salmonella* and *Campylobacter* from humans

a) To monitor, in human clinical isolate trends in the occurrence of resistance to antimicrobial agents relevant for treatment of human *Salmonella* and *Campylobacter* infections, including comparison with food/animal isolates

b) To monitor, in human clinical isolates, trends in the occurrence of resistance to other antimicrobial agents of public and animal health importance, including comparison with food/animal isolates

c) To monitor, in human clinical isolates, the prevalence of ESBL, plasmid-encoded Ambler class C β-lactamases (pAmpC) and carbapenemase phenotypes and genotypes

d) To use antimicrobial resistance patterns to characterise human clinical isolates, i.e. as an epidemiological marker, to support identification of outbreaks and related cases

e) To identify and monitor, in human clinical isolates, genetic determinants of resistance that are important for public health e.g. to aid recognition of epidemic cross-border spread of multi-drug resistant *Salmonella* strains

f) To monitor, in human clinical isolates, trends in the occurrence of resistance to antimicrobial agents that may be needed for future therapeutic use

https://www.ecdc.europa.eu/en/publications-data/eu-protocol-harmonised-monitoring-antimicrobial-resistance-human-salmonella-and-0

EU protocol for harmonised monitoring of antimicrobial resistance in human *Salmonella* and *Campylobacter* isolates - Salmonella

Table 1. List of antimicrobials to be tested for human *Salmonella* spp. isolates

Class	Name (abbreviation*)	Surveillance objectives	Comments
First priority			
Aminoglycosides	Gentamicin (GEN)	b, d	
Aminopenicillins	Ampicillin (AMP)	a, b, d	
Amphenicols	Chloramphenicol (CHL)	a, d	
Carbapenems	Meropenem (MEM)	a, b, c, d, e	EUCAST recommend meropenem as it offers the best compromise between sensitivity and specificity in terms of detecting carbapenemase-producers
Cephalosporins	Cefotaxime (CTX)	a, b, c, d, e	May be insensitive for detection of ceftazidimase-type ESBLs
	Ceftazidime (CAZ)	a, b, c, d, e	Added to increase sensitivity of screening for full range of ESBL with diverse substrate specificities
Dihydrofolate reductase inhibitors	Trimethoprim (TMP)	d	Value as an epidemiological marker, e.g. in the resistance pattern ASuT common among *S.* Typhimurium.
Macrolides	Azithromycin (AZM)	f	May be considered as a last resort drug for invasive salmonellosis.
Polymyxins	Colistin (COL)	b	Last-resort drug in human medicine and extensively used in animal medicine. Plasmid-mediated resistance detected in *E. coli* and *Salmonella* in Europe in 2015. Its chemical properties however cause unreliable results with dilution and render it impossible to test with disk diffusion. Please follow the dilution method agreed between CLSI and EUCAST [10]. Note: Any laboratory that wants to report an isolate as resistant to colistin must get the result confirmed at a reference laboratory that is up to date with the latest method developments for testing of colistin.
Quinolones	Ciprofloxacin (CIP)/pefloxacin (PEF)	a, b, c, d, e	Preferably test ciprofloxacin with broad MIC range. For disk diffusion, EUCAST recommend screening with pefloxacin [11] since ciprofloxacin is poor at detecting low-level fluoroquinolone resistance in *Salmonella* spp. with this method and nalidixic acid is often not detecting plasmid-mediated fluoroquinolone resistance [12]. Only for isolates having the *aac(6')-Ib-cr* gene, pefloxacin does not work well.
Sulphonamides	Sulfamethoxazole (SMX)	d	Value as an epidemiological marker, e.g. in the resistance pattern ASuT common among *S.* Typhimurium. No ECOFF available however due to methodological problems and little harmonisation between disk manufacturers.
Tetracyclines	Tetracycline (TCY)	b, d	Used both in veterinary and human medicine.
	Tigecycline (TGC)	f	
Optional			
Aminopenicillins	Amoxicillin (AMX)		Alternative for testing and reporting if AMP not tested.
Carbapenems	Ertapenem (ETP)		Many human laboratories test for ertapenem so should be possible to report.
Cephalosporins	Ceftriaxone (CRO)	a, b, c, d, e	Alternative for cefotaxime with disk diffusion method as has similar spectrum of activity.
Combination drugs	Trimethoprim + sulfamethoxazole (co-trimoxazole) (SXT)		No need to test if the substances are tested separately.
Quinolones	Nalidixic acid (NAL)		For laboratories using disk diffusion, nalidixic acid (NAL) can be tested in addition to pefloxacin for easier identification of QRDR mutations (*gyr* and *par*) since such mutations may result in clinical treatment failure (Le Hello, Institut Pasteur Paris, personal communication, Sep 2015).

Table 1 lists which objective each antimicrobial fulfils for *Salmonella* (one or more)

Treatment of salmonellosis

- *ciprofloxacin, cefotaxime/ceftazidime, ampicillin, chloramphenicol (typhoid), meropenem, trimethoprim-sulfa (optional)*

Last resort

- *azithromycin, tigecycline*

Used in health care for other pathogens or in animal husbandry

- *gentamicin, tetracycline, colistin*

Epi markers

- *Most of the above plus trimethoprim and sulfamethoxazole*

Recently added in vet panel

- *amikacin*

EU protocol for harmonised monitoring of antimicrobial resistance in human *Salmonella* and *Campylobacter* isolates - *Campylobacter*

Table 2. List of antimicrobials to be tested for human *Campylobacter* spp. isolates

Class	Name (abbreviation*)	Surveillance objectives	Comments
First priority			
Aminoglycosides	Gentamicin (GEN)	a, b	Included for invasive disease monitoring.
Macrolides	Erythromycin (ERY)	a, b	
Quinolones	Ciprofloxacin (CIP)	a, b	
Tetracyclines	Tetracycline (TCY)	a, b	
Optional			
Carbapenems	Meropenem (MEM) Ertapenem (ETP) Imipenem (IPM)	a, c	Include for invasive disease monitoring when MIC values are available. Encourage MSs to send their data (MIC) to EUCAST for the determination of ECOFFs. CLSI criteria exists. Both testing method and related quality control range are needed for disk diffusion.
Combination drug	Amoxicillin + clavulanic acid (AMC)		Currently no standardised method available.
Macrolides	Azithromycin (AZM)	f	Not included at this stage. Option for future.

Table 2 lists which objective each antimicrobial fulfils (one or more)

<u>Treatment of campylobacteriosis</u>

- *ciprofloxacin, erythromycin, tetracycline, gentamicin (invasive inf.)*
- *meropenem/ertapenem/imipenem (so far optional, invasive inf.), amoxi-clav (optional, used in some countries)*

<u>Recently added in vet panel</u>

- *ertapenem, chloramphenicol*

Current situation *Salmonella* – 2021 data

- 26 countries reported
- Most tested – ampicillin (12 080 isolates), all countries
- Least tested – colistin, tigecycline and azithromycin (3 116 – 4 589 isolates), 9 countries
- MDR analysis with 9 classes (excluding COL, TGC, AZM) – 14 countries, 6 867 isolates
- So far, EFSA agreed to exclude colistin in MDR analysis and include tigecycline and amikacin together with similar substances. Therefore only azithromycin differ in EFSA and ECDC analysis.

Current situation *Campylobacter* – 2021 data

- 24 countries reporting
- Almost all test ciprofloxacin, erythromycin and tetracycline - erythromycin (12 630 isolates)
- Least tested – gentamicin (7 633), 16 countries
- MDR analysis with 4 classes – 15 countries 6 867 isolates
- So far, EFSA agreed to use same 4 classes in MDR analysis as ECDC but now has also chloramphenicol and ertapenem in their panel.

What is the issue?

- Countries with less resources have difficulties to test all antimicrobials in the priority panel
- For *Shigella*, in EU surveillance included only antimicrobials used for treatment. Now problem to assess extent of emerging MDR-clones in the EU
- Reducing the priority list will make it more difficult to compare data with vet sector – One Health AMR surveillance gaining importance
- Vet panel now including new substances. Should any of these be added to the priority panel?

To discuss

- Reduce the priority panel to only antimicrobials important for treatment of *Salmonella* and *Campylobacter*?
- Test a smaller subset with the full panel?
- Accept that not all countries can report the full panel and focus on EU situation rather than individual countries?
- Implement WGS from which you can get results for all antimicrobials?
- Other?

Thank you for your attention!