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UK Public Health Resistance Alert: *Salmonella* Typhi resistant to third-generation cephalosporins isolated in England from a traveller returning from Pakistan

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UK Public Health Resistance Alert: *Salmonella* Typhi resistant to third-generation cephalosporins isolated in England from a traveller returning from Pakistan

Salmonella Typhi (_S_. Typhi) resistant to third-generation cephalosporins has been isolated from a traveller returning to the UK from Pakistan. The resistance was conferred via the acquisition of a CTX-M-15 ESBL. The isolate also has mutations conferring resistance to fluoroquinolones.

In response, it is recommended that:

- **Diagnostic laboratories should screen presumptive isolates of _S._ Typhi and _S._ Paratyphi A for resistance to third-generation cephalosporins.**
- **Diagnostic laboratories should continue to refer all isolates of presumptive _S._ Typhi and _S_. Paratyphi to PHE's Gastrointestinal Bacteria Reference Unit (GBRU) to enable continuous surveillance of genetic resistance markers. This is free of charge to the NHS laboratories in England and Wales.**
- **NHS laboratories in Scotland should, instead, forward isolates to the Scottish Salmonella Reference Service, based in the Scottish Microbiology Reference Laboratories, Glasgow.**

Background

Public Health England (PHE) reports approximately 300 cases of laboratory-confirmed enteric fever each year, of which >90% are acquired abroad, the majority from travellers returning to the UK from Pakistan, India and Bangladesh [1]. The majority of *S.* Typhi isolates received by the Gastrointestinal Bacteria Reference Unit (GBRU) are of the globally epidemic and multidrug-resistant (MDR) clone H58, which characteristically shows resistance to chloramphenicol, ampicillin, co-trimoxazole, streptomycin, tetracycline and reduced susceptibility to quinolones [2]. Third-generation cephalosporins are therefore used as first-line therapy to treat complicated cases of enteric fever [3]**.**

Resistance to third-generation cephalosporins has been reported since 2003 from isolated cases in *S*. Typhi from the Indian subcontinent, Middle East, and Africa. More recently, cases of cephalosporin-resistant *S.* Typhi have been reported in travellers returning to Germany and Spain, and a case of *S.* Paratyphi A returning to Japan [4-7]. Of note, given the extent of travel between the UK and Pakistan, there is a large and ongoing outbreak of *S.* Typhi with CTX-M-15 in the Sindh district of Pakistan.

Basis for alert

PHE's GBRU undertakes characterisation of all *Salmonella* isolates using whole genome sequencing (WGS). A presumptive *S.* Typhi isolated from the blood of a traveller returning from Karachi, Pakistan was received in September 2017. The isolate typed as H58 *S.* Typhi and had the following resistance determinants: $bla_{\text{CTX-M -15}}$, $bla_{\text{TEM-1}}$, *gyrA* [83:S-F], *qnrS-1, aac(6')-Iy, aph(6)-Id, strB, strA , dfrA-7, sul2, sul-1 and cat-A.* The CTX-M-15 ESBL gene was associated with an IS*Ecp1* transposable element [4,9].

Antimicrobial susceptibility testing (AST) confirmed the isolate to be resistant to ceftriaxone (MIC >32 mg/L), ceftazidime (>32 mg/L), ciprofloxacin (2 mg/L), and co-trimoxazole (>32 mg/L). It was susceptible meropenem (0.06 mg/L), ertapenem (0.015 mg/L), chloramphenicol (2 mg/L), colistin (0.5 mg/L), azithromycin (8 mg/L; no EUCAST breakpoint, but isolates with MICs ≤16 mg/L are regarded as 'wild-type'), and with a tetracycline MIC <2 mg/L (no EUCAST breakpoint). Supplemental testing confirmed presence of an ESBL and the absence of AmpC.

Action advised

1. Diagnostic laboratories should screen all presumptive isolates of *S*. Typhi and *S*. Paratyphi for resistance to third-generation cephalosporins with discs or gradient strips using EUCAST methodology. Testing ceftriaxone or cefotaxime should be sufficient to detect CTX-M-15, which is the dominant ESBL found in the species.
2. Diagnostic laboratories should continue to refer presumptive isolates of *S.* Typhi and *S.* Paratyphi to PHE's GBRU to enable continuous surveillance of genetic resistance markers. This is free of charge to the NHS laboratories in England and Wales.
3. NHS laboratories in Scotland should, instead, forward isolates to the Scottish Salmonella Reference Service, based in the Scottish Microbiology Reference Laboratories, Glasgow.
4. Consideration should be given to starting empirical combination therapy with ceftriaxone plus azithromycin for cases of complicated enteric fever until AST results are available, particularly if there are epidemiological links with areas where cephalosporin resistance has been well recognised.
5. Targeted treatment in a case with confirmed third-generation cephalosporin resistance should include combination treatment with meropenem (1 g 8 hourly IV in adults) plus oral azithromycin (up to 20 mg/kg/day PO) [10]. As there are historic reports of clinical efficacy with temocillin for treatment of enteric fever [11], consideration might be given to a combination of temocillin plus azithromycin.

For further information please contact Dr Gauri Godbole, PHE Gastrointestinal Bacteria Reference Unit, gauri.godbole@phe.gov.uk

Additional information for NHS Scotland

For Scottish diagnostic laboratories please ensure that all *S.* Typhi and *S.* Paratyphi A isolates are phenotypically tested for ESBL production locally. Then, as per current normal practice, please submit all isolates to the Scottish Salmonella Reference Laboratory, Glasgow.

As part of the new processing of these isolates by Whole Genome Sequencing at the Reference Laboratory, any diagnostic laboratory-detected phenotypic ESBL-positive isolates can be confirmed by Reference Laboratory sequencing methodology.

Additional information for Northern Ireland

For HSCNI diagnostic laboratories, please ensure that all *S.* Typhi and *S.* Paratyphi A isolates are phenotypically tested for ESBL production locally. If suggestive of ESBL production, isolates should be sent to PHE's GBRU via the Belfast Health and Social Care Trust for Category A postage.

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Health Protection Report is a national public health bulletin for England and Wales, published by Public Health England. It is PHE's principal channel for the dissemination of laboratory data relating to pathogens and infections/communicable diseases of public health significance and of reports on outbreaks, incidents and ongoing investigations.

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