Recommendation on aspects of management of shigellosis in Ireland in the context of current antimicrobial resistant *Shigella species* associated with gay, bisexual and men who have sex with men (gbMSM).

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Summary

Shigellosis is an acute diarrhoeal disease associated with species of the genus shigella. The severity of diarrhoea varies from mild to severe diarrhoea with blood and mucous in stools (dysentery). Shigella is shed in humans faeces. Shedding persists for up to six weeks after diarrhoea resolves. Long term shedding is generally not a concern. Most cases are self-limiting. Some cases may develop blood stream infection or severe colonic disease. Severe illness is more likely in immunocompromised hosts. Effective antimicrobial treatment reduces the duration and severity of illness and reduces the duration of shedding.

The organism infects others when ingested. It is primarily spread through contact with infected faeces. Hands contaminated with faeces are likely to be important in spread. Spread can occur directly through personal contact including social contact in household, workplace or school setting. Sexual contact has emerged as a very important means of transmission in recent years particularly amongst gbMSM. Infection can also spread by indirect contact such as contaminated food or surfaces. Hand hygiene after using the toilet plays an important part in reducing spread.

There is evidence of spread of a number of clonal groups of *Shigella flexneri* and *Shigella sonnei* amongst gbMSM in Ireland. Some of these clonal groups are predicted to be resistant to multiple antibiotics including ceftriaxone, ciprofloxacin and azithromycin in addition to older agents. This document was prepared to support clinical and laboratory practice in responding to this issue.

Recommendations for clinical practice

1. Adult male patients who require hospitalisation and are seriously ill with suspected shigellosis (clinical dysentery like illness) or with laboratory confirmed shigellosis should be treated with a carbapenem such as meropenem until there are laboratory results to guide the use of alternative agents such as ceftriaxone, azithromycin or a fluoroquinolone. This may also be a consideration in all patients with suspected or confirmed shigellosis acquired during travel outside of the EU as antimicrobial resistance is also a significant concern in some countries.
2. Adult male patients with laboratory confirmed shigellosis other than those described above should be offered treatment with azithromycin 500mg daily PO for 3 days unless there is a contraindication to use of azithromycin. They should be advised that sexual partners are likely to be at risk and should seek healthcare if they currently have or develop diarrhoea.

3. At the present time, shigellosis in adult males acquired in Ireland appears very strongly associated with being gbMSM. It is important to establish if adult males presenting with shigellosis are gbMSM.

4. gbMSM with shigellosis in whom sexual transmission is the likely source of infection should be advised to avail of testing for *Chlamydia trachomatis*, *Neisseria gonorrhoeae* from rectal site, pharyngeal and genitourinary (first void urine) sites in addition to testing for syphilis, hepatitis C, HIV (where not known to be positive) and Hepatitis B (if not known to be immune).

5. gbMSM with shigellosis in whom sexual transmission is the likely source of infection should be advised to avoid all sexual activity until at least 1 week after complete resolution of diarrhoea. They should be advised that shedding of shigella can persist for up to 6 weeks following resolution of diarrhoea.

6. The local Medical Officer of Health should be informed of all cases of shigella. In this context, all male shigella cases are to be notified, with completion of the Shigellosis Sexual Exposure Incident/Cluster Investigation form for those who identify as gbMSM (circulated by Health Protection Surveillance Centre 19th May 2023), AND the general enhanced surveillance form for all laboratory-confirmed cases of Shigellosis. Both forms are available on the HPSC website here.

Suggestions for laboratory practice

1. Following molecular detection of shigella in faeces laboratories should make every practical attempt to isolate *Shigella species* as quickly as possible and perform susceptibility testing including testing for susceptibility to ceftriaxone (or cefotaxime), azithromycin, ciprofloxacin and meropenem.
2. EUCAST does not provide breakpoints for susceptibility testing of Enterobacterales against Azithromycin but includes the following comment "*Azithromycin has been used in the treatment of enteric infections, primarily with Salmonella Typhi and Shigella species and although wild type distributions vary somewhat, isolates with MICs above 16 mg/L (azithromycin 15 µg disk zone diameters less than 12mm) are likely to have resistance mechanisms.*"
3. In relation to detection of blaCTX-M producing isolates it may be helpful to culture samples on ESBL-Chromagar in addition to usual selective media for *Shigella species*.
4. Send all shigella isolates to the National Reference Laboratory Service as soon as practical to do so.
5. When notifying the isolate to the Department of Public Health, highlight if the organism is resistant to ceftriaxone, azithromycin or fluoroquinolones.

Technical Background

In recent years shigellosis acquired in Ireland has been increasingly detected in gbMSM. Antimicrobial resistance in *Shigella species* is a growing concern internationally. The following

gives a very brief summary of current concerns regarding dissemination of clonal groups of *Shigella species* and antimicrobial resistance plus recommendations for clinical practice.

Shigella flexneri

There are two principal clonal groups of *S. flexneri* that have been detected mainly in gbMSM in Ireland.

SH19-007 represents 58 cases as of end of April 2023. Most representatives of this clonal group **do not have** resistance determinants to either ceftriaxone, azithromycin or fluoroquinolones although 1 had a blaCTX-M-14 and 7 had resistance determinants for azithromycin.

SH20-004 represents 14 isolates as of end of April 2023 of which: **8 have resistance determinants for all 3 of ceftriaxone, azithromycin and fluoroquinolones** (CAF resistance); 4 for ceftriaxone and fluoroquinolones and 3 for fluoroquinolones alone. [14 fluoroquinolone resistant, 11 resistant to ceftriaxone, 8 resistant to azithromycin]

Both clonal groups are exclusively or almost exclusively associated with adult males and within the Dublin region.

Shigella sonnei

There are two clonal groups that have been mainly detected in gbMSM in Ireland.

SH19-005. As of end of April 2023 there were 7 *S. sonnei* SH19-005 isolates this year in adult males. This group frequently **has** a resistance determinant for fluoroquinolones (qnrB19) but **not for** ceftriaxone or azithromycin. It has been detected in samples submitted in Cork and Dublin. There were four isolates of this group before 2023. Three of these 4 earlier isolates were in women (1 in 2018 and 2 in 2019 and associated with travel to Mexico and South America).

SH22-001 In 2023 there were 3 isolates of SH22-001 and 2 in 2022. These 5 isolates **have** resistance determinants for ceftriaxone and fluoroquinolone but not for azithromycin. All cases are adult males.

Comment

The above data indicates 4 chains of transmission, although these may overlap. It is likely that in many cases the antimicrobial resistance is coded on conjugative plasmids that may spread between different species of shigella and to between shigella and other genera.

Early treatment of infection with an effective agent may speed recovery and reduce shedding thus helping to interrupt the chains of transmission.

SH19-007 is the most extensive chain of transmission, but it may be that SH20-004 is the greater concern given the association with predicted AMR to key agents commonly used for treatment. Patients who are seriously ill with suspected shigellosis or with shigellosis confirmed on molecular detection and treated with one of the commonly used empiric agents

(any one of ceftriaxone, azithromycin or fluoroquinolone) could be receiving ineffective therapy if infected with SH20-004 strains with resistance determinants for ceftriaxone, azithromycin and fluoroquinolone.

Notes

1. The designations for the clonal groups are assigned by the National Reference Laboratory based at Galway University Hospital. SH refers to shigella, the numeral following SH (for example 19) indicates they year in which there were sufficient isolates in the database to designate the group as a cluster of interest. The number after hyphen (for example 007) indicates the order of identification of that cluster in that year. SH19-007 therefore refers to the 7th cluster of *Shigella species* recognised in 2019.
2. The National Reference Laboratory characterises *Shigella* species based on whole genome sequencing. Conventional phenotypic susceptibility testing is usually not performed. Antimicrobial resistance is therefore predicted on the basis of bioinformatics analysis of DNA sequence.
3. It is possible that some patients could have mixed infection. This would probably go undetected as a mixed culture of two different *Shigella spp*. would most likely look like a pure culture on inspection of an agar plate. In that case a representative colony could be taken for further characterisation and the strain identified (and subsequent predicted resistance reported) would be based on the colony selected for characterisation.