Risk Assessment Group

CONSULTATIVE SIGNAL ASSESSMENT
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INCREASE IN EXTENSIVELY-DRUG RESISTANT SHIGELLA SONNEI INFECTIONS IN MEN WHO HAVE SEX WITH MEN (MSM), BELGIUM AND EUROPE, FEBRUARY 2022

Date of the signal	Date of the PRA	Signal provider	Experts consultation	Method
27/01/2022	**20/02/2022**	UK/ECDC	**Permanent experts:** Karin Cormann (DGOV), Wouter D'Haeze (AZG), Naïma Hammami (AZG), Christian Huvelle (AViQ), Romain Mahieu (COCOM), Cecile van de Konijnenburg (FOD) **Specific experts :** Pieter-Jan Ceyssens (NRC - Sciensano), Irith De Baetselier (NRC-STI - ITG), Dominique Van Beckhoven (Sciensano), Dieter Van Cauteren (Sciensano), Dorien Van den Bossche (NRC-STI - ITG)	**E-mail consultation**
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Signal	On 27 January 2022, the United Kingdom reported an increase in extensively-drug resistant *Shigella sonnei* infections, mainly in adult men who have sex with men (MSM)[1]. Several European countries (including Belgium) then reported cases (sampling dates from 2020 to 2022) with isolates either closely genetically related by whole genome sequencing (WGS), or with the same or very similar resistance profile. WGS is not routinely performed on all *Shigella* samples in Belgium. Analysis made by the NRC of a random set of resistant *S.sonnei* samples (n=20) identified 4 strains belonging to the UK cluster, isolated from male patients between July and September 2021. Additional sequencing of all *S. sonnei* strains isolated between January 2020 and today is ongoing (ad-hoc funding). Phenotypic AMR assessment of these isolates indicates resistance against azithromycin, ciprofloxacin and cephalosporins for 24% (31/128). Additionally, the NRC identified successive/parallel clusters of drug-resistant *S. sonnei* circulating among MSM (five with the new UK cluster included) in a retrospective analysis of a set of ***S. sonnei*** strains (2017-2019).

Description	
Cause known?	*Shigella* species are highly virulent Gram-negative bacteria belonging to *Enterobacteriaceae* family. Around 300-400 cases are annually reported in Belgium with *S. sonnei* (75%) and *S. flexneri* (21%) being the two most important subgroups. A decrease of *S. sonnei* cases reported occurred between February 2020 and August 2021 (possibly related to the COVID-19 pandemic and the measures taken to limit close contacts). Since September 2021 (lifting measures, travel) numbers are rising again. Transmission occurs via faecal-oral route through direct person-to-person spread or from contaminated food and water. Sexual transmission (oral-anal contact) mainly affects MSM with a high-risk profile of whom isolates often exhibit antibiotic resistance against first line antibiotics[2]. A recent study in Belgium (2013-2019) identified successive/parallel clusters of drug-resistant *S. sonnei* circulating among MSM since 2017. A possible hypothesis for the increase could be the introduction of pre-exposure prophylaxis or PrEP in 2017 to prevent HIV among individuals at high-risk, since screening for STI's is recommended in that context (including *Chlamydia trachomatis* and *Neisseria gonorrhoeae)* with treatment also of asymptomatic infection, leading to an increase in antimicrobial use[3–5].
Unexpected/unusual	**Expected**: Sexual transmission of drug resistant strains among MSM has been documented over the past decade. This trend has particularly been reported since 2015, across continents. **Unusual**: The recent increase in extensive-plasmid borne-drug resistant *S. sonnei* infections in MSM including the international spread is worrisome. The choice for oral antibiotics for treatment of *S. sonnei* has become extremely limited.
Severity	The most common symptoms of *S. sonnei* infection are diarrhoea, abdominal pain/cramps and fever. Other symptoms that may occur are nausea, vomiting, anorexia, headache, malaise. The illness lasts on average 5 days. Complications such as bacteraemia, severe gastrointestinal disease may occur and the infection can be associated with reactive arthritis. Most forms of shigellosis are self-limiting within a couple of days and most healthy people will recover without the need for antibiotics. Antibiotic treatment

	(fluoroquinolones, cephalosporins and macrolides) is recommended for more severe cases, with underlying conditions (immunosuppression).
Dissemination High – MSM Low - General population	The probability of new infections in MSM exposed to high-risk sexual practices, and the spread in Belgium in the coming months is high, as outbreaks among MSM are usually protracted over long time periods and often linked to travel abroad. Also, progressive lifting of measures for COVID-19 (including opening of night life) might impact the sexual risk behaviour of MSM. As awareness increases, more cases may be identified, more strains may be sequenced leading to higher notification numbers. The population is primarily MSM (sexual transmission) but a spill over towards the general population cannot be excluded, especially when transmission among MSM is very high. Transmission in the community could manifest itself as secondary cases among heterosexuals (sexual bridging by men who have sex with men and women) or via non-sexual contacts of infected cases such as foodborne infections after contamination of food items by infected food handlers, and infections transmitted by carers for older people and children (e.g. in long term care facilities or day cares).
Risk of (inter)national spread High	International spread of extensively-drug resistant *S. sonnei* infections is already documented. The (inter)national dimension of the extensively-drug resistant *S. sonnei* infections may be explained by the highly interconnected sexual networks among MSM.
Preparedness and response	
Preparedness	Reporting of shigellosis cases is mandatory in Flanders but not in the other regions of Belgium. A surveillance system is in place in Belgium via the National Reference Center (NRC). Peripheral clinical laboratories voluntarily send isolates to the NRC for subtyping and assessment of AMR. In 2019 the coverage of the NRC surveillance was estimated to be 83-85% for *Salmonella* (same NRC). WGS is not routinely performed on all *Shigella* isolates for financial reasons. Systematic susceptibility testing is for isolates among (clinically) high-risk people is routinely done at the NRC and peripheral labs but without including Azithromycine by the latter (given the absence of clinical breakpoints).
Specific control measures (surveillance, control, communication)	No additional specific control measures have been implemented yet (see recommendations).
Public health impact	
Public health impact in Belgium Low	The public health impact can be considered low for the general public: mostly mild disease, low risk of transmission outside MSM, even if spill over may happen. For MSM, the public health impact can be considered moderate: mostly mild disease but a high risk of transmission of extensive-plasmid borne-drug resistant strains. However, due to the increasing proportion of multidrug resistant sexually transmitted pathogens such as *S. sonnei*, *N. gonorrhoeae* and *M. genitalium* in this key population, untreatable STIs may emerge in the near future.
Recommendations (surveillance, control, communication)	Add shigellosis to the list of mandatory notifiable diseases in Brussels and Wallonia. Include/focus on shigellosis in prevention and awareness campaigns in the MSM community.

Actions	Inform specialized physicians/care centres dealing with STI and inform health professionals in general. Reinforce antimicrobial stewardship among MSM and avoid the usage of macrolides and fluoroquinolones. A national STI plan should be developed. Provide a specific budget to the NRC for sequencing and follow-up of the situation in the international context.
	Information of physicians through the next newsflash (Sciensano). In Flanders, a letter will be sent to all GPs and laboratories will be requested to send all their samples to the NRC (AZG). The information could also be spread through the BCFI/CBPI (Sciensano). Collection of more detailed data on cases (food, travel history, sexual behaviour, PrEP uptake and recent AB treatment for STI). This could be done by the regions, if Shigella would become mandatory notifiable in all regions. An alternative is through a questionnaire send by the NRC to laboratories sending samples, but this would be more complex. Financial support for routine WGS (300-400 cases/year) (up to now financed on internal budget Sciensano). Sciensano will prepare a request for funding. Set-up a prevention campaign of sexually transmitted pathogens including *S.sonnei*, *N.gonorrhoeae* and *M.genitalium* with re-opening of night life. Sensoa will launch a prevention campaign focussing on hygiene measures but also creating awareness about the symptoms and targeting gay festivals. The UK campaign will be used as an example[6]. Make a request to the PrEP network to further explore the effect of testing strategy on the STI resistance among PrEP users. Consider setting up a national STI plan.

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