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MINI-REVIEW

Shigella sonnei: virulence and antibiotic resistance

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Abstract

Shigella sonnei is the emerging pathogen globally, as it is the second common infectious species of shigellosis (bloody diarrhoea) in low- and middle-income countries (LMICs) and the leading one in developed world. The multifactorial processes and novel mechanisms have been identified in *S. sonnei,* that are collectively playing apart a substantial role in increasing its prevalence, while replacing the *S. flexneri* and other Gram-negative gut pathogens niche occupancy. Recently, studies suggest that due to improvement in sanitation *S. sonnei* has reduced cross-immunization from *Plesiomonas shigelliodes* (having same O-antigen as *S. sonnei*) and also found to outcompete the two major species of Enterobacteriaceae family (*Shigella flexneri* and *Escherichia coli),* due to encoding of type VI secretion system (T6SS). This review aimed to highlight *S. sonnei* as an emerging pathogen in the light of recent research with pondering aspects on its epidemiology, transmission, and pathogenic mechanisms. Additionally, this paper aimed to review *S. sonnei* disease pattern and related complications, symptoms, and laboratory diagnostic techniques. Furthermore, the available treatment reigns and antibiotic-resistance patterns of *S. sonnei* are also discussed, as the ciprofloxacin and fluoroquinolone-resistant *S. sonnei* has already intensified the global spread and burden of antimicrobial resistance. In last, prevention and controlling strategies are briefed to limit and tackle *S. sonnei* and possible future areas are also explored that needed more research to unravel the hidden mysteries surrounding *S. sonnei*.

Keywords *Shigella sonnei* · *Shigella flexneri* · *Escherichia coli* · LMICs · Virulence · Antimicrobial resistance

Introduction

The *Shigella* is the Gram-negative rod, facultatively anaerobic, non-spore forming and non-motile bacterial genera belongs to Enterobacteriaceae family and comprise of four major species *S. dysenteriae, S. boydii, S. flexneri and S. sonnei* (Chatterjee and Raval 2019). *Shigella* species stand apart from Enterobacteriaceae due to their unique nature, mechanisms of pathogenesis and evolutionary history (The et al. 2016). Kiyoshi Shiga in 1897 from Japan, first isolated the highly virulent strain *S. dysenteriae* that produce exotoxins (Trofa et al. 1999; Lampel et al. 2018). The other species were discovered later, *S. flexneri* in 1899, *S. sonnei* by Carl Olaf Sonne in 1906 and *Shigella boydii* in 1921 (Barceloux 2008).

Because of diverse antigenicity based on lipopolysaccharides (LPS), O-antigen components in cell wall, *Shigella* species has further serotypes and sub-serotypes. The serotype 1 of *Shigella* dysenteries (formerly *Shigella* bacillus), has 15 types, *S. flexneri* has 19, *S. boydii* has 20, however, *S. sonnei* has just only 1 serotype (Wu et al. 2019). Several studies indicate that, the *Shigella* spp. are geographically distributed based on the economic development of countries (Anderson et al. 2016). The most of the *Shigella* infection are caused by *S. flexneri* as highlighted as an emerging pathogen in a recent review (Nisa et al. 2020). In past, *S. flexneri* infections have been associated worldwide (Gentle et al. 2016), while *S. sonnei* has been found to be in association with the developed world only.

The sequencing of eight housekeeping chromosomal genes showed that the *Shigella* spp. contain three major clades (C1, C2 and C3) and an outgroup member to these clades named *S. sonnei* (Pupo et al. 2000). However, a study assumes that *S. sonnei* emerged later than the other types of *Shigella* spp. and are more in developed world than

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developing world, probably, because low-resource countries show more immunity to *S. sonnei as* exposure of faecal contaminated water that contains *Pleisiomonas Shigelloides* O17 having identical antigen to *S. sonnei* (Shepherd et al. 2000). A more recent genomic study indicated that, *S. sonnei* emerged from *E. coli* in central Europe ~ 1500 AD (Holt et al. 2012) and spread intercontinentally through travellers. *S. sonnei* significantly dependent on economic and industrial development of regions (Qiu et al. 2015) and now showing dominance over *S. flexneri* due to several mechanisms. However, *S. sonnei* rate of infections trend is replacing *S. flexneri* and has been changing substantially over time, shifting towards low- and middle-income countries (LMICs), particularly in Asia (Thompson et al. 2015).

Globally, *Shigella* spp. are strict human pathogens, accounts for shigellosis (bloody diarrhoea) and associated with huge proportion of morbidity and mortality (Khalil et al. 2018; Kotloff et al. 2018). The annual deaths estimated to be 212 438 in group of all ages due to *Shigella* infections and children of age < 5 are more prone to shigellosis leading to 75 million cases each year (Khalil et al. 2018). Moreover, military forces and international travellers are also susceptible to *Shigella* (Porter et al. 2017). The encoding of T6SS in *S. sonnei* favours the propagation and survival efficiently as compare with *S. flexneri* (lacks T6SS), while also commensally target *E. coli* (Anderson et al. 2017).

S. sonnei has been found to adapt and equipped with antimicrobial resistance genes more profoundly through mobile genetic elements (MGEs) such as plasmids, transposons, insertion sequences and genomic islands (Muthuirulandi Sethuvel et al. 2017) as compared with *S. flexneri* (Thompson et al. 2015). The synergistic effect of antimicrobial resistance genes (ARGs) alongside with integrons (genetic elements that acquire or exchange exogenous DNA, called as gene cassettes by site-specific recombination) further increases the emergence and survival rate (Ahmed et al. 2006). In another study ubiquitously existing, free living amoeba called *Acanthamoebae castellanii* has found to phagocytosize *S. sonnei* protecting it from chlorination and environmental damage (Saeed et al. 2009), however, contrary to this, in a recent study, it has been shown that although *A. castellanii* phagocytosize *S. sonnei* but it does not be able to survive or grow in the cytosol of *A. castellanii* (Watson et al. 2018).

Additionally, it has also been found that the O-antigen of *S. sonnei* inhibits internalization, vacuole escape and inflammasome activation, this different approach further stands out *S. sonnei* from other Gram-negative enteropathogenic *E. coli* and *Salmonella* spp. (Watson et al. 2019). Thus, in the light of such versatile weapons, *S. sonnei* has an edge over the closely related and to the different species as well (Starling 2017). Therefore, the spectrum of recent studies actively demands for looking more alternative approaches in determining and characterization of the actual cause of *S. sonnei* infections persistence.

This review aimed to highlight the *S. sonnei*, as an emerging pathogen in the light of recent research and findings. The gaps which recent studies has filled and further urged to look for more possible underlying mysterious mechanisms including epidemiological features, and evolving mechanisms of antimicrobial resistance patterns of *S. sonnei* are discussed. As, the global expansion of ciprofloxacin and fluoroquinolone-resistant *S. sonnei* (De Lappe et al. 2015; Chung The et al. 2016, 2019; The and Baker 2018) exacerbated the antimicrobial resistance issue worldwide. The comprehensive knowledge about *S. sonnei* attempted to be documented here, that lead to establish a clearer picture in understanding of this deadly pathogen as to overcome and tackle it has been a serious emerging problem.

Epidemiological view of *S. sonnei*

S. sonnei accounts for up to 80% of all the *Shigella* infections in developed world, particularly in North America and Europe (Gu et al. 2012) and has caused several outbreaks, for example, in California between 2014 and 2015 (Kozyreva et al. 2016). For instance, *S. sonnie* has significantly contributed to foodborne outbreaks as well in America and Canada, highlighting the food items as the major source (Lee et al. 1991; Naimi et al. 2003; Kimura et al. 2004). In Spain, a study associated the *S. sonnei* infections upon the consumption of fresh pasteurized milk cheese (García-Fulgueiras et al. 2001). In Australia, *S. sonnei* prevalence rate has been identified up to 55.6% of all *Shigella* infections in year 2010 (OzFoodNet Working Group 2012).

In a different study, the foodborne outbreak of *S. sonnei* has also been reported and raw carrots were identified as the potential vehicle among air passengers departed from Hawaii to Japan (Gaynor et al. 2009), pointing towards the expanding landscape of transmission horizon. Prior to this, a study has pinpointed *S. sonnei* (from a packing shed of baby corn in Thailand) as the potential cause of foodborne outbreak in Denmark and Australia (Lewis et al. 2009). Additionally, the foodborne outbreaks due to *S. sonnei* has also been reported in youth-trip from Austria (Kuo et al. 2009) and associated the consumption of raw peas as a potential source of infection in Denmark (Muller et al. 2009).

However, the global trend of infections due to *S. sonnei* has changed drastically over time from developed to developing countries due to evolving mechanisms and different infection causing modes in *S. sonnei* (Torraca et al. 2020). The frequency of outbreaks and respective severity differ across regions due to multifactorial elements based on geography, climate, host–pathogen relationships, and corresponding controlling strategies. A study from Bangladesh, estimated the trending changes of *Shigella* spp. and observed

that the prevalence of *S. sonnei* increased from 7.2% to 25% in 2001–2011, respectively (Ud-Din et al. 2013).

Recently, three main lineages of *S. sonnei* (I, II, III) have been identified. *S. sonnei* evolved rapidly from Europe and spread as multi-drug-resistant (MDR) single lineage to other continents dominantly (Holt et al. 2012; Anandan et al. 2017). The single clone was named as "Global lineage III" (see Table 1).

In Taiwan, the rate of infections caused by *Shigella* is rare, while *S. sonnei* reported cases were 16 from 200 to 2003 and only one case reported in 2006. The genotypic data showed that, the reducing rate of infection was probably due to limited travelling and contact between villages population, lead to conclude that public health intervention as one of the best controlling strategy (Ko et al. 2013). Furthermore, the serotype shift has been documented in a recent research note and accounted the prevalence of *S. sonnei* infections steadily increased from 2003 to 2011 (17.4–58.2%) in China (Qiu et al. 2015).

A recent broad-spectrum study from Korea, investigated the *Shigella* spp. dysentery infections rate and reported the steady increase of *S. sonnei* infections from 1954 to 2004 (50 years), thus concluding the substantial change of *S. flexneri* to *S. sonnei* serotype (Pai 2020). *S. sonnei* also found predominantly in one study from Africa, four in Asia and two in South America (Kahsay and Muthupandian 2016).

Transmission

The very low infectious dose rate of about of 1–100 cells results in severe outbreaks and transmission. *S. sonnei* along with other *Shigella* species shares the common mode of reservoirs and transmission pattern, including water, food, wild animals, birds, insects, and amoeba (Bridle 2013). Humans are the primary host and transmission primarily occurred through fecal–oral route. The infections caused by *Shigella* spp. are highly contagious and considered as most infectious as compared to other bacterial entero-pathogens (DuPont 2014). However, the bacterium cannot survive out long without host for continuous transmission (Niyogi 2005). The contamination of water and food, fomites, poor sanitation, and ecological conditions also aid in the persistence of *S. sonnei* that result in emerging of severe kind of outbreaks (Taneja and Mewara 2016). For instance, only 40% of Indian population has access to good sanitation system, this further escalate the infections rate in the region (The World Bank 2015). *S. sonnei* has ability to turn into viable but non-culturable form (VBNC), thus aiding in the survival and then transmission later on, when conditions become favourable (Nicolò et al. 2011).

Shigella sonnei possess capability to survive seven weeks on soiled linen, 5 days in freshwater environment, while 12–30 h in salt water and carriers can excrete up to 2 weeks after infection or longer occasionally (Nisar et al. 2014). The seasonality also affects the rate of *S. sonnei* infection, as probably high in summer and rain, while in tropical climatic regions, it is present throughout the year (Ashkenazi and Cohen 2013). The bacterium virulence genes become activated and expressed at 30–37 °C, in pH 7.433 and mild osmotic pressure (Dorman and Porter 1998). The *S. sonnei* frequently causes episodes in populated organizations, counting primary schools, military camps (Lee et al. 2003; Wei et al. 2007). Travelling, prison and asylum houses have been significantly attributed to *S. sonnei* transmission and outbreaks (Baker et al. 2016; Al-Dahmoshi et al. 2020). *Muscus domestica* (common house fly) is also a major vector in the transmission of *S. sonnei* infections (Gupta et al. 2012).

Moreover, sexual transmission of *S. sonnei* particularly in gay, bisexual and men sex with men (GBMSM) communities has been reported in Europe, Asia, North America and Oceania (Baker et al. 2015; Mook et al. 2016; Liao et al. 2017). The person-to-person transmission of *S. sonnei* has also been common in Europe, particularly in England (Morgan et al. 2006; McDonnell et al. 2013; Simms et al. 2015), suggesting *S. sonnei* as the major health problem causing the burden of gastrointestinal infections (Dallman et al. 2016). Additionally, four distinct chains of *S. sonnei* infections in United Kingdom (UK) has been identified showing little difference in genetic diversity (Baker et al. 2018a). The HIV (human immunodeficiency virus)-infected patients also serve as a reservoir for the transmission of *S. sonnei*, as due to the use of antiretroviral therapy parasitic pathogens become more common (Wanyiri et al. 2013).

A recent study opened a new dimension of 'gender' to explore the rate of *S. sonnei* infections. The study suggested a different transmissibility pattern of shigellosis among male and females. The female–male transmission has been found dominant, because females generally carry out more tasks such as cooking in the home. While to children (≤ 5 years), the route of transmission were elder people (≥ 60), as grandparents care for children as a custom in China. This highlighted the urgent need of interventions to be applied in females and elder people (Zhao et al. 2020). However, the previous reports also support that the males are more

Table 1 Dissemination of MDR *S. sonnei* Global lineage III from Europe (Holt et al. 2012)

Regions/Country	Year
Korea	1978
South America	1982
Africa	1982
Middle East	1983
Central Asia	1986
Vietnam	1990, 1997

MDR multi-drug resistant

prone to shigellosis and incidence rate is higher than females (Xiao et al. 2014; Chang et al. 2016; Yan et al. 2018). This is supported by a study, indicating that the female sanitary state is more than males (Chompook et al. 2006). But this impact cannot be ignored that the various modes of possible transmission like food, water and inter-personal connection has been interrupted and show relative incidences entirely differently among the different age groups (Hao et al. 2019). In addition, a more recent data on antibiotic-resistant enteric pathogens, suggested investment in WASH (Water, Sanitation, and Hygiene) measures to tackle the global burden of enteric infections (Shakoor et al. 2019).

Pathogenesis and virulence mechanisms of *S. sonnei*

Shigella sonnei possesses multiple well-established and unique pathogenic mechanisms (Caboni et al. 2015; Mahmoud et al. 2016; Anderson et al. 2017) (see Fig. 1). All the four *Shigella* species can cause disease in human (Livio et al. 2014). The survival of *S. sonnei* intracellularly, sabotaging the phagocytic killing and evading of host immune system, particularly inflammatory responses are the fundamental processes of its pathogenesis. For example, inhibition of host pro-inflammatory responses and modulation in the regulation of B-cells and T-cells. These mechanisms and evolving nature of *S. sonnei* can result in the persistence of infection for longer period (Ashida et al. 2015).

Shigella sonnei successful invasion is based on the overcoming of two gut-specific barriers, the gut microbiota and mucus layer (Anderson et al. 2016), as the commensal pathogens competitively act on survival and proliferation. This competitive situation modulates the host immune response, due to the toxins and antimicrobial responses (Baker and The 2018). The invasion plasmid antigen (*ipaH*) and invasion-associated locus (*ial*) facilitates the internalization, survival and growth in intestinal cells (Johnson 2017). A study from Vietnam (Thiem et al. 2004), reported the 100% prevalence of *ipa*H gene in *S. sonnei*, while it is detected very low from Kenya (Nyanga et al. 2017). These genes are the effectors of T3SS (type 3 secretion system).

Interestingly, prior to release, its effector proteins *S. sonnei* first adhere to host cell diligently, despite in the absence of classical adhesins (Killackey et al. 2016). The recent study showed that the surface protein IcsA (actin polymerizing factor), activated by bile salts, function as an adhesin and play a pivotal role in the attachment to host after the initial activation of T3SS (Brotcke Zumsteg et al. 2014). This novel adhesin advances the pathogenesis pattern and further, the g4C (Group 4C) capsule protects from serum-mediated killing. The g4C capsule is made up of unknown lipid anchor, rather than the known lipopolysaccharides (Caboni et al. 2015). The g4C capsule has high molecular weight and due to its similarity with LPS-Ag, referred as O-Ag capsule (Whitfield 2006).

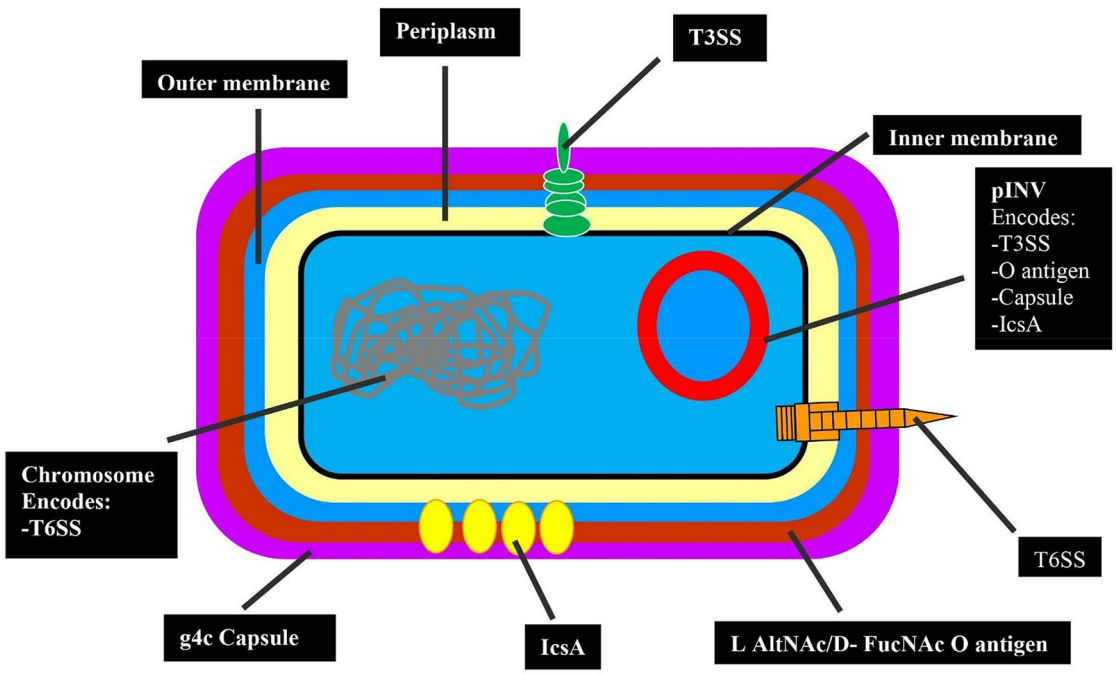

Fig. 1 Schematic representation of *S. sonnei* virulence arsenal (Torraca et al. 2020). *T3SS* host cell invasion, *IcsA* actin based mortility, *T6SS* Bacterial competition and niche occupancy, *g4c and O antigen* resistance to phagocytosis, complement-mediated lysis and phogolysosomal degradtion. *L-AltNAc* 2-acetamido-2-deoxy-L-altruronic acid, *D-FucNAc N*-acetyl-2-acetamido-4-amino-2,4-dideoxy-D-fucose

The effector proteins (OspE1 and OspE2), secretion is further promoted by bile salts, that remain intact with the bacterial outer membrane, thus enhances attachment to other polarized cells (Faherty et al. 2012). Moreover, deoxycholate (bile salt), make the final assembly of T3SS in activation-ready state (Stensrud et al. 2008). At the distal tip end of T3SS are components IpaB, IpaC and IpaD. The IpaD assemble the IpaB and IpaC on to the needle, while IpaB and IpaC are hydrophobic proteins in nature and triggers the formation of pore in host cell to deliver effector proteins (Veenendaal et al. 2007).The host membrane cholesterol play a major role in the interaction with IpaB to facilitate and promote the insertion and T3SS activity (Hayward et al. 2005).

The T3SS components (IpaB and IpaD), promote binding to filopodia (cytoplasmic projections) and aid in interaction and invasion (Romero et al. 2011). The IpaB function as a molecular plug to block the secretion from T3SS prior to its insertion and removed, while inserted into host membrane (Roehrich et al. 2010). The other T3SS-dependent effector virulence factors include IcsB (inhibit autophagy), IpaA (actin depolymerization) and OpsD3 that has entero-toxic activity (Du et al. 2016).

The bacterium reaches its primary target, the colonic epithelium by invading through M cells (microfold) of the gut-associated lymphoid tissue (GALT) and mucosa-associated lymphoid tissue (MALT), located in the Peyer's patches of small intestine (Phalipon and Sansonetti 2007). Then, bacteria cause inflammatory colitis (Ashida et al. 2015). *Shigella sonnei* act against the suppression of inflammation by the host, releasing the effector proteins against MAPK (Mitogen-Activated Protein Kinases) and NF-κB (Nuclear Factors) signaling pathways. In addition, bacterium also inhibit pro-inflammatory cytokines, for example, IL-8 (Interleukin-8) epigenetically (Ashida et al. 2011).

In a genomic study, the sequencing of *S. sonnei* strain revealed that the genome (chromosomal and plasmid DNA) of 4,546,505 bp size containing biosynthetic genes of lipopolysaccharide (Deutsch-Nagy et al. 2018). A recent zebrafish model study of *S. sonnei* infection revealed that *S. sonnei* O-antigen resist acidification by phagolysosome and enhance neutrophils cell death, hence found to be more virulent than *S. flexneri* due to its acquired O-antigen oligosaccharides from environmental bacteria *Plesiomonas shigelliodes*. Additionally, suggesting that the increase of phagolysosomal acidification and frequent innate immune system exposure can decrease *S. sonnei* by neutrophils (Torraca et al. 2019).

There are two distinct unusual sugars are present only on *S. sonnei* O-Ag (-acetamido-2-deoxy-L-altruronic acid and 2-acetamido-2-deoxy-L-fucose) (Liu et al. 2008). Both, lipopolysaccharide, and capsule contain O-Ag, reduce *S. sonnei* uptake, however, a recent study further thrown light in this dimension saying *S. sonnei* has adapted its extracellular lifestyle and survival mode by developing multiple O-Ag layers on its surface (Watson et al. 2019). Furthermore, *S. sonnei* also down-regulate the antimicrobial peptides (ß-defensin hBD-3) and chemokines such as CCL20 (C–C Motif Chemokine Ligand 20), thus turning dendritic cells into defective state (Al-Dahmoshi et al. 2020).

In addition, a large virulence plasmid (pINV) of size 220 kb encodes the proteins that make needle-like macromolecular structure, this enables the transmission of effector proteins from bacterium to host eukaryotic cell directly (Killackey et al. 2016). Type 3 secretion system (T3SS) enables *S. sonnei* to enter in the host epithelial cells by rupturing its vacuolar membrane, then the bacterium proliferates in cytosol and spread cell-to-cell (Mellouk and Enninga 2016). However, the exact molecular nature and mechanism by which the bacteria rupture vacuolar membrane still demands precise understanding (Carayol and Van Nhieu 2013).

In addition to the virulence plasmid, a small region of chromosome "Pathogenicity Islands" also contributes to the pathogenesis and virulence. This pathogenic island is present among *Shigella* spp. and are highly diversified (Yang et al. 2005). A recent study reported the functional type 6 secretion system (T6SS) presence in *S. sonnei* (encoded by chromosome), that gives *S. sonnei* an advantage in a niche-specific environment over *E. coli*, *S. flexneri* and other closely related species. T66S predominate *S. sonnei* colonization in host and help it during interbacterial competition (Anderson et al. 2017). *Shigella sonnei* found to be killing competitors near the surface of colon epithelial cells, thus suggesting T6SS-mediated killing as potential mechanism of uprising its global prevalence.

Pyroptotic cell death (highly inflammatory programmed cell death) play a major role in the pathogenesis of *S. flexneri* (Bergsbaken et al. 2009), that help in escaping the macrophage-mediated killing, inducing local inflammation and evasion of epithelial cells from basolateral side. Likewise, *S. sonnei* also induces macrophages pyroptosis through caspase 1. Additionally, the internalization of *S. sonnei* into macrophages is dominantly found to be through phagocytic uptake of macrophages, rather than evasion through T3SS mechanism, as found predominantly in *S. flexneri* (Watson et al. 2019). Moreover, *S. flexneri* can activate NLR4C and NLRP3 inflammasomes (multiprotein intracellular complex, that detect pathogens and activate pro-inflammatory response) (Suzuki et al. 2014). It is unclear that *S. sonnei* releases the same inflammasome or not and to which its benefit, to host or the bacteria itself.

Shigella sonnei also possess antibacterial mechanisms. *S. sonnei* has potential to enable proton consumption system, resist host antimicrobial peptides (Mattock and Blocker 2017), produce colicins (a toxin produces by coliform bacteria) and mucinases (enzymes to degrade

mucins) that kills small range of phylogenetically related bacteria, thus making *S. sonnei* more favourable in the colicin-mucinase sensitive strains. A study from India reported the 93% presence of at least one colicin-coding plasmid, showing its high level of threatening pathogenic trait (Calcuttawala et al. 2015). Another study from Bhutan showed that, all tested strains of *S. sonnei* carried ColE plasmid, to produce colicins (Ruekit et al. 2014).

A different but homologous *pic* (*S. flexneri* 2A protein) is also expressed by *S. sonnei*, belonging to SPATE (Serine, Protease, AutoTransporters of Enterobacteriaceae) family that secrete another protein (SepA). A study suggested that, SepA play role in the destabilization of host intestinal epithelial integrity (Maldonado-Contreras et al. 2017).

Recently, first time the completely assembled whole genome of a hybrid pathotype Shiga toxin (Stx) producing *S. sonnei* has been documented. *S. sonnei* strain found to be carried Stx1 inducible encoding prophage (genetically *S. sonnei* do not fabricate Shiga toxin), which further draw attention towards the potentially evolving and emerging virulence capabilities of *S. sonnei* (Sváb et al. 2017). Therefore, there is no ambiguity in the fact that, the global shifting pattern of *Shigella* infections are multifactorial and depend on several host, environmental, bacterial rapid mutational, and evolutionary mechanisms. However, in the light of above-mentioned virulence and pathogenic mechanisms, it is easy to inference that *S. sonnei* has become a potential pathogen, increasing its global emergence and burden.

Diseases and other complications

After the invasion of colon epithelial cells, *S. sonnei* cause bloody diarrhoea or "Shigellosis". In response, the host cell releases the pro-inflammatory cytokines (particularly IL-8), and cascades of reaction started at the infection site by recruiting of polymorphonuclear cells (PMNs), such as neutrophils. These PMNs destroy the gut mucosa lining and thus promote further invasion (Williams and Berkley 2018).

There are some other complications, that are resulted in infection due to *S. sonnei* such as seizures, electrolyte imbalance, leukemoid reactions, intestinal perforation, toxic megacolon, arthralgia, rectal prolapse, while in severe cases sepsis and life-threatening haemolytic–uremic syndrome (HUS) (Ashkenazi 2004; Christopher et al. 2010). Immunocompromised, elderly age group people and young children are more prone to complications, like mucosal ulceration, rectal bleeding, and drastic dehydration (Bliven and Lampel 2017). Reiter's syndrome (reactive arthritis ReA) can also develop following the infection from *S. sonnei* (Hannu et al. 2005).

Symptoms and diagnostic techniques

The infectious diarrhoea results in the loss of water and electrolyte imbalance, with an abdominal pain, cramping, fever, vomiting; tenesmus (straining during bowel movements), pus and bloody mucoid stools (Nygren et al. 2013). The usual incubation period is 3 days (normally 1–7 days) and symptoms last for almost about 1–2 weeks (Lampel 2012). In endemic regions, the patients become asymptomatic, developing no infection but shed bacterium in stools for longer duration.

The stool culturing and microscopy are the cheap, fast, and easy method to detect the strains of *S. sonnei*. The PMNs in stools sample can be revealed with the help of methylene blue. The most suitable method to isolate and differentiate *S. sonnei* is microbiological culturing. The pINV plasmid of *S. sonnei* is highly unstable when cultured in vitro, hence *S. sonnei* gives two different appearances when cultured on Congo Red Agar. The small smooth red colonies (retaining plasmid), because of expressing T3SS and O-Ag, while large irregular rough white colonies (loosing plasmid) also formed (Torraca et al. 2020). Multiplex polymerase chain reaction (PCR), technique is also available commercially (Kimberlin et al. 2015). The culture-based approaches inherently possess low sensitivity, as the resistance shown by *S. sonnei* to ciprofloxacin, erythromycin and azithromycin has become a serious problem (Tang et al. 2018).

The routine-based sequencing methodologies and to afford the respective cost of sequencing-based diagnosis is also among the major constraint for the individual health care facilities and institutes apart from research centres in LMICs (low- and middle-income countries). Therefore, it has become very important to evaluate susceptibility pattern and modify treatment according to the results obtained. Pathogen-specific rapid diagnostic assay are now available to detect O-Ag (Gonzalez and McElvania 2018), however, culture-independent diagnostic tests (CIDTs), also do not detect antimicrobial resistance profile (Fang and Patel 2017).

Treatment options

The majority of *Shigella* infections are self-limited but in severe cases can be fatal if left untreated. Serotype-specific protective immunity can also be developed against O-Ag in the host, automatically over the various exposures (Barnoy et al. 2010). Antimicrobial use is the routine way strategy to limit infection, increase recovery and reducing the transmission. Ampicillin, streptomycin, tetracycline, sulphonamide, and trimethoprim are the common drug of choices against *S. sonnei*. But, over the span of time, *S. sonnei* has become resistant to these antimicrobials. In areas, where ampicillin and co-trimoxazole resistant strains are present, the use of

fluoroquinolones and azithromycin were advocated (Tribble 2017).

Ciprofloxacin and fluoroquinolone had been recommended by WHO for the effective treatment purpose. However, the widespread use of ciprofloxacin and fluoroquinolone has led to emerge the resistance to these antimicrobials also. In late 1990s, ciprofloxacin-resistant *S. sonnei* emerged, and spread throughout the Asia within just first decade of century (The and Baker 2018). Rifaximin and rifamycin (nonabsorbable) are effective drug of choice in traveller's diarrhoea (TD), while not helpful in invasive infections. Interestingly, the use of rifamycin potentially reduced the rate of resistance among gut microbiota in comparison to ciprofloxacin treatment (Steffen et al. 2018).

Probiotics has been proved to be as a great source of potential to tackle diarrhoea duration (Basu et al. 2009). Interestingly, using guidelines *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* is recommended for therapeutic purpose (Husby et al. 2012). In another study, 16 out 91 tested lactobacilli showed potent antibacterial activity (Zhang et al. 2011, 2012). But probiotic use and severity level differ with host and are not recommended alternatively over antibiotics in severe and moderate diarrhoea, because of the lack in comprehensive knowledge about probiotic-pathogen specificities (Shakoor et al. 2019). The recombinant probiotics targeting the specific pathogens are in developing phase and if come to clinical use, will effectively reduce the pressure of antibiotics (Mathipa and Thantsha 2017).

To date, there is no licensed vaccine available against *S. sonnei*. The inactivated whole cell and subunit vaccines have also been trialled for the prevention against shigellosis (Kaminski and Oaks 2009), a trial of conjugated vaccine *S. sonnei*-rEPA (Shigella *sonnei* O-specific polysaccharide bound to *Pseudomonas aeruginosa* recombinant exoprotein A), one injection found to provide significant immunity against *S. sonnei* shigellosis (Cohen et al. 1997). An experimental trivalent vaccine has been made containing O-Ag and a pentavalent vaccine also has been proposed, hypothetically that can be effective against majority of shigellosis (Levine et al. 2007).

Phage therapy is another pivotal option against shigellosis caused by *S. sonnei*. Bacteriophages use has several advantages as specificity to bacteria without disturbing the normal microbiota, bactericidal to antibiotic-resistant pathogens, replication at site and self-limiting (Jamal et al. 2015). Nanoparticles (NPs) are also opening a new window to look for more therapeutic options due to their bactericidal activity against the pathogenic bacteria. NPs destroy the structural integrity of cell and generate oxygen free radicals. Copper oxide NPs has recently shown promising approach towards *S. sonnei* and has been recognized as potential antimicrobial agent (Babaei et al. 2017). Organic acids (citric, acetic, lactic, malic) use also has been regarded as safe by the US Food and Drug administration, as they are antimicrobial and inactivate bacteria. The research showed that the synergistic effect of malic and lactic acid significantly reduced *S. sonnei* from 4.53 and 3.25 log CFU/mL, respectively (Zhou et al. 2007). Carvacrol (phenol) and their combinations with organic acids also found to be as potential weapon against *S. sonnei*.

Antimicrobial resistance pattern of *S. sonnei* among different classes of antibiotics

World Health Organization (WHO) first ever published its list of antibiotic-resistant pathogens in 2017 (Tacconelli 2017). *Shigella* was a priority pathogen among other 12 families of bacteria, that pose significant threat to the public health (Tillotson 2018). The horizontal gene transfer mechanisms and dissemination through mobile genetic elements (MGEs), such as resistance plasmids (R-plasmids), integrons, transposon and also the presence of pathogenic islands on chromosomes has risen up the worldwide transmission and emergence of MDR strains of *S. sonnei* (Ranjbar and Farahani 2019). In a study, improving water supplies and dissemination of MGEs are predicted to be as the major cause of *S. sonnei* global expansion (Thompson et al. 2015).

Plasmids are one of the major importance in the process of horizontal genetic exchange, thus facilitating the spread of antimicrobial resistance genes. *S. sonnei* like all enteric pathogens has a potential to adapt and survive in the environment, predominantly in aquatic environments, like sewage and wastewater. The inappropriate sanitation then leads to the contamination of irrigated and drinking water. Thus, resulting in the possible transmission and genetic exchange between strains (Byarugaba 2004). For instance, genes of carbapenemase encoding $bla_{\text{NDM-1,}}$ extended spectrum beta-lactamase $bla_{\text{CTX-M}}$ and currently ongoing challenge of *mcr-1*(resistance to colistin), has revived the issue of antimicrobial resistance horribly (Cantón et al. 2012; Johnson and Woodford 2013; Schwarz and Johnson 2016). Plasmid-mediated transferring of resistance genes (Table 2) in *S. sonnei* has become a common and potential source in the emergence of resistance to antimicrobial regimes (Das and Mandal 2019).

Furthermore, the emergence of resistance to cephalosporins, beta-lactam, macrolides (erythromycin and azithromycin), has left over no empirical choice for treatment (Shakoor et al. 2019). Particularly, in MSM (men sex with men) population the emergence of azithromycin-resistant, ciprofloxacin-resistant, and ceftriaxone-resistant *S. sonnei* has intensified the situation as because of its global transmission (Baker et al. 2015). The resistance to third generation cephalosporins and azithromycin has also been reported from Europe, America and Australia

Table 2 Plasmid-mediated antimicrobial resistance genes prevalence of *S. sonnei* from selected publications

Genes	Prevalence (%)	Country	References
bla-CTX-M-1	78.5 (11/14)	Iraq	(Auda 2014)
	15 (21/140)	China	(Zhang et al. 2014)
bla-CTX-M-15	100, 11	India	(Anandan et al. 2017)
bla-OXA-1	5.8 (1/17)	India	(Pazhani et al. 2008)
	7.8 (11/140), 100	China	(Zhang et al. 2014)
			(Zhu et al. 2018)
bla-TEM-1	20 (3/15)	Brazil	(Peirano et al. 2005)
	2.8 (4/140), 100	China	(Zhang et al. 2014)
			(Zhu et al. 2018)
	59	Chile	(Toro et al. 2005)
*dhfr*1A	49	Spain	(Delgado and Otero 1988)
*Sul*II	100	Brazil	(Peirano et al. 2005)
	56	India	(Anandan et al. 2017)
aac(6')-Ib-cr	5.8 (1/17)	India	(Pazhani et al. 2008)
	100, 4.2 (14/337)	China	(Zhu et al. 2018),
			(Gu et al. 2017)
*qnr*S	100	India	(Anandan et al. 2017)
	2.1 (7/337)	China	(Gu et al. 2017)
*qnr*B	2.7 (1/37)	India	(Bhattacharya et al. 2011)
*qep*A	0.6 (2/337)	China	(Gu et al. 2017)
mcr-1	100	Vietnam	(Thanh et al. 2016)

in MSM and HIV positive population (Baker et al. 2015; Ingle et al. 2019). While, azithromycin resistance measurement has no standard guidelines, thus emanating an issue in its actual surveillance and monitoring (Brown et al. 2017). Additionally, according to a systematic review study, the rate of infections due to ESBL-producing and cephalosporin-resistant *Shigella* spp. particularly *S. sonnei* has increased in Asia than from Europe and America since 1998–2012 (Gu et al. 2015).

Plasmid incompatibility typing of isolates has a potential to give an insight view of genetic diversity and facilitate to understand the local, global and regional expansion whether through multiple molecular relationships between plasmids or due to any one single dominant plasmid type (Das and Mandal 2019). A genomic study indicated the prevalence of a single plasmid in *Shigella*, facilitated by horizontal gene transfer found to be as major culprit in the emergence of existing and new epidemics (Baker et al. 2018b). Another study further affirms that the global expansion of *S. sonnei*-resistant strains was due to a single clone. The study showed that resistance to fluoroquinolone is due to sequential mutations (*gyr*A-S83L, *par*C-S80I, and *gyr*A-D87G) in *S. sonnei* from South Asia around 2007, prior to its distribution in Southeast Asia and Europe. Furthermore, the mutational analysis showed that the clone has a strong adaptiveness towards the oxidative stress that probably reflect its dominance pattern (Chung The et al. 2019).

Therefore, a significant relation exists between the Integron (class II) and developing of resistance towards the different kinds of antimicrobials in *S. sonnei* (Gassama-Sow et al. 2006). The gain of class II integrons by *S. sonnei* and substantial mutational changes create selective pressure on antibiotics, thus resulting in the emergence of resistant strains.

Prevention and controlling strategies

Antibiotics are the best sources to deal with *S. sonnei* infection, having low cost with community-accessible approach. But, due to emergence of resistance, it is very important to use antibiotics rationally with appropriate prescription. The AMR issue, has significant impacts on the ecology and society, as rising of the combined social cost of AMR from the individual cost of antibiotics (Okeke et al. 2007). The implementation of WASH measures gain significance and exhibit supreme importance, where *Shigella* spp. and other enteric pathogens evolve and emerge. "One Health" approach is an ideal way of carefully monitoring the origin, sources of possible transmission and routes in environment, human and animal triad (Heymann et al. 2017). This one health approach works in collaboration among the various disciplines of sciences with multisectoral organization locally, regionally, and globally in the better survival and nourishment of civil society (Kahn 2017; Nadimpalli et al. 2018). The safe and widespread effective vaccines are also welcoming alternative approach to antibiotics and hence will dampen the issue of AMR. Therefore, a continuous endeavour and investment is needed to control and limit the *S. sonnei* infection and shifting spectrum.

Future perspective

There is a lot more work needed to explore further about the *S. sonnei*. As some studies has unfold the several aspects of its pathogenesis and virulence mechanisms, but still lies a gap between its actual origin among *Shigella* spp. The shifting pattern of *S. sonnei* from developed to developing countries still need attention and demands explanation. There might be the existence of other special systems along with T3SS and T6SS. The structural and molecular area of *S. sonnei* needed to be under consideration for the discovery of complex underlying mechanisms. The *S. sonnei* epidemiology in relation with other closely related species needed appropriate surveillance and monitoring, in order of understanding the global risen burden and changing landscape. The IpaB and IpaD protein of *S. sonnei* has been indicated as a potential safe and sound candidate for the vaccine development in a clinical testing against mice (Martinez-Becerra

et al. 2012; Heine et al. 2014, 2015). In recent times, due to advancement of technology, new lab tools, equipment's, protocols and reducing cost of sequencing, the responsibility of healthcare workers and scientists rises than ever to look for better options and developing strategies for the service of mankind.

Conclusion

Shigella has been considered as a priority pathogen by WHO recently, the uniqueness in the structure, pathogenesis and virulence mechanisms stand out Shigella. More recently, the global changing landscape and shifting pattern of species from *S. flexneri* to *S. sonnei* has urged the attention to seek behind the mysterious ongoing pathways. The different sources and routes of transmission, epidemiological variations in relation to anthropogenic activities like travelling and trade has raised many questions regarding the dispersion of *S. sonnei* single clone. Additionally, the growing AMR burden of *S. sonnei* has worsen the therapeutic options as no drug can be considered as standard option. The growing resistance to antimicrobials and the stagnancy in developing of new antibiotics is a horrible scenario. Therefore, rational use of antibiotics, vaccines development, adapting appropriate WASH measures, and meanwhile having eye on the genomic and epidemiological patterns of *S. sonnei* can only dampen the growing problem and tackle this emerging pathogen.

Compliance with ethical standards

Conflict of interest None to declare.

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