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Article

Genetic Determinants of Virulence and Antimicrobial Resistance in Shigella species.: A Comprehensive Review on Virulence Genes, Resistance Mechanisms, and Horizontal Gene Transfer

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Abstract: Shigella spp. are among the enteric pathogens of great morbidity and mortality all over the world particularly in developing countries. Once it has established pathogenesis, a typical large complex array of virulence genes found within chromosomal islands and large virulence plasmids encode invasion proteins, secretion apparatuses,and regulatory factors involved in pathogenesis by epithelial cell invasion plus immune evasion. High prevalence rates of parallel alarming multidrug-resistant (MDR) Shigella strains pose an immediate public health hazard due to complications in treatment and increased risks for outbreaks. This review pauses at the major genetic factors that are associated with Shigella virulence about the ipaH, virF, mxi-spa, and icsA gene clusters. It further reviews at a molecular level how resistance is achieved in Shigella towards antibiotics drawing resistance genes including blaTEM, aadA, tetA, and qnr among many others that are also usually found on plasmids, transposons as well as integrons. Conjugation, transformation, and transduction are horizontal gene transfer (HGT) mechanisms described as means by which resistance plus virulence determinants can very fastly move not only within populations of Shigella but also other populations of enteric pathogens. Synthesizing recent findings, meanwhile emphasizing the dire need to carry out genomic surveillance, therapeutic strategy recalibration, and an antibiotic stewardship program to battle against the evolving genetic landscape of Shigella would be fruitful. The relationship between virulence and resistance interacting at the genetic level must be understood for further research initiatives, clinical management, and vaccine development.

Keywords: Shigella Species, Virulence Genes, Antimicrobial Resistance, Horizontal Gene Transfer, Multidrug Resistance (MDR)

Introduction

Shigella spp. that globally recognized as major causes of bacillary dysentery, within increasing concern lead to their rapid development of multidrug resistance. “Shigella spp. the are resistant to almost all antimicrobial classes are increasing in prevalence as well as becoming globally

dominant"[1]. These pathogens utilize an invasive type III secretion system encoded on the large virulence plasmid pINV, facilitating epithelial invasion as well as cell-to-cell spread [2].Central virulence genes that ipaH, icsA, virF, and mxi-spa orchestrate host cell manipulation and immune evasion: "Key gene clusters such as the ipaH, virF, mxi-spa, and icsA loci" serve as the genetic backbone for Shigella pathogenicity (our review). synthesis of recent genomic studies Equally troubling, antibiotic resistance genes including blaTEM, aadA, tetA, and qnr are frequently harbored on plasmids and mobile genetic elements, compounding treatment challenges. Recent regional studies report the occurrence for PMQR genes: qnrS (52.4 %), qnrA as well as aac(6′)-Ib-cr (33.3 %) as well as qnrB (19.0 %) among Shigella isolates [3]. Horizontal gene transfer via conjugation, transposons, and integrons "contributes to the rapid dissemination of resistance and virulence traits" [40]. Given these evolving threats, this review synthesizes recent advances in understanding the genetic determinants of virulence and resistance in Shigella spp., examines mechanisms of horizontal gene transfer, and discusses implications for genomic surveillance, antibiotic stewardship, and vaccine development.

Virulence Genes in Shigella spp:

Shigella spp. depend on a group of virulence genes on a large plasmid (~210–220 kb) called pINV that is important for invasion of epithelial cells and intracellular persistence [4]. This plasmid harboring a ~30 kb pathogenicity island this encodes that type III secretion system (T3SS) as well as invasion genes including ipaABCD, mxi-spa, all regulated in a hierarchical manner by the master transcription activator virF [5]. Expression of virF activates the downstream regulators virB and icsA (virG) leading to transcription of ipa-, mxi-, and spa-operons thereby production of the invasion proteins (IpaB, IpaC) and the T3SS needle complex [6].

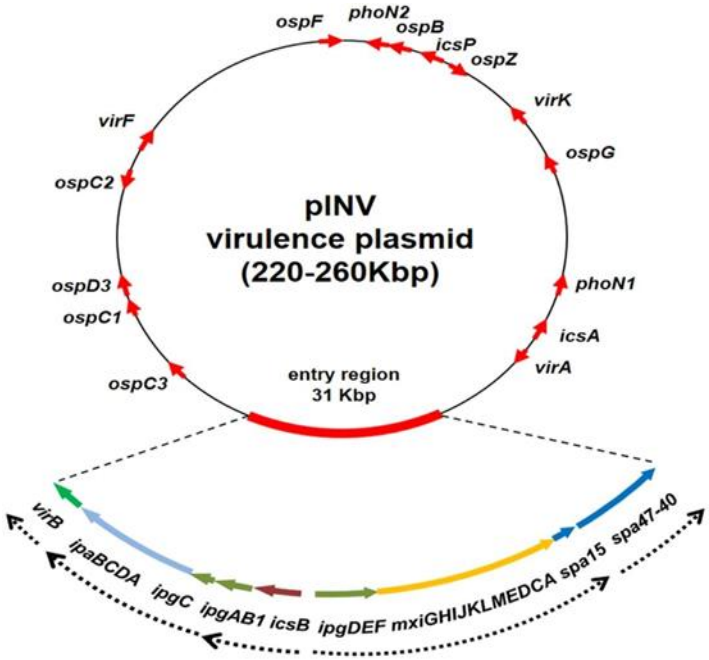

Figure 1. Schematic Map of the pINV Virulence Plasmid in Shigella spp.

This Figure 1 shows the organization of key virulence genes (e.g., ipa, mxi, spa), regulatory genes (virF, virB, icsA), toxin–antitoxin systems, and partition modules on the pINV plasmid that facilitate epithelial invasion and intracellular spread in Shigella.

IcsA also facilitates actin-dependent intracellular movement through recruitment of the host Arp2/3 complex, and intercellular spread is induced [6]. Furthermore, VirB is a transcriptional anti-silencer that inhibits H-NS repression on pINV and creates discrete cytoplasmic foci through DNA interaction [7]. Hierarchical regulation guarantees proper timing of virulence gene expression, thus leading to effective pathogenesis.

The pINV gene structure, typically represented as a circular map, identifies several significant virulence loci clustered in the Entry Region. Together, the pINV-encoded virulence proteins, viz., ipaABCD, mxi‑spa, virF, virB, and icsA, comprise the genetic foundation for Shigella's pathogenicity.

Table1. Major Virulence Genes in Shigella spp. and Their Functions.

Gene Name	Function	Location	Notes
ipaA, ipaB, ipaC, ipaD	Invasion proteins; form the translocon of the T3SS	Pathogenicity Island on pINV	Critical for epithelial cell invasion and membrane disruption
mxi-spa operon	Structural components of the T3SS needle complex	Pathogenicity Island on pINV	Includes 20+ genes; essential for secretion apparatus
virF	Master transcriptional activator	Regulatory region on pINV	Induces virB and downstream ipa/mxi/spa genes
virB	Secondary activator; anti-silencer of H-NS	Downstream of virF on pINV	Activates multiple virulence loci including T3SS
icsA (virG)	Actin polymerization protein for intracellular motility	pINV	Allows Shigella to spread from cell to cell
ipaH	E3 ubiquitin ligase; modulates host immune response	pINV and chromosome	Used as a diagnostic marker in PCR; repetitive gene family
set1A, set1B	Shigella enterotoxins (only in S. flexneri)	Chromosome (SHI-1)	Associated with watery diarrhea
sen (ShET-2)	Shigella enterotoxin 2	pINV	Contributes to enterotoxic effects

Antimicrobial Resistance Genes Found in Shigella Species:

Among 123 cephalosporins-resistant isolates, this dominant extended‑spectrum beta‑lactamase gene was blaTEM‑1, followed via blaCTX‑M, blaOXA‑1, as well as blaSHV‑12. Six subtypes for blaCTX‑M were found, blaCTX‑M‑14 (n = 36) as well as blaCTX‑M‑55 (n = 26) were predominant (Xu et al., 2019). These cephalosporin-resistant Shigella also carried plasmid‑mediated quinolone resistance genes including qnrA, qnrB, qnrS, as well as aac(6')‑Ib‑cr [8].

In Iranian clinical isolates, the prevalence of β‑lactamases, PMQR, and tetracycline resistance genes in Shigella was 80%, 33.3%, and 46.7%, respectively [9].

There is evidence that mediated quinolone resistance genes (PMQR), efflux pump proteins, as well as primary mutations in the drug binding site for gyrA, among others, as well as the primary mechanisms behind is development for drug resistance in Shigella [10].

The emergence of azithromycin resistance is increasingly recognized as a significant issue: A high prevalence of the mph and ermB genes associated with decreased susceptibility to azithromycin (DSA) has been reported in contemporary Shigella strains [11].

A broad meta-analysis on the continent of Africa identified resistance prevalence to be 10.0% for ciprofloxacin and 8.5% for ceftriaxone, cautioning that multidrug-resistant strains now account for as much as 41% of isolates [12].

Genes blaTEM‑1, blaCTX‑M, qnr variants, aac(6')‑Ib‑cr, mph, and ermB, as well as efflux pumps as well as target site mutations, collectively constitute the molecular basis for antimicrobial

resistance in Shigella species. This genes that carried via mobile genetic elements highlights this need of genomic surveillance as well as prudent antibiotic stewardship.

Table 2. Antimicrobial resistance genes for Shigella spp., with the resistance profiles as well as genetic locations.

Gene Name	Resistance Type	Mechanism of Action	Location	Notes
blaTEM-1	β-lactam antibiotics	β-lactamase enzyme hydrolyzing penicillins	Plasmid, Integron	Most prevalent β-lactamase in Shigella spp.
blaCTX-M-14 / -15 / -55	Extended-spectrum cephalosporins	Hydrolyzes 3rd-gen cephalosporins	Plasmid-borne (IncF, IncI1)	Major cause of ESBL phenotypes
blaOXA-1 / blaSHV-12	Broad-spectrum β-lactams	Enzymatic degradation	Plasmid	Co-exists with CTX-M often
qnrA, qnrB, qnrS	Fluoroquinolones	DNA gyrase protection proteins	Plasmid-mediated	PMQR genes
aac(6')-Ib-cr	Fluoroquinolones & aminoglycosides	Acetylation/inactivation of drugs	Integrons, plasmids	Synergizes with qnr genes
mph(A), mph(E)	Macrolides	Phosphotransferase modifies macrolide	Plasmid, transposon	Linked to azithromycin resistance
ermB, ermF	Macrolides, lincosamides	rRNA methylation	Plasmid, integron	Prevents drug binding to ribosome
tet(A), tet(B)	Tetracyclines	Efflux pump	Plasmid, transposon	Common in MDR strains
sul1, sul2	Sulfonamides	Mutant DHPS enzymes	Plasmids, integrons	Frequent with class 1 integrons
dfrA1, dfrA17	Trimethoprim	Altered DHFR enzymes	Class 1/2 integrons	Found in cassette arrays

Horizontal Gene Transfer about Mobile Genetic Elements for Shigella spp:

The passage clearly states: "That mechanism for HGT is threefold: transformation, transduction, as well as conjugation, all for which include various mobile genetic elements (MGEs), about plasmids, bacteriophages, transposons, and integrons" [13]. MGEs can move intercellular DNA; they can also provide antibiotic resistance and virulence characteristics [14].

Integrons are especially important in Shigella: Integrons carrying antimicrobial resistance are important for transferring AMR genes via horizontal transfer through transposons and plasmids to form multi-resistance [15]. Class 1 and 2 integrons take up gene cassettes carrying resistance genes for trimethoprim, streptothricin, and streptomycin (including dfrA1, aadA1, among others) into their gene cassettes [16].

More importantly, MGEs often interact with one another: phage-plasmids can play a key role for the transfer by genes across mobile elements within their hosts, as well as can act as intermediate swithin conversion for one type of element to another [17].by Shigella, plasmid conjugation commonly occurs during co-infections that allow the spread of pINV and other resistance plasmids [18].Also, IS6 family insertion sequences are known to be part of resistance gene clusters as composite pieces which move by horizontal gene transfer [19]. That co-functioning MGEs for an intricate system that is facilitates further spread: That interplay for mobile genetic elements the central to HGT, and

then to the systems for preserving and spreading adaptive features [20]. This multifaceted situation escalates the difficulty in containing the Shigella spread dominated by virulence and resistance factors. Epidemiological Trends And Clinical Impact: Kotloff estimated Shigella continues to impose a substantial global burden being responsible for an estimated 188 million infections and 164 thousand deaths per year. The majority of these deaths are in children under five years old in low to middle income countries [21].What is also concerning is that surveillance data have shown how Shigella sonnei.has been progressively replacing S. flexneri in more developed socio-economic areas, which illustrates a changing epidemiology with increases in S. sonnei and antibiotic resistant strains in older children and adults from developing countries [22]. Outbreak investigation states that "multi–drug resistant (MDR) Shigella outbreaks have been increasingly frequent both in community and institutional settings such as daycare centers and refugee camps [23].

These MDR strains are associated with increased resistance to ciprofloxacin, azithromycin, and ceftriaxone, resulting in prolonged diarrhea, increased hospital admissions, and heightened case fatality rates of up to 5% [24].In developed countries, sexually transmitted Shigella infections have emerged as a concern in MSM populations. "MSM community outbreaks due to Shigella flexneri serotype 2a exhibit high rates of azithromycin resistance which complicates empirical treatment guidance [25].For assessing clinical significance, intervention studies emphasize the need for integrated epidemiological surveillance combining microbiological, genomic, and clinical data to track and respond to Shigella outbreaks in real time [26]. Additionally, cost-benefit analyses conducted for endemic regions indicate this aggressive targeting through enhanced intervention could lower costs via 35% as well as reduce hospitalization via 25% [27]. Current Challenges as well as Future Directions: We see ourselves confronted within the reality where multiple classes for antimicrobials have become or that becoming obsolete when dealing within Shigella spp. that is a pressing requirement of alternative therapies and/or vaccines against shigellosis [28]. That swift emergence for fluoroquinolone- as well as cephalosporin-resistant XDR Shigella strains heightens that need: Since that first report from Vietnam.

While oral carbapenems were encouraging, their prolonged for threatens into hasten resistance to our antibiotics for last resort [29]. Other novel therapies like phage therapy, CRISPR‑Cas antimicrobials, as well as antimicrobial peptides are also encouraging for in the early stages for clinical testing [30]. New strategies must surmount issues like targeted delivery, approval, as well as cost-effectiveness about resource-limited environments [29][30].

Vaccine development continues to be hindered by Shigella antigenic diversity—more than 50 serotypes—and a lack of understanding of correlates of protection. Yet, serotype-specific O-antigen vaccines have revived interest, particularly with intensive funding and WHO leadership [28] [32].Molecular surveillance via whole-genome sequencing and machine learning–powered resistome monitoring provides novel capacity but relies on worldwide standardized data exchange and interoperability [30][31].

Lastly, antibiotic stewardship and public health infrastructure continue to be uneven—especially for low- and middle-income countries—within lax surveillance as well as rampant self-medication driving resistance [31]. Tackling environmental reservoirs and One Health approaches are the next steps forthcoming [31]. Eventually, the future of Shigella control is a unified approach of genomic surveillance, stewardship, novel therapeutics (e.g., phages, CRISPR), and good vaccines—but so with regulatory, financial, and infrastructural challenges.

As more multidrug-resistant in extensively drug-resistant Shigella strains emerge, it is necessary that "a combination of ongoing genomic surveillance, new therapeutic approaches, and international collaboration must be undertaken to avert a public health disaster" [33]. Genomic epidemiology demonstrates that Shigella sonnei with low-fitness XDR plasmids is spreading in sexual networks like MSM communities, illustrating how resistance determinants become established worldwide [34].

AMR high-resolution monitoring through genomics yields real-time actionable data, enabling the detection of developing resistance early and enhancing worldwide response measures [35].

Nevertheless, resource constraints, fragmented data platforms, and bioinformatics capacity gaps in LMICs are still considerable challenges [36].

A few of the newer treatments like phage therapy, CRISPR-Cas antimicrobials, and antimicrobial peptides present encouraging alternatives to conventional antibiotics [37]. Additionally, novel targets like TolC, AcrR, and MdtA are a breakthrough in drug discovery against Shigella spp. [38].

There are difficulties in vaccine development because of antigenic diversity and the absence of well-defined correlates of protection [39]. Howver, reverse vaccinology strategies against outermost membrane proteins such as TolC demonstrate promising immunogenic responses within murine models" [39], [40].

Overall, combating XDR/MDR Shigella requires:

1. Global real-time genomic surveillance.
2. Investing in next-generation antimicrobials.
3. Creation of effective, widely protective vaccines.

Only through such concerted efforts can public health systems hope to turn back the tide of antibiotic-resistant Shigella.

Conclusion

Shigella spp. remain a major global health threat due to the combined impact of potent virulence mechanisms and the rapid rise of multidrug and extensively drug-resistant strains. Core virulence determinants—including ipaH, icsA, virF, and the mxi-spa system encoded on the pINV plasmid—enable efficient epithelial invasion, intracellular spread, and immune evasion. At the same time, resistance genes such as blaTEM, blaCTX-M variants, qnr alleles, aac(6')-Ib-cr, mph, and ermB are increasingly disseminated through plasmids, integrons, transposons, and other mobile genetic elements, driving widespread MDR/XDR emergence. Horizontal gene transfer further accelerates the spread of both virulence and resistance traits, while shifting epidemiological patterns—especially the rise of S. sonnei and recurrent MDR outbreaks—underscore the growing clinical burden. Escalating resistance to ciprofloxacin, ceftriaxone, and azithromycin has significantly narrowed therapeutic options. Future Shigella control requires integrated global efforts: real-time genomic surveillance, investment in novel therapeutics such as phage and CRISPR-based antimicrobials, and accelerated vaccine development capable of overcoming extensive antigenic diversity. Without coordinated international action, antibiotic-resistant Shigella will continue to escalate as a critical public health threat.

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