

Pathogenicity islands in bacteria of upper respiratory tract infection

Rawaa B. J. Al Daamee¹, Rana H. Raheema^{1,*}, Qasim Dawood Yasir Altameemi² and Maan M.N. AL-Naqeeb³

¹ Departments of Medical Microbiology, Faculty of Medicine, University of Wasit, Iraq.

² Departments of Pediatric Faculty of Medicine, University of Wasit, Iraq.

³ College of Biotechnology, Al-Qassim Green University, Iraq.

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Abstract

Children's upper respiratory tract infections (URTIs)—infections of the upper respiratory tract without symptoms of pneumonia—represent a significant socioeconomic and epidemiological issue. The study of microbial pathogenicity, which is a complex multifactorial process complicated by the coordinated activity of genetic regions linked to virulence and resistance determinants, has accelerated due to increased awareness of infectious diseases in humans caused by microbial pathogens. Pathogenicity islands and resistance islands are essential to the evolution of pathogens and seem to work in tandem during the bacterial infection process. While pathogenicity islands encourage the development of illness,

Additionally, pathogenicity islands are part of a vast array of genomic islands that play a vital role in the transmission of bacterial genes. They encode essential characteristics such as virulence, antibiotic resistance, and other supplementary functions.

Keywords: Pathogenicity islands; Upper Respiratory Tract Infection; Microbial pathogens

1. Introduction

Children's upper respiratory tract infections (URTIs)—infections of the upper respiratory tract without symptoms of pneumonia—represent a significant socioeconomic and epidemiological issue. Much like other components of the human anatomy, the upper respiratory tract (URT) quickly becomes populated with a diverse assortment of bacteria following birth, forming the typical microbiota.

The study of microbial pathogenicity, which is a complex multifactorial process complicated by the coordinated activity of genetic regions linked to virulence and/or resistance determinants, has accelerated due to increased awareness of infectious diseases in humans caused by microbial pathogens. Pathogenicity islands, or PAIs, and resistance islands, or REIs, are essential to the evolution of pathogens and seem to work in tandem during the bacterial infection process. While PAIs encourage the development of illness, REIs provide the host with a fitness advantage against a variety of antimicrobial drugs (1).

Additionally, pathogenicity islands are part of a vast array of genomic islands that play a vital role in the transmission of bacterial genes. They encode essential characteristics such as virulence, antibiotic resistance, and other supplementary functions (2). In Iraq, as far as we know, survey of literature showed no information on upper respiratory tract infection Pathogenicity islands. Hence, this review article was presented to highlight the characterized of pathogenicity islands in bacteria of upper respiratory tract infection and some factors which play role in the regulation of virulence genes.

* Corresponding author: Rana H. Raheema.

2. Upper Respiratory Tract Infection

Worldwide, pediatric patients' morbidity and death are mostly caused by respiratory tract infections (3). Wheezing, sore throats, rhinitis, coughs, and fevers are some of the symptoms that can be associated with RTIs. While most pediatric infections are treated in a primary care environment, some can require hospital hospitalizations. Acute respiratory infections account for 25% of all pediatric admissions from developing nations. Other factors that increase the risk of Respiratory Tract Infections (RTIs) in children encompass various aspects. These include the method of infant feeding, the possibility of contracting infections from older siblings at daycare or school, passive smoking exposure, especially from maternal smoking, the presence of specific diseases or congenital conditions like congenital heart disease, immune deficiencies (congenital or acquired), neuromuscular disorders, severe gastroesophageal reflux disease, chronic lung diseases (such as cystic fibrosis or those linked to premature birth), and the requirement for supplementary oxygen therapy at home due to chronic lung diseases associated with premature birth. Furthermore, RTIs can also result from exposure to air pollution, low birth weight, lack of measles vaccination, crowded living conditions, and inadequate nutrition. In underdeveloped nations, low birth weight and malnutrition stand out as primary causes of RTIs in children. (4). Respiratory tract infections are inclusive of any infectious diseases that impact the respiratory system. Particularly in low- and middle-income nations, these infections pose substantial public health challenges due to their capacity to induce severe illness and mortality in both adults and children. (5).

Most viral upper respiratory tract infections (URTIs) tend to resolve without complications, while bacterial infections often require specific antibiotic treatments. Additionally, secondary bacterial infections are commonly observed, especially among undernourished and young children (6). Frequently encountered bacterial pathogens responsible for URTIs include *Streptococcus pneumoniae*, *Corynebacterium diphtheriae*, *Haemophilus influenzae type b (Hib)*, and *Streptococcus pyogenes*. *Neisseria meningitidis*, although not typically associated with URTIs, causes infections affecting the central nervous system (CNS). Its colonization in the pharynx primarily acts as a reservoir, and heightened colonization elevates the risk of CNS-related illnesses.

An estimated 14.5 million cases of severe illness and 826 000 pediatric fatalities are attributed to *S. pneumoniae* each year. Williams and colleagues, (2011). Hib is thought to be responsible for around 3 million cases of severe illness and 400 000 deaths worldwide, mostly affecting children in nations with few resources (7). *Neisseria meningitidis*, *Corynebacterium diphtheriae*, and *Streptococcus pyogenes* have the potential to cause acute effects and, in some cases, may result in long-term consequences such as rheumatic fever. Communities where people live closely together, such as school settings, tend to have higher rates of transmission and carriage of these bacteria. In the bustling neighborhood of the upper respiratory tract, a diverse community of microbes takes up residence. Among them are the friendly neighbors, the commensals, tirelessly working to maintain a healthy epithelial environment. Alongside these good-hearted residents are the enigmatic pathobionts, capable of swinging between benign coexistence and causing trouble when conditions align just right. Factors like family size, the seasonal rhythm, and the vaccination status of these dwellers play a role in their numbers. Among the celebrated commensals gracing this lively community are *Dolosigranulum pigrum*, *Corynebacterium spp.*, *Staphylococcus epidermis*, *Streptococcus mitis/oralis*, and *Haemophilus haemolyticus*. Meanwhile, the pathobionts *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Staphylococcus aureus*, occasionally stir up a bit of mischief amidst this colorful URT neighborhood (8).

Bacteria from the phyla Actinobacteria and *Firmicutes* predominate in the URT microbiota, with lesser percentages of *Proteobacteria* and *Bacteroidetes* species. Different zones in your upper airways (URT) house unique teams of microscopic residents - microbes! Their variety and location depend on the surroundings, like tough skin walls and oil glands near your nostrils (9–11). It's like a diverse city where each district harbors its own community. In contrast, the mucosa of the sino-nasal and nasopharyngeal regions is composed of pseudostratified columnar and ciliated epithelium, facilitating the production of mucus (12). Apart from *Staphylococcus* species, lipophilic skin colonizers such as *Cutibacterium* (previously known as *Propionibacterium*) and *Corynebacterium spp.* are commonly found in abundance within the anterior nares. The nasal mucosa becomes a vibrant ecosystem, teeming with a richer tapestry of bacterial life compared to the guard post at the entrance (nares). *Moraxella*, *Dolosigranulum*, and *Streptococcus* join the party, adding to the diversity. (10,13).

3. Development of the URT Microbiota

The gut isn't the only place impacted! How babies are born and fed can heavily influence the diversity and number of bacteria colonizing their upper respiratory tract, as emphasized by Esposito and [NO_PRINTED_FORM] (14). The predominance of *Staphylococcus*, *Corynebacteria*, and *Cutibacterium* in the anterior nares, coupled with their detection

in the adjacent skin microbiota, suggests skin-to-skin contact as a primary acquisition route for these organisms and raises the possibility of a direct influence of the skin microbiome on URT microbial composition.

In comparison to infants fed formula, those who were breastfed demonstrated a higher prevalence of *Corynebacterium* spp. and a reduced prevalence of *S. aureus* in their upper respiratory tract bacterial profiles (15). In addition to skin contact, breastfeeding is another way that this taxon may colonize an infant during the first few months of life. This is demonstrated by the presence of *Corynebacterium* spp. in the microbiota of maternal breast milk (16).

Although it is less common than the three major species, *D. pigrum* is nonetheless widely distributed. *D. pigrum* is most likely derived from vaginal microbiota received following a vaginal birth while the human upper respiratory microbiota is still in its early stages of development (14). Early on in their growth, *Moraxella* and *Haemophilus* species also colonize the URT, though it's unclear how they do so. Compared to younger babies and older children, pre-schoolers have been demonstrated to have a higher concentration of them in healthy development (17). This observation might shed light on the timing of infants acquiring their upper respiratory tract (URT) microbiota. Understanding the developmental trajectories and functional implications of the upper respiratory tract microbiota during early life could potentially provide valuable predictive biomarkers for the susceptibility and manifestation of respiratory infections in children (18,19) This could have an impact on respiratory health and illness in the future.

3.1. Causative Agent

Runny noses, sinus pressure, earaches, scratchy throats, difficulty swallowing, and voice changes are all signs of upper respiratory tract infections. These illnesses typically affect areas at or above the larynx and are commonly caused by viral infections. Bronchitis, bronchiolitis, and pneumonia are examples of bacterial or viral diseases that occur below the larynx and are categorized as lower respiratory tract infections (20).

Most upper respiratory infections (URIs) are of viral origin. However, in underdeveloped countries, respiratory infections leading to pneumonia in children often arise as a consequence of bacterial infections following viral ones. URIs can be attributed to over 225 diverse pathogens. The bacteria frequently associated with these infections include *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Citrobacter koseri*, *Acinetobacter baumannii*, and *Streptococcus pyogenes* (21).

Streptococcus pyogenes is a facultative anaerobic bacteria that is Gram positive and nonspore forming. Penetration of compromised skin or mucosal membranes by these microorganisms presents a potential gateway for diverse ailments, including rheumatic fever, rheumatic heart disease, pharyngitis, and streptococcal toxic shock syndrome. It is also known as the Lance-field group. The primary bacterial pathogen causing acute pharyngitis in school-age children from lower socioeconomic backgrounds is beta-hemolytic *Streptococcus* (GAS) (Smeesters *et al.*, 2010). Secondary pathogens in respiratory tract infections include *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Enterobacter bugandensis* and *Staphylococcus aureus*. On the other hand, *Escherichia coli* and *Klebsiella pneumoniae* are classified as primary pathogens, as indicated by Karchmer (22). The spread and virulence traits associated with different strains of Group A *Streptococcus* (GAS) are known to fluctuate over time.

Antibiotics have played an immensely beneficial and life-saving role in medicine, significantly reducing mortality rates caused by various bacterial infections. Antibiotics are secondary metabolites manufactured by various microorganisms, functioning as antimicrobial agents (23). These medications primarily act by interfering with cell wall construction, inhibiting protein synthesis, disrupting nucleic acid synthesis, blocking metabolic pathways, and disturbing the integrity of the cell membrane (24).

3.2. Pathogenicity islands

A unique type of genomic islands known as pathogenicity islands (PAIs) are obtained by microbes through horizontal gene transfer. Pathogenic organisms frequently harbor unique genetic elements within their genomes, often absent in nonpathogenic counterparts of the same or closely related species, potentially contributing to their disease-causing capabilities. These mobile genomic elements, which can have a size of 10–200 kb, encode genes that increase the pathogen's pathogenicity. Adherence factors, poisons, iron uptake systems, invasion factors, and secretion systems are typical examples. Pathogenicity islands are distinct genetic units that have insertion sequences, direct repeats, or tRNA genes around them. These sequences serve as locations where DNA may recombine.

Genes encoding adhesins, poisons, or invasins are among the virulence factors that are carried by pathogenicity islands. They might be carried by a plasmid or found on a bacterial chromosome. It may be easier to identify pathogenicity islands within a certain DNA sequence since their GC-content frequently varies from that of the remainder of the

genome. PAIs carry functional genes, such as integrases, transposases, or portions of insertion sequences, to permit insertion into host DNA. They are flanked by direct repeats, meaning that the nucleotides at the two ends of the inserted sequence are identical. Target locations for this integration event include tRNA genes, which are frequently linked to PAIs. They have the ability to be transmitted as a single unit to fresh bacterial cells, giving previously harmless strains pathogenicity.

3.3. Structure of PAI .

The following lists the genetic characteristics of PAI (25):

Sure, here is a breakdown of the provided information:

- Pathogenicity islands (PAIs) can be likened to treasure islands housing valuable virulence genes. Meanwhile, genomic regions resembling PAIs but devoid of these precious virulence genes are akin to islands holding different treasures—metabolic or genomic riches.
- Pathogenic bacterial genomes boast a treasure trove of Pathogenicity Islands (PAIs), whereas their nonpathogenic counterparts from the same or closely related species miss out on these hidden gems.
- PAIs aren't just small pockets but rather sprawling domains within the genomic landscape, stretching across extensive regions that can range from a modest 10 to a hefty 200 kilobases (kb) in size.
- The genetic makeup of PAIs seems to dance to a different tune compared to the core genome. While bacterial DNA typically sways between 25% to 75% in guanine and cytosine (G+C) content, these sneaky PAIs often stand out with G+C levels commonly hitting the 40% to 60% mark. The mystery? Despite their ancient origins, these islands seem to maintain their distinct genetic playlist even after settling in new genomic neighborhoods. Divergent base composition in PAI may also be maintained by other variables, such as particular codon use of the virulence genes or DNA architecture.
- The frequent co-localization of PAI with tRNA genes in bacterial genomes prompted the hypothesis that tRNA loci serve as preferential insertion sites for horizontally acquired foreign DNA during HGT events. The preservation of genes encoding transfer RNAs (tRNAs) across diverse bacterial species offers a potential explanation for their frequent use as insertion sites. Integration of horizontally acquired DNA fragments harboring tRNA genes into the recipient bacterial genome can be facilitated by recombination events occurring between highly conserved tRNA loci, resulting in seamless incorporation of the foreign element.

Additionally, specific bacteriophages target particular insertion sites within the host genome known as tRNA genes. The preferential targeting of tRNA loci for the integration of horizontally acquired DNA fragments underscores their pivotal role as assimilation hotspots for external genetic material within bacterial genomes.

(vi) Mobile genetic elements are commonly linked to PAI. They frequently have direct repeats (DR) on either side. DNA sequences ranging from 16 to 20 base pairs, and sometimes up to 130 base pairs, characterized by complete or nearly perfect repetition are termed Direct Repeats (DR). These DRs might have initially operated as sites recognized for bacteriophage integration, triggering their subsequent duplication.

The presence of direct repeats (DRs) flanking Pathogenicity Islands (PAIs) serves as recognition sites for enzymatic machinery involved in the excision of mobile genetic elements, further promoting the inherent instability of these PAIs. This mechanism may bear resemblance to the processes responsible for the deletion of antibiotic resistance genes under relaxed selection pressure, potentially contributing to the elimination of PAIs. In both scenarios, the deletion results in a smaller genome, shortening the generation time and providing a competitive advantage to the microbe.

PAIs often carry functional mobility genes like transposases or integrases, and sometimes even cryptic ones. Phage integrases exhibit remarkable functional versatility, facilitating both the excision of the integrated prophage to initiate the lytic cycle and the site-specific integration of the phage genome into the host bacterial chromosome, establishing lysogeny. These integrases might have originated from lysogenic bacteriophages. In certain PAIs, these genes remain active, and the proteins they encode may aid in the removal and loss of the PAI. Later in this review, the function of bacteriophages in the spread of PAI is discussed. Genes found in other PAI resemble the transposon integrase and resolvase genes. Transposons have the ability to move from one chromosomal region to another within a plasmid and vice versa, in addition to these mobile genetic components shifting positions within chromosomes. In PAI, insertion sequence (IS) elements are commonly seen. Genes can be rendered inactive by the insertion of IS elements, but longer DNA segments can also be mobilized when two or more IS elements are combined. Pathogenicity islands (PAIs) could encompass integrated plasmids, conjugative transposons, bacteriophages, or portions derived from these components. This broadens their genetic diversity and potential impact on the virulence of the host bacterium.

PAIs often display a tendency for instability and can undergo deletions at varying rates. Some virulence functions encoded within PAIs are lost more frequently than the average mutation rate. Genetic analyses challenge the notion of point mutations within virulence genes of Pathogenicity Islands (PAIs) as the sole source of phenotypic alterations. Instead, they suggest a potential role for large-scale deletions, encompassing significant segments or even the entirety of the PAI, in driving phenotypic diversity. These changes are observable not only when pathogens are cultured in laboratory settings but also in isolates obtained from infected individuals, particularly in cases of chronic infections. This suggests that there is inherent genetic instability in such PAI. Genetic instability in PAI is determined by the same genetic pathways that permit its horizontal gene transfer. Numerous distinctive components, including IS elements, transposases, and integrases, have been found to contribute to both instability and mobilization as previously mentioned.

(viii) Rather of being uniform lengths of DNA that has been acquired horizontally, PAI frequently depict mosaic-like structures. One genetic element may have been inserted into certain PAI. Others have a more intricate structure due to the presence of components from various origins. Numerous genetic components have independently evolved during the course of evolution from various hosts and at various times. Nonetheless, these DNA acquisitions were incorporated into the receiving bacterial cell's chromosome at the same location. This will cause a specific region of the chromosome to accumulate horizontally acquired elements, with the same target structures—such as tRNA genes—serving as a constant platform for the integration of the different elements.

These characteristics are true for many PAI, however it has become evident that prokaryotes have extremely varied mosaic genomes as more genomic sequence data has been obtained. In addition to a core genome that primarily exhibits uniform G+C composition and codon use, mobile genetic components comprise a variable gene pool. Most genes found within the flexible gene pool provide selective advantages to the bacteria upon transfer. However, there are also genes that are self-serving, primarily focused on propagating themselves rather than providing direct benefits to the host bacterium.

The final set of components within this adaptable gene pool comprises insertion elements, specifically restriction/modification systems, and prophets. PAIs are considered part of this flexible gene pool as well. These "islands" are more common than previously believed, according to the sequencing of full bacterial genomes. This finding reinforces the existence of genetic elements present across diverse bacterial genomes. As a result, the term "pathogenicity islands" has evolved to encompass "genomic islands," exhibiting the capacity to encode a broad array of functions and activities. The majority of genomic islands include genes essential to the survival and propagation of microorganisms.

3.4. Evolution and transfer of PAI.

The remarkable conservation of key virulence factors across disparate bacterial taxa suggests a potential role for horizontal gene transfer in the dissemination of these pathogenic determinants. The transmission across bacterial strains and species can be explained by a variety of theories.

3.4.1. Natural transformation.

Some bacteria have the ability to naturally change. Transport mechanisms that enable the absorption of free DNA from the surroundings are expressed at certain stages of development. Although most foreign DNA tends to degrade, specific segments containing "beneficial" genes are integrated into the recipient's genome and persist without degradation. It is plausible that this process permits the reception of DNA from animals that are distantly related and that this DNA will be preserved while the selection pressure favors the recently acquired traits.

3.4.2. PAI and Plasmids

Comparable virulence gene clusters have been found in PAI and on virulence plasmids, suggesting that the same gene cluster may exist in both episomal and chromosomal sites. Certain virulence gene clusters have been shown to be present on virulence plasmids in certain bacteria as well as in the pathogen-associated intracellular matrix (PAI). The virulence plasmid carries the *mxi* and *spa* genes responsible for the Type III Secretion System (T3SS) necessary for *Shigella* spp. to invade epithelial cells, whereas a comparable gene cluster essential for *Salmonella enterica* to be invasive is found in SPI-1 in a chromosomal position. Plasmids can be transferred between bacteria via conjugation. Once within the bacterial genome, these plasmids can multiply autonomously. However, given some circumstances, they can also integrate into the chromosome. On the other hand, it has been documented that certain PAI of *Staphylococcus aureus* generate episomal components. Plasmids may thus represent an additional pathway for the spread of PAI across bacteria.

3.4.3. Transduction

Nearly every type of bacterium has been shown to have bacteriophages; even obligatory intracellular parasites like *Chlamydia* spp. have phages. Bacteriophages has the ability to carry bacterial virulence genes throughout their genomes. Phages can occasionally convey virulence genes to recipient bacteria, enabling them to colonize new environments like host organisms or anatomical locations. Additionally, the bacteriophages can propagate more effectively because to this expansion. Hence, bacteriophages might undergo evolutionary benefits by transmitting bacterial virulence genes present within their viral genome. *Vibrio cholerae*, discussed further below, serves as a well-documented illustration of how bacteriophages have played a role in shaping the evolution of bacterial pathogenicity.

A lot of PAI are too big to fit inside the genomes of bacteriophages as passengers. The gene clusters found on Pathogenicity Islands (PAIs) that encode Type III Secretion Systems (T3SS) or Type IV Secretion Systems (T4SS), for example, typically span 25 to 40 kilobases (kb) of DNA in size. Interestingly, this size range is comparable to the entire genome size of certain bacteriophages. Other methods are feasible under these circumstances. There are bacteriophages that can transduce widely. The efficient multiplication of phage particles within host bacteria necessitates the encapsidation of multiple phage genome copies within specialized protein shells termed capsids or phage heads. Fragmentation of the host DNA occurs during replication. A portion of the host genome can occasionally be mistakenly packed into the phage head by the enzymes that package the phage genome. A fragment of bacterial DNA may be transduced as the produced particles retain the ability to infect a new bacterial host. Recombination may take place if there is enough sequence similarity, in which case the transduced segment integrates into the new host's genome.

3.4.4. Integration sites of PAI

The bacterial chromosome's integration of PAI is a site-specific process. The majority of known PAI have been found to insert at the 3' end of tRNA loci. Moreover, this area is often home to phage attachment sites. Nonetheless, Pathogenicity Islands (PAIs) utilize specific genes and occasionally intergenic regions within operons. The *selC* locus is often a favored site for the insertion of various Pathogenicity Islands (PAIs) within Enterobacteriaceae members, including *E. coli*, *Shigella* spp., and *S. enterica*. PAIs exhibit sequence homology with tRNA loci, specifically localized to the 3' terminal region of tRNA genes, encompassing approximately 15-20 nucleotides. These overlapping sequences encode the 3' portion of the acceptor-T ψ C stem-loop structure of tRNA, extending to the conserved CCA terminus (26). Three possible possibilities explain why tRNA genes are used as integration sites, albeit the molecular basis of this usage is not entirely known.

Indeed, a connection exists between a Pathogenicity Island (PAI) and specific tRNA molecules in such a way that the encoded tRNA has the capability to interpret or read the codons present within the associated PAI. This is demonstrated for the uncommon tRNA^{LeuX} encoded by the *leuX* tRNA gene (27). The production of virulence components encoded on PAI536 requires *leuX* expression. This argument is not supported as *leuX* also modulates fundamental cellular genes unrelated to pathogenicity and because PAI's relationship with certain tRNA genes is unique to this island.

The existence of numerous copies of the tRNA gene, which would provide various insertion sites and amplify pathogenicity factors, would be a second theory. Nevertheless, this doesn't apply to *selC* and *leuX*, as they are present as solitary copies. A compelling hypothesis proposes that highly conserved structural motifs within tRNA genes serve as facilitators for both the integration and excision of phages and Pathogenicity Islands (PAIs) within bacterial genomes (28). This highlights the role of integrases as catalysts for both excision and integration.

3.4.5. PAI OF *Streptococcus* spp

Similar to staphylococci, streptococcal infections are associated with a range of illnesses. Group A streptococci, or *S. pyogenes*, can cause pharyngitis, necrotizing fasciitis, and skin infections. These diseases advance rapidly. Neonatal septic illnesses are often linked to Group B streptococci, namely *Streptococci agalactiae*. *Pneumococci* (*S. pneumoniae*), in addition to their typical commensal presence along the upper respiratory tract's mucosal lining, these organisms have the potential to cause ailments such as otitis media, pneumonia, and several other respiratory tract diseases.

Conversely, *S. aureus*, it appears that Pathogenicity Islands (PAIs) have a lesser impact on the evolutionary process of streptococci towards virulence. Genome sequencing of *S. pyogenes* revealed the absence of PAIs in the genome, however, a significant portion of virulence factors had been obtained via horizontal gene transfer, aided by bacteriophages (29).

Analysis of the *Streptococcus pneumoniae* genome has revealed the presence of a genetic region displaying characteristics reminiscent of a Pathogenicity Island (PAI), typically associated with enhanced virulence in other bacterial species. This specific site is known as pneumococcal pathogenicity island 1 (PPI-1), spans around 27 kilobases

(kb), displaying uniqueness from similar regions in other streptococci. PPI-1 contains genes encoding transposases and recombinases, which might be associated with the mobility or movement of this locus. *Pit2ABCD* encodes an iron absorption mechanism, which has been identified as a virulence component in PPI-1. Even though the *pit1* operon is present outside of the Pathogenicity Island (PAI), both the Pit1 and Pit2 iron absorption systems need to function together for pneumococci to exhibit complete pathogenicity in lung and systemic animal models (30).

4. Conclusion

The *Streptococcus pneumoniae* is a significant pathogen responsible for a number of infections particularly upper respiratory tract infections, the identification of PAIs in streptococcal isolates is a fundamental step towards the selection of appropriate treatment options and accurate differentiation of upper respiratory tract infections.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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