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Commensals upon us

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ABSTRACT

A battle to control and curtail bacterial infectious diseases is being waged in our hospitals and communities through antibiotic therapies and vaccines targeting specific species. But what effects do these interventions have on the epidemiology of infections caused by the organisms that are part of our natural microbial flora? Gram-positive and gram-negative bacteria appear as new disease agents from among commensal flora. These include vancomycin resistant enterococci (VRE), community-associated methicillin resistant *Staphylococcus aureus* (CA-MRSA), non-vaccine invasive serotypes of *Streptococcus pneumoniae*, new strains of non-type b *Haemophilus influenzae* and multi-drug resistant *Escherichia coli*. These examples illustrate how clinical improvements and widespread use and misuse of antibiotics have pushed evolution, allowing normally non-pathogenic strains to become infectious disease threats to human health.

1. Introduction

About 20–40% of children asymptomatically carry nasopharyngeal *Streptococcus pneumoniae*, a leading infectious agent for otitis media, pneumonia, bacteremia, and meningitis in both children and adults [1]. For adults, the carriage rate is 18–29% in homes with children (<6 years old) and 6% in households without children [2]. *Haemophilus influenzae*, which causes mucosal infections (especially in children <5 years old) such as sinusitis, otitis media, and bronchitis, as well as severe diseases including bacteremia and meningitis, is a common constituent of the human respiratory tract. In the intestinal tract, normal microbes are appearing more virulent or as more common agents of disease. *Clostridium difficile* a spore-forming organism that produces pseudomembranous colitis and antibiotic-associated diarrhea has appeared drug resistant and more virulent. New strains of multi-drug resistant *Escherichia coli* populate the human intestinal flora and can be the source of urinary tract infections and septicemias. The enterococci, normal enteric commensals, plague patients undergoing chemotherapy, organ transplantation and other surgeries. Their emergence as vancomycin resistant has increased their threat as pathogens. From the environment, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (gram-negative bacteria of which some are untreatable because they thwart all clinically used antibiotics) become pathogens when they strike immunocompromised people.

What do these organisms have in common? They are all commensals, that is, bacteria that colonize an individual without normally causing disease. Some, however, have the capacity to produce disease (Table 1). In this review we shall focus on these ''pathogenic commensals'' that inflict disease when the host is vulnerable. We distinguish them from the truly non-disease-causing (non-pathogenic) commensals such as some lactobacilli. Since colonization is often a function of age or the status of a person's immune system and a common foreword of disease, we shall consider those organisms that can colonize, for example, *S. pneumoniae* and

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Table 1 – Selected commensals with pathogenic potential

Organism	Notable characteristic(s)
MSSA	Multi-drug susceptible *S. aureus*
MRSA	Methicillin resistant *S. aureus* acquired in the hospital and the community; frequently possess resistance to multiple antibiotics
S. pneumoniae	Serotype diversity complicates targeted vaccine approaches
H. influenzae	While type b strains are targeted by the current vaccine, upper respiratory tract infection from non-type b strains is increasing
E. coli	Multi-drug resistant strains have been found in common community (e.g., UTI) infections
P. aeruginosa	Strains have emerged resistant to all antibacterials
A. baumannii	Strains have emerged resistant to all antibacterials
Enterococcus (VRE)	Multi-drug resistant including resistance to vancomycin
C. difficile	Resistance to metronidazole and vancomycin is documented and more virulent fluoroquinolone resistant strains have recently emerged

Staphylococcus aureus, as well as true opportunistic pathogens like *P. aeruginosa*, which can be regarded as environmental commensals.

There are approximately 10 times more bacteria associated with the normal healthy individual than cells that make up the human body [3]. In most instances, the appearance of commensals that possess the capacity to cause disease is limited by an active immune system and by competition with other organisms occupying the same environmental niche. This balance is disturbed following a change in a person's host defense such as that which occurs in patients undergoing chemotherapy for cancer or those following surgical intervention or organ transplantation.

Two approaches to protect and/or control infection by disease-causing organisms are antibiotics and vaccines. Antibiotics indiscriminately inhibit growth of both beneficial and harmful bacteria while vaccines, especially those targeting individual organisms, e.g., *H. influenzae* type b, are more selective and less disruptive microbiologically. Both types of therapies alter the microbial flora of the human body (Fig. 1). Antibiotics have immediate short-lived effects on microbial growth while vaccines deliver their benefits through a slower but more persistent process.

The mechanisms that govern the selection of new infectious agents following antibiotic or vaccine use are generally distinct, but equally burdensome. For example, single antimicrobial agents can select for co- and cross-resistance phenotypes through the acquisition of novel genes or mutations [4]. Vaccines foster the creation of unique ecological niches that can be occupied by organisms not subject to the vaccine and select for immunologically unreactive disease-causing variants. There are parallels between the two approaches, however, that are noteworthy. In the case of the pneumococci, the first wave following successful vaccination has resulted in decreased disease

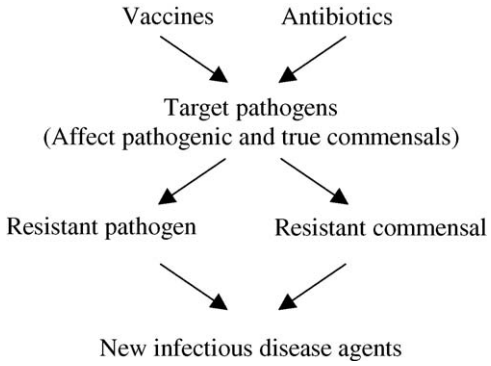

Fig. 1 – Mechanism by which antibiotics and vaccines select for new infectious disease agents. Although antibiotics and vaccines can foster the development of new infectious disease agents, different selective mechanisms are applicable to each therapeutic intervention (see text).

caused by invasive and/or penicillin resistant serotypes much like antibiotics. Subsequently, however, new invasive strains (or isolates like *H. influenzae* that overexpress a vaccine's target) and organisms bearing penicillin or multi-drug resistance have emerged. Thus, complacency in the face of recognized successful vaccination campaigns is ill-advised and continued microbiology monitoring is essential for control of these agents.

2. The effects of vaccines on organisms with capsules

S. pneumoniae and *H. influenzae* are pathogenic commensals against which successful vaccines have been developed. These vaccines are directed against whole organisms and are available in two different forms. Polysaccharide vaccines offer broader protection in adults and children (>5 years old). The principal utilities of conjugate vaccines, which afford protection against a limited spectrum of organisms, are their use and effectiveness in young children (<2 years of age) and their ability to provoke immunologic memory.

A primary determinant of *S. pneumoniae* virulence is its polysaccharide capsule, and there are more than 90 different capsular serotypes[1] [5]. The current pneumococcal conjugate vaccine Prevnar® (Wyeth Pharmaceuticals, Philadelphia, PA) was developed to cover seven (PCV7) of the most commonly encountered serotypes in the United States and was introduced into clinical practice in 2000 [6]. Since these serotypes are not necessarily the most frequent disease-causing agents in other parts of the world [5], newer 9-valent and 11-valent vaccines are being developed. Data from the Active Bacterial Core Surveillance of the Emerging Infectious Program Network (Centers for Disease Control and Prevention) have shown

[1] *S. pneumoniae* are classified into serotypes (numbered consecutively in the United States) based on differences in the chemical composition of their capsules. The serotypes can be further divided into a smaller number of serogroups based on similarities in the immunological reactivity of the capsule.

steep declines in invasive pneumococcal disease among young vaccinated children. Of note, an advantage of this therapy involved other non-vaccinated children and adults in what is termed ''herd protection'' [7,8].

As noted above, PCV7 has demonstrated a profound medical benefit. The selective elimination of particular commensal pneumococcal serotypes, however, has led to the replacement of vaccine with non-vaccine serotypes, a finding noted early during clinical trials [9]. Byington et al. recently reviewed the incidence of invasive pneumococcal disease (IPD) in the intermountain west region of the United States before (1996–2000) and after (2001–2003) introduction of PCV7 [10]. While an approximate 30% decrease in the incidence of IPD due to vaccine serogroups was noted in children <18 years old, a marked increase in IPD by strains not covered by the vaccine was found [10]. While this study has limitations (IPD disease attributed to vaccine serogroups in this region was lower than elsewhere in the United States and pathogen identification was based solely on differing serogroups) the finding illustrates a potential consequence of increasing concern [10].

The use of PCV7 has also positively impacted acute otitis media (AOM) in children [11]. In studies of the microbiology of AOM before and after large-scale use of PCV7, Block et al. found that children in the post-PCV7 cohort were more prone to AOM and were more likely to attend day care centers and to have received recent courses of antibiotics [12]. While significant decreases were seen in the proportion of *S. pneumoniae* isolated, a concomitant and statistically significant increase in the isolation of nontypable *H. influenzae*, including β-lactamase positive organisms, was observed [12]. Casey and Pichichero addressed this issue in a prospective study over a period of 9 years studying the microbiology of AOM and pathogens responsible for treatment failure (non-responsive disease during antibiotic therapy) or persistence (infection after the cessation of antibiotic therapy) of AOM [13]. Prior to vaccination (1995–2000), *S. pneumoniae* was either the primary organism responsible for failure and persistence in AOM or as frequently responsible as *H. influenzae*. During the post-vaccine era (2001–2003), *H. influenzae* have become the predominant pathogen, but *S. pneumoniae* still retain a prominent role. This change in etiology of AOM was also accompanied by a shift in the antibiotic susceptibility of the organisms causing disease. There was a statistically significant increase in β-lactamase positive *H. influenzae*, and a non-significant trend towards penicillin resistant *S. pneumoniae* [13].

Surveying pathogens responsible for AOM between 1998 and 2001, a group of researchers from Israel found that approximately 20% of the cases were caused by *S. pneumoniae* (about 1/3 were from serotypes 35B, 33F, 21, and 15B/C) that would not be covered with a new expanded 11-valent conjugate vaccine (PCV7 and serotypes 1, 3, 5, and 7F) [14]. Of these predominant serotypes, 80% exhibited a penicillin non-susceptible phenotype, but were not multi-drug resistant (MDR) [14]. This finding contrasts with the vaccine serotype strains that were studied of which 23.8% were MDR [14]. The effects of vaccination on the dissemination of non-vaccine related antibiotic resistant strains remains to be determined.

H. influenzae are normal constituents of the human respiratory tract. Encapsulated organisms, which cause respiratory tract infections and invasive disease such as meningitis, are classified primarily according to differing capsular antigens (types a–f). Of all encapsulated *H. influenzae*, type b (Hib) is by far the most frequent disease-causing agent in the group [15]. Thus, the targeting of essentially a single organism, i.e., Hib, with a conjugate vaccine has proven highly efficacious for decades. This selective pathogen elimination has to a large extent not been overly burdened by issues of serotype replacement, but signs of this phenomenon are now appearing.

Prior to the advent of the Hib conjugate vaccine, invasive disease caused by non-Hib strains was minor (<10% of all cases). Notable increases in severe disease caused by *H. influenzae* type f after widespread vaccination, however, have been reported [16]. In one survey, a 17-fold increase in invasive disease caused by Hif was observed over a 5-year period [16]. In another study from Brazil, 165 Hib and 2 *H. influenzae* type a strains were identified in a pre-vaccine strain collection ($n = 167$) and all bacteria were isolated from cerebrospinal fluid [17]. Isolates from CSF, blood, and bronchial secretions in post-vaccine surveys ($n = 62$) included 53% Hib, 18% types a, c–f, and 30% nontypable *H. influenzae*. Thus, Hib still remains an important etiology of invasive disease while disease incidence caused by non-type b strains has increased in this part of the world.

The recent descriptions of Hib true vaccine failure (TVF) in immunized children are instructive and worrisome [18]. The Hib capsulation (*cap*) locus contains the genes responsible for the formation and export of the pathogen's capsule. Present in multiple copies in a number of Hib strains, *cap* is flanked by insertion sequences that impart a recombination potential [19]. Cerquetti and colleagues noted an increased prevalence (approximately three-fold higher) of TVF in children (<60 months old) bearing Hib containing multiple copies of the *cap* locus than in unvaccinated adolescents [18]. Since *cap* amplification parallels decreased susceptibility to host immune defenses, it is speculated that *cap* overproduction contributes to TVF [18].

3. Multiple antibiotic resistant *S. aureus* and their threat to the community

Given that carriage of *S. aureus* is a predisposing factor for infection, it is unsettling that approximately 1/5 of the healthy adult population carries *S. aureus* and another 3/5 will experience transient carriage of this organism [20]. The recent description of intracellular reservoirs of *S. aureus* in patients with persistent rhinosinusitis offers a potential mechanism for long-term persistence of these organisms in the nasal mucosa [21].

The current emergence of community-associated methicillin resistant *S. aureus* (CA-MRSA) began with strains resistant to all β-lactams, but susceptible to most other antibiotics. Now, they are increasingly acquiring other resistances as their numbers increase, such as to macrolides, fluoroquinolones, and tetracyclines [22]. Relative to the multi-drug resistant hospital-associated MRSA, CA-MRSA more frequently possess a unique set of toxin genes that specify the Panton–Valentin leukocidin (PVL) which makes them

Table 2 – Range of infections caused by community-associated methicillin resistant *S. aureus*

Skin and soft tissue	Invasive	Other	Antibiotic resistance profile[a]
Abscess Cellulitis Folliculitis Impetigo	Bacteremia Sepsis Septic arthritis Osteomyelitis Necrotizing fasciitis Necrotizing pneumonia	Wounds Pneumonia	β-Lactams Erythromycin/clindamycin Fluoroquinolones

[a] All MRSA are resistant to the β-lactams and >50% possess erythromycin resistance [25]. In certain strains, resistance to clindamycin, tetracycline, and fluoroquinolones has emerged [22].

more virulent producing a range of infections in healthy individuals (such as athletes and military personnel) as well as those with underlying disease [23,24]. Most CA-MRSA also bear a unique SCC*mec* type IV allele that specifies methicillin and wide β-lactam resistance [25]. The emergence of CA-MRSA is a prescient illustration of the perils of non-hospital based infectious agents that possess a broad antibiotic resistance phenotype (Table 2).

Using a molecular approach, Melles et al. [26] compared the genomic content of *S. aureus* ($n = 1016$) from the Netherlands [including 829 (carriage) isolates obtained from healthy children (<19 years old) and adults (>55 years old), 164 invasive strains, and 40 from children with nonbullous impetigo] to strains of MRSA causing international epidemics. All carriage isolates were clonal and similar to other carriage strains in the United Kingdom. Particular virulent (PVL bearing) clones were favored in instances of severe disease. Unusually, none of the non-epidemic strains (including clinical and non-clinical isolates) possessed the *mec*A gene specifying resistance to methicillin and other β-lactam antibiotics. This finding is a reflection of the low prevalence of MRSA in the Netherlands. MRSA causing international epidemics arose from lineages that also encompass the carriage isolates, illustrating the ease of *mec*A dissemination. The presence of PVL in invasive isolates was 10-fold greater (6%) than in carriage strains (0.6%) and its identification in *S. aureus* producing invasive deep-seated and soft tissue infections, abscesses, and arthritis as compared to the carriage strains in children was also significantly greater [26]. The absence of *mec*A among clinical and non-clinical strains implicitly demonstrates the pathogenic potential of *S. aureus*. In the United States, recent data from the National Health and Nutrition Examination Survey sponsored by the Centers for Disease Control and Prevention have shown that 32% and 0.84% of healthy US citizens carry *S. aureus* and MRSA, respectively, and about 0.4% of the MRSA is CA-MRSA (http://www.cdc.gov/nchs/nhanes.htm).

Hidron and colleagues sampled the anterior nares of patients ($n = 726$) following their admission (<48 h) to an inner city hospital situated in Atlanta, GA; of these, 23.7% tested positive for *S. aureus* and 7.3% bore MRSA [27]. Of the MRSA strains that were seen, 30.2% were CA-MRSA and 94% of these isolates possessed PVL. Of note, 63% of the patients with CA-MRSA did not have an infection at admission. The risk factors for MRSA acquisition in this study included immediate past antibiotic use and prior hospitalization as well as presentation of a skin or soft tissue infection and a positive HIV status in patients not taking antibiotics. Additional studies have also identified HIV status, IV drug use, and infected abscesses as predisposing factors for MRSA carriage [28].

The situation in children is particularly disconcerting. Approximately 1/3 of the CA-*S. aureus* isolated in February 2000 at Texas Children's Hospital (TCH) in Houston was found to be methicillin resistant; later in the same year this percentage jumped to 50% [29]. At Children's Medical Center of Dallas, more than 50% of the *S. aureus* isolates were CA-MRSA [30]. Over a 3-year period (2001–2004), infections (mainly skin and soft tissue) caused by CA-MRSA increased from 71.5% to 76.4% [31]. In this same period, the rate of clindamycin resistance increased significantly in methicillin susceptible *S. aureus* and MRSA [31]. Moreover, resistance to clindamycin, tetracycline, and fluoroquinolones was noted in certain strains [22]. Since CA-MRSA have now acquired resistance to other antibiotics, clindamycin, linezolid, and minocycline (in some circumstances) are some of the few remaining choices for oral therapy of MRSA infections.

4. Competition during microbial co-colonization

Competition among organisms of the human microbial flora has fueled a large number of in vitro and in vivo studies to describe and characterize the behavior of bacteria living in different ecological niches. Recent studies have investigated *S. pneumoniae* and *S. aureus* co-colonization as a means to address the potential impact of widescale pneumococcal vaccination on staphylococcal persistence [32,33]. A sampling of the microbial flora within the nasopharynx of more than 3000 healthy children without previous pneumococcal vaccination revealed a negative correlation between *S. pneumoniae* serotypes targeted by the pneumococcal vaccine (PCV7) and *S. aureus* co-colonization [32]. The same association, however, was not maintained for non-vaccine *S. pneumoniae* serotypes [32]. A similar inverse relationship was noted in children (most of whom had a respiratory tract infection) from four large urban areas in Israel that do not provide pneumococcal vaccination [33]. Carriage of either *S. pneumoniae* or *S. aureus* was lower if the other pathogen was present, although this relationship in adults was not seen [33]. While studies performed with pure cultures have suggested that hydrogen peroxide produced by *S. pneumoniae* interferes with the growth of *S. aureus* [34], the situation in the human nasopharynx is likely to be much more complex when one considers both micro, e.g., chemical, and macro effects, e.g., the presence of other bacteria and health of the human host.

5. Life in the human gastrointestinal tract

The human gastrointestinal (GI) tract, particularly the distal ileum and colon, supports the growth of an innumerable

amount of bacteria. Some organisms, for example, *Lactobacillus* spp. and *Bifidobacterium* spp., are beneficial inhabitants while others, such as *Enterococcus faecalis*, *Helicobacter* spp., *E. coli*, *Clostridium* spp., and *Bacteroides* spp. can cause clinical disease if allowed to proliferate under particular vulnerable conditions [35].

Of recent concern is *C. difficile*-associated diarrhea (CDAD), which is precipitated by antibiotic use, e.g., clindamycin, semi-synthetic penicillins, 1st, 2nd and 3rd generation cephalosporins, and fluoroquinolones, that non-selectively perturbs the intestinal micro-flora [36,37]. In July 2005, the Centers for Disease Control and Prevention issued a preliminary report on a new strain of *C. difficile* that was associated with severe disease and increased mortality. A full description of this phenomenon has now been published [37,38]. This strain produces greater amounts of two exotoxins and is fluoroquinolone resistant [37,38]. While fluoroquinolones are not indicated for the treatment of *C. difficile*, their widespread use in healthcare facilities could favor the propagation of this more virulent resistant isolate. For patients with antibiotic-associated CDAD, current recommendations include therapy with oral vancomycin or metronidazole, yet resistance to both agents has been noted. Since the former is associated with vancomycin resistance development in the enterococci, also normal inhabitants of the human GI tract, front-line use of metronidazole is preferred in most cases.

The enterococci are normal constituents of the human gastrointestinal tract and female genital tract. Of the two clinically prevalent enterococcal species, *E. faecalis* is the predominant pathogen (accounting for up to 90% of all infections) whereas *E. faecium* is a less frequent cause of disease [39]. Both possess resistance to a number of antibiotics, including vancomycin. Since infections caused by *Enterococcus* spp. are especially prevalent in immunodeficient patients and individuals with physical impediments, for example, indwelling catheters, these organisms are a scourge of intensive care units in the United States. Their spread to long-term care facilities outside of the hospital, where they can serve as reservoirs of infection, is also a problem [39]. The epidemiology of VRE carriage within the United States and European populations is strikingly different. In the United States, colonization of otherwise healthy individuals without common risk factors in the community is rare [39]. Among Europeans, however, commensal carriage of VRE, which is thought to be linked to the use of avoparcin (a glycopeptide like vancomycin) in animal husbandry, is widespread [39].

6. Multi-drug resistance in gram-negative bacteria

Infections caused by gram-negative organisms bearing extended spectrum β-lactamases (ESBLs) that afford resistance to oxyimino-β-lactams (i.e., cefuroxime, cefotaxime, ceftriaxone, ceftazidime, and aztreonam) are now a prominent threat to patients and clinicians world-wide [40]. While once confined to relatively few members of the *Enterobacteriaceae*, ESBLs have now spread to other members in this family causing community-acquired infections posing great difficulty in treatment [41].

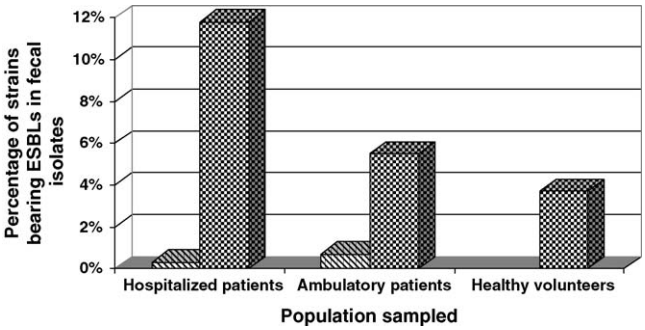

Fig. 2 – Fecal carriage of *Enterobacteriaceae* bearing ESBLs in Spain [42]. Samples were taken in 1999 (striped $n = 305$ and 544 for hospitalized and ambulatory patients, respectively) and 2003 (checkered; $n = 293$, 93, and 108 hospitalized patients, ambulatory patients, and healthy volunteers, respectively). Data from healthy volunteers were not available for 1999.

An analysis of *Enterobacteriaceae* bearing ESBLs isolated from hospitalized, ambulatory, and healthy individuals in Spain during a period (1999–2003) when infection caused by these organisms was low [42] noted a significant increase in ESBLs in patients circulating through the hospital. More notably was the high prevalence of these organisms in healthy individuals, who had not recently (<3 months) received antibiotics or spent time in a hospital (Fig. 2). Among 1000 fecal isolates (namely, normal inhabitants of the bowel) from hospitalized, ambulatory, and institutionalized patients [43] 22 were identified, including *E. coli*, *Enterobacter cloacae*, *Citrobacter freundii*, *Klebsiella* spp., and *Salmonella* spp., expressing an ESBL. This study further demonstrates that ESBL producers are encountered in hospital and community settings and that commensal-like carriage of the resistance gene is a likely important factor for infection. This concept, commensals as reservoirs of antibiotic resistance genes, forms the focus of a National Institutes of Allergy and Infectious Diseases-sponsored ROAR project of the Alliance for the prudent use of antibiotics (http://www.apua.org). Non-pathogens are subject to selection of resistance genes when confronted by antibiotics. The greater numbers of these commensals make them prominent hosts for transferable multiple drug resistance genes.

E. coli can be distinguished into groups with higher or lower potential for causing disease. In this regard, fluoroquinolone resistant *E. coli* (FQREC) causing extraintestinal infections were studied in order to ascertain the virulence potential of antibiotic resistant organisms [44]. The studies showed that FQREC emerged from the relatively less pathogenic phylogenetic groups (A, B1, and D) as compared to the traditional *E. coli* lineages (B2) that cause extraintestinal infection. Moreover, the FQREC did not possess many of the traditional virulence factors associated with other pathogenic *E. coli* (i.e., phylogenetic group B2).

This finding emphasizes the realization that strains within the same species can have differing potential for causing disease. Recognizing such differences could help in the diagnostic distinction between pathogenic and non-patho-

genic commensals. Manges et al. studied the genetic composition and antibiotic susceptibility profiles of *E. coli* isolates causing community-acquired urinary tract infection (UTI) in California and compared these isolates to those causing similar infections in Minnesota and Michigan [45]. Of 255 *E. coli* in the cohort from California, 22% demonstrated resistance to trimethoprim-sulfamethoxazole (TMP-SMX), the drug of choice for this disease. Fifty-one percent of the isolates were derived from a similar genetic lineage (clonal group A [CGA]) and more frequently displayed resistance to multiple antibiotics including TMP-SMX, ampicillin, streptomycin, chloramphenicol, and tetracycline. A high percentage of CGA *E. coli* with resistance to TMP-SMX were also seen in the Michigan and Minnesota cohorts. Additionally, 7% of the 170 *E. coli* causing pyelonephritis belonged to CGA and the majority (83%) were resistant to at least five antibiotics [46]. Although the fluoroquinolones and nitrofurantoin are viewed as therapeutic alternatives to TMP-SMX, an association between fluoroquinolone and nitrofurantoin resistance has been demonstrated recently [47].

P. aeruginosa is an opportunistic pathogen that can cause disease in virtually any enfeebled tissue. Its ubiquitous presence in a number of different environmental settings, e.g., soil and water, presents a serious challenge to the immunocompromised individual, such as those in intensive care units (ICUs). With the emergence of ESBLs and carbapenemases in *P. aeruginosa*, reliance has shifted to the fluoroquinolones especially for the treatment of respiratory and urinary tract infections. The antibiotic susceptibility of more than 35,000 gram-negative aerobic bacterial isolates from patients within ICUs from across the United States during the period from 1994 to 2000 was determined [40]. Susceptibility to ciprofloxacin decreased from 89% in the pre-study period (1990–1993) to 76% in 2000. With respect to *P. aeruginosa* alone, fluoroquinolone resistance rose from 11% (1990–1993) to 32% (2000) and was accompanied by greater overall use of the fluoroquinolones. These strains (as well as *Enterobacter* spp. and *Klebsiella pneumoniae*) were more likely to exhibit resistance to other antibiotics including gentamicin and amikacin, imipenem, and ceftazidime.

ESBL production has been associated with ciprofloxacin resistance in bacteremic patients with *K. pneumoniae* infections [48]. Currently, the surfacing of resistance in *P. aeruginosa*, and other gram-negative bacteria, to all clinical therapies (the pan-resistance phenotype) are of great concern and has forced the use of previously abandoned systemic therapeutics such colistin and polymyxin B [49].

7. Conclusions

The emergence of commensal organisms as pathogens is an expanding and threatening phenomenon of consequence to the infectious disease community. That many are multi-drug resistant further complicates and intensifies the clinical problem. These commensal organisms exist on the skin, oropharynx and intestinal tract without generally causing disease; but under certain circumstances, they become pathogens. Outbreaks of UTI caused by clonal MDR *E. coli* have been observed recently [45]. Severe (invasive) disease and mortality has been associated with CA-MRSA in children and athletes without historically common risk factors, i.e., prior antibiotic use, previous hospital admission, or family members in long-term care facilities [23].

Our attempts to control infection with the use of ''narrow-spectrum'' (conjugate) vaccines have shown a disease prevention benefit in vaccinated and neighboring unvaccinated individuals. However, a shift away from *S. pneumoniae* vaccine serotypes toward non-vaccine serotypes bearing antibiotic resistance determinants has accompanied vaccination programs targeted at children [14]. A similar phenomenon gives advantage to the nontypable *H. influenzae* following use of the Hib vaccine. From the beneficial effects of protective immunity alone, one might have assumed that this approach would be preferable to antibiotics that kill indiscriminately. Large-scale vaccination programs, however, are expensive and are not available to all especially those in developing countries [50]. When implemented, e.g., for polio and small pox, however, they have proven extremely successful. Paradoxically, cheap generic antibiotics are available and often accessible without a physician's consultation. Easy access to antibiotics coupled with transmissible resistance traits fosters the dissemination of resistant organisms [51] and proposals for dealing with the drug resistance problem are cited elsewhere [52].

If we are to garner anything from our experiences with the spread of resistance in our hospitals, it is that our current therapeutic efforts have increased the appearance of commensal organisms in diseases. Unfortunately, commensals are not confined to hospitals, but affect the community as well. Increased awareness and the tracking of commensal emergence should provide insights into improved drug choice and control of infection.

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