Antibacterial cleaning and hygiene products as an emerging risk factor for antibiotic resistance in the community

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Antibiotic resistance within the community setting is an emerging public-health concern. Infection with antibiotic-resistant organisms in the community among people lacking traditional risk factors has been reported. In addition, prevalence studies have identified individuals carrying antibiotic-resistant organisms in the absence of known risk factors. These studies strongly suggest the presence of contributing factors that have yet to be identified. In this paper we review the burden of antibiotic resistance and known risk factors within the community setting, assess the potential role of antibacterial cleaning and hygiene products containing triclosan in the emergence of resistance, and recommend future research on the assessment of household cleaning and hygiene products containing triclosan.

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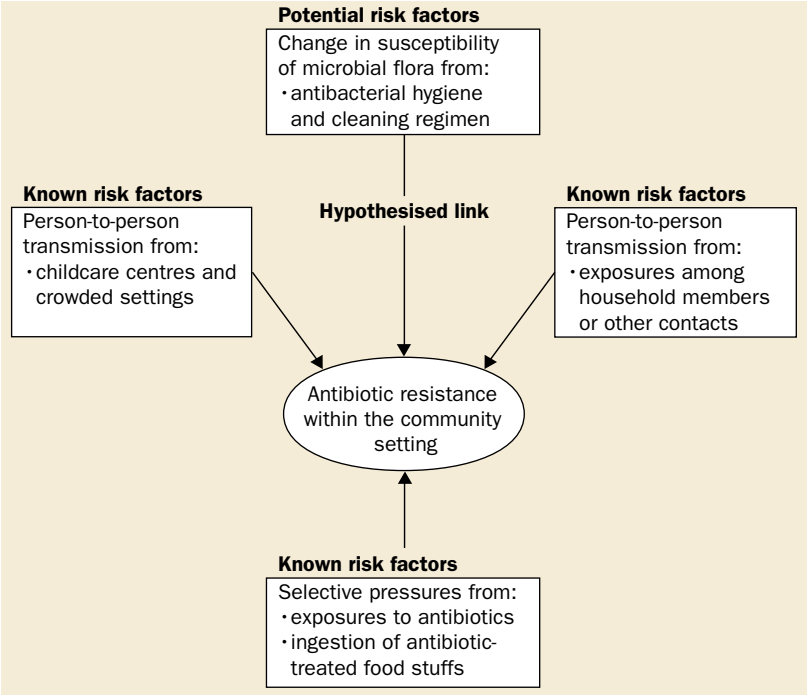

Factors contributing to antibiotic resistance within the community setting.

The emergence of antibiotic-resistant bacteria has been contributed to by factors such as the misuse of antibiotics, increases in day-care centre attendance, use of antibiotics in the food industry, and an increasingly immunocompromised population.[1,2] Antibiotic resistance can result in treatment failure, can alter natural microbial ecology, and lead to higher severity of infections from transmission of multi-antibiotic-resistant bacterial pathogens.[2] Resistance to antibiotics is no longer confined to organisms seen in the hospital setting and is increasingly identified in outpatient populations, urban poor, day-care centres, and in people with no known risk factors for acquiring resistant bacteria.[3–6]

In recent years, there has been a proliferation of household products containing antibacterial agents such as triclosan used for cleaning and disinfection within the home environment.[7,8] Concern over the use of cleaning and hygiene products containing triclosan (2,4,4'-trichloro-2'-hydroxyphenyl ether) has been raised since it has been suggested that these products may contribute to resistance.[9–12] Triclosan has been seen to have mechanisms for killing bacteria similar to those of some systemic antibiotics, and when bacteria are exposed to triclosan in vitro, mechanisms can be elicited that can confer resistance to antibiotics used to treat human disease.[13–19] These findings have led researchers to question whether widespread use of antibacterials could lead to a proliferation of antibacterial-resistant organisms and result in cross-resistance to one or more antibiotics in the home environment.[9–12] Here we review the burden of antibiotic resistance within the community setting and the known risk factors for infection and carriage of antibiotic-resistant bacteria, and assess the potential role that antibacterial cleaning and hygiene products containing triclosan may have in the emergence of antibiotic-resistant organisms within the community. Finally, recommendations for future research regarding the assessment of household

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cleaning and hygiene products containing triclosan will be discussed in the light of current research findings.

The public-health burden of antibiotic resistance

There are two important public-health concerns surrounding infection with an antibiotic-resistant organism. First, infection with a resistant organism may cause a delay in treatment because it can take hours or even days to ascertain the resistance pattern of the infecting organism.[20] Second, infection with antibiotic-resistant organisms leads to treatment failure and can therefore increase transmission potential since the resistant organism is able to thrive and survive within the host for a longer period.[20,21]

Antibiotic resistance within the community setting is becoming an increasing threat to public health. Examples of antibiotic-resistant bacteria that have been associated with increased morbidity and mortality in the community setting include: shigella, salmonella, community-acquired meticillin-resistant *Staphylococcus aureus* (caMRSA), and pneumococci.[1,20,22,23] Since infections with antibiotic-resistant bacteria have been typically confined to the hospital environment, the clinician treating community-onset infections may be less likely to question whether the organism is resistant to the usual therapeutic antibiotics. Recently, the *Global Strategy for Containment of Antimicrobial Resistance*, a report written by the WHO, concluded that high priority should be given to interventions in the general community that can eliminate risk factors for resistance, such as misuse of antibiotic agents.[22]

Known risk factors for the emergence of antibiotic resistance in the community

The primary routes by which an individual may become colonised and subsequently infected with an antibiotic-resistant organism in the community setting include person-to-person transmission of the bacteria and selective pressures from direct exposure to antibiotics (figure). For both of these routes there are established or known risk factors, such as attending day-care centres or other crowded settings, antibiotic use, and consumption of food products treated with antibiotics.

Person-to-person transmission

Child-care centres/crowded living conditions.

There is increased risk for the transmission of antibiotic-resistant organisms in crowded environments, a problem that is best illustrated in child-care centres. For example, the presence of antibiotic-resistant *Streptococcus pneumoniae* in day-care centres has been reported worldwide.[24–29] The use of broad-spectrum antibiotics among susceptible day-care age children as therapy for infections and treatment for recurring infections contributes to the presence and transmission of antibiotic-resistant bacteria within the day-care environment.[1] In addition, MRSA has been isolated from children in day-care centres with no known contact to health-care settings and with no MRSA carriers in the home.[3] Children attending day-care centres may carry resistant organisms into the home environment, facilitating transmission to other susceptible family members.[30] Antibiotic resistance in military settings has also been characterised.[31–33] For example, a high prevalence of pencillin-resistant pnuemococci has been reported among military populations in Washington DC, USA.[33]

Contacts within the household setting

Studies have shown that antibiotic use by one member of a household may lead to the transmission of, and colonisation with, a resistant organism in other members.[34–36] In 1997, a nurse colonised with MRSA caused wide-scale contamination of her home environment and subsequent transmission to two family members. Cleaning and disinfection of the home inhibited further carriage.[37] Transmission of vancomycin-resistant *Enterococcus faecium* (VRE) from health-care workers to their household members has also been shown.[38] An identical pulsed field gel electrophoresis fingerprint of a VRE strain was found in an isolate taken from one health-care worker and household member isolates.[38]

In one study, a significant risk factor for carrying a resistant strain was antibiotic use by the study participant or antibiotic use by people within the participant's household (odds ratio=2·0; 95% CI 1·3–3·2).[34] Another study investigating antibiotic therapy for acne reported that a significantly greater number of household members (parents, siblings, or partners of the antibiotic user) versus controls (no known contact with antibiotic user) carried resistant strains of bacteria ($p < 0{\cdot}05$).[36]

Direct exposure to antibiotics

Outpatient antibiotic use

Antibiotic use has been established as a risk factor for carrying a resistant organism by both individual and ecological study designs. In a study among the urban poor, individuals reporting antibiotic use in the past 12 months were significantly more likely to be colonised with MRSA.[4] By contrast, prior antibiotic use was not associated with carriage of MRSA versus meticillin-susceptible *S aureus* (MSSA) in an American Indian community.[39] In a study among college-age women attending an emergency clinic, current use of any antibiotic and/or use of trimethoprim-sulfamethoxazole (co-trimoxazole) was significantly associated with resistance of urinary coliform isolates.[40] In an ecological study in Sweden, high use of antibiotics in geographically defined areas was significantly correlated with frequency of penicillin-resistant pneumococci isolated from children under 7 years old living in those areas,[41] and in a study in Iceland, antibiotic consumption by geographic area and individual use of antibiotics were significantly associated with carriage of resistant strains of pneumococci.[42]

Use and consumption of animal products

In the USA, most food animals receive antibiotics in either feed, water, or parenterally.[43] Antibiotics used in agriculture are often the same or similar to antibiotic compounds used clinically.[43] For example, there has been an increase in

fluoroquinolone-resistant *Campylobacter jejuni* in both human beings and poultry meat.[44,45] Helms et al[23] reported a 10·3-fold higher rate of death in individuals colonised with the zoonotic strain of quinolone-resistant *Salmonella typhimurium*. Before use in food animals, fluoroquinolone-resistant strains were rarely isolated from people who reported no prior exposure to fluoroquinolones.[22,46] An intensive review of published material by committee members of FAAIR (Facts About Antimicrobials in Animals and Impact on Resistance) concluded that antibiotic use in food animals may have a significant effect on the development of antibiotic resistance.[2] FAAIR has recommended that antibiotics be prescribed by a veterinarian and used in food animals solely as therapy for disease, and that surveillance programmes be implemented to monitor antibiotic use in agriculture.

Infection and carriage of antibiotic-resistant organisms without known risk factors

Of major concern is the recent appearance of infections with MRSA in people in the community setting who lack traditional risk factors.[3,47,48] A review by Salgado et al[49] reported that for a majority of the caMRSA studies among hospital patients, a case was defined as community-acquired if an MRSA-positive isolate was identified within 48 h of hospital admission, with or without other risk factors for MRSA. Since there are several health-care-related risk factors for carrying MRSA in the community setting, it is important to ascertain a wide array of the known health-care-related risk factors to define a case as truly community-acquired. Some studies have sampled directly from the community to assess the prevalence of MRSA carriage while gathering data on past exposure to known risk factors. Of the six community-based studies that collected information on both prior antibiotic use and recent hospitalisation/outpatient visits as well as other risk factors, four reported MRSA colonisation among individuals without such risk factors.[4–6,50–52] It is important to note that only two studies examined contact with health-care personnel or individuals within the home colonised with MRSA.[5,6] Hussain et al[5] examined an extensive list of potential risk factors including contacts among children aged less than 1 month to 16 years presenting to an outpatient facility in Chicago. In this study, they identified three of 122 (2·5%) children lacking known risk factors who were positive for MRSA.

Some of the MRSA strains seen in the community show a unique pattern of antimicrobial susceptibility that differs from patterns seen in the hospital environment.[47,53,54] For example, MRSA strains isolated from the community setting have been reported to be susceptible to various non-β-lactam antibiotics.[6,55] Novel clonal differences in *S aureus* strains isolated from the community setting have been identified.[56–58] Unlike the hospital-acquired isolates, resistance genes other than the *mecA* were absent on a newly identified staphylococcal cassette chromosome (SCC*mec*-type IV), suggesting that this novel genetic type of MRSA isolated from the community has evolved independently of a hospital strain and may have arisen de novo within the community setting.[56–59] Further research is needed to examine factors originating from the community setting that may have an impact on antibiotic resistance. The use of antibacterial cleaning and hygiene products has also been suggested as one potential risk factor for carriage and spread of antibiotic resistance within the community setting (figure).

Potential risk from antibacterial cleaning and hygiene products: changes in the susceptibility of microbial flora?

To assess the risk from antibacterial cleaning and hygiene products, it is important to ascertain the baseline prevalence of antibiotic resistance within the home environment. One small survey[60] of antibiotic resistance in flora isolated from kitchens and bathrooms of 25 households has been reported. There were no isolates of MRSA (n=51 MSSA) and four of 58 (6·9%) enterococcal isolates were resistant to vancomycin. Most (94%) *Escherichia coli* isolates were susceptible to ten antibiotics tested. Similarly, other Gram-negative species were generally susceptible to most antibiotics tested. This study, however, did not report the types or specific duration of antibacterial cleaning and hygiene products used within the home. Since pathogenic microorganisms can survive within the home environment and have the ability to cause cross-contamination,[61] the levels, sources, and routes of transmission of antibiotic resistance within the household should be more thoroughly examined.

Molecular mechanisms of antibacterial cleaning and hygiene products

Although antibiotic use is one of the factors that affects rates of resistance in the hospital and community, antibacterial cleaning and hygiene products can also exert pressure on organisms to develop resistance. Antibiotics act at a specific target within the bacterial cell.[62] Until recently it was thought that most antibacterial agents used in cleaning and hygiene products used multiple targets for both degrading and inhibiting bacteria.[62] For example, products containing alcohols are non-specific and have been used for decades without any concerns of resistance. Although the bactericidal activity of triclosan involves some non-specific mechanisms, recent research has shown that triclosan inhibits bacteria via a specific bacterial target known as the NADH-dependent enoyl-acyl carrier protein (ACP) reductase (Fab 1 enzyme) in *E coli, Pseudomonas aeruginosa,* and *S aureus* or its homologue, the *InhA* gene, in *Mycobacterium smegmatis* and *Mycobacterium tuberculosis.*[13,14,16–18,63–65] Hence, for triclosan, the multiple-target theory is no longer tenable.[14,66] By targeting a specific bacterial site, triclosan inhibits the bacterial fatty acid biosynthetic pathway similar to the mode of some antibiotics and may, therefore, confer cross-resistance. Moreover, triclosan acts as a substrate for a multidrug efflux pump in *E coli* and in *P aeruginosa.*[18,67] This research is important since these findings were the first suggestion that triclosan may confer cross-resistance to clinically relevant antibiotics. Therefore, this discussion focuses primarily on triclosan

because of the shared mechanisms of antibiotic resistance and because triclosan is widely used in the community as an ingredient in antibacterial cleaning and hygiene products.[9,10,18,19,68,69]

Triclosan was first patented as a herbicide.[7] It is a non-ionic, broad-spectrum antimicrobial with limited antiviral and antifungal properties.[8] Triclosan has been used in personal hygiene products such as soap and underarm deodorant in the USA since the 1960s and was first used in the clinical environment as an ingredient in surgical scrubs in 1972.[8] In addition, triclosan has been used in various consumer products, such as dishwashing detergent and liquid hand soaps as well as being imbedded in products such as cutting boards, toys, and chopsticks.[7,10] In a recent study of 23 US national chain stores and groceries, 76% of 395 liquid soaps and 29% of 733 bar soaps (45% of all household soaps) contained antibacterial agents.[69] Most liquid soaps contained triclosan while the bar soaps predominantly contained triclocarban. Triclosan was one of the most frequently detected pharmaceutical contaminants isolated from samples of 139 rivers in the USA and has also been found in human breast milk.[70,71]

Association between resistance to antibacterial cleaning and hygiene products and resistance to antibiotics

Laboratory-based studies have shown that bacteria with low susceptibility to triclosan can foster cross-resistance to antibiotics[16–19] and recently several researchers have suggested a potential molecular-level link between reduced susceptibility to triclosan and antibiotic resistance.[10,18,19,72,73] Chuanchuen et al[18,19] showed that triclosan is a substrate for multidrug efflux pumps and allows selection of pump mutations. Exposure of susceptible *P aeruginosa* (lacking *mexAB-oprM*) to triclosan resulted in the selection of multidrug-resistant strains, including resistance to clinically relevant antibiotics.[18,19] For example, the minimum inhibitory concentration (MIC) for ciprofloxacin was increased 94-fold after exposure to triclosan.[18] In addition, a mutation in the *InhA* gene leads to reduced susceptibility to triclosan in *M tuberculosis* and also causes cross-resistance to the antitubercular treatment isoniazid, which happens to share the same bacterial target as triclosan.[16,17]

Although the potential for cross-resistance is limited since the target for triclosan (enoyl ACP reductase Fab 1 gene) is not shared with clinically relevant antibiotics besides isoniazid, there is still the potential for transferring reduced susceptibility of triclosan because this target is shared among various bacterial species such as *S aureus* and *E coli*. In addition, by acting as a substrate for specific efflux pumps in *P aeruginosa*, triclosan can confer cross-resistance to clinically relevant antibiotics.[18] In turn, efflux pumps may be transferred to other susceptible species or foster proliferation of *P aeruginosa* and related species in the presence of triclosan.[74]

The association between resistance to triclosan and antibiotics within species of bacteria has been investigated primarily within the hospital environment. A study by Cookson et al[75] showed that isolates of MRSA with low levels of triclosan resistance (MIC 2–4 mg/L) from patients who had received daily triclosan baths were also resistant to the antibiotic mupirocin via plasmid-mediated transfer. A more recent study could not confirm these findings.[12] Bamber and Neal[76] reported that in 186 linical specimens of *S aureus,* 14 (7·5%) had high triclosan MICs (one or greater parts per million; ppm), and five (2·7%) showed very high MICs (greater than 4 ppm). However, there were no significant differences in the triclosan MICs between MRSA and MSSA.[76] Suller and Russell[12] examined 33 clinical isolates of *S aureus* and showed that several strains exhibited low rates of resistance to triclosan (as characterised by high MICs) and were also resistant to several antibiotics. However, this association was not consistent since a few strains were resistant to several antibiotics but were more susceptible to triclosan—ie, had low MICs. Despite these correlational studies, there is no evidence to date that the acquisition of the resistance determinant for MSSA is mediated or facilitated by use of triclosan.

A few studies have examined the effects of triclosan-containing toothpaste on the microflora of the mouth in relation to antibiotic susceptibility.[77,78] A double-blinded randomised trial by Walker et al[78] compared a 0·3% triclosan-containing toothpaste with a control toothpaste over a 6 month period among 144 participants. This study reported no significant changes in the antibiotic susceptibility of the microflora at the end of the trial.[78] A study by Sullivan et al[77] examined changes in the microflora of the mouths of nine patients using a 0·3% triclosan-containing toothpaste over a 2-week period. They reported no difference in the antibiotic susceptibility of streptococcal strains over the study period. Although there are only a few studies examining the link between antibiotic resistance and the use of toothpaste that contains triclosan, there is a review of several studies that examine triclosan MICs of the microflora from individuals who used triclosan-containing toothpaste.[79]

Besides the antibacterial agent triclosan, Moken et al[80] showed that *E coli* isolates resistant to household products containing pine oil were also resistant to various antibiotics such as tetracycline, ampicillin, and chloramphenicol. More recently, pine-oil-cleaner-resistant *S aureus* mutants also showed reduced susceptibility to oxacillin and vancomycin.[81] Gram-negative bacteria seen on the chlorhexidine soap dispensers in a New York hospital were resistant to both chlorhexidine and up to 15 different antibiotics.[82] In addition, one study has shown an inverse correlation with intensity of chlorhexidine use and antimicrobial susceptibility of *S aureus*, *Klebsiella pneumoniae*, *P aeruginosa*, *Acinetobacter baumannii,* and *Candida albicans*.[83] MRSA isolates with decreased susceptibility to benzalkonium chloride have also been shown to be resistant to β-lactam antibiotics.[72] Levy[9] noted that exclusive resistance to β-lactam antibiotics among MRSA isolates with decreased susceptibility to benzalkonium chloride matches the susceptibility pattern of the MRSA SCC*mec*-type IV isolates found within the community setting. He suggested that use of benzalkonium chloride may be a contributing factor in the emergence of these community type strains of MRSA.

Russell et al[84] reported that *Pseudomonas stutzeri* adapted to the antiseptic chlorhexidine demonstrated cross-resistance with quarternary ammonium compounds. Loughlin et al[85] showed that *P aeruginosa* cells adapted to benzalkonium chloride exhibited resistance to chloramphenicol and tobramycin but there was no increased resistance to chlorhexidine, triclosan, or the antibiotics ceftazidime, imipenem, and ciprofloxacin. In a study measuring resistance to biocides among antibiotic-resistant hospital bacteria, one of five antibiotic-resistant strains of *K pneumoniae* was also significantly more resistant to a quarternary ammonium compound at its commonly used dilution.[86]

Recommendations

Although there has been recent growth in the use of products—such as soaps and hand lotions—that contain antibacterial ingredients, there are no guidelines or recommendations regarding the use of home hygiene products from any of the major US federal agencies, such as the Environmental Protection Agency, the Centers for Disease Control and Prevention, or Food and Drug Administration (FDA). The American Medical Association (AMA) has recently published a statement with respect to the use of antibacterials within the home environment, which advocates regulation by the FDA for antimicrobials where research has suggested a potential pathway for acquired resistance. The AMA has also called for the removal of antibacterial ingredients in hygiene and cleaning products where mechanism of antibiotic resistance have been characterised.[87]

Although the widespread use of antibiotics probably represents the primary contributing factor to antibiotic resistance, it is clearly not the only explanation. Hence, new factors should be examined, including the use of antibacterial cleaning and hygiene products within the home. Until the potential role of triclosan (and other antibacterial ingredients) in the emergence of antibiotic resistance is better understood, the public has several options. First, individuals can continue to use available antibacterial products for personal hygiene and cleaning.

Search strategy and selection criteria

The Pubmed database was searched and English language studies only were included. Search terms for this review included: "antibiotic resistance", "antimicrobial resistance", "hospital", "day care", "military", "agriculture", "community acquired resistance", "antibacterial", "cleaning", "hygiene", and "triclosan".

Second, use can be limited to products with no known mechanisms for potential transfer of resistance. Third, specific indications within the household could dictate use—eg, antibacterial products may be used when a household member is ill or immunocompromised, or to prevent skin infection. Last, individuals can opt to omit the use of all types of antibacterial products. This last option seems inappropriate and perhaps foolhardy because of the strong temporal association between improved hygiene and health in the developed world and the overwhelming evidence that hygiene practices reduce infections in developing nations.[88]

Nevertheless, the mandate to the scientific and manufacturing communities is clear. The emergence of antibiotic resistance among individuals without known risk factors means that other contributing factors are yet to be identified. Because antibacterial hygiene and cleaning products have been used in most households in the USA for several decades, they warrant examination as an additional possible risk factor. An important next step is to educate the consumer so that there is a clear understanding of the delineation between hygiene and cleaning products containing ingredients that may contribute to antibiotic resistance versus broad-spectrum hygiene and cleaning products that have not been linked to antibiotic resistance. With this information the consumer public can make an informed decision regarding the use of these products within the home.

Conflicts of interest

Neither author has any financial or other conflicts of interest in relation to this review.

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