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Review

Biocide-tolerance and antibiotic-resistance in community environments and risk of direct transfers to humans: Unintended consequences of community-wide surface disinfecting during COVID-19?☆

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ABSTRACT

During the current pandemic, chemical disinfectants are ubiquitously and routinely used in community environments, especially on common touch surfaces in public settings, as a means of controlling the virus spread. An underappreciated risk in current regulatory guidelines and scholarly discussions, however, is that the persisting input of chemical disinfectants can exacerbate the growth of biocide-tolerant and antibiotic-resistant bacteria on those surfaces and allow their direct transfers to humans. For COVID-19, the most commonly used disinfecting agents are quaternary ammonium compounds, hydrogen peroxide, sodium hypochlorite, and ethanol, which account for two-thirds of the active ingredients in current EPA-approved disinfectant products for the novel coronavirus. Tolerance to each of these compounds, which can be either intrinsic or acquired, has been observed on various bacterial pathogens. Of those, mutations and horizontal gene transfer, upregulation of efflux pumps, membrane alteration, and biofilm formation are the common mechanisms conferring biocide tolerance in bacteria. Further, the linkage between disinfectant use and antibiotic resistance was suggested in laboratory and real-life settings. Evidence showed that substantial bacterial transfers to hands could effectuate from short contacts with surrounding surfaces and further from fingers to lips. While current literature on disinfectant-induced antimicrobial resistance predominantly focuses on municipal wastes and the natural environments, in reality the community and public settings are most severely impacted by intensive and regular chemical disinfecting during COVID-19 and, due to their proximity to humans, biocide-tolerant and antibiotic-resistant bacteria emerged in these environments may pose risks of direct transfers to humans, particularly in densely populated urban communities. Here we highlight these risk factors by reviewing the most pertinent and up-to-date evidence, and provide several feasible strategies to mitigate these risks in the scenario of a prolonging pandemic.

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1. Introduction

Since the first reported outbreak in December 2019, the coronavirus disease 2019 (COVID-19) pandemic has caused over 100 million confirmed infections, including more than two million deaths around the globe (WHO, 2021). Contact with virus-contaminated surfaces, or fomites, has been recognized as an effective route of community spread of the novel coronavirus (CDC, 2020; WHO, 2020a). As vaccine doses are being administered to the wider population (Dai et al., 2020; WHO, 2021), infection control and prevention strategies remain in place in most countries. One effective measure to contain the virus spread is to use disinfectants to destroy viral pathogens that are present on common touch surfaces. Public guidelines issued by the World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC) recommend regular cleaning and disinfecting on high touch surfaces in homes and public places by spraying and wiping with disinfectants (CDC, 2021; WHO, 2020b). The U.S. Environmental Protection Agency publishes a list of approved disinfectant

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products for containment of COVID-19 with regular updates (EPA, 2021). Of the 535 products listed, the most commonly used active ingredients are quaternary ammonium compounds (QACs, a group of chemically similar substances), hydrogen peroxide (H_2O_2), sodium hypochlorite (NaClO), and ethyl alcohol (ethanol) (EPA, 2021). In total, the four biocidal agents represent two-thirds of the active ingredients used in current EPA-approved disinfectant products for COVID-19.

Global sales of surface disinfectants totaled $4.5 billion in 2020, representing a dramatic increase (>30%) over the previous year (Lewis, 2021). The intensive and indiscriminate use of chemical disinfectants raised concerns on their potential adverse ecological effects. In a recent discussion, Nabi et al. (2020) pointed out that the massive use of toxic and corrosive disinfectants in outdoor urban environments threatened urban wildlife. Zhang et al. (2020) argued that some disinfectants would end up in aquatic environments and pose acute risks to aquatic biota. Similar views were held by Chu et al. (2020) that the overuse of chlorine-based disinfectants could impair water quality and threaten ecology and human health. Singh (2020) further postulated that the injudicious use of disinfectants and sanitizers could accelerate the emergence of antimicrobial resistance in natural environments, after their eventual discharge or disposal.

Concerning antimicrobial resistance, much of the discussion in recent literature has revolved around the prevalent use and sometimes misuse of antibiotics in the current pandemic (Anonymous, 2020; Bengoechea and Bamford, 2020; Hsu, 2020; Reardon, 2020). Given the fact that patients diagnosed with COVID-19 are often prescribed with antibiotics for treating bacterial co-infections, some warned that excessive use of antibiotics – sometimes even on patients showing no symptom of bacterial infection – can exacerbate the emergence of antibiotic resistance (Anonymous, 2020; Bengoechea and Bamford, 2020; Clancy and Nguyen, 2020; Hsu, 2020; Usman et al., 2020; Yam, 2020). A widely overlooked risk, however, lies in the fact that massive loads of chemical disinfectants are being used on a routine basis in community settings, including many public places with high user occupancy or foot traffic, to reduce the virus spread or as a precautionary measure. In areas with persisting spread of COVID-19, such practices have been put in place for months with no ending yet in sight (CDC, 2021). In this context, antimicrobial resistance emerged from regularly disinfected surfaces and environments in those immediate surroundings may become a realistic risk which has been barely addressed in current regulatory guidelines or scholarly discussions revolving around COVID-19. In this domain, the limited information published to date predominantly focuses on the discharges (*e.g.*, via runoffs) of chemical disinfectants and the induction of antimicrobial resistance in the receiving environments, such as in municipal wastewater, surface water, and soils (Hora et al., 2020; Murray, 2020; Usman et al., 2020). In reality, community-related environments have much closer links with humans, where antimicrobial resistant pathogens emerged under current circumstances could pose risks of direct transfers to humans via contacting surfaces, touching objects, or similar activities. Such risks are not of a speculative nature: ample evidence showed that when exposed to those commonly used biocidal agents, many types of bacterial pathogens could develop increased tolerance and through similar mechanisms, acquire resistance to antibiotics (Russell, 1999). In July 2020, a group of scientists at WHO proposed that the short- and long-term impact of the widespread use of biocides for environmental and personal disinfection, including resistance to antimicrobials, should be included in the current research agenda (Getahun et al., 2020).

The use of chemical agents can radically change the microenvironment the bacteria living in. By exerting constant selective pressures, biocidal agents promote bacterial tolerance over time, especially on those high touch surfaces in public settings where cleaning and disinfecting are routinely performed under the current regulatory guidelines (CDC, 2021; Mc Carlie et al., 2020; WHO, 2020b). Along with their intensive and regular uses during COVID-19, such risks may culminate to unprecedented levels and persist as the current pandemic continues. The frequent and complex interactions between people and their immediate surroundings mean that antimicrobial resistant bacterial pathogens emerged in these settings could pose direct risks to humans, especially in densely populated urban communities.

As the current pandemic passes over the twelve-month mark since the first report to the WHO, and the spread of the virus and new variants continue with the slow vaccine rollouts, fresh concerns have been raised over the widespread and regular use of chemical disinfectants in public spaces and community environments. On January 29, 2021, *Nature* published a feature article where the author combed through existing evidence on fomite transmission of COVID-19 and raised questions over the cleaning and disinfection protocols that have been widely put in place in response to COVID-19 (Lewis, 2021). On the same day, two Australian scientists published a letter in *Science* expressing concerns over the surging use of antimicrobials including disinfectants, sanitizers, and antiseptics during COVID-19, and warned on the potential of disinfectant-facilitated bacterial acquisition of antimicrobial resistance, a widely acknowledged environmental and public health risk (Lu and Guo, 2021). Building on the recent scholarly discussions (Hora et al., 2020; Murray, 2020; Nabi et al., 2020; Usman et al., 2020), this article aims to present the first comprehensive view on this issue in the current literature context, by focusing on the main biocidal active compounds in disinfectant products approved for COVID-19. To this end, we surveyed the active ingredients in disinfectant products currently approved for COVID-19 and the common mechanisms promoting tolerance to biocides in bacteria and resistance to certain antibiotics. By scrutinizing the up-to-date evidence and scholarly discussions, we highlight the risks of exacerbated emergence of biocide-tolerant and drug-resistant bacteria by current practices of regular community-wide chemical disinfecting as well as potential transfers of antimicrobial resistant bacterial pathogens to humans. We also propose feasible strategies to mitigate these risks in the current pandemic and possibly in the post-pandemic era, as such practices may continue as a precautionary measure before the eradication of COVID-19.

2. Biocidal agents in COVID-19 disinfectants and increased tolerance in bacteria

As of March 3, 2021, there are 535 EPA-approved chemical disinfectant products for COVID-19 disinfection (EPA, 2021). Despite the large varieties of products offered to consumers, the majority of these products rely on several biocidal active compounds (*i.e.*, biocidal agents) as active ingredients for COVID-19 disinfection. Of those, the most commonly used biocidal agents are a group of structurally similar quaternary ammonium compounds (QACs), hydrogen peroxide (H_2O_2), sodium hypochlorite (NaClO), and ethyl alcohol (ethanol). Altogether, the four groups of biocidal agents account for two-thirds of the active ingredients found in current EPA-approved disinfectants (Fig. 1). Nearly 81% of the disinfectant products ($n = 431$) use only one biocidal agent, while the rest of them use two ($n = 90$) or more ($n = 14$) in their formulation.

The lack of diversity of active ingredients used in these products increases the likelihood of exposing bacteria to the same type of biocidal agents over and over again on a regular basis, under the

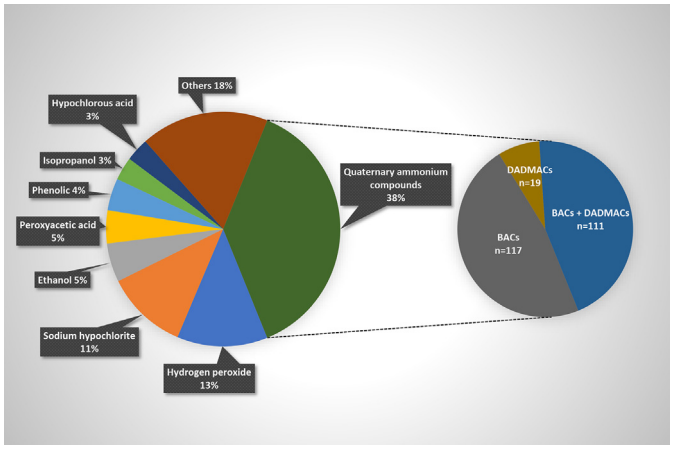

Fig. 1. Active ingredients in EPA-approved disinfectants for COVID-19. As of March 3, 2021, a total of 535 products are listed, with 34 biocidal active compounds contained within. Quaternary ammonium compounds (QACs) were found in 247 products, hydrogen peroxide in 82 products, sodium hypochlorite in 74 products, and ethyl alcohol in 35 products. Other common active ingredients include peroxyacetic acid (30), phenolic (29), isopropanol (21), and hypochlorous acid (21). Most of these approved products contain only one active ingredient ($n = 431$), and some products contain two ($n = 90$) or more ($n = 14$). A QAC product may contain one or several benzalkyl dimethyl ammonium compounds (BACs) and dialkyl dimethyl ammonium compounds (DADMACs), or a combination of both. Specifically, among the 247 QACs products approved, 117 contained only BACs, 19 contained only DADMACs, and 111 products contained both BACs and DADMACs. There are also 49 products containing QACs and other non-QAC biocidal active compound such as ethanol or isopropanol. All products are intended for use on surfaces (not humans). EPA expects them to kill the novel coronavirus (SARS-CoV-2) when used in accordance with their label directions. This list is regularly updated by the EPA (available at: https://cfpub.epa.gov/giwiz/disinfectants/index.cfm).

current practices of regular disinfecting of contact surfaces in community and public settings during COVID-19. QACs, which constitute the highest percentage of biocidal agents in EPA-approved disinfectant products for COVID-19 disinfection, contain a variety of structurally similar compounds. For instance, benzalkyl dimethylammonium compounds (BACs), the most widely used active ingredients in EPA-approved QAC disinfectant products, are benzalkyl dimethyl ammonium compounds (*i.e.*, first-generation QACs) or ethylbenzalkyl dimethyl ammonium compounds (*i.e.*, second-generation QACs) or a combination of both (*i.e.*, third-generation QACs). Dialkyldimethylammonium compounds (DADMACs) are predominantly dioctyl, octyl decyl, or didecyl dimethylammonium chloride or a combination of these, which are often considered as the fourth-generation QACs. Among the 247 QACs products currently approved for COVID-19 disinfection (as of March 3, 2021), 117 products contained only BACs, 19 contained only DADMACs, 111 contained both BACs and DADMACs, and 49 contained QACs with other non-QAC active ingredients such as ethanol or isopropanol (Fig. 1). The fourth-generation QACs (twin or dual-chain QACs) generally have superior antimicrobial performance than the former generations (Gerba, 2015). However, the antimicrobial effects of different QACs are similar, *e.g.*, adsorption and penetration of cell wall, reaction with cell membrane, degradation of proteins and nuclei acids, leakage of cellular content, which involve the positive charged quaternary nitrogen and N-alkyl chain (Buffet-Bataillon et al., 2012b; Gerba, 2015). As a result, bacteria could develop similar mechanisms to increase tolerance to different QACs. In general, if a microorganism is intrinsically tolerant to certain QACs or acquires such tolerance after exposure, it is likely to exhibit cross-tolerance to other QACs (Soumet et al., 2012; Tabata et al., 2003; Voumard et al., 2020).

It should be pointed out that even before the current pandemic, numerous studies had reported the occurrence of biocide-tolerant bacteria in food processing (Langsrud et al., 2003; Zhang et al., 2016), livestock and poultry farm (Bjorland et al., 2005; Long et al., 2016), healthcare (Gebel et al., 2002; Pidot et al., 2018), and domestic environments (Cooper et al., 2008). Many types of bacterial pathogens have shown the ability to adapt and develop increased tolerance to biocidal agents, including the four major active ingredients used in products listed by EPA for COVID-19. For instance, He et al. (2014) isolated bacteria samples from their local community environments, and found that 24% of the isolates ($n = 268$) collected from surfaces frequently disinfected by BAC-containing sprays or wipes showed tolerance to BAC (minimal inhibitory concentration (MIC) > 3 mg/L). In a recent review, Kampf (2018) conducted a systematic literature search to assess the adaptive potential of bacteria on low-level BAC exposure. Most of the reviewed bacterial species ($n = 57$) underwent a multi-fold increase in MIC after adaption. Among those, *Salmonella enterica* serovar Typhimurium showed the highest MIC to BAC (3000 mg/L), followed by *Pseudomonas aeruginosa* (2500 mg/L), *Enterobacter* spp. (1500 mg/L), *Escherichia coli* and *Staphylococcus saprophyticus* (1000 mg/L), which could exceed the BAC concentrations in practice use (Kampf, 2018). Chlorine-tolerant bacteria were often detected in drinking water or drinking water distribution systems. Five chlorine-tolerant bacteria, namely, *Legionella*, *Sphingomonas*, *Mycobacterium*, *Bacillus*, and *Pseudomonas* are most commonly reported in published literature (Luo et al., 2021). Notably, *Sphingomonas TS001*, a chlorine-tolerant bacterium, could withstand 4 mg/L sodium hypochlorite which showed only 5% reduction in viability after 240 min of exposure (Sun et al., 2013). Similar findings were reported on increased alcohol tolerance in healthcare settings. Pidot et al. (2018) tested the alcohol tolerance of *Enterococcus faecium* collected from hospitals, where the *Enterococcus faecium* isolates collected after 2010 were found to be ten-fold more tolerant to alcohol than were older (pre-2004) isolates. The study established a contaminated surface transmission model to assess the clinical relevance and demonstrated that even after disinfection with 70% isopropanol, alcohol-tolerant *Enterococcus faecium* could transmit to mice and colonize in their guts. In a follow-up study, Gebel et al. (2019) pointed out that Pidot et al. applied 0.85 mL isopropanol to cover a 450-cm^2 surface and thus may lead to inadequate surface disinfection. The authors showed that 60% or 70% isopropanol were sufficiently effective to inactivate alcohol-tolerant strain of *Enterococcus faecium* but 23% isopropanol was not. The study concluded that healthcare workers could be reassured that, when used at 60% or 70% (v/v) for the appropriate contact time and with a sufficient volume, isopropanol would be effective against *Enterococcus faecium*. Studies on hydrogen peroxide tolerance are relatively scant, although published data suggested that both group A *Streptococcus* and *Escherichia coli* could develop tolerance to it over a short period of exposure (Dukan and Touati, 1996; Henningham et al., 2015). In addition, other researchers have observed increased bacterial tolerance to phenolic compounds, peroxyacetic acid, isopropanol, and hypochlorous acid (Horinouchi et al., 2017; Nguyen and Yuk, 2013; Nontaleerak et al., 2020; Zou et al., 2019), all of which are used as common active ingredients in current EPA-approved disinfectant products for COVID-19 (Fig. 1).

3. Mechanisms conferring bacterial tolerance to biocidal agents

One of the difficulties in defining the adaptive behaviors of bacteria to biocidal agents is the terminology used in the existing literature. Currently, there is no clear and consensual definition of 'disinfectant resistance' and 'reduced susceptibility' or 'increased

tolerance' in scholarly literature (Cerf et al., 2010; Chapman, 2003a; Langsrud et al., 2003; Maillard, 2018; Maillard et al., 2013; Russell, 1999). A comprehensive definition was proposed earlier by Russell (1999) that bacteria which are (i) insusceptible to a concentration of disinfectant used in practice or (ii) not inactivated (or sometimes not inhibited) by a concentration that inactivates (or inhibits) the majority of strains of that organism are deemed to be in this category. Recently, some scholars argued that the concept of disinfectant resistance or tolerance should be clearer, namely, surviving bacteria after disinfection at recommended concentration should be termed as 'resistant' and bacteria with higher MIC should be termed as 'reduced susceptibility' or 'increased tolerance' (Cerf et al., 2010; Weber et al., 2019). In this article, we adopted the definition by Weber et al. (2019) to avoid ambiguity on terminology.

In general, the tolerance to biocidal agents in bacteria can be categorized as intrinsic and acquired. Intrinsic tolerance is a natural chromosomally controlled property which means that a bacterial species are less susceptible to certain biocides than other bacterial species and often manifests as a permeability barrier reducing the uptake of foreign substances (Ortega Morente et al., 2013; Russell, 1999; Sheldon, 2005). Bacterial spores have been considered as the most biocide-tolerant bacterial species, followed by mycobacteria, Gram-negative bacteria, and Gram-positive bacteria (Fig. 2). The coat or possible cortex of spore, the cell wall of mycobacteria, and the outer membrane of Gram-negative bacteria can confer increased tolerance to biocides, while Gram-positive bacteria is most susceptible (Ortega Morente et al., 2013; Russell, 1999; Sheldon, 2005). In addition, physiological (phenotypic) adaptions could confer intrinsic bacterial tolerance to biocides, and bacterial cells contained within a biofilm are more insusceptible to biocides than planktonic cells (Ortega Morente et al., 2013; Russell, 1999; Sheldon, 2005). Acquired tolerance, which can be effectuated by cellular genetic alterations or acquisition of exogenous mobile genetic elements carrying biocide-tolerant genes, is observed in certain strains of bacteria that are less susceptible to some antimicrobials compared with the average for this bacterial species (Mc Carlie et al., 2020). Specifically, genetic alterations such as mutations or differential gene expression can lead to increased tolerance under antimicrobial stress exerted by biocidal agents (Mc Carlie et al., 2020). Meanwhile, horizontal gene transfers allow mobile genetic elements carrying biocide-tolerant genes, such as plasmids and integrative and conjugative elements (ICEs), to move from the donor cell to the recipient cell (Partridge et al., 2018) (Fig. 3).

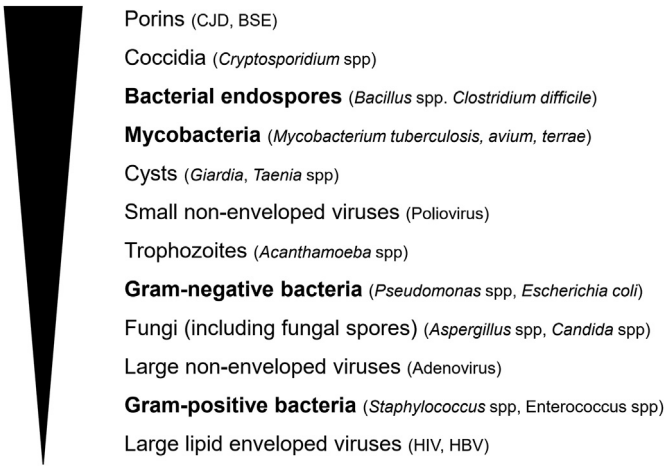

Fig. 2. Classification of microorganisms based on their tolerance of biocidal agents. Groups containing bacteria are highlighted in bold. Adapted with permission of Elsevier from Russell (1999).

3.1. Mutations and horizontal gene transfer

Bacterial mutations are random in nature but can also be driven by selective pressure exerted by antimicrobials (*e.g.*, disinfectants), which could contribute to the development of increased tolerance (Maillard, 2018; Mc Carlie et al., 2020). Kim et al. (2018a) described fixed mutations in the pmrB gene of *Pseudomonas aeruginosa* after continuous culture in the presence of BAC, which reduced the negative charges in the outer membranes and resulted in its increased tolerance to BAC. Horinouchi et al. (2017) exposed *Escherichia coli* to isopropanol (0−500 mM, in 50 mM steps) for adaptive laboratory evolution. The authors found that mutations of *relA*, *marC*, *proQ*, *yfgO*, and *rraA* conferred tolerance to isopropanol and several other alcohols (*e.g.*, ethanol, *n*-propanol, *n*-butanol). Furi et al. (2013) reported that mutations in the promoter region of *norA*, a major facilitator super (MFS) family transporter, resulted in increased expression and conferred increased tolerance to benzalkonium chloride and chlorhexidine.

Horizontal gene transfer is considered to be an important contributor in the development of increased biocide tolerance in bacteria (Mc Carlie et al., 2020). Bacteria can acquire mobile genetic elements (MGEs) bearing biocide-tolerance genes from other bacteria. Among them, insertion sequences, transposons, integrons, and gene cassettes are able to move between DNA molecules within a cell, while ICEs and plasmids could move between bacteria (Fig. 3). Insertion sequences (IS) are discrete DNA segments carrying more than one transposase (Tnp) genes. Two copies of the same or related insertion sequences could bind to both sides of a "passenger" gene to form a composite transposon (Tn) (Mc Carlie et al., 2020; Partridge et al., 2018). Unit transposon is much different to composite transposon, which was bounded by a pair of inverted repeats (IR) rather than insertion sequences, carrying a transposase gene and "passenger" genes (Mc Carlie et al., 2020; Partridge et al., 2018). Insertion sequences and transposon carrying "passenger" genes (*e.g.*, biocide-tolerant genes) can randomly translocate to different locations on the same or other DNA molecules (Mc Carlie et al., 2020; Partridge et al., 2018). Gene cassettes typically contain one promoter-less gene and an *attC* recombination site, which are captured by a lager genetic unit integron (Hall, 2012; Partridge et al., 2009). Integrons are defined as an *attI* recombination site, a promoter (Pc), and an *intI* gene which mediate the insertion and excision of gene cassettes (Hall, 2012). Plasmids are circular or linear extrachromosomal replicons which can carry other mobile genetic elements to transfer between bacteria by conjugation (Shintani et al., 2015). Also known as conjugative transposons, ICEs can integrate into host chromosome and replicate (Carraro and Burrus, 2015; Johnson and Grossman, 2015). Intercellular gene transfers include conjugation/mobilization (mediated by plasmids and ICEs), transformation (uptake of naked extracellular DNA fragments), and transduction (bacteriophages transfer chromosomal DNA and MGEs) (Partridge et al., 2018; von Wintersdorff et al., 2016). The acquisition and stockpiling of MGEs facilitate the rapid evolution of bacteria and accelerate the emergence of biocide tolerance (Mc Carlie et al., 2020). Kim et al. (2018a) reported ICE-mediated BAC tolerance in *Pseudomonas aeruginosa*, which encoded efflux pumps to extrude the biocide molecule. In another study, Elhanafi et al. (2010) found that the BAC tolerance of *Listeria monocytogenes* H7550 was associated with a gene cassette harbored on the plasmid of the strain, pLM80, which included two efflux pump genes (bcrB and bcrC) and a transcriptional regulator (bcrA) that controls the transcription of multidrug efflux systems. Norman et al. (2008) reported that the plasmid pOLA52 in *Escherichia coli* was able to express multidrug efflux

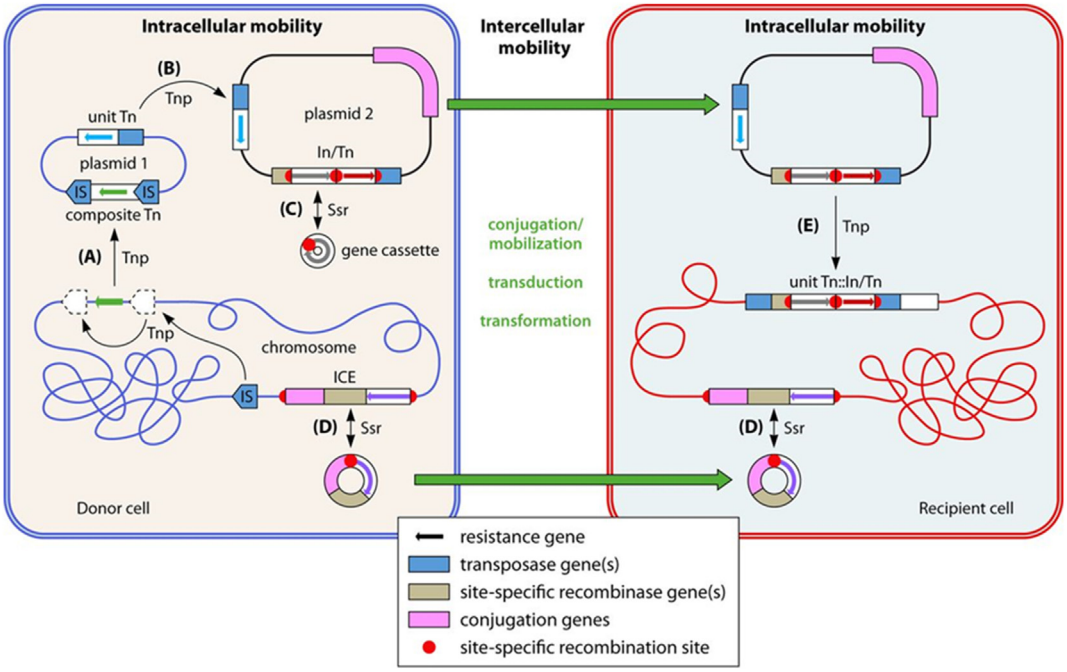

Fig. 3. Intra-cellular and inter-cellular mobility of mobile genetic elements containing resistance genes. Thin black arrow and thick green arrow represent intra-cellular processes and inter-cellular horizontal gene transfer, respectively. (A) A composite transposon bearing a resistance gene could transpose from the chromosome to a plasmid. (B) Transfer of unit transposon between plasmids within the cell. (C) A gene cassette can excise from or insert into an integron via a circular intermediate. (D) Excision of ICE from chromosome in donor cell (reversibly) to form a circular structure, which is capable of conjugative transfer to recipient cell and integrates into recipient chromosome by site-specific recombination. (E) Intercellular transfer of plasmid was mediated by conjugation or mobilization. In addition, it can be mediated by transformation or bacteriophage transduction. Reprint with permission of American Society for Microbiology from Partridge et al. (2018). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

pumps and enhanced its ability to form biofilms. Seier-Petersen et al. (2014) showed subinhibitory concentration (1/4) of ethanol exposure resulted in a five-fold increase in the conjugative transfer frequency of Tn*916* between different *Bacillus subtilis* strains.

3.2. Efflux pump

Efflux pump has been recognized as a major mechanism of biocide tolerance in many bacteria (Gnanadhas et al., 2013). Referred to as multidrug resistant (MDR) proteins, these transmembrane proteins can pump out a wide range of toxic substances, including biocidal agents, from bacterial cells (Buffet-Bataillon et al., 2012b; Poole, 2007). Five efflux pump families have been identified (Fig. 4), namely, the ATP-binding cassette (ABC) family, the major facilitator super (MFS) family, the multidrug and toxin extrusion (MATE) family, the small multidrug resistance (SMR) family, and the resistance-nodulation-cell division (RND) superfamily (Buffet-Bataillon et al., 2012b; Ortega Morente et al., 2013; Putman et al., 2000). Except for ABC family transporters which directly use ATP energy as the driving force, the other four transporter families are powered by the transmembrane H^+ or Na^+ gradient (Wand, 2017). In *Staphylococcus aureus*, chromosomally-encoded biocide efflux pumps include the MepA protein (MATE) and the NorA, NorB, MdeA, LmrS proteins (MFS), while plasmid-encoded biocide efflux pumps include the QacA, QacB proteins (MFS) and the Smr, QacG, QacH, QacJ proteins (SMR). Both the chromosomally-encoded and plasmid-encoded efflux pumps can confer tolerance to QACs in *Staphylococcus aureus* (Costa et al., 2013). These MDR efflux pumps could also extrude other unrelated compounds, including dyes (rhodamine, ethidium bromide) and antibiotics (ciprofloxacin, norfloxacin) (Costa et al., 2013). *Enterococcus faecalis* was found to express the biocide transporter

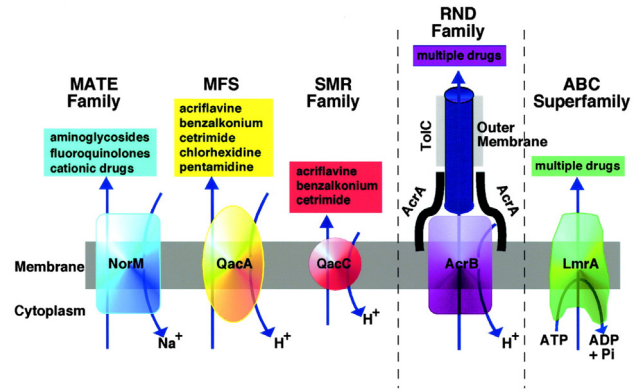

Fig. 4. Schematic of representatives of the five known efflux pump families. The MATE, MFS, SMR and RND families are powered by electrochemical energy (transmembrane ion gradients, *i.e.*, H^+ or Na^+). The ABC superfamily directly utilizes ATP as energy source to pump out disinfectant molecule from the cell. Reprint with permission of American Society for Microbiology from Piddock (2006).

QacA/B (MFS), in addition to QacEΔ1 (SMR) and EfrAB (ABC) (Bischoff et al., 2012; Kazama et al., 1998; Lee et al., 2003). Among the Gram-positive bacteria, the qacA/B (MFS) gene system has the most common QAC-tolerant genes, which are found on plasmids (Jennings et al., 2015). The qacA and qacB genes are closely related with only seven nucleotides being different, resulting in changes in only one amino acid (Paulsen et al., 1996). As a consequence, the QacA transporter utilizes acidic aspartic acid residue to confer tolerance to monovalent and divalent cations via proton motive force, while the QacB transporter with an uncharged residue (alanine) is more specifically tolerant to monovalent cations

(Jennings et al., 2015; Ortega Morente et al., 2013; Paulsen et al., 1996). Efflux pumps and their determinants of biocide tolerance are also widely distributed in Gram-negative bacteria (Poole, 2005). The biocide transporters in *Escherichia coli* include the YdhE, MdtK, NorM efflux pump (MATE), the MdfA, CmlA, CmlB, Cmr efflux pump (MFS), the EmrE, SugE efflux pump (SMR), and the AcrAB-TolC, MdtABC-TolC, MdtEF-TolC, CusCFBA efflux pump (RND) (Anes et al., 2015; Buffet-Bataillon et al., 2012b; Poole, 2005; Slipski et al., 2018). The presence of qacA (MFS), qacΔE, qacE (SMR), and acrA (encode precursor for AcrAB-TolC efflux pump, RND) in Carbapenem-resistant *Klebsiella pneumoniae* could accommodate common biocides including ethanol, chlorhexidine acetate, chlorine-containing '84' disinfectant, and benzalkonium bromide (Guo et al., 2015). In *Pseudomonas aeruginosa*, QacEΔ1, QacF, QacG (SMR) efflux pumps and PmpM (MATE) efflux pumps conferred tolerance to QACs, while MexAB-OprM, MexCD-OprJ, MexEF-OprN, MexJK (RND) efflux pumps conferred tolerance to triclosan (Chuanchuen et al., 2002, 2005; Poole, 2005; Wand, 2017). Recently, Kim et al. (2018a) showed that the increased expression of ICE-harbored efflux genes (*i.e.*, *sugE-A*, *sugE-B* [SMR], ABC transporter related genes, and an RND family member gene) and chromosomally-harbored *muxABC-opmB* genes (RND) are related to BAC tolerance (alkyl (60% C_{12}, 40% C_{14}) dimethyl benzyl ammonium chloride). In *Acinetobacter Baumannii*, biocide transporters included the AbeM efflux pump (MATE), the AdeF efflux pump (MFS), the AbeS efflux pumps (SMR), and the AdeABC, AdeIJK, AbuO efflux pumps (RND) (Wand, 2017).

The proteobacterial antimicrobial compound efflux (PACE) family, a new multidrug efflux pump family recently reported, was first discovered in *Acinetobacter baumannii* and hence named as *Acinetobacter* chlorhexidine efflux protein I (AceI) (Hassan et al., 2013, 2015). AceI transporter and its homologs widely existed in Gram-negative bacteria, such as *Acinetobacter baumannii*, *Vibrio parahaemolyticus*, *Acinetobacter baylyi*, *Pseudomonas aeruginosa*, *Pseudomonas protegens*, *Burkholderia cenocepacia*, *Klebsiella pneumoniae*, *Escherichia coli*, which were shown to confer bacterial tolerance to chlorhexidine, benzalkonium chloride, dequalinium, proflavine, and acriflavine (Hassan et al., 2013, 2015).

3.3. Membrane alteration

Membrane alteration, which includes variations in the composition and content of membrane proteins, fatty acids, and phospholipids, can confer bacterial tolerance to biocides (Maillard, 2018). The porin loss of *Salmonella enterica* serovar Typhimurium, *Acinetobacter baumannii*, and *Escherichia coli* reduce their cell membrane permeability and consequently increase their tolerance to biocides (Coldham et al., 2010; Fernandez-Cuenca et al., 2015; Forbes et al., 2019; Karatzas et al., 2008). Tabata et al. (2003) showed that OprR, an outer membrane protein in *Pseudomonas aeruginosa*, was correlated with BAC tolerance. The authors observed an increase level of OprR expression in BAC-tolerant *Pseudomonas aeruginosa* strains and recovered BAC susceptibility in the corresponding knockout mutant. Some studies showed that QACs induced specific variations in the membrane fatty acid composition of *Pseudomonas aeruginosa* (Guerin-Mechin et al., 1999; Mechin et al., 1999). With a hydrophobic long C-chain, the diffusion and penetration of QACs in cell are closely related to membrane lipids and lipopolysaccharides (Russell and Gould, 1988). Therefore, changes in membrane fatty acid composition could limit the adsorption and penetration of QACs and thus cause a progressive loss of bactericidal efficacy. Kim et al. (2018a) found that the reduction of oprG gene expression decreased OprG, a major outer membrane protein in *Pseudomonas aeruginosa* which mediates the diffusion of small hydrophobic molecules, and prevented the adsorption and penetration of BAC. The change of membrane potential could also result in decreased susceptibility to biocides in *Pseudomonas aeruginosa* (Maillard, 2018). In the study by Kim et al. (2018a), reduced negative charges in the outer membranes of *Pseudomonas aeruginosa* resulted in decreased sorption of positively charged BAC. When exposed to tetradecyltrimethylammonium (TDTMA), *Pseudomonas putida* exhibited a higher membrane negative charge due to increased phosphatidic acid and phosphatidylglycerol contents (Boeris et al., 2007). These phospholipids are the composition of released outer membrane vesicles and thus eliminate QACs molecules attached to the membrane by neutralizing the positive charges of ammonium quaternary moiety (Boeris et al., 2007; Marisa Heredia et al., 2016).

3.4. Biofilm

Biofilms can colonize virtually any biological or inanimate surface and have been identified in industrial, medical, and domestic settings (Hu et al., 2015; Kumar and Anand, 1998; Ledwoch et al., 2018; Rayner et al., 2004). It is established that bacteria within biofilms can endure higher concentration of biocides compared to the same bacteria growing planktonically in suspensions (Cooper and Hanlon, 2010; Kumar and Anand, 1998; Shen et al., 2017; Wong et al., 2010). Smith and Hunter (2008) grew biofilms of two nosocomial pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, on hospital environment-relevant materials and treated them with three hospital disinfectants, namely, BAC (1%), chlorhexidine gluconate (4%), and triclosan (1%). The results showed that these biocides were not effective to kill the bacteria within biofilms when used at their recommended concentrations. After the treatment, 0%–11% and 80% of viable cells were found in MRSA biofilms and *Pseudomonas aeruginosa* biofilms, respectively. For all three disinfectants, the minimum bactericidal concentrations (MBCs) of both organisms living in biofilms were found to be 10–1000 times higher than their planktonic counterparts (Smith and Hunter, 2008).

Biofilms can confer bacterial tolerance to disinfectants through a multitude of mechanisms including reduced diffusion, chemical interactions with biocidal active compounds, reduced growth rates, enhanced mutation and horizontal gene transfer (Bridier et al., 2011; Kumar and Anand, 1998). A characteristic feature of biofilms is their three-dimensional spatial structures consisting of multiple layers of bacteria and extracellular polymeric substances (Fig. 5), which can act as physical diffusion barriers, molecular sieves, adsorbents, and reactants to hamper biocide penetration and react with biocidal active compounds (Bridier et al., 2011; Kumar and Anand, 1998), potentially resulting in exposure to sublethal concentrations of biocides (Chapman, 2003b). Inside biofilms, competition for nutrients and limited access to oxygen result in slow growth and starving cells, which can also contribute to increased bacterial tolerance to biocides (Bridier et al., 2011; Ortega Morente et al., 2013). The slowly growing strains of *Mycobacterium avium* showed higher chlorine tolerance compared with rapidly growing strains (Taylor et al., 2000). Notably, starvation could stimulate the synthesis of glutathione and subsequently promote the chlorine tolerance of some bacteria (Saby et al., 1999). One study found that starving *Klebsiella pneumoniae* required up to 200-fold more chlorine to achieve same six-log number reductions compared with the well-fed cells (Stewart and Olson, 1992). Apart from these effects, biofilms can also promote biocide tolerance in bacteria via mutations or horizontal gene transfer (Conibear et al., 2009; Nguyen et al., 2010). Conibear et al. (2009) reported that *Pseudomonas aeruginosa* cells in biofilms exhibited at least 100-fold increase in mutation frequency compared to planktonic cultures. In an earlier study, Ehlers and Bouwer (1999) demonstrated that the

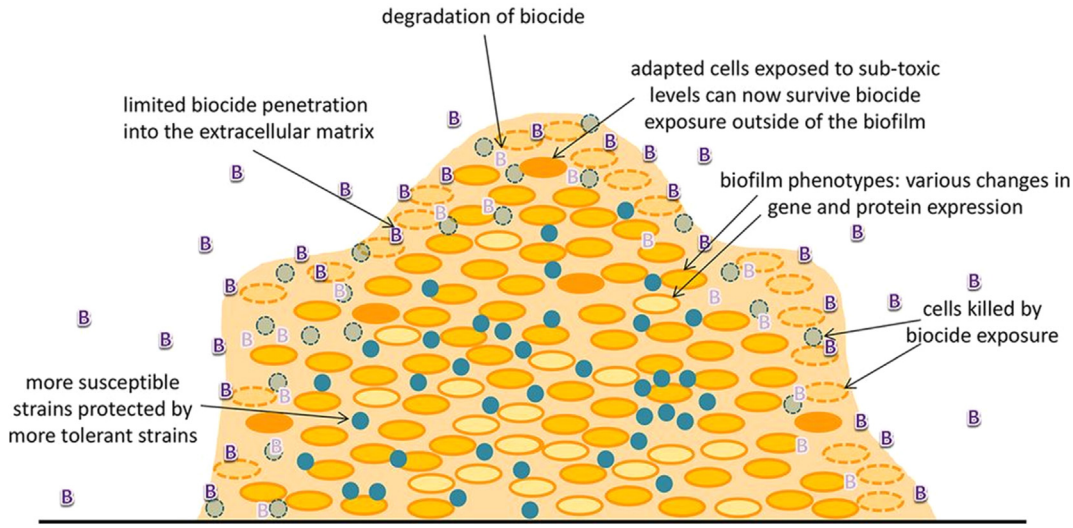

Fig. 5. The dense extracellular matrix of biofilms can degrade biocides and hamper their penetration, protecting the sensitive bacteria inside. In actual environments, some bacteria are exposed to subinhibitory concentrations of biocides. This kind of selective pressure can further increase the propensity to give rise to tolerant cells. Reprint with permission of the Royal College of Paediatrics and Child Health and BMJ from Bock (2019).

physical proximity of bacteria within biofilms could facilitate horizontal gene transfers. The authors reported that the conjugation frequencies between different species of *Pseudomonas* were 1000–50,000 times higher in biofilms compared with planktonic conditions.

3.5. Other mechanisms

Generally, it is unlikely for bacteria to develop tolerance to biocides by target alteration since most biocides have multiple target sites against bacteria. Production of specific enzymes to inactivate the biocide molecule is also uncommon in bacteria (Gilbert and McBain, 2003; Wand, 2017). Nonetheless, there have been some reports in these domains. The most well-known target alteration is the mutations in *fabI* gene which can confer increased tolerance to triclosan (Heath et al., 1999). In this particular case, the function mechanism of triclosan is to inhibit the activity of the enoyl-acyl carrier protein reductase (FabI) and thus prevent fatty acid synthesis (Heath et al., 1998). Mutations in *fabI* gene have been found in *Escherichia coli* (Heath et al., 1999), *Pseudomonas aeruginosa* (Hoang and Schweizer, 1999), *Staphylococcus aureus* (Heath et al., 2000), *Acinetobacter baumannii* (Chen et al., 2009), *Rhodobacter sphaeroides* (Lee et al., 2002), and *Staphylococcus epidermidis* (Skovgaard et al., 2013). Some bacteria are also found to inactivate biocide molecules at low concentrations by synthesizing specific enzymes. For instance, group A *Streptococcus* can synthesize enzymes such as NoxA and AphC oxidase to decompose hydrogen peroxide (Henningham et al., 2015). The presence of superoxide dismutase enzyme and catalase enzyme in *Escherichia coli* increased its tolerance to superoxide and hydrogen peroxide (Demple, 1996; Greenberg and Demple, 1989). Inactivation of phenols, aldehydes and QACs have also been reported in bacteria (Kummerle et al., 1996; Meade et al., 2001; Nishihara et al., 2000).

4. Antibiotic resistance in bacteria induced by exposure to biocidal agents

Inappropriate use of antibiotics has been recognized as the main cause of antibiotic resistance found in bacteria (Chokshi et al., 2019; Fair and Tor, 2014; Levy and Marshall, 2004; Michael et al., 2014; Ventola, 2015). Factors driving the increased drug resistance among pathogens principally acquired in healthcare settings include greater severity of illness in hospitalized patients, presence of more severely immunocompromised patients, increased introduction of resistant pathogens from the community, effective implementation of infection control and isolation practices and compliance, increased use of antimicrobial prophylaxis, increased use of empirical polymicrobial therapy, and a high rate of antimicrobial use per geographic area per unit time (Anonymous, 2021). Meanwhile, factors driving the increased resistance among pathogens principally acquired in the community settings include frequent and often overuse of antibiotics by both providers and patients, widespread use of antibiotics in agriculture and animal production, patient noncompliance with antibiotic therapy, prolonged survival of persons with chronic diseases and altered host defenses, and lack of research on new antibiotics (Anonymous, 2021). The main mechanisms conferring antibiotic resistance to bacteria include reducing the access to the target (*e.g.*, via efflux pump and impermeability), inactivation of antibiotics, and re-programing of its target structure (Blair et al., 2015; Walsh, 2000). In comparison, less attention has been drawn to the fact that exposure to disinfectants could also promote antibiotic resistance and give rise to multidrug resistant (MDR) bacteria (Buffet-Bataillon et al., 2012b; Kim et al., 2018b; Wand, 2017).

A substantial body of published literature has described the linkage between the use of chemical disinfectants and the growth of antibiotic resistance in some bacteria (Elekhnawy et al., 2020; Gilbert and McBain, 2003; Ortega Morente et al., 2013; Russell, 2003; Wand, 2017). Langsrud et al. (2004) observed cross-resistance to BAC and antibiotics in *Escherichia coli* after being exposed to subinhibitory concentrations of BAC. Specifically, enhanced efflux pumps were found to be responsible for the six-fold higher BAC MIC and ten-fold higher chloramphenicol MIC. Mc Cay et al. (2010) reported that after continuous enrichment culturing, *Pseudomonas aeruginosa* became 12 times more tolerant to BAC while at the same time, its resistance to ciprofloxacin increased by a remarkable 265 times – the latter was ascribed to mutations in gyrA. Kim et al. (2018b) elucidated the underlying mechanisms and showed that biocide tolerance genes and

antibiotic resistance genes (ARGs) were located in the same mobile genetic elements, and the mutations in *pmrB* and the upregulation of efflux pump genes contributed to the antibiotic resistance of *Pseudomonas aeruginosa* after being exposed to BACs. Tandukar et al. (2013) also explored the antimicrobial resistance of microbial communities after BAC exposure. The study found that such exposures not only selected BAC-tolerant species but concurrently increased their resistance to several clinically relevant antibiotics. Specifically, degradation and transformation were found to be the predominant mechanisms of their tolerance to BACs and resistance to penicillin G, while efflux pumps largely contributed to their resistance to tetracycline and ciprofloxacin. Similar effects were reported on chlorine-tolerant bacteria. Jin et al. (2020) elucidated the mechanisms of how chlorination promotes the horizontal transfer of ARGs. The study found that the disinfection process enhanced cell membrane permeability and the oxidative stress response of chlorine-tolerant injured bacteria, where competent cells showed a 550 times higher transformation frequency than untreated bacteria and could easily uptake the free ARGs from the ambient environment. In an earlier study, Zhang et al. (2017) found that exposure to subinhibitory concentrations of three commonly used biocidal agents (chlorine, chloramine, and H_2O_2) facilitated the conjugative transfer of ARGs between *Escherichia coli* and further from *Escherichia coli* to *Salmonella enterica* serovar Typhimurium via intracellular ROS formation, SOS response, increased cell membrane permeabilization, altered expressions or regulations of conjugation relevant genes. It is worth noting that exposure to biocidal agents can lead to further drug resistance in antibiotic-resistant bacteria. In an early study, Akimitsu et al. (1999) showed that exposure to QACs promoted oxacillin and β-lactam resistance in methicillin-resistant *Staphylococcus aureus* (MRSA) strains (Akimitsu et al., 1999).

The association between chronic sublethal exposure to biocidal agents and promoted antibiotic resistance has been demonstrated unequivocally in laboratory studies (Jin et al., 2020; Kim et al., 2018b), although real-world situations are often more complicated. Many field studies have been conducted to explore whether there was indeed a correlation between disinfectant use and antibiotic resistance. Khan et al. (2016) isolated 22 genera of bacteria from chlorinated drinking water systems and evaluated the correlation between sodium hypochlorite tolerance and antibiotic susceptibility. The study found consistent correlations between chlorine tolerance and MIC of several clinically antibiotics including tetracycline, sulfamethoxazole and amoxicillin, indicating that drinking water disinfection may indeed induce antibiotic-resistance in surviving bacteria. Liu et al. (2018) investigated the impact of chlorine disinfection on the promotion of antibiotic resistance in a full-scale wastewater treatment plant over one year. The study showed that chlorine dioxide disinfection increased the abundance of both extracellular and intracellular ARGs up to 3.8 folds and 7.8 folds, respectively. In a different setting, Fernandez Marquez et al. (2017) collected 39 *Salmonella* isolates from hen eggshells and found a positive link between biocide tolerance and antibiotic resistance. Among those, a total of 29 isolates (74.4%) showed higher MIC than wild-type strains and were determined as tolerant to biocides including benzalkonium chloride (BAC, 7.7%), cetrimide (CT, 7.7%), hexadecylpyridinium chloride (HDP, 10.3%), triclosan (TC, 17.9%), hexachlorophene (CF, 30.8%), and P3-oxonia (OX, 25.6%). The study found that most of the biocide tolerant isolates were resistant to ampicillin (90.5%), followed by chloramphenicol (61.9%), tetracycline (47.6%), and trimethoprim–sulfamethoxazole (38.1%). Similar results were reported by de Quadros et al. (2020) where the authors assessed the biocide tolerance and antibiotic resistance of *Salmonella* serotypes isolated from a swine slaughterhouse. All tested strains ($n = 25$) were susceptible to 0.5% and 1% peracetic acid and 18 of the 25 tested strain were resistant to 0.5% BAC. The authors found that only four of the tested strains were susceptible to all the seven antibiotics tested, *i.e.*, amoxicillin, chloramphenicol, florfenicol, doxycycline, cefaclor, azithromycin, and enrofloxacin, while other strains showed resistance to one or several antibiotics. Marino et al. (2011) showed that Staphylococci strains isolated from food and food environments were resistant to both QACs and several antibiotics. Fernandez Fuentes et al. (2014) reported that Gram-negative bacteria collected from organic foods were both biocide tolerant and antibiotic resistant, and efflux pumps genes (*e.g.*, *acrB*, *sugE*, *efrA*) and antibiotic resistance genes (*e.g.*, *ereA*, *lsa*) were both detected in those species.

The terms 'co-resistance' and 'cross-resistance' are often used to described the adaptive behaviors of microorganisms that are resistant or less susceptible to biocidal agents and antibiotics, although they do have different meanings (Buffet-Bataillon et al., 2012b; Elekhnawy et al., 2020). Co-resistance means that different tolerance/resistance mechanisms are encoded by the same gene (Buffet-Bataillon et al., 2012b; Elekhnawy et al., 2020). For instance, Kim et al. (2018b) found that, in *Pseudomonas aeruginosa*, biocide tolerance gene and antibiotic resistance gene are located on the same mobile genetic element. Cross-resistance means that one particular mechanism is responsible for biocide tolerance and antibiotic resistance exhibited by a certain microorganism (Buffet-Bataillon et al., 2012b; Elekhnawy et al., 2020). One notable example of cross-resistance is that some QAC transporters can also pump out clinical antibiotics (Table 1). In reality, many clinical and hospital isolates manifested cross-resistance or co-resistance to biocides and antibiotics. Sidhu et al. (2002) found that nearly 50% of clinical staphylococcal strains (118/238) were BAC tolerant, and those strains were more likely be resistant to antibiotics than BAC-sensitive ones. The *qacA/B* and *qacC* genes were widely detected in BAC-tolerant isolates, which could be the reason for their resistance to certain antibiotics (Table 1). Romao et al. (2005) reported that among 35 *Pseudomonas aeruginosa* clinical isolates, 73% showed multidrug resistance to antibiotics (mainly ceftazidime, cefepime) and 43% were BAC tolerant. In a later study, Romao et al. (2011) showed that a total of 124 clinical isolates of *Pseudomonas aeruginosa* were all resistant to antibiotics, and 32 showed resistance to two or more antibiotics. Among the 43 antibiotic-resistant isolates tested for disinfectant susceptibility, twenty isolates also showed tolerance to BAC. Buffet-Bataillon et al.

Table 1
Efflux determinants conferring increased tolerance to QACs and resistance to antibiotics (adopted with modifications from Tezel and Pavlostathis (2015)).

Efflux pumps family	QAC transporters	Typical antibiotic substrates
RND	YhiUV-TolC, AcrAB-TolC, MexAB-OprM, CmeABC, CmeDEF, SdeXY, OqxAB	Aminoglycosides, β-lactams, Chloramphenicol, Erythromycin, Fluoroquinolones, Novobiocin, Rifampin, Tetracyclines, Trimethoprim
MFS	QacA, QacB, NorA, NorB, MdeA, EmeA, MdfA	Aminoglycosides, Chloramphenicol, Erythromycin, Fluoroquinolones, Lincosamides, Novobiocin, Rifampin, Tetracyclines
MATE	MepA, NorM, PmpM	Aminoglycosides, Fluoroquinolones
SMR	QacE, QacEΔ1, QacF, QacG, QacH, QacI, QacJ, smr, EmrE, SugE	Aminoglycosides, Chloramphenicol, Erythromycin, Tetracyclines

Note: Abbreviations used above are RND, the resistance-nodulation-cell division superfamily; MFS, the major facilitator super family; MATE, the multidrug and toxin extrusion family; SMR, the small multidrug resistance family.

(2011) collected 153 blood culture isolates of *Escherichia coli* and assessed the relationship between their QACs MIC and antibiotic resistance. The authors found that cotrimoxazole resistance was correlated with higher MIC of QACs. In a follow-up study, they elucidated the molecular mechanisms that class 1 integron harbored *dfrA/sul1* and *qacEΔ1* gene cassettes which mediated the increased tolerance to QACs and resistance to cotrimoxazole (Buffet-Bataillon et al., 2012a). Similar findings were reported by Kadry et al. (2017) where the authors found that class 1 integron was responsible for the increased tolerance to biocides in multidrug-resistant *Pseudomonas aeruginosa* clinical isolates. In a recent study, Boutarfi et al. (2019) collected 77 *Enterobacter* isolates from hospital environments and showed that they were tolerant to biocides and resistant to clinically antibiotics.

While many filed studies have reported evidence suggesting a link between disinfectant exposure and antibiotic resistance, some studies suggested otherwise (Cole et al., 2003; Maertens et al., 2020; Oggioni et al., 2015; Peyrat et al., 2008; Roedel et al., 2019). In reality, there may not be a simple cause for such linkage, since in 'real-world' situations antibiotics often exist in complex environments and therefore, the use of disinfectants may not be the only or the primary driving force for the occurrence of antibiotic resistance. Overall, current evidence suggests that disinfectant-induced antibiotic resistance is more likely to become a contributing factor when bacteria are repeatedly exposed to subinhibitory concentrations of biocidal agents in disinfectants. This is plausible given that in practice, the concentration of biocides will be in a continuous gradient from zero to the treatment concentration (Gilbert and McBain, 2003). Meanwhile, the actual uses of disinfectants by untrained individuals and the wide variety of receiving surfaces and environments differ from an ideal situation, and many factors could affect the disinfection efficacy, potentially leading to subinhibitory concentration exposure. Common risk factors include inadequate cleaning of the surface to be disinfected, materials with porous or complex internal structures that are difficult to access, presence of biofilms, and failure to follow instructions during product storage and use. A lesser known risk factor in disinfectant-induced antibiotic resistance is that some disinfection byproducts (DBPs) – intermediates often generated in chemical disinfection processes – can have mutagenic activities and contribute to the emergence of antibiotic resistance in microbes (Li and Gu, 2019; Lv et al., 2015). Experiments using three commonly occurring DBPs, namely, trichloroacetic acid, chlorite, and iodoacetic acid, demonstrated that the latter two compounds had antibiotic-like effects and induced antibiotic resistance at both high (near MICs) and low levels (*ca.* 3% of MICs) (Li et al., 2016). Lv et al. (2014) investigated the association between antibiotic resistance and the mutagenic activities of DBPs by exposing *Pseudomonas aeruginosa* to dichloroacetonitrile, dibromoacetic acid, potassium bromate, and 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone. Exposed *Pseudomonas aeruginosa* showed varied degrees of resistance to antibiotics, especially to norfloxacin and polymycin B where the resistance of *Pseudomonas aeruginosa* increased by over 10-fold from control (Lv et al., 2014). Given the complexity of oxidative disinfection processes – many involving condition-specific pathways and byproducts – the antibiotic-like effects and mutagenic activities of DBPs represent a challenging and under-investigated issue that require further studies as part of the understanding of disinfectant-induced antibiotic resistance in bacteria.

5. Bacterial resistance and human transfers from regular surface disinfecting during COVID-19

It is generally accepted that disinfectants and antiseptics should be used when there is scientific evidence demonstrating the benefits of use or when there is a strong rationale for doing so. When used properly, disinfectants have been shown to be effective in reducing microbial contamination (Laustsen et al., 2008; Rutala et al., 2019) and preventing infections (Chmielarczyk et al., 2012; Loo, 2015; Robustillo Rodela et al., 2012), which are particularly important in healthcare settings (Climo et al., 2013; Rutala et al., 2014; Santana et al., 2007). Their uses are essential in high-risk settings such as healthcare facilities in the current pandemic given the large numbers of patients routinely admitted to these facilities and workers at potential risks of exposure to contaminated surfaces or objects. A more cautious approach, however, is needed to weigh the risks and benefits of their prolonged and often non-discriminated use in other low-risk settings. The constant selective pressures exerted by over a handful of disinfecting agents would inevitably give rise to bacteria that can survive in these environments, and consequently increase the risk of exposure to biocide-tolerant and drug-resistant bacteria for people living by or contacting with these surfaces (Fig. 6). Despite the current widespread practice, reports evaluating the correlation between disinfectant use and potential induction of bacterial tolerance or resistance in community-relevant environments are scarce. To date, there has been no study or scholarly discussion on the risk of antimicrobial resistance emerging from the regular use of chemical disinfectants on common touch surfaces in community or public settings, revolving around the current practices during the COVID-19 pandemic or the EPA-approved disinfectants. Pertinent data and findings suggest that one probably should not neglect the emerging risk of community outbreaks of antimicrobial bacteria as unintended consequences of the wide and regular use of chemical disinfectants in a persisting pandemic. In a recent investigation on disinfectant-induced bacterial resistance in confined building environments, Mahnert et al. (2019) identified a significantly lower diversity of microbes with more resistance genes in regularly cleaned and strictly disinfected premises compared with those without such requirements. He et al. (2014) collected 64 samples on common touch surfaces in four fitness centers and two school dormitories in Massachusetts, USA, including weight machines, exercise bikes, dumbbells, boxing gloves, refrigerator door handles, toilet handles, TV remote controls, and bathroom faucet handles. About 9.6% of the isolated bacterial strains ($n = 653$) were BAC-tolerant, and the BAC-tolerant strains of Staphylococci were also resistant to erythromycin, penicillin, and ampicillin. Notably, all BAC-tolerant strains were identified in samples collected from surfaces upon which antibacterial wipes or sprays (containing 0.02%–0.12% BAC) had been frequently applied, while strains isolated from non-antibacterial cleaned surfaces were all susceptible to BAC. In a randomized double-blind trial, 224 households in a northern Manhattan neighborhood completed a twelve-month study on bacterial resistance emerged from the routine use of antibacterial cleaning products containing QACs. Upon completion of the study, BAC-insensitive bacterial isolates were found in households assigned with antibacterial cleaning products, which also exhibited resistance to one or multiple types of clinical antibiotics (Carson et al., 2008). In a recent study conducted during the COVID-19 pandemic, Zheng et al. (2020) found increased QAC concentrations in 40 indoor dust samples collected from residential homes in Indiana, USA. The increased exposure to QACs was associated with the frequent use of disinfectants by occupants during the COVID-19 pandemic (June 2020) and the accumulation of those compounds on indoor atmospheric particulate matter. Similar findings were reported in an earlier study where the concentrations of triclosan, a common phenolic disinfectant, were positively correlated with the abundance of an antibiotic resistance gene in indoor dusts (Hartmann et al., 2016).

One of the particular risk factors associated with community-

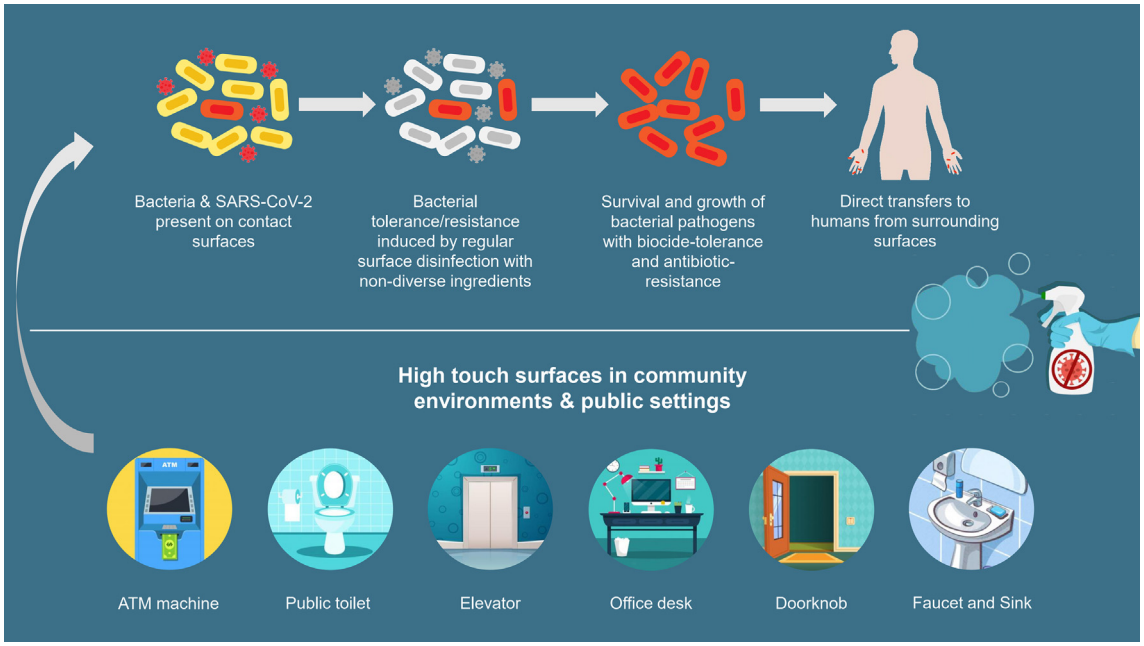

Fig. 6. A schematic illustration on the potential growth of disinfectant-tolerant and antibiotic-resistant bacteria on contact surfaces in community and public settings, posing risks of direct transfers to humans. With a highly non-diverse spectrum of biocidal agents in disinfectant products approved for COVID-19, these unintended consequences may arise from the regular and intensive surface disinfecting during COVID-19 and perhaps extended to the post-pandemic area.

emerged bacterial tolerance or resistance is their direct transfers to humans. There have been plenty of reports on human acquisition of antimicrobial-resistant bacterial pathogens in community and public settings, before the recent outbreak of the COVID-19 pandemic (Kang et al., 2006; King et al., 2006; Morozumi et al., 2010; Peng et al., 2012; Tao et al., 2012; Wise et al., 2011). Adding to this risk, many common bacterial pathogens such as *Enterococcus* spp., *Shigella* spp., *Listeria* spp., *Klebsiella* spp., *Acinetobacter* spp., *Pseudomonas aeruginosa*, and methicillin-resistant *Staphylococcus aureus* (MRSA) could survive for months on dry inanimate surfaces (Kramer et al., 2006). Several routes of microorganism transfers could eventuate from the human interactions with the surrounding environments, of which the surface-to-hand transfer is the most common route. Davis et al. (2012) reported that human infections of MRSA were typically associated with contaminated high touch surfaces in indoor environments. In a six-month study, Lax et al. (2014) demonstrated the close link between the hands of indoor occupants and common touch surfaces (*e.g.*, countertop, floor, door knob), where an occupant's hand shared 84% of genes with those present on a kitchen countertop, suggesting substantial transfers of microorganisms from inanimate surfaces to humans in indoor environments. In a subsequent study, Lax et al. (2017) found high resemblance between the microbiota present on patients' skins and those on in-hospital surfaces, suggesting that bacterial communities can transfer in both directions between humans and the surrounding surfaces (Lax et al., 2017). Rusin et al. (2002) measured the transfer efficiency of pathogens from surface to hands and further from fingers to lips. The highest transfer rates were observed on hard, nonporous surfaces where the number of bacteria transferred from surface to hand could reach up to 10^6 cells with a 10 s contact. Substantial transfers of bacteria from fingers to lips were also found, with rates up to 40% identified in the study. Lastly, it is worth noting that the likelihood of acquired human infection is not only determined by bacterial transfer efficiency or effective doses of bacteria transferred, but the specific type of pathogens being transferred to human. For instance, the minimal infectious dose of *Shigella* spp. was below 10 CFU while an equivalent dose of some *Salmonella* spp. was beyond 10^5 CFU (Gerhardts et al., 2012).

It should be noted that, in practice, disinfectants are often used at concentrations considerably higher than minimum inhibitory concentrations (MICs) or minimum bactericidal concentrations (MBCs) to achieve rapid killing, and it is unlikely for bacteria to survive and develop resistance under normal circumstances (Weber and Rutala, 2006). Further, the antibiotic resistance promoted by exposure to disinfectants, as described in some studies (Langsrud et al., 2004; Zhang et al., 2017), may not be clinically relevant because the test organism may not be a human pathogen, the altered level of antimicrobial susceptibility was within achievable serum levels for the antibiotic, or the antibiotic tested was not clinically used to treat the concerned pathogen. Although strains with reduced susceptibility to disinfectants have been reported outside laboratories (de Quadros et al., 2020; Fernandez Marquez et al., 2017), the concentration of disinfectants used in healthcare settings usually greatly exceeds the concentration required to kill strains with reduced susceptibility to disinfectants. Overall, from the current evidence, reports on disinfectant-promoted antibiotic resistance should not discourage the appropriate use of disinfectants, but more studies should be carried on the proposed linkage between disinfectant uses and antibiotic resistance, particularly in real-life scenarios outside laboratories and under community or environmentally relevant conditions.

Meanwhile, one should also be aware that the actual scenarios of use can vary greatly, and many factors can contribute to the situation where the bacteria may be exposed to sub-lethal levels of biocides from the inappropriate uses of disinfectants. Apart from human errors and misuses (Weber et al., 2019), confounding factors such as the inappropriate dilution of disinfectants, co-existence of biocide-exhausting substances (*e.g.*, due to inadequate cleaning prior to disinfection), insufficient contact, and disturbance during the disinfection process are among the common issues encountered in disinfectant uses (Cerf et al., 2010; Elekhnawy et al., 2020;

Rutala and Weber, 2018; Song et al., 2019). Further, the methods of how disinfectants are applied in practice (*e.g.*, wipe, sprays, or gels) and the characteristics of receiving surfaces or objects (*e.g.*, porous or having complex internal structures) can also influence the efficacy of disinfection (Rutala and Weber, 2018; Song et al., 2019). Under these circumstances, bacteria can be, in theory, exposed to subinhibitory concentrations of biocides. Such risks may be aggravated in the current pandemic due to the widespread and non-discriminated use of disinfectants in non-conventional settings.

6. Conclusion and actions to take

The regular and persisting use of chemical disinfectants in community and public settings under the current circumstance may bring unintended consequences – constant selective pressures exerted on microbiota not only can increase their tolerance to biocidal agents but their resistance to certain antibiotics. Such risks are likely to be exacerbated by the non-diverse portfolio of active ingredients used in current 535 disinfectant products approved for COVID-19. While these risks are widely overlooked in recent scholarly discussions and regulatory guidelines, ample evidence has shown disinfectant-induced resistance in many bacterial pathogens with their mechanisms elucidated under laboratory and environmental relevant settings. For many bacteria, tolerance to biocidal agents can be intrinsic or acquired, specifically, via mutations and horizontal gene transfer, membrane alterations, upregulation of efflux pumps, biofilm formation, as well as other mechanisms conferring tolerance to specific biocides. Importantly, some biocides and degradation byproducts are known to further induce antibiotic resistance in bacteria. While there is a strong suspected link between disinfectant use and community-emerged bacterial resistance, the underlying risks of human acquisition of resistant bacterial pathogens from the surrounding surfaces in community and public settings have been barely assessed in the COVID-19 context. Meanwhile, existing data and evidence suggest that hand contact with contaminated surfaces or objects is a prevalent route of bacterial transfer to humans in these environments, where transfer rates from hard, nonporous surfaces to hands were found to be generally high, with substantial transfers further from fingers to lips. Under current regulatory guidelines, common touch surfaces may become 'hotspots' for the growth of antimicrobial resistant bacteria and subsequent transfers to members of the public, especially in places with high user occupancy or foot traffic.

In the midst of a prolonging pandemic where regular surface disinfection remains an essential means of reducing the virus spread, and that scientific evidence demonstrated that disinfectants are beneficial in reducing microbial contamination and preventing infectious when used properly, we propose the following actions to be considered for mitigating the risks of community-emerged biocide-tolerant and antibiotic-resistant bacteria and consequent transfers to humans from surrounding surfaces and environments. First, it is essential to remove dirt and debris from the surfaces and objects before spraying or wiping them with disinfectants. Then, users must carefully read the labels on disinfectant products prior to their use and comply with the instructions. To avoid exposing microorganisms at subinhibitory conditions, care must be taken to ensure that products are current (non-expired), intact (no leakage or visible damage on packaging), properly stored (*e.g.*, no direct sunlight or excessive heat), and applied on desired surfaces or objects in adequate amounts for sufficient periods of time. Where possible, alternating the use of disinfectant products with unrelated active ingredients can mitigate the emergence of increased biocide tolerance. As a precaution, proper hand hygiene should be maintained by community members to minimize transfers of bacterial pathogens from regularly disinfected touch surfaces or objects to humans. Children and crawling infants should be given more attention to maintain good hand hygiene and minimize hand-to-face bacterial transfers. Lastly, given the fact that regular disinfection also greatly reduces microbial diversity, maintaining natural ventilation and plantation can diminish the competitive advantages of bacterial pathogens selected by biocidal agents, and help restore the microbial diversity in affected environments. As the current pandemic progresses into the twelfth month, and community-wide surface disinfecting remains an essential measure to control the virus spread, we call for attention of regulatory bodies and the scientific community on these underlying risks and mitigation measures. Future studies on the consequences of prolonged and intensive community-wide surface disinfecting could focus on current knowledge gaps on: i) the extent to which the disinfectant-induced bacterial resistance to antibiotics occurred in real-world environments and whether the emerged antibiotic resistance is clinically relevant and to what extent it affects the efficacy of antibiotic treatment; ii) human acquisition of biocide-tolerant and antibiotic-resistant bacterial pathogens from surrounding surfaces and environments, focusing on community and public settings that are in close proximity to humans and most severely impacted by disinfectant use during the current pandemic and possibly into the post-pandemic era.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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