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Surveillance and prevalence of antimicrobial resistant bacteria from public settings within urban built environments: Challenges and opportunities for hygiene and infection control

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ABSTRACT

Antimicrobial resistant (AMR) bacteria present one of the biggest threats to public health; this must not be forgotten while global attention is focussed on the COVID-19 pandemic. Resistant bacteria have been demonstrated to be transmittable to humans in many different environments, including public settings in urban built environments where high-density human activity can be found, including public transport, sports arenas and schools. However, in comparison to healthcare settings and agriculture, there is very little surveillance of AMR in the built environment outside of healthcare settings and wastewater. In this review, we analyse the existing literature to aid our understanding of what surveillance has been conducted within different public settings and identify what this tells us about the prevalence of AMR. We highlight the challenges that have been reported; and make recommendations for future studies that will help to fill knowledge gaps present in the literature.

1. Introduction

As early as the 1970s, the twenty-first century was predicted to see humanity enter a new stage of the epidemiological transition (Omran, 2001), in which individual actions and lifestyle choices as much as the biological and physiochemical characteristics of pathogens would have an increasingly strong influence on our health (Roger and Hackenberg, 1987). Omran's concept of the epidemiological transition – a shift in the global burden of morbidity and mortality from nutritional deficiencies and occasional epidemics to endemic infectious disease and then to chronic non-communicable disease – has always been a reflection of human action. The first epidemiological transition happened alongside the development of agriculture and saw a decline in deaths from starvation and sporadic epidemics as previously nomadic humans settled into farming. The densely populated and often unsanitary settlements made them more vulnerable to endemic infectious disease, however, leading to the emergence and rise of 'crowd infections' that lasted well into the 19th century (Harper and Armelagos, 2010; Rook et al., 2014). The second transition saw a shift away from infectious disease as human civilisation flourished and sanitation, vaccination and medical knowledge improved but a third one occurred as chronic diseases caused by pollution, sedentary lifestyles and, in the latter half of the twentieth century, poor quality, highly processed diets began to take their toll (Ferriman, 2007; Prüss-Üstün et al., 2016) . Beginning in the 1990 s, a focus on human disease ecologies, including the impacts of environmental degradation and rising resistance to existing drugs resulting from their overuse intensified (Barrett et al., 1998). A 1992 report by the Institute of Medicine warned that due to changes in climate, air quality and deforestation, the coming decades were likely to see an increase in the incidence of infectious disease outbreaks (Institute of Medicine (US), 1992; Morens and Fauci, 2012). A subsequent 2003 report warned of added vulnerabilities imposed by populations made more susceptible by ageing, HIV and societal factors including increasing social inequality and conflict (Anderson et al., 2003; Institute of Medicine (US) Committee on Health and Behavior, 2001).

Scholars working in cross-disciplinary areas of health study are increasingly pointing towards the ways in which modern lifestyles create vulnerabilities to disease, amplifying or enabling micro-organsims' pathogenicity. This includes 'disease situations' that stress immune systems and turn otherwise harmless microbes into pathogens; evolutionary perspectives that suggest the pathogens best able to exploit human behaviours and global networks in any given age will arise to cause pandemics; and warnings regarding the impacts of socioeconomic inequality, and the degradation of healthcare systems due to conflict,

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war and corruption (Bingham et al., 2008; Cole, 2014; Dikid et al., 2013; Green, 2020; Hinchliffe et al., 2016; Hotez, 2020; Hotez et al., 2016). The consequences are a world where infectious disease is likely to become more prevalent and harder to control with the medical interventions we came to rely on throughout the twentieth century: both because it will take time to develop vaccines against the novel diseases – which have emerged with increasing frequency in recent decades – and because diseases with which we are already familiar are developing resistance to the drugs we have so far used to hold them at bay (Madhav et al., 2020; Morens et al., 2004; Trovato et al., 2020). Emerging microbial resistance has been identified as one of four major categories of emerging and re-emerging disease and a major threat to global health (Löscher and Prüfer-Krämer, 2009; O'neil, 2014). As we struggle with the aftermath of the COVID-19 pandemic, we welcome the recent call to better understand the role of hygiene in the modern world (Warmbrod et al., 2021), and agree that a refocus on the value of hygiene and other non-medical interventions should be encouraged – not only as a back-up plan but as an integral part of global health security. Such a refocussing is, in turn, dependent on a better understanding of the transmission pathways of pathogens (Bloomfield et al., 2008, 2016) . This includes a better understanding of surface transmissions and how actions taken in relation to contaminated surfaces may drive the development of drug resistance, thus exacerbating rather than improving the problem.

2. The threat from antimicrobial resistance

The rise of antimicrobial resistance (AMR) is a global crisis which threatens the lifesaving role of antibiotics, the use of which is one of the cornerstones of modern medicine (Hutchings et al., 2019). A report by Lord O'Neill (O'neil, 2014), commissioned by the UK government in 2014, estimated that by 2050 10 million people worldwide could die annually from infections that no longer respond to antibiotics, with the economic cost of this could reach USD 100 trillion annually if no concrete global action is undertaken. The rapid increase and spread of AMR is driven by many factors, including the overreliance on and misuse of antibiotics in healthcare settings (Chang et al., 2019; Korenstein et al., 2012; Llor and Bjerrum, 2014) and in agriculture, including in livestock feed as a growth promotor and metaphylaxis or as an "infrastructural" response to poor hygiene, overcrowding and climate stress, (Chandler, 2019; Cole and Desphande, 2019; Gustafson and Bowen, 1997; Martin et al., 2015; Mathew et al., 2007). In response, many countries have introduced policies to minimise the use of antibiotics in those sectors (Cox et al., 2017; Walia et al., 2019; Wiley and Villamizar, 2019) as well as education in the improvement of hygiene to prevent the spread of bacterial infections (Marimuthu et al., 2014). However, to truly understand if these policies are working (or in fact, even if they are appropriate in the first place (Hinchliffe, 2021) will require comprehensive surveillance of AMR bacteria from different ecological niches and environments, to understand how and where resistant bacteria and/or mobile genetic elements that can confer resistance are selected and transmitted, so that appropriate measures can be taken to address this. Microbiologists can then work with behavioural scientists to identify and implement appropriate interventions – which may include the promotion of different prescribing practices (Krockow et al., 2019; Rawson et al., 2017), more targeted hygiene (Bloomfield, 2020; Maillard et al., 2020), or other interventions yet to be identified – and work across disciplines to develop effective implementation programmes. It is especially important to also adapt a "One health" approach (Hernando-Amado et al., 2019) as the emergence and spread of AMR are interconnected between humans, animals and the environment.

To date most AMR surveillance studies have focused on healthcare and agriculture settings, but this does not mean the human environment should be overlooked. Only a few studies (Cave et al., 2019; Kang et al., 2018; Roberts et al., 2013; Shen et al., 2018) have focussed on general public settings in built-up environments but the studies that have been conducted generally shown that public settings have a high abundance of AMR resistance across different species. Some of these species pose a public health risk as they have genetic linkage to isolates that have caused infections in humans and livestock animals (Cave et al., 2021; Xu et al., 2018b; Zou et al., 2019). The main issues with many of these studies (Conceição et al., 2013; Zhou and Wang, 2013; Kahsay et al., 2019) is that they tend to focus on relevant clinical bacteria (including those belonging to the genus *Staphylococcaceae* and *Enterobacteriaceae*), recovered from surfaces and from the air: little is known about the diversity of antimicrobial resistant bacterial species and AMR genes present in public settings and the built environment around the globe, including how bacteria come to be in such environments and the main barriers or enablers of transmission and resistance emergence. Additionally, studies have shown that the external environment (exposome) has a pivotal impact on the internal environment of the human microbiome (Kim and Hong, 2017) and studies in India have started to map the movement of resistant genes between waterways, food fishes and produce markets (Sivaraman et al., 2020, 2021a,b). Changes in the exposome could alter the composition of the human microbiome due to the complex interactions acquired infections tend to have with other microbial communities and their host. Disruption to the current microbial ecology could have a profound impact on human health (Tasnim et al., 2017). It is essential that this interaction is fully understood so that it does not undermine confidence in hygiene at a time when applying it appropriately is more important than ever (Bloomfield et al., 2016).

In this review, we provide insights on AMR bacteria recovered from general public settings within urban built environments including transit systems, universities and schools, athletics facilities, cinemas and supermarkets. We summarise the implications of the findings, review the reasons for a lack of comprehensive studies in this area and identify the knowledge gaps it presents.

3. The rise of antimicrobial resistant bacteria

AMR is not a modern phenomenon; it is a complex challenge and while much attention has been given to Alexander Fleming's prescient warning of its emergence in his acceptance speech for the 1945 Nobel Prize for Medicine, resistance far precedes that observed in the first mass-produced antibiotics. Genes encoding resistance to several antibiotics have been found in 30,000 year old permafrost sediments (D'Costa et al., 2011) and β lactamases, the enzymes that render penicillin-like antibiotics ineffective, are estimated to be 1–2 million years old (Hall et al., 2004). Antibiotics are found in fungus and bacteria as a natural defence mechanism (D'Costa et al., 2011) and may have become a severe problem only as a result of human activities, including their misuse and overuse in healthcare and agriculture (Shallcross and Davies, 2014). In addition to evolution and random mutations driven by selection due to antibiotic pressure or other environmental stress factors, AMR can arise through horizontal gene transfer between species, including the exchange of pathogenicity islands, via plasmids, transposons, chromosomal cassettes or prophages (Malachowa and DeLeo, 2010; Martinez and Baquero, 2000; Munita and Arias, 2016; Fajardo et al., 2008). Resistance genes can then be transmitted to other areas, including where antibiotic usage is significantly lower, via the movement of humans or through the food chain (Sivaraman et al., 2021b) (Fig. 1).

4. Origins of antimicrobial resistance in the environment

The primary source of AMR bacteria is the environment. Most of the genes responsible for AMR did not evolve in clinical or in agriculture settings, but rather long before this, in the natural environment due to the presence of naturally occurring antibiotics (including penicillin, streptomycin, tetracycline and chloramphenicol) derived from soil-dwelling bacteria and fungus as a means to compete with other bacteria for limited resources (Gaynes, 2017; Nelson and Levy, 2011; Waksman and Schatz, 1945). However, as these antibiotic-producing bacteria

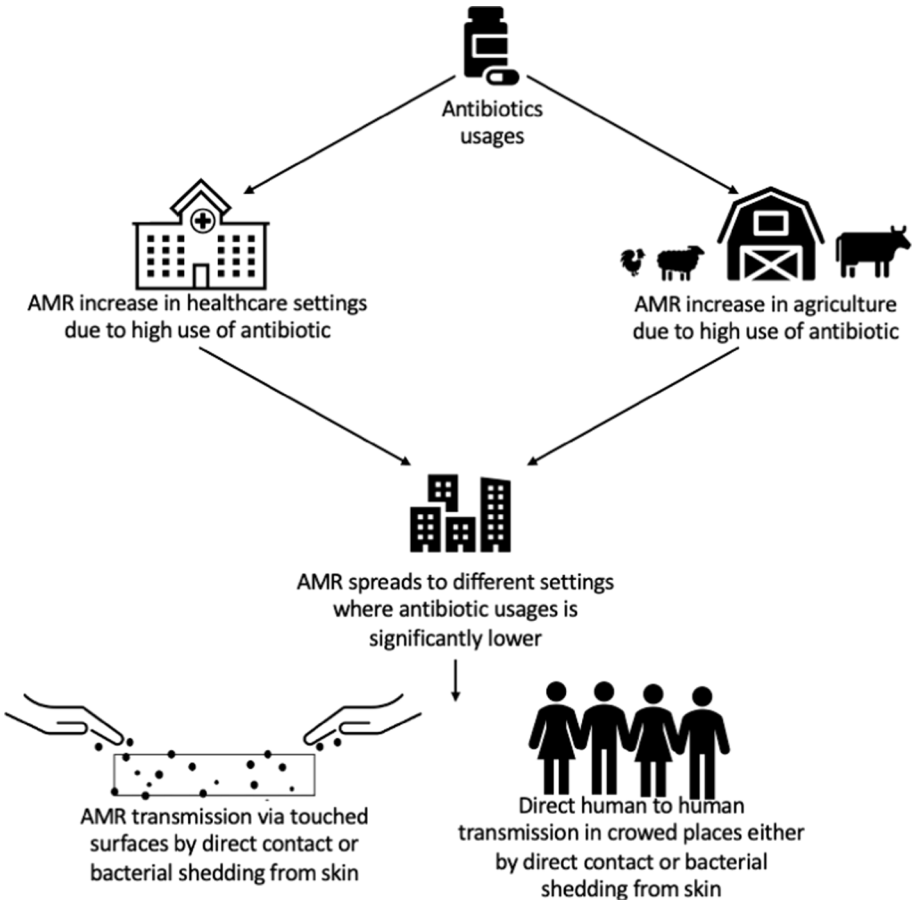

Fig. 1. The transmission of AMR bacteria from high antibiotic usage areas to settings where antibiotic usage is significantly lower and the transmission to humans within public settings.

are physiologically similar to the bacteria they compete with, there is potential for them to be susceptible to others' toxic metabolic compounds and therefore they had to develop defence mechanisms to protect themselves. For example, antibiotic-producing streptomyces transcribes genes for the export mechanisms of antibiotics during the inactive precursor stage of antibiotic synthase to prevent intracellular concentration reaching toxic levels (Benveniste and Davies, 1973; Hopwood, 2007; Humeniuk et al., 2002). Many AMR genes may have originated from these antibiotic producers, disseminated to other bacterial species via horizontal gene transfer over time. Antibiotic resistance may have also arrived from spontaneous mutations that have altered the antibiotic target sites, as well as pre-existing genes encoding the enzymes or transported by efflux pumps and later evolving as a resistance mechanism (Blanco et al., 2016; Chen et al., 2015; Dickinson et al., 2019; Morar and Wright, 2010; Wang et al., 2001).

4.1. The challenge of antimicrobial resistant bacteria surveillance in public settings

The prevalence and distribution of AMR bacteria are on the rise (Barros et al., 2012; Lee et al., 2019) but due to limited resources including time, cost, expertise and the heavy focus on observing clinically important pathogens, it has not been possible to implement a comprehensive AMR surveillance system in public settings for all bacterial species. Surveillance is mainly limited to human and animal bacterial pathogens found within healthcare facilities and agriculture. However, due to the nature of horizontal transfer, even non-pathogenic bacteria that possess AMR genes need to be considered a public health threat as they risk transferring the AMR genes to known pathogens (Hummel et al., 1977; Sivaraman et al., 2021b). In addition, AMR bacteria have been known to spill-over from hospitals and agriculture into public settings such as restaurants, street food stalls and markets (Manyi-Loh et al., 2018; Sivaraman et al., 2020, 2021a). Moreover, inappropriate antibiotic use and self-prescribing within low and middle income countries (LMICs), particularly in lower socioeconomic communities, may also contribute to increased AMR in the community and in public settings (Erku et al., 2017; Saleem et al., 2019) including the carriage of mobile genetic elements by houseflies (Sobur et al., 2019). There is, however, a serious knowledge gap with regard to prevalence in public settings, much of which has gone unreported.

The main limiting factor preventing better surveillance of AMR bacteria in public settings is the current methodology. Biases in traditional culturing methods select only those organisms that can grow within laboratory conditions (Rappé and Giovannoni, 2003). This limits the number of studies to a specific group of microorganisms that have been previously shown to be a public health threat; are culturable in the lab; are easily speciated using molecular typing methods (e.g. multilocal sequence typing (MLST), pulsed field gel electrophoresis (PFGE) and *spa* typing for *Staphylococcus aureus*); are known to contain clinically relevant AMR genes; are detectable by PCR; and can be profiled by a standardised antibiotic susceptibility test (Maugeri et al., 2019). More advanced culture techniques known as culturomics have been used for high throughput analysis to identify and characterise microorganisms in their habitats including unknown species that were previously known as unculturable (Greub, 2012). Culturomics uses a wide range of culture conditions and techniques such as MALDI-TOF and 16S rRNA sequencing for rapid identification of species. Although this technique can expand the repertoire of culturable bacteria, many bacterial species within a habitat are still not detected and it's execution still remains labour intensive, costly and time-consuming (Nowrotek et al., 2019).

Due to more recent advancements and a sharp drop in the cost of next-generation sequencing technologies, however, it is becoming increasingly possible to perform culture-independent metagenomic studies (Forbes et al., 2017). This approach is highly comprehensive with high precision in bacterial species identification, quantification and functional characterisation of genes (Thompson et al., 2017).

The level of detail obtained from metagenomics analysis offers opportunities to use the technology for the development and management of 'smart cities', potentially linking urban design with public health, for instance in the design of more hygienic subways and public transport systems (Mason et al., 2016). Using the information from metagenomics, we can use an interdisciplinary collaborative approach of experts in public health, microbiology, bioinformatics, data science, architecture, material science and social science to better understand the spread of infectious disease and AMR and how to prevent it. The only limiting factor of metagenomic culture-independent studies is that it contains unknown sequences from unidentified microbes and lack of knowledge regarding the phenotypes of isolates that display antibiotic resistance as characterising antibiotic genes alone cannot always correlate to antibiotic resistance phenotype as antibiotic resistance phenotypes can alter due to environmental changes or be influenced by the genetic context of resistance determents (Hughes and Andersson, 2017; Jaillard et al., 2017; Nowrotek et al., 2019). Therefore, culturing methods are still preferred to link antibiotic resistant phenotypes to the bacterial strain and genotype.

Although culture-independent metagenomics studies within public settings remain very limited, a body of knowledge is emerging on, for example, mass transit systems, including in Hong Kong (Kang et al., 2018), Boston (Hsu et al., 2016), and opportunistic pathogens on the New York subway (Afshinnekoo et al., 2015); in atheltic facilities (Fahimipour et al., 2018) and classrooms (Hartmann et al., 2016). However, most studies that investigate built-up environments and non-healthcare public settings still use culture-dependent methods to detect staphylococci and enteric bacteria such as *Enterobacteriaceae*, as these are the most frequently recovered bacteria from such areas that are known to cause infections in humans (Roberts et al., 2013). This perpetuates an incomplete knowledge of not only the microbiome of such environments but also the best ways to design out vulnerabilities to disease transmission and spread. Such understanding could offer benefits to the control of other diseases, including influenza and COVID-19 as well as those caused by AMR bacteria, by identifying where targeted hygiene interventions might be best introduced.

4.2. Factors contributing to the transmission of antimicrobial resistant bacteria in public settings in built environments

Multiple studies have indicated that AMR bacteria can be transmitted to humans in public settings including on buses (Conceição et al., 2013); at railway stations (Lin et al., 2017); on subway trains (Mason et al., 2016) and in university classrooms (Li et al., 2015). These areas typically see high population movement and throughput and, at times, high population density (Batista e Silva et al., 2020). Public settings such as mass transport systems (buses and trains) contain surfaces that are frequently touched by multiple people and so too do shops and leisure facilities, all posing a particular challenge to AMR spread. High-frequency hand-touched surfaces can act as a vector for AMR transmission from person-to-person if they either touch these surfaces directly or via bacterial shedding from one's skin onto a surface which is then transmitted to others who touch the same surface (Fig. 1) (Cave et al., 2019; Conceição et al., 2013; Plipat et al., 2013). Surfaces that are not sanitised regularly and are touched multiple times a day, particularly if this is by people who have poor hand hygiene, could further the transmission of AMR bacteria within the population (Cobrado et al., 2017). Moreover, within overcrowded public settings, AMR bacteria can be transmitted directly, either via the air from bacterial shedding from skin, by direct contact, or through food (Li et al., 2018; Sivaraman et al., 2021b). Some of these factors, including direct contact and aerosolised transmission have been key for transmission of SARS-CoV-2, the virus that has caused the COVID-19 pandemic (Meyerowitz et al., 2020). To successfully combat the transmission, governments across the world have taken measures to educate the public with regards to hand hygiene, to improve cleaning and hygiene practices relating to frequently-touched surfaces to prevent fomite transmission, and have introduced social distancing rules to prevent transmission via aerosols (Chu et al., 2020). Maintaining long-term social distancing in the post-COVID-19 era may the easiest task to undertake due to its adverse physical and mental effects (Di Corrado et al., 2020), along with the economic (Nicola et al., 2020) and social compliance challenges (Hills and Eraso, 2021), however keeping up with good hand hygiene and cleaning/infection control practices will help prevent transmission of infectious diseases including those caused by antimicrobial resistant bacteria.

In this review, we presented and compared studies (Table S1) of bacterial species, including *Staphylococcus* and *Enterobacteriaceae* species, that have mostly been recovered and reported from public settings using traditional culturable, molecular typing methods, whole genome sequencing and metagenomic analysis in different countries.

5. Antimicrobial resistance of *Staphylococcus aureus*

Staphylococci are commonly found in built environments. They are abundant bacteria within human skin flora and can be transmitted on to touched surfaces or shredded in the air (Cave et al., 2019; Madsen et al., 2018; Xu et al., 2018b). Many staphylococcal species are opportunistic pathogens and some have developed resistance to multiple drugs: *Staphylococcus aureus* has been the centre of attention for researchers and clinicians for decades as one of the most common causes of nosocomial and, more recently, increasing numbers of community associated infections (Tong et al., 2015). The most well-known is methicillin-resistant *S. aureus* (MRSA) which historically has been challenging to treat due to its broad resistance to beta-lactam antibiotics, caused by the *mecA* gene found within a mobile genetic element known as a *Staphylococcus* Chromosome Cassette *mec* (SCC*mec*). There formally are 13 different SCC*mec* types (Miragaia et al., 2008), which are defined by the composition of the *mec* complex and chromosome cassette recombinase (*ccr*) complex. Originally, MRSA was categorised into three groups – Healthcare-associated MRSA (HA-MRSA); community-associated MRSA (CA-MRSA) and livestock-associated MRSA (LA-MRSA) (Naimi et al., 2003; Vanderhaeghen et al., 2010). These groups have evolved separately from different clonal backgrounds (Naimi et al., 2003; Vanderhaeghen et al., 2010). The transmission of HA-MRSA isolates occurs in healthcare facilities via patients and healthcare workers; CA-MRSA is isolated from people who have had minimum to no contact with healthcare facilities, and LA-MRSA generally only affects animals in agricultural settings. Only a few studies have reported transmission of LA-MRSA to humans (Vanderhaeghen et al., 2010; Witte et al., 2007) but the potential for spread through infected agricultural workers is nonetheless considered a risk that needs to be taken seriously (Cuny et al., 2013; Kinross et al., 2013). Certain SCC*mec* types, i.e. types I, II and III are associated with HA-MRSA, whereas other SCC*mec* types (IV, V, VI, VII and VIII) are associated with CA-MRSA and LA-MRSA (Ahmad et al., 2009; Köck et al., 2013). Those SCC*mec* types that are associated with CA-MRSA are smaller in size compared to SCC*mec* associated with HA-MRSA, and this contributes to their mobility, making it easier for the *mecA* gene to be disseminated into *Staphylococcus* isolates of diverse genetic background (Daum et al., 2002; Ito et al., 2004).

5.1. Antimicrobial resistant Staphylococcus aureus from fomite surfaces and air in public settings

Increasingly, studies are showing that MRSA can be found outside of clinical settings, in several places frequented by the general public. Studies have, for example, looked at university campuses and

recreational beaches in the USA (Roberts et al., 2013); public buses in Portugal (Conceição et al., 2013), the USA (Lutz et al., 2014) and Ethiopia (Kahsay et al. 2019); transport hubs and metro systems in China (Lin et al., 2017; Peng et al., 2015); and the handles of shopping baskets in Japan (Domon et al., 2015). The prevalence of MRSA isolates recovered from these settings varies from 1.5% to 36%, with public buses in Portugal showing the highest levels of contamination.

Transmission of HA-MRSA onto surfaces found in public buses has been linked to bus routes connected with hospitals, suggesting unintentional spread by patients and hospital workers (Conceição et al., 2013; Lutz et al., 2014). Between May 2011 and May 2012, the authors (Conceição et al., 2013) screened hand touched surfaces of 199 buses in Lisbon, Portugal; 32% were contaminated with MRSA, whereas 15 of the 575 passengers screened carried MRSA on their hands. Another study (Lutz et al., 2014) carried out in a large Midwestern city in the USA between July and October 2010 revealed that hand touched surfaces of 63% (25/40) of the 40 randomly selected buses were contaminated with MRSA. In addition, Lutz et al. (2014) measured multiple variables to determine the association of MRSA contamination of buses including which bus depot they arrived from, routes covered (single, multiple), whether hospitals were served, and number of passengers served within a day; however none of these factors were shown to be associated with MRSA contamination. They did however find there was significant ($p = <0.01$) risk of MRSA contamination on areas considered to be touched more frequently including seats (odds ratio (OR) = 18.8) and seat rails (OR = 16.5) compared to the back door (OR = 6.9) or stanchions (OR = 4.3). The most prevalent strain isolated from bus surfaces and passengers' hands and nasal passages in Lisbon was EMRSA 15 (ST22, SCC*mec* type IV, PFGE type A, *spa* types t2357/t747/t025/t379/t910) which accounted for 29% of MRSA isolates, whereas the most common HA-MRSA isolated from bus surfaces in the United States (US) was USA100 (SCC*mec* type II) which accounted for 22.9% of the isolates. Both EMRSA 15 and USA100 were the predominant strains isolated from healthcare facilities in Portugal (Aires-de-Sousa et al., 2008) and the US (Carrel et al., 2015). Moreover, EMRSA 15 in Portugal has also been shown to be carried within the nasal passages of healthy dogs (Coelho et al., 2011) which suggest that this strain can spread outside of hospital settings and cross between the species barrier to be transmitted to and from humans via surfaces in public settings. Both studies also show that the bus surfaces harbour CA-MRSA clones (26% of MRSA isolates from Lisbon were USA300 or ST8, SCC*mec* type IV and 62.9% of MRSA in the US were USA300 or USA400) that are commonly found to colonise humans in Europe and the US (Glaser et al., 2016).

HA-MRSA transmission patterns have been detected in the metro system in Guangzhou China in November 2013, however, no isolates were identified as CA-MRSA based on their SCC*mec* indicating that MRSA was transmitted from a hospital setting although there was no indication on the proximity of metro lines to the hospitals (Peng et al., 2015). The prevalence was low with only 2.5% of the 220 samples being MRSA. Intriguingly, one of the most common MRSA sequence types identified from surfaces in Guangzhou metro system was a ST398 (37.5% of MRSA isolates) which is rare to find in urban settings due to it mainly colonises animals. This suggests that it was spread into this setting by a passenger who was in contact with animals or meat. Other sequence types from Guangzhou metro station included known hospital associated ST125 (25% of the MRSA isolates); ST5 (12.5% of the MRSA isolates) and ST30 (12.5% of the MRSA isolates). In contrast all 6 (1.58% of the 380 isolates) recovered between December 2013 and January 2014 from railway and bus stations surfaces in Guangzhou were CA-MRSA as they were characterised carrying the community-associated SCC*mec* type IV, except for two that were not typeable (Lin et al., 2017). MRSA isolates recovered on frequently touched surfaces in the public areas of a university campus in the USA between 2009 and 2010 were also similar to healthcare associated clones (ST45, SCC*mec* type I and ST8, SCC*mec* type I), community-associated clones (ST5, SCC*mec* type IV; PFGE type 3; ST8, SCC*mec* IV, PFGE type 1; and ST30, SCC*mec* IV, PFGE type 6) and animal associated clones (ST97, SCC*mec* not typeable (NT), PFGE type 10 and 9), although it is unknown how the transmission of HA-MRSA and MRSA associated with animals onto these surfaces occurred (Roberts et al., 2013), pointing to a need to better understand and track routes of transmission, which could be determined through social science observation, supported by regular surface testing to identify when the contamination first appears and how it was introduced. The literature we reviewed indicates that the public settings are crucibles for various MRSA clones which could further be transmitted to other settings and warrants attention for improving hygiene practices in such public settings to prevent cross transmission of MRSA clones.

Studies that have conducted phenotyping of the antibiotic susceptibility profiles of *S. aureus* recovered from public settings have shown that penicillin is consistently the antibiotic to which resistance is most often found (in 74%– 88% of the isolates) (Lin et al., 2017; Lutz et al., 2014; Peng et al., 2015). This is not surprising, as penicillin is one of the most common antibiotics prescribed globally (Tong et al., 2015; WHO Report on Surveillance of Antibiotic Consumption 2016 - 2018 Early Implementation). For other antibiotics, there is little consensus between studies exploring the prevalence of resistance to them. This may be due to different antibiotic usage in different countries, or because the panel of antibiotics used to test susceptibility varies from study to study. *S. aureus* resistant to multiple antibiotics has also been reported in studies which investigated the resistance patterns of CoNS from public settings in London (Cave et al., 2019; Mkrtchyan et al., 2013; Xu et al., 2018b) and from metro system in Guangzhou (Peng et al., 2015). However, the overall prevalence of *S. aureus* was low, with only 1.78% of total isolates recovered in Xu et al. (2018b), and 2.1% in Cave et al. (2019) being *S. aureus*, whereas in Mkrtchyan et al. (2013) the percentage of the total recovered isolates which were S. aureus was not reported. However, neither Xu et al. (2018b) nor Cave et al. (2019) recovered MRSA, although they reported that (of the antibiotic resistant or multidrug resistant isolates) *Staphylococcus epidermidis* accounted for 26.69% and 30.77% of all isolates respectively. Peng et al. (2015) did not speciate CoNS isolates in their studies, but they did find that 14.88% of the 94.21% of antibiotic resistant staphylococci isolates recovered from the metro system in Guangzhou, China, were *S. aureus*. The low prevalence of *S. aureus* in comparison to CoNS is surprising, considering that 30% of the population are estimated to be asymptomatic carriers of *S. aureus*. However, the low levels of antibiotic resistance in *S. aureus* recovered from surfaces in public environments are likely to be due to such bacteria being more commonly carried in the nasal passages than on hands, and because they can only survive for up to 24 h on dry surfaces (Domon et al., 2015; Tammelin et al., 2003).

Apart from the *mecA* gene, there is a lack of data on antibiotic resistance genes found in *S. aureus* recovered from public settings. Only two studies have reported antibiotic resistance gene profiles: one investigating supermarket basket handles in Osaka prefecture, Japan (Domon et al., 2015) and another focussing on frequently touched surfaces in built environments in the USA (Roberts et al., 2013). In the former study, the authors used PCR to detect six different antibiotic resistance genes, of which 64% of the isolates possessed beta-lactam resistance gene, *blaZ*, whereas in the latter the authors used PCR to identify eight antibiotic resistance genes, of which 82% of the isolates were positive for the kanamycin-resistance gene. *mecA*, *ermA* and *ermC* were the most common genes found in both studies.

In addition to fomites, MRSA and antibiotic-resistant *S. aureus* have previously been identified in air samples, cinemas, hotels, and university classrooms in Tai'an city of Shandong Province in China between March and May 2013 (Li et al., 2015). The authors measured the amount of inhaled and respired *S. aureus* using a six-stage Anderson Sampler; their data showed that cinemas had the highest mean concentration of MRSA (mean 33 CFU/m^3) compared to university classrooms (mean 24 CFU/m^3), hotels (mean 23 CFU/m3) and nurseries (mean 20 CFU/m^3). Although no molecular typing was conducted to determine the possible origins of the airborne MRSA; they were able to determine the location

of the respiratory system deposited by the size of the of airborne bacteria. They found that the highest collection rate was stage 4 (2.1–3.3 μm) and stage 3 (3.3–4.7 μm) of the Anderson Sampler; particle sizes (<57 μm) which could deposit in the lower regions of the human respiratory tract. This suggests that is plausible that indoor air in public settings can cause respiratory tract MRSA infections.

5.2. Prevalence of antimicrobial resistant coagulase-negative staphylococci from hand-touched surfaces and air within public settings

Coagulase-negative staphylococci (CoNS) are less virulent than *S. aureus*, although many species have been identified as nosocomial pathogens and they are a common cause of medical device-associated healthcare infections (MDA-HAI). *S. epidermidis*, *S. haemolyticus* and *S. hominis* are the most frequent CoNS species associated primarily with nosocomial and MDA-HAI infections (Chaves et al., 2005; Cherifi et al., 2013; Czekaj et al., 2015). Similar to *S. aureus,* they too can carry the *mecA* gene, but there are no studies on CoNS methicillin-resistant isolates that focus distinctly on their genotype and phenotype by isolation source. It is believed that these bacteria can be reservoirs for antibiotic resistance and virulence genes for *S. aureus*, contributing to the emergence of rather successful MRSA clones (Otto, 2013) but more research is required to confirm this.

There is only a limited number of studies on the prevalence of CoNS in non-healthcare public settings and the general built environment. These studies have investigated shopping centres (Cave et al., 2019, 2021), train stations (Cave et al., 2019, 2021; Peng et al., 2015; Xu et al., 2018b; Zhou and Wang, 2013), hotel rooms, supermarkets, restaurants, public transport, public libraries (Xu et al., 2018b), around the world; public restrooms (Cave et al., 2019, 2021; Mkrtchyan et al., 2013) and public areas in hospitals in London, UK (Cave et al., 2019, 2021); university campuses in Thailand (Seng et al., 2017), and the metro system in China (Peng et al., 2015; Zhou and Wang, 2013) and food markets in Assam, India (Sivaraman et al., 2020).

In studies that have looked at general public settings in London, the number of antibiotic resistant bacteria reported has varied most likely due to sampling different sites within a relatively large city at different time periods. Mkrtchyan et al. (2013) found that 37.8% of staphylococcus isolates, recovered from 18 public restrooms in four buildings from non-healthcare settings over a period of 24 weeks, were antibiotic resistant. However, Xu et al. (2018b), in a study that collected samples from environmental sites between April 2013 to November 2014 including hotels, baby care facilities, handbags, supermarkets, restaurants, public transport, public library and from the hands of volunteers, found that 94% of the staphylococci isolates were antibiotic resistant. Cave et al. (2019) reported that 46.80% of the samples collected from train stations, shopping centres and public areas in hospitals from East and West London, between November 2016 to September 2017, were multidrug-resistant (MDR) and that the prevalence of multidrug resistant isolates recovered in East London was significantly higher (56.7%) compared to West London (49.96%). A significantly higher number of MDR isolates were also recovered from public areas in hospitals (49.5%) than from public areas within the community (40.66%). The authors concluded that the difference between East and West London was due to the differences in population density, whereas the difference found in public areas in hospitals and public areas in the community is explained by the higher use of antibiotics in hospital settings than in the community.

In studies conducted in London, the proportion of *mecA* positive isolates ranged from 8.17% to 37% (Cave et al., 2019; Mkrtchyan et al., 2013; Peng et al., 2015; Seng et al., 2017; Xu et al., 2018b) with the highest prevalence of *mecA* gene reported from areas examined in public restrooms (Mkrtchyan et al., 2013). Only 6.56% of the isolates recovered from a metro station in China were positive to *mecA* (Peng et al., 2015) but the rate was relatively higher (20.5%) in isolates recovered from a university campus in Thailand (Seng et al., 2017). In addition to this, multilocus sequence types (MLST) of the *mecA* positive *S. epidermidis* isolates were determined by Xu et al. (2018b) and Cave et al. (2019). Xu et al. (2018b) found that all *mecA* positive *S. epidermidis* isolates had novel ST types, however one of the isolates recovered from a hotel room in London belonged to ST59 (Xu et al., 2018a), a sequence type that can cause infection in animals and humans (Argudín et al., 2015). In contrast, Cave et al. (2019) whose study recovered all *S. epidermidis* isolates from public areas in hospitals found that only two out of 17 isolates had novel sequence types. In addition, the authors reported isolates belonging to ST2; a sequence type that has been associated with hospitals and recovered from patients who have an infection caused by an implanted medical device (Argudín et al., 2015; Cave et al., 2019). Isolation of such *S. epidermidis* linages from public areas in hospitals and hotels could potentially pose an as yet unquantified risk to public health. We have not been able to find other studies that have found hospital-associated CoNS in public settings. This may be due to such bacteria not being as virulent and/or prevalent cause of infection compared to *S. aureus* and *S. epidermidis* (Argemi et al., 2019). However, there are many reports in which CoNS infections other than *S. epidermidis* have caused infections within hospitals (Ahmed et al., 2017; Barros et al., 2012; D'mello et al., 2008) and further investigation is needed.

In the studies above, isolates were most often resistant to penicillin (ranging from 65% to 100%). With regard to other antibiotics, two studies conducted in London found a high prevalence of fusidic acid resistance (65% in Xu et al. (2018b) and 72.4% in Cave et al. (2019)), whereas erythromycin resistance dominated in studies evaluating metro systems in China (94.17%) (Peng et al., 2015) and at university campus in Thailand (73.1%) (Seng et al., 2017). Evaluating these reports of staphylococcal isolates recovered from public settings, we found that there was variation between panels of antibiotics that the authors used. Mkrtchyan et al. (2013) did not state which antibiotic(s) the staphylococci isolates recovered from public washrooms were most commonly resistant to, although they did determine that antibiotic resistant staphylococcal isolates had similar antibiograms to different species recovered from the same restroom on different dates. The authors did identify that six isolates belonging to three species recovered from different sites of a single restroom had the same antibiogram and that these antibiograms were also present in other staphylococcal species found in four other restrooms within the same building on different days. This suggested widespread dissemination of resistance determinants in different *Staphylococcus* species and restrooms in the same building.

Antibiotic resistant CoNS isolates were also recovered from air samples taken from public settings in Shanghai metro systems and parks (Zhou and Wang, 2013). In this study, the authors found that within the metro system, CoNS isolates on average were resistant to 2.64 antibiotics; this was significantly higher than isolates taken from a public park (mean 2.03 antibiotic types) but less than those found in hospital treatment rooms (mean 2.94 antibiotic types). High levels of antibiotic resistance found in these areas appears to be linked to closed, crowed environments where there is increased physical contact and AMR genes are able to exchange: the metro system had a higher number of isolates with the *mecA* and *qacA/B* (28 and 40% respectively) compared to those found in parks (5.56% for both genes). In the study by Zhou and Wang, (2013), the antibiotics to which the recovered isolates were most often resistant were bactrim (sulfamethoxazole and trimethoprim) (38.95%), nitrofurantoin (36.28%) and penicillin (30.49%). The CoNS isolates found in metro systems were most resistant to nitrofurantoin (52% of the isolates), whereas those recovered from parks were most resistant to oxacillin (36% of isolates). The statistics behind the prevalence of antibiotics in different settings may well be associated with the history of antimicrobial chemotherapy of park visitors or metro system users (although there will be a crossover between both groups) or that environmental factors may be key drivers for the presence of certain AMR bacteria in different settings. However, it is not well studied why certain AMR bacteria can be found in higher abundance in different settings

without further looking into the environmental impact as a driver (e.g. air pollution) (Hussey et al., 2017), the presence of antibiotic producing microorganisms (Peterson and Kaur, 2018), spatial relationships with the sites where antibiotics are used in high abundance (e.g. healthcare) (Chang et al., 2019) and agriculture (Manyi-Loh et al., 2018) and social interaction of people who could transmit AMR bacteria into these settings.

5.3. Antimicrobial resistant Enterobacteriaceae species recovered from fomite surfaces and air in public settings

Enterobacteriaceae are a group of microorganisms usually associated with the gut but also known to contaminate food, water and the environment (Ashbolt, 2015; Baker et al., 2018; Denis et al., 2016; Manshadi et al., 2013). The presence of these bacteria is usually a sign of faecal contamination, with strains of *Escherichia coli* and species of *Enterobacter, Shigella*, *Salmonella* and *Klebsiella* associated with various types of infections (Clements et al., 2012; Giannella, 1996; Guentzel, 1996; Hale and Keusch, 1996). Treating diseases caused by *Enterobacteriaceae* pathogens can be difficult as many of them are resistant to multiple antibiotics (Agyepong et al., 2018; Kayode et al., 2020). To combat these bacterial infections in clinical settings, last resort antibiotics such as carbapenem and colistin have frequently had to be used (Sekyere, 2019). In recent years carbapenem-resistant *Enterobacteriaceae* (CRE) have emerged which harbour the extended-spectrum β-lactamase (ESBL) and mobile colistin resistance (*mcr*) genes, the presence of which makes many multidrug resistant *Enterobacteriaceae* potentially untreatable, with dire consequences for human health (Drew et al., 2013; Elbediwi et al., 2019; Lerner et al., 2015; Wang et al., 2018).

ESBL is caused by β-lactamase, an enzyme which can hydrolase oxyimino-beta-lactam antibiotics. It was first described in 1983 in *Enterobacteriaceae*, but since then more than 350 ESBL variants have emerged (Bajpai et al., 2017; Knothe et al., 1983). ESBLs are mainly plasmid-borne, and can be characterised into nine distinct groups based on their amino acid sequences and evolutionary history: TEM, SHV, CTX-M, PER, VEB, GES, BES, TLA, and OXA (Rahman et al., 2018). Today, CTX-M is the most predominant of the ESBLs genes, found in humans and disseminated across various epidemiological niches (Rahman et al., 2018). CTX-M was originally derived from the genus *Kluyvera* and has horizontally transferred to other *Enterobacteriaceae* species via recombinant plasmids (Sarria et al., 2001). Epidemiological CTX-M is the most prevalent ESBL gene. First reported in Japan in 1988 (Matsumoto et al., 1988), it has now disseminated globally, with over 170 variants recorded (Ramadan et al., 2019). CTX-M can be found in many ecological niches including healthcare facilities, community settings, livestock and companion animals, wildlife and river water (Azam et al., 2016; Bachiri et al., 2017; Lewis et al., 2007; Ruppé et al., 2009; Sun et al., 2010; Tamang et al., 2013).

CRE is mainly caused by a gene encoded by carbapenem-hydrolysis enzymes, although carbapenem resistance can also result from the over-expression of efflux pumps. The Ambler classification system has classified carbapenemases into four groups, three of which (A, B and D) belong to *Enterobacteriaceae* (Hall and Barlow, 2005). A Class C carbapenemases have also been described; however, they are not considered true carbapenemases as they have a low enzyme's catalytic efficiency and a permeability defect, which only gives them a slight reduction in susceptibility to carbapenems (Bedenić and Sardelić, 2018). Class A carbapenemases are associated with *K. pneumoniae* (KPC) as are the less common non-metallocarbapenemase type A (NMC-A) and SME enzymes; Class B carbapenemases are associated with metallo-β-lactamases (MBL) including New Delhi metallo-β-lactamases (NDM), the IMP family of carbapenemases, and the Verona integron–encoded metallo-β-lactamases (VIM). Class D carbapenemases are associated with OXA-48-like carbapenemases. Currently only two of the CRE genes (KPC and NDM) are widely spread, with KPC being the most widely disseminated, with 13 known variants of the gene (Perez and Van Duin, 2013). First isolated in North Carolina, USA in 1996, the KPC variants have spread globally and transferred across to other *Enterobacteriaceae*, including *E. coli*, *K. oxytoca*, *Enterobacter*, *Serratia*, and *Salmonella* species. NDM was first isolated in 2008 from a Swedish patient of Indian descent who had recently visited New Delhi and although predominantly found in the Indian subcontinent, it soon disseminated to other regions of the world (Yong et al., 2009) In addition to clinical settings, KPC and NDM genes have both been recovered from community settings, livestock, companion animals and rivers (Ahammad et al., 2014; Bayssari et al., 2015; Poirel et al., 2012a,b; Pulss et al., 2018; Shaheen et al., 2013; Song et al., 2019; Souli et al., 2010; Tafoukt et al., 2017; Wang et al., 2012) but how it transfers from one environment to another is not well understood and requires further research.

The *mcr* gene was first identified in China in 2015 from a pig, although historical data for the gene in *E. coli* can be traced back to the 1980s (Liu et al., 2016; Shen et al., 2016). *Mcr* genes have been found to horizontally transfer across other *Enterobacteriaceae* species via a conjugation plasmid and this is known to have transmitted to humans and disseminated around the world (Liu et al., 2016; Wang et al., 2018). To date, there are nine variations of the *mcr* genes of which all but *mcr-6* and *mcr-7* have been recovered from humans. These genes have mainly been determined *in E.coli* (*mcr-1* to *mcr-5*) recovered in three different continents (Africa, Asia and Europe), whereas the *mcr-1* gene has been identified in six continents and is carried by at least 1 of the 10 known *Enterobacteriaceae* species (Gharaibeh and Shatnawi, 2019). The spread of *mcr* genes is believed to be through the food chain as there is a higher prevalence of *mcr* in food samples than in human samples (Luo et al., 2020) but further investigation of food systems is required to fully understand this. In addition, *mcr* has been recovered from wildlife, companion animals and the environment (Ahmad et al., 2009; Lei et al., 2017; Zheng et al., 2017) suggesting complex and possibly intersecting transmission chains that need to be more fully understood.

In total, there are only a few studies that have looked at antibiotic resistant *Enterobacteriaceae* bacteria in public areas in the built environments. These studies include isolates recovered from public buses in Ethiopia; public transport systems and public hired bicycles in China (Shen et al., 2018; Zou et al., 2019; Kahsay et al., 2019). Kahsay et al. (2019) recovered antibiotic resistant *E. coli* and *Enterobacter* spp. from buses in Mekelle city, Tigray, Ethiopia, although the authors only identified isolates' resistance profiles, not any key antibiotic resistance genes and did not test for carbapenem or colistin resistance. They did, however, determine that antibiotic-resistant *E. coli* and *Enterobacter* spp. were recovered less often (4% and 1.3% respectively) than *S. aureus* (18%) from the same sites. Although there was a low recovery rate of *Enterobacteriaceae*, this does suggest contamination of bus surfaces with faecal matter (although *E. coli* can sometimes be found naturally in other environments including tropical soil) containing bacteria that potentially can cause various infections. In addition, all the enteric bacteria recovered from buses were resistant to ampicillin and 75% of all isolates were resistant to chloramphenicol.

In another study, Shen et al. (2018) reported that 3.53% of the isolates recovered from public transport in Guangzhou, China were *mcr-1* positive; 76.9% of the *mcr-1* isolates were recovered from areas that had a high density of hospitals nearby or heavy traffic. Conceição et al. (2013) reported similar findings when they recovered MRSA from public buses linked to hospitals. This may indicate that the *mcr-1* positive isolates recovered in Shen et al. (2018) are likely to have been transmitted onto public transport systems via hospital workers and patients (Lin et al., 2017; Lutz et al., 2014). Future collaborations including social scientists could help to determine commuter routes, visitor travel patterns and hand hygiene en route, map transmission and suggest interventions – such as the most appropriate positioning of hand sanitiser stations or the introduction of touch-free surfaces.

The *Mmcr-1* gene was only identified in *E. coli* (n = 23) and *K. pneumoniae* (n = 3). In addition, *mcr-1* isolates had high resistance rates to ampicillin (96.2%), cefotaxime (80.8%), amoxicillin-clavulanate

(73.1%), fosfomycin (61.5%) and gentamicin (57.7%), indicating a concerningly high level of multidrug resistance (Shen et al., 2018).

Whole genome sequencing analysis has demonstrated the presence of the ESBL gene $bla_{\text{CTX-M-55}}$ and $bla_{\text{CTX-M-99}}$ in 15 of *E. coli* isolates and $bla_{\text{CTX-M-3}}$ in all three *K. pneumoniae* isolates. The *mcr-1* positive *(mcr-1*$^{+}$*) E. coli* isolates belonged to various sequence types of which the most notable was ST2253, which has previously been isolated from patients with bloodstream infections, indicating that the presence of these isolates in public settings may pose a risk to public health. However, not all lineages were associated with humans: for example ST101, a lineage reported to be associated with water, sewage and poultry, and the ST10 complex were recovered from animals, patients and the environment (Shen et al., 2018).

Zou et al. (2019) reported that 19.7% of shared bikes parked near metro stations in Beijing were positive for Enterobacteriaceae, of which 40% of isolates were resistant to at least one antibiotic and 2.7% were considered multidrug-resistant, including *E. coli* (n = 8), *S. marcescens* (n = 2) and *K. pneumoniae* (n = 1). The overall resistance rate was low (0.5–6%) for 9 out of 10 antibiotics tested including colistin (3.6%). Only sulfamethoxazole-trimethoprim was detected at a high resistance rate (31.5%). Unlike Shen et al. (2018), the authors (Zou et al., 2019) did not detect the *mcr-1* gene. They did, however, detect that three *E. coli* isolates were positive for the ESBL-associated gene $bla_{\text{CTX-M-199}}$ and two *E. coli* isolates were positive for the CRE associated gene $bla_{\text{NDM-5}}$. Interestingly, univariant ($p < 0.2$) and multivariable logistic analysis ($P < 0.05$) showed a significant association of antibiotic-resistant Enterobacteriaceae isolated from bikes stationed near hospitals (2 km diameter), suggesting that this may be a key site for hygiene-based interventions. Additionally, several species of antibiotic-resistant *Enterobacteriaceae*, including *K.* pneumoniae, *Pantoea calida*, *E. hormaechei*, *P. stuartii*, *P. rettgeri*, *P. vermicola*, *Raoultella terrigena*, and *Kosakonia radicincitan* were recovered from bikes stationed near hospitals, but not from other hire bike stations. The authors also found that bikes stationed near hospitals had higher or similar resistance rates to eight of the 10 tested antimicrobial agents. These results were consistent with the findings by Shen et al. (2018) as both studies detected higher rates of antibiotic resistant *Enterobacteriaceae* near hospitals, which offers further opportunities for the development of targeted hygiene interventions.

5.4. Other bacterial species found in general public built environments and opportunities offered by metagenomic analysis.

Apart from *Staphylococcus* and *Enterobacteriaceae*, other bacteria commonly isolated from public settings in built environments include *Bacillus*, *Propionibacterium, Streptococcus, Corynebacterium*, *Pseudomonas*, *Micorococcus* (Afshinnekoo et al., 2015; de Sousa, 2020; Fahimipour et al., 2018; Hartmann et al., 2016; Hsu et al., 2016; Mkrtchyan et al., 2013; Wu et al., 2021). The authors of the majority of these studies have evaluated public transport systems in the relevant city. However, all these studies have limitations and provide little information on the antibiotic resistance profiles of the isolates or genes responsible for resistance (Afshinnekoo et al., 2015; Hsu et al., 2016; Kang et al., 2018). The reasons for not conducting detailed investigation of these isolates remains unexplained as various species belonging to *Streptococcus, Pseudomonas* and *Corynebacterium* commonly found in public settings are known human pathogens and would have warranted further investigation. A plausible reason for the lack of reporting may be due technological limitations. Newer, sequence-based metagenomics approaches can now capture both taxonomic composition and specific features such as resistance and virulence factors, however to date there are few studies that use sequence-based metagenomics in public settings.

This shortfall was highlighted in Hsu et al. (2016), which reported the metagenomic analysis of bacteria found on surfaces in the Boston metropolitan transit system. The authors found that human skin and oral commensals, and opportunistic pathogens such as *Propionibacterium*, *Corynebacterium*, *Staphylococcus*, and *Streptococcus*, were commonly recovered from the surfaces. However, overall a minimal level of antibiotic resistance genes was detected from sequence reads (average reads per kilobase per million reads (RPKMs) per sample for antibiotic resistance markers was 1.72, with values ranging from 0 to 46.67) in comparison to those found in the human gut, with low levels of genes responsible for tetracycline and beta-lactamase resistance.

Afshinnekoo et al. (2015) examined the New York subway and found that 31% of the bacteria were opportunistic pathogens: 12% of the isolates were identified as *Pseudomonas stutzeri*, followed by strains belonging to *Enterobacter* and *Stenotrophomonas*. However, the authors reported only the presence of the mecA gene, without further analysis of the data. Across their samples, they reported 0.2 × –32 × coverage of the gene and five of the 18 subway stations they tested harboured unidentified bacteria which were resistant to one of three antibiotics used in the study (kanamycin, chloramphenicol, and ampicillin).

Kang et al. (2018) conducted metagenomic analysis of inner- and intercity traffic flow on the Hong Kong metro line and found higher abundance (322.6 ± 62.1 RPM) of antibiotic resistance genes compared to the study conducted in Boston by Hsu et al. (2016). The authors stated that the relative abundance of AMR was higher than that found in drinking water and marine sediments they had previously detected in Hong Kong (Guo et al., 2016) but lower than was reported for the samples recovered from human gut samples in China (Yu et al., 2017). Many of these antibiotic resistance genes encoded for antibiotics used in clinical settings, including vancomycin, erythromycin and methicillin. Furthermore, Kang et al. (2018) found that 8 out of 10 most common bacterial species recovered from surfaces were human skin commensals, of which 40.13% ± 6.25% were opportunistic pathogens (*P. acnes, A. baumannii, S. epidermidis, E. coli, and S. aureus*). The authors determined a time signature for the emergence of the AMR genes: during the afternoon and evening (pm) the abundance of genes responsible for resistance to antibiotics widely used in clinic increased, including genes that confer resistance to tetracycline, vancomycin, erythromycin and methicillin. It was theorised that this is mostly likely due to increased human traffic at these times, but social-science informed observational studies should be developed to test this hypothesis. In addition to this, the authors found that the inter-city train connecting Hong Kong to Shenzhen in mainland China had a significant day-to-day increment of clinically important antibiotic resistance genes (24.1%), indicating possible cross-border transmission of antibiotic resistant bacteria. Studies focussed on the movement and behaviour of people that can tie specific actions to the environmental spread of bacteria and resistant genes are clearly needed to fully understand these transmission pathways.

A recent metagenomic study of mass transit systems across 60 cities around the world has also found a low abundance of antibiotic resistance genes (Danko et al., 2021). The authors used metagenomics to identify that 2,210 out of 4,728 samples had AMR gene sequences, of which the most common antibiotic resistance detected was for macrolides, lincosamides, streptogamines (MLS), and beta lactams; some of the most commonly used antibiotics to treat bacterial infection in humans. Overall, there was a low abundance of AMR genes detected from all cities (AMR classes ranging from 0.1 to 1 Reads Per Kilobase Million (RPKM)) compared to housekeeping genes (10-100RPKM). However, this low RPKM could be explained by AMR classes containing many genes: if individual genes were measured, the RPKM is likely to be higher. In addition, Danko et al. (2021) suggest that these samples may contain undetected AMR genes that have not been previously characterised. The samples contained sequences from hundreds of distinct AMR genes, those these were not distributed evenly across cities. This may be due to differences in the amount of antibiotics used in these areas, urban geographical differences such as population density, as well as the difference in the cities' individual microbiomes, all of which suggests avenues for further study. Overall, the three most common bacterial phyla across the 60 cities were *Proteobacteria, Actinobacteria*

and *Firmicutes* and many of the taxa found in these areas can be associated with human infections including *Staphylococcus, Streptococcus, Corynebacterium, Klebsiella* and *Enterobacter* species. None of the three studies was able to link the antibiotic resistance genes to the bacterial species, however, suggesting that if bacteria recovered from mass public transit areas are species that can cause infections, then they still may be a risk to public health.

Metagenomic studies from other public settings have also suggested that the level of antibiotic resistance is relatively low. Hartmann et al. (2016) found that dust samples recovered from mixed-use athletic and educational facilities had a median RPKM per sample of 23.24 attributed to AMR genes, of which the most abundant were tetracycline-resistance *tet(W)*, extended-spectrum beta-lactamase blaSRT-1, and macrolide-resistance *erm(B)* genes. Moreover, there was a correlation with the use of the disinfectant triclosan, 23S rRNA methyltransferase gene *erm (X)* and efflux pump *tet(K)* and *vga(A)*, as well as correlation with the disinfectant methylparaben and the *erm(33)*, *erm(c)* and *cmr* efflux pump. These results showed no suggestion that these AMR genes may benefit bacterial survival due to the presence of tricon and methylparaben; however the use of disinfectants could be the cause of AMR presence (Mahnert et al., 2019) as conducting metagenomics analysis the authors found that there was a reduced bacterial diversity and high levels of AMR in areas that was highly maintained for cleanliness (intensive care unit) compared to other built environments. Similar findings were reported by Fahimipour et al. (2018) who were able to demonstrate a correlation between the increased abundance of triclosan- and triclocarban in indoor athletics arenas in the USA and the increased number of Gram-positive bacteria with diverse drug resistance genes recovered from dust. In that study, the most common taxa recovered from these settings were *Propionibacterium acnes*, *Pseudomonas* sp. and *Massilia* spp. However, *Micrococcus luteus* was considered the most antimicrobial enriched species recovered, with genes that have transferred resistance to disinfectants (*qnr* and *ftsH*). Other species the authors found to be antimicrobial enriched included *Finegoldia magna ocuria rhizophila*, *Eubacterium rectale*, *Gardnerella vaginalis*, and *Lactobacillus crispatus.* Not all bacteria found in areas of high triclosan- and triclocarban carried AMR genes, however, for example, the human skin commensals *Corynebacterium tuberculostearicum*, *C. pseudogenitalium*, *C. amycolatum C.tuberculostearicum*, *C. pseudogenitalium*, *C. amycolatum*, and *C. genitalium* were found in areas where high levels of triclosan- and triclocarban were detected but they carried no AMR genes. Apart from performing metagenomic analysis, isolates were also cultured, of which 71.7% of colonies (unidentified) displayed no resistance to three antibiotics (ampicillin, clarithromycin and tetracycline). However, the study did find that 41 of 42 buildings tested harboured at least one bacterium (cultured) showing resistance to at least one antibiotic. There is clearly a bigger picture here, and the quantity of isolates than can be studied using metagenomic techniques can help to illuminate this.

6. Conclusion and recommendation

From the literature we reviewed for AMR bacteria in public settlings and built environments and our own previous research; we identified a threat to human health from *Staphylococcus* spp. and *Enterobacteriaceae* recovered from the surfaces found in many public settings including, hotels (Xu et al., 2015), washrooms (Mkrtchyan et al., 2013) and general public settings (Cave et al., 2019, 2021), university campuses and recreational beaches in the USA (Roberts et al., 2013); public transport (Conceição et al., 2013; Lin et al., 2017; Lutz et al., 2014; Peng et al., 2015; Kahsay et al., 2019); and shopping baskets in Japan (Domon et al., 2015) as well as from rivers (Ahammad et al., 2014; Tafoukt et al., 2017) and companion animals (Pulss et al., 2018; Shaheen et al., 2013)

The number of studies available is not large, but it appears many of the AMR isolates that show resistance to clinically important antibiotics may well transmit from hospitals through high-touch surfaces associated with public transport on which staff and patients travel to and from healthcare settings, or hired bicycles used by similar groups. This suggests that with more robust data on such settings, investigations of the efficacy of targeted hygiene interventions could be warranted, perhaps leading to the encouragement of long-term adoption of the frequent hand sanitising that has become common during COVID-19 and the permanent introduction of sanitiser stands at the entrance to train stations, on buses and at bike hire points close to healthcare facilities. Indoor areas have also been found to have a particularly high prevalence of AMR bacteria, which may be due to high levels of disinfectant use, with some AMR genes demonstrating a crossover resistance to disinfectants (Buffet-Bataillon et al., 2015; Kampf, 2018). Metagenomic analysis carried out in mass transport systems, athletics facilities and schools – which are less frequently subjected to the deep cleaning with stringent disinfectants used in indoor arenas – has shown a low abundance of antibiotic resistance in these settings compared with environments where stronger disinfectants are used. The impact of this on the human microbiome, and the potential to drive further resistance to sanitising products is however unknown and should form part of future studies. We also need to consider how much sanitation is warranted as we need to consider the "hygiene hypothesis" (Apostol et al., 2020; Strachan, 1989) in that the underexposure to microbes in the environment in early life can lead to immune-related disease and that being "too clean" can be harmful as it can reduce the diversity of microbes in environment important in training our immune system.

Overall, very little remains known about AMR bacteria from public settings within built environments, including whether resistance is increasing or decreasing in these settings as there have been no longitudinal studies. Most of the studies conducted have looked primarily at public transport systems, but very little is known about AMR bacteria in hand touched surfaces, dust and air samples within other public settings such as cinemas, shops, restaurants, pubs, bars and cafes as well as the prevalence of livestock associated resistance genes in settings close to farms and agricultural land.

There is limited information about the public health risk these AMR bacteria pose, as many of the metagenomic studies conducted have not so far linked the AMR genes detected to bacterial taxa. This may be due to sequencing technology producing only short-reads, which can only qualify genes and not contextualise them, although new assemblies and algorithms have been developed to help contextualise short-read metagenomic data (Nurk et al., 2017; Olekhnovich et al., 2018). Moreover, recently, new long-read sequence technology can further link genes to the bacterial species they belong to and their molecular typing (Arango-Argoty et al., 2019), which opens possibilities for future studies in this area: to better determine and link AMR genes to their host bacterial species, and to focus on a wider range of pathogenic bacteria. The existing literature suggests that the *mcr,* NDM and KPC genes warrant particular attention to better understand how they transfer between environments. In addition, such technology may help to determine if current policies around hygiene, cleaning, use of disinfectants and hand sanitisers have helped to reduce AMR in public settings and built environments. Better of understanding the current situation will require short-term studies to determine current baselines and long-term longitudinal studies to identify trends, areas of vulnerability and priorities for intervention, with a notable role for social science collaboration to identify behaviours and movements that may contribute to or amplify spread.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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