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REVIEW

Strategic measures for the control of surging antimicrobial resistance in Hong Kong and mainland of China

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Antimicrobial-resistant bacteria are either highly prevalent or increasing rapidly in Hong Kong and China. Treatment options for these bacteria are generally limited, less effective and more expensive. The emergence and dynamics of antimicrobial resistance genes in bacteria circulating between animals, the environment and humans are not entirely known. Nonetheless, selective pressure by antibiotics on the microbiomes of animal and human, and their associated environments (especially farms and healthcare institutions), sewage systems and soil are likely to confer survival advantages upon bacteria with antimicrobial-resistance genes, which may be further disseminated through plasmids or transposons with integrons. Therefore, antibiotic use must be tightly regulated to eliminate such selective pressure, including the illegalization of antibiotics as growth promoters in animal feed and regulation of antibiotic use in veterinary practice and human medicine. Heightened awareness of infection control measures to reduce the risk of acquiring resistant bacteria is essential, especially during antimicrobial use or institutionalization in healthcare facilities. The transmission cycle must be interrupted by proper hand hygiene, environmental cleaning, avoidance of undercooked or raw food and compliance with infection control measures by healthcare workers, visitors and patients, especially during treatment with antibiotics. In addition to these routine measures, proactive microbiological screening of hospitalized patients with risk factors for carrying resistant bacteria, including history of travel to endemic countries, transfer from other hospitals, and prolonged hospitalization; directly observed hand hygiene before oral intake of drugs, food and drinks; and targeted disinfection of high-touch or mutual-touch items, such as bed rails and bed curtains, are important. Transparency of surveillance data from each institute for public scrutiny provides an incentive for controlling antimicrobial resistance in healthcare settings at an administrative level.
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INTRODUCTION

The World Health Organization (WHO) global report on surveillance of antimicrobial resistance in 2014[1] stated that, 'a post-antibiotic era—in which common infections and minor injuries can kill—far from being an apocalyptic fantasy, is instead a very real possibility for the 21st Century. The report makes a clear case that resistance to common bacteria has reached alarming levels in many parts of the world and that in some settings, few, if any, of the available treatments options remain effective for common infections'. In September 2014, the US government issued a national policy for the White House national strategy for combating antibiotic-resistant bacteria[2] and set up a task force for combating antibiotic-resistant bacteria. Despite the rising antimicrobial resistance in Hong Kong and mainland China, a corresponding effort to combat this huge public health threat is not apparent. Here, we review the burden of this problem, its origin, its transmission dynamics and control measures, using data from local and mainland China where possible.

MAGNITUDE OF THE PROBLEM

Survey of antibiotic producing bacteria for antibiotic resistance genes showed the existence of a vast environmental pool of resistance genes with the potential to be captured and amplified in human flora if given the correct circumstances.[3] No wonder that the battle between human use of antimicrobials and development of resistance in microbes started soon after the discovery of sulphonamide and penicillin. Penicillin resistance rapidly emerged in *Staphylococcus aureus* in the 1940s when penicillin was widely used in humans.[4] While community-acquired penicillin-resistant *Streptococcus pneumoniae*[5] and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae[6] have been increasingly reported in the last two decades, methicillin-resistant *Staphylococcus aureus* (MRSA)[7] and vancomycin-resistant Enterococcus (VRE)[8] have now become endemic in many hospitals. Recently, the emergence of carbapenem-resistant *Acinetobacter baumannii* (CRAB), multidrug-resistant A*cinetobacter baumannii*[9] and carbapenemase-producing Enterobacteriaceae (CPE)[10,11] have been reported in many parts of the world. The increasing or persistent trends of MRSA, ESBL-producing *Escherichia coli*, CRAB and carbapenem-resistant *Pseudomonas aeruginosa* in a teaching hospital in Hong Kong between 1998 and 2012 are illustrated in Figure 1.

The burden of antibiotic resistance is serious in mainland China. According to data from the Shanghai Bacterial Resistance Surveillance Project involving 23 hospitals since 1989, and CHINET, a national

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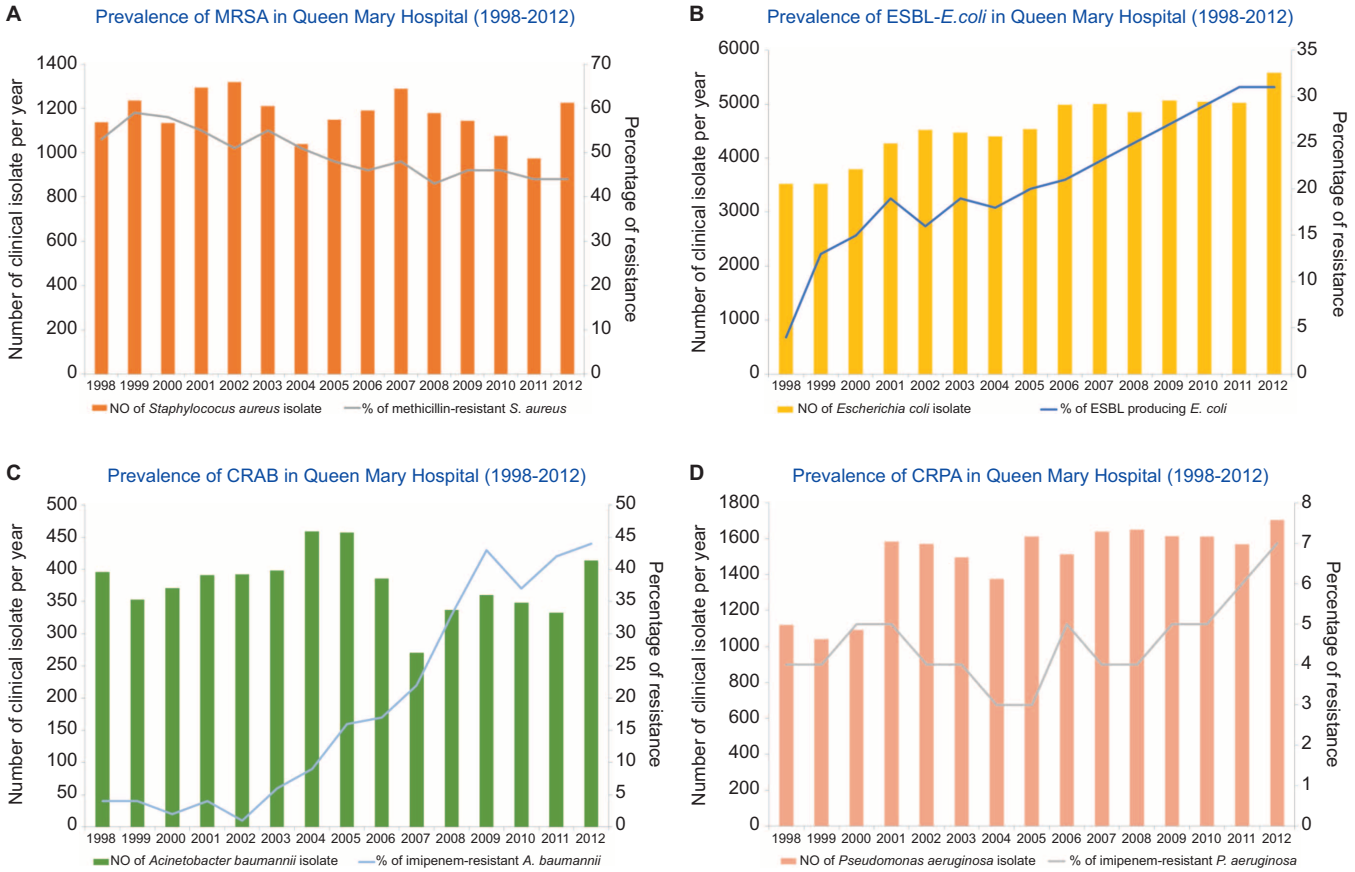

Figure 1 The prevalence of MRSA (**A**), ESBL-*E. coli* (**B**), CRAB (**C**) and CRPA (**D**) in Hong Kong, using laboratory data from Queen Mary Hospital as a surrogate marker between 1998 and 2012. Non-duplicate isolates selected from the first isolate for the same patient with the same specimen collected from blood, urine, and respiratory system were recruited for analysis, and interpreted according to Clinical and Laboratory Standards Institute. CRPA, carbapenem-resistant *Pseudomonas aeruginosa*.

bacterial resistance surveillance project in China involving 15 tertiary hospitals (13 university hospitals and 2 children's hospitals) since 2005, the prevalence of MRSA has gradually increased from less than 10% in the 1980s to 50%–70% in the 2000s, while the prevalence of ESBL-producing *E. coli* has increased from 30% in 2000 to 60% in 2012. The CTX-M genotype constituted 98.1% of the 158 strains of ESBL-producing *E. coli* being tested.[12] Enterobacteriaceae with decreased susceptibility to carbapenems were also observed in mainland China. Of the 49 Enterobacteriaceae isolates with decreased susceptibility to carbapenems collected from 2004 to 2008 in 16 teaching hospitals, CPE was noted in 33% (16/49), *Klebsiella pneumoniae* carbapenemase (KPC-2) was found in six isolates, and imipenemase-4 (IMP-4) and imipenemase-8 (IMP-8) were identified in eight and two strains, respectively.[13] The dissemination of CTX-M and carbapenemase-type resistance involves both the expansion of successful clones and acquisition of resistance plasmids. Clonal expansion is the main mechanism for KPC dissemination, especially in healthcare settings. Qi *et al* reported that *K. pneumoniae* ST11 (a variant of the pandemic ST258 clone) was the dominant KPC-producing clone among 95 isolates from 15 hospitals in nine cities covering five provinces in China during 2006–2009.[14] In contrast, transmissible plasmids or transposons with integrons are the main vehicles through which the New Delhi metallo-β-lactamase (NDM) and IMP-type of genes spread in the community and hospitals.[15–18] In China, self-transmissible IncX3 plasmids seem to be a common vehicle mediating the spread of NDM-1. IncX3 plasmids carrying NDM-1 have been detected in patients with epidemiological links to Guangzhou, Hunan, Haifeng and Dongguan[19] and have been reported to cause nosocomial outbreaks in a Beijing hospital.[20] IncX3 plasmids carrying NDM have also been reported from India and the United Arab Emirates. Of the >35 different IMP alleles, IMP-4 occurred most frequently among isolates from China, and the gene was often carried on broad host-range plasmids, such as IncN and IncA/C groups, with the ability to shuttle into and out of Enterobacteriaceae, *P. aeruginosa* and *A. baumannii*.[17,18,21] Among non-glucose fermenters, the prevalence of carbapenem-resistant *P. aeruginosa* was found to be 29% in 2011. The proportion of CRAB also increased from 50% to 60% from 2009 to 2011, and OXA-23 was the most prevalent plasmid-encoded carbapenemase among CRAB isolates in China, which were found in 97.7% (216/221) of imipenem-resistant clinical isolates collected from 11 teaching hospitals.[22] Moreover, NDM-1-producing *A. baumannii* has recently been reported in four different provinces in mainland China.[22]

MORTALITY RELATED TO MULTIDRUG-RESISTANT ORGANISMS

Resistance against commonly used antibiotics in pathogens isolated from invasive infections is associated with increased morbidity and mortality.[23–25] In community-acquired infections, mortality from invasive pneumococcal pneumonia was significantly associated with penicillin minimum inhibitory concentrations of 4.0 mg/L or higher and cefotaxime minimum inhibitory concentration of 2.0 mg/L or higher, as shown in a cohort of 5837 cases in 1995 through 1997 in

the United States.[26] Patients with pneumococal bacteremia and meningitis due to a non-susceptible antibiotic strain have an increased risk of mortality[27,28] Inadequate initial antimicrobial therapy was shown to be an independent risk factor for mortality in patients with ESBL-producing Enterobacteriaceae infections, as illustrated in two retrospective cohort studies involving almost 400 subjects in the United States and Italy.[29,30] Mortality following bacteremia caused by ESBL-producing *E. coli* was significantly higher than non-ESBL-producing *E. coli* regardless of whether the infection was acquired in the community or in hospitals.[31]

In hospital-acquired infections, patients with non-pneumonic MRSA infections had a higher 90-day mortality compared with patients with non-pneumonic methicillin sensitive *Staphylococcus aureus* infections, independent of the severity of the patients' underlying illnesses.[32] In addition, patients with nosocomial MRSA bacteremia had a crude mortality of 50%, according to a large cohort of 1148 patients over 15 years.[33] Even in critically ill patients, those with MRSA bacteremia had a significantly higher attributable 30-day mortality rate (53.2% *vs.* 18.4%) and in-hospital mortality rate (63.8% *vs.* 23.7%) than patients with methicillin sensitive *Staphylococcus aureus* bacteremia, after accurate adjustment for disease severity.[34]

Carbapenem-resistant gram-negative organisms also carried significant mortality in hospitalized patients. The 30-day mortality in patients with CRAB in intensive care units was as high as 80%.[35] Similarly, the in-hospital mortality of patients associated with carbapenem-nonsusceptible *Klebsiella pneumoniae* and *E. coli* in intensive care units was found to be 50% in a nationwide multicenter study in Taiwan.[36] Nineteen (29%) of 66 isolates had genes encoding carbapenemases, including KPC-2 (n=14), IMP-8 (n=1), Verona integron-encoded metallo-β-lactamase (VIM) (n=3) and NDM-1.

HEALTHCARE COSTS RELATED TO MULTIDRUG-RESISTANT ORGANISMS

Multidrug-resistant organisms complicate clinical treatment and increase cost. Hospital antibiotic costs were higher in the penicillin-resistant *S. pneumoniae* group compared with penicillin-susceptible *S. pneumoniae* (Canadian dollars 211 *vs.* 74; P=0.02) in a case-control study.[37] In a case-control analysis from Israel for patients with ESBL-producing Enterobacteriaceae, the median length of stay after bacteremia was 11 days for cases (interquartile range: 5–21) versus 5 days for controls (interquartile range: 3–9) (P<0.001). The average hospital cost was Israeli shekels 65 509 for cases versus 23 538 for controls (P<0.001). After adjusting for differences between groups using multivariable analysis, ESBL production remained a significant predictor for increased length of hospital stay (1.56-fold; P=0.001) and increased cost (1.57-fold; P=0.003).[38]

Cost analysis of patients with nosocomial MRSA infections also showed that MRSA infection was independently associated with higher hospitalization costs (median of US$18129.89 *vs.* US$4490.47; P<0.001) and higher post-discharge healthcare-associated financial costs (median of US$337.24 *vs.* US$259.29; P=0.021) in a matched case–control study in an endemic area.[39]

The impact of carbapenem resistance on cost outcomes among patients with *P. aeruginosa* and *A. baumannii* infection was also studied. Compared with patients infected with imipenem-susceptible *P. aeruginosa*, patients infected with imipenem-resistant *P. aeruginosa* had longer hospitalizations (15.5 days *vs.* 9 days; P=0.02) and greater hospital costs (US$81 330 *vs.* US$48 381; P<0.001).[40] The average total cost of hospitalization among patients with CRAB was significantly higher than that among patients with carbapenem-susceptible *A. baumannii* in a multivariate analysis (adjusted cost, US$11 359 *vs.* US$7049; P<0.001).[41] The cost of a medical intensive care unit closure due to an outbreak of CRAB in a hospital was estimated to be €216 553, while the cost of waste elimination and cleaning procedures was about €12 000. The cost of drug and non-cleanable equipment destruction was approximately €36 000, and the estimated direct cost of the intensive care unit closure was €264 553.[42]

CONSUMPTION OF ANTIMICROBIALS IN ANIMALS AND HUMANS

The increasing trend of antibiotic consumption in animal husbandry was associated with the spread of antimicrobial resistance.[43] In an earlier study, the intestinal flora of the farm personnel has changed after the use of tetracycline-supplemented feed on a chicken farm. As expected, the intestinal flora of the chicken consisted almost entirely of tetracycline-resistant organisms within one week of starting tetracycline-supplemented feed. Furthermore, 31.3% of the weekly fecal samples from farm dwellers converted to an intestinal flora consisting of greater than 80% of tetracycline-resistant bacteria within 5 to 6 months. Selective pressure by tetracycline-supplemented feed in chickens appeared to extend to human in contact with chickens and the feed, resulting in a change to a predominant tetracycline-resistant intestinal flora.[44] The occurrence of acquired resistance to antimicrobials used for growth promotion among bacteria isolated from swine, cattle and poultry was demonstrated in Denmark during October 1995 to September 1996.[45] In fact, there was a clear and significant increase in the amount of resistance genes in the fecal metagenomes from Spanish, Danish, and American subjects for antibiotics approved for animal use by the Food and Drug Administration of the United States and for other antibiotics that have historically been used in the market.[46] According to a survey in 2007, China produced and consumed the largest quantity of antimicrobials by country.[47] The estimated annual antimicrobial production in China was 210 million kg, and 46% of these were used in the livestock industry. In a recent analysis of antimicrobial consumption in the United States, the estimated annual antibiotic use in livestock was 13.54 million kg, followed by humans (3.29 million kg), aquaculture (0.15 million kg), pets (0.15 million kg) and crops (0.07 million kg), with approximately 80% of antibiotics being consumed in agriculture and aquaculture.[48]

The use of antibiotics in human also correlated with increasing isolation of multidrug resistant organisms (MDROs). The association of CRAB infection with hospital antimicrobial usage between 2003 and 2011 was assessed in a tertiary care hospital in northeast China. It was found that the rates of CRAB increased significantly from 11.3% to 59.1%. The quarterly use of carbapenems, but not other classes of antibiotics, was correlated strongly with the increase of quarterly isolation of CRAB (β=1.661; P<0.001).[49] Similarly, a significant increase in the usage of carbapenems was strongly correlated with the isolation of imipenem- and meropenem-resistant *P. aeruginosa* (P<0.001).[50] Such high incidences of MDROs are likely to be related to the inappropriate use of antimicrobial agents in mainland China. A study conducted in mainland China—the first of its kind—examined 230 800 prescriptions written between 2007 and 2009 at 784 community health institutions in 28 cities across China and revealed substantial overprescribing, including twice as many prescriptions for antibiotics as recommended by the WHO.[51] Another observational study conducted in the Sichuan province, an agricultural and economically developing province in western China, collected and analyzed a total of 3059 prescriptions from 30 township health centers. Approximately 85% of the prescriptions contained antibiotics, of which 25% contained

two or more types of antibiotics. Such irrational prescription practice is due to the pursuit of maximal monetary profits in the township health centers, as well as a lack of medical knowledge about rational prescription practice among rural doctors and the lack of diagnostic medical laboratory services in these township health centers.[52] In fact, antimicrobial abuse in China is not driven by patients' demands but is mainly a supply-driven phenomenon, as illustrated in an audit study. In this study, paired simulated patients with identical flu-like symptoms visited the same physician; simulated patient A asked questions that showed knowledge of appropriate antibiotic use, whereas patient B said nothing beyond describing the symptoms. It was interesting to note that patients who displayed knowledge of appropriate antibiotic use were prescribed fewer antibiotics.[53]

ANTIMICROBIAL RESIDUES AND RESISTANCE GENES IN SEWAGE AND FOOD

The nondiscretionary use of antibiotics in agriculture and human medicine has led to the discharge of many residual antimicrobial compounds and their derivatives into the sewage system, which is considered an emerging environmental niche for the dissemination of antimicrobial resistance genes. The coastal water of Bohai Bay in northern China was investigated for the presence of 21 antibiotics from six different classes. Antibiotic levels in the north Bohai Bay were generally higher than those in the South, highlighting the remarkable effects of high-density aquaculture activities on the exposure of the environment to antimicrobials. The antibiotic levels found in the six rivers flowing into the Bohai Bay were generally higher than those in Bohai Bay, reflecting the importance of river discharge as the source of these antibiotics.[54] In eastern China, the occurrence and dissipation of 14 selected antibiotics, including tetracyclines, sulfonamides, macrolides, fluoroquinolones and chloramphenicol, were investigated in two swine wastewater treatment systems. As anticipated, highest contamination by tetracycline, oxytetracycline, chlortetracycline, doxycycline and sulfadiazine was noted in the sample tested, with maximum concentrations reaching 41.6, 23.8, 13.7, 685.6 and 98.8 μg/L, respectively.[55] In southern China, fluoroquinolones (ciprofloxacin, norfloxacin and ofloxacin), macrolides (dehydroerythromycin, roxithromycin and clarithromycin), sulfonamides (sulfamethoxazole and sulfamethazine) and trimethoprim were ubiquitous in wastewater. Fluoroquinolones (norfloxacin) were the most abundantly detected antibiotic in raw sewage, with a maximum concentration of up to 6.415 μg/L. A median percentage of 67% of sulfonamides and 86% of macrolides remained in the final effluent after treatment in sewage treatment plants.[56] In the urban regions of southern China, sulfamethoxazole was the most frequently detected antibiotic residue in the Guangzhou section of the major Pearl River. The maximum concentration of sulfamethoxazole reached 5.597 μg/L in the raw wastewater from a large-scale sewage treatment plant in Guangzhou.[57] In Hong Kong, a study revealed that cephalexin, amoxicillin, ofloxacin and erythromycin were ubiquitous in seawater throughout Victoria Harbor, indicating their continuous discharge into the environment.[58] In the sewage treatment plants in Hong Kong, cephalexin, ofloxacin and erythromycin were found in concentrations of 1.020-5.640, 0.142-7.900, 0.243-4.740 μg/L in influent, respectively.[59] This degree of contamination was comparable to levels reported in urban regions in mainland China.

As expected, these residual antibiotics in wastewater will select for and enrich resistance genes in the environmental bacteria; these, in turn, could eventually enter the food chain via food animals and agricultural produce, which are in close contact with the soil and water that are inevitably contaminated by animal and human sewage. In China, the occurrence and diversity of many different transmissible genes conferring fluoroquinolone resistance (*qnrA, qnrD, oqxA* and *aac(6′)-Ib-cr*) and ESBLs (CTX-M-27 and CTX-M-14) co-existed in different isolates and serovars of non-typhoidal Salmonella from food-producing animals. The presence of MDROs in food-producing animals may carry a risk for the global dissemination of antibiotic resistance.[60] In Hong Kong, longitudinal studies have confirmed the endemic presence of ESBL-producing *E. coli* isolates in the major food-producing animals (chickens, pigs and cattle) with increasing prevalence from 2008/2009 to 2012/2013.[61–63] In 2012–2013, approximately seven out of 10 live chickens, eight out of 10 pigs and five out of 10 cattle were found to carry these bacteria (Figure 2). Among the ESBL-producing isolates carried by the animals, co-resistance to other classes of antimicrobials (tetracyclines, aminoglycosides, sulphonamides and fluoroquinolones) that are widely used in animal feed or veterinary treatment was also detected. Molecular epidemiological investigation further demonstrated that the predominant resistance determinants associated with resistance to expanded-spectrum cephalosporins ($bla_{\text{CTX-M}}$), aminoglycosides (*aacC2*) and sulphonamides (*sul*) at the level of the gene allele, integron cassette or plasmid vehicle in the animal isolates were identical or highly similar to those carried by asymptomatic humans, and to those in clinical *E. coli* isolates from Hong Kong.[63–67]

CONTROL OF ANTIBIOTIC RESISTANCE ON FARMS

In light of the association between antibiotics used on farms and the subsequent identification of MDROs in food animals and food products, the control of antibiotic use in farms has become one of the most important upstream control measures (Figure 3). Restriction of antibiotic use as growth promoters in farms was first introduced in Sweden in 1986. Swedish farmers supported the ban because the consumer confidence in meat safety dropped when the public learned that 30 tons per year of antibiotics had been used in Sweden for food animal production. Similarly, because of consumers' concerns regarding antimicrobial resistance, farmers in Denmark voluntarily stopped all antimicrobial use as growth promoters in 1999, after the government banned the use of avoparcin in 1995 and virginiamycin in 1998, respectively. The avoparcin ban in 1995 was followed by a decrease in the occurrence of glycopeptide-resistant *E. faecium* in broilers from

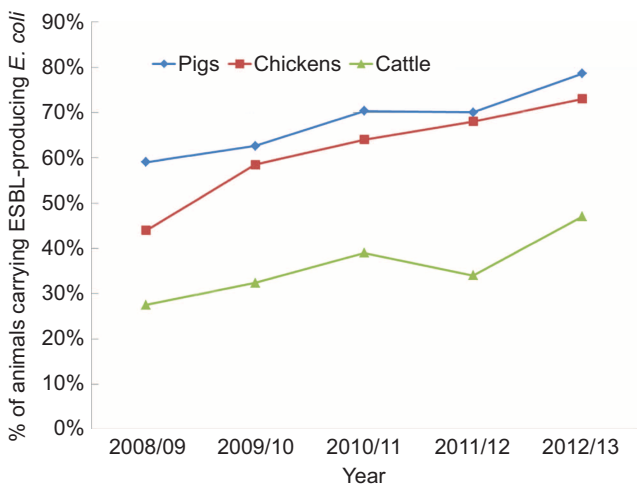

Figure 2 Prevalence of fecal samples carrying ESBL-producing *E. coli* in food animals (1260 chickens, 610 pigs, and 590 cattles), in Hong Kong, 2008–2013.

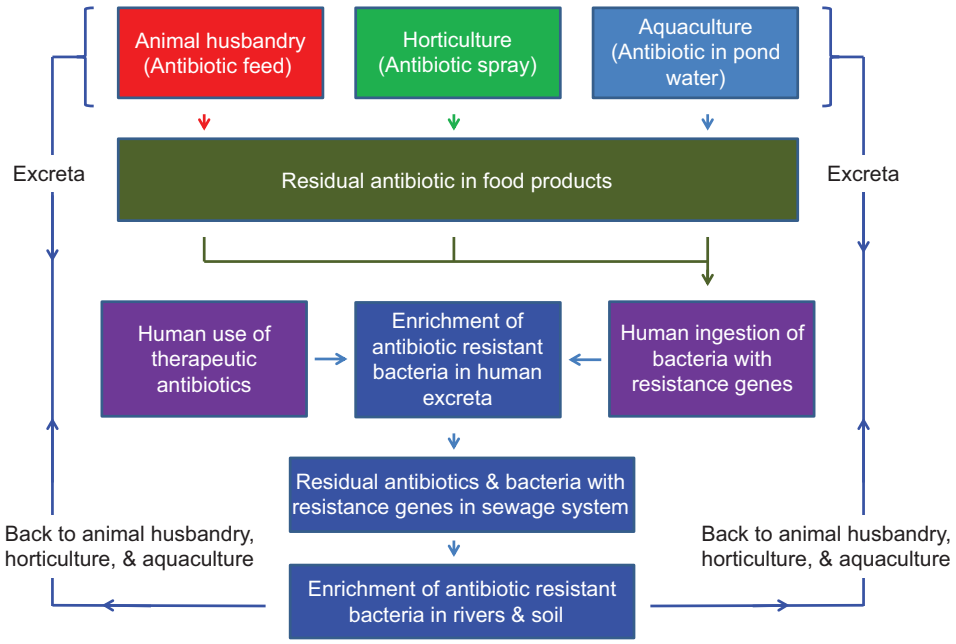

Figure 3 Transmission cycle of antibiotic resistance between humans and the environment.

72.7% in 1995 to 5.8% in 2000, and the occurrence of virginiamycin resistance decreased from 66.2% in 1997 to 33.9% in 2000.[68] Many European countries have demonstrated marked decreases in antimicrobial resistance after the restriction of antimicrobial use in food animals.[69] Consequently, the use of certain antimicrobial agents (avoparcin, tylosin, spiramycin, bacitracin and virginiamycin) as animal growth promoters have been banned by the European Union in 2001, and the Health Ministries in the European Union have subsequently agreed to discontinue the use of all antimicrobial growth promoters.[70] There is an urgency to perform intensive surveillance on the type, the amount and indications for use of antibiotics in farming. Such data must be transparent to the public, and their usage must be audited. Use of antibiotics for growth promotion must be banned (Table 1). Animal health is better served by better biosecurity than antimicrobial abuse.

CONTROL OF ANTIMICROBIALS IN EFFLUENTS OF WASTEWATER OR SEWAGE TREATMENT PLANTS

Wastewater or sewage treatment plants are designed to improve the quality of water before it is discharged from urban, industrial and agricultural facilities into the natural environment. However, treatment processes at wastewater treatment plants do not eradicate MDROs. Water samples were collected and cultured weekly over a 10-week period from 11 sites throughout the wastewater network in a city in France to detect the amount of ESBL-producing *E. coli*. Although the quantity of ESBL-producing *E. coli* was lower in the treated water than untreated water (22 *vs.* 481 colony forming unit (CFU)/mL), the proportion of ESBL-producing *E. coli* was significantly higher in the effluent than in the influent (0.6% *vs.* 0.3%, $P=0.017$).[71] Similarly, another study evaluated the risk of dissemination of antibiotic-resistant *P. aeruginosa* from a hospital to the environment via the wastewater network. With the same study design, water treatment is effective in removing *P. aeruginosa* from the effluent, but does not decrease the proportion of antibiotic-resistant strains. Therefore, treated water and sewage sludge still pose a risk for environmental contamination.[72] Further studies should be focused on methodologies for eliminating MDROs from the effluent of wastewater treatment plants.

CONTROL OF ANTIBIOTIC RESISTANCE IN THE COMMUNITY: CONTROL OF OUTPATIENT USE OF ANTIMICROBIALS

Antibiotic consumption in the community was strongly associated with an increase in antibiotic resistance. In a recently published meta-analysis on the relationship between the antibiotic resistance patterns of bacteria circulating in the community and the consumption of antibiotics in the community, it was shown that increased antibiotics not only produce greater antimicrobial resistance at the level of individual patients, but may also produce greater resistance in the community as a whole.[73] Antibiotic consumption increased by 36% (from 54 billion standard units to 73.6 billion standard units) between 2000 and 2010 according to the drug sales data in 71 countries. Brazil, Russia, India, China and South Africa accounted for 76% of this increase.[74]

Education for physicians in private care is an important strategy for controlling antibiotic use (Table 1). In a study using mixed qualitative and quantitative evaluation of a randomized controlled community-wide educational intervention in 16 Massachusetts communities, physicians in the intervention communities received locally endorsed guidelines, group educational sessions, and biweekly newsletters. Physicians in the intervention arm reported decreased antibiotic prescription from 2000–2003 compared with control physicians (75% *vs.* 58%, $P=0.03$).[75] Moreover, patient and parent education that aims to enhance knowledge and awareness about antibiotic resistance and appropriate antibiotic use is equally important.

CONTROL OF ANTIBIOTIC RESISTANCE IN THE COMMUNITY: THE RELEVANCE OF FOOD HYGIENE

In addition to the traditional education targeting physicians, patients, and parents, a clear health message has to be disseminated to the general public that ready-to-eat, undercooked food items should be avoided, especially during antibiotic therapy. In a study investigating

Table 1 Summary of control measures to combat the dissemination of multidrug-resistant organisms (MDROs)

	Strategic control measures
Control of antibiotic resistance in farms and animals	Non-therapeutic use of antibiotics for growth promotion should be banned. Increase farm productivity by improving biosecurity. Audit the appropriateness of antibiotics for the treatment of sick animals or in the control of outbreaks among animals.
Control of resistant bacteria in wastewater	Surveillance of sewage discharge for antimicrobial residues and resistance genes. Research and develop more effective methods to eliminate MDROs in wastewater treatment plants before discharge into the environment.
Control of antibiotic resistance in the community	For medical professionals: Provision of up-to-date antibiotics prescription guidelines, and physician education to reduce unnecessary antibiotic prescriptions in outpatient clinics. Regular auditing on antibiotic usage in the community. Health warning on antibiotics prescription bags to emphasize the importance of hand and food hygiene during antibiotics treatment. For the public: Educate on the appropriate indications of antibiotics to eliminate misconceptions on antibiotic use. This will help to reduce irrational demand for antibiotics by patients. Educate on avoidance of ingestion of uncooked or undercooked food items, especially during antibiotic therapy. Educate on kitchen hygiene to prevent cross contamination of food. Promote hand hygiene practices and use of alcohol-based hand rub, especially during antibiotic therapy.
Control of antibiotic resistance in hospital or healthcare institutions	Antimicrobial stewardship programs with an aim to reduce antibiotic selective pressure by reducing unnecessary antibiotic use. Proactive surveillance culturing of high risk patients for early identification of patients with asymptomatic colonization by MDROs. Contact precautions with single room isolation of patients colonized or infected with MDROs. Decolonization of MDROs where applicable. Environmental decontamination of frequently and mutually touched surfaces or items by healthcare workers, patients, and visitors. Provision of pamphlets for hospitalized patient and visitors to enhance compliance with infection control measures for personal protection against nosocomial acquisition of MDROs. Hand hygiene with alcohol-based hand rub if hands are not visibly soiled. Practice of "entry and exit" control by implementing directly observed hand hygiene for conscious patients before oral hygiene, ingestion of meals and medications, and after using the toilet.
Administrative and government support	Hospital-based measures: Incorporation of infection control compliance into core component of human resource policy in health care institutions. Employ independent audit team to monitor the infection control performance, including hand hygiene compliance and environmental cleanliness in healthcare institutions. Investment in new technology, such as electronic immediate feedback devices for monitoring and increasing awareness of practicing hand hygiene. National/regional-based measures: Formation legislation to illegalized use of antibiotics as growth promoters in farms. National policy to mandate the surveillance of MDROs in animals, humans and the environment. Active surveillance and audit of antimicrobial consumption in hospitals and the community. Surveillance of the number of hospital-acquired MDROs per 1000 patient-days across different hospitals with regular reporting to the public. Regular health promotion campaign in the community to promote awareness of appropriate antibiotics use, food and personal hygiene among the population. Formation of an antimicrobial resistant working group, under the local government, to oversee the surveillance data and above measures, as well as setting further goals and initiatives for continual control in antibiotic resistance in the community as a whole.

the influx of enterococcal antibiotic resistance and virulence genes from ready-to-eat food into the human digestive tract, it was estimated that the influx of *tet* genes in the human digestive tract is 3.8×10^5 gene copies per meal of chicken salad. The influx of antibiotic resistance genes was associated with ready-to-eat foods because they are commonly consumed and may play a role in the acquisition of antibiotic-resistant bacteria in the human digestive tract.[76] Similarly, bacteria carrying antibiotic resistance genes were also found in carrots (organic and non-organic) and salad vegetables. Thus, uncooked vegetables are another potential source of highly resistant opportunistic pathogens.[77] In a French survey on antibiotic-resistant bacteria in 399 types of organic and conventional fruits and vegetable, irrespective of their modes of production, 13% carried bacteria producing extended-spectrum β-lactamases; hence, both organic and conventional fruits, as well as vegetables, may constitute significant sources of resistant bacteria and resistance genes.[78]

While still rare, carbapenemase-producing bacteria have been reported in food-producing animals and their environment. *E. coli* producing VIM-1 carbapenemase was isolated in a pig farm,[79] and *Salmonella enterica* subsp. *Enterica* producing VIM-1 carbapenemase was isolated from livestock farms in Germany.[80] Nine of the 50 cattle sampled in France carried the carbapenemase-producing *A. lwoffii* $bla_{\text{OXA-23}}$ gene.[81] The identification of a $bla_{\text{NDM-1}}$-carrying strain of *A. lwoffii* in swab samples from chickens collected from 15 animal farms and one slaughterhouse in eastern China revealed the potential of $bla_{\text{NDM-1}}$ transmission from animals to human.[82] A survey of gram-negative bacteria from pigs, chickens and ducks was conducted in southern China (Guangdong province) from November 2011 to May 2012. Of the 1293 samples collected from five commercial pig farms, three commercial chicken farms and one duck farm, one single *A. baumannii* isolate from a lung sample of a pig with pneumonia and sepsis was positive for $bla_{\text{NDM-1}}$.[83] Although there are anecdotal reports, carbapenemases are not routinely tested for in bacterial isolates from non-human sources because many veterinary laboratories have not currently adopted methods that recommend screening for CPE. In Hong Kong, targeted testing of 4766 fecal *E. coli* isolates from

4764 animals (1260 chickens, 610 pigs, 590 cattle, 1161 cats and 1143 dogs) from September 2008 to August 2013 revealed that only two (0.04%) isolates were nonsusceptible to ertapenem (i.e., disc inhibition diameter <22 mm). The two isolates were polymerase chain reaction-negative for KPC, NDM, VIM, IMP and OXA-types of carbapenemase genes (PL Ho *et al*, unpublished data, 2015).

The presence of MDROs in food animals and food items should alert the general public to comply with good hand hygiene practices and to avoid eating raw and undercooked foods, especially while receiving antimicrobial therapy. Antibiotic resistance in animals may be transferred to humans from direct contact with animals, contaminated food and water, and also through indirect contact with contaminated environment. Given the abundance of antimicrobial-resistant *E. coli* in food animals and meat products, it would be informative to assess the risk of human exposure. In a summer camp outbreak of foodborne Salmonella gastroenteritis, two multi-resistant *E. coli* strains were found along with *S. enterica* in nine of the 22 investigated individuals,[84] raising the possibility that contaminated food or water were the vehicles for simultaneous dissemination of Salmonella and resistant *E. coli* to the campers. Investigators from Spain evaluated this possibility further by investigating stool samples from 905 people involved in another 132 episodes of acute gastroenteritis outbreaks and from 226 outbreak-related food handlers from 2003-2004. In 31 of the 132 outbreaks, one or more of the investigated subjects carried one or more ESBL-producing bacteria. In 10 outbreaks, two or more diners were found to share the same ESBL-producing bacteria, and in four of them, the strain was identical to the bacteria isolated from the food handlers.[85] Using a mathematical model, Depoorter *et al*.[86] assessed the risk of human exposure to antimicrobial-resistant *E. coli* through consumption of broiler meat in Belgium, and 35% of the *E. coli* strains isolated from live broilers were resistant to third-generation cephalosporins. Using baseline data estimates, the probability of exposure to 1000 CFUs or more of resistant *E. coli* during consumption of a meal containing chicken meat was calculated to be 1.5%. The risk is mainly attributed to cross-contamination in the kitchen rather than undercooking. Given the much higher frequency of ESBL-producing Enterobacteriaceae in the live poultry in Hong Kong, this model predicted that the chance of consuming resistant bacteria in a serving of broiler meat could be as high as 4.3%–9.3% at exposure levels of 10–100 CFUs. In a recent study in Scandinavia, 21% (90/430) of the returning travelers had fecal colonization by ESBL-producing Enterobacteriaceae. The risk was higher among those who had travelled to South Asia and were taking antimicrobials.[87]

In theory, ingestion of plasmids or DNA fragments containing the resistance determinants might also pose a risk because the human microbiota may acquire the resistance genes by transformation. However, the risk of resistance emerging from this route of exposure seems to be exceedingly low, at least for members of the gut microbiota that are not naturally competent to free DNA, such as *E. coli* and *Klebsiella* spp. In an animal model using *Acinetobacter baylyi*, which is competent to free DNA, extensive ingestion of plasmid DNA (100 μg per day) encoding resistance genes did not produce antibiotic-resistant transformants among the aerobic microbiota (detection limit <1 transformants per 1.1×10^8 cultured bacteria).[88] The content within the rodent gastrointestinal tract may have shielded or adsorbed the plasmid DNA, preventing exposure of food-derived DNA fragments to competent bacteria.[89] The observed lack of DNA uptake by gut bacteria might also be related to the lack of expression of bacterial competence inside the gut, insufficient free DNA concentrations, suboptimal biochemical conditions for transformation that the use of assay methods were not sensitive enough for detecting low levels of transformation. These findings suggested that ingestion of plasmid DNA does not lead to fecal colonization, thus eating food that has been cooked or heated immediately before consumption with good attention to prevent cross-contamination in the kitchen may help safeguard against intestinal colonization by food-acquired MDROs. Because determinants conferring resistance to several different classes of antibiotics are often found together on the same mobile genetic elements (plasmids and transposons), switching to a different class of antibiotics may not reduce the antibiotic selective pressure. Therefore, it is important to reduce the overall use of antibiotics in humans and animals.

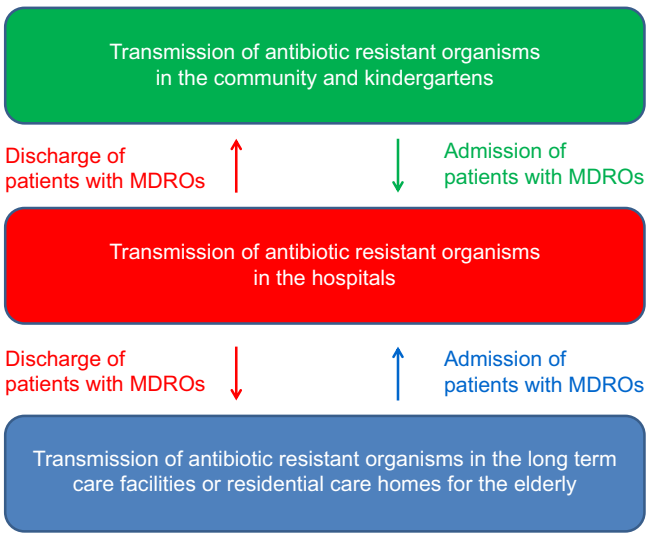

Figure 4 Transmission cycle of antibiotic resistance between hospitals and the community.

CONTROL OF ANTIBIOTIC RESISTANCE IN HOSPITALS OR HEALTHCARE INSTITUTIONS: PROACTIVE SCREENING, INFECTION CONTROL AND PATIENT SELF-PROTECTION

Proactive infection control measures must be in place to prevent nosocomial dissemination of MDROs, especially in the context of ongoing complicated MDRO transmission dynamic between hospitals and the community (Figure 4). For MDROs that are not yet endemic in hospitals, pro-active surveillance cultures allow for early recognition of patients with asymptomatic colonization of MDROs (Table 1). In Hong Kong, we adopt the 'whom TO screen model' as previously described,[90,91] where T represents a history of hospitalization outside Hong Kong (medical tourism) and O represents a history of receiving surgical operation outside Hong Kong within the preceding 12 months admission, especially in areas in mainland China where NDM-1-positive Enterobacteriaceae is reported.[11] However, travel history alone without contact with medical care may become a potential risk factor for acquisition of MDROs, as NDM-1-producing bacteria were found in 99 water samples collected from river water, treated drinking water, water samples from pools and sewage from 4 comprehensive hospitals in Beijing[92] and NDM-1 was identified in two of 50 drinking-water samples and 51 of 171 seepage samples from New Delhi, India.[93] Acquisition of CPE (two OXA-181, one NDM-1) was recently documented in three healthy travelers returning from India without any healthcare contact.[94] Patients with histories of admissions to local hospitals in the preceding three months were also included in the active surveillance. An education pamphlet was delivered to all patients upon

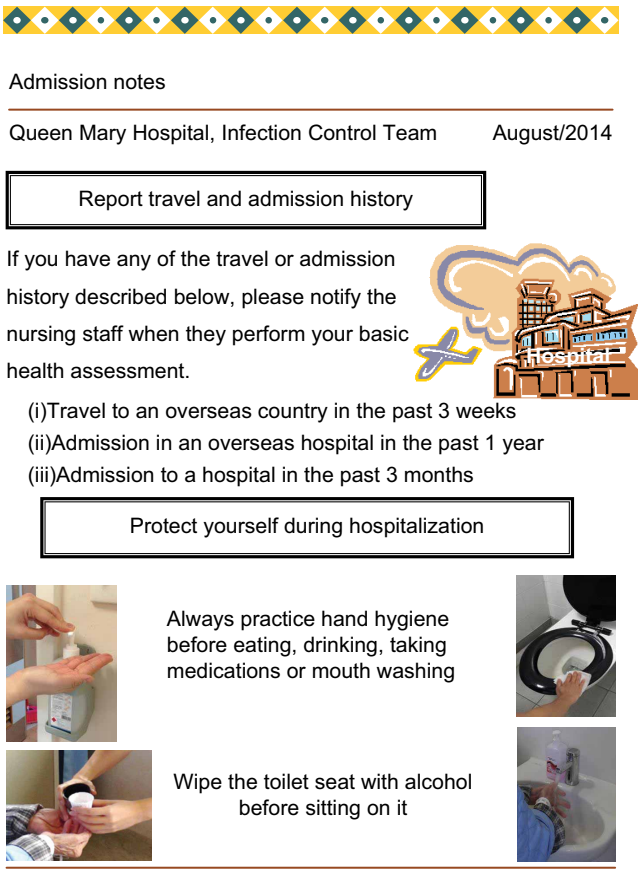

Figure 5 Pamphlet given to patients on admission for triage to educate them about infection control. Patients required to report travel or admission history in (i) because of the Ebola outbreak in West Africa, Middle East Respiratory Syndrome Coronavirus in Middle East, and avian influenza A H7N9 in mainland China; (ii) because of the median duration of colonization of MDROs of less than 1 year; (iii) because of workload consideration.

admission as a reminder of some important infection control practices (Figure 5). Rectal swabs were collected from patients who fulfilled the aforementioned criteria to identify patients with asymptomatic gastrointestinal carriage of VRE, CRAB and CPE, which are not yet endemic in Hong Kong. Because carriage of MDROs may be unmasked by subsequent prolonged antibiotic use after hospitalization,[95,96] a 'safety net' to screen patients hospitalized for 14 days or more, as well as inpatients with stool sent for *Clostridium difficile* cytotoxin or culture, was implemented as previously described[90,97,98] to enhance detection. For newly diagnosed patients carrying VRE or CPE, bedside assessment is carried out by the infection control team to coordinate and ascertain that strict contact precautions and isolation of these patients in single rooms are implemented. Extensive contact tracing for secondary cases is performed when an index VRE or CPE patient has been hospitalized for more than 48 h in an open cubicle. The duration of extensive contact tracing includes the entire duration of hospitalization of the index patient, covering all potentially exposed patients. Immediate rectal swab screening is conducted for all potentially exposed patients who are still hospitalized within the same hospital. Discharged but exposed patients are labeled as 'VRE or CPE contact patients' in the hospital computer system by infection control nurses, and screening for VRE or CPE are performed upon hospital readmission. For exposed patients discharged to residential care homes for the elderly, site visits and collection of rectal swabs are performed by community geriatric assessment teams within one week. If a secondary VRE- or CRE-positive case is confirmed in a residential care home for the elderly, all residents in that residential care home for the elderly will be screened for asymptomatic gastrointestinal carriage of VRE or CPE. In fact, vigorous screening and isolation of MRSA was performed by the Scandinavians and the Dutch in the late 1980s,[99,100] and their prevalence of MRSA remain less than 1% in admission screening, while the prevalence in the US and other parts of Europe is much higher.[101] Their experience strongly supports the concept of proactive screening, isolation and decolonization, also called a 'search and kill' strategy. Mandatory surveillance is also useful even in an endemic setting where MRSA bacteremia in England was reduced from over 7000 to less than 2000 cases per year.[102] In addition, active surveillance played an important role in the control of a hospital-wide outbreak of carbapenem-resistant *K. pneumoniae* infection Israel. Of 12 391 days of contact precautions, 4713 (38%) were added as a result of active surveillance.[103] However, infection control measures should not be limited to an institution. A nationwide intervention has to be launched to contain MDROs, as illustrated in the containment of a country-wide outbreak of carbapenem-resistant *K. pneumoniae* in Israeli hospitals via a nationally implemented intervention where the monthly incidence of nosocomial carbapenem-resistant *K. pneumoniae* was significantly reduced from 55.5 cases per 100 000 patient-days in March 2007 to 11.7 cases per 100 000 patient-days in May 2008 ($P<0.001$).[104]

Hand hygiene is always considered a critical component of infection control practices. Promotion in the 'Five Moments' in the WHO recommendation—namely, before patient contact, before an aseptic task, after body fluid exposure risks, after patient contact and after contact with patient surroundings—is a key measure to reduce the risk of nosocomial transmission of MDROs, but compliance is often limited to the first four moments and not the 5th moment. Therefore, MDROs can be easily transmitted via contact with mutually touched items by healthcare workers, conscious patients, and visitors in institutional environments (Figure 6). Although hand hygiene monitoring demonstrated compliance of over 70% in our center, manual observation of hand hygiene practice may be overestimated due to the Hawthorne effect. When hand hygiene compliance was continuously and unobtrusively monitored by an electronic monitoring system, the overall compliance was found to be less than 40%,[105] which was consistent with previous findings.[106] The concept of infection control is simple, but compliance is difficult. Introduction of directly observed

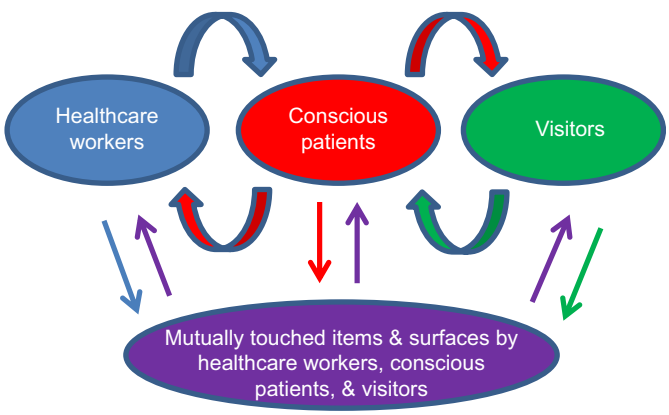

Figure 6 The transmission cycle of antibiotic-resistant organisms by contact with mutually touched items by healthcare workers, conscious patients and visitors in an institutional environment.

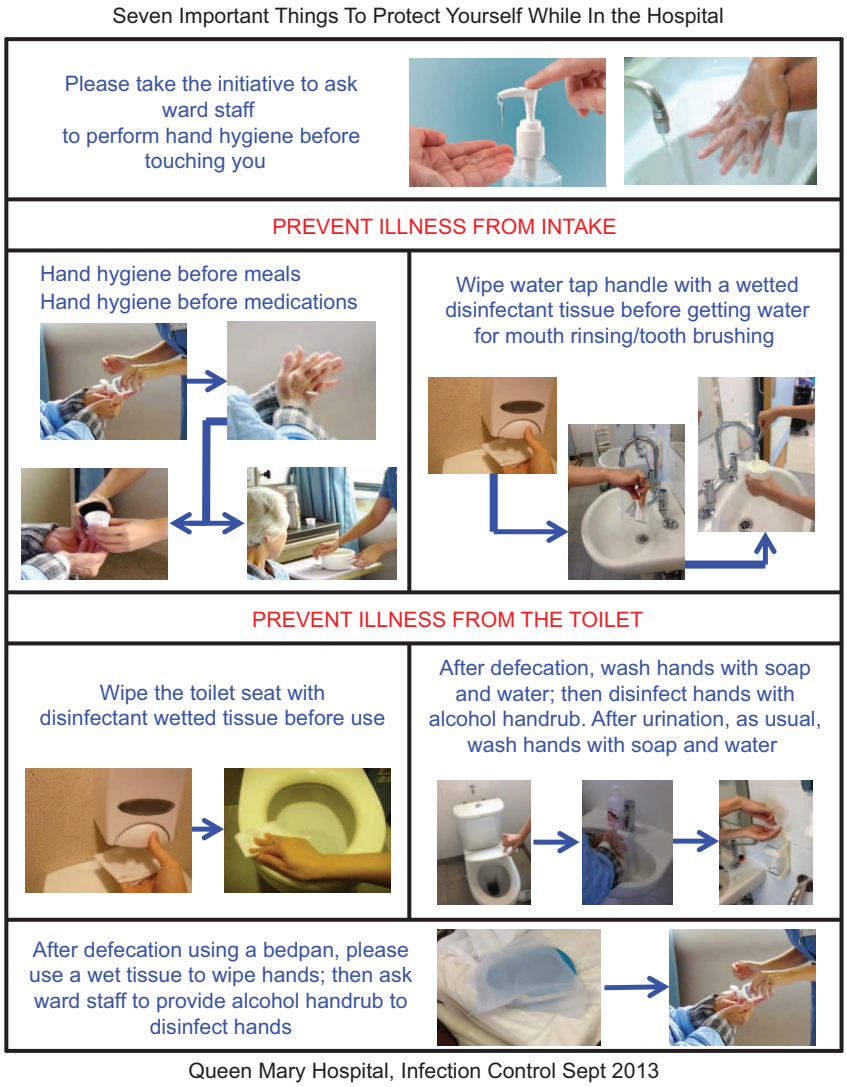

Figure 7 Bedside poster to remind patients about infection control on personal protection from hospital-acquired infections.

hand hygiene in clinical settings may be a better option, where a designated healthcare assistant or nurse delivers alcohol-based hand rub to all conscious patients and healthcare workers once every 2–3 h. This practice appeared to be useful in the prevention of nosocomial outbreaks due to epidemiologically important viruses or MDROs in our setting.[90,91,97,107–112]

Figure 8 Education pamphlet for self-protection during antibiotic therapy.

Because there are many more patients than healthcare workers in clinical areas, hand hygiene practice in conscious patients is equally important. Directly observed hand hygiene in patients was promoted as a new core infection control component, and alcohol-based hand rub was delivered to all conscious patients before meals and medications. In addition, alcohol foam and hand rub was also made available in patients' bathrooms. Patients were encouraged to disinfect toilet seats prior to use and to clean their hands after using the toilet (Figure 7). A slogan of 'entry and exit control' was used in this campaign to highlight the key measures for breaking the fecal–oral transmission of VRE and CPE during hospitalization.[91] This strategic measure of 'entry and exit control' was shown to be effective in controlling endemicity of multidrug-resistant *Acinetobacter baumannii* ST457 in our locality.[113] In addition, educational pamphlets on precautionary measures during antimicrobial therapy were distributed by the admissions office to in-patients and through pharmacy to out-patients when they are prescribed antibiotics (Figure 8).

To control endemic MDROs such as MRSA, an antimicrobial stewardship program to reduce antibiotic selective pressure and

environmental disinfection with focus on frequently touched areas should be enforced.[114,115] MRSA-positive cases are best nursed in isolation rooms.[111] However, with limited number of isolation facilities in many hospitals, innovative measures should be implemented to prioritize the utilization of isolation rooms. Our study previously found higher transmissibility of MRSA with certain spa types,[116] and the use of broad-spectrum antibiotics could increase bacterial loads leading to an increased risk of environmental contamination by patients with asymptomatic colonization of MRSA;[95] therefore single room isolation is reserved for MRSA patients with the aforementioned characteristics. For other MRSA-positive patients, implementation of 2% chlorhexidine gluconate daily bathing, in addition to the hand hygiene campaign and contact precautions in open cubicles, could limit nosocomial transmission of MRSA in our highly endemic setting.[117] Decolonization of MRSA may reduce the burden of MRSA. The use of a 5-day regimen of nasal mupirocin ointment, chlorhexidine mouth rinse and whole-body wash with didecyldimonium chloride gave an eradication rate of 65% (33/51) after a median follow-up of 13 months, compared with a spontaneous clearance rate of 22% (6/27) in the non-decolonized group.[118] Recently, a study involving 74 adult intensive care units suggested that universal decolonization may be more effective than targeted decolonization or screening and isolation in reducing the rates of clinical MRSA isolates and bloodstream infections due to any pathogen.[119] In contrast to MRSA decolonization, VRE decolonization is more controversial. Bacitracin-containing regimens given orally or via a gastrostomy tube for 10 to 29 days have been reported.[120–124] Although the overall observed rate of VRE clearance was found to be 43%–100% in patients treated with these bacitracin-containing regimens,[120,122,124] long-term follow-up showed that persistent decolonization of VRE was observed in 33%–53% of patients at three weeks post-treatment.[121,123] The use of *Lactobacillus rhamnosus* GG or *Lactobacillus rhamnosus* Lcr35 had been attempted to decolonize VRE patients, but the results were variable.[125–127] The failure of these regimens is likely to be related to the lack of an effective decolonization regimen, and prolonged asymptomatic carriage of VRE in the gastrointestinal tract will perpetuate the endemicity of VRE in healthcare settings. We have recently introduced a novel regimen for VRE decolonization. Sustained decolonization of gastrointestinal carriage of VRE has been achieved by a combination of environmental disinfection, patient isolation, bowel preparation to wash-out the fecal bacterial population using polyethylene glycol, a five-day course of oral absorbable linezolid and non-absorbable daptomycin to suppress any remaining VRE, and subsequent oral *Lactobacillus rhamnosus* GG to reinstate colonization resistance.[128] This strategy should be further studied in settings of low VRE endemicity with limited isolation facilities.

Residential care homes for the elderly are considered potential reservoirs for MDROs in many parts of the world.[129,130] In Hong Kong, residents from residential care homes for the elderly account for an estimate of 7% of acute hospital admissions. In a recent prevalence study, the rate of asymptomatic nasal MRSA carriage was 21.6% among 40 residential care homes for the elderly in Hong Kong. Transmission of MRSA within the residential care homes for the elderly was found to be three times higher than in the hospital.[131] Therefore, infection control measures must be implemented in residential care homes for the elderly in order to reduce the burden of MRSA carriers in healthcare settings.

CONCLUDING REMARKS

In summary, control of antimicrobial resistance in Hong Kong and mainland China depends on more intensive surveillance of farms, wastewater treatment plants, outpatient clinics and healthcare institutions. Parameters including antimicrobial consumptions, environmental contaminations, and antimicrobial resistance should be monitored with appropriate follow up action. Antimicrobial use animals must be banned, and biosecurity measures on farms should be strengthened. Sewage and wastewater treatment should be improved to prevent resistant bacteria from getting into the water, soil and fertilizers. Antimicrobial treatment in healthcare settings should only be given according to evidence-based guidelines, and regular auditing should be in place to reduce the inappropriate usage and duration of antibiotic treatment. Heightened public awareness about combating antimicrobial resistance and compliance with food and personal hygiene are important to decrease the acquisition of antimicrobial resistance, especially while taking antibiotics. Educational pamphlets should be handed to patients and relatives while awaiting hospital admission or drug prescriptions at the pharmacy. The combination of proactive 'added testing' for emerging MDROs, directly observed hand hygiene, and the 'entry and exit' control strategy are important additional measures to control and prevent new antimicrobial resistance in our hospitals. Interventions in healthcare setting should be regionally coordinated where patients, staff and visitors are often transferred between acute hospital service, convalescent hospital and elderly residential homes. Data of hand hygiene compliance, broad-spectrum antibiotic consumption, and incidence of newly diagnosed and hospital-acquired MDROs should be regularly released to public so that the performance of the individual hospitals are subject to auditing by the public from time to time.

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