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Review

Infection control in the post-antibiotic era

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Abstract. There are enormous challenges facing infection control in the 21st century. Countries across the world are confronted by ageing populations, restricted healthcare resources, demands for modern medicine and increasing antimicrobial resistance. Problem pathogens in the community are set to invade hospitals, and those created in hospitals are seeding into the community. Continued consumption of antimicrobial agents is generating and consolidating resistance to nearly all classes of drugs. New resistance mechanisms arising in one locality rapidly spread across the 'global village' courtesy of migration, conflict and international travel. We are facing unprecedented threats to the management of infection both in healthcare and communities across the world. This review summarises the current challenges for infection control and proposes a range of solutions encompassing novel strategies and technologies aimed at protecting us against untreatable infection.

Additional keywords: antimicrobial stewardship, decontamination, healthcare-associated infection, hospital hygiene, infection control.

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Introduction

Infection control faces radical challenges at the beginning of the third millennium.[1] Infection remains the second most common cause of death worldwide, with healthcare-associated infection (HAI) affecting at least 1 in 10 patients admitted into hospital. Advanced healthcare increases the risk of infection – with invasive technologies and immunosuppression – while fuelling high patient expectations of modern medicine.[2] Most countries are experiencing ageing populations, along with continued restrictions on healthcare resources.[3] Healthcare tourism, along with migrant workers, refugees, business and holiday travellers illustrate the ease by which pathogens traverse the aptly named 'global village'.[4]

These socioeconomic, medical and population issues have coincided with the present backdrop of steadily-increasing antimicrobial resistance.[3,5,6] Some pathogens are termed multi-drug resistant (MDR), with a few treatment choices; others, with one major drug class available, are classified 'extreme-resistant' (XDR); and finally, there are organisms termed 'pan-resistant (PDR), because there are no remaining agents with which to treat patients.[7]

Additional organisms attract attention by virtue of pathogenic determinants and/or superlative transmission ability. These include *Clostridium difficile* and a wide range of viruses.[3,8] Resistance issues have already been heralded with *C. difficile* (low-level resistance to metronidazole) and some influenza strains appear to be developing resistance to oseltamivir.[9,10] As for norovirus, new genotypes regularly appear, causing a wave of outbreaks across a region, which then spread elsewhere.[11] Such genomic plasticity illustrates a persistent threat, because it means that viruses could mutate into a strain impossible to contain, particularly if combined with exceptional virulence.[12] Indeed, all microbial categories have this capacity for mutation.

Despite current concern over resistance, antimicrobial development and immunotherapy appear to have frozen.[13,14] There are economic reasons for this, since short-term anti-infectives do not generate much profit, but it is possible that there are only a finite number of microbial targets accessible for antimicrobial exploration.[15] It is also the case that regulatory bodies are not necessarily helping smooth the tortuous pathway from drug discovery to licensing.[16]

With diminishing options for treating infection, control of transmissible pathogens has ignited international interest.[17] Multiple organisations have begun to formulate policies, but these efforts are challenged on every level by national, political, criminal and economic restraints.[5,17–19] Without international recognition and collaboration, successful interventions in one part of the world will ultimately be compromised by control deficits in another. This article highlights current problems with microbial pathogens and offers a range of strategies for the future delivery of infection control. A return to the pre-antibiotic era, when normal healthy people died from infection, is not inevitable, even if

Implications

- This opinion piece summarises current challenges for the prevention and control of infection.
- It proposes a range of novel strategies and technologies aimed at protecting us against untreatable infection.
- We need to prepare for a world without antibiotics.

a 21st century solution for treating infection takes its time to emerge.

Current problems with control methods

Healthcare

Solutions for controlling healthcare-associated infection are not all possible, practical, affordable, acceptable or even evidence-based.[20] The usual response is to implement a 'bundle' of infection-control strategies, and hope that the overall effect will have the desired result.[20–22] Exactly what effect each individual strategy has against a particular pathogen is usually unknown because we lack this level of evidence. Post-outbreak analysis often only provides a cause-and-effect relationship rather than data supporting single interventions. Thus, designing infection-control studies is fraught with confounders as well as being subject to ethical constraints.[23]

Formulating guidelines and policies on infection control has never been so popular but stating what we should do, and doing what is stated, can be a world apart on a busy ward.[24,25] When clinical staff are overstretched, time for patient care is compromised, and integral to this is infection control.[26,27] Good practice is reliant on personal choices. The 'zero tolerance' policy aimed at healthcare workers and their hand hygiene practices has not necessarily resulted in 100% compliance and there are compelling reasons for its failure.[28,29] In addition, the success of antimicrobial stewardship programs depends on support by committed prescribers.[30]

Outside of outbreak situations, routine infection control remains low priority, since it is impossible to cost something that may not happen.[31,32] By its very nature, infection prevention conflicts with the priorities of managers, keen to lower the overheads of their organisations.[33,34] Running a hospital at 100% bed occupancy, for example, or underestimating staffing levels, is an invitation for pathogens to spread.[33,35] Infection-control practitioners must engage with management and convince them of the importance of early implementation of control activities.[36] It is unacceptable that avoidable fatalities have to occur before anyone takes any notice of hygiene deficits. Ultimately, the responsibility of determining the quality of healthcare rests with governing bodies at national level.[37]

Whilst many hospitals have set up epidemiology and surveillance programs to aid infection control, the components of these may lack definition, which means that surveillance data cannot be compared between countries, or even between regions.[3] Similar problems exist at molecular level, where strain types may be disputed by international agencies and impede global attempts at monitoring spread.[38]

Community

Poor infection control encourages and concentrates pathogen reservoirs in hospitals, which eventually permits spillage into the community. Since the street between the hospital and the community runs both ways, patients colonised or infected with hospital organisms then return them back to hospital.[2,39,40] Carriers contaminate the healthcare environment, which serves as a reservoir for others.[41] In contrast, pathogens originating in the community are capable of spreading through hospitals following introduction by both staff and patients.[42] Resistant coliforms can be acquired through different community reservoirs and carried long-term in the gut, particularly amongst the elderly.[40,43] Older patients do not retain immunological defences capable of eradicating these microbes, which results in an accumulation of pathogens among people who frequently, and ultimately, require healthcare.

Patients not only desire the best and most modern of treatments, they also expect a 'pill for every ill', which makes it difficult to withhold antimicrobial drugs for the worried well. Time constraints in community clinics do not permit the explanation, reassurance and education required for non-infected patients, especially parents who want something for a sick child.[44] Indeed, rigid stewardship in the community occasionally compromises the management of a patient who really does need timely antimicrobial therapy.[45] This is compounded by poor access to diagnostic microbiology laboratories, which forces clinicians to prescribe broad-spectrum therapy and ultimately encourages antimicrobial resistance.[46]

There seems to be a current trend for waging war on the germs.[47,48] Germs are a 'buzzword' for a danger that people wish to eliminate from their surroundings.[47] This has resulted in a flourishing market of antibacterial products for use in the community.[49,50] Antibacterial products were developed to prevent transmission of pathogens among patients, particularly in hospitals, but they are now being added to products used in healthy households, even though additional health benefits have not been demonstrated.[51] Some antibacterial agents promote resistance and cross-resistance antibiotics.[52,53] We should remember that 'nature abhors a vacuum and will fill it up if she can'; this means that using microbiocidal products might remove susceptible microbes, but the space created could attract a new population of something worse.[46,48] We cannot rid ourselves of bacteria.

Whilst affluent countries exercise their choice of disinfectant, there are places in the world which lack even basic sanitation and clean water. This compromises hygiene, facilitates infection and furthers the spread of resistant pathogens.[54,55] Underfunded or inaccessible healthcare also

encourages the creation of resistant organisms, such as tuberculosis, with transmission facilitated by social and housing deficits, HIV and war zones.[56] Benefits accrued from antimicrobial restrictions and infection-control policies will be eroded by practices elsewhere in the world. Without international understanding and cooperation, national strategies are compromised when people purchase antimicrobial agents over-the-counter from local pharmacists or from internet sources.[57–59] There exists a 'black market' for 'antimicrobial' medicines, for anyone keen enough to pay. The sudden emergence or recognition of a novel 'superbug' reignites irrational behaviour, reminiscent of long-gone quackery.[60]

Veterinary and agricultural contributions

The consequences of antimicrobial exposure outside hospitals do not originate solely from human consumption because industry, agriculture and the veterinary profession also use antibiotics in various ways.[46] Resistant organisms are shed in excreta without antimicrobial pressures.[61] Faeces entering, or bypassing, sewage systems can disperse organisms throughout the wider environment and sewage acts as a suitable vehicle for the transmission of resistance genes.[55,62] Antibiotics given to animals contribute towards emergence of resistant bacteria in people, some of which may cause disease.[63–65] The ST398 strain of methicillin-resistant *Staphylococcus aureus* (MRSA) that causes skin infections and sepsis in farm workers has evolved its resistance profile within a farm animal reservoir.[65]

Other resistant organisms originating in livestock enter the food chain and can be shown on foodstuffs at point of sale.[43] A Dutch study demonstrates the spread of antibiotic-resistant *E. coli* from animals to people, firstly farmers and ultimately meat consumers.[66] Similar findings have been reported from the UK.[67] The US Food and Drug Administration recently announced new restrictions on using preventive antibiotics in livestock, but the rules cover a subset of drugs constituting just 0.2 per cent of antibiotics used on farms.[68] As a result they are not expected to have much effect.[69]

Veterinary contribution does not rest solely on antimicrobial consumption or pathogen reservoirs, but with infection control practices as well.[70] Hygiene measures are required to limit the transmission of resistant organisms between animals, just as they are for humans.[71–73] Since some infection control practices in human healthcare remain controversial, similar evidence-based activities to limit spread among animals will take time to become established.

Short-term control policies

There are practices that could be implemented or improved in the short-term, in order to minimise transmission of resistant organisms. These strategies are already employed to a greater or lesser extent within healthcare systems throughout the world. They include cleaning, screening, hand hygiene, barrier and contact precautions, antimicrobial stewardship, surveillance, laboratory access, education, monitoring and feedback, research, managerial engagement, national policy making, and international collaboration.[74] If these activities are already in place, what more could we do to deter antimicrobial resistance and transmissible infection?

Hygiene

Given that impeding transmission reduces the risk of infection, hygiene is key, with emphasis on prevention, rather than control.[48] Failed or faltering hand hygiene campaigns can be re-ignited with repeated educational and advertising campaigns, supported by personal electronic reminders.[75] The hospital environment can receive the attention it has needed for years, with targeted and revised cleaning strategies for general surfaces and clinical equipment.[76,77] We should initiate scientific monitoring of surface-level cleanliness in hospitals, with application of infection risk-based standards similar to that in the food industry.[78–80] Cleaning in healthcare will thus achieve a status never witnessed before, with a tiered professional structure based on certified courses for janitorial staff. These could include practical and accredited qualifications aimed at decontamination of clinical equipment and other surfaces currently cleaned by nurses.[81] Sufficient cleaning hours, determined by staff and patient consortia, can be implemented throughout the healthcare system despite current lack of evidence.[78]

All hospitals should increase the proportion of single en-suite rooms, with isolation units for pan-resistant pathogens and novel ventilation methods, such as air ionisers and high-intensity UV light.[82,83] There could be greater use of silver and similar non-antibiotic coatings for clinical equipment and devices.[84] 'Natural' products such as hydrogen peroxide, ozone, steam and electrolysed water can be integrated into cleaning and decontamination strategies, despite concern over the efficacy of some.[78,85,86] Healthcare facilities could also make good use of natural (cross) ventilation and the germicidal properties of sunlight, since earlier work on these appears to have been forgotten.[87,88] Use of antiseptics or disinfectants shown to encourage cross-resistance with antibiotics should be discouraged in healthcare facilities.[51–53]

To assist the campaign for cleaner hospitals, there are antimicrobial surfaces and easy-clean furniture, but despite future promise, traditional cleaning methods should not be relaxed even if the whole hospital is coated with bioactive veneer.[78,89,90] No one single process will remove all relevant microbial soil from the hospital. Coating constituents can wear off, degrade, or simply fail due to accumulation of organic soil. There might be health and safety issues, including toxic effects on the environment. Futuristic surfaces might seem appropriate for a 21st century hospital, but they could proffer false assurance if not properly tested over time. All require a comprehensive assessment in association with patient outcome before widespread adoption for healthcare.[78]

Antimicrobial stewardship

Antimicrobial stewardship requires further restrictions, with electronic monitoring, mixed prescribing and diagnostic

frameworks aimed at reducing anti-infective use in hospital and community.[91] It takes courage to say 'no' to a request for antimicrobials, but if a patient is systemically well, the benefits of treatment for the individual should be weighed against safeguarding treatment options for future patients.[92,93] Antibiotic prophylaxis should be regarded as a privilege. Prescribing penalties for clinicians, along with financial incentives, would focus management on reducing antimicrobial consumption.[93,94] Other initiatives are mandatory antimicrobial restrictions and testing in veterinary practices and agriculture, including imported livestock and foods, implemented and monitored on a global basis. Food producers should not use growth-promoting antimicrobial agents. There is no strong evidence of actual economic benefit and the potential for harm from antimicrobial resistance is high.[95,96] International understanding, cooperation and support will be required to terminate over-the-counter drugs, electronic purchase and exchange of surveillance and research data.[2,18]

Laboratories, surveillance and screening

Good access to routine diagnostic laboratories requires continued support, with rapid diagnostic molecular methods introduced into routine practice.[97] Electronic transmission of data will deliver results to clinicians for immediate appropriate management.[98] For countries lacking accessible laboratories, the resources required should become a national priority, with additional support from charitable healthcare organisations. One affluent country could 'adopt' another of similar population and help construct an infection-control framework including laboratories, computer technology and data capture.

International agencies should agree on standardised definitions for surveillance in order to compare and contrast resistance rates all over the world.[3,7,99] Screening may be expensive, and vulnerable to definition, but you cannot control what you do not know about. There has been much debate over MRSA screening. Perhaps it is time to introduce routine screening for other resistant microbes, with programs reflecting local hotspots or burgeoning risk depending on geography, institution and speciality.[100]

Education

Implementation of these strategies requires robust educational grounding for healthcare workers and the general public. Public health personnel could initiate and supervise structured delivery of mandatory hygiene education for school children and students, with courses made available for mothers, teachers, food handlers, farmers and people who work with animals, beauticians, sports coaches, supermarket and food shop staff, amongst others.[101] Infection-control education can be strengthened within student curricula, and introduced for healthcare-staffing groups who have not previously been included. Advertising campaigns using national and local media would support this, extolling the benefits from restricting antimicrobial agents and keeping hands and surfaces clean, although no government will be able to challenge domestic squalor of necessity, design or choice.[16,102]

Research

Relevant research initiatives need higher status, with better-quality original studies, surveillance, epidemiological investigation, drug discovery and trials, industry and business partnerships, and international cooperation.[1,2,17,18,23] Current emphasis on cancer and heart disease has meant that hygiene projects have not, so far, received the priority they deserve. Escalating drug-resistant infection should encourage work on phage-based therapies,[103,104] antimicrobial peptides,[105–107] bacterial interference,[108] probiotics, toll-like receptor and quorum sensing blockers,[109] nanoparticles,[110] bacterial reversal agents,[111,112] novel vaccines and immunotherapy,[113,114] maggots,[115] tea tree oil,[116] and potential antimicrobial constituents in herbs, spices and foodstuffs, amongst other innovations.[117] Almost certainly, scientists will return to the soil-searching of old in pursuit of new antimicrobial agents.[118]

Managerial and political engagement

Managerial responsibilities regarding infection control should continue to be formalised with professional networking to ignite and maintain political interest.[36] Healthcare data on quality, outcome and mortality from regional managers delivered on a regular and timely basis should be accessible to the public, and serve to focus the political agenda. Once MRSA became an electoral issue in the UK, screening, surveillance and mandatory reporting helped prioritise its control with nationwide benefit.[119] National leaders should identify an independent forum for long-term policy planning, including support for assisting research innovation into practice.[36] International collaboration already exists but needs encouragement, commitment and support from institutional heads and politicians.

Infection control in the future

The initiatives described make the most of what is already known. Should these be insufficient, then we require additional interventions to aid control. Some of the following suggestions may seem incredible now, but not for a world without antibiotics. Most are unsupported by scientific evidence.

Healthcare

Perhaps the most contentious proposal is the premise that all prescribers should have a supplementary antimicrobial-prescribing licence. Challenging doctors' and veterinarians' right to prescribe will not be popular. It is likely that electronic prescribing with in-built antimicrobial alerts will be introduced, with formal regulation and monitoring. If antibiotics become obsolete, it is hoped that there would be other types of anti-infective drugs forthcoming.[107,110] We can be confident that human initiative will prevail.[120] Use of

new agents should be severely restricted and monitored if resistance is biologically possible.

In hospitals, futuristic strategies might include robot healthcare delivery; or user-friendly 'space' suits to shield staff managing infected patients. Staff and patients would be further protected by compulsory shower and changing facilities when traversing different hospital wards or units (as occurs in food factories). Could staff be irradiated with a microbiocidal light source, if safe for human health? Even ordinary sunlight has untapped capacity for decontamination.[88] There is no doubt that hand hygiene compliance will become a major issue – if it isn't already – with mandatory monitoring and video surveillance in clinical areas.[75,121] It is hoped that disciplinary issues on hygiene misdemeanours do not escalate into witch hunts, encouraged by ensuing panic over untreatable infection.

Given the potential for airborne transmission, novel ventilation systems will be needed to deliver frequent air-changes based on clinical risk. Accurate airflow visualisation techniques are essential to understand how aerosolised or airborne infection may be dispersed and, equally importantly, how it may be prevented.[122] Less well-resourced healthcare facilities will contemplate outdoor wards and clinics, as regularly practiced before the discovery of antibiotics.[87] There could be 24 h specialist infection-control cleaning teams, using steam, UV light and hydrogen peroxide when necessary, supplementing high frequency manual cleaning with or without bio-coated surfaces.[78,89]

Hospitals would benefit from multiple isolation 'bubble' room design, with antechamber, separate ventilation, plumbing and waste disposal systems, and strip-panel delivery of germicidal light in these rooms and other patient areas.[83] In the diagnostic laboratory, tests could be devolved to critical areas within the hospital, such as polymerase chain reaction microarrays and other rapid molecular techniques for routine use in emergency departments.[123] These might render the benefits from electronic transfer of clinical data obsolete, but not necessarily quicker diagnosis of infected wounds using electronic 'nose' or glowing wound technology.[124]

Natural resources can and should be used to run our hospitals, with minimal adverse effects on the environment. Microbiocidal properties of sunlight, air and water can be exploited and delivered where possible. If homes and healthcare continue to rely upon disinfectants, nature's 'balloon' expands to fill the vacuum. There is no guarantee that the microbes which proliferate will always be controlled by disinfectants, nor, indeed, by current antimicrobial agents.[48,125]

Community

In the community, national and private laboratory resources will prioritise infection research, investigating bioengineering, pathogen transmission, disinfectant testing, antimicrobial surfaces, coatings, cements & textiles, and cleaning equipment & methods. No doubt business and industry will create marketable items for 'eliminating' infection risk in peoples' homes and elsewhere.[47] Supermarkets will make use of UVC-based decontamination of consumables and bio-coated wrappers for both raw and processed food. Environmental health teams will use species-specific pathogen adenosine triphosphate (ATP)-detecting kits for food-producing premises, cafes and restaurants. Community health centres will create their own infection-control strategies, with specialist nurses responsible for managing patients in a variety of community healthcare settings.[126] A framework of guidelines, policies and procedures for outbreak detection, contact tracing and intervention will be overseen by public health teams, supported by diagnostic laboratories and local clinical staff.[127]

Mobile decontamination and cleaning firms will provide hygiene services for the community, with automatic drive-in washer-disinfectors for public transport and ambulances. Local community initiatives will provide hygiene and health evening classes, with find-and-treat vans roaming the streets for patients with MDR tuberculosis and other infections.[128] Whole families can be quarantined at home, if one or more members are sick, with computer technology aiding education and job commitments. Public health legislation will support incarceration of people with untreatable transmissible infection, similar to the situation with syphilis a century ago.[56] Travellers might have to undergo quarantine conditions, depending on origin and destination, or perhaps people might choose simply to stay at home. The prospect of untreatable malaria would quickly remove the gloss from an exotic holiday.

Veterinary and agricultural interventions will be monitored with systematic surveillance programs shared across the world, with regular updates and international reporting.[129,130] Perhaps a long time coming, but nonetheless welcome, would be a global strategy to provide clean water for everyone. The obvious addition to this would be a complete ban on routine and emergency sewage discharge into free-flowing water courses or the sea, with appropriate sewage management for all countries.[54]

Conclusion

Darwinian evolution will compromise all our antimicrobial policies over time. Microbes readily exchange survival mechanisms between themselves, as well as from environmental sources.[131] The latter will always be capable of producing a resistance mechanism against any biological agent introduced into clinical practice.[46,132] Once selected, the capability for resistance persists long-term whether or not the original stimulus continues.[133] Resistant organisms so generated then spread throughout the world in a chosen niche accelerated by 21st century trends, travel and technology. This is well illustrated by the recent appearance of New Delhi metallo-β-lactamase enterobacteria (NDM-1), complete with encoded carbapenemase. The emergence of this gene is a catastrophe, because it edges bacteria to the brink of being completely untreatable. Since the gene resides in organisms

that colonise people without necessarily causing symptoms, NDM-1 has been a hidden assault, crossing borders and entering hospitals without being detected.[4,134]

The real challenge for infection control over the next few years will be raising its profile to those not actively involved in healthcare. Engaging policy makers and budget holders at all levels will require repeated debate, since investment in infection control will hardly be a priority in the current economic climate. Action depends upon altruistic individuals with vision, who can influence political drive, governmental mandate and international collaboration. People will die from untreatable infection before the resources are found to control activities and research.

There is still time to prepare for a world without antibiotics. The need to revisit hygiene values of the past will not set pulses racing in an age of microchips and space travel.[135,136] We have a duty to reverse complacency over infection prevention and control in the 21st century.

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