His assertion that these practitioners were spreading disease was largely ignored for many years, until, in 1843, the young Boston physician, Oliver Wendall Holmes, presented a review of the literature, including Gordon’s treatise, and results of his extensive correspondence with colleagues, entitled The Contagiousness of Childbed Fever. His research revealed the widespread, often guilty, suspicion among some doctors that they, themselves, were responsible for the spread of childbed fever, between patients or from bodies of dead patients, which they had recently dissected. Many described their attempts to prevent this by strict ablutions and changing clothes between patients. But Holmes stated publicly that: ‘occurrence of three or more closely connected cases, in the practice of one individual . . . is prima facie evidence that he is the vehicle of contagion’ and when his paper was republished, in 1854, it provoked abuse and scorn from several influential academics, who could not countenance the possibility that a physician could be responsible for transmission of disease.

Meanwhile, in 1847, another controversial physician/obstetrician entered the fray. Ignaz Semmelweis was assistant lecturer at the first obstetrical division of the Vienna General Hospital. He became greatly concerned by the persistently much higher (up to 10-fold) maternal mortality from childbed fever in the first, compared with the second obstetrical division, although the only obvious difference between them was that the latter was staffed by midwives and the former, by doctors and medical students. Semmelweis spent months systematically investigating every conceivable explanation, without success, until the death of his mentor – the pathologist, Jacob Kolletschka – provided a breakthrough. Kolletschka had died from sepsis, following a scalpel wound sustained during an autopsy; the pathological findings at his autopsy were essentially similar to those of childbed fever victims. Semmelweis realised that Kolletschka had died from ‘cadaverous material’ being introduced into his wound. He reasoned that similar material was the cause of childbed fever and ‘that the transmitting source of the cadaver particles was . . . the hands of the students and attending physicians’, each of whom who performed several autopsies a day and moved freely between the mortuary and wards where they examined women in labour. Hand washing was perfunctory and failed to remove the cadaverous smell.

Semmelweis ordered his students and colleagues to wash their hands in chloride of lime between the autopsy room and examining patients. The next year (1848), the maternal mortality in the first obstetrical division fell from more than 10% to an unprecedented low of 1.2% – almost identical with that (1.3%) of life-threatening illnesses for which they were admitted were often infectious diseases – of which smallpox was the most prominent and feared – and hospital outbreaks were common. Specialised ‘smallpox’ – or, later, ‘fever’ – hospitals partly relieved the pressure, but outbreaks of infectious diseases still occurred in the overcrowded, dirty, verminous wards where patients often shared beds. The lice that infested patients’ beds spread louse-borne typhus (‘hospital’ fever) and outbreaks of dysentery and respiratory infections were common. As barber surgeons became more ambitious, surgical sepsis and gangrene became more common, with mortality rates, after amputations, up to 40%.

Women hoping for assistance during childbirth were much more likely to die from childbed fever in hospital than if they delivered at home. Surgical sepsis and childbed fever were recognised, by many practitioners, as epidemiologically linked and much more likely to occur in hospitals; some had begun to suspect their own roles in transmission, despite the prevailing belief in miasmas as the vectors of disease.

In 1789, the Scottish obstetrician Alexander Gordon, in A Treatise on the Epidemic Puerperal Fever of Aberdeen, linked clusters of childbed fever cases to certain doctors’ or midwives’ practices. His assertion that these practitioners were spreading disease was largely ignored for many years, until, in 1843, the young Boston physician, Oliver Wendall Holmes, presented a review of the literature, including Gordon’s treatise, and results of his extensive correspondence with colleagues, entitled The Contagiousness of Childbed Fever. His research revealed the widespread, often guilty, suspicion among some doctors that they, themselves, were responsible for the spread of childbed fever, between patients or from bodies of dead patients, which they had recently dissected. Many described their attempts to prevent this by strict ablutions and changing clothes between patients. But Holmes stated publicly that: ‘occurrence of three or more closely connected cases, in the practice of one individual . . . is prima facie evidence that he is the vehicle of contagion’ and when his paper was republished, in 1854, it provoked abuse and scorn from several influential academics, who could not countenance the possibility that a physician could be responsible for transmission of disease.

Institutions for the care of the sick and relief of the poor date back at least to ancient Egypt and Greece. In Europe they were generally run by religious communities (Fig. 1), until the Reformation, in the 16th Century, when many passed from Church, to secular control. ‘Modern’ hospitals, which would become centres of medical innovation, research and training, were first established during the Enlightenment, in the 18th Century, funded by wealthy benefactors, specifically for care of the sick.

These 18th Century hospitals were a mixed blessing for patients. The life-threatening illnesses for which they were admitted were often infectious diseases – of which smallpox was the most prominent and feared – and hospital outbreaks were common. Specialised ‘smallpox’ – or, later, ‘fever’ – hospitals partly relieved the pressure, but outbreaks of infectious diseases still occurred in the overcrowded, dirty, verminous wards where patients often shared beds. The lice that infested patients’ beds spread louse-borne typhus (‘hospital’ fever) and outbreaks of dysentery and respiratory infections were common. As barber surgeons became more ambitious, surgical sepsis and gangrene became more common, with mortality rates, after amputations, up to 40%. Women hoping for assistance during childbirth were much more likely to die from childbed fever in hospital than if they delivered at home. Surgical sepsis and childbed fever were recognised, by many practitioners, as epidemiologically linked and much more likely to occur in hospitals; some had begun to suspect their own roles in transmission, despite the prevailing belief in miasmas as the vectors of disease.

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The critical difference between divisions, which Semmelweis had overlooked before, was that midwives did not perform autopsies! Until many years after his death, Semmelweis’ evidence-based hand hygiene practice was misunderstood or angrily rejected by the medical establishment, even after he belatedly published his findings, in 1861, in *Die Aetiologie, der Bergriff und die Prophylaxis des Kindbettfiebers (The Etiology, the Concept and the Prevention of Puerperal Fever).* But Semmelweis’ strategy for implementing practice change was far from ideal:

*Insult your enemies, accuse your superiors of causing the deaths of mothers... refuse to publish, but when you do so write incomprehensibly, use public humiliation and haranguing to change behaviour, and be arrogant and angry. This will not work every time...* 

Fortunately, prevention of hospital-acquired infections did not rest only with Semmelweis. Florence Nightingale reduced hospital cross-infection by enforcing strict hygiene – clean linen (boiled to destroy lice) for each patient; disposal of sewage; fresh-air ventilation (Fig. 2). Joseph Lister, influenced by the work of Pasteur and Koch on the germ theory of disease, introduced antiseptic principles of surgery: use of carbolic acid spray in the operating theatre and carbolic acid wound dressings to kill bacteria, with dramatic reduction in surgical sepsis.

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**Figure 1.** Triptych showing the Hôtel Dieu in Paris, about ad 1500. The comparatively well patients (on the right) were separated from the very ill (on the left). [http://commons.wikimedia.org/wiki/File:Hotel_Dieu_in_Paris_about_1500.gif](http://commons.wikimedia.org/wiki/File:Hotel_Dieu_in_Paris_about_1500.gif) (accessed 23 December 2013).

**Figure 2.** ‘Nightingale’-style open ward. Fairfield Infectious Diseases Hospital, Melbourne.
Despite these improvements, infectious diseases remained the most common cause of premature death, until the first half of the 20th Century, when safe and effective vaccines and antibiotics were developed. Together, they changed the course of medical (and arguably global and military) history to such an extent that, in 1967, the US Surgeon General, William Stewart, is reputed to have said: ‘It is time to close the book on infectious disease’. This widely held view remained largely unchallenged until the 1980s when the emergence of AIDS and other ‘new’ infectious diseases proved how misguided it had been.

By then, hospital infections were no longer taken very seriously. When outbreaks of virulent penicillin-resistant *Staphylococcus aureus* infection occurred in newborn nurseries in the 1950s, shortly after penicillin was introduced, methicillin and its derivatives were developed; when methicillin-resistant *S. aureus* first began to spread in hospitals, in the 1970s, vancomycin was used. Ampicillin, then successive generations of cephalosporins, aminoglycosides and carbapenems were introduced to manage infections due to *E. coli* and other Gram-negative bacteria, as they became progressively more resistant to one antibiotic after another or, more commonly, to several different antibiotic classes simultaneously. The emergence of multiresistant bacteria has been insidious, like climate change, and warnings of ‘the end of the antibiotic era’ were often dismissed as alarmist – at least until recently, when the flow of new antibiotics has largely dried up.

Viral infections also are amplified and spread in the hospital environment. The importance of blood-borne viruses (BBV) only became apparent in the 1970s, when hepatitis B virus (HBV) was identified and outbreaks of HBV infection occurred among patients, in which healthcare workers (HCW) were the source. Serological surveys showed that HCW, especially those frequently exposed to blood, were several times more likely to have been infected with HBV than the general population. The HBV vaccine has virtually eliminated the risk, but hepatitis C, HIV and other BBV remain potential risks for HCWs and patients exposed to blood or blood products in healthcare settings.

Meanwhile, hospital outbreaks of other vaccine preventable diseases still occur, even in countries where immunisation uptake is high. Measles, pertussis and varicella, introduced by an infected HCW or patient, can cause serious, potentially fatal illness in highly vulnerable patients; even a single mild case can cause major disruption, while contacts are traced and quarantined. The risk can be reduced by mandatory HCW immunisation with routine childhood vaccines, as introduced, with moderate success, in New South Wales, in 2007. Also, regular hospital outbreaks of gastrointestinal and respiratory viral infections, of which influenza is the most serious, occur each year. Mandatory annual HCW influenza immunisation remains controversial and logistically difficult, but voluntary uptake is often poor.

It is easy to dismiss the gradual increase in rates of healthcare-associated infection (HAIs) due to multiresistant bacteria or regular seasonal outbreaks of viral infection, as unavoidable collateral damage inherent in modern hospital practice. But the estimated burden of HAIs and the associated morbidity, mortality and excess healthcare costs is huge: an estimated 1.7 million HAIs and 99,000 deaths at a cost of US$10–25 billion, in the USA, annually. Approximately 50% or more of these HAIs are preventable, using simple measures, of which hand hygiene – as advocated with relatively little success by Semmelweis, but recently embraced by healthcare authorities, worldwide – is the most important. Despite the simplicity and logic of hand hygiene and massive international efforts to facilitate and promote it, compliance by HCW remains patchy and often inadequate. HAI prevention is an urgent ethical issue, but it remains a relatively low priority in many countries, including Australia, with increasingly expensive, sophisticated healthcare systems.

Occasionally, unexpected events seriously challenge our complacency. In February 2003, a Chinese doctor with a mysterious respiratory illness checked into the Metropole Hotel, Hong Kong, where he infected 12 people, who subsequently travelled to several countries where they, in turn, infected another 350 people with a disease that became known as severe acute respiratory syndrome (SARS), due to a novel coronavirus. More than 8000 people (one-fifth of whom were HCW) were infected and nearly 800 died from SARS before the outbreak was controlled. Two of the people infected at the Metropole Hotel were Canadians. One, an elderly woman from Toronto, died at home; her son, who became ill while caring for her, was admitted to a Toronto hospital where, directly or indirectly, he infected 84 people, including 37 HCW of whom three died. After strict precautions were implemented the outbreaks appeared to have been controlled and the Ontario government eased restrictions, under pressure because of serious disruption to medical services, businesses and tourism. However, new cases had been occurring, unrecognised, in another hospital and a second epidemic wave affected 118 people (including 64 HCWs), causing 17 deaths. Overall, in Ontario, there were 375 cases (72% in healthcare settings), including 44 deaths (Fig. 3). This was in stark contrast to what occurred in British Columbia where there were only four proven SARS cases and no deaths after the other Canadian, who had been infected at the Metropole Hotel, was admitted to hospital in Vancouver.
The SARS Commission, established in 2006 to investigate these tragic events, revealed that in Toronto the index patient waited in the busy Emergency Department for 16 hours and was not placed in respiratory isolation until 21 hours after his arrival at the hospital. The Commission described a poor worker safety culture, dissociated from infection control, and described the Ontario public health system as ‘...broken, neglected, inadequate and dysfunctional’. In contrast, British Columbia had a well-rehearsed pandemic plan, awareness among HCW of infection control, including appropriate use of N95 masks, and a proactive workplace regulator. However, the Commission conceded:

No one foresaw the sudden emergence of an invisible unknown disease with no diagnostic test, no diagnostic criteria, uncertain symptoms, an unknown clinical course, ... incubation period, ... duration of infectivity, ... method of transmission...[etc.] ... no known treatment and no known vaccine19.

SARS should have been a wakeup call to healthcare organisations everywhere. The events in Toronto could have occurred in any hospital system with inadequate infection control emergency plans, including many in Australia. It could happen again. In September 2012, the discovery was announced of a new coronavirus that caused a SARS-like illness in humans – the Middle Eastern respiratory syndrome (MERS) coronavirus. By November 2013, 175 confirmed or probable cases had been reported, of which 97 resulted from human-to-human transmission, including at least 60 in healthcare settings20. Despite the lessons of SARS, healthcare settings will continue to harbour and amplify established and, potentially, new pathogens and the resistance genes by which they resist our dwindling therapeutic arsenal, unless the whole healthcare community accepts the moral responsibility of protecting the patients in our care.

References

**In Focus**

Antibiotic susceptibility testing methods and emerging bacterial resistance in hospitals

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Clinical microbiology laboratories, whether in hospitals or private institutions, have the important task of performing antimicrobial susceptibility testing on significant bacterial pathogens isolated from a variety of specimens. The aim of all this testing is to detect possible emerging antimicrobial drug resistance in unusual and common pathogens so that infections are treated with the appropriate antibiotics. Microbiologists and clinicians in hospitals are today more dependent on results from *in vitro* susceptibility testing. This signifies the importance of the diagnostic laboratory in clinical medicine. Hospital laboratories have the responsibility of reporting the antimicrobial agent(s) that are most appropriate for the organism(s) isolated, for the site of infection and the hospital pharmacy formulary.

**Definitions used to describe antimicrobial resistance in hospitals**

Antimicrobial resistance is the capacity of bacteria to survive exposure to a defined concentration of an antimicrobial substance. However, in hospitals antimicrobial resistance may have multiple definitions according to the scientific discipline and the goals involved:

- **Clinical definition:** the bacteria survive an adequate treatment with an antibiotic.
- **Pharmacological definition:** the bacteria survive a range of concentrations expressing the various amounts of an antibiotic present in the different compartments of the body when the antibiotic is administered at the recommended dose.
- **Microbiological and molecular definition:** the bacteria have a mechanism or gene that governs a higher minimum inhibitory concentration (MIC) than the original or wild bacteria. In hospitals this may become an infection control issue with plasmid mediated resistant organisms and requires molecular testing, for example, detection of various genes such as *MecA* in *Staphylococcus aureus*, VanA or VanB genes in *Enterococcus* species, with carbapenemase resistance in *Enterobacteriaceae* family or *Pseudomonas* species with the detection of beta-lactamase resistant genes such as *blaIMP-VIM*, *blaNDM*, *blaKPC* etc.
- **Epidemiological definition:** any group of bacterial strains that can be distinguished from the normal (Gauss) distribution of MIC(s) to an antibiotic.

In the past, for many clinical cases, hospital infections could be treated empirically based on the medical microbiologist’s past experiences. However, this has become more difficult recently with the emergence of new unpredictable resistances both in hospital and community patients. Empirical treatment continues to be...