



Gram-negative resistance: can we combat the coming of a new “Red Plague”?

Coordinated action is urgently needed to tackle a looming public health crisis

David F M Looke

FRACP, FRCPA,
MMedSci(ClinEpidemiol),
Infectious Diseases
Physician and Clinical
Microbiologist¹

Thomas Gottlieb

MB BS, FRACP, FRCPA,
Infectious Diseases
Physician and Clinical
Microbiologist²

Cheryl A Jones

MB BS, PhD, FRACP,
Paediatric Infectious
Diseases Specialist³

David L Paterson

MB BS, PhD, FRACP,
Infectious Diseases
Physician and Clinical
Microbiologist⁴

¹Infection Management
Services, Princess
Alexandra Hospital,
Brisbane, QLD.

²Department of
Microbiology and Infectious
Diseases, Concord Hospital,
Sydney, NSW.

³Department of
Microbiology and Infectious
Diseases, The Children's
Hospital at Westmead,
Sydney, NSW.

⁴Infectious Diseases Unit,
Royal Brisbane and
Women's Hospital,
Brisbane, QLD.

david_looke@
health.qld.gov.au

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Everybody knows that pestilences have a way of recurring in the world; yet somehow we find it hard to believe in ones that crash down on our heads from a blue sky. There have been as many plagues as wars in history; yet always plagues and wars take people equally by surprise. Albert Camus, *The plague*, Part 1¹

Infectious diseases scourges in history have had devastating effects on unprepared human populations. Bubonic plague, or the “Black Death”, killed more than a third of Europe’s population from 1346 to 1351, and the “White Plague” (tuberculosis) became epidemic in Europe throughout the 19th century. These plagues provide many lessons from which we can learn if we are to contain the spread of gram-negative resistance — the coming of a new “Red Plague”.

In 1884, Danish bacteriologist Hans Christian Gram published a stain method for distinguishing bacteria. Gram-negative bacteria do not retain a blue dye (crystal violet) and are stained pink or red by use of a counterstain, hence the term “red”. In clinical use, “gram-negative” largely refers to the common human pathogens such as *Escherichia*, *Klebsiella*, *Enterobacter*, *Proteus* and *Pseudomonas* species. These organisms cause infections such as urinary tract infections, peritonitis, biliary tract infection, hospital-acquired pneumonia, and less common but more serious infections such as liver abscess and neonatal meningitis, among others.

While antimicrobial agents were initially highly successful in treating these infections, their unfettered use in both humans and animals has seen rates of antimicrobial resistance rise alarmingly, especially in the developing world. In a 2009 study, > 50% of *Escherichia coli* in China and > 70% in India were extended-spectrum β -lactamase-producing strains, indicative of high-level resistance.² It is now estimated that up to 100–200 million people in India may harbour gram-negative bacteria that carry the New Delhi metallo- β -lactamase (NDM-1) enzyme that renders the bacteria virtually untreatable.³ It is not known how many have experienced infections from these organisms. Poor sanitation and uncontrolled antibiotic overuse in health and agriculture are the likely culprits.

Australia and the rest of the developed world are not immune to these developments. Antibiotic-resistant gram-negative bacterial infections were once thought to be simply “hospital-acquired infections”, but people with community-acquired multiresistant gram-negative bacte-

rial infections are now presenting to general practices and emergency departments. Comprehensive Australia-wide surveillance of resistance trends in gram-negative bacilli is lacking, however. Though rates of resistance are lower in Australia than in the United States, southern Europe and much of Asia, resistance (eg, to third-generation cephalosporins and fluoroquinolones) is rising. The Australian Group on Antimicrobial Resistance surveillance of community-acquired gram-negative isolates has shown that multiresistant *E. coli* isolates rose from 4.5% in 2008 to 7.2% in 2010.⁴ Moreover, virtually all key mechanisms of multidrug-resistance in gram-negative bacilli found worldwide have now been detected in Australia.^{5–8}

Establishment of gram-negative resistance in Australia is likely to have several consequences, including the need to treat previously simple infections, such as uncomplicated urinary tract infections, with intravenous instead of oral antimicrobial therapy; the need to treat severe community-acquired sepsis with antibiotics of last resort upfront, and a growing ineffectiveness of surgical antibiotic prophylaxis. The impact of increased resistance would be seen across all age groups, leading to significant costs to the community in both human and economic terms. This shift has already become apparent in children and adults with no prior hospital exposure presenting with infections acquired during travel to countries where resistance is endemic.⁹ The impact on health care-associated sepsis is likely to be substantial.

Are new antibiotics waiting in the wings to save the day? Unfortunately, antibiotic development has all but stalled, and candidate antibiotics in development have limited activity against these resistant pathogens. Two basic strategies remain: enhancing traditional infection control, including hand hygiene and isolation of carriers in hospital; and antibiotic stewardship, where “selection pressure” on bacterial flora is mitigated by reduction in the volume of antibiotics used in clinical practice. Infection control and antibiotic stewardship programs are now mandated in all hospitals through accreditation, but their effectiveness in halting the spread of gram-negative resistance is unknown.

What must be done?

Without a coordinated effort at government level across all human and animal health care sectors, we are likely doomed to failure. We need to implement national surveillance to map and track the true extent and impact of these infections. We need to proactively implement the princi-

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ples of stewardship across all sectors from “high-tech” hospitals to country general practices, to eliminate the many, mostly non-evidence-based, ways that antimicrobials and disinfectant products are used within the community, hospitals and industry. We need to support and fund research into new antimicrobial compounds and other innovative strategies to combat resistance. We need to think outside the square and embrace innovative trials of preventive strategies, such as vaccines; newer methods of disease treatment, such as using interventional radiology and minimalist surgical techniques instead of traditional surgery; and farm production methods developed with techniques that do not require antimicrobial agents. Most importantly, we need to appreciate the significance of this growing outbreak of gram-negative resistance in the same way that we appreciate and plan for outbreaks of infections such as avian influenza.

In 2011, the World Health Organization declared antimicrobial resistance to be the theme for World Health Day, and governments around the world have begun to face up to this threat. A major positive step has been taken by the Australian Government with the recent formation of the Antimicrobial Resistance Standing Committee, which reports to the Australian Health Protection Committee. This, for the first time, has created a dialogue that allows involved agencies and groups to tackle this challenge together.

All of us — government and public health institutions, universities, human and animal health professional groups, and the community — have to recognise gram-negative resistance as a looming public health crisis and a social challenge: a new plague. We need to be brave enough to make difficult decisions to re-regulate antibiot-

ics. Without intervention, many of the greatest advances in the practice of medicine — such as transplantation, joint replacement surgery or critical care medicine — will be under significant threat.

We have one great advantage over the past plagues of history: we need not be caught unprepared. We have the vast armamentarium of science now working for us. Using this knowledge, we have the capacity to counter ignorant practices and galvanise public and governmental action. Past plagues teach us to take effective steps before it is too late.

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