

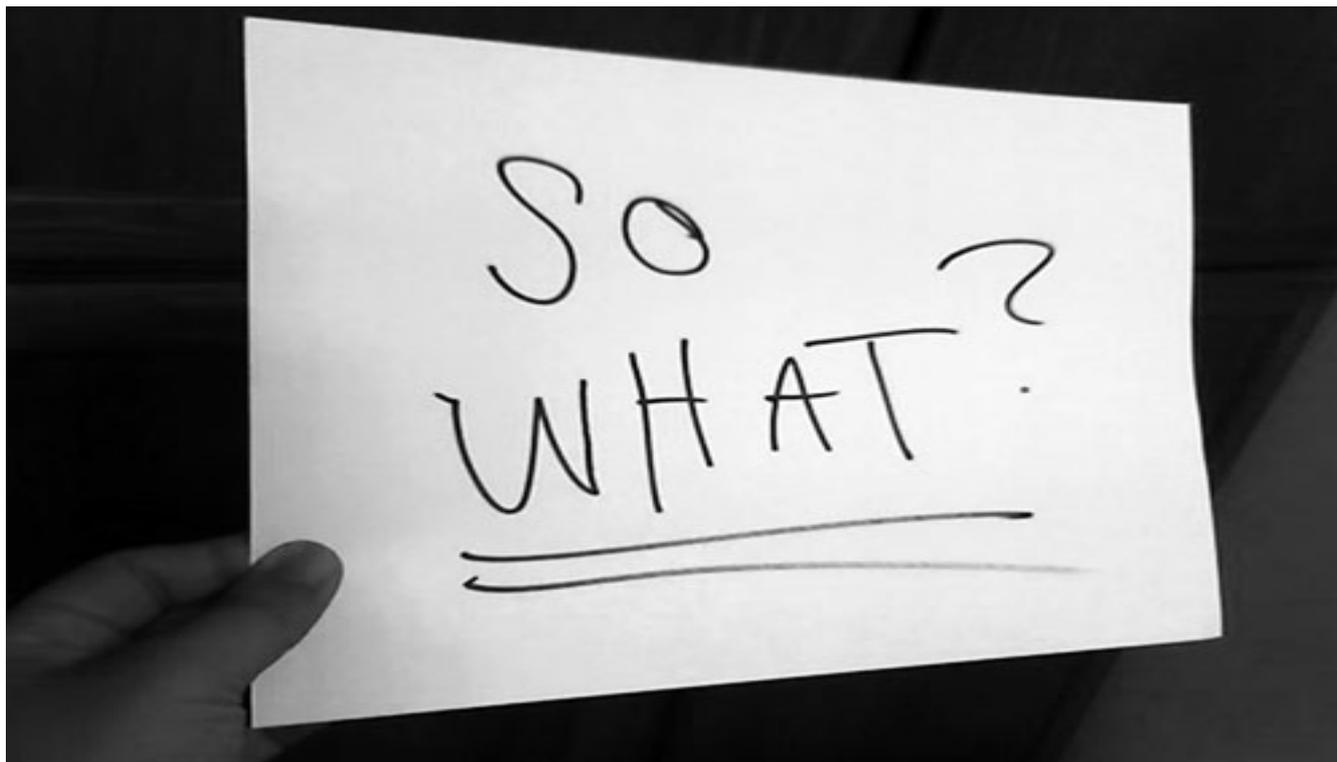
Antimicrobial resistance – A major public health threat of our time

Prof Benjamin Howden

Microbiological Diagnostic Unit Public Health Laboratory

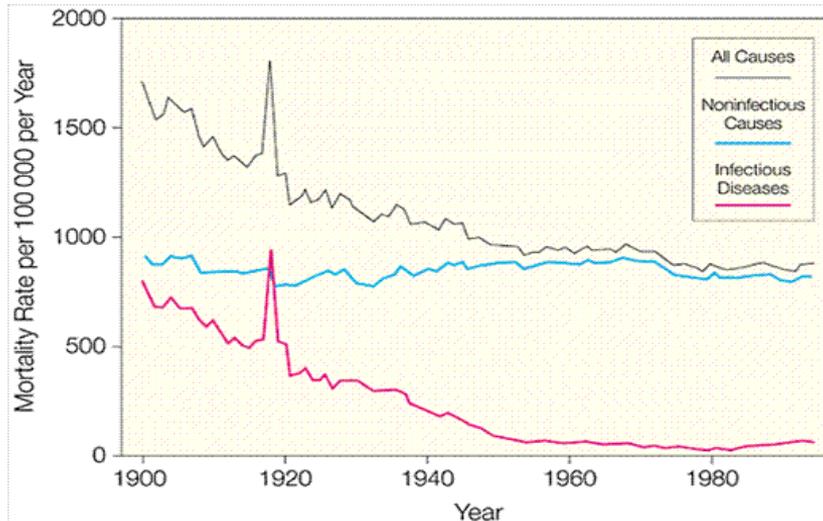
The University of Melbourne

- Antibiotic resistance
- The link between antibiotic use and resistance
- Antimicrobial stewardship
- Addressing antibiotic resistance



The “miracle” of antibiotics

- Discovery of penicillin by Sir Alexander Fleming and its subsequent development by Florey & Chain revolutionised treatment of infectious disease
- Life expectancy has \uparrow due to ability to treat infection



Crude mortality rates for all causes, noninfectious causes and infectious diseases over the period 1900-1996.

Antibiotics save lives every day...

- Ability to control infection is critical to other advances in medicine
 - Neonatal care
 - Transplantation
 - Chemotherapy for malignancy
 - Immunosuppression
 - Safe surgery
 - Safe obstetric care
 - Intensive care interventions



Penicillin, 1944: a new drug that saved lives



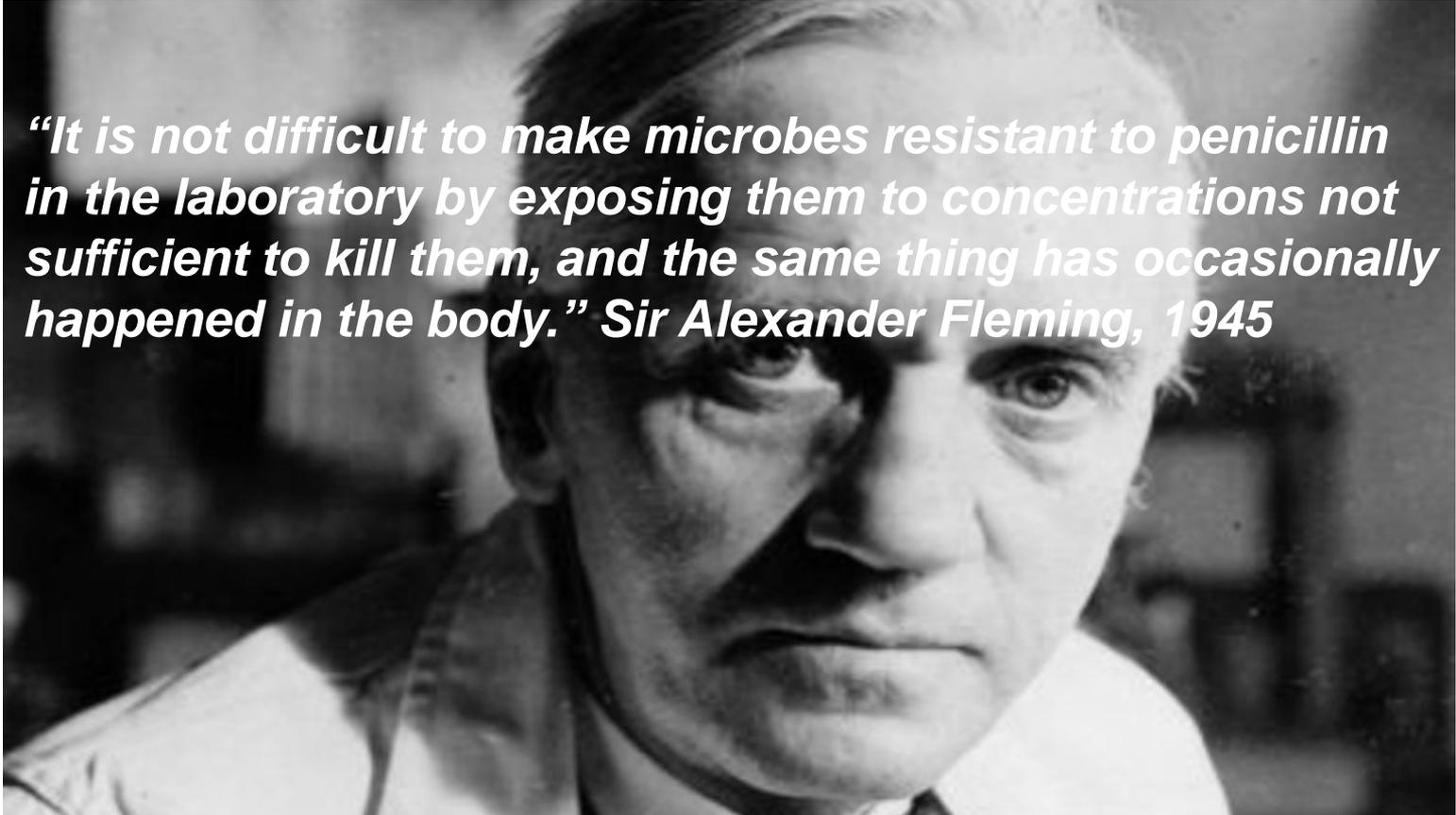
Thanks to **PENICILLIN**
...He Will Come Home!



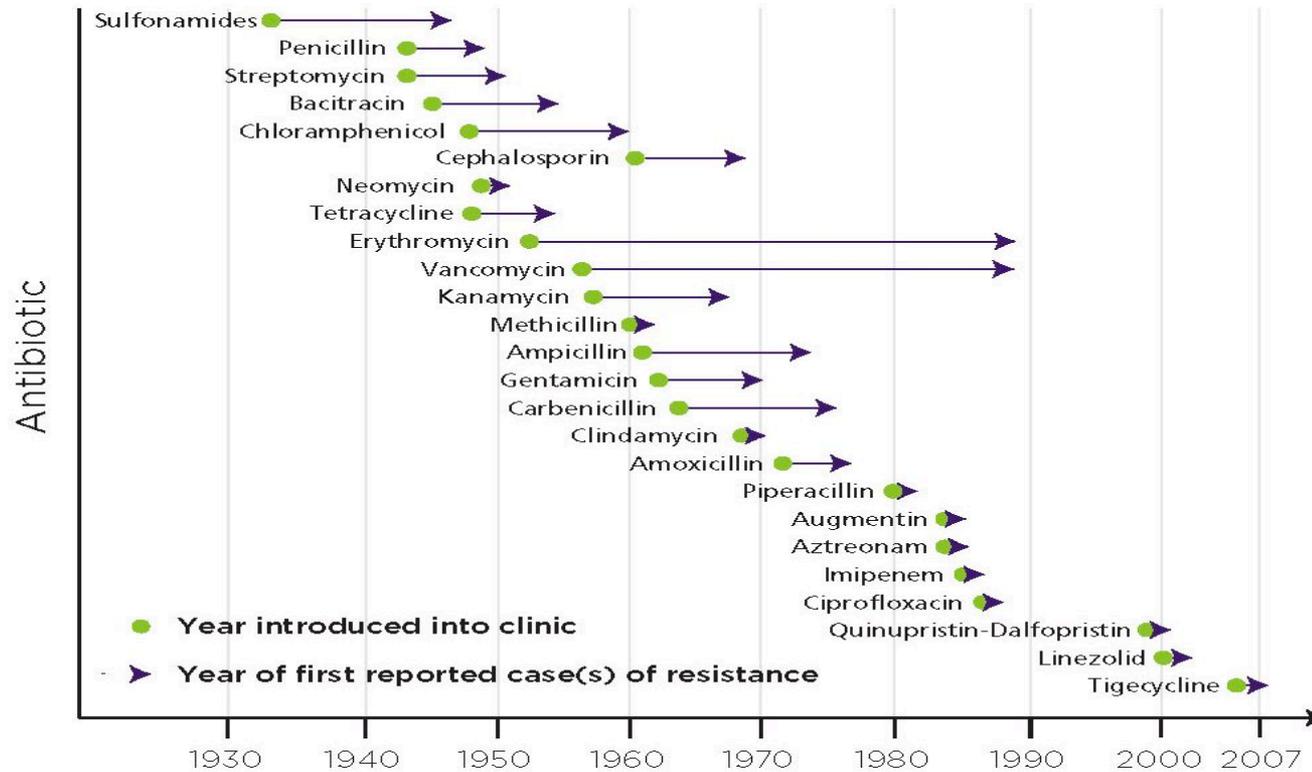
Sources: <http://www.nationalworldmuseum.org/learn/education/for-teachers/lesson-plans/thanks-to-penicillin/lesson-plan> and
A 1944 poster attached to a curbside mailbox offering advice to World War II servicemen. Courtesy photo: Wildmediz

Emergence of antibiotic resistance

“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.” Sir Alexander Fleming, 1945

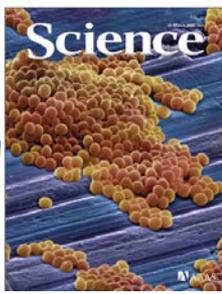


Emergence of antibiotic resistance

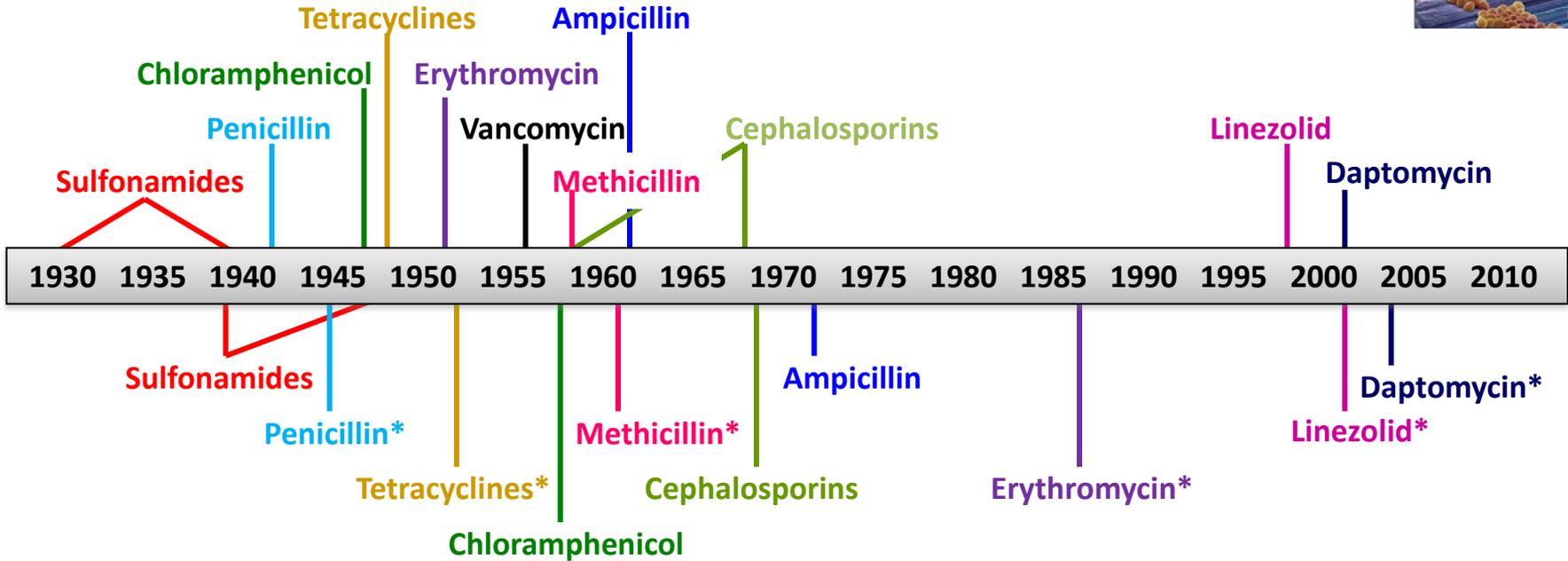


From: Pray L (Antibiotic R&D,
Cambridge Healthcare Institute, Needham, MA, 2008).

Staphylococcus aureus



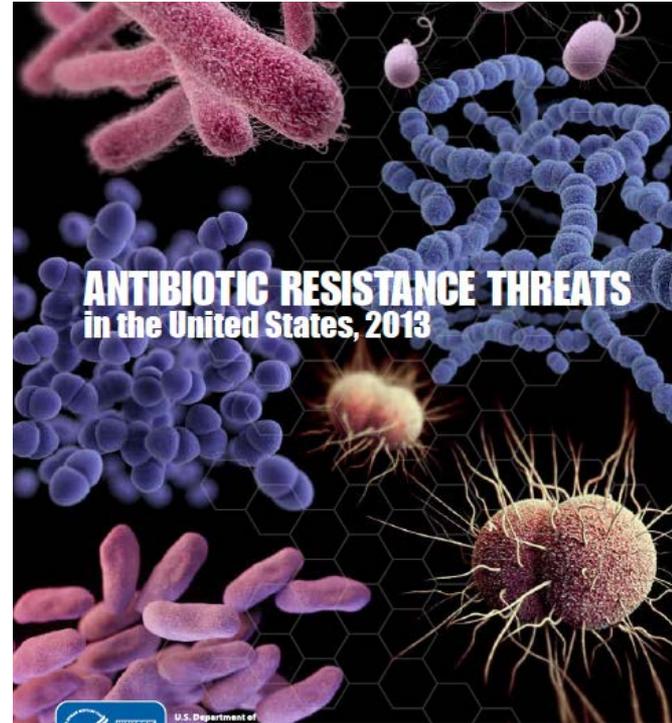
Year of Antibiotic Release



Year of Reported Resistance

Antimicrobial resistance

- One of the greatest public health threats of modern times
- Increasingly difficult to treat many common infections



Key Points

- Threatens the effective prevention and treatment of a wide range of infections caused by bacteria, parasites, viruses, fungi
- Higher morbidity, mortality, healthcare costs
- Serious threat to global public health



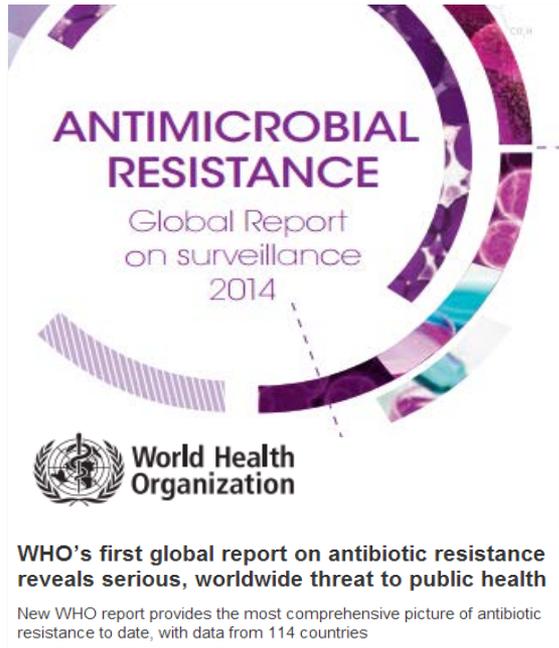
**World Health
Organization**

Impact of resistance

- Increased morbidity/ mortality
 - Evidence across many pathogens
- Untreatable infections
 - Now being encountered
- Increased costs
 - \$18-29,000 US/patient
 - Excess length of stay
 - 6.4 – 12.7 days/patient



Antibiotic Resistance is a Global Issue



CDC Threat Levels

Urgent



Serious



others



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Real people are affected



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Patient Stories

Many patients and their families have suffered the debilitating effects of antibiotic-resistant infections. Indeed, many patients have lost their lives due to these infections. The compelling and heart-wrenching stories below engender a strong sense of urgency to address drug-resistant infections and the lack of new antibiotic development. If you would like to share your story, please contact [Diana Olson](#).



Ricky Lannetti

A healthy 21-year old football player at Lycoming College in Williamsport, Pennsylvania who contracted MRSA and did not survive the infection.

[ADDIE RERECICH](#) [JOSH NAHUM](#)
[CARLOS DON](#) [RICKY LANNETTI](#)

TAKE ACTION!

What can you do to help? Urge Congress to pass legislation to spur research and development of new antibiotics, as part of the Prescription Drug User Fee Act (PDUFA) reauthorization bill. [Send an email](#) to your congressional representatives today.

See All Patient Stories



Addie Rerecich

A healthy 11-year-old girl from Tucson, Ariz., who spent months in the hospital fighting several antibiotic-resistant infections and needed a lung transplant to save her life.



David Ricci

A 19-year-old from the Seattle area battles several NDM-1 positive antibiotic-resistant infections as he recovers from a train accident that cost him his right leg.



Josh Nahum

A 27-year-old skydiving instructor in Colorado who died from an antibiotic-resistant Enterobacter aerogenes infection.



Carlos Don

A healthy 12-year old athlete from Southern California who died of pneumonia caused by an MRSA infection.



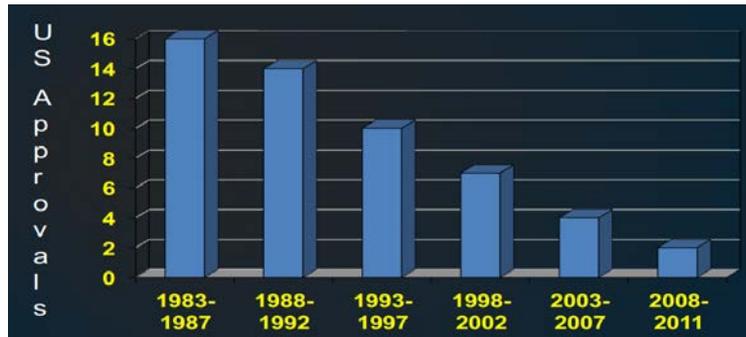
Brock Wade



Tom Dukes

Antibiotics are a limited resource

- We have.....
 - Growing rates of resistance
 - Inappropriate use
 - Decreasing pipeline of new antibiotics

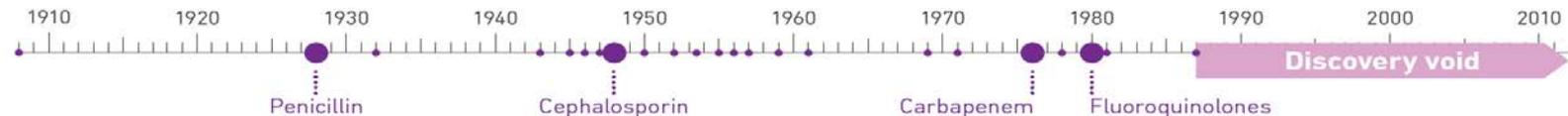


Declining FDA approvals of new antibiotics in United States¹

www.idsociety.org

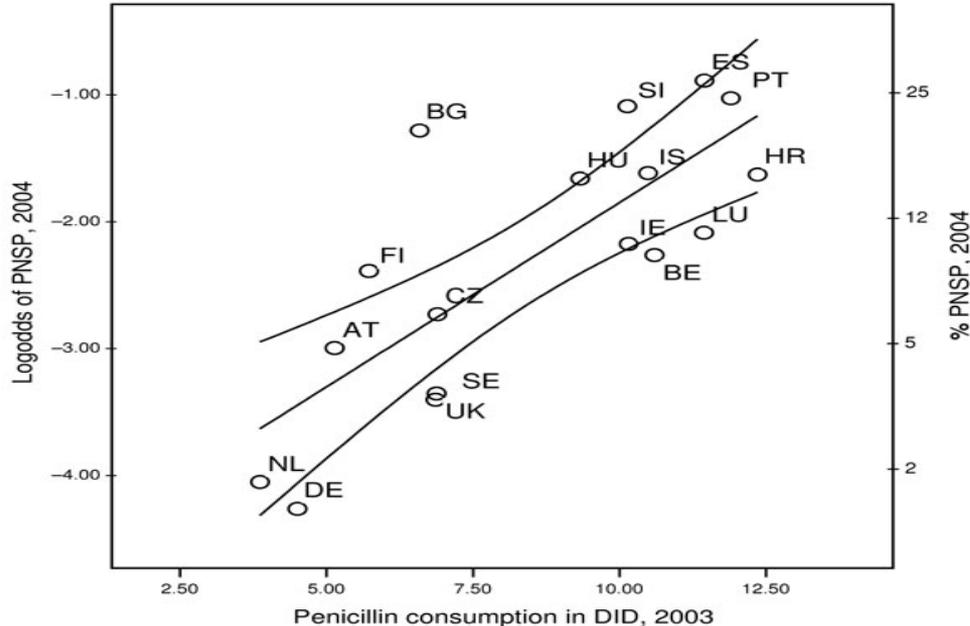


Over the last 30 years, no major new types of antibiotics have been developed



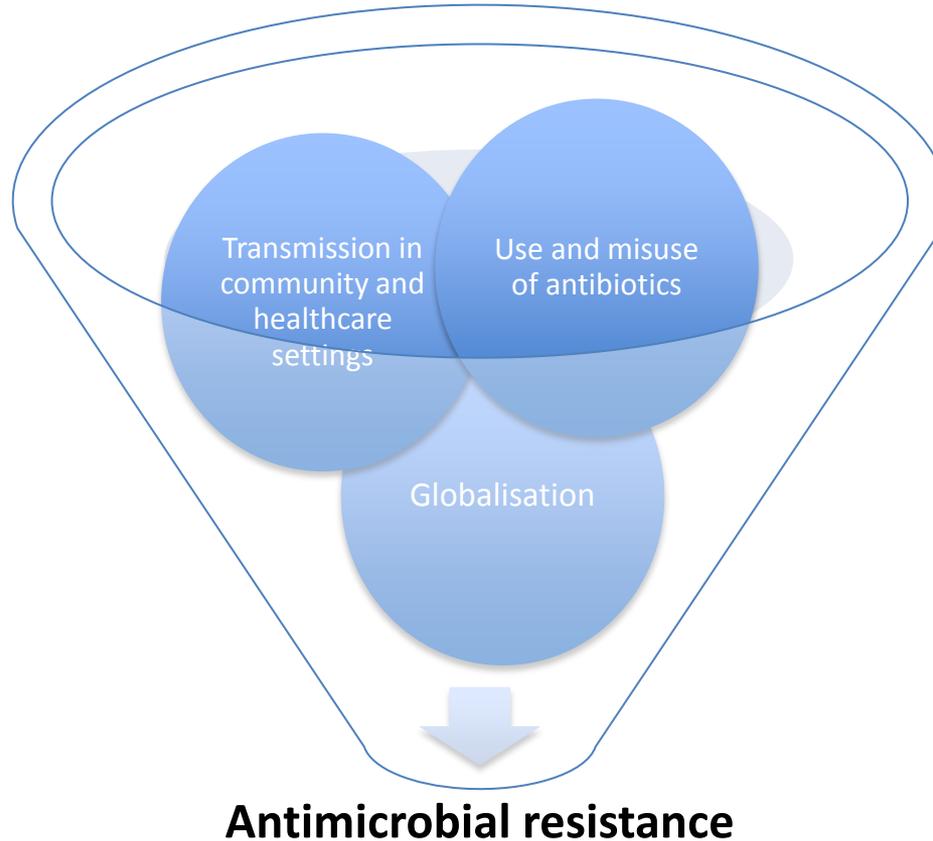
The link between antibiotic resistance and antibiotic use

Countries with high penicillin consumption also have high rates of penicillin resistance in pneumococci

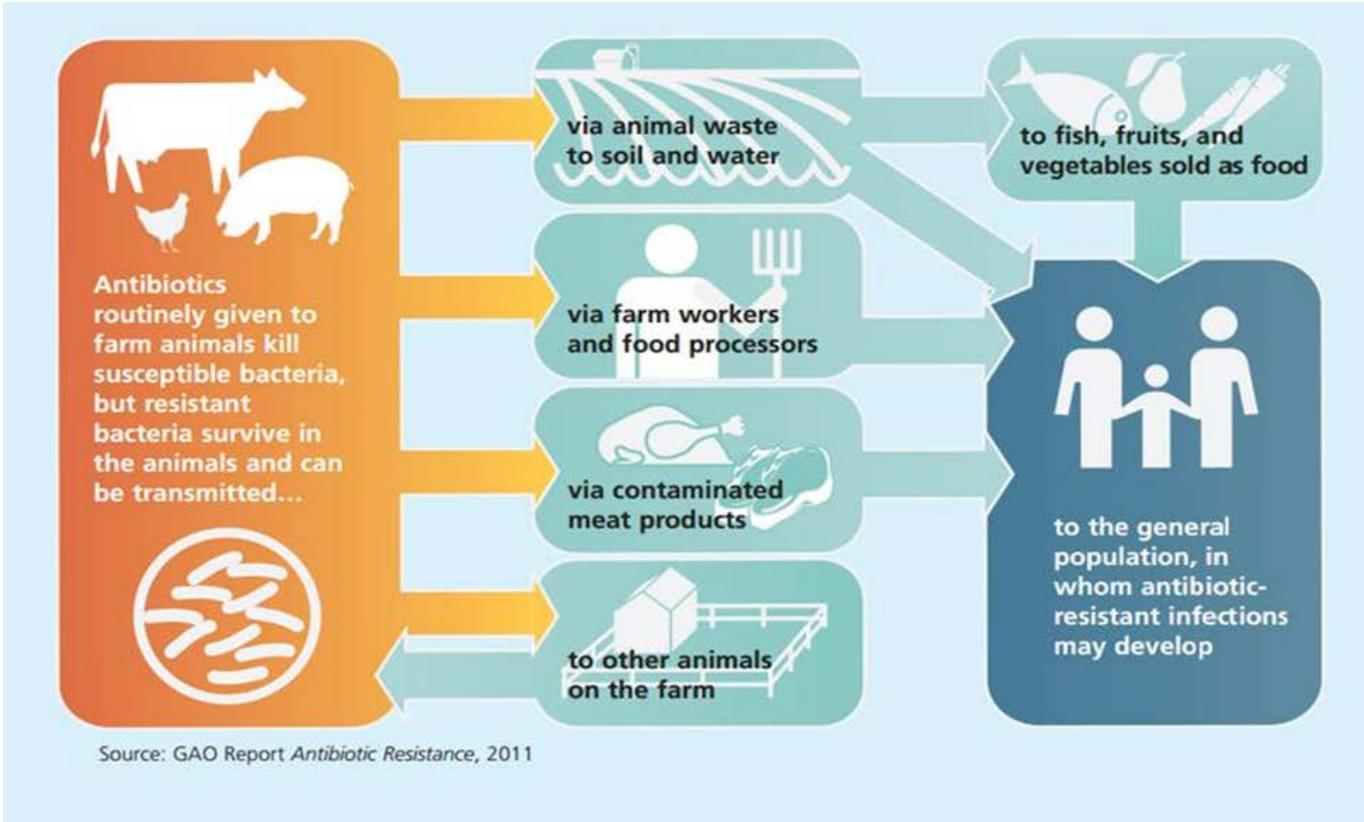


Occurrence of penicillin-nonsusceptible Streptococcus pneumoniae (PNSP) versus outpatient use of penicillins in 17 European countries.

Antimicrobial resistance in Australia



One Health Issue



Source: GAO Report *Antibiotic Resistance*, 2011

THE LANCET Infectious Diseases

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The Lancet Infectious Diseases, Volume 13, Issue 8, Pages 641 - 643, August 2013 [< Previous Article](#) | [Next Article >](#)

Superbugs in food: a severe public health concern

Monaco et al. *BMC Infectious Diseases* 2013, **13**:258
<http://www.biomedcentral.com/1471-2334/13/258>

BMC
Infectious Diseases

RESEARCH ARTICLE

Open Access

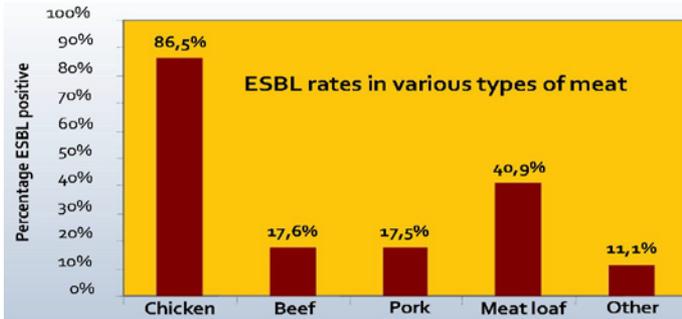
Livestock-associated methicillin-resistant *Staphylococcus aureus* responsible for human colonization and infection in an area of Italy with high density of pig farming

Monica Monaco^{1*}, Palmirino Pedroni², Andrea Sanchini^{1,3,4}, Annalisa Bonomini², Annamaria Indelicato² and Annalisa Pantosti¹

Extended-Spectrum β -Lactamase Genes of *Escherichia coli* in Chicken Meat and Humans, the Netherlands

Ilse Overdeest, Ina Willemsen, Martine Rijsburger, Andrew Eustace, Li Xu, Peter Hawkey, Max Heck, Paul Savelkoul, Christina Vandenbroucke-Grauls, Kim van der Zwaluw, Xander Huijsdens, and Jan Kluytmans

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 7, July 2011



Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

Timothy R Walsh, Janis Weeks, David M Livermore, Mark A Toleman



171 environment swabs
- 51/171 (29.8%) NDM-1+

50 potable water samples
- 2/50 (4%) NDM-1+

Resistance in Australia gains public attention...



THE SUNDAY AGE

NEWS

JUNE 9, 2013 3

Australia running out of time to combat the rise of the superbugs

JILL STARK

Australia urgently needs a national centre to manage the threat of deadly superbugs, and must start screening all imported meat and seafood to prevent their spread, a Senate inquiry has recommended.

Tighter monitoring of the use of antibiotics in animals bred for food should also be introduced, along with national standards for hospital infection control.

The federal inquiry, instigated by Greens senator and former GP Richard Di Natale, was set up in response to an

alarming increase in antibiotic resistance and rising rates of superbug infections.

Doctors told the inquiry that while the bugs had once affected mostly people with weakened immune systems, such as cancer or transplant patients, healthy Australians were increasingly contracting superbugs through routine medical procedures due to the proliferation of antibiotic-resistant bacteria.

The widespread use of antibiotics in intensive farming, particularly in meat, poultry and seafood imported from countries such as China and Viet-

nam, has been pinpointed as one likely factor fuelling the trend.

"This is a problem that the medical community and infectious diseases and public health specialists have known about for a decade but there just hasn't been an adequate response from successive governments. But we must act because... the rise of superbugs has the potential to take us to a pre-industrial age era in medicine where we just don't have antibiotics," Dr Di Natale said.

The inquiry's findings, released on Friday, have been welcomed by infectious diseases experts who say there

will be dire health consequences if the government does not adopt them.

"We have time to fix this but we don't have much time. We have about five years to get this right before it's really going to be a major problem," said Professor Lindsay Grayson, director of infectious disease at Austin Health.

"If the superbug situation gets much further out of control then we won't be able to do transplantations, a lot of chemotherapy for cancer will need to stop, neonatal intensive care units won't be able to look after kids any more because all of those fantastic

advances in human healthcare have only been made possible because we've been able to treat the inevitable routine infections that occur with antibiotics. If now, instead of our infection being one of the easy-to-treat bugs it's a superbug that doesn't respond to antibiotics, it's suddenly very difficult."

Increased surveillance and reporting of antibiotic use in hospitals and in the community is also being urged.

Professor Grayson said was vital in preventing the spread of deadly bugs, and had proved successful with national hand hygiene protocols.

"That would mean that it doesn't matter if you're in a hospital in Queensland or Victoria, the standards will be the same. The way you put in an IV drip and the way urinary catheters are inserted should be the same

an effective way of minimising the spread of infection," he added.

"We take all these sick people and put six of them in a room together and then we're surprised when they spread diseases to each other. We need a system of one burn per toilet because a lot of these superbugs are actually spread from person to person because the toilet becomes contaminated. In the

Superbug discovery triggers new health alarm

BY DAN HARRISON

Researchers have confirmed long-held fears that a drug-resistant bug that is increasingly common in Australia can spread from person to person.

In a finding that could carry major implications for how hospitals control infections, British researchers have provided the first proof the debilitating bug, *Mycobacterium abscessus*, can be transmitted between patients.

The bug, which accelerates decline in lung function and can prevent safe lung transplantation, has become increasingly prevalent in Australia over the past decade, a previous study found. It must be treated with an extended course of a poorly tolerated combination of antibiotics and treatment often fails.

The findings, published on Friday, come as a committee examines response to the problem; resistant infections.

The study authors say their findings carry major implications for how hospitals care for patients and raise questions about the adequacy of current infection control measures.

The researchers conducted DNA analysis of samples collected from 31 patients at a cystic fibrosis centre in Britain and concluded the bug had frequently been transmitted between patients, despite infection-control measures. Previously, it had been thought people caught the bug from their environment. While experts had been concerned about the possibility of the bug spreading between people, the study provides the first proof.

Researchers were unable to

identify exactly how it had been transmitted, but suggested it may have spread through contaminated clothing or bedding or through airborne water droplets.

England's chief medical officer, Dame Sally Davies, recently called for worldwide action to combat antibiotic-resistant bacteria, saying superbugs posed a "catastrophic threat" to human health that should be likened to terrorism.

Austin Hospital head of infectious diseases Professor Lindsay Grayson told the inquiry if authorities did not move to contain existing superbugs and prevent new ones emerging over the next three to five years, infections would increase dramatically.

turning the problem around.

If we don't, we face the prospect of a world without antibiotics, where people will die of simple infections," he said.

He described evidence to the inquiry as "alarming" and the government needed to make tackling the problem a priority.

The federal government has set up a committee, comprising public servants, the chief medical officer and the chief veterinary officer to look at the problem.

Austin Hospital head of infectious diseases Professor Lindsay Grayson told the inquiry if authorities did not move to contain existing superbugs and prevent new ones emerging over the next three to five years, infections would increase dramatically.

The full story...

Enter Keywords Here SEARCH

Chief medical officer calls on govt and science communities to combat antibiotic resistance

Tony Eastley reported this story on Wednesday, July 10, 2013 06:12:00

Superbugs Potential catastrophe for human health

Surgery could soon become deadly

Julia Medew
Health Editor

Superbugs could soon make routine surgical procedures deadly for healthy people if authorities do not start introducing measures to tackle them, doctors say.

The warning comes as England's chief medical officer, Dame Sally Davies, called for worldwide action to combat antibiotic-resistant bacteria that she said posed a "catastrophic threat" to human health that should be likened to terrorism.

In submissions to an Australian Senate inquiry into the problem, microbiologists and infectious disease experts called for better

cleaning of hospitals and more testing of animals and food.

Head of infectious diseases at the Austin Hospital Professor Lindsay Grayson said if authorities did not move to contain existing superbugs and prevent the emergence of new ones over the next three to five years, infections would increase dramatically.

While superbugs were already a routine daily feature of healthcare for many, Professor Grayson said if nothing was done, they would become the norm in coming years, especially for immunocompromised patients such as transplant recipients, sick infants and those being treated for cancer.

Although it is currently unusual for healthy people to fall ill with superbug infections, he said urinary tract infections were increasingly becoming difficult to treat. Five years ago, he said, about 5 per cent of such infections among Victorian women were resistant to many antibiotics - now it was more than 20 per cent.

"[Urinary tract] infections were something previously GPs could easily manage," he said. "Now we're increasingly seeing them resistant to all the antibiotic tablets available and we're having to use intravenous antibiotics... Even then, we're very restricted in terms of which ones will work."

Proliferation of the bugs could also make routine surgery, particularly bowel surgery, potentially deadly for people.

The Australian Society for Microbiologists also called for more funding to develop new antibiotics, saying the global pharmaceutical industry had "dropped the ball" in favour of making other, more profitable drugs.

Greens senator Richard Di Natale - a medical doctor who instigated the inquiry - said he was hopeful a new government steering committee, with senior bureaucrats, the chief medical officer and chief veterinary officer on it, would help relieve the problem.



Senator

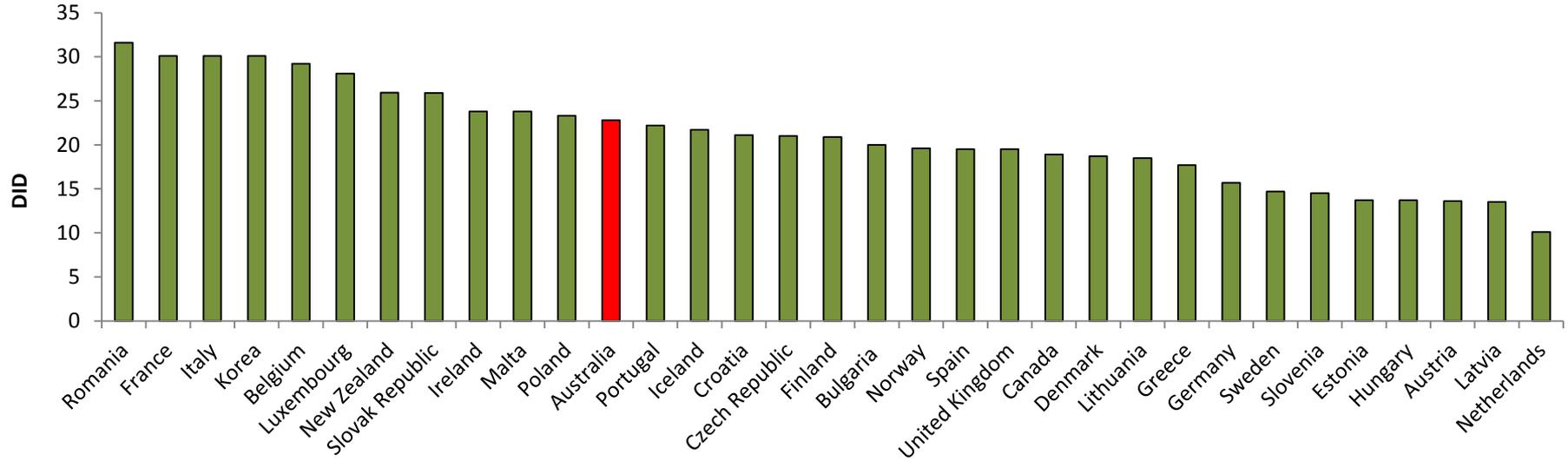
What are superbugs?

A micro-organism such as a bacteria resistant to antibiotics. Caused by:

- ▶ Inappropriate use of antibiotics.

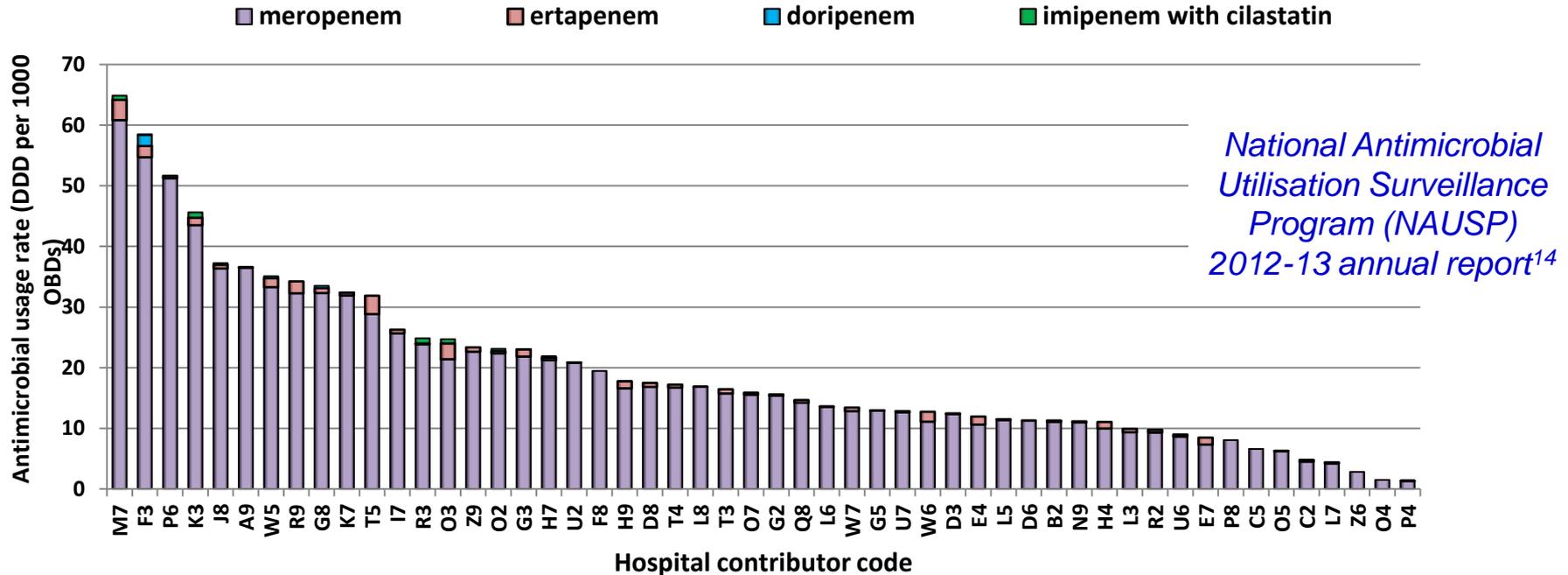
- ▶ Poor infection control, healthcare workers not wearing gowns and inadequate hospital cleaning.
- ▶ Weak or absent surveillance systems of antibiotic use and infections.
- ▶ Insufficient research to develop new antibiotics and vaccines.

Antibiotic use in Australia is high



Antibiotic usage varies between hospitals

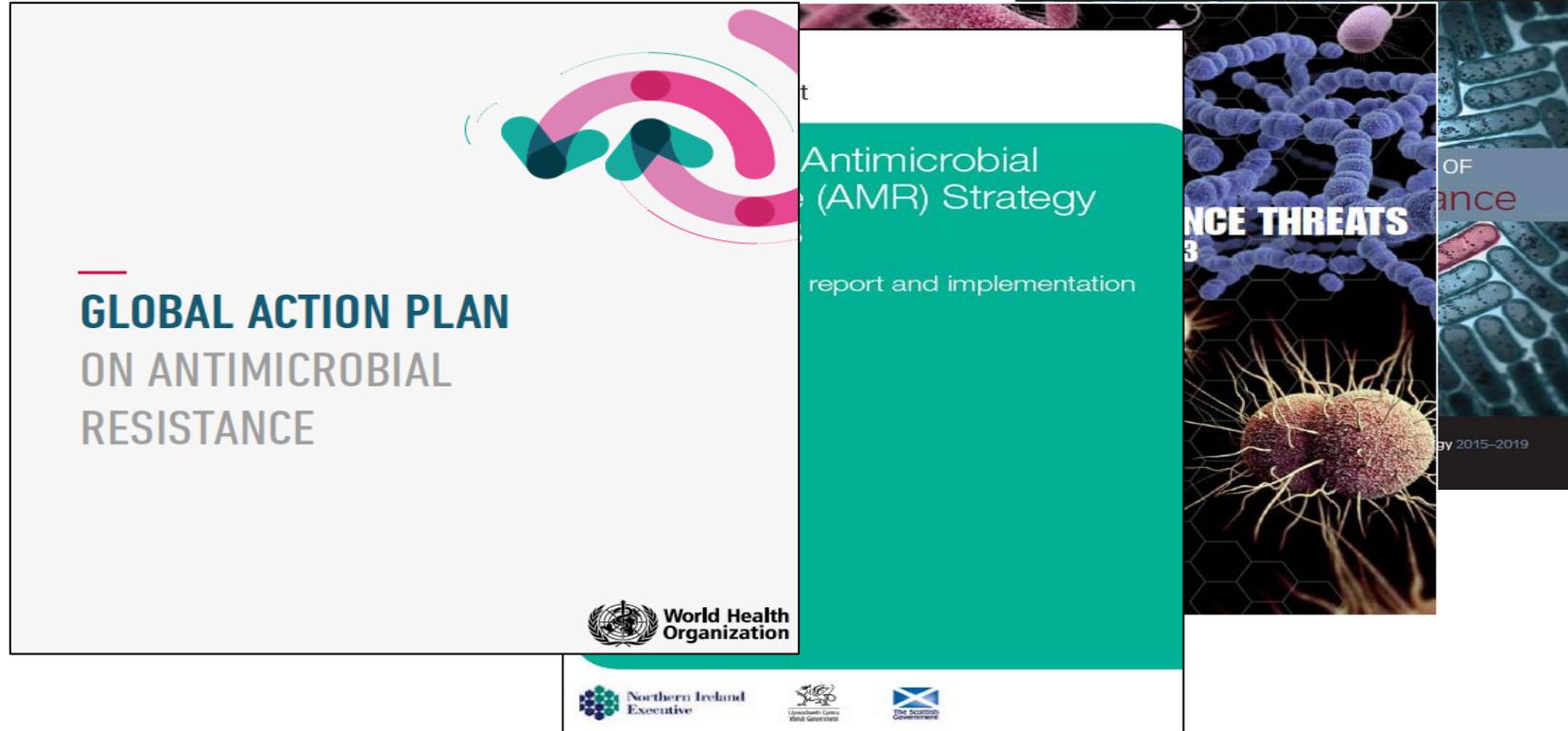
Even within a country – huge inter-hospital variation in antibiotic consumption
e.g. Meropenem use – **10-fold variation** across 52 Australian hospitals



What is inappropriate use ?

- Unnecessary prescription of antibiotics, (viral infections or for prolonged prophylaxis)
- Using broad-spectrum antibiotics when narrow-spectrum antibiotics are effective
- Wrong dose
- Continuing treatment for longer than necessary
- Not prescribing according to microbiology results
- Omitting or delaying administration of doses
- Prescribing intravenous therapy when oral therapy is known to be effective and clinically safe
- Not taking antibiotics as prescribed

What can be done??



**GLOBAL ACTION PLAN
ON ANTIMICROBIAL
RESISTANCE**

World Health Organization

**Antimicrobial
Resistance (AMR) Strategy**
report and implementation

EMERGING ANTIBIOTIC RESISTANCE THREATS

OF
Resistance

by 2015–2019

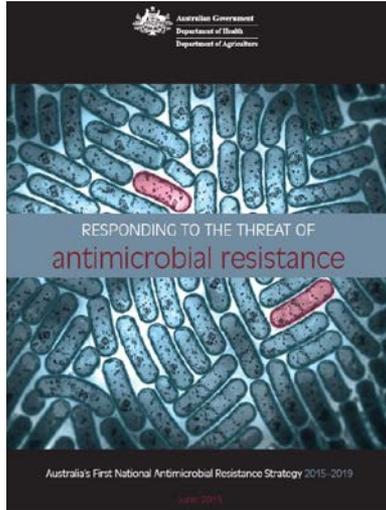
Australian Government
Department of Health
Department of Agriculture

Northern Ireland Executive

Department of Health
Department of Agriculture

Scottish Government

Australian Response



Objective One

Increase awareness and understanding of antimicrobial resistance, its implications and actions to combat it, through effective communication, education, and training

Objective Two

Implement effective antimicrobial stewardship practices across human health and animal care settings to ensure the appropriate and judicious prescribing, dispensing and administering of antimicrobials

Objective Three

Develop nationally coordinated One Health surveillance of antimicrobial resistance and antimicrobial usage

Objective Four

Improve infection prevention and control measures across human health and animal care settings to help prevent infections and the spread of resistance

Objective Five

Agree a national research agenda and promote investment in the discovery and development of new products and approaches to prevent, detect and contain antimicrobial resistance

Objective Six

Strengthen international partnerships and collaboration on regional and global efforts to respond to antimicrobial resistance

Objective Seven

Establish and support clear governance arrangements at the local, jurisdictional, national and international levels to ensure leadership, engagement and accountability for actions to combat antimicrobial resistance

- Involves cooperation between human health professionals, veterinarians, farmers, policy makers from health and agriculture and other related experts to develop strategies to contain antibiotic resistance
- National work has commenced to progress a “One Health” approach in Australia, through an Antimicrobial Resistance Prevention & Containment Strategy.

- Infection prevention and control
 - Hand hygiene
 - Standard and transmission based precautions
 - Environmental cleaning
 - Aseptic technique
 - Workforce immunisation
- Antimicrobial stewardship

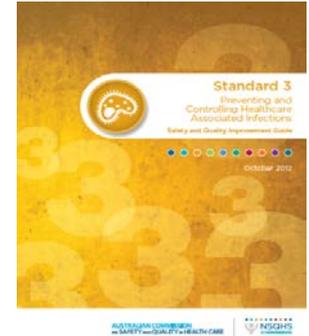
Antimicrobial stewardship (AMS)

- Aim is to optimise use of antibiotics taking into account:
 - Evidence of efficacy
 - Toxicity
 - Ecologic harm (effect on resistance)
- Requires team work at all levels:
 - Executive and clinical leadership
 - Prescribers, clinicians, pharmacists

Essential elements: treatment guidelines, formulary with restrictions, selective susceptibility reporting of isolates, effective audit and feedback to prescribers

Actions required:

- 3.14.1** An AMS program is in place
- 3.14.2** The clinical workforce prescribing antimicrobials have access to endorsed Therapeutic Guidelines on antibiotic usage
- 3.14.3** Monitoring of antimicrobial usage and resistance is undertaken
- 3.14.4** Action is taken to improve the effectiveness of AMS



AMR pathogens in Australia

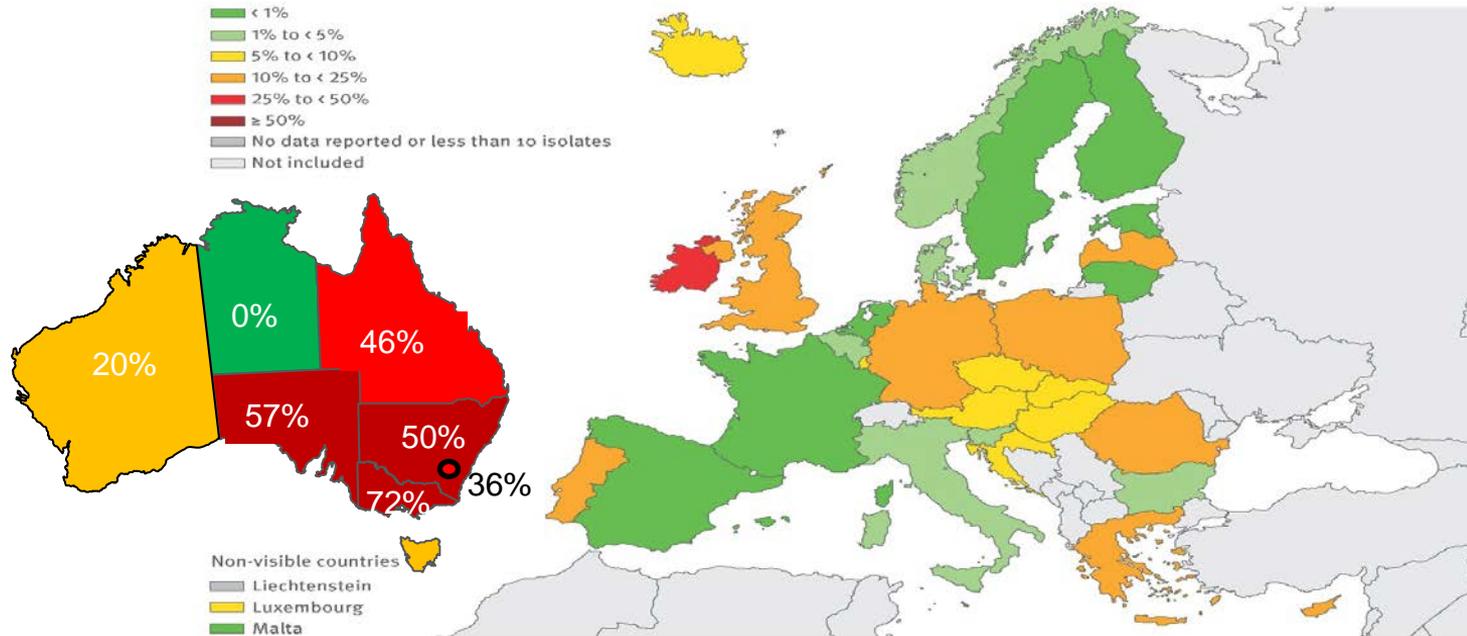
Pathogen	Seen in Australia?
MDR and XDR TB	✓
3GC-resistant <i>S. pneumoniae</i>	✓
3GC-resistant <i>N. gonorrhoeae</i>	A couple
Hypervirulent <i>C. difficile</i>	✓
Vancomycin-resistant enterococci	✓
Carbapenemase producing GNs	✓
Community-MRSA	✓
3GC-resistant Salmonella	✓

Major Problems in Australia - VRE



Australian Group on Antimicrobial Resistance (AGAR)

Enterococcus faecium. Percentage (%) of invasive isolates resistant to vancomycin, by country, EU/EEA countries, 2013



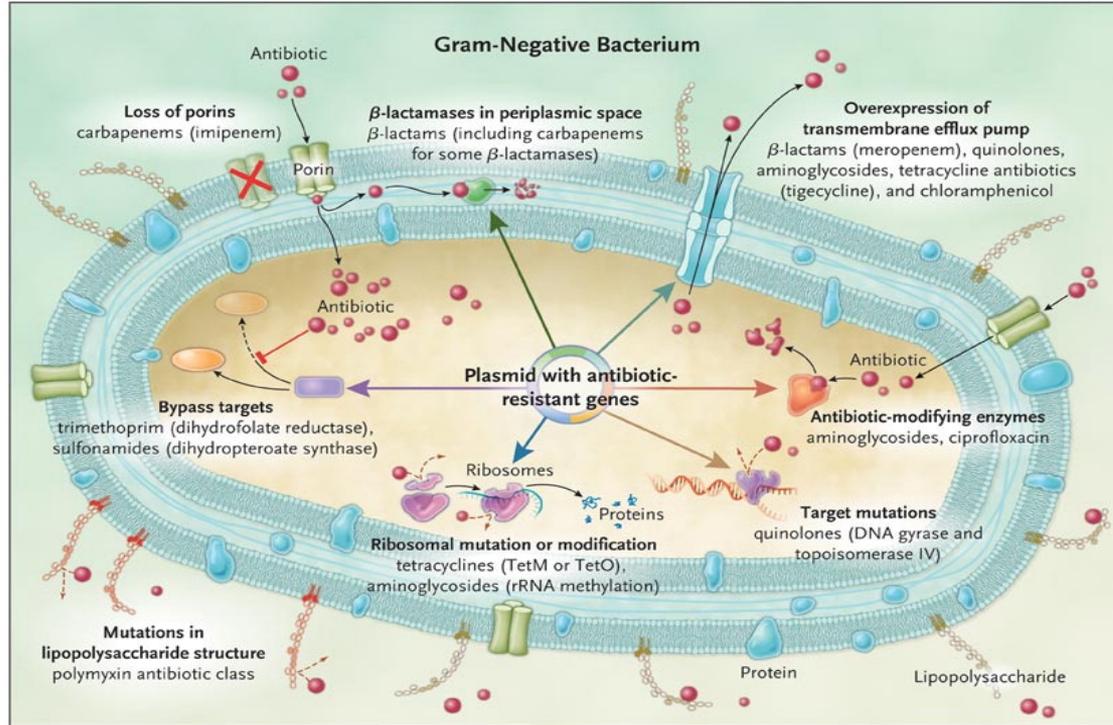
Source: European Centre for Disease Prevention and Control, Antimicrobial resistance surveillance in Europe 2013. Stockholm: ECDC, 2014.
© European Centre for Disease Prevention and Control, 2014.

Major Problems in Australia – “The Red Plague”

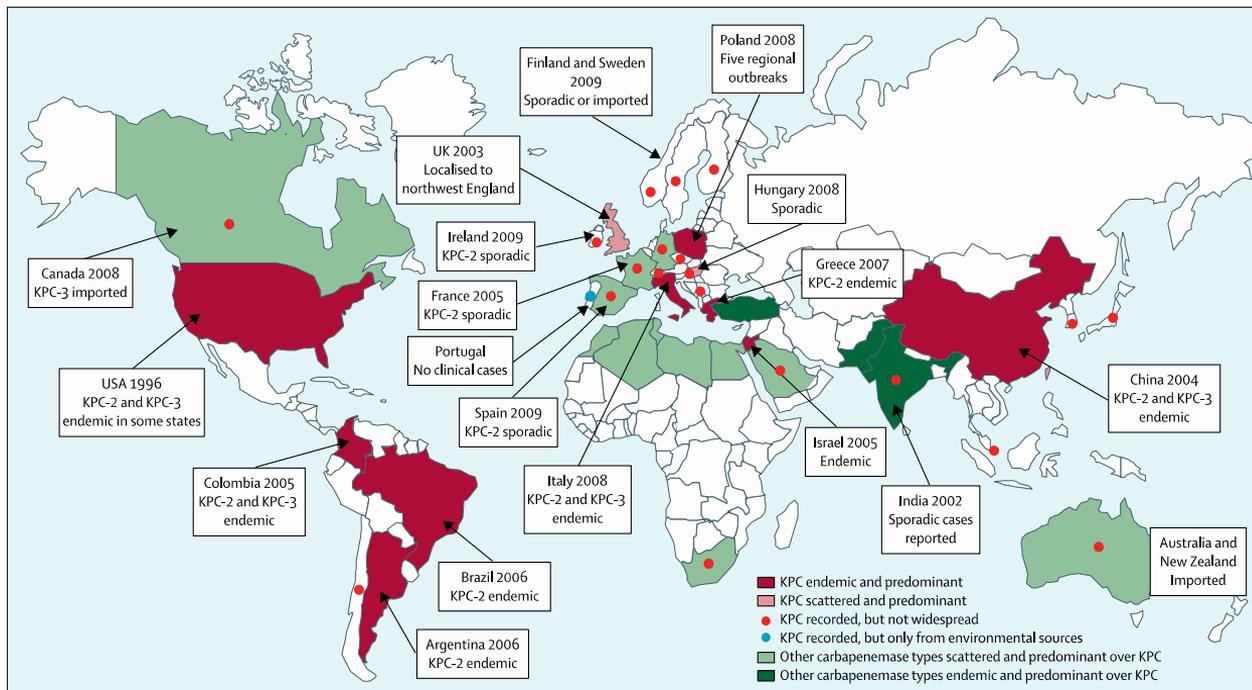
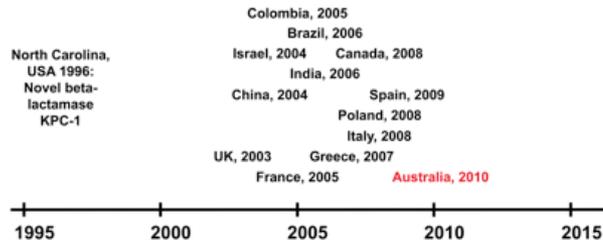
- Refers to emerging resistance in Gram negative organisms (*E. coli*, *Klebsiella spp.*)
- Cause common infections e.g. UTI in community
- High rates of resistance in Asia-Pacific region
- Some strains pan-drug resistant



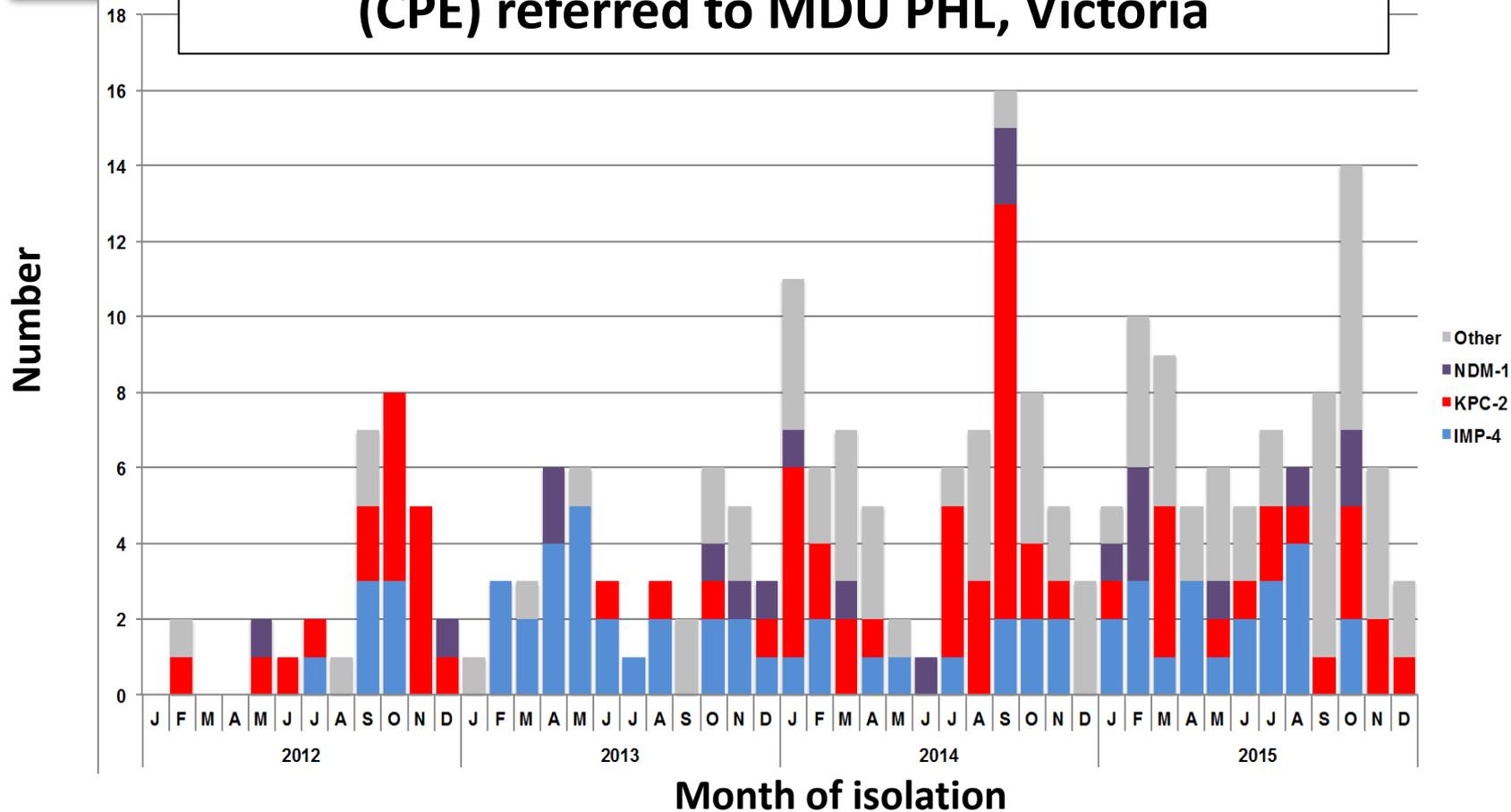
Resistance mechanisms in gram negative bacteria

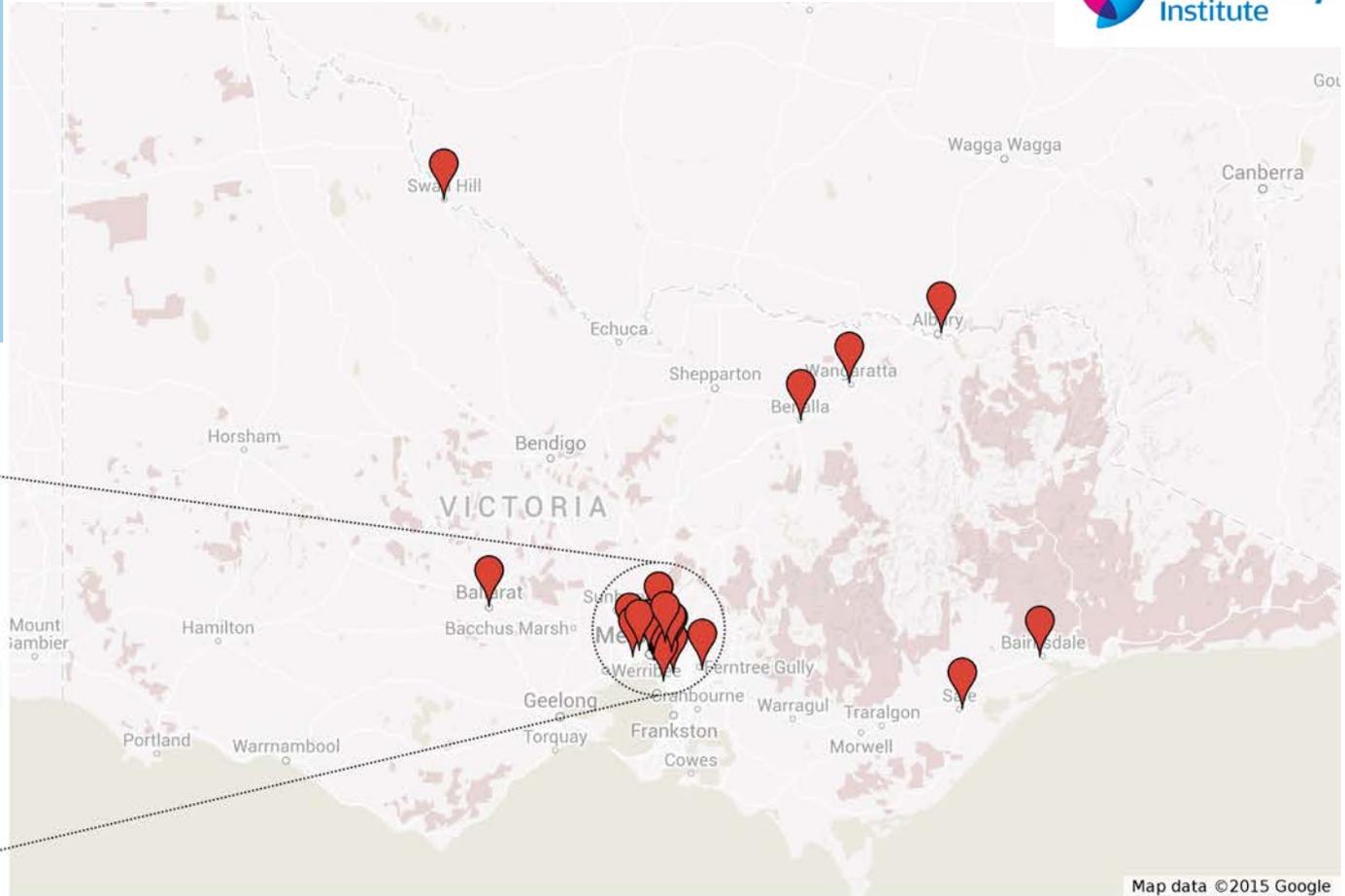


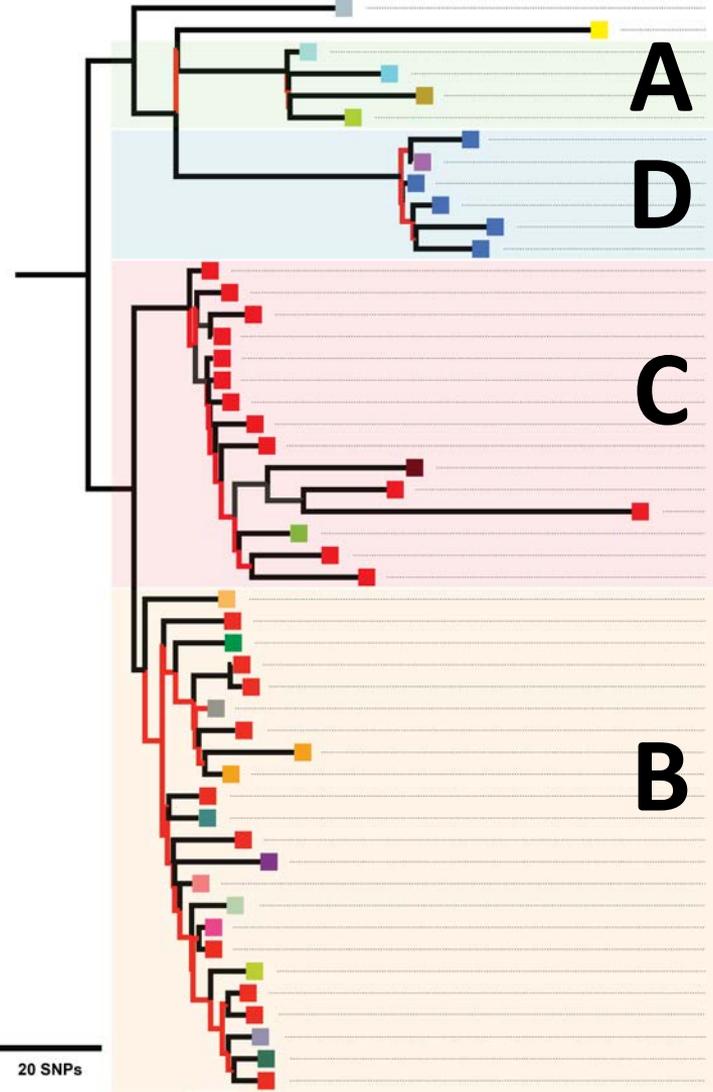
Emergence of KPC
K. pneumoniae in Victoria



Carbapenemase-producing Enterobacteriaceae (CPE) referred to MDU PHL, Victoria







Specimens

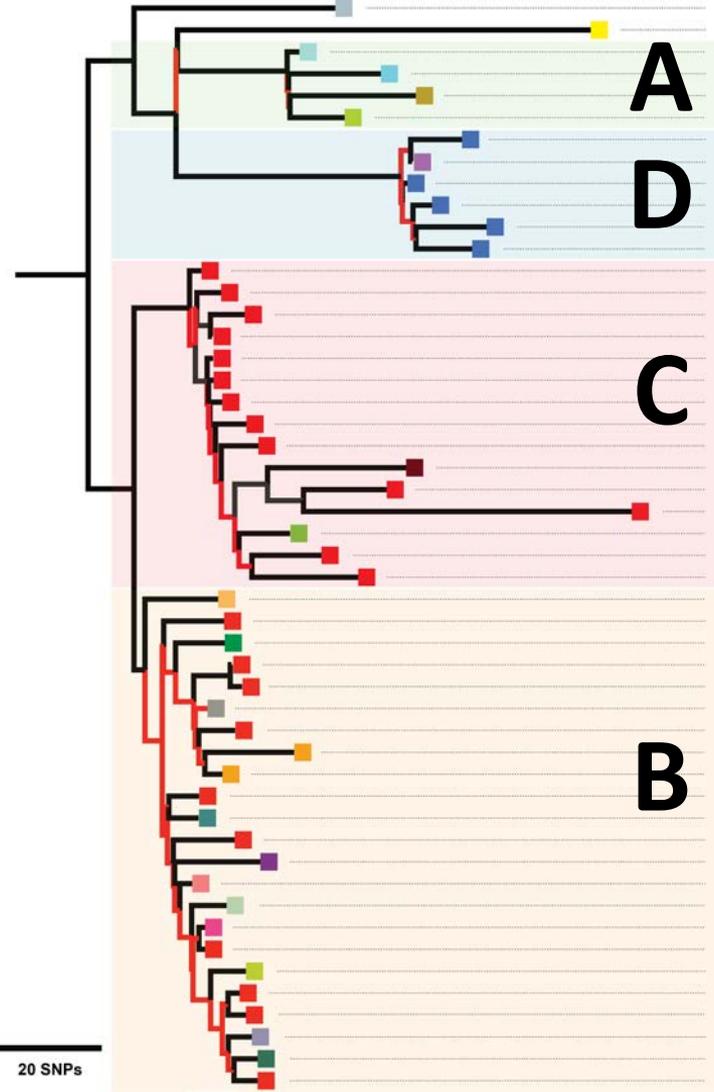
- n = 61 episodes
- 57 patients
- Mostly admitted or ED
- 21 healthcare institutions

Patient Demographics

- 54% male
- Median age = 73 (20-94)

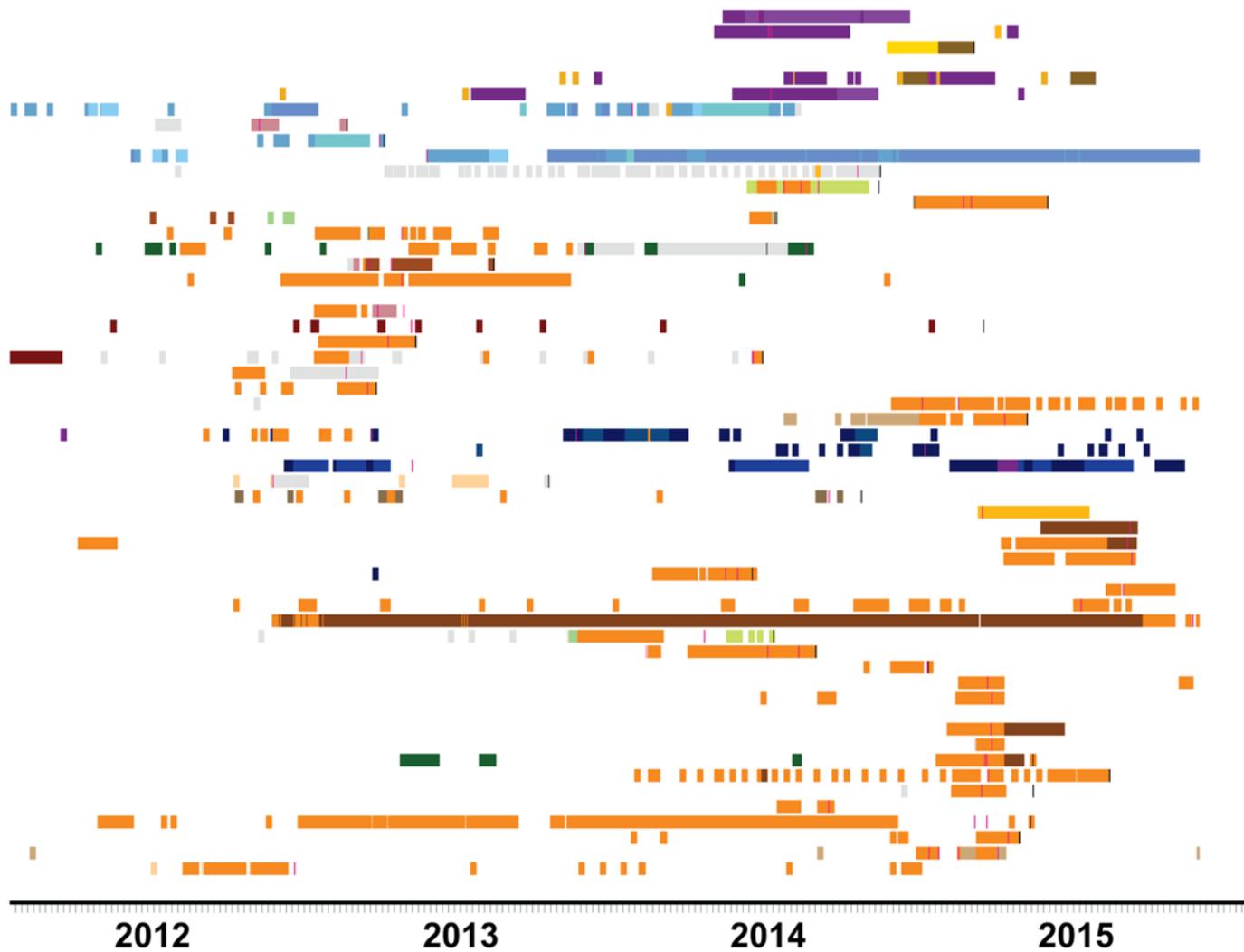
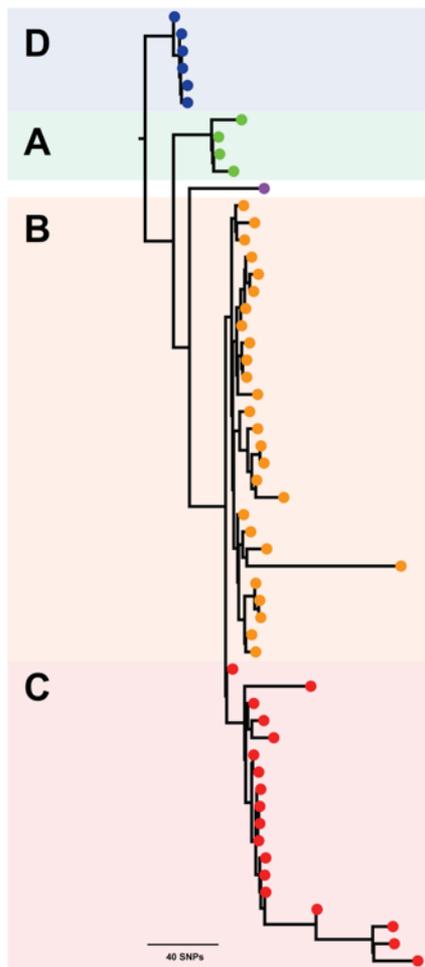
Comorbidities

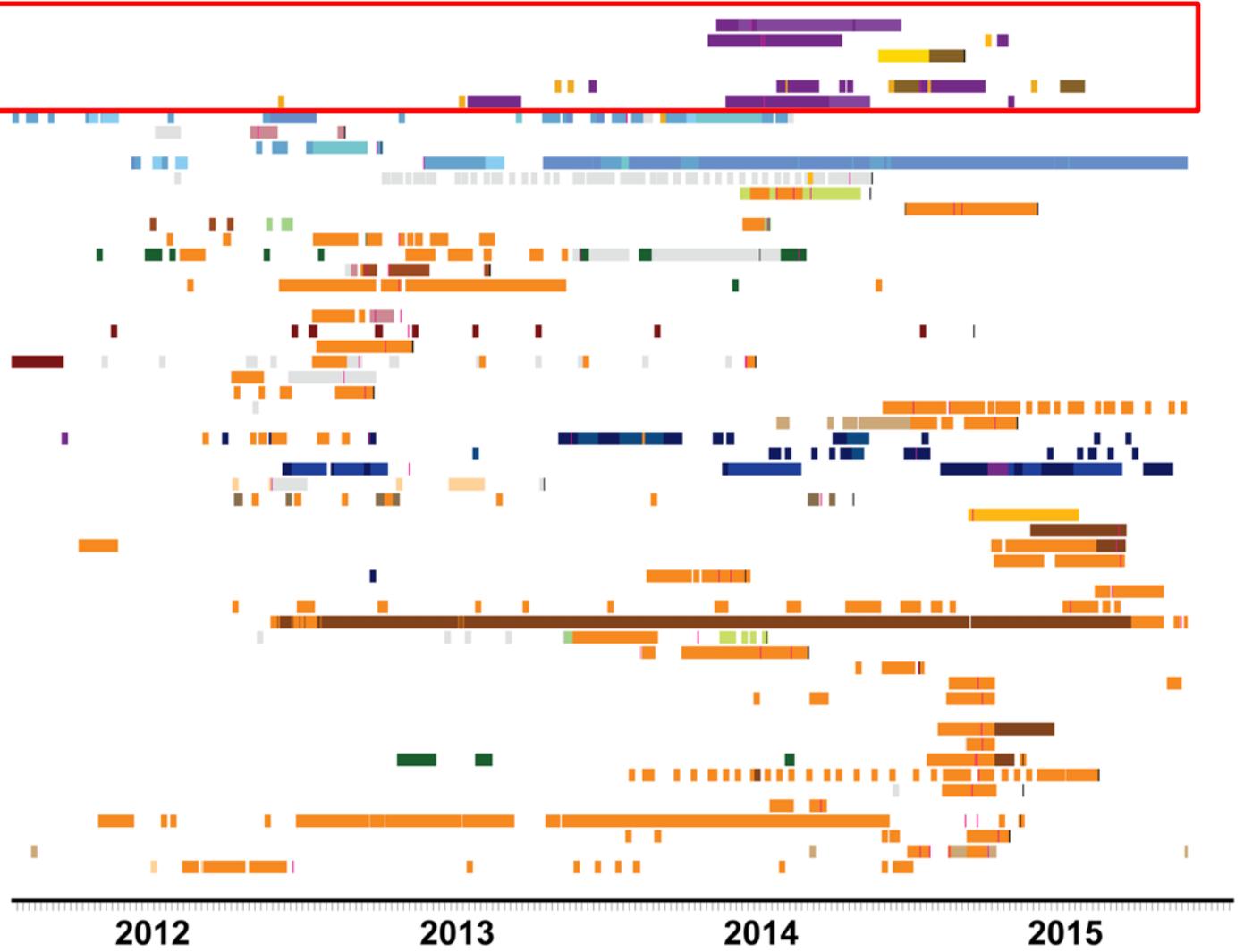
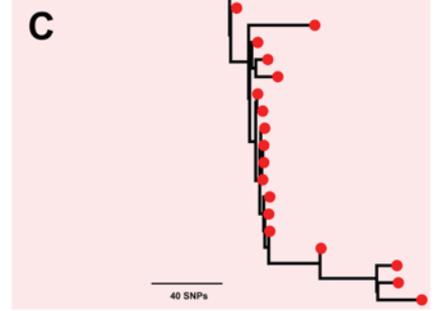
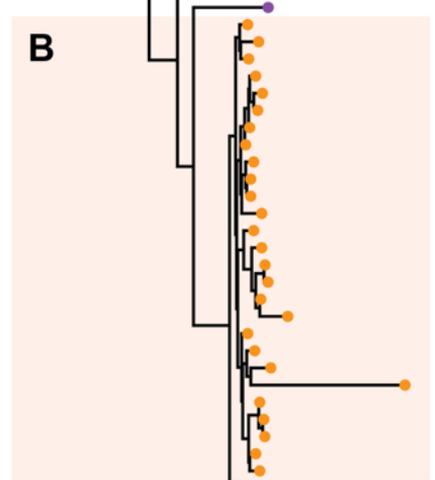
- 60% kidney disease
- 40% immunocompromised

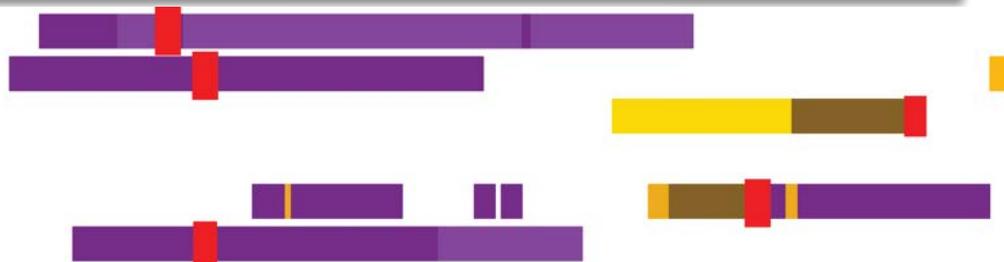
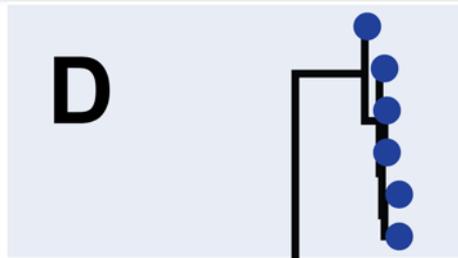


Travel since 1996

- 39% patients
- Most clusters
- All non-clustered isolates
- No patients in Cluster A
- Italy & Greece







Very similar
by WGS

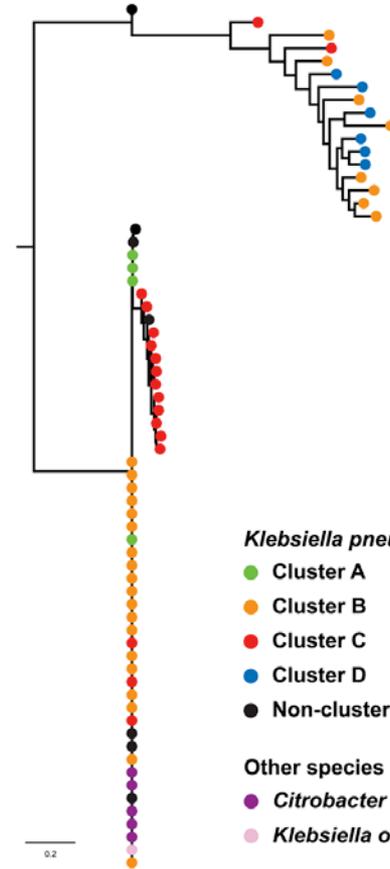
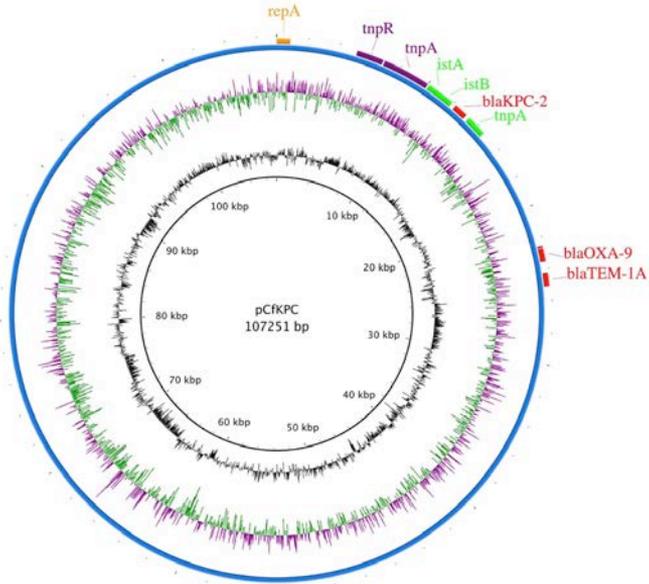


Initial
transmission



Secondary
transmission

 First isolation of KPC-2 producing organism



Klebsiella pneumoniae

- Cluster A
- Cluster B
- Cluster C
- Cluster D
- Non-clustered

Other species

- *Citrobacter farmeri*
- *Klebsiella oxytoca*

- Combination of genomic and epidemiologic investigation defined transmission networks
- Multiple introductions of clones from Greece/Italy
 - Subsequent local transmission
 - Majority are CC258 *K. pneumoniae*
 - KPC-2 carriage on an IncFII-type plasmid
- Ongoing surveillance is required, given the reservoir of undetected colonisation

Victorian guideline on
carbapenemase-producing
Enterobacteriaceae

For health services
December 2015

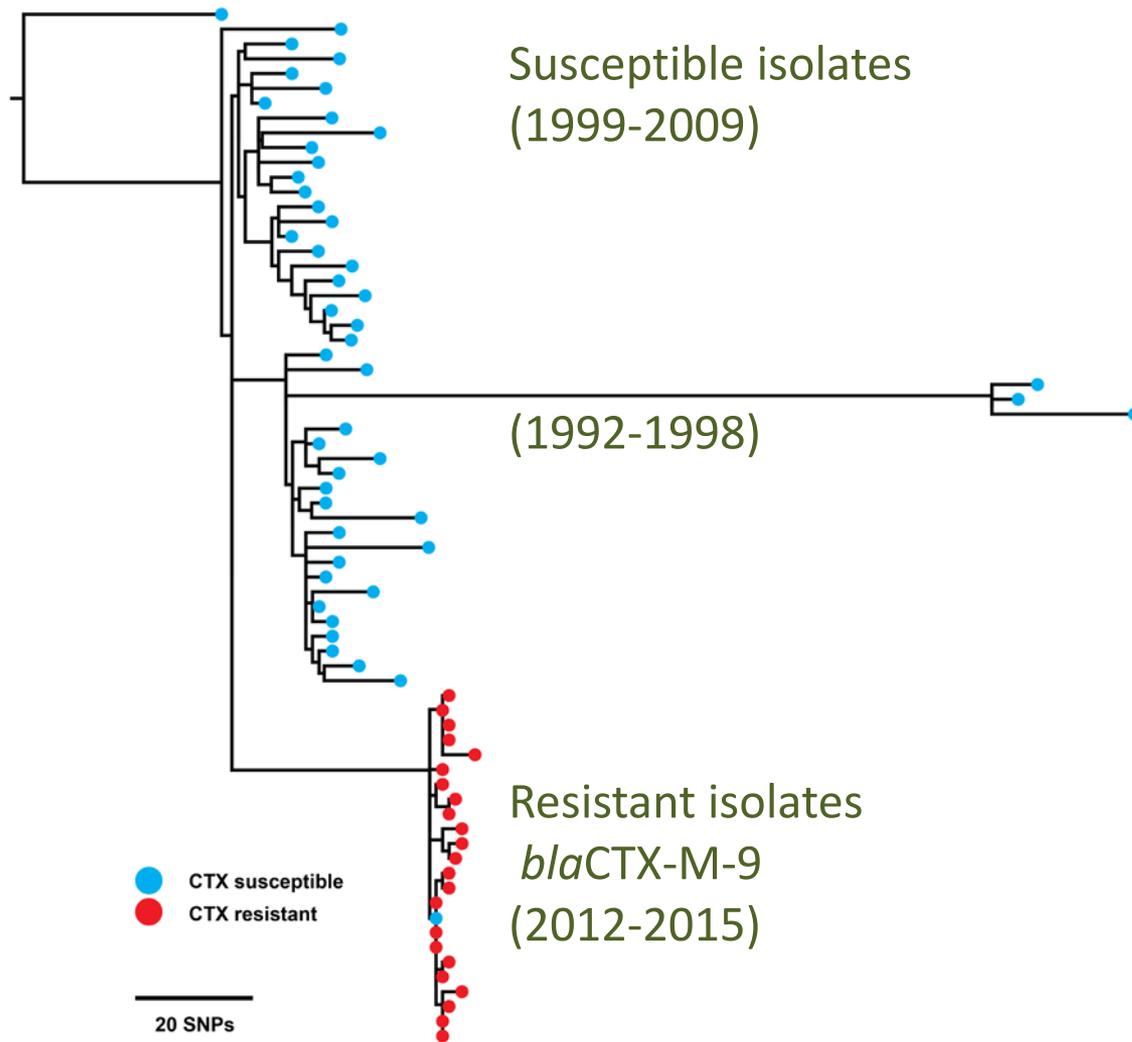
- Inclusion of genomics in outbreak definition:

“2 or more confirmed cases of genetically closely related CPE that are compatible with local transmission and with a plausible epidemiological link, without an alternative explanation”

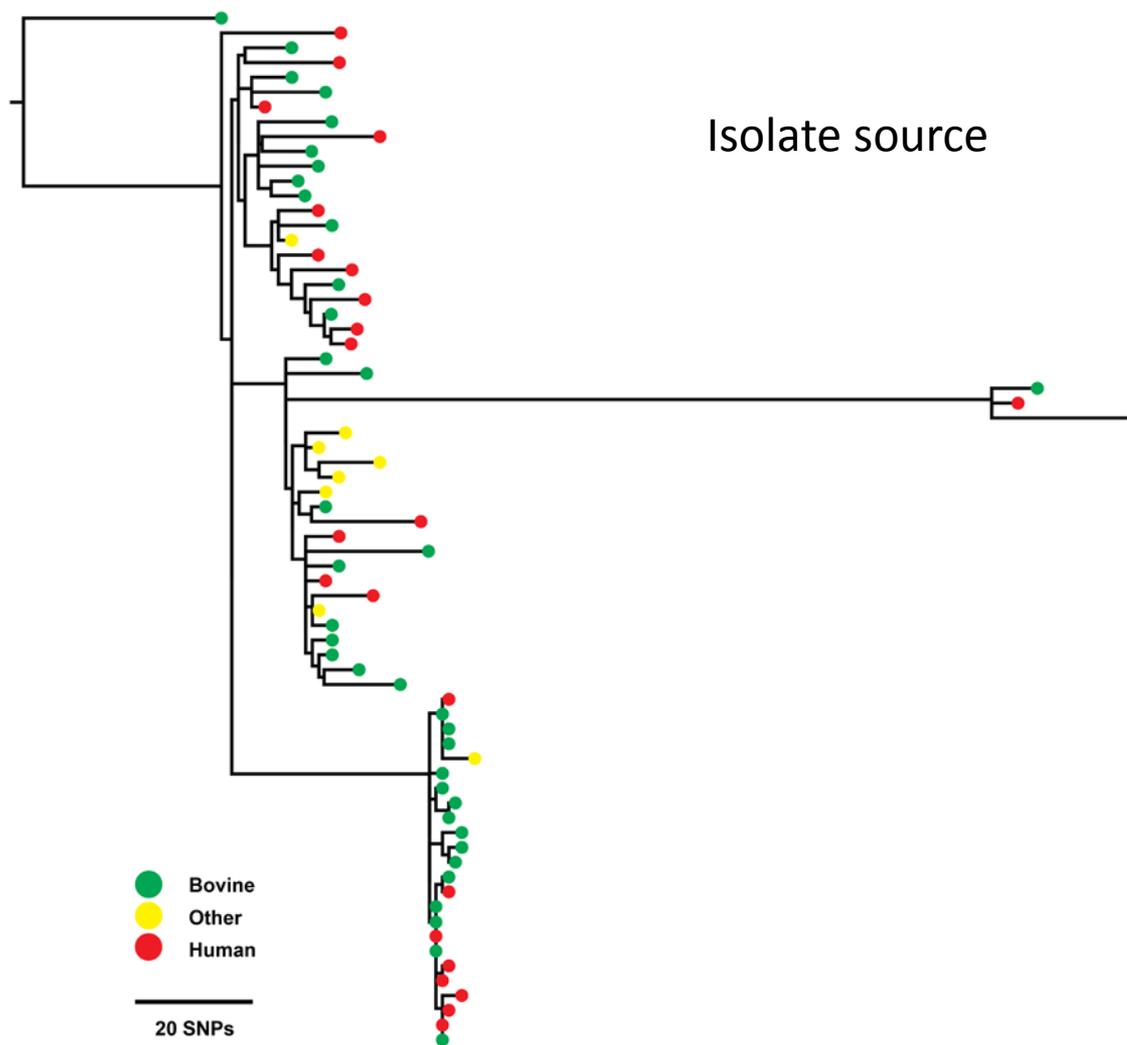


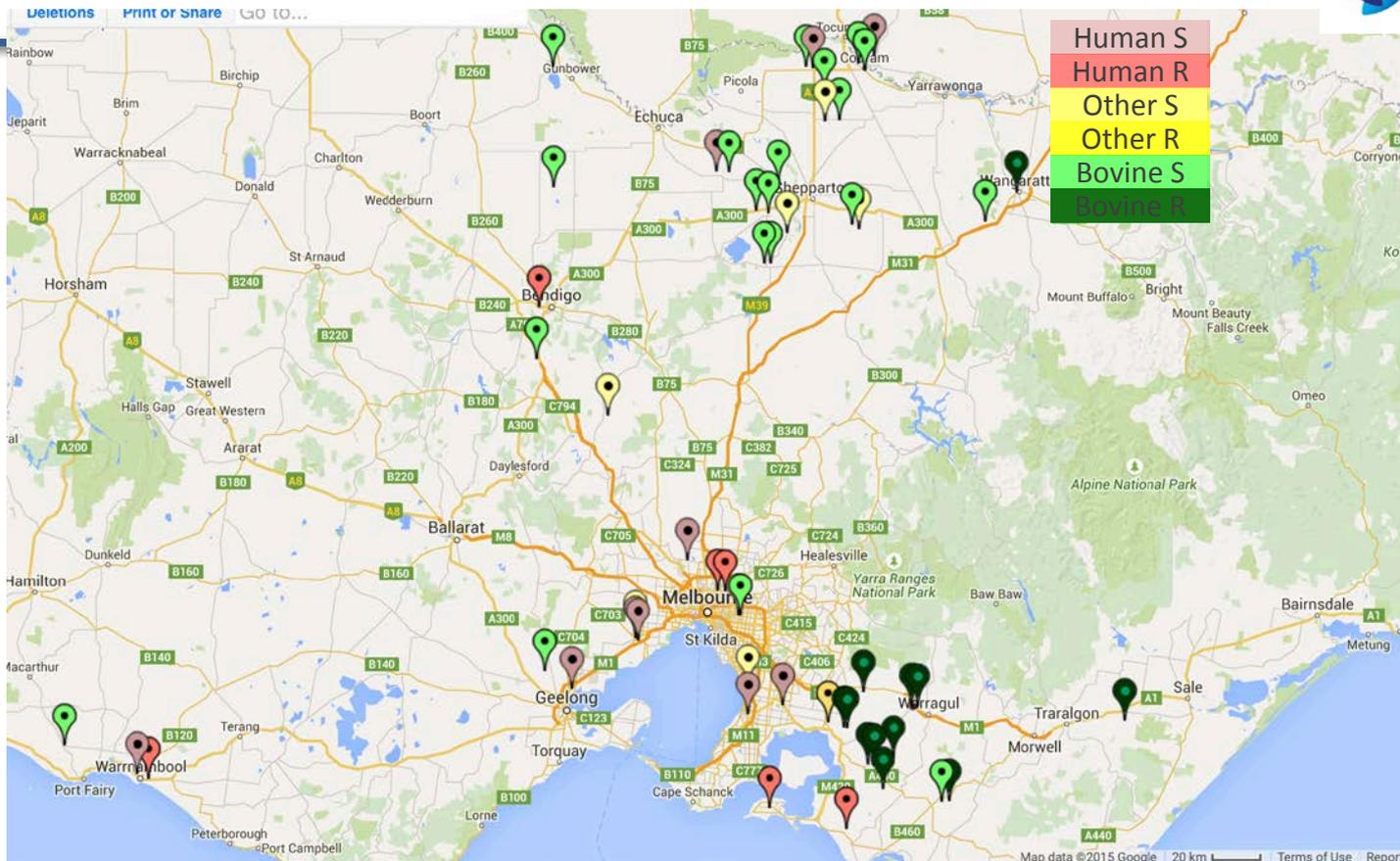
Salmonella Typhimurium
Ceftriaxone
Resistant





Isolate source





Summary and main themes

- Increase awareness
- Implement effective antimicrobial stewardship across human and animal health
- Develop nationally coordinated surveillance of antimicrobial resistance and usage across human and animal populations
- Improve infection prevention and control
- Agree a national research agenda
- Strengthen international partnerships and collaboration
- Establish and support clear governance and accountability

Thank you and questions