One Health Aspects of Antimicrobial Resistance

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1. One Health
2. Carbapenemase-producing Gram-negative bacteria
3. Transferable oxazolidinone resistance in Gram-positive cocci
4. Concluding remarks

One Health

What is One Health?

The **One Health** concept recognizes that the health of people is connected to the health of animals and the environment.

All three sectors are interconnected and none of the three sectors can solve its problems alone

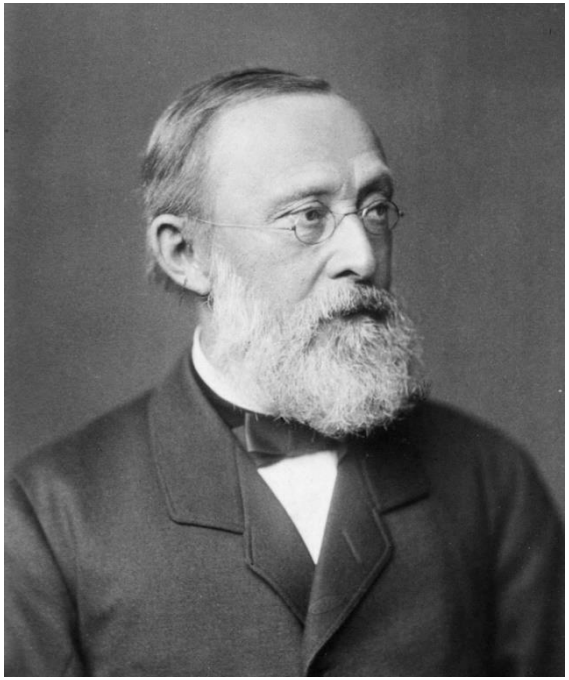
Interdisciplinary collaborations and communications in all aspects of healthcare of humans, animals and the environment are necessary.

One Health History

Although the term "One Health" is fairly new, the concept has long been recognized, both nationally and globally.

Since the 1800s, scientists have noted the similarity in disease processes among animals and humans, but human and animal medicine were practiced separately until the 20th century.

One Health History

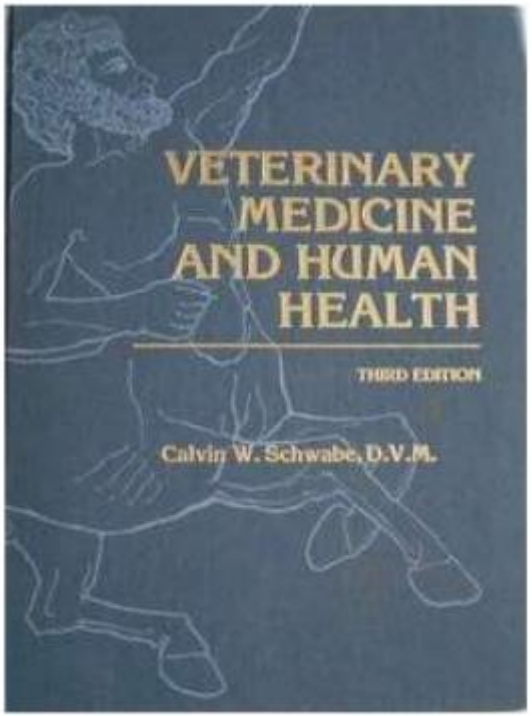


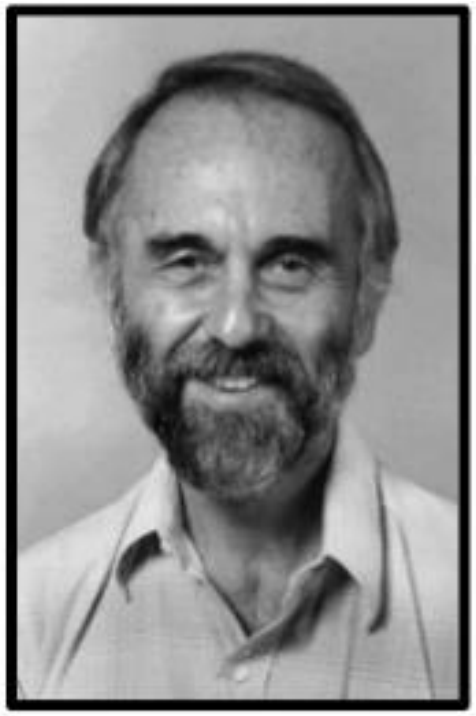
Rudolf Virchow, MD (1821 – 1902), was one of the most famous physicians of the 19th century. Dr. Virchow was a German pathologist who became interested in the linkages between human and veterinary medicine while studying a roundworm, *Trichinella spiralis*, in swine.

He coined the term "zoonosis" to indicate an infectious disease that is passed between humans and animals.

He emphasized, "Between animal and human medicine there are no dividing lines, nor should there be. The object is different, but the experience obtained constitutes the basis of all medicine."

One Health History





Dr. Calvin Schwabe (1927 – 2006) was the founding chair of the Department of Epidemiology and Preventive Medicine at the Veterinary School at the University of California in Davis.

In his textbook, *Veterinary Medicine and Human Health*, Dr. Schwabe coined the term "**One Medicine**."

The term emphasized the similarities between human and veterinary medicine and the need for collaboration to effectively cure, prevent, and control illnesses that affect both humans and animals.

One Health History

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- Nowadays, "**One Medicine**" is commonly referred to as "**One Health**" worldwide. This change in terminology occurred during the first decade of the 21st century.
- "**One Health**" recognizes that humans do not exist in isolation, but are a part of a larger whole, a living ecosystem, and that activities of each member affect the others.

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What are the One Health drivers?

Every individual does not live in isolation – humans and animals are often part of larger communities

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What are the One Health drivers?

Humans have different interactions with animals: private and occupational contact. Pet/companion animals are often considered as family members.






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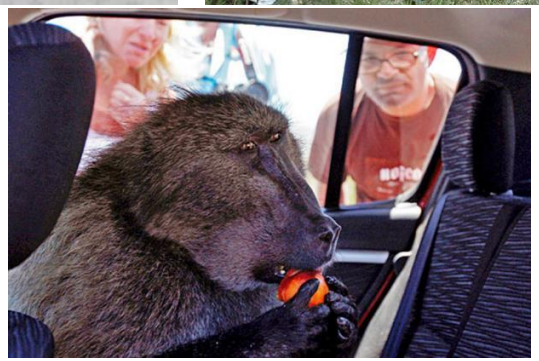
What are the One Health drivers?

As our population expands, wildlife habitats are disappearing and the contact between humans and wild animals increases, introducing the risk of exposure to new viruses, bacteria and other disease-causing pathogens.





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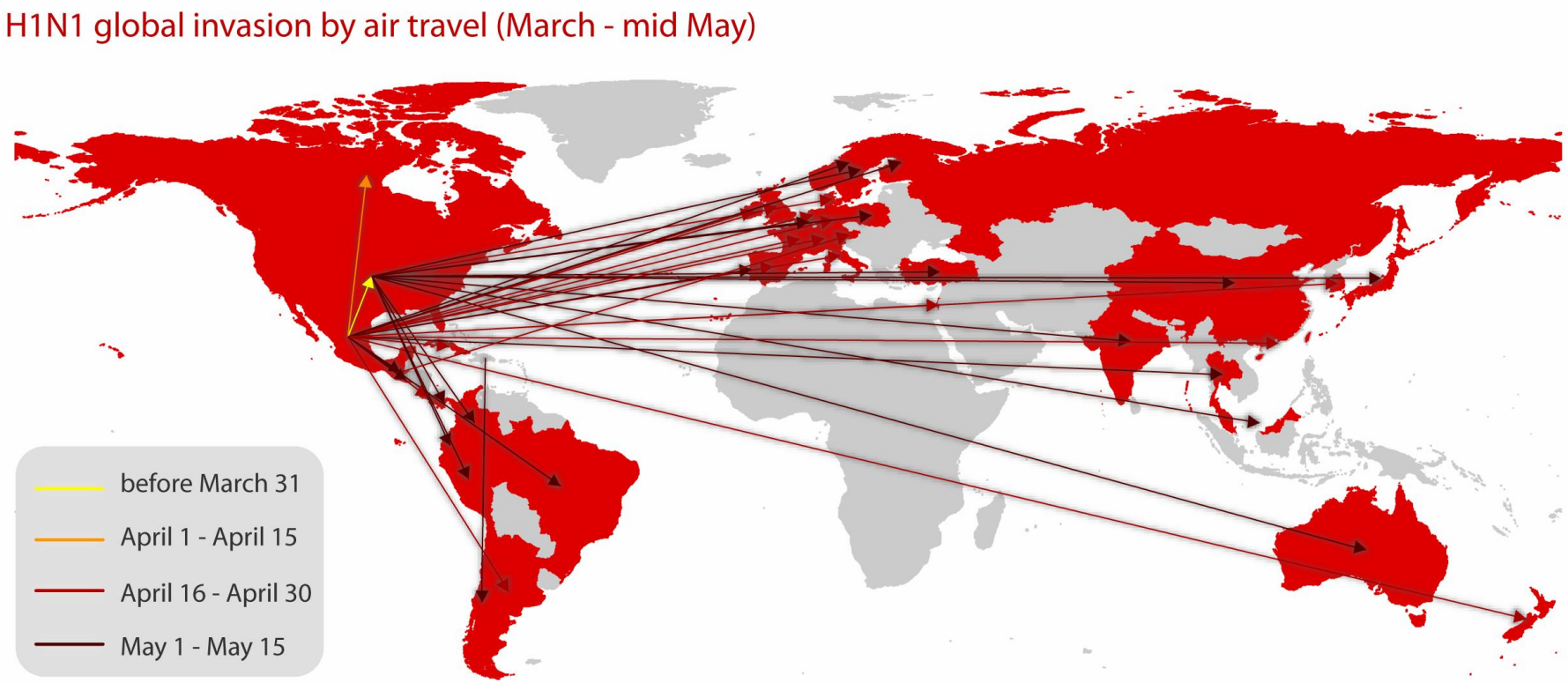
What are the One Health drivers?

Global trade is easy and global travel is fast. Viruses and bacteria do not stop at borders, giving previously isolated outbreaks a pandemic potential.



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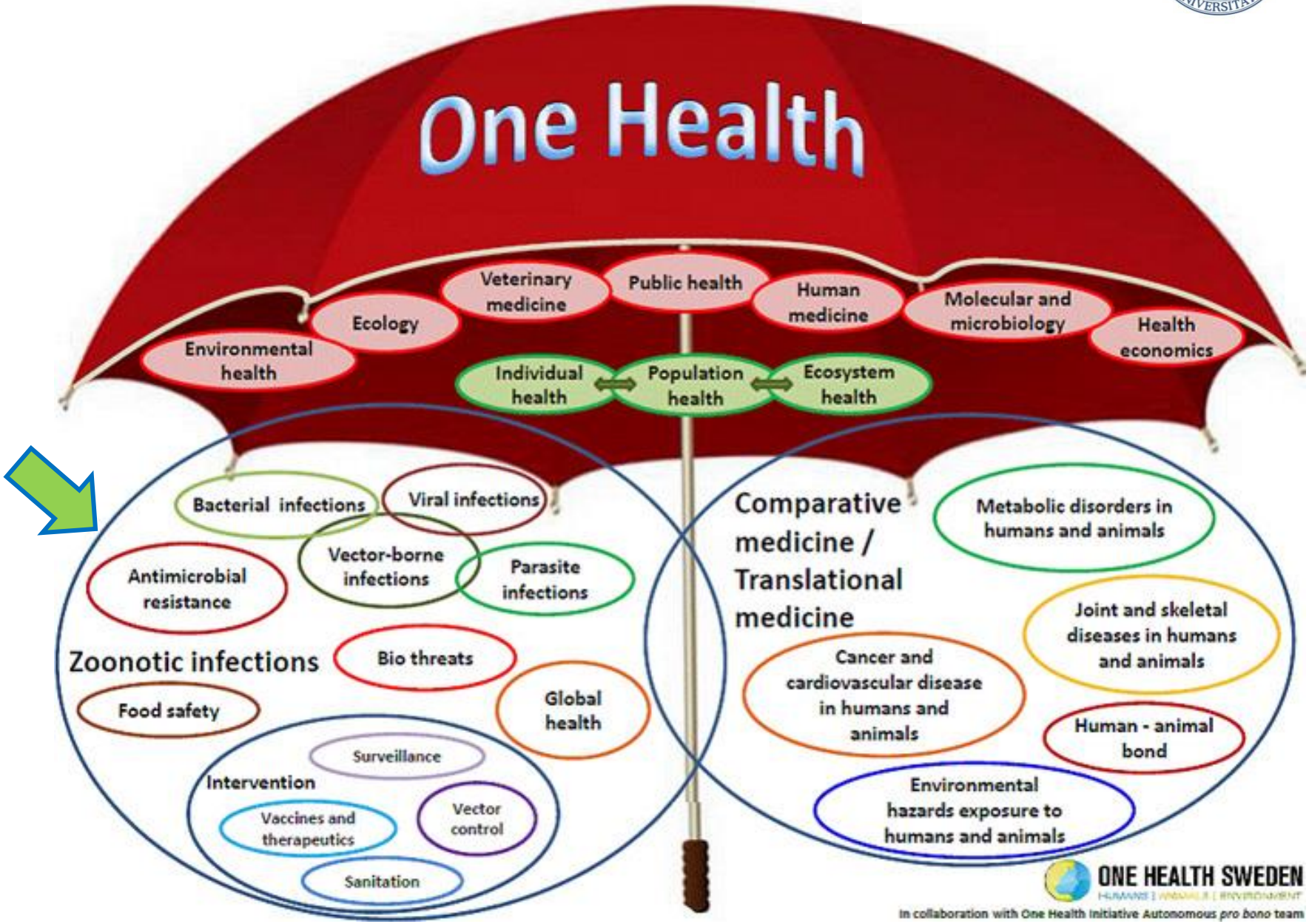
What are the One Health drivers?

The world's total population is expected to exceed 9 billion by 2050 and will require the food supply to double. Only healthy food-producing animals will provide high quality food.


One Health
Veterinary medicine
Public health
Human medicine
Molecular and microbiology
Health economics
Ecology
Environmental health
Individual health
Population health
Ecosystem health
Bacterial infections
Viral infections
Vector-borne infections
Parasite infections
Antimicrobial resistance
Zoonotic infections
Bio threats
Food safety
Global health
Surveillance
Intervention
Vaccines and therapeutics
Vector control
Sanitation
Comparative medicine / Translational medicine
Metabolic disorders in humans and animals
Joint and skeletal diseases in humans and animals
Cancer and cardiovascular disease in humans and animals
Human - animal bond
Environmental hazards exposure to humans and animals
ONE HEALTH SWEDEN
HUMANS | ANIMALS | ENVIRONMENT
In collaboration with One Health Initiative Autonomous pro bono team

Carbapenemase-producing Gram-negative bacteria

Carbapenems

- Carbapenems (imipenem, ertapenem, meropenem) are **NOT** approved for use in veterinary medicine.

- **Carbapenems must not be used in food-producing animals.**

- Carbapenems **may be used in companion and pet animals** in defined cases according to AMDUCA (Animal Medicinal Drug Use Clarification Act), i.e. when no other suitable antimicrobial approved for veterinary use is available.

- **Carbapenem resistance** is based on the expression of various *bla* genes, e.g. bla_{KPC}, $bla_{OXA\text{-}23,\ -48,\ -58}$, $bla_{VIM\text{-}1,\ -2}$, $bla_{IMP\text{-}4,\ -45}$, $bla_{NDM\text{-}1}$, which are often co-located with other resistance genes on the same mobile genetic element.

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K. pneumoniae, E. coli **OXA-48**

Stolle et al., 2013

E. cloacae, K. oxytoca, C. freundii **OXA-48**

Ewers et al., in preparation

A. gandensis **OXA-23**

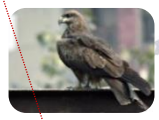
Smet et al., 2012

A. baumannii, **OXA-23/OXA-66**

Ewers et al., 2017

Salmonella Corvallis **NDM-1**

Fischer et al., 2013



A. baumannii **OXA-23**

Pomba et al., 2014

Acinetobacter 15TU **OXA-23**

Poirel et al., 2012

A. indicus-like **OXA-23**

Ewers et al., in preparation

E. coli, Salmonella **VIM-1**

Fischer et al., 2012, 2013

Farm environment

A. lwoffii **NDM-1**

Wang et al., 2012

E. coli **NDM-1**

Shaheen et al., 2013

A. baumannii **OXA-23/-58**

Al Bayasari et al., 2015

P. aeruginosa **IMP-45**

Wang et al., 2014

A. baumannii **NDM-1**

Zhang et al., 2013

E. coli **IMP-4**

Dolejska et al., 2016

P. aeruginosa **VIM-2**

Al Bayasari et al., 2015

Salmonella Typhimurium **IMP-4**

Abraham et al., 2016

J Antimicrob Chemother 2014
doi:10.1093/jac/dku133
Advance Access publication 28 April 2014

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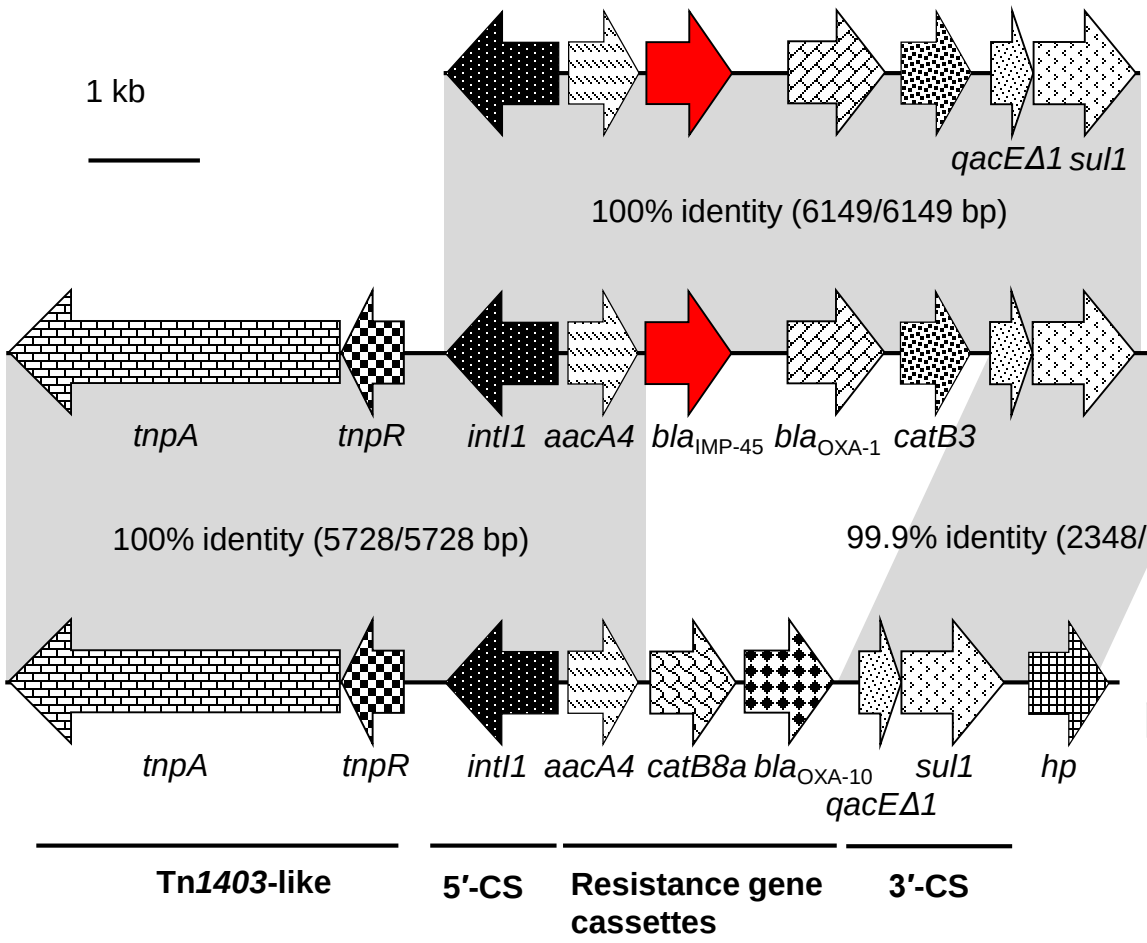
IMP-45-producing multidrug-resistant *Pseudomonas aeruginosa* of canine origin

Yang Wang[1]†, Xin Wang[1]†, Stefan Schwarz[2], Rongmin Zhang[1], Lei Lei[1], Xiaoyu Liu[1], Degui Lin[3] and Jianzhong Shen[1]*

[1]*Beijing Key Laboratory of Detection Technology for Animal-Derived Food Safety, College of Veterinary Medicine, China Agricultural University, Beijing 100193, P. R. China;* [2]*Institute of Farm Animal Genetics, Friedrich-Loeffler-Institut (FLI), Höltystr. 10, 31535 Neustadt-Mariensee, Germany;* [3]*Department of Small Animal Clinical Sciences, College of Veterinary Medicine, China Agricultural University, Beijing 100193, P. R. China*

*Corresponding author. Tel: +86-10-62732803; Fax: +86-10-62731032; E-mail: sjz@cau.edu.cn
†These authors contributed equally to this study.

P. aeruginosa isolate M140A was obtained from the anal swab of a healthy 3-month-old female German Shepherd dog admitted in June 2013 to the Animal Teaching Hospital of the China Agricultural University in Beijing, China, for routine vaccination against canine parvovirus infection.



Human *P. aeruginosa* B3 plasmid In*786* class 1 integron, Guangzhou, China

Canine *P. aeruginosa* M140A IMP-45 segment, Beijing, China

Human *P. aeruginosa* plasmid pOZ176, Guangzhou, China

Veterinary Microbiology 171 (2014) 290–297

Contents lists available at ScienceDirect

Veterinary Microbiology

journal homepage: www.elsevier.com/locate/vetmic

An emerging public health problem: Acquired carbapenemase-producing microorganisms are present in food-producing animals, their environment, companion animals and wild birds

Beatriz Guerra *, Jennie Fischer, Reiner Helmuth

Federal Institute for Risk Assessment (BfR), Department of Biological Safety, Max-Dohrn Strasse 8-10, D-10589 Berlin, Germany

Freie Universität Berlin

J Antimicrob Chemother 2014; **69**: 1155–1157
doi:10.1093/jac/dkt518 Advance Access publication 6 January 2014

Journal of Antimicrobial Chemotherapy

Carbapenemase-producing bacteria in companion animals: a public health concern on the horizon

Sam Abraham[1]*, Hui San Wong[1], John Turnidge[2,3], James R. Johnson[4] and Darren J. Trott[1]

[1]School of Animal and Veterinary Sciences, University of Adelaide, South Australia 5371, Australia; [2]Women's and Children's Hospital, Adelaide, South Australia 5006, Australia; [3]Departments of Pathology, Paediatrics and Molecular and Biomedical Sciences, University of Adelaide, Adelaide, South Australia, Australia; [4]Veterans Affairs Medical Center and University of Minnesota, Minneapolis, MN, USA

*Corresponding author. Tel: +61-8-83137850; Fax: +61-8-830337979; E-mail: sam.abraham@adelaide.edu.au

The emergence of carbapenemase-producing bacteria in companion animals is of great concern because of the close contact between humans and their pets, and the potential for cross-species transmission.

J Antimicrob Chemother 2014
doi:10.1093/jac/dku054
Advance Access publication 26 February 2014

Freie Universität Berlin

The carbapenemase threat in the animal world: the wrong culprit

Laurent Poirel[1]*, Roger Stephan[2], Vincent Perreten[3] and Patrice Nordmann[1]

[1]Medical and Molecular Microbiology Unit, Department of Medicine, Faculty of Science, University of Fribourg, Fribourg, Switzerland; [2]Institute for Food Safety and Hygiene, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland; [3]Institute of Veterinary Bacteriology, Vetsuisse Faculty, University of Bern, Bern, Switzerland

*Corresponding author. E-mail: laurent.poirel@unifr.ch

The real threat related to carbapenem resistance in humans comes from:

(1) the increased consumption of carbapenems in humans worldwide, and

(2) the overall increase in human population movements worldwide, including migration and tourism.

J Antimicrob Chemother 2014
doi:10.1093/jac/dku054
Advance Access publication 26 February 2014

Freie Universität Berlin

The carbapenemase threat in the animal world: the wrong culprit

Laurent Poirel[1]*, Roger Stephan[2], Vincent Perreten[3] and Patrice Nordmann[1]

[1]Medical and Molecular Microbiology Unit, Department of Medicine, Faculty of Science, University of Fribourg, Fribourg, Switzerland; [2]Institute for Food Safety and Hygiene, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland; [3]Institute of Veterinary Bacteriology, Vetsuisse Faculty, University of Bern, Bern, Switzerland

*Corresponding author. E-mail: laurent.poirel@unifr.ch

Taking into account the paucity of reports of carbapenemase producers in animals, and the fact that carbapenems are not used in food-producing animals, the risk to public health remains marginal.

Conclusion I

- Carbapenemase-producing Enterobacteriaceae, but also non-Enterobacteriaceae occur in food-producing animals, pet and companion animals and even wild animals.
- As carbapenems are forbidden in food-producing animals and are rarely used in non-food-producing animals, carbapenem resistance in animals may be the result of a „spill-over“ from humans or from environmental contaminations.
- Actually, we do not know whether carbapenem resistance in animals is a rare finding or the „tip of an iceberg“, which may point to a larger public health problem.

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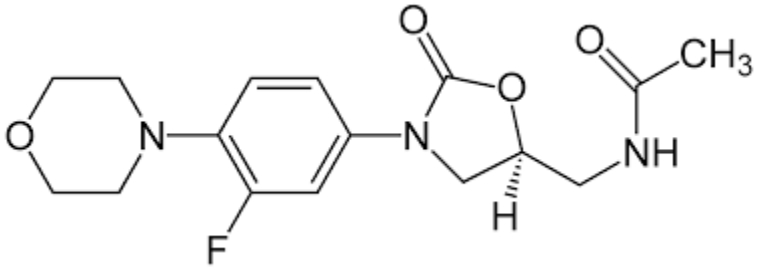
Transferable linezolid/tedizolid resistance in Gram-positive cocci

Oxazolidinones - Linezolid

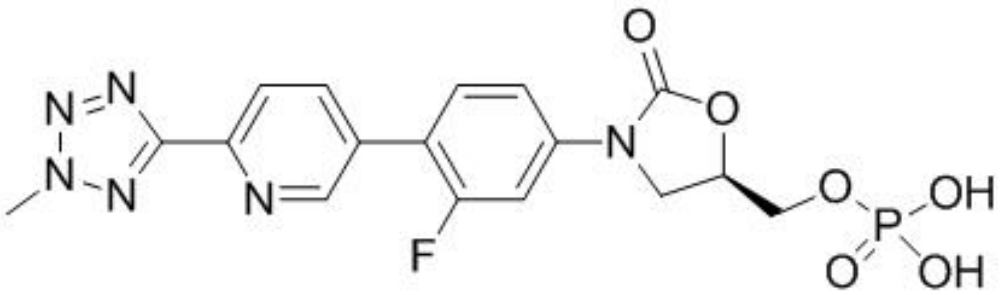
- Linezolid (Zyvox®) was the first oxazolidinone approved for use in human medicine (April 2000)
- Linezolid is a last resort antimicrobial agent for the control of severe infections due to Gram-positive bacteria, e.g. MRSA, VRE
- Linezolid is **NOT** approved for use in veterinary medicine



Linezolid

Oxazolidinones - Tedizolid

- Tedizolid (Syvextro®) was the second oxazolidinone approved for use in human medicine (June 2014)
- Tedizolid has improved activity against *cfr*-carrying bacteria
- Tedizolid is **NOT** approved for use in veterinary medicine



Tedizolid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First tedizolid resistance gene

J Antimicrob Chemother 2015; **70**: 2182–2190
doi:10.1093/jac/dkv116 Advance Access publication 14 May 2015

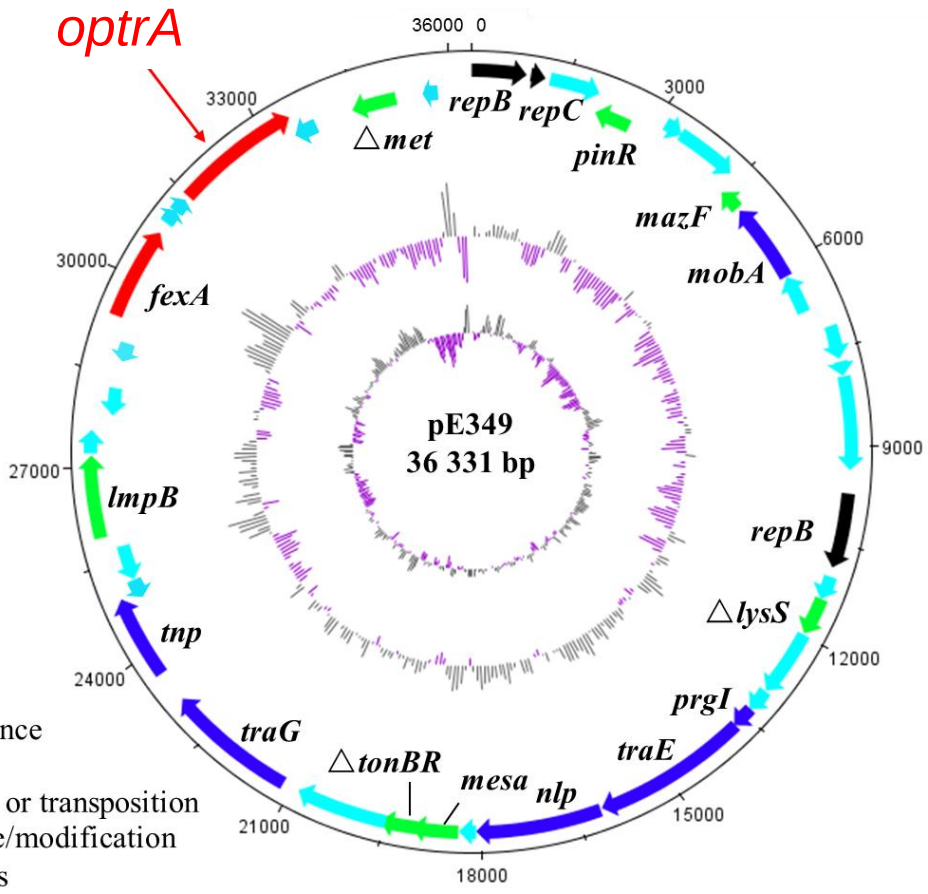
Journal of Antimicrobial Chemotherapy

A novel gene, *optrA*, that confers transferable resistance to oxazolidinones and phenicols and its presence in *Enterococcus faecalis* and *Enterococcus faecium* of human and animal origin

Yang Wang[1]†, Yuan Lv[2]†, Jiachang Cai[3]†, Stefan Schwarz[4]†, Lanqing Cui[2], Zhidong Hu[5], Rong Zhang[3], Jun Li[1], Qin Zhao[1], Tao He[1], Dacheng Wang[6], Zheng Wang[1], Yingbo Shen[1], Yun Li[2], Andrea T. Feßler[4], Congming Wu[1], Hao Yu[6], Xuming Deng[6], Xi Xia[7] and Jianzhong Shen[1]*

Transferable tedizolid resistance

- The gene *optrA* codes for a 655-aa ABC-F protein that confers combined resistance not only to linezolid and tedizolid, but also to phenicols.



Wang *et al.* (2015) J. Antimicrob. Chemother. 70: 2182-90.

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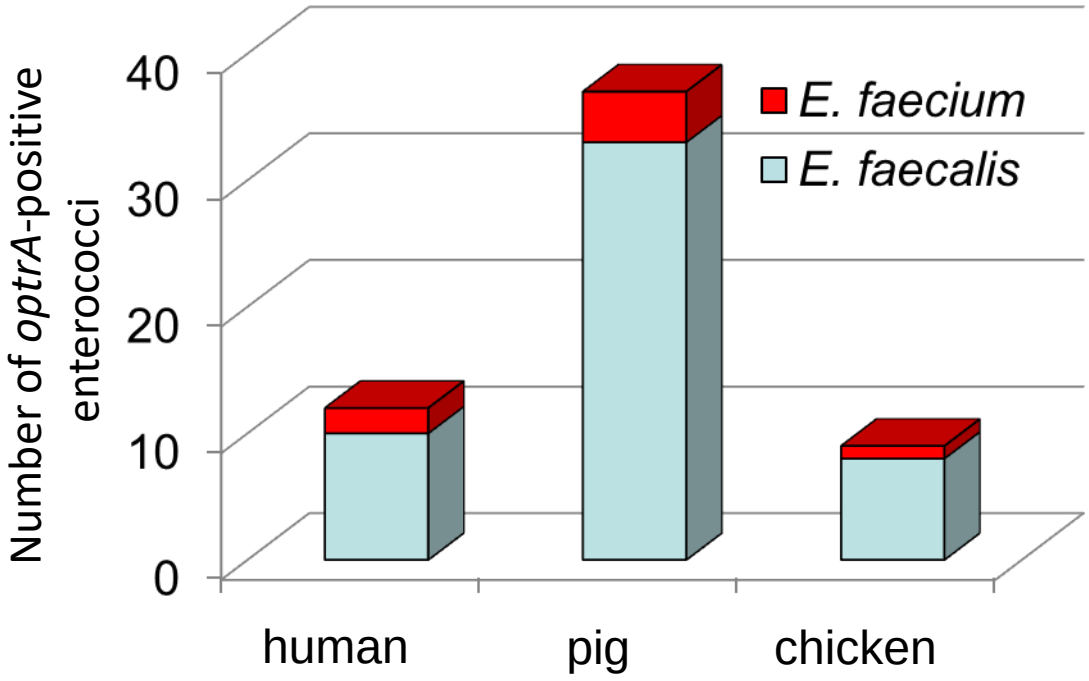
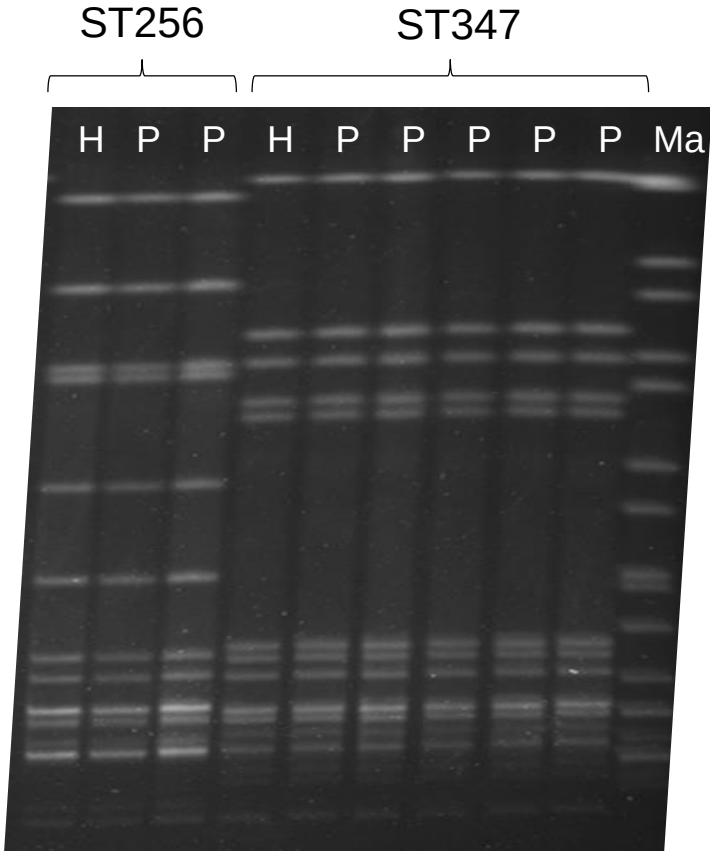
optrA among enterococci from humans and animals



- 12/595 (2.0%) entero-cocci from clinical infections of humans (1998-2014) were *optrA*-positive
- 37/149 (24.8%) enterococci from pigs and 9/141 (6.4%) enterococci from chickens (2009-2013) were *optrA*-positive

Wang *et al.* (2015) J. Antimicrob. Chemother. 70: 2182-90.

Comparison of *optrA*-positive *E. faecalis* isolates from humans and animals



E. faecalis isolates from humans (H) and pigs (P) exhibiting the same MLST type and indistinguishable PFGE patterns

Exchange of the respective isolates between humans and animals

Wang *et al.* (2015) J. Antimicrob. Chemother. 70: 2182-90.

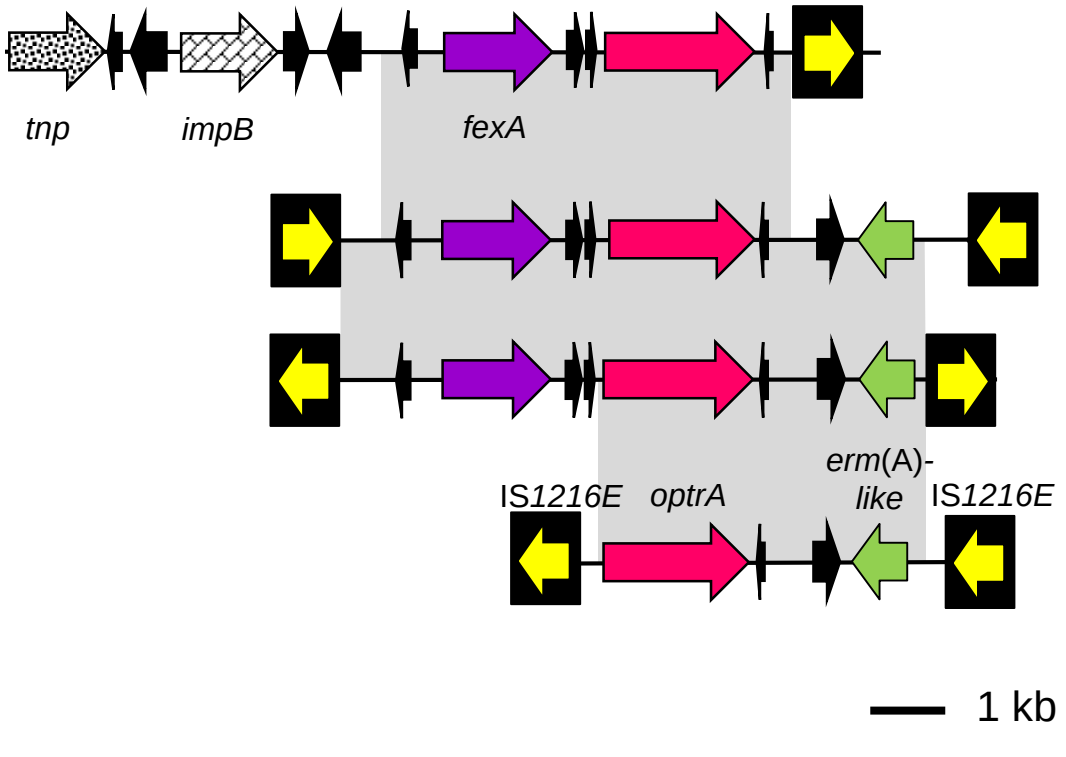
Comparison of *optrA*-carrying plasmids of *E. faecalis* from humans and animals

pXY17 (pig, ST27) ,
pE161 (human, ST585),
pE071 (human, ST480)

pSF35 (chicken, ST330),
pG22 (pig, ST116)

pE419 (human, ST480)

pFX13 (human, ST622)



Comparison of *optrA*-carrying plasmids of *E. faecalis* from humans and animals

pXY17 (pig, ST27) ,
pE161 (human, ST585),
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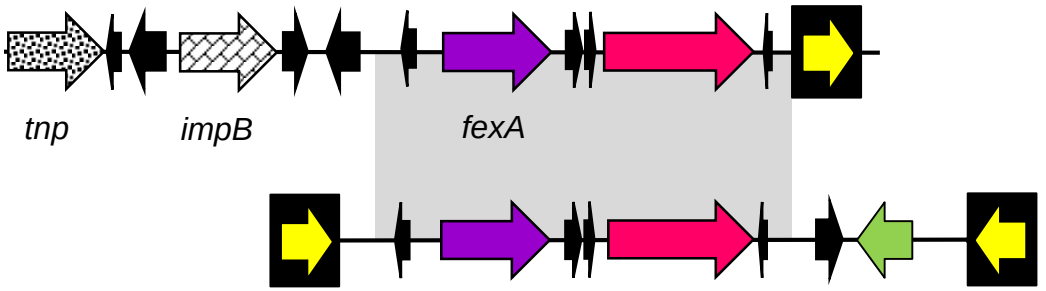
pSF35 (chicken, ST330),
pG22 (pig, ST116)



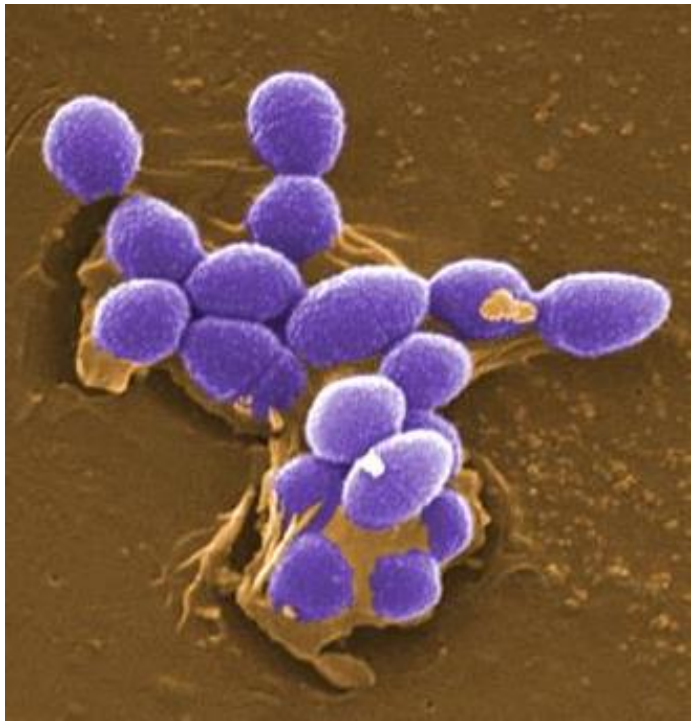
Plasmids of similar size that carry the same *optrA* gene region were found in *E. faecalis* isolates of diverse MLST types and diverse origins.

Horizontal transfer of mobile resistance genes

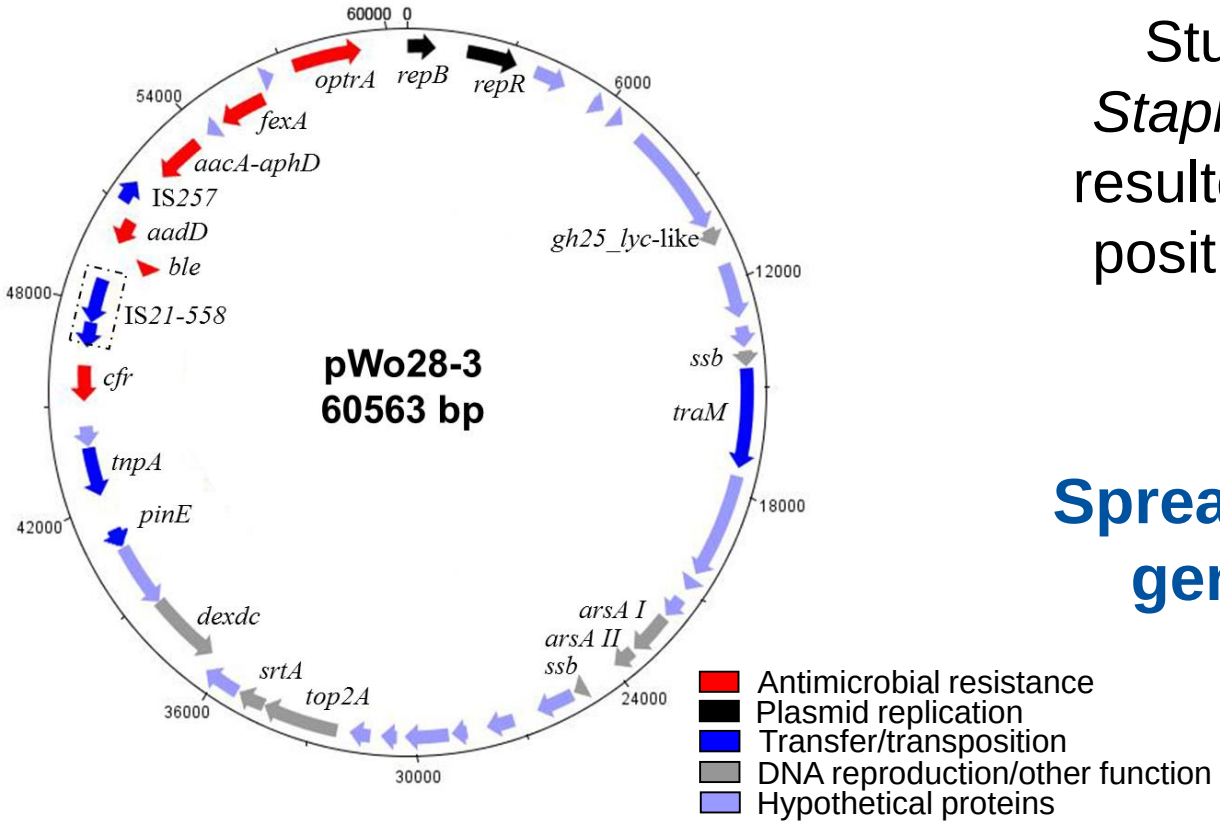
intraspecies transfer
(*E. faecalis* ↔ *E. faecalis*) ✓ *optrA*

interspecies transfer
(*E. faecalis* ↔ *E. faecium*) ✓ *optrA*

intergenus transfer
(*E. faecalis* ↔ *Staphylococcus)* ✓ *optrA*



Intergenus transfer of *optrA* from enterococci to staphylococci



Study on 50 porcine *Staphylococcus* isolates resulted in a single *optrA*-positive *S. sciuri* isolate

Spread of *optrA* across genus boundaries

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Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother
doi:10.1093/jac/dky009

Presence and molecular characteristics of oxazolidinone resistance in staphylococci from household animals in rural China

Chengtao Sun[1], Peng Zhang[1], Xing Ji[1], Run Fan[1], Baoli Chen[2], Yang Wang[1], Stefan Schwarz[1,3] and Congming Wu[1]*

[1]Beijing Advanced Innovation Centre for Food Nutrition and Human Health, College of Veterinary Medicine, China Agricultural University, Beijing, China; [2]Shandong Provincial Key Laboratory of Infectious Disease Control and Prevention, Shandong Centre for Disease Control and Prevention, Jinan, Shandong, China; [3]Institute of Microbiology and Epizootics, Centre for Infection Medicine, Department of Veterinary Medicine, Freie Universität Berlin, Berlin, Germany

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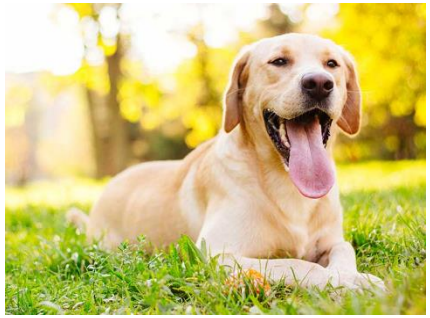
Received 8 September 2017; returned 31 October 2017; revised 28 November 2017; accepted 2 January 2018

Detection of *optrA* in CoNS from pigs, dogs and cats

Staphylococcus sciuri,
Staphylococcus simulans



Staphylococcus sciuri

Staphylococcus sciuri

Sun *et al.* (2018) J. Antimicrob. Chemother. 73: 1194-1200.

Conclusion II

- Oxazolidinone resistance is often based on resistance genes, such as *cfr* and *optrA* (horizontal & vertical gene transfer).
- Oxazolidinone-resistant bacteria can be exchanged among humans, animals and the environment.
- Plasmids play an important role in the dissemination of oxazolidinone resistance genes.
- Although oxazolidinones are not approved for veterinary use, oxazolidinone resistance genes are present among bacteria of animals.
- Direct selection and co-selection by other antimicrobial agents are of major relevance in the dissemination of oxazolidinone resistance genes.

Concluding remarks

One Health and antimicrobial resistance

Antimicrobial resistance is the „**example par excellence**“ that illustrates how humans, animals and the environment are interconnected.

One Health and antimicrobial resistance

Virtually the same classes of antimicrobial agents are used in **human medicine**, **veterinary medicine**, and - in part - also in **horticulture** to combat bacterial infections.

One Health and antimicrobial resistance

- There is transmission of resistant bacteria (and their resistance genes) between animals, humans, and the environment.





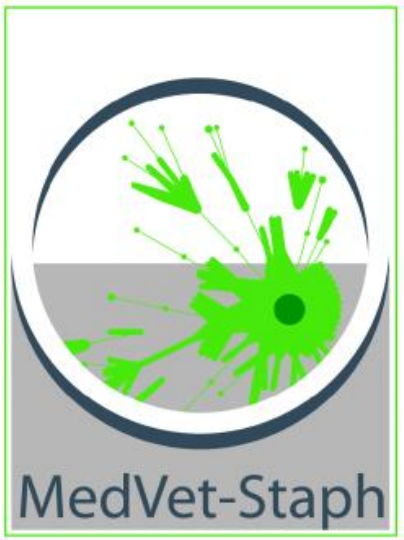


One Health and antimicrobial resistance

- A One Health approach dealing with antimicrobial resistance will require a better understanding of the relative importance of humans, animals and the environment in:
  - the evolution of antimicrobial resistant bacteria and their genetic determinants,
  - the ways in which they interact, and
  - the transmission routes and mechanisms involved.

One Health and antimicrobial resistance

- National research consortia in which groups from human and veterinary medicine interact:



- International research consortia in which groups from human and veterinary medicine interact:

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