La resistenza agli antibiotici: un problema prioritario di Sanità Animale e di Sanità Pubblica Veterinaria

Antonio Battisti

Direzione Operativa Diagnostica Generale, Centro di Referenza Nazionale per l'Antibioticoresistenza

National Reference Laboratory for Antimicrobial Resistance (Reg. 882/2004/EC)

Roma, Regione Lazio

28 novembre 2011

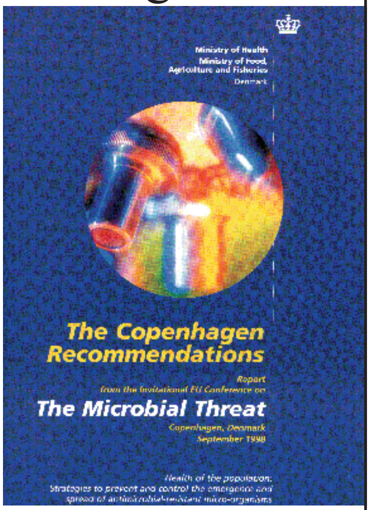
Antibiotici: Passato e Presente

- L'uso degli antibiotici ha svolto un ruolo decisivo negli ultimi 70 anni, nel campo umano ed in quello animale
- Ruolo decisivo nella salvaguardia e nello sviluppo delle Produzioni Animali
- Ruolo chiave nell'assicurare fonte proteica di origine animale salubre ed a costi sostenibili
- Oggi, il problema della resistenza agli antibiotici costituisce un problema emergente di Sanità Pubblica (WHO, EU, FDA) e di SPV (OIE)
- Dir. 2003/99/EC: Resistenza agli antibiotici come zoonosi trasversale!

A. Battisti, 2005

Il “problema” Resistenza agli antibiotici

- E’ un fenomeno noto ed in continua crescita da almeno 40 anni (dall’”invenzione” degli antimicrobici…)
- E’ una priorità di Sanità Pubblica globale da almeno 15 anni… (The Microbial Threat, The Copenhagen Recommendations, EU 1998)



E’ una priorità della Commissione Europea, (Direttorato Salute e Protezione del Consumatore) da almeno 10 anni

EUROPEAN COMMISSION
DIRECTORATE GENERAL XXIV
CONSUMER POLICY AND CONSUMER HEALTH PROTECTION
Directorate B - Scientific Health Opinions
Unit B3 - Management of scientific committees II

OPINION OF THE

SCIENTIFIC STEERING COMMITTEE

ON

ANTIMICROBIAL RESISTANCE

28 May 1999

Il “monitoraggio” dell’antibioticoresistenza

- E’ una priorità di Sanità Pubblica (Umana e Veterinaria) della Comunità Europea da almeno 7 anni
- Dir. 99/2003 (recepita con DLvo 191/2006 in Italia)
- L’antibioticoresistenza è considerata “zoonosi trasversale”
- Obbligatorio per i MS il monitoraggio e il reporting dell’AR negli agenti zoonosici (Salmonella, Campylobacter), fortemente raccomandato il monitoraggio degli indicatori (E. coli, Enterococci) nelle specie zootecniche

La sorveglianza (RMOs?) dell’antibioticoresistenza

E’ una opportunità per la Sanità Pubblica Veterinaria negli ultimi 7 anni:

- Reg. 2160/2003 (Controllo e riduzione agenti zoonosici nella produzioni primarie: per ora obbligatorio per Salmonella, **nelle filiere avicole (e suine?)**
- **Le Dec Comm relative prevedono la produzione di dati di AR sugli isolati di Salmonella e Campylobacter**

- **Reg. 1177/2006** (Control methods in poultry)

Article 2

Use of antimicrobials

1. **Antimicrobials shall not be used as a specific method to control salmonella in poultry**

Antimicrobial resistance and zoonotic infections

October 2009

Joint Opinion on antimicrobial resistance (AMR) focused on zoonotic infections[1]

Scientific Opinion of the European Centre for Disease Prevention and Control; Scientific Opinion of the Panel on Biological Hazards; Opinion of the Committee for Medicinal Products for Veterinary Use; Scientific Opinion of the Scientific Committee on Emerging and Newly Identified Health Risks[2,3]

By alphabetical order:

European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden.

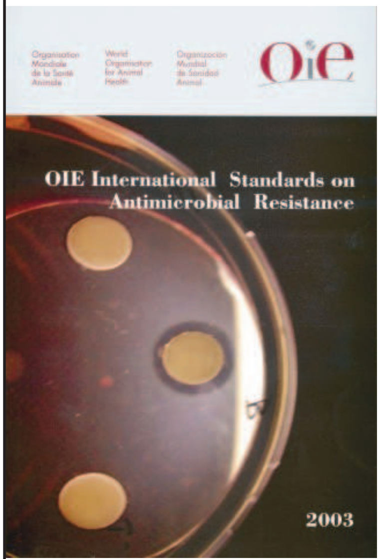
European Food Safety Authority (EFSA), Parma, Italy

European Medicines Agency (EMEA), London, United Kingdom.

Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Brussels, Belgium

Key words: Antimicrobial resistance, usage of antimicrobials, biocides, *Campylobacter*, cephalosporins, *E. coli*, emerging risks, foodborne zoonoses, macrolides, MRSA, multidrug resistance, quinolones, *Salmonella*, veterinary medicines.

E' una Priorità di Sanità Animale



Rev. sci. tech. Off. int. Epiz., 2001, 20 (3), 829-839

Antimicrobial resistance: responsible and prudent use of antimicrobial agents in veterinary medicine

F. Anthony, J. Acar, A. Franklin, R. Gupta, †T. Nicholls, Y. Tamura, S. Thompson, E.J. Threlfall, D. Vose, M. van Vuuren & D.G. White

Food and Agriculture Organization of the United Nations

World Health Organization

World Organisation for Animal Health

Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials

Report of the FAO/WHO/OIE Expert meeting
FAO, Rome, Italy
26-30 November 2007

E' una priorità anche per le Animal Health Industries:
Conservare l'efficacia terapeutica delle molecole registrate per la terapia veterinaria, che si configurano anche come "CIA, HIA, IA", poiché usati anche in terapia umana:

non ci sono vantaggi economici per l'industria riguardo gli investimenti nel settore della ricerca!

E' una Priorità nel settore delle Produzioni, del Commercio e del Consumo degli alimenti

codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Viale delle Terme di Caracalla 00153 ROME Tel: 39 06 57051 www.codexalimentarius.net Email: codex@fao.org Facsimile: 39 06 5705 4593

Agenda Item 1

CX/AMR 08/2/1
August 2008

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

AD HOC CODEX INTERGOVERNMENTAL TASK FORCE ON ANTIMICROBIAL RESISTANCE

Second Session
Seoul, Republic of Korea, 20-24 October 2008

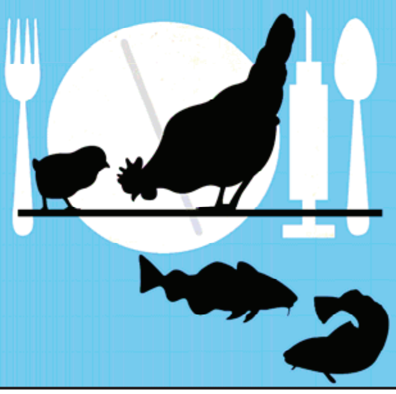
WHO-FAO TF AMR

- Mandato: produrre linee –guida per i Paesi Membri (WHO e anche WTO!) “***on antimicrobial resistance arising from non-human antimicrobial use***..."
- I documenti prodotti per i processi decisionali riguardano:
- Risk Profiling
- Risk Assessment
- Risk Management: proposta di varie RMOs

Questi includono anche linee guida circa **il monitoraggio e la sorveglianza sull’uso** degli antibiotici nel sistema (agro)-zootecnico.

World Health Organization Europe

Tackling antibiotic resistance from a food safety perspective in Europe



Antibiotics have revolutionized the treatment of infectious diseases. But their use and misuse have resulted in the development and spread of antibiotic resistance. This is now a significant health problem: each year in the European Union alone, over 25 000 people die from infections caused by antibiotic-resistant bacteria. Antibiotic resistance is also a food safety problem: antibiotic use in food animals –for treatment, disease prevention or growth promotion – allows resistant bacteria and resistance genes to spread from food animals to humans through the food-chain.

This publication explores the options for prevention and containment of antibiotic resistance in the food-chain through national coordination and international cooperation, including the regulation and reduction of antibiotic use in food animals, training and capacity building, surveillance of resistance trends and antibiotic usage, promotion of knowledge and research, and advocacy and communication to raise awareness of the issues.

This publication is primarily intended for policy-makers and authorities working in the public health, agriculture, food production and veterinary sectors, and offers them ways to take a holistic, intersectoral, multifaceted approach to this growing problem.

Uso degli di antimicrobici in Medicina Veterinaria

Antimicrobici utilizzati per TRE scopi:

- Profilassi (metafilassi)
- Terapia
- Growth promoters (digestive enhancers):

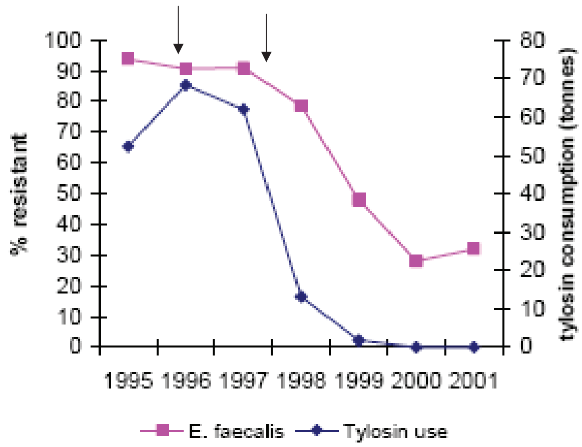
Uso bandito dalla EU dal 2000 (2006)

Residui di antibiotici eliminati con le deiezioni nell'ambiente

Per ognuno, la P selettiva sull'ecosistema (intestino, ambiente) fa emergere Resistenze

A. Battisti, 2005

Trends in tylosin use for growth promotion and erythromycin resistance among Enterococcus faecalis isolated from pigs at slaughter from 1995 to 2001 (WHO 2003; Aarestrup et al. 2001).



http://www.who.int/gfn/en/Expertsreportgrowthpromoterdenmark.pdf

Problematiche derivanti dall'uso di antimicrobici in Veterinaria[2]

- Agenti patogeni R, provocano **<u>costi aggiuntivi per 4-5 milioni $</u>** l'anno in USA, soltanto nell'uomo
- problemi analoghi in Medicina Veterinaria
- Aumento di morbilità, mortalità, costi associati a malattia
- Spesso usati come ***profilassi, metafilassi, terapia, con somministrazioni non individuali, di massa***
- "Non devono mai essere usati per compensare o mascherare cattivo management in allevamento o cattive pratiche veterinarie"
- (<u>Da linee guida su prudent use WVA/IFAP/COMISA, 1999</u>)

http://www.poultry-health.com/library/antimicrobials/wvacoifa.htm

A. Battisti, 2005

Costi annuali malattie da AMR-bacteria in USA:

4-5 M USD l'anno

Special Issue

Economic Impact of Antimicrobial Resistance

John E. McGowan, Jr.
Emory University School of Medicine, Atlanta, Georgia, USA

One reason antimicrobial-drug resistance is of concern is its economic impact on physicians, patients, health-care administrators, pharmaceutical producers, and the public. Measurement of cost and economic impact of programs to minimize antimicrobial-drug resistance is imprecise and incomplete. Studies to describe and evaluate the problem will have to employ new methods and be of large scale to produce information that is broadly applicable.

One reason antimicrobial-drug resistance has recently become a concern is its economic impact. The Institute of Medicine estimates the annual cost of infections caused by antibiotic-resistant bacteria to be U.S.$4 to $5 million (1). However, methods for measuring economic impact of resistance are in their infancy, and the studies leave many questions unanswered (2). In this review, I examine perspectives from which economic impact of resistance is important, assess available data about economic methods used for evaluating economic effect, and suggest issues important for these assessments, as well as approaches for further study.

Economic Impact: Differing Viewpoints

Several viewpoints toward antimicrobial-drug resistance and its impact include those of physicians, patients, health-care businesses, the drug industry, and the public (Table 1).

Table 1. Perspectives of economic impact of antimicrobial-drug resistance*

	Focus	Outcome	Time	Motivation	Approach
Physician	Individual	Health	Short	Profes-sional-ism	Treatment
Patient	Individual	Health	Short	Health	Treatment
Provider	Care group	Lower cost	Short	Profit	Cost contain-ment
Industry	Clients	Sales	Short, long	Profit	New drugs, viable old drugs
Public	Population	Health	Long	Social good	Lower chance of resistance

*Cordell RL, Solomon SL, Scott RD, McGowan JE Jr, unpub. data.

WVA/Comisa/IFAP Basic Principles http://www.poultry-health.com/library/antimicrobials/wvacoifa.htm

WVA	FIPA/IFAP	COMISA
representing VETERINARIANS	representing FARMERS	representing the ANIMAL HEALTH INDUSTRY

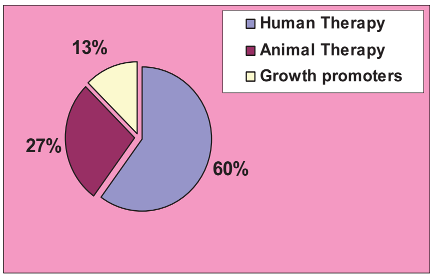
Prudent Use of Antibiotics: Global Basic Principles

This paper presents a set of principles governing the prudent use of antibiotics in animals, elaborated jointly by the international representative organisations of veterinarians, farmers, and the pharmaceutical industry. It may form the backbone of and/or guide in the elaboration of more specific guidelines.

Total amount of antibiotics used in Europe (IFAH, 2003)

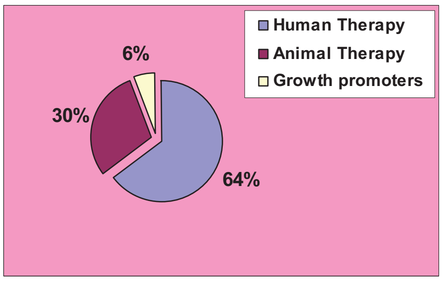
1997

Total amount: 12752 tons



1999

Total amount: 13216 tons



A. Battisti, 2005

Stime riportate nel booklet WHO 2011: nel 2010 nel mondo

Metà degli AM utilizzati nel settore agro-zootecnico (page 8, Ch. 1.)

AR: quali strumenti per contrastarla?

- Nei decenni scorsi, aumento delle conoscenze di fisiologia dei batteri con sviluppo di AM “ad hoc” Lo sviluppo di un AM può richiedere fino a

  <u>400 milioni $</u> e **<u>dieci anni di ricerche</u>**

- Dall’avvento dei Fluorochinolonici, non sono stati più scoperti nuovi “target sites” né nuove classi di AB, (Industria investe meno in ricerca)
- Nuove strategie: inattivazione R factors, distruzione mRNA, modifica classi precedenti(?)

A. Battisti, 2005

Come siamo arrivati a questo punto?

- **Antibioticoresistenza: Fenomeno biologico naturale**

  Gruppi di microrganismi (es: *Streptomycetes*) producono sostanze inibenti contro i competitori per lo stesso substrato

Basi biologiche dell'antibioticoresistenza

- Negli ultimi trenta anni il fenomeno è stato **enormemente amplificato** dall'uso degli antibiotici in medicina umana e veterinaria (R in ogni classe)
- La pressione selettiva esercitata con l'uso nell'Uomo e negli animali fa emergere e diffondere geni di resistenza e cloni resistenti nelle popolazioni batteriche

A. Battisti, 2005

Esempi di basi genetiche e modalità di diffusione

- **Mutazioni puntiformi nel DNA del cromosoma**
  mantenimento del trait nella progenie e

disseminazione per diffusione clonale (successo evolutivo del clone)

- **Trasferimento orizzontale di geni di resistenza:**

-Trasformazione, Trasduzione, Coniugazione

Non implica necessariamente successo del clone

Trasferimento anche tra specie diverse: Commensali & patogeni (anche zoonosici)

ecdc efsa European Food Safety Authority emea

16 June 2009

Joint scientific report of ECDC, EFSA and EMEA on meticillin resistant *Staphylococcus aureus* (MRSA) in livestock, companion animals and food[1].

Summary of the scientific Opinion of the Panel on Biological Hazards (EFSA/BIOHAZ) on "*Assessment of the Public Health significance of meticillin resistant Staphylococcus aureus (MRSA) in animals and foods*" and the Reflection paper of the Committee for Medicinal Products for Veterinary Use (EMEA/CVMP) on "*MRSA in food producing and companion animals and in the European Union: Epidemiology and control options for human and animal health*"

La pressione selettiva favorisce l'emergenza e la diffusione di **cloni R**

(o in altri casi, di geni di resistenza su elementi in MGE)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2010
EMA/CVMP/SAGAM/736964/2009
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on meticillin-resistant *Staphylococcus pseudintermedius*

Agreed by SAGAM (Scientific Advisory Group on Antimicrobials)	2 June 2010
Adoption CVMP for release for consultation	15 September 2010
End of consultation (deadline for comments)	30 November 2010

Comments should be provided using this template to vet-guidelines@ema.europa.eu

KEYWORDS	*Staphylococcus pseudintermedius, antimicrobial resistance, meticillin[1] - resistance, S. intermedius, veterinary medicinal product.*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2009, p. 1709–1711 Vol. 53, No. 4
0066-4804/09/$08.00+0 doi:10.1128/AAC.01014-08
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Transmission of IncN Plasmids Carrying $bla_{CTX\text{-}M\text{-}1}$ between Commensal *Escherichia coli* in Pigs and Farm Workers▽†

Arshnee Moodley* and Luca Guardabassi

Department of Veterinary Pathobiology, Faculty of Life Sciences, University of Copenhagen, Frederiksberg C, Denmark

Received 29 July 2008/Returned for modification 1 November 2008/Accepted 25 January 2009

CTX-M-1-producing *Escherichia coli* were isolated from 56 pigs, three farm personnel, two manure samples, and two air samples from two Danish pig farms where an association between prophylactic ceftiofur use and the occurrence of cephalosporin resistance was previously demonstrated. Human, animal, and environmental strains displayed high genetic diversity but harbored indistinguishable or closely related IncN plasmids carrying $bla_{CTX\text{-}M\text{-}1}$, indicating that IncN plasmids mediating cephalosporin resistance were transmitted between pigs and farm workers across multiple *E. coli* lineages.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2005, p. 833–835 Vol. 49, No. 2
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.2.833–835.2005
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Extended-Spectrum β-Lactamases in *Escherichia coli* Isolated from Dogs and Cats in Rome, Italy, from 2001 to 2003

Alessandra Carattoli,[1] Sarah Lovari,[2] Alessia Franco,[2] Gessica Cordaro,[2] Paola Di Matteo,[2] and Antonio Battisti[2]*

Istituto Superiore di Sanità[1] and Istituto Zooprofilattico Sperimentale delle Regioni Lazio e Toscana,[2] Rome, Italy

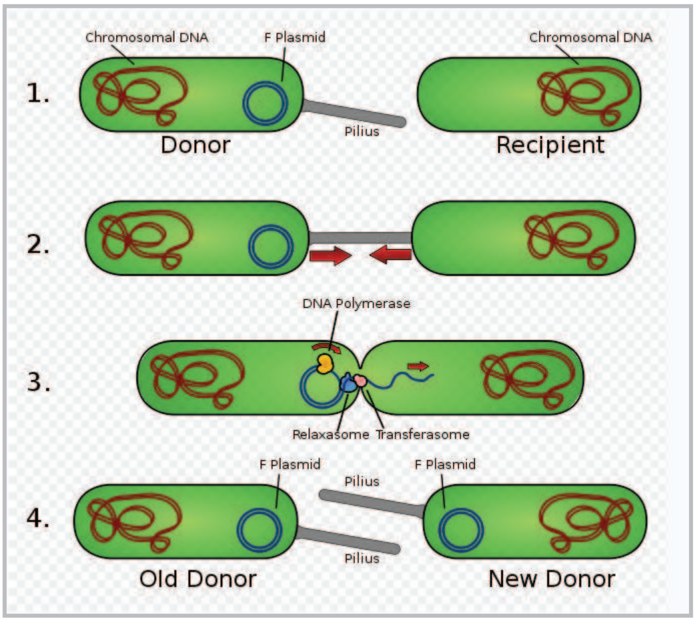
Received 23 July 2004/Returned for modification 6 September 2004/Accepted 12 October 2004

We report expanded-spectrum cephalosporin resistance in *Escherichia coli* from dogs and cats in Rome, Italy. Three major β-lactamases (CMY-2, SHV-12, and CTX-M-1) are reported for the first time in *E. coli* from sick and healthy dogs and cats. Molecular characterization suggests the presence of several combinations of β-lactamase genes in *E. coli* from companion animals.

TABLE 1. Characteristics of *E. coli* isolates recovered from sick and healthy dogs and cats in Rome, Italy from 2001 to 2003

Isolate	Species	Source[a]	Origin	Resistance pattern[b]	PFGE profile[c]	$bla_{SHV\text{-}12}$	$bla_{CMY\text{-}2}$	$bla_{CTX\text{-}M\text{-}1}$	bla_{TEM}[d]
18196	Dog	Organs	Kennel A	AMP AMC CTX FOX KAN SUL SXT TET	A	−	+	−	−
16117	Dog	Feces	Kennel B	AMP AMC CHL CTX FOX GEN	B	−	+	−	−
20432	Dog	Organs	Kennel B	AMP AMC CHL CTX ENO FOX KAN NAL STR SUL SXT TET	C	−	−	+	+
14083	Dog	Organs	Kennel B	AMP AMC CHL CTX ENO FOX KAN NAL STR SUL SXT TET	ND	−	−	+	+
331	Dog	Feces	Kennel B	AMP AMC CHL CTX ENO FOX GEN KAN NAL STR SUL SXT TET	D	−	−	+	+
1092	Dog	Infection	Kennel B	AMP AMC CHL CTX FOX GEN KAN NAL SPT STR SUL SXT TET	E	−	−	+	+
31038	Rat	Gut contents	Kennel B	AMP AMC CTX FOX GEN STR SUL SXT TET	F	−	+	+	−
24623	Dog	Feces	Kennel B	AMP AMC CHL CTX ENO FOX NAL SUL SXT TET	G	−	−	+	+
1599B	Dog	Gut contents	Kennel C	AMP CTX ENO GEN KAN NAL STR SUL SXT TET	G	+	−	+	+
1599C	Dog	Organs	Kennel C	AMP CTX ENO GEN NAL SUL SXT TET	G	+	−	+	+
1599D	Dog	Organs	Kennel C	AMP CTX ENO GEN NAL STR SUL SXT TET	G	+	−	−	+
17795	Dog	Gut contents	Kennel C	AMP CHL CTX ENO NAL SUL SXT TET	G	−	−	+	+
1599A	Dog	Gut contents	Kennel C	AMP CHL CTX ENO NAL STR SUL SXT TET	H	−	−	+	+
1599E	Dog	Organs	Kennel C	AMP CHL CTX ENO NAL STR SUL SXT TET	H	−	−	+	+
322	Dog	Organs	Kennel D	AMP CTX STR SUL SXT TET	I	−	−	+	+
11361	Dog	Organs	Private owner	AMP CHL CTX KAN SPT STR SUL SXT TET	L	+	−	−	+
362	Dog	Feces	Private owner	AMP AMC CHL CTX ENO FOX KAN NAL SUL SXT TET	ND	−	−	+	+
17419	Cat	Organs	Private owner	AMP AMC CHL CTX ENO FOX KAN NAL STR SUL SXT TET	C	−	−	+	+
3050	Dog	Organs	Private owner	AMP AMC CTX ENO FOX NAL STR SUL SXT TET	M	−	−	+	+
34430	Cat	Organs	Private owner	AMP CTX ENO FOX NAL SUL SXT TET	M	−	−	+	−
8113	Cat	Organs	Private owner	AMP AMC CHL ENO FOX KAN NAL SPT STR SUL SXT TET	N	−	−	−	+

[a] Gut contents and organs are from necropsy specimens.
[b] AMP, ampicillin; AMC, amoxicillin-clavulanic acid; CHL, chloramphenicol; CTX, cefotaxime; ENO, enrofloxacin; FOX, cefoxitin; GEN, gentamicin; KAN, kanamycin; NAL, nalidixic acid; SPT, spectinomycin; STR, streptomycin; SXT, sulfometoxazole-trimethoprim; SUL, sulfonamides; TET, tetracycline.
[c] ND, not determined. PFGE patterns differing for more than three DNA fragments were classified as different profiles.
[d] bla_{TEM} genes were identified by PCR, although several amplicons were sequenced identifying $bla_{TEM\text{-}1a}$ and $bla_{TEM\text{-}1b}$ gene variants.



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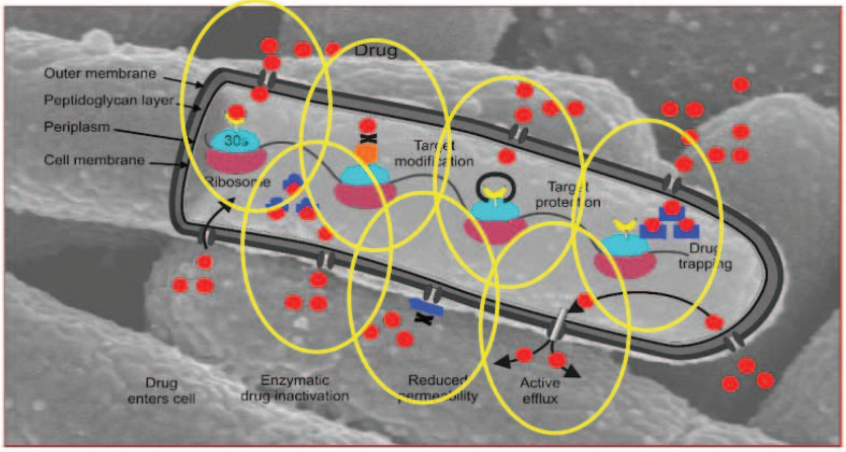
Antibiotics: Modes of resistance



National Food Institute

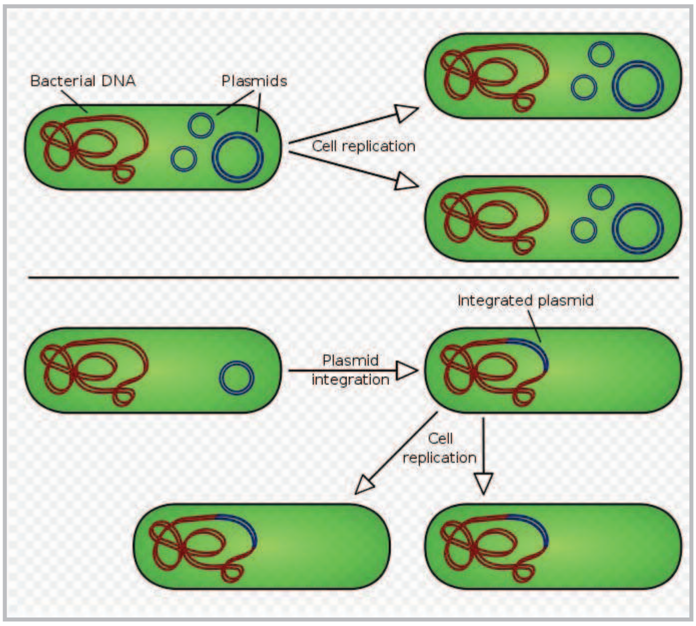
Nel mondo dei batteri, si stimano almeno 25.000 meccanismi diversi di resistenza agliantibiotici!

DTU

AR: considerazioni ecologiche[1]

Enterobacteriaceae (Salmonella):

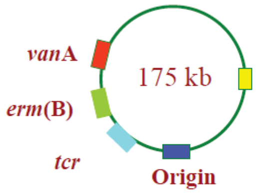
- Anni '60: self transfer R factors, **monoresistenze** in seguito all'inizio dell'uso massivo di AB
- Fine '70, **MultiResistenze** (transposizioni e formazioni di cointegrati - grandi plasmidi).
- Sistemi efficienti di trasferimento a 22°C e 37°C
- Anni '80, sotto massiccia e K Pressione selettiva: **integrazione cromosomica**



Concetto di co-selezione delle resistenze

20

Co-selection of resistance



tcr=Transferable copper resistance

Usage of copper or erythromycin selects for presence of vancomycin resistance

National Food Institute

DTU

Concetto di “multifunzione” di meccanismi di resistenza

- Determinanti di resistenza per alcune classi di antibiotici di che <u>“estendono” su altre classi di antibiotici</u>
- Meccanismi <u>“non-drug specific”</u> come efflux pumps:

(transporters anche in Gram +ve bacteria)

AR: le tendenze

- **E' aumentato il pool di geni di R**
- E' aumentato anche il rischio di trasferimento di molti di essi all'Uomo (zoonosici e umani)
- Da monoresistenze ('50 e '60) a Resistenze Multiple (MR), dalla fine degli anni '70
- **Oggi osserviamo:**

-Aumento significativo delle R multiple

-Emergenza <u>e in alcuni casi alta prevalenza</u> di R alle <u>più recenti</u> classi di antibiotici (cefalosporine di 3a generazione, fluorochinolonici, macrolidi)

A. Battisti, 2005

Trends of antimicrobial resistance in humans (CDC –USA)

http://www.cdc.gov/drugresistance/about.html

- Reports of **methicillin-resistant Staphylococcus aureus (MRSA)**—a potentially dangerous type of staph bacteria that is resistant to certain antibiotics and may cause skin and other infections—in persons with no links to healthcare systems have been observed with increasing frequency in the United States and elsewhere around the globe.
- Multi-drug resistant ***Klebsiella*** species and ***Escherichia coli*** have been isolated in hospitals throughout the United States.
- Antibiotic-resistant ***Streptococcus pneumoniae*** infections <u>have significantly declined,</u> but remain a concern in some populations.

Problematiche derivanti dall'uso di antimicrobici in Veterinaria[3]

Terapia:

- Problema etico legato al concetto di Animal Welfare: Fornire la terapia più efficace possibile (<u>non la molecola più recente esistente!)</u>
- AR <u>causa **fallimento terapeutico**</u> in Medicina Veterinaria, a livello di "caso clinico": <u>il cattivo uso ne aumenta le probabilità</u>
- <u>**Fondamentale strumento del "prudent use": diagnosi eziologica e test di sensibilità agli antibiotici**</u>

Decisivo nella corretta gestione di casi clinici e del gruppo (**anamnesi storica in allevamento**)

Problematiche derivanti dall'uso di antimicrobici in Veterinaria[4]

- Eticamente, l'emergenza dell'AR va contrastata dal Veterinario, <u>per gli agenti patogeni animali, e non solo</u>
- Altra ragione etica:

  I fattori di R, selezionati in patogeni od in commensali degli animali, <u>diffondono agli agenti zoonosici ed ai patogeni umani puri</u>
- Dopo la registrazione di apramycina e chinoloni, aumento notevole di R in *Salmonella* dimostrato in Programmi di Sorveglianza (es. in Germania)

<u>Priorità nella sorveglianza</u> di AMR in SPV:

Agenti zoonosici

Per ora il documenti EU usano il temine "monitoraggio"

es. Dec Comm 407/2007/EC

Antimicrobial resistance and zoonotic infections

October 2009

Joint Opinion on antimicrobial resistance (AMR) focused on zoonotic infections[1]

Scientific Opinion of the European Centre for Disease Prevention and Control; Scientific Opinion of the Panel on Biological Hazards; Opinion of the Committee for Medicinal Products for Veterinary Use; Scientific Opinion of the Scientific Committee on Emerging and Newly Identified Health Risks[2,3]

Possibili livelli di intervento

- Implementazione "Salute" degli animali:

(buone pratiche di allevamento, investimenti strutturali, misure di biosicurezza, prevenzione vaccinale….)

⇓

Può ridurre quantità AB usati nelle produzioni primarie

Purtroppo ancora oggi l'uso non prudente degli antibiotici fornisce "una scorciatoia", economicamente non svantaggiosa

Possibili Livelli di Intervento

- Implementare linee guida condivise sull'uso prudente e responsabile degli AB
- Formularia! (es. Società di veterinari clinici et al.)

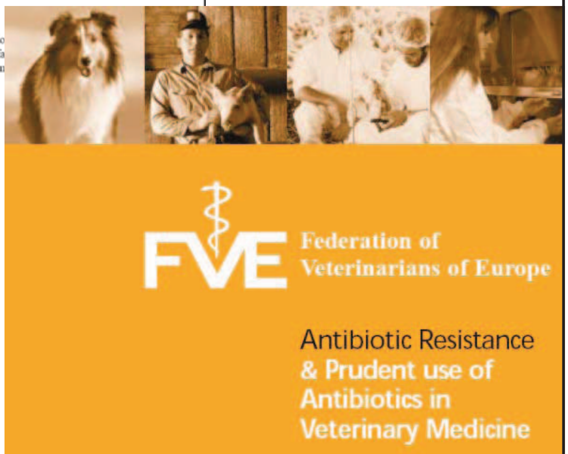
Discussione a livello EU su:

- Incentivi alla produzione primaria con limitato uso di antibiotici?
- Disincentivi alle prescrizioni e distribuzioni (vendita) inappropriate?
- Formazione…


WVA representing VETERINARIANS
FIPA/IFAP representing FARMERS
COMISA representing the ANIMAL HEALTH INDUSTRY

Prudent Use of Antibiotics: Global Basic Principles

This paper presents a set of principles governing the prudent use of antibio
jointly by the international representative organisations of veterinarians, fa
industry. It may form the backbone of and/or guide in the elaboration of m



http://www.fve.org/news/publications/pdf/antibioen.pdf

Il Sistema Produttivo (agro)-zootecnico (veterinari inclusi)

- E’ chiamato <u>in qualità di “co-responsabile”</u> ad un impegno comune per:
- controllare e ridurre la diffusione dei batteri resistenti e dei determinanti (geni) di resistenza lungo le filiere produttive, fino al consumatore finale
- La DG SANCO <u>ha voluto schemi armonizzati per il monitoraggio (emergenza, prevalenza, trend) dell’AR</u> nella EU <u>in funzione di conoscenza</u> per le decisioni di politica sanitaria comunitaria

Domani: da monitoraggio a sorveglianza…?

In rapporto a:

- [informazioni sulle quantità di antibiotici usati nelle diverse linee produttive] e
- stime di prevalenza e trend di antibioticoresistenza nelle diverse linee produttive

Valutare e mettere in atto azioni volte a ridurre il rischio negli animali e nell'Uomo

Mantenimento dell'efficacia ed uso controllato di Critically Important Antimicrobials

Classi di antibiotici indispensabili per la terapia di infezioni invasive nell'uomo causate anche da agenti zoonosici emergenti o ad incidenza rilevante (es. Salmonella, Campylobacter, E. coli etc).

- Cefalosporine a spettro esteso (3th – 4th generation)
- Fluorochinolonici
- Macrolidi

Restricted/controlled use in primary productions?

2.2 THE WHO LIST OF CRITICALLY IMPORTANT ANTIMICROBIALS

The WHO list of critically important antimicrobials was based on the following criteria for categorization as developed by two Expert Meetings (WHO, 2005; WHO, 2007):

- **Criterion 1** Sole therapy or one of few alternatives to treat serious human disease.
- **Criterion 2** Antibacterial used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases causes by organisms that may acquire resistance genes from non-human sources.

The definitions of the different categories were as follows:

Critically important antimicrobials are those that meet criteria 1 and 2

Highly important antimicrobials are those that meet criteria 1 or 2

Important antimicrobials are those that meet neither criteria 1 nor 2

The detailed explanations of the reasoning of the WHO Expert Meetings were as follows.

Table 5. Example of Approach III for prioritization for risk assessment purposes of the combination of antimicrobial agent, the species of animal, and the foodborne bacterium

Report of the Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials, 26–30 Nov. 2007 17

Drug	Bacterial species	Animal species	Rationale (available information for the four criteria) *1. Frequency and severity of human disease* *2. Exposure to hazard through food* *3. Frequency and severity of animal disease* *4. International trade*
Fluoro-quinolones	Campylobacter	Pigs	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and is a preferred empiric treatment for a frequently occurring gastrointestinal disease. 2. The food is consumed worldwide. The Campylobacter species found in pigs is *C. coli*, which accounts for approximately 5% of human infection. Resistance is very frequent. 3. Used for short-term treatment for a range of porcine diseases, which may vary widely between countries. Used to treat individual animals. Is not licensed in some countries. 4. Pork traded to a large extent worldwide.
Macrolides	Campylobacter	Poultry	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and is a preferred empiric treatment for a frequent gastrointestinal disease. 2. One of the foods most consumed worldwide. The pathogen is very frequently found in the food product and a high prevalence of resistance can be found in some countries. Resistant varies widely between countries. 3. May be used in feed. 4. Poultry traded to a large extent worldwide.
Macrolides	Campylobacter	Cattle	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and is a preferred empiric treatment for a frequent gastrointestinal disease. 2. The food is frequently consumed. The pathogen is frequently found, primarily in ground product and less in whole meats in some countries. Resistance is not as frequent as in other commodities and may be particularly low in some countries 3. Infrequently used in the individual animal. 4. Beef traded to a large extent worldwide.
Macrolides	Campylobacter	Pigs	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and is a preferred empiric treatment for a frequent gastrointestinal disease. 2. The food is consumed worldwide. The *Campylobacter* species found in pigs is *C. coli*, which accounts for approximately 5% of human infection. Resistance is very frequent. 3. Used for growth promotion and group treatment for a range of porcine diseases, which may vary widely between countries. Used in feeds. 4. Pork traded to a large extent worldwide.

efsa

Analysis of the baseline survey on the prevalence of *Campylobacter* in broiler batches and of *Campylobacter* and *Salmonella* on broiler carcasses in the EU, 2008

Table 3. Prevalence of *Campylobacter*-colonised broiler batches, by country and in the EU*, 2008

Country	N (No of broiler batches)	% prevalence[3]	95% CI[3]
Austria	408	47.8[4]	41.5[4] - 54.2[4]
Belgium	337	31.0	23.6 - 39.4
Bulgaria	275	29.6	21.9 - 38.6
Cyprus	375	30.6	25.7 - 36.0
Czech Republic	422	61.3	56.1 - 66.3
Denmark	396	19.0	15.9 - 22.6
Estonia	102	2.0[1]	0.5[1] - 7.5[1]
Finland	411	3.9	3.8 - 4.0
France	422	76.1	70.4 - 81.0
Germany	432	48.9	40.3 - 57.7
Hungary	321	50.1	44.5 - 55.7
Ireland	394	83.1	75.2 - 88.8
Italy	393	63.3	54.5 - 71.3
Latvia	122	41.0	17.0 - 70.2
Lithuania	374	41.5	40.7 - 42.2
Luxembourg	12	100	73.5[2] - 100[2]
Malta	367	96.8	95.0 - 98.0
Netherlands	429	24.4	20.3 - 29.0
Poland	419	78.9	74.1 - 83.0
Portugal	421	82.0	76.3 - 86.6
Romania	357	77.0	63.9 - 86.4
Slovakia	422	73.6	63.6 - 81.6
Slovenia	413	78.2	78.1 - 78.2
Spain	389	88.0	84.0 - 91.2
Sweden	410	13.2	8.0 - 21.0
United Kingdom	401	75.3	69.9 - 80.1
EU (26 MS)*	**9,224**	**71.2**	**68.5 - 73.7**
Norway	396	3.2	2.1 - 4.8
Switzerland	296	59.0	55.0 - 62.9

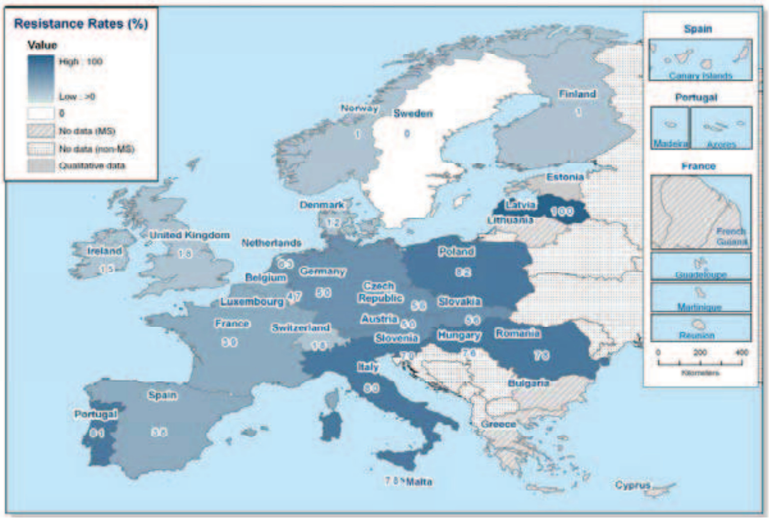
[1] As one slaughterhouse contributed to the entire survey, point estimate and 95% CI are based on logistic regression.
[2] Exact binomial CI, the clustering of data is not taken into account.
[3] Prevalence estimates and CIs at national as well as at EU level were obtained taking into account correlation among observations within the same slaughterhouse. In addition, at EU level, prevalence estimates and CIs were weighted for the national numbers of slaughtered broilers during 2008.
[4] Results assuming independent covariance structure.
* Greece did not participate in the baseline survey and two non-MSs, Norway and Switzerland, participated.

Prevalenza Campylobacter zoonosici in broilers, EU baseline study 2008:

Italy >60%

Spatial distribution of ciprofloxacin resistance among *Campylobacter jejuni* from ***Gallus gallus*** in countries

reporting quantitative data in 2008



Impatto Salmonella AMR e MultiR

Antimicrobial resistance and zoonotic infections

4.4. The burden of disease of resistant infections in humans, e.g. in comparison with sensitive infections

In the EU, *Salmonella* is the second most common human food-borne pathogen. From 2005 to 2006, EFSA Community Summary Reports show that resistance to nalidixic acid in *S.* Enteritidis increased from 13% to 15%, but resistance to ciprofloxacin remained stable at 0.4% - 0.6%. AMR in *Salmonella* has been associated with higher frequency and duration of hospitalisation, longer illness, a higher risk of invasive infection and a two-fold increase risk of death in the two years following infection. Infections with antimicrobial-resistant *S.* Typhimurium are associated with increased risk of invasive disease and death compared to susceptible infections and several studies have shown that patients infected with MDR *S.* Typhimurium definitive phage type (DT) 104 may have worse outcomes. Treatment failures, increased hospitalisation and higher risk of death have been reported for MDR *S.* Typhimurium DT104 exhibiting quinolone resistance.

4.5. To which extent humans are exposed to the resistance agent through food or contact (e.g. pets) with the relevant species – exposure estimate?

Foods have been implicated in several major national and international outbreaks of *S.* Typhimurium exhibiting epidemiological resistance to ciprofloxacin. Eggs contaminated with nalidixic acid-resistant *S.* Enteritidis have been linked to numerous outbreaks of salmonellosis in several European countries since 2000, although it was not possible to precisely ascertain how many infections have been associated with contaminated eggs. A series of studies in Denmark have demonstrated imported poultry and Danish eggs were important sources for quinolone-resistant *Salmonella*, and that travel was associated with the acquisition by consumers, of both MDR and quinolone-resistant *Salmonella*. Although infections with quinolone-resistant *Salmonella* associated with contact with domestic pets appear to be uncommon, concern has been expressed about the possibility of pet animals acting as reservoirs of antimicrobial-resistant *Salmonella*, including quinolone-resistant strains, particularly as antimicrobials, including fluoroquinolones, are used commonly in small animal veterinary practices.

Impatto Campylobacter AMR e MultiR

Antimicrobial resistance and zoonotic infections

7.4. The burden of disease of resistant infections in humans, e.g. in comparison with sensitive infections

Direct data comparing infections due to macrolide-resistant and macrolide-susceptible isolates are limited. In 2006 2.3% of all *C. jejuni* and 10% of *C. coli* were resistant to erythromycin and multidrug resistance, defined as resistance to $\geq$4 antimicrobials, was reported in 8% of *C. jejuni* and 17% of *C. coli* isolates. Infections with macrolide-resistant *Campylobacter* are associated with an increased frequency of adverse events, including invasive illness and death compared to susceptible infections.

7.5. To which extent humans are exposed to the resistance agent through food or contact (e.g. pets) with the relevant species – exposure estimate?

Studies have demonstrated the occurrence of erythromycin-resistant *Campylobacter*, including *C. jejuni*, in retail raw meat samples and various foods, including chicken, raw milk, and the environment. A significant proportion of isolates were resistant to erythromycin, including 16% of isolates from chickens. From pets, similar proportions of erythromycin-resistant *C. jejuni* have been reported. Since onward transmission from domestic pets to humans is a recognised risk for contracting campylobacteriosis, this may be an important factor in the dissemination of macrolide-resistant strains of this pathogen.

Grazie dell’attenzione….Domande?