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Interlifescience
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La resistenza agli antibiotici richiede un approccio One-Health

Manno, 8 novembre 2018

Concetto One-Health

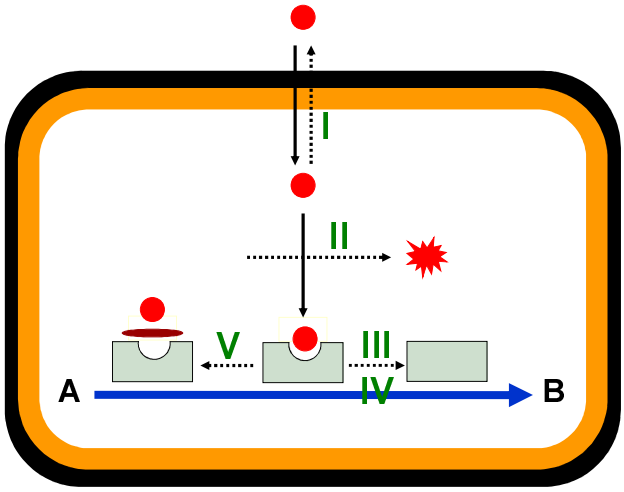
Concetto olistico con il quale si riconosce che la salute degli esseri umani è strettamente legata a quella degli animali, dell'ambiente, dell'ecosistema

→ Lotta contro la AMR: approccio One-Health

Temi considerati

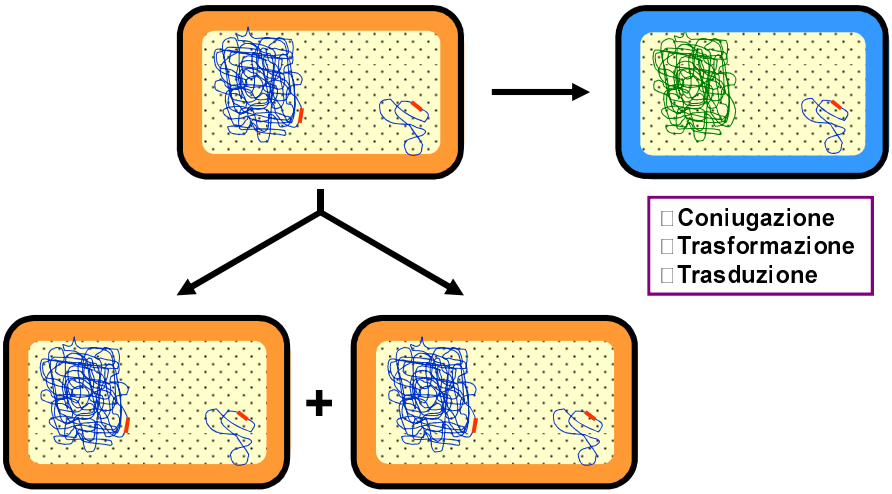
- Batteri resistenti: meccanismi fisiologici e genetici
- Evoluzione batterica verso la (multi)resistenza
- Batteri e geni di resistenza nell'ecosistema
- L'esempio della resistenza alla colistina
- Deboli concentrazioni di antibiotici (<CMI) e resistenza
- Una battaglia multisettoriale

I 5 meccanismi della resistenza agli antibiotici



I: Diminuzione della concentrazione
II: Inattivazione, distruzione
III: Modifica del bersaglio
IV: By-pass
V: Protezione del bersaglio

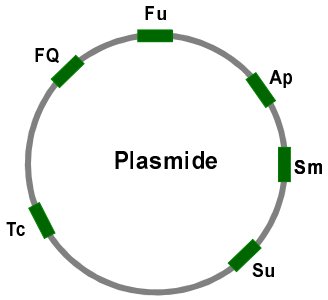
Mobilità genetica della resistenza agli antibiotici

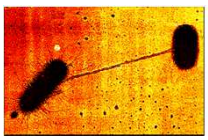


- Coniugazione
- Trasformazione
- Trasduzione

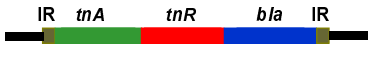
Trasmissione orizzontale
Trasmissione verticale

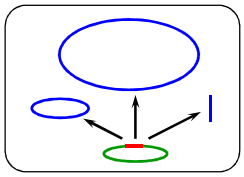
Mobilità genetica della resistenza agli antibiotici. La multiresistenza.



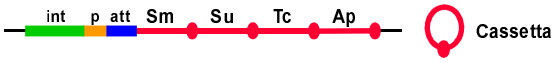


Trasposone Tn*3*





Integrone



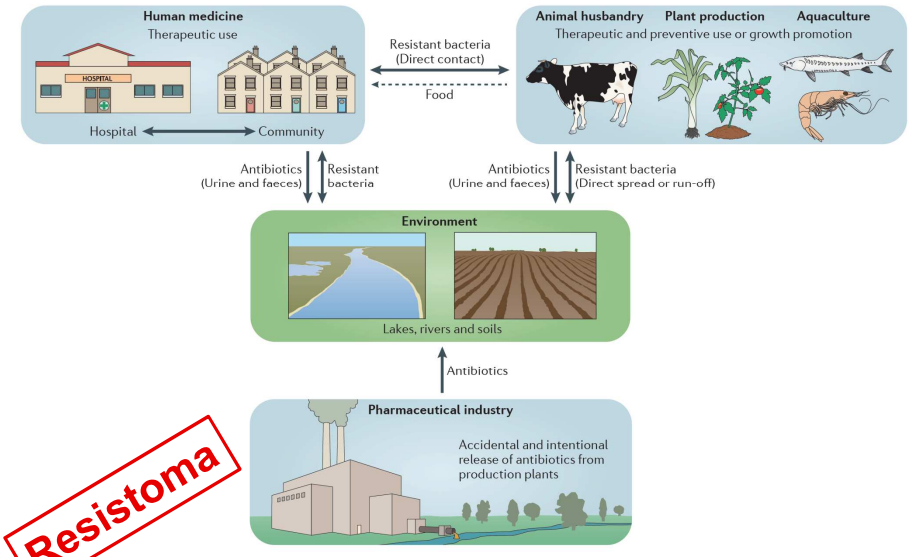
Batteri: le variazioni genotipiche → cambiamenti massicci e rapidi

Antibiotici

- Numero elevato di individui
- Tempo di generazione corto
- Pressioni di selezione spesso forti
- Trasferimenti genetici
  - Trasformazione
  - Trasduzione
  - Coniugazione
  - Plasmidi
  - Trasposoni
  - Integroni

"Batteri":
Totale: $\approx 10^{30}$
Suolo: $\approx 10^{29}$
Acqua: $\approx 10^{28}$
Umani: $\approx 10^{23}$
Individuo: $\approx 10^{13}$

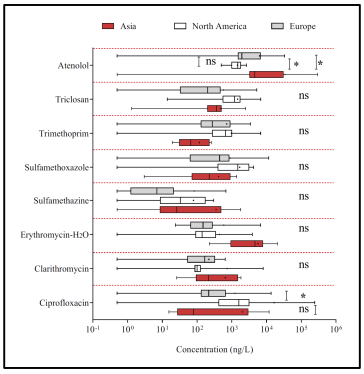
Ecologia degli antibiotici e della resistenza



Resistoma

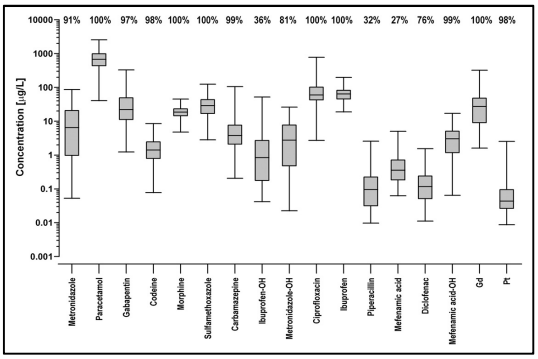
Andersson D.I. & Hughes D., Nature Rev. Microbiol., 12:465 (2014)

Concentrazioni di alcuni contaminanti in acque affluenti di impianti di depurazione in diverse regioni geografiche



Tran N.H. et al., Water Research 133: 182 (2018)

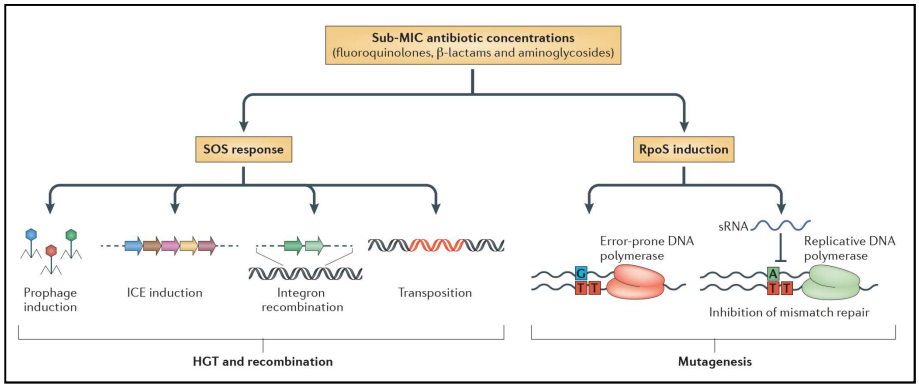
Concentrazioni di alcuni contaminanti in acque effluenti dello stabile principale dei HUG



Daouk S. et al., Sci. total. environ. 547: 244 (2016)

Ma le deboli concentrazioni di antibiotici (<CMI) possono promuovere la resistenza?

Impatto de concentrazioni di antibiotici <CMI sul trasferimento orizzontale di geni (HGT), la ricombinazione e la mutageni



Andersson D.I. & Hughes D., Nature Rev. Microbiol., 12:465 (2014)

Fitness cost!

OXFORD FEMS JOURNALS investing in science

FEMS Microbiology Letters, 363, 2016, fnw034

doi: 10.1093/femsle/fnw034
Advance Access Publication Date: 11 February 2016
Commentary

COMMENTARY – Pathogens & Pathogenicity

Antibiotic resistance: the emergence of plasmid-mediated colistin resistance enhances the need of a proactive one-health approach

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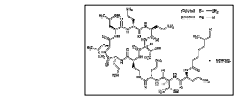
One sentence summary: The recent emergence in Gram-negative bacteria of a transferable gene encoding resistance to colistin, a last resort antibiotic, emphasises the need of a holistic approach to fight antimicrobial resistance.

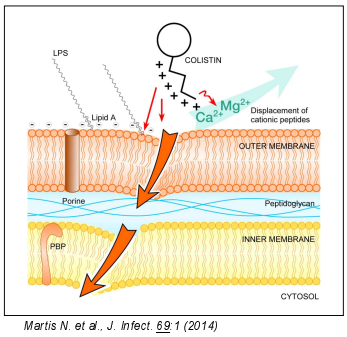
Editor: Arnoud van Vliet

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

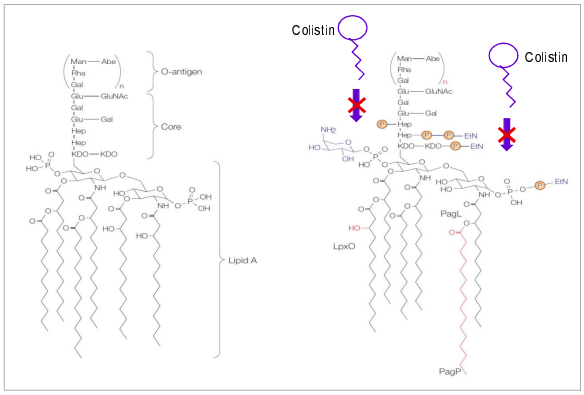
Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*

Liu Y.-Y. et al., Lancet Infect. Dis. 16:161 (2016)

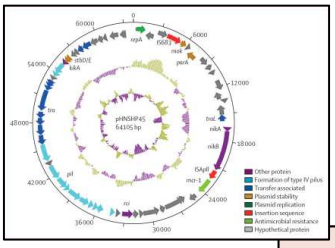




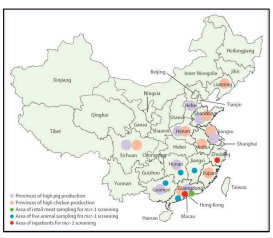
Martis N. et al., J. Infect. 69:1 (2014)



Ex Miller S.I. et al., Nature Rev. Microbiol. 3:36 (2005)



> 40 paesi, 5 continenti!



	Year	Positive isolates (%)/number of isolates
Escherichia coli		
Pigs at slaughter	All	166 (20·6%)/804
Pigs at slaughter	2012	31 (14·4%)/216
Pigs at slaughter	2013	68 (25·4%)/268
Pigs at slaughter	2014	67 (20·9%)/320
Retail meat	All	78 (14·9%)/523
Chicken	2011	10 (4·9%)/206
Pork	2011	3 (6·3%)/48
Chicken	2013	4 (25·0%)/16
Pork	2013	11 (22·9%)/48
Chicken	2014	21 (28·0%)/75
Pork	2014	29 (22·3%)/130
Inpatient	2014	13 (1·4%)/902
Klebsiella pneumoniae		
Inpatient	2014	3 (0·7%)/420

Table 2: **Prevalence of colistin resistance gene *mcr-1* by origin**

Liu Y.-Y. et al., Lancet Infect. Dis. 16:161 (2016)

Search of the plasmid-mediated colistin resistance (*mcr-1* gene)

TABLE

Colistin resistant and mcr-1 positive commensal *Escherichia coli* strains from French livestock, France, 2007–2014

Year	Animals	*E. coli* strains tested for MIC N	*E. coli* strains resistant to colistin N	Proportion of *mcr-1* positive (n) among colistin-resistant *E. coli* strains (N) n/N	Prevalence of *mcr-1* positive *E. coli* strains % (95%CI)
2014	Turkeys	239	14	14/14	5.9 (2.9–8.8)
	Broilers	227	4	4/4	1.8 (0.1–3.5)
2013	Pigs	196	1	1/1	0.5 (0.0–1.5)
	Broiler	193	3	3/3	1.6 (0.0–3.3)
2012	Pigs	194	0	N.a.	N.a.
	Broiler	201	0	N.a.	N.a.
2011	Pigs	200	1	1/1	0.5 (0.0–1.5)
2007	Turkeys	ND[a]	ND[a]	0/246[a]	0 (0.0–1.2)
Total	**All**	**1,450**	**23**	**N.a.[a]**	**N.a.[a]**

Perrin-Guyomard A. et al., Eurosurveillance 21, 11 February 2016

Numbers of extended spectrum beta-lactamase and AmpC-producing E. coli isolates obtained and analysed by WGS from chicken meat, humans and carbapenemase-producing isolates from humans tested for mcr-1 using ResFinder, Denmark, November 2015 (n=914)

Isolate origin	No. of isolates analysed by WGS	No. of sequences positive for *mcr-1*
ESBL- and AmpC-producing *E. coli* isolates from Danish chicken meat (2012–2014)	125	0
ESBL- and AmpC-producing *E. coli* isolates from imported chicken meat (2012–2014)	255	5
ESBL- and AmpC-producing *E. coli* isolates from human bloodstream infections (January 2014– beginning of November 2015)	417	1
Carbapenemase-producing isolates from humans (January 2014– beginning of November 2015)	117	0

Hasman H. et al., Eurosurveillance 20, 10 December 2015

UK: >24'000 Gram-negative genome sequences:
- 10 *Salmonella* human isolates
- 2 *Salmonella* Para B poultry isolates
- 3 *E. coli* human isolates

Public Health England, 2015

Asia (China, Malaysia, Thailand, Laos, Vietnam)
Americas (Canada)
Africa (Algeria)
Europe (DK, D, F, NE, CH, BE, UK)

Origin of the isolates	N isolates with the *mcr-1* gene
74 ESBL* *Enterobacteriaceae* from 21 Swiss rivers and lakes	1
60 ESBL* *Enterobacteriaceae* from imported vegetables (India, Thailand, Vietnam)	2

	Strain OW3E1	Strain H226B	Strain 2SK1
Sample type	River water sampled in Switzerland	Cha-om imported from Thailand	Basil leaves imported from Vietnam
Year	2012	2014	2014
Species	*E. coli*	*E. coli*	*E. coli*
Phylogroup	B1	A	B1
Sequence type	ST359	ST167	ST4683
bla_{ESBL}	SHV-12	CTX-M55	CTX-M-65
MIC for colistin (μg/mL)	6	6	6
AM	R	R	R
AMC	S	S	R
CF	R	R	R
CTX	R	R	R
CIP	R	R	R
GM	S	R	R
TE	R	R	R
S	R	R	R
C	R	S	R
K	S	R	S
NA	R	R	R
SMZ	R	R	R
TMP	R	S	R

ampicillin(AM), amoxicillin-clavulanic acid (AMC), cephalothin (CF), cefotaxime (CTX), ciprofloxacin (CIP), gentamicin (GM), tetracycline (TE), streptomycin (S), chloramphenicol (C), kanamycin (K), nalidixic acid (NA), sulfamethoxazole (SMZ), and trimethoprim (TMP)
R: resistant, S: susceptible

Zurfuh K. et al., Antimicrob. Agents Chemother., 16 February 2016

Distribuzione geografica del gene *mcr-1*

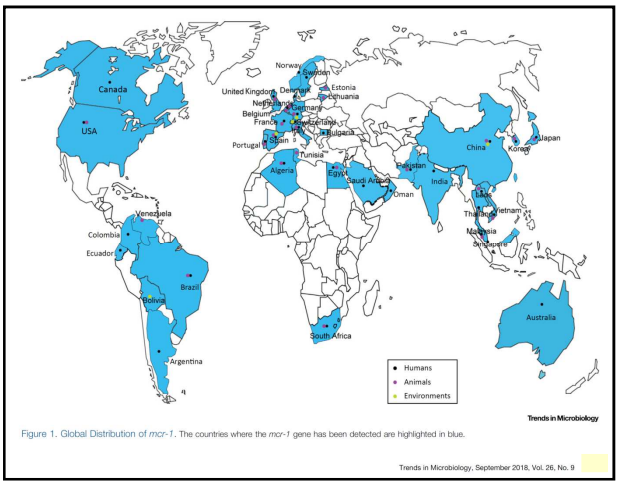
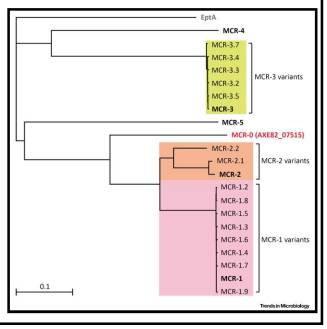


Figure 1. Global Distribution of *mcr-1*. The countries where the *mcr-1* gene has been detected are highlighted in blue.

Trends in Microbiology, September 2018, Vol. 26, No. 9

Sun J. et al, Trends Microbiol. 26:794 (2018)

Filogenia dei varianti dell'enzima mcr



Alcune misure da attuare: un approccio One-Health

- Aumento delle conoscenze sui potenziali serbatoi dei geni di resistenza e dell'efficienza della loro trasmissione
- Scoperta di nuove molecole antibatteriche
- Sviluppo di tecniche rapide di diagnosi
- Sviluppo di misure d'intervento (prevenzione) efficienti

→ **Migliore gestione degli antibiotici / Diminuzione del consumo di antibiotici**

What Switzerland is doing

1999	Ban of antibiotics as feed additives (growth promoters)
2001	NRP 49 “Antibiotic Resistance” (CHF 12 millions)
2015	StAR (Strategy on Antibiotic Resistance)
2015	NRP 72 “Antibiotic Resistance: a one-health approach” (CHF 20 millions)
2017	World Antibiotic Awareness Week (WHO)
2017	RT on Antibiotics: Appeal by science and industry to make more effective use of Switzerland's innovative capacity to fight antibiotic resistance and to develop new antibiotics

Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)

New Drugs for Bad Bugs" (ND4BB)

DRIVE-AB (Driving reinvestment in R&D for antibiotics and advocating their responsible use)

WHO's "Global Action Plan on Antimicrobial Resistance"

etc.

La Strategia contro le resistenze agli antibiotici (StAR) ha l’obiettivo di assicurare a lungo termine l’efficacia degli antibiotici. Nella sua attuazione sono coinvolti l’uomo, gli animali e l’ambiente. L’USAV è responsabile delle misure che interessano gli animali.

Approccio One-heath: 4 settori che interagiscono (umano, animale, agricolo, ambientale)

Grazie per l’attenzione!