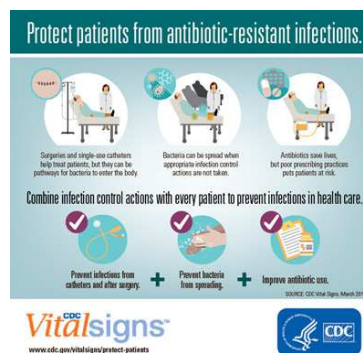


Prevenzione delle resistenze negli ospedali

Enos Bernasconi

Servizio Malattie Infettive
Dipartimento di medicina
Lugano e Ginevra

Manno, 08 novembre 2018



- Note introduttive
- Caso clinico recente
- Depistaggio e prevenzione
- Studio COMPASS
- Conclusione



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Chiaramente gli antibiotici fanno la differenza



Koch

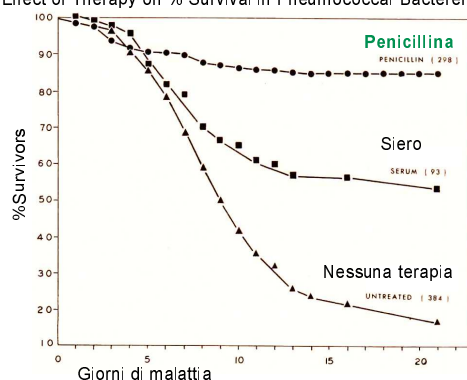


Fleming



Ehrlich

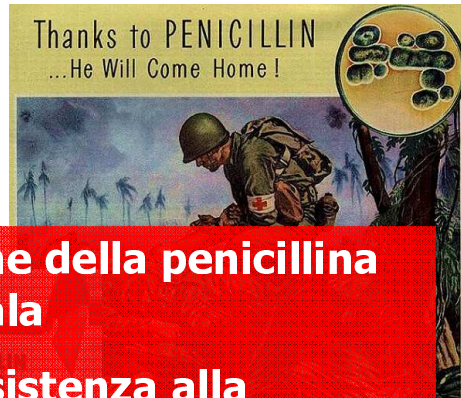
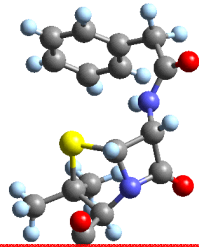
Effect of Therapy on % Survival in Pneumococcal Bacteremia



Austrian & Gold. Ann Int Med 60:759, 1964



Penicillina (Fleming, 1928)



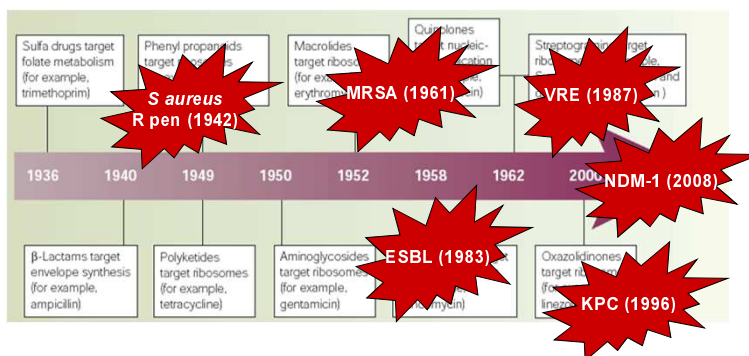
- 1945 distribuzione della penicillina su larga scala
- 1946 Tasso di resistenza alla penicillina, *S. aureus* = 6%



The collage features several headlines related to antibiotic resistance:

- The Washington Post:** "Superbug" stalked NIH hospital last year
- MailOnline:** MRSA found in our milk: Superbug strain can cause serious infections in humans is resistant to antibiotics
- Le Matin:** LES ANTIBIOTIS BIEN TÔT INUTILES (Antibiotics soon useless)
- The Scientist:** Superbug Sickens Dozens in Illinois

La «linea temporale» degli antibiotici



Walsh (2003). Nat Rev Microbiol 1:65-70



La vera «linea del tempo» degli antibiotici

- Homo sapiens*
0.2 milioni di anni
- Daptomicina**
30 milioni di anni
- Vancomicina**
240 milioni di anni
- Streptomicina**
610 milioni di anni
- Eritromicina**
880 milioni di anni
- Beta-lattamasi**
> 2 miliardi di anni



Wright (2007), Nat Rev Microbiol /Hall et Barlow (2004), Drug Resist Updat



The Shared Antibiotic Resistome of Soil Bacteria and Human Pathogens

Kevin J. Forsberg,^{1*} Alejandro Reyes,^{1*} Bin Wang,^{1,2} Elizabeth M. Selleck,³
Morten O. A. Sommer,^{4,5}† Gautam Dantas^{1,2}†

Soil microbiota represent one of the ancient evolutionary origins of antibiotic resistance and have been proposed as a reservoir of resistance genes available for exchange with clinical pathogens. Using a high-throughput functional metagenomic approach in conjunction with a pipeline for the de novo assembly of short-read sequence data from functional selections (termed PARFuMS), we provide evidence for recent exchange of antibiotic resistance genes between environmental bacteria and clinical pathogens. We describe multidrug-resistant soil bacteria containing resistance cassettes against five classes of antibiotics (β -lactams, aminoglycosides, amphenicols, sulfonamides, and tetracyclines) that have perfect nucleotide identity to genes from diverse human pathogens. This identity encompasses noncoding regions as well as multiple mobilization sequences, offering not only evidence of lateral exchange but also a mechanism by which antibiotic resistance disseminates.

Forsberg et al. *Science*. 2012 Aug 31;337(6098):1107-11



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Alte Frau, 1925

- Residente a Stoccarda in vacanza a Morcote
- Pronto Soccorso: stato febbrile, sospetta infezione delle vie urinarie
- 3 settimane prima **ricovero in un ospedale di Stoccarda**
 - Escissione di 2 carcinomi squamocellulari alle gambe
 - A destra infezione cutanea, prescrizione di **ciprofloxacina e co-amoxicillina**

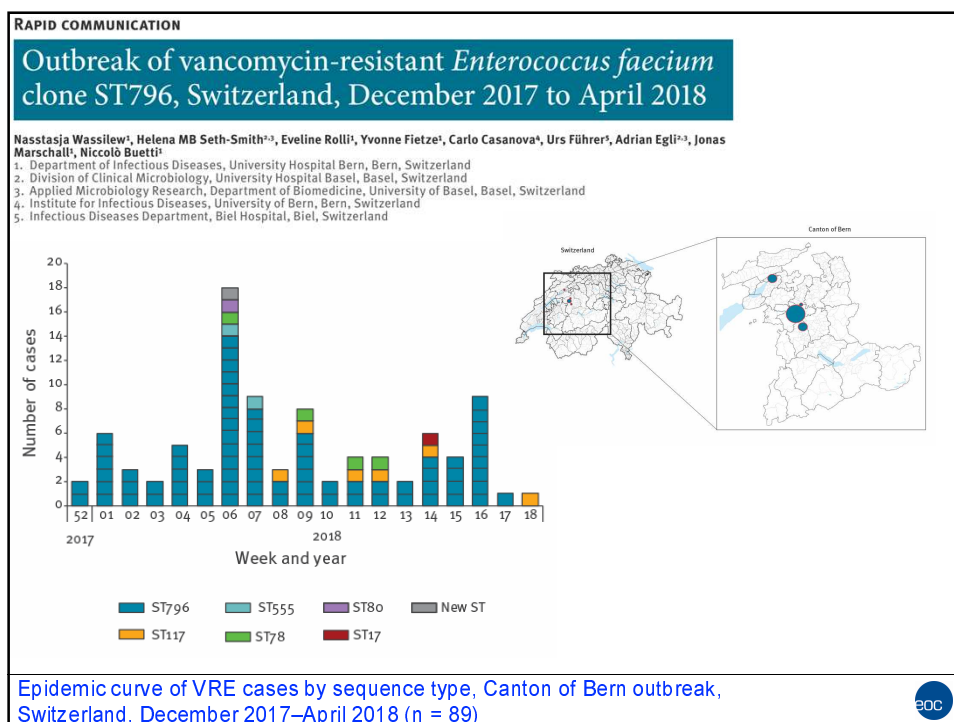
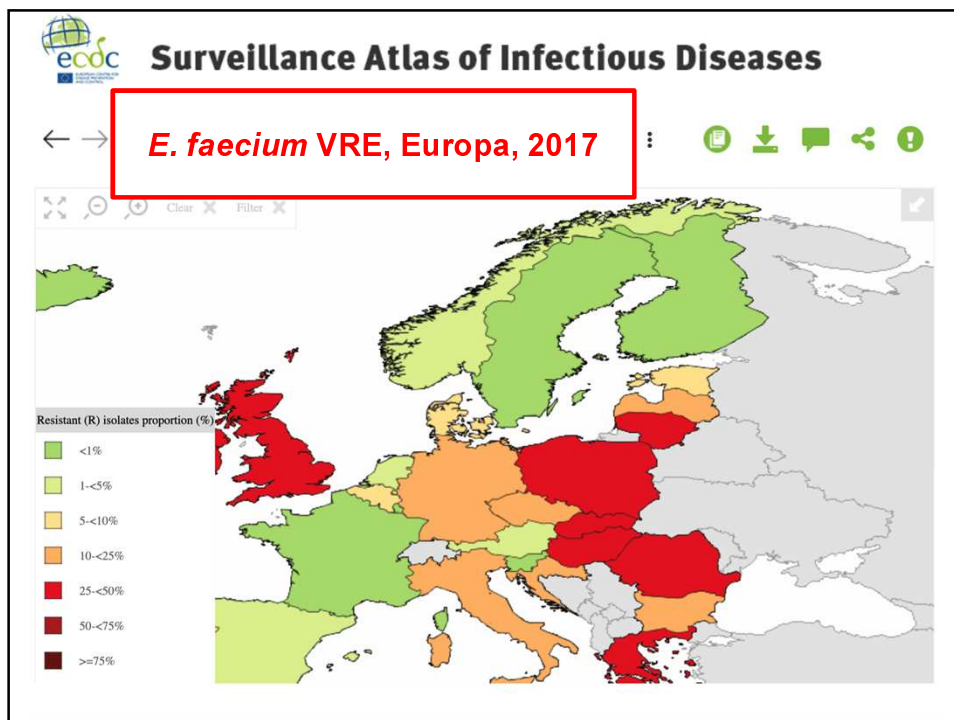
Siete preoccupati per un eventuale rischio epidemiologico?



La «sorpresa» nello striscio ferita

- **Screening VRE: POSITIVO** (*E. faecium* Van B)
- **Screening ESBL: POSITIVO** (*E. coli* ESBL)
- **Screening CRE: NEGATIVO**, ma **P. aeruginosa multiresistente** (S solo amicacina e colistina)

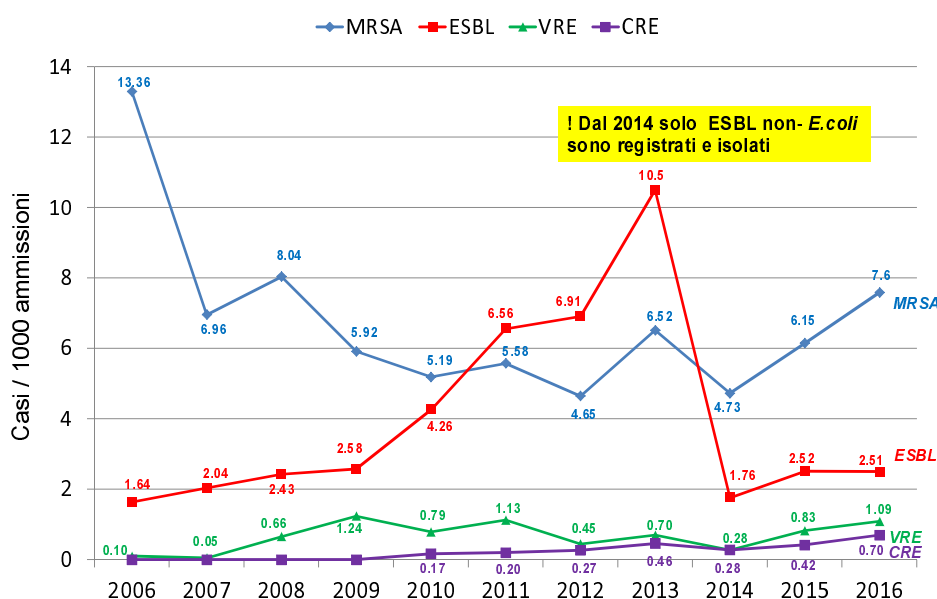




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Incidenza germi multiresistenti (EOC)





Misure di depistaggio e controllo dei germi multiresistenti (MR)

- Screening pazienti a rischio (**diapositiva screening**)
- Pazienti portatori di MDR:
(ad es. MRSA, VRE, ESBL-non *E.coli*, CRE):
 - Precauzioni contatto/ ev. goccioline
- Sistema di allerta informatico per pazienti MR

Nome anagra	Unità	Tagliati	17.09.18 07.27 REG.11	11.09.18 18.11 PG REG.12	04.10.18 21.05 PG REG.12
Dato	mmHg	136 - 146	139	138	137
Frequenza	mmHg	3,5 - 5,1	4,0	4,0	4,0
Giorno	mmHg	4,1 - 6,1		5,5	6,4
Ura	mmHg	2,0 - 6,1	3,2	4,4	5,5
Cholesterol	mg/dL	61 - 100	66	66	59
GPA (Formula DSD EPD)	mg/dL	> 60	58	43	
Cl	mg/L	< 180			102
Cl-crea	mg/L	< 1,4			1
Tropomina I	mg/L	< 0,09			0,02
Proteina Creativita (COP)	mg/L	< 5	6	29	
ALAT (GPT)	mg/L	10 - 39			12
Proteina sierica	mg/L	100 - 1300			63

Cortesia C. Balmelli



Misure di depistaggio e controllo dei germi multiresistenti (MR) - 2

- **Investigazione dei contatti (stessa camera)**
 - Se ≥ 3 casi: annuncio UMC
 - Se > 5 casi info a Swissnoso
- **Set di screening di controllo per dichiarare il paziente negativo (2-5)**
- **Segnalazione germi MR (lettera di dimissione)**

Cortesia C. Balmelli



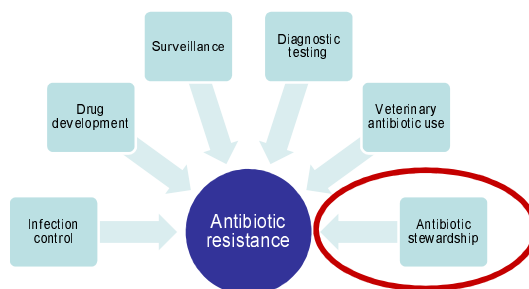
Screening pazienti a rischio MR (MRSA, VRE, ESBL-non *E. coli*, CRE)

- Se possibile isolamento preventivo in attesa dei risultati
- Pazienti trasferiti da un ospedale estero
- Pazienti ricoverati in un ospedale estero negli ultimi 6-12 mesi (implementazione difficile)
- Pazienti noti in passato per uno dei germi MR
- Pazienti che sono oggetto di un indagine di contatto (in camera con paziente risultato MR+)

Cortesia C. Balmelli



Lotta alle resistenze microbiche



Laxminarayan et al. Lancet Infect Dis. 2013 Dec;13(12):1057-98



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The goals of antibiotic stewardship

Antibiotic stewardship seeks to achieve optimal clinical outcomes... and limit the selection of antimicrobial resistance”



http://www.idsociety.org/stewardship_policy




Policy statement on antimicrobial stewardship (SHEA, IDSA, PIDS), 2012

Antimicrobial stewardship refers to coordinated interventions designed to improve and **measure the appropriate use of antimicrobials**....


... by promoting the selection of **the optimal antimicrobial drug regimen, dose, duration of therapy**, and route of administration.

http://www.idsociety.org/stewardship_policy





Antimicrobial Resistance
National Research Programme
A one-health approach



COMPASS

COMPUterized Antibiotic Stewardship Study

Background



Antimicrobial Resistance
National Research Programme
A one-health approach


Call for proposals

Module 1: Potential reservoirs and mechanisms of transmission

Module 2: Rapid diagnostic techniques, novel antimicrobial molecules

Module 3: Implementation measures and public health recommendations...

Stratégie Antibiorésistance



StAR

Utilisation optimisée des antibiotiques

Utilisés à mauvais escient ou de manière excessive, les antibiotiques favorisent le développement de résistances. De nouveaux processus et aides à la décision doivent permettre aux médecins, vétérinaires et agriculteurs d'en faire un usage plus ciblé.

Projets approuvés

Procalcitonin and lung ultrasonography point-of-care testing to decide on antibiotic prescription in patients with lower respiratory tract infection at primary care level: cluster randomised trial
Dr. Noémie Bollat Blanco, Université de Lausanne


Routine antibiotic prescription and resistance monitoring in primary care physicians: A nationwide pragmatic randomized controlled trial
Prof. Heiner C. Bucher, Universität Basel


Improvement of antibiotic use in hospitals through pragmatic, multifaceted, computerized interventions: a multicentre cluster-randomized trial
Dr. Benedikt Huttner, Université de Genève

Potentials of incentive-based instruments to an animal-friendly reduction of antibiotics usage
Dr. Stefan Mann, Forschungsanstalten Agroscope

A novel concept for veal calf production: "the outdoor veal calf"
Prof. Mireille Meylan, Universität Bern

AntibioticScout: Online tool for antimicrobial stewardship in veterinary medicine
Prof. Hanspeter Naegeli, Universität Zürich

Impact of routine audit and feedback on the use of protected antibiotics: a multicenter, randomized trial
Dr. Laurence Senn, Université de Lausanne 



Problems with existing antibiotic stewardship interventions

- Resource intensive
- Cover often only a minority of antibiotic prescriptions
- Often limited to regular work hours
- Are often “back-end” interventions
 - i.e. occurring after the prescription (and the potential damage) has been made



Problems with existing antibiotic stewardship interventions

Informatics-based interventions: a potential solution ?

- Resource intensive
 - in the long run probably cheaper than “manual” interventions => sustainability
- Cover often only a minority of antibiotic prescriptions
 - Can cover a large proportion of prescriptions
- Often limited to regular work hours
 - Available 7/7 - 24/24
- Are often “back-end” interventions
 - Can be “front-end”

Generalizability?

Unintended consequences ?

*Acceptability by prescribers
(physician autonomy) ?*

Few high-quality studies



Open-label, parallel-group, cluster randomized superiority trial

Study question: "Can overall antibiotic exposure in hospitalized patients be reduced through a multimodal computerized antibiotic stewardship intervention?"

Population	<p>Adult patients hospitalized in acute-care wards of three secondary and tertiary care centers</p> <p>Physicians prescribing antimicrobials for these patients</p>
Intervention	<p>Multimodal, computerized antibiotic stewardship intervention</p> <ul style="list-style-type: none"> implemented on the ward level
Control	" Standard-of-care " antibiotic stewardship
Outcome	<p>Overall antibiotic exposure</p> <ul style="list-style-type: none"> measured in days of therapy per admission
Time	12 months



Benedikt HUTTNER
(antibiotic stewardship)



Enos BERNASCONI
(ID & internal medicine)



Stephan HARBARTH
(antibiotic stewardship)



Rodolphe MEYŠER
(Informatics)



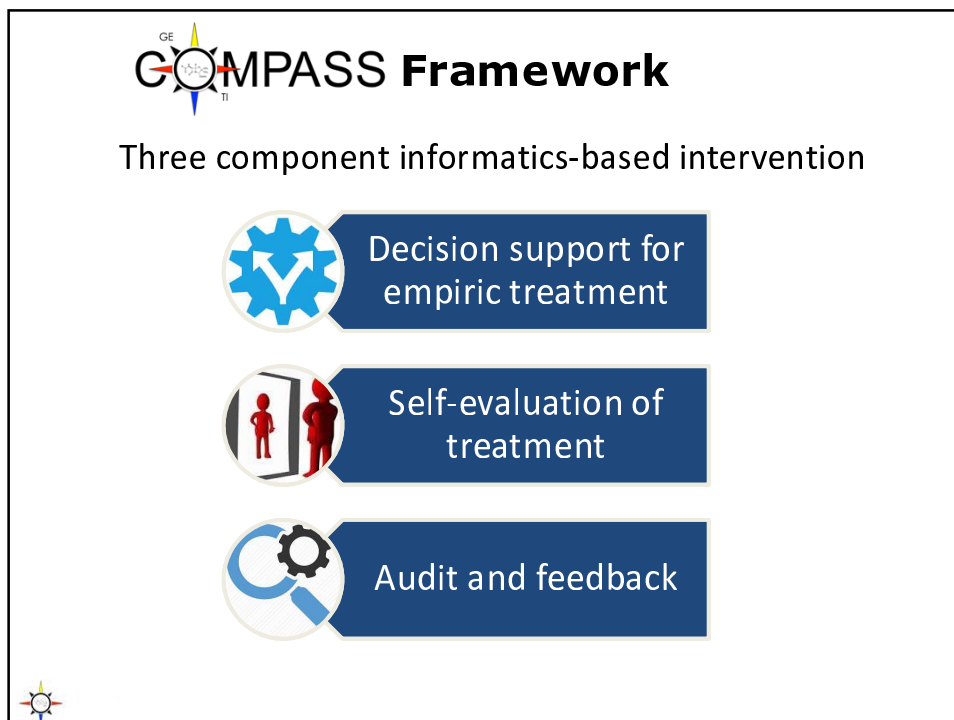
Laurent KAISER
(infectious diseases)


Study site	acute-care beds	admissions to medicine/surgery wards per year	approximate overall antibiotic use (DDD/100 PD)
(1) HUG	1'100	about 26'000	59
(2) ORL	306	about 8'000	50
(3) OSG	229	about 6'000	42



DDD: defined daily doses
PD: patient-days





(1) Decision support for empiric treatment 



A- Selezione del tipo di trattamento

Terapia antibiotica




empirico
mirato
profilassi chirurgica
profilassi medica

Nuovo episodio

Diagnosi...

La resistenza aux antimicrobians
Programme national de recherche

Hôpitaux
Universitaires
Genève

(1) Decision support for empiric treatment

B- Inserimento dell'indicazione della terapia antibiotica

Co-Amoxi Mepha 2200 mg flac
(amoxicillin (2000 mg) + clavulanic acid (200 mg))

Combinazione Riserva Condizionale Pre-op Post-op

Terapia antibiotica

empirico mirato profilassi chirurgica profilassi medica

Nuovo episodio

Polmonite extraospedaliere
ricovero in reparto

Data inizio episodio infettivo Data

Raccomandazioni



(1) Decision support for empiric treatment

C- Supporto decisionale per la terapia antibiotica

Clindamycin Pfizer 300 mg caps
(clindamycin)

Combinazione Riserva Condizionale Pre-op Post-op

Terapia antibiotica

empirico mirato profilassi chirurgica profilassi medica

Nuovo episodio

Episodio 1 dal 09.04.2018
Piele diabetico infetto
con segni di gravità o ulcera da decubito

Aggiorna diagnosi episodio...

Data inizio episodio infettivo dal: 09.04.2018

Raccomandazioni

Durata	Parenterale	Enterale
7-X giorni	ertapenem i.v. 1g 1x/die	ciprofloxacina per os o SNG 500-750mg 1x/12h + clindamicina per os o SNG 300mg 1x/6h

Misure particolari



(2) Accountable justification



Fornire una giustificazione in caso di deviazione dalle raccomandazioni

Farmaco e/o via prescritti non corrispondono alle raccomandazioni

Giustificazione

- Secondo antibiogramma/diagnosi microbiologica
- Colonizzazione da germe multiresistente
- Germe resistente alla terapia raccomandata
- Altra raccomandazione da parte dell'infettivologo
- Intolleranza, allergia e/o altre controindicazioni
- Immunosoppressione
- Terapia orale non possibile
- Recente terapia antibiotica



72 La resistenza aux antibiotiques
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Genève

(2) Self-evaluation of treatment (72h)



Rivalutazione (microbiologia?) e durata del trattamento

Cu-Amoxi Mepha 1200 mg fac. 1200 1200 0 1200 [99%] [5] [4] [28/10/2018]

+ NaCl 0,9% 50 50 0 50 [99%]

Esplorazione [1]

STOP

Raccomandazioni	Parenterale	Enterale
Durata	5-15 giorni	
	amoxicillina/clav. Lv. 1200-2200mg 1x12h +/- claritromicina Lv. 500mg 1x12h	amoxicillina/clav per os 1000mg 1x12h +/- claritromicina per os 500mg 1x12h o amoxicillina/clav per os 625mg 1x12h +/- claritromicina per os 500mg 1x12h o ceftriaxone per os 500mg 1x12h +/- claritromicina per os 500mg 1x12h o levofloxacina per os 750mg 1x12h o moxifloxacina per os 400mg 1x12h

Misure particolari
Diagnostica: antigene urinario per legionella e pneumococco; se antigene legionella negativo: considerare stop claritromicina. Eseguire Gram/batteriologia esportato se materiale rappresentativo; emocolture, eventualmente PCR multiplex germi respiratori (soprattutto se paziente immunocompromesso). Durata terapia pneumonia batterica 10-15 giorni (prima di interrompere il paziente deve essere asintomatico da almeno 2 giorni o PCR = 1/3 valore iniziale; se polmonite da S.aureus/Gram negativo: 14 giorni; se polmonite atipica: 10-14 giorni; se polmonite da Legionella: 14-21) giorni.

La durata non corrisponde alle raccomandazioni

Giustificazione

- Altra raccomandazione da parte dell'infettivologo
- Durata minima raccomandata non sufficiente
- Immunosoppressione
- Persistenza del focolaio infettivo

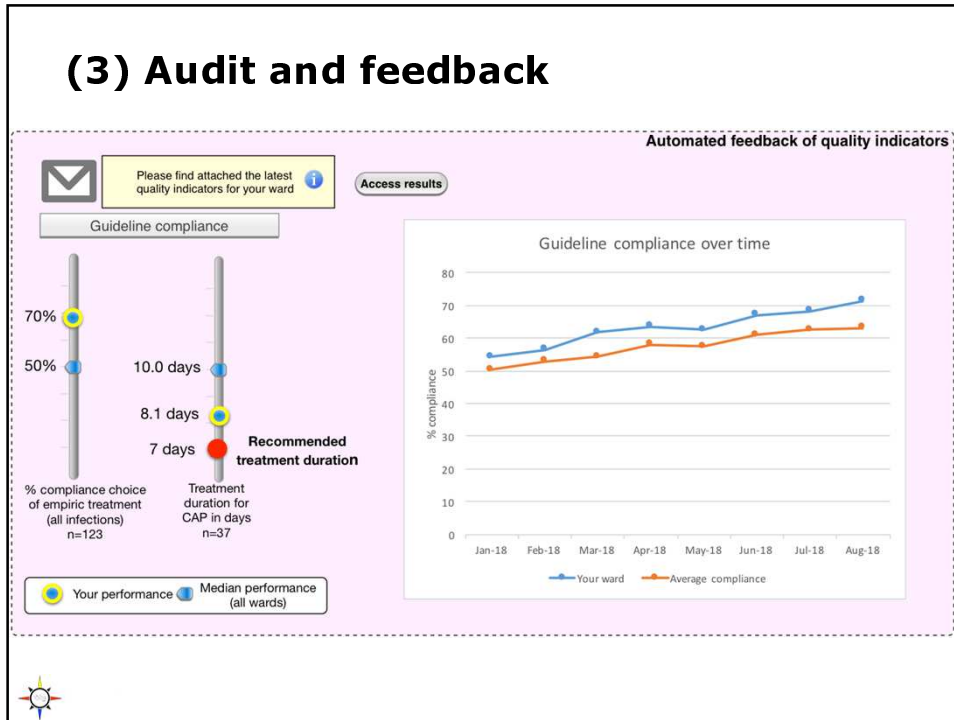


72 La resistenza aux antibiotiques
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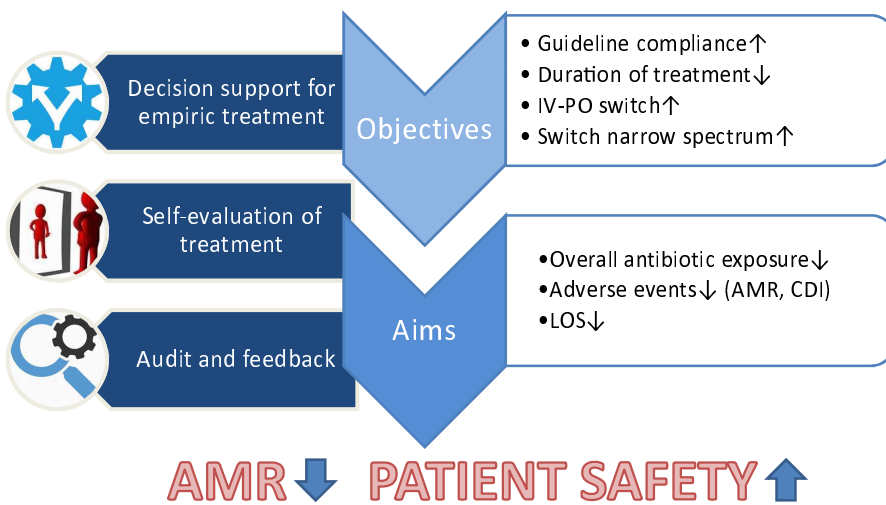


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(3) Audit and feedback



GE COMPASS Framework



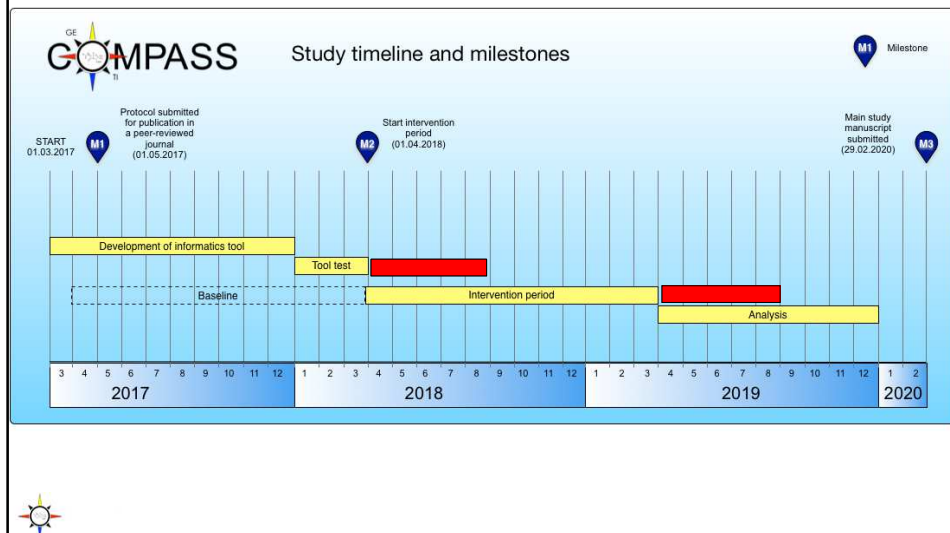
Randomization scheme



PRIMARY OUTCOME

- Systemic antibiotic treatment in days of therapy by admission
 - Objective
 - Reliably and objectively assessable in both intervention and control group
 - Ability to detect a meaningful difference given the achievable sample size

Timeline



BMJ Journals

Open access

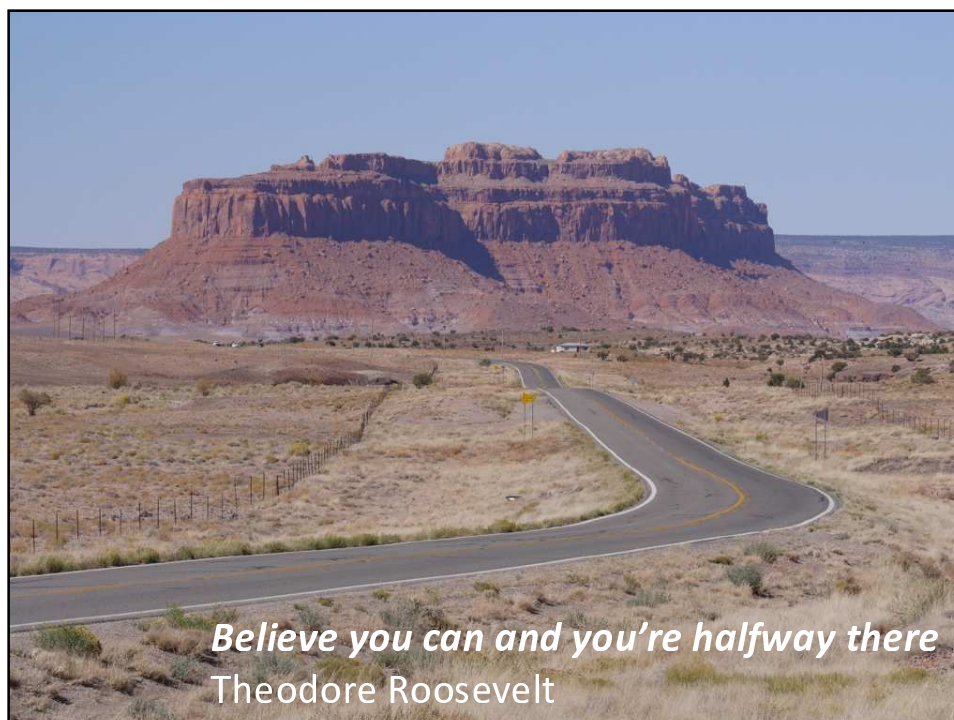
Protocol

BMJ Open Study protocol for a multicentre, cluster randomised, superiority trial evaluating the impact of computerised decision support, audit and feedback on antibiotic use: the COMPuterized Antibiotic Stewardship Study (COMPASS)

Gaud Catho,¹ Marlieke De Kraker,² Brigitte Waldispühl Suter,³ Roberta Valotti,⁴ Stephan Harbarth,^{1,2} Laurent Kaiser,¹ Luigia Elzi,⁵ Rodolphe Meyer,⁶ Enos Bernasconi,⁴ Benedikt D Huttner^{1,2}

BMJ Open, 27 June 2018

Grazie di cuore al Dr. Carlo Balmelli e al team COMPASS!



Believe you can and you're halfway there
Theodore Roosevelt