Le concept "Antibiotic stewardship"

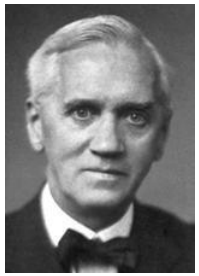
Enos Bernasconi

Service de maladies infectieuses
Departement de medicine
Lugano et Genève

Bellinzona, 9 novembre 2017

Clairement, les antibiotiques font une différence

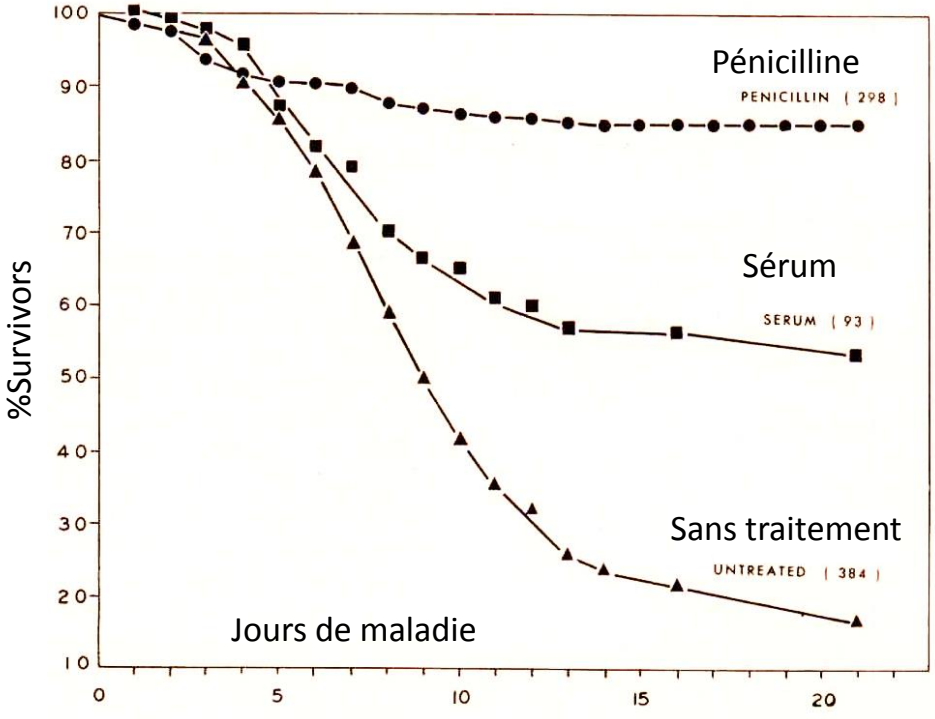
Koch



Fleming

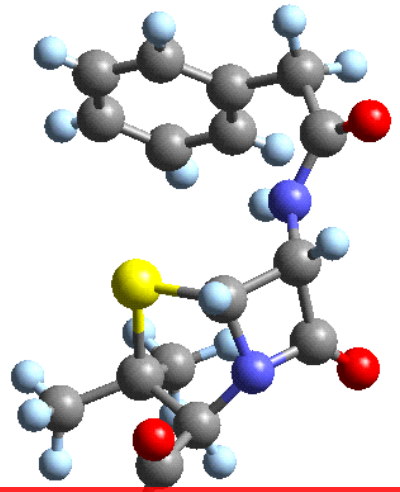
Ehrlich

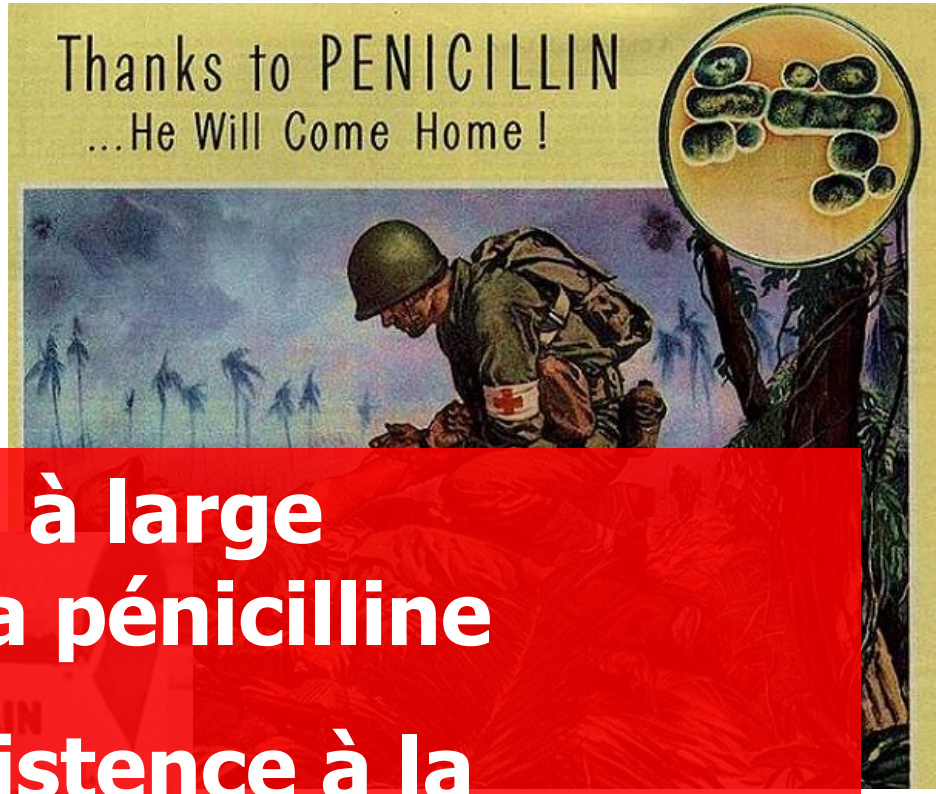
Effect of Therapy on % Survival in Pneumococcal Bacteremia



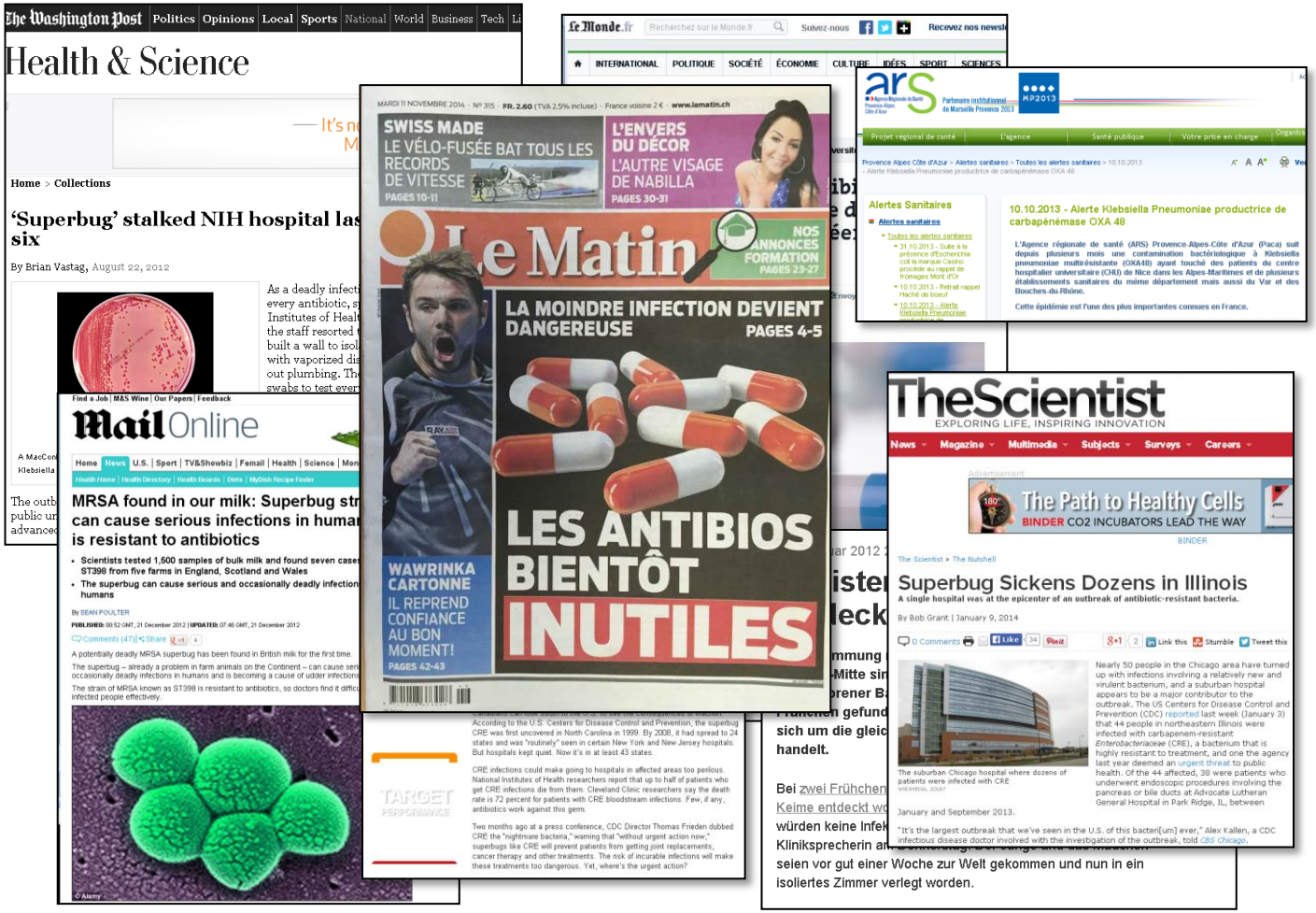
Austrian & Gold. Ann Int Med 60:759, 1964

Pénicilline (Fleming, 1928)





- 1945 Distribution à large échelle de la pénicilline
- 1946 Taux de resistence à la pénicilline, *S. aureus* = 6%



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Health & Science

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‘Superbug’ stalked NIH hospital las
six

By Brian Vastag, August 22, 2012

Le Monde.fr

INTERNATIONAL | POLITIQUE | SOCIÉTÉ | ÉCONOMIE | CULTURE | IDÉES | SPORT | SCIENCES

ars — Agence Régionale de Santé Provence-Alpes-Côte d'Azur — Partenaire institutionnel de Marseille Provence 2013

Projet régional de santé | L'agence | Santé publique | Votre prise en charge

Alertes Sanitaires

10.10.2013 - Alerte Klebsiella Pneumoniae productrice de carbapénémase OXA 48

L'Agence régionale de santé (ARS) Provence-Alpes-Côte d'Azur (Paca) suit depuis plusieurs mois une contamination bactériologique à Klebsiella pneumoniae multirésistante (OXA48) ayant touché des patients du centre hospitalier universitaire (CHU) de Nice dans les Alpes-Maritimes et de plusieurs établissements sanitaires du même département mais aussi du Var et des Bouches-du-Rhône.

Cette épidémie est l'une des plus importantes connues en France.

MARDI 11 NOVEMBRE 2014 · Nº 315 · FR. 2.60 (TVA 2,5% inclus) · France voisine 2 € · www.lematin.ch

SWISS MADE
LE VÉLO-FUSÉE BAT TOUS LES RECORDS DE VITESSE
PAGES 10-11

L'ENVERS DU DÉCOR
L'AUTRE VISAGE DE NABILLA
PAGES 30-31

Le Matin

NOS ANNONCES FORMATION
PAGES 23-27

LA MOINDRE INFECTION DEVIENT DANGEREUSE
PAGES 4-5

LES ANTIBIOS BIENTÔT INUTILES

WAWRINKA CARTONNE
IL REPREND CONFIANCE AU BON MOMENT!
PAGES 42-43

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MRSA found in our milk: Superbug str
can cause serious infections in humar
is resistant to antibiotics

- Scientists tested 1,500 samples of bulk milk and found seven case ST398 from five farms in England, Scotland and Wales
- The superbug can cause serious and occasionally deadly infection humans

By SEAN POULTER

PUBLISHED: 00:52 GMT, 21 December 2012 | UPDATED: 07:46 GMT, 21 December 2012

Comments (47) | Share

A potentially deadly MRSA superbug has been found in British milk for the first time.

The superbug – already a problem in farm animals on the Continent – can cause seri occasionally deadly infections in humans and is becoming a cause of udder infection

The strain of MRSA known as ST398 is resistant to antibiotics, so doctors find it diffic infected people effectively.

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The Path to Healthy Cells
BINDER CO2 INCUBATORS LEAD THE WAY

BINDER

The Scientist » The Nutshell

Superbug Sickens Dozens in Illinois

A single hospital was at the epicenter of an outbreak of antibiotic-resistant bacteria.

By Bob Grant | January 9, 2014

0 Comments | Like 34 | Pinit | +1 2 | Link this | Stumble | Tweet this

The suburban Chicago hospital where dozens of patients were infected with CRE

WIKIMEDIA, JOHN7

Nearly 50 people in the Chicago area have turned up with infections involving a relatively new and virulent bacterium, and a suburban hospital appears to be a major contributor to the outbreak. The US Centers for Disease Control and Prevention (CDC) reported last week (January 3) that 44 people in northeastern Illinois were infected with carbapenem-resistant *Enterobacteriaceae* (CRE), a bacterium that is highly resistant to treatment, and one the agency last year deemed an urgent threat to public health. Of the 44 affected, 38 were patients who underwent endoscopic procedures involving the pancreas or bile ducts at Advocate Lutheran General Hospital in Park Ridge, IL, between January and September 2013.

"It's the largest outbreak that we've seen in the U.S. of this bacter[um] ever," Alex Kallen, a CDC infectious disease doctor involved with the investigation of the outbreak, told *CBS Chicago*.

According to the U.S. Centers for Disease Control and Prevention, the superbug CRE was first uncovered in North Carolina in 1999. By 2008, it had spread to 24 states and was "routinely" seen in certain New York and New Jersey hospitals. But hospitals kept quiet. Now it's in at least 43 states.

CRE infections could make going to hospitals in affected areas too perilous. National Institutes of Health researchers report that up to half of patients who get CRE infections die from them. Cleveland Clinic researchers say the death rate is 72 percent for patients with CRE bloodstream infections. Few, if any, antibiotics work against this germ.

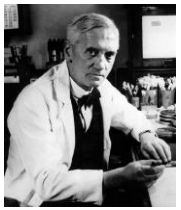
Two months ago at a press conference, CDC Director Thomas Frieden dubbed CRE the "nightmare bacteria," warning that "without urgent action now," superbugs like CRE will prevent patients from getting joint replacements, cancer therapy and other treatments. The risk of incurable infections will make these treatments too dangerous. Yet, where's the urgent action?

TARGET PERFORMANCE

Bei zwei Frühchen
Keime entdeckt wo
würden keine Infek
Kliniksprecherin ar
seien vor gut einer Woche zur Welt gekommen und nun in ein isoliertes Zimmer verlegt worden.

sich um die gleic
handelt.

L'histoire des antibiotiques et l'histoire de la résistance bactérienne



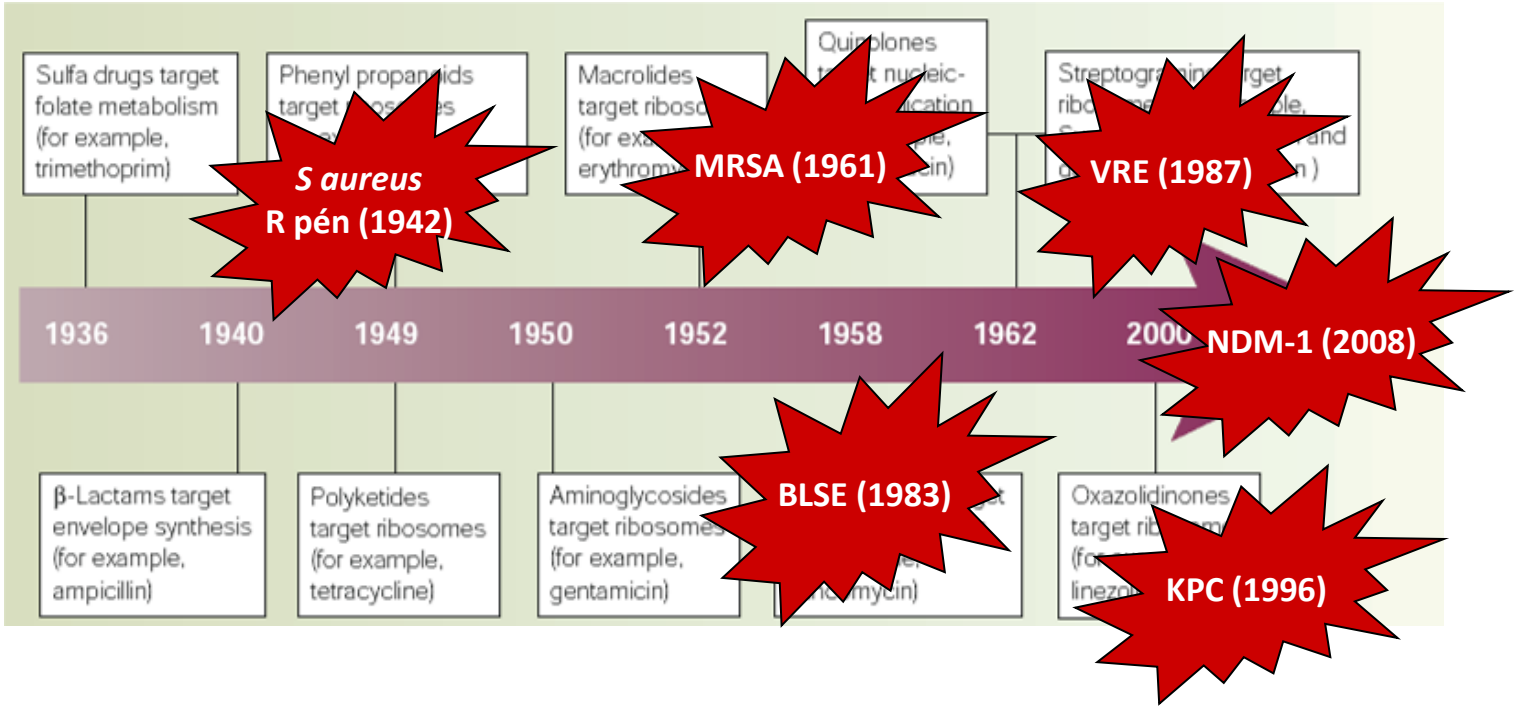
- "There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

- "Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin."

- "He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies."

Alexander Fleming, Nobel Lecture, December 11, 1945

La ligne du temps des antibiotiques



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

La vraie ligne du temps des antibiotiques

Homo sapiens
0.2 millions d'années

Daptomycine
30 millions d'années

Vancomycine
240 millions d'années

Streptomycine
610 millions d'années

Erythromycine
880 millions d'années

Béta-lactamases
> 2 millards d'années

Wright (2007), Nat Rev Microbiol 5:175-186/Hall et Barlow (2004), Drug Resist Updat 7:111–23

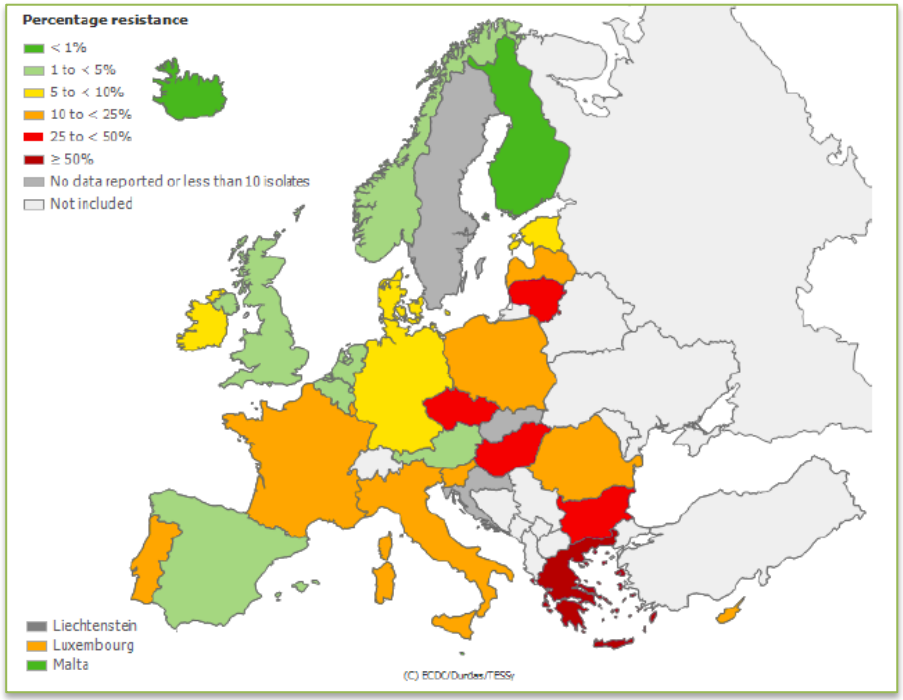
The Shared Antibiotic Resistome of Soil Bacteria and Human Pathogens

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†]

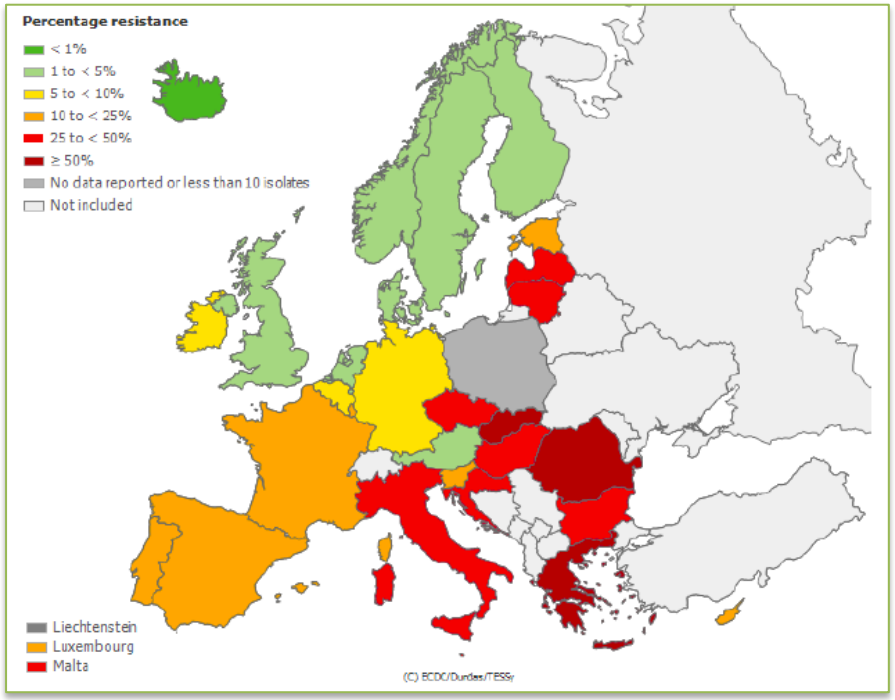
Soil microbiota represent one of the ancient evolutionary origins of antibiotic resistance and have been proposed as a reservoir of resistance genes available for exchange with clinical pathogens. Using a high-throughput functional metagenomic approach in conjunction with a pipeline for the de novo assembly 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

Klebsiella pneumoniae, R to 3$^{gen.}$ cephalosporins, fluoroquinolones, aminoglycosides

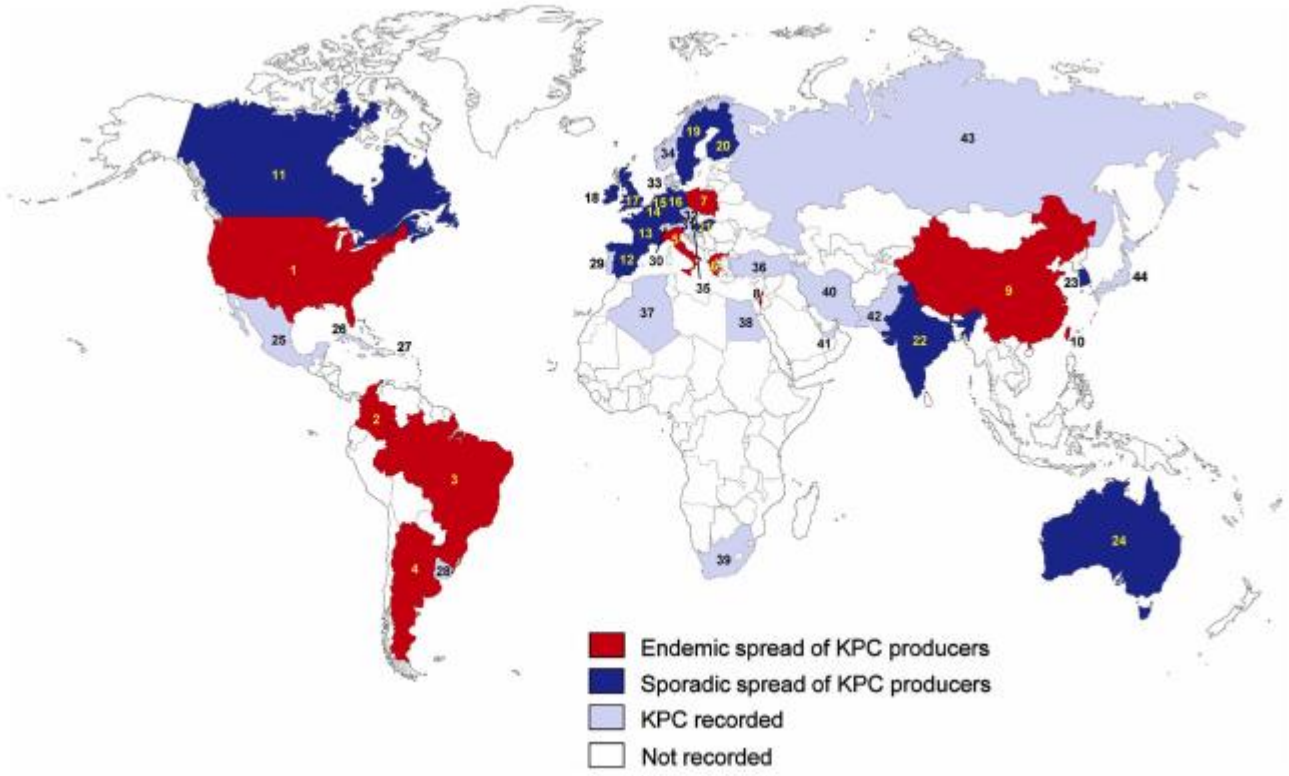


2009



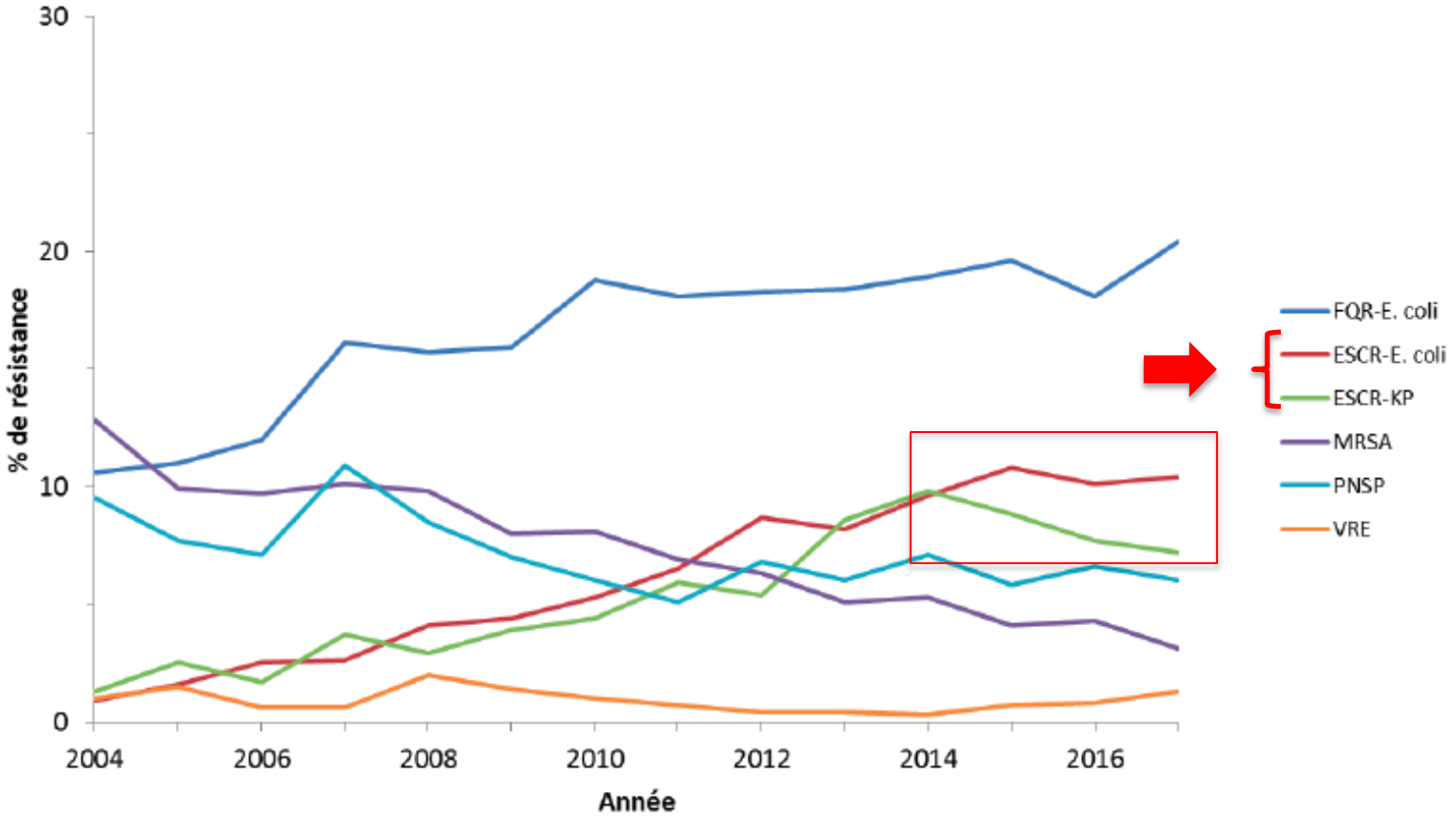
2014

Global Dissemination of Carbapenemase-Producing *Klebsiella pneumoniae*



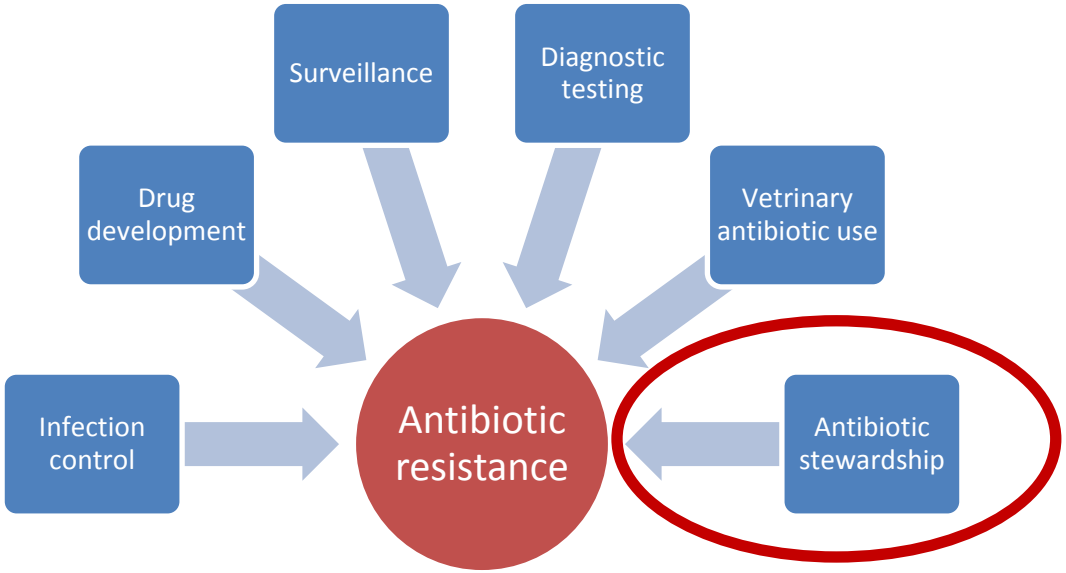
Lee et al. Front Microbiol. 2016 Jun 13;7:895

Steady increase of *E.coli* and *K. pneumoniae* ESBL in Switzerland



PREVENTION
IS BETTER
THAN
CURE

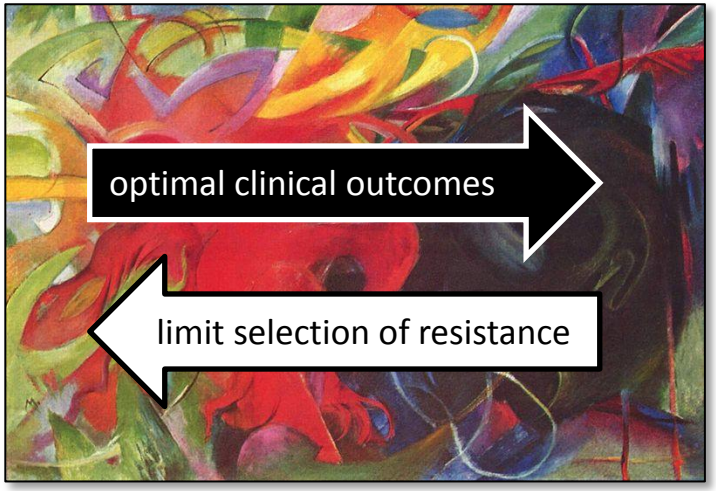
Combatting antimicrobial resistance



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

The goals of antibiotic stewardship

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



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.

72 NRP Antimicrobial Resistance
National Research Programme

A one-health approach

COMPuterized Antibiotic Stewardship Study

Background

72 NRP

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 approuvé

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 Boillat 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

CHUV

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	**Adult patients** hospitalized in acute-care wards of three secondary and tertiary care centers **Physicians** prescribing antimicrobials for these patients
Intervention	Multimodal, **computerized antibiotic stewardship intervention** • implemented on the ward level
Control	**“Standard-of-care”** antibiotic stewardship
Outcome	Overall **antibiotic exposure** • measured in days of therapy per admission
Time	12 months

Benedikt HUTTNER
(antibiotic stewardship)

Enos BERNASCONI
(ID & internal medicine)

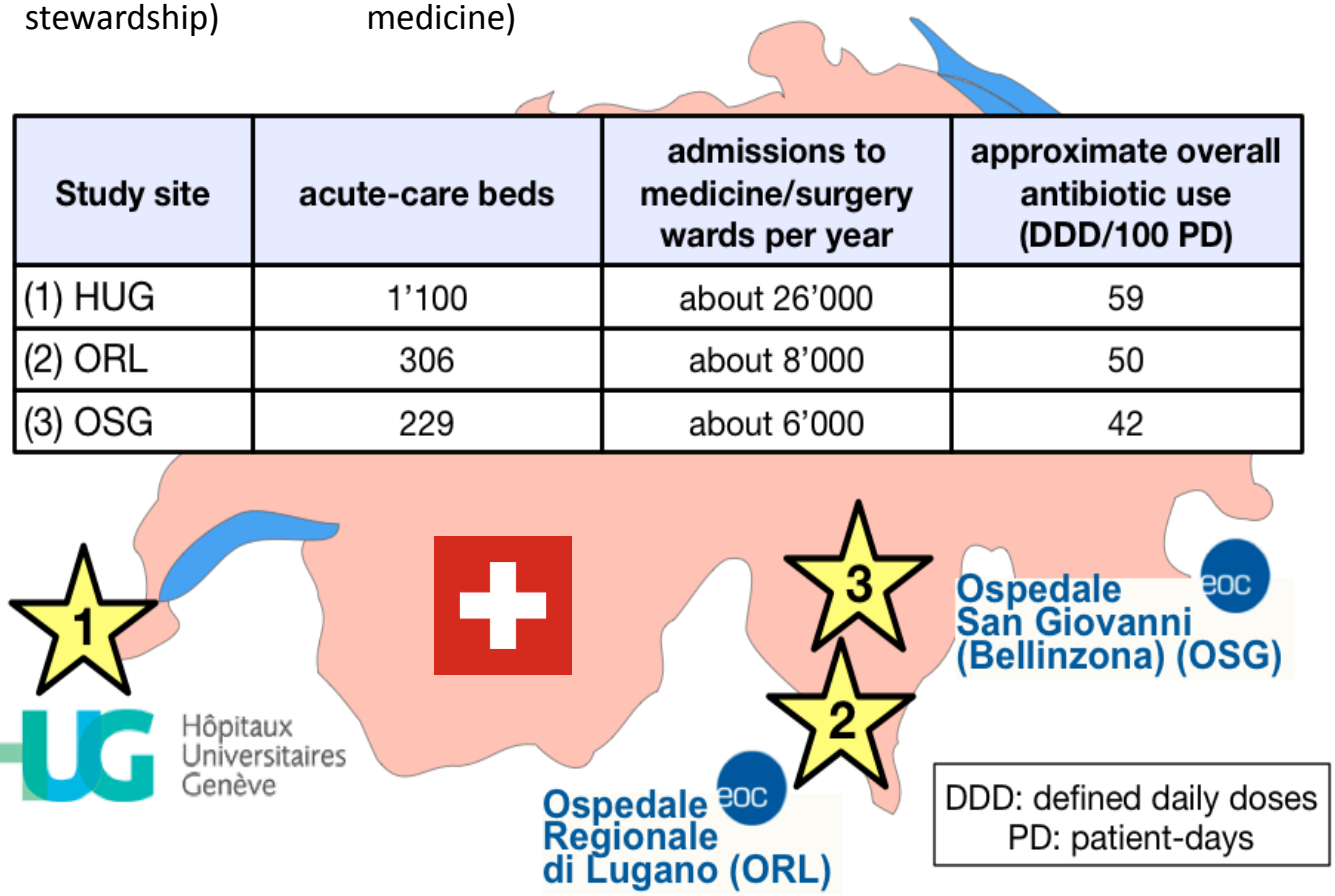
GE COMPASS TI

Stephan HARBARTH
(antibiotic stewardship)

Rodolphe MEYSER
(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



COMPASS Framework

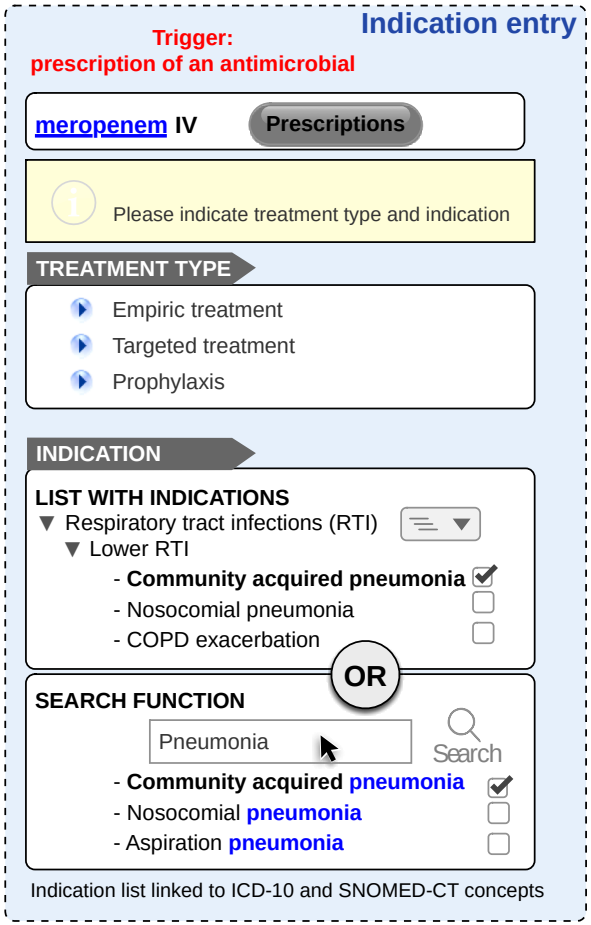
Three component informatics-based intervention

Decision support for empiric treatment

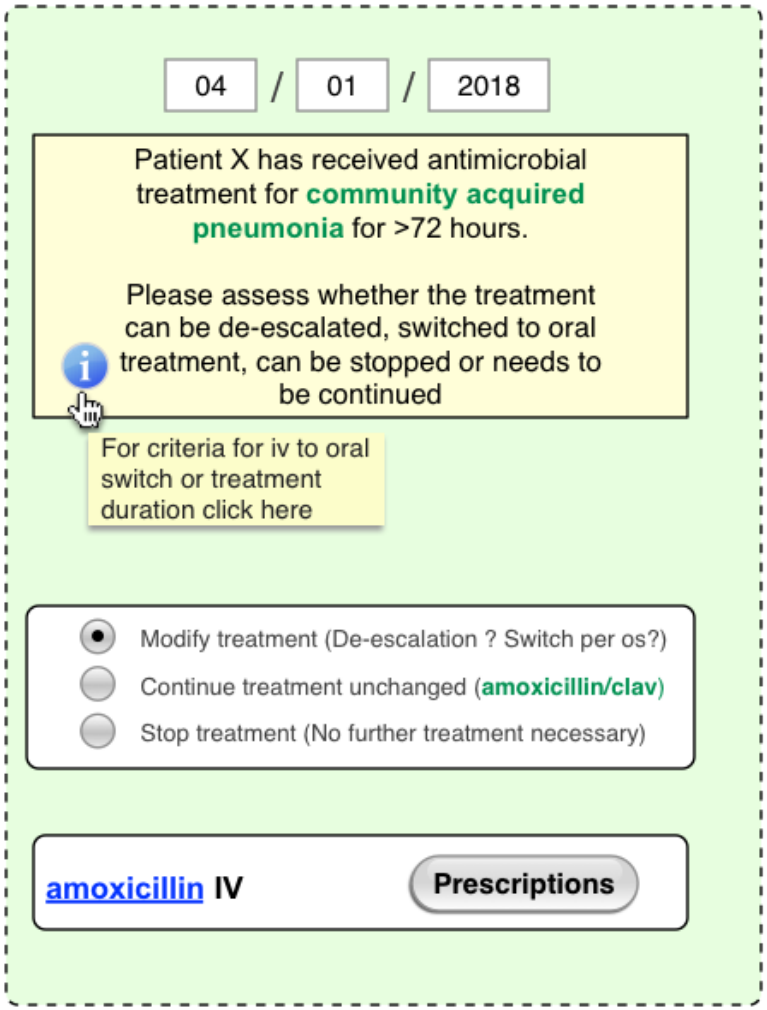
Self-evaluation of treatment

Audit and feedback

Decision support for empiric treatment and limitation of duration to max 4 days



(2) Self-evaluation of treatment (72-96h)



(3) Audit and feedback

Automated feedback of quality indicators

Please find attached the latest quality indicators for your ward

Access results

Guideline compliance

70%

50%

% compliance choice of empiric treatment (all infections) n=123

10.0 days

8.1 days

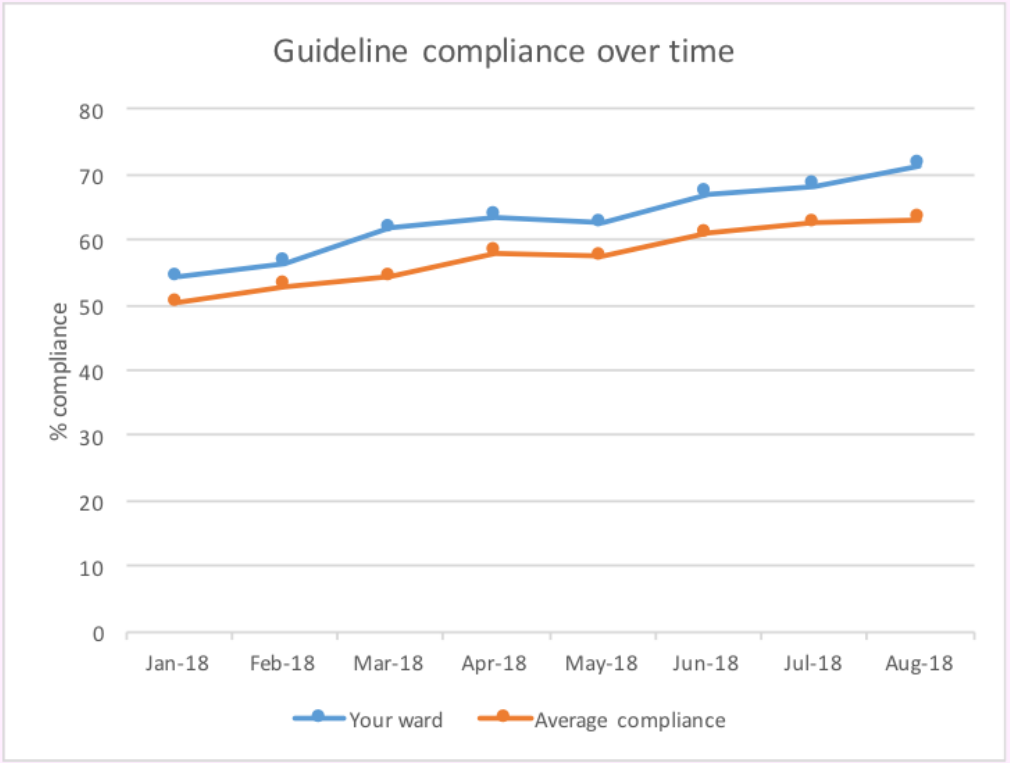
7 days

Recommended treatment duration

Treatment duration for CAP in days n=37

Your performance

Median performance (all wards)



COMPASS Framework

Decision support for empiric treatment

Self-evaluation of treatment

Audit and feedback

Objectives

- Guideline compliance↑
- Duration of treatment↓
- IV-PO switch↑
- Switch narrow spectrum↑

Aims

- Overall antibiotic exposure↓
- Adverse events↓ (AMR, CDI)
- LOS↓

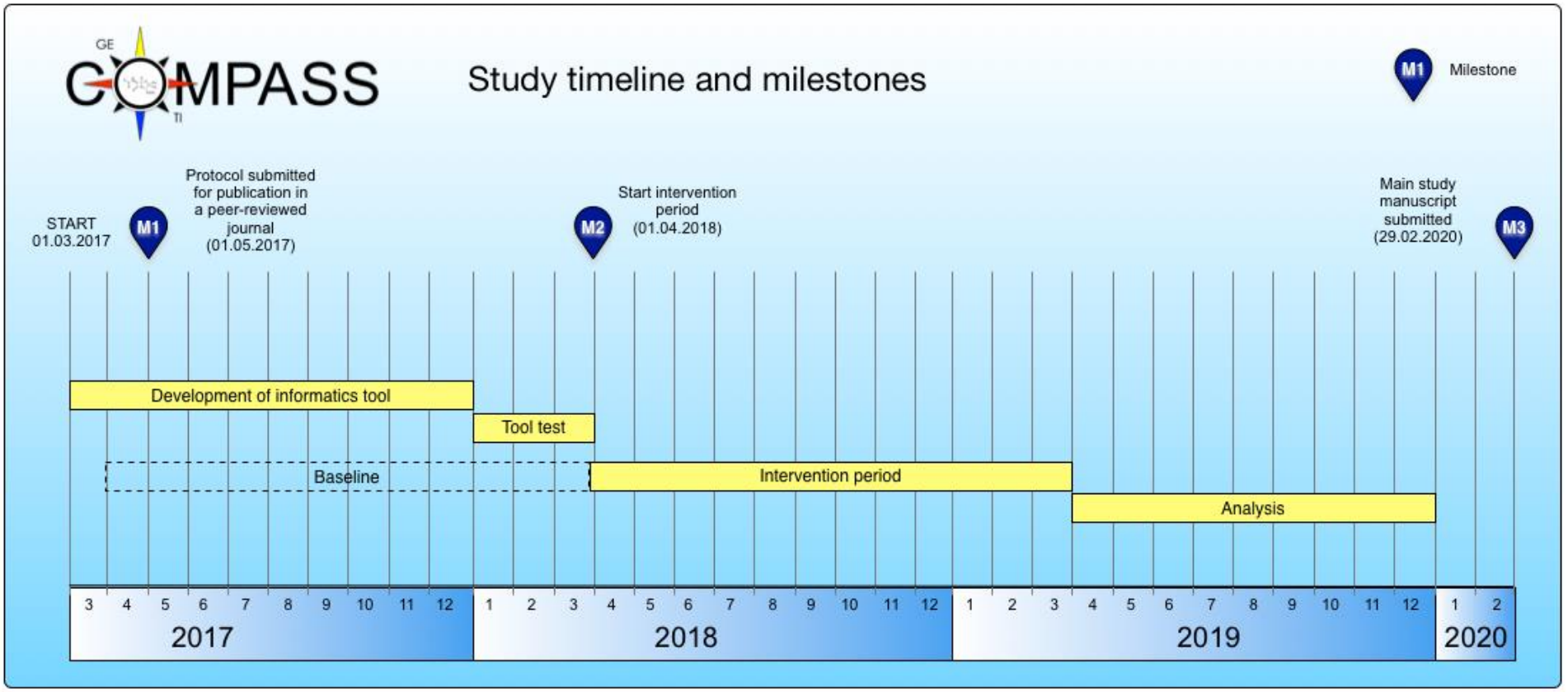
AMR↓ PATIENT SAFETY↑

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


GE
COMPASS
TI
Study timeline and milestones
M1 Milestone
START
01.03.2017
M1
Protocol submitted for publication in a peer-reviewed journal (01.05.2017)
M2
Start intervention period (01.04.2018)
Main study manuscript submitted (29.02.2020)
M3
Development of informatics tool
Tool test
Baseline
Intervention period
Analysis
3 4 5 6 7 8 9 10 11 12
2017
1 2 3 4 5 6 7 8 9 10 11 12
2018
1 2 3 4 5 6 7 8 9 10 11 12
2019
1 2
2020

Questions

Un grand merci à Benedikt Huttner pour avoir contribuer à cette présentation