university of groningen

University Medical Center Groningen

Resistance prevention in a connected world

Alex W. Friedrich
Medische Microbiologie
UMCG
www.mmb-umcg.nl

Contributions to UMCG priorities

- Patient care for **Transplantation, Oncology, Acute&Critical Care**
  - Prevent were possible, Detect fast and treat optimal all infections

- Research in **Healthy Ageing**
  - Research programme “Microbes for Health&Disease”

- **Internationalization**
  - 7 EU projects on Bacteriology, Infection Prevention/AMR, OneHealth
  - 2 H2020 Cofunds for 18 international PhD students

- Top Priorities in **Quality of Care, Patient Safety, Regional Care**
  - Prevent Infections, Maintain antibiotic therapy, Regional Network

MMB – umcg
Medische Microbiologie & Infectiepreventie

Microbes in Health&Disease


Prof. Van Dijl

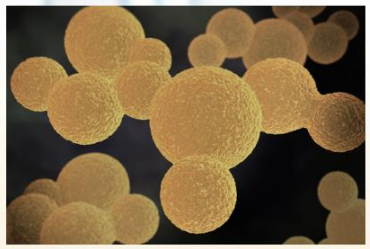

Prof. Smit

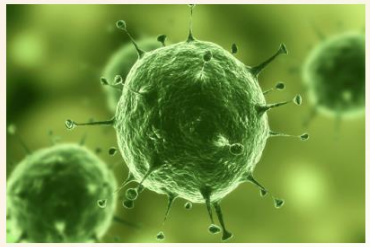

Prof. Huckriede

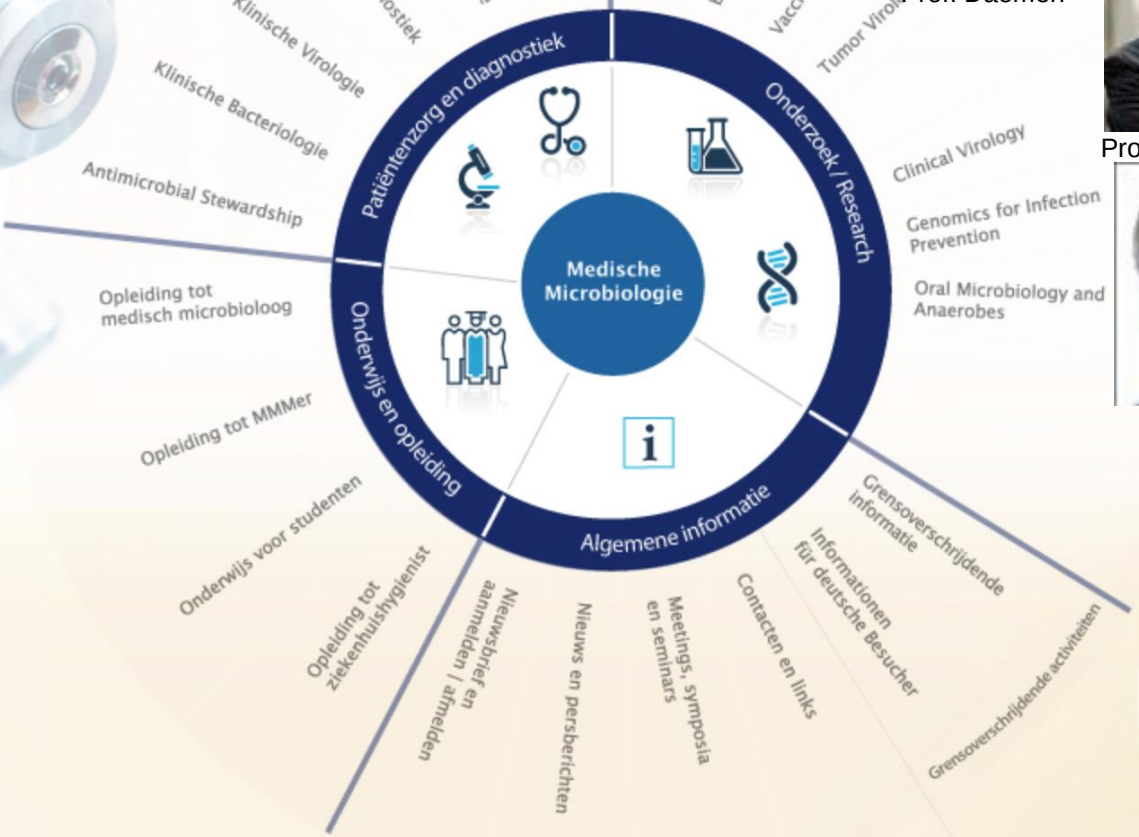

Prof. Daemen


Prof. Niesters

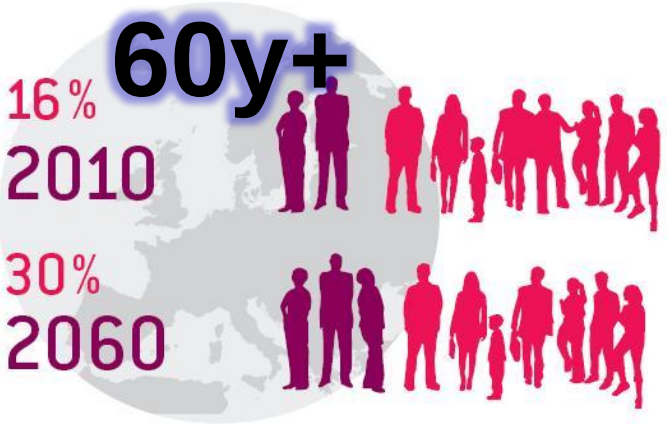

Prof. Sinha







50-30-60



„Silver Generation“

Are you **YOPI ?**

>83 years

<8 months

Prevent infections, Maintain optimal antimicrobial therapy


Micronaut.ch

Healthcare-associated infections and antimicrobial resistance

Alex W. Friedrich
Medical Microbiology and Infection Prevention
UMCG

EU 2016

The Netherlands EU Presidency 2016

AMR Next

EU Antimicrobial Resistance One Health ministerial conference 2016

Veterinary Health
Human Health
One Health

Introduction

Antimicrobial Resistance. from intentions to action

Minister of Health, Welfare and Sport, Schippers

Minister for Agriculture, Van Dam

From the very beginning the European Union continuously faced political, social and economic challenges. Today the migration crisis, terrorism, climate change and international tensions demand our immediate response and continuing attention. At the same time we cannot afford to neglect Antimicrobial Resistance, a threat that is evolving slowly but progressively, jeopardising the health of all people.

If antibiotics are not effective anymore, modern healthcare is at stake. Without antibiotics, common infections can no longer be treated. Even routine operations will be too risky. Already 25,000 people die every year in Europe due to untreatable bacterial infections.

Alarming signals

Infection prevention and prudent use of antibiotics, both in human and animal healthcare, are crucial in the fight against Antimicrobial Resistance. We need new antibiotics or other effective medicines against infections. This requires new business models. Also, we need to develop new, affordable and quick diagnostic instruments. Commitment is important, but commitment alone will not stop the spread of multiresistant bugs. It is alarming that recent data of the European Centre for Disease Prevention and Control show that Antimicrobial Resistance is still progressing in the EU. It is time to act!

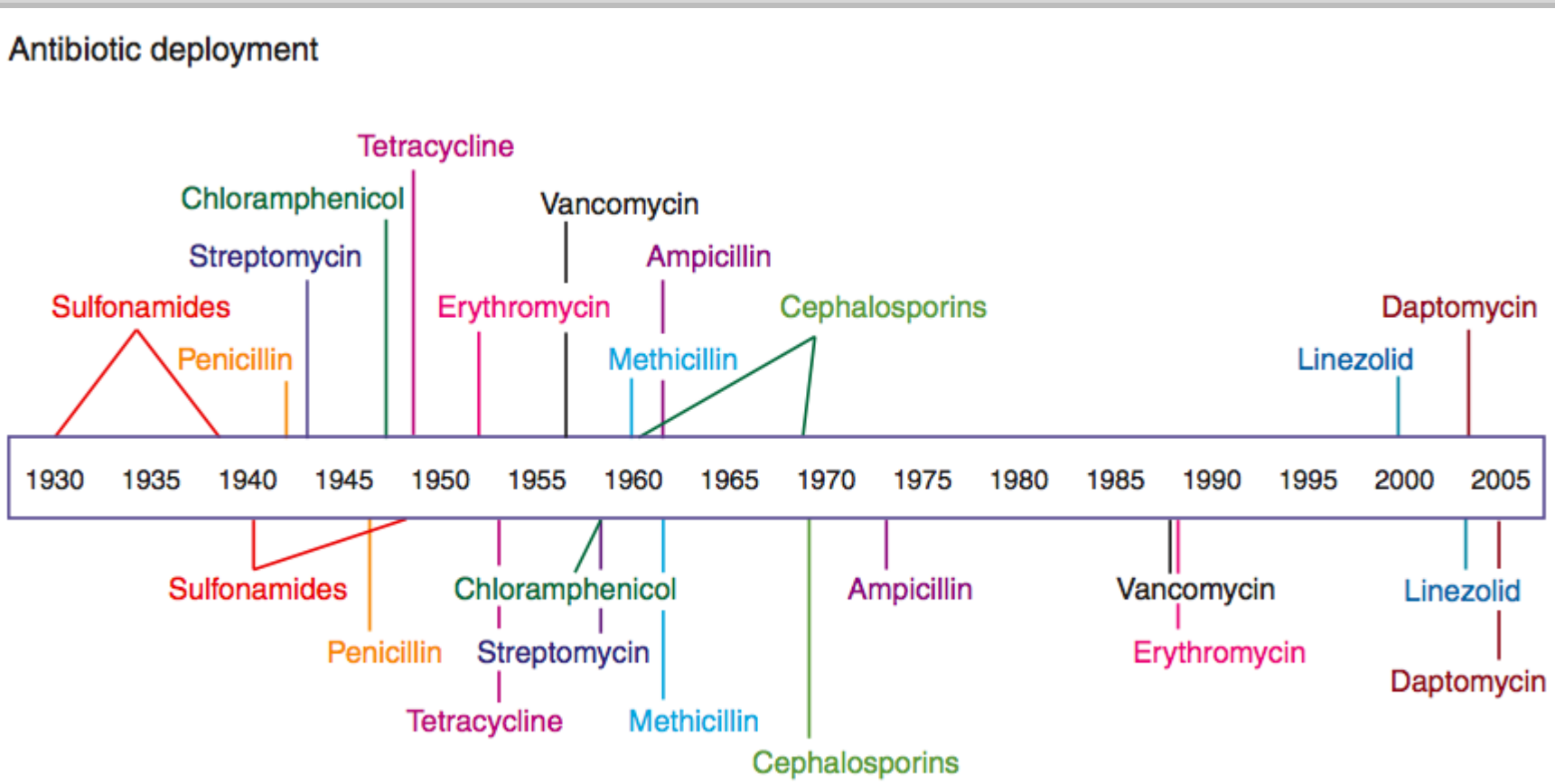
the One Health approach, when all discip work together, is crucial in combating Ant Resistance.

'Commitment is impor but commitment alone not stop the spread of multiresistant bugs'

This newspaper is meant as a source of inspira It provides good practices both from the huma healthcare sector and the veterinary sector of different Member States. It shows that we are not powerless in the fight against Antimicrobial Resistance and that joining forces within the EU allows tailor-made solutions fitting individual Member States.

Realistic dilemmas

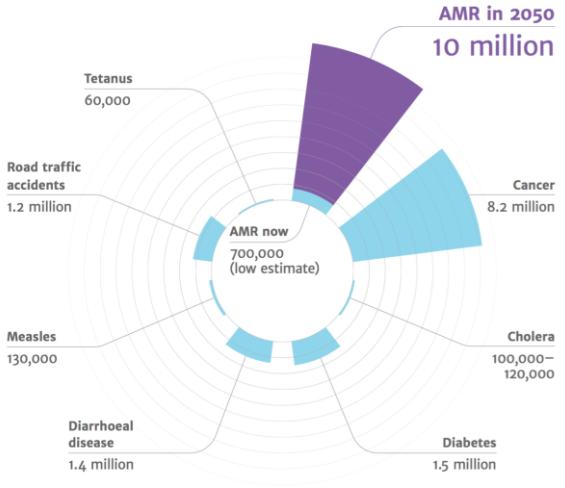
You will also find a sneak preview of our program which includes a scenario-based policy discussion that will confront us with realistic dilemmas on the topic of Antimicrobial Resistance. This is an important part of the conference. Our experience is that an interactive approach supports us in moving from intentions to actions. We are looking forward


Antibiotic deployment
Tetracycline
Chloramphenicol
Vancomycin
Streptomycin
Ampicillin
Sulfonamides
Erythromycin
Cephalosporins
Daptomycin
Penicillin
Methicillin
Linezolid
1930
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
Sulfonamides
Chloramphenicol
Ampicillin
Vancomycin
Linezolid
Penicillin
Streptomycin
Erythromycin
Daptomycin
Tetracycline
Methicillin
Cephalosporins
Antibiotic resistance observed

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

DEATHS ATTRIBUTABLE TO AMR EVERY YEAR



TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

MAY 2016

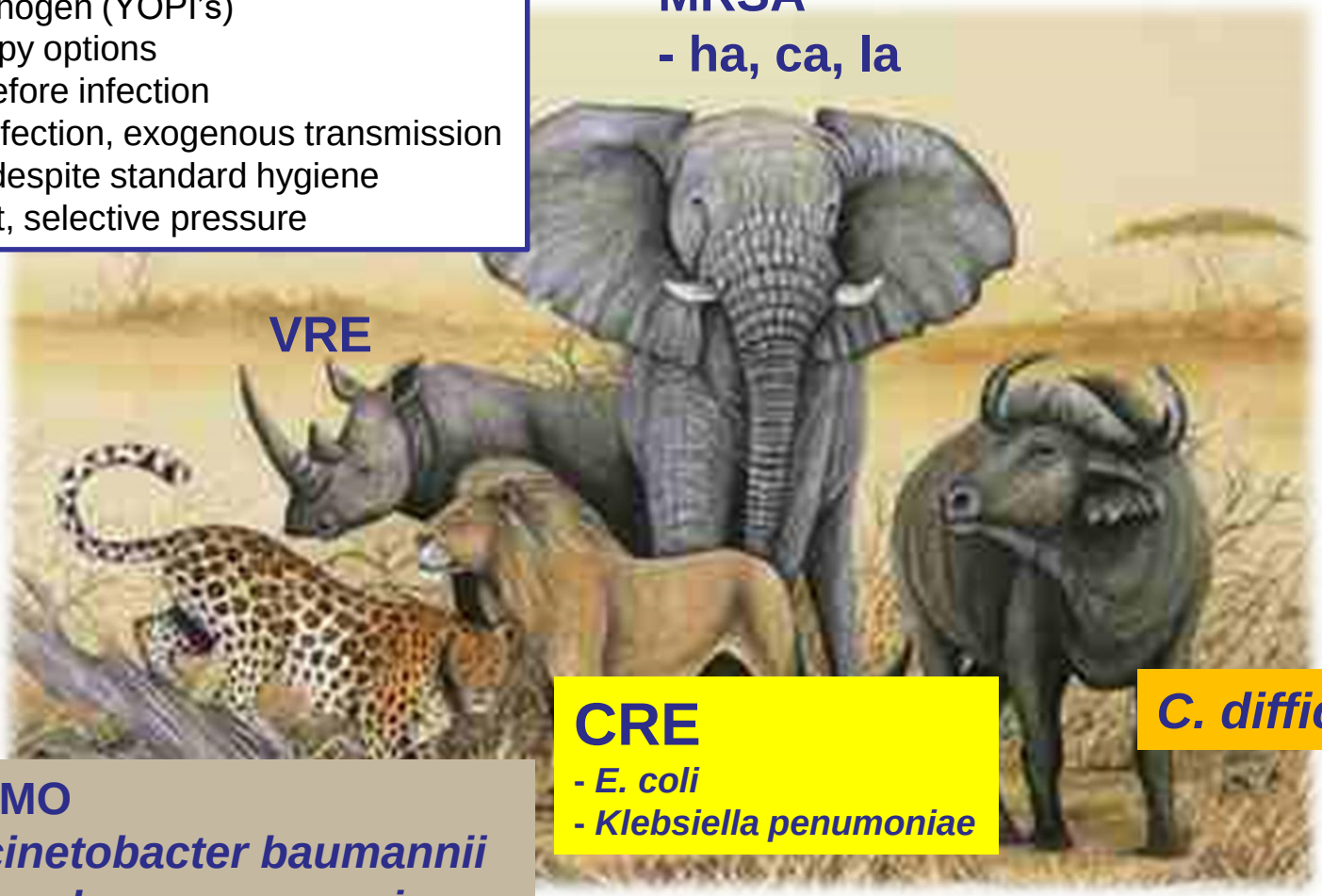
The UK Prime Minister commissioned the Review on Antimicrobial Resistance to address the growing global problem of drug-resistant infections. It is chaired by Jim O'Neill and supported by the Wellcome Trust and UK Government, but operates and speaks with full independence from both.

wellcome trust

HM Government

„The big Five“

- Facultative pathogen (YOPI’s)
- Reduced therapy options
- Colonisation before infection
- Endogenous infection, exogenous transmission
- Transmittable despite standard hygiene
- Cohort, contact, selective pressure



MRSA
- ha, ca, la

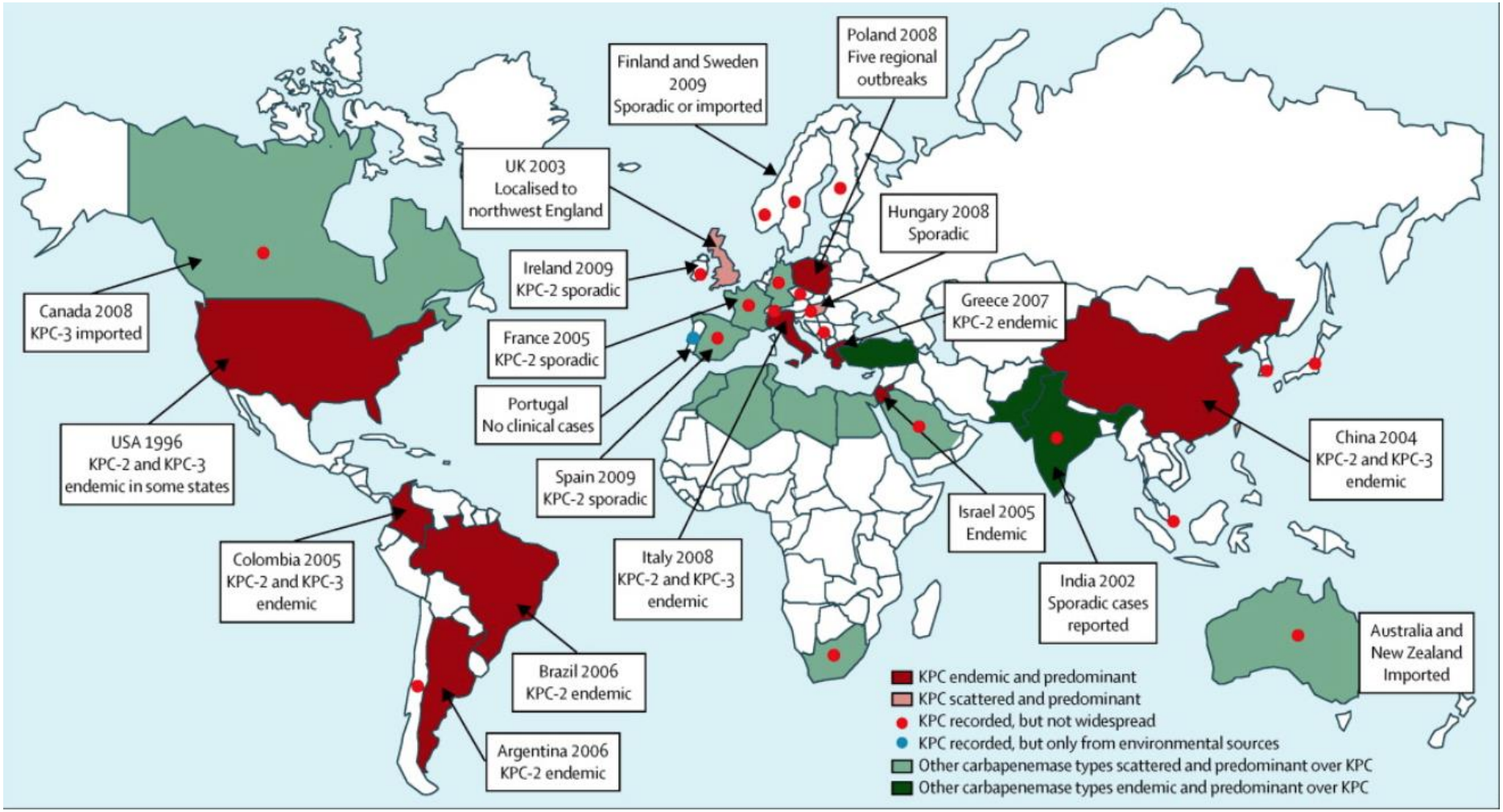
VRE

CRE
- E. coli
- Klebsiella penumoniae

C. difficile

CR-MO
- Acinetobacter baumannii
- Pseudomonas aeruginosa

Global epidemiology of CRE

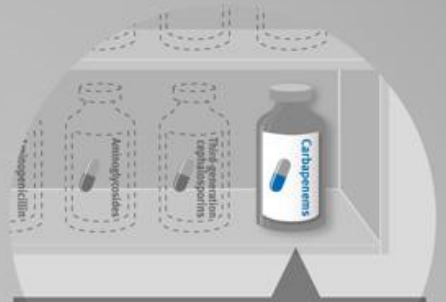


Munoz-Price, LS, LID 2013

Growing resistance to last-line antibiotics

Carbapenems are a major last-line class of antibiotics to treat bacterial infections. The spread of carbapenem-resistant infections is a threat to healthcare and patient safety in Europe as it seriously curtails the ability to cure infections.

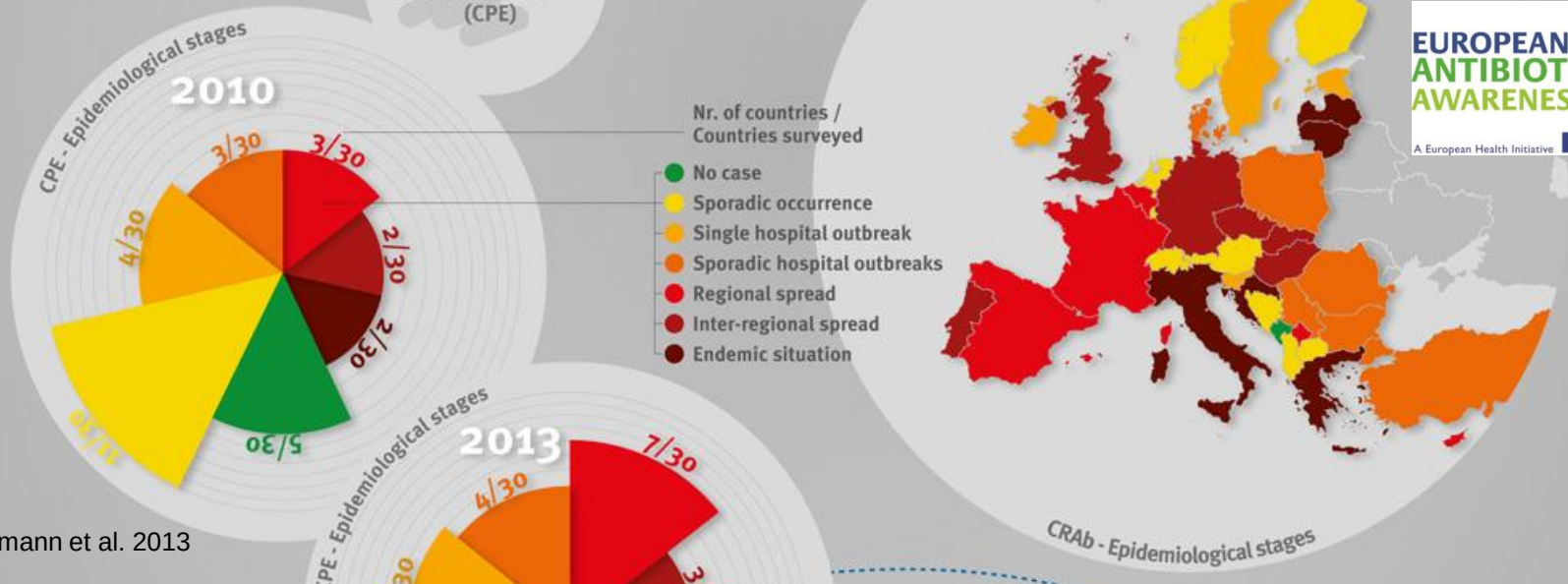
Each year, 30 EU/EEA countries report data on antimicrobial resistance to the European Antimicrobial Resistance Surveillance Network (EARS-Net) and on antimicrobial consumption to the European Surveillance of Antimicrobial Consumption network (ESAC-Net). Both networks are hosted at ECDC. For the first time, 18 countries reported data on *Acinetobacter* spp. to EARS-Net. In addition, experts in 38 European countries participated in the European Survey on Carbapenemase-Producing *Enterobacteriaceae* (EuSCAPE) done for ECDC by the University Medical Centre Groningen, The Netherlands.



Carbapenems are one of doctors' last possible choice of antibiotics to treat infections due to bacteria resistant to multiple antibiotics.

Carbapenemase-producing *Acinetobacter baumannii* (CRAb)

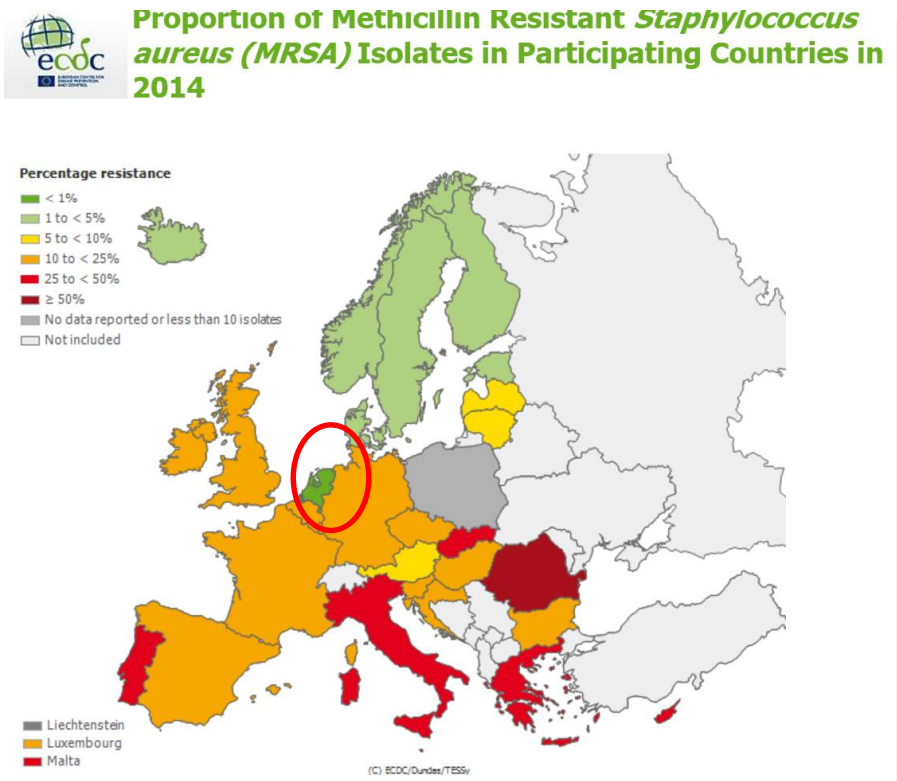
Carbapenem-resistant *Enterobacteriaceae* (CPE)



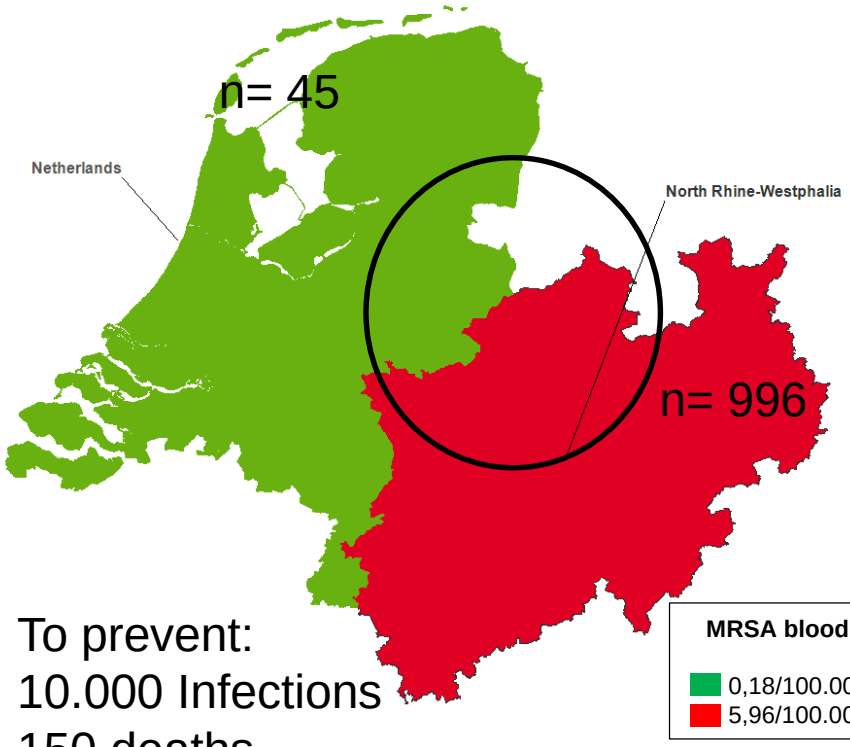
EUROPEAN ANTIBIOTIC AWARENESS DAY
A European Health Initiative

Grundmann et al. 2013

Learn from differences



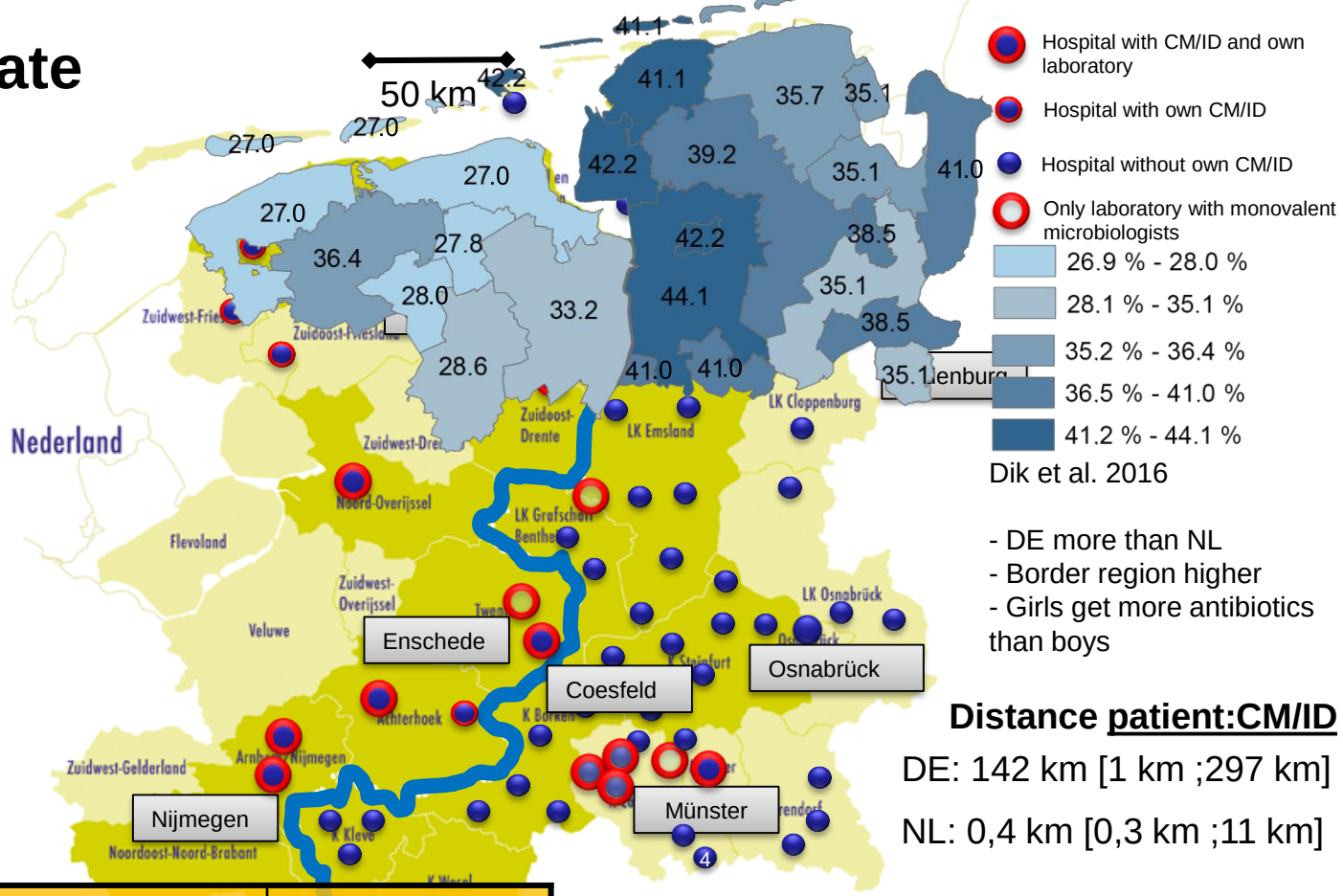
MRSA Blood cultures



To prevent:
10.000 Infections
150 deaths
120 Mio € per y

Köck et al&Friedrich. JHI. 2009
van Cleef BA, et al& Friedrich AW. PLoS One. 2012

Borders stimulate questions



Dik et al. 2016

- DE more than NL
- Border region higher
- Girls get more antibiotics than boys

Distance <u>patient:CM/ID</u>

DE: 142 km [1 km ;297 km]

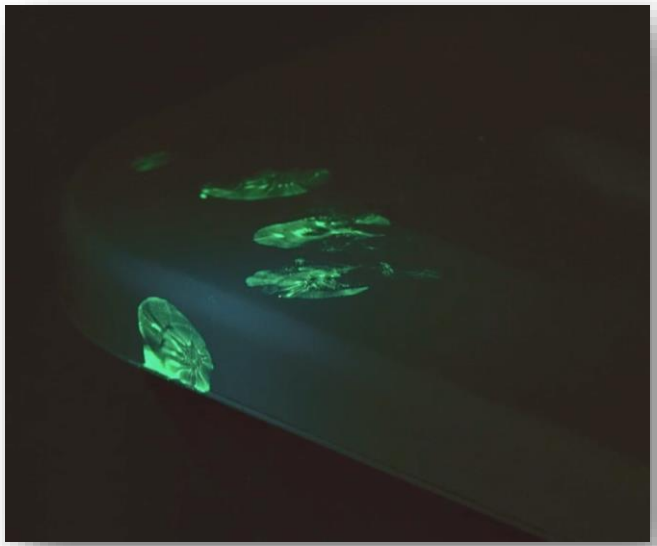
NL: 0,4 km [0,3 km ;11 km]

Parameters	Euregio-NL	Euregio-DE
Inhabitants	3,6 Mio	2,8 Mio
Acute care hospitals (beds)	22 (10813)	69 (17839)
Beds per 1000 inh	3,3	6,1
GP's/ 1000 inh	0,44	1,5
HCW:patient ratio (on ICU)	1 : 1,5	1 : 3,2
CM-ID /1000 beds	37 (3,6)	17 (1,0)
Hospitals with own CM/ID	95%	3%

Preventive approach

- **Infection prevention**
  - optimal treatment of underlying disease (good doctors!)
  - strict indication for medical treatment (aggressive waiting)
  - Aseptic procedures/desinfection

- **Resistance prevention**
  - Reduce selective pressure (ASP)
  - Early identification of carriers
  - Reduce transmission

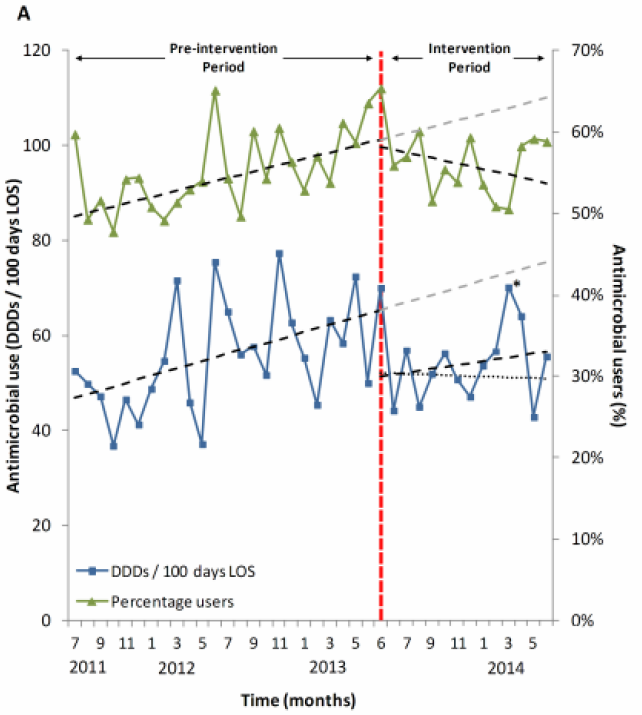


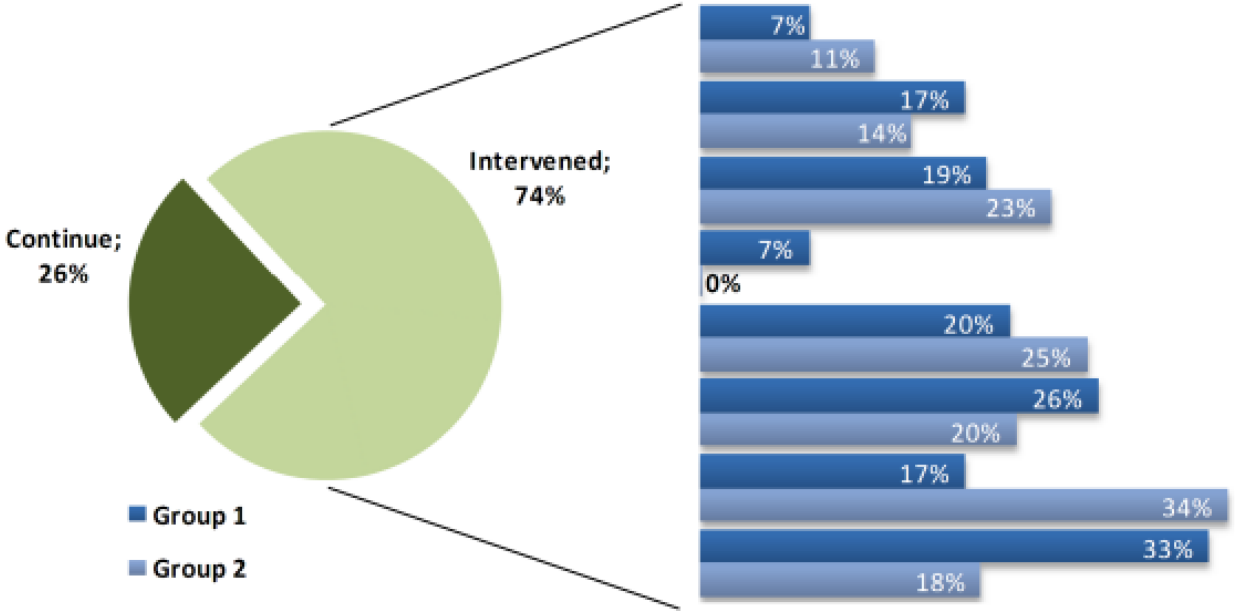
UMCG Instruction movie “Eyes for the invisible” 2016

ORIGINAL RESEARCH ARTICLE
Front. Microbiol. | doi: 10.3389/fmicb.2015.00546

Automatic day-2 intervention by a multidisciplinary Antimicrobial Stewardship-Team leads to multiple positive effects

Automatischer Emal-alert nach 48h Ab-Therapie bei Patienten
Ungefragtes vor-Ort-Konsil durch A-Team
RoI = 5,9





Dik et al. & Sinha 2015

Adjuvant
Cost-efficiency studies

PLOS ONE

RESEARCH ARTICLE

Cost-Analysis of Seven Nosocomial Outbreaks in an Academic Hospital

Jan-Willem H. Dik[1], Ariane G. Dinkelacker[1,2], Pepijn Vemer[3,4,5], Jerome R. Lo-Ten-Foe[1], Mariëtte Lokate[1], Bhanu Sinha[1], Alex W. Friedrich[1]*, Maarten J. Postma[3,4,5]

1 Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, **2** Department of Medical Microbiology, University Hospital Tübingen, Tübingen, Germany, **3** Department of Pharmacy, Unit of PharmacoEpidemiology & PharmacoEconomics, University of Groningen, Groningen, the Netherlands, **4** Institute of Science in Healthy Aging & healthcaRE (SHARE), University Medical Center Groningen, Groningen, the Netherlands, **5** Department of Epidemiology, University Medical Center Groningen, Groningen, the Netherlands

* alex.friedrich@umcg.nl

CrossMark click for updates

Abstract

OPEN ACCESS

Citation: Dik J-WH, Dinkelacke Ten-Foe JR, Lokate M, Sinha B Analysis of Seven Nosocomial Academic Hospital. PLoS ONE doi:10.1371/journal.pone.0149

Editor: Olivier Baud, Hôpital R

Received: December 9, 2015

Accepted: January 28, 2016

Published: February 10, 2016

Data Availability Statement: within the paper.

Funding: This work was partly European Union, the German s Westphalia and Lower Saxony provinces Overijssel, Gelderlan

7 outbreaks 2012-2014

Costs/out 10.778-356.756 Euro

Per pos. patient/outbreak day:
546 Euro

PLOS ONE

RESEARCH ARTICLE

Cost-Minimization Model of a Multidisciplinary Antibiotic Stewardship Team Based on a Successful Implementation on a Urology Ward of an Academic Hospital

Jan-Willem H. Dik[1], Ron Hendrix[1,2], Alex W. Friedrich[1]*, Jos Luttjeboer[3], Prashant Nannan Panday[4], Kasper R. Wilting[1], Jerome R. Lo-Ten-Foe[1], Maarten J. Postma[3,5], Bhanu Sinha[1]

1 Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, **2** Certe Laboratory for Infectious Diseases, Groningen, the Netherlands, **3** Department of Pharmacy, Unit of PharmacoEpidemiology & PharmacoEconomics, University of Groningen, Groningen, the Netherlands, **4** Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, the Netherlands, **5** Department of Epidemiology, University Medical Center Groningen, Groningen, the Netherlands

* alex.friedrich@umcg.nl

CrossMark click for updates

48h-ASP bundle
74% changed

RoI: 5,9

Real-time *in vivo* imaging of invasive- and biomaterial-associated bacterial infections using fluorescently labelled vancomycin

Marleen van Oosten, **Tina Schäfer**, **Joost A. C. Gazendam**, **Knut Ohlsen**, **Eleni Tsompanidou**, **Marcus C. de Goffau**, **Hermie J. M. Harmsen**, **Lucia M. A. Crane**, **Ed Lim**, **Kevin P. Francis**, **Lael Cheung**, **Michael Olive**, **Vasilis Ntziachristos**, **Jan Maarten van Dijl** & **Gooitzen M. van Dam**

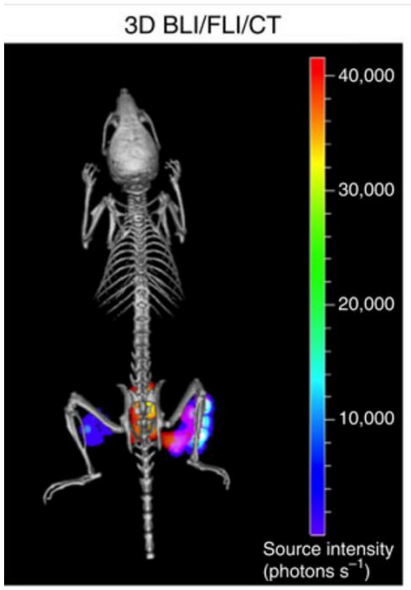
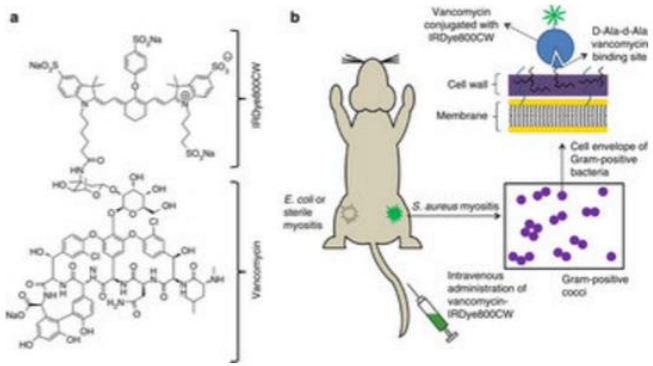
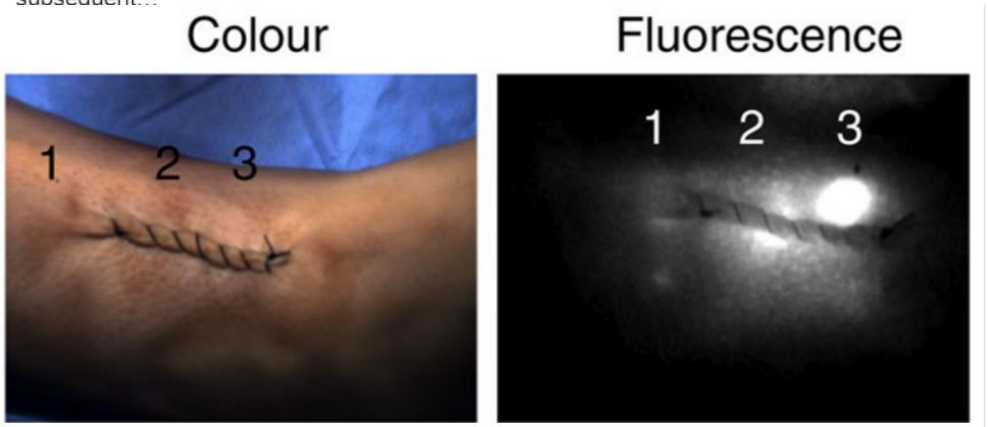


Figure 1: Vancomycin-IRDye 800CW and the experimental approach.



(**a**) Structure of vanco-800CW. (**b**) Schematic representation of the experimental approach for imaging mice injected with either *S. aureus* (*S. aureus* myositis), *E. coli* (*E. coli* myositis) or Cytodex beads (sterile myositis), and subsequent…



…targeted/intelligent antibiotics

Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
Journal of Magnetism and Magnetic Materials 293 (2005) 483–496
Journal of magnetism and magnetic materials
www.elsevier.com/locate/jmmm

Review

Superparamagnetic nanoparticles for biomedical applications: Possibilities and limitations of a new drug delivery system

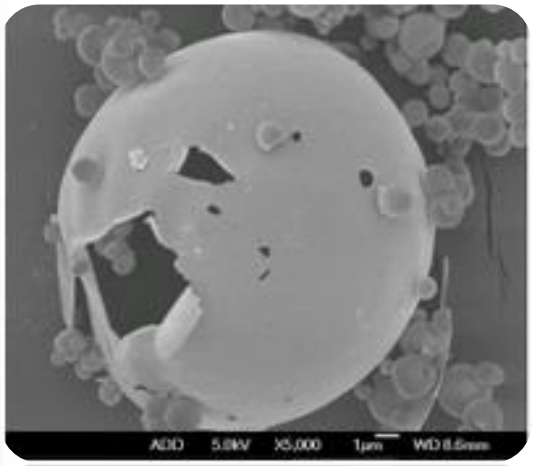
Tobias Neuberger[a], Bernhard Schöpf[a], Heinrich Hof… [b]
Margarete Hofmann[c], Brigitte von Rechenberg[a]

[a]*Musculoskeletal Research Unit, Equine Hospital, Vetsuisse Faculty Zurich, University of Zurich, 8057 Zurich, Switzerland*
[b]*Laboratory of Powder Technology, Institute of Materials, Swiss Federal Institute of Technology, EPFL,*
[c]*MatSearch Pully, Chemin Jean Pavillard, 14, CH-1009 Pully, Switzerland*

Available online 2 March 2005

Abstract

Nanoparticles can be used in biomedical applications, where they facilitate labora… medical drug targeting. They are used for in vivo applications such as contrast agent for ma… (MRI), for tumor therapy or cardiovascular disease. Very promising nanoparticles fo… superparamagnetic nanoparticles based on a core consisting of iron oxides (SPION) that … external magnets. SPION are coated with biocompatible materials and can be functionalize… plasmids. In this review, the characteristics and applications of SPION in the biomedical s… discussed.



Proceedings of the National Academy of Sciences of the United States of America
PNAS
CURRENT ISSUE // ARCHIVE // NEWS & MULTIMEDIA // FOR AUTHORS // ABOUT PNAS COLLECTED ARTICLES / BROWSE BY TOPIC / EARLY EDITION

Early Edition > Nazila Kamaly

Development and in vivo efficacy of targeted polymeric inflammation-resolving nanoparticles

Nazila Kamaly[a,1], Gabrielle Fredman[b,1], Manikandan Subramanian[b], Suresh Gadde[a], Aleksandar Pesic[a], Louis Cheung[a], Zahi Adel Fayad[c], Robert Langer[d,2], Ira Tabas[b,2], and Omid Cameron Farokhzad[a,2]

Author Affiliations

Contributed by Robert Langer, February 22, 2013 (sent for review December 20, 2012)

Abstract

Excessive inflammation and failed resolution of the inflammatory response are underlying components of numerous conditions such as arthritis, cardiovascular disease, and cancer. Hence, therapeutics that dampen inflammation and enhance resolution are of considerable interest. In this study, we demonstrate the proresolving activity of sub–100-nm nanoparticles (NPs) containing the anti-inflammatory peptide Ac2-26, an annexin A1/lipocortin 1-mimetic peptide. These NPs were engineered using biodegradable diblock poly(lactic-*co*-glycolic acid)-*b*-polyethyleneglycol and poly(lactic-*co*-glycolic acid)-*b*-polyethyleneglycol collagen IV–targeted polymers. Using a self-limited zymosan-induced peritonitis model, we show that the Ac2-26 NPs (100 ng per mouse) were significantly more potent than Ac2-26 native peptide at limiting recruitment of polymononuclear neutrophils (56% vs. 30%) and at decreasing the resolution interval up to 4 h. Moreover, systemic administration of collagen IV targeted Ac2-26 NPs (in as low as 1 μg peptide per mouse) was shown to significantly block tissue damage in hind-limb ischemia-reperfusion injury by up to 30% in comparison with controls. Together, these findings demonstrate that Ac2-26 NPs are proresolving in vivo

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Published online before print March 26, 2013, doi: 10.1073/pnas.1303377110
PNAS March 26, 2013

Classifications
Biological Sciences
Medical Sciences

Access
Abstract
Full Text (PDF)
Full Text + SI (Combined PDF)
Supporting Information

Article Tools
Article Alerts
Export Citation

- Targeted therapy
- Personalized drug delivery
- Photodynamic activation of antibiotics

Interventional Clinical Microbiology

Courtesy: BD/Kiestra

Different labordiagnostic markers
(e.g. Na+/Ka+)
Microbiological biomarkers (microbes)

a.) are transmittable
b.) have own evolution and change

Courtesy: NVMM

a. Tailor-made diagnostics

b. On demand/Real-Time (<12h)

c. Early detection and Prevention

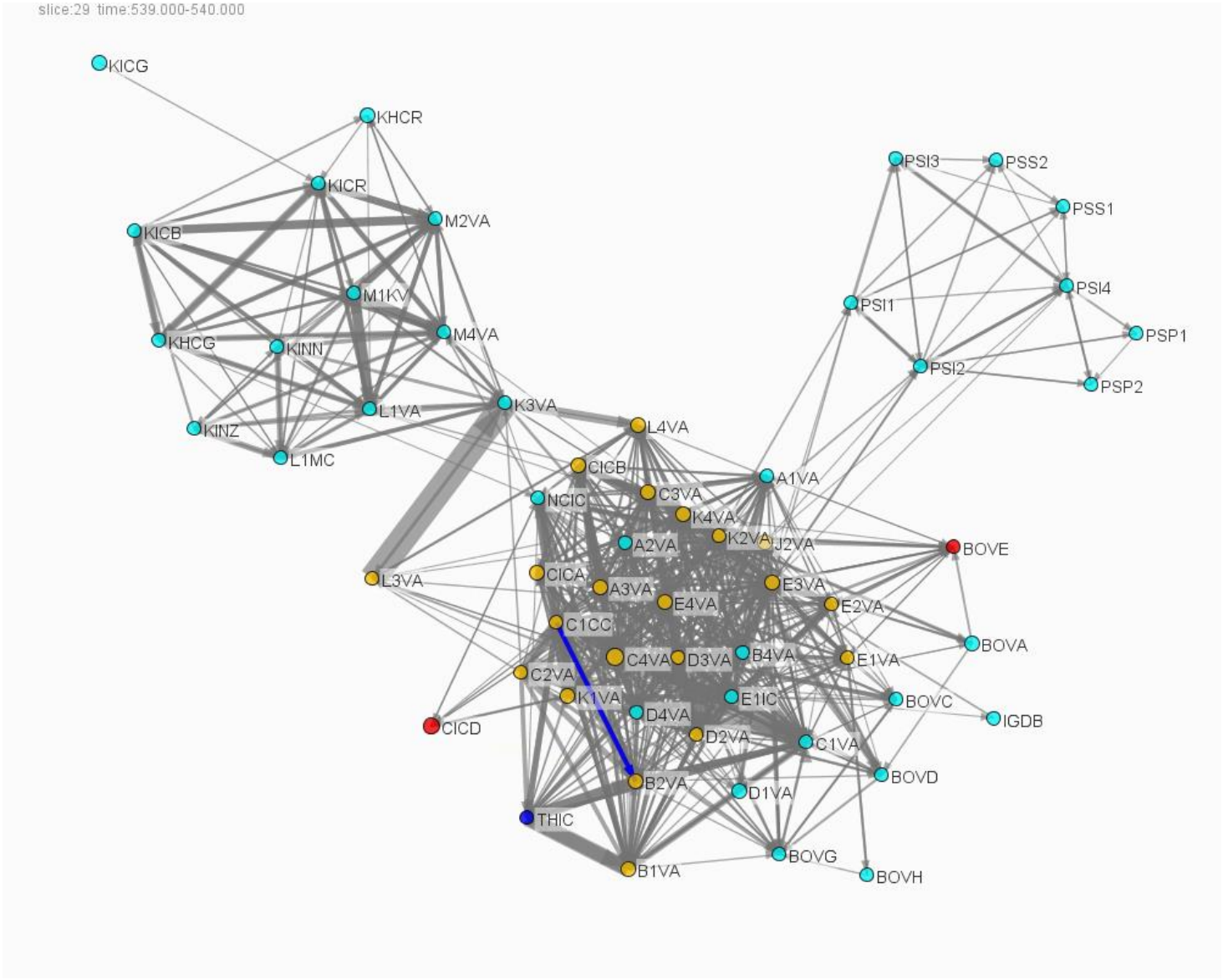
d. Regional uitbreak control

-

KPNEU Outbreak analysis based on Intra-Hospital transmission network and TYPING

Day-by-day patient transfer

Start: 29.5.2012



Ward without KPNEU patient

ward with exposed patients

KPNEU GT1 (11)

KPNEU GT2 (5)

KPNEU sporadic (11)

ward with positive patients

<10

10-50

>50

International Journal of Medical Microbiology

Available online 13 March 2013

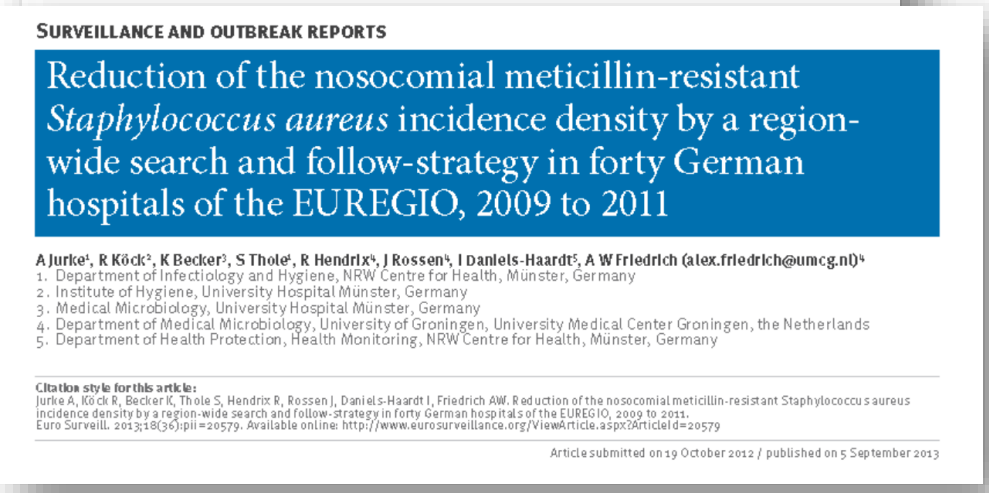
In Press, Corrected Proof — Note to users

Infection prevention in a connected world: The case for a regional approach

Open Access Article

Mariano Ciccolini[a], Tjibbe Donker[a], Robin Köck[b], Martin Mielke[c], Ron Hendrix[d], Annette Jurke[e], Janette Rahamat-Langendoen[a], Karsten Becker[f], Hubert G.M. Niesters[a], Hajo Grundmann[a], Alexander W. Friedrich[a].

[a] Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands



SURVEILLANCE AND OUTBREAK REPORTS

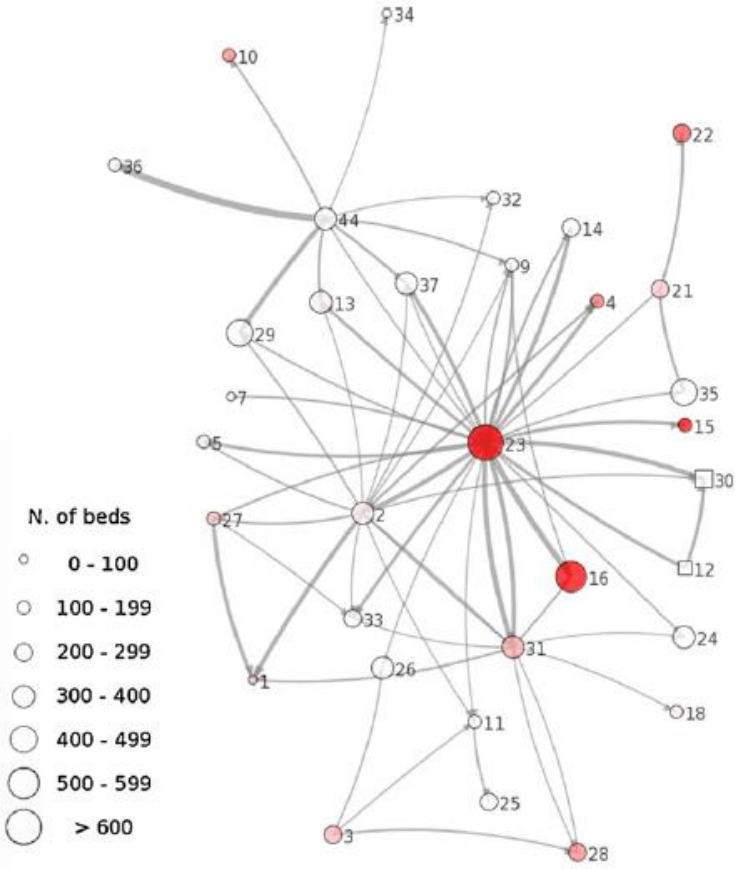
Reduction of the nosocomial meticillin-resistant *Staphylococcus aureus* incidence density by a region-wide search and follow-strategy in forty German hospitals of the EUREGIO, 2009 to 2011

A Jurke[1], R Köck[2], K Becker[3], S Thole[4], R Hendrix[4], J Rossen[4], I Daniels-Haardt[5], A W Friedrich (alex.friedrich@umcg.nl)[4]

1. Department of Infectiology and Hygiene, NRW Centre for Health, Münster, Germany
2. Institute of Hygiene, University Hospital Münster, Germany
3. Medical Microbiology, University Hospital Münster, Germany
4. Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, the Netherlands
5. Department of Health Protection, Health Monitoring, NRW Centre for Health, Münster, Germany

Citation style for this article:
Jurke A, Köck R, Becker K, Thole S, Hendrix R, Rossen J, Daniels-Haardt I, Friedrich AW. Reduction of the nosocomial meticillin-resistant Staphylococcus aureus incidence density by a region-wide search and follow-strategy in forty German hospitals of the EUREGIO, 2009 to 2011. Euro Surveill. 2013;18(36):pii=20579. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20579

Article submitted on 19 October 2012 / published on 5 September 2013



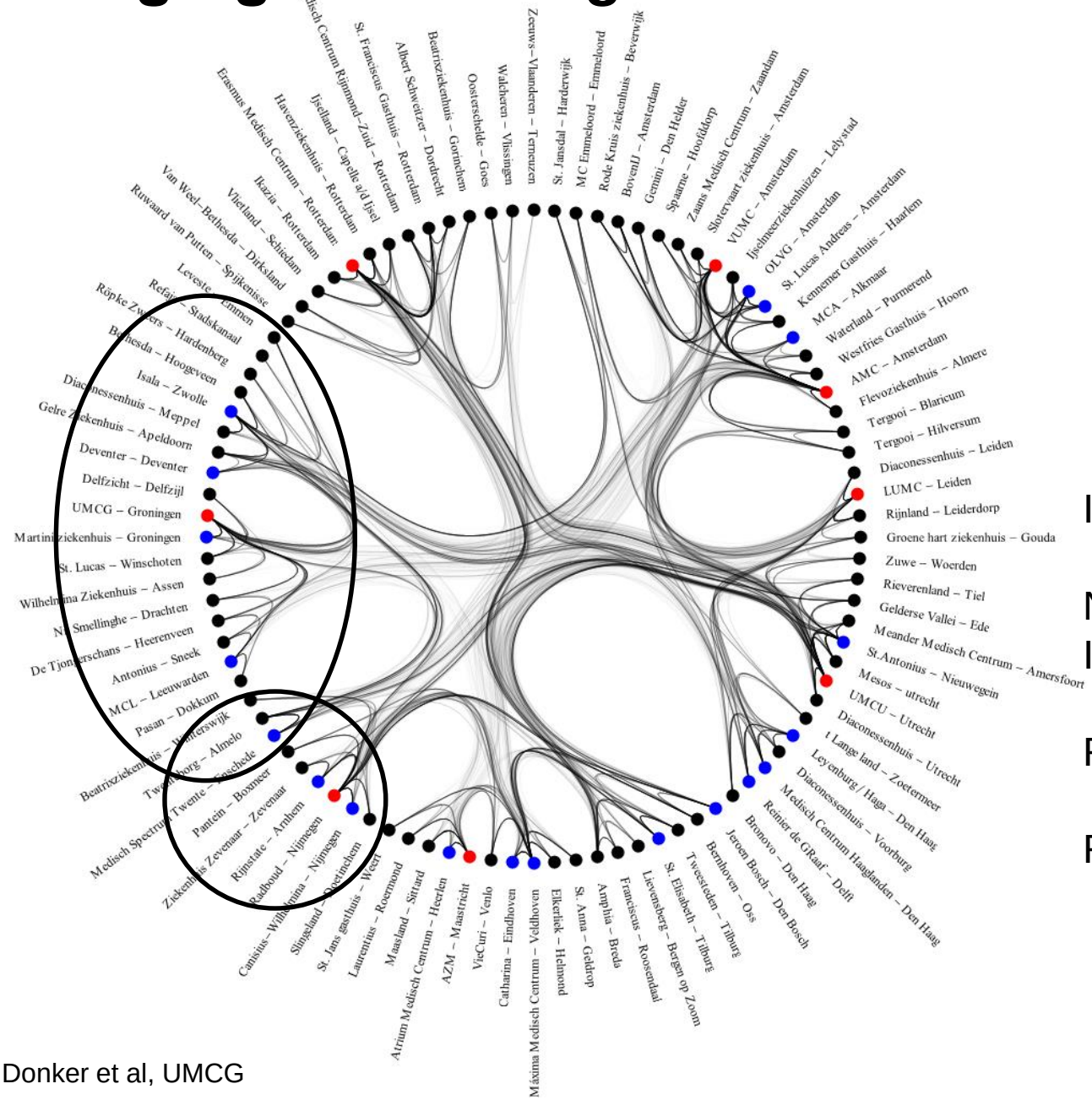
“Healthcare communities”

- Patients are shared within a definable healthcare communities
- Not size, but centrality decides on importance and necessary impact
- Regional intervention can reduce rate also in low-IC performing hospitals
- Hubs of the community have higher responsibility

Zorgregio‘s en zorgclusters in NL

Structuur:
7 zorgregio‘s
20 zorgclusters

20 regionale centra
45 lokale centra



Interdependency

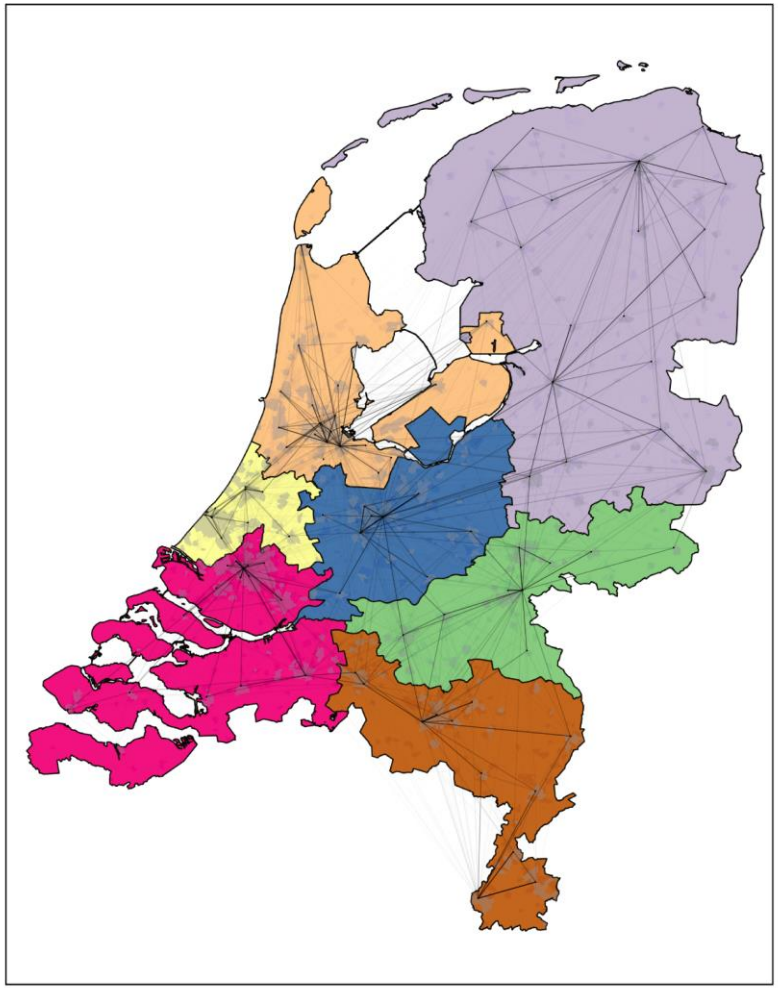
No benchmarking between Institutions within one cluster

Regional quality

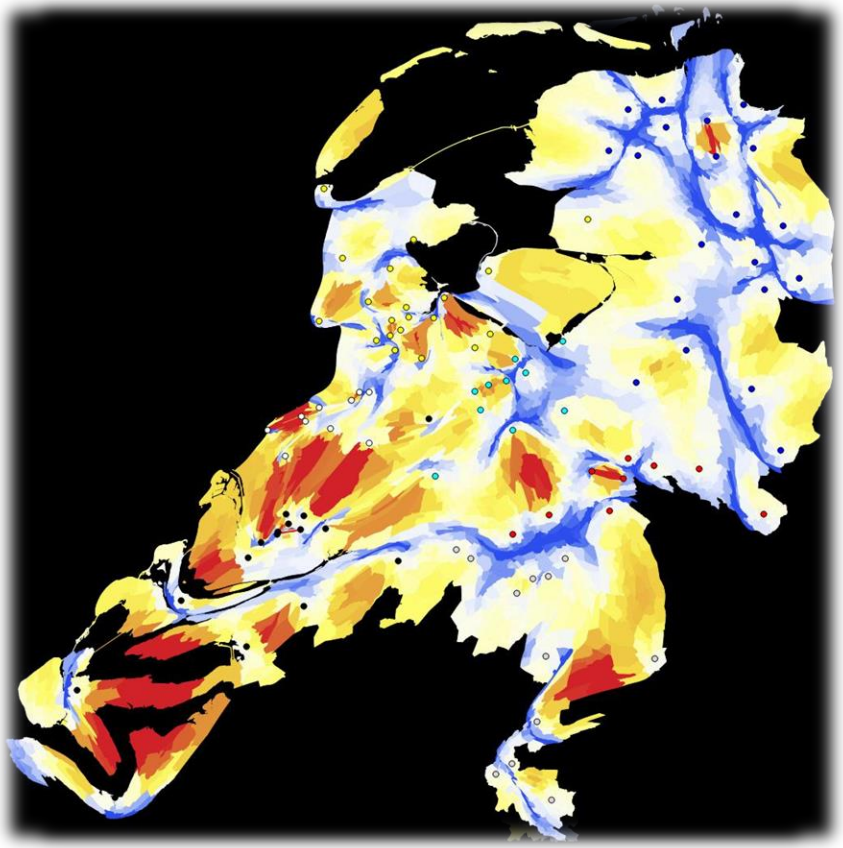
Regional prevention budget

Donker et al, UMCG

Regional Healthcare Networks



Healthcare network map



zeer kort

neutraal

zeer groot

Heat map of epi-distance by geo-distance

Tjbbe Donker, UMCG 2014

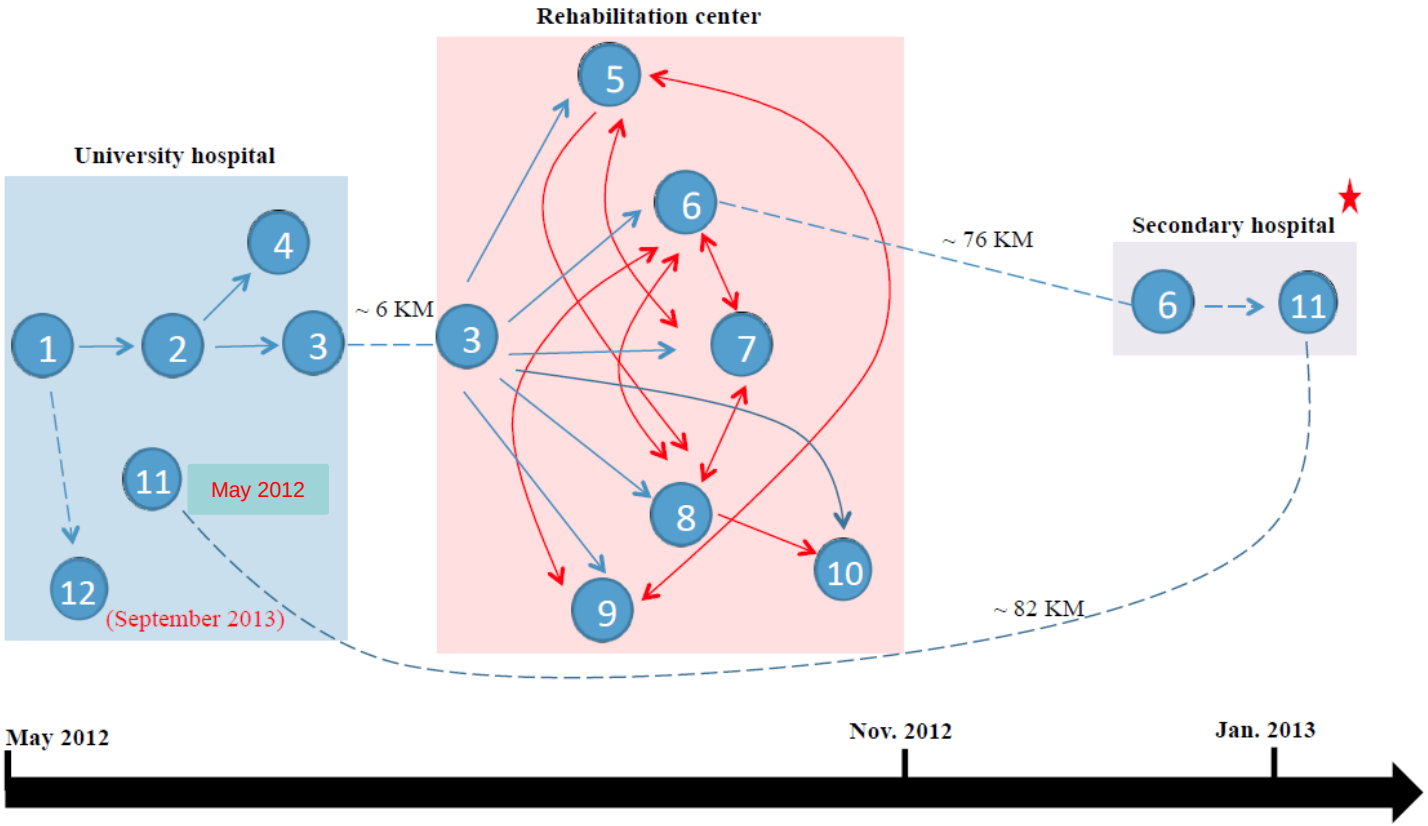
SCIENTIFIC REPORTS

OPEN

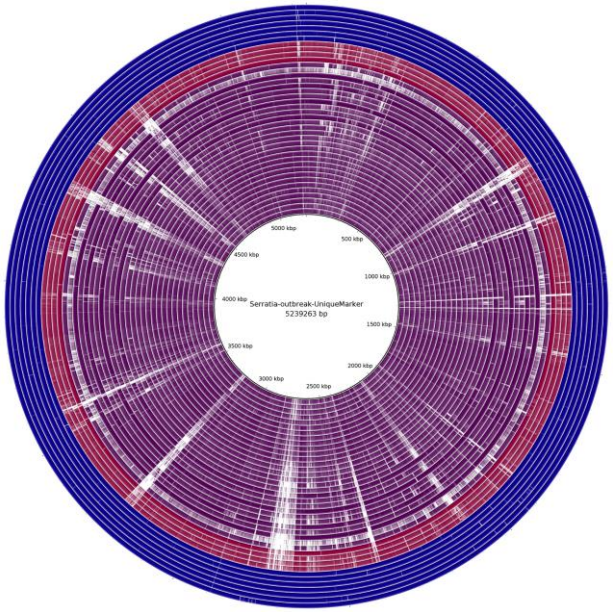
Use of whole-genome sequencing to trace, control and characterize the regional expansion of extended-spectrum β-lactamase producing ST15 *Klebsiella pneumoniae*

Received: 03 November 2015
Accepted: 13 January 2016
Published: 11 February 2016

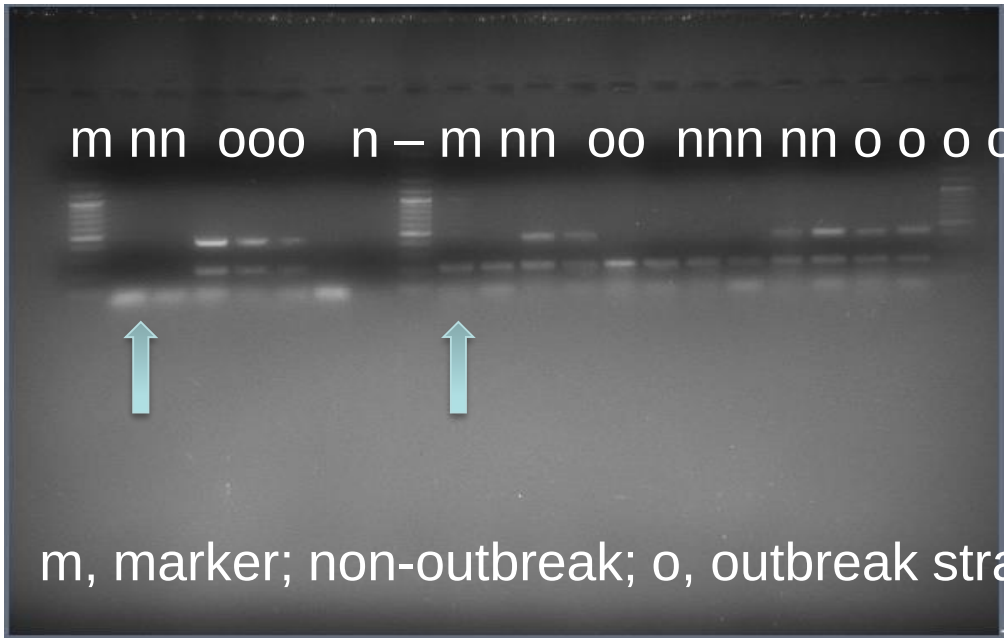
Kai Zhou[1,3], Mariette Lokate[1], Ruud H. Deurenberg[1], Marga Tepper[2], Jan P. Arends[1], Erwin G. C. Raangs[1], Jerome Lo-Ten-Foe[1], Hajo Grundmann[1], John W. A. Rossen[1,*] & Alexander W. Friedrich[1,*]



On demand Dgn-test

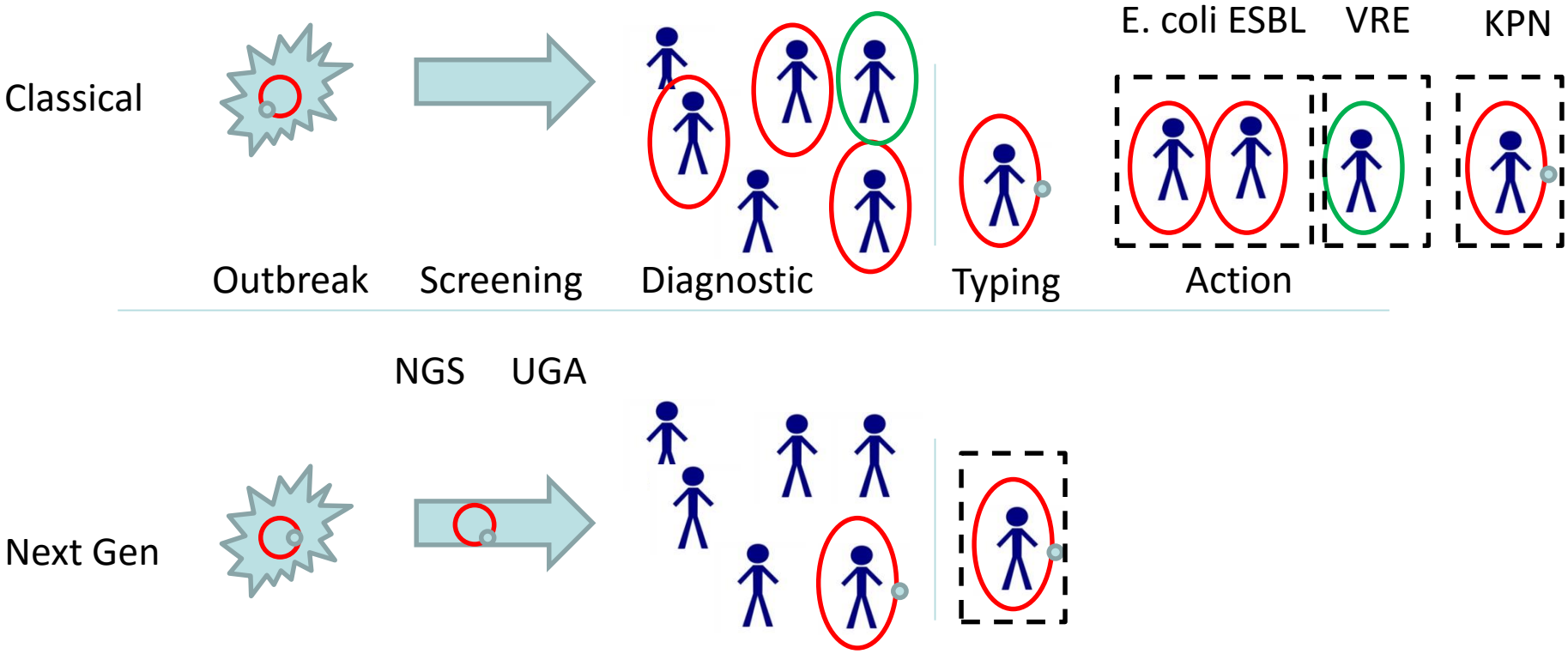


- Designing primers to amplify Unique marker(s)
  - CDS for hypothetical proteins
  - *luxS* gene: modulates virulence and antibiotic production via extracellular signaling
  - *irp2* gene: encoding the iron regulatory protein 2



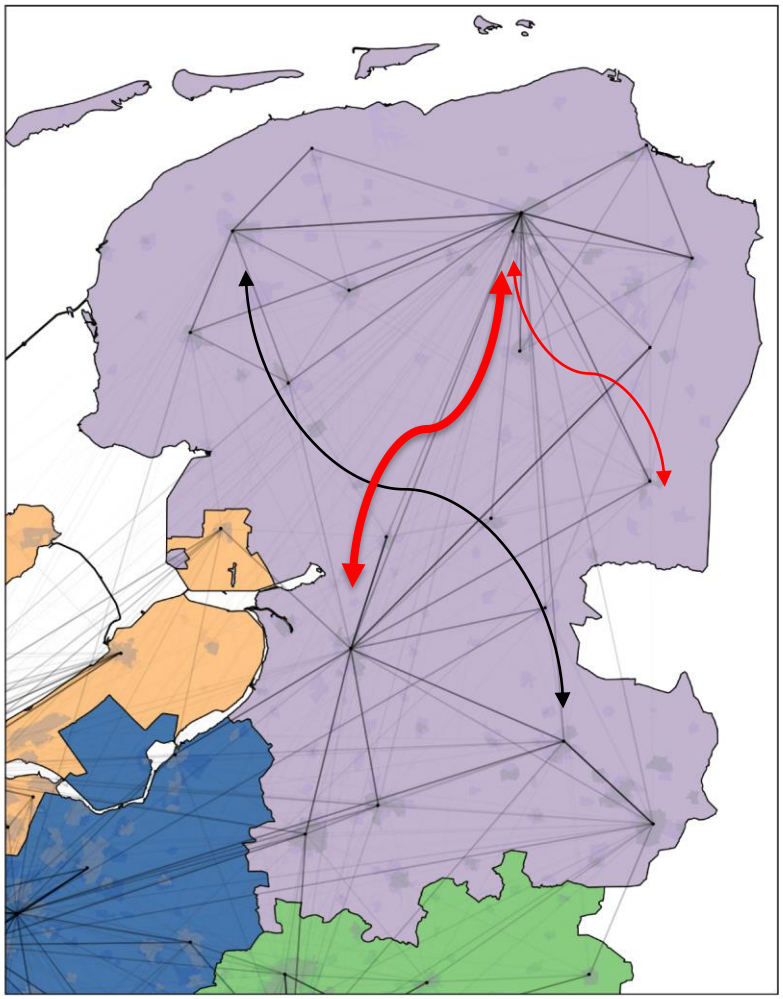
Zhou et al. Nat Scient Rep 2015

Tailor-made diagnostics using unique gene signatures at the UMCG



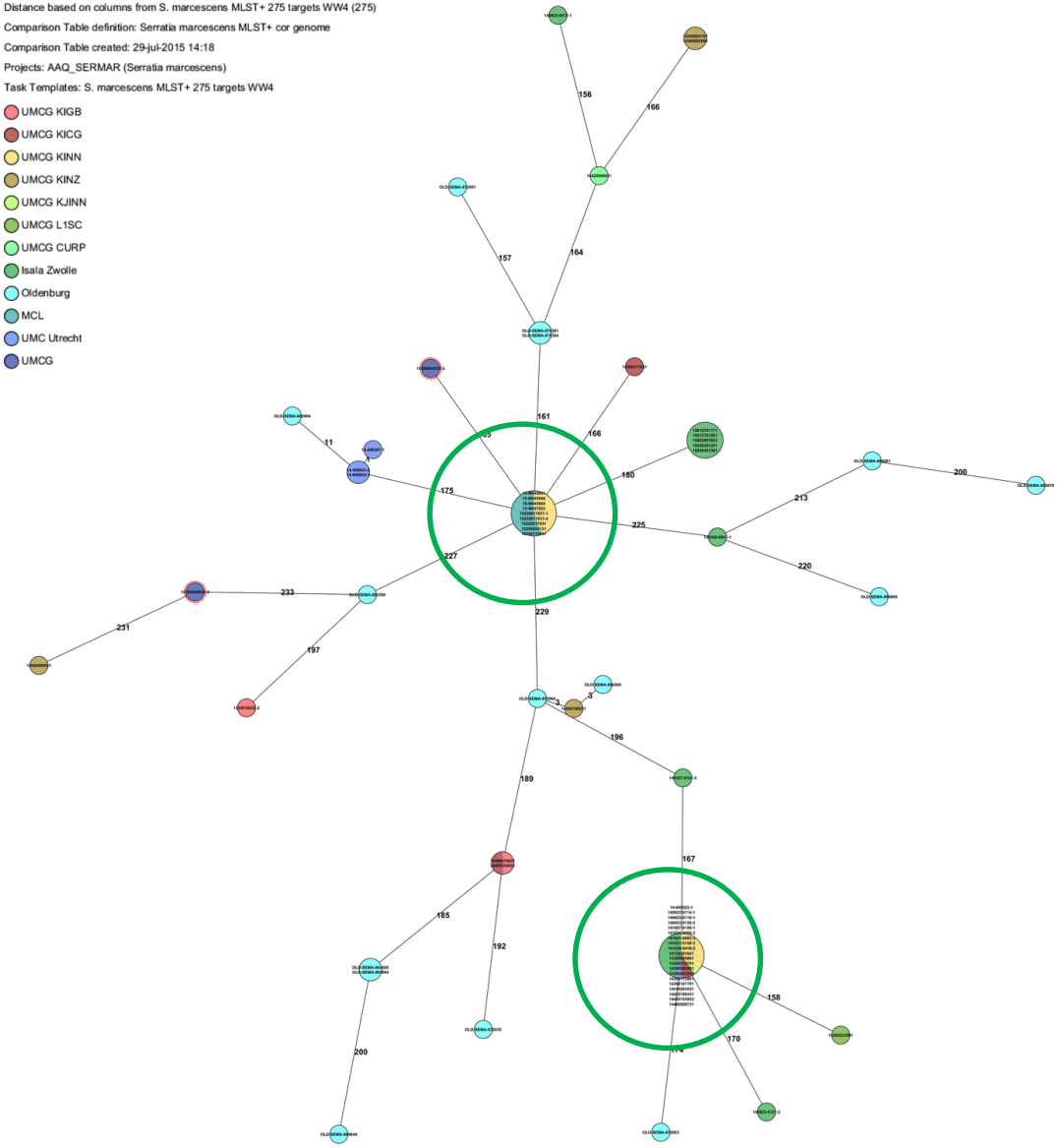
Type first and <u>not</u> afterwards

Interventional Microbiology



MST for 68 Samples based on 275 columns, pairwise ignoring missing values
Distance based on columns from S. marcescens MLST+ 275 targets WW4 (275)
Comparison Table definition: Serratia marcescens MLST+ cor genome
Comparison Table created: 29-jul-2015 14:18
Projects: AAQ_SERMAR (Serratia marcescens)
Task Templates: S. marcescens MLST+ 275 targets WW4

- UMCG KIGB
- UMCG KICG
- UMCG KINN
- UMCG KINZ
- UMCG KJINN
- UMCG L1SC
- UMCG CURP
- Isala Zwolle
- Oldenburg
- MCL
- UMC Utrecht
- UMCG



Crossborder healthcare in the the Dutch-German Euregio

12 Mio inhabitants
241 hospitals
10 universities

Kooperation Kinderherzen mit Groningen
12. Januar 2012

Ein erfolgreiches Fazit für eine medizinische grenzüberschreitende Kooperation zwischen Oldenburg und Groningen wurde am 12. Januar 2012 in der Kinderklinik gezogen. Auf dem Foto von rechts nach links:

Winterswijkse patiënten in Bocholt behandeld

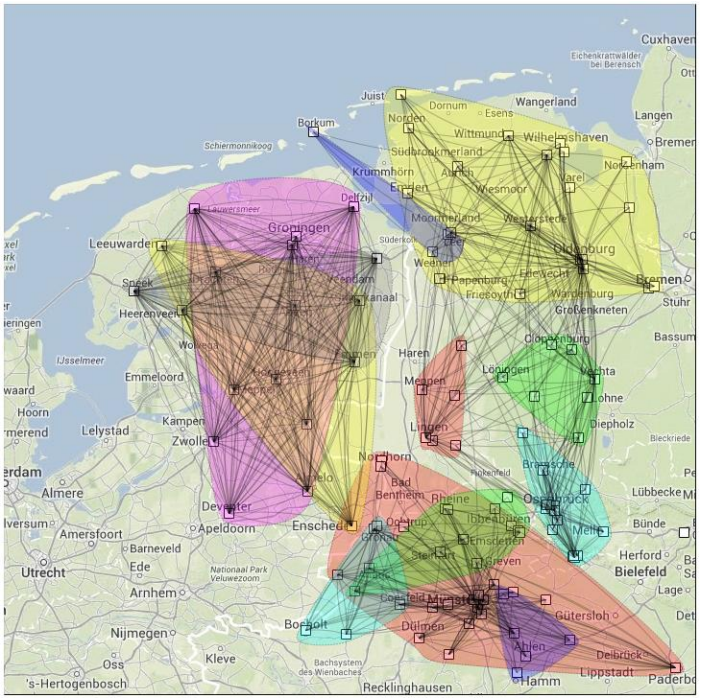
23 februari 2014 | Laatste update: 23 februari, 15:28

SKB stuurt spoeddotters over de grens

EUROPEAN MEDICAL SCHOOL

Outbreak simulation in the regio

24 Month- Transmission simulation under hub-conditions



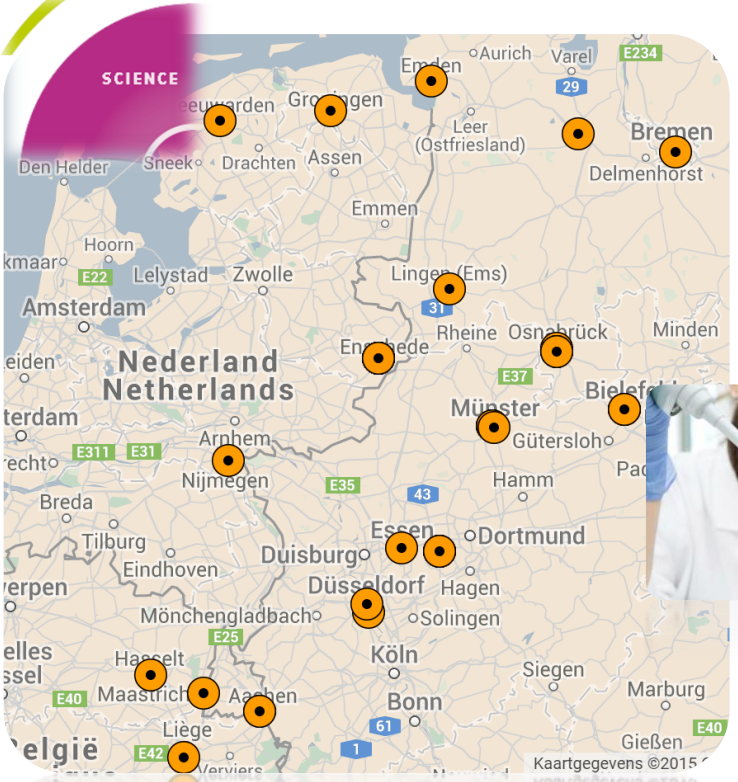
Crossborder innovation

71 Partner
30 SME's
41 Universities, Health partners, authorities

EurHealth-1Health

Euregional Prevention Against Antibiotic Resistance and Infections

HEALTH i CARE



INTERREG Deutschland Nederland

Europäische Union
Europese Unie

- **Sustainable and Smart antibiotics**

- **Infection- &Resistance prevention**
- **Personalized microbiology**

- **Regional Healthcare Networks**

- **Crossborder innovation**