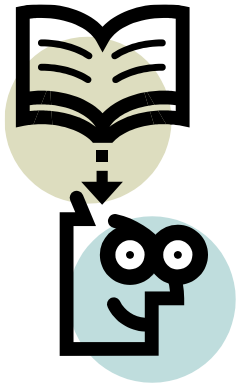


# Antimicrobial stewardship



Leonardo Pagani, MD

*ESCMID Fellow*

*WHO Expert Advisor*

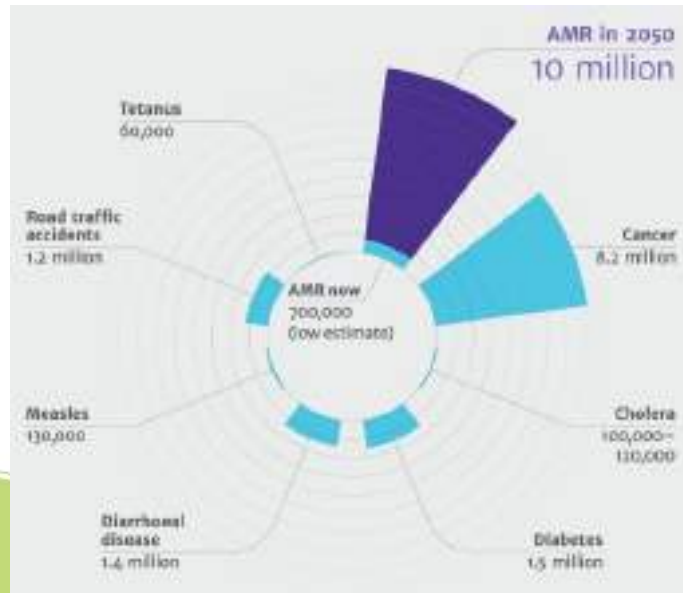
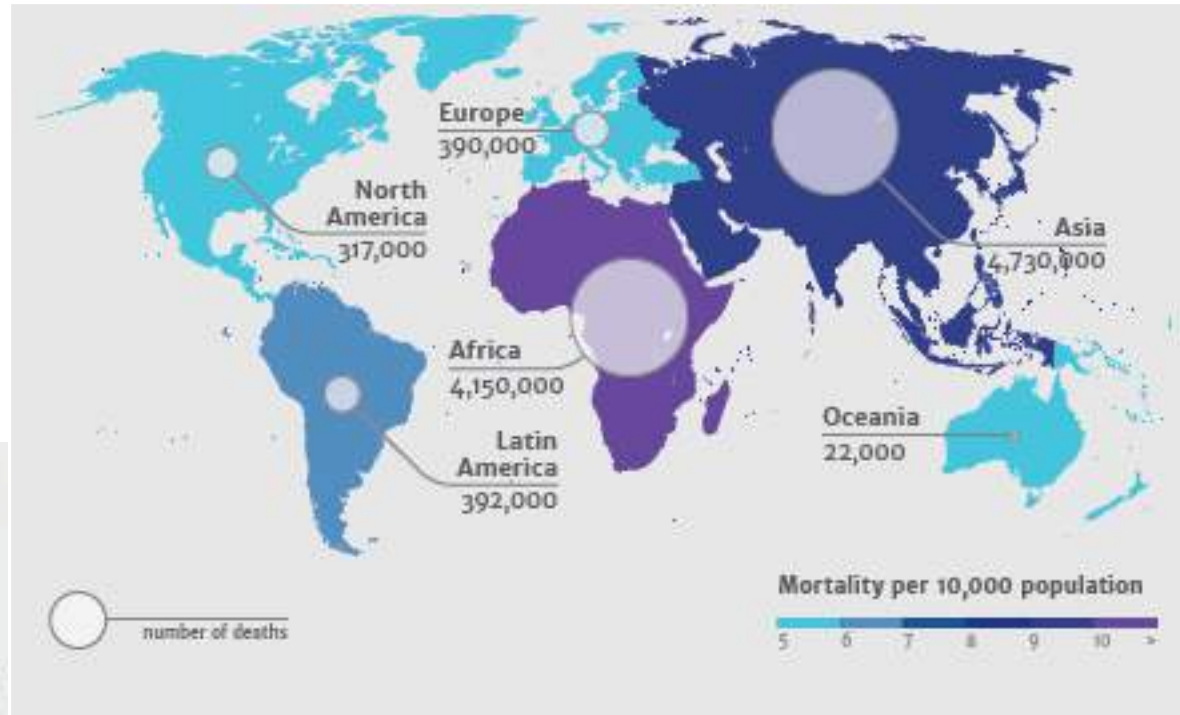
*Executive Board GAIS*

15.06.2023

# The perfect storm is approaching..

*O'Neill report,  
UK, 2014*

## Deaths attributable to AMR every year by 2050



...and this scenario did not even take into account the upcoming pandemic “era” ...

# The homogenisation of prescribing “just in case” prescribing, often saves the day in uncertainty

But some daily experiences are ‘just in case’

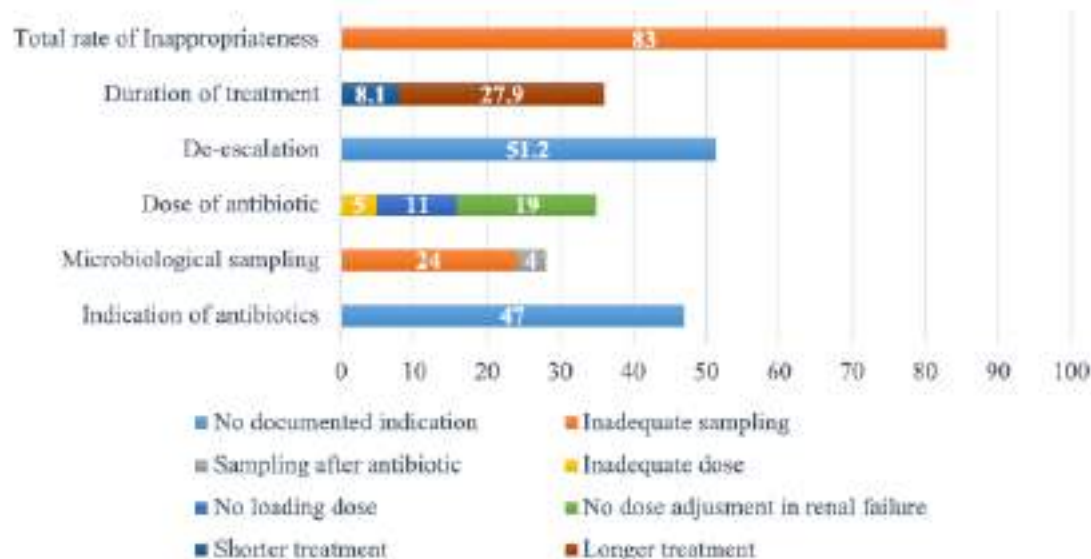
- meropenem in ICU
- ceftriaxone in heart failure
- prolonged orthopaedic prophylaxis
- confusion is caused by a UTI
- wound culture report implies need for treatment
- a few more days treatment may help, etc..



Thomas Jefferson  
drafting  
an audit on  
ceftriaxone use



## Reasons for Inappropriate Use of Antibiotics



**Fig. 1** Reasons for inappropriate use of antibiotics

### RESEARCH ARTICLE

### Open Access

## Inappropriate use of antibiotics effective against gram positive microorganisms despite restrictive antibiotic policies in ICUs: a prospective observational study



Hüsnü Selçuk Özger<sup>1</sup>, Döküny Merve Fakıoğlu<sup>2</sup>, Kübra Erbay<sup>3</sup>, Aslınur Albayrak<sup>2</sup> and Kenan Hoel<sup>1</sup>

Maybe we have a problem...



# **FIGHT ERRORISM !!**

## **Tackle AMR: Antimicrobial Stewardship**

- An activity that optimizes antimicrobial management and includes selection, dosing, route and duration of antimicrobial therapy
- Used to reduce inappropriate antimicrobial use, improve patient outcomes and reduce adverse consequences (AMR, toxicity and unnecessary costs)
- **Along with infection control, hand hygiene and surveillance**, a key strategy in local and national programs to prevent the emergence of AMR



**PATIENT SAFETY !**

# Who ? ..and what for...??

- AS teams
- ID clinicians
- IPC staff
- Clinical pharmacists
- Public health officials
- Global health workers
- Veterinary and agricultural professionals

Work in action:

AS is for our children's children...

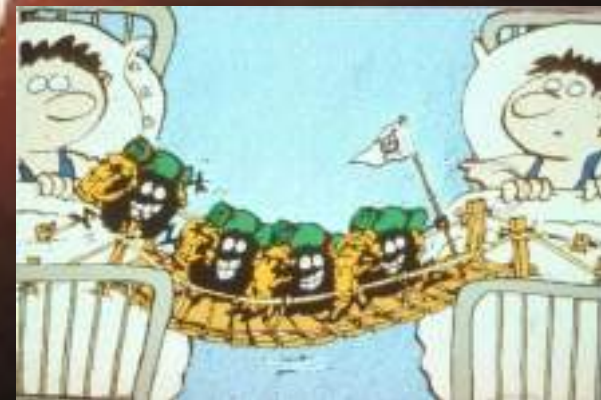
We all need to be stewards of antibiotics

*“The future belongs to preventive health care. This science, going hand in hand with curative health care will bring undoubted benefits to mankind.”*

*N.I. Pirogov (1810–1881)*



# Hand hygiene...



If hospital bugs would look like this - compliance with hand hygiene would be 100%



This is unfortunately still not the case...

# How to maximize positive outcomes and improve safety of our patients?



**Mug**



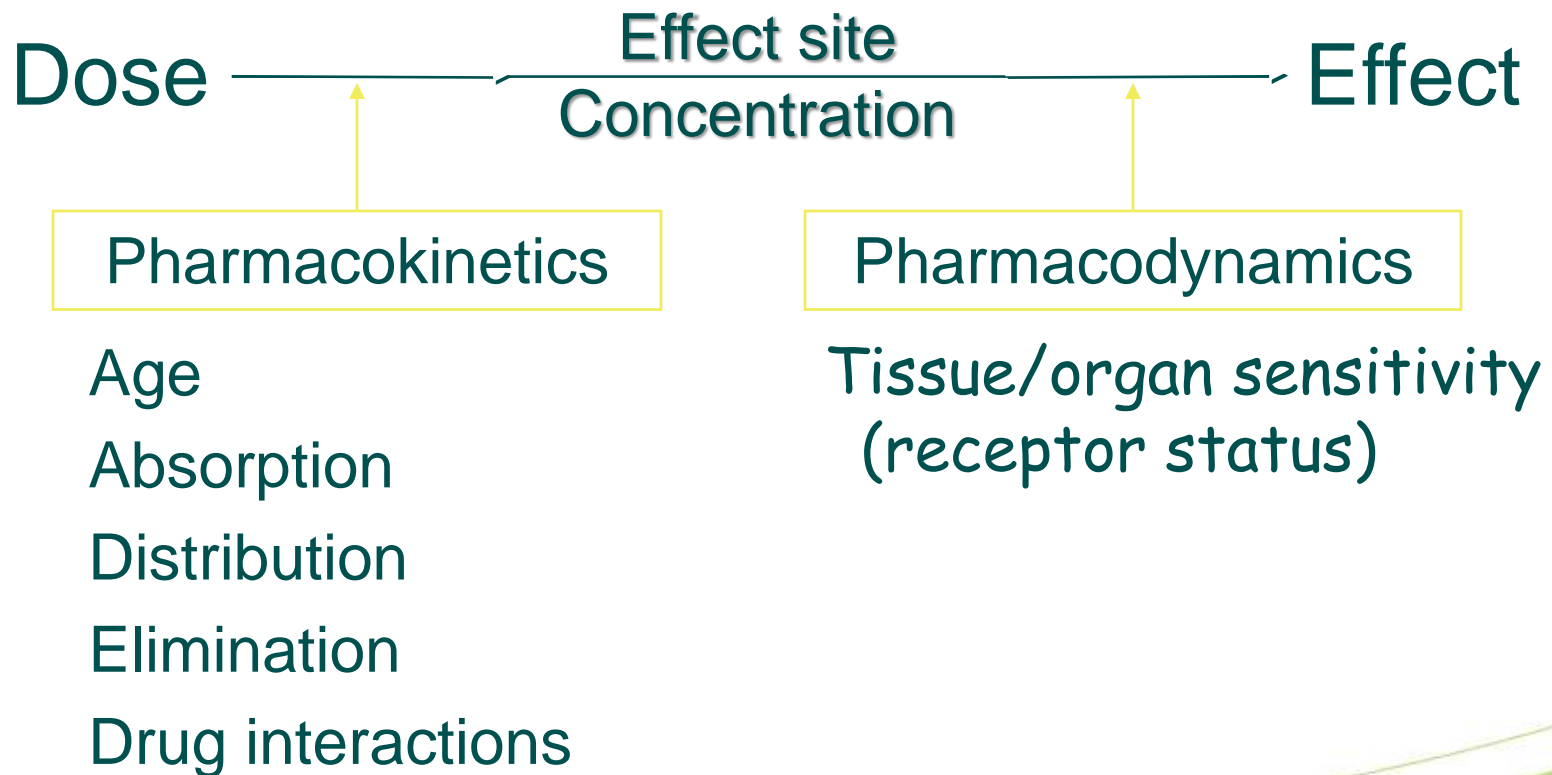
The 'players' in this challenging match

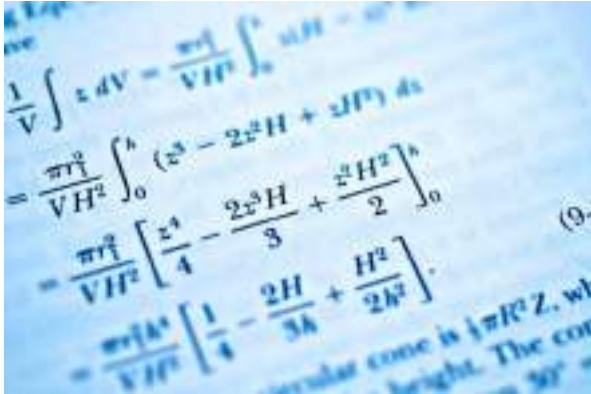
**Drug**

**Bug**



# Relating Dose to Effect *In Vivo*





## Antimicrobial pharmacodynamics: Interaction between antibiotics and their effects on pathogens

- The study of antimicrobial pharmacodynamics has proved useful for
  - establishing newer optimal dosing regimens for currently available drugs
  - developing new antimicrobials and new formulations (EMA rules)
  - establishing susceptibility breakpoints (New EUCAST rules)
  - formulating guidelines for empirical therapy of infections



# EUCAST

EUROPEAN COMMITTEE  
ON ANTIMICROBIAL  
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

The new definitions of S, I and R emphasize the close relationship between the susceptibility of the organism and the exposure of the organism at the site of infection. Following the change there are two levels of susceptible and one of resistant, as compared to before when there were two levels of resistant and one of susceptible. The term “non-susceptible” now encompasses only resistant organisms.

- **S - Susceptible, standard dosing regimen:** A microorganism is categorised as “Susceptible, standard dosing regimen”, when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
- **I - Susceptible, increased exposure:** A microorganism is categorised as “Susceptible, Increased exposure” when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
- **R - Resistant:** A microorganism is categorised as “Resistant” when there is a high likelihood of therapeutic failure even when there is increased exposure.

**Dose** is the amount of agent given to the patient whereas **exposure** includes dose, mode of administration, and both general pharmacokinetics and pharmacokinetics at the site of the infection. The doses against which breakpoints were reviewed and revised to match the new definitions are listed in a specific document ([EUCAST: Clinical breakpoints and dosing of antibiotics](#)), also part of the breakpoint table.

# Routine collection, analysis and feedback of information about AMR and MICs



Mandatory, before planning any **intervention**

# AmpC vs. ESBL vs. MBL

Pagani L, et al. *Infect Drug Resist* 2014

|  | AmpC                              | ESBL      | MBL       |
|--|-----------------------------------|-----------|-----------|
| Penicillins  | Resistant                         | Resistant | Resistant |
| Cephalosporins   | Resistant<br>(except<br>cefepime) | Resistant | Resistant |
| Aztreonam  | Resistant                         | Resistant | Sensitive |
| $\beta$ -lactamase<br>inhibitors<br>(tazobactam,<br>clavulanic, etc) | Resistant                         | Sensitive | Resistant |



# Decision making in antimicrobial choice

Adequate prescription demands consideration of:

- Bacteriology (susceptibility testing)
- PK/PD (kinetics and dynamics)
- Tolerance & predisposition
- Ecology (impact on AMR)
- Costs



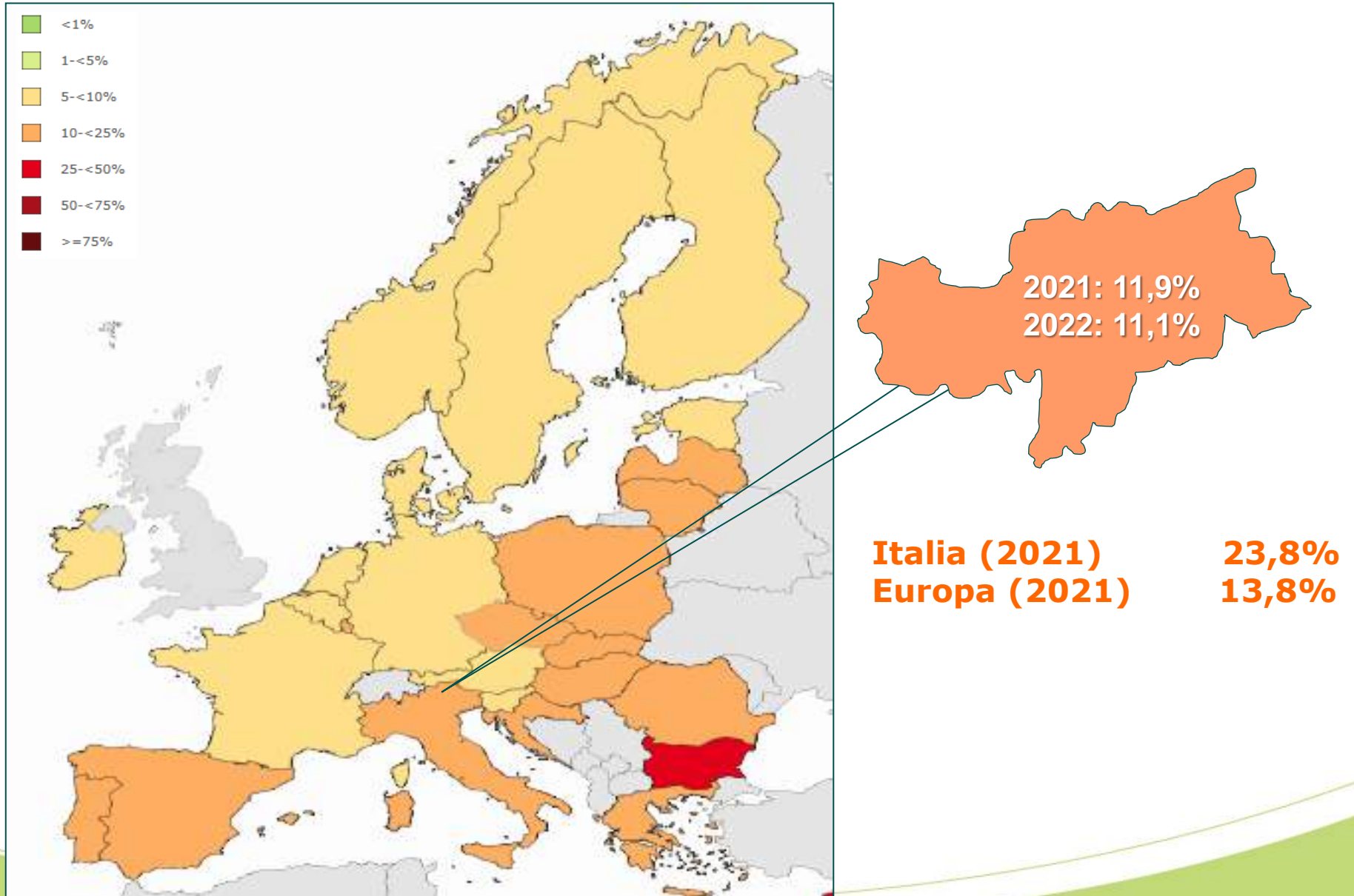
# Measures of Antibiotic Policy Change

- Process
  - Promoted and restricted antibiotics
  - Compliance with policy
- Outcome
  - *C difficile* infection
  - **Resistance**
  - Mortality (30 day) for medical and surgical admissions
  - Drug related toxicity [nephrotoxicity]

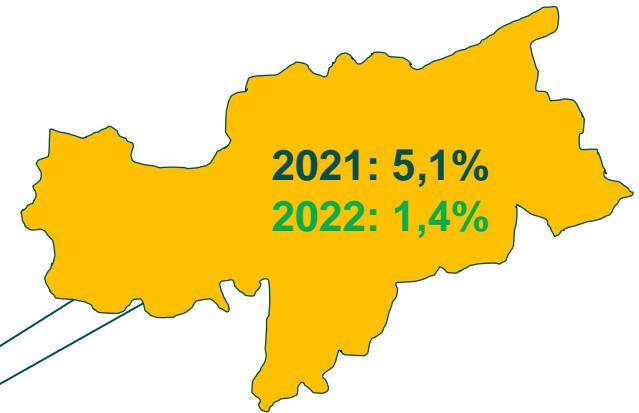
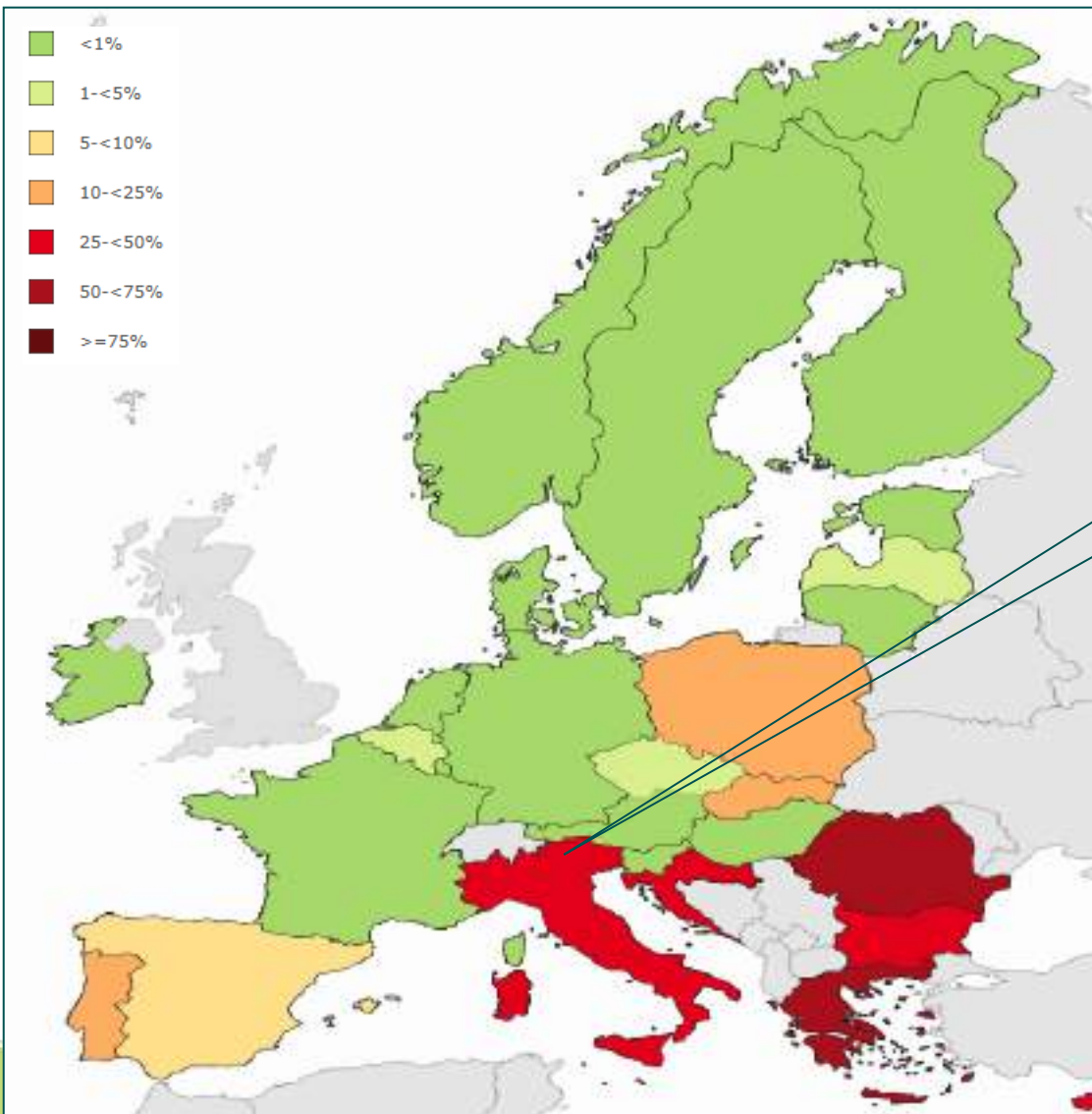
# What have we done until now..??

- Unit for Hospital Antimicrobial Chemotherapy (UHAC), officially approved and acting since 2007
  - *The first Italian multidisciplinary working Unit on Antimicrobial Stewardship within a healthcare institution*
  - *Pioneering what others have done far later, based on our experience*
  - *Still working much better than any other...*

## *E. coli* ESBL, sangue/liquor, 2021

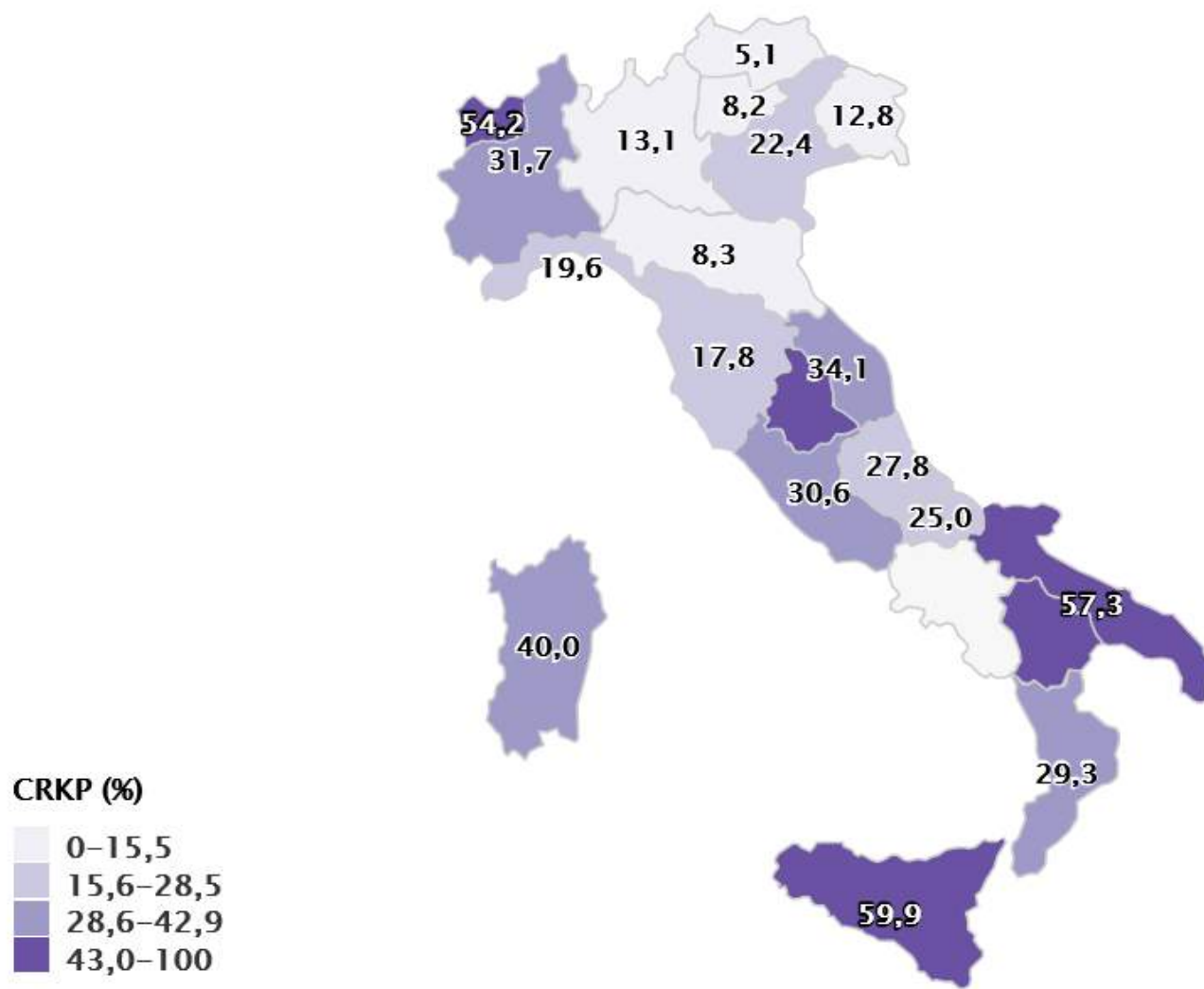


# *K. pneumoniae* Carba-R, sangue/liquor

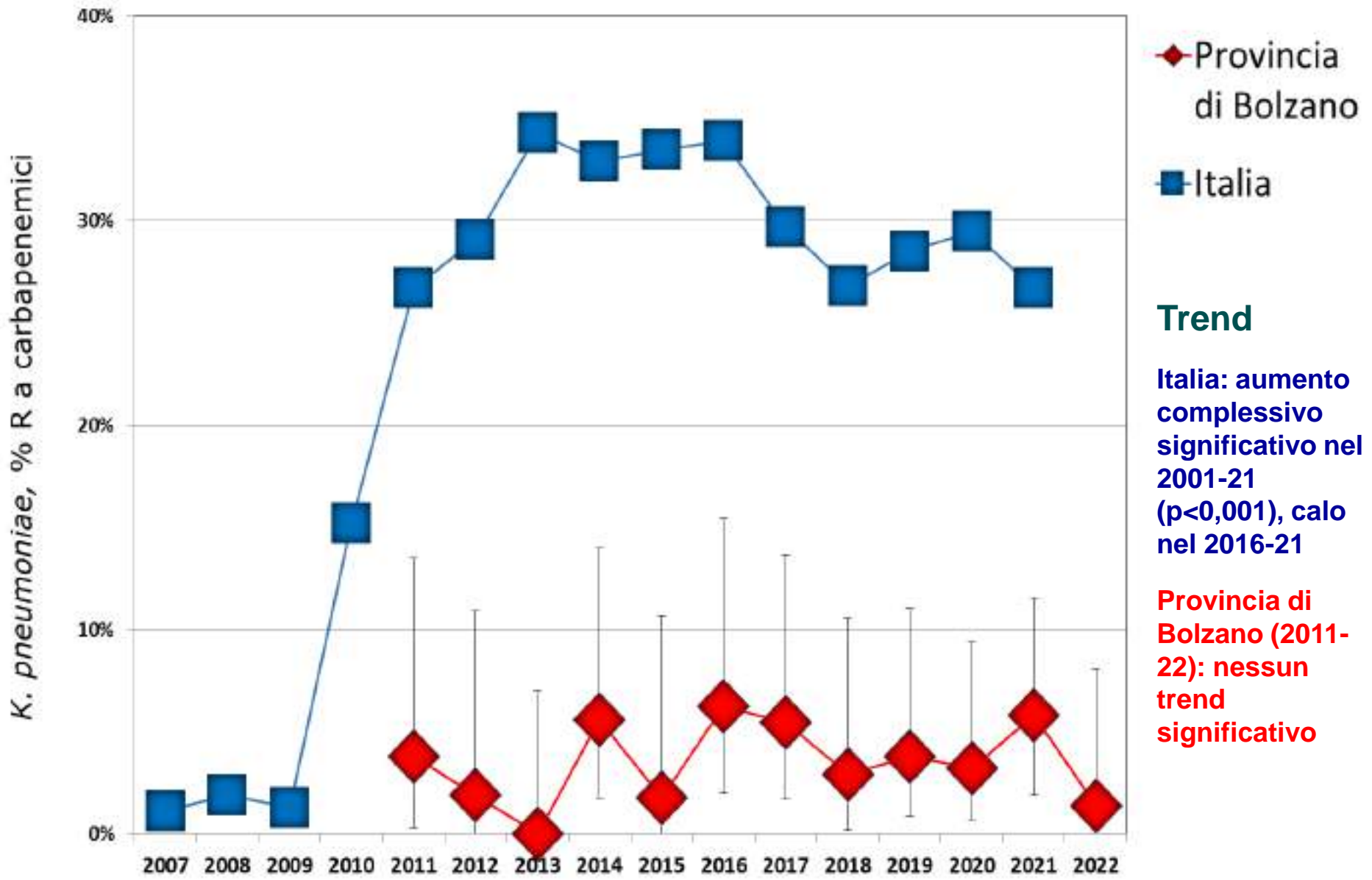


**Italia (2021) 26,7%**  
**Europa (2021) 11,7%**

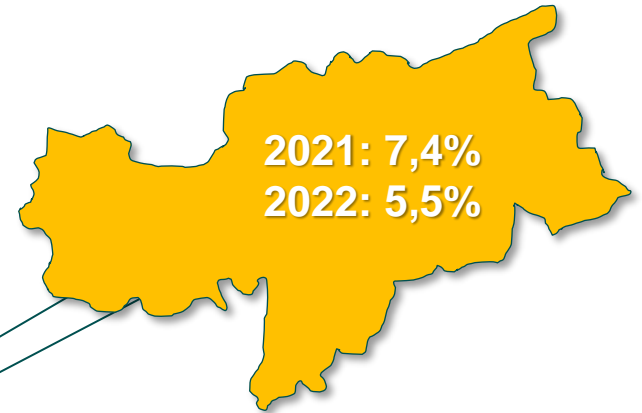
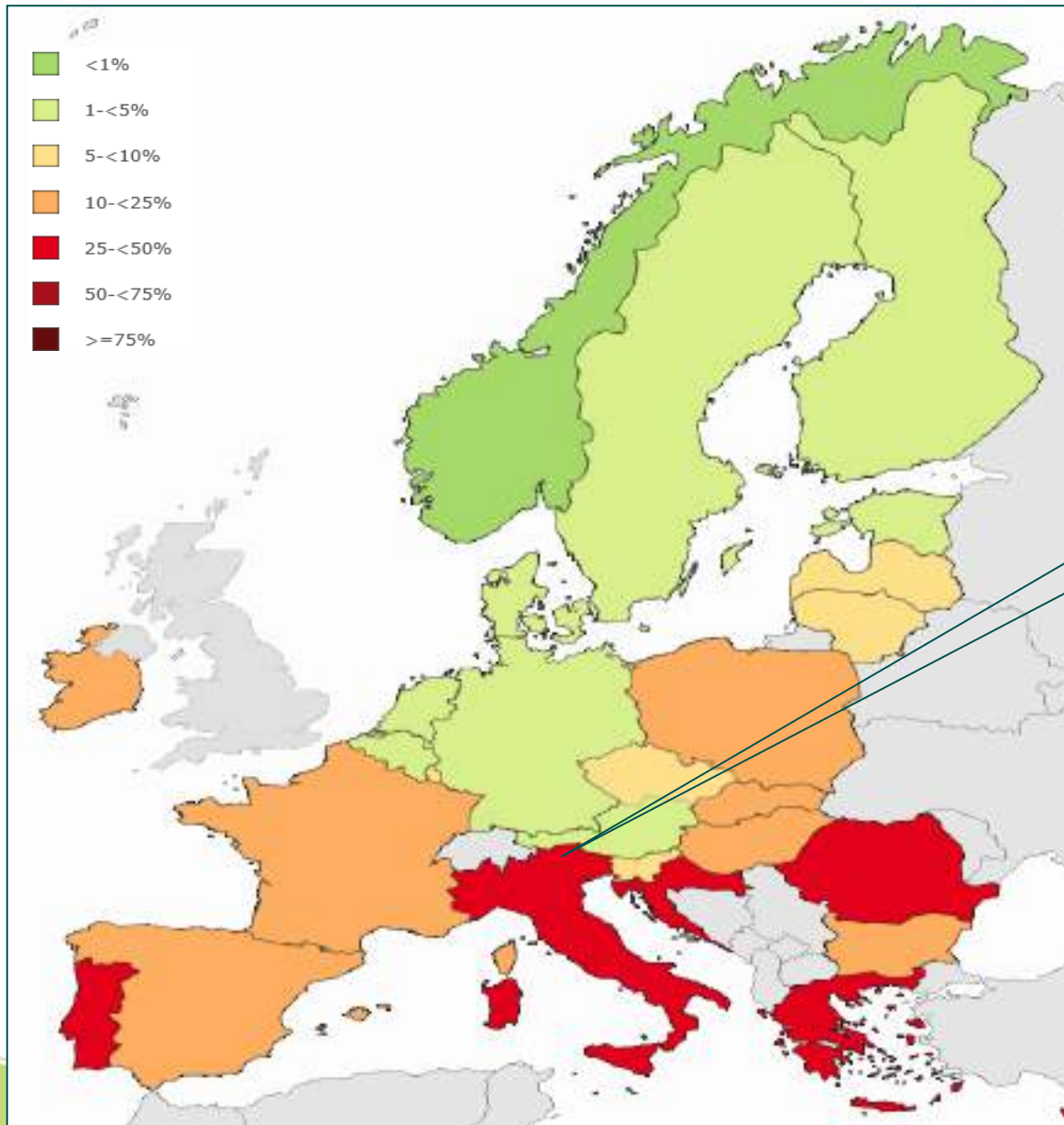
# *K. pneumoniae* Carba-R, sangue/liquor, 2021



# *K. pneumoniae* Carba-R, sangue/liquor, trend



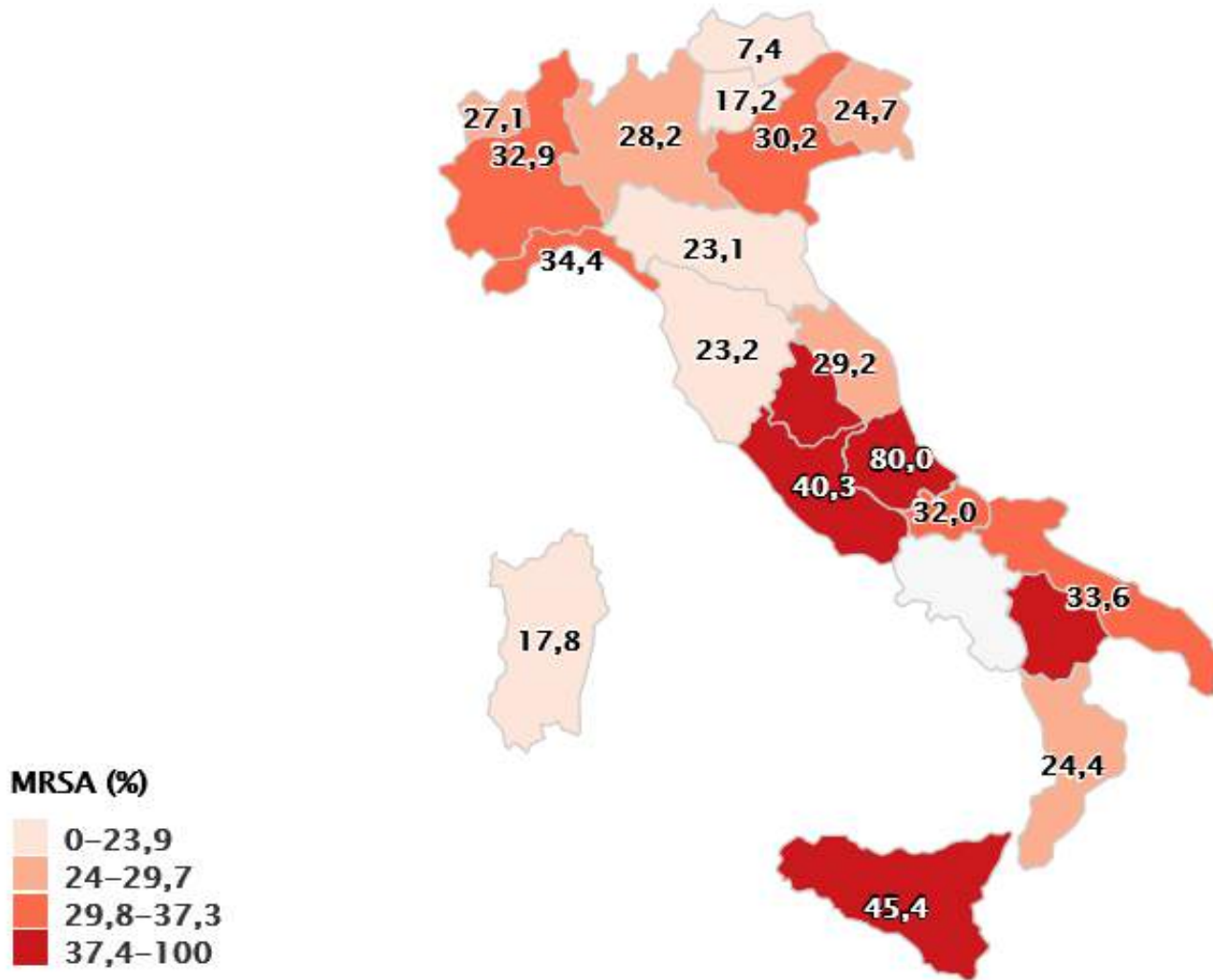
# **MRSA, sangue/liquor, 2021**



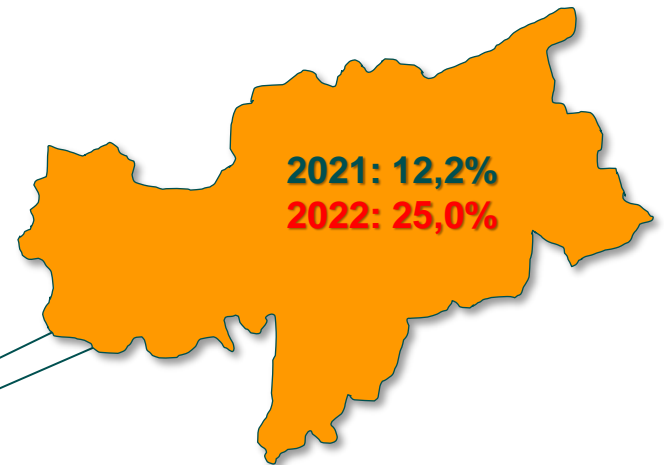
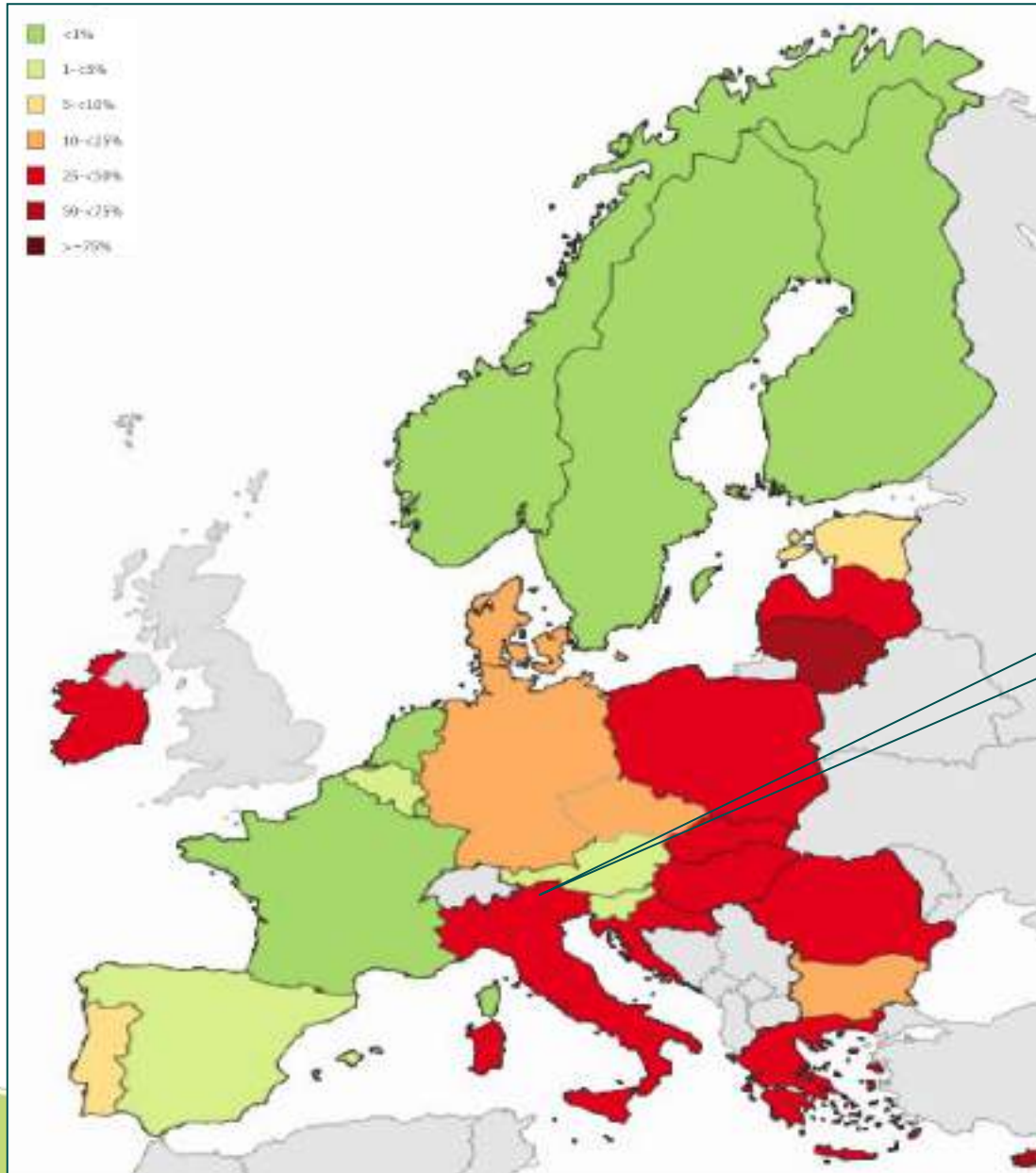
**Italia (2021) 30,0%**  
**Europa (2021) 15,8%**



# ***MRSA***, sangue/liquor, 2021



# VRE, sangue/liquor, 2021



**Italia (2021) 28,2%**  
**Europa (2021) 17,2%**

# Measures of Antibiotic Policy Change & Quality in Healthcare

- Process
  - Promoted and restricted antibiotics
  - Compliance with policy
- Outcome
  - *C difficile* infection...okay, but old-fashioned
  - **Resistance Rates in your healthcare institution**
  - Mortality (30 day) for medical and surgical admissions
  - Drug related toxicity [nephrotoxicity]

# Different approaches for different targets

- Highly protocolized
- Impositive
- Outbreak (or budget) oriented
- Quite easy and definite
- No special skills required
- Ideal for turnaround
- Broad coverage of domain
- Progressive education
- Clinically oriented
- Time and effort consuming
- High-level expertise
- Dedicated team

Cheng WCC et al. *Eur J Clin Microbiol Infect Dis* 2009;28:1447-1456

Palmer HR et al. *Am J Health-Syst Pharm* 2011;68:2170-2174

Long term, outcome-centered asset

“Low-hanging fruit” approach

## Finally, ...

- ✓ While ASP have consistently shown improvement in AB usage, there are few studies examining meaningful clinical outcome measures
  - ✓ LOS, mortality rates or even quality indicators (e.g., patient satisfaction)
- ✓ The relative paucity of outcome data demonstrating the benefits of ASP is likely due to its infancy: ASP today are where IC programs were 40 years ago
- ✓ In the absence of outcome monitoring, ASP are nothing more than programs to reduce AB use, with a largely unproven effect on patient care and safety



## Conclusions

Observations from this ECDC country visit confirm that the AMR situation in Italian hospitals and regions poses a major public health threat to the country. The levels of carbapenem-resistant *Enterobacteriaceae* (CRE) and *Acinetobacter baumannii* have now reached hyper-endemic levels and, together with methicillin-resistant *Staphylococcus aureus* (MRSA), this situation causes Italy to be one of the Member States with the highest level of resistance in Europe.

During conversations in Italy, ECDC often gained the impression that these high levels of AMR appear to be accepted by stakeholders throughout the healthcare system, as if they were an unavoidable state of affairs.

The factors that contribute negatively to this situation seem to be:

- Little sense of urgency about the current AMR situation from most stakeholders and a tendency by many stakeholders to avoid taking charge of the problem;
- Lack of institutional support at national, regional and local level;
- Lack of professional leadership at each level;
- Lack of accountability at each level;
- Lack of coordination of the activities between and within levels.

If the current trends of carbapenem resistance and colistin resistance in gram-negative bacteria such as *Klebsiella pneumoniae* and *A. baumannii* are not reversed, key medical interventions will be compromised in the near future. Untreatable infections following organ transplantation, intensive care or major surgical interventions are now a significant possibility in many Italian hospitals.

Infections caused by resistant bacteria are associated with increased morbidity, mortality, length of hospital stay, and costs.<sup>6</sup> If unrelenting attention to infection control practices is crucial, the administration of antimicrobials should no longer be considered a single's pledge, as clearly demonstrated by these recent Italian experiences. AMPs are rightly aimed at a more appropriate prescription of antimicrobials and trigger a virtuous circle through tight collaborative efforts and ever-improving educational plans: we are bound to be geared up in helping caregivers avoid collateral damage related to antimicrobial misuse while ultimately improving patient safety. In Italy, we should really start thinking about effective antimicrobial policies rather than deeming antimicrobial resistance and inappropriate antimicrobial therapy as our inescapable fate.

Leonardo Pagani, MD

Richard Aschbacher, MBSc

Antimicrobial Management Program, Unit for Hospital Antimicrobial Chemotherapy (UHAC), Bolzano Central Hospital, Bolzano, Italy

*Am J Infect Contr*  
2009

The scientific man does not aim at an immediate result.

He does not expect that his advanced ideas will be readily taken up.

His work is like that of the planter—for the future.

His duty is to lay the foundation for those who are to come, and point the way.

Nikola Tesla

As scientists, we believe  
that this must also be:

our strategy  
our mission  
our vision

[lpagani.id@gmail.com](mailto:lpagani.id@gmail.com)

