# Diagnosing infection in the ICU.

# A new dawn?

## Kyiv 2016

Dr David Brealey
University College Hospital
London, UK

# Infection and Sepsis

- It's a bit of a problem and we don't seem to be doing very well
  - Incidence is increasing
  - No new interventions since antibiotics
  - Rise in multi-drug resistant bacteria
- To manage a condition we need to know what to treat

# Everything starts with the definition

- Sepsis is an ancient Greek term
- It means ‘decomposition’
- …and they described it perfectly:
  - ‘A local lesion, heated by humor afflux, makes the whole body become feverish. One can die because of this….’
  - ‘A darkening and a faster sedimentation of the form component of blood’

# So lets imagine……

Feverish, tachycardic and unwell

What you do about it depends a little in which century you live

# Two golden ages of sepsis

## 14th Century

- Make an assumption they are septic (Greek definition)
- Put to bed and wash with vinegar
- Blood letting
- Eat bread, fruit and veg
- Try
  - Tie a hen around their waist
  - Drink their urine
  - Warm treacle and beer

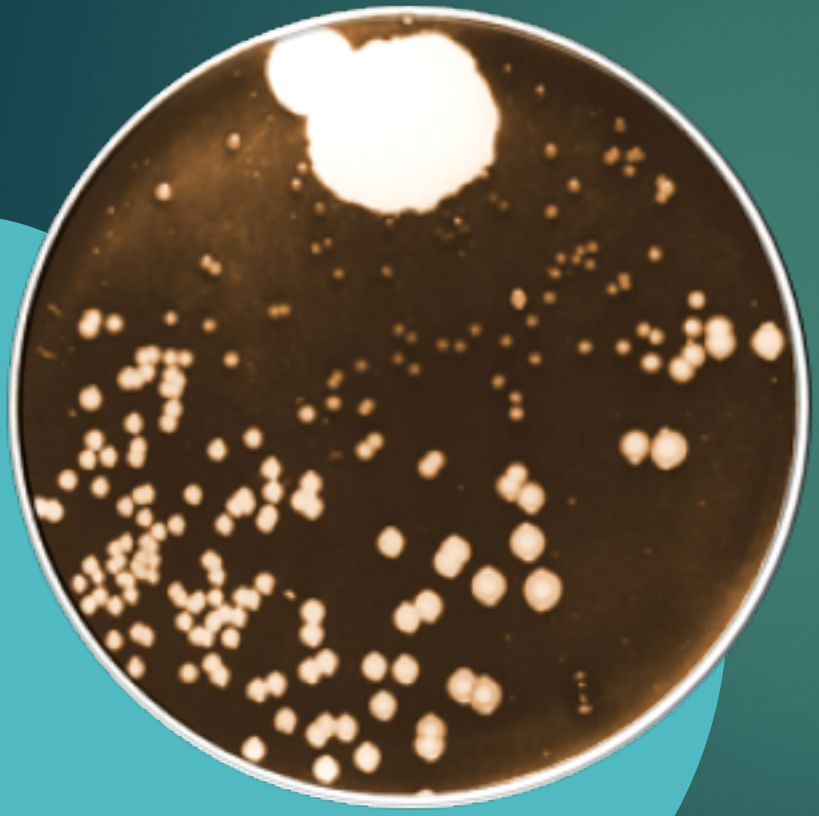
## 21st Century

- Make an assumption they are septic (give antibiotics)
- Put to bed and wash with chlorhexidine
- Tolerate a Hb>60g/l
- Start early nutrition
- Try
  - Activated Protein C
  - Talactoferrin (breast milk)
  - Steroids

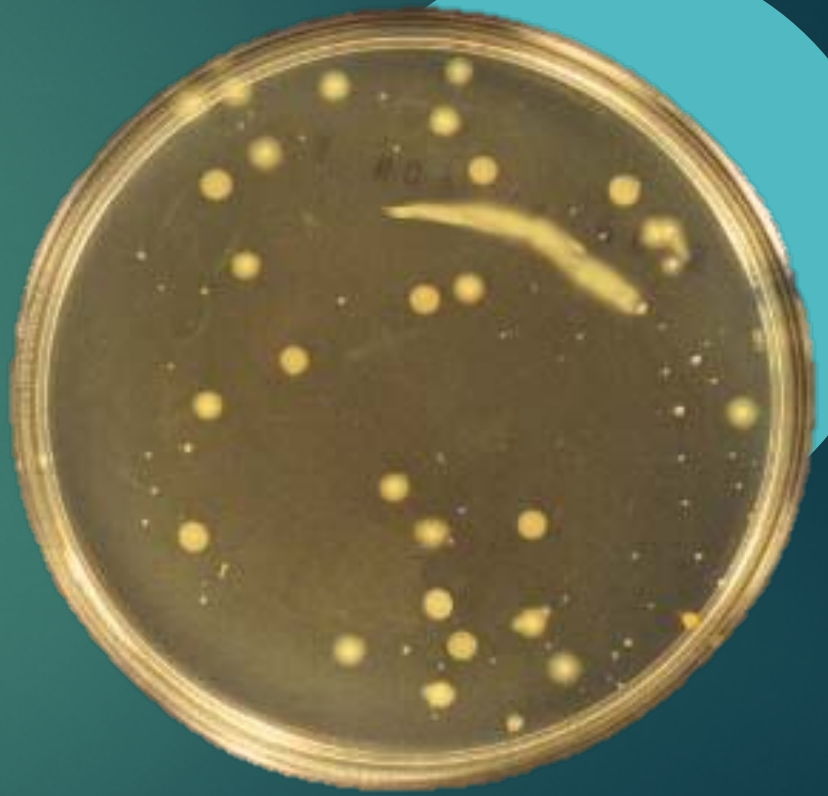
# What has changed?

- The clinical definition of sepsis in ancient Greece or Kyiv today:
  - Is highly non-specific
  - Does not isolate when the septic process started
  - Let alone what is causing it
- Our understanding has improved markedly
  - Mitochondria
  - Reactive oxygen/nitrogen species
  - Cell death etc etc
- But still held back by diagnostic uncertainty

# Not Rapid Pathogen Detection

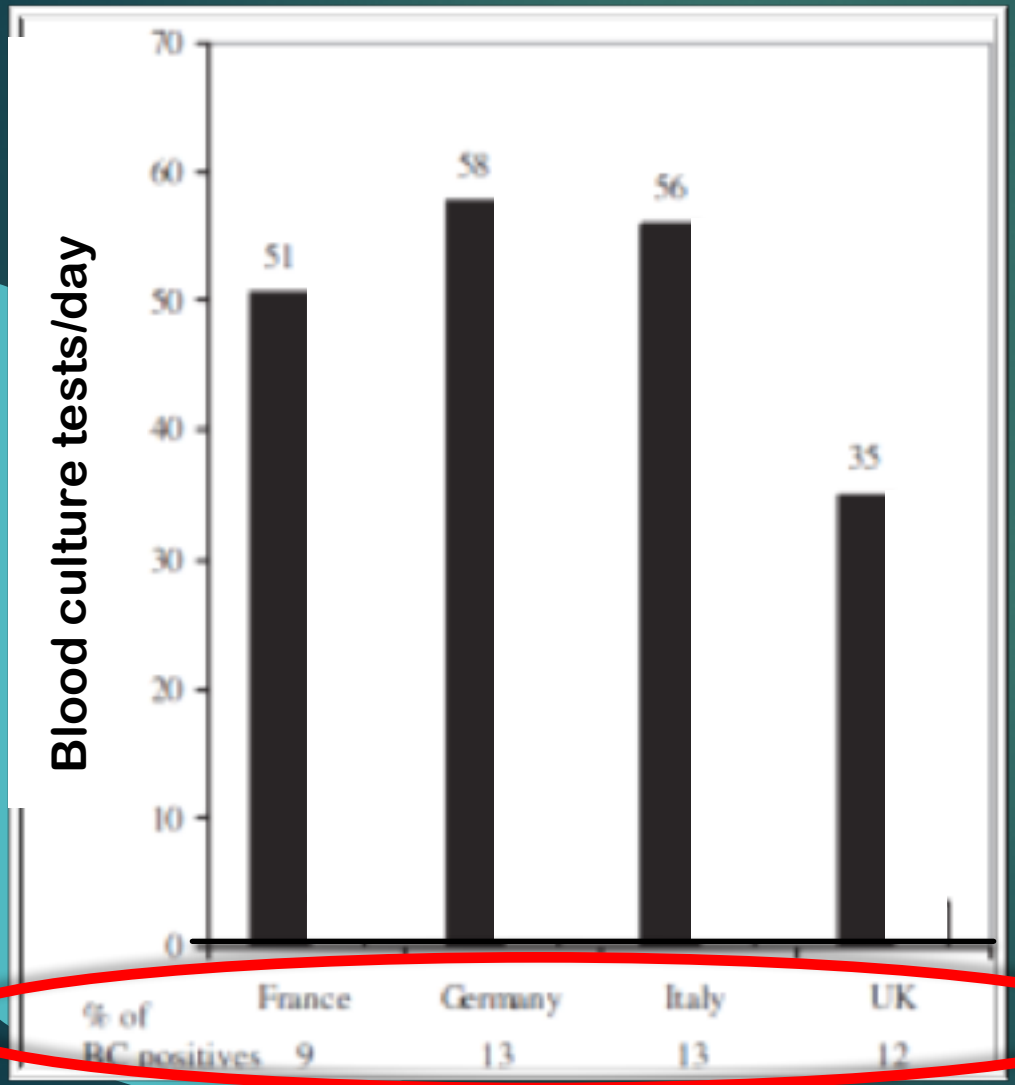


1928



2015

# The yield from blood cultures are negligible




Schmitz et al. Critical Care 2013, 17:R248
http://ccforum.com/content/17/5/R248

CRITICAL CARE

RESEARCH Open Access

Quality of blood culture testing - a survey in intensive care units and microbiological laboratories across four European countries

Roland PH Schmitz[1,2†], Peter M Keller[3,4†], Michael Baier[3], Stefan Hagel[5,6], Mathias W Pletz[5,6] and Frank M Brunkhorst[1,2,6,7*]

# When we are sure…we are not

- ARISE: 1600 patients with severe sepsis, 38% cultures were positive
- PROCESS: 1351 patients with severe sepsis, 31% cultures were positive
- ProMISe: 1260 patients with severe sepsis, 56% able to identify a pathogen
- SOAP study (observational European study): 1177 patients with infection, 468 had a pathogen identified (39%)
- Canada/US: 2,731 patients with Septic Shock – 37% had positive blood cultures (Kumar Crit Care Med 2006)

# So why is that?

- Often prior use of antibiotic
- Viral aetiology
- Inappropriate culture technique
- Fragile organisms (e.g. pneumococcus)
- Patient is not septic!
- Sensitivity of blood culture is approximately 40% (specificity ~95%)

# They make no difference

- 414 patients in ED with pneumonia
- Blood cultures taken and antibiotics started
- 7% blood cultures positive (26/414)
- Of those 26:
- 11/26 continue empiric therapy, though 8 could de-escalate
- 11/26 de-escalate
- 4/26 broaden therapy

Kennedy et al. Annals of Emergency Medicine 2005

# They make no difference

- 760 patients with community pneumonia, all had blood cultures
- 43 (5.7%) were positive
- Culture suggested a step down in antibiotics in 17
- Of those 17 only 6 followed the recommended course of action

Cambell et al. Chest; 2003

# No other area tolerates this level of imperfection

- Cardiologists would not stent all with chest pain
  - High sensitivity Troponin T 90% sensitivity with baseline
  - ST elevation on ECG 88-98% specific
- Stroke doctors would not thrombolyse everyone with a weak arm
- Oncologists would not give ‘chemotherapy’ to everyone with a mass on CT
- Why should we give antibiotics to everyone who may just be septic?

# Perhaps because…

A retrospective cohort analysis of **760** patients with severe sepsis*

**31%** received inappropriate antibiotic treatment

In **58%,** therapy was delayed

**42%** had resistance to the antibiotic administered

**Patients who progress to septic shock have a 7.6% increase in mortality every hour while not on appropriate therapy****

* Shorr AF et al. *Crit Care Med*. 2011;39(1):46-51. *Kumar A et al. *Crit Care Med*. 2006;34(6):1589-1596.

# How big a problem is empiric prescribing?

- Pneumonias comprise the largest single group (22.8%) of all hospital-acquired infections in UK.
- Standard empiric treatment is piptazobactam or carbapenems
- Look at organism ID and susceptibility and these drugs achieve 85-86% coverage
- But 49% of pathogens could have been covered by amoxicillin-clavulanate and 27% by ampicillin or amoxicillin.
- Thus, empirical piperacillin-tazobactam or imipenem amounts to under treatment in 14-15% of cases and over-treatment in 27-49%.

# Not just the UK

- European study of 3,147 ICU admissions identified an infection (clinically or microbiologically defined) in 37%
  - 64% received an antibiotic
- In an Israeli teaching hospital infection could only be defined in 54% of cases where antibiotics were being used
  - Length of antibiotic course was the same if infection was defined (11.5 days) or undefined (10.7 days)
  - Even when clinician certainty was low, antibiotics continued
  - 658 antibiotic days could have been saved in the 4 month study period

SOAP Study. Crit Care Med 2006

Levin et al J.Hosp Med 2012

# So what's the big deal?

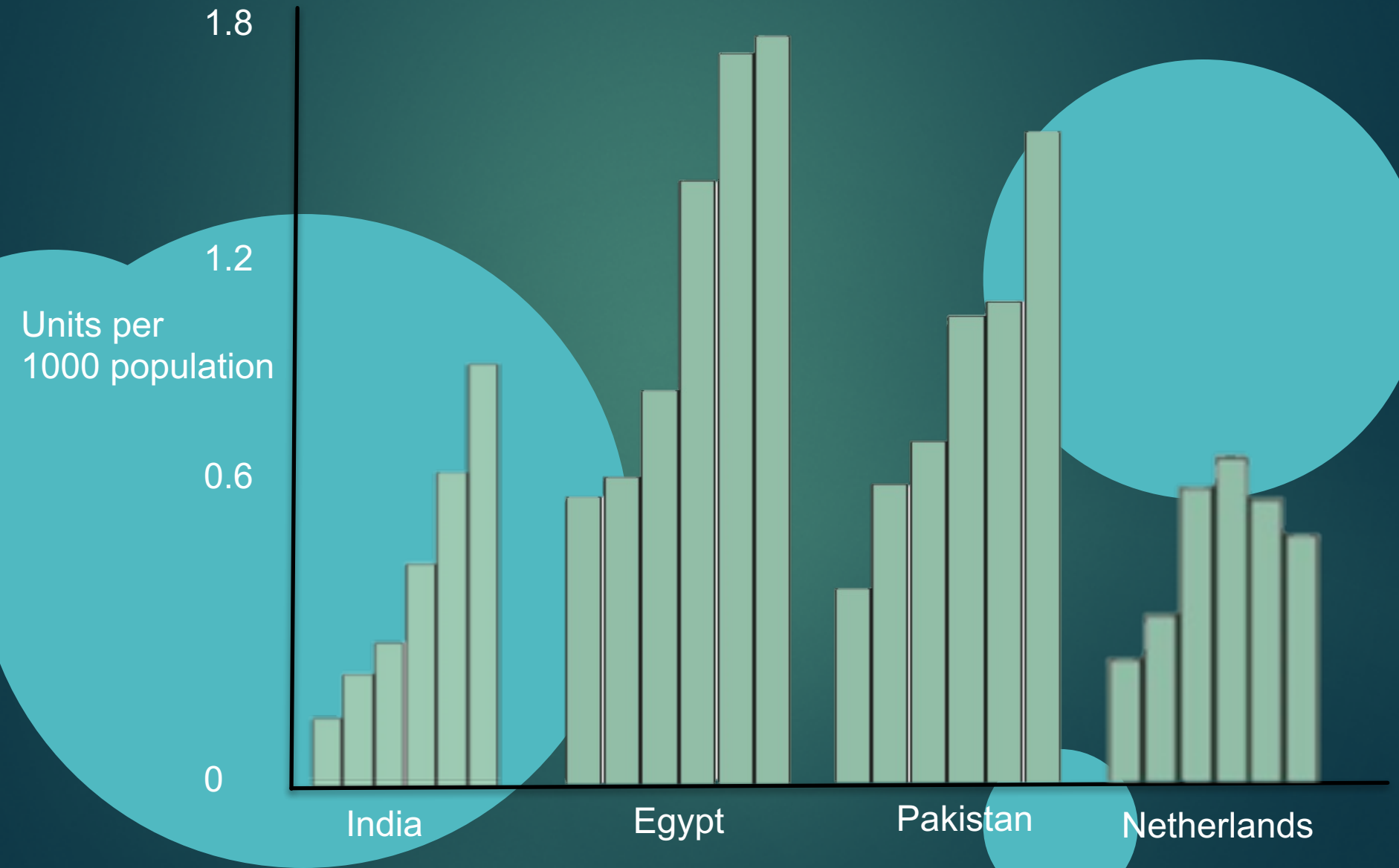
# Quite a lot really…

- Simple diarrhoea, rash etc
- Drug induced nephritis and cholestatic liver impairment
- Mitochondrial impairment – potentiating organ dysfunction
- Destruction of gut flora (C.difficile infection)
- Anaphylactic reactions
- Pressure on bacteria to develop drug resistance

# Antibiotic resistance

- The liberal use of broad spectrum antibiotics is leading to a rapid rise of highly resistant bacteria across the World
- Ultimately one of the biggest challenges to healthcare in the coming decades

# Meropenem sales 2005-2010



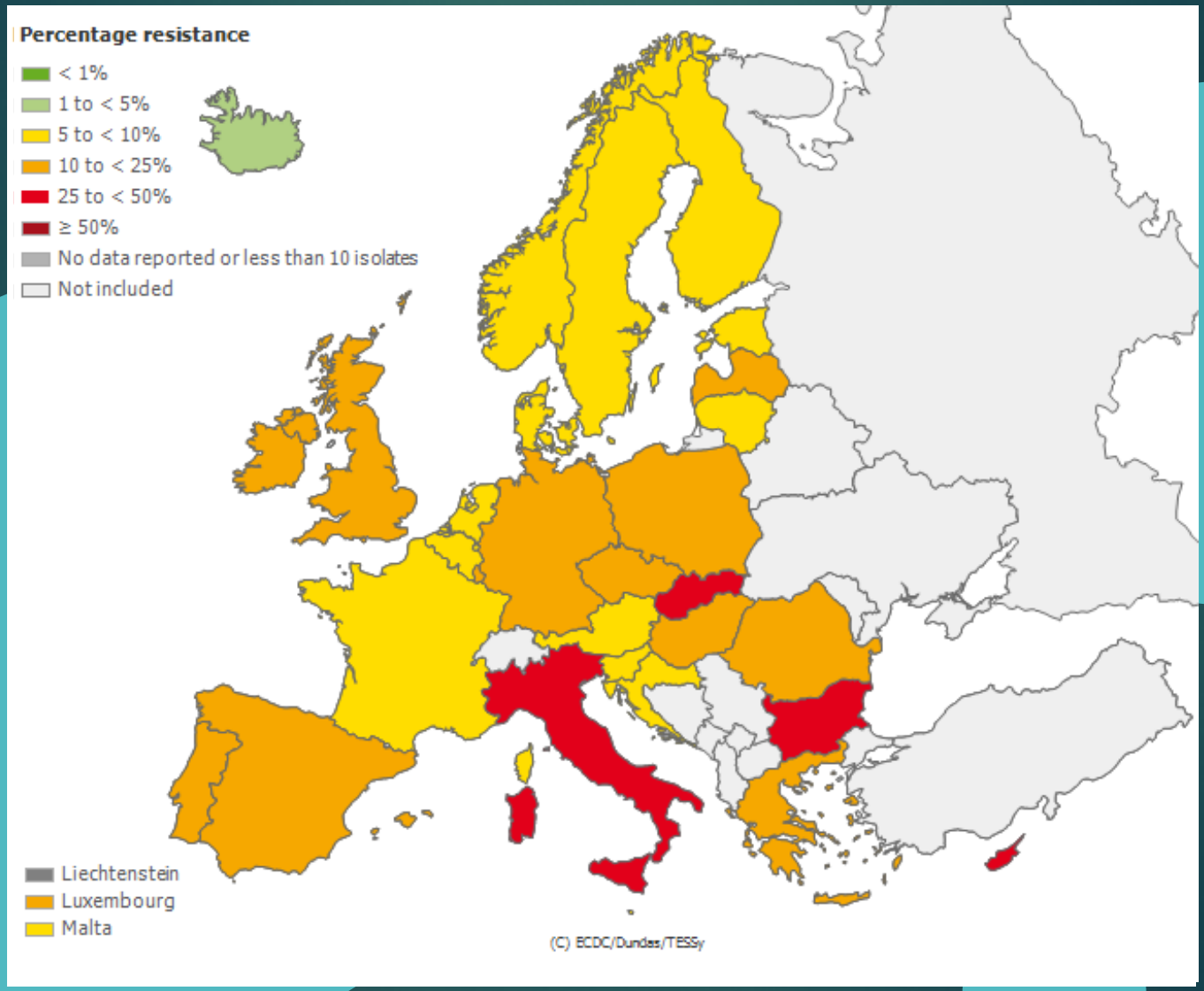
# UK from 2010-2013

46% rise in piptazobactam use

37% rise in meropenem use

Public Health England

# *E.Coli* resistance to cephalosporins 2001-2013

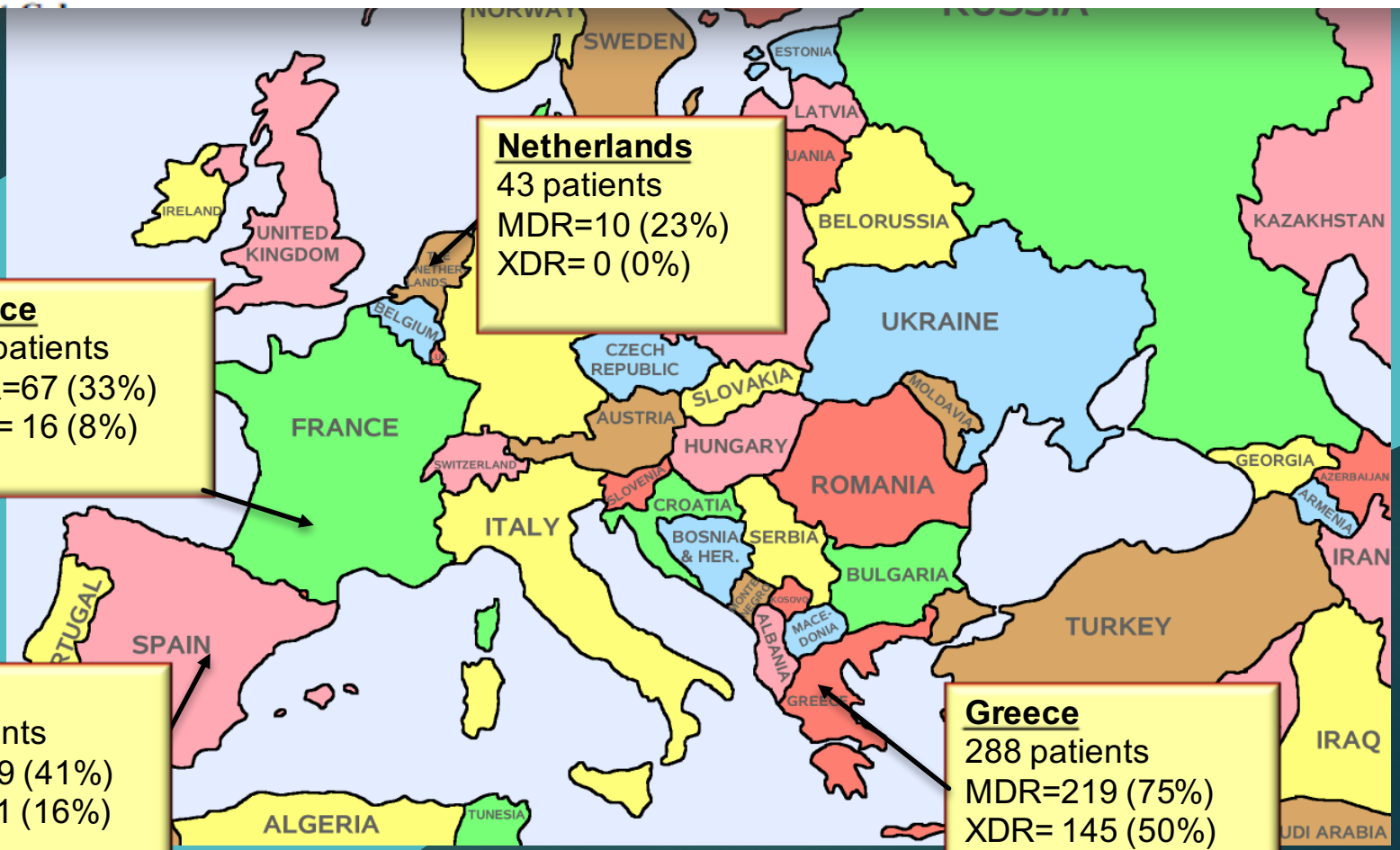


Intensive Care Med (2012) 38:1930–1945
DOI 10.1007/s00134-012-2695-9

SPECIAL ARTICLE

Alexis Tabah
Despoina Koulenti
Kevin Laupland
Benoit Misset
Jordi Valles
Frederico Bruzzi de Carvalho
José Artur Paiva

# Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study




**Netherlands**
43 patients
MDR=10 (23%)
XDR= 0 (0%)

**France**
206 patients
MDR=67 (33%)
XDR= 16 (8%)

**Spain**
70 patients
MDR=29 (41%)
XDR= 11 (16%)

**Greece**
288 patients
MDR=219 (75%)
XDR= 145 (50%)

# Cost of multi-resistant bacteria

| European Union<br>*population 500m* | Thailand<br>*population 70m* | United States<br>*population 300m* |
|---|---|---|
| 25,000 deaths per year | >38,000 deaths | >23,000 deaths |
| 2.5m extra hospital days | >3.2m hospital days | >2.0m illnesses |
| Overall societal costs<br>(€ 900 million, hosp. days)<br>Approx. €1.5 billion per year | Overall societal costs<br>US$ 84.6–202.8 mill. direct<br>>US$1.3 billion indirect | Overall societal costs<br>Up to $20 billion direct<br>Up to $35 billion indirect |
|  |  |  |
| *Source: ECDC 2007* | *Source: Pumart et al 2012* | *Source: US CDC 2013* |

…developing new antibiotics will not address this growing problem

# There seems to be a conflict…

## Drive to spot and treat sepsis

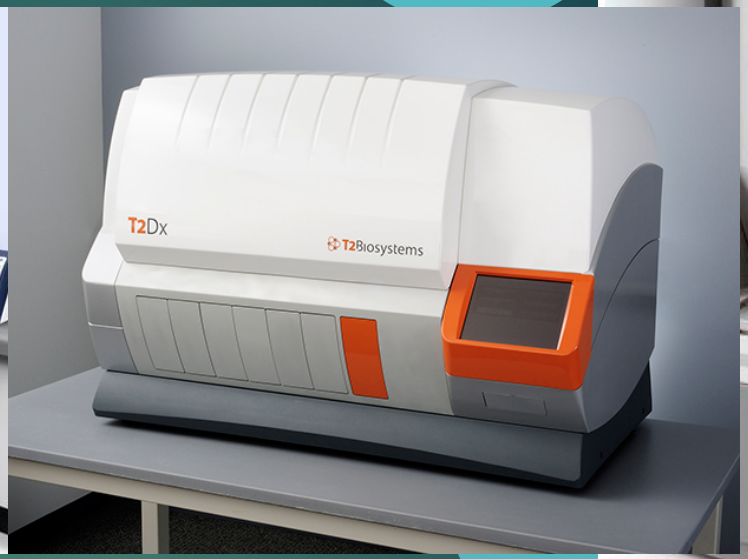

Vs

## Drive to control antibiotic misuse

# We desperately need to…

- Identify the pathogen faster and more reliably than you (or Sir Alexander Flemming) can
- Identify the inflammatory response is to an infection
  - Currently best markers are pro-calcitonin or C-reactive protein
  - Both are rubbish
- Field is now changing very fast indeed

# Where are we now?

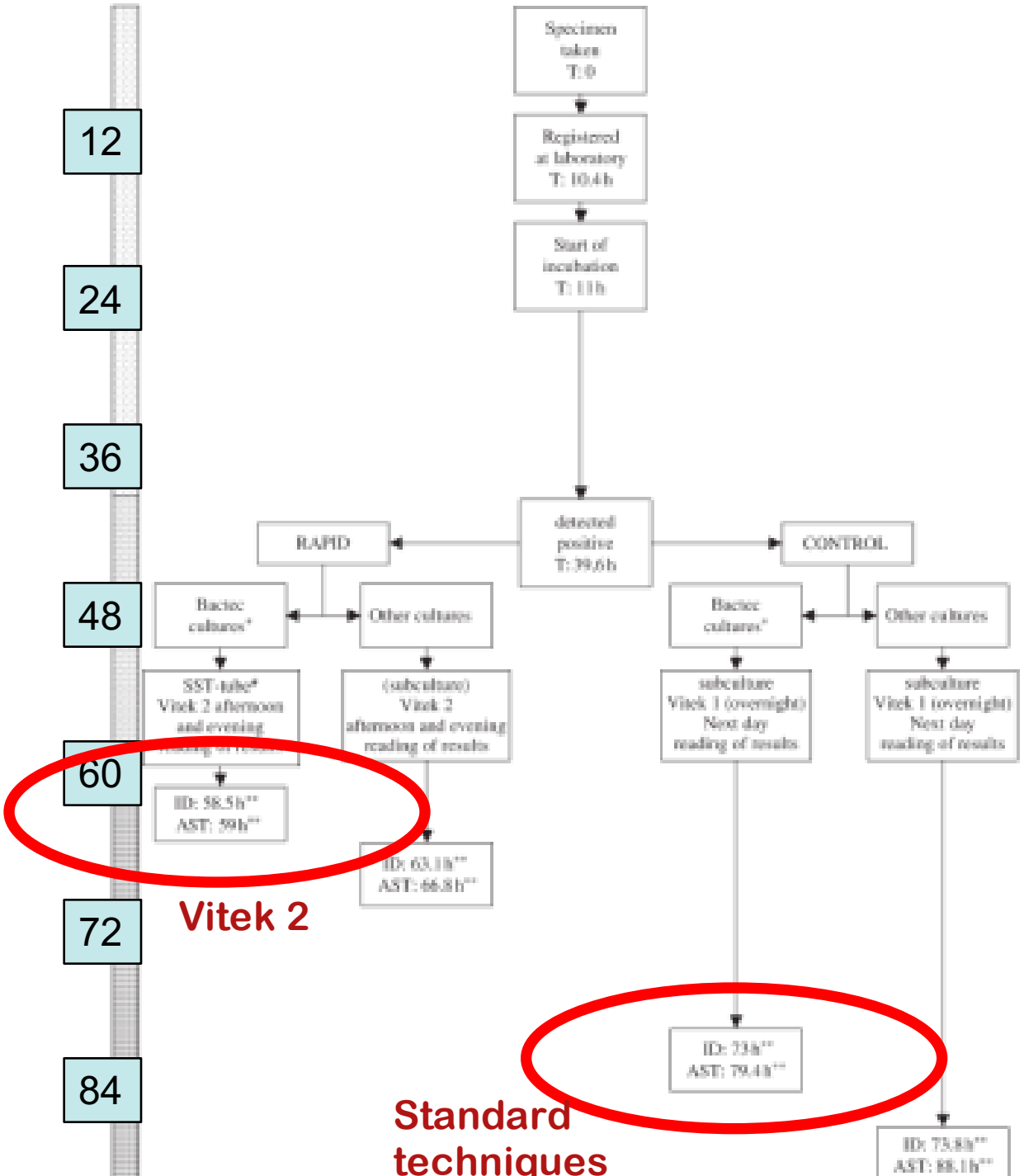




- Pre-culture techniques
  - Iridica, SeptiFast, T2 Biosystems
  - Able to deliver results within a few hours
  - New and currently not very common (at least no

# Any evidence?

- Kerremans et al J.Antimicrob Chemother 2008
- Prospective RCT of 1498 patients with positive culture from sterile compartments
- Rapid pathogen detection (Vitek2) vs standard culture
- Intervention group
  - Identification reduced by 13h and 20h for susceptibility testing (P<0.001)
  - Lower DDD of antibiotics.
  - No difference length of stay and mortality
- However, large number of protocol violations (~15%)

Timeline (hours)



# Any evidence?

- Galar et al J Infec 2012.
- 290 patients with positive culture guided by the results from Vitek 2
- Compared to 284 historical controls (bit of a flaw!)
- Vitek 2 led to:
  - Reduced Time to ID and sensitivities 9.4 h (±1.2) vs 27.0 h (± 9.1) for the($P < 0.001$)
  - Time result received within 48hr of culture of specimen: 81% vs 52%
  - Reduced time in ward 7.7 ± 14.6 vs 10.1 days ± 16.3 p=0.003
  - Decreased need for intubation7.9% vs 14.4% p=0.017
  - Decreased number of investigations
  - Decreased cost s €12,402 vs €15,990

# Any evidence?

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- A pre–p
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- Time to
- Reduce
- Reduce
- Reduce

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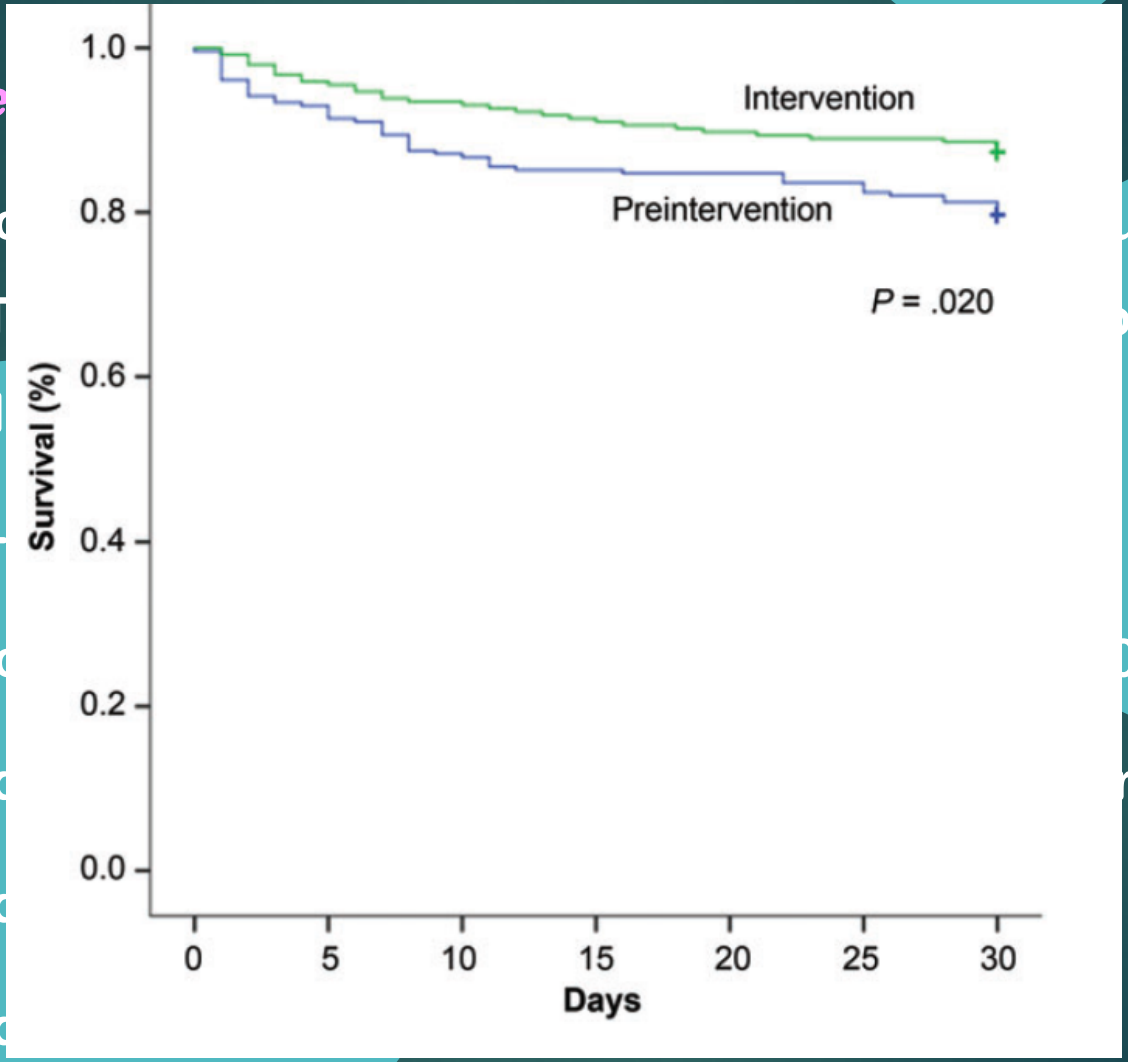


# Having said that

- All these studies have fairly major methodological flaws
- Had to rely an organism being cultured
- All had fairly long time to ID an organism and effect treatment
- But all showed some sort of benefit we would like to see and perhaps a taster of what is possible

# What about pre-culture techniques?

- Promise of much faster turns around times
- Panels including bacteria, fungi or viruses
- Unaffected by antibiotics
- Impressive observational trials
- Concerns that DNA does not equal infection:
  - Dead bacteria
  - DNA Translocation

# IRIDICA

- New PCR/ESI MS developed by Abbott
- Can detect over 1,200 pathogens
  - Bacteria
  - Viruses
  - Fungi
- Limited, but expanding resistance profile
  - MEC-A, VAN-A/B, KPC
- Direct from blood, BAL, CSF etc
- Result within 6-8 hours

# IRIDICA

# Does it work?

# The RADICAL Study

## Rapid Diagnosis of Infection in the Critically Ill, a Multicenter Study of Molecular Detection in Bloodstream Infections, Pneumonia, and Sterile Site Infections

Jean-Louis Vincent, MD, PhD, FCCM[1]; David Brealey, MD[2]; Nicolas Libert, MD[3]; Nour Elhouda Abidi, MD[4]; Michael O'Dwyer, MD[5]; Kai Zacharowski, MD[6]; Malgorzata Mikaszewska-Sokolewicz, MD[7]; Jacques Schrenzel, MD[8]; François Simon, MD[9]; Mark Wilks, PhD[5]; Marcus Picard-Maureau, PhD[10]; Donald B. Chalfin, MD, MPH[11]; David J. Ecker, PhD[11]; Rangarajan Sampath, PhD[11]; Mervyn Singer, MD[2]; the Rapid Diagnosis of Infections in the Critically Ill Team

- Critical Care Medicine. August 2015

# Methodology

- To compare the performance of PCR/ESI-MS with standard hospital culture techniques
- A pragmatic prospective, observational trial
- Patient population: Any adult patient under the care of the critical care team being investigated for potential sepsis

# Of the 625 blood samples…

| | Culture | PCR/ESI-MS |
|---|---|---|
| Positive | 68 (11%) | 228 (36%) |
| Negative | 557 (89%) | 397 (64%) |

- PCR/ESI-MS has a yield 3x that of culture
- Positive blood culture rate similar to literature

# Of the 625 blood cultures…

| Performance | | Culture | |
|---|---|---|---|
| | | Positive | Negative |
| PCR/ESI-MS | Positive | 55 (9%) | 173 (28%) |
| | Negative | 13 (2%) | 384 (61%) |

- Negative predictive value: 97%
- Positive predictive value: 24%
- Sensitivity: 81% Specificity: 69%

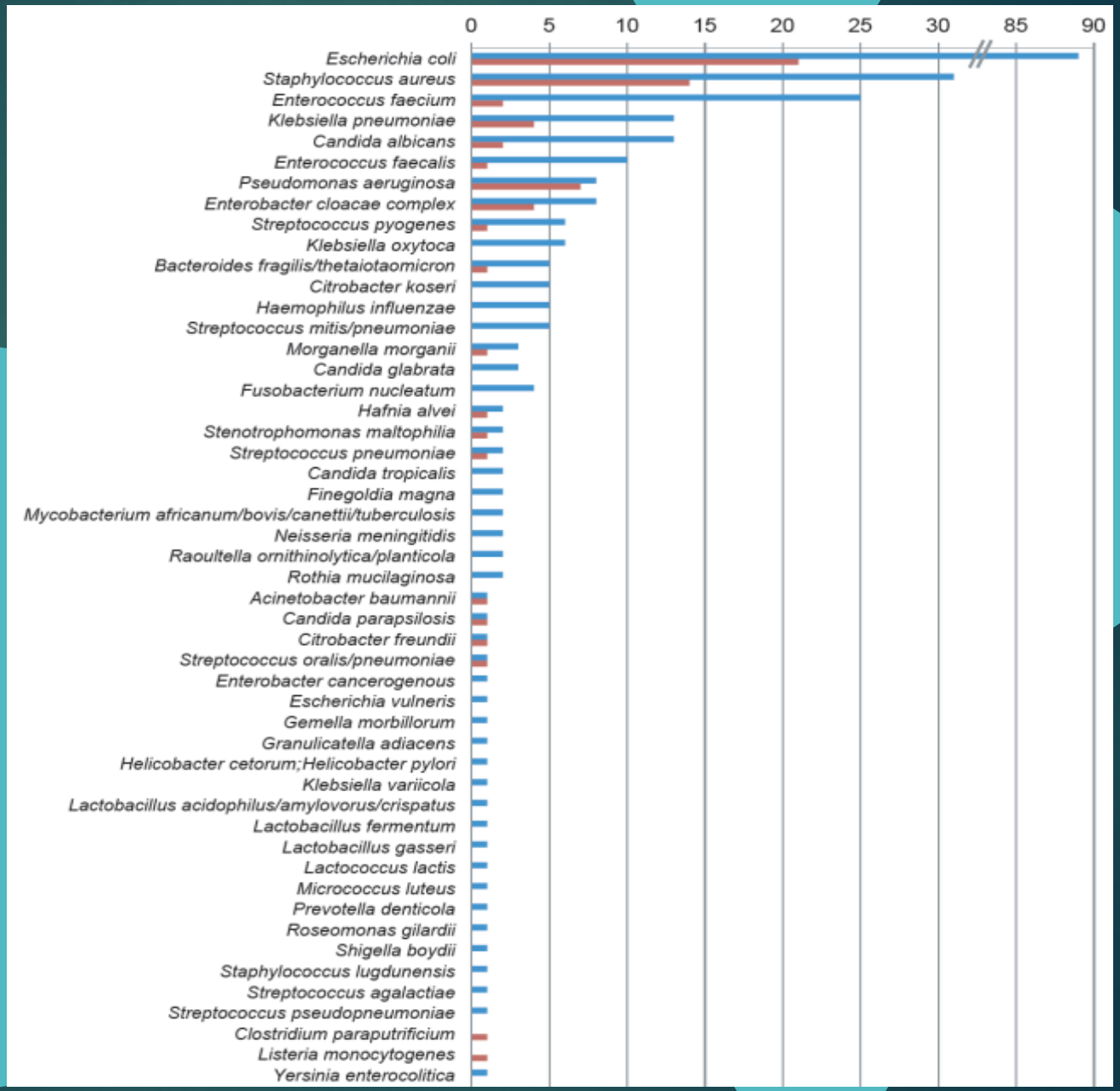
# A little caution…

- Sensitivity and specificity are about comparing to a gold standard
- Blood cultures are standard but they are not golden
- This is a recurrent problem as we start to replace old biomarkers and definitions
  - Creatinine – renal failure
  - Chest x-ray – pneumonia
  - CRP – sepsis diagnostics

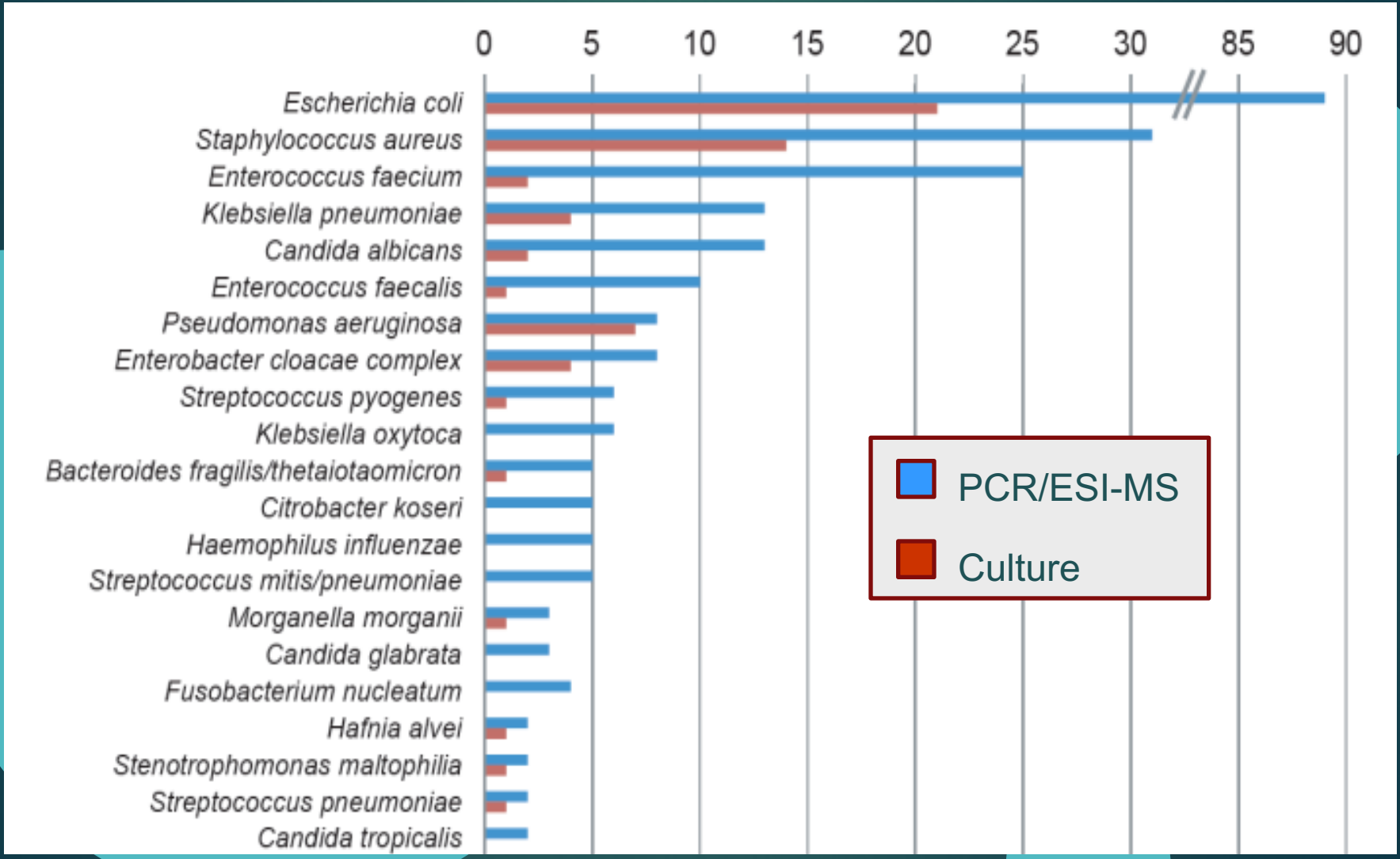
Perhaps its picking up irrelevant DNA?

# Organisms within the blood

- Iridica
- Culture



# Organisms within the blood



# Replicate sampling

- 169 had replicate blood sampling (e.g. 2 venepunctures)
  - PCR/ESI-MS concordance in 83%
  - Culture concordance in 55%
- 151 had sampling from 2 sites (e.g. respiratory & blood)
  - PCR/ESI-MS Concordance in 57%
  - Culture concordance in 12%

# Independent case review

- A panel of 3 doctors, independent of the trial, reviewed results
- Asked to comment if the PCR/ESI-MS results would alter antibiotic prescription if they had known about the result
- 442 summaries reviewed
- 42% of the time the PCR/ESI-MS result would have affected their decision
- Rising to 57% if the PCR/ESI-MS result was positive

# Final thoughts

If implemented carefully, these devices may revolutionise the way we manage infection and sepsis in a way we have not seen for decades

# кінець
# (The End)

# Of the 185 respiratory samples…

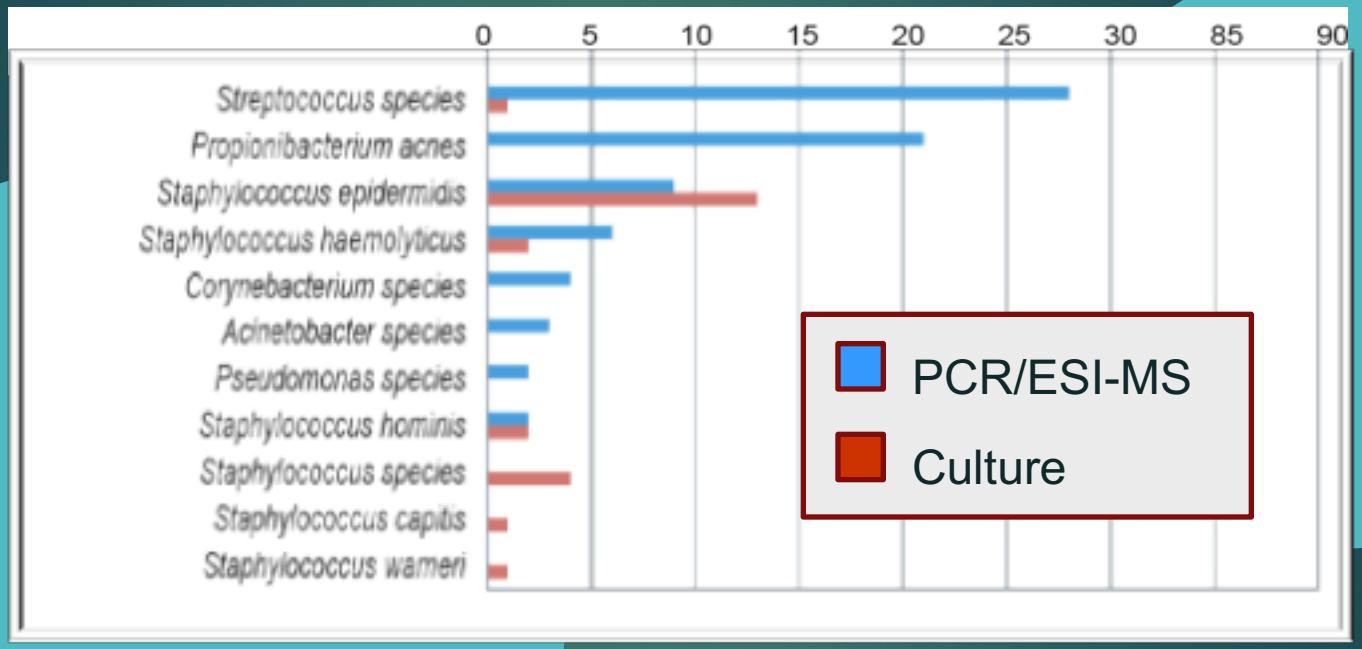
| | Culture | PCR/ESI-MS |
|---|---|---|
| Positive | 81 (44%) | 117 (63%) |
| Negative | 104 (56%) | 68 (37%) |

## Performance

| | | Culture | |
|---|---|---|---|
| | | Positive | Negative |
| PCR/ESI-MS | Positive | 68 (37%) | 49 (26%) |
| | Negative | 13 (7%) | 55 (30%) |

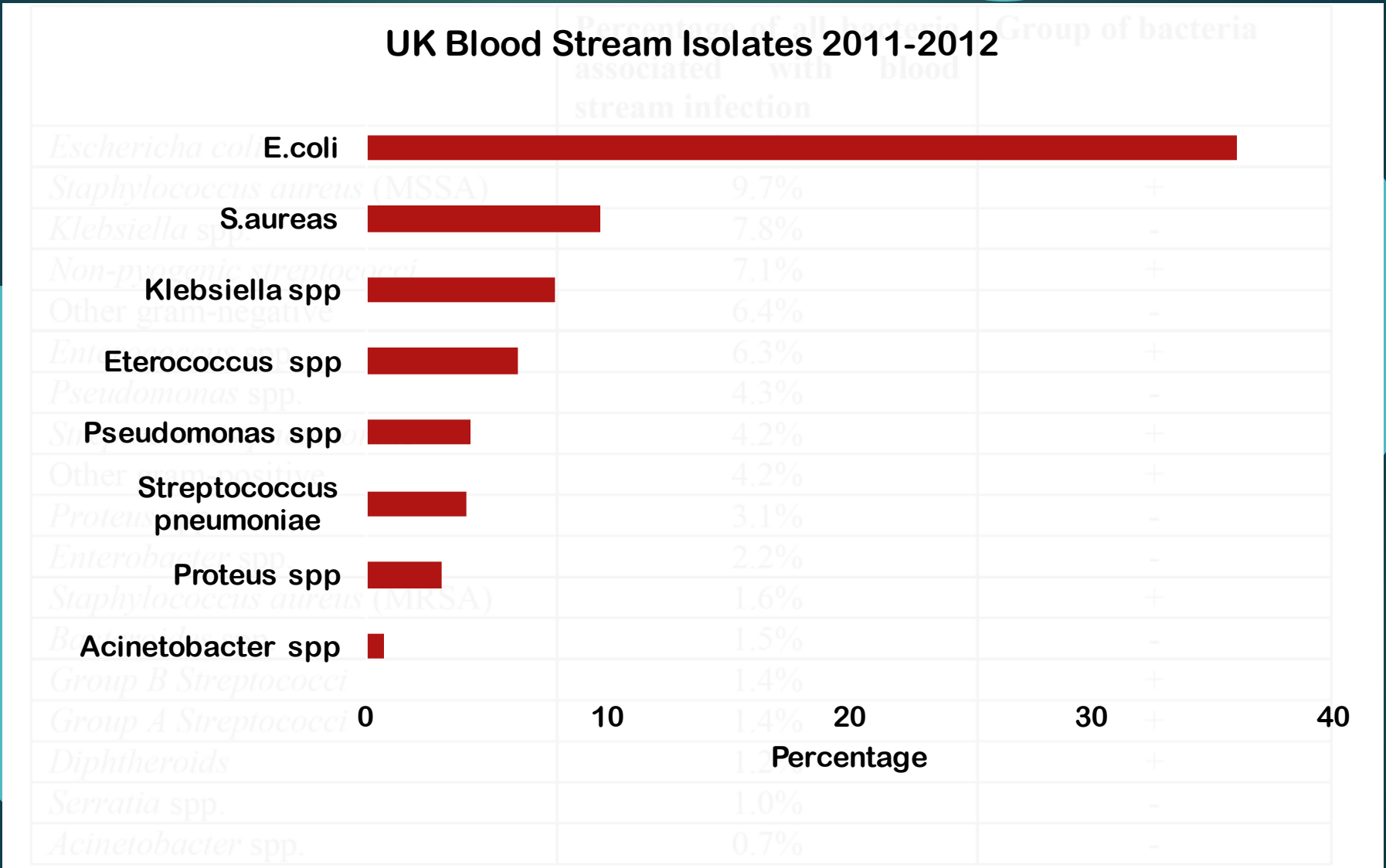
- Negative predictive value of 81%

# Where is the *Staph. Epi?*




- **Presumed contaminants (excluded from analysis)**

# UK Blood Stream Isolates 11-12

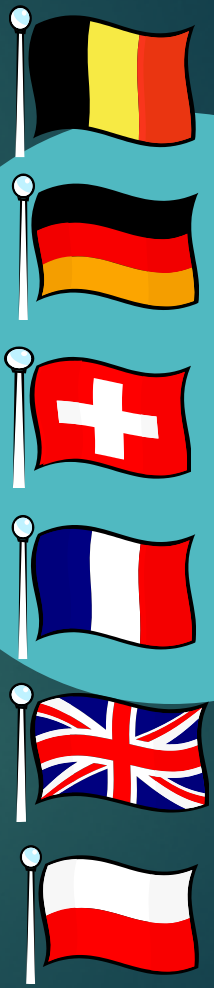


# Samples taken

- Simultaneous samples for PCR/ESI-MS paired with:
  - Blood culture
  - BAL or endotracheal aspirate
  - Fluid from other sterile body cavities
    - CSF
    - Pleural
    - Ascitic
  - Excluding urine, sputum and faeces
- PCR/ESI-MS samples were frozen and batch analysed
- Clinicians blinded to result

# 8 European Centres

- University College London Hospitals, London
- Barts Health, London
- Hospital Erasme, Brussels
- Hôpitaux Universitaire Genève
- Hôpital Militaire du Val de Grace, Paris
- Child of Christ Hospital, Warsaw
- Universitätsklinikum Frankfurt
- Hôpital St Louis, Paris



# Results

- 543 patients recruited – 529 included in analysis
- >900 samples taken
  - 625 blood samples
  - 88 broncho alveolar lavages
  - 96 tracheal aspirates
  - 11 CSFs
  - 36 intra-peritoneal fluid
  - 14 pleural fluid
  - 13 tissue
  - 37 other samples

# Characteristics

- Age 60.4 ± 18.8 years
- Gender
  - Male 61.2%
  - Female 38.8%
- Source of ICU admission
  - Emergency Department 32%
  - Ward 25%
  - Theatres 16%
- Immune status
  - Competent 83.4%
  - Incompetent 16.6%
- Antibiotics
  - Started following enrolment 22.1%
  - Within the last 30 days 75.4%
- SOFA
  - 7.9 ± 4