Febrile neutropenia & antibiotic resistance

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Definitions & epidemiology

Definition of febrile neutropenia

- Febrile
  - T >= 38.3°C
  - T >= 38.0°C sustained over 2 hours
- Neutropenia
  - ANC < 0.5 x 10^E9/L
  - ANC expected to drop below 0.5 x 10^E9/L within 48h

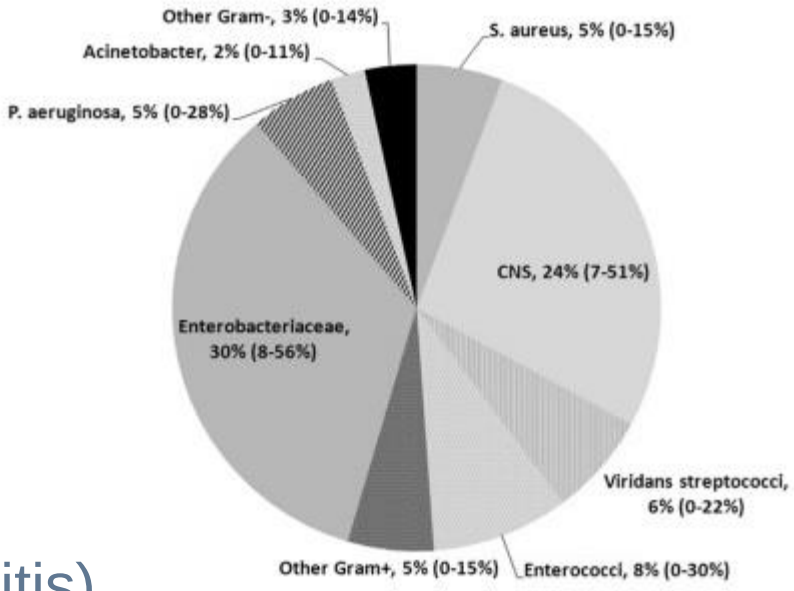
Epidemiology of febrile neutropenia

- Solid tumours 10-50%
- Haematological malignancies +/- 80%
  - Mortality in the 1960s: 90%
  - Mortality in the 21st century: 5-10%

- Microbiologically documented 10-25%
- Clinically documented 20-30%
- Unknown origin 45-70%

The usual suspects

- Gram - (GI translocation)
  - Escherichia coli
  - Klebsiella species
  - Enterobacter species
  - Pseudomonas aeruginosa
  - Citrobacter species
  - Acinetobacter species
- Gram + (IV access or oral mucositis)
  - Coagulase- staphylococci
  - Staphylococcus aureus *(including MRSA)*
  - Enterococcus species *(including VRE)*
  - Viridans group streptococci



Mikulska et al. Journal of Infection 2014;68:321-331.

Current guidelines

Risk stratification

Table 1. MASCC Risk Index Factors and Weights

CHARACTERISTIC	WEIGHT
Burden of febrile neutropenia with no or mild Symptoms[1]	5
No hypotension (systolic BP > 90 mm Hg)	5
No chronic obstructive pulmonary disease[2]	4
Solid tumor or hematological malignancy with no previous fungal infection[3]	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate Symptoms[4]	3
Outpatient status	3
Age <60 years	2

[1] Burden of febrile neutropenia refers to general clinical status as influenced by the febrile neutropenic episode. It is evaluated in accordance with the following scale: no symptoms (5), mild symptoms (5), moderate symptoms (3), severe symptoms (0), moribund (0).

[2] Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in FEVs, need for oxygen therapy and/or steroids and/or bronchodilators.

[3] Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

[4] The points attributed to the variable "burden of febrile neutropenia" are not cumulative. Thus, the maximum theoretical score is therefore 26. A score of ≥ 21 is considered low risk and a score of < 21 as high risk (positive predictive value of 91%, specificity of 68%, and sensitivity of 71%).

Multinational Association of Supportive Care in Cancer

- High risk
  - Prolonged profound neutropenia (> 7 days, < 0.1 x 10^E9/L)
  - Clinical instability (hypotension, hypoxia, neurological, …)
  - Co-morbidities (age, WHO/ECOG, COPD, …)

Klastersky et al. J Clin Oncol 2000; 18:3038-3051.

Empiric antibiotic therapy

- Low risk
  - Oral broad spectrum (amoxicillin-clavulanate)
  - Inpatient observation (4-24h) versus outpatient
- High risk
  - IV broad spectrum (antipseudomonal β-lactam)
  - Combination therapy with aminoglycoside
    - Complicated infection: shock, pneumonia
    - Antimicrobial resistance suspected/proven
  - Combination therapy with vancomycine
    - Complicated infection: shock, pneumonia
    - Skin / soft tissue / catheter-related

ESMO Guidelines. Klastersky et al. Ann Oncol 2016; 27 (Suppl 5):v111-v118.
IDSA Guidelines. Freifeld et al, Clin Infect Dis 2011; 52:e56-e93.

Combination therapy

- Intuitive appeal
  - Broaden empiric coverage
  - To exploit synergy between to agents
  - To prevent/delay emergence of resistance

- Possible harmful effects
  - Increased microbial resistance
  - Adverse effects
  - Cost

Tamma et al. Cin Microbiol Reviews 2012; 25(3):450-470.

Combination therapy and emergence of resistance

- Meta-analysis of 8 randomized controlled trials comparing β-lactam versus β-lactam + aminoglycoside
  - Primary outcome: emergence of resistance:
    - Equivalent odds ratio (0.90; 95% CI 0.56 - 1.47)
  - Secondary outcome: development of a superinfection
    - β-lactam mootherapy was associated with fewer superinfections
    - Odds ratio 0.62; 95% CI 0.42 - 0.93)

Bliziotis et al. Clin Infect Dis 2005; 41:149-158.

Combination therapy in neutropenic patients

- Failure to cover resistant pathogens, including ESBL-producers, significantly and independently impairs outcomes for haemato-oncology patients

- Combination therapy increases the chance of empirical therapy covering resistant bacteria

Microorganism	No./total no. (%) receiving:		OR (95% CI)	*P*
	Combination	β-Lactam		
Non-ESBL *E. coli*	242/248 (98)	2,454/2,489 (99)	0.6 (0.2–1.7)	0.3
ESBL *E. coli*	21/28 (75)	62/122 (51)	2.9 (1.07–8.2)	0.02
Non-ESBL *K. pneumoniae*	62/63 (98)	393/420 (94)	4 (0.7–177)	0.2
ESBL *K. pneumoniae*	18/20 (90)	38/63 (60)	2 (1.2–4.2)	0.01
P. mirabilis	10/10 (100)	116/118 (98)		1
Salmonella spp.	15/15 (100)	108/109 (99)		1
AmpC organisms	78/82 (95)	258/326 (79)	5.1 (1.8–20)	0.001
P. aeruginosa	133/143 (93)	201/319 (63)	7.8 (3.8–16)	<0.0001
Other nonfermenters	24/51 (47)	53/105 (51)	0.9 (0.4–1.8)	0.7
Miscellaneous	18/18 (100)	105/114 (92)		0.4

Martinez et al. Antimicrob Agents Chemother 2010; 54(9):3590-3596.

Combination therapy in neutropenic patients

- Risk factors for infection with resistant bacteria
  - Prolonged hospital stay and/or repeated hospitalizations
  - Previous exposure to broad-spectrum antibiotics
  - Nosocomial infection
  - Older age

- Factors predicting a complicated clinical course
  - Advanced age
  - Inpatient status
  - Prolonged and severe aplasia
  - Co-morbidities (bleeding, organ failure, chronic illness)

Klastersky et al. J Clin Oncol 2000; 18:3038-3051.
Gonzalez-Barca et al. Eur J Clin Microbiol Infect Dis 2009.

Duration of antibiotic therapy: guidelines

- ESMO:
  - If ANC ≥0.5 × 10^9/L, afebrile for 48h, negative blood cultures.
  - If ANC ≤0.5 × 10^9/L, no complications, afebrile for 5-7 days. Except high-risk cases (acute leukemia following intensive chemotherapy): continue for up to 10 days or until ANC is ≥0.5 × 10^9/L.
- IDSA:
  - In patients with clinically or microbiologically documented infections appropriate antibiotics should continue for at least the duration of neutropenia (until ANC > 500 cells/mm^3)
  - In patients with unexplained fever, it is recommended that the initial regimen be continued until there are clear signs of marrow recovery (ANC > 500 cells/mm^3)

ESMO Guidelines. Klastersky et al. Ann Oncol 2016; 27 (Suppl 5):v111-v118.
IDSA Guidelines. Freifeld et al, Clin Infect Dis 2011; 52:e56-e93.

Duration of antibiotic therapy: studies

- 3-Day imipenem for FUO during prolonged neutropenia in haematology patients on fluoroquinolone prophylaxis

Patients (n=169)	Relapse of fever	Infection	Death
Neutropenia ≥ 10 d (mean 20.5 d)	**0**	**0**	**3 (2%)** 1 aspergillosis 1 severe typhlitis 1 progressive AML

- Cefepime & imipenem in the empirical treatment of febrile neutropenia in patients treated for haematological malignancies

Patients	Relapse of fever	Infection	Death
Still neutropenic (n=49)	**9 (18%)**	-	**2 (4%)** 1 progressive lymphoma 1 invasive fungal infection
Neutrophils recovered (n=11)	**2 (18%)**	-	**0**

Slobbe et al. Eur J Cancer 2009; 45(16):2810-2817.
Cherif et al. Scand J Infect Dis 2004; 36(8):593-600.

Definition escalation / de-escalation approach

- Escalation
  - Initial empirical monotherapy that covers Enterobacteriaceae & P. aeruginosa, except multidrug resistant (MDR) strains
  - If patient deteriorates or resistant pathogen is isolated, therapy is escalated to an antibiotic (combination) with broader spectrum
- De-escalation
  - Very broad initial empiric regimen, aiming to cover even highly resistant pathogens
  - Step-down to a narrower spectrum therapy once laboratory does not report on resistant pathogen

Averbuch et al. Haematologica 2013;98 (12):1826-1835.

Pro & con of escalation approach

- Pro
  - Avoids early use of broadest-spectrum antibiotics
    - Less toxicity & cost
    - Less selection of carbapenem resistance
- Con
  - If initial empirical therapy fails to cover the pathogen, prognosis is significantly worse

- Preferred strategy
  - Uncomplicated presentation
  - Without risk factors for resistant pathogens
  - In centres where infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia

Averbuch et al. Haematologica 2013;98 (12):1826-1835.

Pro & con of de-escalation approach

- Pro
  - More likely to achieve cover in the first 48h
- Con
  - Leads to unnecessary use of broad-spectrum antibiotics in many patients
    - Common failure to de-escalate
    - Consequent risk of selecting for resistance

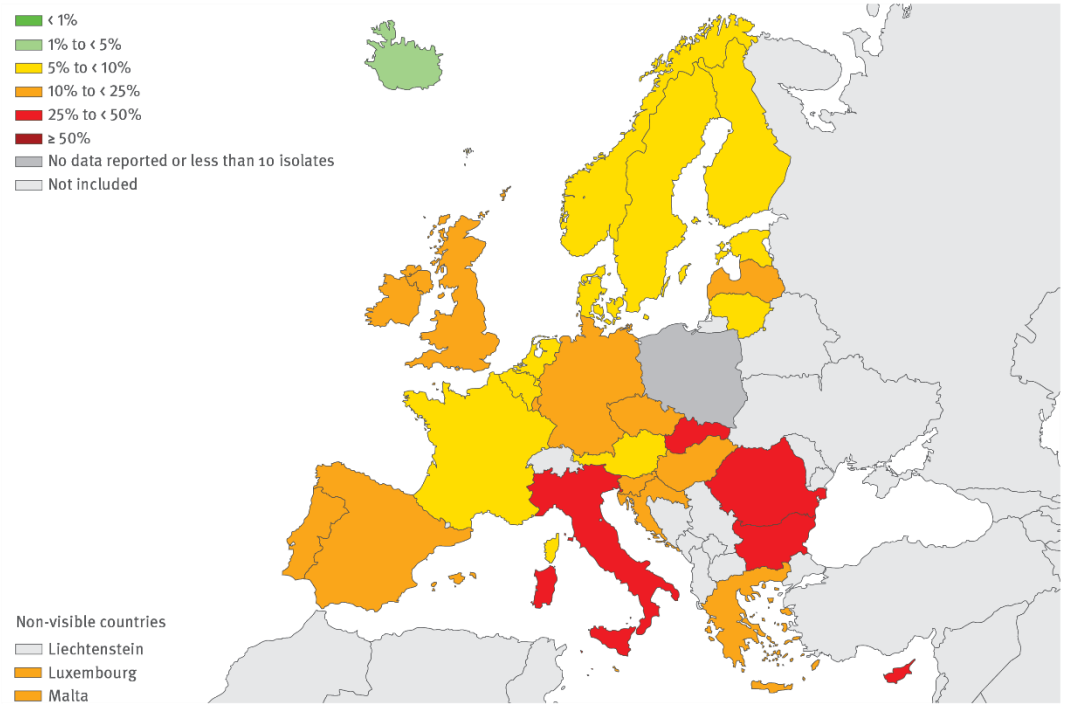
- Preferred strategy
  - Complicated presentation
  - With individual risk factors for resistant pathogens
  - In centres where infections due to resistant pathogens are regularly seen at the onset of febrile neutropenia

Averbuch et al. Haematologica 2013;98 (12):1826-1835.

Antibiotic resistance

ECDC – Antimicrobial resistance surveillance

Escherichia coli. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins, by country, EU/EEA countries, 2014

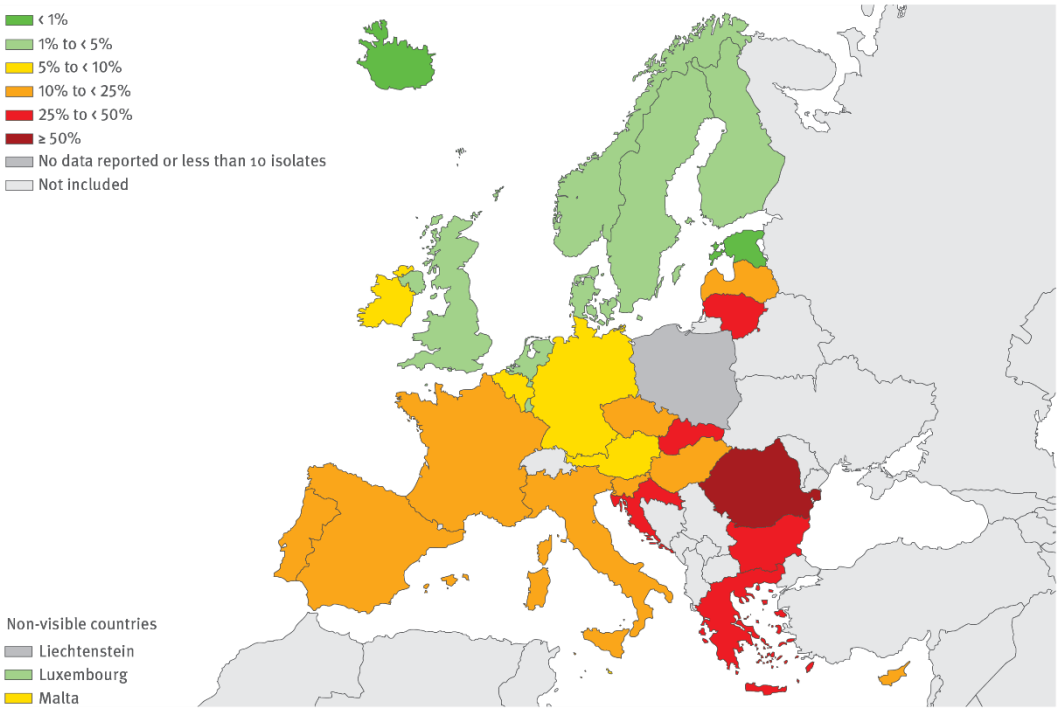


Source: European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Stockholm: ECDC, 2015

www.ecdc.europa.eu

ECDC – Antimicrobial resistance surveillance

Pseudomonas aeruginosa. Percentage (%) of invasive isolates with combined resistance (resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems), by country, EU/EEA countries, 2014

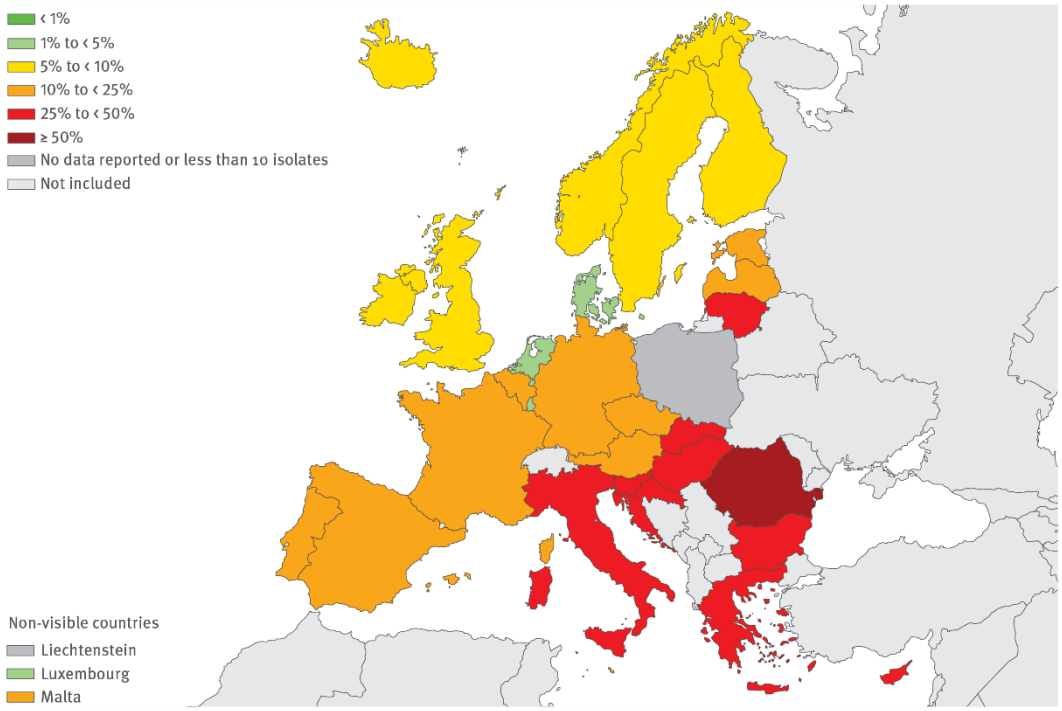


Source: European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Stockholm: ECDC, 2015

www.ecdc.europa.eu

ECDC – Antimicrobial resistance surveillance

Pseudomonas aeruginosa. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2014



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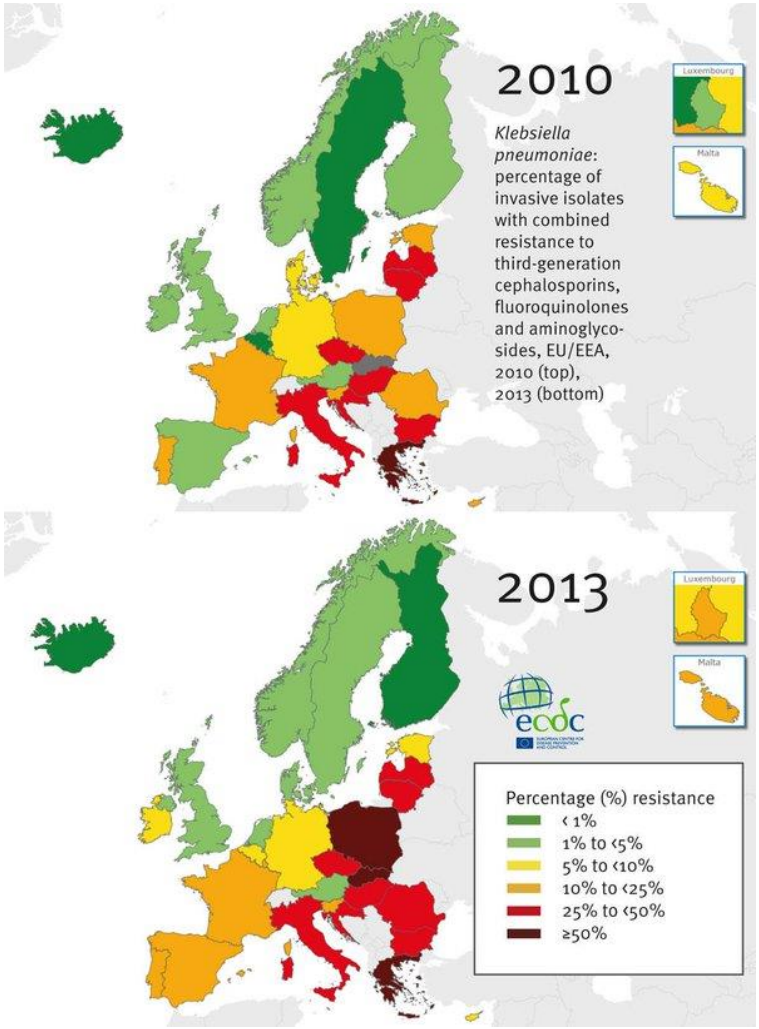
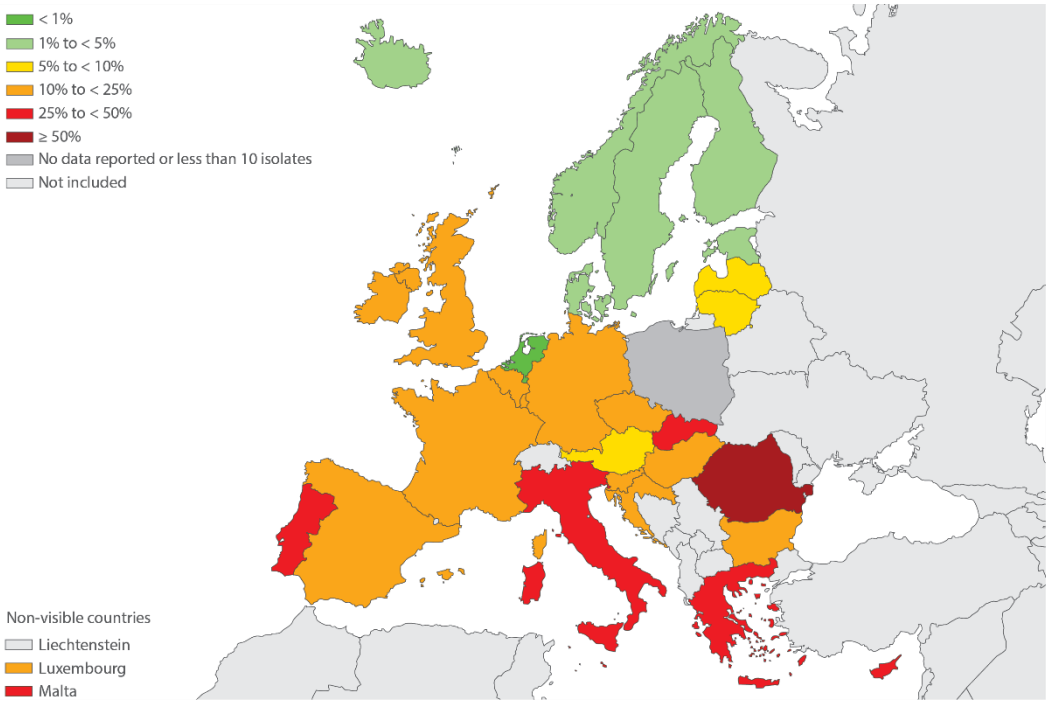
ECDC – Antimicrobial resistance surveillance



ECDC Antimicrobial resistance and healthcare-associated infections 2014.

ECDC – Antimicrobial resistance surveillance

Staphylococcus aureus. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), by country, EU/EEA countries, 2014

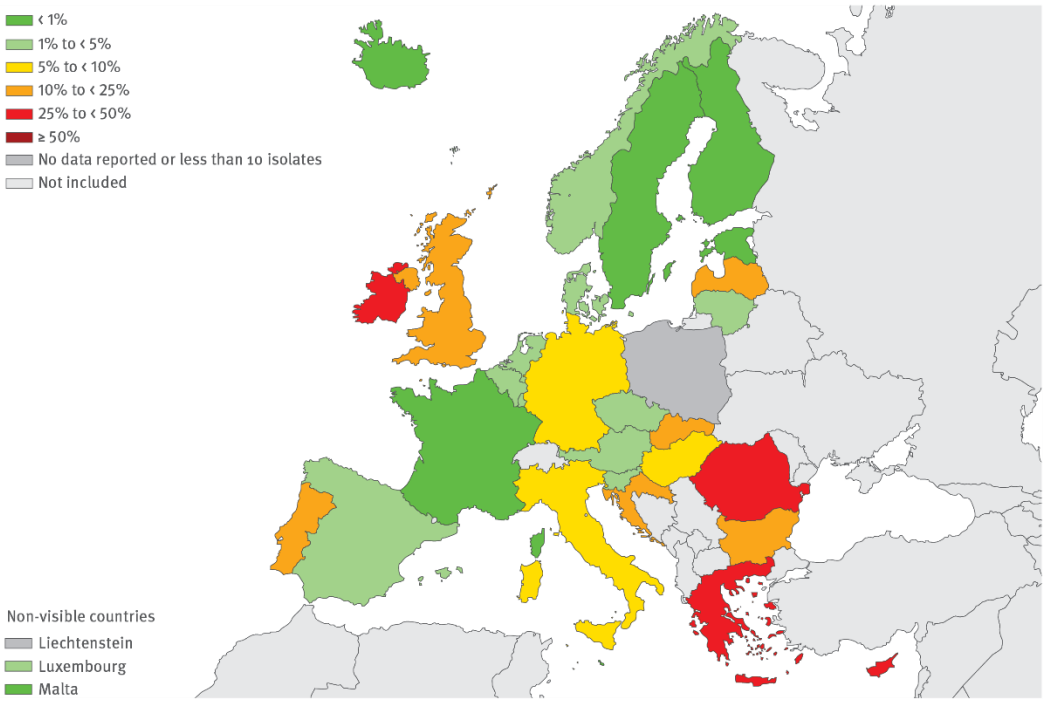


Source: European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Stockholm: ECDC, 2015

www.ecdc.europa.eu

ECDC – Antimicrobial resistance surveillance

Enterococcus faecalis. Percentage (%) of invasive isolates with resistance to vancomycin, by country, EU/EEA countries, 2014



Source: European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Stockholm: ECDC, 2015

www.ecdc.europa.eu

Resistance in bacteraemias in haematology patients

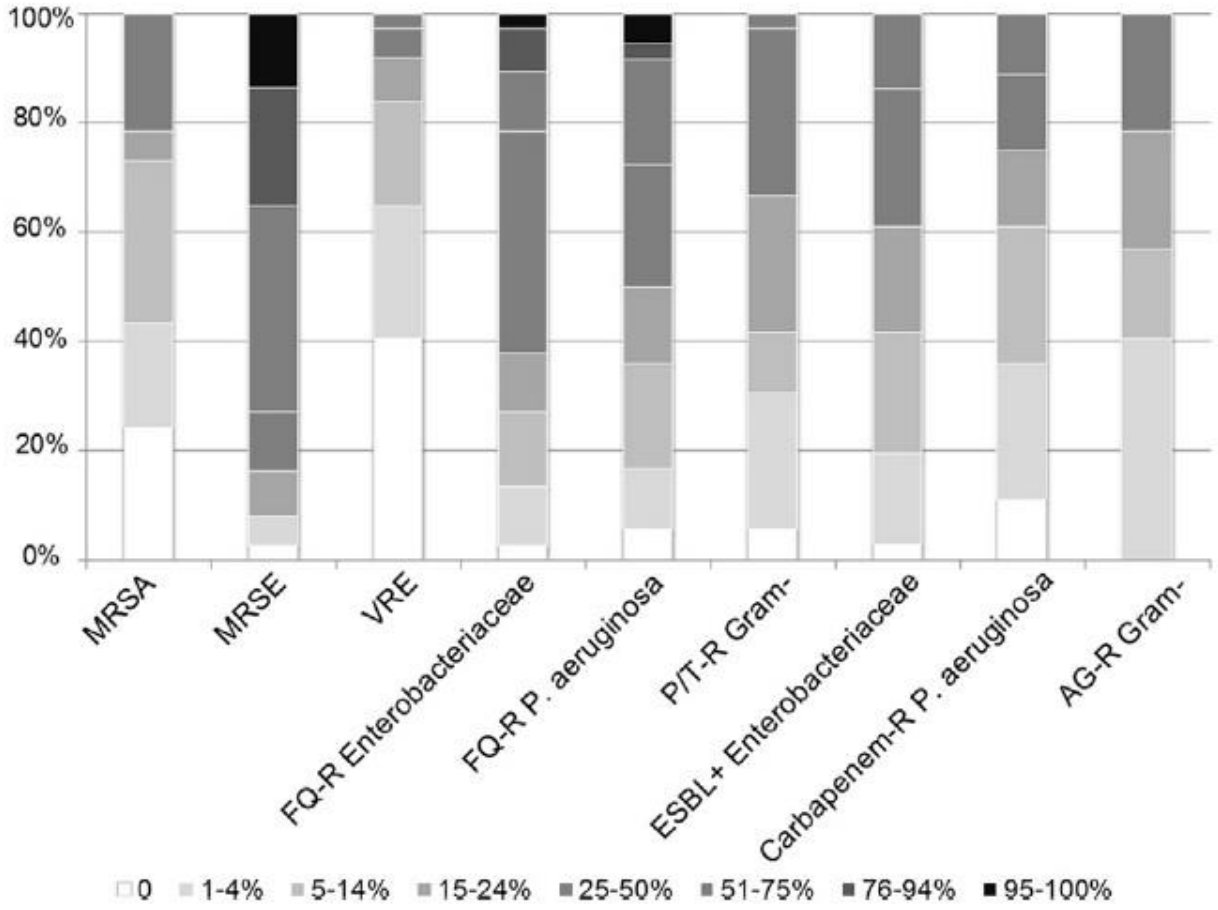
Table 3 Median rates of resistance to different antibiotics in pathogens causing bacteraemias in haematology-oncology adults and children, based upon literature reports.

Pathogen and studies	Type of resistance	Adults median rate of resistance (range)	Children median rate of resistance (range)
S. aureus	MRSA	56% (18–100%)[a]	0% (0–26%)[b]
CNS	MR-CNS	80% (33–100%)[c]	38% and 39%[d]
Enterococci	VRE	23% (0–50%)[e]	0%[f]
Gram-negatives	Fluoroquinolone-resistant	41% (18–74%)[g]	7% and 32%[t,h]
Gram-negatives	Carbapenem-resistant	20% (11–72%)[i]	9% and 10%[h]
Gram-negatives	Aminoglycoside-resistant	28% (6–41%)[j]	Gentamicin-resistant 26% (25–28%)[k]
Gram-negatives	Ceftazidime-resistant	43% (17–45%)[l]	18% and 27%[h]
Enterobacteriaceae	ESBL-producing	34% (16–44%)[m] + 42% of *E. coli*[n]	18%[o]
Enterobacteriaceae	Fluoroquinolone-resistant	56% (28–87%)[p] + 63% of *E. coli*[n]	4%[o]
P. aeruginosa	Fluoroquinolone-resistant	53% (7–72%)[q]	18%[r]
P. aeruginosa	Carbapenem-resistant	44% (3–66%)[s]	25%[r]

Abbreviations: CNS, coagulase-negative staphylococci; ESBL, extended-spectrum beta-lactamase; MRSA, meticillin-resistant *S. aureus*; MR-CNS, meticillin-resistant CNS; VRE, vancomycin-resistant enterococci.

Mikulska et al. Journal of Infection 2014;68:321-331.

Resistance in bacteraemias in haematology patients



Mikulska et al. Journal of Infection 2014;68:321-331.

Antimicrobial stewardship

Key aspects

- Local surveillance of antibiotic resistance, antibiotic consumption and patient outcomes
- Multidisciplinary protocols and algorithms on the diagnosis, prevention and treatment of infections
- Swift reporting of positive cultures and implementation of rapid techniques for bacterial identification and resistance patterns
- Re-assessment of the antibiotic therapy and its duration
- Optimization of dosing regimens using pharmacodynamic principles
- Frequent multidisciplinary rounds

Gyssens et al. Haematologica 2013;98:1821-1825.

Our experience

Combination therapy with amikacin

- Ceftazidime/Vancomycin → Cefepime/Amikacin

Table 2 Changes in antibiotic reduced susceptibility rates (%) for all cultured inducible Enterobacteriaceae per year

Antibiotic	*1994 n = 36*	*1995 n = 37*	*1996 n = 26*	*1997 n = 20*	*P value*[a]
Imipenem	0	0	0	5.0	—
Amikacin	36.1	18.9	0	5.0	0.009
Cotrimoxazole	50.0	33.3	11.5	10.0	0.0027
Cefepime	13.9	0	7.7	0	0.208591
Ceftriaxone	72.2	36.1	23.1	15.0	0.00004
Ceftazidime	75.0	35.1	30.8	15.0	0.000016
Ciprofloxacin	52.8	24.3	15.4	10.0	0.0015

[a]Comparison between 1994 and 1997.

- Reduction of resistance may be related at least in part to the combined use of cefepime together with an aminoglycoside.
- It is possible to reverse bacterial resistance by modifying the antibiotic regimen used.

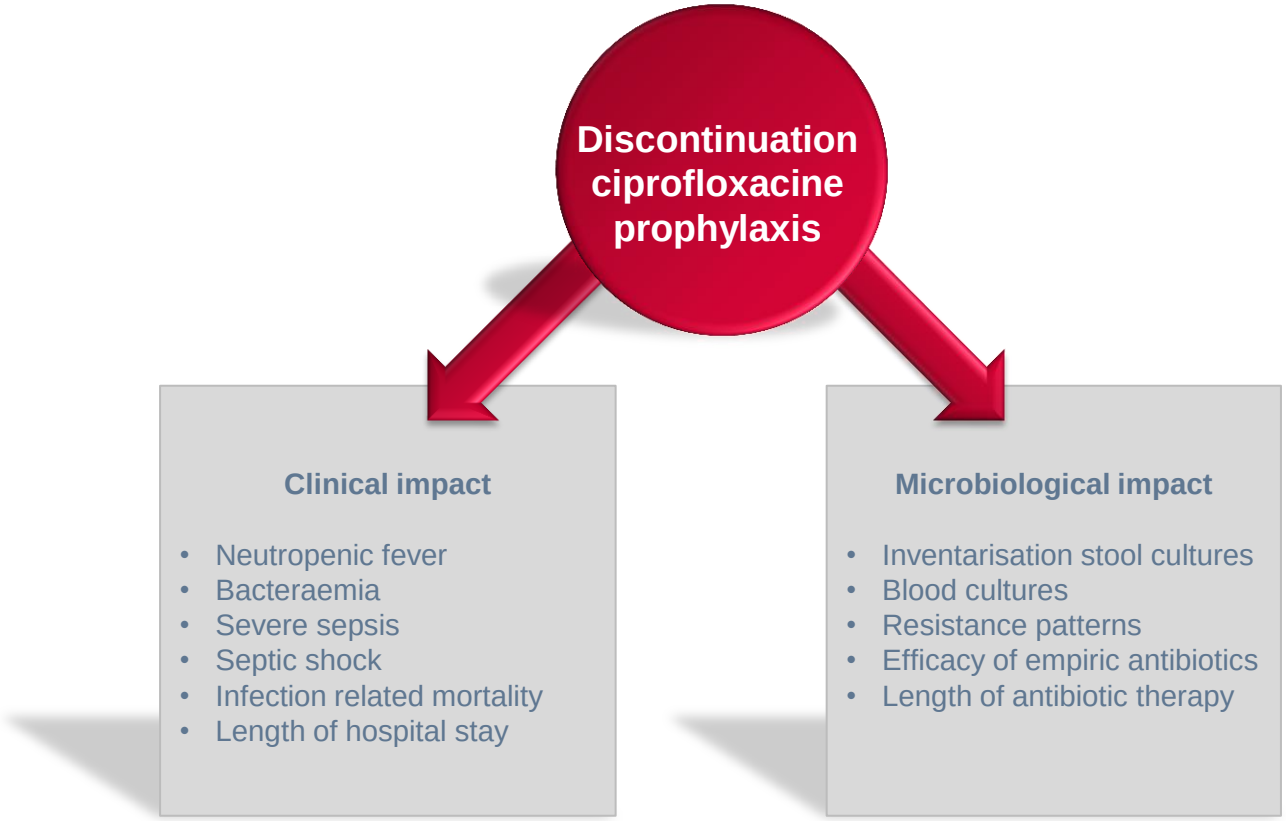
Mebis et al. Leukemia 1998;12:1627-1629.

Fluoroquinolone prophylaxis

- Meta-analysis by Imran et al (Eur J Clin Microbiol Infect Dis 2008)
  - ↓ Neutropenic fever RR 0.76 [CI 0.55-1.03]
  - ↓ All cause mortality RR 0.76 [CI 0.54-1.08]
    - Subgroup analysis: haematology inpatients and stem cell transplant recipients (high risk of febrile episodes / 83%-100%) less responsive

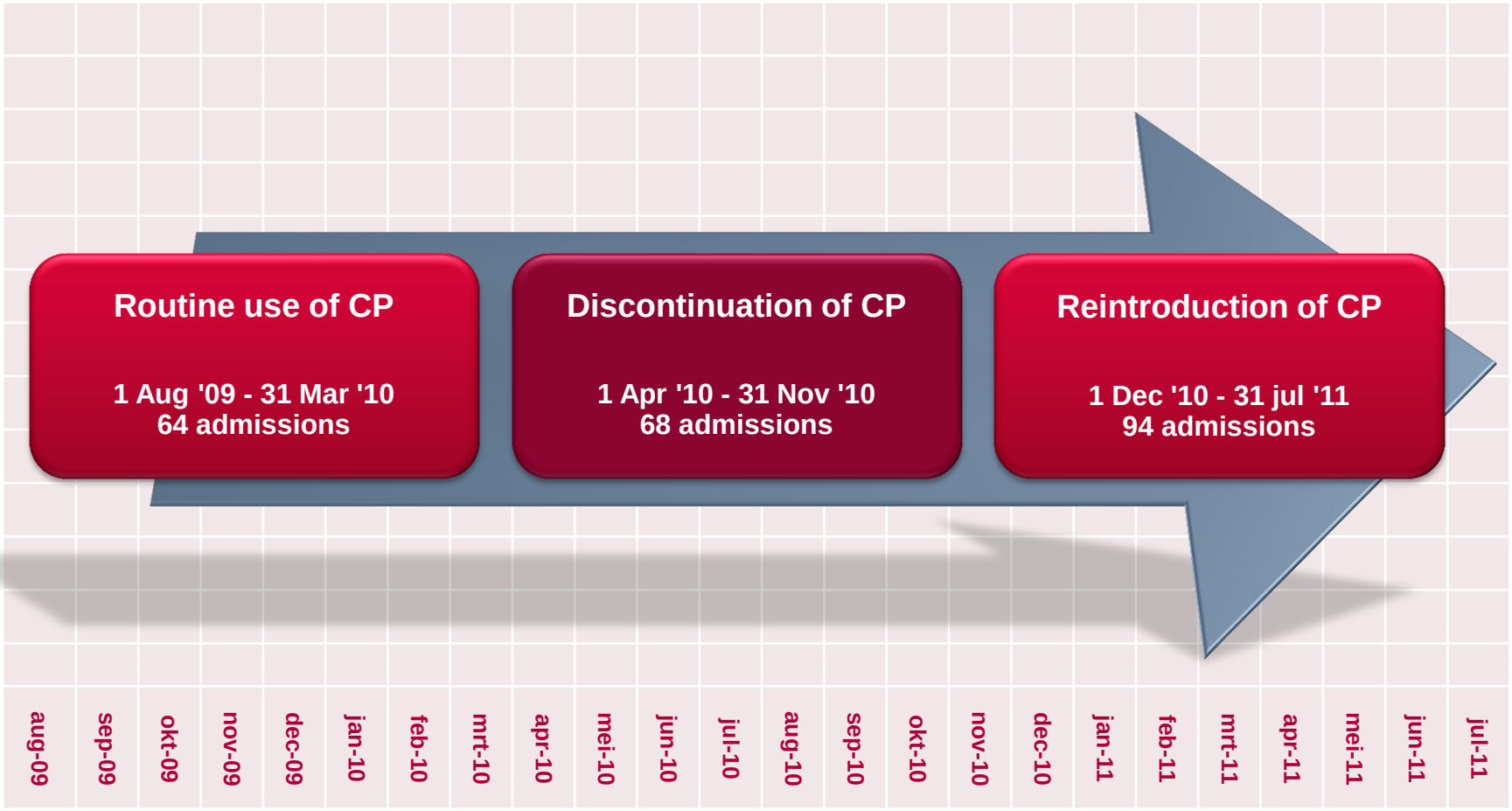
- Meta-analysis by Gafter-Gvili et al (J Antimicrob Chemother 2007)
  - ↑ Colonization with resistant organisms RR 1.68 [CI 0.71-4.00]
  - = Infections caused by resistant pathogens RR 1.04 [CI 0.73-1.50]

Cipro Stop Study – Objectives



Verlinden et al. Eur J Haematol 2014;93(4):302-8.

Cipro Stop Study – Study design



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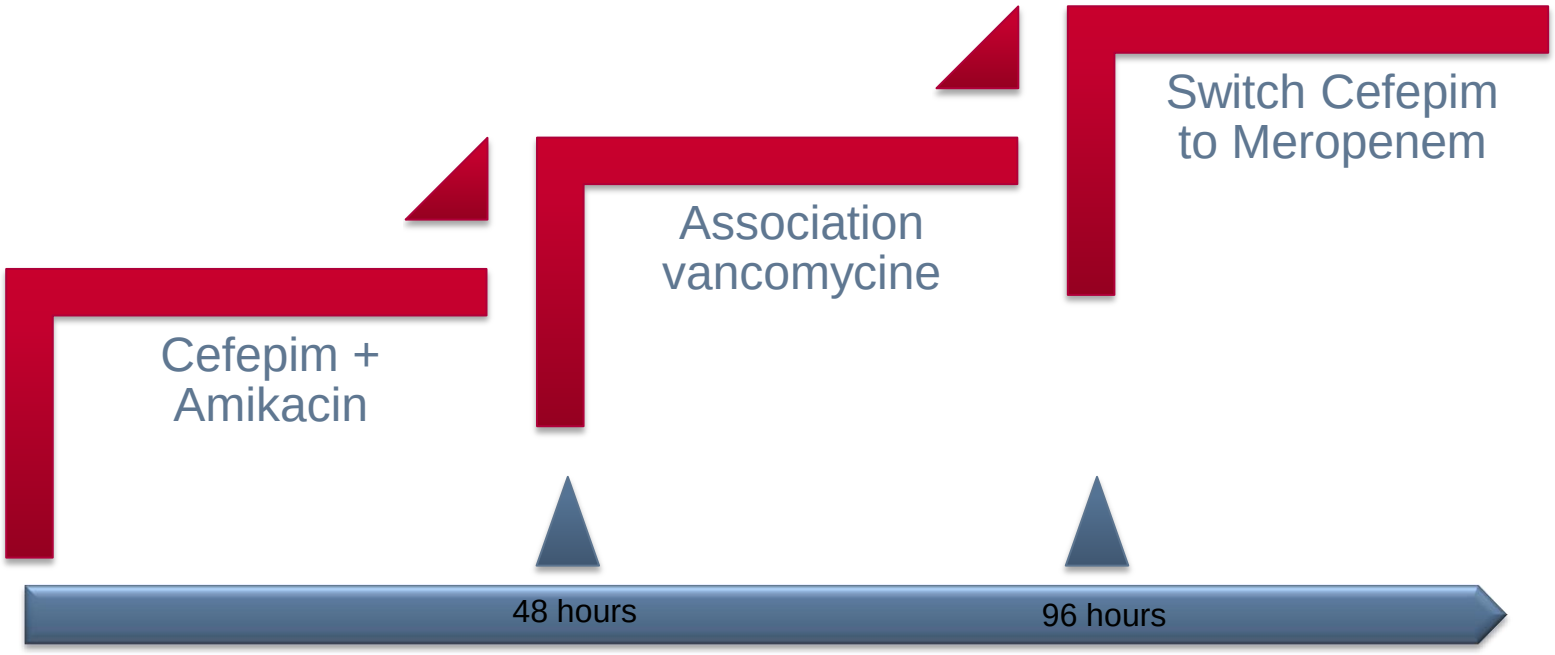
Cipro Stop Study – Empiric antibiotic treatment



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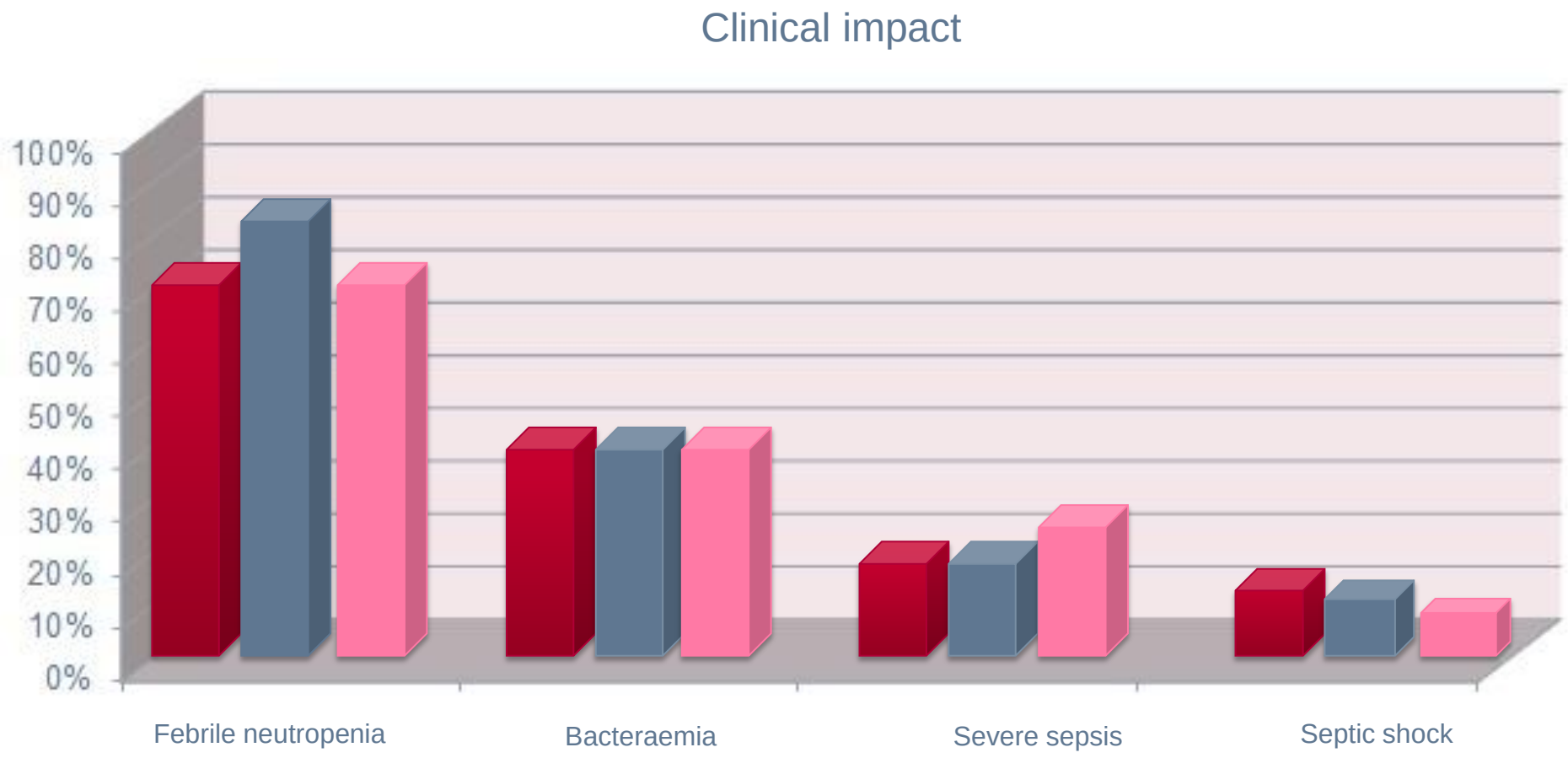
Cipro Stop Study – Results



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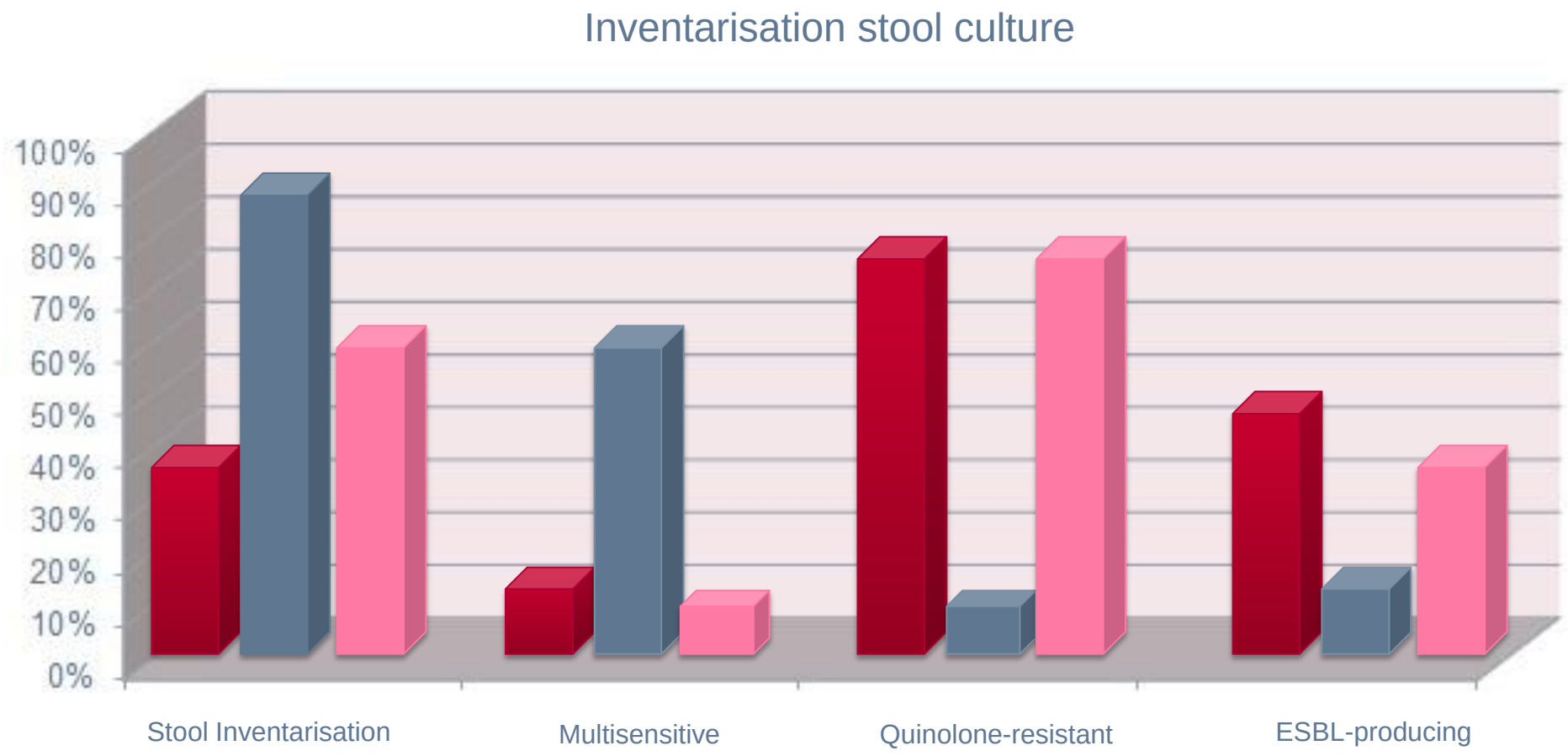

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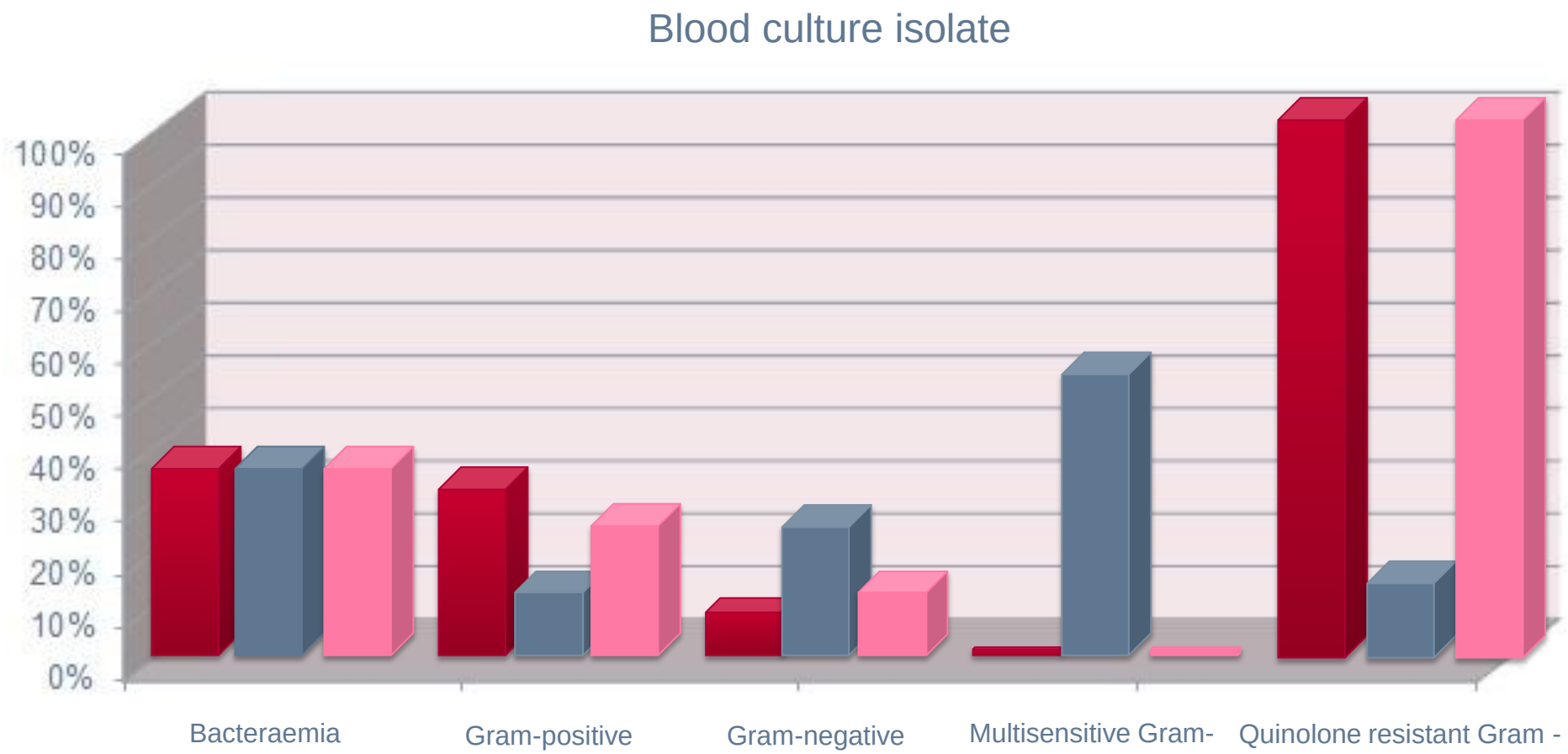

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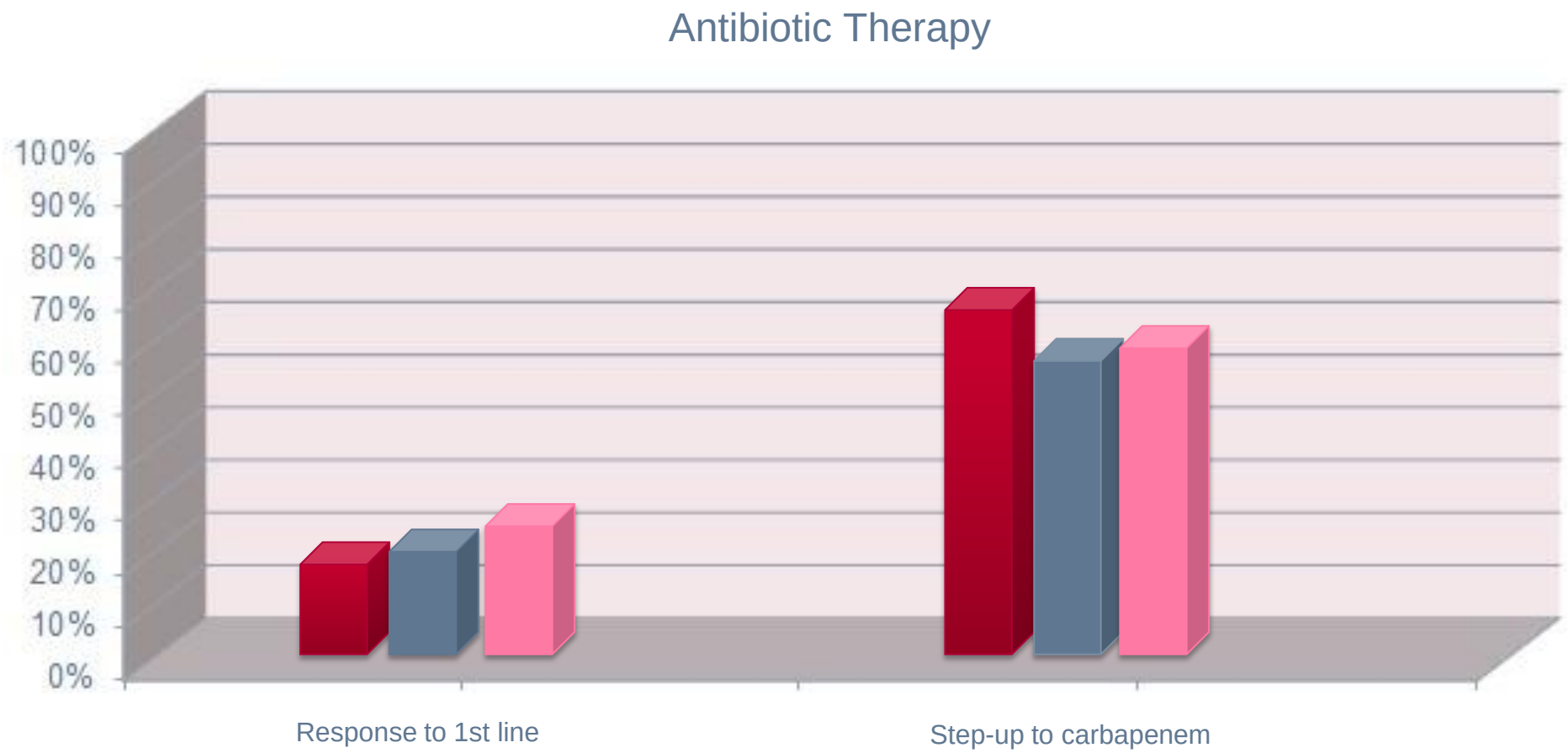

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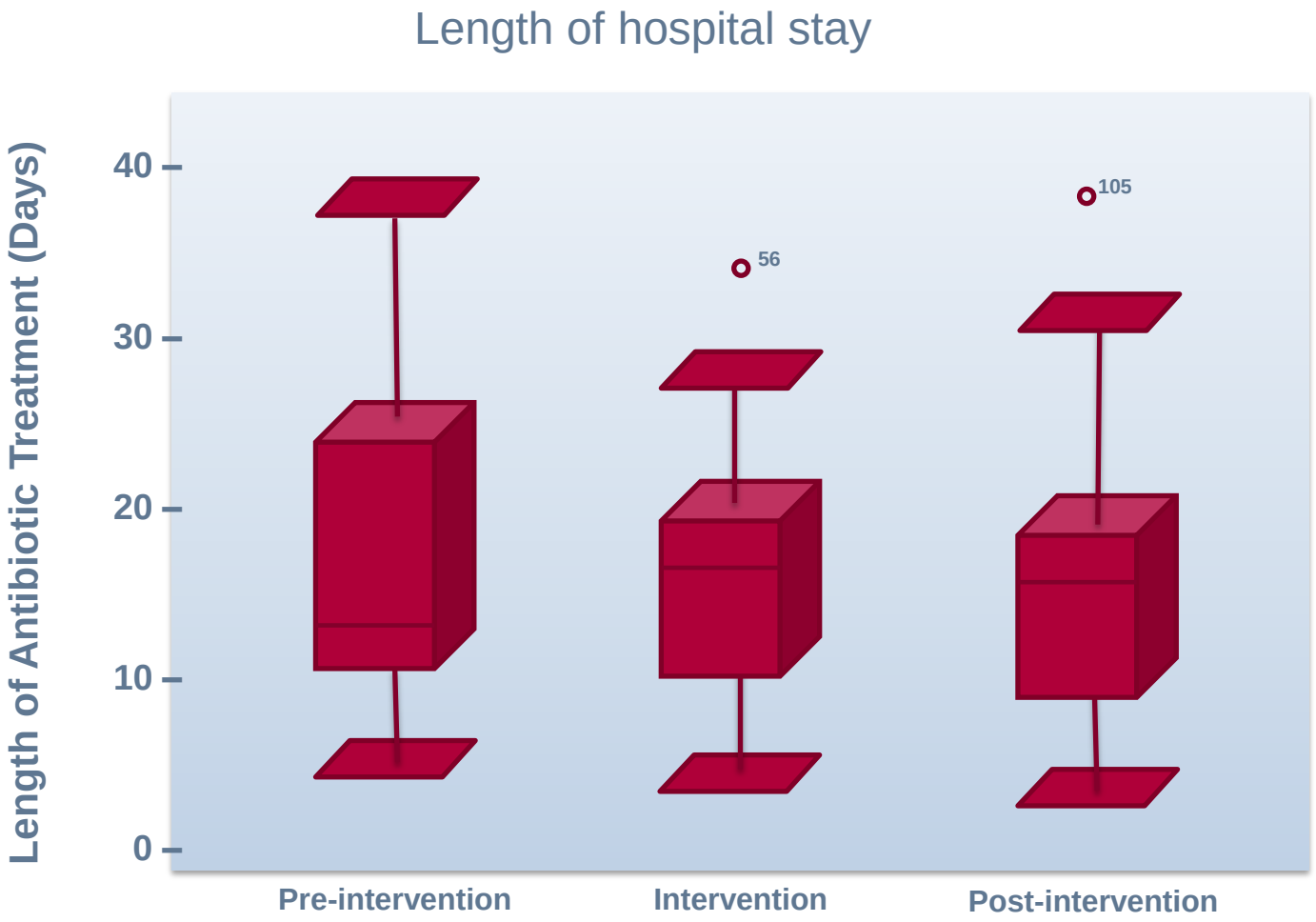

Verlinden et al. Eur J Haematol 2014;93(4):302-8.

Cipro Stop Study – Conclusions

- ↑ Episodes of neutropenic fever
  - Not resulting in more episodes of severe sepsis or septic shock
- ↑ Stool culture isolates
  - Significantly less colonization with resistant organisms
- ↑ Blood culture isolates
  - Significantly less infections caused by resistant pathogens
- = Efficacy first-line empiric antibiotics
- = Length of antibiotic treatment
- = Length of hospital stay

Verlinden et al. Eur J Haematol 2014;93(4):302-8.

Evolution decreased susceptibilities

- Cefepime/Amikacin → Meropenem/Amikacin
- Discontinuation of fluoroquinolone prophylaxis

	1/11/2008-31/10/2011	1/11/2011-31/12/2013
E. coli	**n = 28**	**n = 32**
Amikacin	0 %	0 %
Ciprofloxacine	42,9 %	25 %
Cefepime	3,8 %	0 %
Meropenem	0 %	0 %
Amoxi-clavulaanzuur	11,1 %	6,5 %
P. aeruginosa	**n = 11**	**n = 12**
Amikacin	36,4 %	8,3 %
Ciprofloxacine	36,4 %	0 %
Cefepime	36,4 %	16,7 %
Meropenem	36,4 %	8,3 %

Verlinden et al. Unpublished data.

What's next?

- 5 year follow-up after fluoroquinolone discontinuation
- Antimicrobial stewardship program in a stepwise approach
  - 2016:
    - Reducing vancomycin use
    - Shortening amikacin use from 5 to 3 days
    - Treating low risk patients with amoxicilline-clavulanate
    - Step down to narrow spectrum in case of multisensitive positive culture
  - 2017:
    - Shortening the length of antibiotic therapy
  - 2018:
    - Back to a less broad spectrum first-line?