INFEZIONI DA GERMI MDR IN PEDIATRIA

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DISCLOSURES

- **Research grants paid to my Institution by Abbott, GSK, Sanofi, Vifor**

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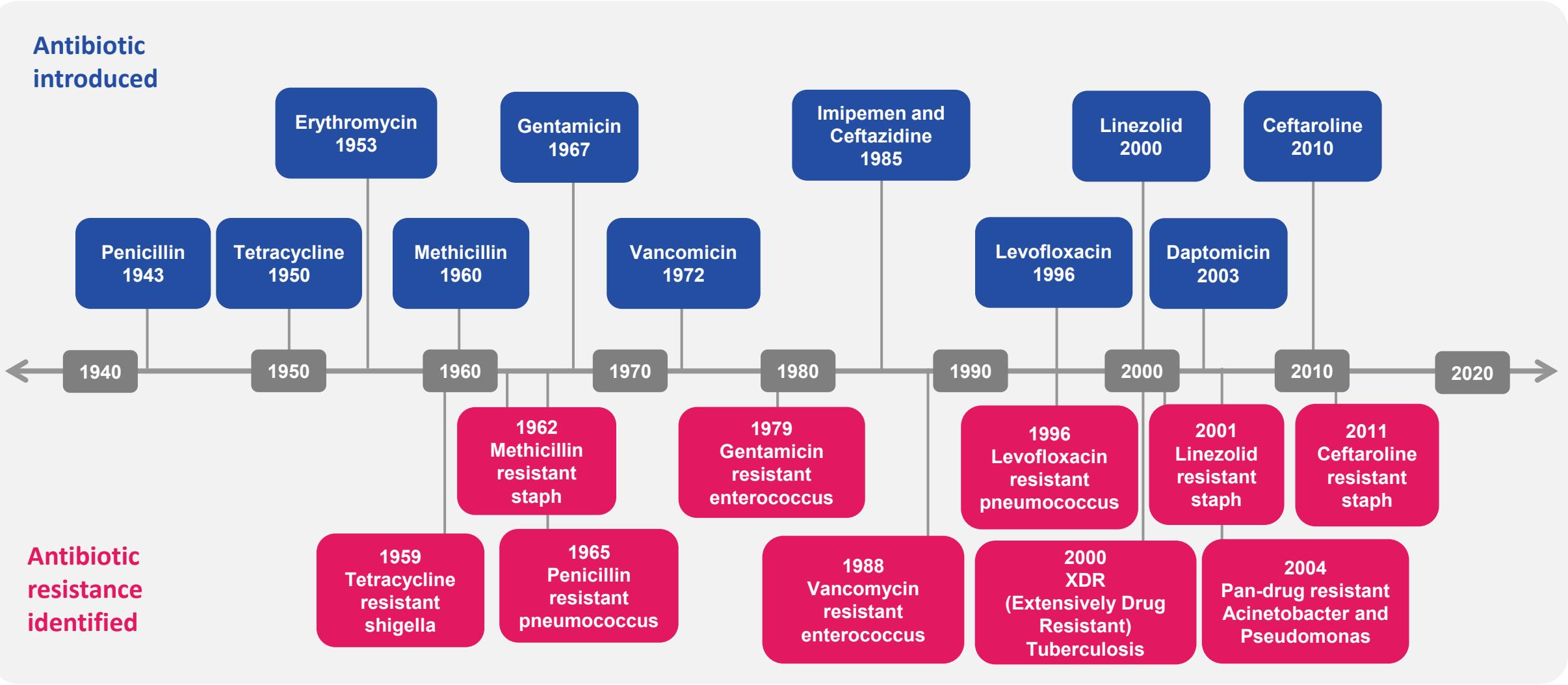
Agenda

- Consequences of inappropriate use of antibiotics in children
- Principles of appropriate use of antibiotics in children
- What happens in real-world practice
- Education by HCPs for caregivers

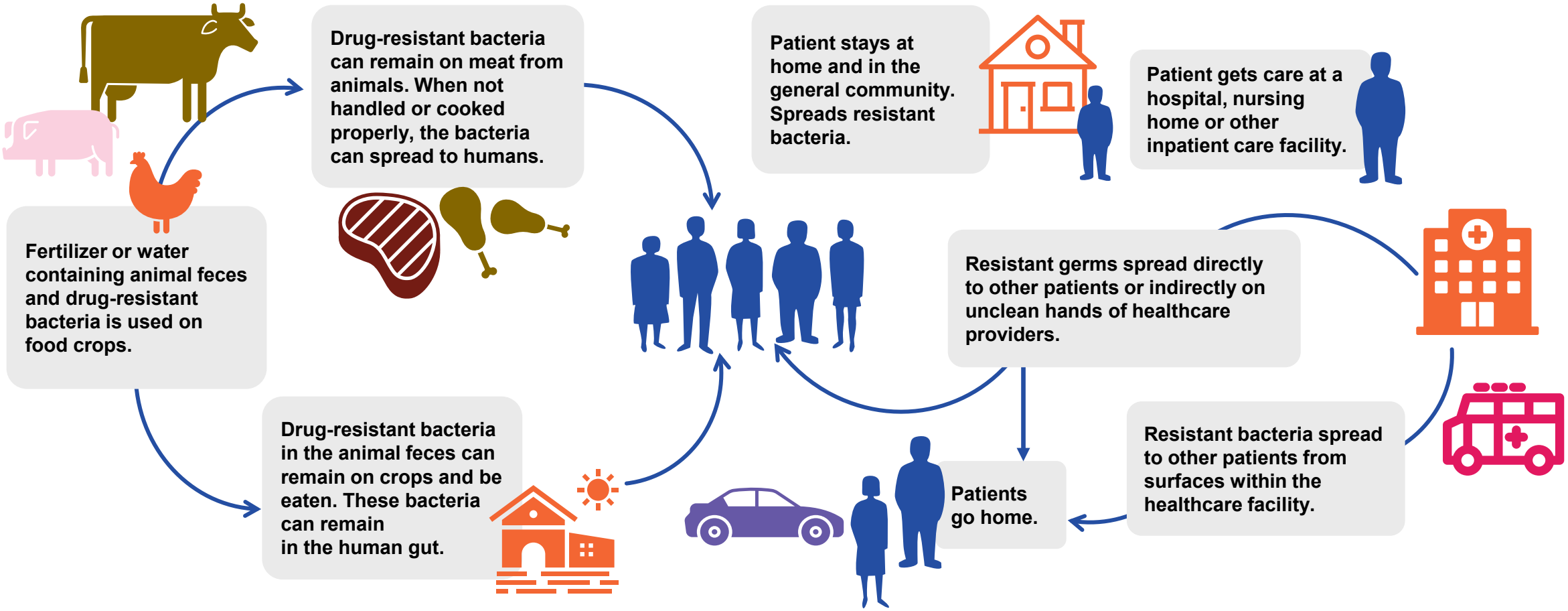
HCPs, healthcare professionals

Antibiotic use drives resistance



.
Annunziato G. *Int J Mol.Sci* 2019;20:5844.

Examples of how antibiotic resistance spreads



Simply using antibiotics creates resistance. These drugs should only be used to treat infections

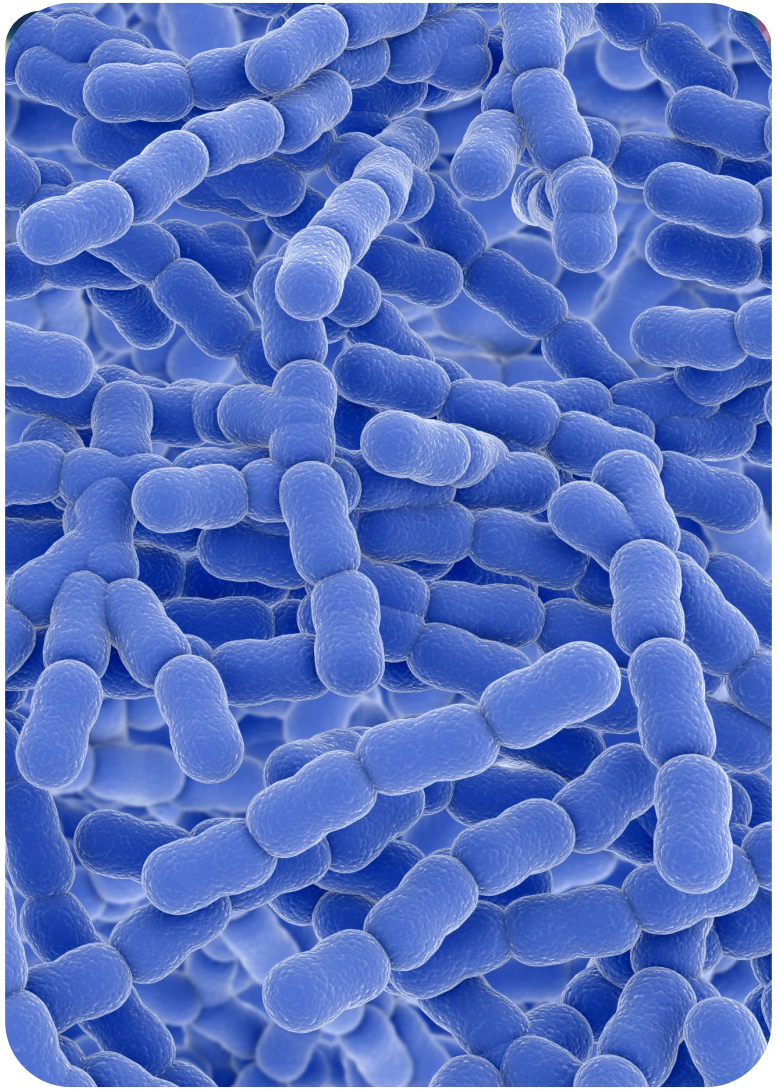
CDC. Antibiotic resistance and NARMS surveillance. Available from: https://www.cdc.gov/narms/faq.html. Accessed October 2022

AMR – quantifying the effect

AMR is a health problem at least as large as HIV or malaria …potentially **much larger**

4·95 million deaths were associated with bacterial AMR, of these,

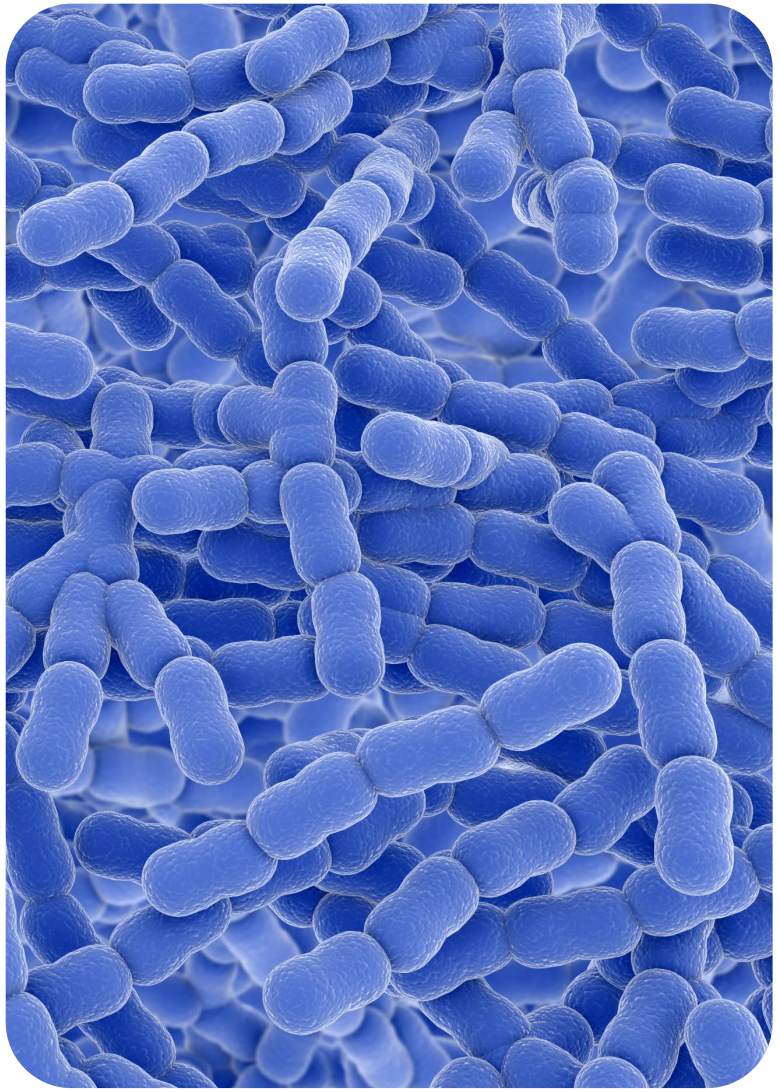
1·27 million deaths were directly attributable to bacterial AMR



AMR, antimicrobial resistance

Antimicrobial Resistance Collaborators. *Lancet* January 20, 2022 https://doi.org/10.1016/ S0140-6736(21)02724-0.

AMR – quantifying the effect



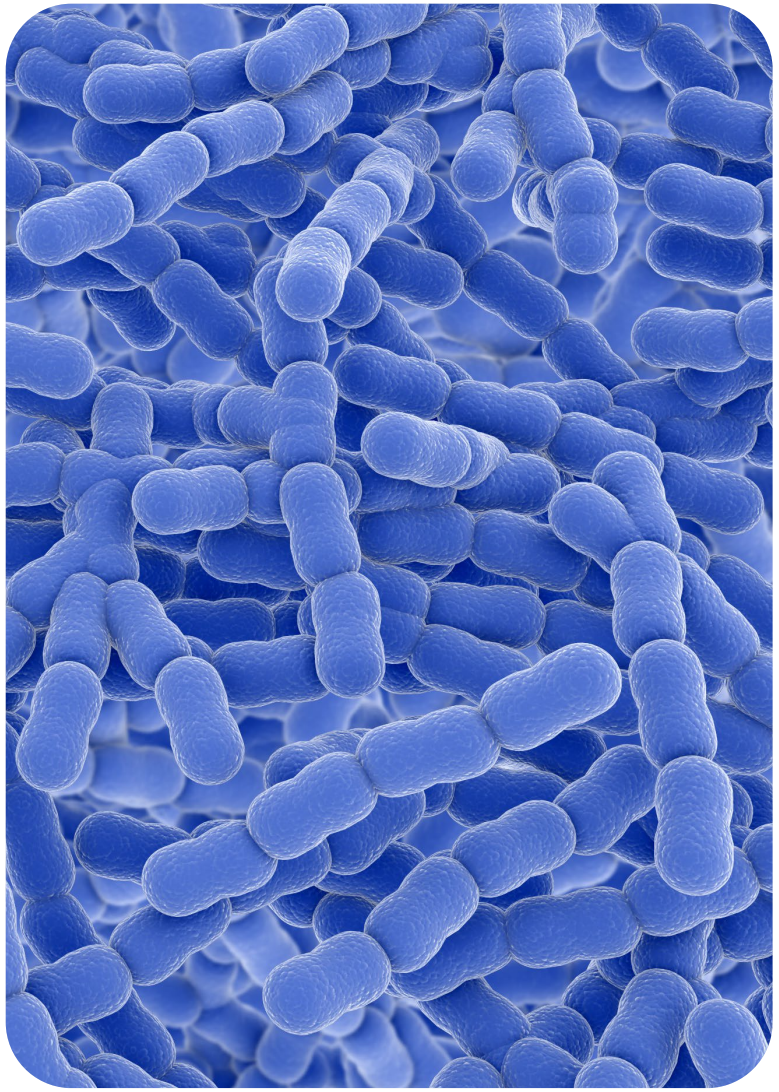
The most common infection was LRTI (>1·5 million deaths) followed by bloodstream infections and intra-abdominal, these 3 making up **78.8%** of the total

73·4% of all deaths due to bacterial AMR were caused by: *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa*

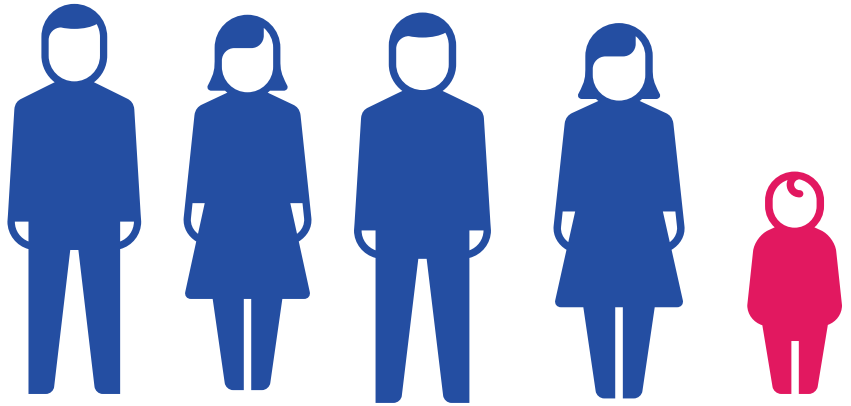
AMR, antimicrobial resistance; LRTI, lower respiratory tract infection.

Antimicrobial Resistance Collaborators. *Lancet* January 20, 2022 https://doi.org/10.1016/ S0140-6736(21)02724-0.

AMR and child death



In 2019, 1 in 5 people who died due to AMR were **children under 5 years old**



AMR, antimicrobial resistance

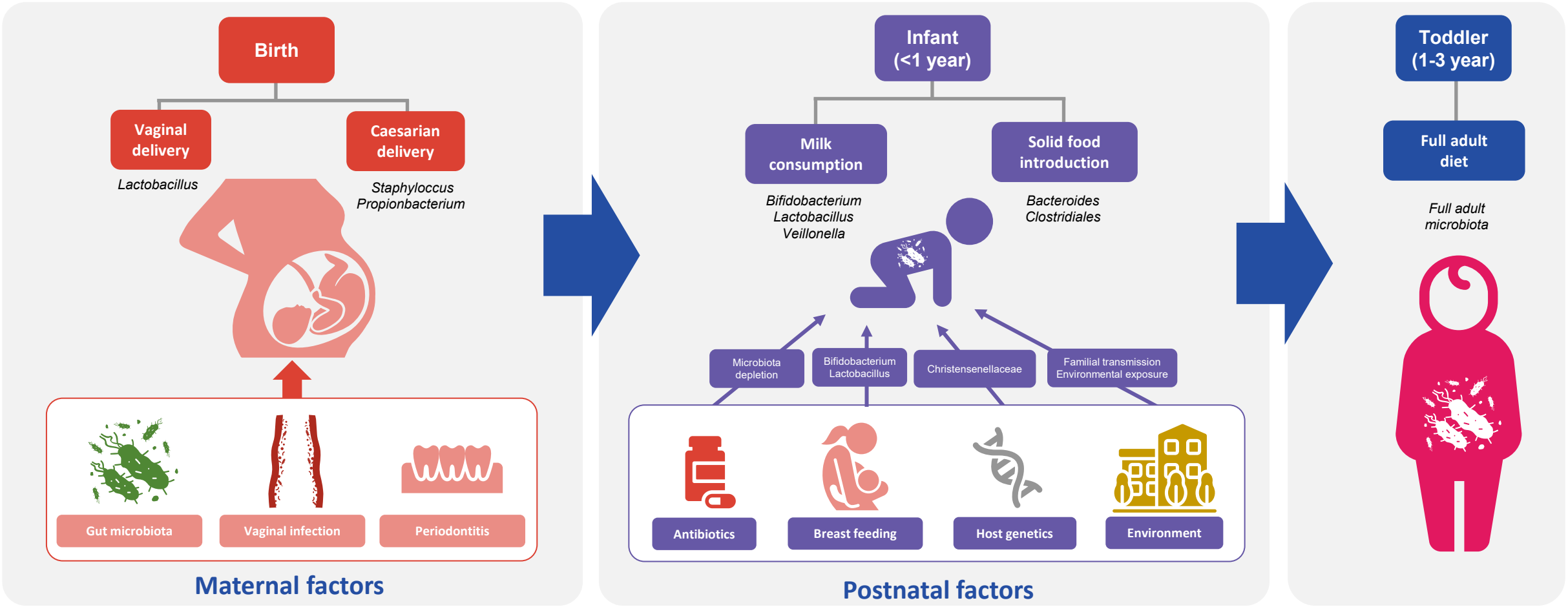
Antimicrobial Resistance Collaborators. *Lancet* January 20, 2022 https://doi.org/10.1016/ S0140-6736(21)02724-0.

Unintended consequences of antibiotic use: adverse events

- Adverse events range from minor to severe
- 140,000 emergency department visits occur nationally per year from antibiotic-associated adverse events
- Antibiotic use associated with allergic, autoimmune, and infectious diseases likely through disruption of the normal microbiome

Linder JA. *Clin Infect Dis* 2008;47(6):744–6.
Shehab N, *et al*. *JAMA* 2016:316:2115–25.
Vangay P, *et al*. *Cell Host Microbe* 2015;17(5):553–64.

Summary of the origin and transmission of the microbiome



Tamburini S, *et al. Nature Medicine* 2016;;22:713–22.

Potential effect on beneficial bacteria

Antibiotic overuse: Stop the killing of beneficial bacteria

Blaser; Nature, 2011, Vol 476: 393-394

Evidence is accumulating that our welcome residents do not recover completely from antibiotics or are replaced in the long term by resistant organisms

Overuse of antibiotics could be fueling the dramatic increase in conditions such as obesity, type 1 diabetes, inflammatory bowel disease, allergies and asthma, which have more than doubled in many populations

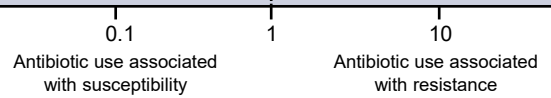
Stop the killing of beneficial bacteria

Concerns about antibiotics focus on bacterial resistance – but permanent changes to our protective flora could have more serious consequences

Blaser M. *Nature*. 2011;476:393-4.

Effect of antibiotic prescribing in primary care on antibiotic resistance

Time period, study	Antibiotic exposure	Resistance in unexposed (control) group (%)	Odds ratio (9.5 CI)	Odds ratio(9.5 CI)
0-1 month				
Donnan[17]	Trimethoprim	NR		4.45 (3.78 to 5.21)
Hillier[19]	Trimethoprim	20		4.85 (2.63 to 8.94)
Hillier[19]	Amoxicillin	20		3.11 (1.57 to 6.17)
Pooled odds ratio				4.40 (3.78 to 5.12)
Test for Heterogeneity:	I^2–0.0%, P–0.576			
0-3 months				
Donnan[17]	Trimethoprim	NR		2.60 (2.04 to 3.33)
Hillier[19]	Trimethoprim	39		2.62 (1.69 to 4.07)
Hillier[19]	Amoxicillin	39		2.26 (1.41 to 3.62)
Hay[18]	Any antibiotic	20		1.93 (1.06 to 3.51)
Pooled odds ratio				2.06 (2.06 to 2.98)
Test for Heterogeneity:	I^2–0.0%, P–0.796			
0-6 months				
Steinke[23]	Any antibiotic*	19		1.36 (1.14 to 1.61)
Donnan[17]	Trimethoprim	NR		1.67 (1.32 to 2.10)
Steinke[23]	Trimethoprim	19		3.95 (3.04 to 5.12)
Hillier[19]	Amoxicillin	28		1.83 (1.39 to 2.42)
Donnan[17]	Any antibiotic*	NR		1.65 (1.10 to 2.46)
Hillier[19]	Trimethoprim	28		2.57 (1.83 to 3.61)
Metlay[24]	ST	28		4.10 (2.20 to 7.50)
Pooled odds ratio				2.18 (1.57 to 3.03)
Test for Heterogeneity:	I^2–89.2%, P–0.000			
0-12 months				
Donnan[17]	Trimethoprim	NR		1.22 (1.16 to 1.28)
Donnan[17]	Any antibiotic*	NR		1.18 (1.06 to 1.32)
Hillier[19]	Amoxicillin	19		1.62 (1.18 to 2.23)
Hay[18]	Any antibiotic*	38		1.13 (0.79 to 1.63)
Hillier[19]	Trimethoprim	19		2.36 (1.59 to 3.50)
Pooled odds ratio				1.33 (1.15 to 1.53)
Test for Heterogeneity:	I^2–71.9%, P–0.007			



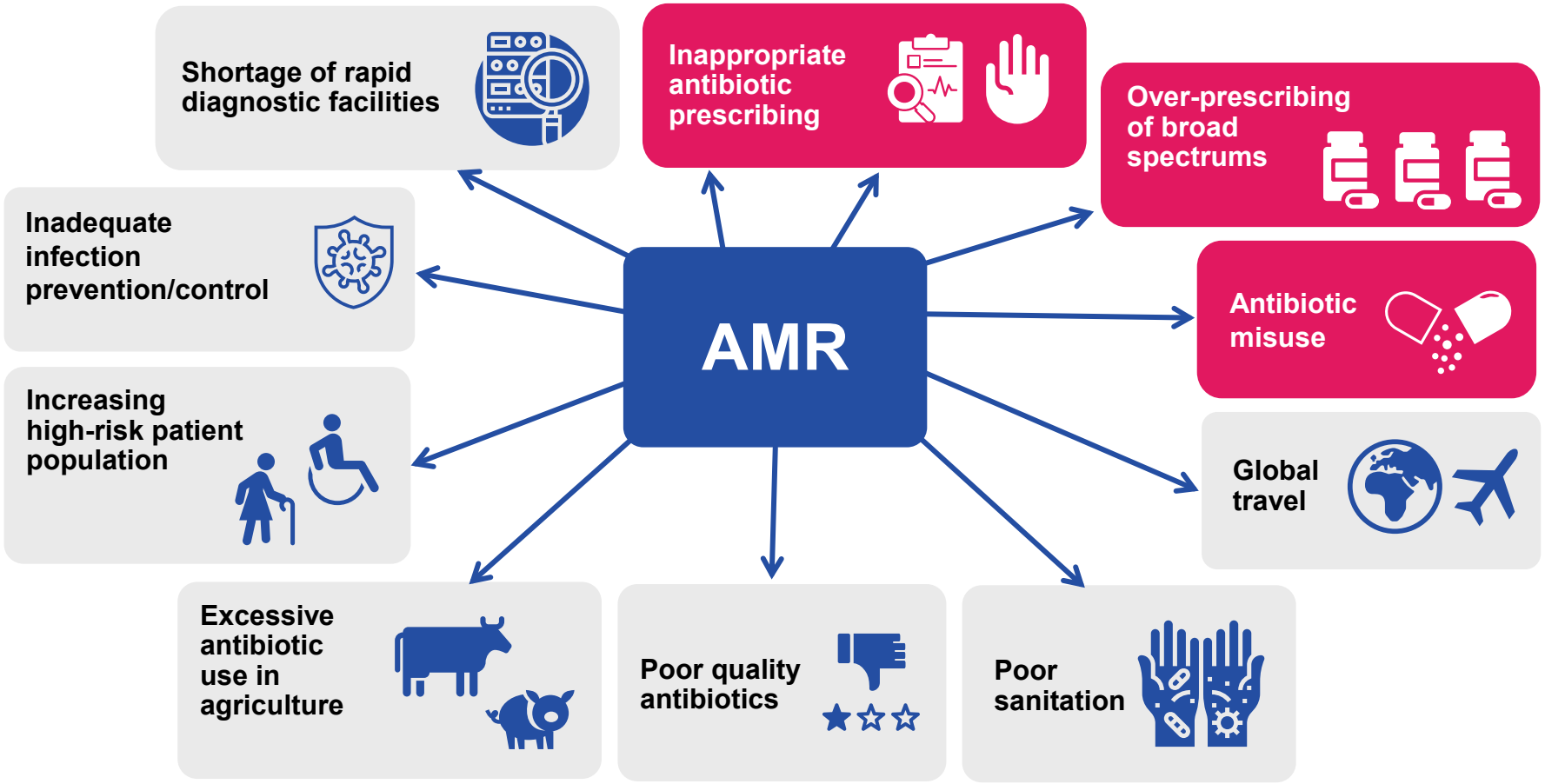
Costelloe C, *et al. BMJ* 2010;340:c2096 doi:10.1136/bmj.c2096

Antibiotics in Italian hospitalized children with lower respiratory tract infections

	Bronchitis		Wheezing		Pneumonia	
	2-4 y	> 5 y	2-4 y	> 5 y	2-4 y	> 5 y
Cephalosporins	19.3	9.8	11.3	20.6	50.7	25.8
Cephal+macrol	6.4	9.7	7.4	6.8	15.2	24.8
Macrolides	40.3	43.1	41.3	27.5	14.7	25.9
Amino+inhibit	22.5	9.8	15	3.4	13.8	9.5
No antibiotic	9.6	21.5	22.6	37.9	1.9	2.3

Esposito S. EJCMID; 2001:20:647

Major drivers of the development and spread of AMR[1–3]



'The world urgently needs to change the way it prescribes and uses antibiotics. Even if new medicines are developed, without behaviour change, antibiotic resistance will remain a major threat'

WHO 2020[4]

AMR, antimicrobial resistance; WHO, World Health Organization.

1. Watkins RR, *et al. Infect Dis Clin N Am* 2016;30:313–22. 2. Laxminarayan R, *et al. Lancet Infect Dis* 2013;13(12):1057–98.
3. ECDC Surveillance of antimicrobial resistance in Europe 2017. https://www.ecdc.europa.eu/sites/portal/files/documents/EARS-Net-report-2017-update-jan-2019.pdf. Accessed 03/10/2022.
4. WHO antibiotic resistance Fact sheet July 2020. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance. Accessed 10/10/2022.

Guidelines for the Diagnosis and treatment of Acute Subacute Rhinosinusitis in Children

S. Esposito

Updated Guidelines for the Management of Acute Otitis Media in Children by the Italian Society of Pediatrics

Paola Marchisio *et al*

Management of Acute Pharyngitis in Children: Summary of the Italian National Institute of Health Guidelines

Elena Chiappini *et al*

Guidelines for the Management of Acute Sore Throat

ESCMID Sore Throat Guideline Group

C. Pelucchi *et al*

British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011

Michael Harris *et al*

Antibiotic use for community-acquired pneumonia in neonates and children: WHO evidence review

Shrey Mathur *et al*

Understanding the burden of CAP in paediatric patients and unmet needs

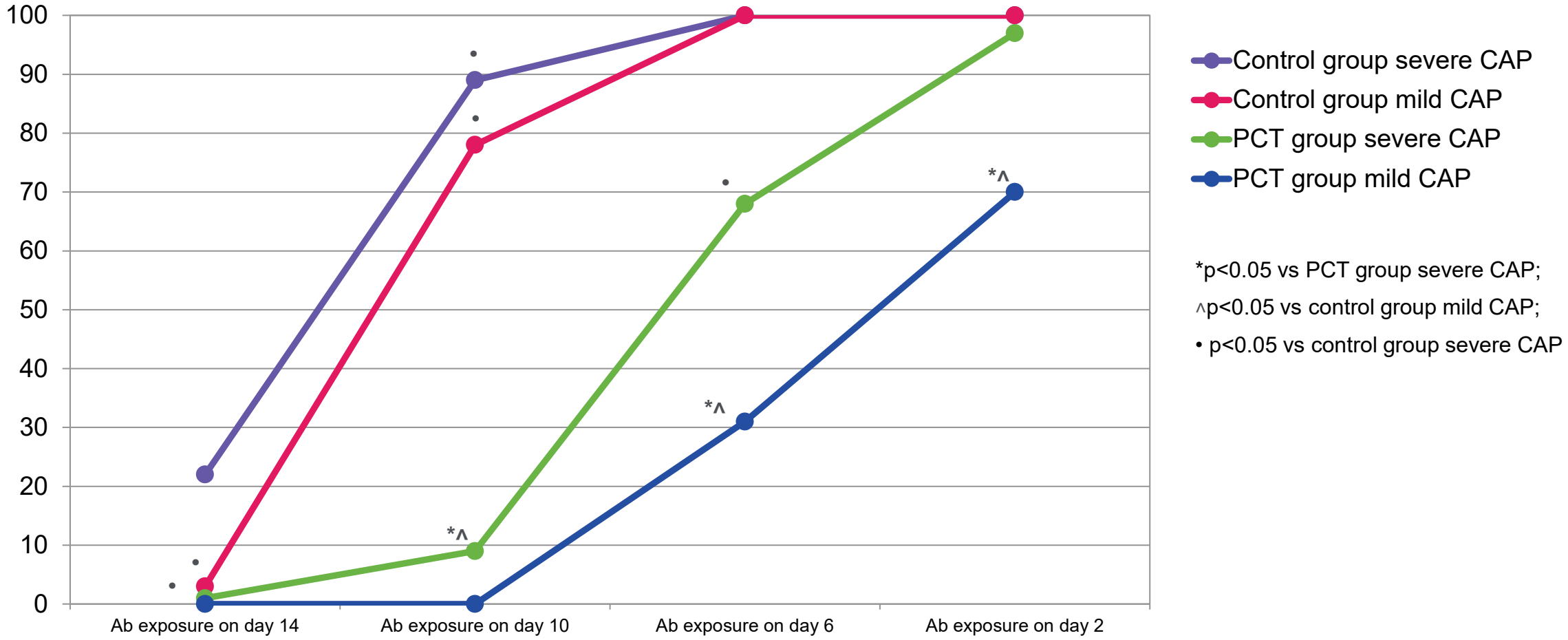
Burden

- Globally, CAP has been found to be the leading cause of death in children under 5 years of age[1]
- In the US, the prevalence of CAP in children is reported to be 1,000 to 4,000 cases/100,000 children/year[2]
- Risk factors for CAP in children <15 years of age were found to include lower age, asthma and previous respiratory tract infections[3]

Unmet needs

- The most common bacterial pathogen associated with CAP in adults and children is Streptococcus pneumoniae; however, *Haemophilus influenzae* and *Staphylococcus aureus*, including MRSA and MSSA, are also aetiological agents
- The emergence of drug-resistant pneumococcal and staphylococcal isolates has limited the effectiveness of currently available agents
- Newer agents with activity against drug-resistant strains of *S. pneumoniae* and MRSA are needed for the management of patients with CAP

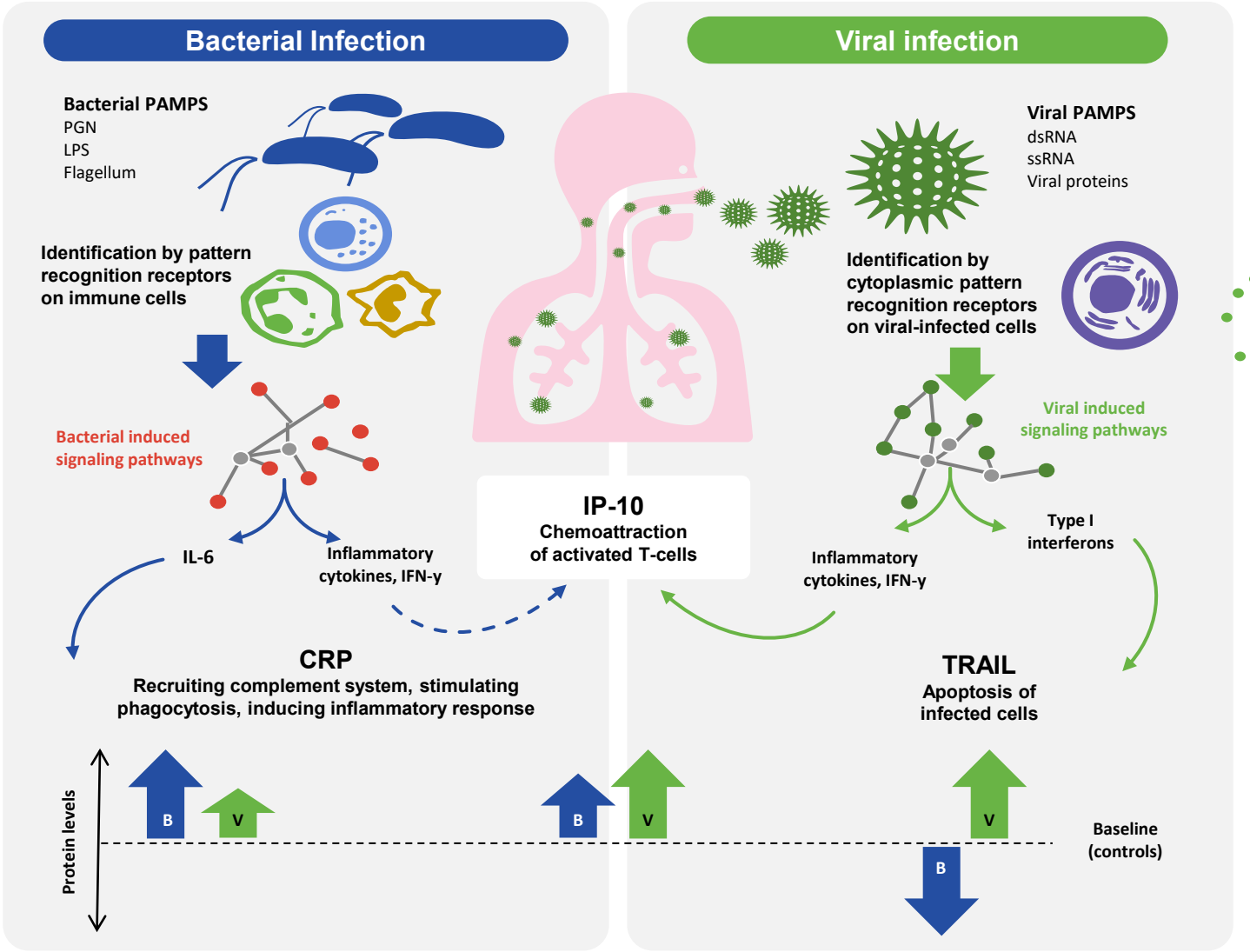
Antibiotic exposure by treatment group and CAP severity



CAP, community-acquired pneumonia; Ab, antibiotic; PCT

Esposito S et al. *Respir Med* 2011;105:1939–1945. This graph has been created by GSK from the original data.

Novel host-immune signature for distinguishing between bacterial and viral infections

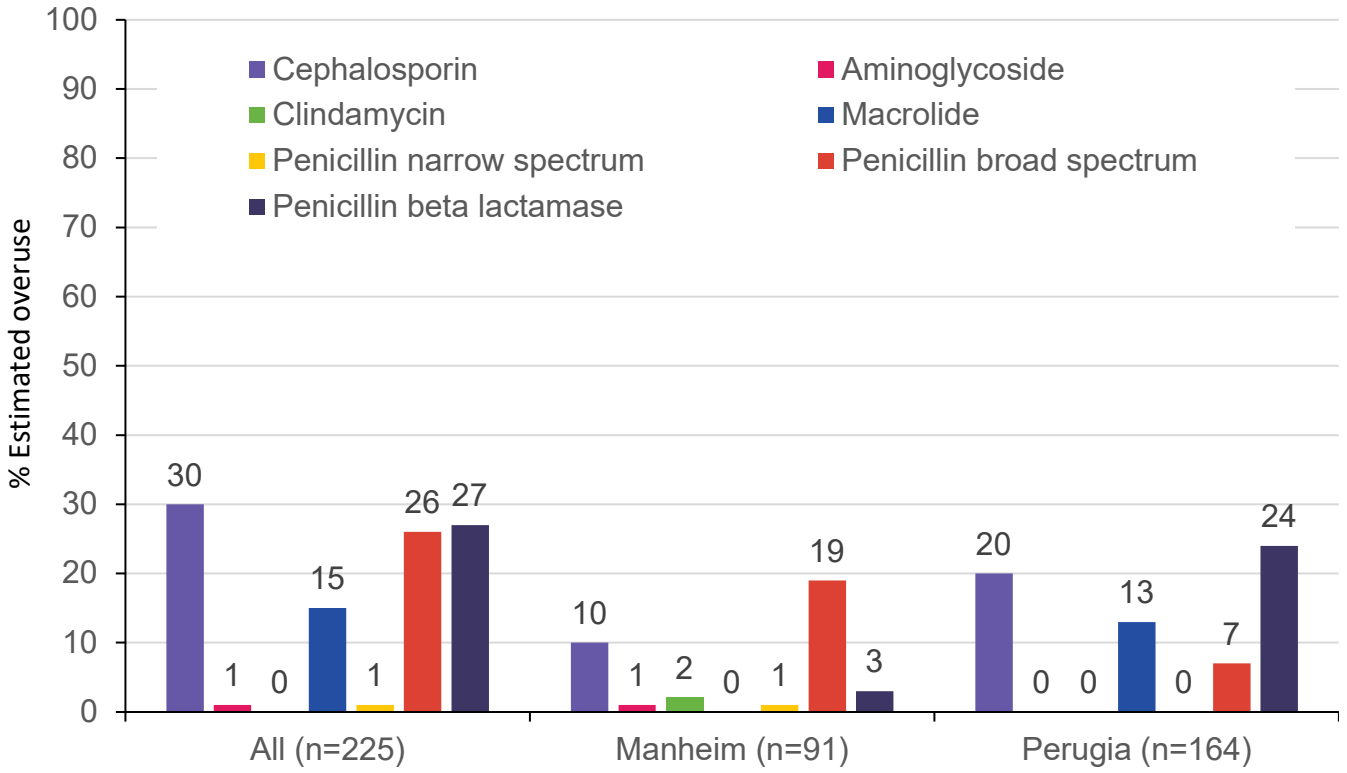


Oved K, et al. *PLOS One* 2015; https://doi.org/10.1371/journal.pone.0120012

How to differentiate between viral and bacterial infections?

Estimated impact of the signature on misuse and antibiotic overuse types across different cohorts. Current practice overuse was defined as viral patients receiving antibiotics, underuse as bacterial patients not receiving antibiotics or receiving delayed treatment

	Overuse (Viral=628)	Underuse (Bacterial=104)
Current practice	30%	9%
Current practice (index test)	9%	7%



CMI CLINICAL MICROBIOLOGY AND INFECTION
ESCMID

Original Article

A host signature based on TRAIL, IP-10, and CRP for reducing antibiotic overuse in children by differentiating bacterial from viral infections: a prospective, multicentre cohort study

Cihan Papan [1,2,†], Alberto Argentiero [3,†], Marian Porwoll [1], Ummaya Hakim [1], Edoardo Farinelli [3], Ilaria Testa [3], Maria Bruna Pasticci [3], Daniele Mezzetti [3], Katia Perruccio [3], Liat Etshtein [4], Niv Mastboim [4], Einat Moscoviz [4], Tahel Ilan Ber [4], Asi Cohen [4], Einav Simon [4], Olga Boico [4], Liran Shani [4], Tanya M. Gottlieb [4], Roy Navon [4], Eran Barash [4], Kfir Oved [4], Eran Eden [4], Arne Simon [5], Johannes G. Liese [6], Markus Knuf [7], Michal Stein [8], Renata Yacobov [8], Ellen Bamberger [9,10], Sven Schneider [11], Susanna Esposito [12,§], Tobias Tenenbaum [1,*,§]

Papan C, et al. *Clin Microbiol Infect* 2022;28: 723–730

Ceftarolin fosamil - Paediatric dose selection

- Adult dosing regimen for ceftaroline fosamil:[1]
  - 600 mg q12h by IV injection for the treatment of CAP and cSSTI
- Paediatric patients require different dosing to adults for ceftaroline due to differences in PK between children and adults[2]
  - The renal clearance and distribution volumes of β-lactams vary depending on age in paediatric patients
  - Incorrect dosing could lead to over- or under-dosing
- Population PK models have been developed for ceftaroline using paediatric study data. These provide the basis for the FDA and EMA dose recommendations in children (see next slide)[1,2]
  - PK model used data from five paediatric studies, including over 300 children with ABSSSI and CABP treated with ceftaroline
  - Model simulations were used to predict exposures for the paediatric doses
  - These analyses suggest that paediatric exposures would be similar to the exposures in adults treated with 600 mg ceftaroline fosamil q12h and would maintain high PK/PD target attainment in children at the breakpoints for *S. aureus* and *S. pneumoniae*
- Recent PK analyses and clinical data acquired from a multiple-dose neonatal study support a ceftaroline fosamil dosage regimen of 6 mg/kg q8h for patients aged <2 months[3,4]

The recommended dose regimen for treatment of cSSTI in adults due to *S. aureus* for which the ceftaroline MIC is 2 or 4 mg/L is 600 mg every 8 hours using 2 hourly infusions[1]

ABSSSI, acute bacterial skin and skin-structure infection; CABP, community-acquired bacterial pneumonia; CAP, community-acquired pneumonia; cSSTI, complicated skin and soft-tissue infection; EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; q8h, every 8 hours; q12h, every 12 hours

1. Zinforo® Summary of Product Characteristics, 2019; 2. Riccobene TA, *et al*. *J Clin Pharmacol*. 2017;57(3):345–55; 3. Chan PLS, *et al*. Poster presented at: ECCMID, 13–16 April 2019. Poster O106. 4. Bradley J, *et al*. Poster presented at: ECCMID, 13–16 April 2019. Poster P1171.

Summary – Ceftaroline fosamil

- Ceftaroline fosamil was shown to be effective and well-tolerated in paediatric patients for the treatment of CAP[1–3]
  - Paediatric patients have reported a similar overall tolerability with ceftaroline as with other cephalosporins[1–3]
- The indication for ceftaroline fosamil is now extended to neonates for the treatment of CAPI[4]
  - Safety in neonates is consistent with the known safety profile for ceftaroline fosamil[5,6]
- Ceftaroline fosamil may provide a useful empirical treatment option for children with CAP[3]

CAP, community-acquired pneumonia; cSSTI, complicated skin and soft-tissue infection

1. Cannavino CR, *et al*. *Pediatr Infect Dis J*. 2016;35:752–9; 2. Korczowski B, *et al*. *Pediatr Infect Dis J*. 2016;35:e239–e247 3. Blumer JL, *et al*. *Pediatr Infect Dis J*. 2016;35:760–6; 4. Zinforo® Summary of Product Characteristics, 2019; 5. Bradley J, *et al*. Poster presented at: ECCMID, 13–16 April 2019. Poster P1171;
6. Chan PLS, *et al*. Poster presented at: ECCMID, 13–16 April 2019. Poster O106.

- 840/1801 cases (46.7%) were due to antimicrobial-resistant uropathogens → 83 (4.7%) to ESBL, 119 (6.7%) to MDR and 4 (0.2%) to XDR bacteria
- The most frequent **ESBL** pathogens were ***E. coli*** (62/83, 74.7%), ***K. pneumoniae*** (10/83, 12.0%)
- The most frequent **MDR** pathogens were ***E. coli*** (68/119, 57.1%), ***P. aeruginosa*** (12/119, 10.1%), ***K. pneumoniae*** (7/119, 5.9%), ***Proteus mirabilis*** (6/119, 5.0%);
- **XDR** pathogens were ***E. coli*** (3/4) and ***K. pneumoniae*** (1/4);
- **Having ESBL or MDR/XDR uropathogens was significantly associated with treatment failure**

Risk factors for the development of febrile urinary tract infection (UTI) due to resistant bacteria

- The most reported predisposing factors for the development of resistant febrile UTI were the **presence of urinary system structural or functional abnormalities**, including vesicoureteral reflux (VUR), **recurrent UTI**, and **administration of continuous antibiotic prophylaxis**, particularly when based on cephalosporins.
- **Antibiotic therapy within 30 days before infection** was the only independent risk factor for the development of a resistant UTI (OR 3.92, 95% CI 1.76-8.7).
- In children with previous episodes of UTI and/or well-defined structural or functional abnormalities of the urinary tract, the risk of resistance is high, and the choice of antibiotic therapy must take into consideration the aetiology of previous episodes and local antimicrobial resistance data.
- Taking into account the increase in the incidence of ESBL cases, Italian guidelines have recently been updated, and an **amoxicillin/clavulanic acid combination** has been indicated as the drug of choice for paediatric UTI treatment, highlighting that **first- to third-generation cephalosporins are, in many cases, ineffective against ESBL-producing strains.**

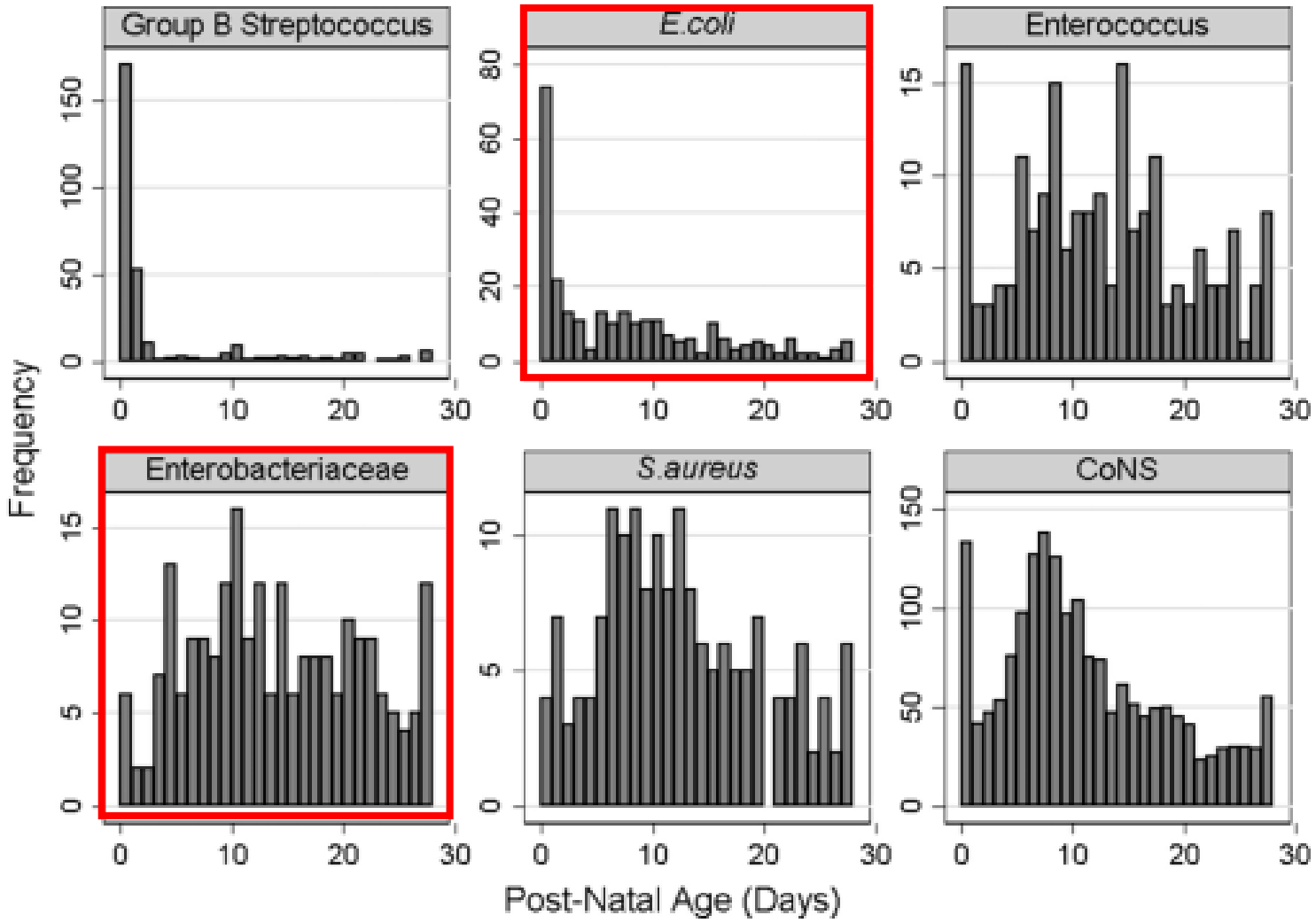
Esposito et al., Antibiotics 2021

RESULTS

Table 4. Univariate logistic regression analysis of risk factors for failure of discordant empirical treatment.

Parameter	Odds Ratio (OR)	95 % CI	*p* Value
Male	0.69	0.35–1.36	0.29
Age groups			
<3 months	1.00		
3 months–2 years	1.94	0.89–4.20	0.09
2–6 years	1.76	0.53–5.88	0.35
>6 years	2.20	0.73–6.65	0.16
History of recurrent UTIs	3.23	1.13–9.98	<0.05
VUR	1.67	0.42–7.44	0.42
Urological malformations	1.98	0.55–7.97	0.23
Pyelectasis	1.54	0.69–3.45	0.25
Antibiotic prophylaxis	1.10	0.28–4.58	0.88
Antibiotic therapy in previous 30 days	5.02	1.46–21.82	<0.01
ESBL	1.36	0.51–3.70	0.49
MDR/XDR	1.85	0.79–4.40	0.12
Simple resistance pattern	0.51	0.22–1.16	0.08
Escherichia coli	0.80	0.35–1.81	0.55
Pseudomonas aeruginosa	7.30	1.85–62.10	<0.05
Klebsiella spp.	1.34	0.36–5.10	0.61
Enterobacter spp.	0.62	0.13–2.57	0.45
Discordant treatment with penicillin/beta-lactamase inhibitor combinations	1.94	0.94–4.03	0.05
Discordant treatment with 3rd-generation cephalosporins	0.80	0.32–2.00	0.61
Discordant treatment with penicillins + aminoglycoside	0.56	0.23–1.34	0.15
Intravenous route of administration	0.59	0.26–1.34	0.17

Incidences of common pathogens causing infections in 30 neonatal units in the neonIN network.

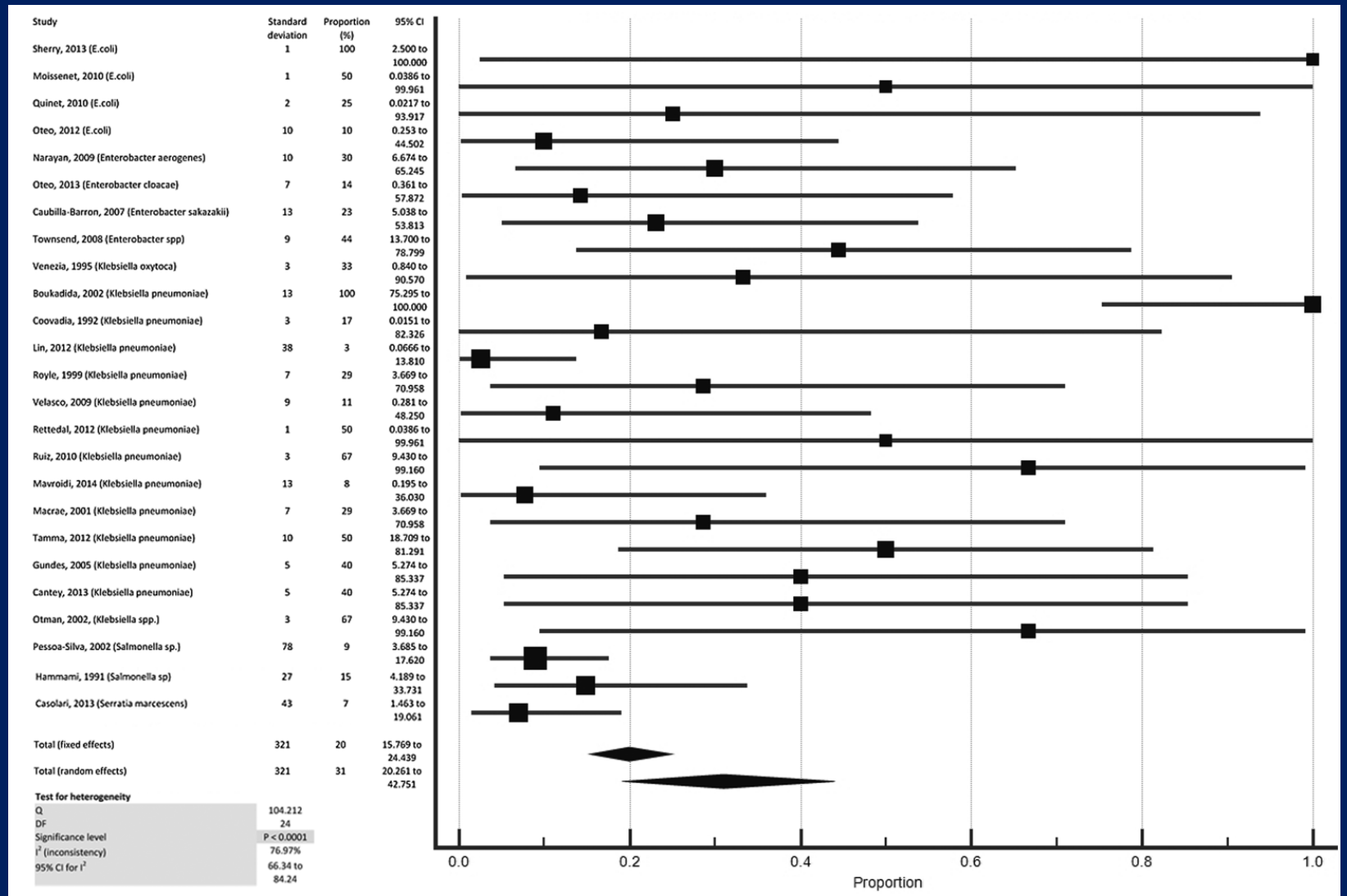


Benjamin Cailes et al. Arch Dis Child Fetal Neonatal Ed 2018;103:F547-F553

FN

Meta-analysis of proportion of neonates with infections due to ESBL-producing *Enterobacteriaceae* who died

(From Stapleton PJM et al., Arch Dis Child Fetal Neonatal Ed. 2016)

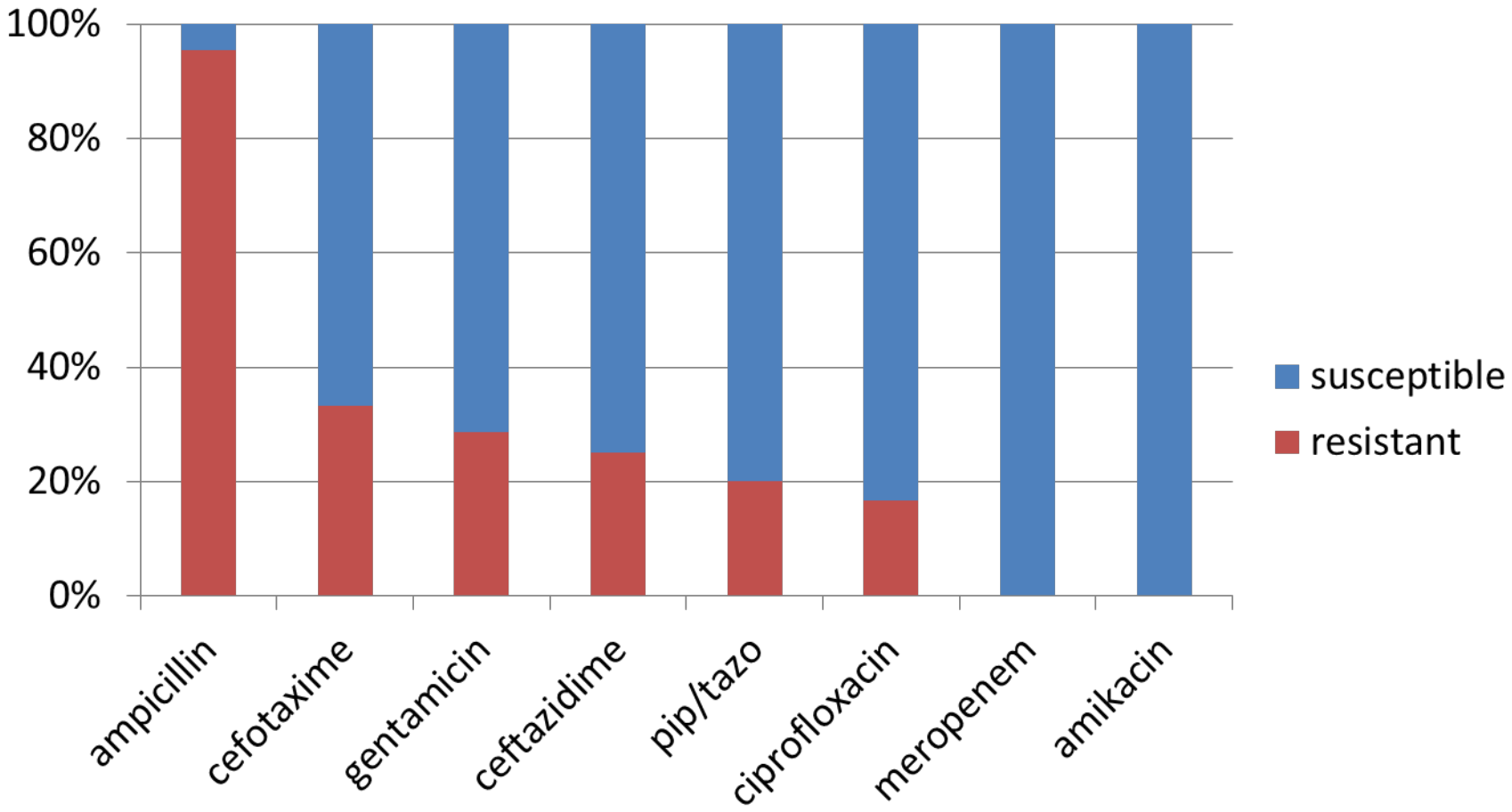


Study	Standard deviation	Proportion (%)	95% CI
Sherry, 2013 (E.coli)	1	100	2.500 to 100.000
Moissenet, 2010 (E.coli)	1	50	0.0386 to 99.961
Quinet, 2010 (E.coli)	2	25	0.0217 to 93.917
Oteo, 2012 (E.coli)	10	10	0.253 to 44.502
Narayan, 2009 (Enterobacter aerogenes)	10	30	6.674 to 65.245
Oteo, 2013 (Enterobacter cloacae)	7	14	0.361 to 57.872
Caubilla-Barron, 2007 (Enterobacter sakazakii)	13	23	5.038 to 53.813
Townsend, 2008 (Enterobacter spp)	9	44	13.700 to 78.799
Venezia, 1995 (Klebsiella oxytoca)	3	33	0.840 to 90.570
Boukadida, 2002 (Klebsiella pneumoniae)	13	100	75.295 to 100.000
Coovadia, 1992 (Klebsiella pneumoniae)	3	17	0.0151 to 82.326
Lin, 2012 (Klebsiella pneumoniae)	38	3	0.0666 to 13.810
Royle, 1999 (Klebsiella pneumoniae)	7	29	3.669 to 70.958
Velasco, 2009 (Klebsiella pneumoniae)	9	11	0.281 to 48.250
Rettedal, 2012 (Klebsiella pneumoniae)	1	50	0.0386 to 99.961
Ruiz, 2010 (Klebsiella pneumoniae)	3	67	9.430 to 99.160
Mavroidi, 2014 (Klebsiella pneumoniae)	13	8	0.195 to 36.030
Macrae, 2001 (Klebsiella pneumoniae)	7	29	3.669 to 70.958
Tamma, 2012 (Klebsiella pneumoniae)	10	50	18.709 to 81.291
Gundes, 2005 (Klebsiella pneumoniae)	5	40	5.274 to 85.337
Cantey, 2013 (Klebsiella pneumoniae)	5	40	5.274 to 85.337
Otman, 2002, (Klebsiella spp.)	3	67	9.430 to 99.160
Pessoa-Silva, 2002 (Salmonella sp.)	78	9	3.685 to 17.620
Hammami, 1991 (Salmonella sp)	27	15	4.189 to 33.731
Casolari, 2013 (Serratia marcescens)	43	7	1.463 to 19.061
Total (fixed effects)	321	20	15.769 to 24.439
Total (random effects)	321	31	20.261 to 42.751

Test for heterogeneity	
Q	104.212
DF	24
Significance level	P < 0.0001
I^2 (inconsistency)	76.97%
95% CI for I^2	66.34 to 84.24

Resistance rates of *Enterobacteriaceae*

(Lutsar I et al., Eur J Pediatr 2014)

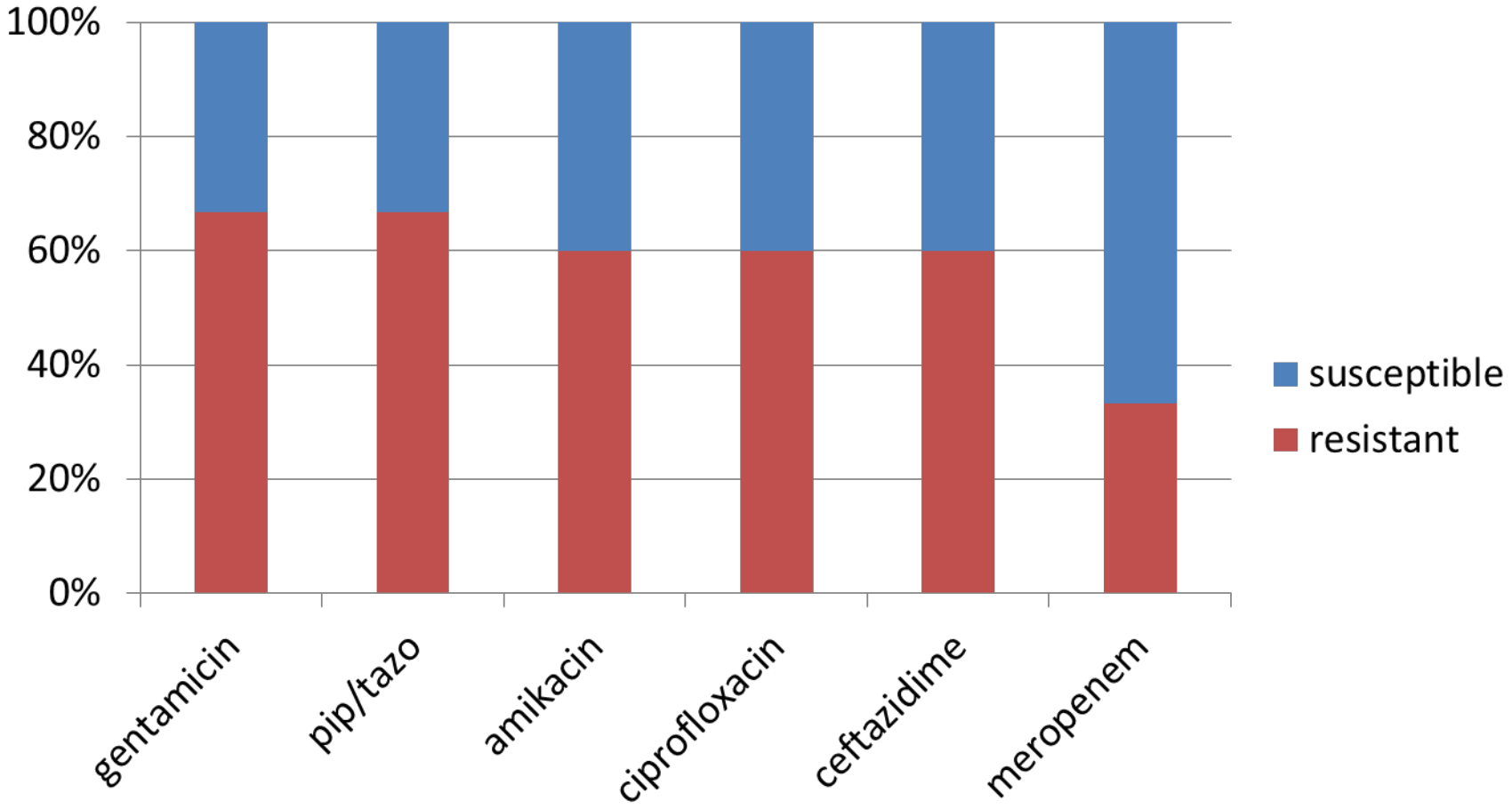


R contains also IR strains
Number of strains appr. 20

38% resisitant to AMP+GENT and 32% to CTX+GENT

Resistance rates of Gram-negative non-fermetative organisms

(Lutsar I et al., Eur J Pediatr 2014)



R contains also IR strains

43 different AB regimens were used

First line of ATB (i)	Total N=113
AMPICILLIN	1 (1%)
AMPICILLIN\Gentamicin	**7 (6%)**
AMPICILLIN\NETILMICIN	1 (1%)
Amikacin	2 (2%)
Amikacin\Cefotaxime	2 (2%)
Amikacin\Colistin	1 (1%)
Amikacin\Meropenem	2 (2%)
Amikacin\PenicillinG	1 (1%)
Amikacin\Teicoplanin	1 (1%)
Amikacin\Vancomycin	10 (9%)
Amikacin\Vancomycin\Meropenem	1 (1%)
AmpicillinSulbactam	1 (1%)
AmpicillinSulbactam\NETILMICIN	1 (1%)
CEFEPIME	4 (4%)
CEFEPIME\Teicoplanin	1 (1%)
CEFEPIME\Vancomycin	1 (1%)
Cefotaxime	4 (4%)
Cefotaxime\Gentamicin	**1 (1%)**
Cefotaxime\Gentamicin\PenicillinG	2 (2%)
Ceftazidime	1 (1%)
Ceftazidime\Teicoplanin	2 (2%)
Ceftazidime\Vancomycin	8 (7%)
Cefuroxime	2 (2%)
Cefuroxime\Meropenem\Vancomycin	1 (1%)
Colistin	1 (1%)
Gentamicin	3 (3%)
Gentamicin\Meropenem\Vancomycin	1 (1%)
Gentamicin\PIPERACILLINTazobact	2 (2%)
Gentamicin\PIPERACILLINTazobact\PenicillinG	1 (1%)

First line of ATB (ii)	Total N=113
Gentamicin\PenicillinG	2 (2%)
Gentamicin\Vancomycin	2 (2%)
IMIPENEM\Metronidazole\NETILMICIN\Colistin	1 (1%)
Meropenem	**10 (9%)**
Meropenem\Teicoplanin	1 (1%)
Meropenem\Vancomycin	13 (12%)
Metronidazole	1 (1%)
NETILMICIN\Vancomycin	1 (1%)
PIPERACILLINTazobact\Gentamicin\Meropenem	1 (1%)
Teicoplanin	1 (1%)
Teicoplanin\CEFEPIME	1 (1%)
Vancomycin	9 (8%)
Vancomycin\CIPROFLOXACIN	1 (1%)
Vancomycin\NETILMICIN	2 (2%)
Vancomycin\PIPERACILLINTazobact	1 (1%)

(Lutsar I et al., Eur J Pediatr 2014)

Al-Iawama *et al. Ann Clin Microbiol Antimicrob (2016) 15:8*
DOI 10.1186/s12941-016-0126-4

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RESEARCH Open Access

Intravenous Colistin in the treatment of multidrug-resistant Acinetobacter in neonates

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Abstract

Background: Neonatal sepsis caused by multidrug-resistant gram-negative bacteria has been reported in di erent parts of the world. It is a major threat to neonatal care, carrying a high rate of morbidity and mortality. While Colistin is the treatment of choice, few studies have reported its use in neonatal patients.

Methods: A retrospective descriptive study of all neonatal patients who had multidrug-resistant Acinetobacter sepsis and were treated with Colistin over a 2-year period. Patients' charts and hospital laboratory data were reviewed.

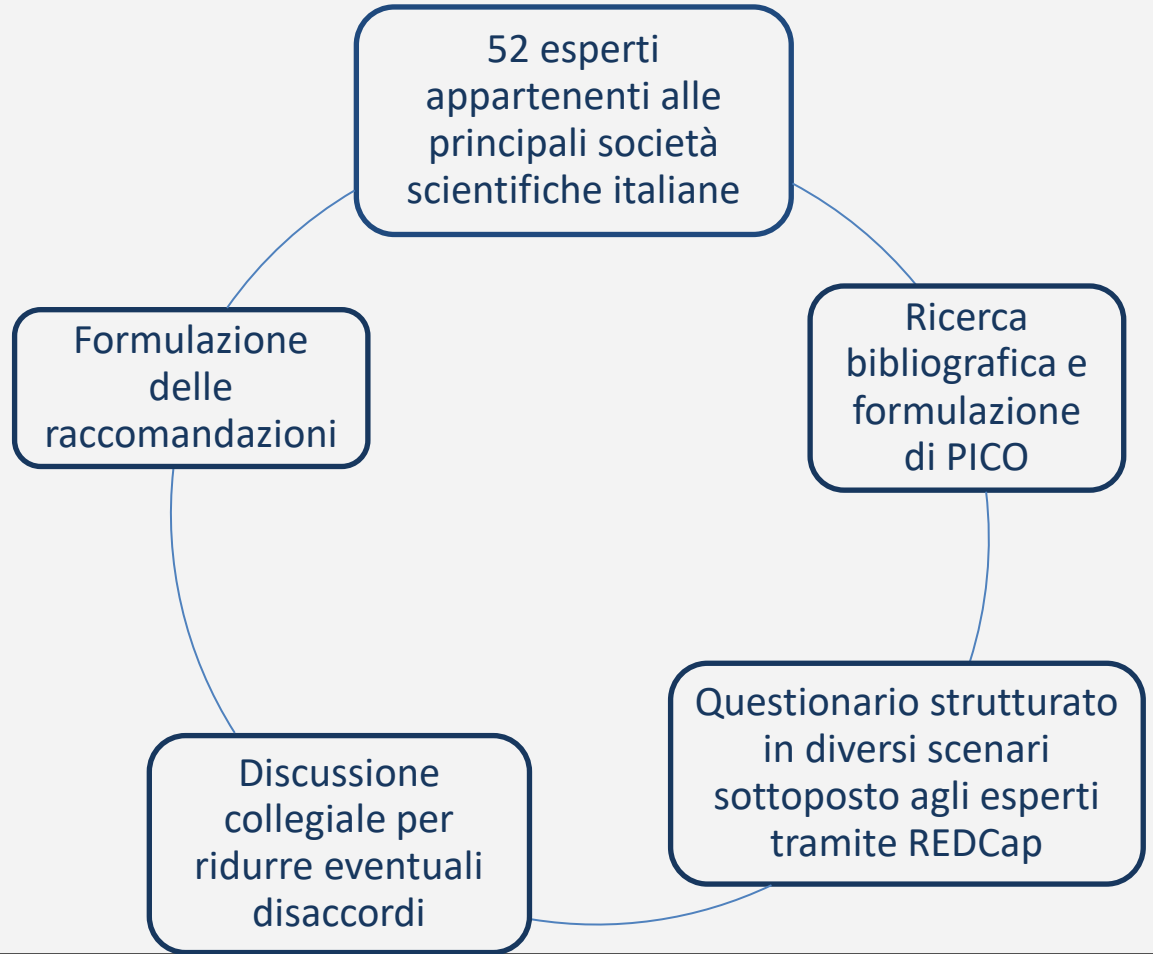
Results: During the study period, 21 newborns were treated with Colistin. All had sepsis evident by positive blood culture and clinical signs of sepsis. The median gestational age and birth weight were 33 weeks (26–39) and 1700 g (700–3600), respectively. Nine (43 %) were very low birth weight infants. Eighteen (86 %) were preterm infants. Nineteen (91 %) newborns survived. No renal impairment is documented in any of our patients. Fourteen (67 %) of our patients had elevated eosinophil counts following Colistin treatment, for those patients, the average eosinophilic counts ± standard deviation before and after Colistin therapy were 149.08 ± 190.38 to 1193 ± 523.29, respectively, with a p value of less than 0.0001.

Conclusion: Our study showed that Colistin was both e ective and safe for treating multidrug-resistant Acinetobacter neonatal sepsis. This is a retrospective study. No universal protocol was used for the patients. The factors that might a ect the response or cause side e ects are di cult to evaluate.

Keywords: Colistin, Sepsis, Neonate, Multidrug-resistant Acinetobacter, Eosinophilia

METODI

Il documento è stato realizzato con il metodo di appropriatezza RAND/UCLA (Research and Development Corporation dell'Università della California - Los Angeles)

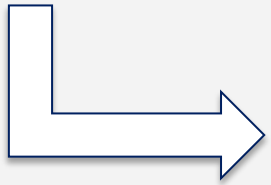


RISULTATI


Chirurgia cardiotoracica
Chirurgia ortopedica
Neurochirurgia
Chirurgia ORL
Chirurgia addominale
101 raccomandazioni
Chirurgia oculistica
Chirurgia urologica
Chirurgia plastica
Chirurgia maxillo-facciale
Chirurgia nei pazienti speciali

SCREENING E COLONIZZAZIONE BATTERICA

Lo screening dei patogeni multi-resistenti (es. MRSA) deve essere effettuato nei casi di **chirurgia cardiotoracica e ortopedica**, in linea con quanto indicato per i pazienti adulti, ed in caso di ospedalizzazione prolungata.
Fortemente raccomandato in **contesti ad alto rischio** di infezione da MRSA (interventi di neurochirurgia)



Profilassi chirurgica con CEFAZOLINA (30 mg/kg) + VANCOMICINA (15mg/kg) 30 min prima dell'intervento

Nei pazienti colonizzati è possibile effettuare decolonizzazione 5 giorni prima dell'intervento

Bianchini S et al. Surgical Antimicrobial Prophylaxis in Neonates and Children with Special High-Risk Conditions: A RAND/UCLA Appropriateness Method Consensus Study. *Antibiotics (Basel)*. 2022.

PAZIENTI IN TERAPIA O PROFILASSI

Seguire le indicazioni fornite per il singolo intervento e aggiungere la profilassi con cefazolina da somministrare 30 minuti prima dell'intervento, se questo non è già previsto

PAZIENTI PRECEDENTEMENTE OPERATI O OSPEDALIZZATI

Effettuare uno screening tramite tampone nasale per la ricerca di colonizzazione da *S. aureus* (sia MSSA che MRSA) e si raccomanda di seguire le indicazioni per la profilassi relative all'intervento specifico.

Bianchini S et al. Surgical Antimicrobial Prophylaxis in Neonates and Children with Special High-Risk Conditions: A RAND/UCLA Appropriateness Method Consensus Study. *Antibiotics (Basel)*. 2022.

Antimicrobial stewardship in pediatrics

Main strategies

- Review and analyze antibiotic use after they have been prescribed
- Reach consensus on antibiotic use before they are prescribed

Problems that must be considered for national antibiotic use

- Prompt initiation of antibiotic use when indicated
- Avoiding use of antibiotic for conditions not due to bacteria
- Choice of the first- and second-line drugs for the demonstrated or supposed bacterial etiology responsible for the disease that requires treatment
- Identification of proper dose, fractioning, and duration of antibiotic and switch from intravenous to per as according to the patient and disease
- Choice of conditions for which antibiotic prophylaxis is needed

Methods to rationalize antibiotic therapy

- Education (i.e., lectures, handbooks, educational conferences, guidelines)
- Use of antibiotic order forms
- Formation of multidisciplinary antimicrobial stewardship team
- Obtaining administrative and leadership support
- Continuous and transparent monitoring of antibiotic use
- Adequate use of diagnostic tests, including point-of-care tests
- Knowledge of local resistance rates for different pathogens

Principi N & Esposito S. *BMC Infect Dis* 2016;16:424

Improving the quality of hospital antibiotic use:

Impact on multidrug-resistant bacterial infections in children

- Point prevalence survey on anti-infective drugs
- Aware (Access, Watch, Reserve)
- Pre-prescription authorization & post-prescription review
- Guidelines & diagnostic algorithms
- Antibiotic cycling
- Rapid diagnostic tests
- Computerized prescribers order entry
- Therapeutic drug monitoring

Fanelli U et al. *Front. Pharmacol*. 2020;11:745. doi: 10.3389/fphar.2020.00745

Role of artificial intelligence in fighting antimicrobial resistance

AI application in fighting antimicrobial resistance	Advantages	Limitations
AI, health industry and antibiotics		
1. Antimicrobial peptides	• low risk of resistance development; • multiple antimicrobial mechanisms of action; • ease of synthesis thanks to AI.	• high toxicity to eukaryotic cells; • high cost of large-scale production; • initial appearance of cross resistance associated with widespread use; • onset of allergic reactions.
2. Discovery of new antibiotics	• ability to develop new molecules with targeted and broad-spectrum bioactivity; • reduced time and labor costs for development.	• need for training libraries to contain molecules with physicochemical properties consistent with those of antibacterial drugs yet • sufficiently diverse; • need for selection of the most appropriate approach compound development and minimizing toxicity.
AI, pediatric practice and infectious diseases		
Prediction of antibiotic resistance	• ability to exploit genomic information to predict the bacterial phenotype (VAMPr); • ability to help the clinician select the correct antibiotic	• lack of complete genotypes in the NCBI database for each microorganism • need for integrating large amounts of data (laboratory, clinical, geographical)
Appropriate prescription of antibiotics	• automated decision support systems for the review of antimicrobial prescriptions at hospital level; • ability to receive feedback for automatic and continuous improvement • guideline-based operation	• lack of staff in systems management; • need for available health funds.
Prediction of infection severity	• ability to distinguish infectious diseases, including sepsis, from non-infectious diseases • provision of decision support for the doctor; • ability to reduce mortality	• need for accurate and complete data collection; • inability to obtain laboratory data from the beginning of illness.

Fanelli U, et al. *Antibiotics* 2020, 9, 767; doi:10.3390/antibiotics9110767

Antibiotic awareness for caregivers

6 Smart facts about antibiotics

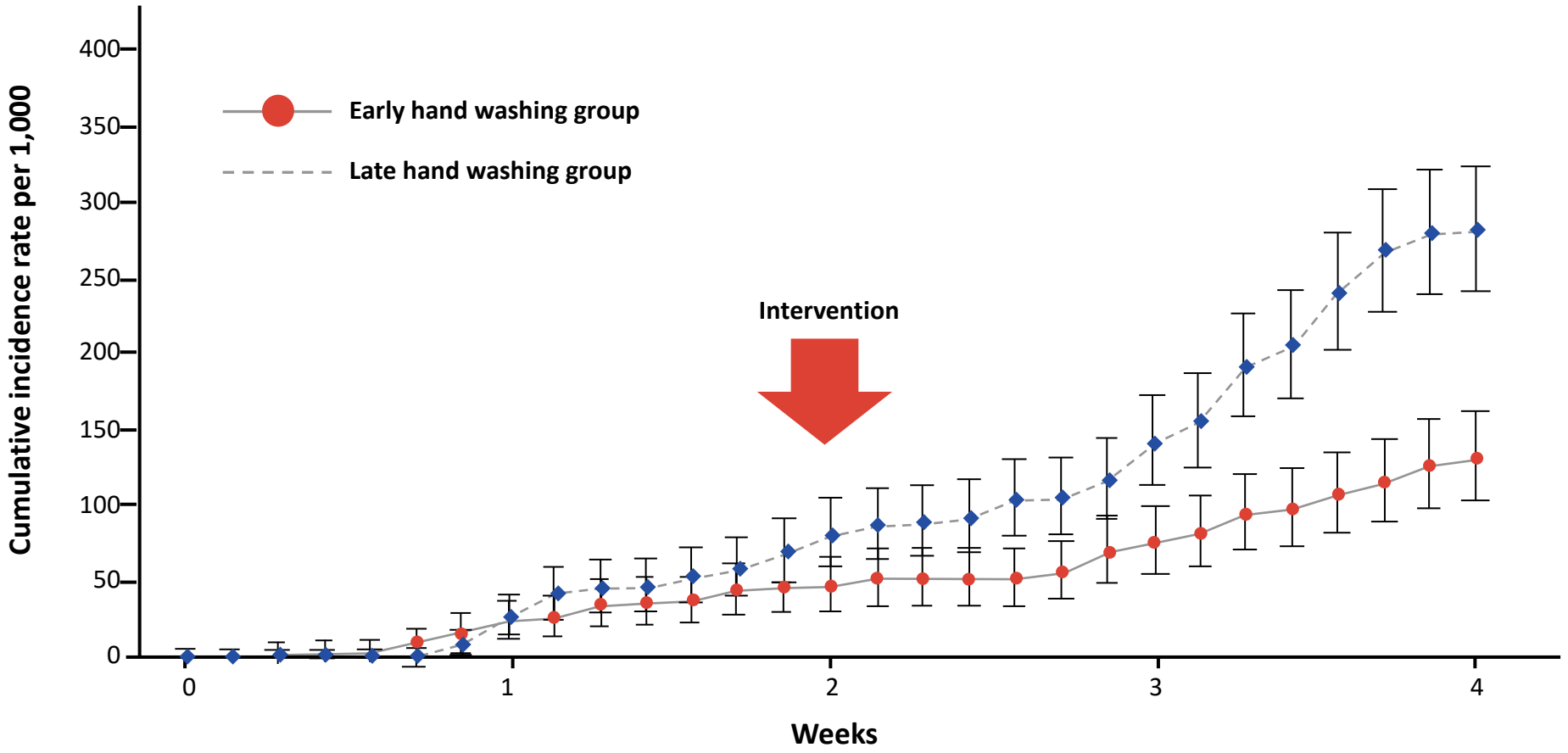
1. **Antibiotics are life-saving drugs**
2. **Antibiotics only treat bacterial infections**
3. **Some ear infections do not require an antibiotic**
4. **Most sore throats do not require an antibiotic**
5. **Green coloured mucus is not a sign that an antibiotic is needed**
6. **There are potential risks when taking any prescription drug**

Talk to your healthcare provider about when and how to safely use antibiotics

North Carolina Public Health Dept. Available from : https://epi.dph.ncdhhs.gov/cd/antibiotics/campaign.html. Accessed October 2022

Prevention of infection: handwashing

Early and late hand washing and emergence of respiratory infectious diseases



Kim HK et al. *Medicine (Baltimore)* 2018; 97:30(e11594).

Take-home messages

- To fight antimicrobial resistance represents a priority that requires a multi-level commitment
- Use of new anti-infective drugs should be based on the careful analysis of well-conducted clinical studies
- Multidisciplinary antimicrobial stewardship programs for hospital and community setting, including the use of new biomarkers and technologies, appear useful also in pediatrics
- Synergism between scientific society & political/institutional level is mandatory to fight antimicrobial resistance
- AI-driven health interventions could lead to improved health outcomes in pediatric infectious diseases management
- High vaccination coverage is extremely important to reduce antimicrobial resistance

Messieurs, c'est les microbes qui auront le dernier mot.

Louis Pasteur
1822-1895