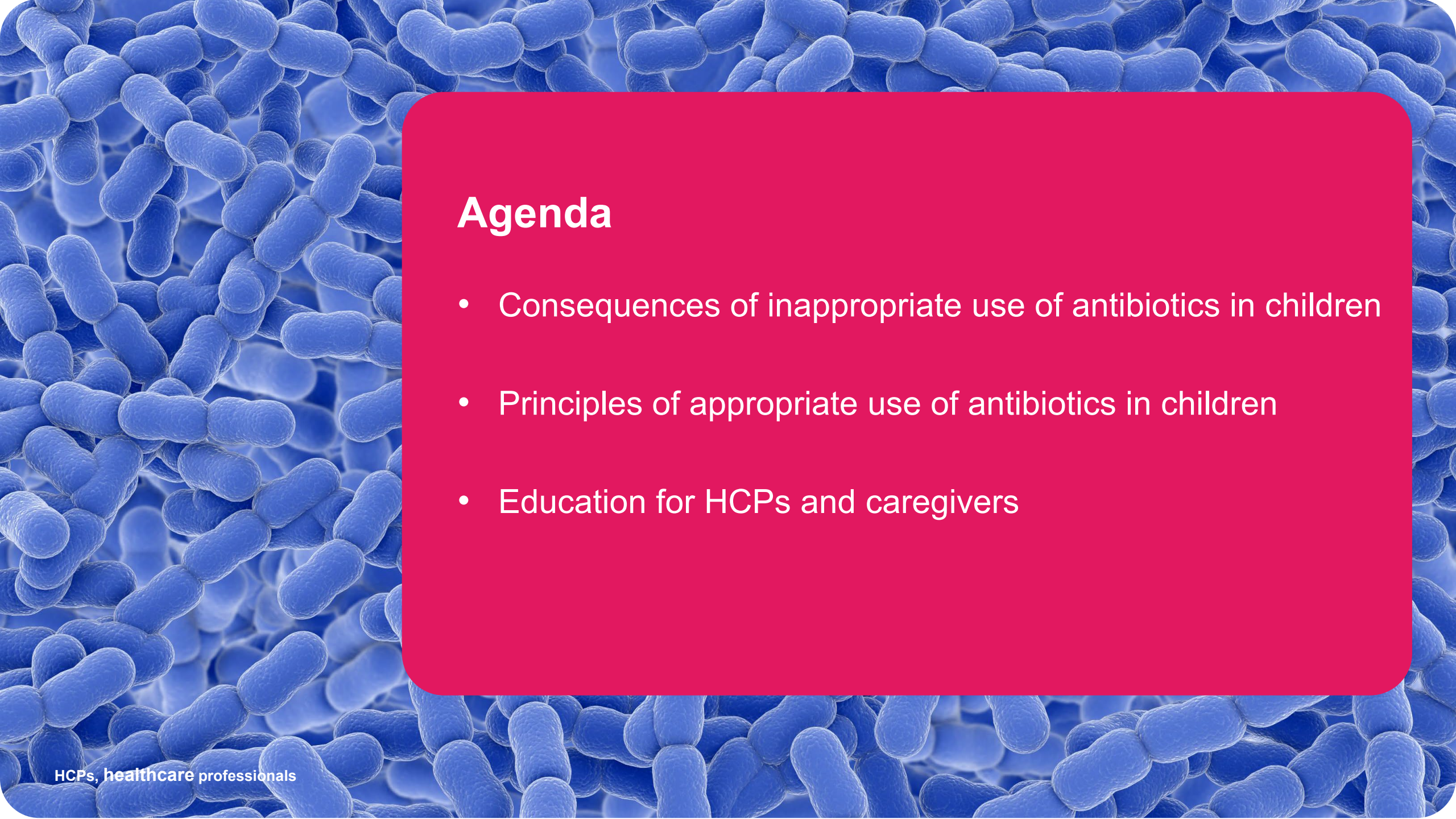
# Si utilizzano i nuovi antibiotici in pediatria? Quali e perché?

**Susanna Esposito**

*Clinica Pediatrica*
*Ospedale dei Bambini Pietro Barilla*
*Università di Parma, Parma*



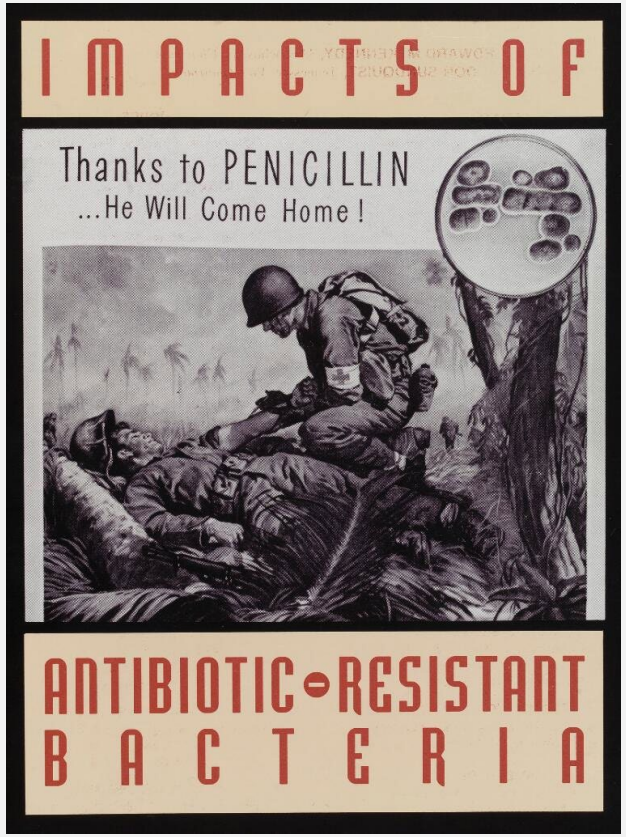
# Agenda

- Consequences of inappropriate use of antibiotics in children
- Principles of appropriate use of antibiotics in children
- Education for HCPs and caregivers

HCPs, healthcare professionals

# A very short life-span

**1944**

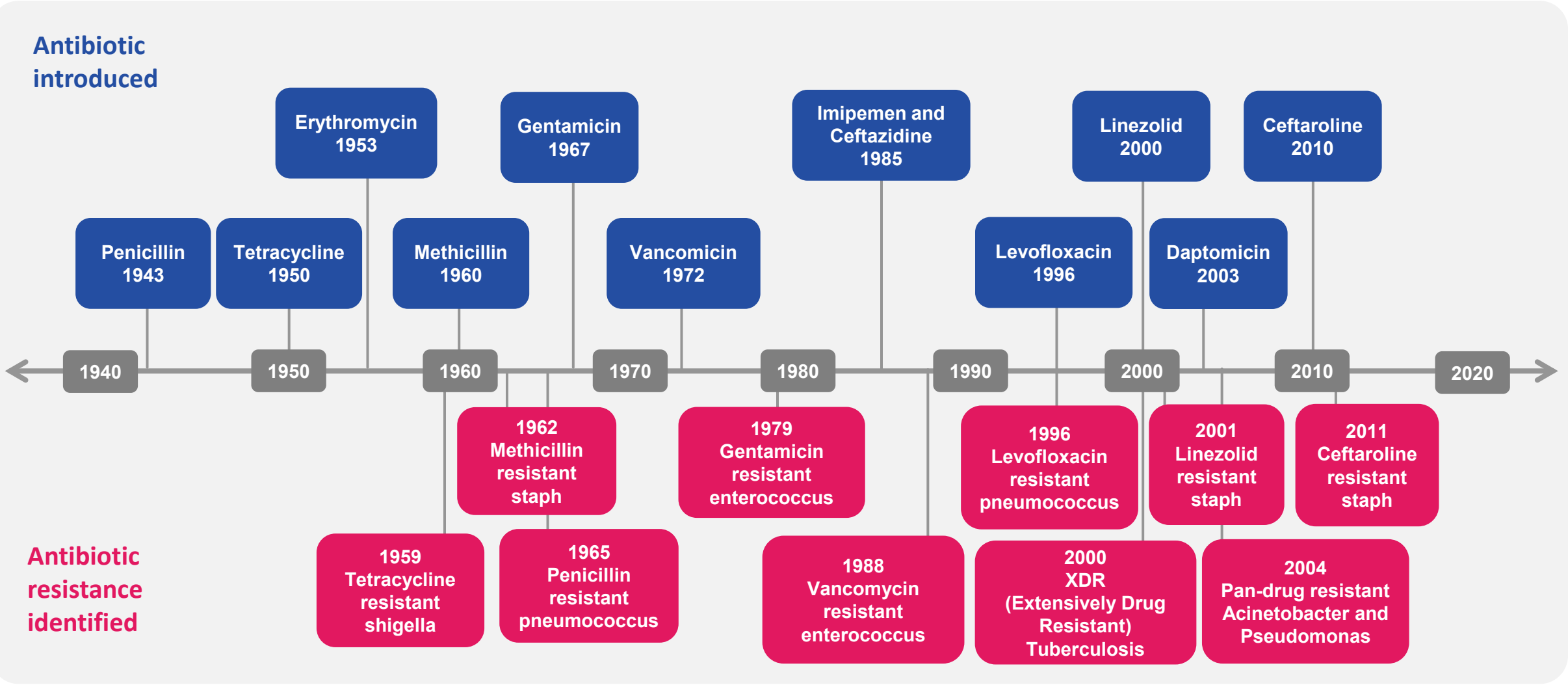



**Wellcome Collection**. Available at: https://wellcomecollection.org/works/hvnh4r46. Accessed October 2022

**2016**

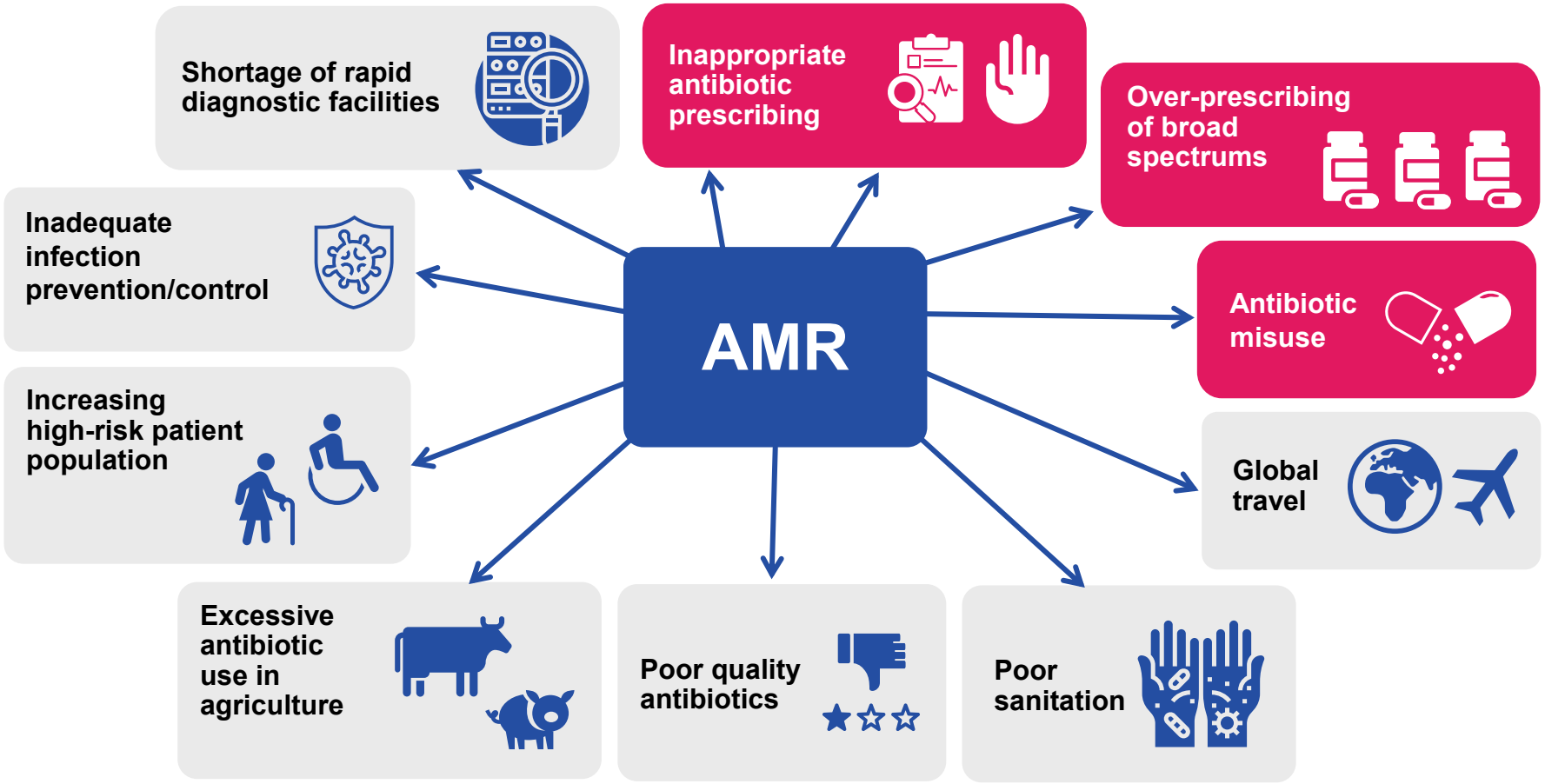

**The Economist:** May 21st 2016. Available at: https://www.economist.com/weeklyedition/2016-05-21. Accessed October 2022

# Antibiotic use drives resistance




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

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



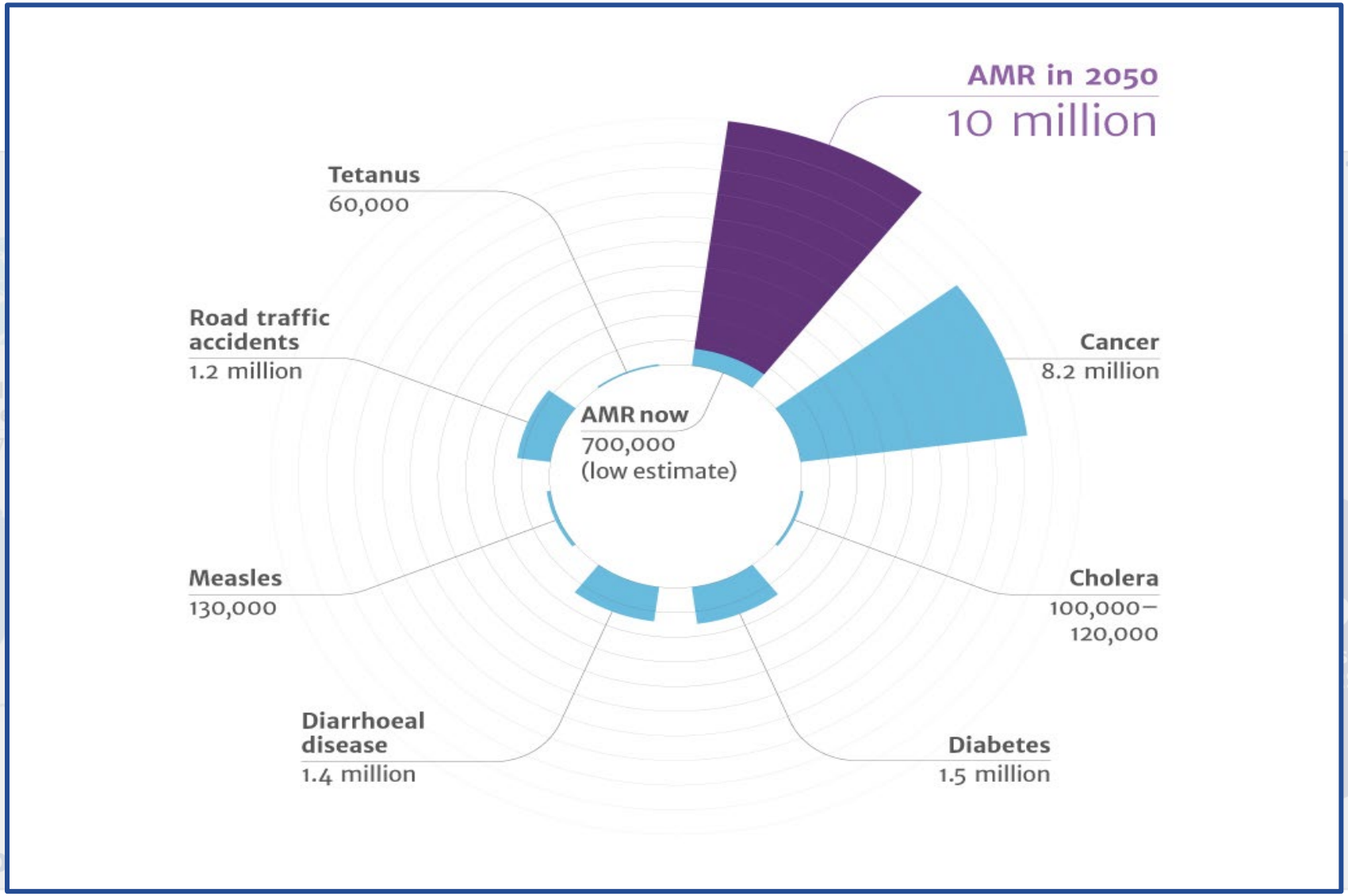

'The world urgently needs to change the way it prescribes and uses antibiotics. Even if new medicines are developed, without behaviour change, antibiotic resistance will remain a major threat'

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.

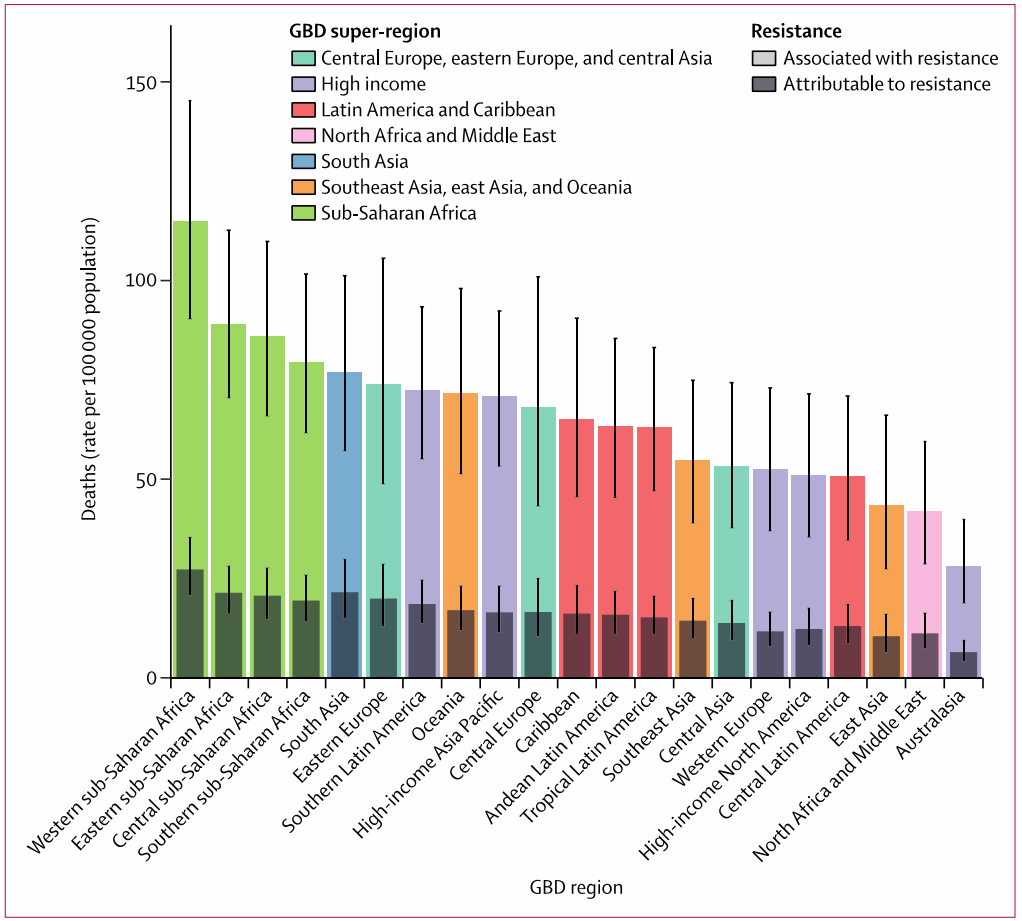
# La resistenza antimicrobica è una delle 10 minacce alla salute globale che l'umanità deve affrontare




https://amr-review.org

# AMR non è un problema solo del futuro….ma un problema attuale

## Morti globali attribuibili e associate ad AMR, 2019




- 4.95 millioni di morti **associate** ad AMR
- 1.27 millioni di morti **attribuibili** ad AMR

**Tasso di mortalità attribuibile** ad AMR :

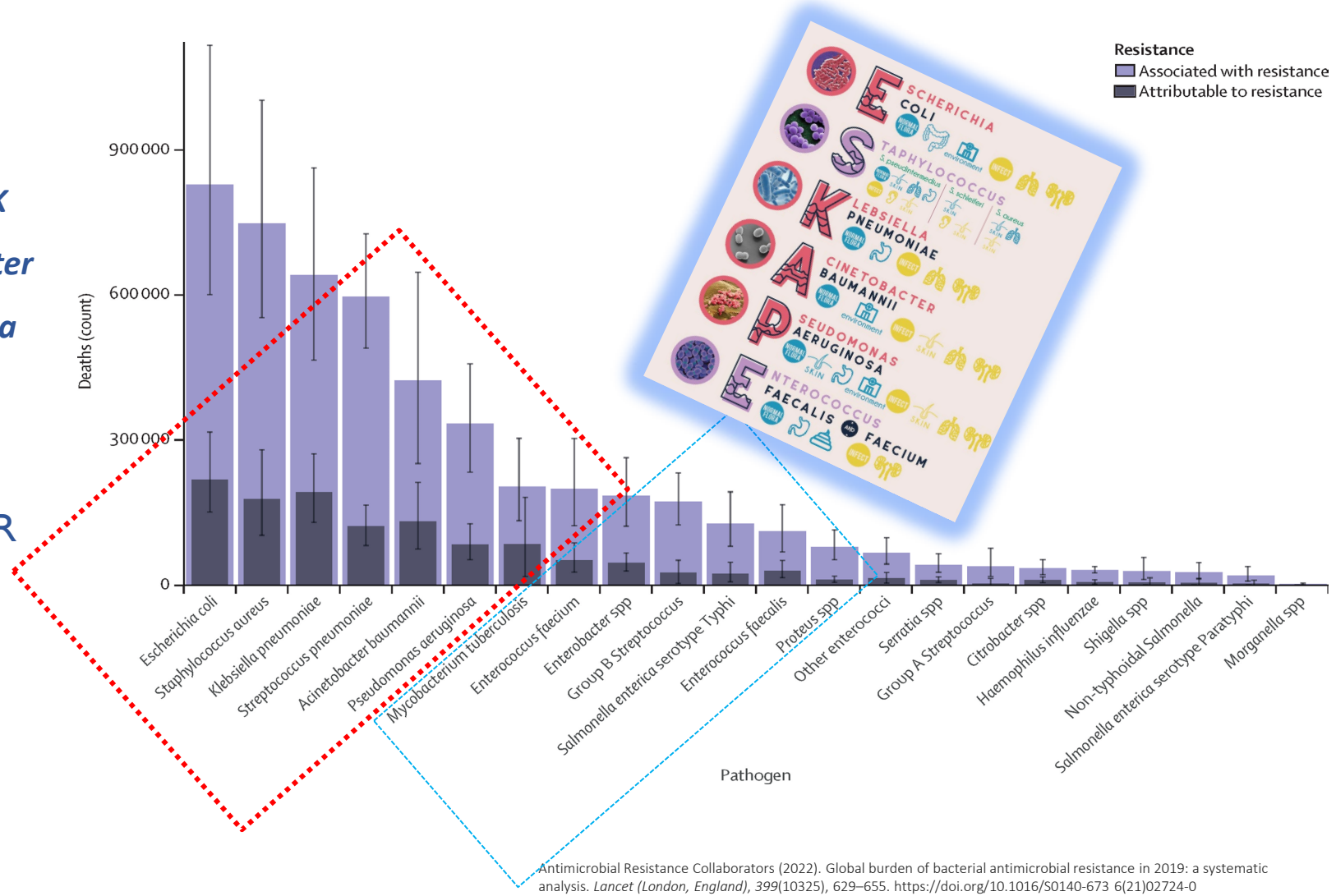
- **Più alto nell'Africa sub-sahariana occidentale** (27.3 morti per 100 000)
- Più basso in Australia (6.5 morti per 100 000).

**Infezioni delle basse vie respiratorie, batteriemie e infezioni intra-addominali** rappresentano il **78.8%** (95% UI 70.8–85.2) delle morti

Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022

- **Sei patogeni** sono responsabili di più di **250.000 morti**.
  - ***Escherichia coli, Staphylococcus aureus, K pneumoniae, S pneumoniae, Acinetobacter baumannii,*** **and** ***Pseudomonas aeruginosa***

- Altri **sei patogeni** sono responsabili di 100.000 – 250 000 morti associate ad AMR
  - *Mycobacterium tuberculosis, Enterococcus faecium, Enterobacter* spp, *Streptococcus agalactiae* (group B *Streptococcus*), *S* Typhi, and *Enterococcus faecalis*



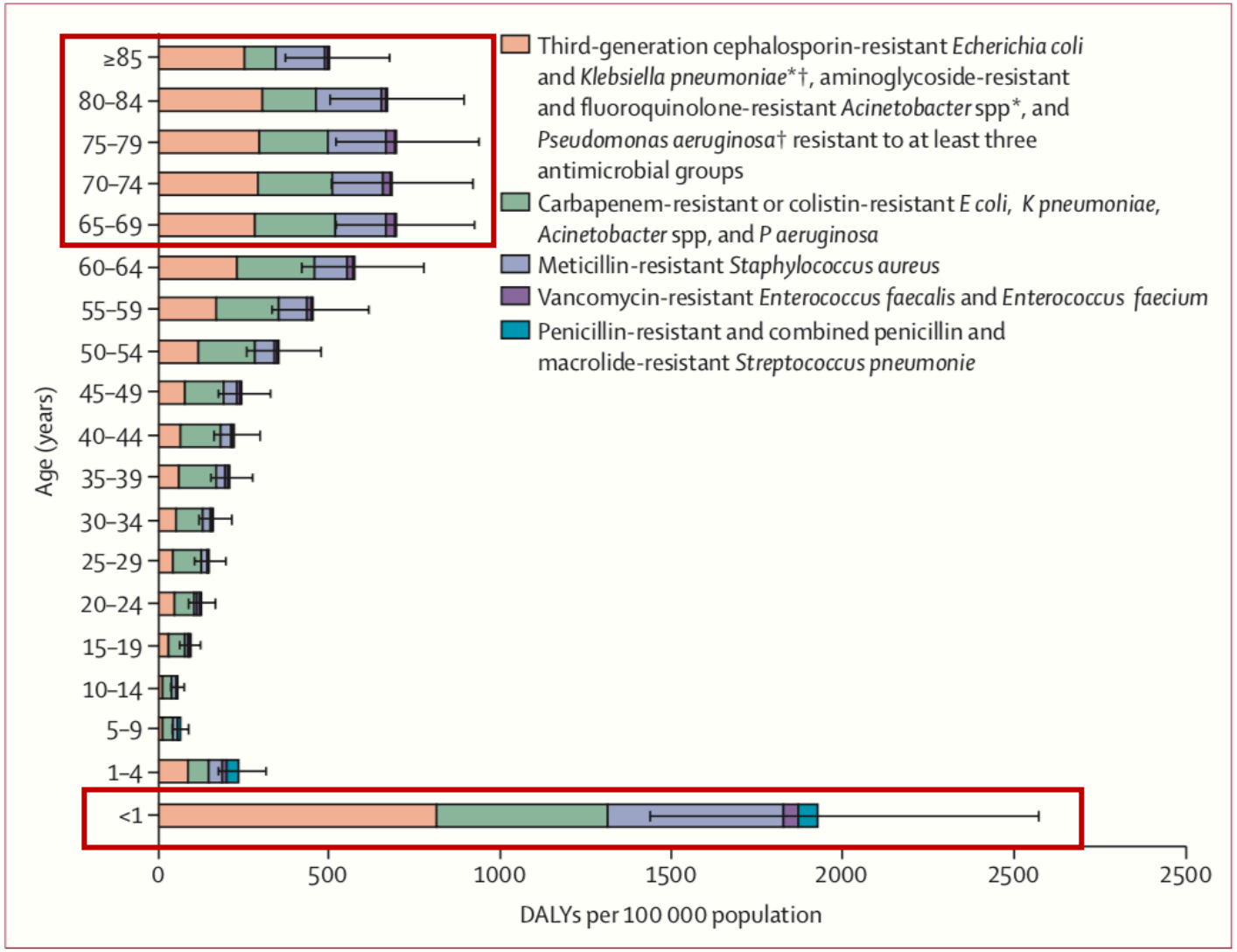

Antimicrobial Resistance Collaborators (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet (London, England)*, *399*(10325), 629–655. https://doi.org/10.1016/S0140-673 6(21)02724-0

# AMR – Non è un problema solo degli adulti

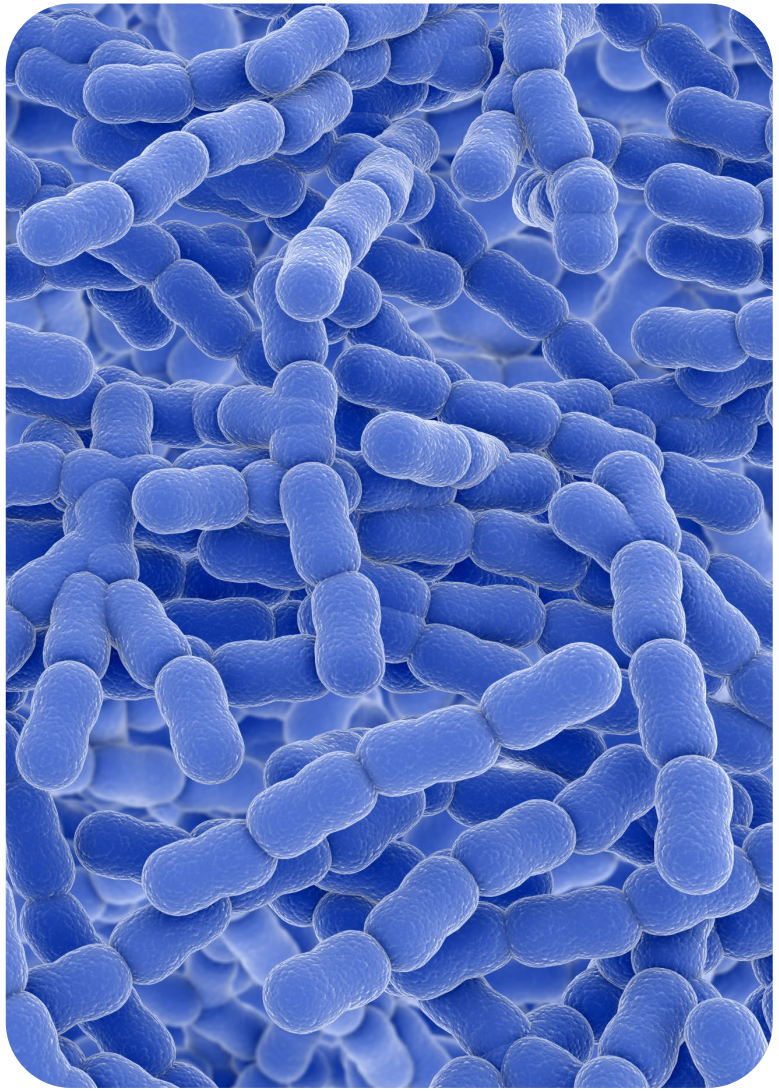
**Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis**

*Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira, Marc J Struelens, Carl Suetens, Dominique L Monnet, and the Burden of AMR Collaborative Group**

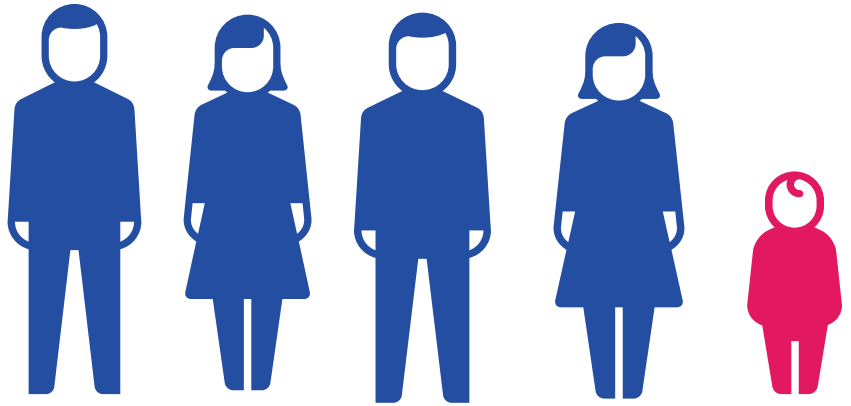
**Maggiormente colpiti i lattanti (<1 anno di età)**
e gli adulti > 65 anni



# 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.

# Consumo di antibiotici in Europa secondo AWaRe

Elevato consumo ospedaliero di antibiotici Watch

Maggior consumo territoriale di antibiotici Access

**Figura 7.4** Variabilità per Paese del consumo ospedaliero (DDD/1000 ab *die*) degli antibiotici sistemici (J01) p
dell'OMS nel 2020

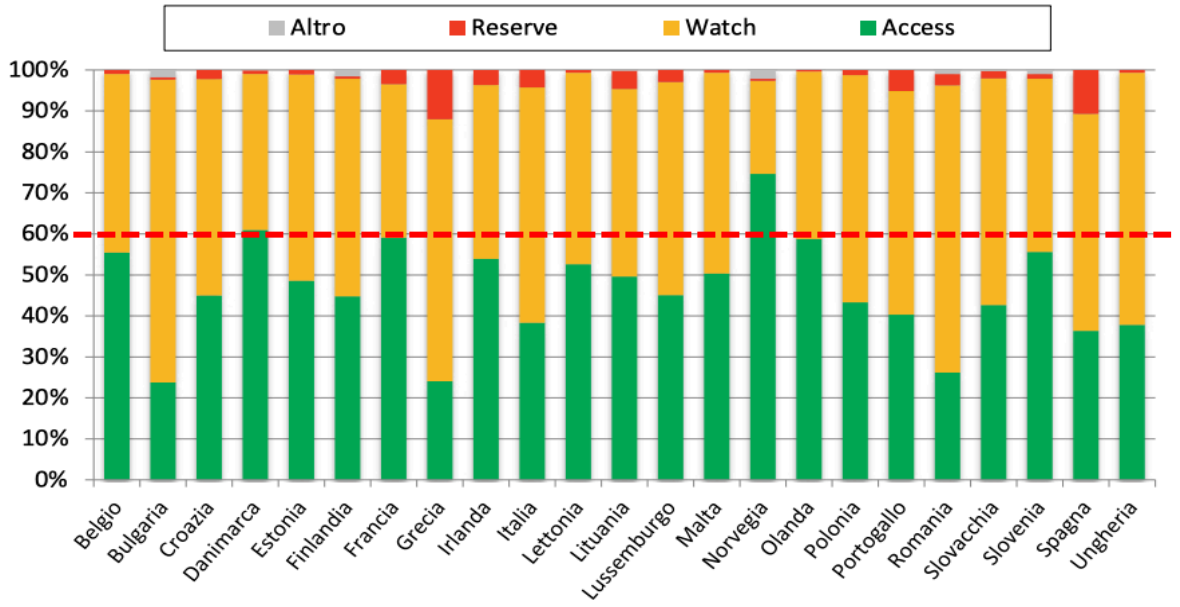



**Figura 7.2** Variabilità per Paese del consumo territoriale (DDD/1000 ab *die*) degli antibiotici sistemici (J01) p
dell'OMS nel 2020

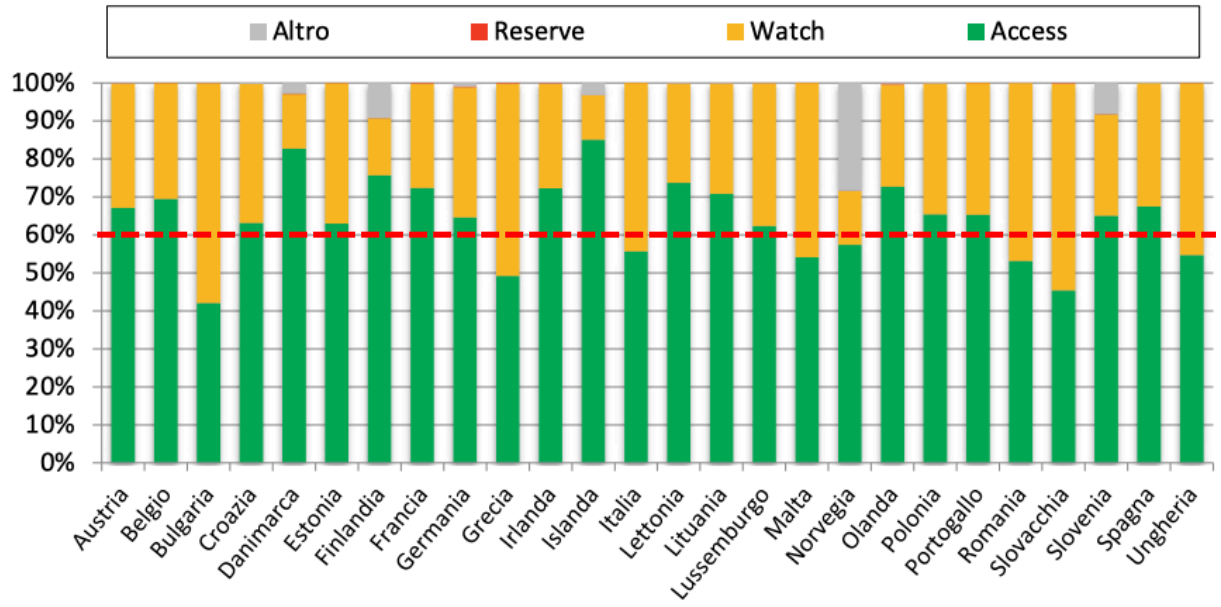


**Tabella 1.5.4** Primi 20 principi attivi per consumo in età pediatrica nel 2021

| ATC I | Principio attivo | Confezioni (per 1000 ab.) | Δ % 21-20 | Δ % 20-19 | Consumi (%)* | | Inc. cum**% |
|---|---|---|---|---|---|---|---|
| | | | | | maschi | femmine | |
| J | amoxicillina/acido clavulanico | 179,1 | -5,8 | -46,6 | 53,7 | 46,3 | 17,4 |
| A | colecalciferolo | 84,2 | 22,0 | -5,7 | 49,3 | 50,7 | 25,6 |
| H | betametasone | 81,1 | 30,6 | -42,3 | 57,5 | 42,5 | 33,5 |
| J | azitromicina | 71,5 | 19,4 | -35,5 | 54,0 | 46,0 | 40,4 |
| R | beclometasone | 70,5 | 30,5 | -38,3 | 55,3 | 44,7 | 47,3 |
| J | amoxicillina | 70,0 | -7,5 | -53,1 | 53,0 | 47,0 | 54,1 |
| R | salbutamolo | 60,7 | 15,7 | -39,6 | 60,5 | 39,5 | 60,0 |
| R | cetirizina | 57,0 | 3,7 | -5,0 | 61,8 | 38,2 | 65,5 |
| R | budesonide | 56,9 | 48,9 | -42,8 | 56,2 | 43,8 | 71,1 |
| J | cefixima | 53,4 | 2,8 | -44,7 | 50,2 | 49,8 | 76,3 |
| N | acido valproico | 51,5 | -1,3 | 0,2 | 66,8 | 33,2 | 81,3 |
| J | claritromicina | 29,8 | -23,5 | -49,7 | 54,5 | 45,5 | 84,2 |
| R | fluticasone | 26,5 | -0,9 | -27,4 | 63,6 | 36,4 | 86,7 |
| R | salbutamolo/ipratropio | 25,8 | 40,2 | -47,9 | 55,2 | 44,8 | 89,3 |
| R | montelukast | 24,0 | -19,9 | -14,1 | 63,9 | 36,1 | 91,6 |
| J | cefpodoxima | 21,1 | -10,8 | -51,9 | 53,2 | 46,8 | 93,6 |
| H | somatropina | 21,0 | -5,3 | 3,9 | 60,6 | 39,4 | 95,7 |
| H | levotiroxina | 15,5 | 1,9 | -0,4 | 38,7 | 61,3 | 97,2 |
| N | carbamazepina | 14,9 | 4,1 | 3,4 | 56,1 | 43,9 | 98,6 |
| P | mebendazolo | 14,1 | -6,1 | -9,8 | 48,1 | 51,9 | 100,0 |
| | **Totale** | **1028,4** | **6,6** | **-37,2** | **55,6** | **44,4** | **100,0** |

* calcolati rispetto al totale dei consumi della molecola in età pediatrica

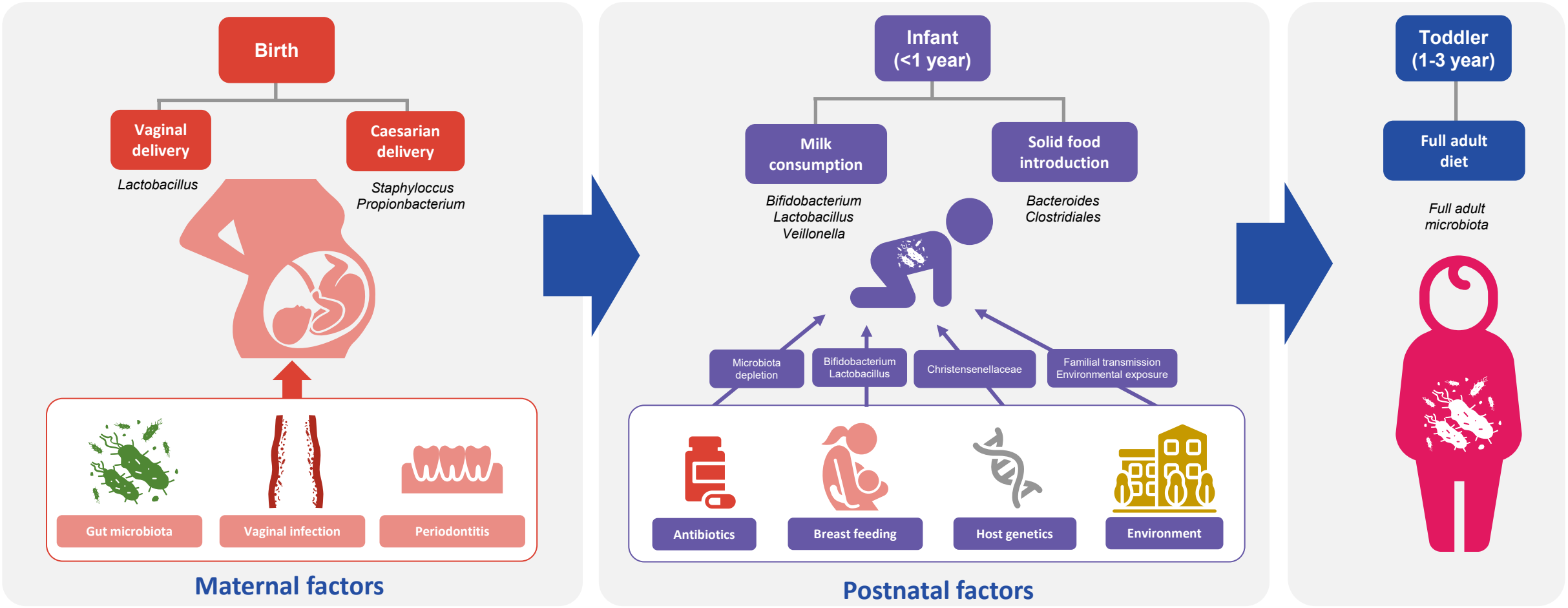
** calcolata su consumi totali in età pediatrica

## Guardando all'età pediatrica…

L'uso dei Farmaci in Italia
Rapporto Nazionale
Anno 2021

AIFA
AGENZIA ITALIANA DEL FARMACO

# 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

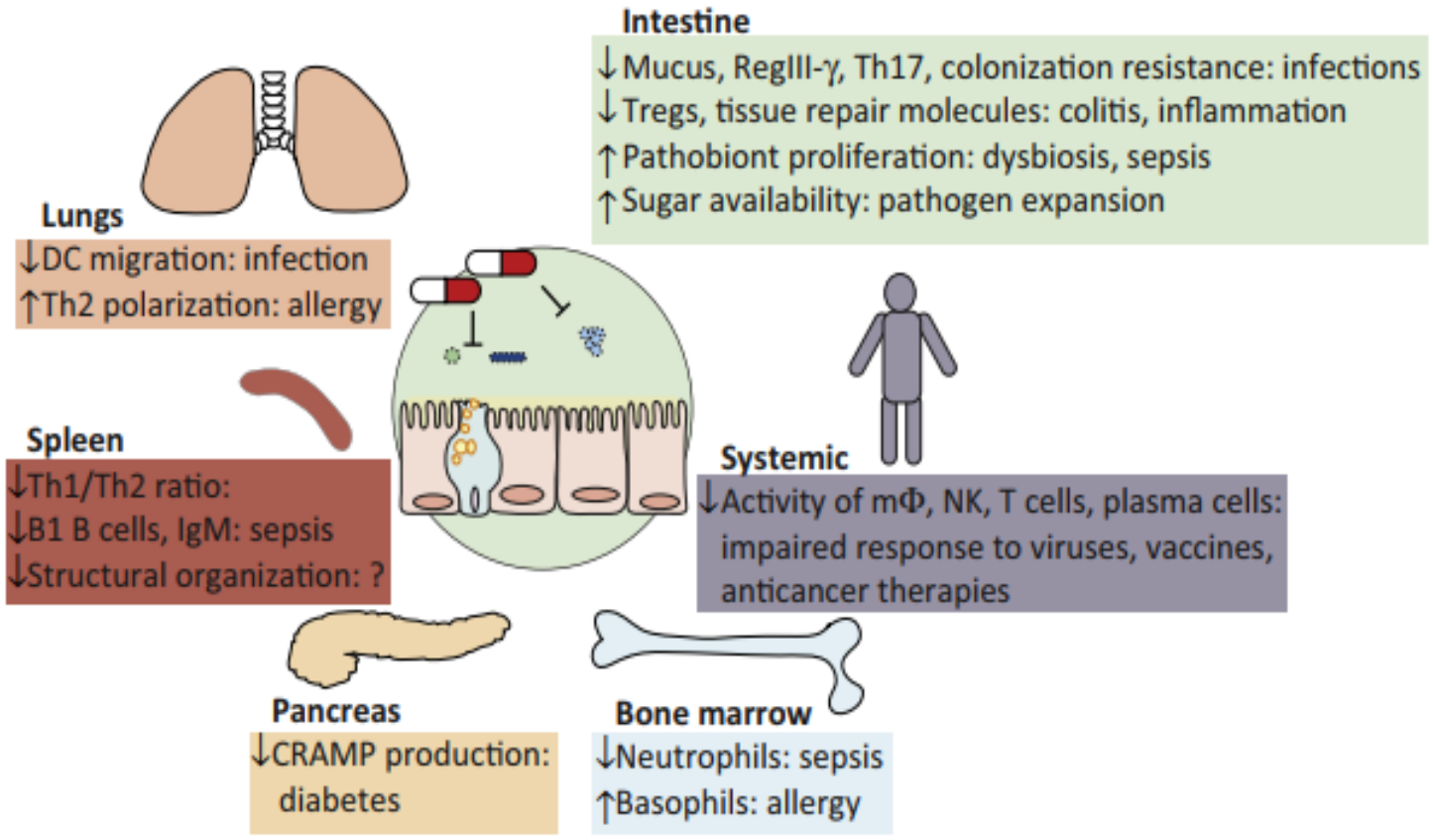
Overuse of antibiotics could be fueling the dramatic increase in conditions such as obesity, type 1 diabetes, inflammatory bowel disease, allergies and asthma, which have more than doubled in many populations

**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.

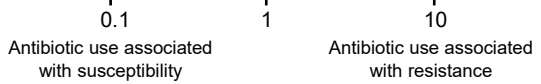
# Antibiotic-mediated microbiota depletion causes disease in multiple organs




Trends in Molecular Medicine

# 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 | | | |



# 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 |

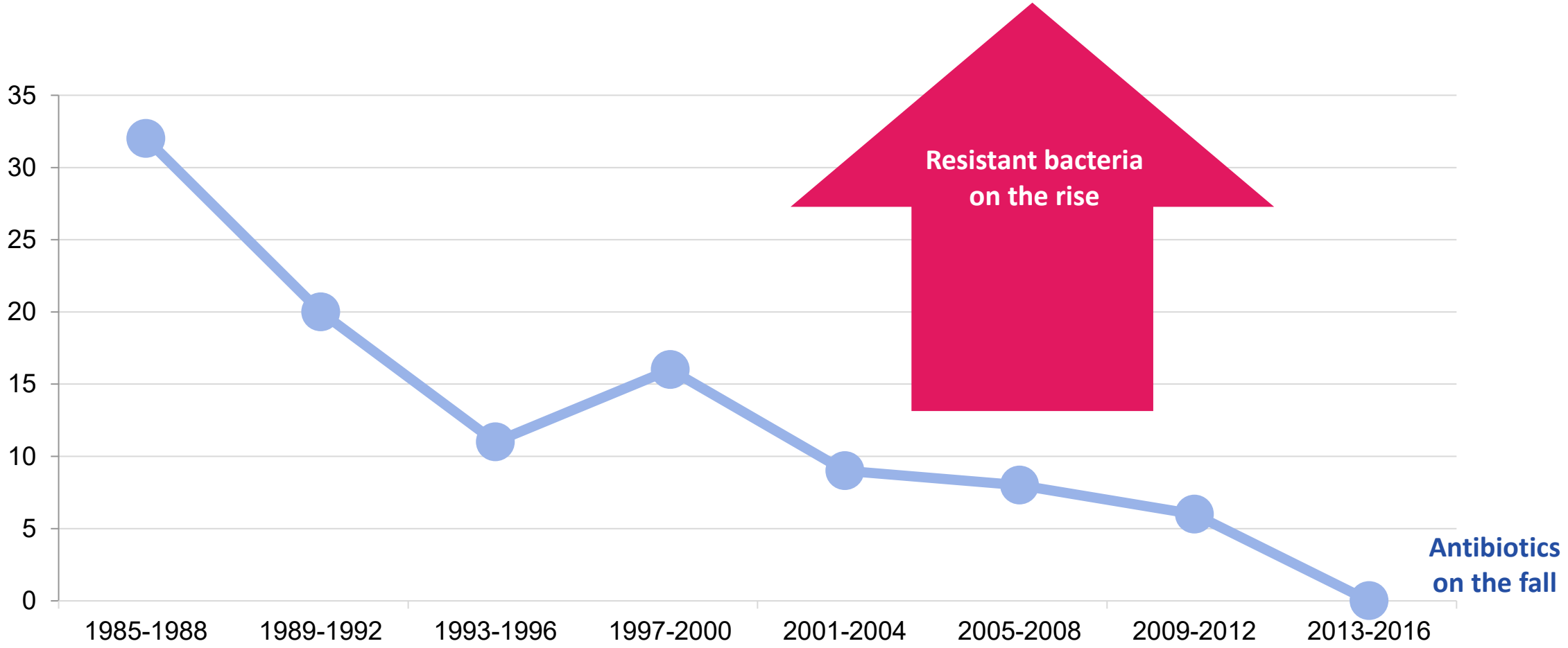
Esposito S. EJCMID; 2001:20:647

# 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.

# Antimicrobial development




Schäberle F & Hack IM. *Trends Microbiol* 2014;22:165-7. This graph has been created by GSK from the original data.

**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*

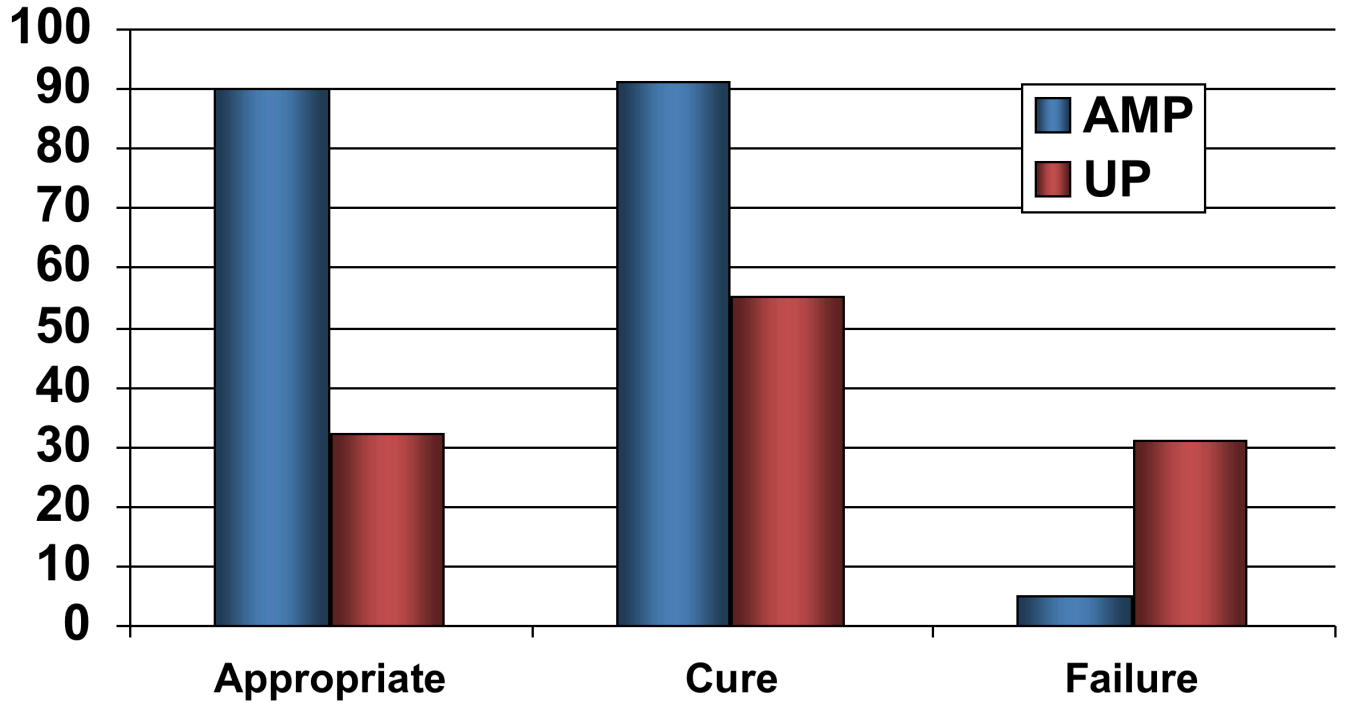
OTTIMIZZARE L'OUTCOME DEL PAZIENTE

# ASPs hanno dimostrare di migliorare l'outcome del paziente

**Studio randomizzato controllato**

Pazienti trattati da gruppi in cui è stato implementato un progetto di stewardship (AMP) e da gruppi in cui viene applicata la pratica usuale (UP)

Pazienti trattati da gruppi in cui è stato implementato un programma di stewardship antibiotica hanno un più **alto tasso di appropriatezza della terapia, di successo di cura e un più basso tasso di fallimento terapeutico**

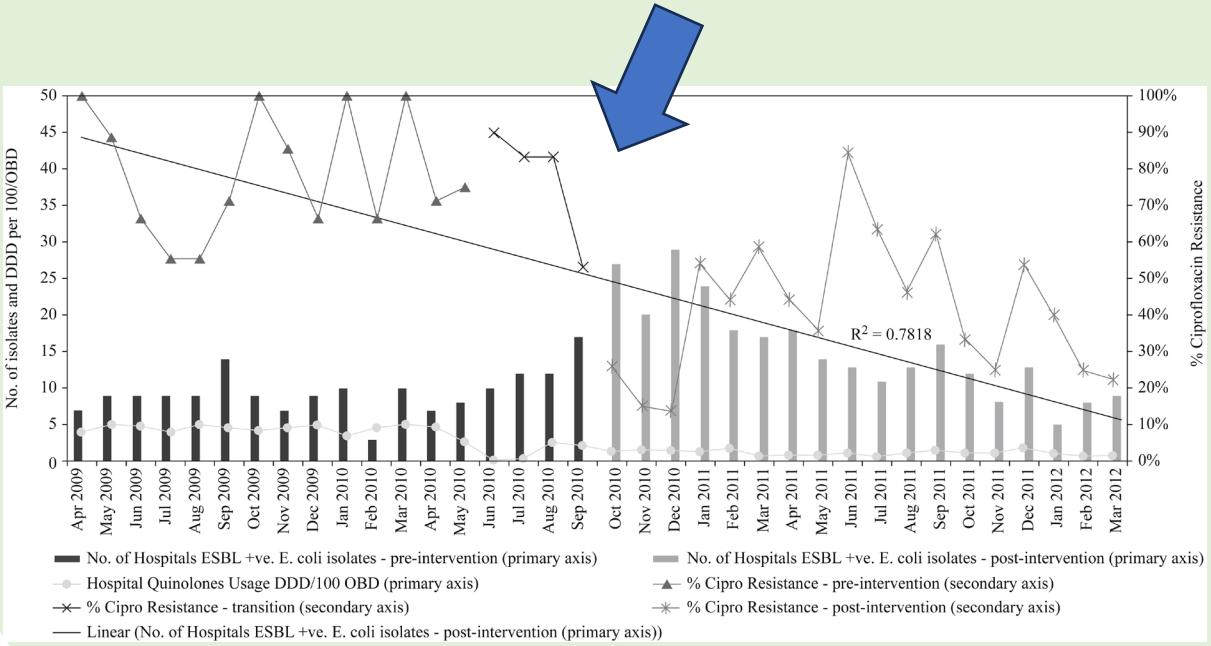



Adapted from Fishman N. Antimicrobial stewardship. Am J Infect Control. 2006 Jun;34(5 Suppl 1):S55-63; discussion S64-73. doi: 10.1016/j.ajic.2006.05.237. PMID: 16813983.

RIDUZIONE DELLE RESISTENZE

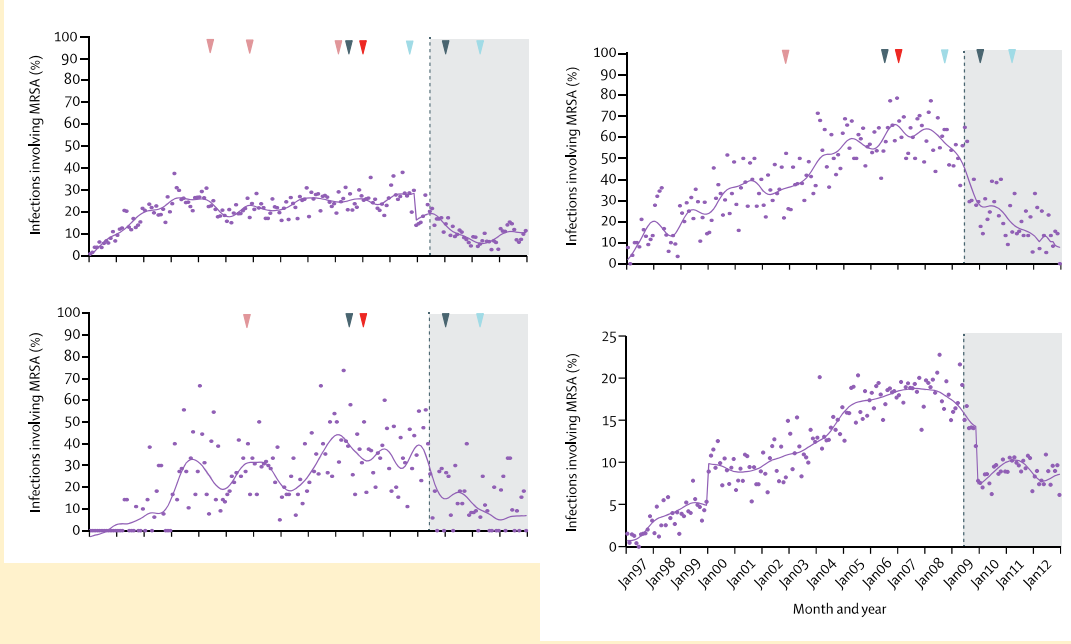
# ASPs hanno dimostrato di ridurre le resistenze

## Effetto della restrizione delle fluorchinoloni (dal 2007 al 2012) sulle Enterobacteriaceae resistenti: analisi della serie temporale interrotta.




Sarma JB, et J Hosp Infect. 2015

## Effetto delle strategie nazionali di gestione degli antibiotici e di controllo delle infezioni sulle infezioni da Staphylococcus aureus meticillino-resistente




Lawes T, et al Lancet Infect Dis. 2015

RIDUZIONE DELLE RESISTENZE

# ...e le infezioni da C. difficile

**Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis**

*David Baur*, Beryl Primrose Gladstone*, Francesco Burkert, Elena Carrara, Federico Foschi, Stefanie Döbele, Evelina Tacconelli*

**L'implementazione di programmi di stewardship antibiotica è associata ad una significativa riduzione nell'incidenza di infezioni da C. difficile nei pazienti ospedalizzati**

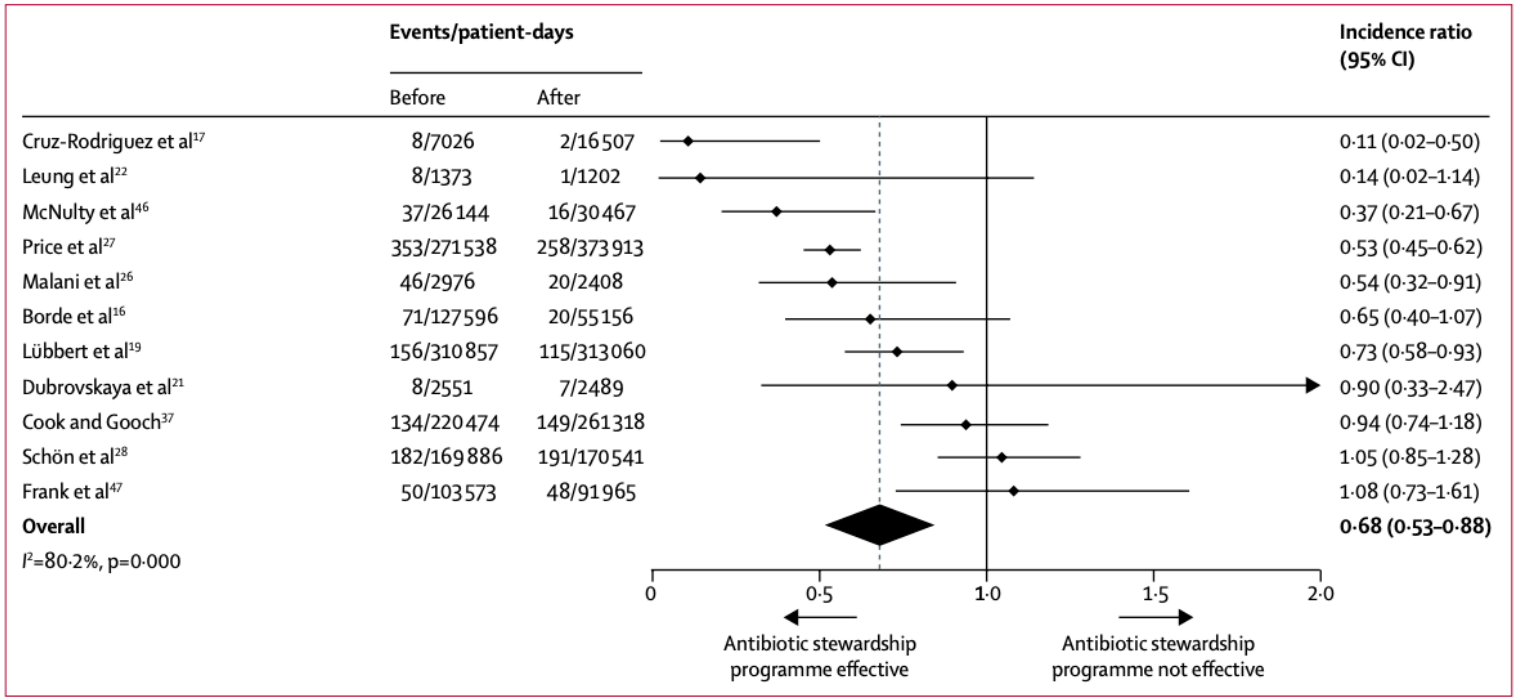
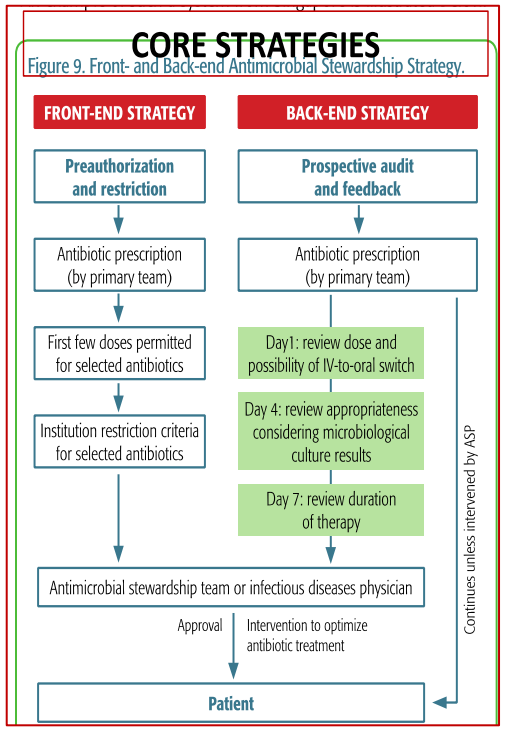



***Figure 4:*** **Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of *Clostridium difficile* infections**

Si segnala importante eterogeneità tra gli studi (>80%)

RIDUZIONE O CONTROLLO DEI COSTI

# ASPs hanno dimostrato un risparmio fino ad 800,000$/anno




| Strategia | Tipo di istituto | Risparmio annuale |
|---|---|---|
| Approvazione pre-prescrizione | Ospedale universitario territoriale | **$803,910** |
| | Ospedale di III livello | **$302,400** |
| Revisione post-prescrizione | Ospedale di III livello | **Riduzione costo antibiotici per paziente ($1287 vs. $1873, p<0.04)** |
| | Ospedale territoriale (175 letti) | **$200,000-250,000** |
| | Ospedale territoriale (120 letti) | **$177,000** |
| | Ospedale argentino (250 letti) | **$913,236** |


White AC et al. Clin Infect Dis. 1997;25:230-239. Fishman N. Am J Med. 2006;119:S53-S61.
Fraiser GL et al. Arch Intern Med. 1997;157:1689-94. Gentry CA et al. Am J Health Syst Pharm. 2000;57:268-74.
LaRocco A. Clin Infect Dis. 2003;37:742-3; Bantar C et al. Clin Infect Dis. 2003;37:180-6.
Carling P et al. Infect Control Hosp Epidemiol. 2003;24:699-706.

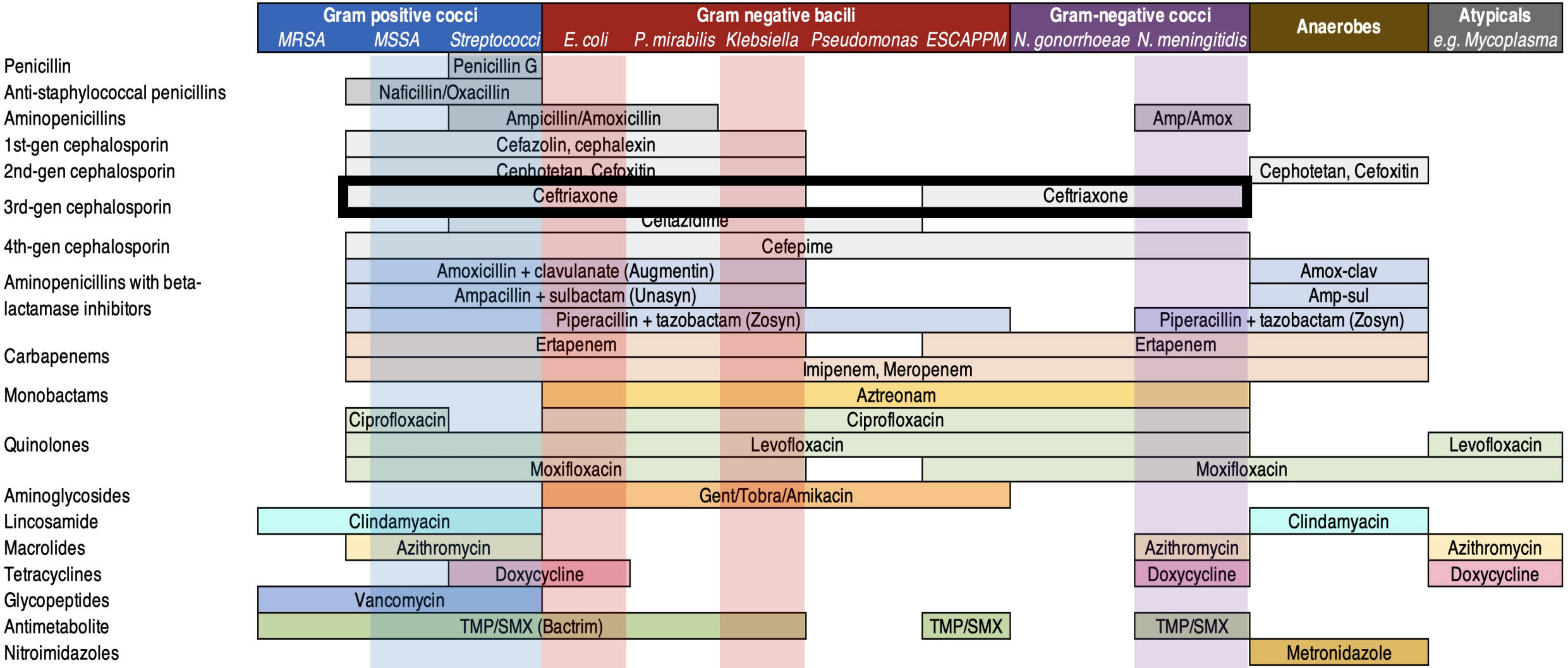
*BMJ* 2015;350:h3017 doi: 10.1136/bmj.h3017 (Published 9 June 2015)

# Sepsis in children

CLINICAL REVIEW

Adrian Plunkett *consultant paediatric intensivist*[1], Jeremy Tong *consultant paediatric intensivist*[2]

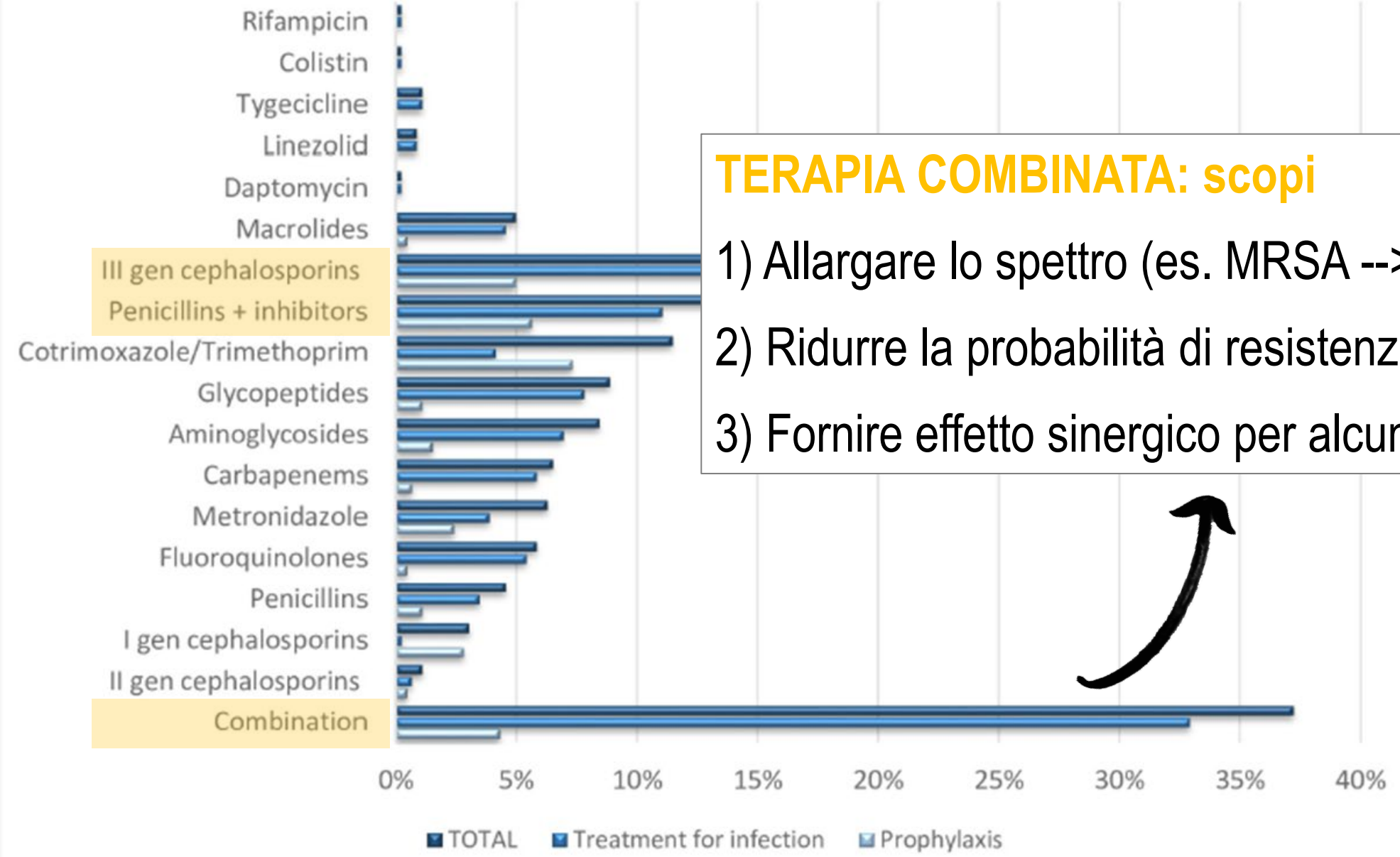
For infants and young children, empirical antibiotic regimens should include cover for the most common prevailing organisms (such as *Staphylococcus*, *Streptococcus*, *Neisseria meningitides*, and *Haemophilus influenzae*). For community acquired infection, a third generation cephalosporin (such as cefotaxime or ceftriaxone) is a suitable first line option. For hospital acquired


Gram positive cocci
MRSA
MSSA
Streptococci
Gram negative bacili
E. coli
P. mirabilis
Klebsiella
Pseudomonas
ESCAPPM
Gram-negative cocci
N. gonorrhoeae
N. meningitidis
Anaerobes
Atypicals
e.g. Mycoplasma
Penicillin
Penicillin G
Anti-staphylococcal penicillins
Naficillin/Oxacillin
Aminopenicillins
Ampicillin/Amoxicillin
Amp/Amox
1st-gen cephalosporin
Cefazolin, cephalexin
2nd-gen cephalosporin
Cephotetan, Cefoxitin
3rd-gen cephalosporin
Ceftriaxone
Ceftriaxone
Ceftazidime
4th-gen cephalosporin
Cefepime
Aminopenicillins with beta-lactamase inhibitors
Amoxicillin + clavulanate (Augmentin)
Amox-clav
Ampacillin + sulbactam (Unasyn)
Amp-sul
Piperacillin + tazobactam (Zosyn)
Piperacillin + tazobactam (Zosyn)
Carbapenems
Ertapenem
Ertapenem
Imipenem, Meropenem
Monobactams
Aztreonam
Quinolones
Ciprofloxacin
Ciprofloxacin
Levofloxacin
Levofloxacin
Moxifloxacin
Moxifloxacin
Aminoglycosides
Gent/Tobra/Amikacin
Lincosamide
Clindamyacin
Clindamyacin
Macrolides
Azithromycin
Azithromycin
Azithromycin
Tetracyclines
Doxycycline
Doxycycline
Doxycycline
Glycopeptides
Vancomycin
Antimetabolite
TMP/SMX (Bactrim)
TMP/SMX
TMP/SMX
Nitroimidazoles
Metronidazole

# *Non tutte le cefalosporine sono uguali*

| | CEFOTAXIME | CEFTRIAXONE | CEFTAZIDIME |
|---|---|---|---|
| E. fecalis | - | +/- | - |
| S. Aureus (MSSA) | + | + | - |
| S. Aureus (MRSA) | - | - | - |
| CoNS | + | + | - |
| Group A Strepto | + | + | + |
| S. Pneumoniae | + | + | + |
| Neisseria Meningitidis | + | ++ | + |
| Haemophilus Influenzae | ++ | ++ | + |
| M. catarrhalis | + | + | + |
| Salmonella | + | + | + |
| E.coli | + | ++ | + |
| Pseudomonas | - | - | ++ |
| Campylobacter | - | - | - |

# Terapia antibiotica in Ospedali Italiani (dati ARPEC)




## TERAPIA COMBINATA: scopi

1) Allargare lo spettro (es. MRSA --> Vanco)

2) Ridurre la probabilità di resistenza di singoli agenti

3) Fornire effetto sinergico per alcuni patogeni

De Luca - PLoS One. 2016

# Monoterapia o associazione?

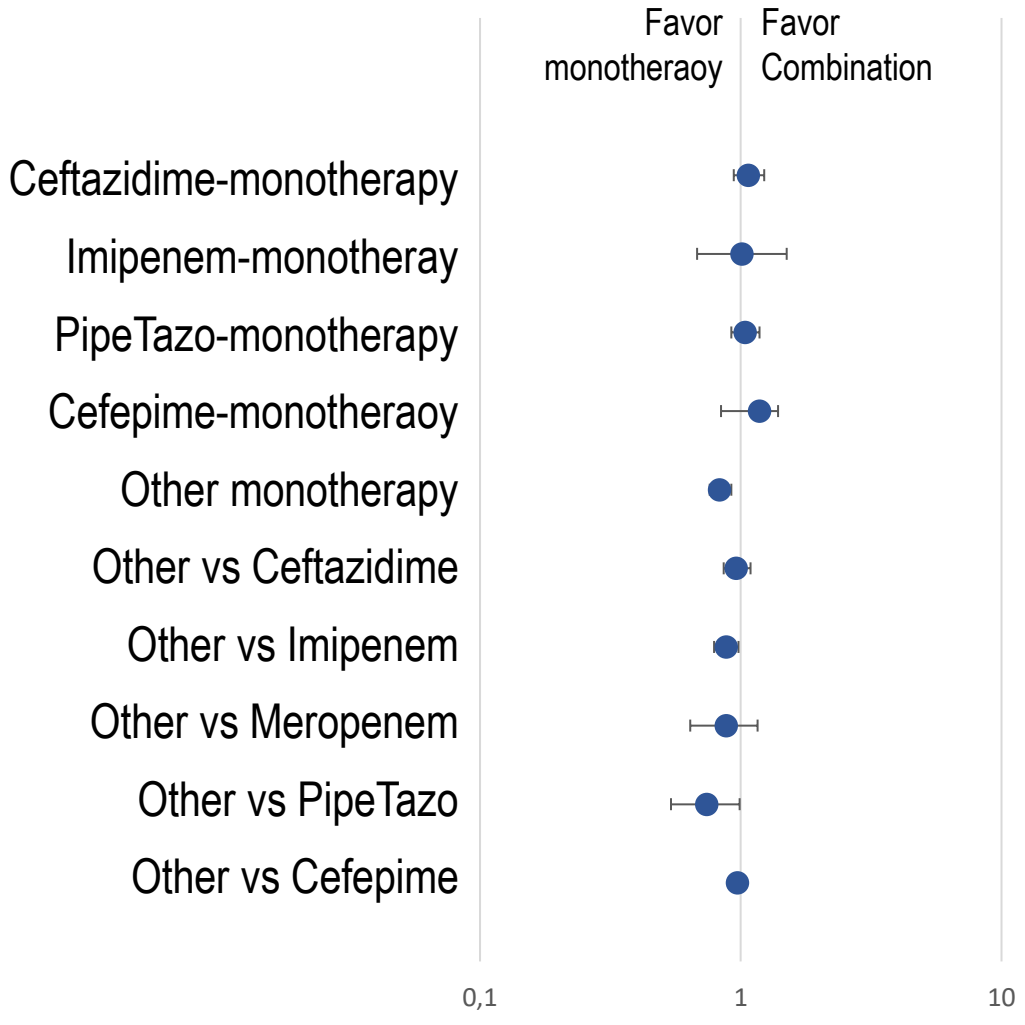
Betalattamici + / - aminoglicosidi nella sepsi del bambino oncologico

| Study or subgroup | Monotherapy n/N | Combination therapy n/N | Risk Ratio M-H, Fixed, 95% CI | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **11.1.1 children** | | | | | |
| Agaoglu 2001 | 2/30 | 0/57 | | 0.12% | 9.35[0.46,188.82] |
| Ahmed 2007 | 2/63 | 3/66 | | 0.99% | 0.7[0.12,4.04] |
| Duzova 2001 | 0/45 | 2/45 | | 0.85% | 0.2[0.01,4.05] |
| Hung 2003 | 2/39 | 3/37 | | 1.04% | 0.63[0.11,3.57] |
| Jimeno 2006 | 1/23 | 0/26 | | 0.16% | 3.38[0.14,79] |
| Morgan 1983 | 1/26 | 3/24 | | 1.05% | 0.31[0.03,2.76] |
| Petrilli 2003 | 2/68 | 3/68 | | 1.01% | 0.67[0.12,3.86] |
| Smith 1990 | 0/47 | 0/53 | | | Not estimable |
| Zengin 2011 | 0/37 | 0/35 | | | Not estimable |
| **Subtotal (95% CI)** | **378** | **411** | | **5.22%** | **0.8[0.39,1.64]** |
| Total events: 10 (Monotherapy), 14 (Combination therapy) | | | | | |

Paul – Cochrane 2016

# **Monoterapia o associazione**?

Betalattamici + / - aminoglicosidi nella sepsi del bambino oncologico




Combinazione **associata** a:

- Maggiori effetti collaterali (NNH = 4)
- Maggiore nefrotossicità
- Maggiore sovra-infezione fungina
- Maggiore interruzione di terapia

Paul – Cochrane 2016

# Linee guida Sepsi 2020

10) In children without immune compromise and without high risk for multidrug-resistant pathogens, we suggest against the routine use of empiric multiple antimicrobials directed against the same pathogen for the purpose of synergy (weak recommendation, very low quality of evidence).

11) In children with immune compromise and/or at high risk for multidrug-resistant pathogens, we suggest using empiric multi-drug therapy when septic shock or other sepsis-associated organ dysfunction is present/suspected (weak recommendation, very low quality of evidence).

# **Scenari clinici**: Terapia empirica ragionata

| PAZIENTE | 1° LINEA | Altri fattori | 2° LINEA / ADD ON |
|---|---|---|---|
| **Paziente immunodepresso** | PIPERACILLINA/TAZOBACTAM<br>CEFEPIME / CEFTAZIDIME | • Neutropenia o Trapianto | Vedi ICA |
| **Paziente ospedalizzato**<br>Sepsi correlata all'assistenza | PIPERACILLINA/TAZOBACTAM<br>+ VANCOMICINA | • Neutropenia o Trapianto<br>• Immunodepresso o Steroidi<br>• Pregressa Candidemia | Se in shock settico<br>+ ECHINOCANDINE<br><br>Altri rivalutare a 48-72 h |
| **Paziente con CVC** | PIPERACILLINA/TAZOBACTAM +<br>VANCOMICINA | | Se in shock settico<br>+ ECHINOCANDINE<br><br>Altri rivalutare a 48-72 h |
| **Paziente** post intervento addominale o con probabile **localizzazione addominale** | CEFTRIAXONE O CEFOTAXIME<br>+ METRONIDAZOLO/CLINDA<br>+ GENTA/AMIKACINA<br><br>PIPERACILLINA/TAZOBACTAM<br>+ GENTA/AMIKACINA | • Ricovero in rianimazione<br>• Pregresso da Gram neg MDR<br>• Colonizzazione Gram neg MDR | MEROPENEM +<br>GENTAMICINA/AMIKACINA |
| Paziente sottoposto a **chirurgia ortopedica o neurochirurgia** | CEFTAZIDIME + VANCOMICINA | | |

# Nuovi e vecchi farmaci… per le infezione gravi da batteri multi-resistenti

## Anti GRAM Neg

### Ceftazidime-Avibactam (*Zavicefta®*)

AIFA

**Intra-addominali complicate**
Bradley - PIDJ 2019

**IVU complicate**
Bradley - PIDJ 2019

**Klebsiella MDR**
Iosifidis - PIDJ 2019

### Ceftolozane-Tazobactam (Zerbaxa®)

AIFA

**Intra-addominali complicate**
Larson – Antim Age Chemother 2019

**IVU complicate**
Larson – Antim Age Chemother 2019

**Pseudomonas**
Larson – Antim Age Chemother 2019

### Ceftaroline (Zinforo®)

AIFA

**Cute & tessuti molli**
Yim - Infect Dis Ther 2017

**Polmonite complicata**
Yim - Infect Dis Ther 2017

### Tigeciclina (Tygacil®)

AIFA > 8 anni

**Intra-addominali complicate**
Mastrolia - Ex Rev Anti Inf Ther. 2017
Ye - Eur J Pediatr. 2018
Sharland – PIDJ 2019

**Cute & Tessuti molli**

### Colistina

**Enterobacteriacae ESBL & CRE**

### Fosfomicina

**Enterobacteriacae ESBL & CRE**

## Anti GRAM Pos

### Daptomicina (Cubicin®)

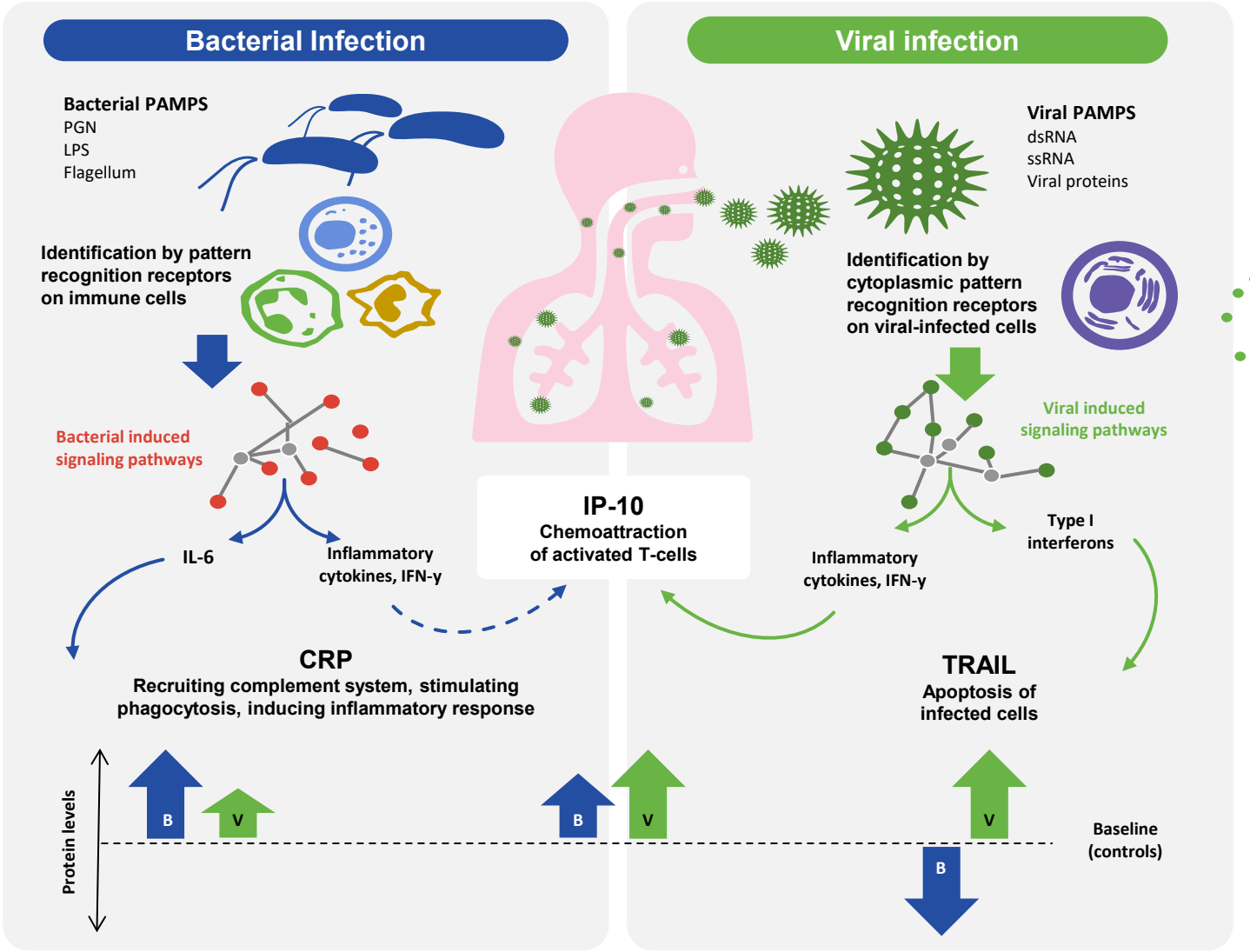
AIFA

**Cute & tessuti molli**
Bradley Pediatrics 2017, Syrogiannopoulos PIDJ 2017

**Batteriemia SA, Endocarditi**
Arrieta PDIJ 2018

### Telavancin (Vibativ®)

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

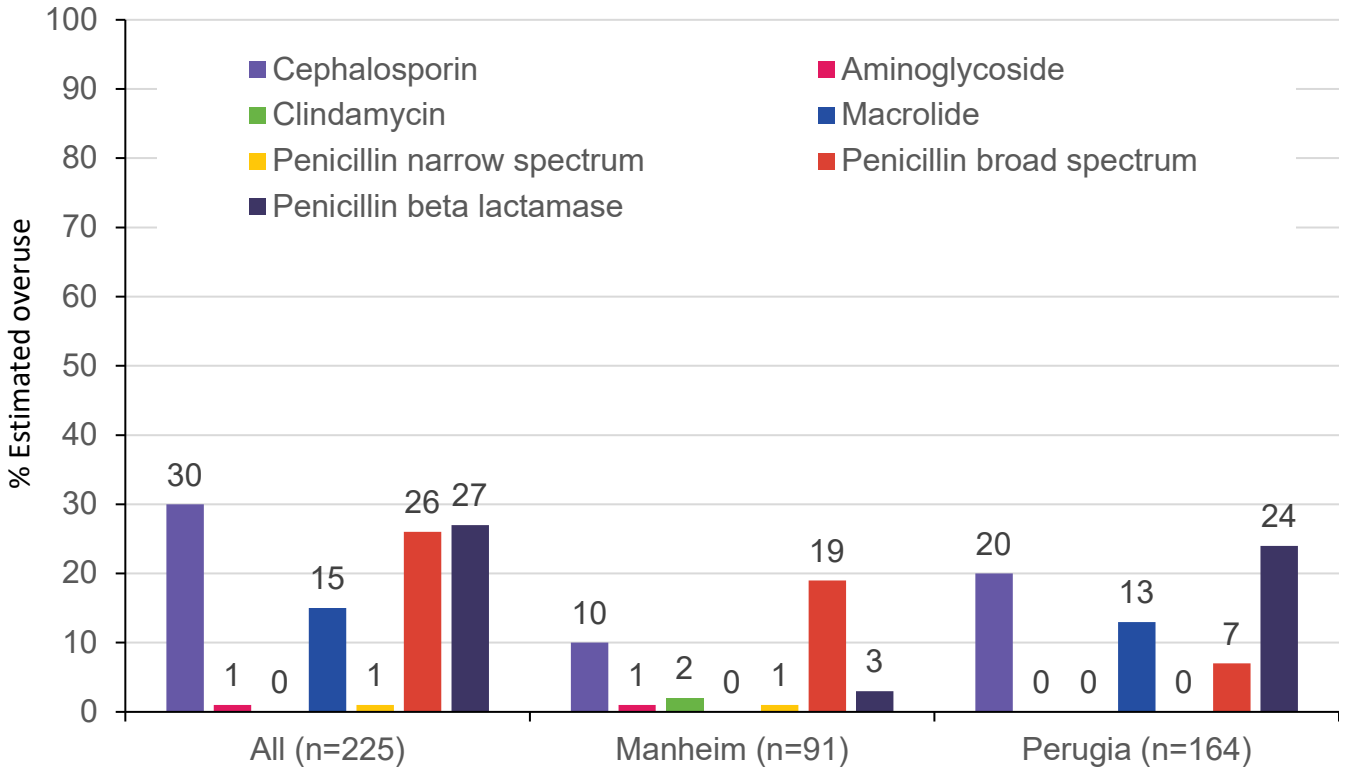



Oved K, et al. *PLOS One* 2015; https://doi.org/10.1371/journal.pone.0120012

# 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

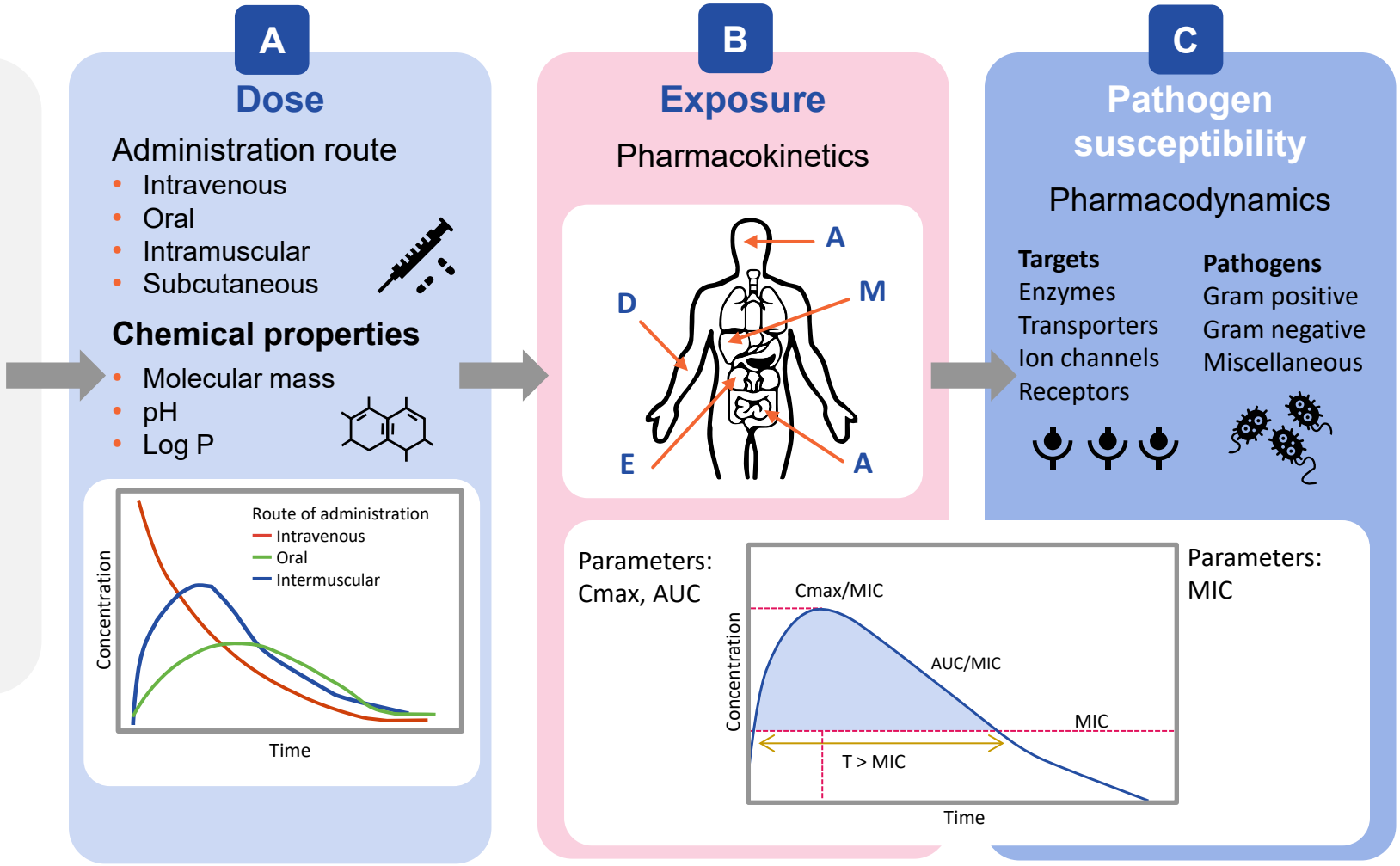
# PK/PD concepts and dose rationale

**Determinants of the antibacterial activity and clinical response**

**A. Dose:**
Fomulation properties, administration route and regimen

**B. Exposure:**
Pharmacokinetic processes and parameters:
A - Absorption (e.g. bioavailability)
D - Distribution (e.g. volume of distribution, Cmax )
M - Metabolism (e.g. clearance, AUC)
E - Excretion (e.g. clearance, AUC)

**C. Etiological agent:**
Susceptibility of pathogens to the drug




Cmax, peak concentration; AUC, area under the concentration-time curve; MIC, minimal inhibitory concentration; T > MIC, time above MIC; PK, pharmacokinetics; PD, pharmacodynamics.

Van Donge T, *et al. Front Pediatr 2018*;6:325. doi: 10.3389/fped.2018.00325.

# Education

- Provide regular updates on antimicrobial prescribing, antibiotic resistance, and infectious disease management
- Address both national and local issues
- Choose format based on receptiveness at your institution:
- Didactic presentations
- Posters. flyers. newsletters, emails
- ASP website
- Review de-identified cases where changes in antimicrobial therapy could have been made

# 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

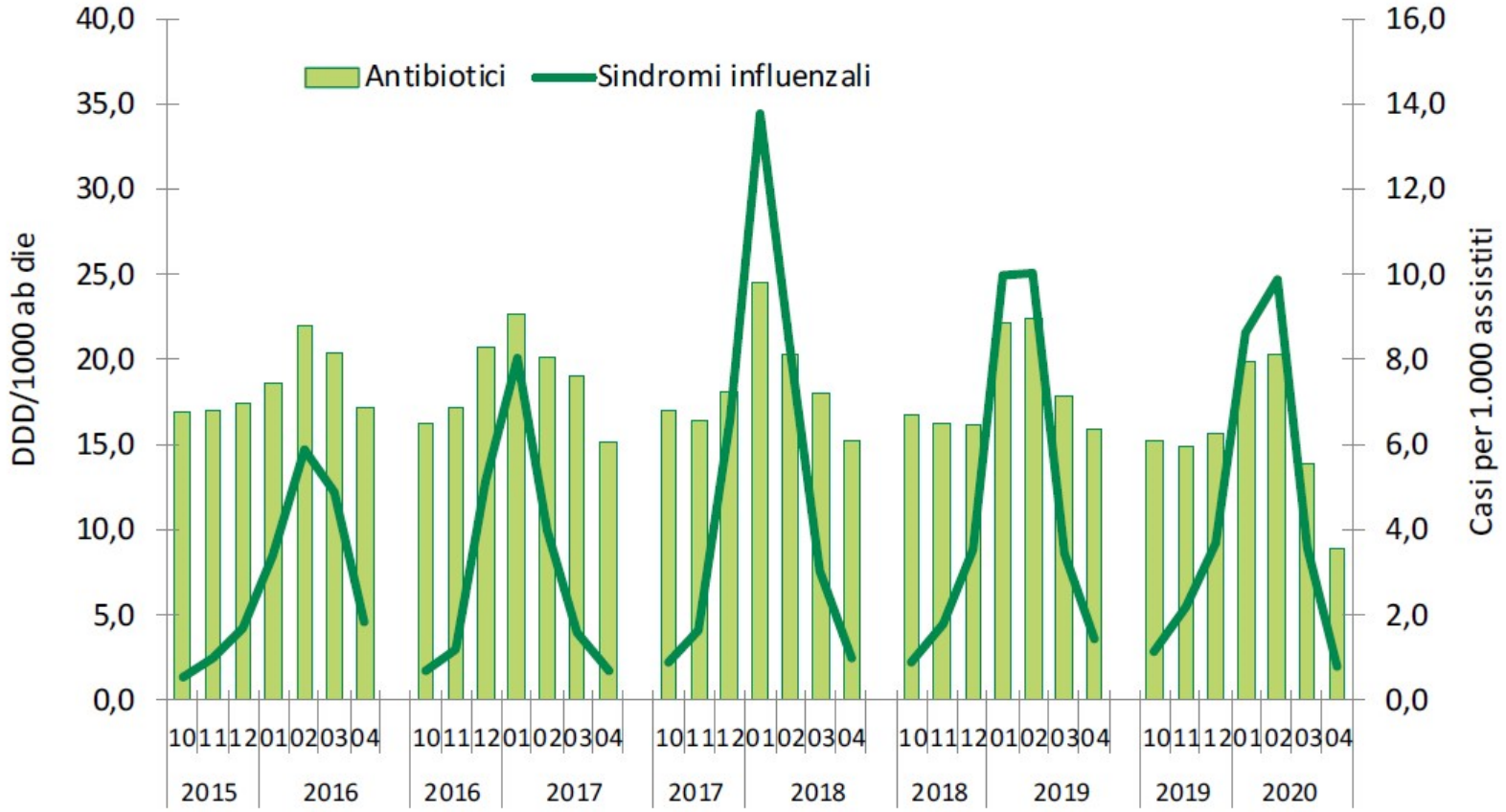
| | | | | |
|---|---|---|---|---|
| 6. Contrastare le infezioni e le ICA attraverso la vaccinazione | 6.1 Favorire il raggiungimento degli obiettivi di copertura vaccinale nella popolazione generale e nei gruppi a rischio e predisporre interventi specifici dedicati a chi opera nei servizi di assistenza e cura e agli operatori del settore veterinario | MdS, NITAG, Regioni/ PPAA, Società scientifiche | Per tutta la durata del Piano | NAZIONALE<br>Secondo gli obiettivi del PNPV |

Ministero della Salute

PER UN USO CONSAPEVOLE ANTIBIOTICI EFFICACI

# Piano Nazionale di Contrasto all'Antibiotico-Resistenza (PNCAR) 2022-2025

Correlazione tra consumo (DDD/1000 ab *die*) di antibiotici sistemici (J01) in assistenza convenzionata e incidenza di sindromi influenzali (casi per 1000 assistiti) nel periodo 2015-2019, in Italia




Agenzia Italiana del Farmaco *Rapporto Nazionale 2019*

# 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;<br>• multiple antimicrobial mechanisms of action;<br>• ease of synthesis thanks to AI. | • high toxicity to eukaryotic cells;<br>• high cost of large-scale production;<br>• initial appearance of cross resistance associated with widespread use;<br>• onset of allergic reactions. |
| 2. Discovery of new antibiotics | • ability to develop new molecules with targeted and broad-spectrum bioactivity;<br>• reduced time and labor costs for development. | • need for training libraries to contain molecules with physicochemical properties consistent with those of antibacterial drugs yet<br>• sufficiently diverse;<br>• 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);<br>• ability to help the clinician select the correct antibiotic | • lack of complete genotypes in the NCBI database for each microorganism<br>• 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;<br>• ability to receive feedback for automatic and continuous improvement<br>• guideline-based operation | • lack of staff in systems management;<br>• need for available health funds. |
| Prediction of infection severity | • ability to distinguish infectious diseases, including sepsis, from non-infectious diseases<br>• provision of decision support for the doctor;<br>• ability to reduce mortality | • need for accurate and complete data collection;<br>• inability to obtain laboratory data from the beginning of illness. |

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

# Take-home messages

- Use of new anti-infective drugs should be based on the careful analysis of well-conducted clinical studies in pediatrics
- To fight antimicrobial resistance represents a priority that requires a multi-level commitment
- To implement multidisciplinary antimicrobial stewardship programs for hospital and community setting is mandatory 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

Children are the only
future the human race has.
Treat them well!