ANTIMICROBIAL STEWARDSHIP IN ETA' PEDIATRICA

Susanna Esposito
UOC Clinica Pediatrica, Ospedale dei Bambini Pietro Barilla, Università di Parma, Parma

AGENDA

How antimicrobial resistance is frequent in Italy and why

Consequences of antibiotic abuse and misuse in primary care and in the hospital

Prevention of antmicrobial resistance

Focus on the neonates

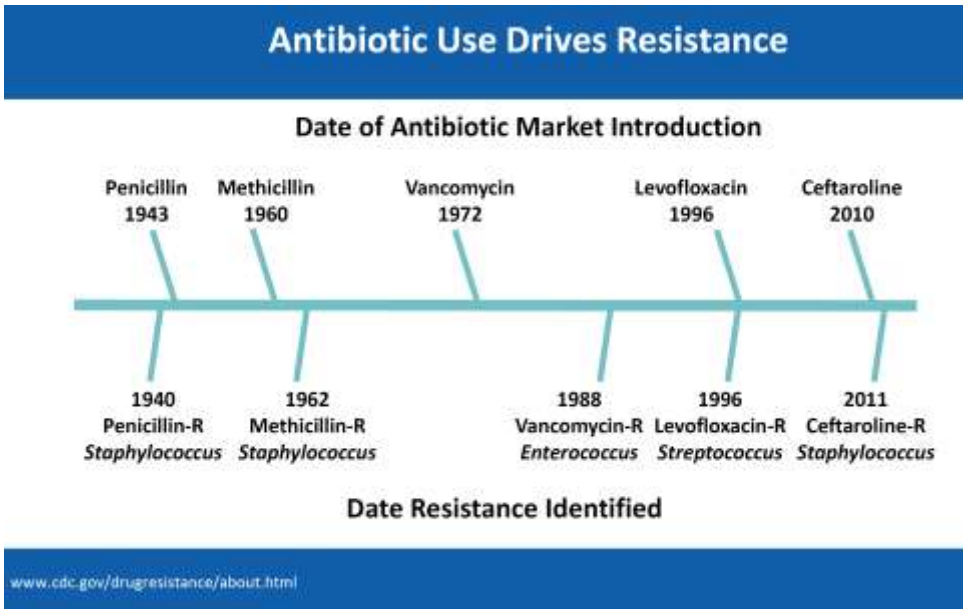
Potential impact of vaccination

A very short life-span

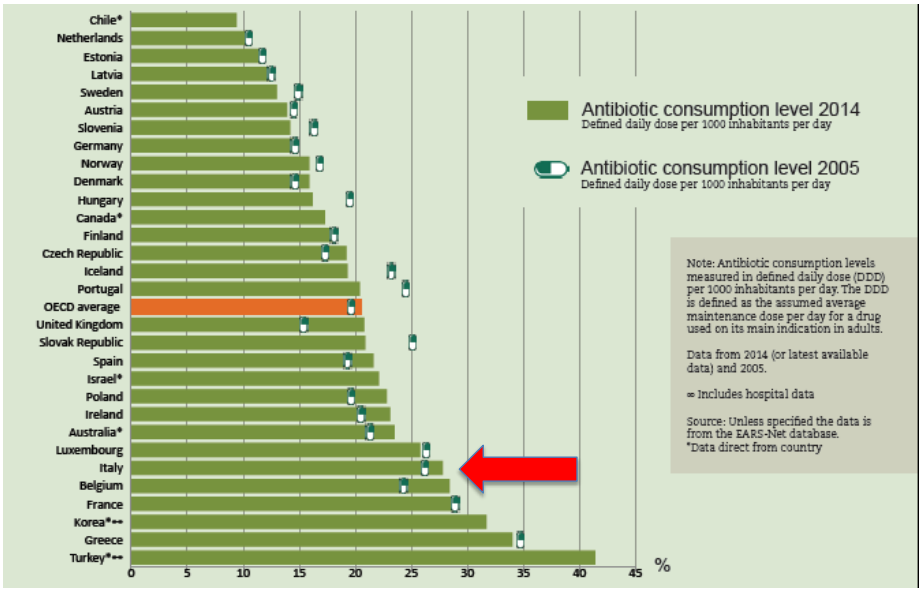
1944

"The greatest ..event of WWII may well be the discovery & development of penicillin"

2016



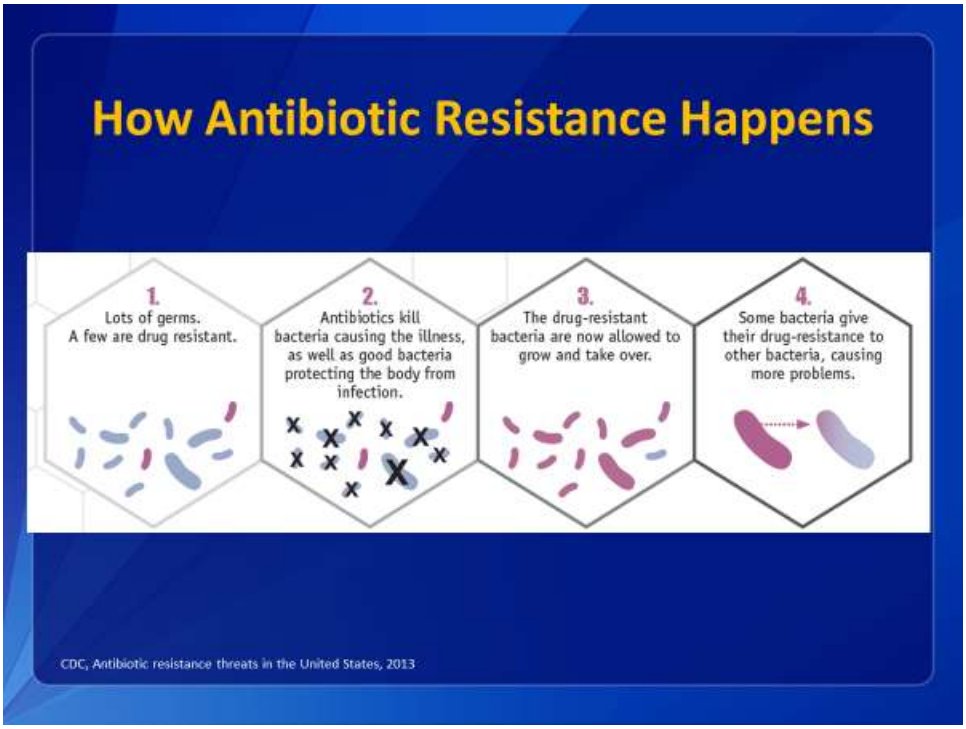
Antibiotic Consumption, Europe

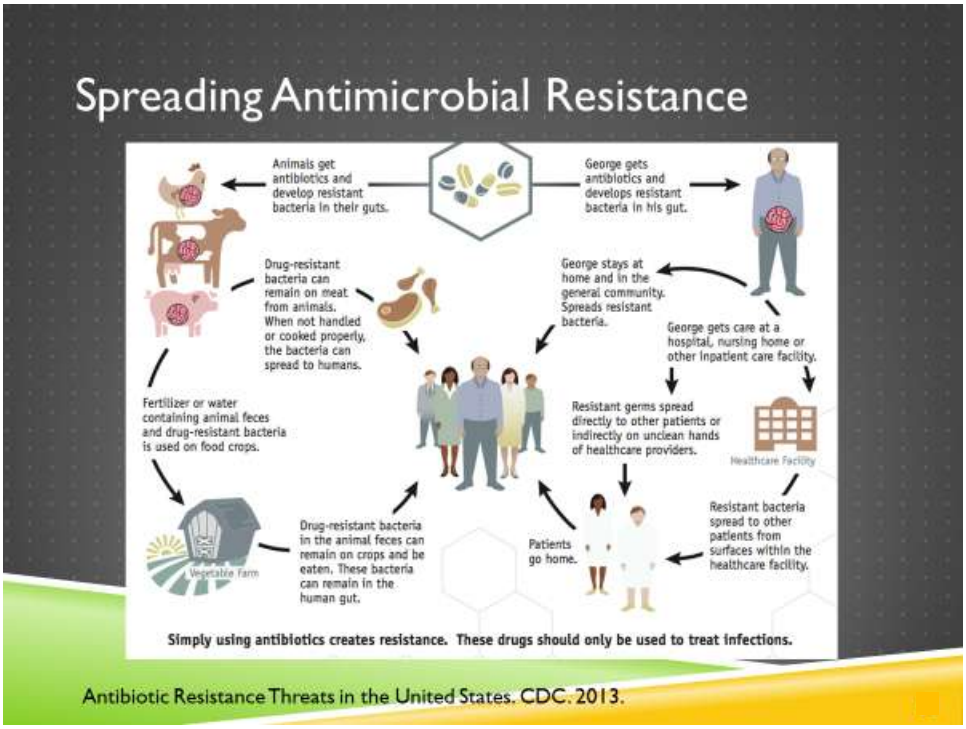


OECD 2016

AMR, Europe

OECD 2016


How Antibiotic Resistance Happens
1.
Lots of germs.
A few are drug resistant.
2.
Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.
3.
The drug-resistant bacteria are now allowed to grow and take over.
4.
Some bacteria give their drug-resistance to other bacteria, causing more problems.
CDC, Antibiotic resistance threats in the United States, 2013


Spreading Antimicrobial Resistance
Animals get antibiotics and develop resistant bacteria in their guts.
George gets antibiotics and develops resistant bacteria in his gut.
Drug-resistant bacteria can remain on meat from animals. When not handled or cooked properly, the bacteria can spread to humans.
George stays at home and in the general community. Spreads resistant bacteria.
George gets care at a hospital, nursing home or other inpatient care facility.
Fertilizer or water containing animal feces and drug-resistant bacteria is used on food crops.
Resistant germs spread directly to other patients or indirectly on unclean hands of healthcare providers.
Healthcare Facility
Vegetable Farm
Drug-resistant bacteria in the animal feces can remain on crops and be eaten. These bacteria can remain in the human gut.
Patients go home.
Resistant bacteria spread to other patients from surfaces within the healthcare facility.
Simply using antibiotics creates resistance. These drugs should only be used to treat infections.
Antibiotic Resistance Threats in the United States. CDC. 2013.

ANTIMICROBIAL RESISTANCE AND USE OF ANTIBIOTICS

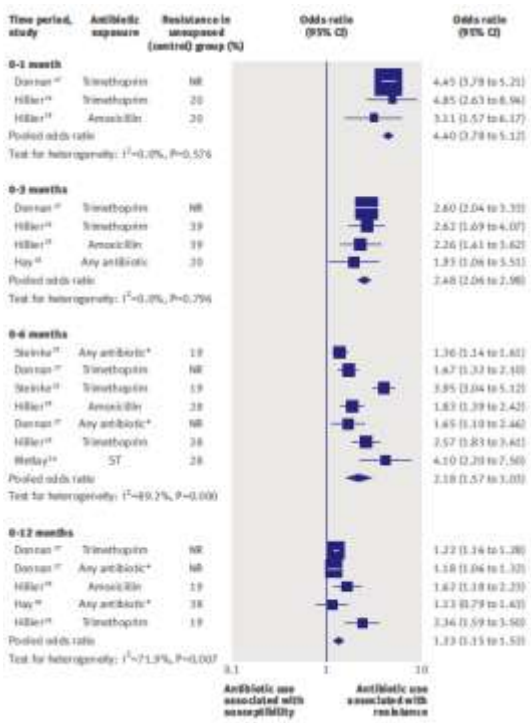
a) ABUSE: prescriptions for diseases not due to bacterial infection

b) MISUSE: use with inappropriate dosage and duration of administration

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



Effect of antibiotic prescribing in primary care on antibiotic resistance

(From Costelloe C et al. BMJ 2010)

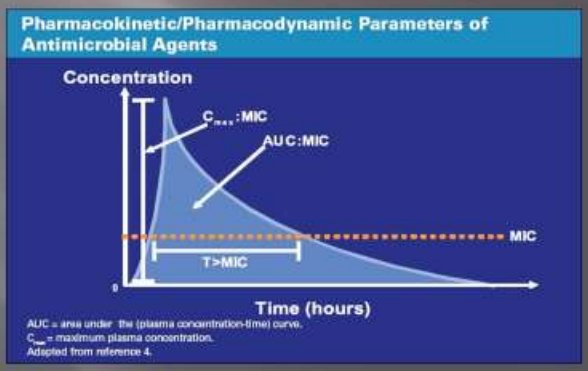
ANTIBIOTIC IN ITALIAN HOSPITALIZED CHILDREN WITH LOWER RESPIRATORY TRACT INFECTIONS

	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

(from Esposito S, EJCMID, 2001; 20:647)

Inappropriate Dosing May Lead to Resistance

- Data pooled from 4 studies
  - Gram-negative pneumonia
  - Ciprofloxacin resistance associated with AUC/MIC <100



Thomas JK, et al. Antimicrob Agents Chemother. 1998;42:521-527.

Dosing Matters – Penicillin Example

- Penicillin half-life is only 30-45 minutes
- Retrospective review of Streptococcal infective endocarditis
  - Penicillin given every 4 hours was associated with successful treatment vs every 6 hours (OR 2.79; 95%CI 1.43-5.62)

Sandoe JAT, et al. J Antimicrob Chemother. 2013; June 13 [Epub ahead of print]

Unintended Consequences of Antibiotic Use: Adverse Events

- Adverse events range from minor to severe
- 200,000 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 Sep 15;47(6):744–6
Shehab N, Lovegrove MC, Geller AI, et al. *JAMA* 2016;316:2115–25
Vangay P, Ward T, Gerber JS, et al. *Cell Host Microbe* 2015 May 13; 17(5): 553–564

Are Antibiotics Really Benign?

ANTIBIOTICS ARE RESPONSIBLE FOR ALMOST

1 OUT OF 5

EMERGENCY DEPARTMENT VISITS FOR ADVERSE DRUG EVENTS

ANTIBIOTICS ARE THE MOST COMMON CAUSE OF EMERGENCY DEPARTMENT VISITS FOR ADVERSE DRUG EVENTS IN CHILDREN UNDER 18 YEARS OF AGE.

CDC. Threat Report 2013. http://www.cdc.gov/drugresistance/threat-report-2013/

Antibiotic Resistance

Estimated minimum number of illnesses and deaths caused annually by antibiotic resistance*:

At least **2,049,442** illnesses,

23,000 deaths

**bacteria and fungus included in this report*

Annual excess direct healthcare cost: $20 billion
Additional annual cost of lost productivity: >$35 billion

www.cdc.gov/drugresistance/threat-report-2013/

Clostridium Difficile Infection: Consequence of Antibiotic Use

- **453,000 infections and 15,000 deaths in the United States annually**
- ***C. difficile* infections can be recurrent and are costly and potentially fatal consequences of antibiotic use**
- **Prevention of *C. difficile* infections is key**

Lessa FC, Bamberg WM, Beldavs ZG, et al. *N Engl J Med.* 2015 Feb 26;372(9):825–34

Table 1 CDC Assessment of Antibacterial Resistance Threats[5]

Urgent Threats
- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

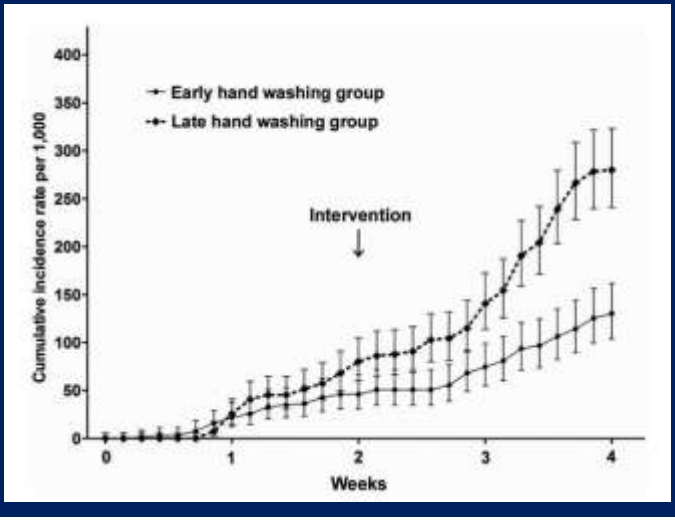
Serious Threats
- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant Enterococci (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* Typhimurium
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

Prevention of infection: handwashing

Early and late hand washing and emergence of respiratory infectious diseases

(from Kim HS et al., Medicine 208)



Tracking

- Monitor antibiotic use prescribing
  - Identify opportunities for improvement
  - Assess impact of efforts
- Process measures
- Antibiotic use
  - Controversy regarding best methods for monitoring use
  - DDD = defined daily dose
  - DOT = days of therapy
- Outcomes measures

CDC. Core Elements of Hospital Antibiotic Stewardship Programs. 2014.

Antimicrobial Stewardship

- **Strategic multidisciplinary and facility specific efforts to optimize antimicrobial prescribing**
  - Right drug
  - Right dose
  - Right duration
  - Recognize when not needed

Infectious Diseases Expert Resources

Methods to Improve Antimicrobial Use

- Passive prescriber education
- Standardized antimicrobial order forms
- Formulary restrictions
- Prior approval to start/continue
- Pharmacy substitution or switch
- Multidisciplinary drug utilization evaluation (DUE)
- Interactive prescriber education
- Provider/unit performance feedback
- Computerized decision support/online ordering

➢ *Link to: SHEA / IDSA: Guidelines for the Prevention of Antimicrobial Resistance in Hospitals*

Use Antimicrobials Wisely
Use local data

Fact:
The prevalence of resistance can vary by time, locale, patient population, hospital unit, and length of stay.

Surgical prophylaxis

- Surgical antimicrobial prophylaxis reduce the risk of SSI
- Surgical antimicrobial prophylaxis timing is crucial
- Prophylaxis should use narrow-spectrum antibiotic
- Control of the adherence to the National Guidelines
- National surveillance system of adverse events of antibiotic prophylaxis, including *C. difficile*
- Communication and educational programmes to increase awareness of adverse events, including AMR, due to inappropriate use of antibiotics for surgical prophylaxis

Menichetti F et al. Int J Antimicrob Agents. 2018 Aug;52(2):127-134

Medical prophylaxis in patients at risk of infections

- Prevention of endocarditis in dental procedures
- Prevention of post-splenectomy sepsis syndrome
- Prevention of Rheumatic Fever
- Prevention of relapsing cellulitis in lymphedema
- Prevention in close contact of *N.meningitidis*
- Prevention of sepsis in febrile neutropenia (?)
- Prevention of sepsis in multi-colonized pts (?)

Menichetti F et al. Int J Antimicrob Agents. 2018 Aug;52(2):127-134

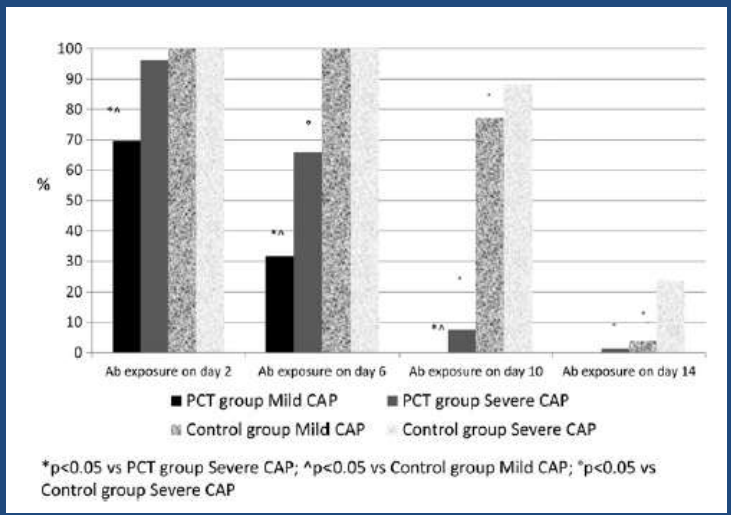
Appropriate use of antimicrobials
Surrogate markers: procalcitonin (PCT)

- PCT help to identify bacterial infections
- PCT-guided antibiotic therapy significantly reduce: days of antibiotic exposure, drug-related side-effects and rate of antibiotic resistance.
- The early dynamic of PCT values (48-72 hrs) is a reliable predictor of survival and efficacy of antibiotic therapy.
- PCT may help to distinguish between Gram-neg. & Gram-pos. infection and support the suspicion of fungal infection
- Low PCT levels in sepsis suggest: deep abscesses, meningitis/ventriculitis, endocarditis, atypical pneumonia, etc.

Menichetti F et al. Int J Antimicrob Agents. 2018 Aug;52(2):127-134

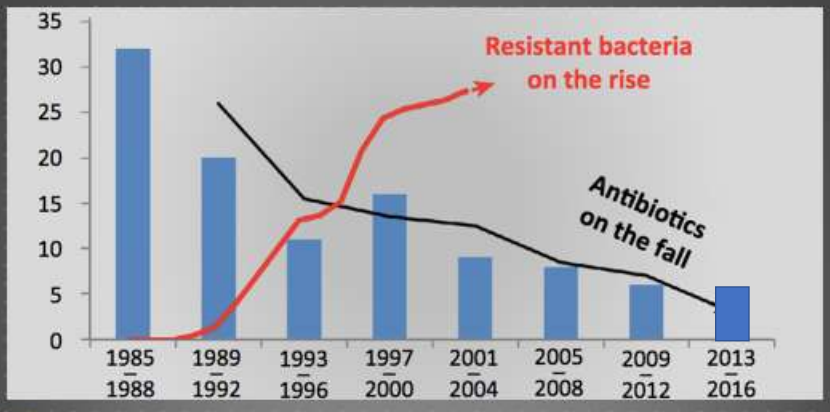
ANTIBIOTIC EXPOSURE BY TREATMENT GROUP AND CAP SEVERITY

(From Esposito S et al., Resp Med 2011)



AutoPilot-Dx consortium – collaboration between industry and academia

Antimicrobial Development



Trends In Microbiology. 2014;22(4):165-167.

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HOSPITAL ANTIBIOTIC PRESCRIBING
(Porta et al., Eur J Clin Pharmacol 2010)

OFF LABEL ANTIBIOTICS USED IN NICU

		London	Milan	Athens*
ABX off label for AGE	% Patients	6.5%	5.3%	40.0%
	% Prescriptions	2.3%	2.2%	22.2%
ABX off label for DOSE	% Patients	67.7%	89.4%	90.0%
	% Prescriptions	37.8%	51.7%	44.4%
ABX off label for INDICATION	% Patients	45.1%	47.3%	50.0%
	% Prescriptions	23.3%	38.5%	25.9%

*Athens neonatal data are not comparable

HOSPITAL ANTIBIOTIC PRESCRIBING
(Porta et al., Eur J Clin Pharmacol 2010)

OFF LABEL ANTIBIOTICS USED FOR AGE IN NICU

UNITED KINGDOM:	ITALY:	GREECE*:
4/62 neonates treated with Off Label antibiotics (6.5%): •3 male – 1 female •39.5 days of life (17 – 89)	2/38 neonates treated with Off Label antibiotics (5.3%): •1 male – 1 female •24 days of life (21 -27)	4/10 neonates treated with Off Label antibiotics (40%): •3 male, 1 female • 64 days of life (34-104)
4/172 antibiotic prescriptions (2.3%): •4 meropenem	2/91 antibiotic prescriptions (2.2%): •2 meropenem	6/27 antibiotic prescriptions (22.2%): •3 imipenem, 2 meropenem, 1 ciprofloxacin
4 different indications to treatment: •4 Sepsis	2 different indications to treatment: •2 Sepsis	4 different indications to treatment: •2 Sepsis •1 LRTI •1 UTI
		*Athens neonatal data are not comparable.

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)

SEPSIS DIAGNOSIS

(Expert Meeting on Neonatal and Paediatric Sepsis; 8 June 2010, EMA, London)

Diagnosis on the basis of the presence of **at least two clinical and two laboratory criteria** in the previous 24 hours.

Clinical criteria

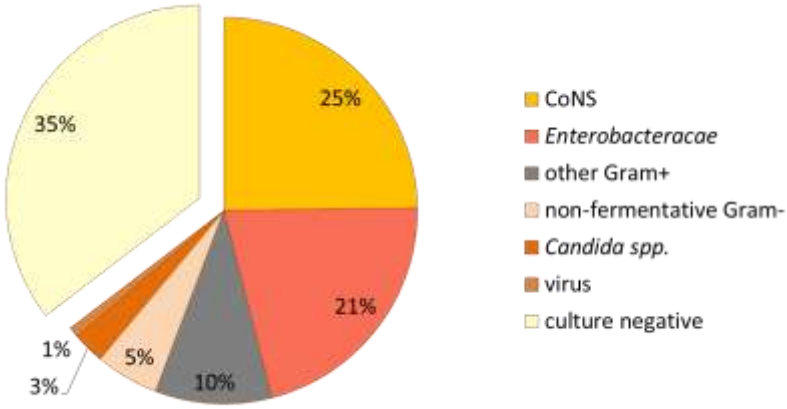
- 1) hyper- or hypothermia or temperature instability;
- 2) reduced urinary output or hypotension or mottled skin or impaired peripheral perfusion;
- 3) apnea or increased oxygen requirement or increased requirement for ventilator support;
- 4) bradycardia spells or tachycardia or rhythm instability;
- 5) feeding intolerance or abdominal distension;
- 6) lethargy or hypotonia or irritability;
- 7) skin and subcutaneous lesions such as petechial rash or sclerema.

Laboratory criteria

- 1) a white blood cell (WBC) count of <4 or >20 x 109 cells/L;
- 2)an immature to total neutrophil ratio (I/T) of >0.2;
- 3) a platelet count of <100 x 10^9/L;
- 4) C-reactive protein (CRP) levels of >15 mg/L or procalcitonin levels of ≥2 ng/mL;
- 5) glucose intolerance when receiving normal amounts of glucose (8-15 g/kg/day) as expressed by blood glucose values of >180 mg/dL or hypoglycemia (<40 mg/dL) confirmed at least twice;
- 6) acidosis, as characterised by a base excess (BE) of <-10 mmol/L or lactate levels of >2 mmol/L.

Causative pathogens of LOS

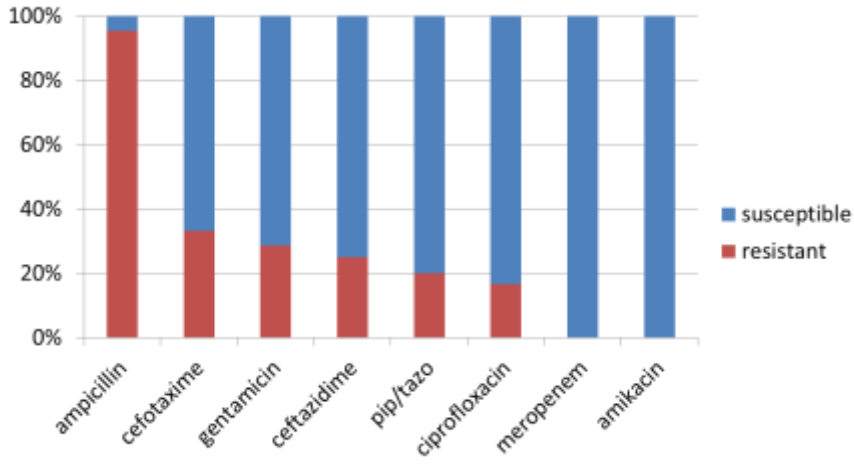
(Lutsar I et al., Eur J Pediatr 2014)



Overall 65% of cases were culture-positive

Resistance rates of *Enterobacteriaceae*

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

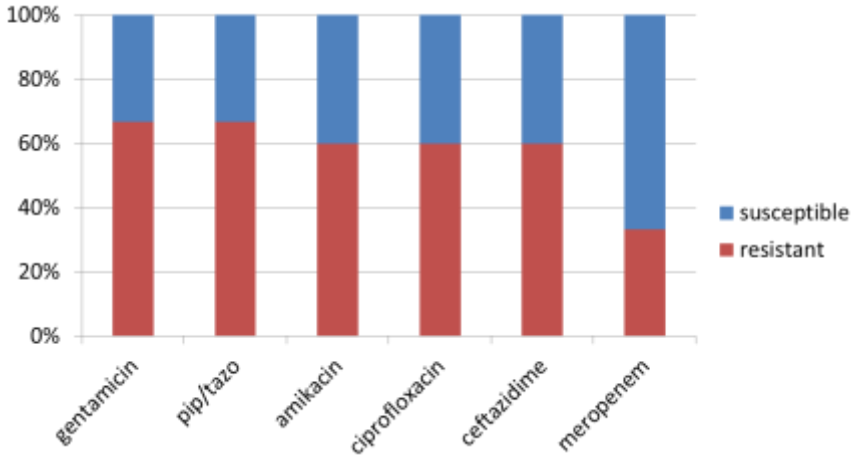


R contains also IR strains
Number of strains appr. 20

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

Resistance rates of Gram-negative non-fermetative organisms

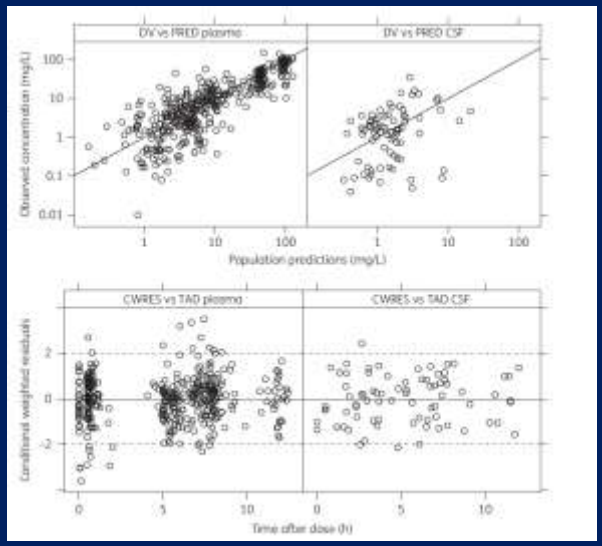
(Lutsar I et al., Eur J Pediatr 2014)



R contains also IR strains

Observed vs predicted concentrations of meropenem in neonates

(From Germonsek E et al., JAC 2018)



Appropriate use of antimicrobials
Optimizing antibiotic use by the pharmacology lab.

- Suggest the most appropriate administration modality according to the PK/PD of the drug, the etiologic agent & the site of infection
- Consider possible pharmacokinetic modifications due to patient underlying pathophysiological status.
- Assess serum antimicrobial concentrations (TDM)
- Assess serum bactericidal activity (SBA) for combination therapy

Menichetti F et al. Int J Antimicrob Agents. 2018 Aug;52(2):127-134

Appropriate use of antimicrobials
Strategy for de-escalating antibiotic therapy

- Reduce the selective pressure on intestinal microbial flora
- Decrease the emergence of resistant bugs
- Reduce the risk of potential microbiological antagonism
- Reduce adverse-events *(C. difficile*)
- Reduce costs

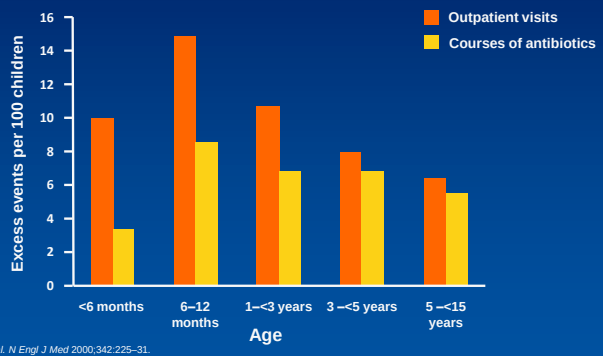
Menichetti F et al. Int J Antimicrob Agents. 2018 Aug;52(2):127-134

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

Louis Pasteur
1822-1895

Effect of Age on Healthcare Burden

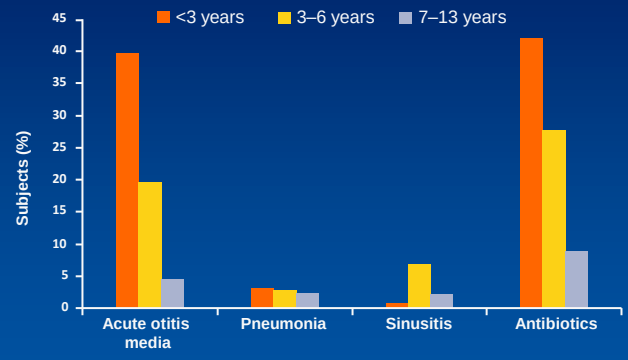
Excess treatment events in otherwise healthy children under 15 years of age; data over 19 consecutive seasons (US)



Neuzil KM, *et al. N Engl J Med* 2000;342:225–31.

Children Under 3 Years of Age are Most Likely to Develop Acute Otitis Media and Require Antibiotics

Complications of influenza in different age groups, prospective cohort study, Turku, Finland, 2000–2002



Heikkinen T, *et al. J Infect Dis* 2004;190:1369–73.

Clinical Outcomes and Drug Use by Influenza A Subtypes

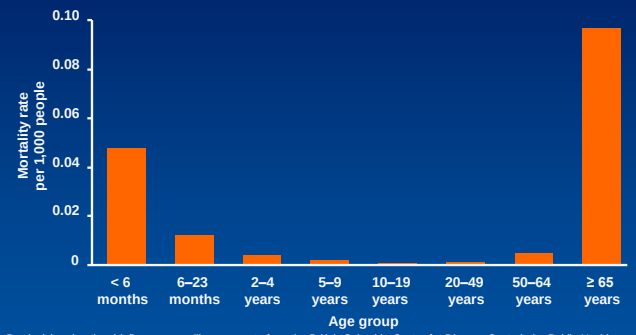
	Season 2007/2008 Seasonal A/H1N1 (n=126)	Season 2008/2009 Seasonal A/H3N2 (n=486)	Season 2009/2010 Pandemic A/H1N1 (n=389)
CLINICAL OUTCOME			
Hospitalisation rate, n (%)	4 (3.1)°*	79 (16.3)	51 (13.1)
Duration of hospitalisation, mean days ± SD	5.1 ± 3.5°*	7.5 ± 4.4*	9.1 ± 7.5
Absence from school, mean days ± SD	5.9 ± 4.7°*	7.5 ± 3.4*	8.9 ± 5.3
DRUG USE, n (%)			
Antibiotics	99 (78.6)°	466 (95.9)	297 (76.3)°
Antivirals	0 (0.0)*	0 (0.0)*	16 (4.1)
Antipyretics	100 (79.4)°*	460 (94.6)	383 (98.5)
Aerosol therapy	30 (23.8)°*	203 (41.8)	157 (40.4)
Steroids	6 (4.8)	36 (7.4)	23 (5.9)

° p<0.01 vs seasonal A/H3N2 influenza; *p<0.01 vs pandemic A/H1N1 influenza

Esposito S, *et al. J Infect* 2011;63:300–7.

Mortality Rates due to Influenza and Pneumonia

Age-associated rates of influenza-related deaths; data from British Columbia, Canada, 1998–2004 influenza seasons

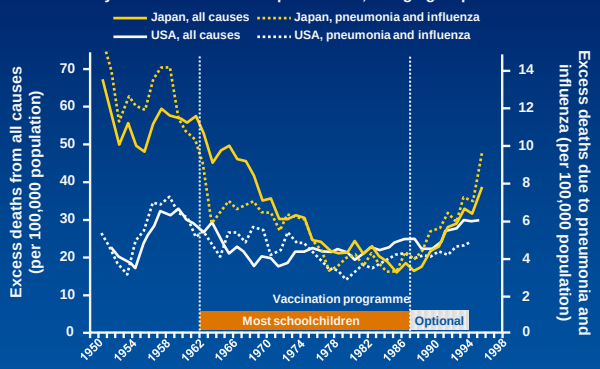


Provincial and national influenza surveillance reports from the British Columbia Centre for Disease Control, the Public Health Agency of Canada's FluWatch Program, and the Canada Communicable Disease Report (CCDR) were analysed from 1 Sep 1998 to 31 Aug 2004, to determine influenza-related deaths in British Columbia, Canada.

Sebastian R, *et al. Vaccine* 2008;26:1397–1403.

Impact on the Community of Childhood Influenza Vaccination in Japan and the USA

Vaccination of school children against influenza, Japan, 5-year moving average excess mortality due to influenza and pneumonia, all age groups



Reichert TA, *et al. N Engl J Med* 2001;344:889–96.

Influenza vaccination recommendations

WHO/Europe

Recommend that member states vaccinate **all individuals ≥6 months**[1]

EU

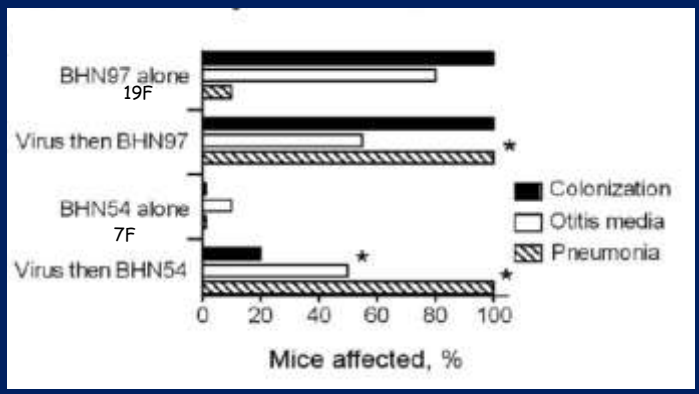
Member states currently **recommend paediatric vaccination**;[2,3,4] recommendations vary by country:

- 6 months to <18 years of age: Austria, Estonia and Slovakia
- 6–35 months: Finland
- 6–24 months: Slovenia, Latvia
- 24 months-10 yrs: UK

USA, Canada and PAHO countries

- US: All individuals ≥6 months of age[5]
- Canada: Children 6–24 months of age, and encourages all individuals ≥6 months of age to be vaccinated[6]
- Currently, 27 PAHO countries and territories recommend paediatric seasonal influenza vaccination[7*]

STREPT. PNEUMONIAE AND INFLUENZA VIRUSES (From Mc Cullers JA et al., J Infect Dis 2010)

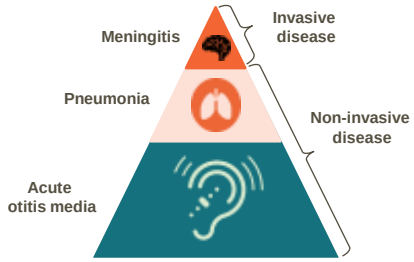


PCV programmes have the potential for substantial public health impact

Reduction in pneumococcal meningitis hospitalisation[1]

Reduction in otitis media cases[2] and HCP consultations[3]

Reduction in antibiotic prescriptions[4]

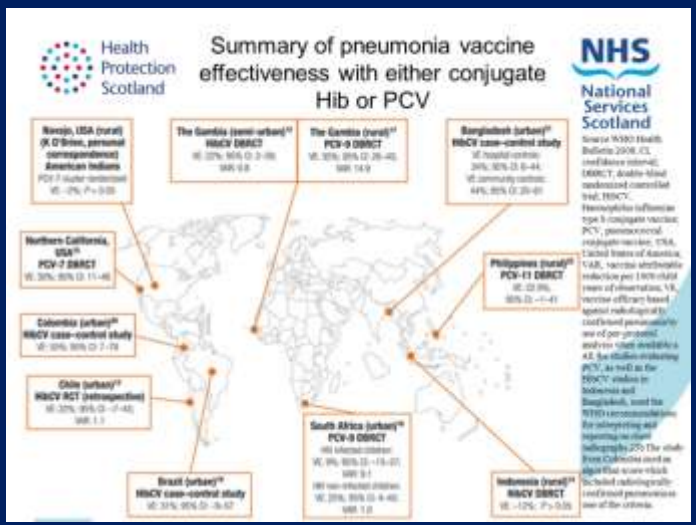


GSK Symposium at the ESPID 2019 Annual Meeting

HCP, healthcare professional; PCV, pneumococcal conjugate vaccine
1. Caceres DC, et al. *Hum Vaccin Immunother* 2018;14:1230–1233; 2. Poehling KA, et al. *Pediatrics* 2007;119:707–715; 3. Fireman B, et al. *Pediatr Infect Dis J* 2003;22:10–16; 4. Breton MC, *et al*. 2018. Poster session presented at IDWeek 2018; October 3–7, 2018; San Francisco, CA

Prevention of infections: use of vaccines

Immediate reduction of IPD after conjugate vaccine introduction



MAIN VACCINES AGAINST RSV

(Esposito & Di Pietro, Future Microbiol 2016)

Take home messages

- AMR: a call for action
- A multi-level committment (strong political advocacy and clear institutional engagement)
- Multidisciplinary clinical governance
- ASP for hospital and community setting
- Synergism between scientific society & political/institutional level


Pediatria
PARMA 2020
5/6 GIUGNO 2020
SALA AUREA DELLA CAMERA
DI COMMERCIO DI PARMA