Antimicrobial Stewardship

Implications for Primary Health Care, and how it can work

Petrozavodsk, Nov 2019

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Basic acronyms

- AMR – antimicrobial resistance
  - Resistance to drugs against microbes: bacteria, virus, protozoan, fungus
  - The most widely used antimicrobials are commonly called antibiotics, or sometimes antibacterials
- ABR – antibiotic resistance or antibacterial resistance
- ABS (AMS); antibiotic (antimicrobial) stewardship
  - Wider sense: ”any work to keep antibiotics working” (including e g WASH, IPC..)
  - Narrower sense: ”work for rational use of antibiotics”
  - Here: mostly use ABS, in the more narrow sense, focus on how we use AB:s

Outline

Why ABS?

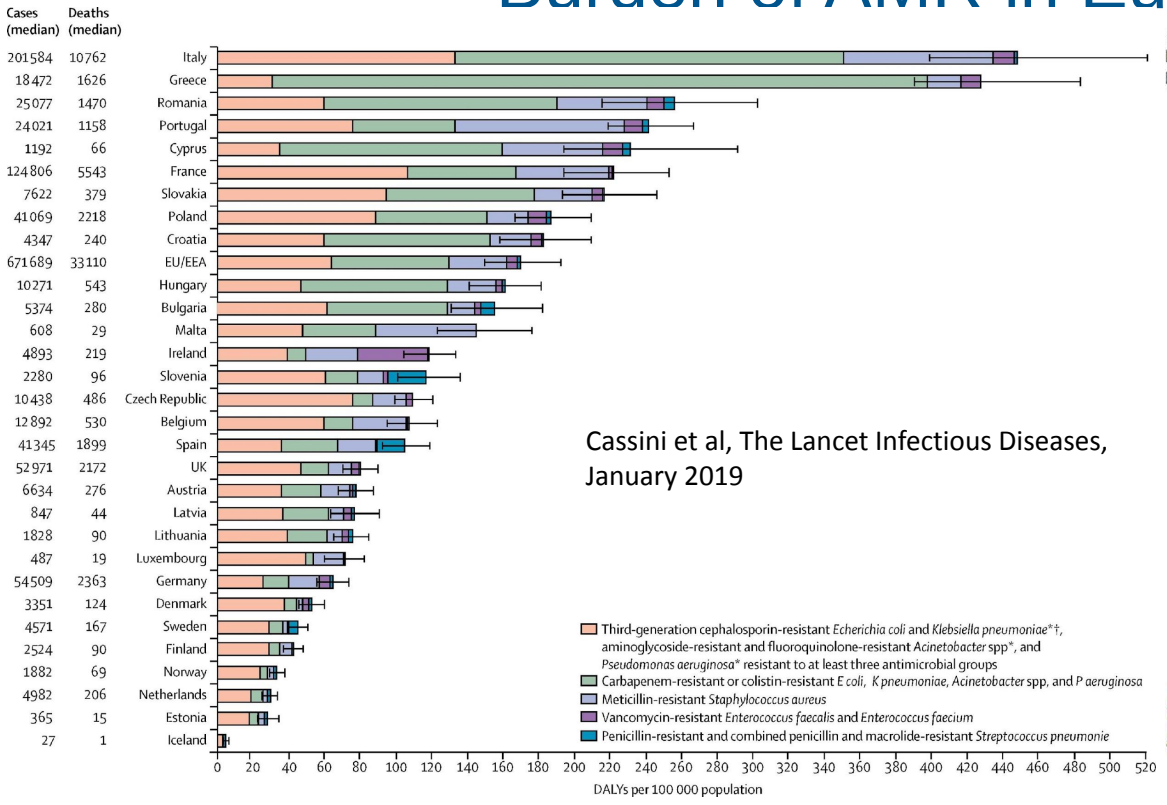
1. AMR is an increasing problem
2. Antibiotics are a limited resource
3. We need to buy us time until new classes of antibiotics become available
4. And when they do, we must have learnt a way to work so that we do not quickly loose them also
5. One important way to achieve 3 and 4 is ABS

What is ABS?

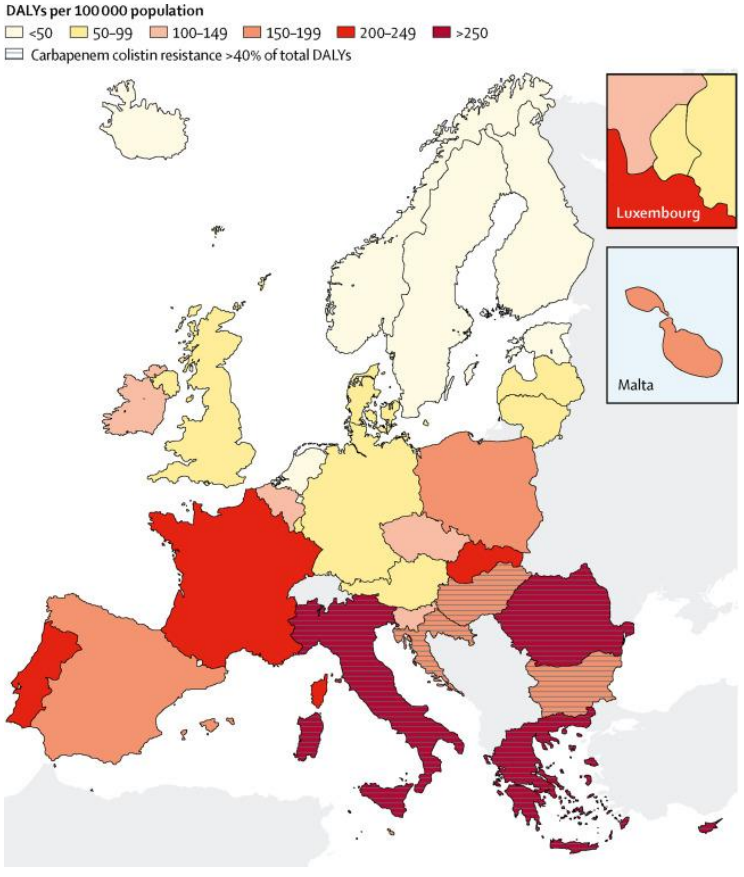
1. To give todays patients optimal therapy;
2. while causing as little ”antibiotic resistance pressure” as possible
   - AB:s only when indicated – quantity comes down
   - AB choice – consider spectrum, thus minimizing ”collateral damage”
3. We call this ”rational therapy”

Ways to get there

Burden of AMR in Europe – a recent update



Cassini et al, The Lancet Infectious Diseases, January 2019



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

There is an increasing problem with AMR – it is mostly measured in HIC:s, but burden is high also in LMIC:s

Klein EY, Tseng KK, Pant S, *et al*
Tracking global trends in the effectiveness of antibiotic therapy using the Drug Resistance Index
BMJ Global Health 2019;**4**:e001315.

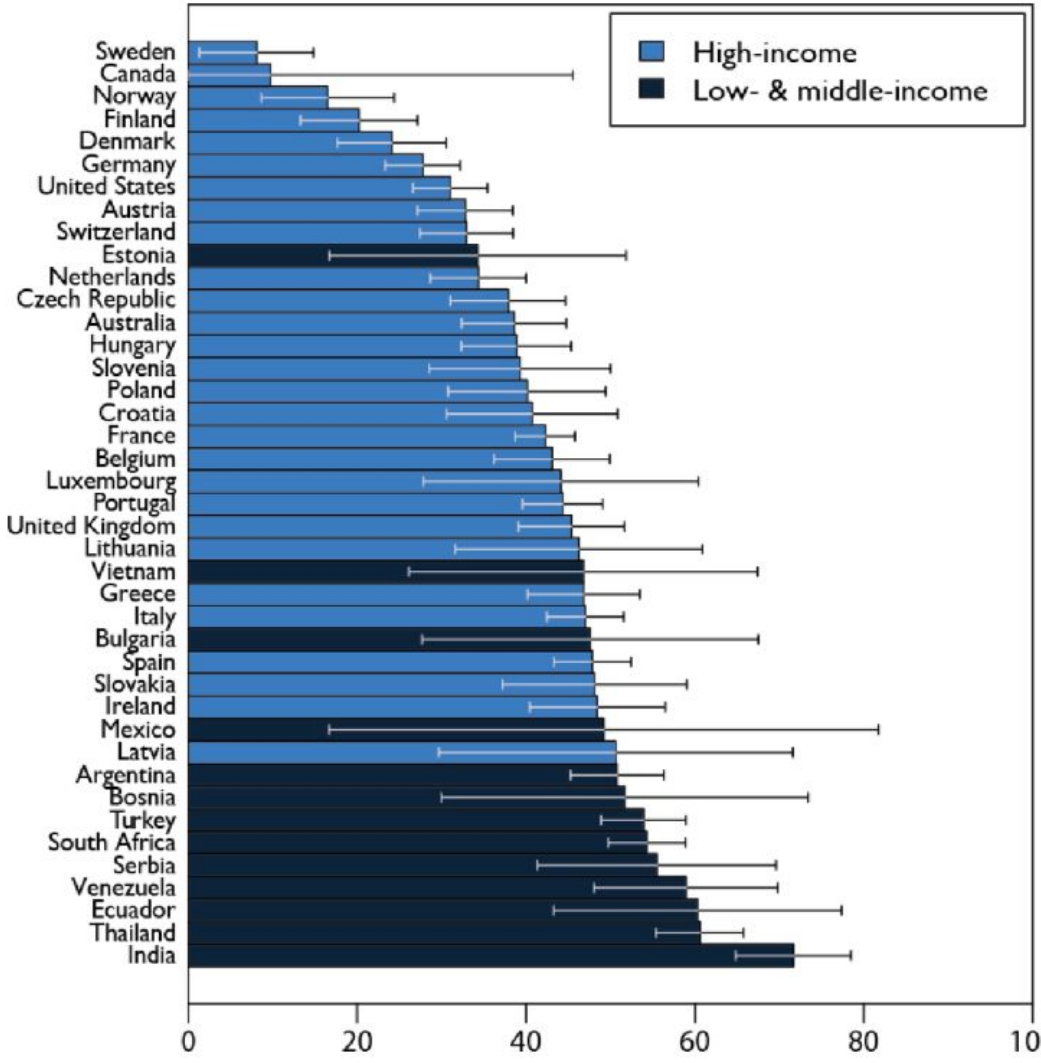


Figure 2 Drug Resistance Index (DRI) across countries. Each bar reports the DRI for countries reporting antibiotic resistance for 5 or more pathogens and for 15 or more pathogen–antibiotic combinations for at least 1 year between 2012 and 2015. Data for the most recent year are shown. All countries included had resistance data for all seven antibiotic classes except Vietnam, which did not have resistance data for glycopeptides. Country income classifications were based on World Bank analytical classifications for fiscal year 2015.

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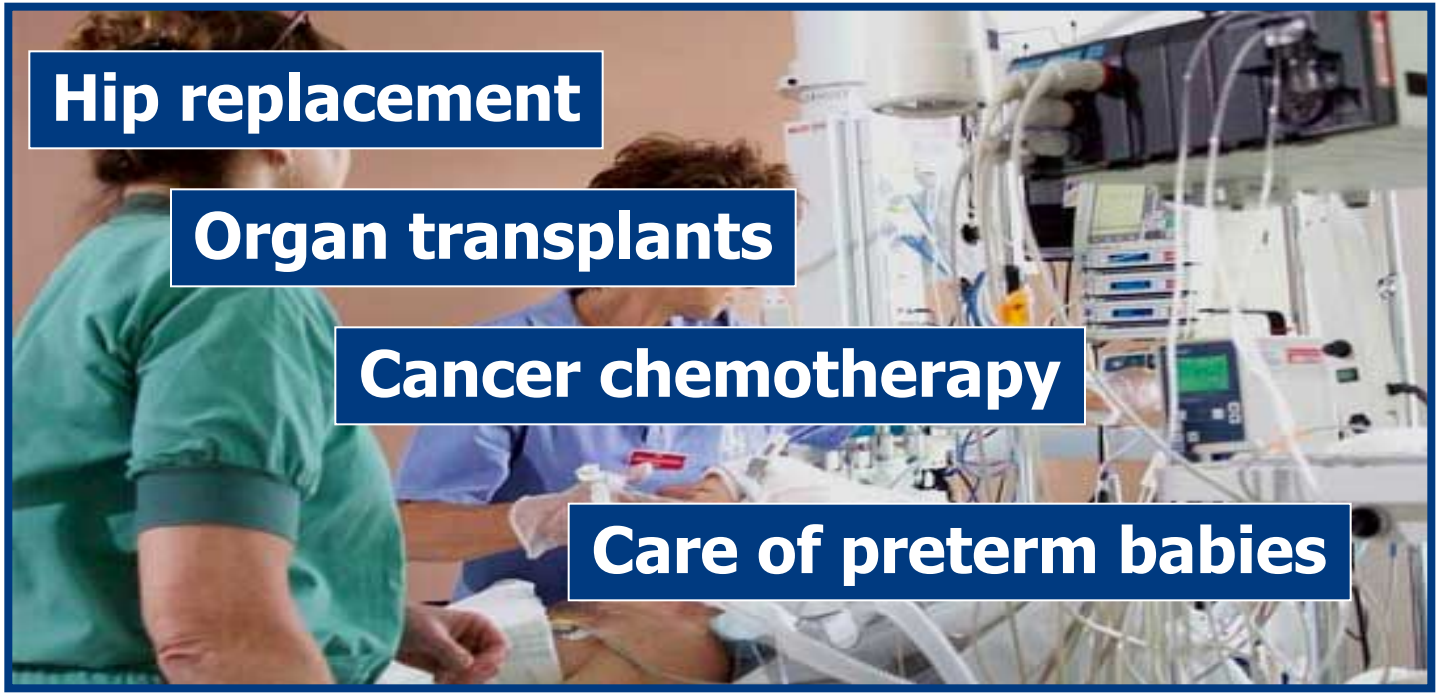
Some of the Blessings of Modern Medicine that would not be possible without Antibiotics



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MAKMAX/IACMAC 2009, Feb 18-19, Omsk

Outbreaks of colistin-resistant and colistin-susceptible KPC-producing *Klebsiella pneumoniae* in a Brazilian intensive care unit

I. Rossi Gonçalves [a,*], M.L. Ferreira [a], B.F. Araujo [a], P.A. Campos [a], S. Royer [a], D.W.F. Batistão [b], L.P. Souza [a], C.S. Brito [a], J.E. Urzedo [c], P.P. Gontijo-Filho [a], R.M. Ribas [a,c]

Findings: In all, 111 patients with CRE were identified during the surveillance period; *K. pneumoniae* was the major isolate (77.13%). The two outbreaks were identified when infection rates (KPC per 1000 patient-days) exceeded the background level. Rates of carbapenem and colistin consumption were high. Control measures (bedside alcohol gel, contact precautions, regular rectal swabs) did not curtail the outbreaks. Mortality rates were 42.9% and 44.4% for ColS-KPC- and ColR-KPC-infected patients, respectively. After the death of four infected patients with ColR-KPC, the unit was closed to new admissions. ***Conclusion:*** Our experience demonstrates the serious risks presented by KPC, and especially ColR-KPC, in Brazilian AICUs. Selective pressure from excessive antibiotic use and transmission on healthcare workers' hands were likely the major factors in transmission.

I. Rossi Gonçalves et al. / Journal of Hospital Infection 94 (2016) 322–329

The resulting outbreak of KPC-2-*Kp* with a mortality rate of more than 40% had dramatic consequences not only for the affected patients, but also for the structure, hygiene management, and costs at LUH.[5,7,8] Moreover, the phylogenetic analysis suggested ongoing transmission of the outbreak strain in surrounding hospitals. Why Western Saxony did not develop into a KPC-endemic area due to the Leipzig outbreak[25] remains unanswered, but we assume that bacterial fitness factors and delayed, but consistent implementation of overall hygiene standards played a role.

Kaiser T, Finstermeier K, Häntzsch M, Faucheux S, Kaase M, Eckmanns T, et al. Stalking a lethal superbug by whole-genome sequencing and phylogenetics: Influence on unraveling a major hospital outbreak of carbapenem-resistant Klebsiella pneumoniae. Am J Infect Control. 2018;46(1):54-9.

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Brief Report

Clinical outcome of dual colistin- and carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections: A single-center retrospective study of 75 cases in India

Amarjeet Kaur MD [a], Sumanth Gandra MD [b], Priyanka Gupta MBBS [a], Yatin Mehta MD [c], Ramanan Laxminarayan PhD [b,d], Sharmila Sengupta MD [a,*]

[a] *Department of Microbiology, Medanta, The Medicity Hospital, Gurgaon, Haryana, India*
[b] *Center for Disease Dynamics, Economics & Policy, New Delhi, India*
[c] *Department of Critical Care & Anesthesiology, Medanta, The Medicity Hospital, Gurgaon, Haryana, India*
[d] *Princeton Environmental Institute, Princeton, NJ*

Key Words:
Colistin resistance
Klebsiella
Carbapenem resistance
India

In this study, we retrospectively evaluated clinical outcomes of 75 patients with dual colistin- and carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections over a 5-year period in a single tertiary care hospital in India. We observed a high in-hospital mortality rate of 69.3%. Our findings indicate the urgent need for new antibiotics to treat these infections.

A fatal outbreak of ST11 carbapenem-resistant hypervirulent *Klebsiella pneumoniae* in a Chinese hospital: a molecular epidemiological study

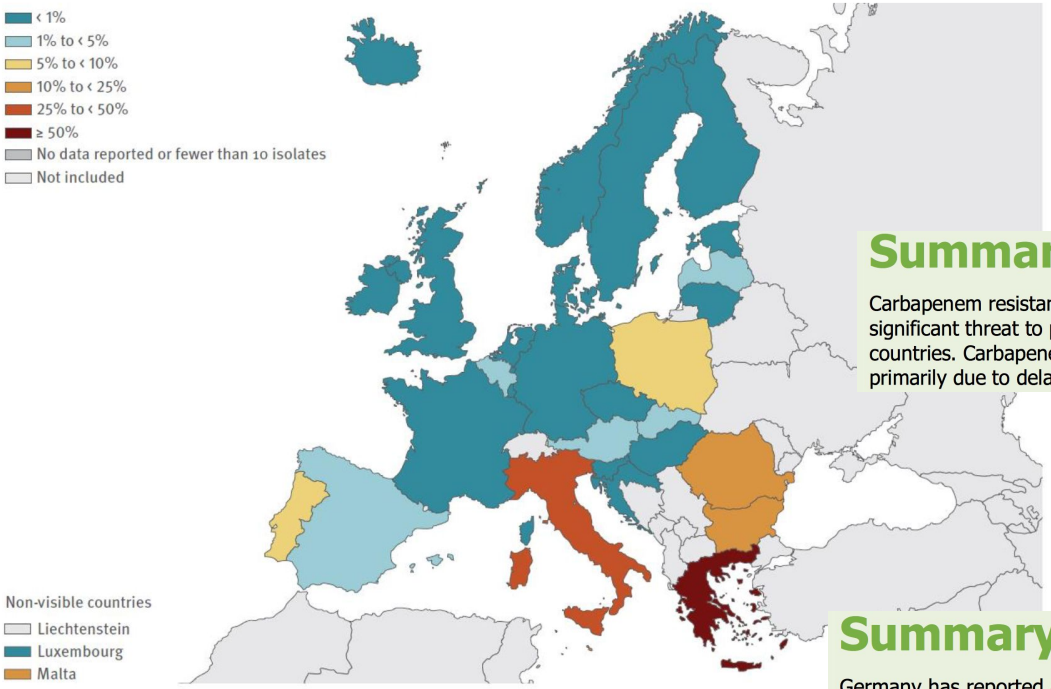
Danxia Gu, Ning Dong*, Zhiwei Zheng, Di Lin, Man Huang, Lihua Wang, Edward Wai-Chi Chan, Lingbin Shu, Jiang Yu, Rong Zhang, Sheng Chen*

Summary

Background Hypervirulent *Klebsiella pneumoniae* strains often cause life-threatening community-acquired infections in young and healthy hosts, but are usually sensitive to antibiotics. In this study, we investigated a fatal outbreak of ventilator-associated pneumonia caused by a new emerging hypervirulent *K pneumoniae* strain.

www.thelancet.com/infection **Published online August 29, 2017** http://dx.doi.org/10.1016/S1473-3099(17)30489-9

Figure 1. Percentage of invasive *K. pneumoniae* isolates with resistance to carbapenems, EU/EEA, 2017 [1]



Note: EARS-Net data are based on invasive isolates from blood and cerebros… infection or colonisation are not included.

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RAPID RISK ASSESSMENT

Carbapenem-resistant Enterobacteriaceae – second update

26 September 2019

Summary

Carbapenem resistance in Enterobacteriaceae such as *Klebsiella pneumoniae* and *Escherichia coli* poses a significant threat to patients and healthcare systems in all European Union/European Economic Area (EU/EEA) countries. Carbapenem-resistant Enterobacteriaceae (CRE) infections are associated with high mortality, primarily due to delays in administration of effective treatment and the limited availability of treatment options.

RAPID RISK ASSESSMENT

Outbreak of carbapenemase-producing (NDM-1 and OXA-48) and colistin-resistant *Klebsiella pneumoniae* ST307, north-east Germany, 2019

28 October 2019

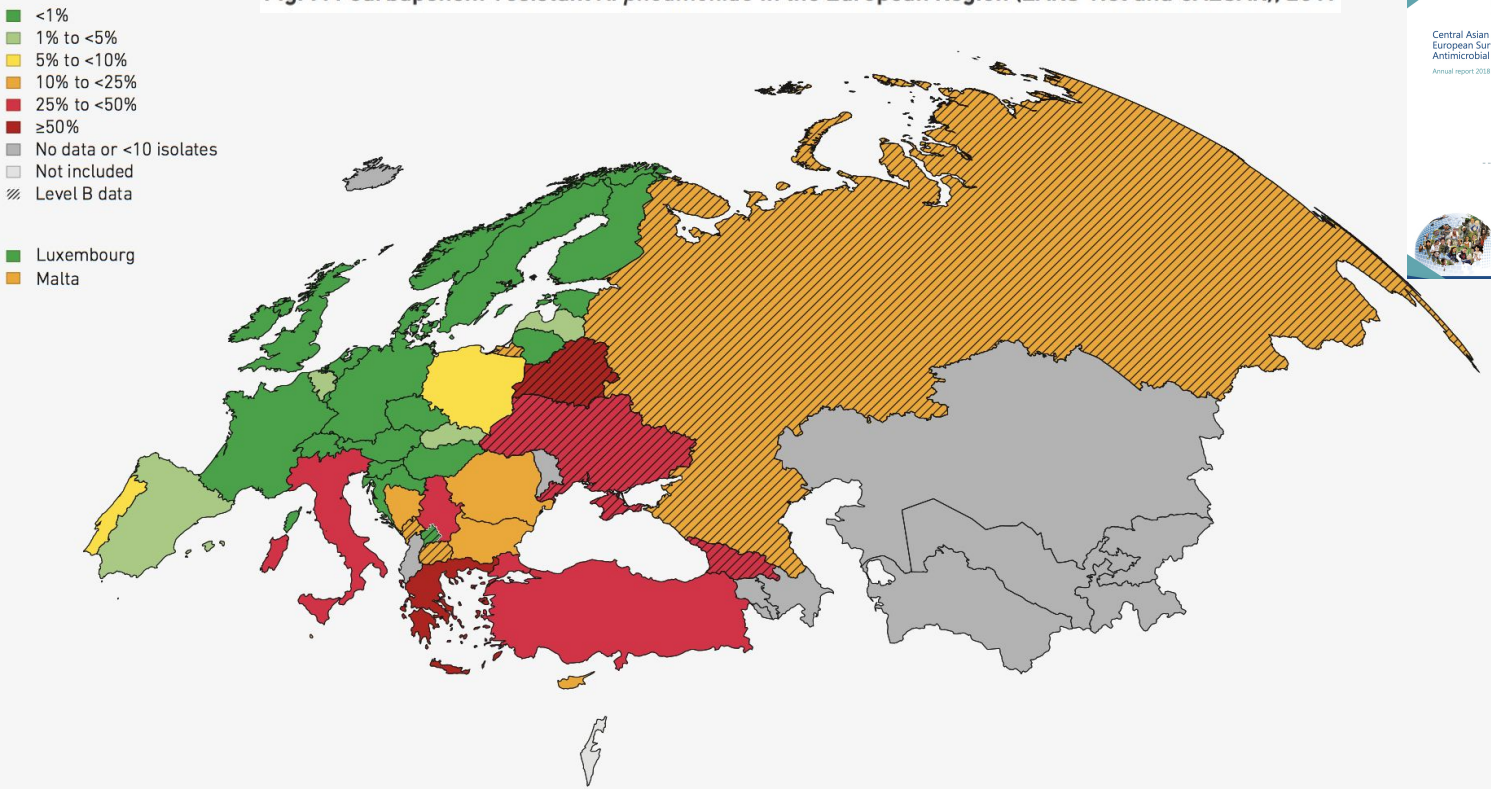
Summary

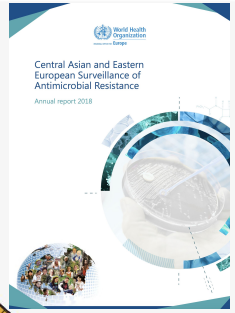
Germany has reported an outbreak of carbapenemase-producing (NDM-1 and OXA-48) and colistin-resistant *Klebsiella pneumoniae* sequence type (ST) 307. As of 21 October 2019, 17 patients in three hospitals and one rehabilitation clinic in Mecklenburg-West Pomerania in north-east Germany have been affected. Six of the 17 cases presented with clinical symptoms of infection, while 11 were identified as be carriers.

This is the first reported outbreak in Germany of *K. pneumoniae* that produce both NDM-1 and OXA-48 while also involving the emerging clone ST307. The outbreak strain is closely related to a *K. pneumoniae* ST307 isolate producing the same carbapenemases detected earlier in Finland from a patient previously hospitalised in Russia, yet there is no epidemiological link between the Finnish case and the outbreak in Germany.

K. pneumoniae ST307 is a high-risk clone expanding globally, including in the EU/EEA. The specific German outbreak strain carries virulence markers associated with increased ability to cause disease. Genetic

Fig. 7.4 Carbapenem-resistant *K. pneumoniae* in the European Region (EARS-Net and CAESAR), 2017





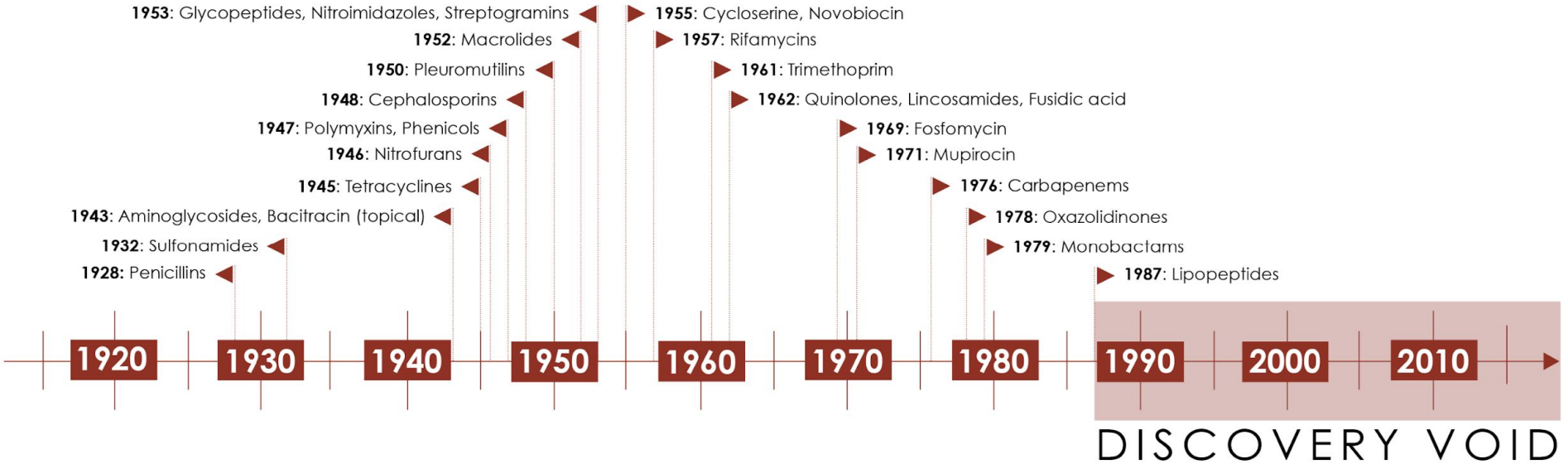
Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country or area. See section 4.2 for more information about levels of evidence, which are only provided for CAESAR countries and areas.

EARS–Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.
CAESAR countries and areas: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, the former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo (in accordance with United Nations Security Council resolution 1244 (1999)).

Data sources: 2017 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2018) and 2017 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2018).

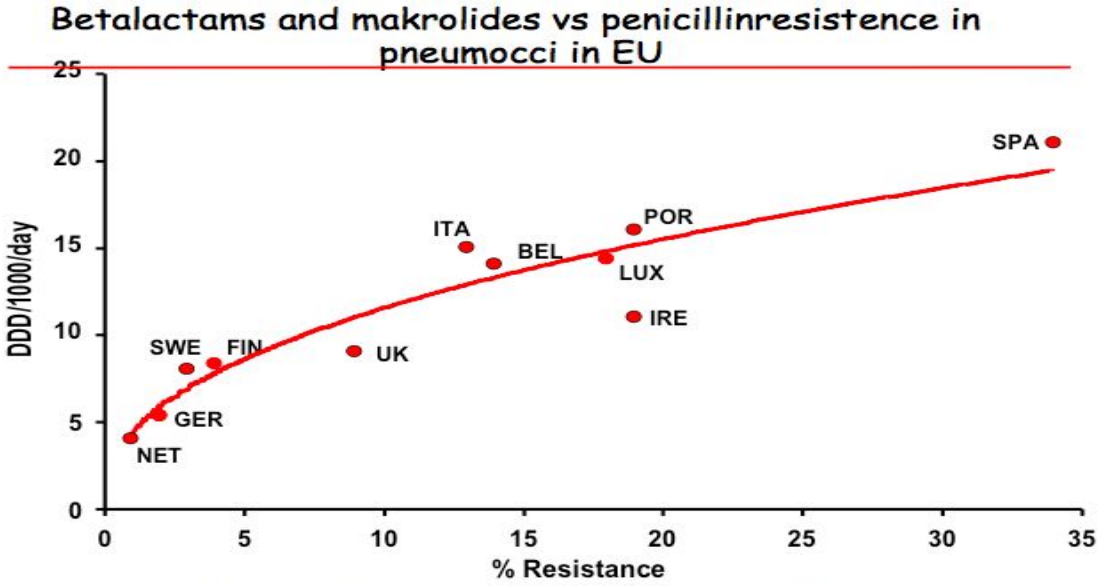
Fig. 7.4 Carbapenem-resistant *K. pneumoniae* in the European Region (EARS-Net and CAESAR), 2017

2. Antibiotics are a limited resource



3. We need to buy us time until new classes of antibiotics become available

Antibiotic consumption drives antibiotic resistance



Bronzwaer SL, Cars O, Buchholz U, *et al.* A European study on the relationship between antimicrobial use and antimicrobial resistance. *Emerging Infectious Diseases* 2002; **8**:278–282.

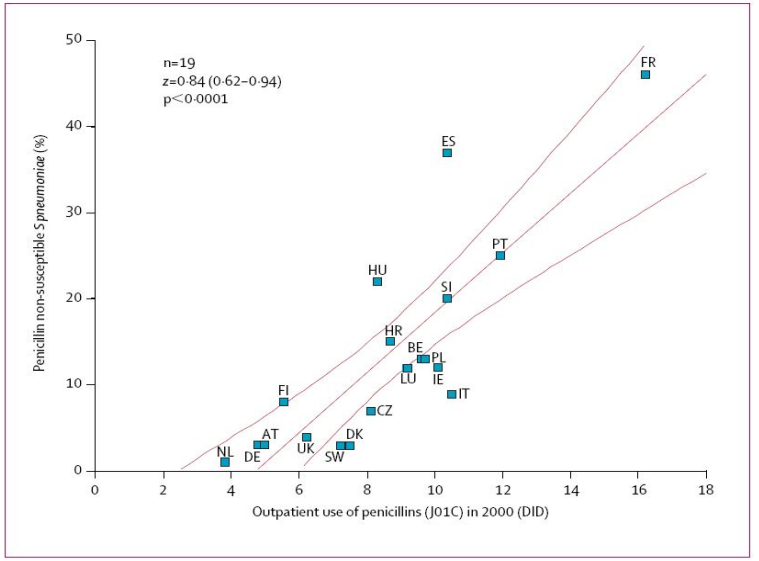


Figure 6: **Correlation between penicillin use and prevalence of penicillin non-susceptible *S pneumoniae***
AT, Austria; BE, Belgium; HR, Croatia; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; HU, Hungary; IE, Ireland; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland; PT, Portugal; SI, Slovenia; ES, Spain; UK, England only.

H. Goossens ***Lancet*** **2005; 365: 579–87**

Antibiotic consumption drives antibiotic resistance, 2; at all levels: patient, community, country, regional and global

BMJ

Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis

Céire Costelloe, research associate,[1] Chris Metcalfe, senior lecturer in medical statistics,[2] Andrew Lovering, consultant clinical scientist,[3] David Mant, professor of general practice,[4] Alastair D Hay, consultant senior lecturer in primary health care[1]

…

Conclusions: Individuals prescribed an antibiotic in primary care for a respiratory or urinary infection develop bacterial resistance to that antibiotic. The effect is greatest in the month immediately after treatment but may persist for up to 12 months. This effect not only increases the population carriage of organisms resistant to first line antibiotics, but also creates the conditions for increased use of second line antibiotics in the community.

BMJ 2010;340:c2096
doi:10.1136/bmj.c2096

Bell *et al. BMC Infectious Diseases* 2014, **14**:13
http://www.biomedcentral.com/1471-2334/14/13

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance

Brian G Bell[1*], Francois Schellevis[2,3], Ellen Stobberingh[4], Herman Goossens[5] and Mike Pringle[1]

Conclusions: Using a large set of studies we found that antibiotic consumption is associated with the development of antibiotic resistance. A subsequent meta-analysis, with a subsample of the studies, generated several significant predictors. Countries in southern Europe produced a stronger link between consumption and resistance than other regions so efforts at reducing antibiotic consumption may need to be strengthened in this area. Increased consumption of antibiotics may not only produce greater resistance at the individual patient level but may also produce greater resistance at the community, country, and regional levels, which can harm individual patients.

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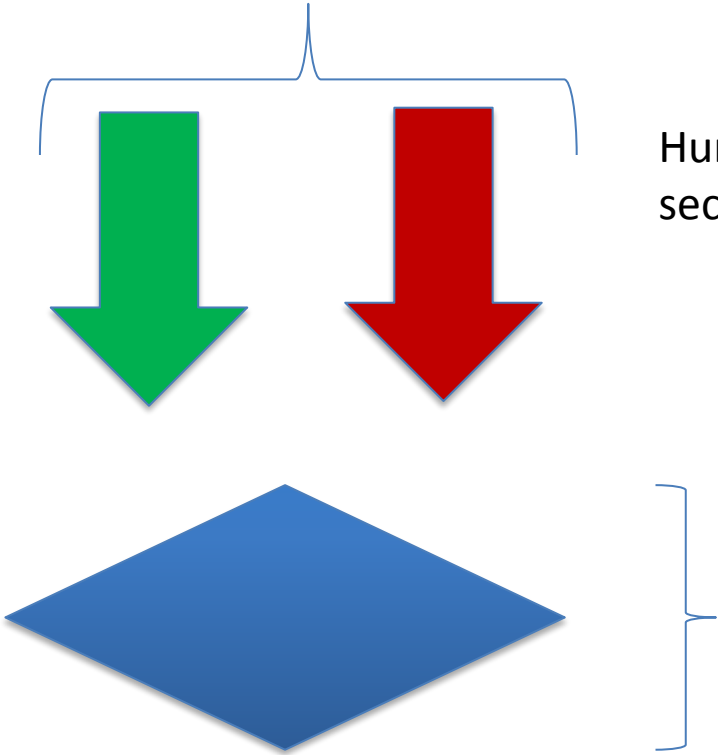
Where to work with ABS?

- Infectious disease clinics – highly qualified, but small part of all antibiotic use
- To achieve some impact on the resistance selection pressure, influence OTHER major clinics: general surgery, general internal medicine
- AND – most antibiotics used are used by patients OUTSIDE hospitals, much prescribed at level of Primary Health Care
- Raise awareness among public, especially if non-prescription use is common; then also work towards a prescription-only policy

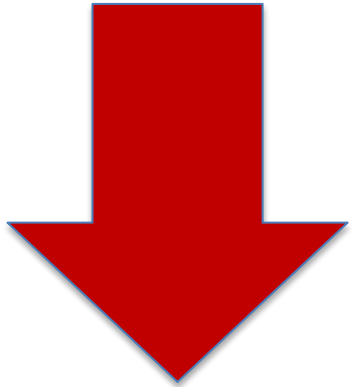
Total antibiotic pressure

Agri/Vet side

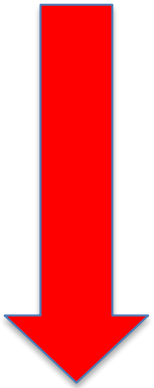


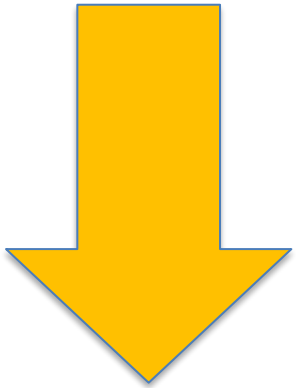
Human health sector

Country X



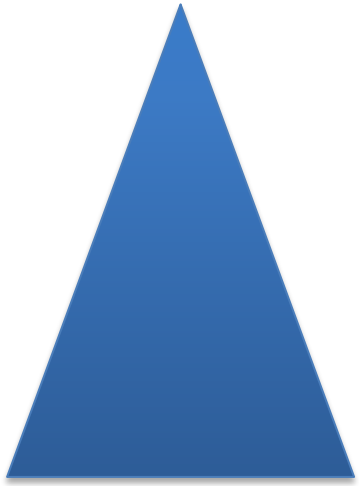
Hospital/in-patient use





Community use

The paradox of seriousness of infection type versus amount of antibiotic use it causes, and thus ”resistance drive”



Seriousness of the infection for the patient

DIAGNOSIS:

Upper Resp Tract Infection - URTI

Lower UTI

Pneumonia

Pyelonephritis

Sepsis

Bacterial meningitis

Antibiotics spent on the diagnosis in society as a whole

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The aim is effective treatment for the present patient with his/her present illness – with no or minimized collateral harm for the next patient; AND for the present patient on next occasion

Reduced amount in total

- No antibiotics where damage outweighs benefit
- No antibiotics for viral infections
- No antibiotics for many self-limited bacterial infections

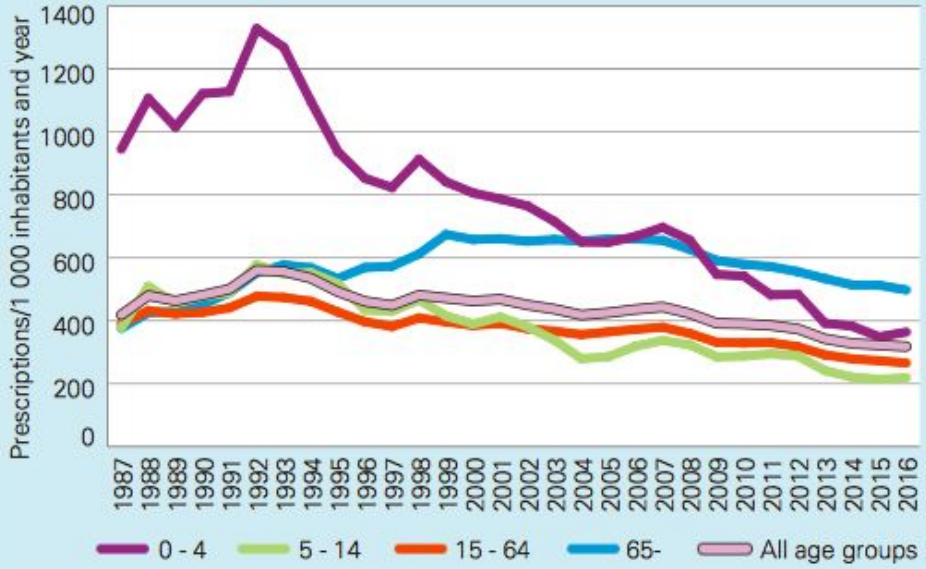
Spectrum – narrow but effective

- Optimally: know the causing agent and resistance patterns for each patient – not possible, so:
- *Empiric treatment* – treat according to *clinical treatment guidelines,* based on:
  - Knowledge of common infections; what are the important causing bacteria?
  - Knowledge of local resistance pattern among important pathogens
  - Knowledge on ”ABR drive” of the various choices

Total use – much to gain from stopping treatment of all **viral** respiratory infections

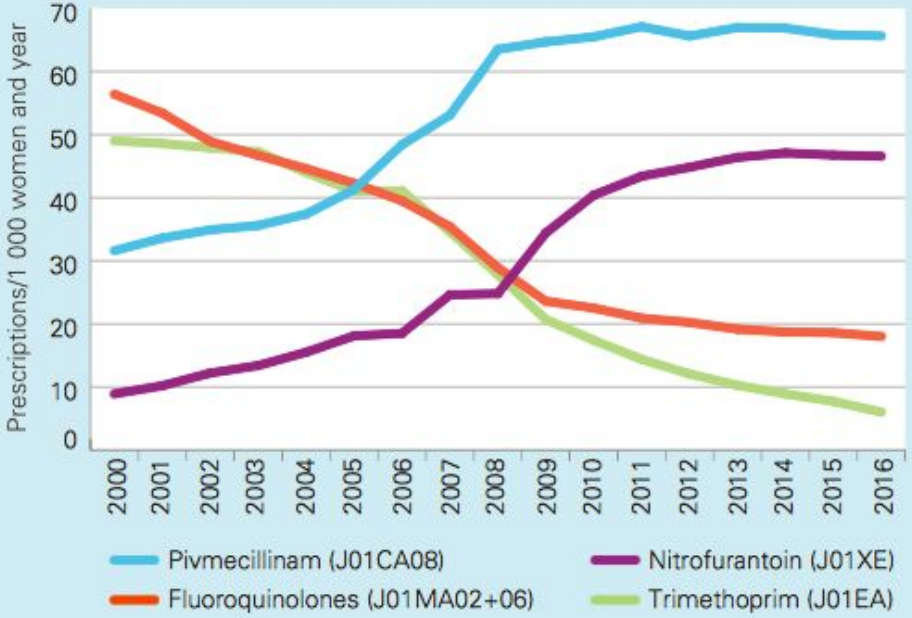
From wide to narrow spectrum – much to gain from switching from quinolones in lower UTI:s/uncomplicated cystitis (and to never start with quinolones for respiratory tract infections, at least outside hospitals..)

FIGURE 1.3. The sales of antibiotics for systemic use in out-patient care (sales on prescriptions) 1987- 2016, prescriptions/1 000 inhabitants and year, both sexes, different age groups.



Swedres-Svarm 2016. Consumption of antibiotics and occurrence of resistance in Sweden. Solna/Uppsala ISSN1650-6332

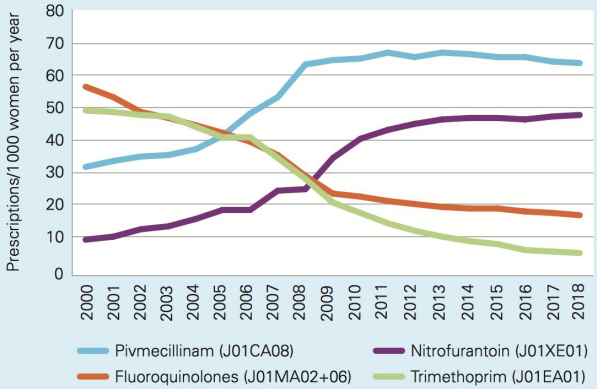
FIGURE 1.9 Sales of antibiotics commonly used to treat lower urinary tract infections in women (sales on prescriptions), 18-79 years, 2000-2016, prescriptions/1 000 women and year.



Antimicrobial consumption/pressure drives antimicrobial resistance; the SPECTRUM aspect

The TOTAL USE is easier to grasp and measure; but SPECTRUM is at least equally important

Figure 1.6. Sales of antibiotics commonly used to treat urinary tract infections in women, outpatient care, humans, 2000-2018, per year, prescriptions/1 000 women per year.



ORIGINAL ARTICLE BACTERIOLOGY

Collateral damage from oral ciprofloxacin versus nitrofurantoin in outpatients with urinary tract infections: a culture-free analysis of gut microbiota

Clin Microbiol Infect 2015; 21: 344.e1–344.e11

http://dx.doi.org/10.1016/j.cmi.2014.11.016

WHO EML AWaRe classification

- ACCESS – first and second choice antibiotics for the empiric treatment of most common infectious syndromes;
- WATCH – antibiotics with higher resistance potential whose use as first and second choice treatment should be limited to a small number of syndromes or patient groups; and
- RESERVE – antibiotics to be used mainly as 'last resort' treatment options.

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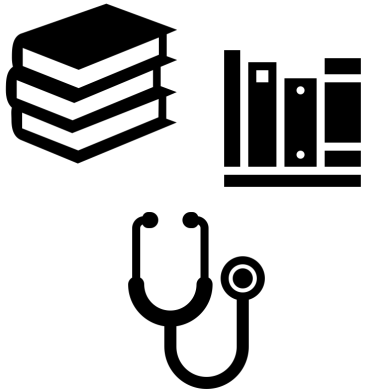
Rational antibiotic use

1. **The right antibiotic** (for the disease, bacterium, patient condition..)
2. **At the right time** (not too late – pneumonia..)
3. **In the right dose** (patient characteristics – weight, renal function, interactions..)
4. **For the right duration** (for the disease to be cured..)



Obviously, the decisions on what is rational treatment should be taken on purely medical grounds, independent from pharma industry or other economic interests.

Site of Infection		Skin and soft tissue			Respiratory	Gastrointestinal / Urinary							Gut anaerobes
"Common pathogens"		MRSA	MSSA	*Beta-hemolytic streptococci*	*Streptococcus pneumoniae*	*Enterococcus faecalis*	*Enterococcus faecium*	*E. coli*	*Klebsiella*	Resistant Gram-negatives: *Pseudomonas*	Resistant Gram-negatives: ESCAPPM	Resistant Gram-negatives: ESBLs	
Penicillins	Penicillin			+									
	Amoxicillin / Ampicillin			+	+	+							
	Cloxacillin		+	+	+/-								
Cephalosporins	Cephalexin / Cefazolin		+	+				+/-	+/-				
	Ceftriaxone / Cefotaxime			+	+			+	+				
	Ceftazidime							+	+	+			
Beta-lactam / beta-lactamase inhibitors	Co-amoxiclav		+	+	+	+		+	+				+
	Piperacillin-tazobactam		+	+	+	+		+	+	+			+
Carbapenems	Ertapenem		+	+	+			+	+		+	+	+
	Meropenem / Imipenem		+	+	+			+	+	+	+	+	+
Glycopeptides	Vancomycin	+	+	+	+	+	+						
Miscellaneous	Doxycycline	+	+		+/-			+/-	+/-		+/-	+/-	
	Trimethoprim-sulfamethoxazole	+	+					+/-	+/-		+/-	+/-	
	Moxifloxacin		+	+	+	+		+	+				+/-
	Ciprofloxacin	+/-	+/-					+/-	+/-	+/-	+/-	+/-	
	Aminoglycosides							+	+	+	+	+/-	
	Daptomycin / Linezolid	+	+	+	+	+	+						
	Clindamycin	+/-	+/-	+/-									+/-
	Polymyxin / Colistin*							+	+	+	+/-	+	
	Metronidazole												+

* Serratia, Proteus, Providencia, Morganella, B. cepacia are intrinsically resistant to polymyxin/colistin.

Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries. A practical toolkit. Geneva: World Health Organization; 2019.

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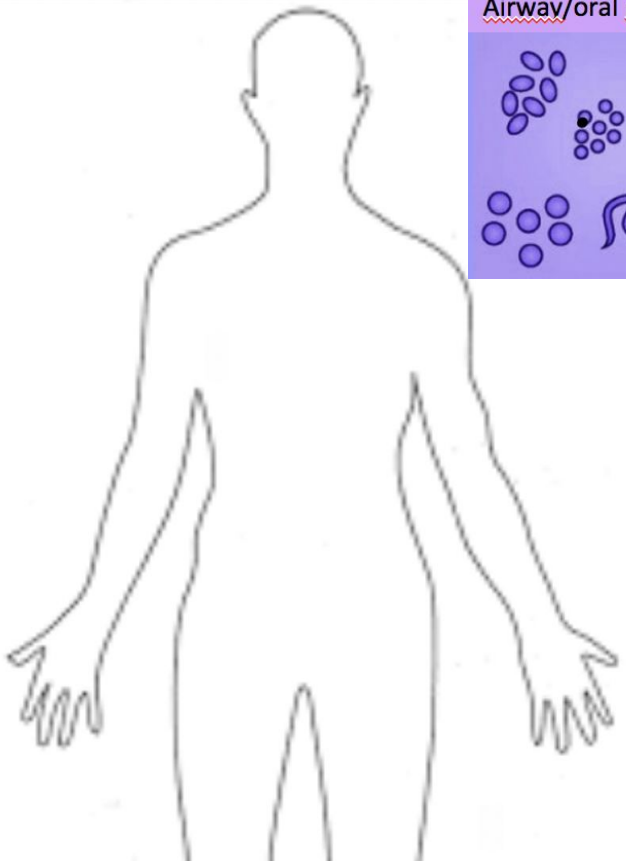

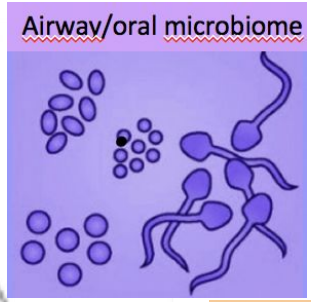

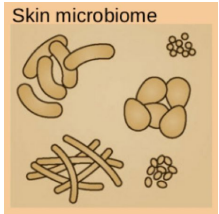

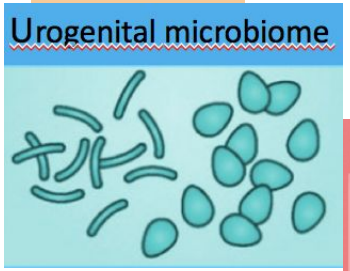

Tonsillopharyngitis: Strep A - 100 % sensitive to penicillin. We use pc V. Amoxicillin works as well

AOM, sinusitis, pneumonia: Pneumococci, to high degree S to penicillin. We use pc V. Amoxicillin works as well.

Erysipelas: Strep A. See tonsillitis.

Other skin infections, wound infections: Staph aureus. We use cloxacillin/flucloxacillin.

E. coli, Klebsiella pn:
For lower UTI/cystitis, we use mecillinam or nitrofurantoin
For acute pyelonephritis we use ciprofloxacin

Of all the first choices above, only ciprofloxacin/f-quinolones have a significant impact on the gut flora. Amoxicillin some, but limited.

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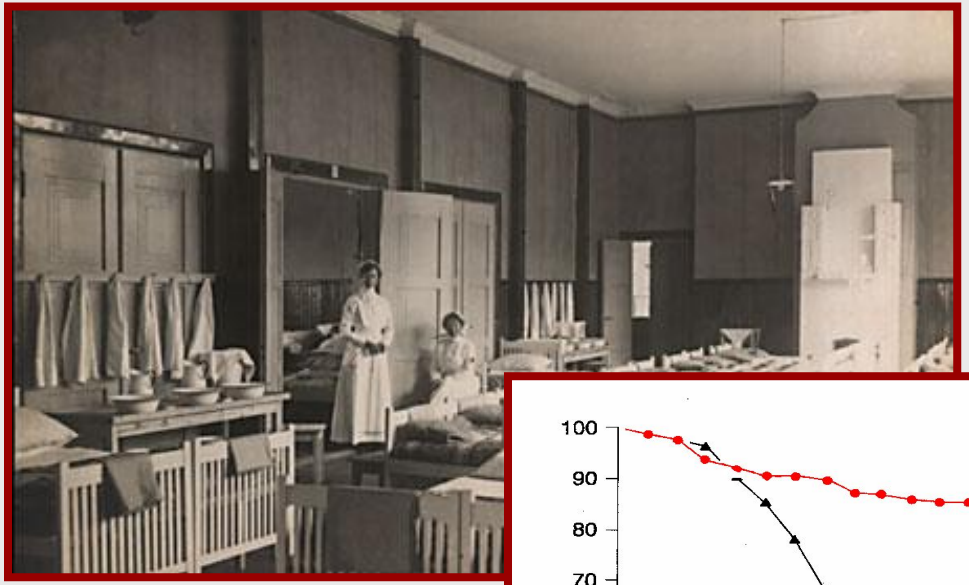


Patients with pneumonia and bacteria in blood

Penicillin increased the chance of survival from 10% to 90%

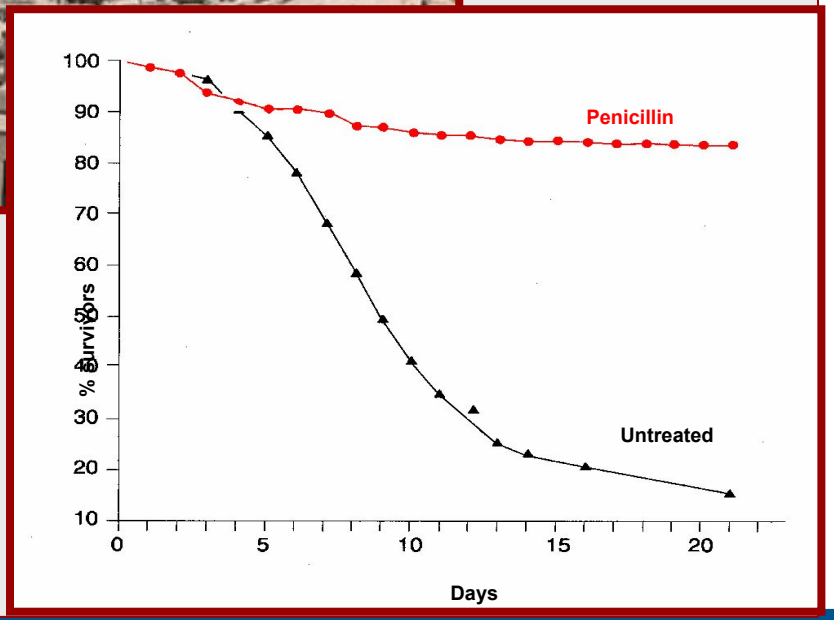


Table 5.27 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in the Russian Federation, 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[a]	18	28*
Cefotaxime/ceftriaxone (R)[b]	18	0*
Cefotaxime/ceftriaxone (I+R)[b]	18	22*
Levofloxacin/moxifloxacin (R)[c]	18	0*
Erythromycin/clarithromycin/azithromycin (R)[d]	18	22*
Erythromycin/clarithromycin/azithromycin (I+R)[d]	18	22*
Multidrug resistance (I+R)[e]	18	22*

* A small number of isolates were tested (N < 30), and the percentage resistance should be interpreted with caution.
a Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.
b Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.
c Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.
d Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.
e Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Svebar
Svensk bevakning av antibiotikaresistens

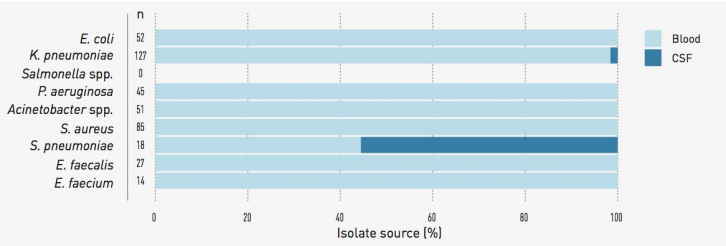
Tabell 1: Urval av resistensbestämningsdata

Analys	Blododling Aerob Anaerob
Provmaterial	Blododlingsprov
Lab	10 av 26 i Sverige
Befolkningstäckning	54,6 %
Start.datum	2013-01-01
Slutdatum	2017-12-31
Antal positiva odlingar	160119
Antal negativa odlingar	1054568
Antal odlingar	1214687

Swedish resistance surveillance build on c:a 240 000 blood cultures/year

https://www.folkhalsomyndigheten.se/contentassets/e76b47c98f1a44058f22cfd4795a2c45/blod_ecoli_2017_nat.pdf

Swedish resistance surveillance in pneumococci c:a 1300 invasive isolates per year.



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MRSA in the European Region (EARS-Net and CAESAR), 2017

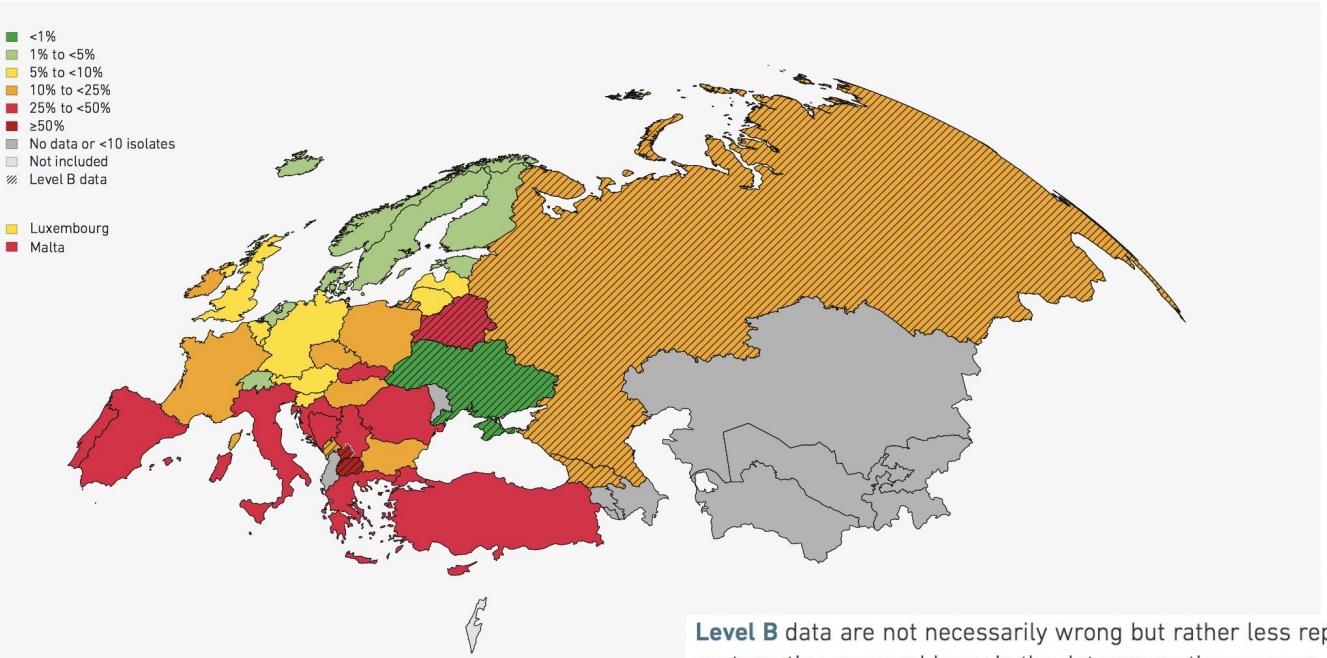


Fig. 7.6 MRSA in the European Region (EARS-Net and CAESAR), 2017

Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or are attain a more valid assessment of the magnitude and trends of AMR in the country or area. See section 4.2 for more

EARS–Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.
CAESAR countries and areas: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Tajikistan, the former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo (in accordance with United Nations Security Council resolution 1244 (1999)).

Data sources: 2017 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2018) and 2017 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2018).

Level B data are not necessarily wrong but rather less representative for the target population due to systematic errors or biases in the data generation process. Nevertheless, presenting level B data allows for the critical evaluation of sources of error and bias, which should be seen as a starting point to further improve and develop the surveillance system. The magnitude of resistance presented is biased and thus precludes the use of data for guiding empirical antibiotic treatment choices.

Table 5.26 Percentages of resistance for *S. aureus* among blood and CSF isolates in the Russian Federation, 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[a]	85	16
Ciprofloxacin/levofloxacin/ofloxacin (R)[b]	85	22
Vancomycin (R)	85	0
Rifampicin (R)	85	2
Linezolid (R)	85	0

[a] MRSA is calculated as resistance to cefoxitin or, if not available, oxacillin.

[b] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

ACCESS GROUP

This group includes antibiotics and antibiotic classes that have activity against a wide range of commonly encountered susceptible pathogens while showing lower resistance potential than antibiotics in Watch and Reserve groups. Access antibiotics should be widely available, affordable and quality-assured to improve access and promote appropriate use.

Selected Access group antibiotics (shown here) are included on the WHO EML as essential first-choice or second-choice empirical treatment options for specific infectious syndromes.

- Amikacin
- Amoxicillin
- Amoxicillin + clavulanic acid
- Ampicillin
- Benzathine benzylpenicillin
- Benzylpenicillin
- Cefalexin
- Cefazolin
- Chloramphenicol
- Clindamycin
- Cloxacillin
- Doxycycline
- Gentamicin
- Metronidazole
- Nitrofurantoin
- Phenoxymethyl-penicillin
- Procaine benzylpenicillin
- Spectinomycin
- Sulfamethoxazole + trimethoprim

WATCH GROUP

This group includes antibiotics and antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials (CIA) for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. Watch group antibiotics should be prioritized as key targets of national and local stewardship programmes and monitoring.

Selected Watch group antibiotics (shown here) are included on the WHO EML as essential first-choice or second-choice empirical treatment options for a limited number of specific infectious syndromes.

- Azithromycin
- Cefixime
- Cefotaxime
- Ceftazidime
- Ceftriaxone
- Cefuroxime
- Ciprofloxacin
- Clarithromycin
- Meropenem
- Piperacillin + tazobactam
- Vancomycin

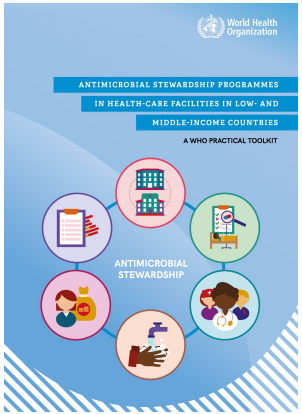
RESERVE GROUP

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi drug-resistant organisms, and treated as "last-resort" options. Their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. They could be protected and prioritized as key targets of national and international stewardship programmes, involving monitoring and utilization reporting, to preserve their effectiveness.

Selected Reserve group antibiotics (shown here) are included on the WHO EML when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List, notably carbapenem-resistant Enterobacteriaceae.

- Ceftazidime + avibactam
- Colistin
- Fosfomycin (intravenous)
- Linezolid
- Meropenem + vaborbactam
- Plazomicin
- Polymyxin B

- review/update national EMLs with AWaRe groups;
- review/update Sustainable Development Goals with AWaRe groups;
- align empirical antibiotic treatment guidelines with ACCESS antibiotics;
- target WATCH and RESERVE groups for AMS;
- review antimicrobial consumption and use surveillance data with AWaRe; and/or
- include in health professional curricula.



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Clinical Treatment Guidelines/Treatment Protocols in infections

Generation I

- Focus on infections dangerous to **society**
- Examples: shigella, typhoid, salmonella, meningococcal infection
- Based on already proven microbiological etiology or”nosologic form”
- Therefore covering few pts..

Generation II

- Focus on infections dangerous to **patient**
- Syndrome based rather than microbiological
- Evidence based
- Considering the normal etiology for a given syndrome – e g purulent meningitis, or bacterial pneumonia
- Covering more patients..

Generation II/AMR

- Focus on infections responsible for largest **flows of antibiotics**
- Syndrome based (e g URTI, tonsillitis, sinusitis, otitis media, pneumonia, lower UTI)
- Clarifying which antibiotic to use for which **syndrome**
- Also clarifying when **NOT** to treat with antibiotics

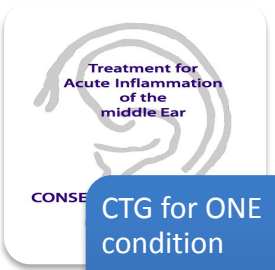
The process of developing Clinical Treatment Guidelines into a format useful in the clinical PHC setting; simplified example of Sweden

Challenge:
Finding the balance between depth and width; keeping in mind that a GP/PHC physician cannot allocate the same amount of time to for example an otitis media as a hospital specialist; and has to cover virtually ALL specialties..

- Balance of experts in ”Guideline Boards”
- Balanced, condensed versions of the full guidelines

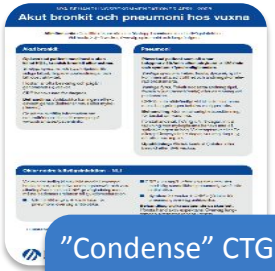
Development of CTG

- National Board with high credibility – hospital and PHC specialists for the topic in question
- Internat. and local evidence and literature



CTG for ONE condition

- Evidence based
- Adapted to local situation



”Condense” CTG

- Usable format
- Balance for PHC; brief but true*
- Short booklet, card, or algorithm
- *Observe medicolegal aspects

Aggregate condensed CTG:s

- Usable format
- Balance for PHC
- Short booklet often with algorithms
- Especially useful if other heatlch care personnel categories are to use it

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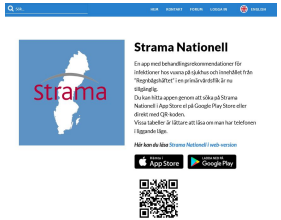
Challenge: Local implementation!

- Getting the CTG:s in place is not enough
- Nothing changes until antibiotic use is changed on the ground
- Distribute to each remote corner
- Adaptability to local situation – ”culture eats strategy”..

Info in ”App” format

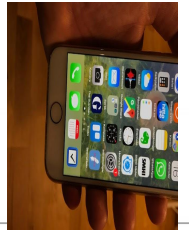


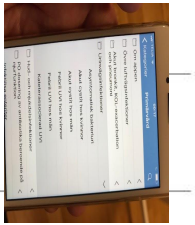
Strama working lunch meeting:

- Discuss PRESCRIPTION DATA; for PHC Centre, for County/Region, for nation
- Distribute individual data; when possible diagnose related
- Go through new guidelines
- Discuss cases

Expedited antibiotic prescriptions per 1000 inhab. and year for various age groups in Sweden 1987 – 2018

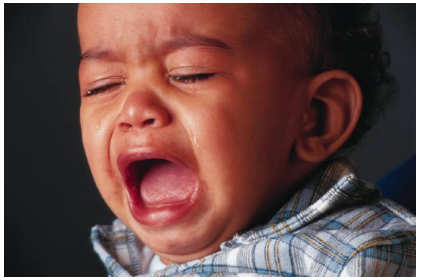
Data source: Apoteket AB and the Swedish eHealth Authority

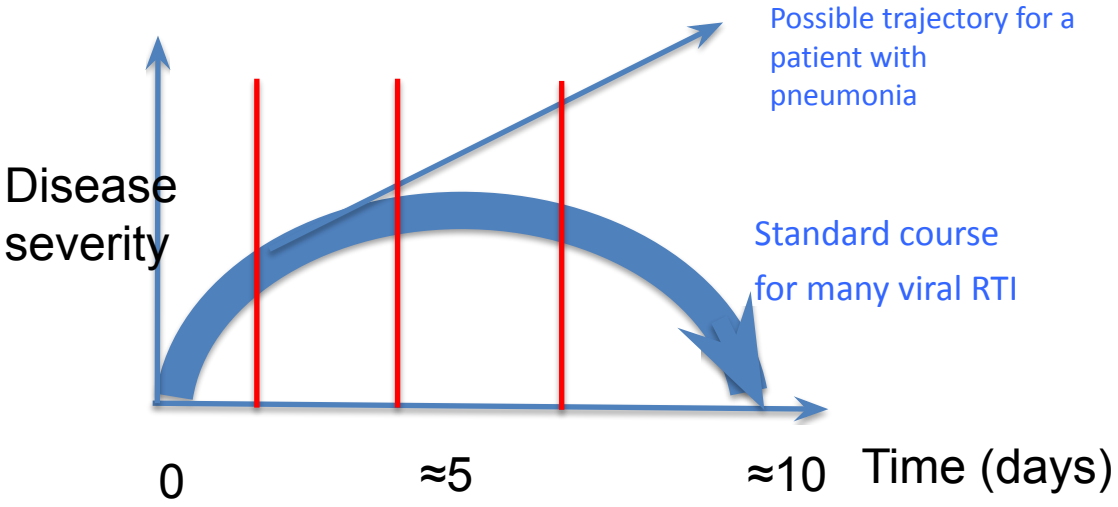




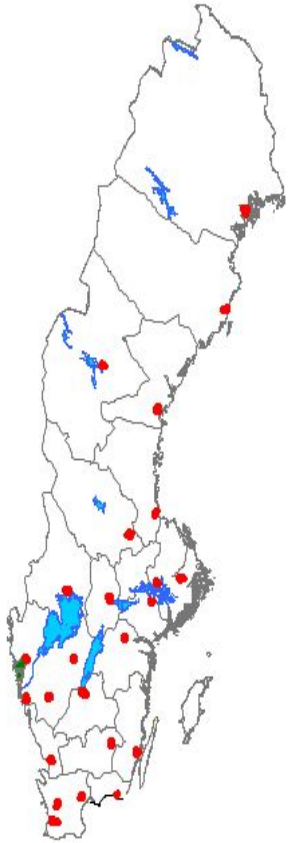
Slide courtesy of dr Christer Norman, PHC "Salem", Sthlm, and PHA

To diagnose and treat a pediatric pneumonia (among many febrile/viral/flu patients) in time takes training, skill, and a very accessible Primary Health Care





1. Patient comes in late – easy
2. Patient comes in early – impossible; must be reassured, and given chance to return – if to withhold treatment more than a parent would
3. The more skilled the doctor, the better the chance



Strama

Lessons learnt during 20 years of the Swedish strategic programme against antibiotic resistance

Sigvard Mölstad,[a] Sonja Löfmark,[b] Karin Carlin,[b] Mats Erntell,[c] Olov Aspevall,[b] Lars Blad,[d] Håkan Hanberger,[e] Katarina Hedin,[f] Jenny Hellman,[b] Christer Norman,[b] Gunilla Skoog,[b] Cecilia Stålsby-Lundborg,[g] Karin Tegmark Wisell,[h] Christina Åhrén[i] & Otto Cars[b]

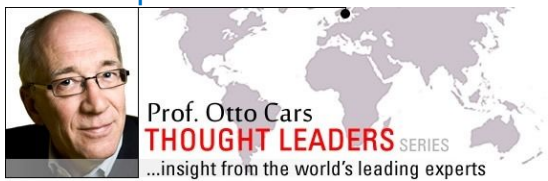
Bull World Health Organ 2017;95:764–773

- **Strama-groups were formed, 1995 in every county (21 counties)**
- **The County Medical Officers for Communicable Diseases Control took a leading role in these groups which include specialists from different medical fields**
- **A main objective is to evaluate the use of antibiotics and antibacterial resistance in the region and to improve prescribing patterns**

The local (regional) Strama groups (typically):

- ✔ County medical officer
- ✔ Pharmacist
- ✔ Microbiologist
- ✔ General practitioner
- ✔ Infectious diseases specialist
- ✔ Infection control
- ✔ ENT, paediatrician, geriatrician, dentist…

”Champions”..



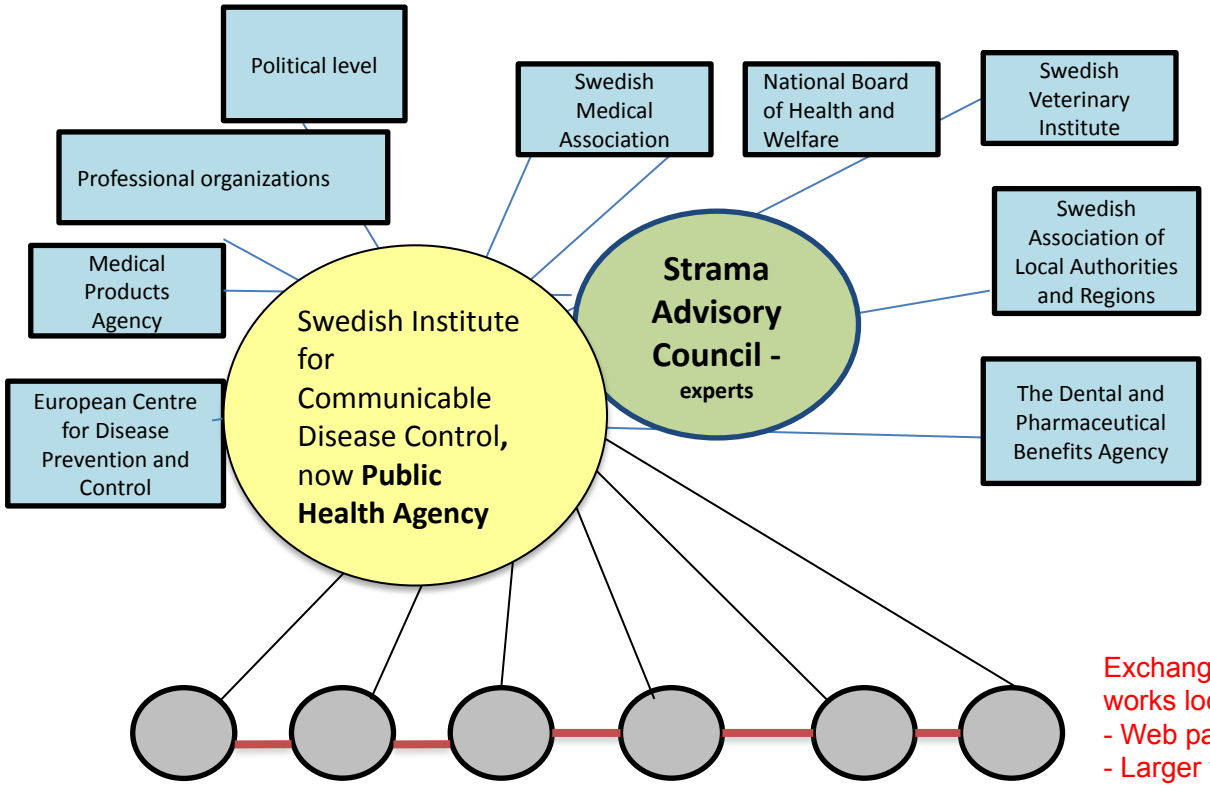
Sigvard Mölstad, Professor and PHC clinician

Gunnar Kahlmeter, Professor Clin. Microbiology

Strama

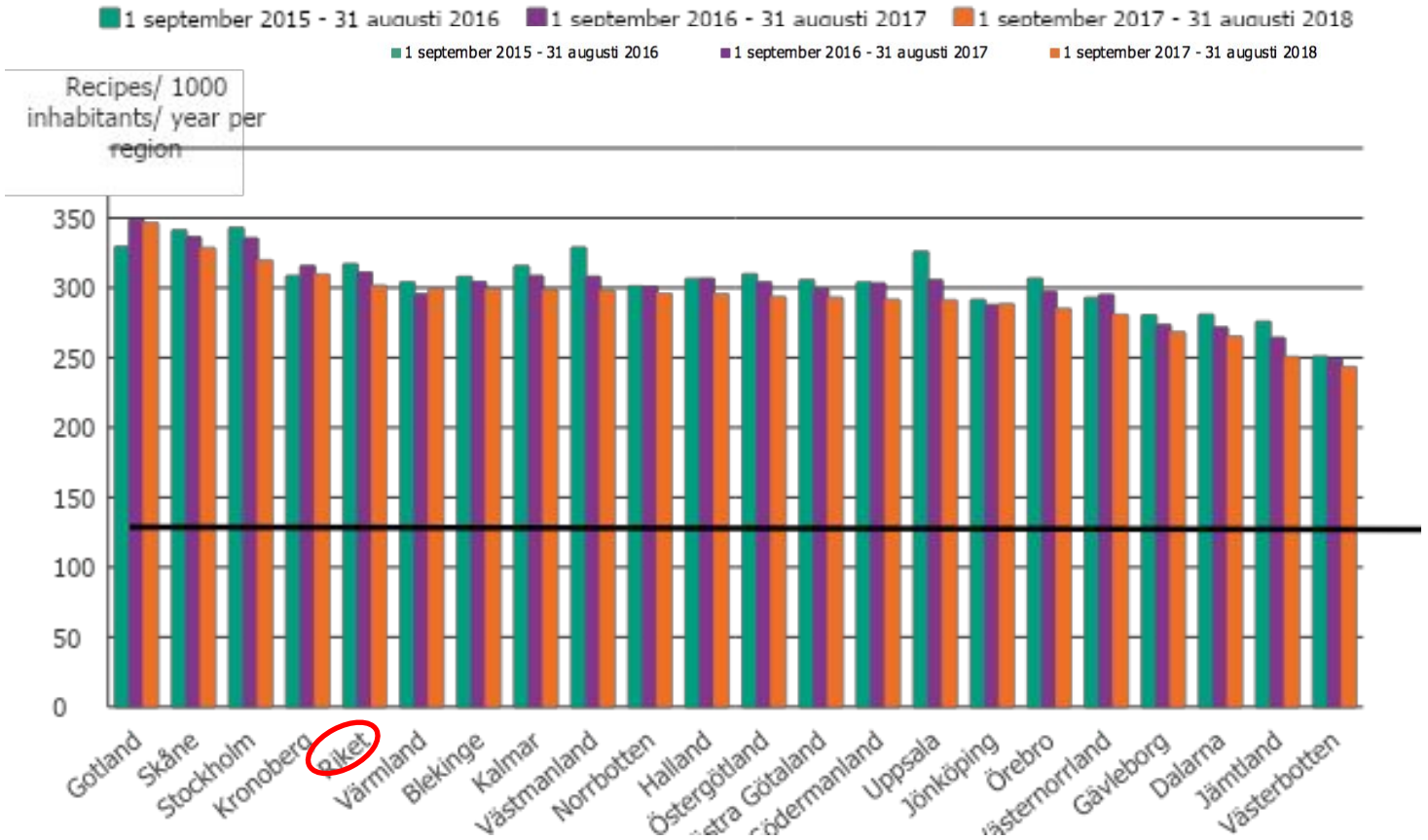
coordination and feedback

National coordination has always been there but the forms have shifted



Exchange ideas - What works locally?
- Web page
- Larger yearly meetings

Open benchmarking at all levels
(regions, municipalities, GP-station, hospital…)



Some LEAD WORDS – possible success factors in the implementation work of Strama

- ∀ Local engagement
- ∀ Network: bottoms-up, top-down, lateral sharing
- ∀ Early and strong government support
- ∀ Cooperation – multidisciplinary, multisectoral
- ∀ Champions
- ∀ Credibility
- ∀ Adaptability
- ∀ Long term perspective

Peace >200 years..

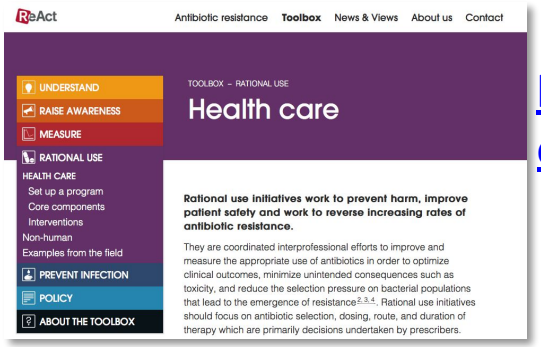
Useful resources

https://www.who.int/medicines/publications/essentialmedicines/en/

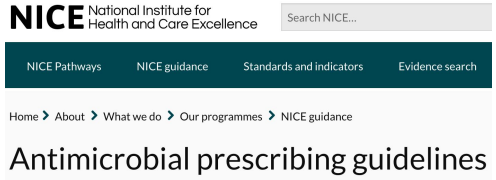
https://www.who.int/antimicrobial-resistance/ru/

http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance

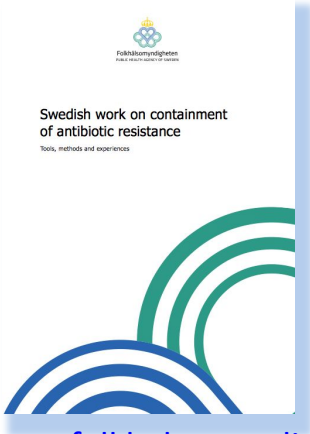
https://openwho.org/courses/AMR-competency



https://www.reactgroup.org/toolbox/rational-use/health-care/



https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/antimicrobial-prescribing-guidelines



https://www.folkhalsomyndigheten.se/pagefiles/17351/Swedish-work-on-containment-of-antibiotic-resistance.pdf

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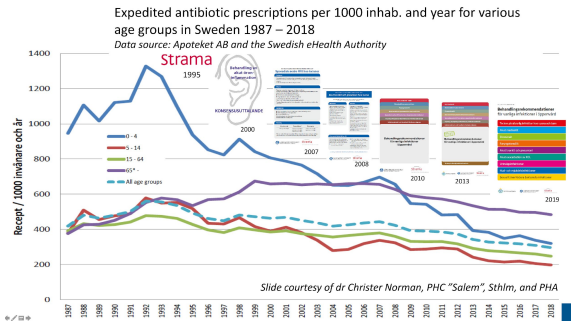
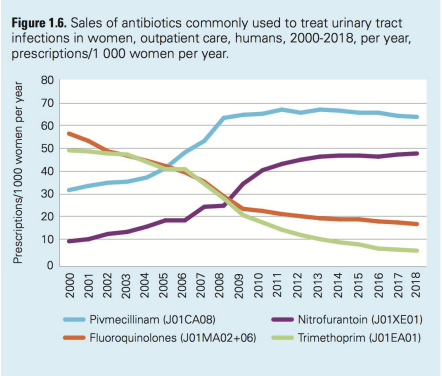




WHO Model List of Essential Medicines

WHO Model List of Essential Medicines for Children

AWaRe classification

- ACCESS – first and second choice antibiotics for the empiric treatment of most common infectious syndromes;
- WATCH – antibiotics with higher resistance potential whose use as first and second choice treatment should be limited to a small number of syndromes or patient groups; and
- RESERVE – antibiotics to be used mainly as 'last resort' treatment options.

Thank you for your attention!

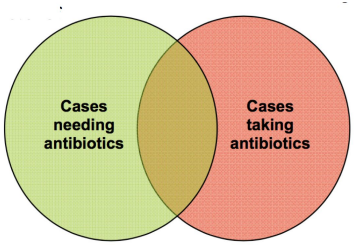
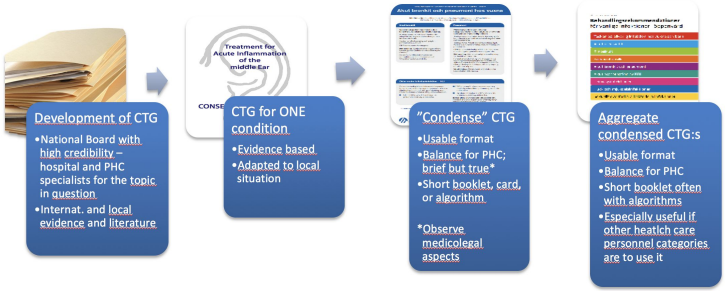


Figure 2. The overlapping relationship between patients who need antibiotics and those who take antibiotics. Källander 2005.



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