Malattie Infettive e Geriatria

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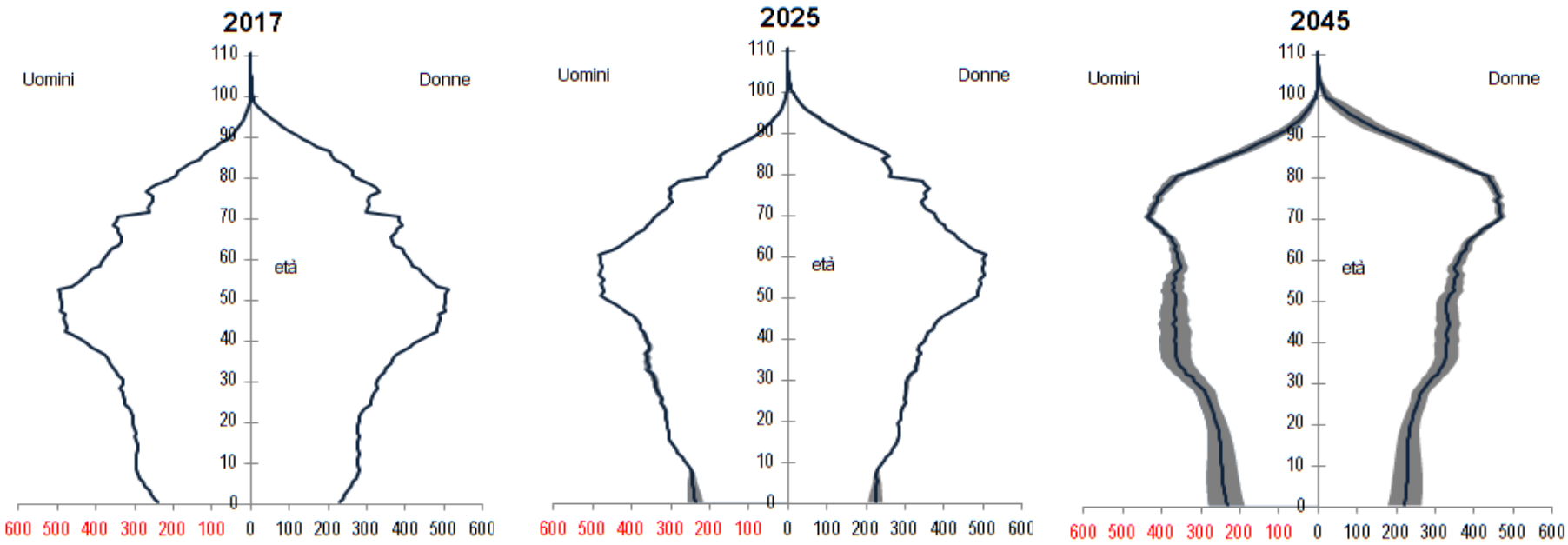
Disclosure

Dr Bonfanti has received grants from:

- ViiV Healthcare
- Gilead
- Jannsen
- Merck

Italy: demographic transition



Source: ISTAT

Outline

- **Increased risk for infection**
  - Alterations in quantitative and qualitative immune responses
  - Higher prevalence of MDRO in elderly
- **Presentation of disease**
  - Fever definition
  - Suspicion for infection
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  - Inappropriate use
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  - Dosing and PK considerations
- **Specific infectious syndromes**
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Why are the elderly at increased risk for infection?

- Decreased immunity
- Immunosuppressive drugs
- Poor nutrition
- Decrease in usual protective barriers (cough, skin)
- Chronic illness
- Increased exposure to organisms, especially in LTCFs
- Increased use of invasive devices

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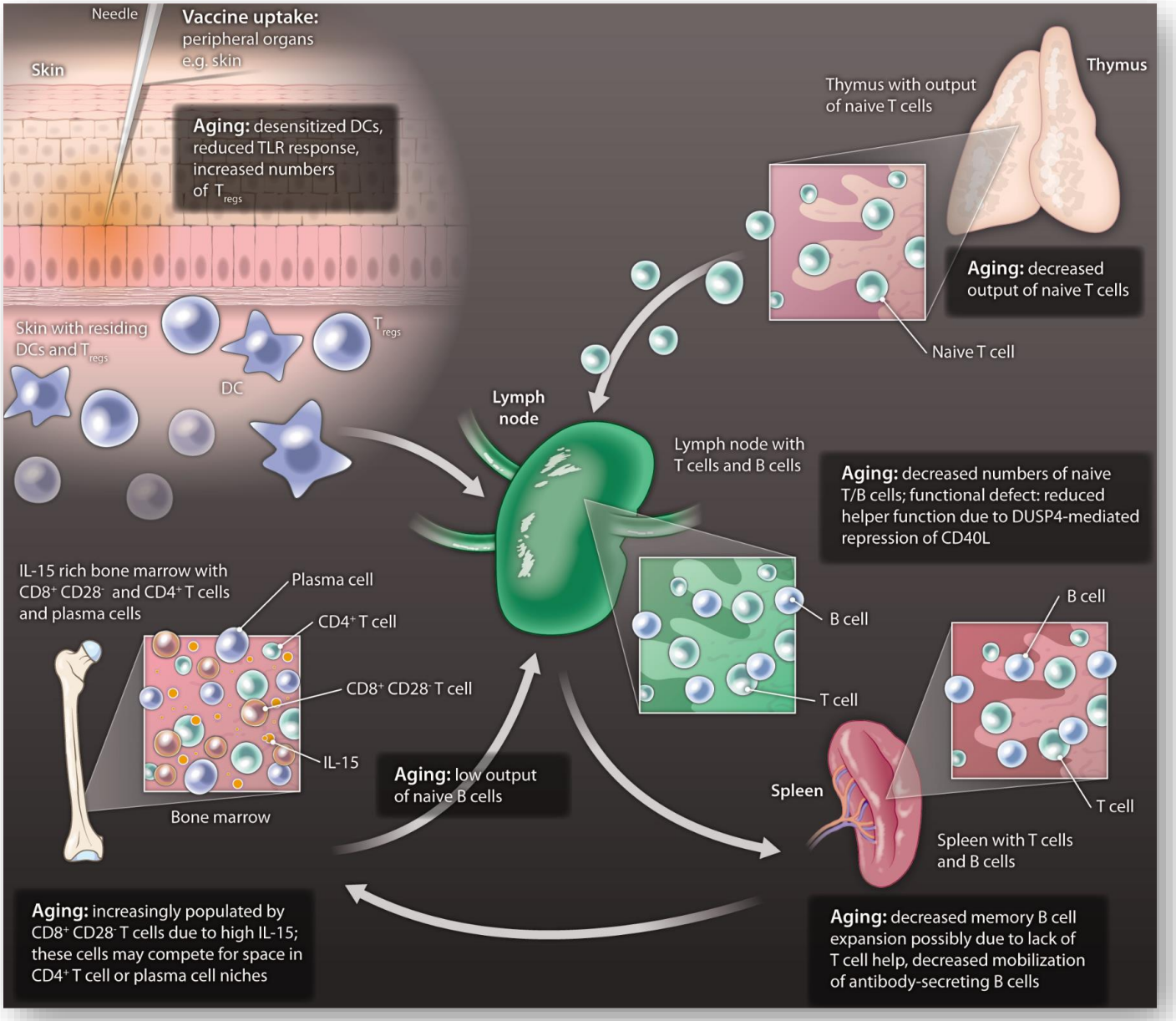
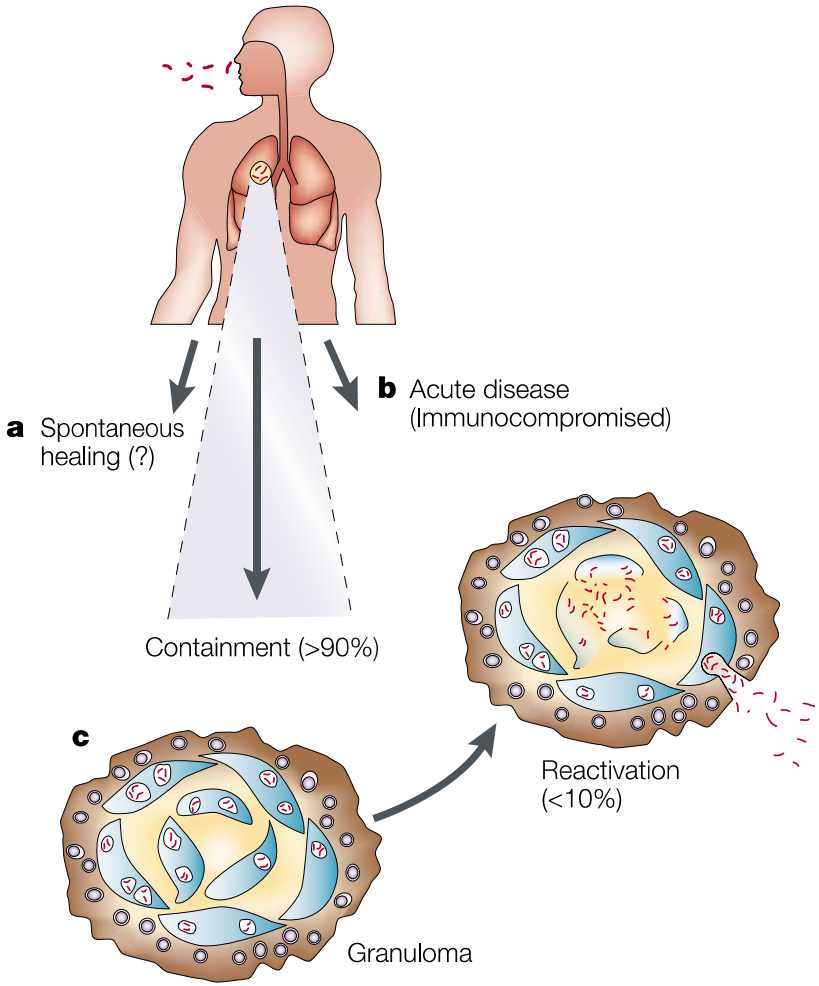
The immunization pathways in the elderly



Boraschi D et al, *Sci Transl Med 2013*

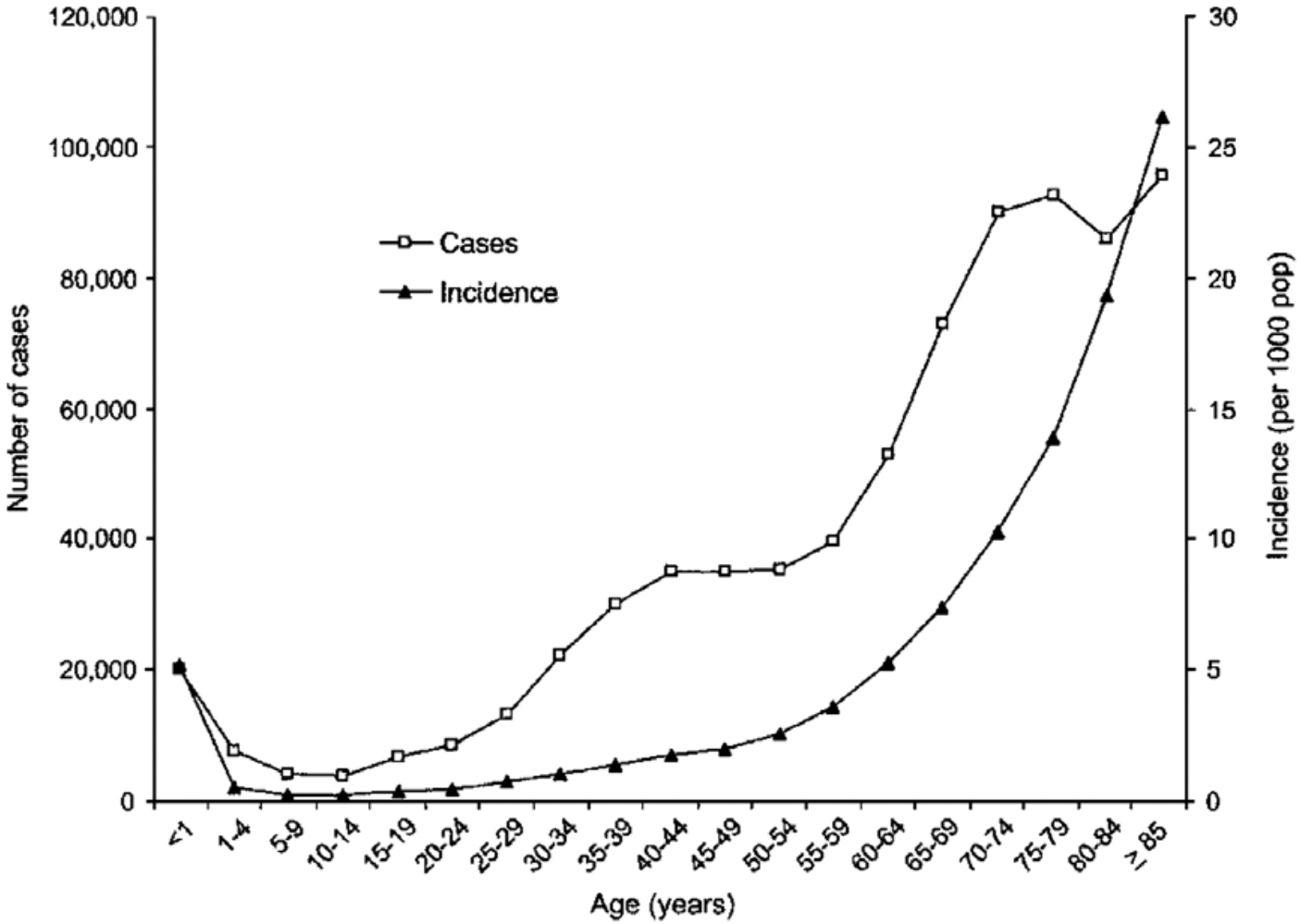
TB in the Elderly

- The majority of TB in the elderly is secondary to reactivation of latent TB infection
- With age, the T-cell mediated immune response wanes allowing for latent TB to become active.



Kaufmann SHE. *Nature Reviews Immunology 2001*

Incidence of severe sepsis by age



Angus DC et al, *Crit Care Med 2001*

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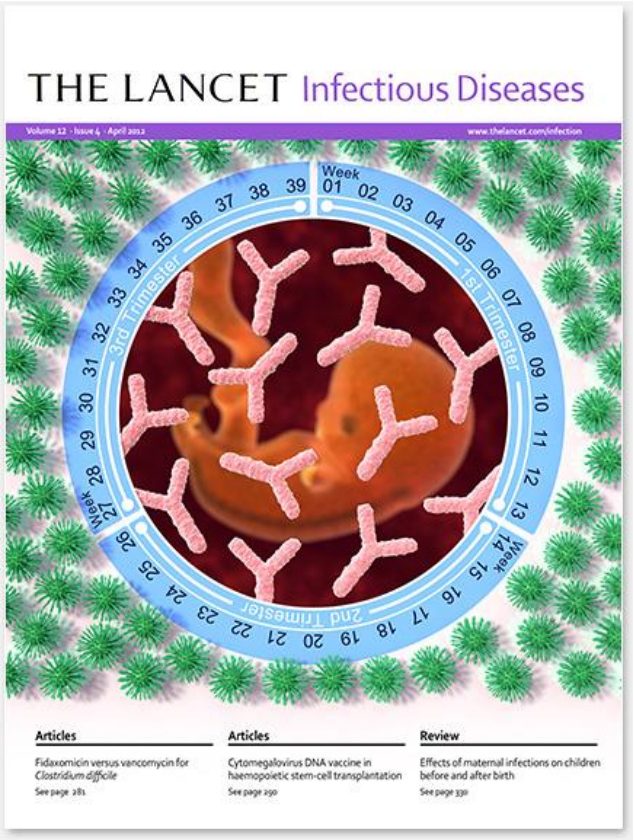
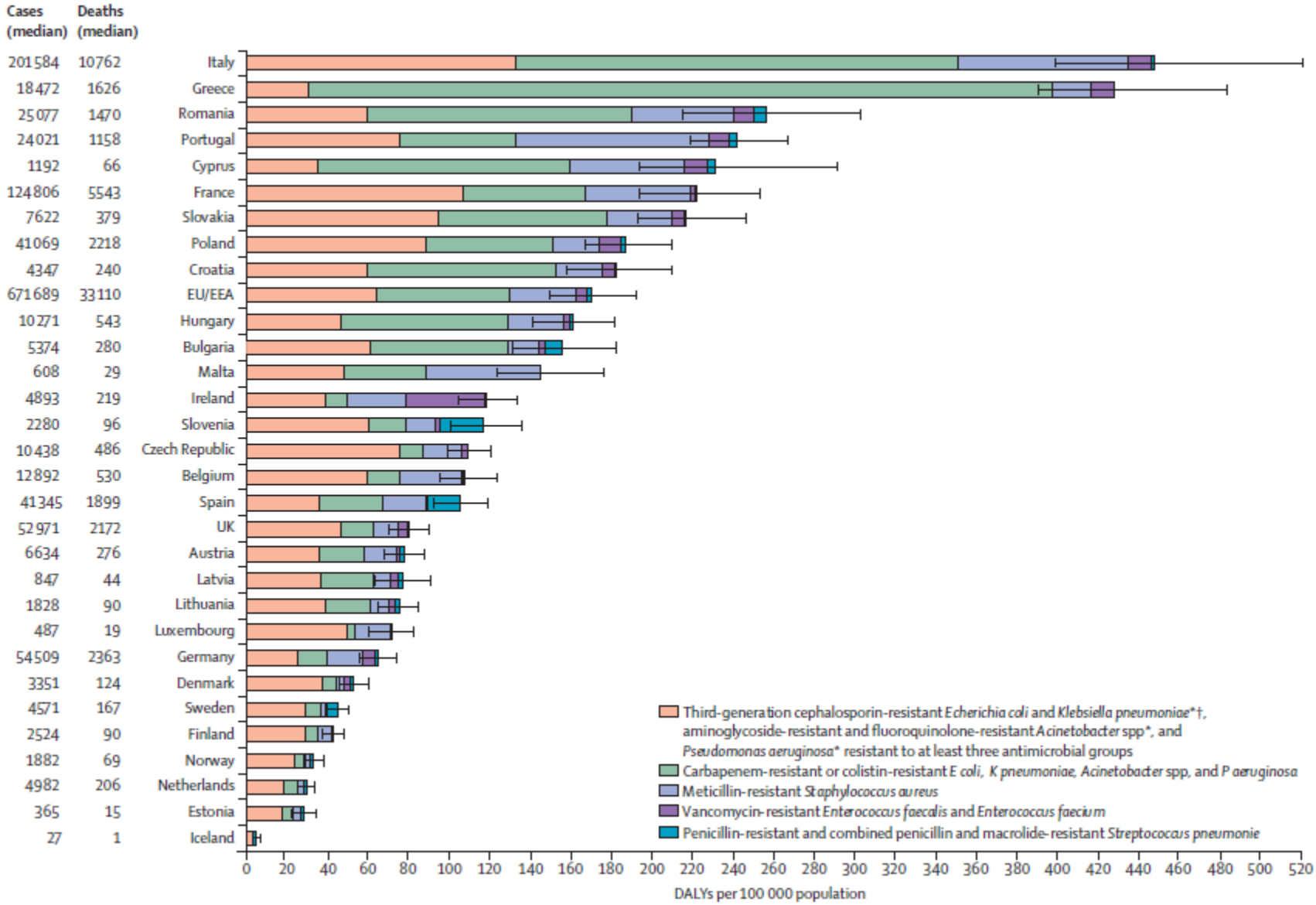
Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

*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**

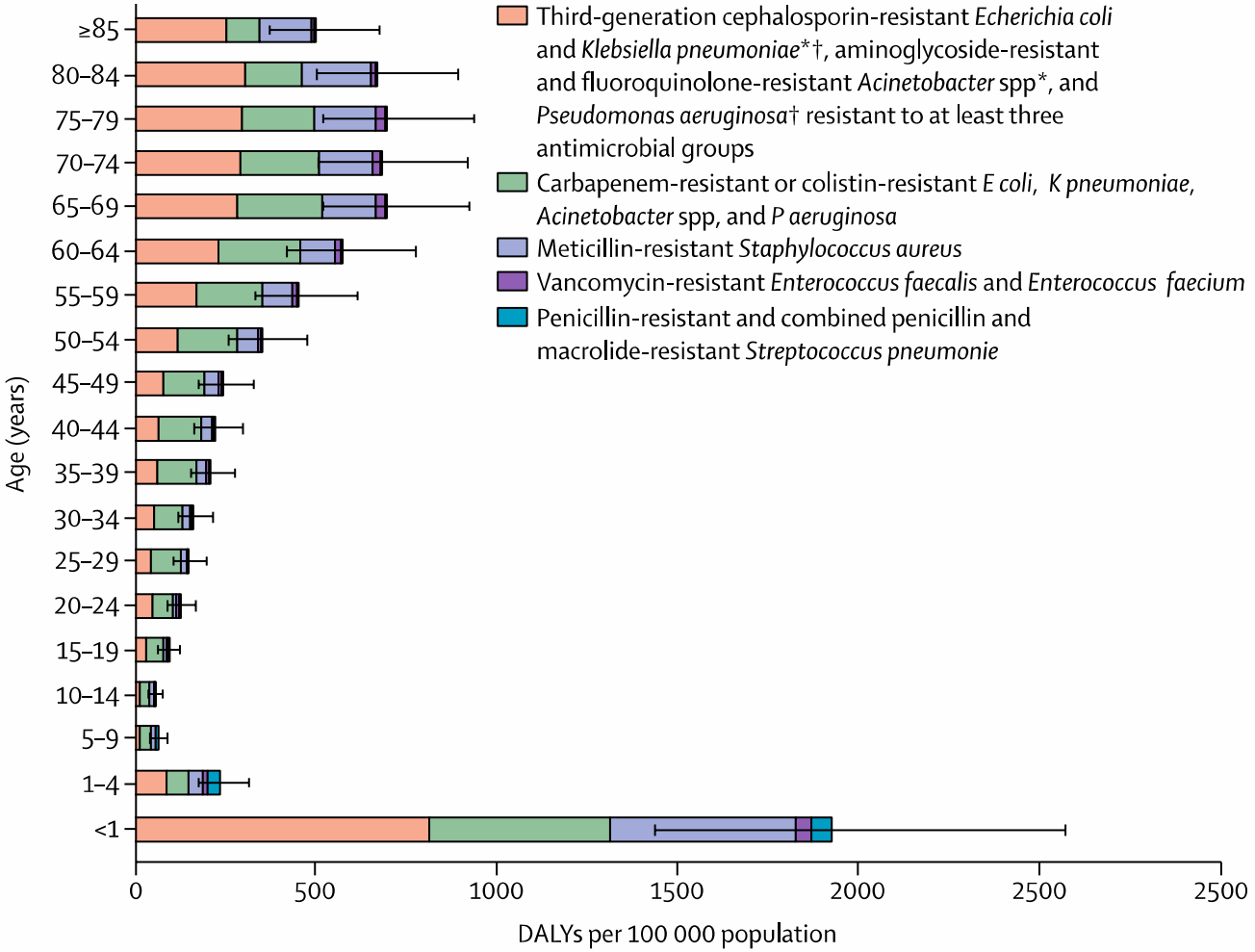


Lancet Infect Dis 2018



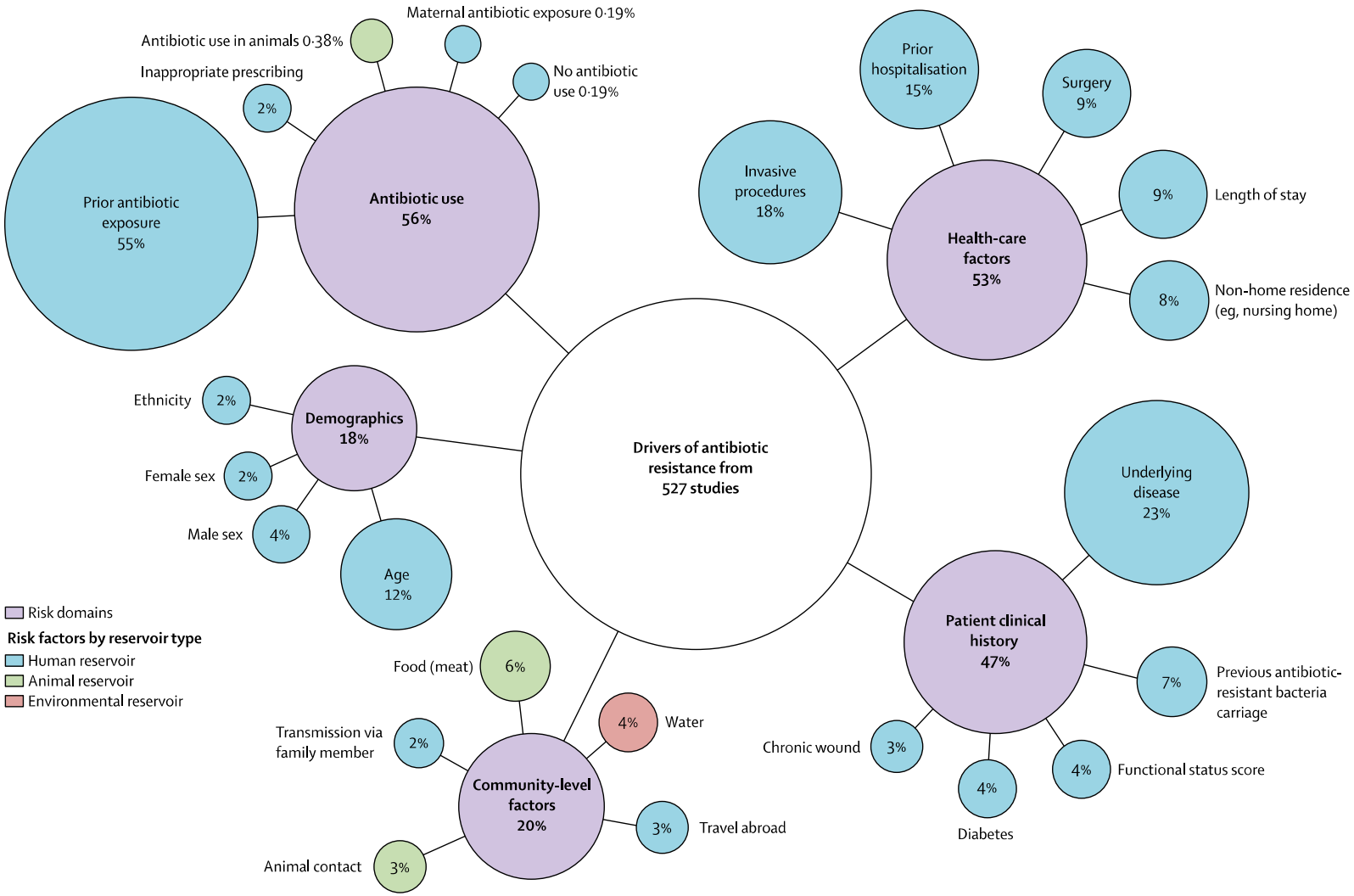
Cassini A et al, *Lancet Infect Dis 2018*

Burden of infections with antibiotic-resistant bacteria of public health importance in DALYs, by age group, EU and European Economic Area, 2015



Cassini A et al, *Lancet Infect Dis 2018*

Drivers of antibiotic resistance in humans



Chatterjee A et al, *Lancet Infect Dis 2018*

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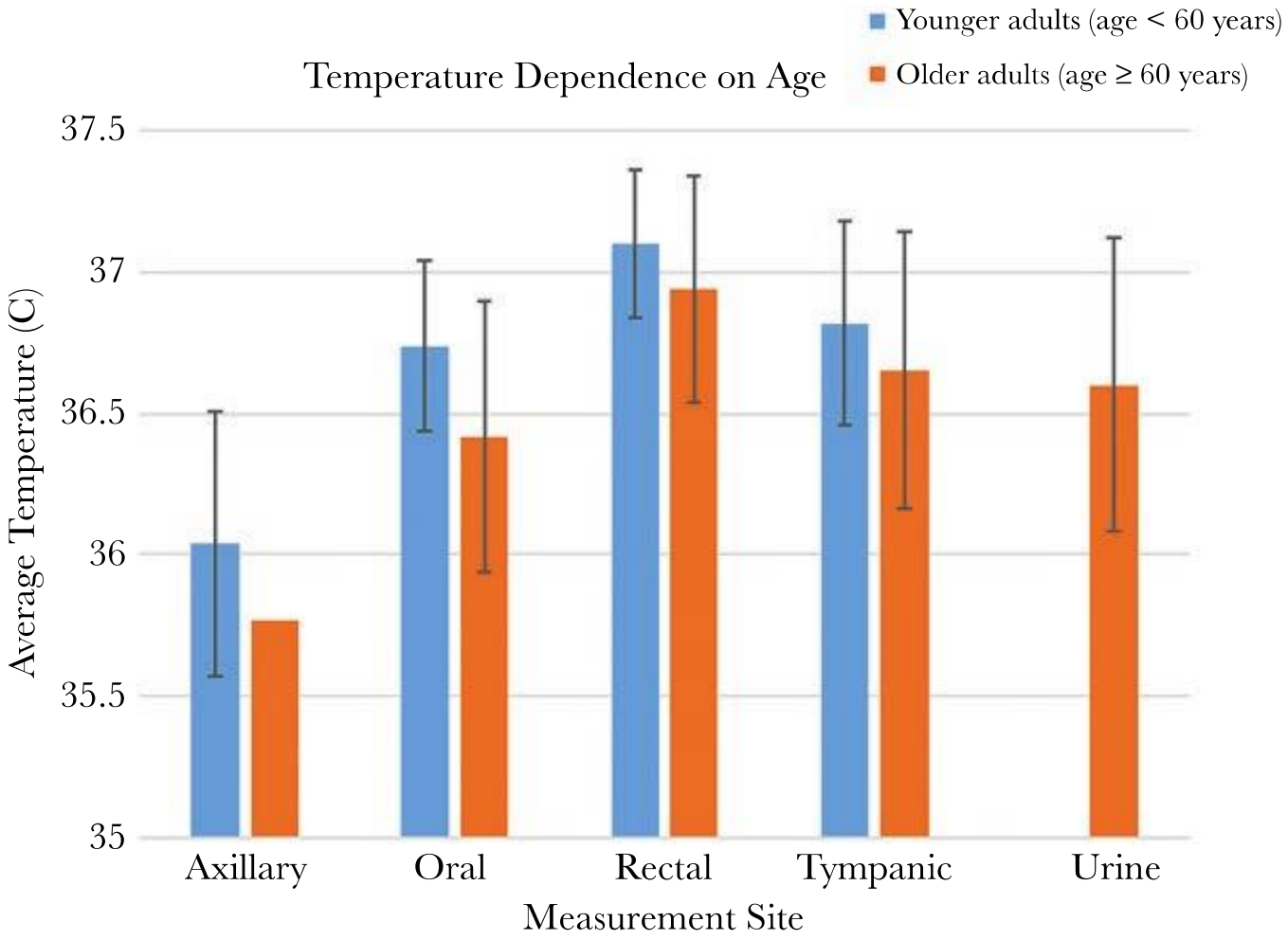
Normal Body Temperature: A Systematic Review



Geneva I et al, *OFID 2019*

Presentation of disease: fever in older adults

- In frail, older adults, fever is absent in 30 to 50 percent, even in the setting of serious infections such as pneumonia or endocarditis.
- It is appropriate use a lower threshold for fever in frail, older patients:
  - **Single oral temperature >37.8° C**
  - **Persistent oral or tympanic membrane temperature ≥37.2° C**
  - **Rise in temperature of ≥1.1° C above baseline temperature**

High KP et al, *Clin Infect Dis 2009*

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Nonspecific Symptoms Lack Diagnostic Accuracy for Infection in Older Patients in the Emergency Department

Characteristic/symptom	OR	(95% CI)	*P* value	Sensitivity, %	Specificity, %	PLR	NLR
Altered mental status							
Delirium: positive CAM-ICU	2.14	(0.72-6.38)	.168	6.7 (2.2-15)	97 (94-98)	2.07 (0.74-5.79)	0.96 (0.90-1.03)
Patient report: confusion or altered mental status	1.46	(0.67-3.13)	.319	13 (6.4-23)	91 (87-94)	1.41 (0.72-2.74)	0.96 (0.87-1.05)
ED chart: confusion or altered mental status	2.73	(1.16-6.43)	.022	12 (5.5-21)	95 (93-97)	2.53 (1.16-5.51)	0.93 (0.85-1.01)
Aggregate variable: CAM-ICU positive, patient report or ED chart confusion or altered mental status	1.49	(0.77-2.88)	.234	18 (10-29)	87 (83-90)	1.4 (0.81-2.42)	0.94 (0.84-1.05)
Malaise/lethargy							
Patient report: malaise, lethargy, or fatigue	1.75	(1.07-2.88)	.027	54 (43-66)	59 (54-65)	1.34 (1.06-1.71)	0.77 (0.59-0.99)
ED chart: malaise, lethargy, or fatigue	1.42	(0.78-2.58)	.244	23 (14-34)	82 (78-86)	1.33 (0.83-2.11)	0.93 (0.82-1.06)
Aggregate variable: patient report or ED charted malaise, lethargy, or fatigue	1.63	(0.98-2.70)	.057	61 (49-72)	51 (46-56)	1.25 (1.01-1.53)	0.76 (0.57-1.03)
Fever (cutoff ≥38.0°C)							
Patient report: fever ≥38.0°C in the prior 24 h	6.24	(2.90-13.44)	<.001	21 (12-32)	96 (93–98)	5.15(2.63-10.10)	0.83 (0.73-0.93)
Initial ED temperature ≥38.0°C	1.00	(Perfectly predictive)		7.9 (2.9-16)	100 (99-100)	NA	0.92 (0.86-0.98)
Any ED temperature ≥38.0°C	20.11	(4.18-96.81)	<.001	10 (4.6-20)	99 (98-100)	18.1 (3.92-83.60)	0.90 (0.83-0.97)
Aggregate variable: patient report or any ED temperature ≥38.0°C	6.77	(3.29-13.94)	<.001	25 (16-36)	95 (93-97)	5.35 (2.89-9.92)	0.79 (0.69-0.90)
Fever (cutoff ≥37.2°C)							
Initial ED temperature ≥37.2°C	4.31	(2.02-9.20)	<.001	18 (10-29)	95 (92-97)	3.71 (1.91-7.20)	0.86 (0.77-0.96)
Any ED temperature ≥37.2°C	3.11	(1.61-6.01)	<.001	22 (13-33)	92 (88-94)	2.64 (1.53-4.56)	0.85 (0.75-0.96)
Aggregate variable: patient report of fever ≥38.0°C or any ED temperature ≥37.2°C	3.90	(2.18-7.01)	<.001	32 (22-44)	89 (85-92)	2.96 (1.9-4.6)	0.76 (0.65-0.89)

Caterino JM et al , *J Am Geriatr Soc 2019*

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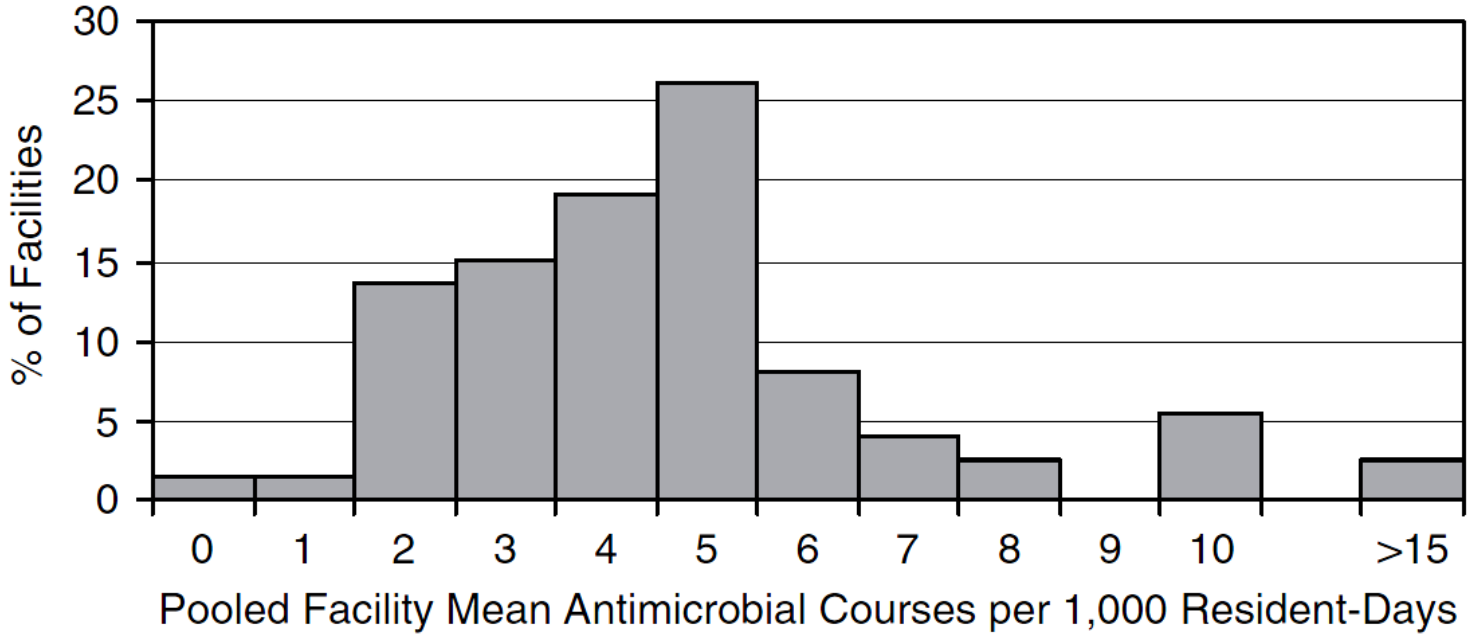
25% to 75% of systemic antimicrobials are inappropriately prescribed in LTC settings.



The extreme variability in antimicrobial prescribing between facilities, it is fair to assume that some of this use was inappropriate

Costelloe C. et al., *BMJ 2010; 340* , Nicolle LE, Bentley DW, Garibaldi R, et al. Antimicrobial use in long-term-care facilities. SHEA Long-Term-Care Committee. *Infect Control Hosp Epidemiol*. 2000;21(8):537-545, Zimmer JG, Bentley DW, Valenti WM, Watson NM. Systemic antibiotic use in nursing homes. A quality assessment. *J Am Geriatr Soc*. 1986;34(10):703-710, Loeb M. Antibiotic use in long-term-care facilities: many unanswered questions. *Infect Control Hosp Epidemiol*. 2000;21(10):680-683, Roumie CL, Halasa NB, Edwards KM, et al. Differences in antibiotic prescribing among physicians, residents, and nonphysician clinicians. *Am J Med*. 2005;118(6):641-648. Benoit et al JAGS 2008; 56:2039

VIEWPOINT

Antimicrobials at the End of Life
An Opportunity to Improve Palliative Care and Infection Management

- Close to 90% of hospitalized patients with advanced cancer receive antimicrobials during the week prior to death.
- 42% of nursing home residents with advanced dementia are prescribed antimicrobials during the last 2 weeks of life.

Juthani-Mehta M et al, *JAMA 2015*

Summary of Core Elements for Antibiotic Stewardship in Nursing Homes

Leadership commitment
Demonstrate support and commitment to safe and appropriate antibiotic use in your facility

Accountability
Identify physician, nursing and pharmacy leads responsible for promoting and overseeing antibiotic stewardship activities in your facility

Drug expertise
Establish access to consultant pharmacists or other individuals with experience or training in antibiotic stewardship for your facility

Action
Implement **at least one** policy or practice to improve antibiotic use

Tracking
Monitor **at least one process** measure of antibiotic use and **at least one outcome** from antibiotic use in your facility

Reporting
Provide regular feedback on antibiotic use and resistance to prescribing clinicians, nursing staff and other relevant staff

Education
Provide resources to clinicians, nursing staff, residents and families about antibiotic resistance and opportunities for improving antibiotic use

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Antibiotic Management

Choice of agent

- The choice of initial antibiotic is the same as in younger patients for most routine infections, and prompt institution of antibiotics is important.
- Consideration for **broader empiric coverage** may be warranted for older adults for the following reasons:
  - Increased risk of **infection with drug-resistant organisms**, due to residence in an institution, recent hospitalization, dialysis treatment, recent antibiotic exposure, or indwelling devices
  - Broader initial coverage may be appropriate in **seriously ill older** adults in whom sepsis, severe pneumonia, or other life-threatening infections are more likely to be suspected
- **Antibiotic interactions** are also a major consideration in antibiotic selection, as these may occur with many medications commonly prescribed in older adults

Wang L et al, Eur J Clin Microbiol Infect Dis 2012; Flannery EL et al, Clin Infect Dis 2011; Kollef MH, Am J Med 2003

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Changes in pharmacokinetic factors associated with aging

PK parameter	Consideration in elderly patients	Impact on drug PK	Potential effects on antimicrobial dosing	Examples
Absorbtion	Decreased gastric acid production	Impaired drug dissolution	Decreased bioavailability of drugs	Azithromycin, erythromycin, cefaclor, ceftibuten, itraconazole, ketoconazole, sulfonamides, dapsone, pyrimethamine
	Decreased gastric motility	Decreased absorption of drugs	Standard dose may be inadequate	Cefpodoxime proxetil
	Decreased small bowel surface area			
	Decreased splanchnic blood flow			

Giarratano A et al, *Clin Interv Aging 2018*

Changes in pharmacokinetic factors associated with aging

PK parameter	Consideration in elderly patients	Impact on drug PK	Potential effects on antimicrobial dosing	Examples
Distribution	Increased proportion of adipose tissue	Impaired drug dissolution	Increased distribution of lipid-soluble drugs	Rifampin, fluoroquinolones, macrolides, oxazolidinones, tetracyclines, amphotericin B, imidazole antifungals
	Decreased lean body mass	Decreased distribution of water-soluble drugs	Increased plasma concentration	Aminoglycosides, glycopeptides, beta-lactams
	Malnutrition/proteinuria leading to hypoalbuminemia	Increased concentration of free drug	Drug toxicity	Penicillins, ceftriaxone, sulfonamides, clindamycin

Giarratano A et al, *Clin Interv Aging 2018*

Changes in pharmacokinetic factors associated with aging

PK parameter	Consideration in elderly patients	Impact on drug PK	Potential effects on antimicrobial dosing	Examples
Metabolism	Liver disease; normal physiological effects of aging on the liver	• Decreased hepatic blood flow • Decreased P450 CYP enzyme activity	Prolonged drug half-life of hepatically metabolized drugs	Macrolides, fluoroquinolones, azole antifungals, antiretrovirals
	Polypharmacy	Competition for CYP P450 hepatic enzymes	Variable drug activity	Macrolides, fluoroquinolones, azole antifungals, antiretrovirals

Giarratano A et al, *Clin Interv Aging 2018*

Changes in pharmacokinetic factors associated with aging

PK parameter	Consideration in elderly patients	Impact on drug PK	Potential effects on antimicrobial dosing	Examples
Elimination	Decreased renal function/ renal disease	• Decreased renal blood flow • Decreased glomerular filtration rate • Decreased drug removal	• Prolonged drug half-life • Accumulation of drug in plasma • High serum concentrations • Increased risk of toxicity	Beta-lactams, glycopeptides, aminoglycosides, daptomycin, ciprofloxacin, levofloxacin, trimethoprim/ sulfamethoxazole
	Renal replacement therapy	Increased drug removal	Dose adjustment required	

Giarratano A et al, *Clin Interv Aging 2018*

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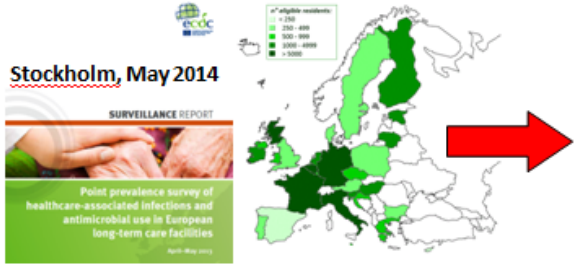

HALT projects: point prevalence survey from May to September 2010 in 722 LTCFs across 28 European countries (HALT 1) and from April to May 2013 in 1181 LTCFs in 19 European countries (HALT 2)

Most frequently reported types of Healthcare-Associated Infections in European Long-Term Care Facilities Project (HALT)

Type of infection	(%) HALT 1 2010	(%) HALT 2013	(%) HALT 2 2013 - ITALY
Respiratory tract infections	33.6	31.2 ↓	38 ↑
Urinary tract infections	22.3	31.2 ↑	29 ↓
Skin and soft tissue infections	21.4	22.8 ↑	16 ↓
Eye, ear, nose and mouth infections	8.0	5.9 ↓	5 ↓
Gastro-intestinal infections	4.6	5.1 ↑	5 ↓
Others	10.1	3.8 ↓	7 ↑

Antibiotic management of urinary tract infection in elderly patients in primary care and its association with bloodstream infections and all cause mortality: population based cohort study

Myriam Gharbi,[1,2] Joseph H Drysdale,[3] Hannah Lishman,[1,2] Rosalind Goudie,[1,2,4] Mariam Molokhia,[5] Alan P Johnson,[1,6] Alison H Holmes,[1] Paul Aylin[1,2]

- 157 264 adults aged 65 years or older presenting to a general practitioner with at least one diagnosis of suspected or confirmed lower UTI from November 2007 to May 2015.
- The **rate of hospital admissions** was about double among cases with no antibiotics (27.0%) and deferred antibiotics (26.8%) compared with those prescribed immediate antibiotics (14.8%; P=0.001).
- The **risk of all cause mortality** was significantly higher with deferred antibiotics and no antibiotics than with immediate antibiotics at any time during the 60 days follow-up
- Men older than 85 years were particularly at risk for both **bloodstream infection** and 60 day all cause mortality.

BMJ 2019;364:l525

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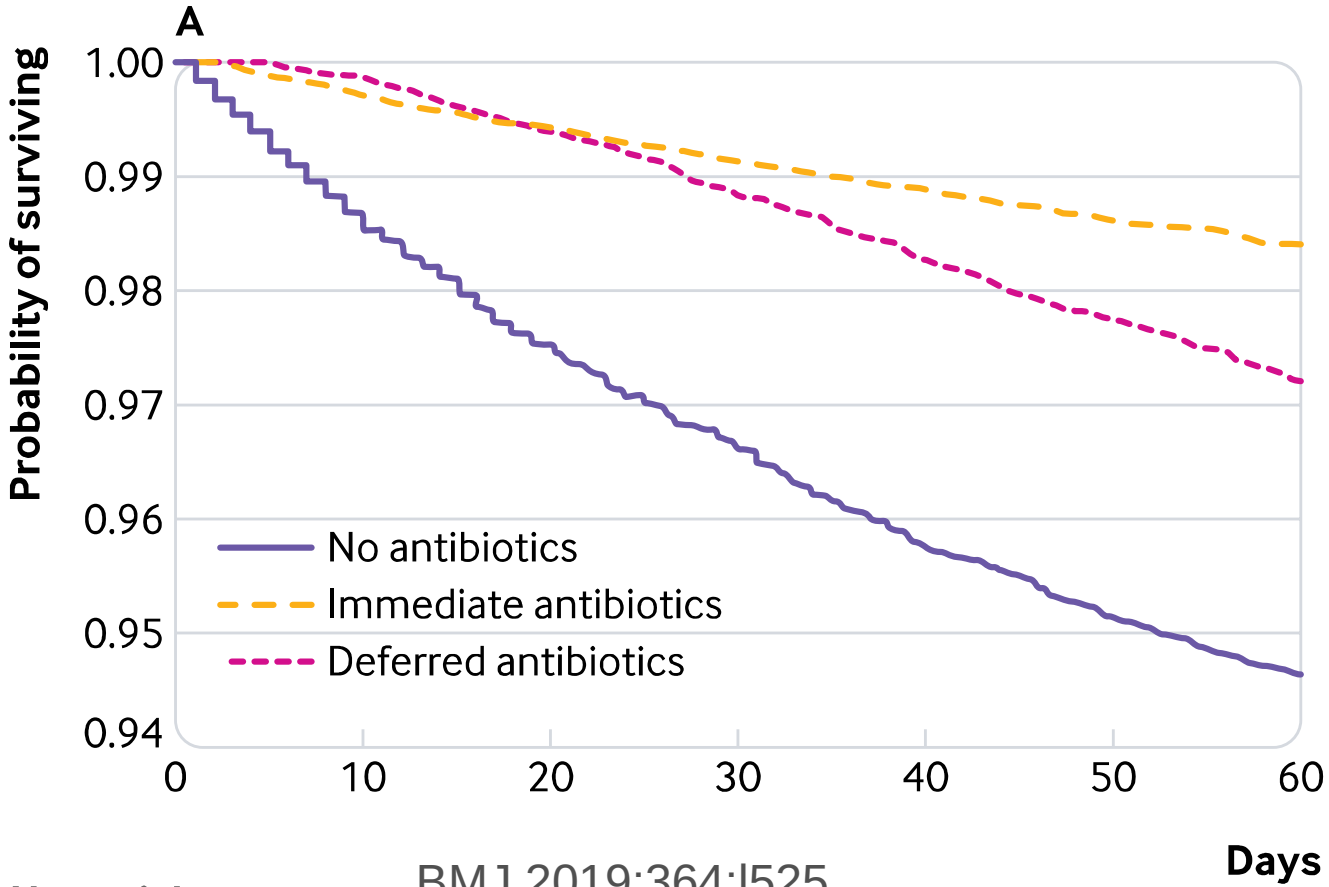
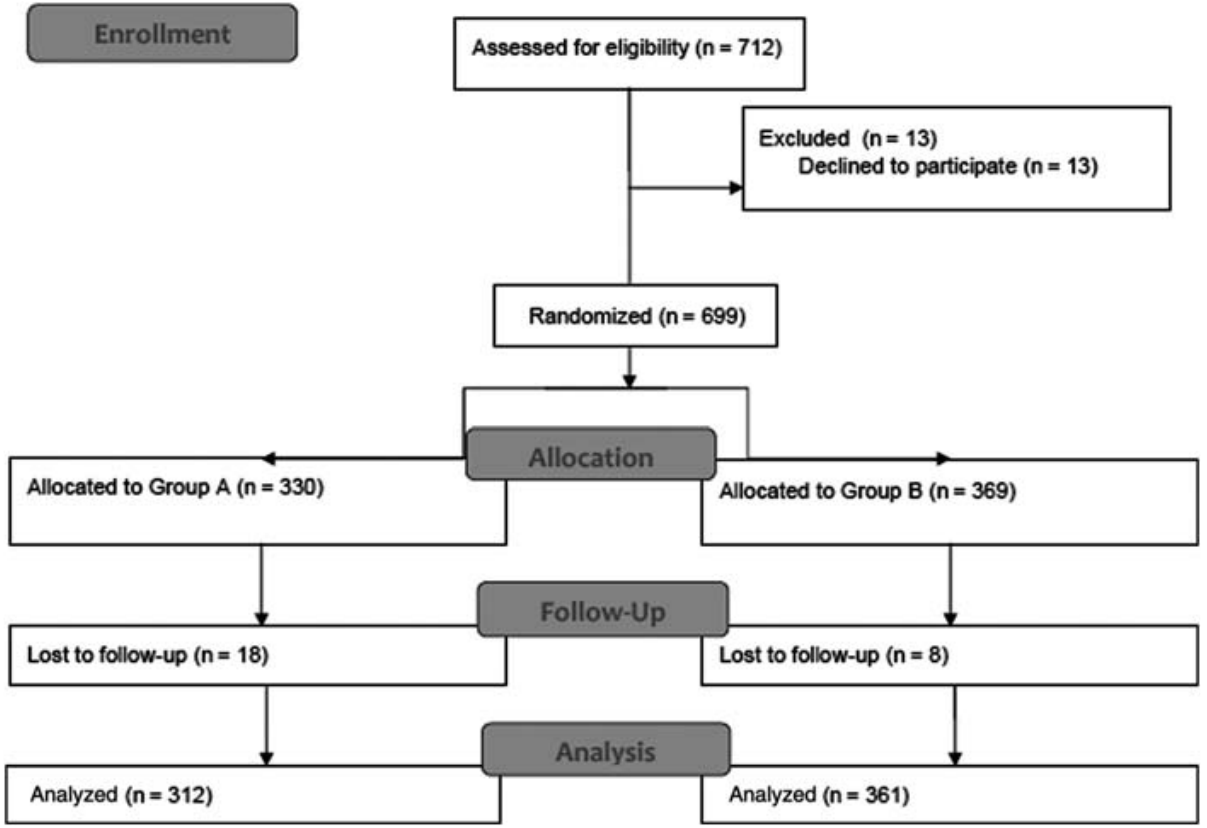


BMJ 2019;364:l525

The Role of Asymptomatic Bacteriuria in Young Women With Recurrent Urinary Tract Infections: To Treat or Not to Treat?

Tommaso Cai,[1] Sandra Mazzoli,[2] Nicola Mondaini,[3] Francesca Meacci,[2] Gabriella Nesi,[4] Carolina D'Elia,[1] Gianni Malossini,[1] Vieri Boddi,[5] and Riccardo Bartoletti[3]

[1]Department of Urology, Santa Chiara Hospital, Trento; [2]Sexually Transmitted Disease Centre, Santa Maria Annunziata Hospital, Florence; [3]Department of Urology, [4]Division of Pathological Anatomy, Department of Critical Care Medicine and Surgery, and [5]Department of Public Health and Epidemiology, University of Florence, Italy



Clinical Infectious Diseases 2012;55(6):771–7

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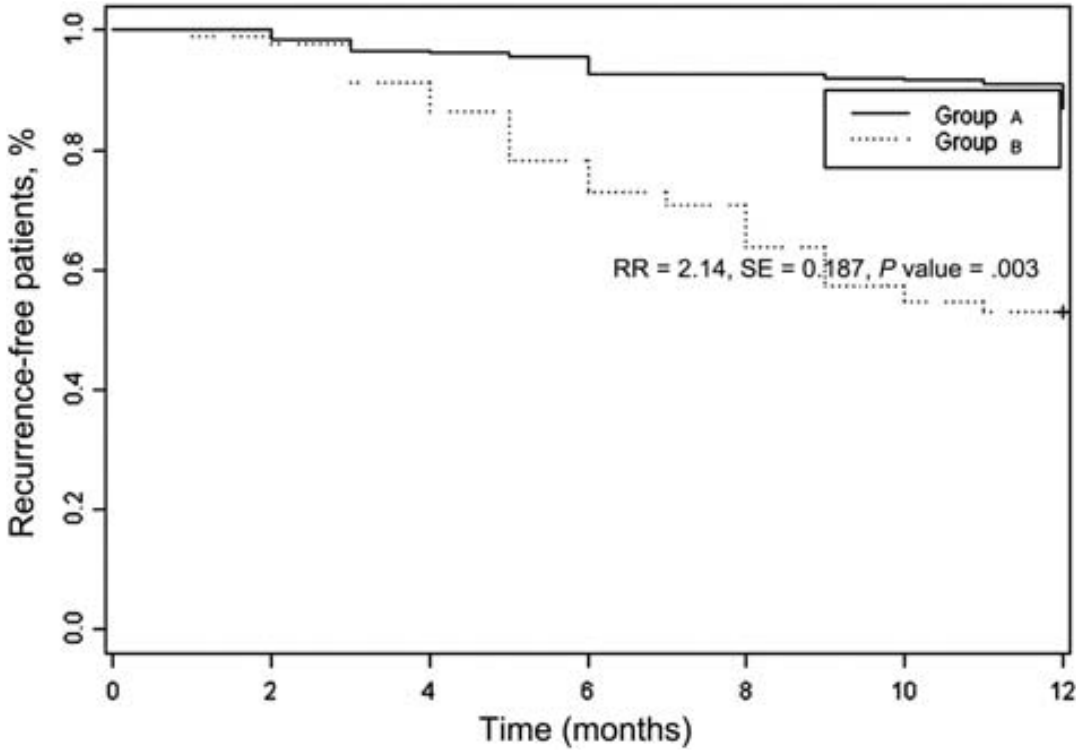


Clinical Infectious Diseases 2012;55(6):771–7

Study results of Asymptomatic Bacteruria in young healthy women

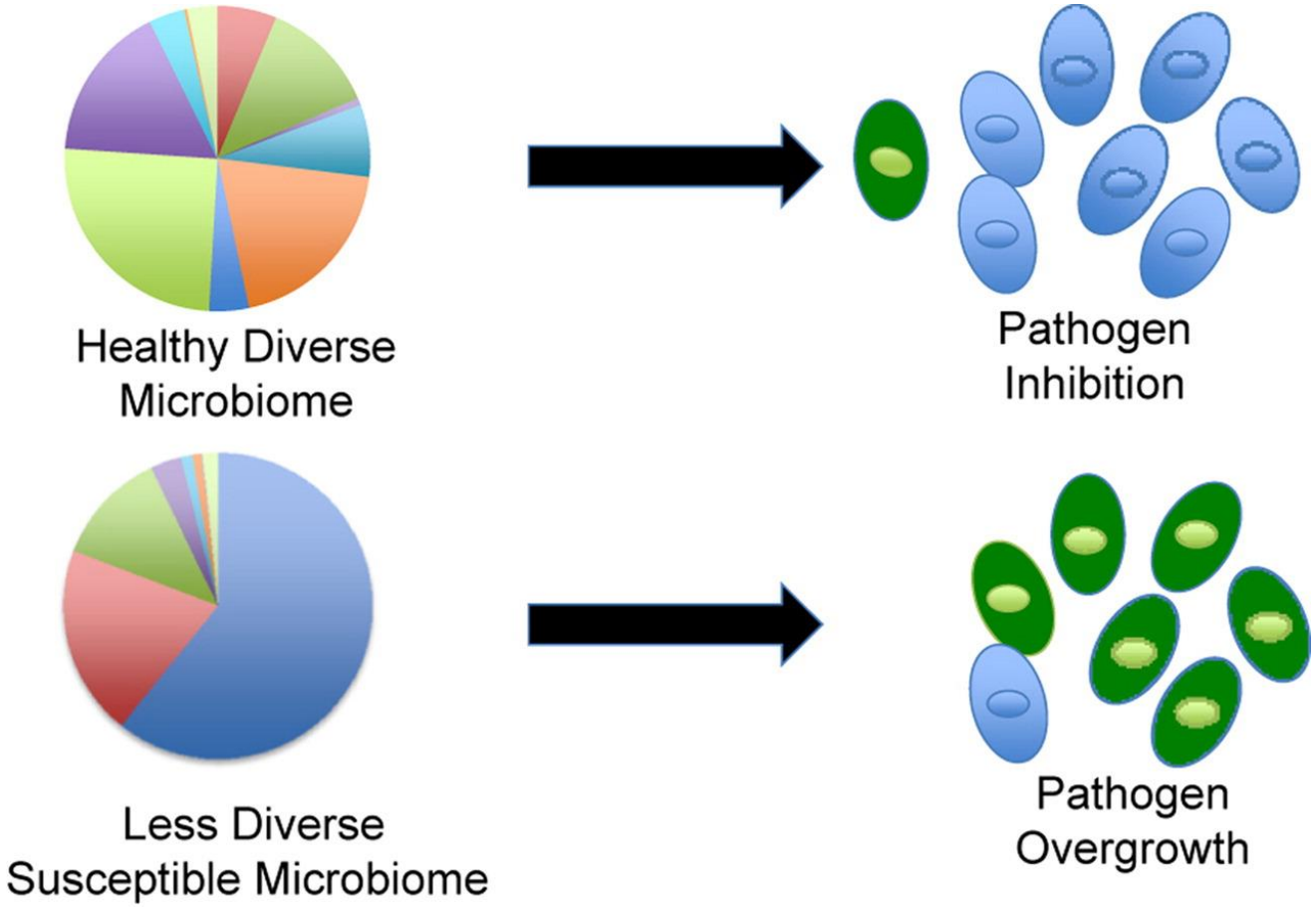
Results after one year of observation:

- Those **treated** for ABU - 46.8% had a symptomatic UTI later during the year
- Those **not treated** for ABU - only 13.1% had another UTI!

Conclusion: The paradoxical result was **increased incidence of symptomatic UTIs in patients given antimicrobials for asymptomatic bacteruria!**

Clinical Infectious Diseases 2012;55(6):771–7

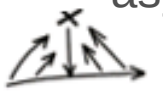
Decreased microbiota diversity associated with urinary tract infection in a trial of bacterial interference



Horwitz D et al, J Infect 2015

Summary

- Older adults are at greater infection risk due to immune senescence, comorbidities, and communal residence.
- Institutionalized older adults are at increased risk for antibiotic resistance, particularly those with indwelling devices
- Typical signs or symptoms of infection, including fever, may be absent in older adults. Furthermore, nonspecific symptoms such as increased confusion, falling, and anorexia are common manifestations of infection.
- Antibiotic dosing should take into account reduced renal function with aging. However, it is important that older adults with serious infection receive the appropriate therapeutic dose.
- UTI is common in older adults, and in general it is managed in the same way as in the general population. However, the diagnosis is complicated by the higher prevalence of chronic urinary symptoms, cognitive impairment, and asymptomatic bacteriuria.



GRAZIE PER L’ATTENZIONE!

Edouard Boubat – *Boulevard Saint-Germain, Paris,* 1948