Cystic Fibrosis and Bacteriology

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11/12/2018

KU LEUVEN

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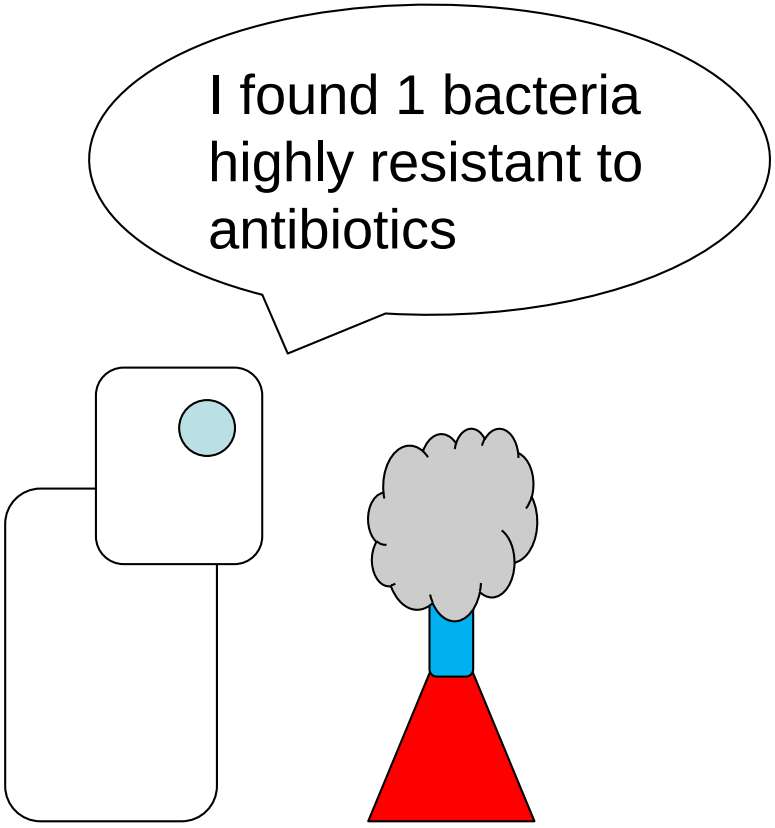
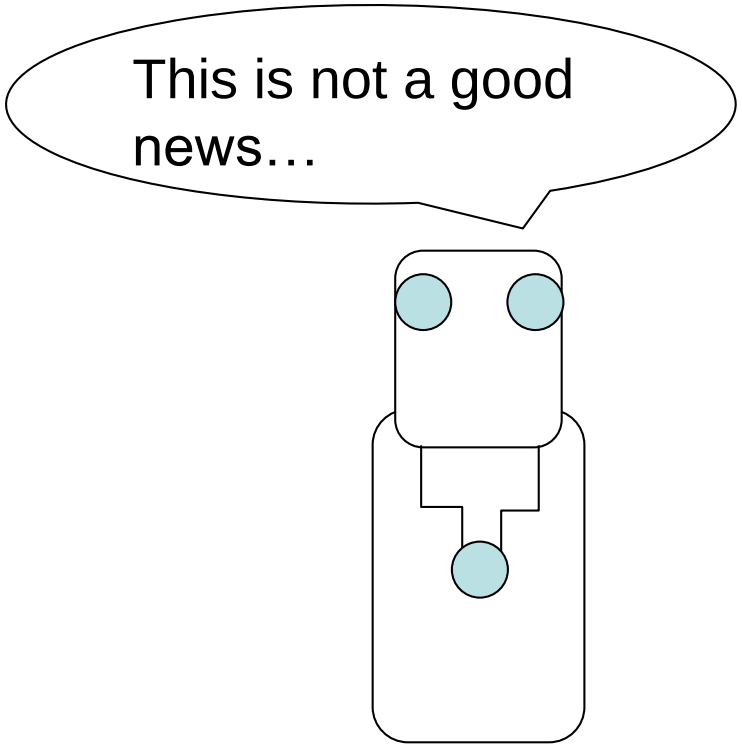


The microbiologist

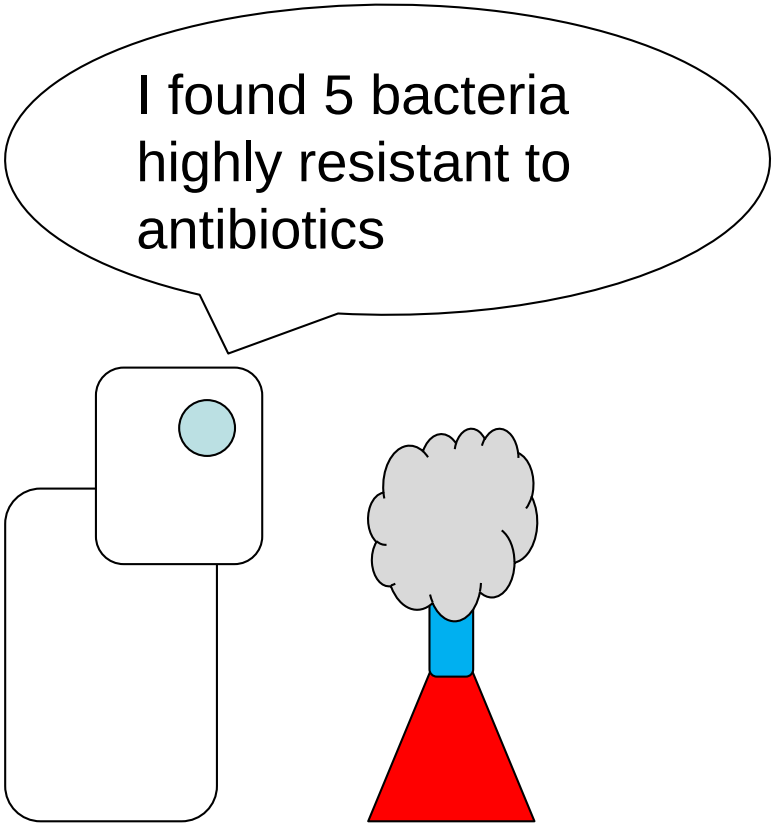


The Clinician

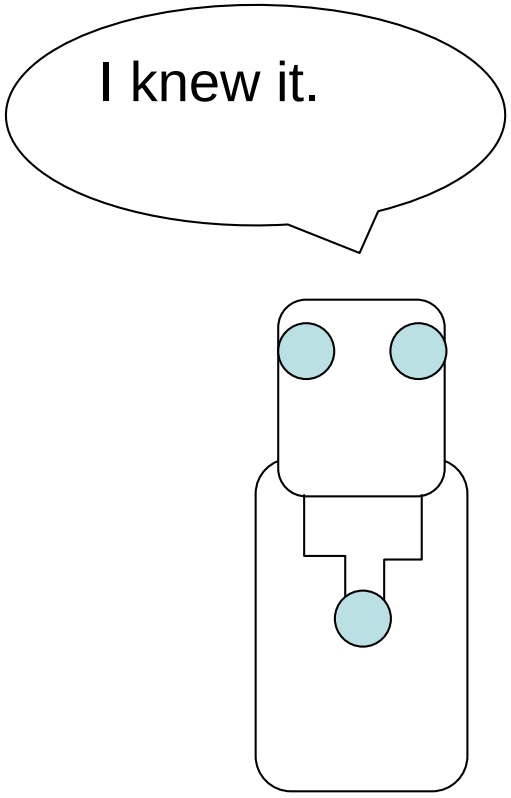
Chronic infection

Predictable emergence of drug resistance

Transmission



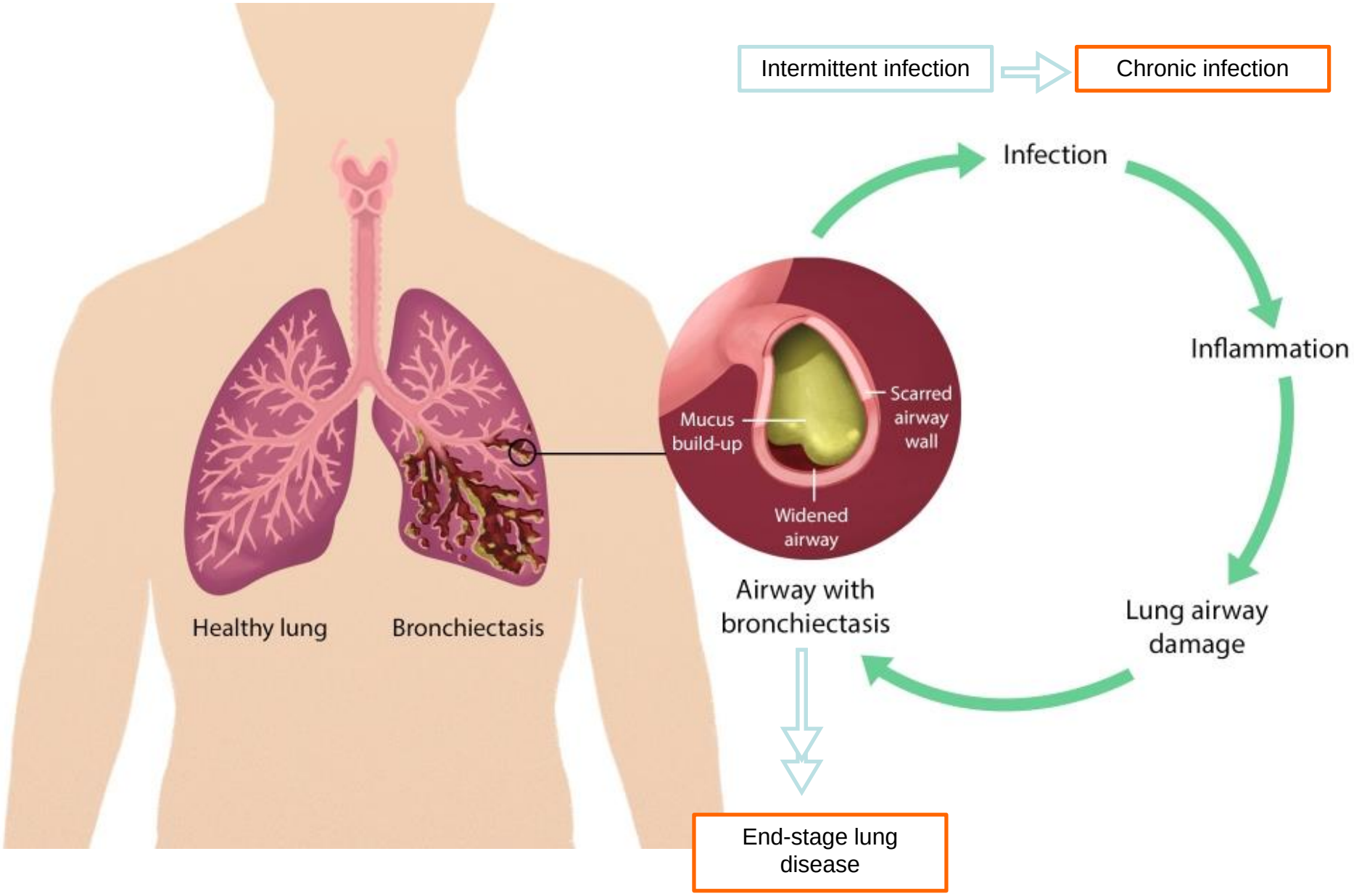
The microbiologist



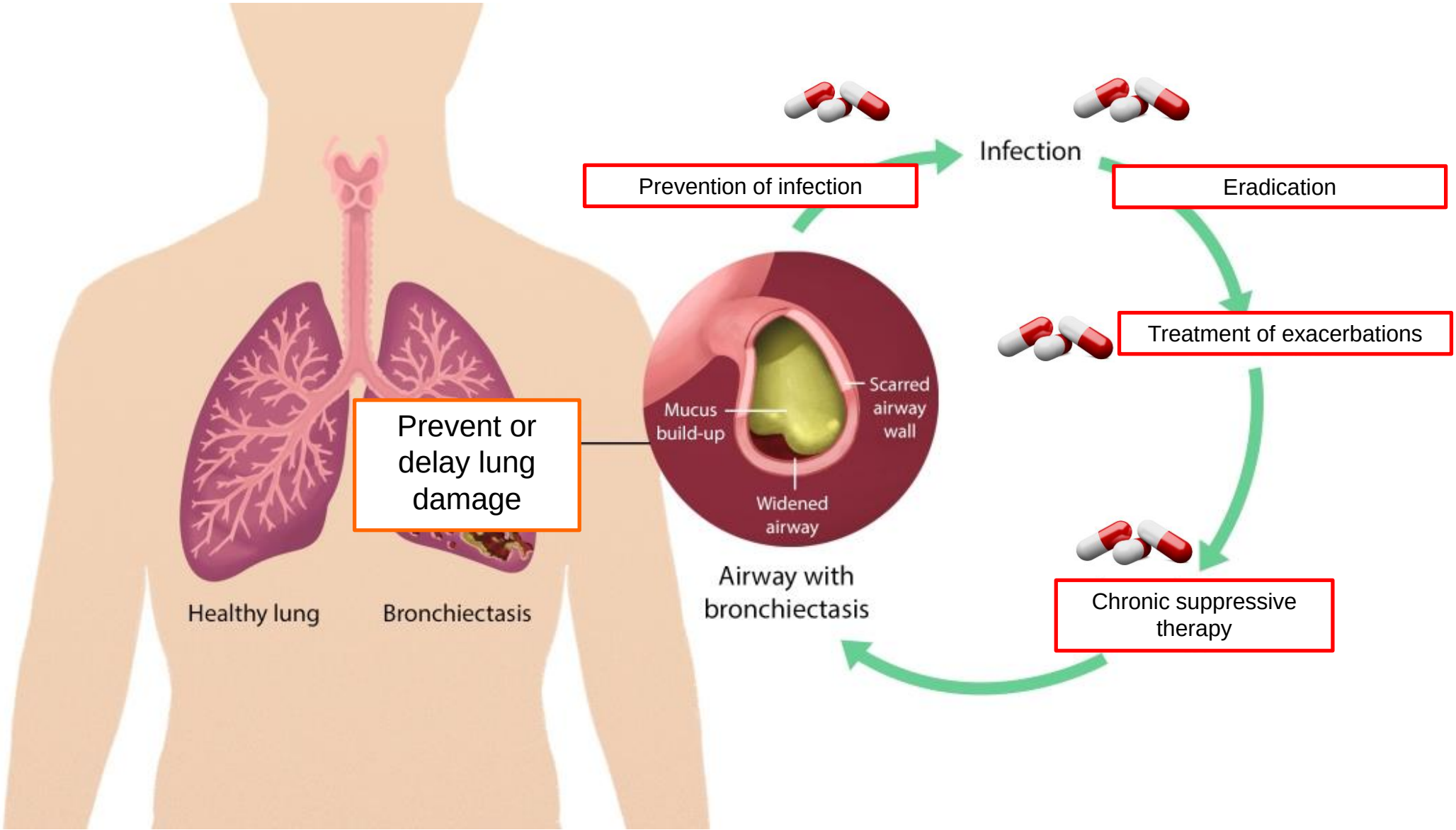
The CF Clinician

WHY DO WE USE (SO MANY) ANTIBIOTICS IN CYSTIC FIBROSIS?

Physiopathology



Role of antibiotics



THE (BACTERIAL) STORY OF A 18 YEAR OLD PATIENT

The early age

- 2001 (1 year old) :
  - *Staphylococcus aureus* (sensitive)
  - *Acinetobacter lwoffii*, *Enterobacter cloacae*
- 2003 (3 years old):
  - *Pseudomonas aeruginosa* (sensitive)
  - *Stenotrophomonas maltophilia* (instrinsically resistant to Meropenem)
- 2006 (6 years old):
  - *Streptococcus pneumoniae*

The evolution

- 2007 (7 years old)
  - *Staphylococcus aureus* becomes resistant to erythromycin and clindamycine
- 2010 (10 years old):
  - *Serratia marcescens* (instrinsically resistant to amoxicillin-clavulanate and colistine)
- 2011 (11 years old)
  - *Achromobacter xylosoxydans* (intrinsically resistant to aminoglycosides)

Getting out of ressources

- 2014 (14 years old)
  - *Mycobacterium abscessus* (multidrug-resistant)
  - *Staphylococcus aureus* becomes resistant to fluoroquinolones (still resistant to oxacillin)
- 2018 (18 years old)
  - *Pseudomonas aeruginosa* becomes resistant to aminoglycosides, fluoroquinolones and meropenem

WHAT IS IMPORTANT ?

Key elements of CF bacteriology

- Identification of a new pathogen
  - Drug resistance
  - Particular phenotype
  - Transmission?

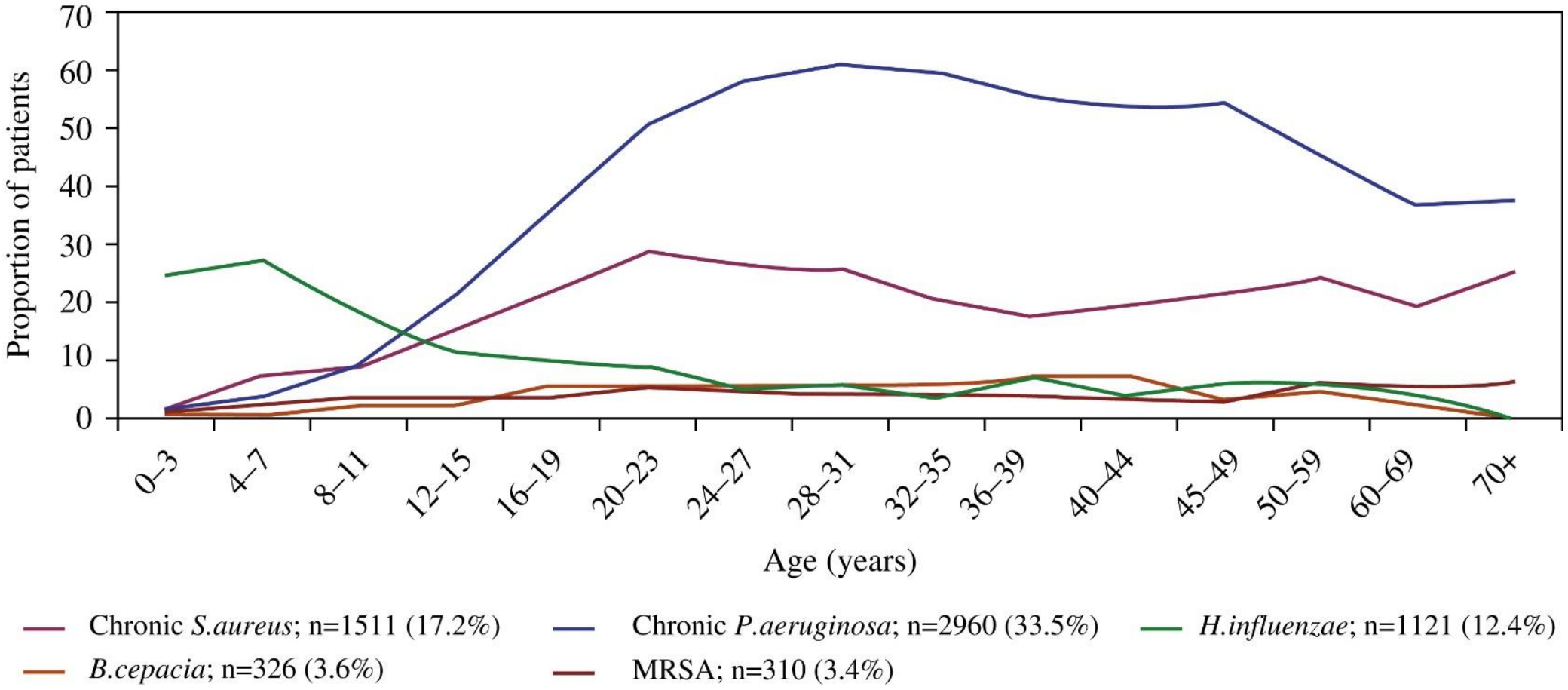
- Follow the evolution in time
  - (New) drug resistance
  - (New) phenotype

- Treatment guidance
  - Choice of therapy
  - Eradication
  - Intermittent/chronic infection
  - Re-infection?

- Prognosis
  - Impact on lung health
  - Usefulness/efficacy of treatment

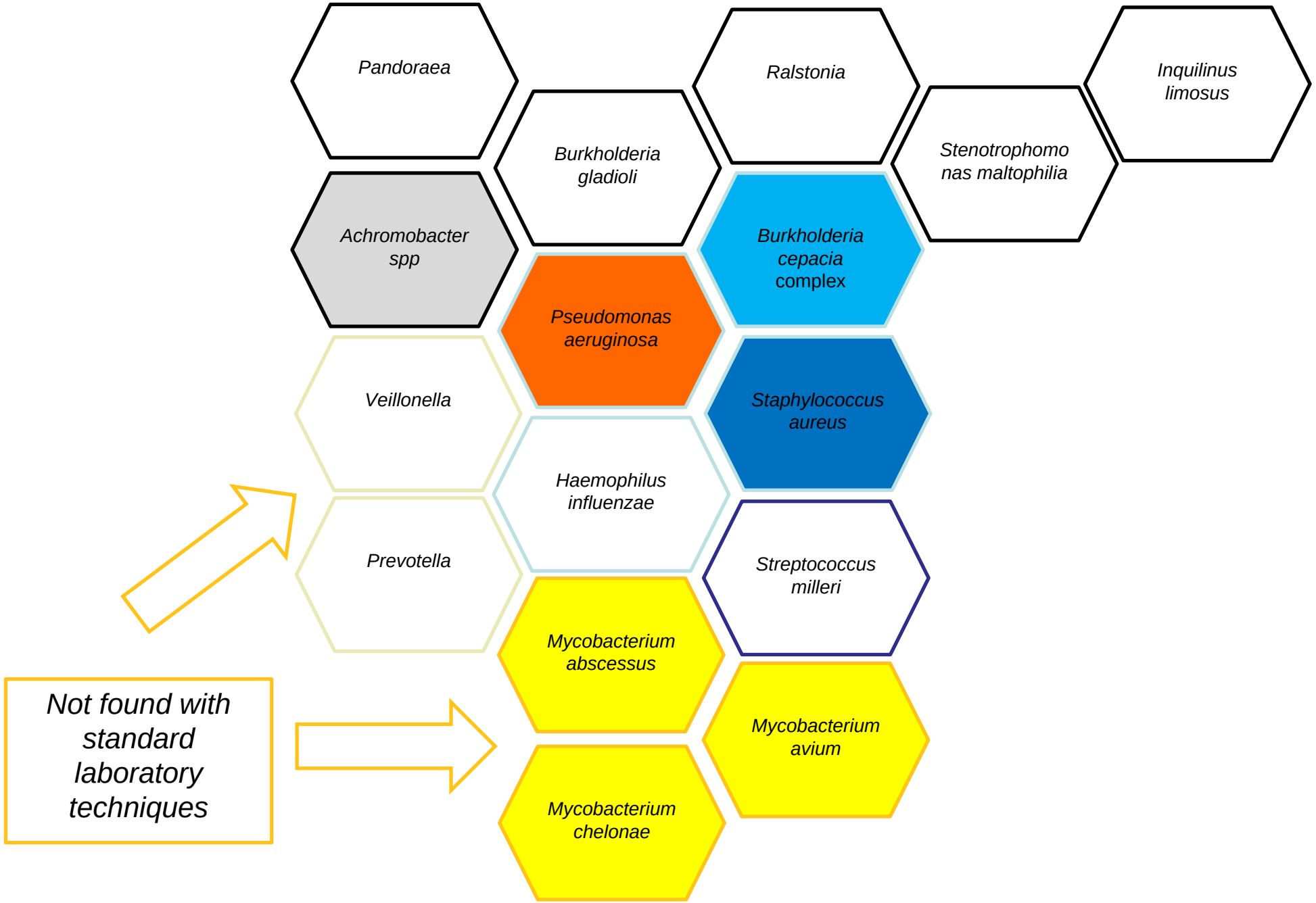
WHICH BACTERIA ARE PATHOGENIC IN CYSTIC FIBROSIS?

Bacterial pathogens



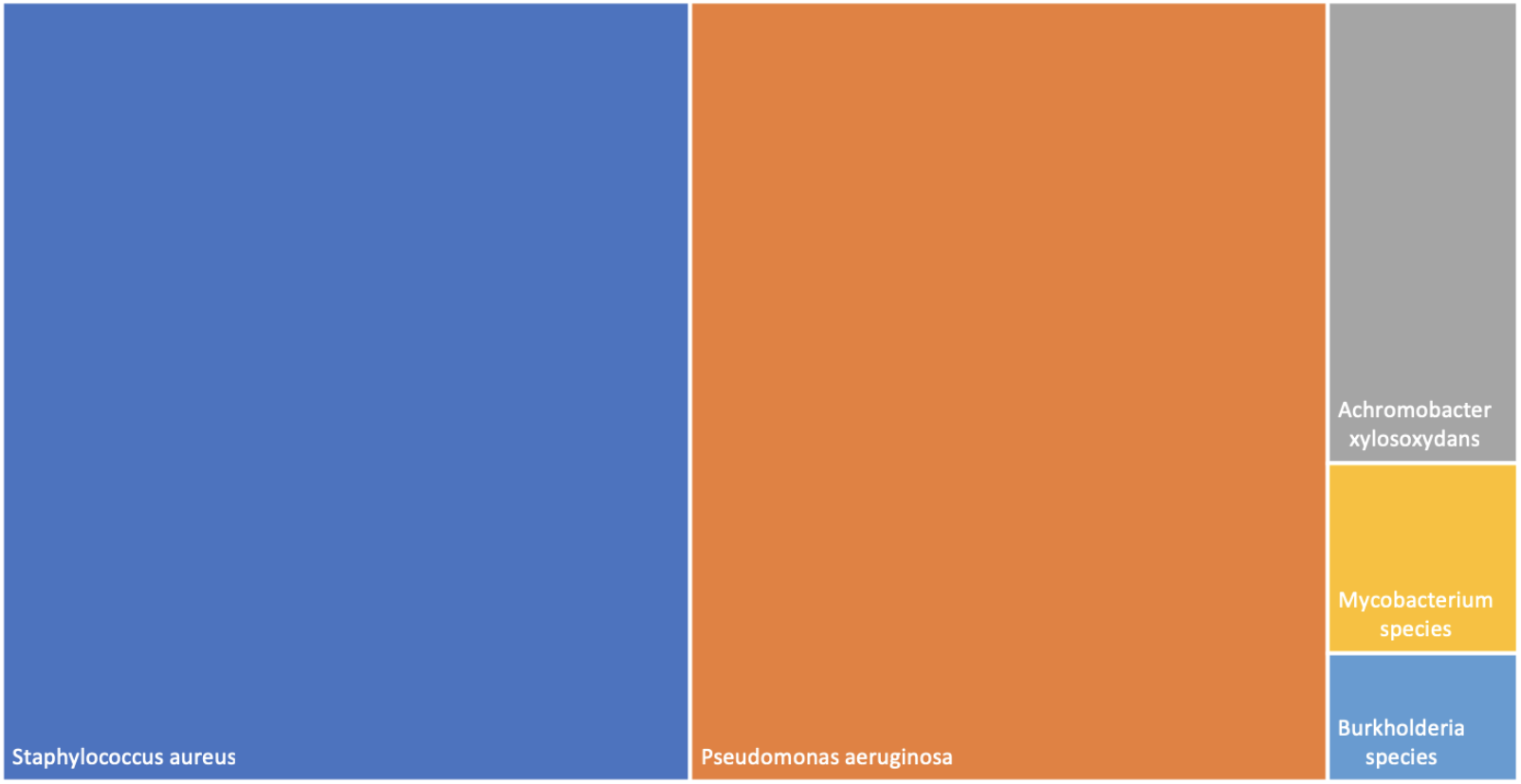
Journal of Hospital Infection 2015 89, 309-313DOI: (10.1016/j.jhin.2015.02.005)

Bacterial pathogens



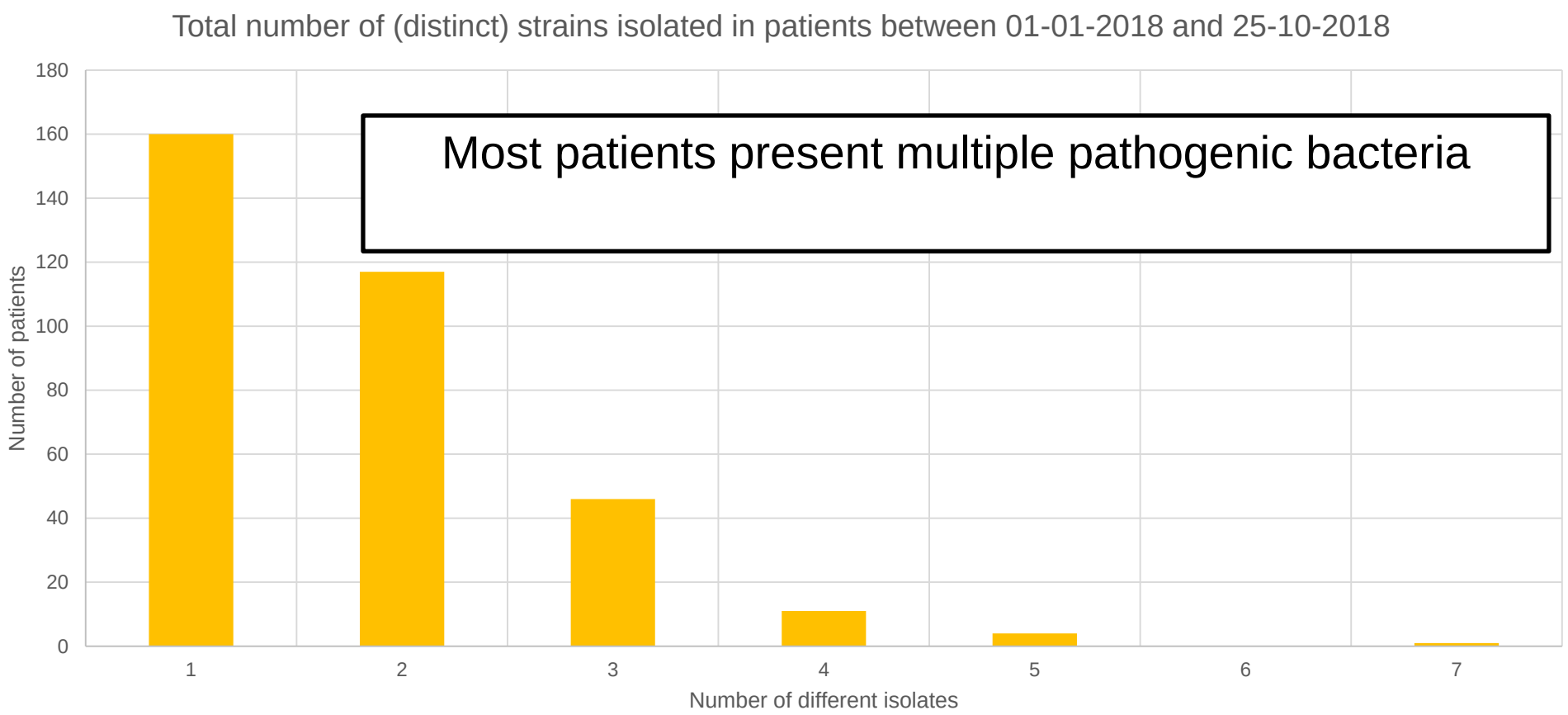
Our experience

In 2018:
339 patients with CF
Frequency of the main bacterial pathogens



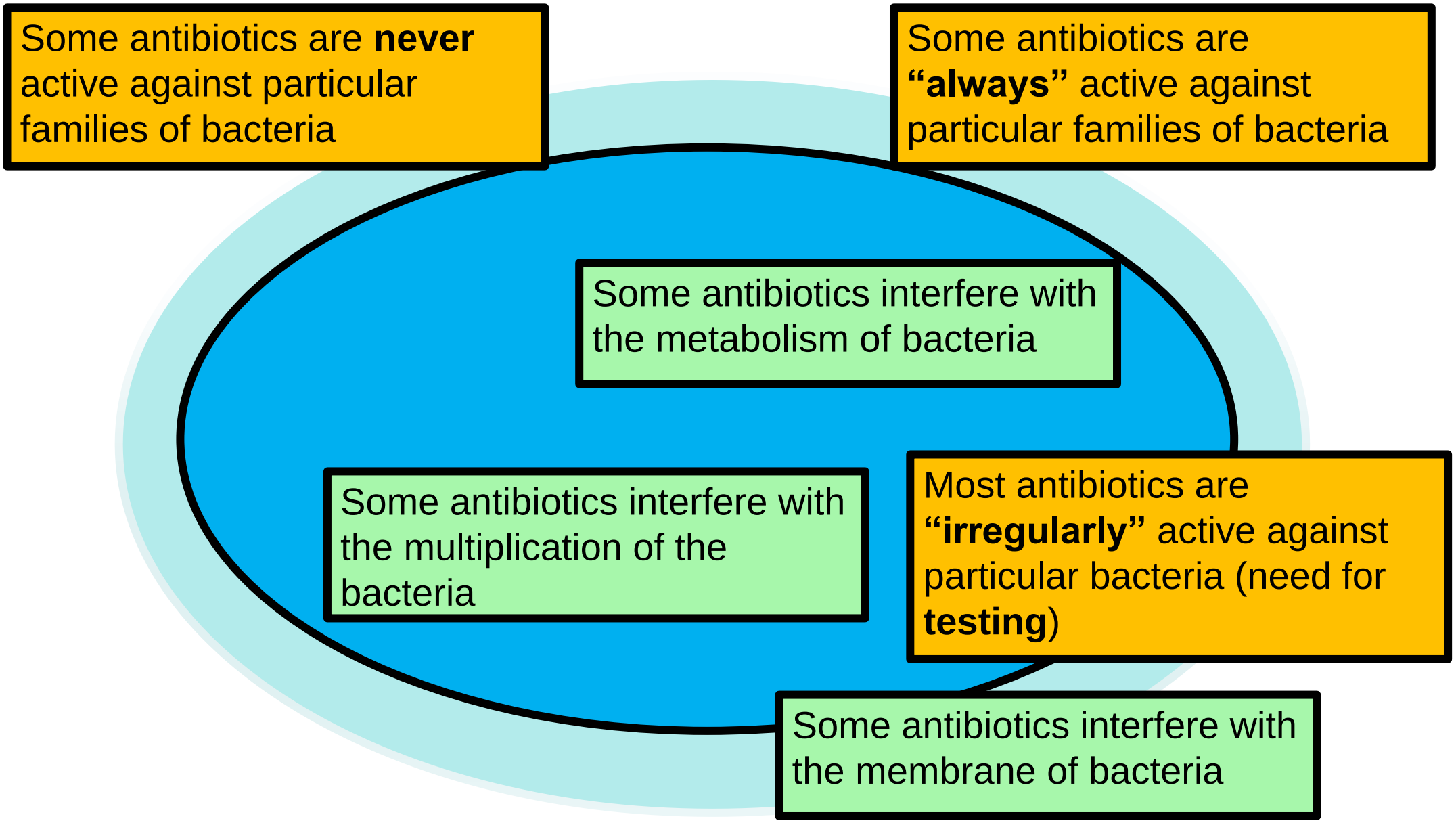
Our experience

In 2018:
339 patients with CF
Number of pathogenic strains per patient

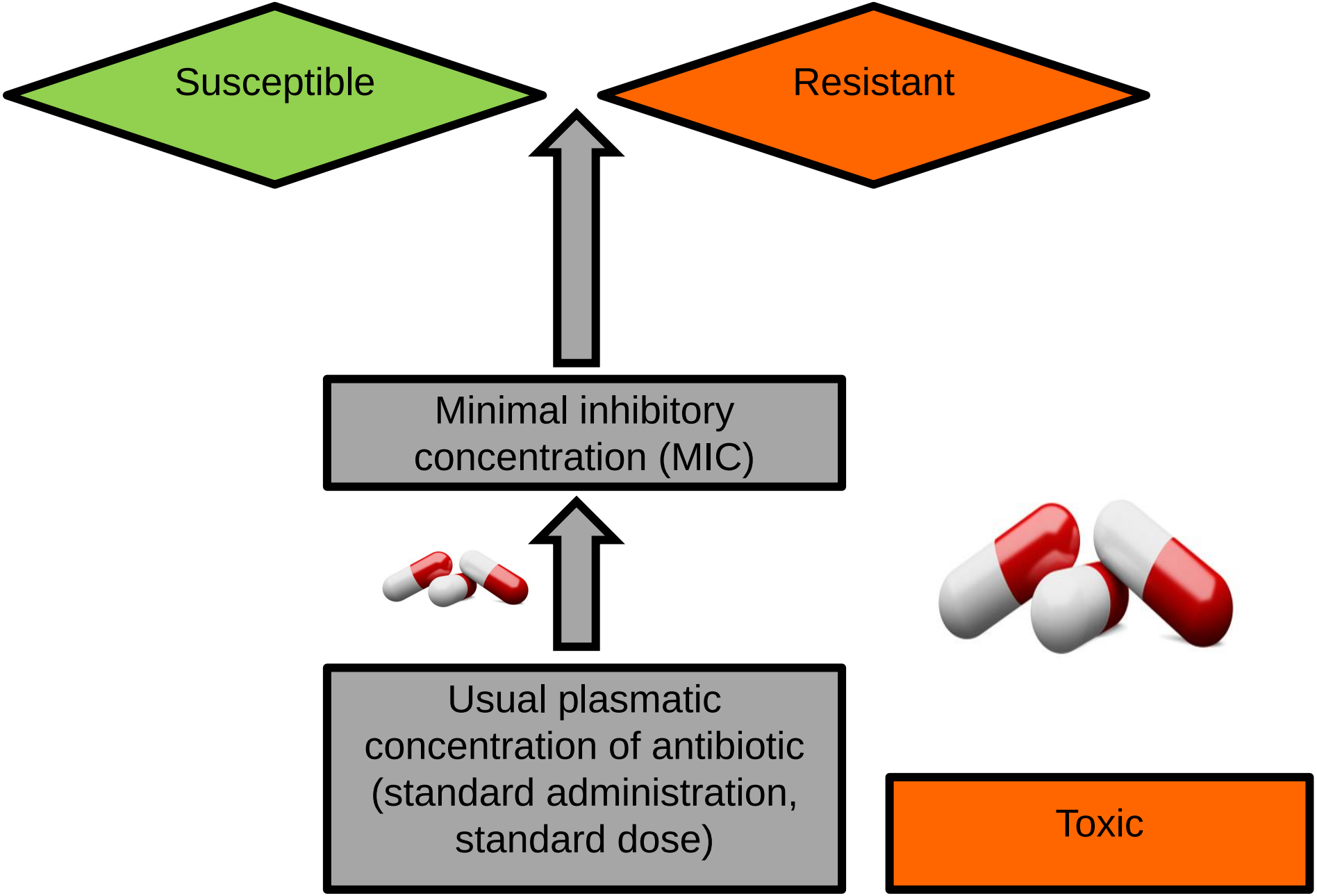


HOW DO WE (USUALLY) CHOSE THE ANTIBIOTIC TO GIVE?

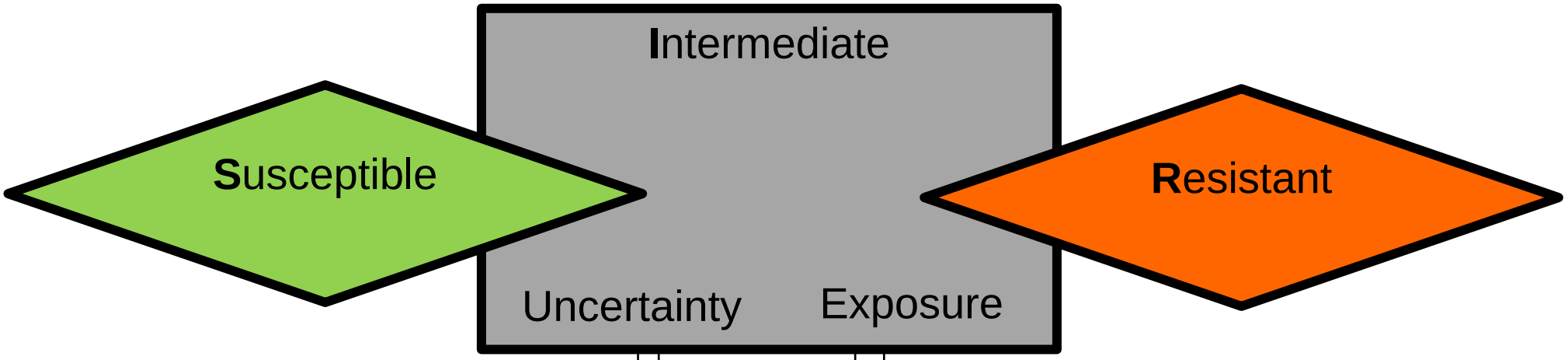
Different classes of antibiotics



Choice of antibiotics



Choice of antibiotics (2)



Optimal therapeutic effect?

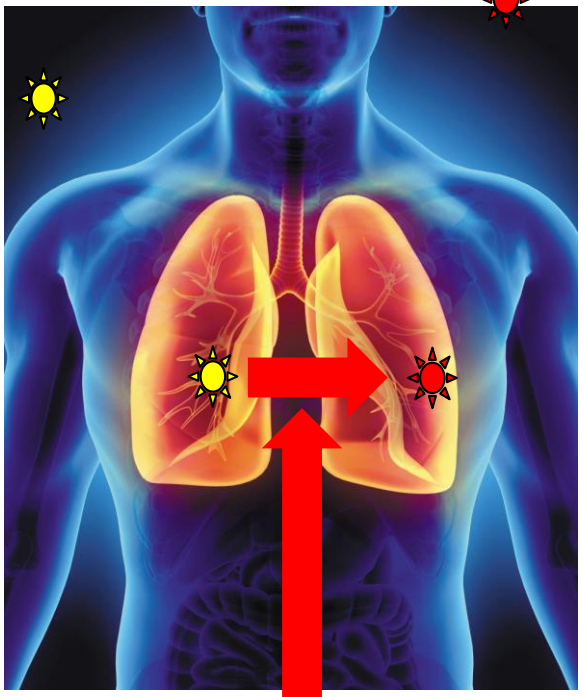
Accurate laboratory result (imprecision)?

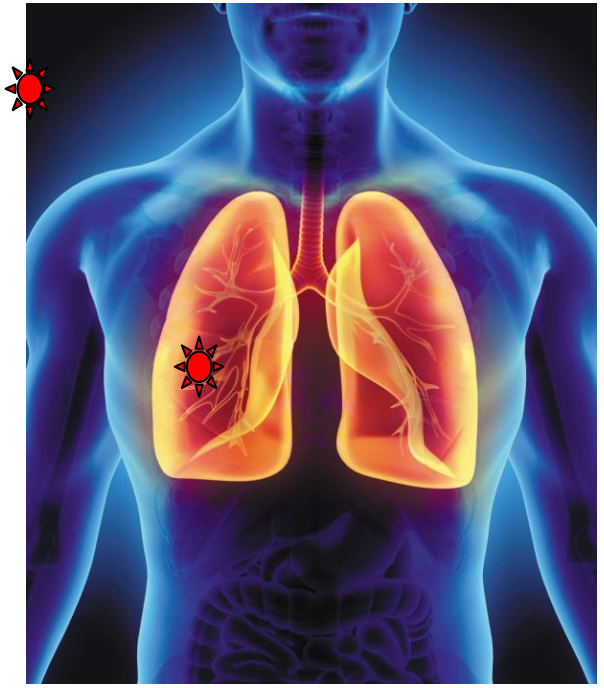
What is the actual **concentration of antibiotic at the site of infection** ?

Did we use the usual mode of administration at the usual dose?

HOW DOES THE USE OF ANTIBIOTICS CONTRIBUTE TO THE EMERGENCE OF RESISTANT BACTERIA?

Bacterial resistance





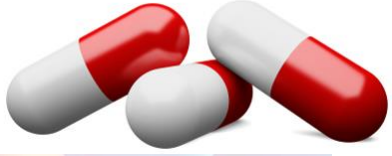
Impact of antibiotics

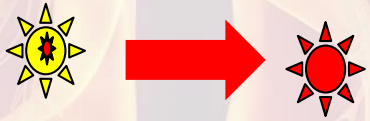
Prevention of infection (prophylaxis)

Eradication

Treatment of exacerbations

Chronic suppressive therapy

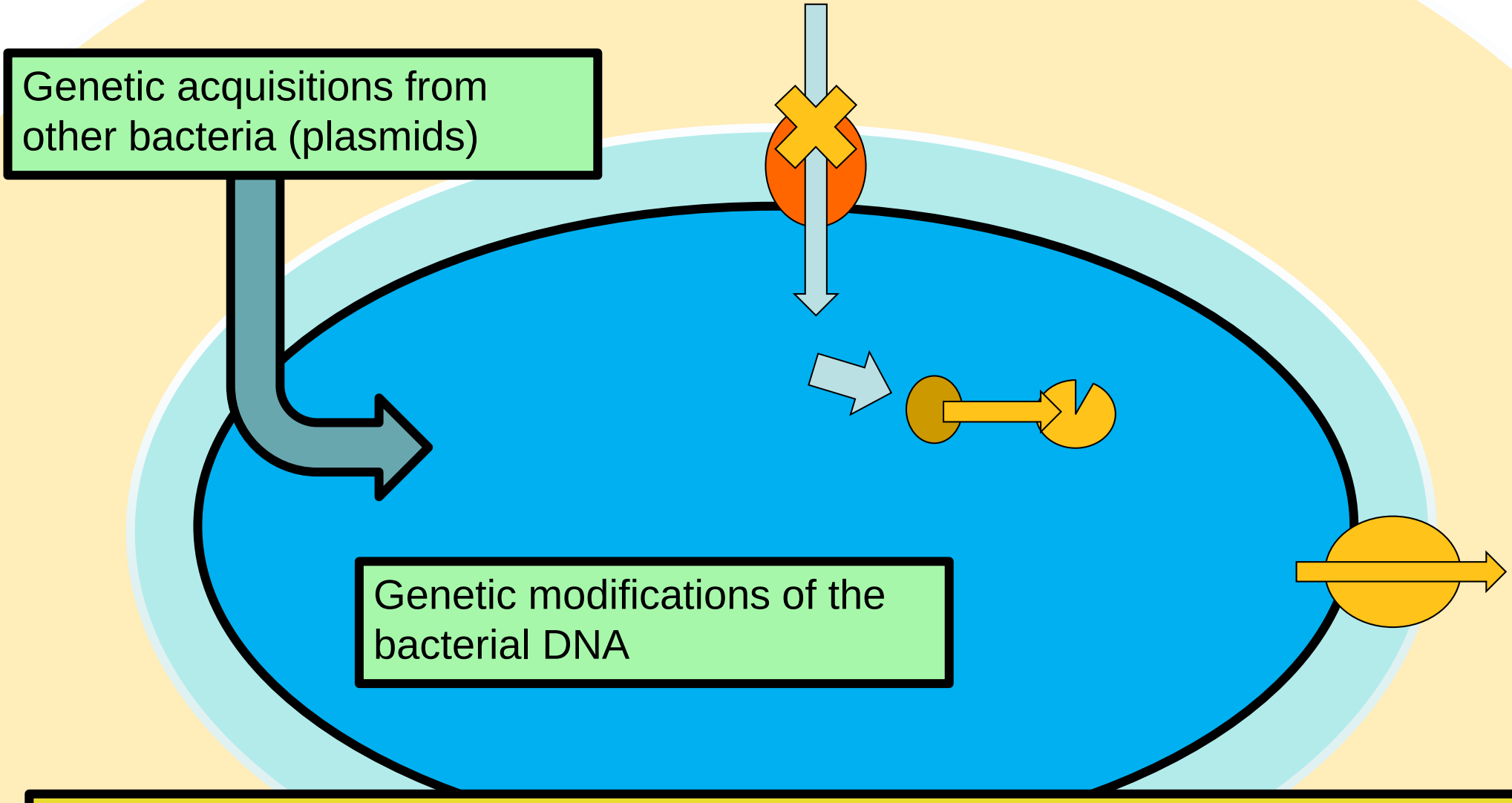




Emergence of resistant bacteria

Selection of resistant bacteria

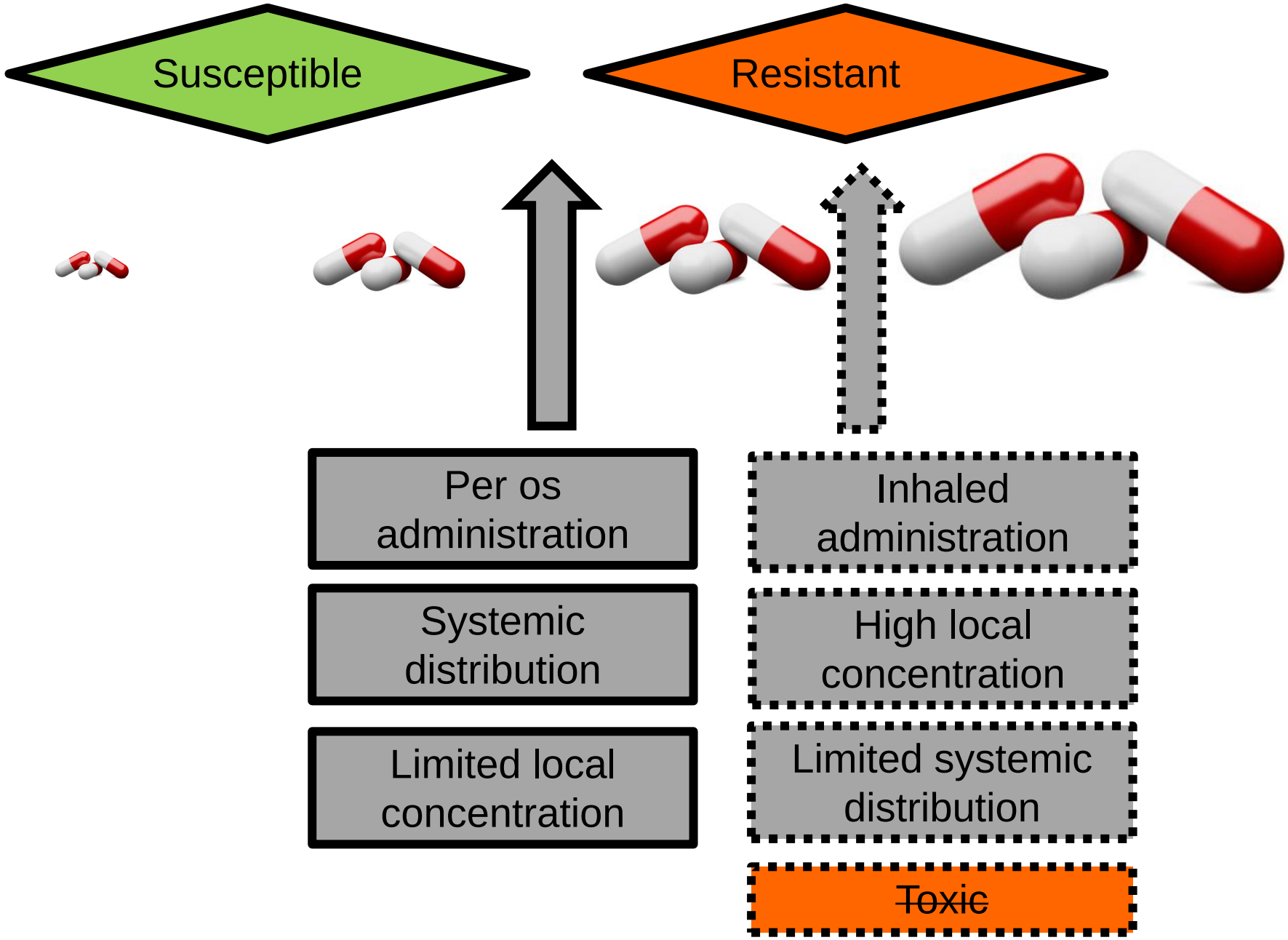
Drug resistance mechanisms



(1) The antibiotic cannot enter (biofilm and/or porins)
(2) The antibiotic is pumped out of the bacteria (efflux pumps)
(3) The antibiotic target site is absent (instrinsic resistance) or altered

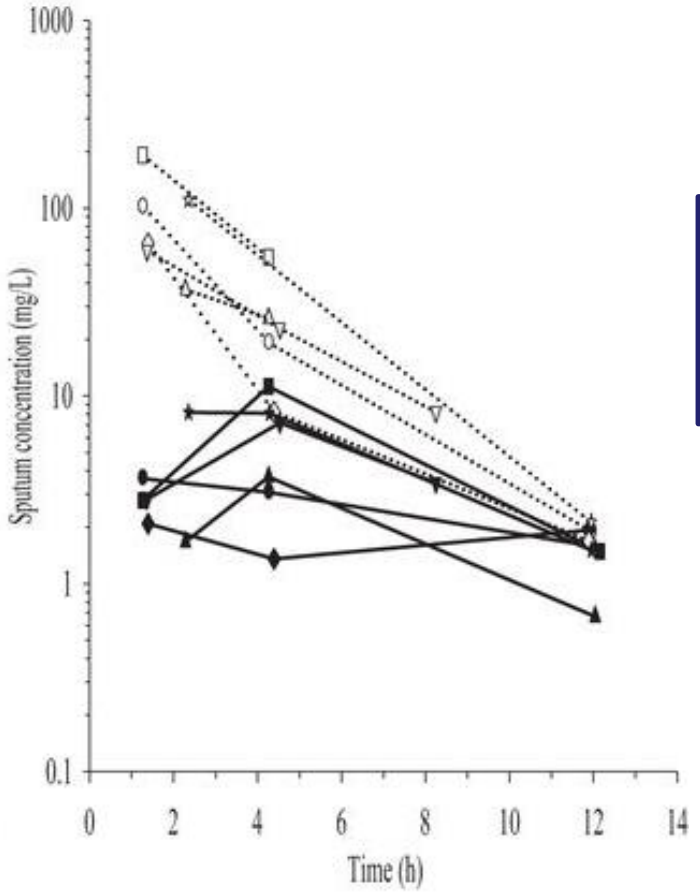
CAN WE OVERCOME DRUG RESISTANCE?

Inhaled antibiotics



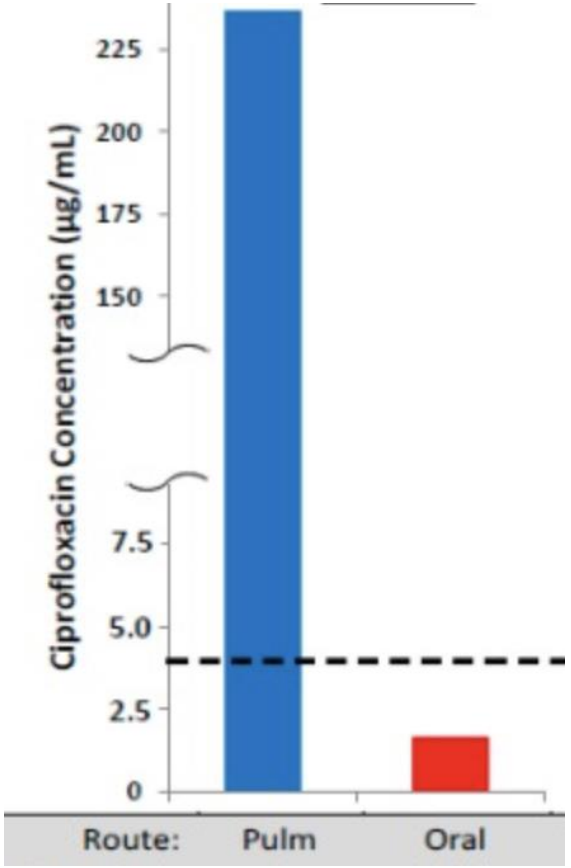
Inhaled antibiotics

Sputum concentration of colistin after intravenous *versus* nebulized administration



Need for adapted clinical breakpoints?

Sputum concentration of ciprofloxacin after oral *versus* nebulized administration



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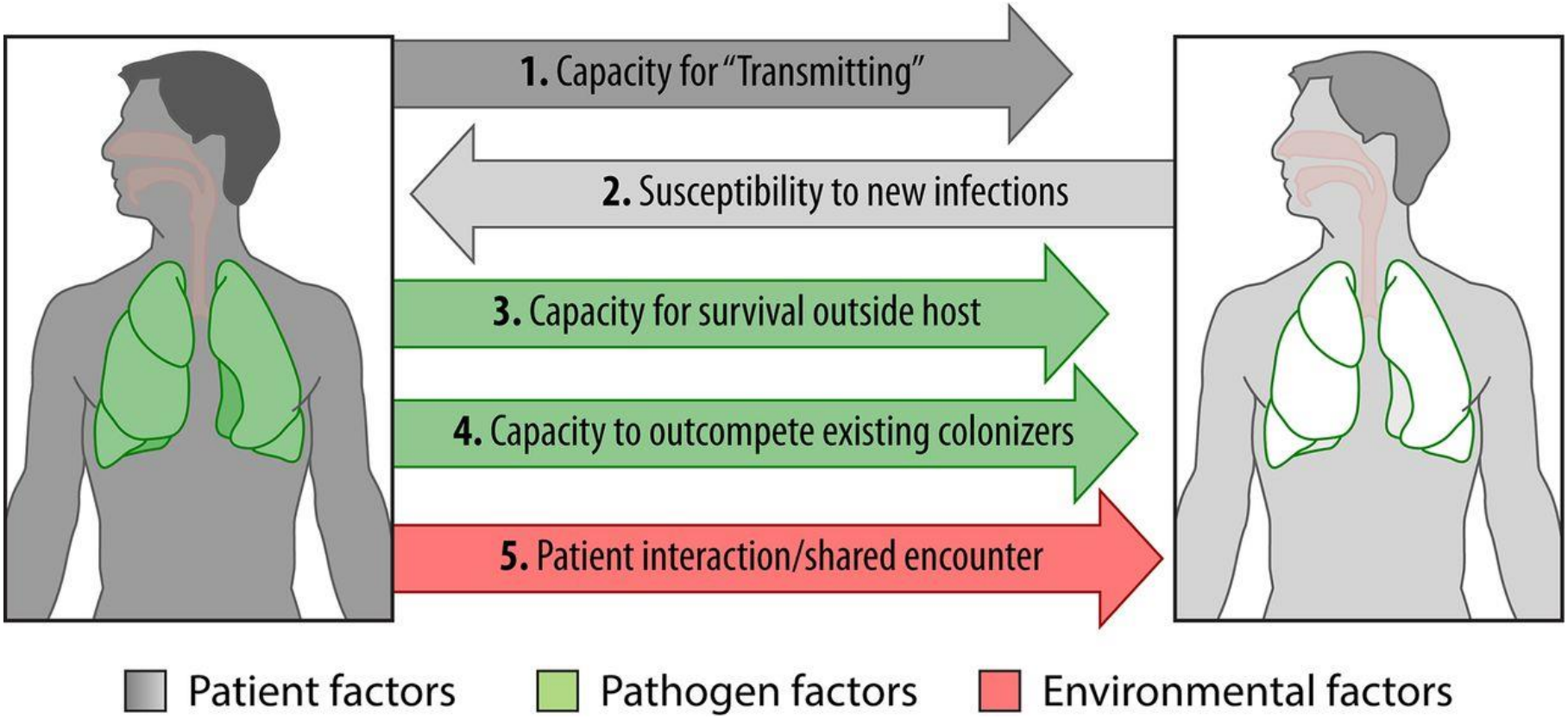
Cipolla D, Blanchard J, Gonda I. Development of Liposomal Ciprofloxacin to Treat Lung Infections. *Pharmaceutics*. 2016;8(1):6. Published 2016 Mar 1. doi:10.3390/pharmaceutics8010006

IS THERE ANYTHING WE CAN DO TO PREVENT INFECTION AND TRANSMISSION?

Bacterial transmission



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doi:10.1128/CMR.00019-18

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Journal of Cystic Fibrosis 7 (2008) 30–36

Journal of Cystic Fibrosis

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Transmission of *Pseudomonas aeruginosa* in children with cystic fibrosis attending summer camps in The Netherlands

R.W. Brimicombe [a,*], L. Dijkshoorn [b], T.J.K. van der Reijden [b], I. Kardoes [a], T.L. Pitt [d], P.J. van den Broek [b], H.G.M. Heijerman [c]

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Received 16 October 2006; received in revised form 28 February 2007; accepted 13 April 2007
Available online 25 May 2007

Abstract

Background: Cross-infection of *Pseudomonas aeruginosa* has been reported to occur at holiday camps for children with Cystic Fibrosis (CF) with varying frequency. The study aimed to establish the degree of transmission resulting in subsequent infection of *P. aeruginosa* among CF children ($n=80$) attending holiday camps in The Netherlands.

Methods: The study was performed in the summer of 2001 in four camps organised simultaneously at different locations. Sputum was collected on day 1 of the holiday, and three and six months later. Different morphotypes of *P. aeruginosa* from sputum were genotyped by AFLP™ analysis. Criteria were defined for the degree of evidence of transmission.

Results: There were 18 cases possible, 2 cases of probable transmission and 1 case of highly probable transmission. Two predominant types of *P. aeruginosa* were found (types 18 and 23). Type 18 was already prevalent on day 1 mostly in younger children and was involved in eleven cases of transmission; type 23 was involved in six cases of transmission among older children.

Conclusions: There was a considerable risk of transmission of *P. aeruginosa* during holiday camps for CF children in The Netherlands. Two genotypes of *P. aeruginosa* appeared to be easily transmissible, one of which seemed common in the Dutch CF population.

Whole-genome sequencing to identify transmission of *Mycobacterium abscessus* between patients with cystic fibrosis: a retrospective cohort study

Josephine M Bryant, Dorothy M Grogono*, Daniel Greaves, Juliet Foweraker, Iain Roddick, Thomas Inns, Mark Reacher, Charles S Haworth, Martin D Curran, Simon R Harris, Sharon J Peacock, Julian Parkhill, R Andres Floto*

Summary

Background Increasing numbers of individuals with cystic fibrosis are becoming infected with the multidrug-resistant non-tuberculous mycobacterium (NTM) *Mycobacterium abscessus*, which causes progressive lung damage and is extremely challenging to treat. How this organism is acquired is not currently known, but there is growing concern that person-to-person transmission could occur. We aimed to define the mechanisms of acquisition of *M abscessus* in individuals with cystic fibrosis.

Method Whole genome sequencing and antimicrobial susceptibility testing were done on 168 consecutive isolates of *M abscessus* from 31 patients attending an adult cystic fibrosis centre in the UK between 2007 and 2011. In parallel, we undertook detailed environmental testing for NTM and defined potential opportunities for transmission between patients both in and out of hospital using epidemiological data and social network analysis.

Findings Phylogenetic analysis revealed two clustered outbreaks of near-identical isolates of the *M abscessus* subspecies *massiliense* (from 11 patients), differing by less than ten base pairs. This variation represents less diversity than that seen within isolates from a single individual, strongly indicating between-patient transmission. All patients within these clusters had numerous opportunities for within-hospital transmission from other individuals, while comprehensive environmental sampling, initiated during the outbreak, failed to detect any potential point source of NTM infection. The clusters of *M abscessus* subspecies *massiliense* showed evidence of transmission of mutations acquired during infection of an individual to other patients. Thus, isolates with constitutive resistance to amikacin and clarithromycin were isolated from several individuals never previously exposed to long-term macrolides or aminoglycosides, further indicating cross-infection.

Interpretation Whole genome sequencing has revealed frequent transmission of multidrug resistant NTM between patients with cystic fibrosis despite conventional cross-infection measures. Although the exact transmission route is yet to be established, our epidemiological analysis suggests that it could be indirect.

Funding The Wellcome Trust, Papworth Hospital, NIHR Cambridge Biomedical Research Centre, UK Health Protection Agency, Medical Research Council, and the UKCRC Translational Infection Research Initiative.

Lancet 2013; 381: 1551–60

Published Online
March 29, 2013
http://dx.doi.org/10.1016/S0140-6736(13)60632-7

See **Comment** page 1517

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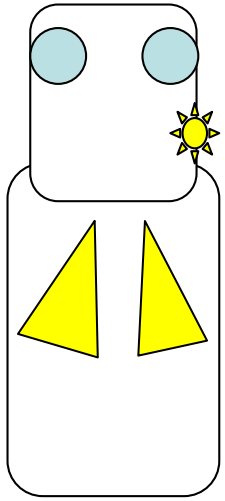
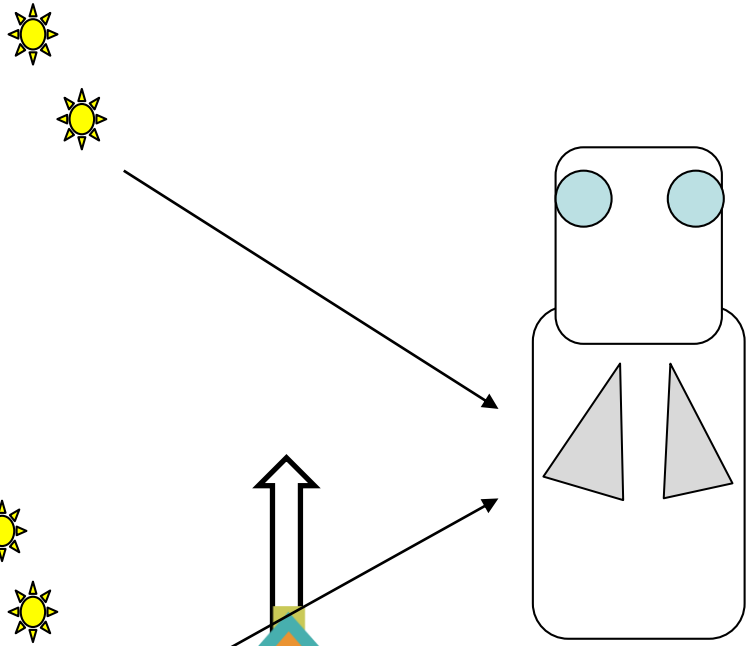
Preventing infection





Use of antibiotics to control the “source” of infection

Use of antibiotics to prevent infection

Limitation of contacts (direct and indirect)

Do these measures work?

Towards a new workflow

New isolate
- Drug susceptibility testing

Transmission? Environmental acquisition?

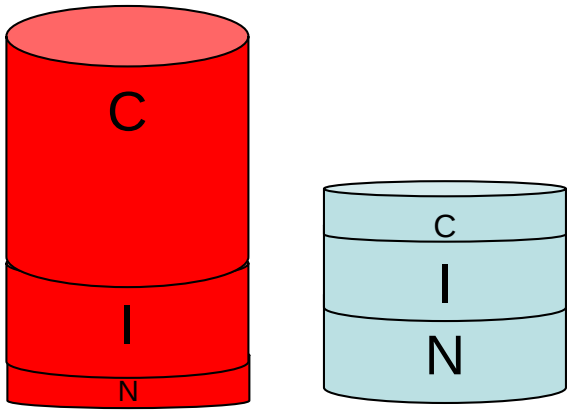
Introduction of WGS in clinical routine

Intermittent infection
- Drug susceptibility testing (3M)

Early genetic determinants of treatment success or evolution towards chronicity?

Chronic infection
- Drug susceptibility testing (1Y)

Genetic determinants of late bacterial adaptations (change in resistance patter, change in phenotype)



WHAT SHOULD WE URGENTLY IMPROVE IN THE FIELD OF MICROBIOLOGY TO IMPROVE THE HEALTH OF PATIENTS WITH CYSTIC FIBROSIS?

- Better diagnostic tools
  - Early identify different bacterial pathogens
  - Correct treatment guidance
  - Early identification of transmission

- Better predictive tools
  - Prediction of evolution towards chronicity
  - Prediction of impact on lung health

Any questions?

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