



Inhaled antibiotics in Cystic Fibrosis

Current state and future perspectives

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Presenter's disclosures

Clinical Trials

Aradigm corporation; Novartis; Zambon; Vertex; Insmed

Consultancies

Astrazeneca; Grifols; Zambon; Vertex; Chiesi

Outline

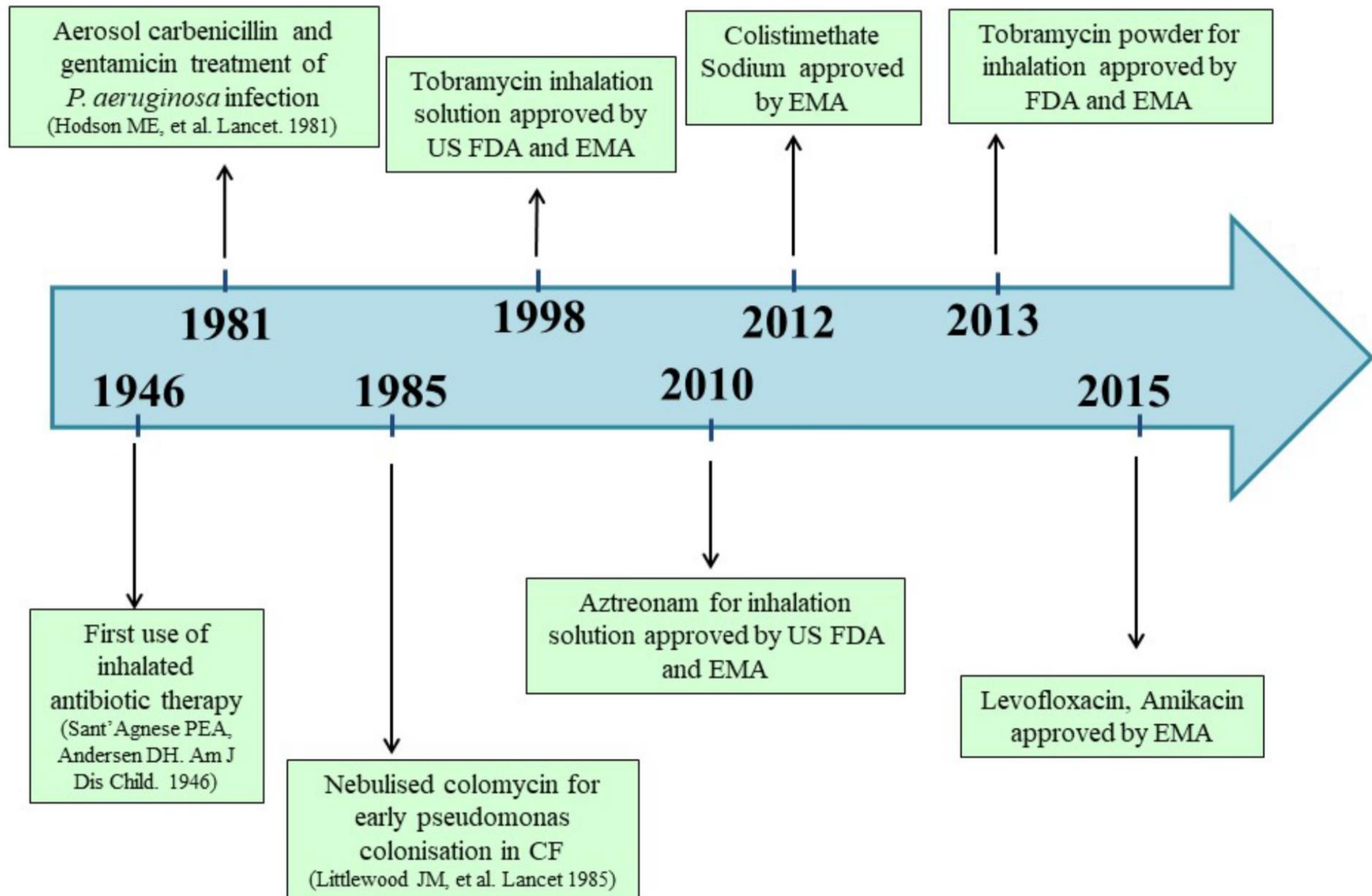
- 1) What's the background now?**
- 2) What's needed most?**
- 3) What are the limitations for further development?**

Outline

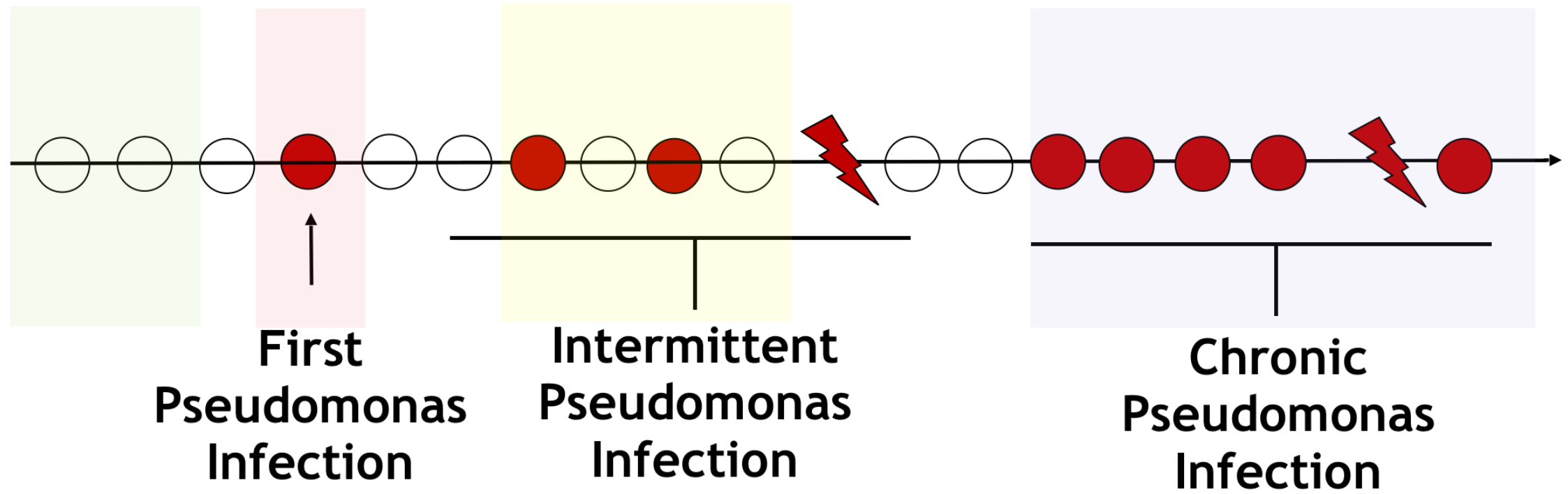
1) What's happening now?

- Current position of inhaled antibiotics in CF care

State-of-art in inhaled antibiotics in CF care



A Drug for All Seasons



ERADICATION TREATMENT

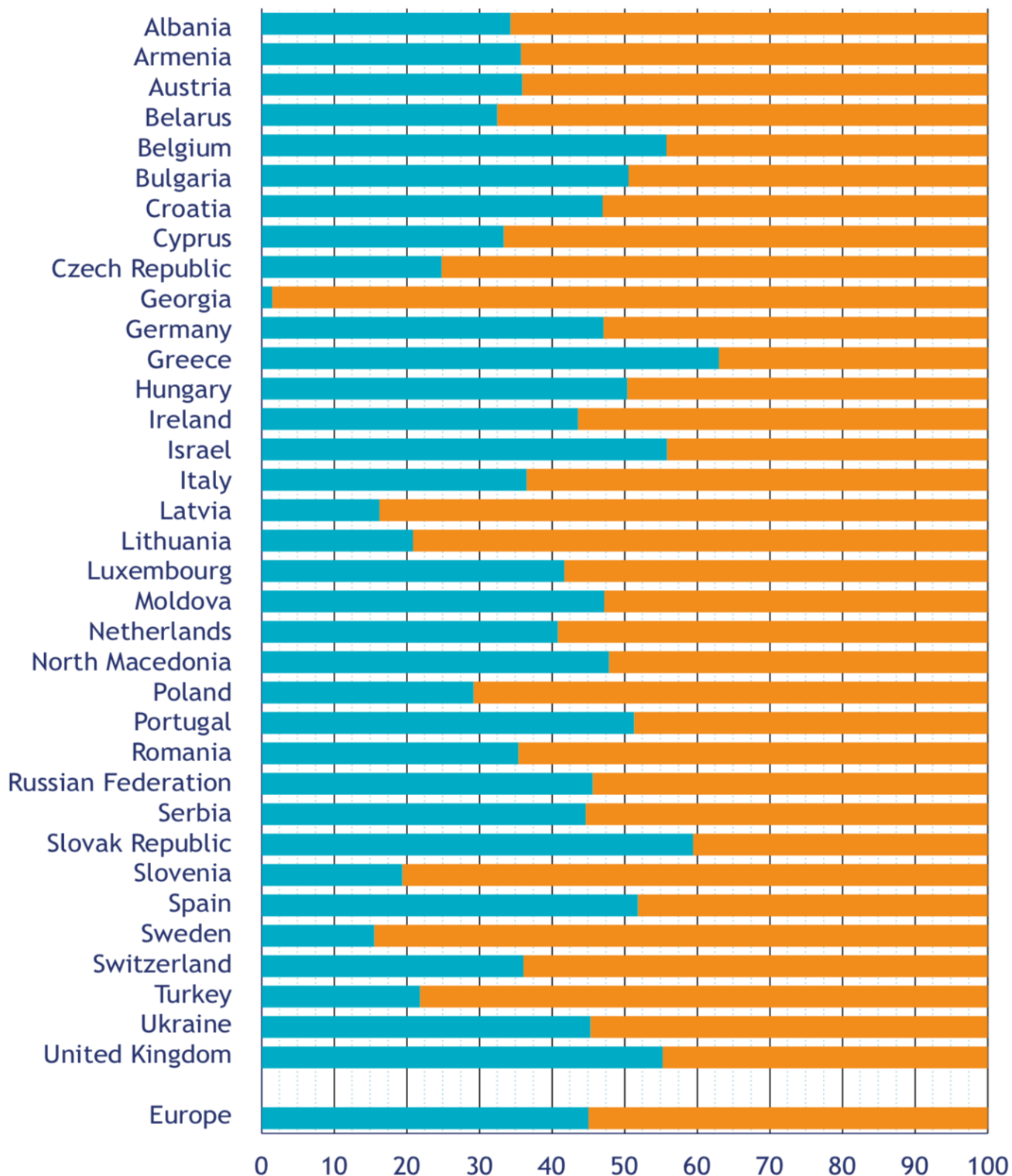
SUPPRESSIVE TREATMENT

Data from patient registries



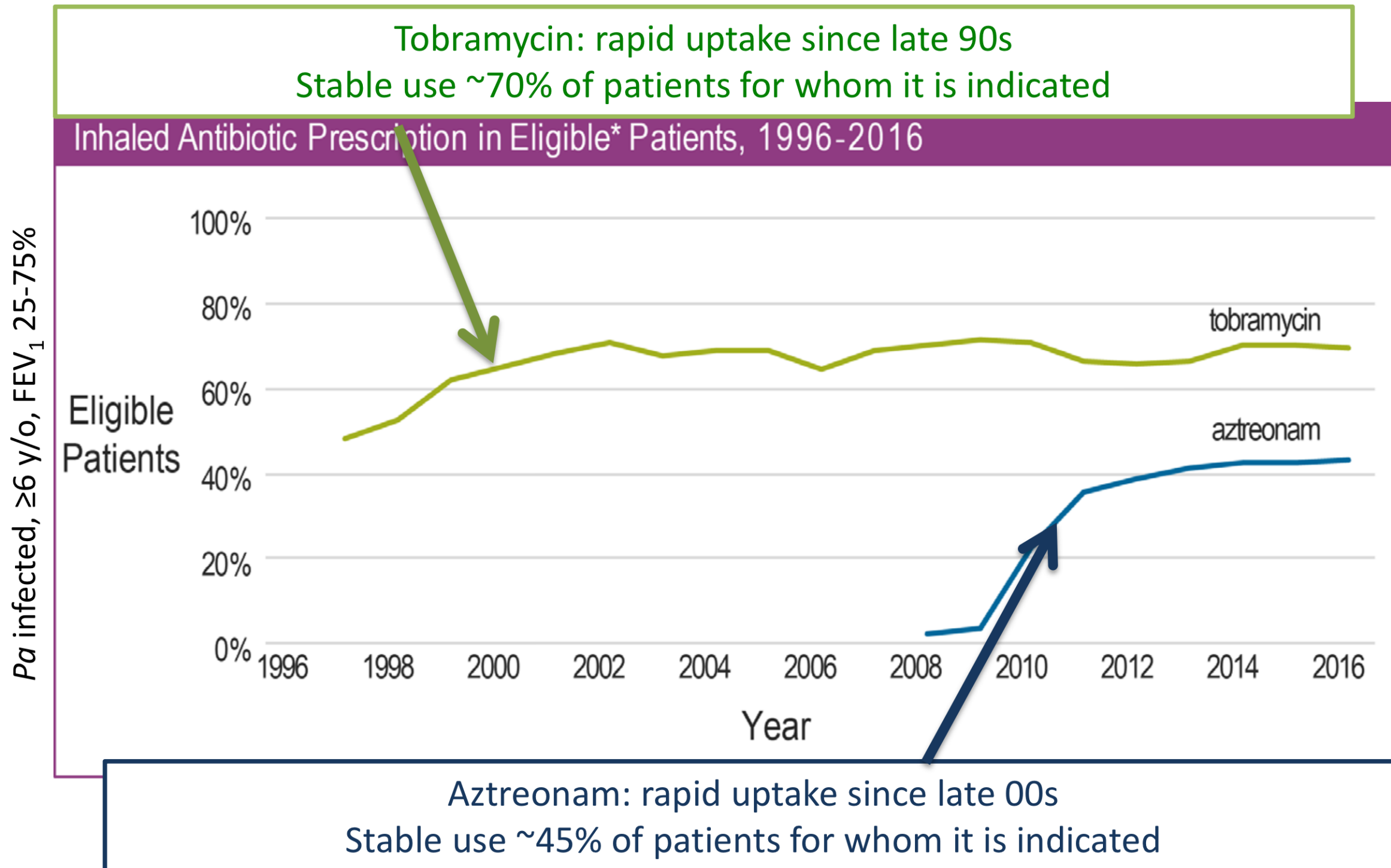
% of people with CF
who use inhaled antibiotics*

Yes
No



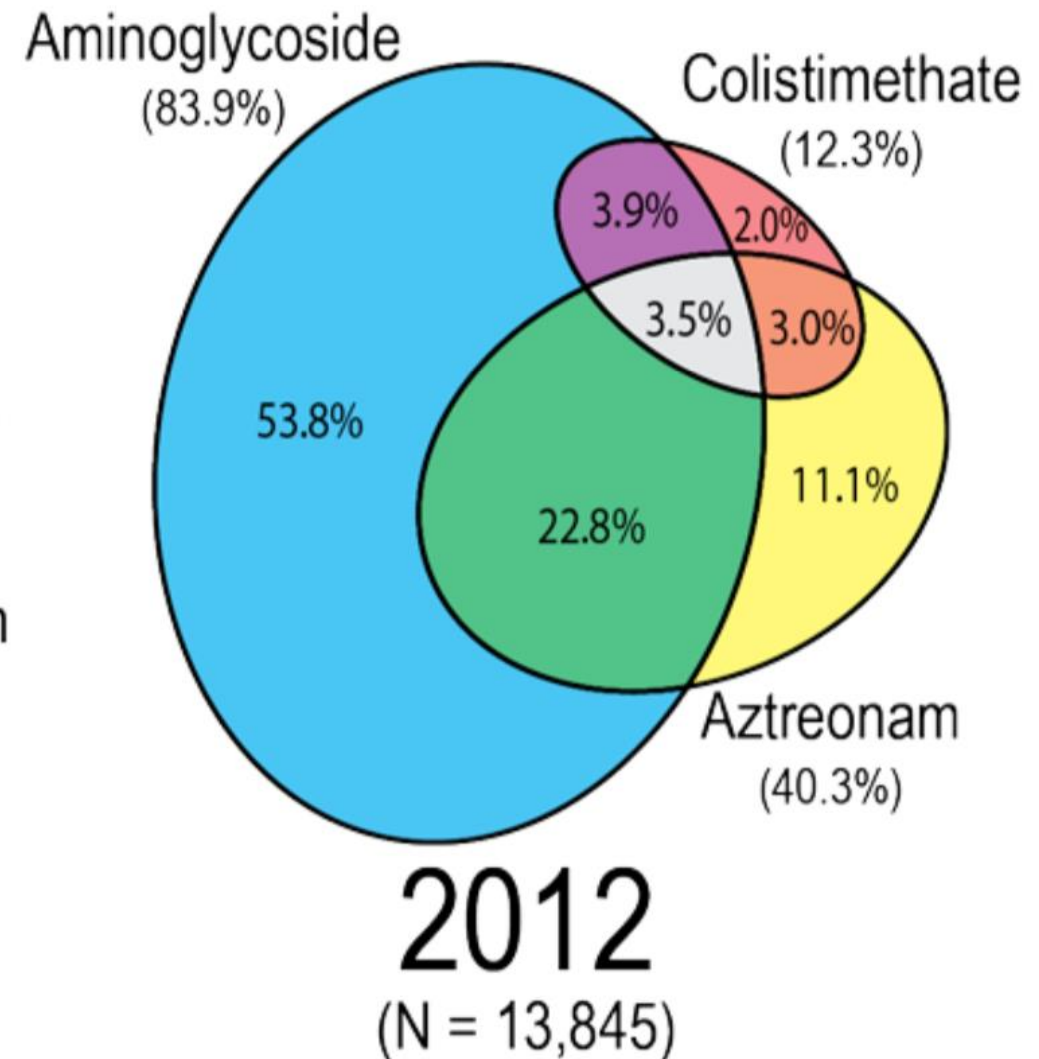
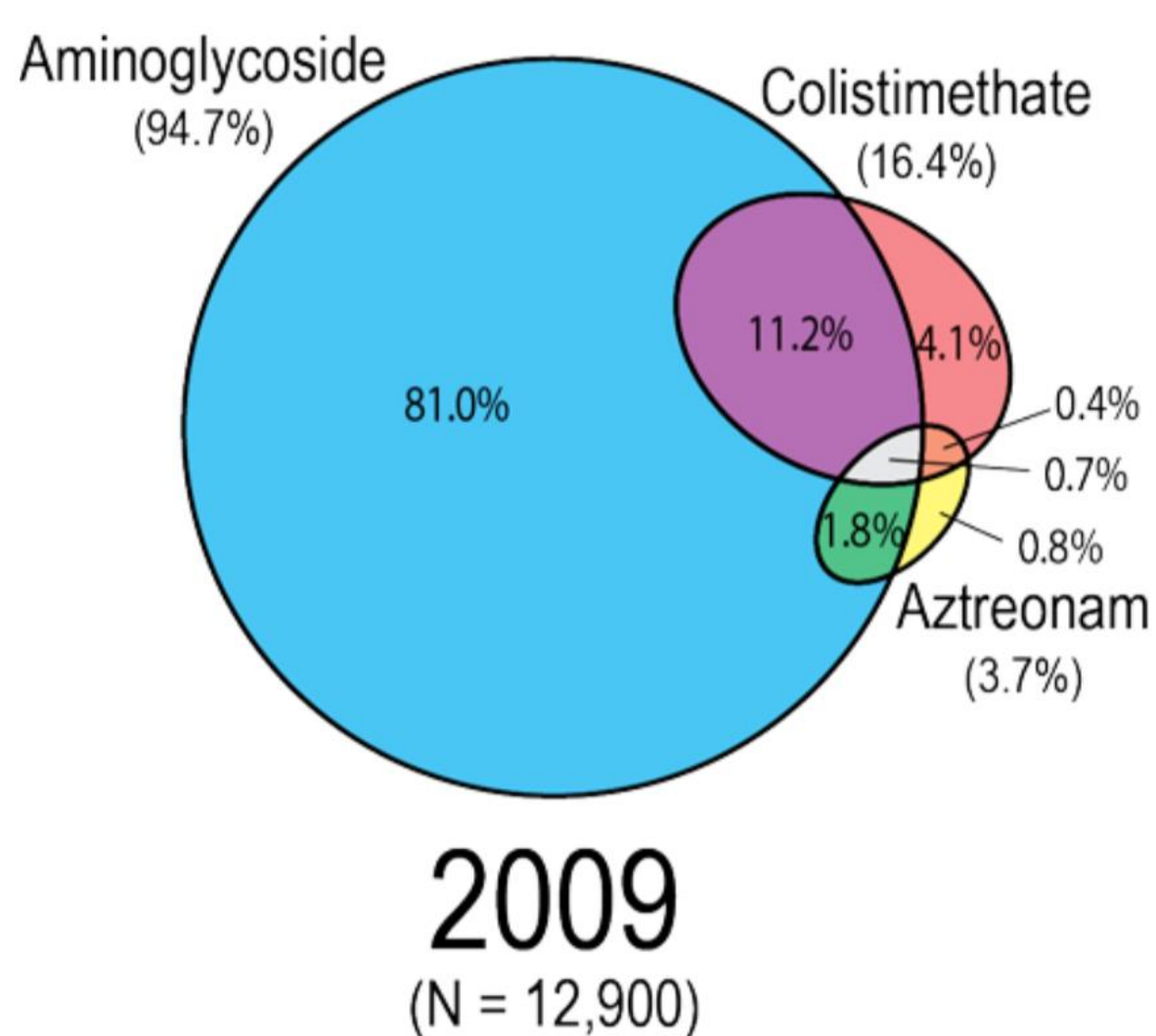
- *at least 3 months/year*
- *ranging from 30% to 50%*
- *overlapping PA epidemiology*
- *issues in terms of availability across Europe*

Data from patient registries



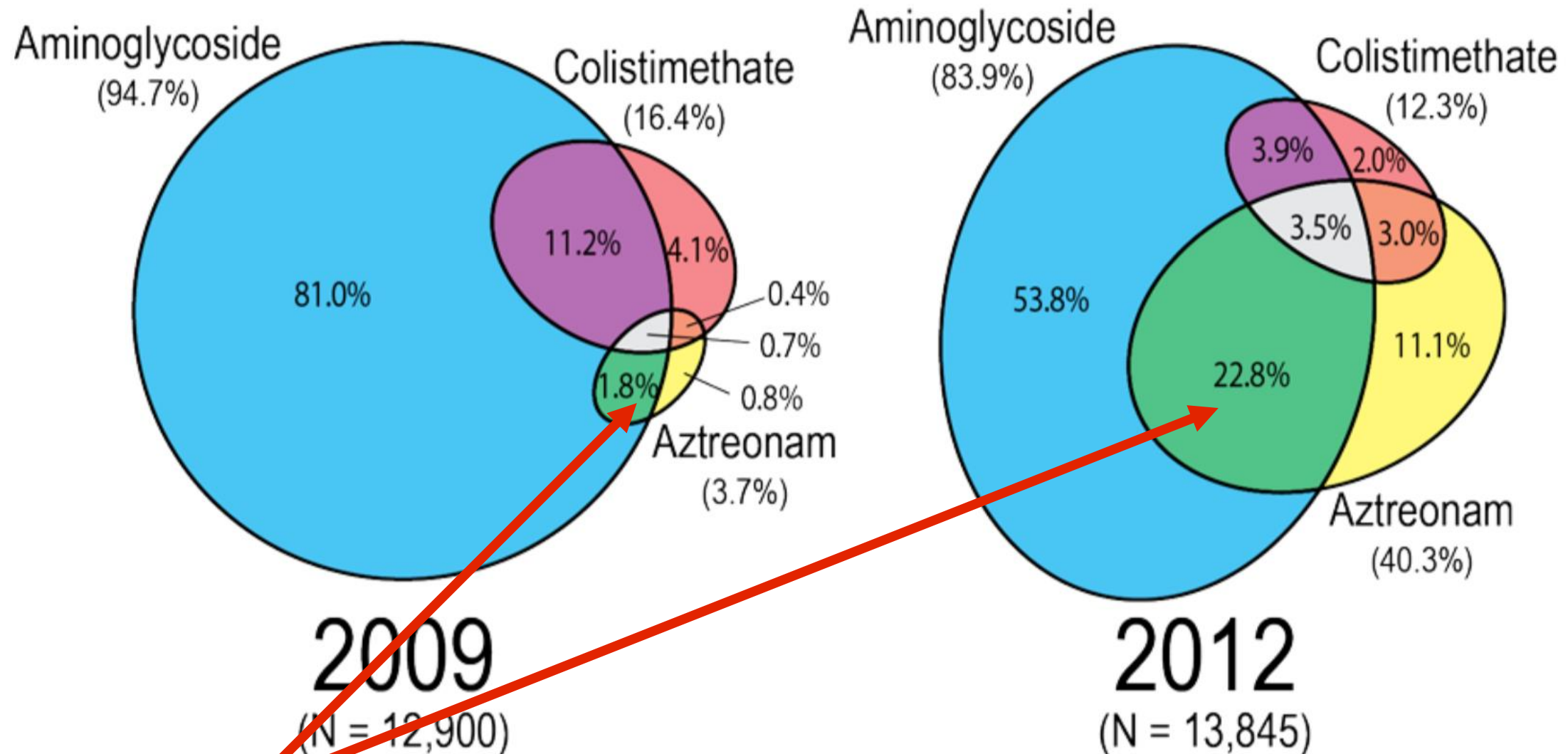
Data from patient registries

2016



Data from patient registries

2016



Continuous Alternating Treatment

Targeting patients with severe lung disease

Continuous Alternating Therapy (CAT)

- **User profiling**

- Adult age
- Lower pulmonary function
- Chronic *P. aeruginosa* respiratory infection
- Higher number of pulmonary exacerbations

Targeting patient's characteristics

Inhaled drug	Nebuliser	DPI
Hypertonic saline (7%)	+	-
Mannitol	-	+
Dornase alpha	+	-
Bronchodilators	+	+
Inhaled corticosteroids	+	+
Tobramycin	+	+
Colistin	+	+
Aztreonam	+	-
AmBisome	+	-
Liposomal amikacin	+	-
Ciprofloxacin	-	+
Vancomycin	-	+
Clarithromycin	-	+

State-of-art in inhaled antibiotics in CF care



- Mostly developed between 20 and 10 years ago
- All target the same pathogen
- High prescription rate and long-term exposure
- Often with no reliable monitoring of clinical endpoints
- adherence issue

Outline

1) What's the background now?

- Current position of inhaled antibiotics in CF care

2) What's needed most?

- Unmet needs for inhaled antibiotics in CF care

Unmet needs for inhaled antibiotics

- **Eradication of first *P. aeruginosa* isolation**
 - two effective treatment options
 - shared guidelines
 - systemic antibiotics in case of eradication failure

More need ? NO

Unmet needs for inhaled antibiotics

- **Persistent *P. aeruginosa* with no clinical decline**
 - several effective treatment options
 - several drug delivery options
 - shared guidelines and centre SOPs
 - CAT

More need ? NO (more or less)

Unmet needs for inhaled antibiotics

- **Chronic *P. aeruginosa* and declining patient**
 - long-term exposure to existing agents
 - CAT not always effective in prevention of clinical decline
 - no new antibiotic classes

More need ? YES

Unmet needs for inhaled antibiotics

- **Other (less common) pathogens and declining patient**
 - more data about pathogenicity
 - increasing prevalence and incidence
 - unproven use of off-label inhaled antibiotics
 - safety and efficacy issues

More need ? YES

Some consideration on lesser common pathogens

- Increase in prevalence according to CF registries
- increase with age and severity of lung disease
- MRSA in US from 7% in 2011 to 26% in 2016
- NTM increasing across US and European countries (estimated 10-12%)
- *S. maltophilia* with data about pathogenicity (series of papers by Waters, JCF)
- empirical approach with inhaled antibiotics towards other rare pathogens

Unmet needs for inhaled antibiotics

- **Treating beyond traditional microbiology**
 - microbiota is rather consistent in CF lungs
 - correlation with age and lung disease
 - not prone to change during antibiotic
 - preliminary short-term data during AZLI and TOB

(Heirali AA, JCF 2019 and Thorax 2020)

More need ? YES

Outline

1) What's the background now?

- Current position of inhaled antibiotics in CF care

2) What's needed most?

- Unmet needs for inhaled antibiotics in CF care

3) What are the limitations for further research?

- how to improve evidence for inhaled antibiotics in CF care

Inhaled antibiotic CFF pipeline

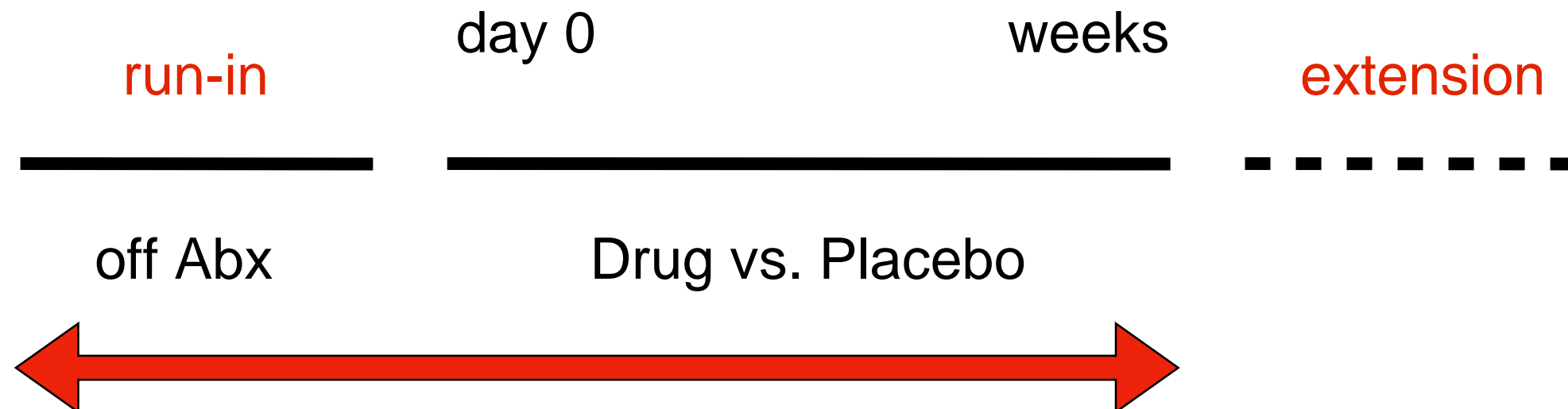


how to put into practice?

Barriers in Clinical Research

- **Limitations in Study Design**

- Best scenario: to measure the effects of an inhaled antibiotic versus placebo after a run-in period with no inhaled antibiotics

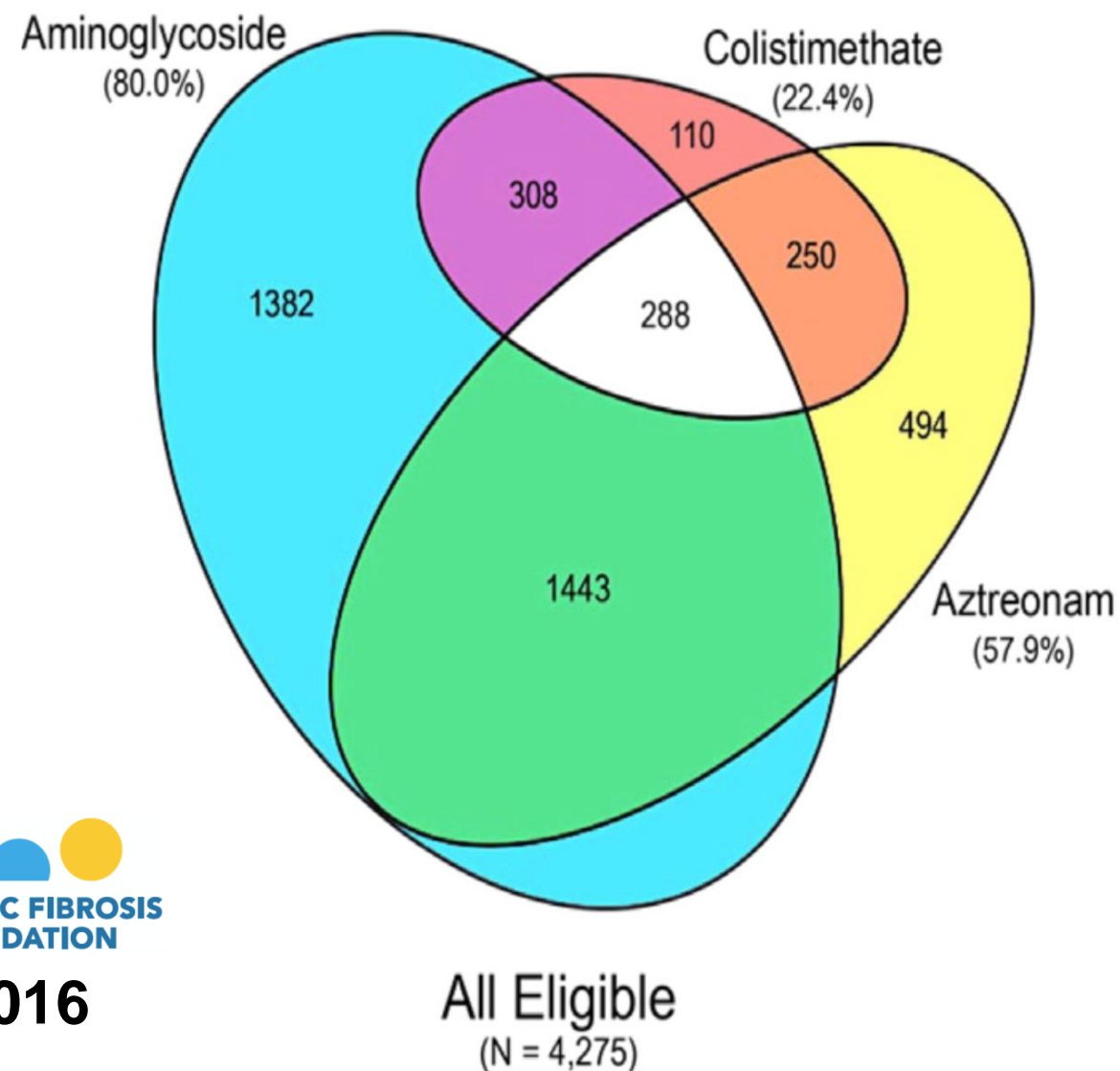


placebo = ethical issues

Barriers in Clinical Research

- **Difficult case finding**

- Inclusion criteria from prior RCTs: age >12 yo; ppFEV1 25-75; PEX 1+



54% of patients are at least on 2+ inhaled antibiotics

Barriers in Clinical Research

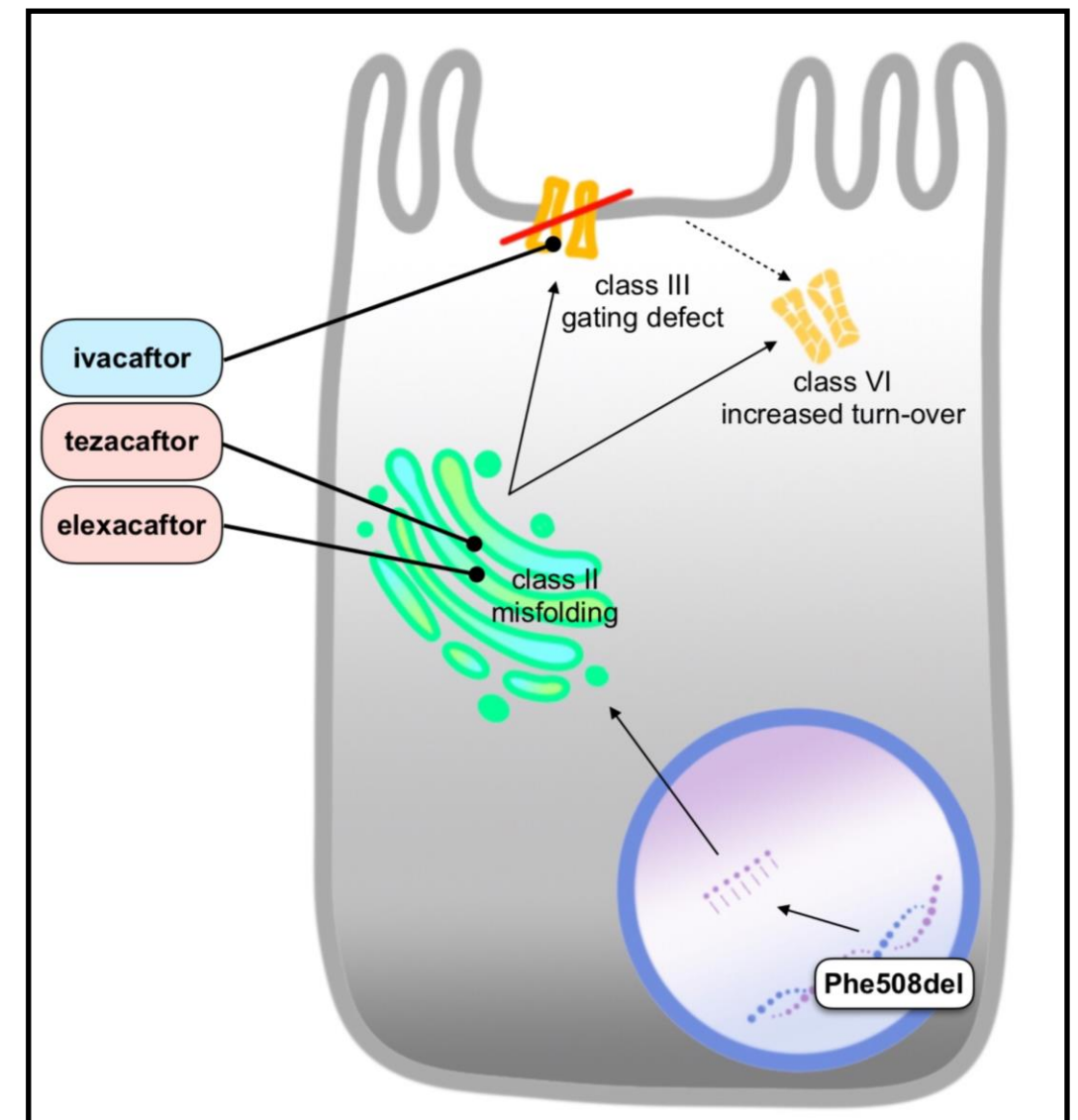
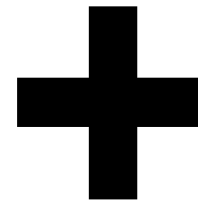
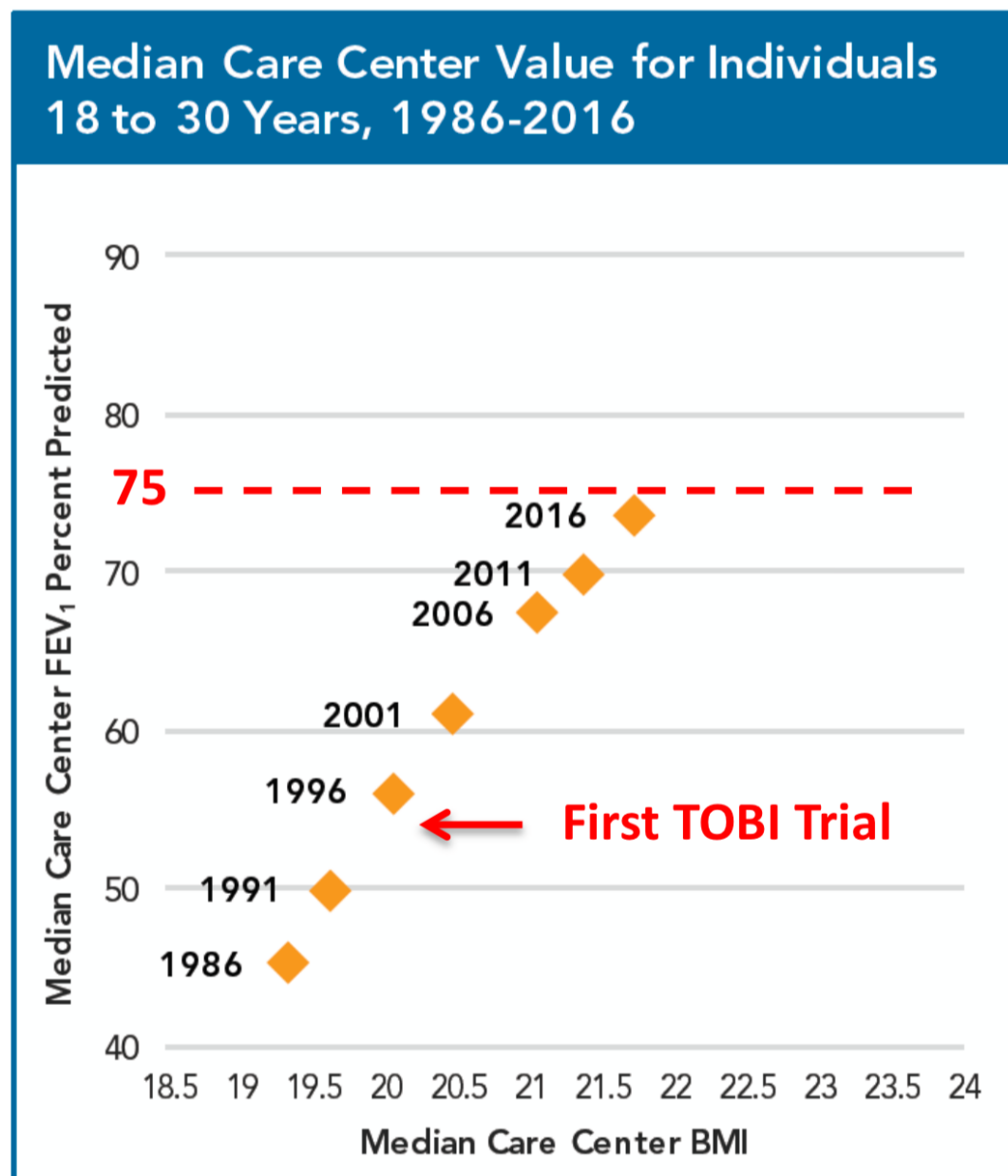
- **What if ... an active comparator in the context of an open label study?**
 - Necessary to avoid the burden of blinding
 - Blinding might fail in patient groups familiar with inhale antibiotics
(taste, smell, appearance before and when nebulized)
 - high impact of confounders
 - High complexity/costs for sponsors
 - Higher risk of bias

Barriers in Clinical Research

- **What if ... a non-inferiority trial?**
 - need to fix an a priori margin to measure the primary outcome
 - lack of robust clinical data to estimate the efficacy of CAT (the comparator)
 - high impact of confounders
 - less appealing for regulatory authorities

Barriers in Clinical Research

- What is the best clinical endpoint?
 - ppFEV1 is the traditional endpoint in CF trials, but...



A Summary of possible Solutions

- **Strong pre-clinical data supporting rationale**
 - CF relevant models / clinical isolates.
 - microbiota analysis and integrative metagenomics

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- **short (4w) placebo-controlled studies to test efficacy**
 - careful choose of clinical outcomes
 - conduct in those settings where it is thought ethical

A Summary of possible Solutions

- **Strong pre-clinical data supporting rationale**
 - CF relevant models / clinical isolates.
 - microbiota analysis and integrative metagenomics
- **short (4w) placebo-controlled studies to test efficacy**
 - careful choose of clinical outcomes
 - conduct in those settings where it is thought ethical
- **longer open label, active comparator studies**
 - focus on safety and duration of effects
 - taking accounts of real-life scenarios
 - adherence



BRONCHIECTASIS CLINIC



ADULT CF CENTER



Bronchiectasis Clinic, Respiratory Unit and Adult CF center

Prof. Blasi; Prof. Aliberti; Dr Gramegna; Dr Pizzamiglio; Dr Amati, Dr Contarini, Dr Franceschi, Dr Nava, Dr Borsa; FT Bellofiore, FT Cerutti



Otorino
Dr Gaffuri



**Immunologo/
Reumatologo**
Dr Vigone



**Laboratorio di
Genetica**
Dr Seia



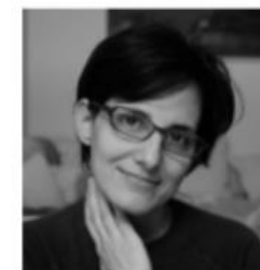
**Laboratorio di
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Dr Porcaro



Pneumologi / Villa Marelli / TB-NTM
Dr Codecasa, Dr Ferrarese, Dr Castellotti



Radiologo
Dr Vespro



Chirurgo toracico
Prof. Nosotti



Gastroenterologo
Dr Caprioli



Gastroenterologo
Dr Basilisco



Microbiologo
Dr Cariani



Endocrinologo
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Psichiatra
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Genetista
Dr Bianchi



Infettivologo
Dr Carugati