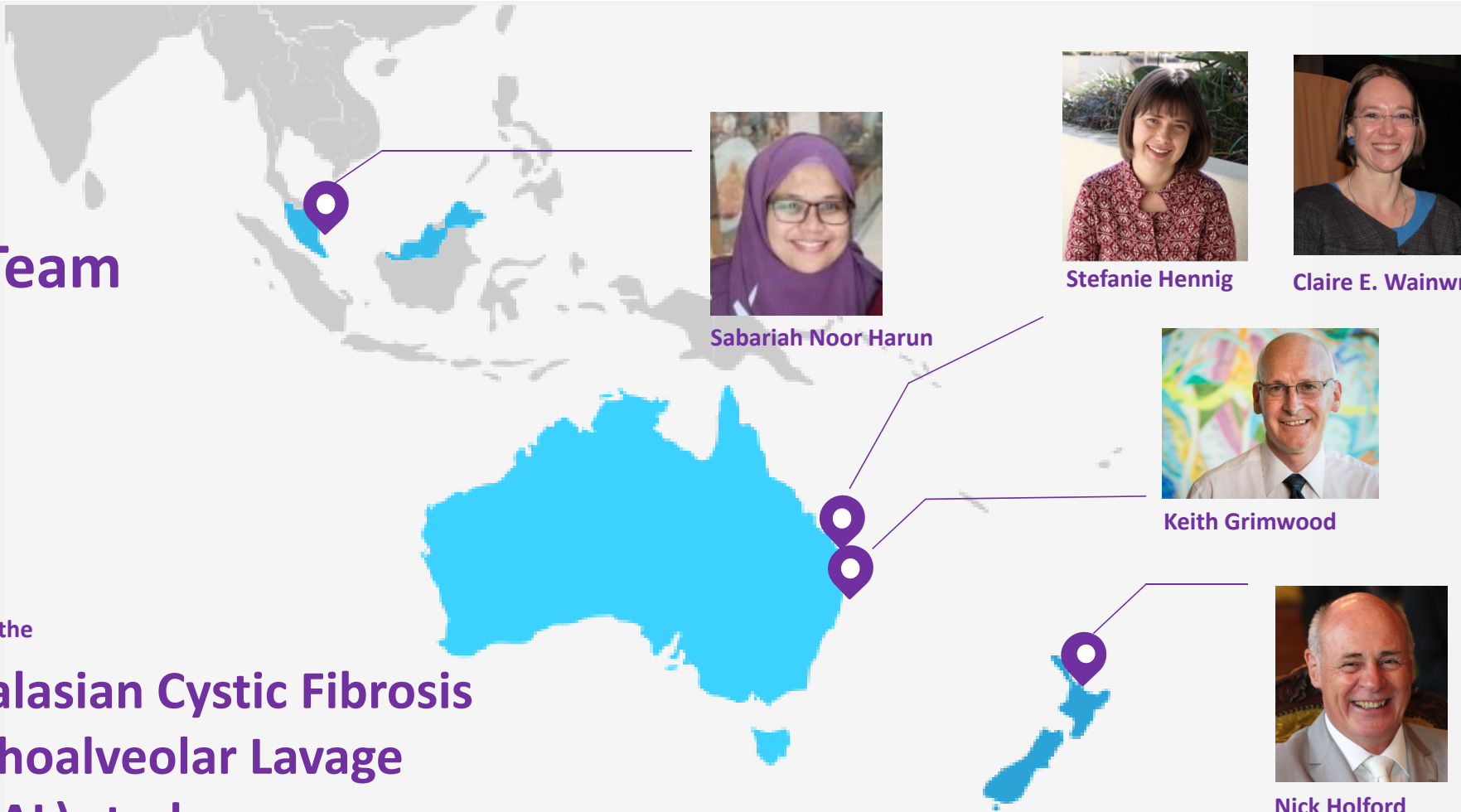


The Team

on behalf of the

Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study group



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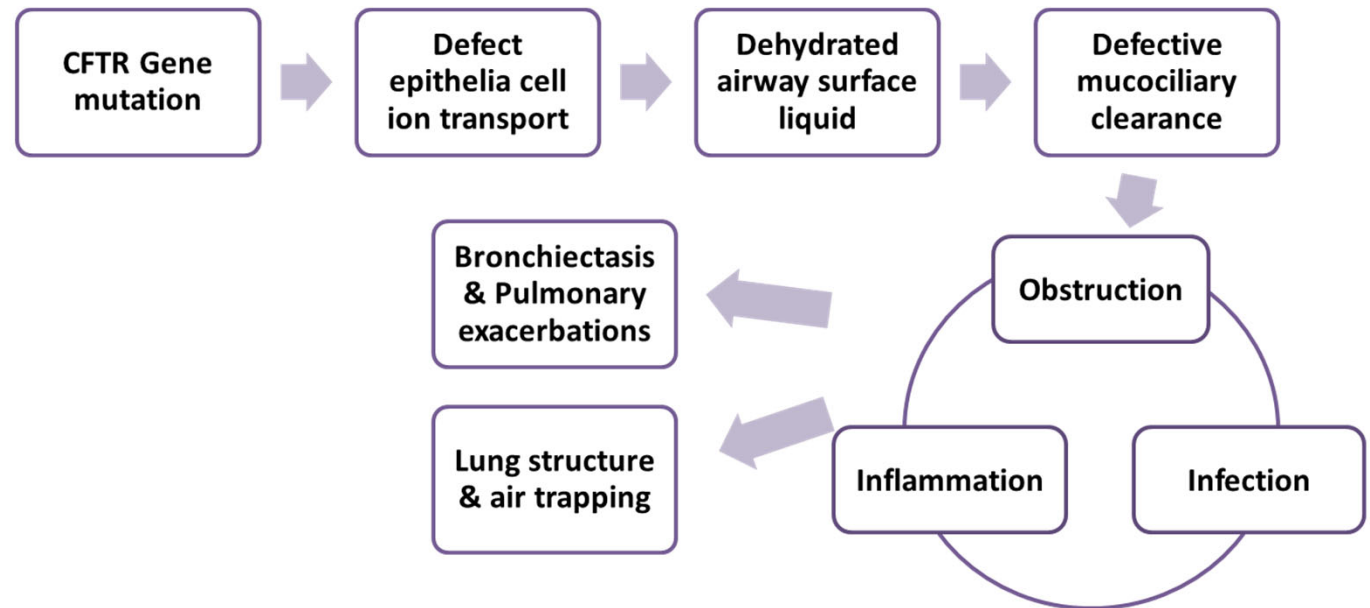
Nick Holford



Cystic Fibrosis

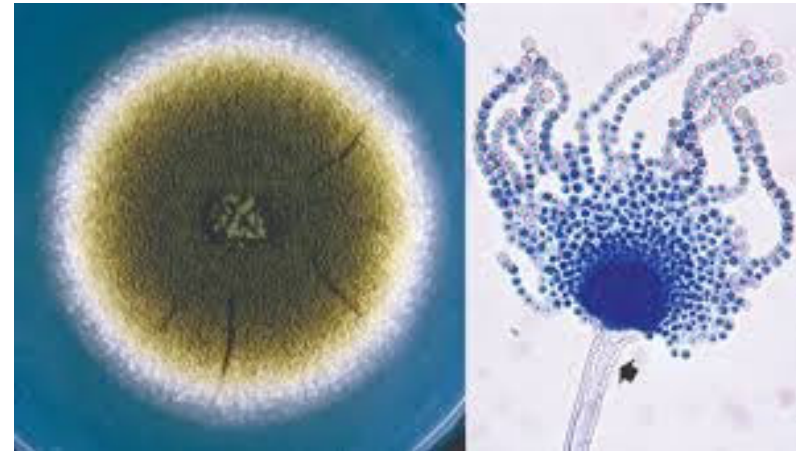
- One of the most common genetic diseases
- Premature death due to lung disease (>90%)
- Endobronchial infection determines mortality

CF Pathogenesis



Pathogens

Pseudomonas aeruginosa (*P. aeruginosa*) *Aspergillus* spp



-> Repeated interval censored event data over 5 years

P. aeruginosa

- **Predominant** pathogen causing chronic infection in CF
- Once established, *P. aeruginosa* is difficult to eradicate and associated with
 - increased symptoms and treatment burden
 - reduced Quality of Life and lung function
 - decreased survival
- Treated repeatedly with intensive antibiotic therapy

Pseudomonas
infections have steadily declined
over the last 20 years
from about
60%
in 1994 to
48%
in 2014.

Source: USA CF Foundation



Aspergillus spp

- **Predominant** fungus isolated
- Prevalence appears to be increasing
- Long-term use of inhaled antibiotics and increased patient survival showed the emergence of *Aspergillus spp*
- Persistence associated with more frequent pulmonary exacerbations in older children (>5 y) & adults with CF

-> *What about younger children?*



ACFBAL study

A multicentre, randomized, parallel group study (Wainwright 2011)

- In 8 CF centers across Australia and New Zealand
- 157 infants diagnosed with cystic fibrosis following newborn screening
- Followed till 5-years of age
- Aim of the original study: Does therapy based on culture results from **bronchoalveolar lavage (BAL)** compared to **oropharyngeal culture (OP)** reduce infection and lung injury?
- Result: At age 5 years **NO** difference between standard-OP/BAL groups

-> *Unexpected study outcome:*

- *Increased Aspergillus detection rates of 45% in children < 5y*
- *27% of children treated for P. aeruginosa had Aspergillus*



Wainwright CE, et al. Effect of bronchoalveolar lavage-directed therapy on Pseudomonas aeruginosa infection and structural lung injury in children with cystic fibrosis: a randomized trial. JAMA 2011;306:163-71

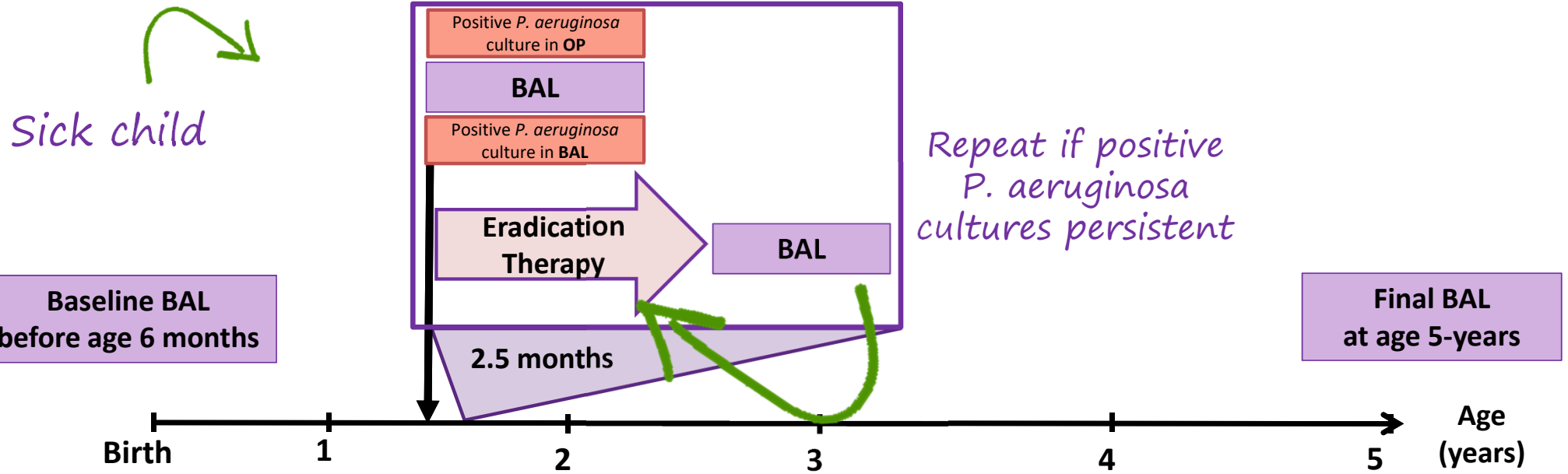
Objectives

Quantify the hazard of acquiring recurrent positive *Aspergillus* BAL cultures in the first 5-years of life

Evaluate the influence of *P. aeruginosa* eradication therapy on the hazard of acquiring *Aspergillus* positive cultures



ACFBAL Study Design – BAL group



Eradication Therapy

1. 2-weeks of intravenous tobramycin and either intravenous ticarcillin-clavulanate or ceftazidime
2. followed by 4-weeks of oral ciprofloxacin & 8-weeks of nebulised tobramycin solution for inhalation

Children in BAL group underwent BAL when:

1. Before age 6 months and 5-years of age
2. With positive *P. aeruginosa* OP cultures
3. At the end of eradication treatment for *P. aeruginosa*
4. When hospitalized for a pulmonary exacerbation

Patients

- 80 children in BAL-directed therapy group (48.8% females)
- Age
 - at enrolment: 0.26 years
 - at last BAL: 5.06 years
- *P. aeruginosa* events
 - Children with 1-5 events: 56.2%
- *Aspergillus spp* events
 - Children with 1-4 events : 45.0%



Methods

Longitudinal parametric survival analysis was performed using interval-censored repeated time-to-event (RTTE) models for:

- *P. aeruginosa* BAL cultures
- *Aspergillus spp* BAL cultures

Joint model developed to allow for the influence of the *P. aeruginosa* eradication therapy (ET) on the hazard of having *Aspergillus spp* positive cultures

Interval-censored RTTE

Describes the time course of the hazard

All events interval censored
(only detected at time of BAL)

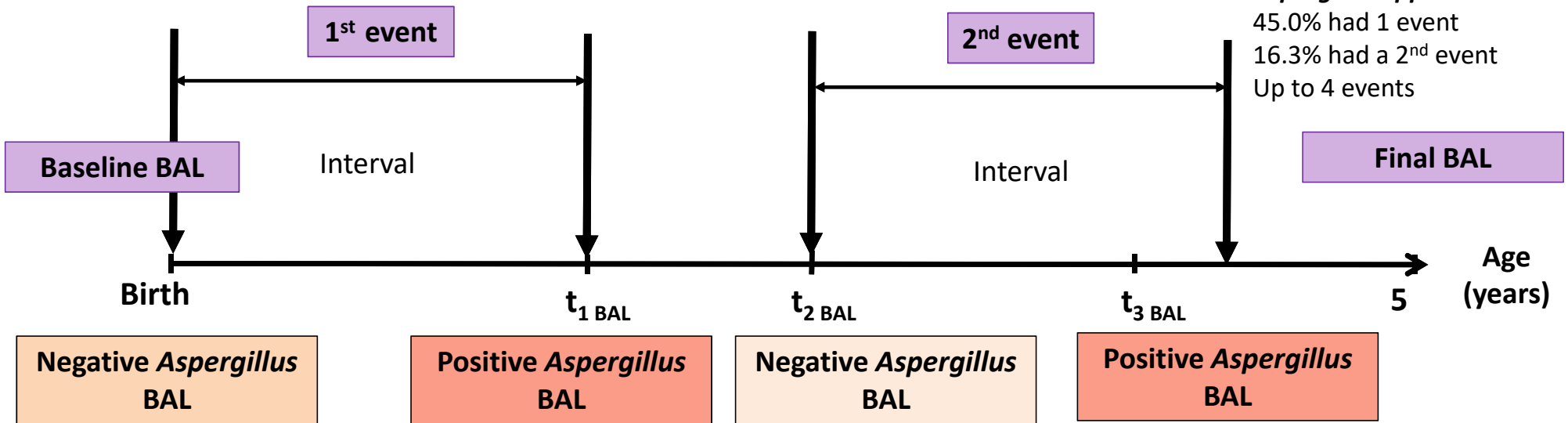
Repeated events

P. aeruginosa

56.0% had 1 event
32.5% had a 2nd event
15.0% had a 3rd event
Up to 5 events

Aspergillus spp

45.0% had 1 event
16.3% had a 2nd event
Up to 4 events



Results - *P. aeruginosa*

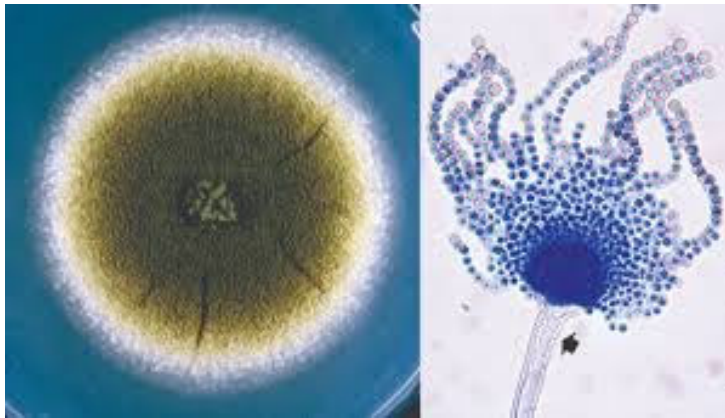


- 1st *P. aeruginosa* event at median age of 2.4-years
- During year 1 the hazard of acquiring *P. aeruginosa* was low
HR 0.39 (95%CI 0.18, 0.59)
- Hazard did not change with time
- Hazard increased with subsequent *P. aeruginosa* infections
HR 138 (95%CI 50.6, 1236)
- *P. aeruginosa* hazard decreased after completing ET
HR 0.15 (95%CI 0.00, 0.79)

-> Suggests a potential lasting clinical benefit of ET

HR is hazard relative to baseline hazard

Results – *Aspergillus* spp



- 1st *Aspergillus* event at median age of 3.7-years
- During year 1 the hazard of acquiring *Aspergillus* was very low, increasing with time (Gompertz)
- Hazard increased dramatically after having had the first *Aspergillus* event
 - 2nd event: HR of 7.29×10^5
 - 3rd event: HR of 5.97×10^5
- Hazard increased after completing *P. aeruginosa* ET
HR of 2.75 (95%CI 1.45, 5.41)

-> Suggests that either eliminating or suppressing *P. aeruginosa* may be a key reason for acquiring *Aspergillus* spp

-> Limitation: *P. aeruginosa* infection events confounded with ET



HR is hazard relative to baseline hazard

Model evaluation

Using Kaplan-Meier (KM) Visual Predictive Checks

- A joint model of *P. aeruginosa* and *Aspergillus* events was required for simulation, as *Aspergillus* event hazard is changed if a *P. aeruginosa* event occurred
- BAL observation restricted to *P. aeruginosa* events, ET occurred only after that
- Joint model allowed for the correct design order
- The same joint model was used for estimation

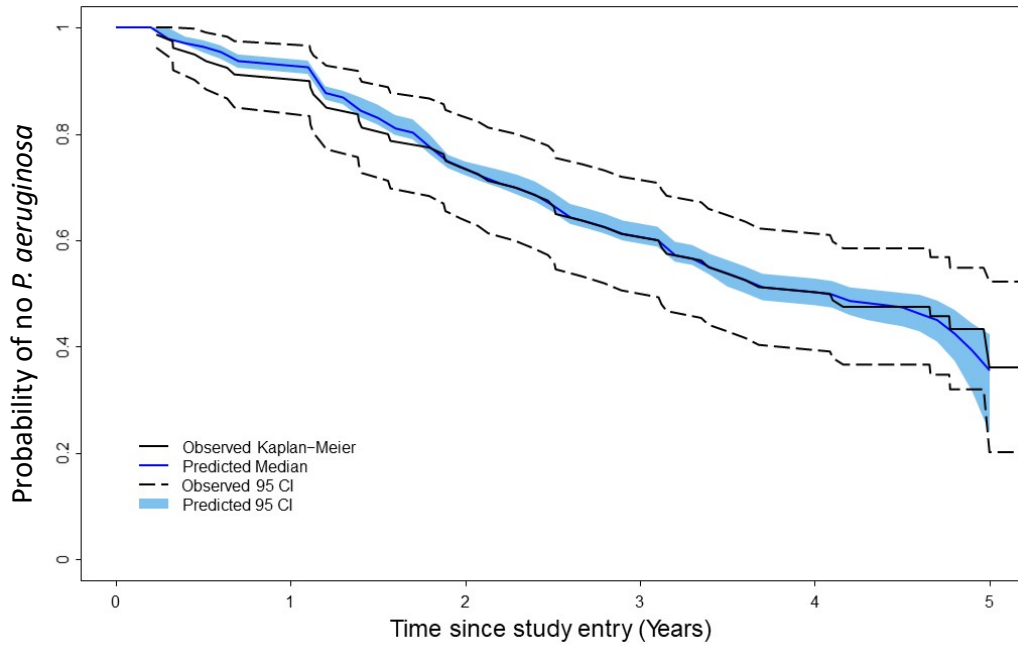
KM plot limitation

- The KM plot method in  using `Surv()` assumes exact event times for both simulated and observed events
- The KM plot method in  when `Surv()` uses interval censoring exists but does not give sensible results
- KM VPC here use exact event times for the evaluation
- Justification: same “error” is applied to both simulated and observed events, which are compared

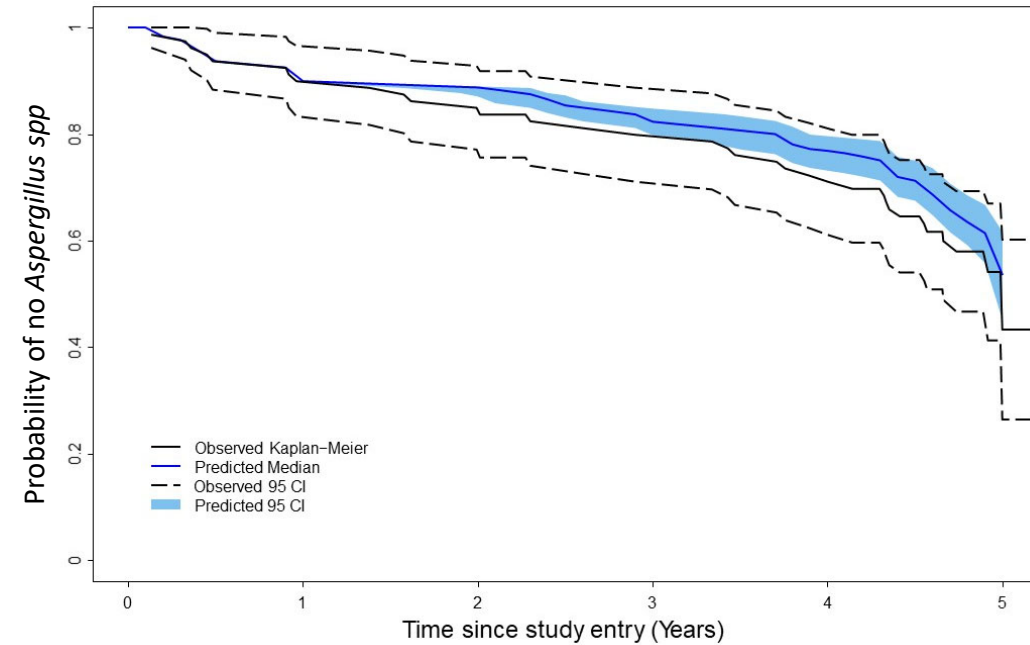
Model evaluation

Only first event presented here

P. aeruginosa



Aspergillus spp



Conclusions

Risk of acquiring Aspergillus spp events in young children with CF increases with completing intensive P. aeruginosa eradication treatment and having experienced a previous Aspergillus spp event



Acknowledgements

- The Team
- The ACFBAL study group
- All participating patients and parents/carers
- Australian Centre for Pharmacometrics
- Humboldt Foundation, Germany

Thank you very much for your attention

Questions

