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COMBACTE CARE

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Time-to-event case-control designs: An efficacious tool for cohort studies on nosocomial infections when resources are limited

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Facts & Figures

Start date	01/03/2015
End date	28/02/2020
Contributions	
IMI funding	23 871 500 €
EFPIA in kind	59 833 500 €
Other	1 408 336 €
Total Cost	85 113 336 €
Project website	www.combacte.com
Social media	twitter.com/combacte

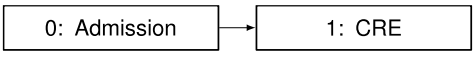
Challenge

- Antimicrobial resistance (AMR) is threat to global health, but currently AMR is rare in parts of Europe
- Challenges for researchers investigating incidence and effect of rare exposures (AMR) are manifold:
  - Randomized clinical trials are problematic; microbiology confirmation is required prior to recruitment resulting in low recruitment rates
  - Matching with control patients with carbapenem-susceptible *Enterobacteriaceae* (CSE) or non-infected admitted patients (ADM)
  - Matched by centre, type of infection, hospital service and acquisition (nosocomial/community)
  - Batch effect in microbiological analysis available
  - Time-to-event methods required for censoring
- **EURECA** (*EU*ropean prospective cohort study on Enterobacteriaceae showing *RE*sistance to *CA*rbapenems) is COMBACTE-CARE study in 50 sites,11 countries (*Gutíerrez-Gutíerrez et al. BMJ Open 2017;7:e015365*)
- EURECA aims to assess mortality and length of stay of patients with target infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE)

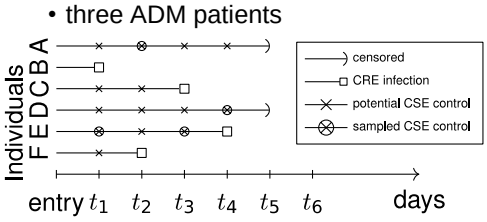
Approach & Methodology

Method 1: Nested case-control design (NCC)

- Cox model $\alpha(t|Z_i(t)) = \alpha_0(t)\exp(\beta^T Z_i(t))$



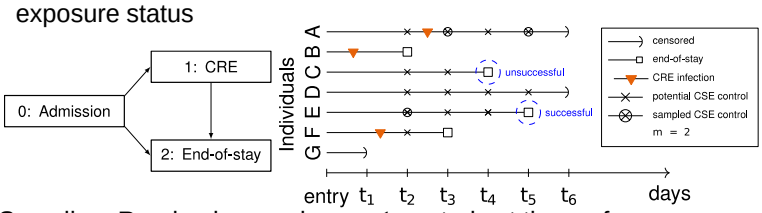
- NCC is established method to use limited resources efficiently (CRE infection is rare)
- NCC successfully applied in EURECA study to identify risk factors for CRE infection
- Sampling: For each CRE patient, randomly sample **at time of sample verification**:
  - one CSE patient, and
  - three ADM patients



- Weighted, stratified analysis takes over the role of a full cohort analysis

Method 2: Nested exposure case-control design (NECC)

- Novel methodological extension of NCC funded by DFG
- Motivated by EURECA study to investigate effect of rare time-dependent exposure on subsequent event
- Identify predictors for negative outcomes caused by CRE
- **Sampling at outcome time** but dependent on the previous exposure status



Sampling: Randomly sample $m-1$ controls at time t_j from persons still at risk, for

- every CRE patient with observed 1 to 2 transition at t_j
- every CSE or ADM with observed 0 to 2 transition at t_j, where Bernoulli experiment with probability $q(t_j|\mathbf{expo})$ is successful

Inclusion probability $q(t)$ important adjusting screw, here $q(t) \equiv q$ i.e. independent of time. But, other designs also possible

Results

- NECC **methodology validated** by application to SIR3 (*S*pread of nosocomial *I*nfections and *R*esistant pathogens cohort study) at Charité University Hospital, Berlin, Germany
- **SIR3** aims to investigate effect of nosocomial pneumonia (time-dependent) on length of hospital stay (discharge alive or death)
- Study recruited 1313 patients admitted to intensive care unit
- 8% acquire nosocomial pneumonia, i.e. rare exposure but common outcome event (98%) similar to EURECA
- To validate NECC, bootstrap **simulation undertaken to compare NECC to full cohort Cox regression**

Sampling design		$exp(\hat{\beta})$	95% CI	$\widehat{SE}$	$SE(\hat{\beta})$	#dist
$q(t)$	Full cohort	0.61	0.50-0.74	0.11	0.10	1313.00
0.1	1:2NECC	0.64	0.41-1.07	0.24	0.25	441.67
	1:4NECC	0.61	0.42-0.92	0.20	0.20	567.91
0.07	1:2NECC	0.64	0.39-1.20	0.28	0.29	378.01
	1:4NECC	0.61	0.40-0.99	0.23	0.23	491.35
0.05	1:2NECC	0.65	0.36-1.41	0.33	0.34	332.97
	1:4NECC	0.61	0.38-1.07	0.26	0.26	435.05

Value of IMI collaboration

- Establishes unprecedented **partnership** between industry, academia and biotech organizations
- Helps to ensure the success of **highly innovative studies** (EURECA) and **methodology** (NECC)
- Enables **collaboration** between normally disjointed research fields (e.g. clinical infectious diseases and statistics)

Impact & take home message

- **NECC addresses censoring appropriately, avoids time-dependent bias** and **performs very well in baseline covariates estimation**
- **NECC competitively analyses the effect of time-dependent exposure with reduced resources** (individuals, determined covariates) to a full cohort analysis
- Procedures **applicable for future studies** in AMR and other areas of scientific and medical research
- More powerful NECC designs (e.g. history-dependent) possible

imi innovative medicines initiative efpia

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