Attributable mortality due to nosocomial infections: a simple and useful application of multistate models

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Outline

- Introduction and basic definitions
- Multistate modelling approach
- SIR 3-study on nosocomial infections
- Conclusions

Basic quantities in a cohort study

- $P(D|E^+)$: conditional probability of developing the disease (D) (of death), given exposure to risk factor (E^+)
- $P(D|E^-)$: conditional probability of developing the disease (D) (of death), given no exposure to risk factor (E^-)

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- $RR = \frac{P(D|E^+)}{P(D|E^-)}$: relative risk

Measures of attributable risk (mortality)

- $P(D|E^+) - P(D|E^-)$

  risk difference, attributable risk, absolute excess risk

- $P(E^+)\left[P(D|E^+) - P(D|E^-)\right]$

  population attributable risk

- $P(E^+)\dfrac{\left[P(D|E^+) - P(D|E^-)\right]}{P(D)} = PAF$

  population attributable fraction

Alternative representations of PAF

- $PAF = \frac{P(D) - P(D|E^-)}{P(D)}$
- $PAF = \frac{P(E)[RR-1]}{P(E)[RR-1]+1}$
- $PAF = P(E^+|D)\frac{[RR-1]}{RR}$

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- $$PAF = \frac{P(E)[RR - 1]}{P(E)[RR - 1] + 1}$$
- $$PAF = P(E^+|D)\frac{[RR - 1]}{RR}$$
- In case-control studies, the latter formula ist used thereby replacing RR through the corresponding odds ratio

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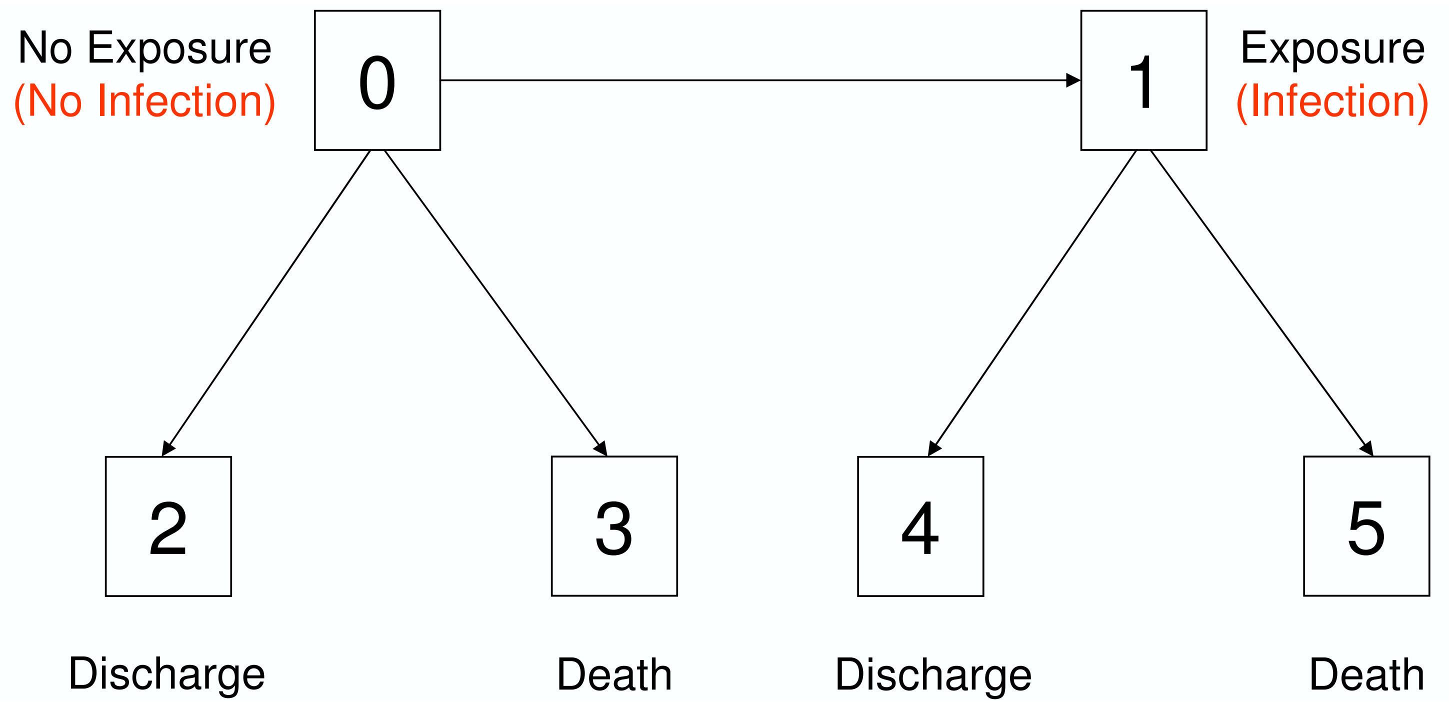
- How should one estimate PAF and related quantities if mortality is of interest, competing events (e.g. discharge) and potential censoring have to be taken into account?

The model: Progressive Disability Model



Multistate modelling approach (1)

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- Time-dependent exposure status

$$\Big\{E(t) = 1\Big\} \;=\; \Big\{X_t = 1\,,4\,,5\Big\} \qquad \Big(\text{"}E(t) = 1\text{"} : E^{+}\Big)$$

$$\Big\{E(t) = 0\Big\} \;=\; \Big\{X_t = 0\,,2\,,3\Big\} \qquad \Big(\text{"}E(t) = 0\text{"} : E^{-}\Big)$$

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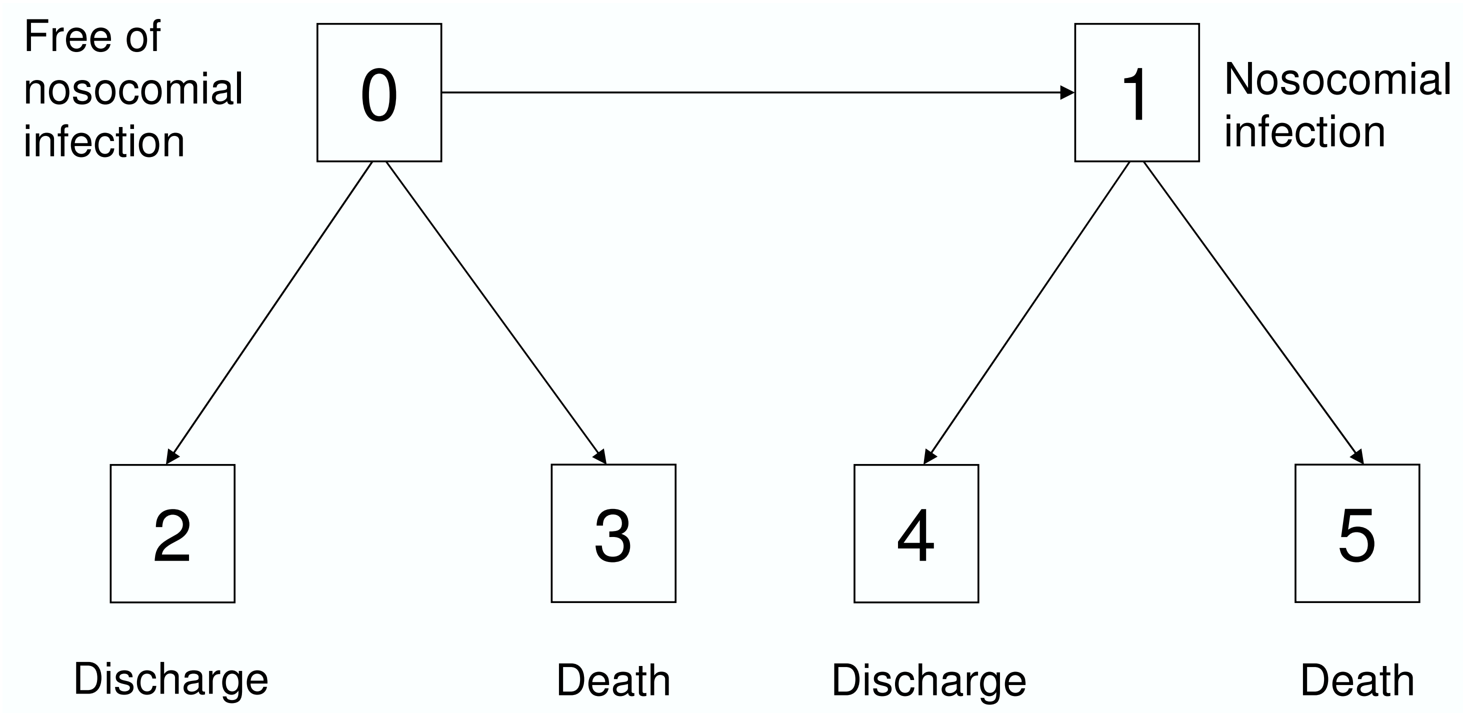

The model: Progressive Disability Model

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- exposure known at $t = 0$: $P(X_0 = 0) = P(E^-)$

$P(X_0 = 1) = P(E^+)$

and $P_{01}(t) \equiv 0$

(infections on admission)

Multistate modelling approach (2)

- $P(D,t) = P(D(t)=1) = P(X_t = 3,5)$

$$= P(X_0 = 0) \cdot P(X_t = 3,5 | X_0 = 0) + P(X_0 = 1) P(X_t = 3\ ,\ 5 | X_0 = 1)$$

$$= P(X_0 = 0) \Big[P_{03}(t) + P_{05}(t) \Big] + P(X_0 = 1) P_{15}(t)$$

- $P(D|E^-,t) = P(D(t) = 1 | E(t) = 0)$

$$= \frac{P(X_t = 3 \cap X_0 = 0)}{P(X_t = 0,2,3, \cap X_0 = 0)} = \frac{P_{03}(t)}{P_{00}(t) + P_{02}(t) + P_{03}(t)}$$

- $P(D|E^+,t) = P(D(t) = 1 | (E(t) = 1) = \ldots$

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- $P(D,t) \quad , \quad P(D|E^-,t) \quad , \quad P(D|E^+,t)$

- $P(D|E^+,t) - P(D|E^-,t)$ "Attributable Mortality"

- $PAF(t) = \dfrac{P(D,t) - P(D|E^-,t)}{P(D,t)}$ "Population Attributable Fraction"

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- $PAF(t) = \dfrac{P(D, t) - P(D|E^-, t)}{P(D, t)}$ "Population Attributable Fraction"
- Estimation with Aalen-Johansen estimator of transition probabilities will properly account for censoring; standard errors via bootstrap

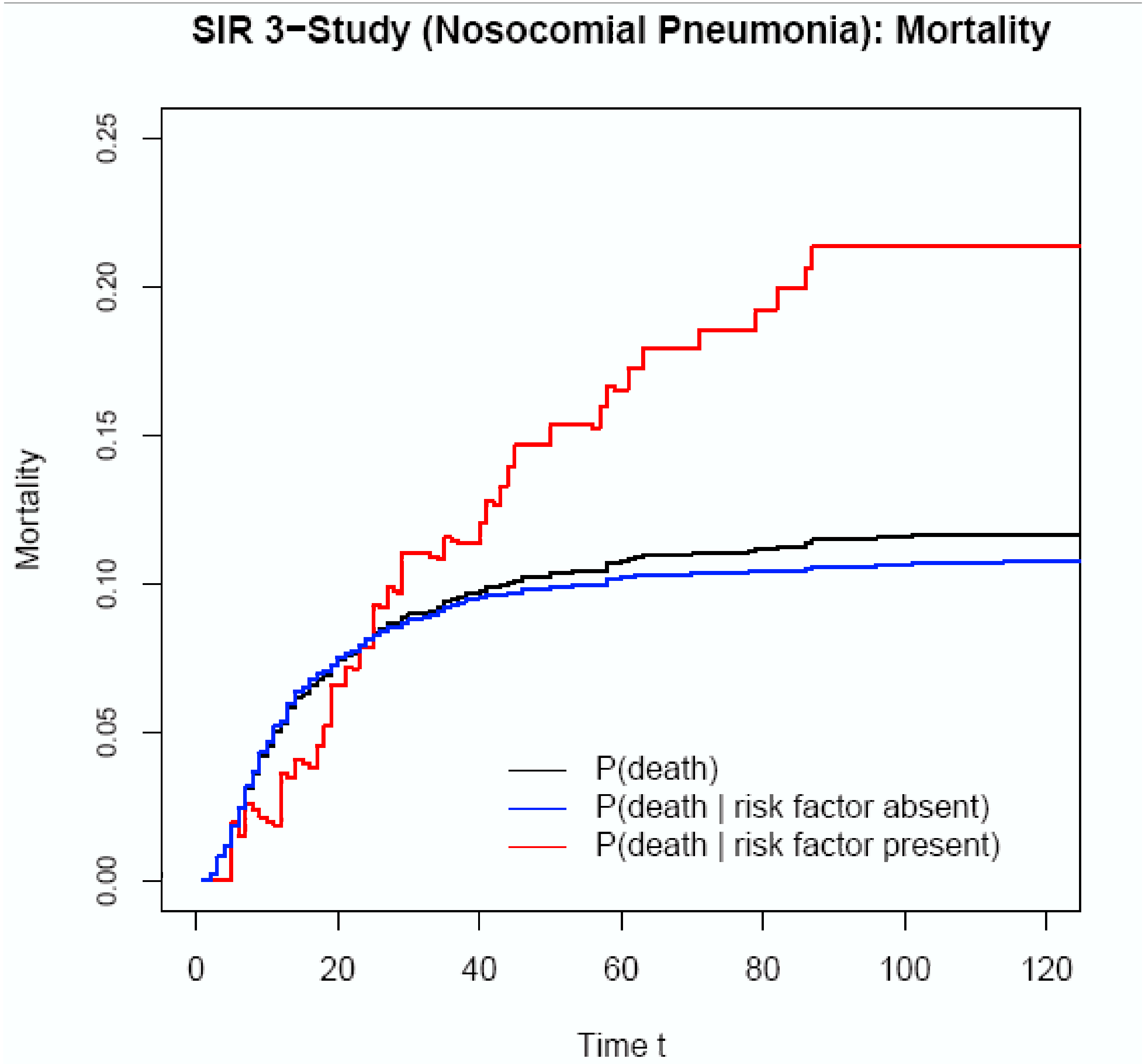
SIR 3-study

- Prospective cohort study on the incidence of nosocomial infections in intensive care unit (ICU) patients.
- All patients who stayed 48 hours or longer in the ICUs were included and followed until discharge or death on ICU (1.6% censored).
- 5 ICUs (72 ICU beds); study period 2/2000 - 7/2001.
- Study has been conducted within the network ”Spread of nosocomial infections and resistant pathogens (SIR)”.

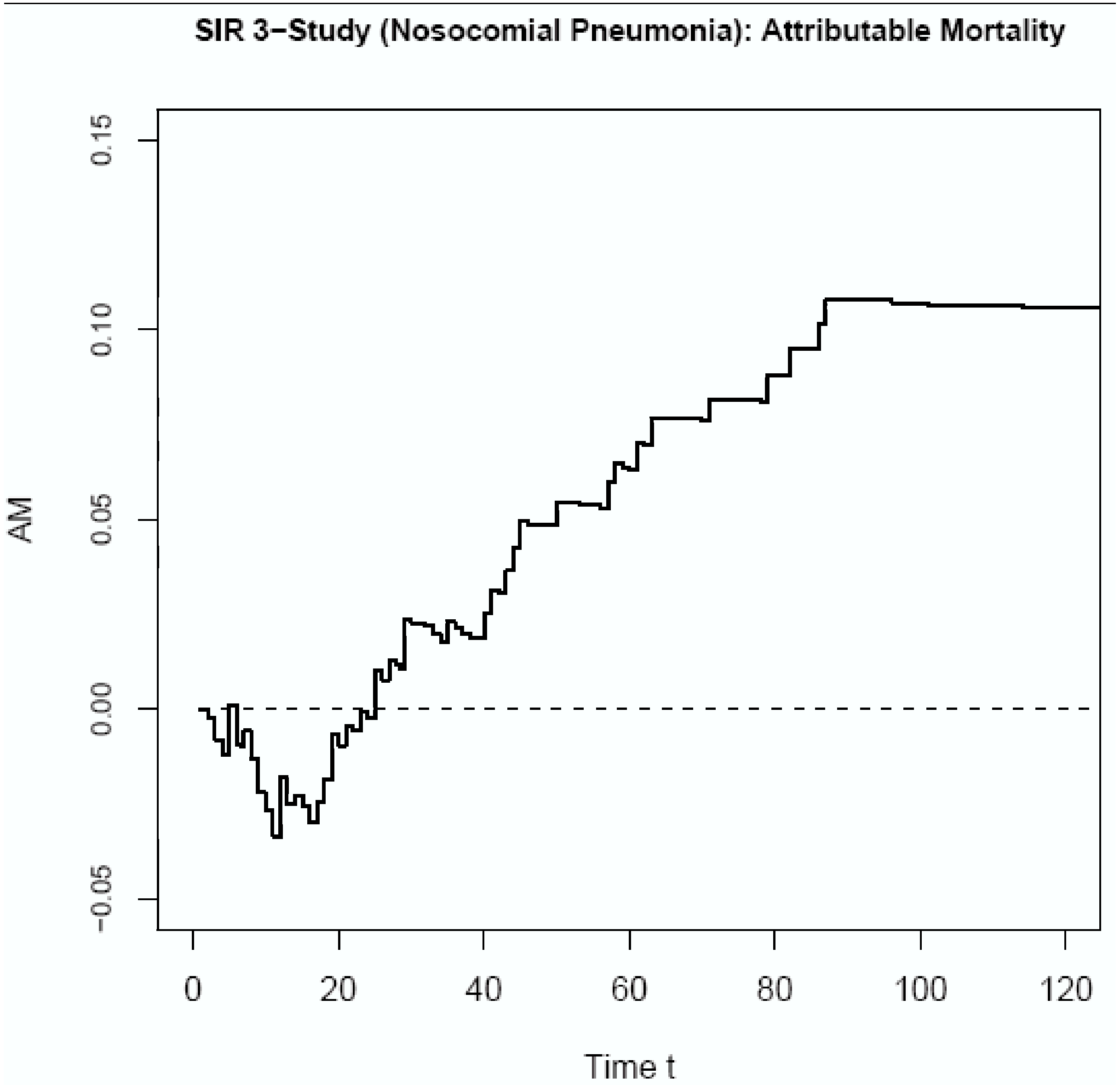
SIR 3-study

		# deaths	(%)
1876	admissions	214	(11.4)
220	pneumonia on admission (POA)	48	(21.8)
1656	no POA	166	(10.0)
158	nosocomial pneumonia (NP)	33	(20.9)
1718	no NP	181	(10.5)

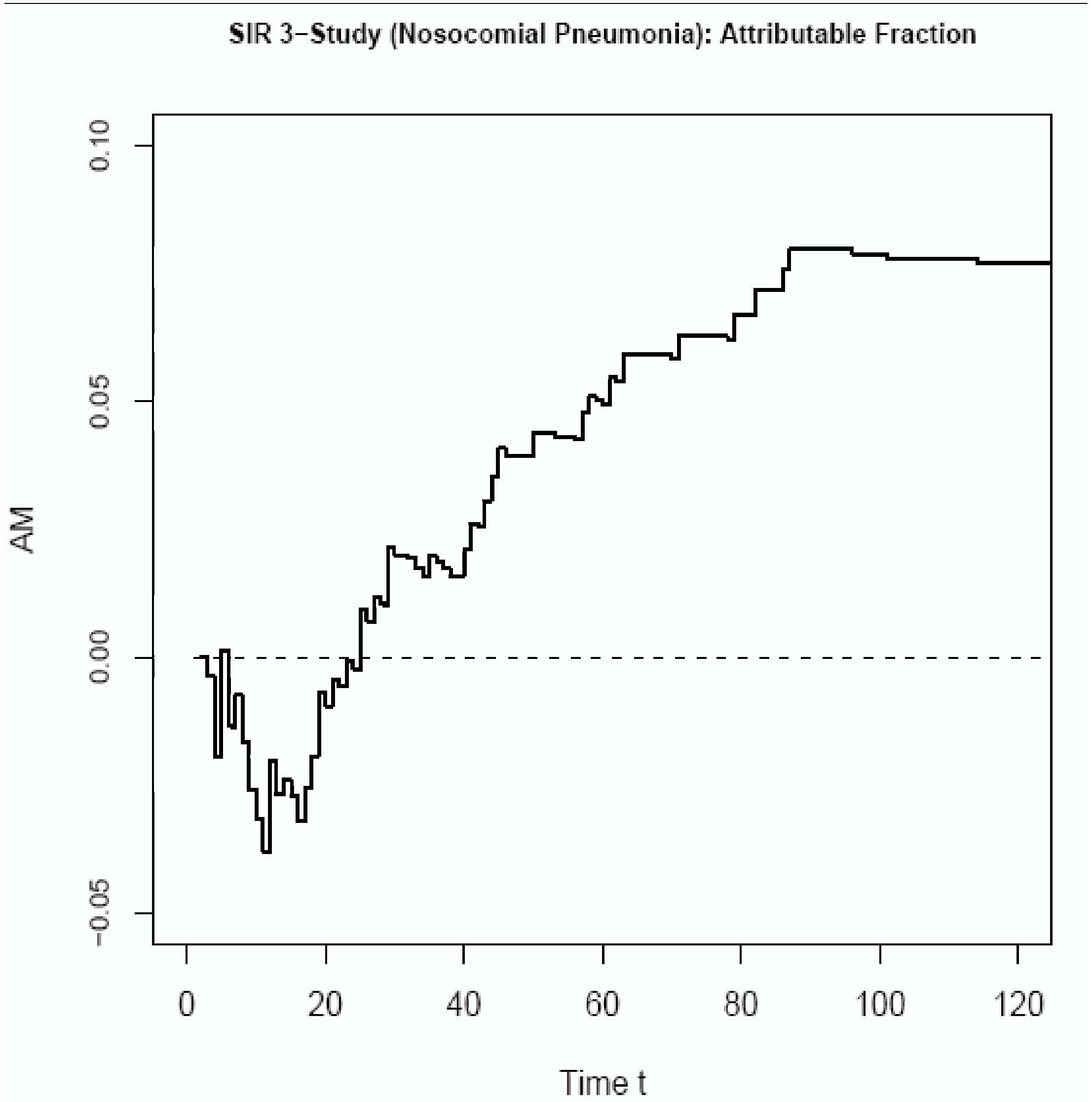
SIR 3-study (NP): Mortality



SIR 3-study (NP): Attributable Mortality



SIR 3-study (NP): Population Attributable Fraction



SIR 3-study: Summary of results

	NP	
	Multistate model	Crude rate
$P(D, t = 120)$	0.117	0.114
$P(D\|E^-, t = 120)$	0.108	0.105
$P(D\|E^+, t = 120)$	0.213	0.209
$P(D\|E^+, t = 120) - P(D\|E^-, t = 120)$	0.106	0.104
$PAF(t = 120)$	0.077	0.077
$SE(PAF(1 = 120))$	0.026	0.027

Conclusions

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- The multistate model provides a general framework for both time dependent exposure and exposure known at $t = 0$.
- If there is no (or little) censoring, crude rates lead to identical (similar) results for large t.
- So far, exposure to single risk factors has only been considered in isolation; in order to properly adjust for confounding, a simultaneous analysis, e.g. based on a suitable regression model, is necessary. (SIR 3-study: nosocomial pneumonia, pneumonia on admission, SAPS II-categories at admission)

Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: Excess length of stay, extra costs, and attributable mortality. JAMA 1994; 271:1598-1601.

- ”Case-control study” in surgical ICU (Matched cohort study) (4002 admitted patients, 107 with nosocomial sepsis)
- ”Cases”: patients with nosocomial sepsis
  ”Controls”: patients without nosocomial sepsis, matched for age, sex, length of stay to infection, comorbidities etc.
- Attributable mortality

  = mortality rate of cases - mortality rate of controls

  $= 43/86 - 13/86 = 50\% - 15\% = 35\%$
- PAF (reconstructed)

  $$= 0.0267 \cdot \frac{0.35}{0.16} = 0.058 \quad (= 5.8\%)$$

Garcia-Martin M et al. Proportion of hospital deaths potentially attributable to nosocomial infection. Infect Control Hosp Epidemiol 2001; 22:708-714.

- Case-control study in a 800-bed, tertiary care, hospital

- "Cases": patients dying in hospital (524 deaths)
  "Controls": patients discharged alive after 48 hours, matched for primary diagnosis and date of admission

- PAF (via Odds-Ratio formula, adjusted for various factors)

All NI's	:	21.3%
Lower respiratory tract	:	5.3%
Bacteremia or sepsis	:	7.7%

Kaoutar B. et al. for the French Hospital Mortality Study Group. Nosocomial infections and hospital mortality: a multicentre epdemiological study. Journal of Hospital Infection 2004; 58:268-275.

- Case study in 16 northern French hospitals (14222 beds)
- ”Cases”: All patients who died at least 48 hours after admission ($n = 1945$ deaths, review of patient’s charts and interview of patient’s treating physician by infection-control practioner)
- ”NI-associated mortality” (AM)

$$= \frac{\text{\# deaths associated with NI}}{\text{\# deaths included into the study}}$$

All NI’s	:	26.6%
Lower respiratory tract	:	10.3%
Bacteremia or sepsis	:	4.5%

”Associated Mortality”

$$P(E^+|D) = \frac{P(E^+ \cap D)}{P(D)} = AM$$

”Percent deaths associated (attributable) to risk factor”

Relationship to PAF:

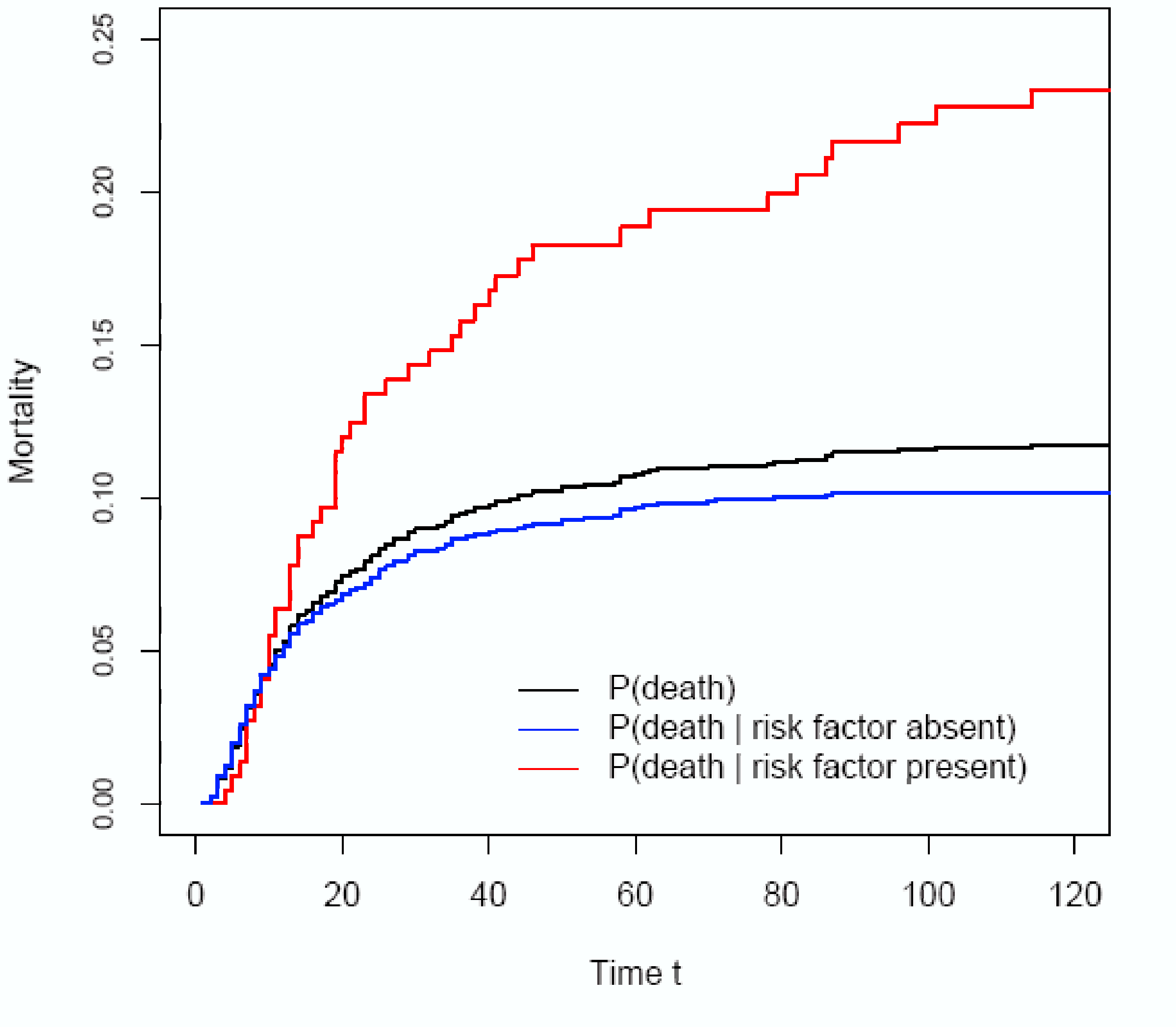
$$\begin{aligned} PAF &= AM - \frac{P(E^+)}{1 - P(E^+)}(1 - AM) \\ &= AM\frac{[RR - 1]}{RR} \end{aligned}$$

Escolano S, Golmard JL, Kormek AM, Mallet A. A multi-state model for evolution of intensive care unit patients: prediction of nosocomial infections and deaths. Statistics in Medicine 2000; 19: 3465-3482.

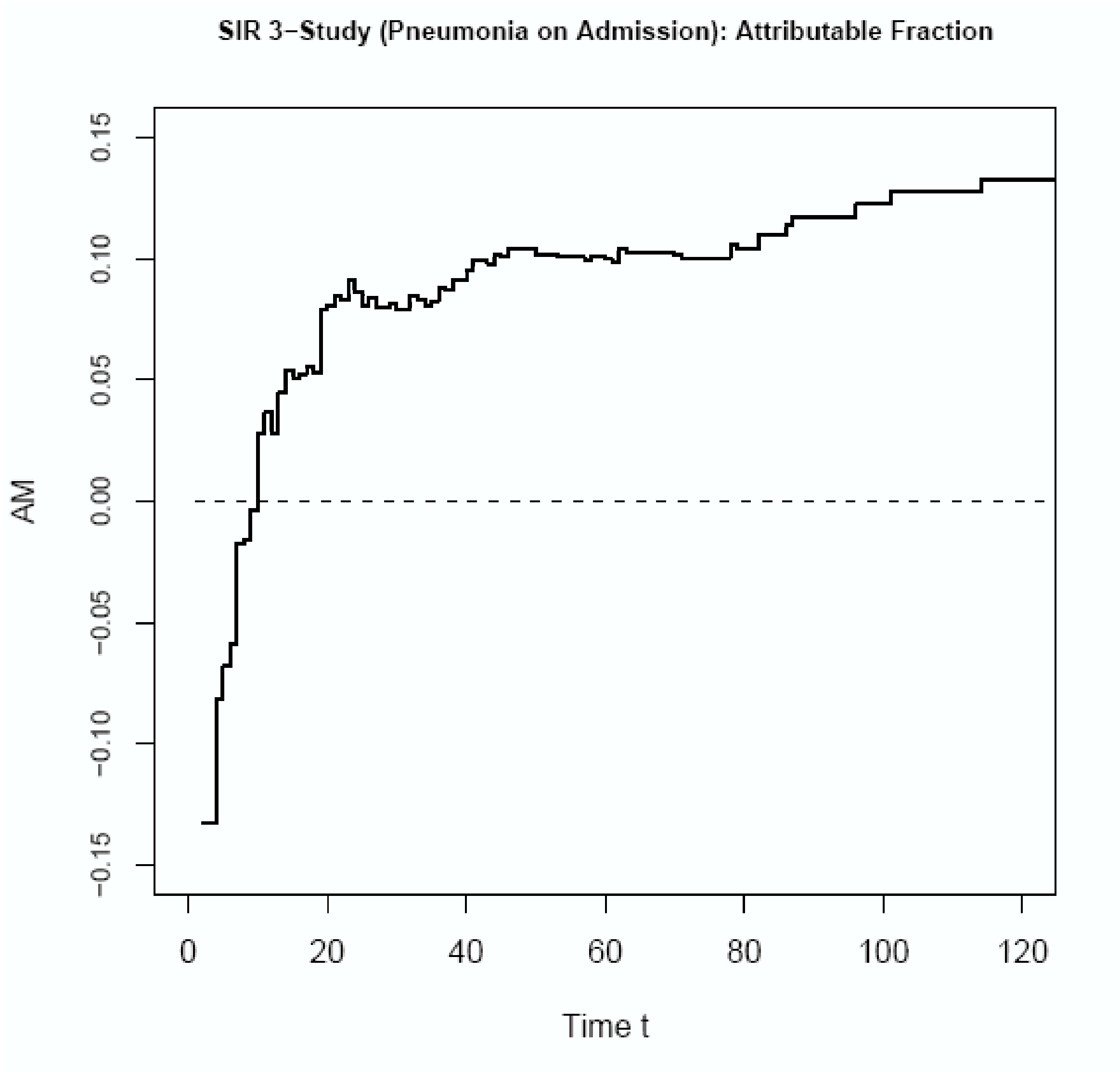
- Cohort study in surgical ICU
  (676 admitted patients, 383 patients with NI, 176 deaths)
- PAF (for all NI's; reconstructed)

$$= 0.57 \frac{0.285 - 0.228}{0.26} = 0.125 \quad (= 12.5\%)$$

SIR 3-study (POA): Mortality



SIR 3-study (POA): Population Attributable Fraction



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$P(D\|E^-, t = 120)$	0.102	0.100	0.108	0.105
$P(D\|E^+, t = 120)$	0.234	0.218	0.213	0.209
$P(D\|E^+, t = 120) - P(D\|E^-, t = 120)$	0.132	0.118	0.106	0.104
$PAF(t = 120)$	0.132	0.121	0.077	0.077
$SE(PAF(1 = 120))$	0.030	0.033	0.026	0.027