Issues in Pharmacoepidemiology:

with special attention to immortal time bias

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Topics

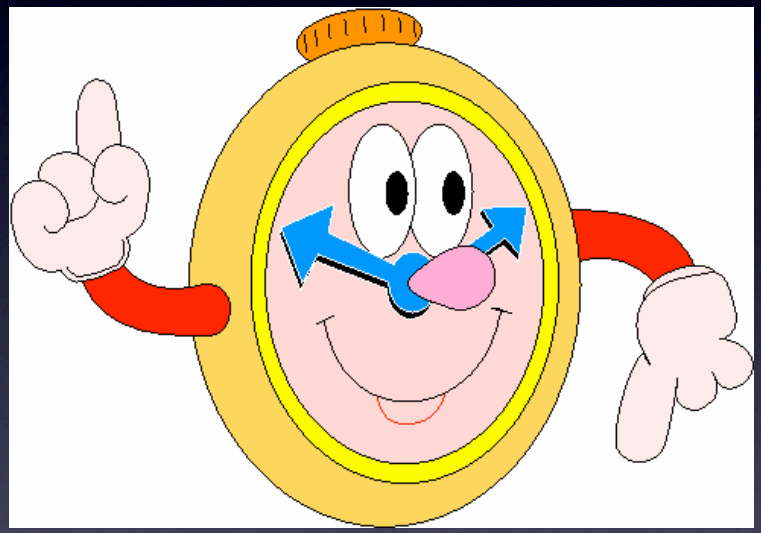
- Examples
- Cohort Definitions
- Control of Confounding
- Immortal Time Bias
- General Advice

The ideal study

- Enroll a large number of subject at risk
- Well-characterized with good baseline data
- Randomized them
- Complete long-term follow-up for events

Only two obstacles to that !!

A Couple of Obstacles



Time

Money

Faster Cheaper Alternative

- Use existing cohort(s) with disease and exposure information collected over time
- Advantages: relative ready dataset
- Disadvantages: not collected for research -- or at least not for your question

Treatment dispensed based on clinical rationale

Data collected for clinical, administrative or billing

Myriad Challenges

- Selecting subjects
- Data verification
- Valid comparisons

Follow-Up Time

- Defined start of follow-up for subjects
- Can be
  - Event based (enrolled after MI),
  - Age based (all subjects at least 50)
  - Date based (Jan 1, 1988)
- Choice attuned to your questions
- Wary of requiring FU (> 10 yr FU).
  What if someone dies 3 years into Kaiser?

Confounding

- The largest threat to validity: confounding by indication
- Impossible to fully eliminate
- May have limited and uneven confounder data
- May have better predictor data on cases then controls: more visits, more attention

Keep in Mind

- Only a confounder if associated with exposure among the cases
- Two stage methods
- Verify or collect confounder data on random subset
- Can be incorporated into a regression analysis
- Only a confounder if associated with exposure among the cases

Immortal Time Bias

Why is this woman smiling?

*Annals of Internal Medicine
134: 955-962, 2001

Or can she?

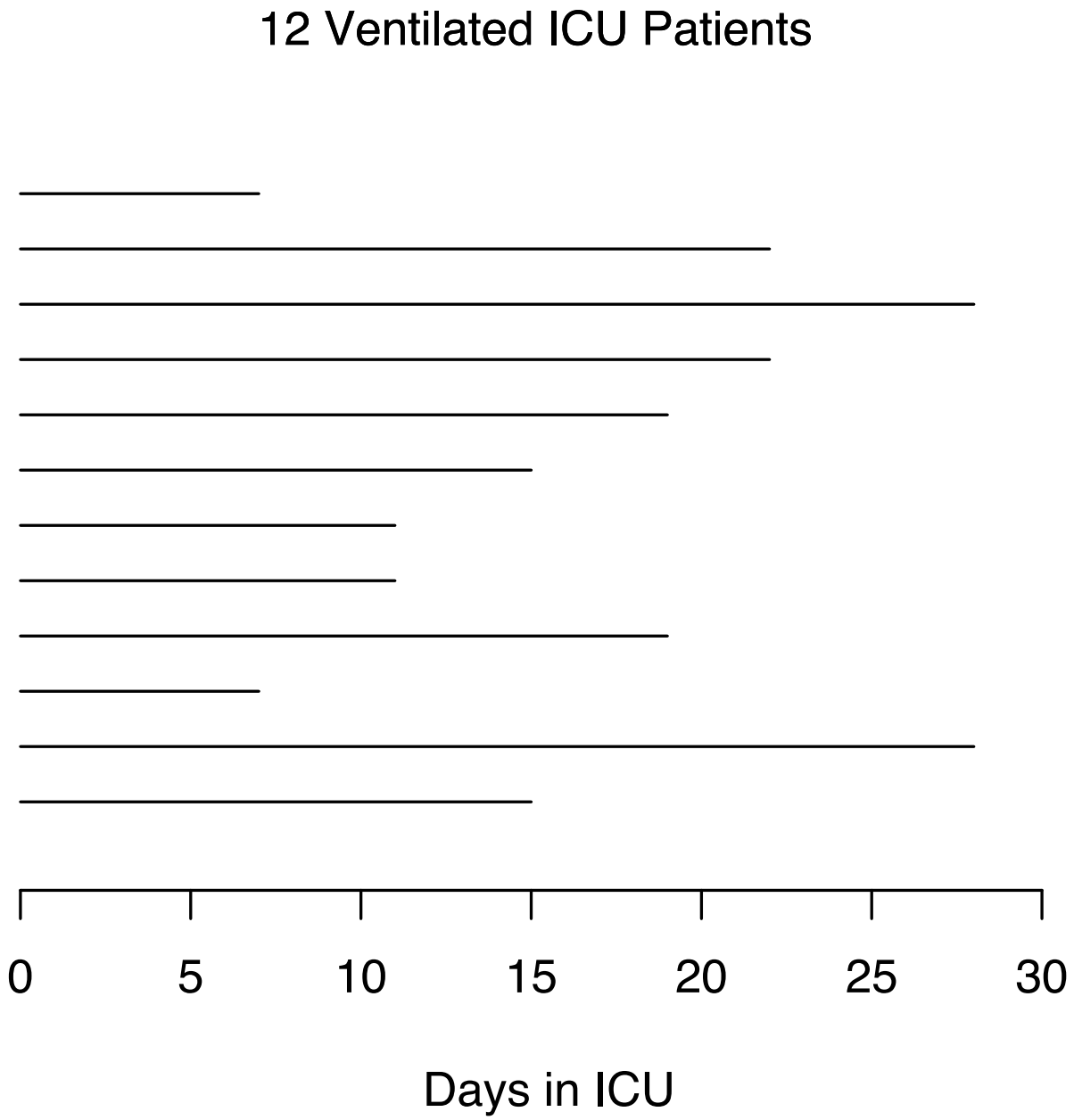
more on this later.....

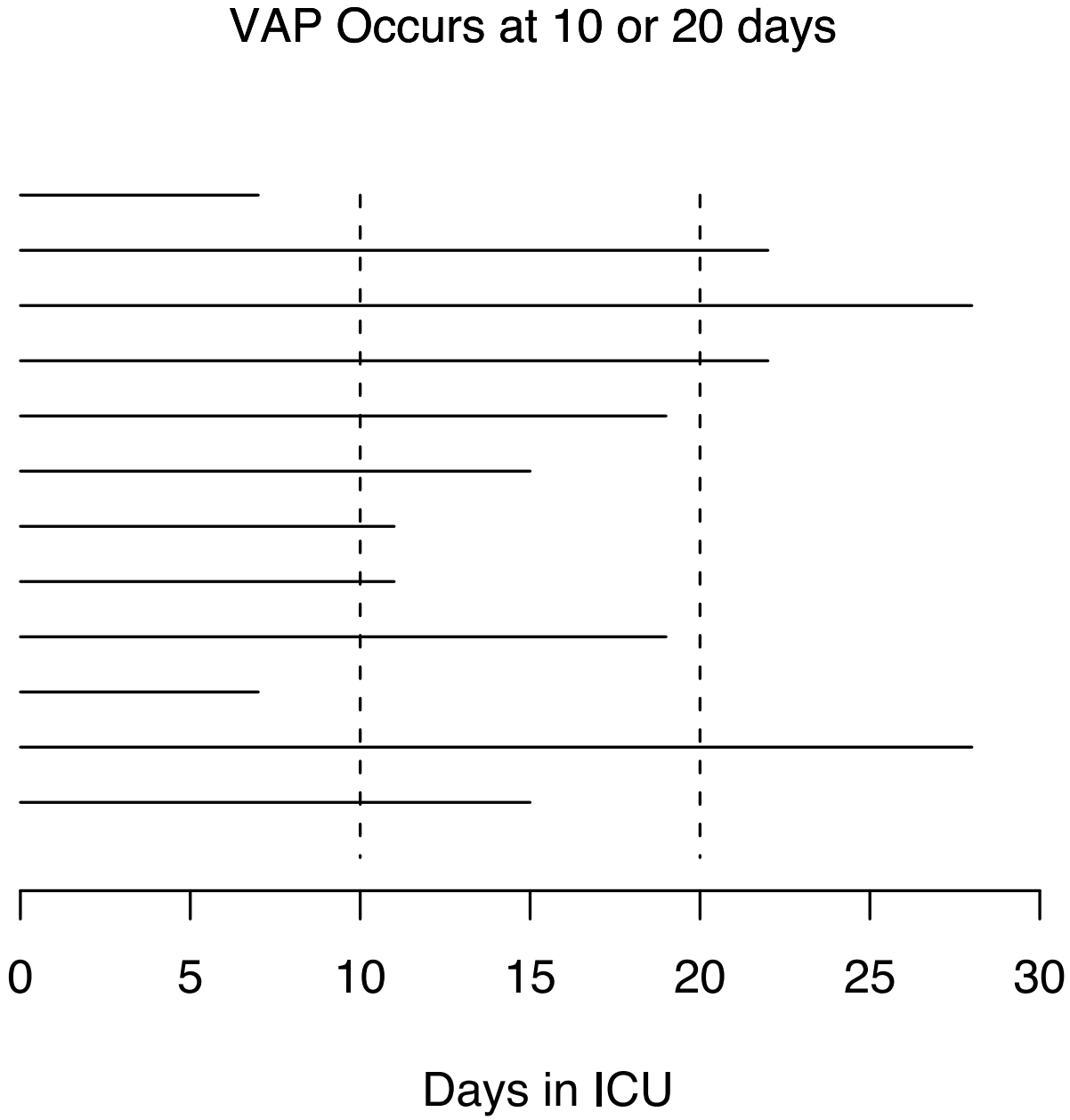
Data Example

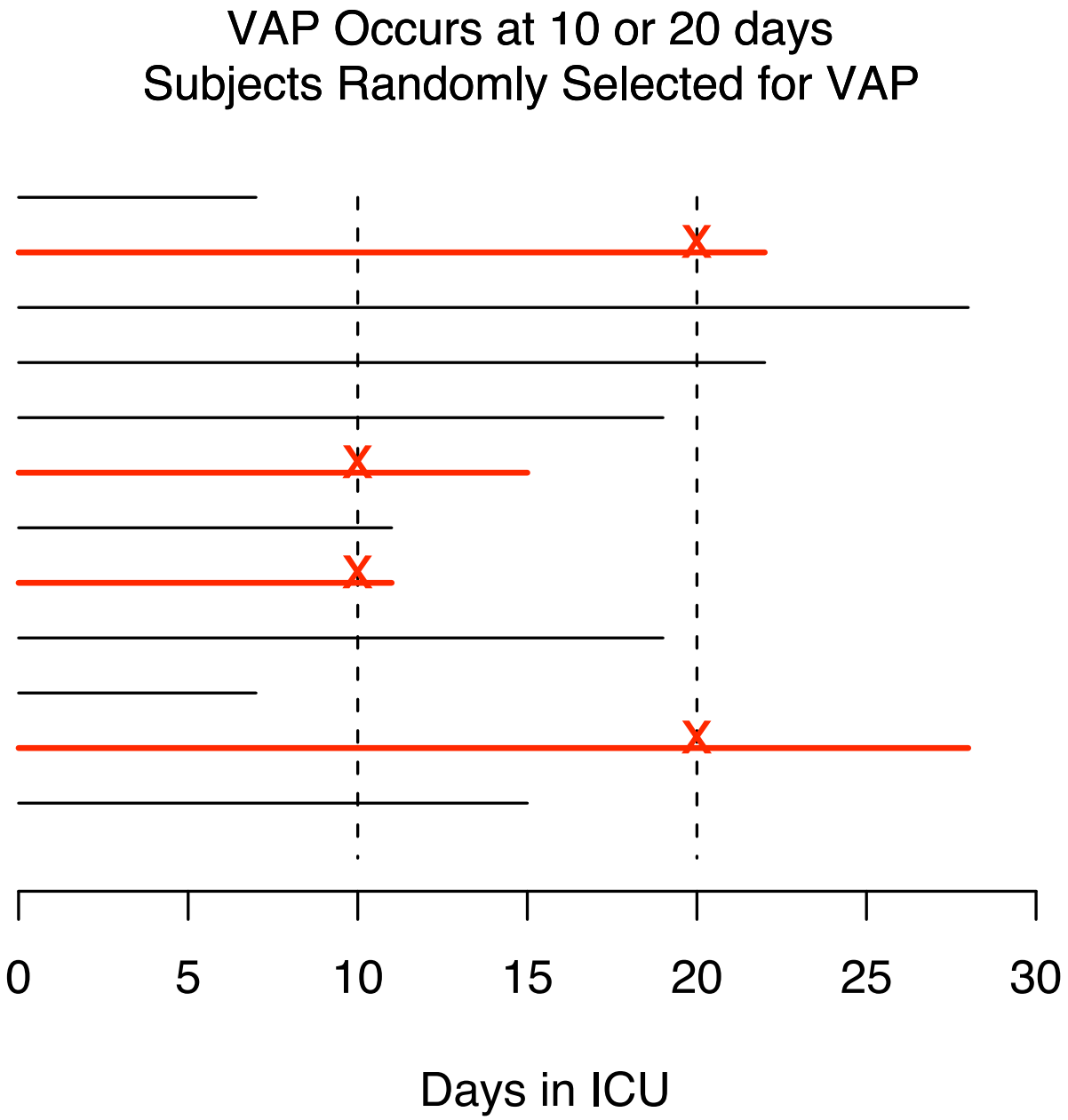
- Collaboration with ICU investigators
- Cohort of ventilated patients
- Ventilator assisted pneumonia (VAP)
- Does it extend time on the ventilator?
  Does it increase risk of death?
- VAP develops over clinical course in ICU

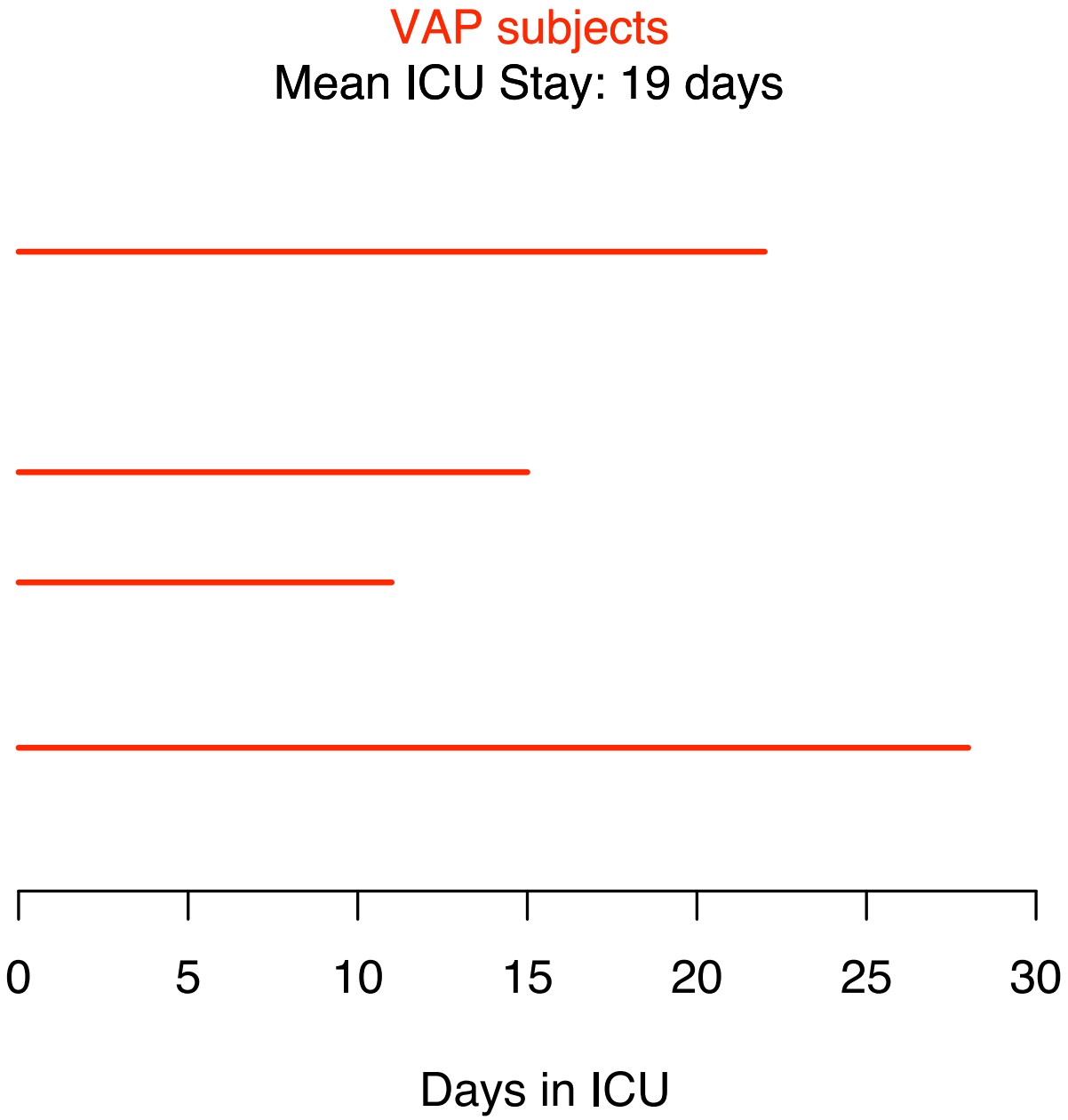
Simplistic Example

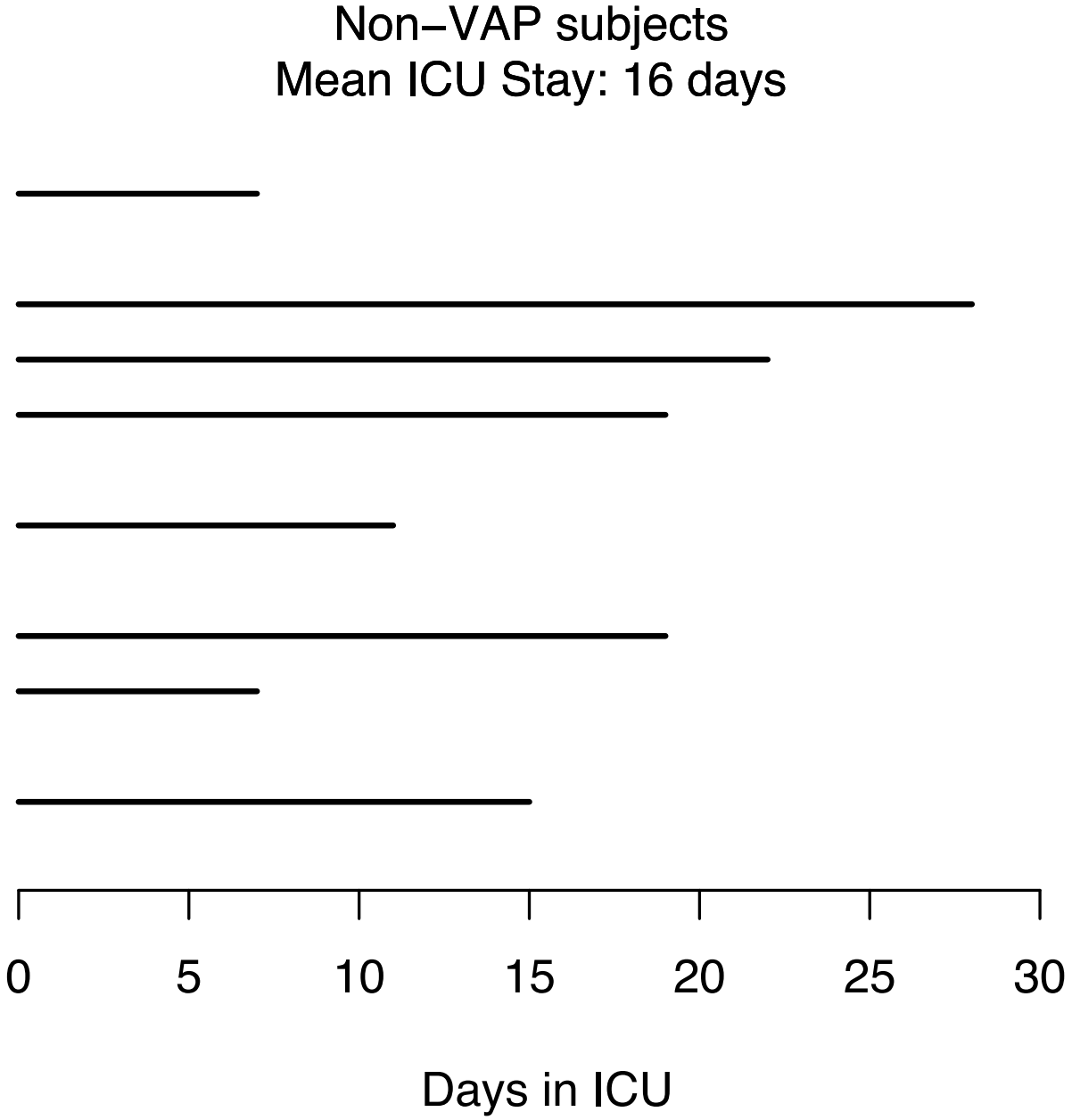
- Consider 12 ventilated patients
- VAP occurs at 10 or 20 days into ICU
- Do VAP patients have longer stay
- An example of immortal time bias

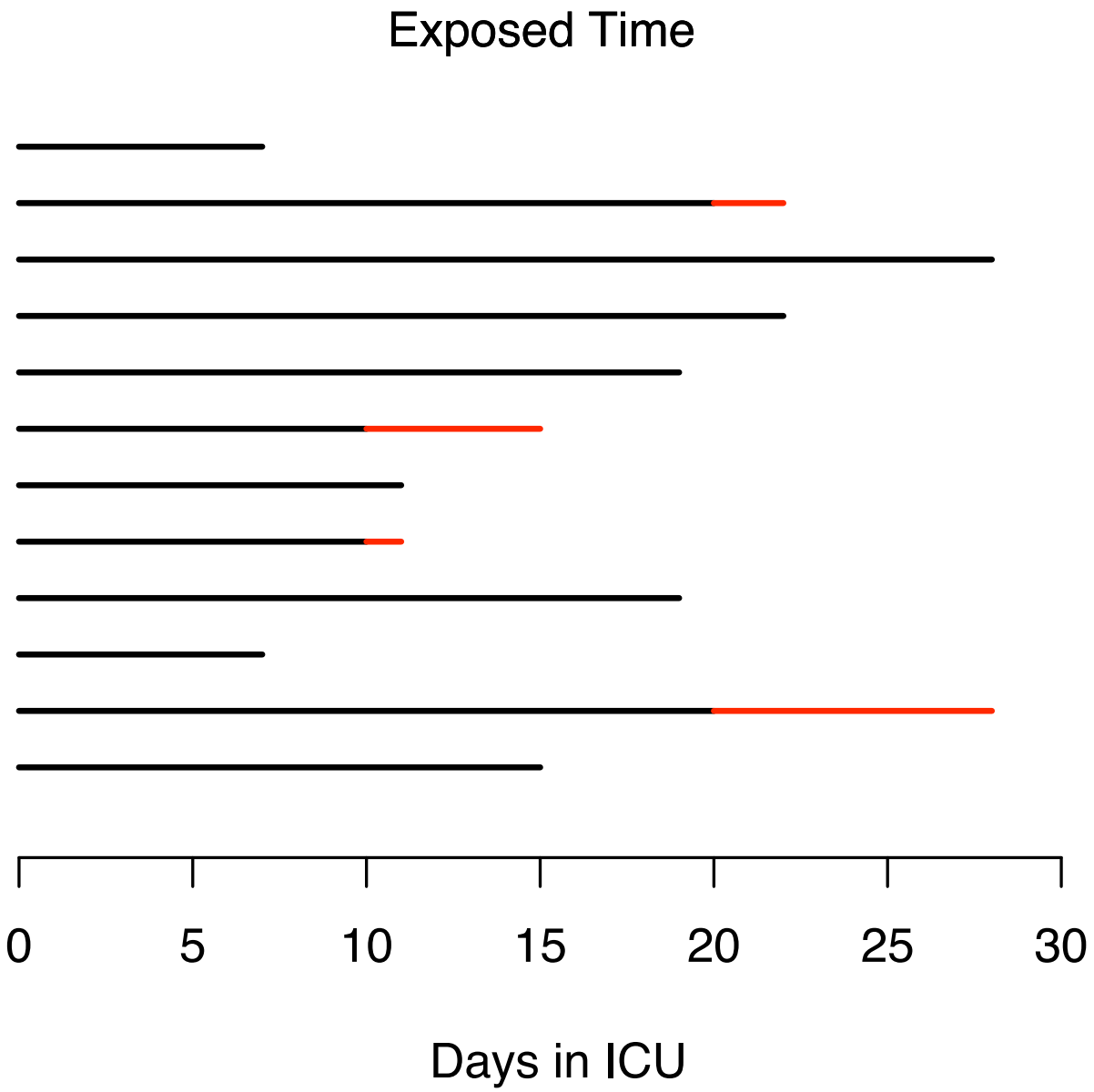

12 Ventilated ICU Patients
0
5
10
15
20
25
30
Days in ICU

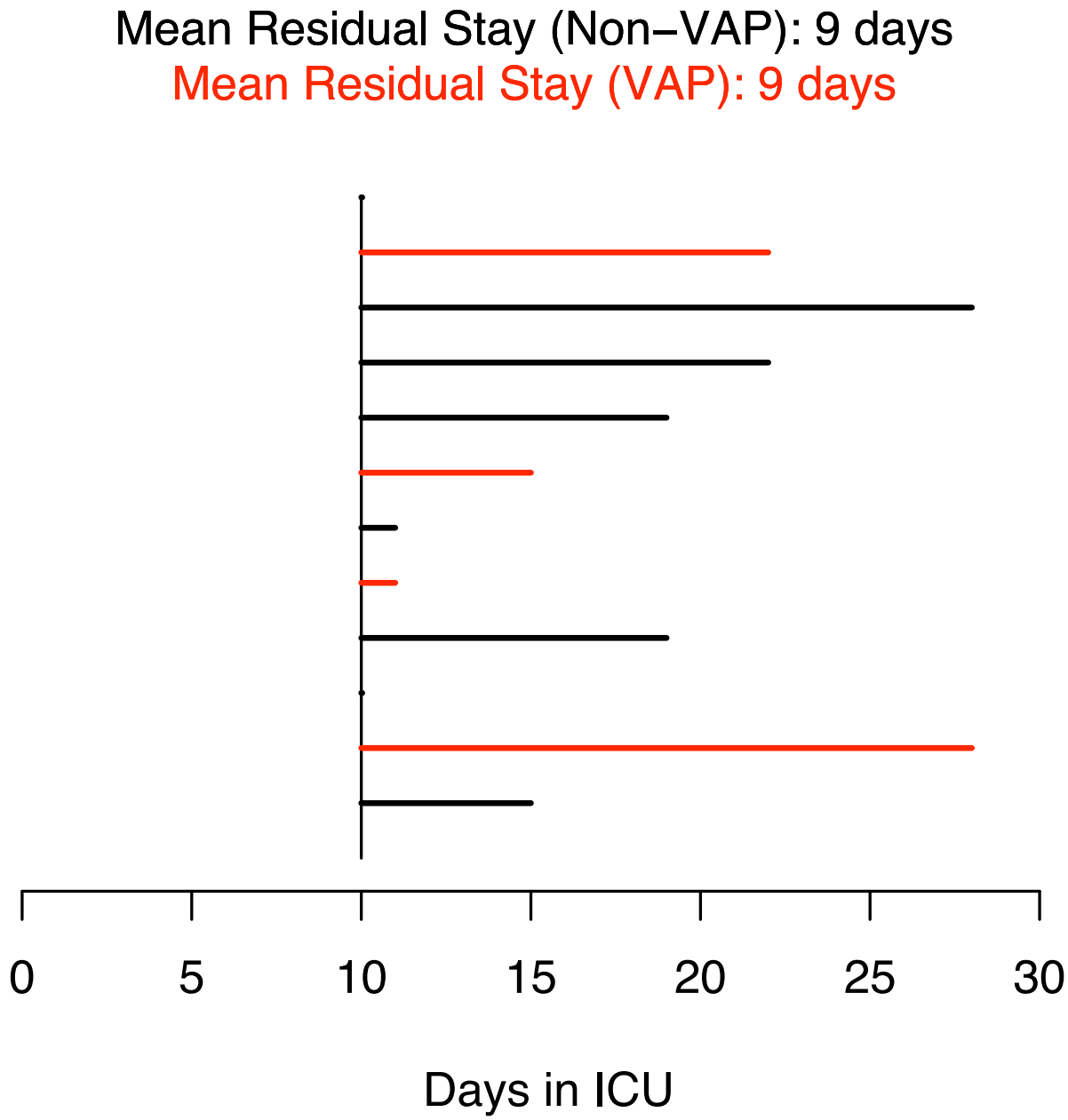

VAP Occurs at 10 or 20 days
0
5
10
15
20
25
30
Days in ICU

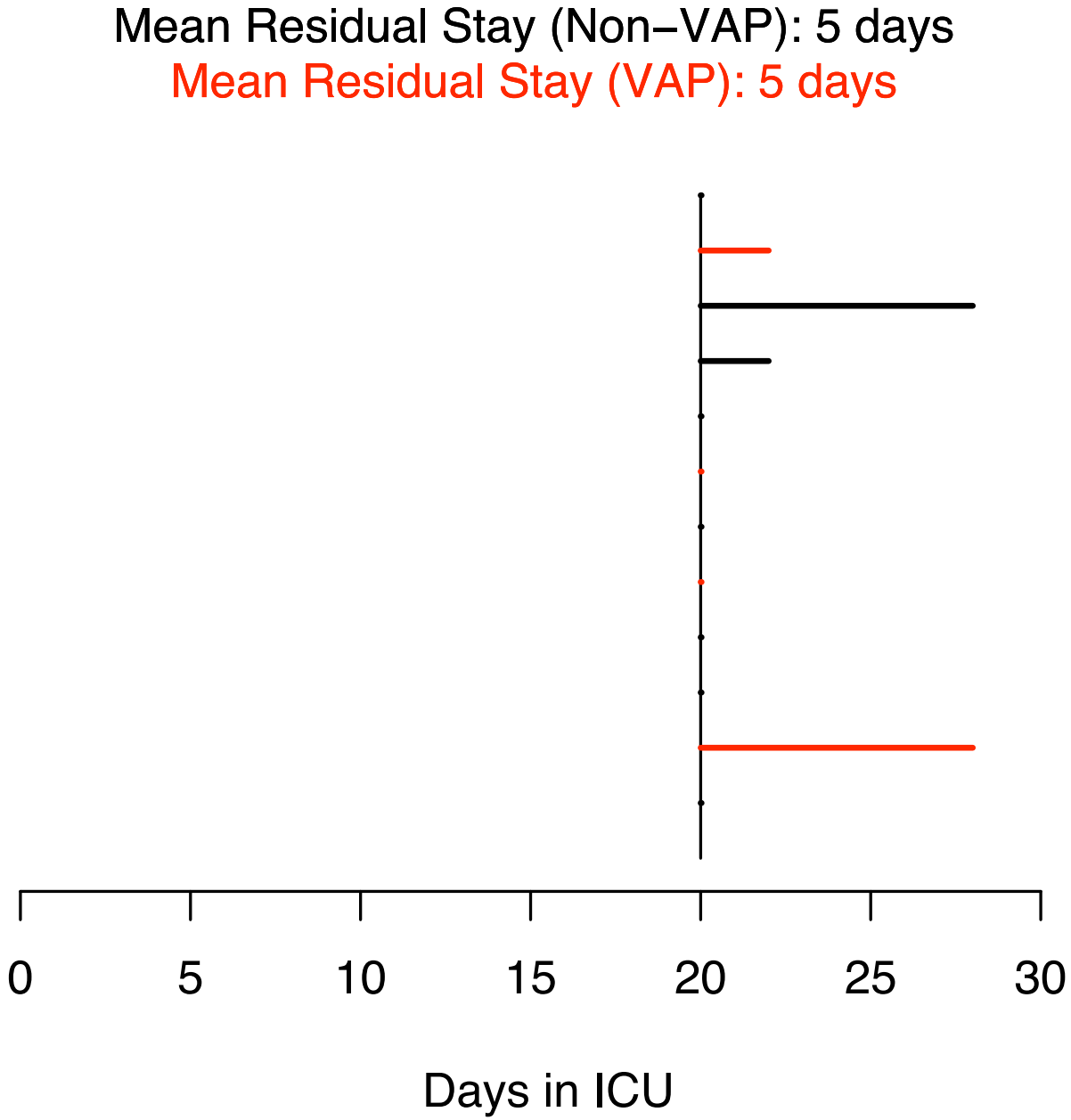

VAP Occurs at 10 or 20 days
Subjects Randomly Selected for VAP
0
5
10
15
20
25
30
Days in ICU


VAP subjects
Mean ICU Stay: 19 days
0
5
10
15
20
25
30
Days in ICU


Non−VAP subjects
Mean ICU Stay: 16 days
0
5
10
15
20
25
30
Days in ICU


Exposed Time
0
5
10
15
20
25
30
Days in ICU


Mean Residual Stay (Non–VAP): 9 days
Mean Residual Stay (VAP): 9 days
0
5
10
15
20
25
30
Days in ICU


Mean Residual Stay (Non–VAP): 5 days
Mean Residual Stay (VAP): 5 days
0
5
10
15
20
25
30
Days in ICU

Example

- Patients ever exposed to VAP vented longer
- VAP patients: two kinds of vent time
- Time before VAP: longer than non-VAP
  the so-called immortal time
- Time after VAP: same as VAP- subjects
- Should time before VAP count toward VAP+?

Other Examples

- PTLD increase risk of death in kidney tx?
- Does heart tx extend life in listed patients?
- Do OSCAR winners live longer?
- Common thread: exposure occurs sometime after follow-up
- PTLD, transplants, awards occur over time

Immortal Time Bias

Jean's Study

- Statin subjects develop BCC after starting statins: FU time before statins is immortal
- Adds time to statin+ group
- Will underestimate BCC rate in statin
- How can we handle this?

Steroids in COPD
A more subtle example

- Cohort patients discharged after COPD-related illness
- Exposure: inhaled corticosteroids (ICS)
- Outcome: death or hospitalization in 1 yr
- Exposed if filled ICS prescription in 90 days
- That 90 days leads to the bias

Two Classic Approaches

- Matching
- Regression

Matching

- Jean identifies cases of BCC
  Case #156: BCC at 6 years, no statins
- Has matched control(s)
  Cont. #156-1: BCC- at 6 years,
  2 years statin use (years 8-10)
- Control is unexposed! Only count statin exposure up to year 6
- Fair: don't count statin exposure after BCC

Careful Matching

- Matched controls can become cases
- Control for case #156 selected at random from those with no BCC after 8 years
- Choosing from no BCC after 10 years induces slight bias
- If disease is rare, bias is negligible

Analysis

- Matched design requires matched analysis
- Conditional logistic regression (binary)
- Stratified Cox model (time-to-event)
- Makes comparisons within pairs only

Time Dependent Covariates

A time-dependent covariate is a predictor whose values may vary with time

....and measured during the study

Regression Approach

- Creates exposure variable:
  1: statins 0: no statins
- Acknowledges that exposure changes
- Time prior to exposure, statin=0
- Time after exposure: statin=1
- Time-dependent covariate!

Time dependent covariate

Treat statin as a time-dependent covariate

$$\text{statin} = \begin{cases} 0 & \text{before initiating statins} \\ 1 & \text{after initiating statins} \end{cases}$$

$$\text{risk} = \begin{cases} \text{baseline risk before statins} \\ \text{RR*baseline risk after statins} \end{cases}$$

two groups but membership changes

Two patients

- Case #156: BCC at 6 years, no statins
- Cont. #156-1: BCC- at 10 years,
  2 years statin use (years 8-10)
- Can code as time-dependent covariates

Data

	idno	t_from	t_to	statin	bcc
218.	156	0	4	0	0
219.	156	4	6	1	1
200.	156-1	0	8	0	0
221.	156-1	8	10	1	0

idno: indicates subjects

t_from: start of interval

t_to: end of interval

statin: statins in interval

bcc: bcc in interval

Time-Dependent Covs

- Can be incorporated into Cox regression
- Use all the FU data
  doesn't discard FU just for matching
- Takes duration into account
- Some delicate modeling issues
- Doesn't work for all outcomes
  e.g., *ventilator free days*

Bad News

- Survival of OSCAR winners
  reanalysis show 1 year survival advantage
  not significant
- Inhaled steroids in COPD
  extensively studied and debated
  appears advantage due to immortal time
- Suissa (2007) documents 20 studies with this possible bias

Principles

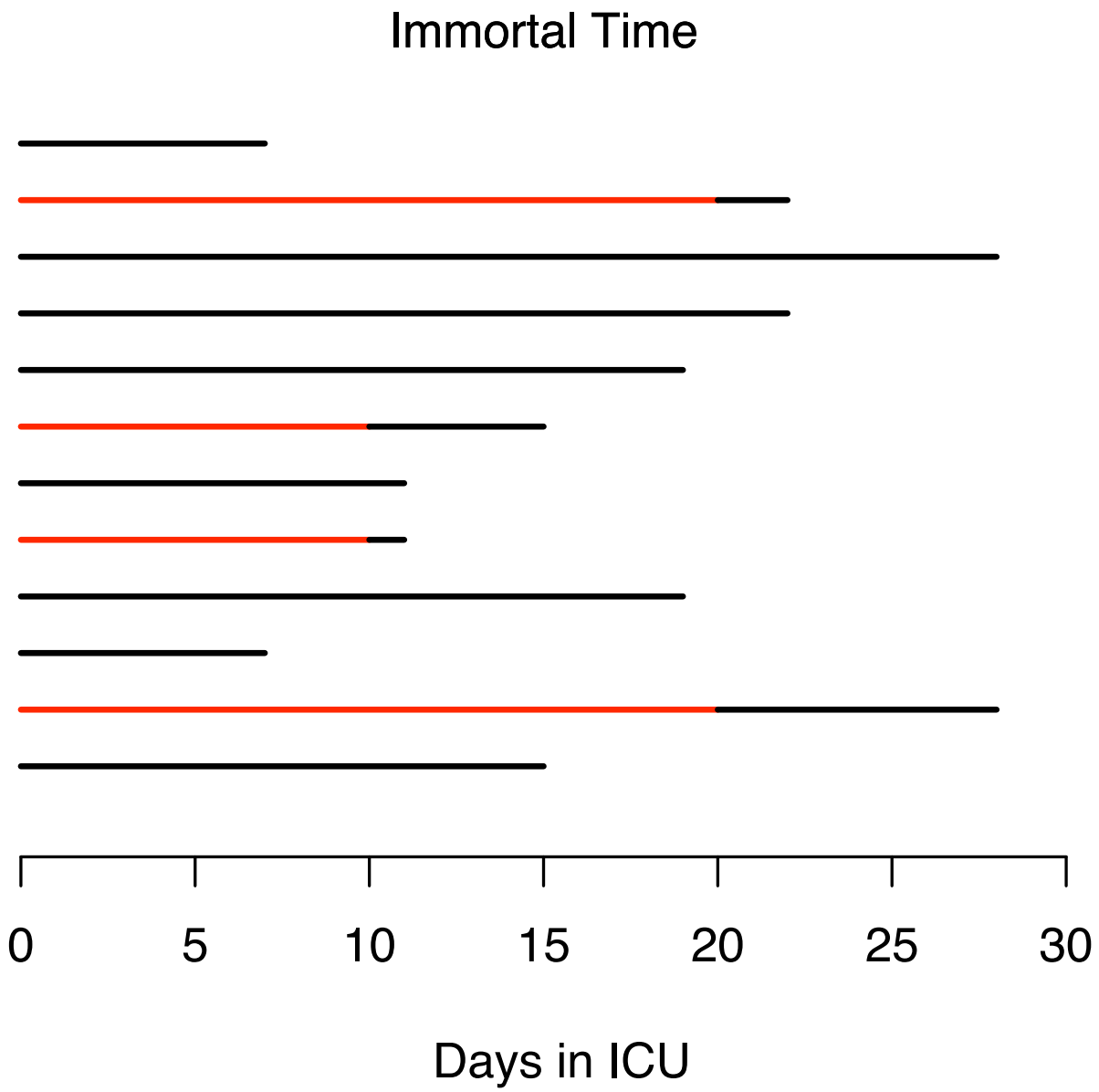
- Predictors can vary with time
  use time-dependent covariate approach
- Beware of defining groups using future
  patients with VAP vs. never developing VAP
  patient using drug at baseline v. never
- Recall, exposure implies survival

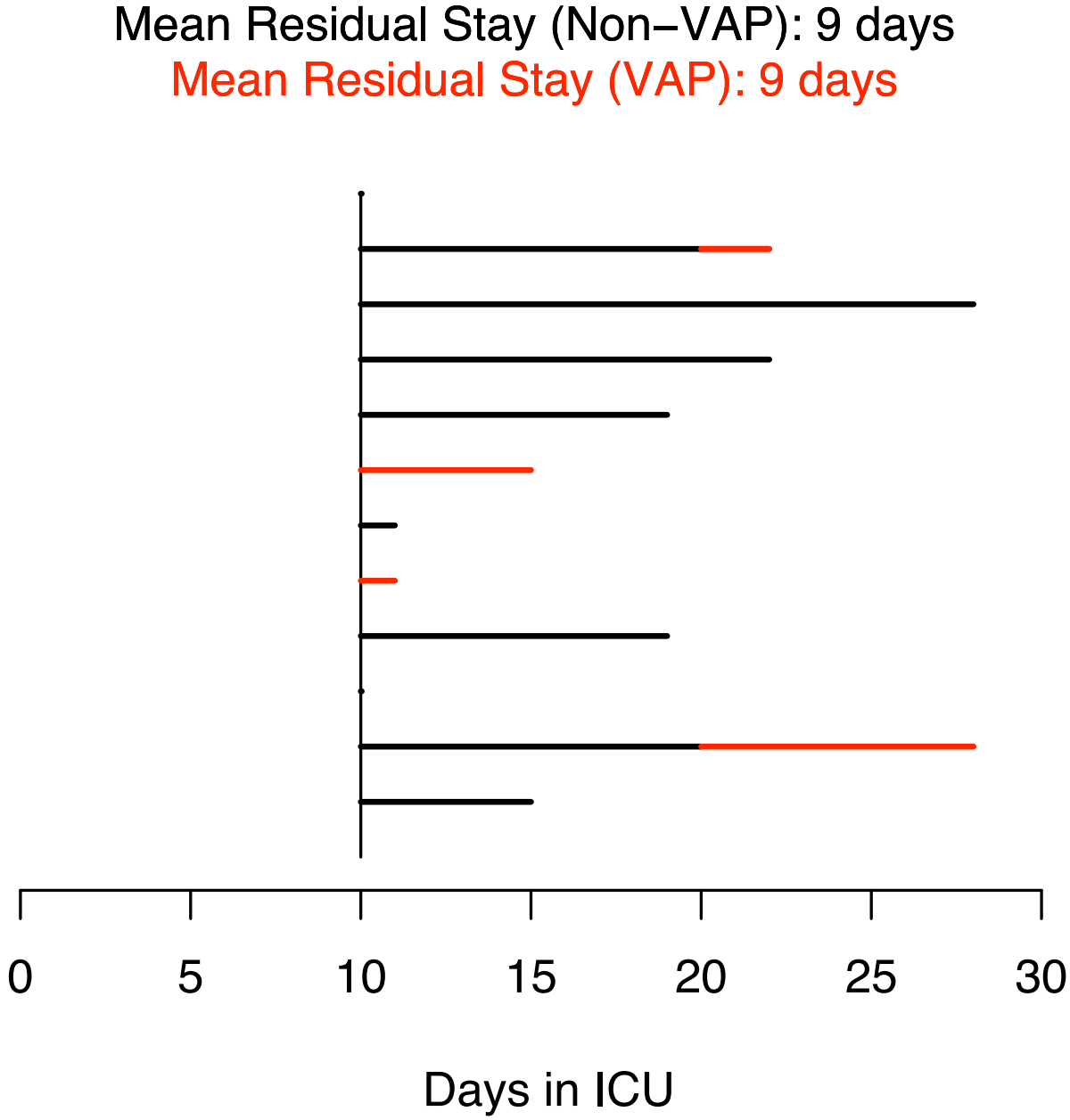
Readings

Suissa, S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiol Drug Saf. 16(3): 241 - 249, 2007

Suissa, S. Observational studies of inhaled corticosteroids in chronic obstructive pulmonary disease: misconstrued immortal time bias. Am J Respir Crit Care Med. 173(4):464, 2006

Pharmacoepidemiology. Wiley: 2005.


Immortal Time
0
5
10
15
20
25
30
Days in ICU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