

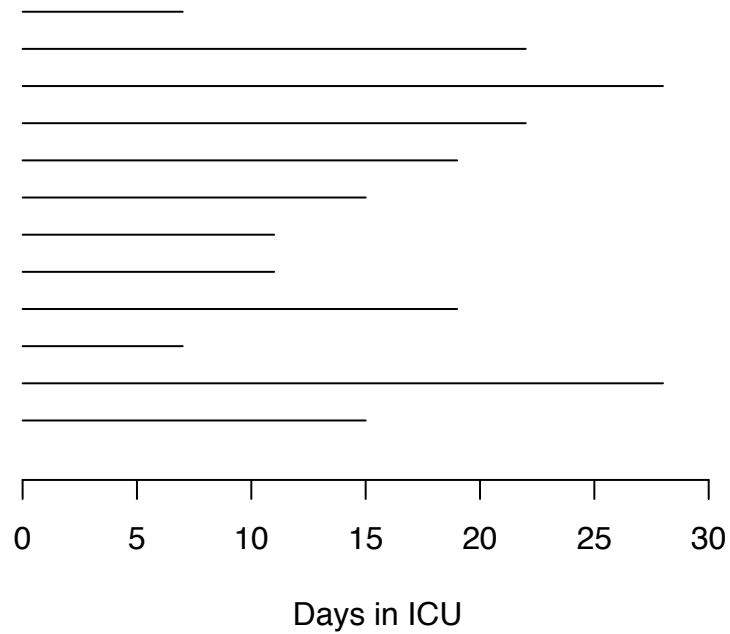
Time Dependent Covariates

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Biostatistics 210

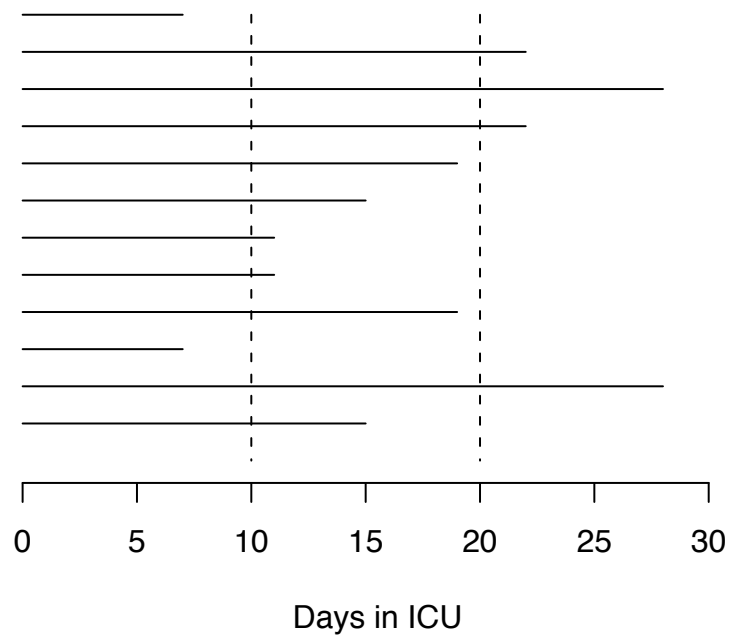
Data Example

- 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

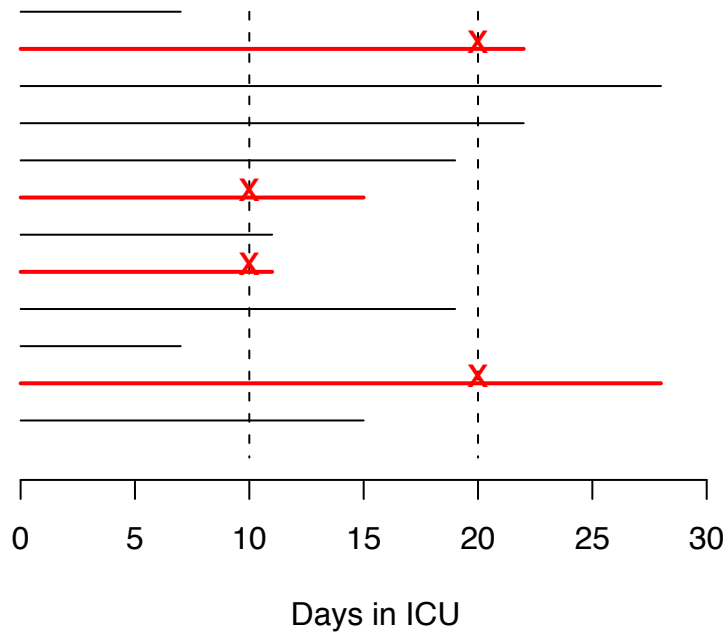
12 Ventilated ICU Patients



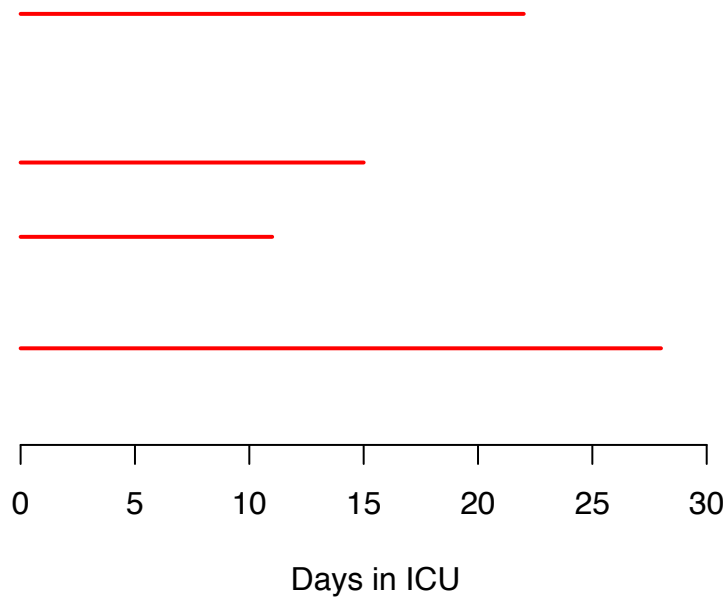
VAP Occurs at 10 or 20 days



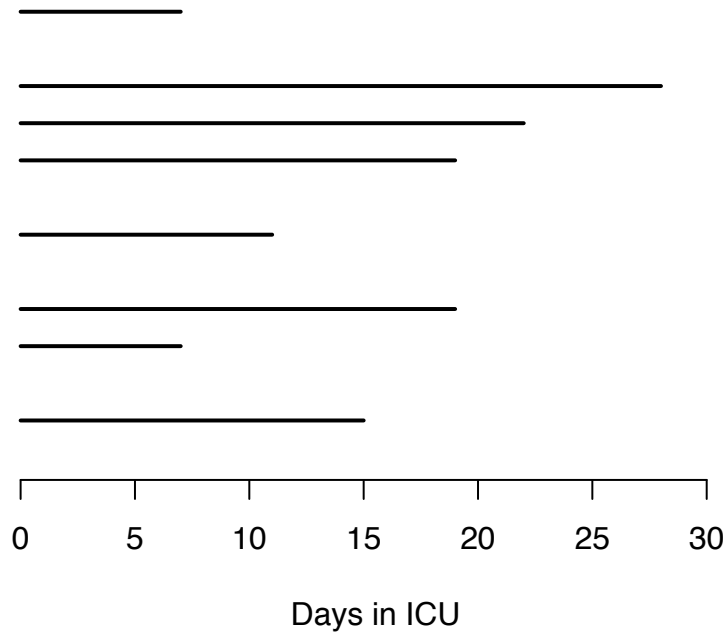
VAP Occurs at 10 or 20 days
Subjects Randomly Selected for VAP



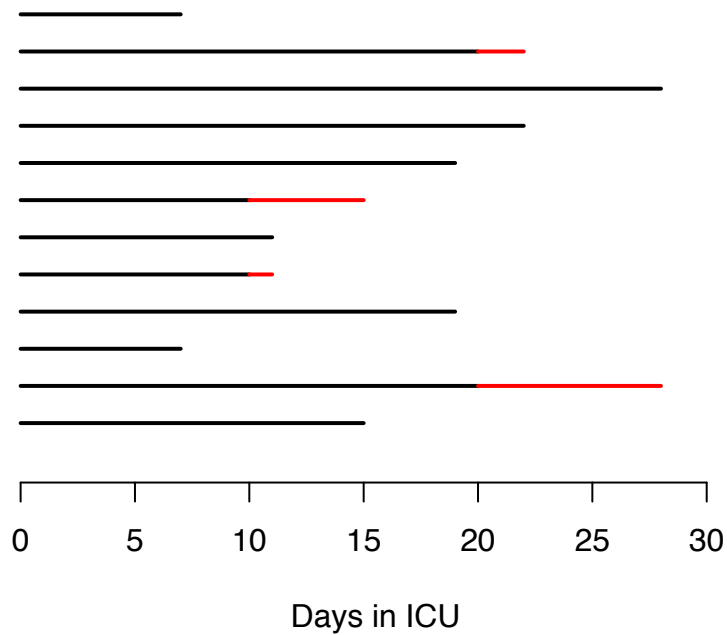
VAP subjects
Mean ICU Stay: 19 days



Non-VAP subjects
Mean ICU Stay: 16 days



Exposed Time



The Bias

- 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

SCC and voriconazole

- Solid organ transplant recipients
- Immune suppression
- Given voriconazole for fungal prophylaxis
- voriconazole introduced ~10 years ago
- Recent reports: may be associated with onset of squamous cell carcinoma (SCC)

UCSF Retrospective Cohort

- 380 Patients with Lung Transplant at UCSF
- Between 23 Oct '91 and 26 Dec '10
- Followed through mid 2011
- 54 patients developed SCC during FU
 - 17% in those with voriconazole*
 - 9% in those with no voriconazole*

Patient 1123

Example

- Transplanted 4/25/05
- SCC free and alive on 10/31/06
554 days after
- 4/28/05 - 6/16/05: 49d @ 400mg/day =
 $49 * 400 / (400 * 365) = 0.13$
- 9/7/05 - 11/10/06: @ 400mg/day
419 days thru 10/31 = 1.15
- Cumulative exposure = 1.36 year of 400mg
- Need this for every person

Analysis Framework

- Cox model for rate of SCC
- Predictor: exposure to voriconazole
- Bad way:
 - fixed predictor
- Better way
 - break up follow up: td predictor

Fixed Predictor

abpatientcode	time	event	evervori	totaldose	ageattp
1123	837	2	1	1.36	64

Ever Voriconazole

fixed time covariate

No. of subjects =	379	Number of obs =	8433
No. of failures =	54		
Time at risk =	413146		
Log likelihood =	-250.63795	LR chi2(1) =	3.47
		Prob > chi2 =	0.0625

_t	Haz. Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
evervori_f~d	1.787881	.5859601	1.77	0.076	.9405156 3.398689

ever voriconazole versus never

Dose of Voriconazole

fixed time covariate

Cox regression -- Breslow method for ties

No. of subjects =	379	Number of obs =	8433
No. of failures =	54		
Time at risk =	413146		
Log likelihood =	-252.23301	LR chi2(1) =	0.28
		Prob > chi2 =	0.5970

_t	Haz. Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
totaldose	1.051435	.0973257	0.54	0.588	.8769829 1.260589

per year at 400 mg dose

Time-Dependent Covariate

TDC

- Predictors whose value may vary with time
- And measured as a part of the study
- Longitudinal data in a predictor
- Outcome is usually longitudinal
GEE or a mixed model
- Or as a part of a Cox model

Td predictor

abpatientcode	from	to	event	cumdose	ageattp
1123	0	91	0	0.13	64
1123	91	198	0	0.31	64
1123	198	263	0	0.48	64
1123	263	398	0	0.85	64
1123	398	405	0	0.87	64
1123	405	447	0	0.99	64
1123	447	545	0	1.26	64
1123	545	554	0	1.28	64
1123	554	590	0	1.31	64
1123	590	637	0	1.36	64
1123	637	638	0	1.36	64
1123	638	723	0	1.36	64
1123	723	761	0	1.36	64
1123	761	800	0	1.36	64
1123	800	817	0	1.36	64
1123	817	837	2	1.36	64

The Cox Model

with time-dependent covs

- $h(t|x_1, \dots, x_p) = h_0(t) \exp(\beta_1 x_1 + \dots + \beta_p x_p)$
- Model hazard (like a rate) function
- baseline hazard not specified
- Predict effect acts multiplicatively on hazard
- $h(t) = h_0(t) \exp(\beta_1 x_1(t) + \dots + \beta_p x_p(t))$
allows the predictors to vary with time

Why use time-dependent covariate?

- Factor or exposure is time varying
- Can increase predictive power
e.g., viral load in HIV
- Aligning timing of exposures & outcomes
avoiding *immortal time bias*

Defining Exposure

- Created exposure variable:
 $x(t)$ dose-days of voriconazole through t
- Acknowledges that exposure changes
- Time prior to exposure, $x(t)=0$
- After exposure accumulates through t
- If exposure stops: $x(t)$ doesn't increase

Time-Dependent Covariate

- Data management is biggest hurdle
- Need a long record dataset for each person
- Need know for series of time periods
 - Did person get SCC or get censored?
 - What was value of td cov for that period?
- Series of time points -- observed times of SCC

Td predictor

abpatientcode	from	to	event	cumdose	ageattp
1123	0	91	0	0.13	64
1123	91	198	0	0.31	64
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1123	637	638	0	1.36	64
1123	638	723	0	1.36	64
1123	723	761	0	1.36	64
1123	761	800	0	1.36	64
1123	800	817	0	1.36	64
1123	817	837	2	1.36	64

Cox Model w/ TD Cov

- Patient #37: SCC 554d after transplant
received 1.01 years of voriconazole
- Think of him as a “case”
*to be compared to a set of controls
matched on follow-up*
- More vori exposure than typical case?
- How much vori in those SCC-free 554 days?

stset

- `stset to, failure(event==1) id(abpatientcode)`
- “from” is not need but helps me keep track
- event: 0 censored, 1 SCC, 2 death
if want Cox on SCC, set event to 1
- Must use id for multiple events data
- Then just apply Cox
- Not good for anything else!
multiple records foul all else up

Ever Voriconazole

as a time-dependent covariate

```
stcox evervori_td
```

```
Cox regression -- Breslow method for ties
```

```
No. of subjects =          379          Number of obs   =          8433
No. of failures =           54
Time at risk    =        413146
Log likelihood   =       -248.1054          LR chi2(1)      =           8.53
                                          Prob > chi2       =          0.0035
```

_t	Haz. Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
evervori_td	2.444013	.8028329	2.72	0.007	1.283786 4.6528

Dose of Voriconazole

as a time-dependent covariate

```
stcox cumdose
```

```
No. of subjects =          379          Number of obs   =          8433
No. of failures =           54
Time at risk    =        413146
Log likelihood   =       -249.4083          LR chi2(1)      =           5.93
                                          Prob > chi2       =          0.0149
```

_t	Haz. Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
cumdose	1.311188	.1346107	2.64	0.008	1.072205 1.603438

per year at 400 mg dose

TD CoVs Eliminates ITB

- Behind the scenes it's implementing the matching approach
comparing comparable follow-up
looking at effects after exposure
- But using all the data in a flexible way
no artificial matches
all available data used

Sparsity

- HIV chemoprophylaxis
with anti-viral drug emtricitabine+tenofovir
- Risk of HIV high associated with levels
pill taking fluctuates, drugs levels per 24w
- Week 24: 10.5 fmol/ 10^6 cells
- Week 48: 18.5 fmol/ 10^6 cells
- What is the level at Weeks 32, 54?

Paradox

reverse causation in smoking exposure

- Coronary artery surgery study
smoking status per 6 months
- Current smoking: reduced risk of death
not statistically significant
- Most deaths among smokers
but had stopped smoking just prior to death
- Hospitalization/CHF lead quitting before death
- Their soln: lag smoking by 6 month

Histories

- BCC study: voriconazole hx over many years
- Which part is relevant for risk of BCC?
current voriconazole
current dose
total accumulated voriconazole
accumulated exposure in last year
- Combine subject-matter knowledge
and can see what fits better

Ever vs. Cumulative Voriconazole

```
. stcox cumd evervori_td
```

No. of subjects =	379	Number of obs =	8433
No. of failures =	54		
Time at risk =	413146		
Log likelihood =	-247.51186	LR chi2(2) =	9.72
		Prob > chi2 =	0.0077

_t	Haz. Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
cumdose	1.155081	.1469683	1.13	0.257	.9001372	1.482232
evervori_td	2.026276	.7556136	1.89	0.058	.9756167	4.20841

ever vs. cumulative -- ever appears stronger

Three Things to Think Of

1. May be gaps in exposure (sparsity)
2. Can introduce additional confounding
some td covs can even be mediators
3. Have to distill a complex history
rich modeling choices

Baseline Covariates

- Osteoporosis study
- Baseline BMD predicts fracture over 3 years
- That, in itself, is powerful
- Prognostic over many years powerful
- Baseline and td cov analyses complimentary
- A baseline value can be just fine

Recognizing ITB

- Carefully examine when and how people enter a “group” or accrue their exposure
- Is there a time-related requirement?
if yes, ITB
- Based on classification @ time 0 or later?
if later, ITB
- TD covs can account for this

TD Cogs

- Clarifying exposure and events
- Addresses immortal time bias
- Dataset construction can be tedious
- Fitting model is easy
- Mindful of inverse associations and mediators
- Rich choices for incorporating hx