Medical University of Graz

Sample size calculations and the temporal dependency between an infection and its sequela in randomised controlled trials

S.A. Herzog, A. Berghold

Institute for Medical Informatics, Statistics an Documentation,
Medical University of Graz, Austria

ROeS 2013
Thursday September 12

Infection and sequela

Medical University of Graz

- *Chlamydia trachomatis* (chlamydia)
  - Sexually transmitted
  - Usually asymptomatic
- Pelvic inflammatory disease (PID)
  - Ectopic pregnancy, infertility
  - On average chlamydia present at diagnosis in 30% of PID cases[§]
  - More than 750'000 PID episodes per year in USA[*]

[§]**Holmes** Sexually Transmitted Diseases 2008, **Low** Int J Epidemiol 2009; [*]CDC Fact Sheet 2011

Screening for chlamydia

Medical University of Graz

- Screening to detect and treat asymptomatic chlamydia is recommended to prevent PID (USA, UK)*
- Objectives of screening for chlamydia
  - Lower prevalence of chlamydia (population level)
  - Prevent complications (individual level)

*CDC MMWR 2010, NCSP Standards 6th ed. 2012

3

Prevention of pelvic infection (POPI) trial, 2004-2006

Medical University of Graz

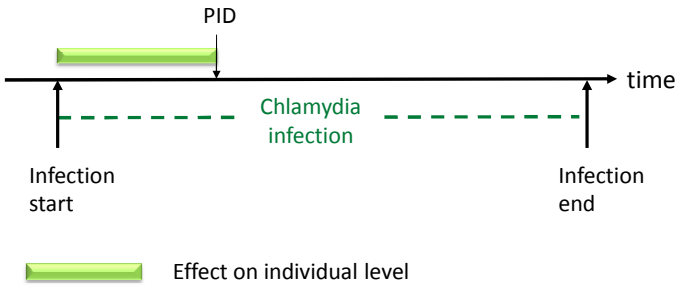
- Randomized controlled trial
  - Outcome: PID incidence after 12 months period of follow-up
  - Intervention: One round screening for chlamydia
    - Intervention group: tested & treated immediately
    - Control group: tested after one year
- Sample size calculation
  - First calculation: 2% PID incidence, 0.48 RR → 4122 in both groups
  - Re-calculation: 3% PID incidence, 0.44 RR → 2274 in both groups
- Result
  - Relative risk 0.65 (95% CI 0.34-1.22) with N=2377

Oakeshott et al. BMJ 2010

4

Objective

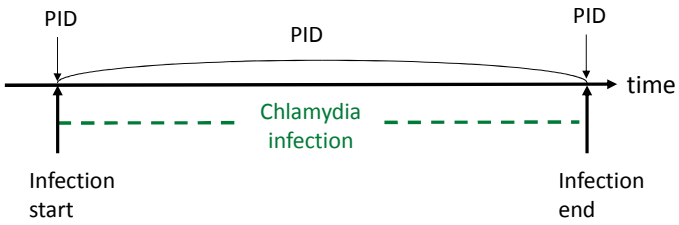
> Investigating how different temporal dependency assumptions can influence the sample size calculation



5

Progression to PID

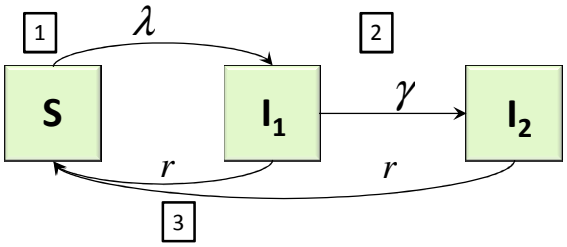
> Hypothetical processes:
  - Immediately after infection (immediate)
  - At a constant rate throughout the infection (constant)
  - At the end of the infection period (end)



6

Mathematical model

Progression to PID



Process	Incidence
1 Immediate	f*λ*S
2 Constant	f*γ*I_1
3 End	f*r*(I_1 + I_2)

S = Susceptible

I_1 = Infected without PID

I_2 = Infected with PID

λ = force of infection (constant)

1/r = duration of infection

γ= rate $I_1 \rightarrow I_2$

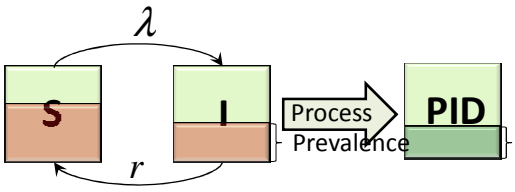
f= fraction of infected developing PID

Model similar to **Herzog et al** BMC Infect Dis 2012

7

Incidence and relative risk

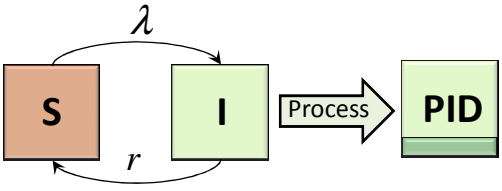
Control group



Given Incidence

Calculate Fraction f

Intervention group



Use Fraction f

Calculate RR

S = Susceptible

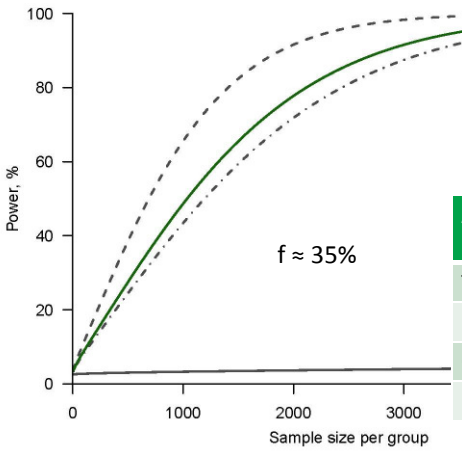
I = Infected

λ = force of infection

1/r = duration of infection

8

Result: First calculation



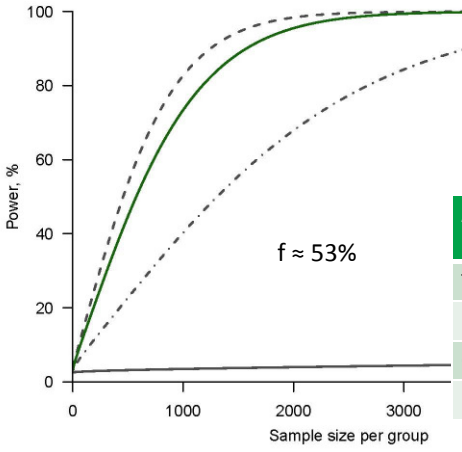
First calculation
Incidence 2%
Relative risk 0.48

Approach	Sample size per group#	RR
Two proportion*	2115	0.48
Immediate	-	1.03
Constant	2436	0.51
End	1408	0.38

for 80% power; *as used in POPI trial

9

Result: Re-calculation



Re-calculation
Incidence 3%
Relative risk 0.44

Approach	Sample size per group#	RR
Two proportion*	1174	0.44
Immediate	-	1.03
Constant	2670	0.60
End	932	0.38

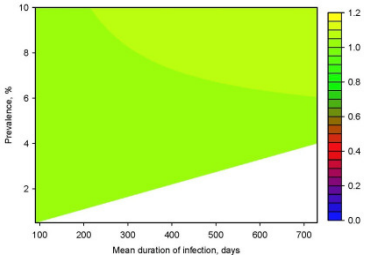
for 80% power; *as used in POPI trial

10

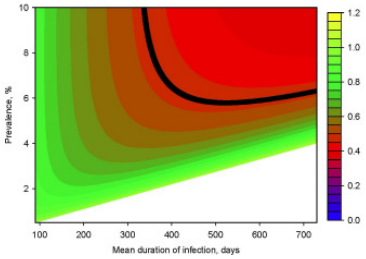
Result: Relative risk of processes

Medical University of Graz

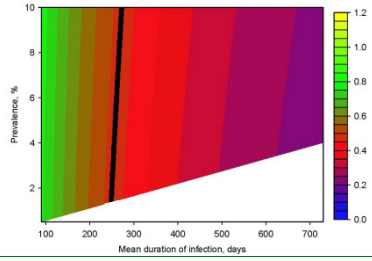
Immediate



Constant



End



First calculation

Incidence 2%

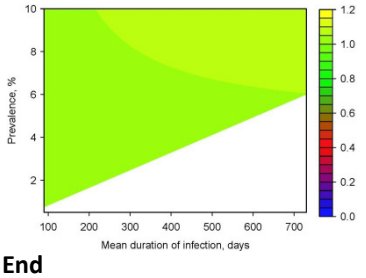
Relative risk 0.48

11

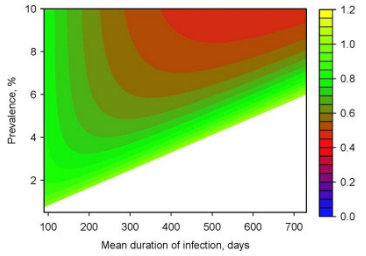
Result: Relative risk of processes

Medical University of Graz

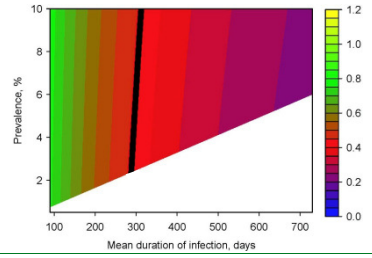
Immediate



Constant



End



Re-calculation

Incidence 3%

Relative risk 0.44

12

Discussion

- Sample size needed per group vary considerably
- Relative risks differ between hypothetical processes
- Strength
  - Studying 3 hypothetical processes in same simple modelling framework
  - Used an empirical example
- Limitation
  - Not all PID cases caused by chlamydia
  - Treatment failure

13

14

Randomized controlled trials

Medical University of Graz

Study, Design, Dates, Place	Study population	Intervention	Control
Scholes et al. Individual RCT 1990 – 1992 USA*	Women, 18–34 years Selected as being at high risk of chlamydia	Invitation to be screened for chlamydia	Usual care
Østergaard et al. Cluster RCT 1997 – 1998 Denmark*	Women and men, mean age 18 years, 17 schools	Home sampling kits sent. Information about chlamydia. PN for positive cases	Usual care Offer of free chlamydia testing Information about chlamydia. No PN advice
Andersen et al. Individual RCT 1997 Denmark*	Women and men, 22-24 years	Invitiation to be screened for chlamydia	Usual care
Oakeshott et al. Individual RCT 2004 – 2006 UK	Women, sexually active students	Swab tested immediately	Swabs tested after one year

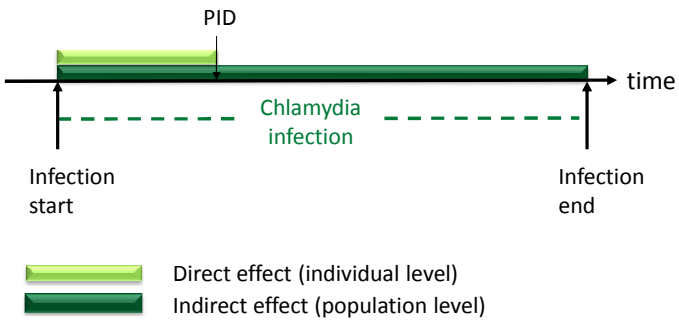
* Registered based screening

15

Effect of screening

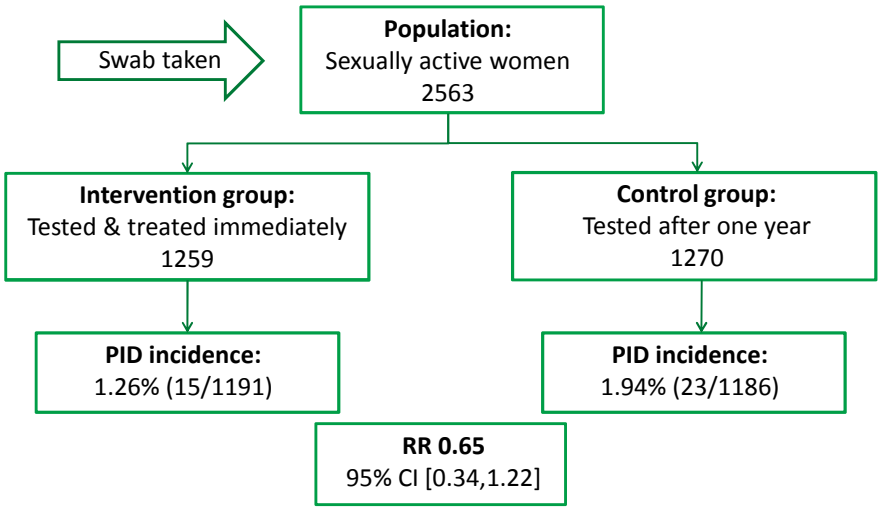
Medical University of Graz

> Effect of screening: direct and indirect



16

POPI trial result



Oakeshott P. et al. BMJ 2010

17

Parameters used

- Force of infection: calibrated to baseline prevalence
- Baseline prevalence: 5.7% (Data*)
- Infection duration: 1 year (Althaus et al. 2010, Heijne et al. 2011)
- Fraction f: fitted incidence

- In the trial
  - Testing uptake: about 22% in both groups
  - Chlamydia: 30/38 PID cases in chlamydia negative
    68 chlamydia cases in intervention group
    75 chlamydia cases in control group

*__Oakeshott P. et al__. BMJ 2010

18

Formulae RR

Medical University of Graz

Immediate progression

$$\begin{aligned} \text{cum}_{\text{Int}} &= fN_I p\left(p - e^{-\frac{r}{1-p}t_1}p + rt_1\right) \\ \text{cum}_{\text{Cont}} &= fN_C p r t_1 \\ \text{RR} &= \frac{N_I\left(p - e^{-\frac{r}{1-p}t_1}p + rt_1\right)}{N_C r t_1} = \frac{\left(p - e^{-\frac{r}{1-p}t_1}p + rt_1\right)}{rt_1} \end{aligned}$$

Constant progression

$$\begin{aligned} \text{cum}_{\text{Int}} &= \frac{fp}{f-p}N_I\left(-\left[-1+e^{-\frac{r}{1-f}t_1}\right]f^2 + p + e^{-\frac{r}{1-p}t_1}(-1+p)p\right. \\ &\quad \left. + f\left[-1+e^{-\frac{r}{1-f}t_1} + rt_1\right] - p(p+rt_1)\right) \\ \text{cum}_{\text{Cont}} &= fN_C p r t_1 \\ \text{RR} &= \frac{\left(-\left[-1+e^{-\frac{r}{1-f}t_1}\right]f^2 + p + e^{-\frac{r}{1-p}t_1}(-1+p)p + f\left[-1+e^{-\frac{r}{1-f}t_1} + rt_1\right] - p(p+rt_1)\right)}{(f-p)rt_1} \end{aligned}$$

End progression

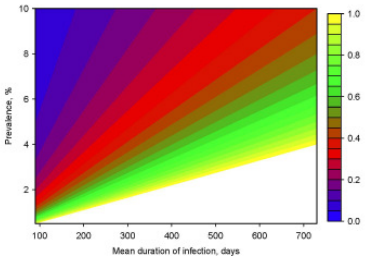
$$\begin{aligned} \text{cum}_{\text{Int}} &= e^{-\frac{r}{1-p}t_1} fN_I p\left(1 - p + e^{\frac{r}{1-p}t_1}(-1+p+rt_1)\right) \\ \text{cum}_{\text{Cont}} &= fN_C p r t_1 \\ \text{RR} &= \frac{e^{-\frac{r}{1-p}t_1}\left(1 - p + e^{\frac{r}{1-p}t_1}(-1+p+rt_1)\right)}{rt_1} \end{aligned}$$

19

Result: Relative risk of processes

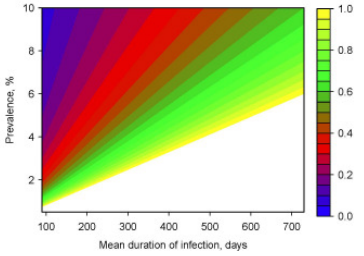
Medical University of Graz

Fraction f – First calculation



First calculation
Incidence 2%
Relative risk 0.48

Fraction f – Re-calculation



Re-calculation
Incidence 3%
Relative risk 0.44

20