Zinc acetate lozenges may improve the recovery rate of common cold patients: an IPD meta-analysis

Supplementary File 2

This is supplementary material to a paper by Hemilä et al. (2017).
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http://www.mv.helsinki.fi/home/hemila/Zinc.htm (papers on zinc and the common cold)

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Statistical analyses of the studies are described in this file.
The data set used in the study is printed at the end of this file.

This file contains:

Table 2 analyses: Effect of zinc acetate lozenges on the recovery rate from the common cold

Petrus (1998)

```
> PetrusCox   <- coxph(PetrusSurv ~ Petrus_1998$Zinc , method = "efron")
> PetrusCox
Call:
coxph(formula = PetrusSurv ~ Petrus_1998$Zinc, method = "efron")

                  coef exp(coef) se(coef)    z      p
Petrus_1998$Zinc 0.573     1.774    0.214 2.68 0.0073

Likelihood ratio test=7.3  on 1 df, p=0.00691
n= 101, number of events= 101
> exp(confint(PetrusCox))
                 2.5 % 97.5 %
Petrus_1998$Zinc  1.167    2.696
```

Test for constant RR assumption

```
> cox.zph(PetrusCox)
                      rho chisq     p
Petrus_1998$Zinc 0.0619 0.415 0.519
```

the cox.zph procedure is described on p 22-23 of
https://cran.r-project.org/web/packages/survival/survival.pdf

If p > 0.05, then the data are consistent with constant RR assumption.

Thus, the above p = 0.519 indicates that the constant RR assumption is appropriate.

Prasad (2000)

```
> Prasad_2000Cox   <- coxph(Prasad_2000Surv ~ Prasad_2000$Zinc , method = "efron")
> Prasad_2000Cox
Call:
coxph(formula = Prasad_2000Surv ~ Prasad_2000$Zinc, method = "efron")

                   coef exp(coef) se(coef)    z       p
Prasad_2000$Zinc 2.017     7.519    0.381 5.29 1.2e-07

Likelihood ratio test=30.2  on 1 df, p=3.99e-08
n= 48, number of events= 48
> exp(confint(Prasad_2000Cox))
                  2.5 % 97.5 %
Prasad_2000$Zinc  3.56    15.9
```

Test for constant RR assumption, see p. 2.

```
> cox.zph(Prasad_2000Cox)
                      rho chisq     p
Prasad_2000$Zinc -0.177  1.19 0.275
```

Prasad (2008)

```
> Prasad_2008Cox   <- coxph(Prasad_2008Surv ~ Prasad_2008$Zinc , method = "efron")
> Prasad_2008Cox
Call:

coxph(formula = Prasad_2008Surv ~ Prasad_2008$Zinc, method = "efron")
                    coef exp(coef) se(coef)    z       p
Prasad_2008$Zinc  3.100    22.201    0.539 5.75 8.7e-09

Likelihood ratio test=46.6  on 1 df, p=8.57e-12
n= 50, number of events= 50
> exp(confint(Prasad_2008Cox))
                  2.5 % 97.5 %
Prasad_2008$Zinc  7.72   63.8
```

Test for constant RR assumption, see p. 2.

```
> cox.zph(Prasad_2008Cox)
                       rho chisq     p
Prasad_2008$Zinc -0.0635 0.163 0.686
```

Table 2 analyses: Effect of zinc acetate lozenges on the recovery rate from the common cold

Cox model; mixed effects pooling, study as a random effect for zinc efficacy

```
> zIPDme <- coxme(zincIPDsurv ~ Study + Zinc + (Zinc-1|Study), ties = "efron")
> zIPDme
Cox mixed-effects model fit by maximum likelihood

  events, n = 199, 199
  Iterations= 5 23
                NULL Integrated Fitted
Log-likelihood -858       -833   -831

                  Chisq  df        p  AIC  BIC
Integrated loglik  50.4 4.0 2.99e-10 42.4 29.2
 Penalized loglik  54.2 3.8 3.54e-11 46.6 34.1

Model:  zincIPDsurv ~ Study + Zinc + (Zinc - 1 | Study)
Fixed coefficients
             coef exp(coef) se(coef)    z       p
StudyP2000 0.0944      1.10    0.221 0.43 6.7e-01
StudyP2008 0.4510      1.57    0.222 2.04 4.2e-02
Zinc       1.1459      3.15    0.205 5.59 2.3e-08

Random effects
 Group Variable Std Dev Variance
 Study Zinc     0.2185  0.0478
> confint_zIPDme<-c(1.1459-1.96*0.205, 1.1459+1.96*0.205)
> exp(confint_zIPDme)
[1] 2.1 4.7
```

The above statistical model is based on the instructions by Stewart et al (2012) in PLOS One:
http://dx.doi.org/10.1371/journal.pone.0046042
Supplementary file of that paper describes the appropriate model in the R-code.
http://dx.doi.org/10.1371/journal.pone.0046042.s003

The first page of the supplementary file, Model 1 shows the code for
"One-stage random-effects model:
Here treatment effect varies across trials, distributed normally around the overall effect θ, with heterogeneity tau^2."

"R code: glmer(event~trial+treat+(treatn-1|trial), family= binomial)"

Thus, Study(=trial) is included in our model as a random effect for zinc effect in the last term, but Study is also included as a variable alone as the first term.
Adding Study as a random variable for the zinc effect means that variation in the true zinc effect is allowed between the Studies.
Adding Study as an independent explanatory variable means that the Studies may have different baseline risks.
In our case the R-program is different (not "glmer"), but the structure of the model is the same.

Table 2 analyses

Cox model; pooling stratified by study

```
> zStrata <- coxph(zincIPDsurv ~ zincIPD$Zinc + strata(zincIPD$Study), method = "efron")

> zStrata
Call:
coxph(formula = zincIPDsurv ~ zincIPD$Zinc + strata(zincIPD$Study),
    method = "efron")


              coef exp(coef) se(coef)    z       p
zincIPD$Zinc 1.274     3.575    0.178 7.17 7.4e-13

Likelihood ratio test=55.4  on 1 df, p=1.01e-13
n= 199, number of events= 199

> exp(confint(zStrata))
             2.5 % 97.5 %
zincIPD$Zinc  2.52   5.06
```

Table 2 analyses

Cox model; pooling ignoring study as a clustering variable

```
> zIPDCox   <- coxph(zincIPDsurv ~   Zinc , method = "efron")
> zIPDCox
Call:
coxph(formula = zincIPDsurv ~ Zinc, method = "efron")


      coef exp(coef) se(coef)   z     p
Zinc 0.948     2.580    0.150 6.3 3e-10

Likelihood ratio test=39.3  on 1 df, p=3.58e-10
n= 199, number of events= 199
> exp(confint(zIPDCox))
     2.5 % 97.5 %
Zinc  1.92   3.47
```

In pooling ignoring the study as a clustering variable, the constant RR assumption was assessed by calculating the RR for each day.
All the single day RR confidence intervals are consistent with the above overall estimate RR = 2.58.

	Placebo			**Zinc**			**Rate Ratio (RR)**	**95%CI**	
Day	Number at risk	Number events	Rate	Number at risk	Number events	Rate		**Low**	**High**
2	97	3	0.031	102	10	0.098	**3.17**	**0.81**	**17.9**
3	94	3	0.032	92	23	0.250	**7.83**	**2.37**	**40.7**
4	91	10	0.110	69	21	0.304	**2.77**	**1.25**	**6.59**
5	81	10	0.123	48	17	0.354	**2.87**	**1.24**	**7.01**
6	71	12	0.169	31	12	0.387	**2.29**	**0.94**	**5.6**
7	59	21	0.356	19	8	0.421	**1.18**	**0.45**	**2.8**
8	38	14	0.368	11	6	0.545	**1.48**	**0.46**	**4.1**
9	24	8	0.333	5	1	0.200	**0.60**	**0.01**	**4.5**
10	16	3	0.188	4	1	0.250	**1.33**	**0.02**	**16.6**

Kaplan-Meier estimates for the pooled data of the 3 trials

```
> KM_zincIPD <- survfit(zincIPDsurv ~ zincIPD$Zinc)
> summary(KM_zincIPD)
Call: survfit(formula = zincIPDsurv ~ zincIPD$Zinc)

                zincIPD$Zinc=0
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    2     97       3   0.9691  0.0176       0.9352        1.000
    3     94       3   0.9381  0.0245       0.8914        0.987
    4     91      10   0.8351  0.0377       0.7644        0.912
    5     81      10   0.7320  0.0450       0.6489        0.826
    6     71      12   0.6082  0.0496       0.5185        0.714
    7     59      21   0.3918  0.0496       0.3057        0.502
    8     38      14   0.2474  0.0438       0.1749        0.350
    9     24       8   0.1649  0.0377       0.1054        0.258
   10     16       3   0.1340  0.0346       0.0808        0.222
   11     13       2   0.1134  0.0322       0.0650        0.198
   12     11       3   0.0825  0.0279       0.0425        0.160
   13      8       2   0.0619  0.0245       0.0285        0.134
   14      6       2   0.0412  0.0202       0.0158        0.108
   15      4       4   0.0000     NaN           NA           NA

                zincIPD$Zinc=1
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    2    102      10   0.9020 0.02944      0.84606       0.9616
    3     92      23   0.6765 0.04632      0.59151       0.7736
    4     69      21   0.4706 0.04942      0.38304       0.5781
    5     48      17   0.3039 0.04554      0.22657       0.4077
    6     31      12   0.1863 0.03855      0.12416       0.2795
    7     19       8   0.1078 0.03071      0.06171       0.1885
    8     11       6   0.0490 0.02138      0.02085       0.1152
    9      5       1   0.0392 0.01922      0.01501       0.1025
   10      4       1   0.0294 0.01673      0.00965       0.0897
   11      3       2   0.0098 0.00976      0.00139       0.0689
   12      1       1   0.0000     NaN           NA           NA
```

Table 3 analyses

The statistical model for treatment-subgroup interaction on the following pages are based on the instructions by Stewart et al (2012) in PLOS One:
http://dx.doi.org/10.1371/journal.pone.0046042
Supplementary file of that paper describes the appropriate model in the R-code.
http://dx.doi.org/10.1371/journal.pone.0046042.s003

The first page of the supplementary file, Model 4 shows the code for
"One-stage random-effects model with treatment-covariate interaction (Simmonds (2005)):
This model allows for independent effects of the covariate on risk across trials"

"R code: glmer(event~trial*covar+treat*covar+(treatn-1|trial), family= binomial)"

In our case the "trials*covar" term corresponds to the "study*subgroup" term, so that "subgroup" is sex, age, etc.

The subgroup may have different own effects on the rate of recovery and those own effects may vary between studies. Adding the "study*subgroup" term to the above model allows the program to adjust for variations between the studies.

The next two pages show the modification of zinc effect by sex as an example.
Other tests of zinc effect modification are similar.

Age-zinc interaction was analyzed also as a continuous variable (p. 11),
and it was analyzed also within the 3 trials by dichotomizing by the median level (Table S2, p. 13).

Table 3 analyses: Effect of zinc acetate lozenges, effect modification by sex as an example

Zinc effect RR = 3.613 below indicates the effect of zinc lozenges on males
Interaction RRR = 0.816 below indicates the ratio between the RR for males and the RR for females
Zinc effect RR = 2.948 on females is calculated on the next page, p. 10.
Thus RRR = 0.816 = 2.948/3.613
The RRR indicates the ratio of two complementary RRs. If there is no difference in the effect in thw two subgroups, RRR = 1.00.

All the RRR values for subgroup comparisons are shown on p. 12.

```
> zmeSex   <- coxme(zincIPDsurv ~ Study*Sex + Zinc+Sex + (Zinc-1|Study), ties = "efron")
> zmeSexI   <- coxme(zincIPDsurv ~ Study*Sex + Zinc*Sex + (Zinc-1|Study), ties = "efron")
> zmeSexI
Cox mixed-effects model fit by maximum likelihood

  events, n = 199, 199
  Iterations= 23 118
              NULL Integrated Fitted
Log-likelihood -858       -832   -830

                  Chisq   df        p  AIC   BIC
Integrated loglik  51.1 8.00 2.50e-08 35.1  8.76
 Penalized loglik  55.6 7.92 3.15e-09 39.7 13.64

Model:  zincIPDsurv ~ Study * Sex + Zinc * Sex + (Zinc - 1 | Study)
Fixed coefficients
                 coef exp(coef) se(coef)     z       p
StudyP2000      0.172     1.187    0.309  0.56 5.8e-01
StudyP2008      0.504     1.656    0.317  1.59 1.1e-01
Sex             0.205     1.227    0.259  0.79 4.3e-01
Zinc            1.285     3.613    0.284  4.53 6.0e-06
StudyP2000:Sex -0.180     0.836    0.365 -0.49 6.2e-01
StudyP2008:Sex -0.147     0.864    0.363 -0.40 6.9e-01
Sex:Zinc       -0.203     0.816    0.294 -0.69 4.9e-01

Random effects
 Group Variable Std Dev Variance
 Study Zinc     0.2508  0.0629
> anova(zmeSex,zmeSexI)
Analysis of Deviance Table
 Cox model: response is  zincIPDsurv
 Model 1: ~Study * Sex + Zinc + Sex + (Zinc - 1 | Study)
 Model 2: ~Study * Sex + Zinc * Sex + (Zinc - 1 | Study)
  loglik Chisq Df P(>|Chi|)
1   -833
2   -832  0.47  1      0.49
> confint_zmeAgI<-c(-0.203-1.96*0.294, -0.203+1.96*0.294)
> exp(confint_zmeAgI)
[1] 0.459 1.452
```

Table 3 analyses: Effect of zinc acetate lozenges, effect modification by sex as an example

Compare with the previous sheet
Zinc effect RR = 2.948 below indicates the effect of zinc lozenges on females
Interaction RRR = 1.225 below indicates the ratio between the RR for females and the RR for males
Zinc effect RR = 3.613 on males is calculated on the previous page
Thus, RRR = 1.225 indicates the ratio 3.613/2.948

```
> zmeWoman    <- coxme(zincIPDsurv ~ Study*Woman + Zinc+Woman + (Zinc-1|Study), ties = "efron")
> zmeWomanI   <- coxme(zincIPDsurv ~ Study*Woman + Zinc*Woman + (Zinc-1|Study), ties = "efron")
> zmeWomanI
Cox mixed-effects model fit by maximum likelihood

  events, n = 199, 199
  Iterations= 24 123
              NULL Integrated Fitted
Log-likelihood -858       -832   -830

                  Chisq   df        p  AIC   BIC
Integrated loglik  51.1 8.00 2.50e-08 35.1  8.76
 Penalized loglik  55.6 7.92 3.15e-09 39.7 13.64

Model:  zincIPDsurv ~ Study * Woman + Zinc * Woman + (Zinc - 1 | Study)
Fixed coefficients
                     coef exp(coef) se(coef)     z       p
StudyP2000       -0.00804     0.992    0.274 -0.03 9.8e-01
StudyP2008        0.35751     1.430    0.268  1.34 1.8e-01
Woman            -0.20492     0.815    0.259 -0.79 4.3e-01
Zinc              1.08124     2.948    0.246  4.40 1.1e-05
StudyP2000:Woman  0.17966     1.197    0.365  0.49 6.2e-01
StudyP2008:Woman  0.14672     1.158    0.363  0.40 6.9e-01
Woman:Zinc        0.20328     1.225    0.294  0.69 4.9e-01

Random effects
 Group Variable Std Dev Variance
 Study Zinc     0.2508  0.0629
> anova(zmeWoman,zmeWomanI)
Analysis of Deviance Table
 Cox model: response is  zincIPDsurv
 Model 1: ~Study * Woman + Zinc + Woman + (Zinc - 1 | Study)
 Model 2: ~Study * Woman + Zinc * Woman + (Zinc - 1 | Study)
  loglik Chisq Df P(>|Chi|)
1   -833
2   -832  0.47  1      0.49
> confint_Woman<-c(1.08123-1.96*0.24567, 1.08123+1.96*0.24567)
> exp(confint_Woman)
[1] 1.82 4.77
> confint_WI<-c(0.203-1.96*0.2937, 0.203+1.96*0.2937)
> exp(confint_WI)
[1] 0.689 2.179
```

Table 3 analyses: Effect zinc acetate lozenges, effect modification by age as a continuous variable.

Table 3 of the main text shows the analysis by age dichotomized at the median of 27 years.
Age was also analyzed as a continuous variable, so that the null point of age was set at 31.2 years which is mean age, since then the baseline zinc effect RR corresponds to the effect on patients of mean age. In addition, age was measured in 10 year period since then the coefficient is more practical.

Below, zinc effect RR = 2.99 indicates the effect of zinc lozenges on common cold recovery rate in patients aged 31.2 years (ie when Age10Mean =0).
The interaction between age and zinc, RR=1.19 indicates that patients with the age of:
41.2 years have an estimated effect of RR = 3.56 = 2.99*1.19
21.2 years have an estimated effect of RR = 2.51 = 2.99/1.19
However the 95%CI of the interaction between age and zinc is wide and the Analysis of Deviance Table indicates that the inclusion of the interaction between age and zinc does not improve the model, P = 0.21.

```
> zmeAg    <- coxme(zincIPDsurv ~ Study*Age10Mean + Zinc+Age10Mean + (Zinc-1|Study), ties = "efron")
> zmeAgI   <- coxme(zincIPDsurv ~ Study*Age10Mean + Zinc*Age10Mean + (Zinc-1|Study), ties = "efron")
> zmeAgI

Cox mixed-effects model fit by maximum likelihood
  events, n = 199, 199
  Iterations= 5 27
                 NULL Integrated Fitted
Log-likelihood -857.9     -830.4 -830.3

                  Chisq   df         p   AIC   BIC
Integrated loglik 55.14 8.00 4.144e-09 39.14 12.79
 Penalized loglik 55.18 7.01 1.384e-09 41.17 18.09

Model:  zincIPDsurv ~ Study * Age10Mean + Zinc * Age10Mean + (Zinc - 1 | Study)
Fixed coefficients
                        coef exp(coef) se(coef)     z       p
StudyP2000            0.4556    1.5771   0.2097  2.17 3.0e-02
StudyP2008            0.6575    1.9299   0.2023  3.25 1.2e-03
Age10Mean            -0.1532    0.8579   0.1378 -1.11 2.7e-01
Zinc                  1.0955    2.9906   0.1593  6.88 6.1e-12
StudyP2000:Age10Mean -0.1502    0.8605   0.1760 -0.85 3.9e-01
StudyP2008:Age10Mean  0.1102    1.1165   0.1546  0.71 4.8e-01
Age10Mean:Zinc        0.1762    1.1927   0.1227  1.44 1.5e-01

Random effects
 Group Variable Std Dev   Variance
 Study Zinc     0.0171525 0.0002942
> anova(zmeAg,zmeAgI)
Analysis of Deviance Table
 Cox model: response is  zincIPDsurv
 Model 1: ~Study * Age10Mean + Zinc + Age10Mean + (Zinc - 1 | Study)
 Model 2: ~Study * Age10Mean + Zinc * Age10Mean + (Zinc - 1 | Study)
  loglik Chisq Df P(>|Chi|)
1   -831
2   -830  1.58  1      0.21
> confint_zmeAgI<-c(0.1762-1.96*0.1227, 0.1762+1.96*0.1227, 0.176)
> exp(confint_zmeAgI)
[1] 0.9377 1.5169 1.1924
```

Table S1. Difference in zinc acetate lozenge efficacy between subgroups: Calculation of the ratio of RRs between the subgroups (RRR). Compare this table with Table 3 in the main text.

Subgroup	**No. common cold patients**	**Difference in the subgroup effects**		
		RRR *	**95% CI**	**Test of interaction (P)**
Age (yr)				
17-27	100	ref.		0.15
28-61	99	1.6	0.9-2.9	
Sex				
Male	82	ref.		0.5
Female	117	0.816	0.459-1.452	
Ethnic group **				
White	132	ref.		0.4
Black	47	1.3	0.6-2.7	
Allergy				
No	137	ref.		0.5
Yes	62	1.2	0.6-2.3	
Smoker				
No	70	ref.		0.8
Yes	28	1.1	0.4-2.8	
Severity of the common cold at the baseline ***				
Below the median	102	ref.		0.2
Above the median	97	0.69	0.4-1.2	

* The RRR estimate of subgroup difference is the ratio of the RRs between the 2 compared subgroups. For example, the RRR = 0.816 indicates that the RR estimate of the zinc acetate lozenge effect in females is 18.4% lower compared with the RR estimate of the zinc lozenge effect in males, see pp. 10-11.

Table S2. Effect of zinc lozenges on recovery rate by age subgroups within the 3 trials

Since the age ranges of the Prasad and Petrus studies differed substantially, and the average RR of the studies differed substantially, the interaction between age and zinc effect was calculated also within each of the 3 trials so that age was dichotomized by the median.
In each study, older participants had on average greater benefit of zinc acetate lozenges, but the difference over age was not significant. Although the direction was consistent, there was no significant age interaction when all trials were analyzed together (Table 3 and Table S1).

Study	**No. common cold patients**	**Effects in subgroups**		
		RRR	**95% CI**	**Test of interaction (P)**
Petrus (1998)				
Age (yr)				
18-22	51	ref.		0.8
23-54	50	1.1	0.50-2.5	
Prasad (2000)				
Age (yr)				
18-37	25	ref.		0.3
38-61	23	2.0	0.6-6.6	
Prasad (2008)				
Age (yr)				
17-34	25	ref.		0.6
35-60	25	1.4	0.4-4.4	

Three zinc gluconate lozenge trials:

References to the two zinc gluconate trials with survival data available:

Eby (1984)
http://dx.doi.org/10.1128/AAC.25.1.20
https://www.ncbi.nlm.nih.gov/pubmed/6367635

Mossad (1996)
http://dx.doi.org/10.7326/0003-4819-125-2-199607150-00001
https://www.ncbi.nlm.nih.gov/pubmed/8678384

The extraction of data and the generation of data set for the survival analysis is described in:
Hemilä (2011)[2]: Supplementary material 3, which is available at:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969/bin/TORMJ-5-51_SD1.zip

Small later modifications were done for the Mossad (1996) data set to reach slightly closer fit between the data set and the published survival curves.

A third zinc gluconate trial did not publish survival data.

Godfrey (1972)
http://imr.sagepub.com/content/20/3/234
http://dx.doi.org/10.1177/030006059202000305

Nevertheless, survival of the zinc group could be inferred from Figure 1 of the Godfrey (1992) report.
Furthermore, the number of patients cured by day 7 was reported on p. 237.
“At day 7, five of the 35 ZGG-treated patients had a total of 15 symptoms, whereas 17 of the 38 placebo-treated patients had a total of 45 symptoms. ”

This corresponds to 30 zinc gluconate participants of 35 having recovered and
21 placebo participants of 38 having recovered.

Calculation of the RR and the survival curve of the zinc group are shown on p. 19.

Calculation of RR and NNT for the Eby (1984) and Mossad (1996) trials

Eby (1984)

```
> EbyCox.efron <- coxph(EbyCox ~ Eby$Zinc, method = "efron")
> EbyCox.efron
Call:
coxph(formula = EbyCox ~ Eby$Zinc, method = "efron")

           coef exp(coef) se(coef)    z     p
Eby$Zinc 1.246     3.476    0.335 3.72 2e-04

Likelihood ratio test=15.5  on 1 df, p=8.1e-05
n= 65, number of events= 45
> exp(confint(EbyCox.efron))
          2.5 % 97.5 %
Eby$Zinc   1.80    6.70
```

```
> KM_Eby <- survfit(EbyCox ~ Eby$Zinc)
> summary(KM_Eby)
Call: survfit(formula = EbyCox ~ Eby$Zinc)

                Eby$Zinc=0
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    2     28       2    0.929  0.0487        0.838        1.000
    3     26       3    0.821  0.0724        0.691        0.976
    4     23       1    0.786  0.0775        0.648        0.953
    5     22       2    0.714  0.0854        0.565        0.903
    6     20       1    0.679  0.0883        0.526        0.876
    7     19       4    0.536  0.0942        0.379        0.756

                Eby$Zinc=1
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
  0.5     37       4    0.892  0.0510       0.7972        0.998
  1.0     33       4    0.784  0.0677       0.6618        0.928
  2.0     29       6    0.622  0.0797       0.4834        0.799
  3.0     23       3    0.541  0.0819       0.4016        0.728
  4.0     20       7    0.351  0.0785       0.2268        0.544
  5.0     13       2    0.297  0.0751       0.1812        0.488
  6.0     11       4    0.189  0.0644       0.0971        0.369
  7.0      7       2    0.135  0.0562       0.0598        0.305
```

Calculation of the NNT for the Eby (1984) trial

Day	Proportion of patients still sick on the given day			NNT
	Zinc	Placebo	Difference	
4	0.351	0.786	0.435	2.3
5	0.297	0.714	0.417	2.4
6	0.189	0.679	0.490	2.0

NNT, the number of patients needed to be treated for one patient to become cured by the given day.

Mossad (1996)

```
> MossadCox.efron <- coxph(MossadCox ~ Mossad$Zinc, method = "efron")
> MossadCox.efron
Call:
coxph(formula = MossadCox ~ Mossad$Zinc, method = "efron")

              coef exp(coef) se(coef)    z       p
Mossad$Zinc 1.039     2.827    0.239 4.35 1.3e-05

Likelihood ratio test=19.5  on 1 df, p=9.87e-06
n= 99, number of events= 90
> exp(confint(MossadCox.efron))
             2.5 % 97.5 %
Mossad$Zinc  1.77   4.51

> KM_Mossad <- survfit(MossadCox ~ Mossad$Zinc)
> summary(KM_Mossad)
Call: survfit(formula = MossadCox ~ Mossad$Zinc)

                Mossad$Zinc=0
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    2     50       4   0.9200  0.0384       0.8478        0.998
    3     46       3   0.8600  0.0491       0.7690        0.962
    4     43       5   0.7600  0.0604       0.6504        0.888
    5     38       2   0.7200  0.0635       0.6057        0.856
    6     36       5   0.6200  0.0686       0.4991        0.770
    7     31       3   0.5600  0.0702       0.4380        0.716
    8     26       5   0.4523  0.0713       0.3320        0.616


                Mossad$Zinc=1
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    1     49       4   0.9184  0.0391       0.8448        0.998
    2     45       5   0.8163  0.0553       0.7148        0.932
    3     40       6   0.6939  0.0658       0.5761        0.836
    4     34       8   0.5306  0.0713       0.4078        0.690
    5     26       4   0.4490  0.0711       0.3292        0.612
    6     22       6   0.3265  0.0670       0.2184        0.488
    7     16       7   0.1837  0.0553       0.1018        0.331
    8      9       3   0.1224  0.0468       0.0579        0.259
```

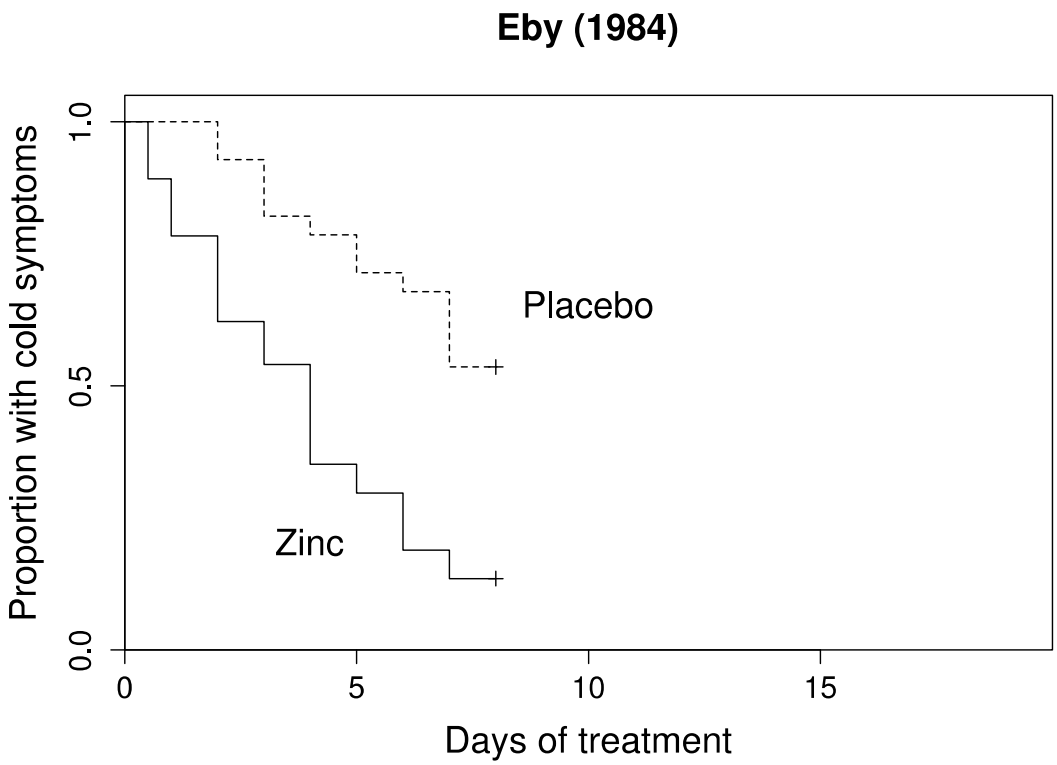
Calculation of the NNT for the Mossad (1996) trial

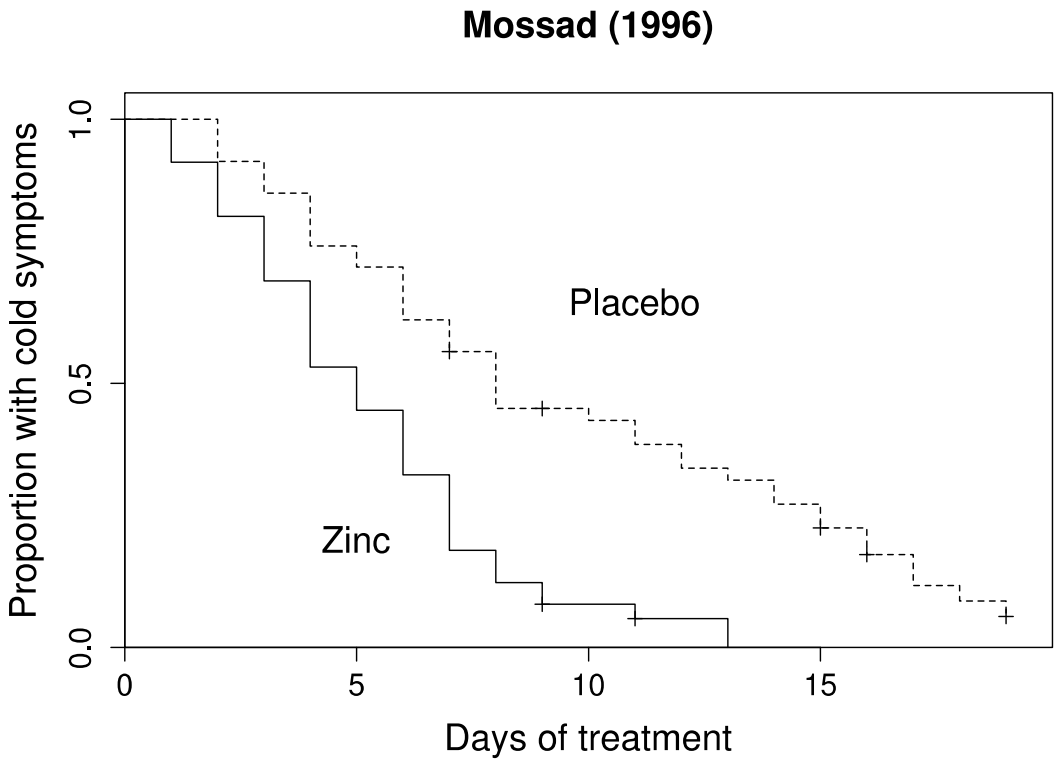
Day	Proportion of patients still sick on the given day			NNT
	Zinc	Placebo	Difference	
4	0.531	0.760	0.229	4.4
5	0.449	0.720	0.271	3.7
6	0.326	0.620	0.294	3.4
7	0.184	0.560	0.376	2.7
8	0.122	0.452	0.330	3.0

NNT, the number of patients needed to be treated for one patient to become cured by the given day.

Kaplan-Meier curves for the Eby (1984) and Mossad (1996) trials

In the Eby (1984) trial, 20 observations were censored, out of 65 patients,
and in the Mossad (1996) trial, 8 observations were censored, out of 100 patients.
Censored observations are marked by the + mark.





Calculation of RR and NNT for day 7 of the Godfrey (1992) trial

```
> riskratio(Godfrey_day7, rev="c")
$data
          Outcome
Treatment Still cold Cured Total
  Placebo         17    21    38
  Zinc             5    30    35
  Total           22    51    73

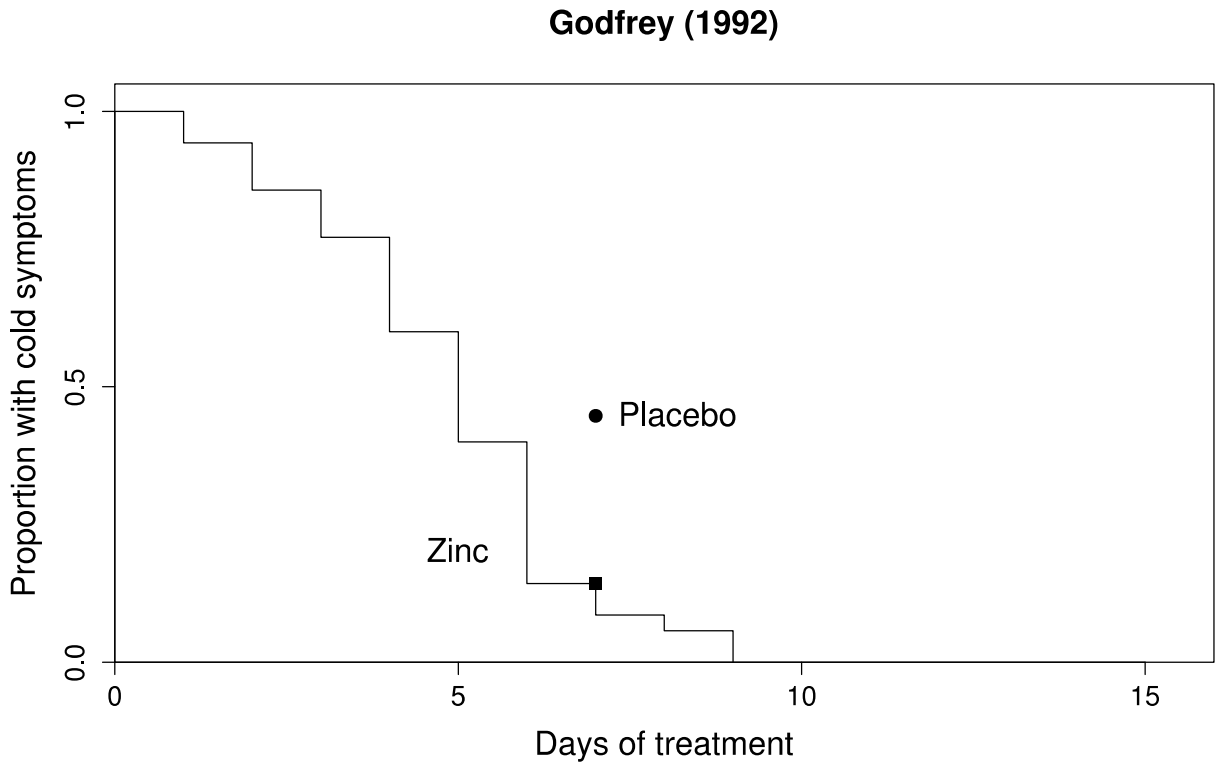
$measure
          risk ratio with 95% C.I.
Treatment estimate  lower  upper
  Placebo    1.000     NA     NA
  Zinc       1.551 1.1303 2.1283

$p.value
          two-sided
Treatment midp.exact fisher.exact chi.square
  Placebo         NA           NA         NA
  Zinc     0.0052124    0.0054615  0.0046163
```

NNT:

```
> NNT <- (1/(30/35 -21/38))
> NNT
[1] 3.284
```

The data points for day 7 were reported (p. 237) and the zinc group survival curve could be calculated from Godfrey's Fig. 1.



The following two pages show the data set that was analyzed in the study

Most of the variables are evident.

The definition of severity is described in Supplementary file 1 and the continuous scale was transformed to binary outcome “SeveBin” at the medians of the three studies.

“Duration” indicates the duration of common cold episodes

“Study” variable indicates the studies, so that Petrus indicates the Petrus (1998) study [10], P2000 indicates the Prasad (2000) study [11], and P2008 indicates the Prasad (2008) study [12].

“NA” indicates not available.

The data set can be copy pasted as a CSV file eg to a spreadsheet program.

```
"","ID","Age","Black","Sex","Allergy","Smoker","Severity","SeveBin","Zinc","Duration","Cured","Study"
"1",103,21,NA,0,0,NA,10,1,1,8,1,"Petrus"
"2",105,18,0,0,1,NA,2,0,1,3,1,"Petrus"
"3",106,40,1,1,0,NA,7,0,1,4,1,"Petrus"
"4",107,37,0,0,1,NA,7,0,1,7,1,"Petrus"
"5",109,42,0,1,0,NA,4,0,1,6,1,"Petrus"
"6",111,21,0,1,0,NA,7,0,1,4,1,"Petrus"
"7",115,22,0,0,1,NA,7,0,1,7,1,"Petrus"
"8",119,21,0,1,0,NA,6,0,1,5,1,"Petrus"
"9",121,22,0,0,1,NA,12,1,1,7,1,"Petrus"
"10",122,20,0,1,1,NA,8,1,1,6,1,"Petrus"
"11",123,30,0,1,0,NA,2,0,1,2,1,"Petrus"
"12",125,22,0,1,0,NA,7,0,1,8,1,"Petrus"
"13",127,22,0,0,1,NA,5,0,1,12,1,"Petrus"
"14",128,20,0,0,1,NA,14,1,1,4,1,"Petrus"
"15",129,22,0,0,1,NA,12,1,1,7,1,"Petrus"
"16",132,25,1,1,0,NA,5,0,1,4,1,"Petrus"
"17",133,20,0,0,0,NA,4,0,1,2,1,"Petrus"
"18",137,24,0,0,1,NA,8,1,1,5,1,"Petrus"
"19",139,24,1,1,0,NA,10,1,1,5,1,"Petrus"
"20",141,23,1,1,0,NA,5,0,1,4,1,"Petrus"
"21",142,19,NA,0,0,NA,2,0,1,7,1,"Petrus"
"22",144,47,0,1,0,NA,4,0,1,11,1,"Petrus"
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"188",337,56,1,1,1,1,11,1,0,9,1,"P2000"
"189",338,43,1,0,0,0,6,0,0,7,1,"P2000"
"190",339,54,1,0,0,1,9,0,0,8,1,"P2000"
"191",340,18,0,0,1,0,6,0,0,8,1,"P2000"
"192",341,38,0,1,0,0,6,0,0,8,1,"P2000"
"193",342,42,0,0,0,0,8,0,0,9,1,"P2000"
"194",343,33,1,1,0,0,11,1,0,6,1,"P2000"
"195",344,40,1,0,0,1,7,0,0,8,1,"P2000"
"196",345,52,0,1,0,0,3,0,0,8,1,"P2000"
"197",346,31,NA,1,0,0,15,1,0,7,1,"P2000"
"198",347,23,0,1,0,0,6,0,0,5,1,"P2000"
"199",348,37,0,1,0,0,7,0,0,9,1,"P2000"
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