Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage

Harri Hemilä

Supplementary File 2

Nov 20, 2016

This file contains

- transformation of common cold duration (days) to the relative scale

- additional forest plots

Normalization of the common cold duration to the scale of Placebo group = 100%

The values on the right hand side are used. These values are calculated by dividing the figures on the left hand side by the mean common cold duration in the placebo group on the left side. This leads to percentage scale so that all the differences between Zn and placebo groups are percentage effects.

Trial [ref]	Duration is based on: [a]	Duration of colds (days)				Duration of colds (% of the placebo level)			
		Zn		Placebo		Zn		Placebo	
		mean	SD	mean	SD	mean	SD	mean	SD
Zinc acetate									
Petrus 1998 [22]	Data set	5.288	2.569	7.061	3.907	74.9	36.4	100	55.3
Prasad 2000 [23]	Report+Fig	4.44	1.56	8.09	1.81	54.9	19.3	100	22.3
Prasad 2008 [24]	Report	4.00	1.04	7.12	1.26	56.2	14.6	100	17.7
Zinc gluconate									
Eby 1984 [1]	Fig	3.92	2.61	7.54	3.18	52.0	34.7	100	42.2
Godfrey 1992 [20]	from t	4.86	2.70	6.13	2.70	79.3	44.0	100	44.0
Mossad 1996 [21]	Fig	5.20	2.83	9.20	5.32	56.6	30.7	100	57.8
Turner 2000 [25]	Fig	7.41	3.88	7.55	3.96	98.1	51.4	100	52.5

[a] **"Report"** indicates that the mean and SD were reported in the study report.
"from t" indicates that the t value was reported and the corresponding SD was calculated from it.
"Fig" indicates that the results were reported as a survival curve in the study reports: see [2] for the calculation of the mean and SD:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969/bin/TORMJ-5-51_SD1.zip

The Mossad (1996) data were reanalyzed which led to small differences compared with the 2011 analyses, see p. 7 of this Supplementary file.

The Petrus (1998) study mean and SD values were calculated from the data set that was made available by Dr. Petrus. The outcome in this analysis was the longest common cold symptom.

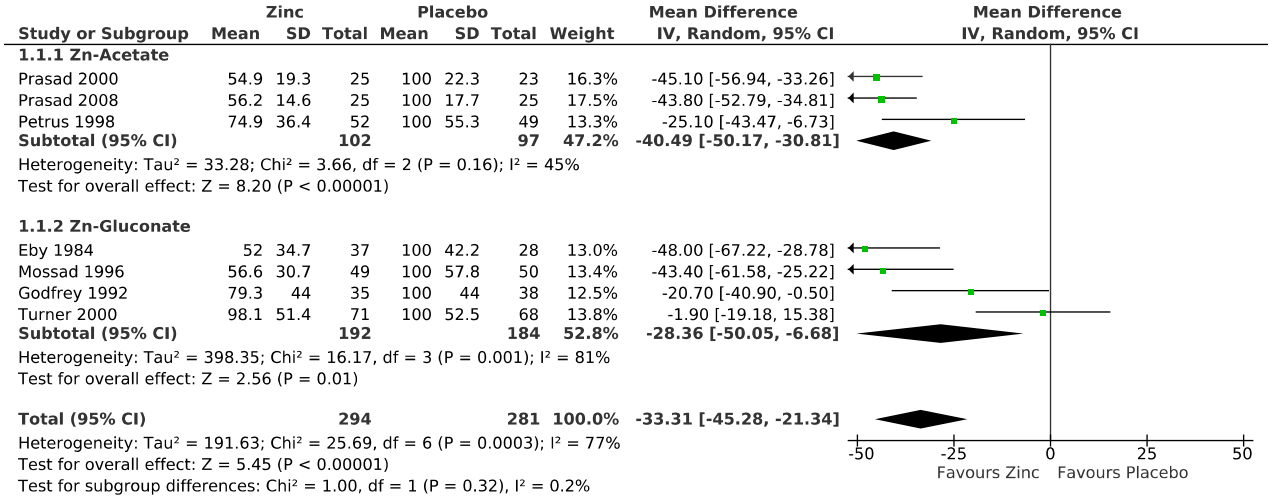
Duration of the common cold:
These forest plots were constructed with the RevMan program (http://tech.cochrane.org/revman)

7 trials: comparison of Zn acetate and Zn gluconate

Overall effect is **33.31%** shorter duration of colds.

Zn **acetate** lozenges shortened colds by 40.49%
Zn **gluconate** lozenges shortened colds by 28.36%

There is no evidence that the two subgroups differ, with $I^2 = 0\%$ (P = 0.33)
There is strong evidence that the 7 trials are heterogeneous, with $I^2 = 77\%$ (P = 0.0002)

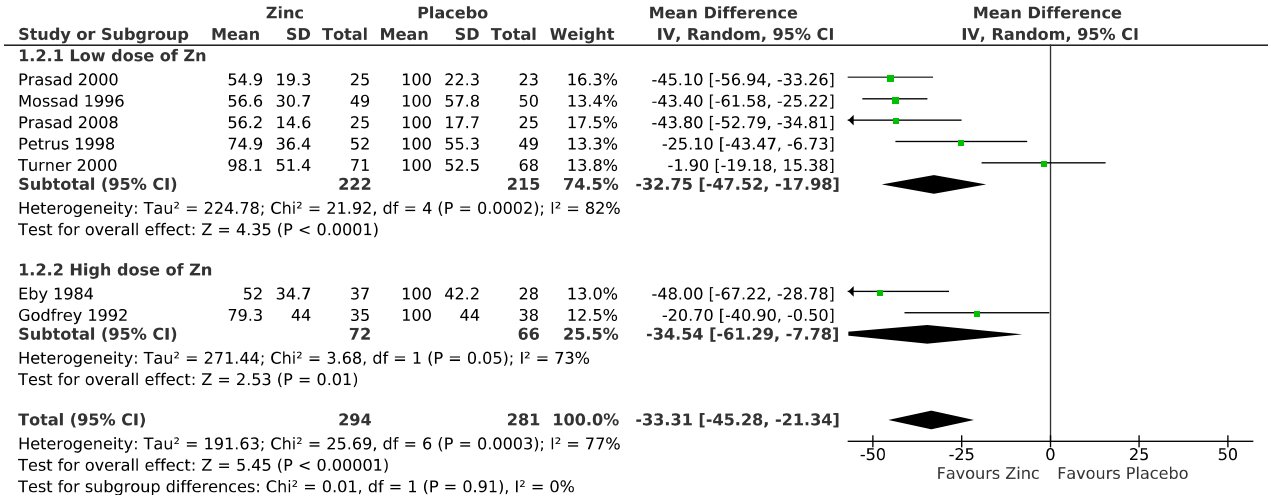


7 trials: comparison of low dose vs. high dose lozenges

Overall effect is **33.31%** shorter duration of colds.

Low dose lozenges shortened colds by 32.75%
High dose lozenges shortened colds by 34.54%

There is no evidence that the two subgroups differ, with $I^2 = 0\%$ (P = 0.92)
There is strong evidence that the 7 trials are heterogeneous, with $I^2 = 77\%$ (P = 0.0002)



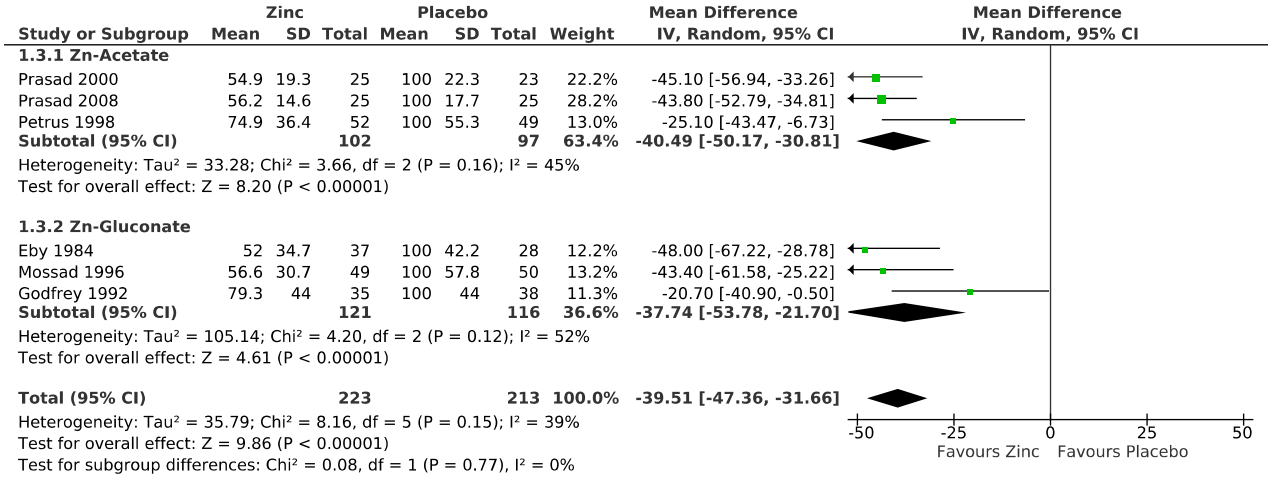
Exclusion of the Turner (2000) trial as an outlier

Turner (2000) excluded: comparison of Zn acetate and Zn gluconate

Overall effect of zinc lozenges is **39.51%** shorter duration of colds.

Zinc **acetate** shortened colds by 40.49%
Zinc **gluconate** shortened colds by 37.74%

There is no evidence that the subgroups differ, with I^2 = 0% (P = 0.81)
There is no significant heterogeneity over the 6 zinc lozenge trials, with I^2 = 39% (P = 0.14)



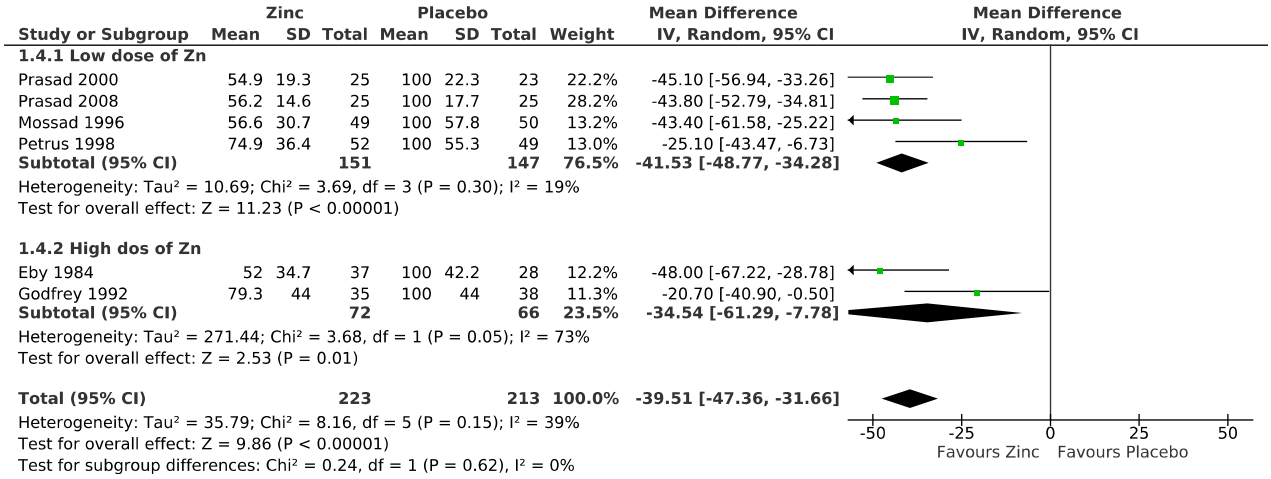
Exclusion of the Turner (2000) trial as an outlier

Turner (2000) excluded: comparison of low dose vs. high dose lozenges

Overall effect of zinc lozenges is **39.51%** shorter duration of colds.

Low doses of zinc shortened colds by 41.53%
High doses of zinc shortened colds by 34.54%

There is no evidence that the subgroups differ, with $I^2 = 0\%$ (P = 0.61)
There is no significant heterogeneity over the 6 trials differ, with $I^2 = 39\%$ (P = 0.14)



Mossad (1996) imputation of censored observations and calculation of cold durations.

Mossad (1996) survival curve was measured in Hemilä (2011)[2], see Supplementary material 3 in:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969/bin/TORMJ-5-51_SD1.zip
This is a new 2016 imputation of the days of the censored observations, with small changes compared with the 2011 imputations. This new version is used for calculating the mean and SD values. Censored observations were replaced with the duration as the day of censoring.

Zinc group

Mossad 1996
Zn (n=49)

Day	pixels 100%= 2274	To Fig scale (0 to 100%)	To persons	Based on censoring, (-1 participant censored) rescaling on the days 9th	11th	**The bold No:s are reported in Mossad's figure** To person integers	Cured per day	Censored	**Calculation of Kaplan-Meier estimates from the inferred figures** This column	**Difference** between measured and calculated **Relative**	**Absolute**
0	213	100,0	49			**49**	0				
1	384	91,7	44.93			45	4		91,84	1.001	0.14
2	589	81,8	40.06			40	5		81,63	0.998	-0.13
3	850	69,1	33.86			**34**	6		69,39	1.004	0.30
4	1180	53,1	26.01			26	8		53,06	1.000	-0.02
5	1345	45,1	22.09			22	4		44,90	0.996	-0.18
6	1598	32,8	16.07			**16**	6		32,65	0.995	-0.15
7	1893	18,5	9.06			9	7		18,37	0.994	-0.12
8	2018	12,4	6.09			6	3		12,24	0.985	-0.18
9	2102	8,3	4.09	> x3/4 >	3.07	**3**	2	1	8,16	0.978	-0.19
10	2102	8,3	4.1		3.07	**3**	0				
11	2168	5,1	2.5	1.89	> x1/2 > 0.95	**1**	1	1	5,44	1.058	0.30
12	2168	5,1	2.5	1.9	0.95	**1**	0				
13	2274	0,0	0.0			**0**	1				
14											
15											
16											
17											
18											
19											
					n =	47		**2**			

The measurement of the Mossad (1996) study number of patients who recovered from the colds is described on page v of Supplementary Material 3 for Hemilä (2011)

This is a new calculation of the corresponding recovery from the common cold and censoring data

Mossad reported:
2 Zn participants dropped out after 7 to 16 days
The days were not reported and 9 and 11 days are inferred from the Kaplan-Meier curves

On the right side of this table is the comparison of the measured curve and the Kaplan-Meier estimates based on the imputations
The differences are minor and consistent with inaccuracy of drawings

Placebo group

Placebo (n=50)

Day	pixels	To Fig scale (0 to 100%)	To persons	Based on censoring, (-1 participant censored) rescaling on the days 7th	15th	16th	**The bold No:s are reported in Mossad's figure** To person Integers	Cured per day	Censored	**Day**	**Calculation of Kaplan-Meier estimates from the inferred figures** This column	Difference between measured and calculated Relative	Absolute
0	213	100,0	50				**50**	0		**0**			
1	213	100,0	50				50	0		**1**			
2	382	91,8	45.90				46	4		**2**	92	1.002	0.20
3	502	86,0	42.99				**43**	3		**3**	86	1.000	0.02
4	710	75,9	37.94				38	5		**4**	76	1.002	0.11
5	792	71,9	35.95				36	2		**5**	72	1.001	0.09
6	996	62,0	31.00				**31**	5		**6**	62	1.000	-0.01
7	1116	56,2	28.09	> x27/28 >	26.09		26	3	**2**	**7**	56	0.997	-0.19
8	1334	45,6	22.8		21.18		21	5		**8**	45,63	1.000	0.02
9	1379	43,4	21.7		20.16		**20**	1		**9**	43,56	1.003	0.13
10	1414	41,7	20.9		19.37		19	1		**10**	41,38	0.992	-0.35
11	1511	37,0	18.5		17.19		17	2		**11**	37,02	1.000	0.00
12	1603	32,6	16.3		15.1		**15**	2		**12**	32,67	1.003	0.11
13	1644	30,6	15.3		14.2		14	1		**13**	30,49	0.997	-0.08
14	1732	26,3	13.1		12.2		12	2		**14**	26,13	0.994	-0.17
15	1835	21,3	10.7		9.9 > x9/10 > 8.90		**9**	2	1	**15**	21,78	1.023	0.48
16	1938	16,3	8.2		7.6	6.81 > x6/7 > 5.84	6	2	**1**	**16**	16,94	1.039	0.64
17	2050	10,9	5.4		5.0	4.5	4	2		**17**	11,29	1.039	0.42
18	2101	8,4	4.2		3.9	3.5 3.01	3	1		**18**	8,47	1.009	0.08
19							**0**	**1**	**2**	**19**			

Mossad reported:
4 placebo participants dropped out after 7 to 16 days
The days were not reported and 7, 15 and 16 days are inferred from the Kaplan-Meier curves

2 had censored data on the 19th day and 1 was cured on the 19th day **n =** 44 **6**