

SUPPLEMENTARY MATERIAL 3

Zinc Lozenges May Shorten the Duration of Colds: A Systematic Review

Harri Hemilä

Department of Public Health, University of Helsinki, Helsinki, Finland

Table S3. Calculation of the Mean and SD for the Common Cold Duration from the Reported Survival Curves

The following sheets describe the calculation of the mean and SD values for the trials that had reported duration of colds as survival curves

Six of the comparisons did not find significant difference between zinc and placebo, yet the mean and SD are needed to include them in Fig. (1).

In these six trials which found no effect, inaccuracy in the estimation of the mean and SD causes only variation in the weight of those trials in Fig. (1), but cannot lead to spurious emergence of difference between the study groups.

Mossad (1996) found benefit of zinc. Imputation of recovery time was needed only for two placebo participants and none zinc participants. Thus, minimal imputation was needed.

Eby (1984) found benefit of zinc. Much imputation was needed, which makes the estimated mean and SD values inaccurate.

Therefore a sensitivity test was carried out leaving the Eby (1984) trial out of the high-dose non-acetate trials, see Results section of the paper.

The Measurement of the Mean and SD from the Survival Curves was Carried out as Follows:

- 1) the published figures were digitalized; curves are available at: <http://www.ltdk.helsinki.fi/users/hemila/Zn/ZnFigs.htm>
 - 2) the height of the curves were then measured as pixels
 - 3) the pixel values were transformed to the figure scale ["to Fig scale"] (0 to 100% scale or 0 to 1.0 scale)
 - 4) the value on the figure scale was transformed to the cumulative number of persons recovered (or still sick) ["To persons"]
 - 5) the number of persons was rounded to the closest integer ["To person integers"]
 - 6) the number of participants recovered on the day N was calculated as the difference between the cumulative number of participants recovered by days N and N-1 ["Cured per day"]
- The day of recovery gives the duration of the cold for the person, since all colds started on day 0
- 7) the mean and SD for the distribution of the common cold cold duration was calculated from the distribution

An Example:

In the placebo group of Eby (1984) [7], 4675 pixels in the particular enlargement corresponded to 100% (= 28 participants), and 448 pixels to 0% (= 0 participants).

On day 7, the height of curve is 2404 pixels, which corresponds to 54.1% of participants still remaining ill (= $[4675-2404]/[4675-448]$).

54.1% of 28 means that 15 participants (0.541×28) were still ill on day 7, which is consistent with Eby's report: 46% (= 13/28) were cured by the 7th day (p.21 [7]).

In most curves, a few participants were not cured by the last time point of the follow-up.

The rate of recovery after the last time point was assumed to be similar to the preceding trend in the graph (marked as "imputed" on the following tables).

The effect of this assumption was tested with sensitivity analysis described on the next sheet.

In the sensitivity analysis, a faster and a slower rate of recovery were assumed.

In addition to the survival curves, Eby (1984), Smith (1987) and Mossad (1996) reported explicit data for the number of participants that had recovered by certain days.

Prasad (2000) reported both the mean and SD, and the survival curves. The mean and SD calculated from the survival curve are the same as those reported.

Sensitivity analysis	1: Rapid Recovery assumption				2: Slow Recovery assumption				3: Fig. 1 imputations			
	all participants who were ill at the last time point are assumed to be cured on the following day				rate of recovery is assumed to be half of the rate assumed on the following pages				These are the mean and SD values calculated on the following pages			
	This leads to:				This leads to:							
	Zn		Placebo		Zn		Placebo		Zn		Placebo	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Eby 1984 [7]	3.86	2.51	6.46	2.13	4.00	2.77	8.79	4.62	3.92	2.61	7.54	3.18
Smith 1989 [19]	6.60	1.53	6.51	1.96	8.07	3.44	8.89	4.49	7.23	2.29	7.57	3.01
Turner A 2000 [23]	7.28	3.61	7.37	3.61	7.50	4.08	7.66	4.23	7.41	3.88	7.55	3.96
Mossad 1996 [24]	5.20	2.83	9.34	5.39	5.20	2.83	9.46	5.63	5.20	2.83	9.38	5.47
Turner B 2000 [23]	6.82	3.19	7.37	3.61	6.92	3.44	7.66	4.23	6.89	3.35	7.55	3.96
Macknin 1998 [27]	9.33	4.72	9.50	4.53	9.42	4.94	9.51	4.55	9.37	4.81	9.50	4.53
Weissmann 1990 [28]	7.16	2.62	6.72	2.29	7.20	2.67	6.75	2.35	7.16	2.62	6.72	2.29
Turner C 2000 [23]	7.58	3.62	7.37	3.61	8.12	4.75	7.66	4.23	7.90	4.25	7.55	3.96
All 13 comparisons												
Test of heterogeneity	χ^2 (12 df) =		116				102				109	
	I ² =		90%				88%				89%	

Imputation involves subjective decisions and therefore sensitivity analysis was carried out to test the effect of the assumed recovery rate. The above tests of heterogeneity (1 and 2) show that irrespective of the imputation approach, there is very strong evidence of heterogeneity over all the trials. Except for the Eby (1984) and the Smith (1989) trials, there are only small changes in the mean and SD values in the “rapid” and “slow” recovery assumptions showing that the mean and SD values for the other trials are robust for the assumptions for the imputations. Eby (1984) and Smith (1989) needed imputation of recovery days for over half of the placebo participants, which explains their sensitivity to the imputation approach. Because of this problem, as a separate sensitivity analysis, Eby (1984) and Smith (1989) trials were excluded from the pooling of the five high-dose non-acetate trials, see the end of the Results section of the paper.

Eby 1984		The bold No:s are reported in Eby's paper					The bold No:s are reported in Eby's paper					
Zn (n=37)		Placebo (n=28)										
Day	pixels 100%= 4675	To Fig scale (0 to 100%)	To persons	To person integers	Cured per day	Day	pixels	To Fig scale (0 to 100%)	To persons	To person Integers	Cured per day	
0	448	100	37.0	37	0	0	448	100	28.0	28	0	
0.5	892	89.5	33.1	33		4	0.5	448	100	28.0	28	0
1	1354	78.6	29.1	29		4	1	448	100	28.0	28	0
2	2035	62.5	23.1	23	6	2	736	93.2	26.1	26	2	
3	2383	54.2	20.1	20	3	3	1198	82.3	23.0	23	3	
4	3187	35.2	13.0	13	7	4	1346	78.8	22.1	22	1	
5	3421	29.7	11.0	11	2	5	1651	71.5	20.0	20	2	
6	3880	18.8	7.0	7	4	6	1799	68.0	19.1	19	1	
7	4112	13.3	4.9		5	2	7	2404	53.7	15.0		15
8					Imputed:	3	8				Imputed:	3
9					Imputed:	2	9				Imputed:	3
10							10				Imputed:	3
11							11				Imputed:	3
12							12				Imputed:	3
		Duration of colds			n =	37		Duration of colds			n =	28
		mean	3.92					mean	7.54			
		SD	2.61					SD	3.18			

Macknin 1998											
Zn (n=123)						Placebo (n=124)					
Day	pixels	To	To	To	Cured	Day	pixels	To	To	To	Cured
	100%= 287	Fig	persons	person	per			Fig	persons	person	per
		scale		integers	day			scale		Integers	day
		(0 to 100%)						(0 to 100%)			
0	1919	0.0	0.0	0	0	0	1919	0.0	0.0	0	0
1	1884	2.1	2.6	3	3	1	1909	0.6	0.8	1	1
2	1884	2.1	2.6	3	0	2	1895	1.5	1.8	2	1
3	1803	7.1	8.7	9	6	3	1895	1.5	1.8	2	0
4	1708	12.9	15.9	16	7	4	1734	11.3	14.1	14	12
5	1510	25.1	30.8	31	15	5	1580	20.8	25.8	26	12
6	1321	36.6	45.1	45	14	6	1396	32.0	39.7	40	14
7	1187	44.9	55.2	55	10	7	1286	38.8	48.1	48	8
8	1132	48.2	59.3	59	4	8	1141	47.7	59.1	59	11
9	1080	51.4	63.2	63	4	9	930	60.6	75.1	75	16
10	907	62.0	76.3	76	13	10	826	67.0	83.0	83	8
11	764	70.8	87.0	87	11	11	740	72.2	89.6	90	7
12	676	76.2	93.7	94	7	12	706	74.3	92.2	92	2
13	580	82.0	100.9	101	7	13	650	77.8	96.4	96	4
14	536	84.7	104.2	104	3	14	554	83.6	103.7	104	8
15	492	87.4	107.5	108	4	15	530	85.1	105.5	106	2
16	464	89.2	109.7	110	2	16	516	86.0	106.6	107	1
17	464	89.2	109.7	110	0	17	464	89.2	110.6	111	4
18	440	90.6	111.5	112	6	18	440	90.6	112.4	112	10
19				Imputed:	3	19				Imputed:	3
20				Imputed:	3	20					
21				Imputed:	1	21					

Macknin reported:

7 Zn students' colds did not resolve during the period of observation

3 placebo students' colds did not resolve during the period of observation

The number of participants recovered on day 18 was increased to fit the total number of participants in the groups.

Duration of colds	n = 123	Duration of colds	n = 124
mean	9.37	mean	9.50
SD	4.81	SD	4.53

Mossad 1996 Zn (n=49)						Placebo (n=50)					
The bold No:s are reported in Mossad's figure						The bold No:s are reported in Mossad's figure					
Day	pixels 100%= 2274	To Fig scale (0 to 100%)	To persons	To person integers	Cured per day	Day	pixels	To Fig scale (0 to 100%)	To persons	To person Integers	Cured per day
0	213	100.0	49.0	49	0	0	213.0	100.0	50.0	50	0
1	384	91.7	44.9	45	4	1	213.0	100.0	50.0	50	0
2	589	81.8	40.1	40	5	2	382.0	91.8	45.9	46	4
3	850	69.1	33.9	34	6	3	502.0	86.0	43.0	43	3
4	1180	53.1	26.0	26	8	4	710.0	75.9	37.9	38	5
5	1345	45.1	22.1	22	4	5	792.0	71.9	36.0	36	2
6	1598	32.8	16.1	16	6	6	996.0	62.0	31.0	31	5
7	1893	18.5	9.1	9	7	7	1116.0	56.2	28.1	28	3
8	2018	12.4	6.1	6	3	8	1334.0	45.6	22.8	23	5
9	2102	8.3	4.1	3	3	9	1379.0	43.4	21.7	20	3
10	2102	8.3	4.1	3	0	10	1414.0	41.7	19.2	19	1
11	2168	5.1	2.5	1	2	11	1511.0	37.0	17.1	17	2
12	2168	5.1	2.5	1	0	12	1603.0	32.6	15.0	15	2
13	2274	0.0	0.0	0	1	13	1644.0	30.6	14.1	14	1
14						14	1732.0	26.3	12.1	12	2
15						15	1835.0	21.3	9.8	9	3
16						16	1938.0	16.3	6.9	7	2
17						17	2050.0	10.9	4.6	5	2
18						18	2101.0	8.4	3.5	4	1
19						19				Imputed:	2
						20					2
Mossad reported: 2 Zn participants dropped out after 7 to 16 d						6 placebo participants dropped out after 7 to 16 d because of these drop-outs, the "To persons" column was rescaled: at 10 d and 16 d to fit the preceding reported value					
Duration of colds						Duration of colds					
n = 49						n = 50					
mean		5.20				mean		9.38			
SD		2.83				SD		5.47			

Prasad 2000											
Zn (n=25)						Placebo (n=23)					
Day	pixels	To	To	To	Cured	Day	pixels	To	To	To	Cured
	100%= 2612	Fig scale	persons	person integers	per day			Fig scale	persons	person Integers	per day
		(0 to 100%)						(0 to 100%)			
0	687	100	25.0	25	0	0	687	100	23.0	23	0
1	687	100	25.0	25	0	1	687	100	23.0	23	0
2	835	92.3	23.1	23	2	2	687	100	23.0	23	0
3	1369	64.6	16.1	16	7	3	687	100	23.0	23	0
4	1678	48.5	12.1	12	4	4	698	99.4	22.9	23	0
5	2061	28.6	7.2	7	5	5	858	91.1	21.0	21	2
6	2373	12.4	3.1	3	4	6	1015	83.0	19.1	19	2
7	2612	0.0	0.0	0	3	7	1358	65.1	15.0	15	4
8						8	1837	40.3	9.3	9	6
9						9	2344	13.9	3.2	3	6
10						10	2428	9.6	2.2	2	1
11						11	2435	9.2	2.1	2	0
12						12	2612	0.0	0.0	0	2
		Duration of colds			n = 25			Duration of colds			n = 23
		mean	4.44				mean	8.09			
		SD	1.56				SD	1.81			
Prasad (2000)											
reported:		mean	4.5				mean	8.1			
		SD	1.6				SD	1.8			

Smith 1989											
Zn (n=57)						Placebo (n=53)					
Smith reported that on day 7, there was 12.6% difference between the groups, consistent with figures below (29/53-24/57 = 0.1261)											
Day	pixels	To	To	To	Cured	Day	pixels	To	To	To	Cured
	100%= 2724	Fig scale	persons	person integers	per day			Fig scale	persons	person Integers	per day
		(0 to 100%)						(0 to 100%)			
0	452	100	57.0	57	0	0	452	100	53.0	53	0
1	452	100	57.0	57	0	1	502	97.79	51.8	52	1
2	452	100	57.0	57	0	2	536	96.30	51.0	51	1
3	532	96.47	55.0	55	2	3	632	92.07	48.8	49	2
4	760	86.44	49.3	49	6	4	944	78.34	41.5	42	7
5	980	76.76	43.8	44	5	5	1192	67.42	35.7	36	6
6	1412	57.74	32.9	33	11	6	1322	61.70	32.7	33	3
7	1776	41.72	23.8	24	9	7	1506	53.60	28.4	29	4
8				Imputed:	6	8				Imputed:	6
9				Imputed:	6	9				Imputed:	6
10				Imputed:	6	10				Imputed:	6
11				Imputed:	6	11				Imputed:	6
12						12				Imputed:	5
		Duration of colds		n =	57			Duration of colds		n =	53
		mean	7.23					mean	7.57		
		SD	2.29					SD	3.01		

Turner 2000																								
Placebo (n=71)					A Zn gluconate (n=68)					B Zn acetate 11.5 mg (n=68)					C Zn acetate 5 mg (n=72)									
Day	pixels	To	To	To	Cure d	Day	pixels	To	To	To	Cure d	Day	pixels	To	To	To	Cure d	Day	pixels	To	To	To	Cure d	
	100%= 2984 (0 to 100%)	Fig scale	persons integers	person integers	per day			Fig scale (0 to 100%)	persons	person integers	per day			Fig scale (0 to 100%)	persons	person integers	per day			Fig scale (0 to 100%)	persons	person integers	per day	
0	380	100.0	71.0	71	0	0	380	100.0	68.0	68	0	0	380	100.0	68.0	68	0	0	380	100.0	72.0	72	0	
2	523	94.5	67.1	67	4	2	651	89.6	60.9	61	7	2	577	92.4	62.9	63	5	2	555	93.3	67.2	67	5	
4	1225	67.5	48.0	48	19	4	1120	71.6	48.7	49	12	4	1208	68.2	46.4	46	17	4	1100	72.4	52.1	52	15	
6	1826	44.5	31.6	32	16	6	1865	43.0	29.2	29	20	6	2004	37.6	25.6	26	20	6	1692	49.6	35.7	36	16	
8	2249	28.2	20.0	20	12	8	2218	29.4	20.0	20	9	8	2384	23.0	15.7	16	10	8	2198	30.2	21.7	22	14	
10	2404	22.3	15.8	16	4	10	2500	18.6	12.6	13	7	10	2601	14.7	10.0	10	6	10	2532	17.4	12.5	13	9	
12	2679	11.7	8.3	8	8	12	2664	12.3	8.4	8	5	12	2853	5.0	3.4	3	7	12	2579	15.6	11.2	11	2	
13.5	2716	10.3	7.3	7	1	13.5	2745	9.2	6.2	6	2	13.5	2853	5.0	3.4	3	0	13.5	2618	14.1	10.1	10	1	
15.5				Imputed: 6		15.5				Imputed: 6		15.5					Imputed: 3	15.5					Imputed: 6	
17.5				Imputed: 1		17.5				Imputed: 1		17.5					Imputed: 1	17.5					Imputed: 4	
	Duration of colds				n = 71	Duration of colds				n = 68	Duration of colds				n = 68	Duration of colds				n = 72				
	mean		7.55			mean		7.41			mean		6.89			mean		7.90						
	SD		3.96			SD		3.88			SD		3.35			SD		4.25						

Weismann 1990											
Zn (n=61)					Placebo (n=69)						
Day	pixels	To	To	To	Cured	Day	pixels	To	To	To	Cured
	100%= 2726	Fig scale (0 to 1.0)	persons	person integers	per day			Fig scale (0 to 1.0)	persons	person Integers	per day
0	536	1	61.0	61		0	536	1	69.0	69	
1	562	0.98	60.3	60	1	1	536	1	69.0	69	0
2	600	0.97	59.2	59	1	2	561	0.98	68.2	68	1
3	716	0.91	56.0	56	3	3	690	0.92	64.1	64	4
4	941	0.81	49.7	50	6	4	899	0.83	57.6	58	6
5	1310	0.64	39.4	40	10	5	1216	0.68	47.6	48	10
6	1383	0.61	37.4	38	2	6	1672	0.48	33.2	33	15
7	1675	0.47	29.3	30	8	7	2054	0.30	21.2	22	11
8	1890	0.38	23.3	23	7	8	2261	0.21	14.7	15	7
9	2149	0.26	16.1	16	7	9	2302	0.19	13.4	14	1
10	2605	0.05	3.4	4	12	10	2605	0.05	3.8	4	10
11				Imputed: 4		11				Imputed: 4	
	Duration of colds				n = 61	Duration of colds				n = 69	
	mean		7.16			mean		6.72			
	SD		2.62			SD		2.29			