SUPPLEMENTARY MATERIAL 3

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

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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 x 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:

|    | Zn mean | Placebo mean | Zn mean | Placebo mean | Zn mean | Placebo mean |
|----|---------|--------------|---------|--------------|---------|--------------|
| Eby 1984 [7] | 3.86 | 2.51 | 6.46 | 2.13 | 4.00 | 2.77 |
| Smith 1989 [19] | 6.60 | 1.53 | 6.51 | 1.96 | 8.07 | 3.44 |
| Turner A 2000 [23] | 7.28 | 3.61 | 7.37 | 3.61 | 7.50 | 4.08 |
| Mossad 1996 [24] | 5.20 | 2.83 | 9.34 | 5.39 | 5.20 | 2.83 |
| Turner B 2000 [23] | 6.82 | 3.19 | 7.37 | 3.61 | 6.92 | 3.44 |
| Macknin 1998 [27] | 9.33 | 4.72 | 9.50 | 4.53 | 9.42 | 4.94 |
| Weissmann 1990 [28] | 7.16 | 2.62 | 6.72 | 2.29 | 7.20 | 2.67 |
| Turner C 2000 [23] | 7.58 | 3.62 | 7.37 | 3.61 | 8.12 | 4.75 |

All 13 comparisons

\[
\chi^2 (12 df) = 116 \quad 102 \quad 109
\]

\[
I^2 = 90\% \quad 88\% \quad 89\%
\]

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

| Day | pixels | To | To | To | Cured | Day | pixels | To | To | To | Cured |
|-----|--------|----|----|----|-------|-----|--------|----|----|----|-------|
|     | 448    | 100| 37.0|37 | 0     | 048 | 100    | 28 | 28 | 0   |
| 0.5 | 892    | 89.5|33.1|33 | 4     | 048 | 100    | 28 | 28 | 0   |
| 1   | 1354   | 78.6|29.1|29 | 4     | 148 | 100    | 28 | 28 | 0   |
| 2   | 2035   | 62.5|23.1|23 | 6     | 2736|93.2    | 26 | 26 | 2   |
| 3   | 2383   | 54.2|20.1|20 | 3     | 31198|82.3    | 23 | 23 | 3   |
| 4   | 3187   | 35.2|13.0|13 | 7     | 41346|78.8    | 22 | 22 | 1   |
| 5   | 3421   | 29.7|11.0|11 | 2     | 51651|71.5    | 20 | 20 | 2   |
| 6   | 3880   | 18.8|7.0 | 7  | 4     | 61799|68.0    | 19 | 19 | 1   |
| 7   | 4112   | 13.3|4.9 | 5  | 2     | 72404|53.7    | 15 | 15 | 4   |
| 8   | 3     | 8   |     |     |       | 8   | 8     |     |     |     |
| 9   | 2     | 9   |     |     |       | 9   | 9     |     |     |     |
| 10  | 10    |     |     |     |       | 10  |     |     |     |     |
| 11  | 11    |     |     |     |       | 11  |     |     |     |     |
| 12  | 12    |     |     |     |       | 12  |     |     |     |     |

Duration of colds  n = 37  Duration of colds  n = 28

| Mean | SD   | Mean | SD   |
|------|------|------|------|
| 3.92 | 2.61 | 7.54 | 3.18 |
Macknin 1998

|       | Zn (n=123) | Placebo (n=124) |
|-------|------------|-----------------|
| Day   | pixels     | To person day   | pixels | To person day   |
|       | 100%       | Fig persons     | Fig    | Integers day   |
|       | scale      | integers day    | scale  | Integers day   |
| (0 to 100%) |        | (0 to 100%)    |        |                |
| 0     | 1919       | 0.0             | 1919   | 0.0            |
| 1     | 1884       | 2.1             | 1909   | 0.6            |
| 2     | 1884       | 2.1             | 1895   | 1.5            |
| 3     | 1803       | 7.1             | 1895   | 1.5            |
| 4     | 1708       | 12.9            | 1734   | 11.3           |
| 5     | 1510       | 25.1            | 1580   | 20.8           |
| 6     | 1321       | 36.6            | 1396   | 32.0           |
| 7     | 1187       | 44.9            | 1286   | 38.8           |
| 8     | 1132       | 48.2            | 1141   | 47.7           |
| 9     | 1080       | 51.4            | 930    | 60.6           |
| 10    | 907        | 62.0            | 826    | 67.0           |
| 11    | 764        | 70.8            | 740    | 72.2           |
| 12    | 676        | 76.2            | 706    | 74.3           |
| 13    | 580        | 82.0            | 650    | 77.8           |
| 14    | 536        | 84.7            | 554    | 83.6           |
| 15    | 492        | 87.4            | 530    | 85.1           |
| 16    | 464        | 89.2            | 516    | 86.0           |
| 17    | 464        | 89.2            | 464    | 89.2           |
| 18    | 440        | 90.6            | 440    | 90.6           |
| 19    |            |                 | 464    |                |
| 20    |            |                 | 440    |                |
| 21    |            |                 | 440    |                |

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            |
| SD    | 4.81            | SD              |
|       | 9.50            | 4.53            |
Mossad 1996

Zn (n=49) are reported in Mossad's figure

| Day | pixels | To Cured | Placebo (n=50) are reported in Mossad's figure |
|-----|--------|----------|---------------------------------------------|
|     |        |          |                                             |
| 0   | 213    | 100.0    | 213.0 50.0 50.0 0                           |
| 1   | 384    | 91.7     | 44.9 4 1 213.0 100.0 50.0 50.0 0            |
| 2   | 589    | 81.8     | 40.1 5 2 382.0 91.8 45.9 46 4               |
| 3   | 850    | 69.1     | 33.9 34 6 350.2 86.0 43.0 43 3               |
| 4   | 1180   | 53.1     | 26.0 8 4 710.0 75.9 37.9 38 5               |
| 5   | 1345   | 45.1     | 22.1 22 4 792.0 71.9 36.0 36 2               |
| 6   | 1598   | 32.8     | 16.1 16 6 996.0 62.0 31.0 31 5               |
| 7   | 1893   | 18.5     | 9.1 9 7 1116.0 56.2 28.1 28 3               |
| 8   | 2018   | 12.4     | 6.1 6 3 1334.0 45.6 22.8 23 5               |
| 9   | 2102   | 8.3      | 4.1 3 3 1379.0 43.4 21.7 20 3               |
| 10  | 2102   | 8.3      | 4.1 3 0 1414.0 41.7 19.2 19 1               |
| 11  | 2168   | 5.1      | 2.5 1 2 1511.0 37.0 17.1 17 2               |
| 12  | 2168   | 5.1      | 2.5 1 0 1603.0 32.6 15.0 15 2               |
| 13  | 2274   | 0.0      | 0.0 0 1 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     | 1345     | 9.1 9 3 Imputed: 2                        |
| 20  | 20     | 1379.0   | 43.4 21.7 20 3                           |

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

|            | n =  |        |            | n =  |
|------------|------|--------|------------|------|
| mean       | 5.20 |        | mean       | 9.38 |
| SD         | 2.83 |        | SD         | 5.47 |
### Prasad 2000

| Day | Zn (n=25) | Placebo (n=23) |
|-----|-----------|----------------|
|     | pixels    | Cured | pixels    | Cured |
| 0   | 687       | 100   | 687       | 100   |
| 1   | 687       | 25.0  | 687       | 23.0  |
| 2   | 835       | 92.3  | 687       | 23.0  |
| 3   | 1369      | 64.6  | 858       | 91.1  |
| 4   | 1678      | 48.5  | 698       | 99.4  |
| 5   | 2061      | 28.6  | 1015      | 83.0  |
| 6   | 2373      | 12.4  | 1358      | 65.1  |
| 7   | 2612      | 0.0   | 1358      | 15.0  |
| 8   | 1837      | 40.3  | 1837      | 9.3   |
| 9   | 2344      | 13.9  | 2344      | 3.2   |
| 10  | 2428      | 9.6   | 2428      | 2.2   |
| 11  | 2435      | 9.2   | 2435      | 2.1   |
| 12  | 2612      | 0.0   | 2612      | 0.0   |

#### Duration of Colds

|          | n = 25 |          | n = 23 |
|----------|--------|----------|--------|
| mean     | 4.44   | mean     | 8.09   |
| SD       | 1.56   | SD       | 1.81   |

Prasad (2000) reported:
- Duration of colds
  - mean: 4.5
  - SD: 1.6
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 100% | Fig | persons | pixels | To 100% | Fig | persons |
|-----|--------|---------|-----|---------|--------|---------|-----|---------|
|     | (0 to 100%) | (0 to 100%) |
| 0   | 452    | 100     | 57.0| 57      | 0      | 0      | 452 | 100     |
| 1   | 452    | 100     | 57.0| 57      | 0      | 1      | 502 | 97.79   |
| 2   | 452    | 100     | 57.0| 57      | 2      | 2      | 536 | 96.30   |
| 3   | 532    | 96.47   | 55.0| 55      | 2      | 3      | 632 | 92.07   |
| 4   | 760    | 86.44   | 49.3| 49      | 6      | 4      | 944 | 78.34   |
| 5   | 980    | 76.76   | 43.8| 44      | 5      | 5      | 1192| 67.42   |
| 6   | 1412   | 57.74   | 32.9| 33      | 11     | 6      | 1322| 61.70   |
| 7   | 1776   | 41.72   | 23.8| 24      | 9      | 7      | 1506| 53.60   |

Imputed: 6
8
Imputed: 6
9
Imputed: 6
10
Imputed: 6
11
Imputed: 6
12
Imputed: 5

Duration of colds
n = 57
mean 7.23
SD 2.29
n = 53
mean 7.57
SD 3.01
### Turner 2000

| Represents | Placebo (n=71) | Zn gluconate (n=60) | Zn acetate 11.5 mg (n=68) | Zn acetate 3mg (n=72) |
|-----------|----------------|---------------------|---------------------------|----------------------|
| Days      | Pixels         | To                  | To                        | To                   |
| 0.00      | 380            | 100.0%              | 0                         | 0                    |
| 1.00      | 523            | 92.4%               | 2                         | 2                    |
| 2.00      | 1225           | 71.6%               | 4                         | 4                    |
| 3.00      | 1826           | 31.6%               | 8                         | 8                    |
| 4.00      | 2249           | 20.0%               | 12                        | 12                   |
| 5.00      | 2404           | 15.8%               | 16                        | 16                   |
| 6.00      | 2679           | 11.7%               | 18                        | 18                   |
| 7.00      | 2716           | 7.3%                | 20                        | 20                   |
| 8.00      | 15.5           | 6.2%                | 22                        | 22                   |
| 9.00      | 17.5           | 6.2%                | 24                        | 24                   |
| 10.00     | 17.5           | 6.2%                | 26                        | 26                   |

**Duration of Colds**

- **Placebo**: 
  - Mean: 7.55 days
  - SD: 3.96

- **Zn gluconate**: 
  - Mean: 7.48 days
  - SD: 3.88

- **Zn acetate 11.5 mg**: 
  - Mean: 6.59 days
  - SD: 3.35

- **Zn acetate 3mg**: 
  - Mean: 7.90 days
  - SD: 4.25

### Weismann 1990

#### Zn (n=61)

| Day | Pixels | To  | To | To | To |
|-----|--------|-----|----|----|----|
| 0   | 536    | 1   | 61 | 61 | 0  |
| 1   | 562    | 0.98| 60.3| 60 | 1  |
| 2   | 600    | 0.97| 59.2| 59 | 1  |
| 3   | 716    | 0.91| 56.0| 56 | 3  |
| 4   | 941    | 0.81| 49.7| 50 | 6  |
| 5   | 1310   | 0.64| 39.4| 40 | 10 |
| 6   | 1383   | 0.61| 37.4| 38 | 2  |
| 7   | 1675   | 0.47| 29.3| 30 | 8  |
| 8   | 1890   | 0.38| 23.3| 23 | 7  |
| 9   | 2149   | 0.26| 16.1| 16 | 7  |
| 10  | 2605   | 0.05| 3.4 | 4  | 12 |

**Duration of Colds**: Mean 7.16 days

**SD**: 2.62

#### Placebo (n=69)

| Day | Pixels | To  | To | To | To |
|-----|--------|-----|----|----|----|
| 0   | 380    | 100.0%| 0  | 0  | 0  |
| 1   | 523    | 90.6% | 2  | 2  | 2  |
| 2   | 1120   | 71.6% | 4  | 4  | 4  |
| 3   | 1865   | 43.0% | 8  | 8  | 8  |
| 4   | 2218   | 29.4% | 12 | 12 | 12 |
| 5   | 2500   | 18.6% | 16 | 16 | 16 |
| 6   | 2664   | 12.3% | 20 | 20 | 20 |
| 7   | 2745   | 9.2%  | 24 | 24 | 24 |
| 8   | 2853   | 5.0%  | 28 | 28 | 28 |
| 9   | 2963   | 1.4%  | 32 | 32 | 32 |

**Duration of Colds**: Mean 6.72 days

**SD**: 2.29