**Supplementary Online Content**

Rosendahl J, Valkama S, Holmlund-Suila E, et al. Effect of higher vs standard dosage of vitamin $D_3$ supplementation on bone strength and infection in healthy infants: a randomized clinical trial. *JAMA Pediatr*. Published online May 29, 2018. doi:10.1001/jamapediatrics.2018.0602



This supplementary material has been provided by the authors to give readers additional information about their work.

 

## eAppendix 1. Supplementary Methods

### Family background data

We collected family demographics, including data on health and lifestyle factors, with self-administered research questionnaires at recruitment. Data on gestation and delivery, and on infant demographics, came from electronic hospital records. Season of birth was categorized as in winter (December, January, February), spring (March, April, May), summer (June, July, August) or autumn (September, October, November).

Maternal body mass index (BMI, $kg/m^2$) was calculated from weight and height measured before pregnancy. We collected data on maternal use of vitamin D supplements (brand name, dosage, and date of commencement), and calculated average daily vitamin D intake from supplements for the last 2 months of pregnancy. Parents' educational level from the questionnaires was graded from 1 (=comprehensive school) to 6 (university degree) and then re-categorized into 2 levels: low educational level (=less than a bachelor's degree) and high educational level (=at least a bachelor's degree). Data also included parental smoking before pregnancy and after the delivery.

At the 24-month follow-up, we collected data with structured questionnaires on family lifestyle factors, child's daycare attendance, and household annual income using structured questionnaires. Household annual income was graded into 9 categories: 0-12,999 euro, 13,000-19,999, 20,000-39,999, 40,000-59,999, 60,000-89,000, 90,000-109,999, 110,000-139,999, 140,000 or above, and unknown and further re-categorized into low income (below 40,000), medium income (40,000-109,999), and high income (110,000 and above).

### Nutritional data

Dietary intakes of vitamin D and calcium were determined at 12 months from a 3-day food record administered by the parents or daycare personnel. Families were instructed to record all foods and beverages consumed by the child with the amounts and detailed description of the food item, as well as breastfeeding. Amounts of each food item were estimated by household measurements or by weighing on a scale. Completed food records were reviewed by a nutritionist, and nutrient intakes were processed with AivoDiet software (Aivo Oy Finland, Turku, Finland), which utilizes Fineli, the National Food Composition Database maintained by Finland's National Institute for Health and Welfare. The volume of breast milk consumed was unknown, meaning that calculated total vitamin D and calcium intakes included no intake from breast milk.

Duration of breastfeeding came from repeated questionnaires incorporated in to the study diaries. For mothers still breastfeeding at the 24-month follow-up, the duration of breastfeeding was recorded as 24 months.

### Anthropometric measurements

Follow-up visits were arranged at the study clinic at Kätilöopisto Helsinki Maternity Hospital, Finland, at the child's $6^{th}$, $12^{th}$, and $24^{th}$ month of age (+/- 1 month). At each follow-up visit, the child was measured for weight (kg) with a scale (Seca®, Hamburg, Germany) and for length (cm) with a table-top meter. Length at follow-up was expressed as standard deviation score (SDS) and weight as length-adjusted weight using age- and sex-specific Finnish reference values.[1]

### Laboratory analyses

25-hydroxyvitamin D concentration was analyzed with an IDS-iSYS fully automated immunoassay system with chemiluminescense detection (Immunodiagnostic Systems Ltd., Bolton, UK). Cord plasma 25-hydroxyvitamin D concentrations were corrected with an equation (19.13 + 0.897 * cord plasma 25-hydroxyvitamin D value) to be comparable with serum 25-hydroxyvitamin D concentrations. The equation was based on comparison of 25-hydroxyvitamin D measurements in samples from 84 study subjects for whom both cord plasma and serum samples were available. In addition, because of manufacturer's changes in the IDS-iSYS system between 2014 and 2016, the cord serum 25-hydroxyvitamin D concentrations were corrected by a linear regression equation (correct value (nmol/L)

 

= [(initial value) – 8.2] / 0.99), provided by the manufacturer (see eAppendix 2). We re-analyzed a subsample of 77 samples and verified the correction (adjusted correlation coefficient = 0.922, standard error of the estimate = 9.2 nmol/L).

All samples were analyzed between 2014 and 2016 with intra-assay variation <13% for cord blood and <5% for 12- and 24-month samples. Accuracy of the serum 25-hydroxyvitamin D analysis was monitored by continued participation in the vitamin D External Quality Assessment Scheme (DEQAS, Charing Cross Hospital, London, UK). This method showed a constant <8% positive bias based on the NIST (National Institute of Standards and Technology) Reference Measurement Procedure during 2014 and 2016.

The IDS-iSYS immunoassay also served to analyze intact parathyroid hormone (PTH) from 12- and 24-month serum samples. The reference range for PTH was 11.5-78.4 ng/L; the lowest detection limit was 4.5 ng/L. PTH values less than that were coded as 4.4 ng/L.

Plasma ionized calcium, adjusted to pH 7.40, was analyzed from capillary samples at 6 months and from serum samples at 12 and 24 months at the Central Laboratory of Helsinki University Hospital (HUSLAB) with the blood gas analyzer ABL 90 FLEX or ABL 835 FLEX. The reference range for ionized calcium at 6 and 12 months was 1.16-1.39 mmol/L and at 24 months 1.17-1.35 mmol/L.

 

**eAppendix 2. The Report from Immunodiagnostic Systems Containing the Linear Regression Equation for Correction of Cord Blood 25-Hydroxyvitamin D Concentration**

October 23th, 2014

RE: DEQAS July 2014 25-hydroxyvitamin D positive bias

Dear Valued Customer,

The 25-Hydroxyvitamin DEQAS - July 2014 distribution report indicates that the results obtained with the IDS-iSYS 25-Hydroxy Vitamin $D^S$ assay were outside the ± 25% criteria.

Immunodiagnostic Systems launched an internal investigation by verifying the alignment between the IDS-iSYS 25-Hydroxy Vitamin $D^S$ and the ID-LC-/MS/MS 25(OH)D Reference Method Procedure (RMP) using the single donor serum samples from the Vitamin D Standardization Program (VDSP). The DEQAS July 2014 distribution and our internal serum samples panels were also measured in multiple reagent lots and systems.

We have confirmed a bias in DEQAS - July 2014 distribution. The regression slope between the IDS-iSYS assay and the RMP is slightly higher than previously communicated in the Product Notification NIS2700S/04 (1.06 vs. 1.04); the mean % bias is 12% versus -2%. The bias occurred due to the implememenging of a new internal serum panel preparation with target value slightly higher than the LC-MS/MS value.

From kit lot 2191 and onward, we have adjusted the internal serum panel target value to correct the bias. The summary of IDS-iSYS 25-Hydroxy Vitamin $D^S$ Traceability is enclosed for your references. The results confirm the alignment against the ID-LC-/MS/MS 25(OH)D Reference Method Procedure (RMP).

Immunodiagnostic Systems strives to provide you with products of the highest quality. We value your business and thank you for your continued support. Please contact your local IDS representative if you have any further questions regarding this information.

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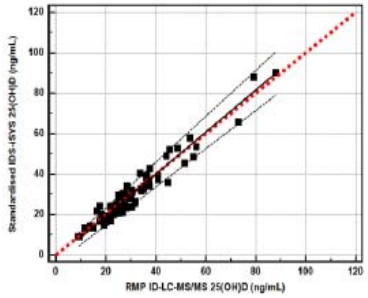
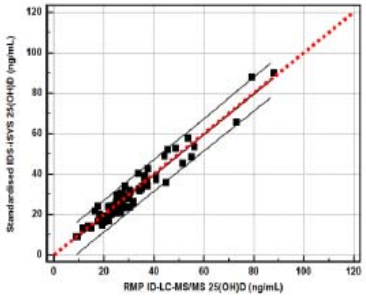
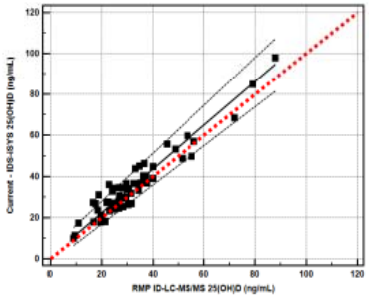
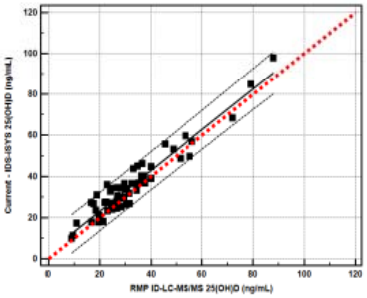
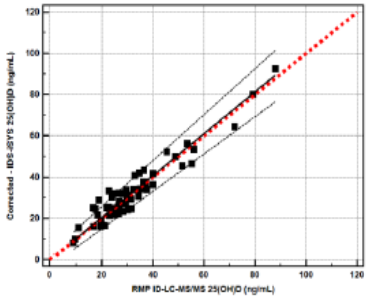
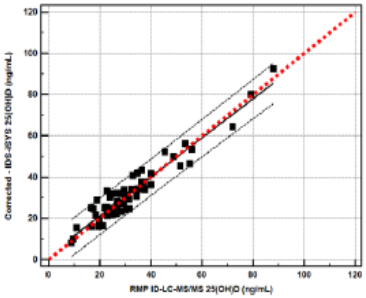
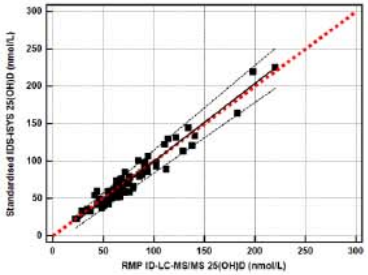
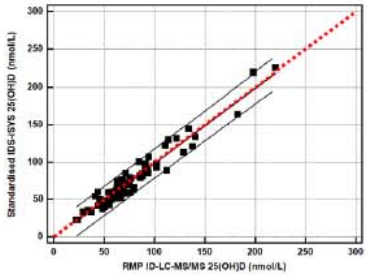
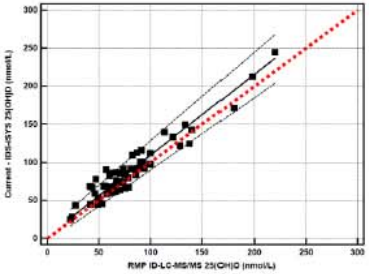
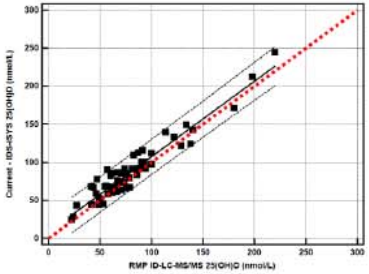
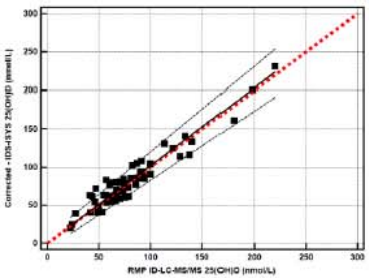
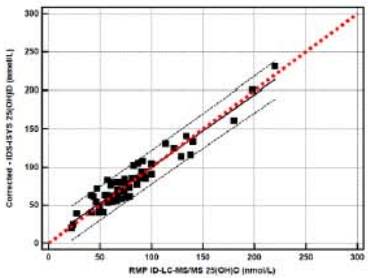
## IDS-iSYS 25-Hydroxy Vitamin D$^{S}$ (ng/mL) VDSP Traceability

The single donor serum samples (n = 70) with RMP ID-LC-MS/MS 25(OH)D target value ranging from 9.0 – 79.2 ng/mL from the Vitamin D Standardization Program (VDSP) were used to verify the IDS-iSYS alignment in May 2014. The same samples were measured in September 2014 to confirm the assay traceability. From kit lot 2191 onward, we have adjusted the internal serum panel target value to correct the bias.

| | Passing-Bablok regression | Linear regression | Statistical summary |
|---|---|---|---|
| Product Notification NIS2700S/04 May 2014 |  |  | The Passing-Bablok regression between the IDS-iSYS (y) and the RMP ID-LC-MS/MS (x) is:<br>IDS-iSYS = 1.04 x (RMP) -1.6 ng/mL<br>95 % CI. slope: 0.95 to 1.13<br>95 % CI. intercept: -4.2 to 0.5 ng/mL<br>Pearson corr. coeff. r: 0.967 (0.948 to 0.980), P<0.0001<br>Mean %bias: -2.0%<br>The linear regression equation is:<br>IDS-iSYS = 1.00 x (RMP) – 0.8 ng/mL<br>95 % CI. slope: 0.94 to 1.07<br>95 % CI. intercept: -3.0 to 1.4 ng/mL |
| Alignment verification September 2014 |  |  | Although the Passing-Bablok regression yields a slope >1.05, the slope of linear regression is 0.99.<br>The Passing-Bablok regression is:<br>IDS-iSYS = 1.06 x (RMP) +1.0 ng/mL<br>95 % CI. slope: 0.95 to 1.17<br>95 % CI. intercept: -2.2 to 4.6 ng/mL<br>Pearson corr. coeff. r: 0.954 (0.932 to 0.970), P<0.0001<br>Mean %bias: 12.0%<br>The linear regression equation is:<br>IDS-iSYS = 0.99 x (RMP) + 3.3 ng/mL<br>95 % CI. slope: 0.91 to 1.07<br>95 % CI. intercept: 0.6 to 6.0 ng/mL |
| Corrected - October 2014 |  |  | After the correction, the Passing-Bablok regression yields a slope of 1.02 and the linear regression slope is 0.95. The Passing-Bablok regression is:<br>IDS-iSYS = 1.02 x (RMP) -0.0 ng/mL<br>95 % CI. slope: 0.91 to 1.11<br>95 % CI. intercept: -3.0 to 3.0 ng/mL<br>Pearson corr. coeff. r: 0.954 (0.932 to 0.970), P<0.0001<br>Mean %bias: 3.1%<br>The linear regression equation is:<br>IDS-iSYS = 0.95 x (RMP) + 2.1 ng/mL<br>95 % CI. slope: 0.87 to 1.02<br>95 % CI. intercept: -0.5 to 4.7 ng/mL |

## IDS-iSYS 25-Hydroxy Vitamin $D^S$ (nmol/L) VDSP Traceability

The single donor serum samples (n = 70) with RMP ID-LC-MS/MS 25(OH)D target value ranging from 23 – 198 nmol/L from the Vitamin D Standardization Program (VDSP) were used to verify the IDS-iSYS alignment in May 2014. The same samples were measured in September 2014 to confirm the assay traceability. From kit lot 2191 onward, we have adjusted the internal serum panel target value to correct the bias.

| | Passing-Bablok regression | Linear regression | Statistical summary |
|---|---|---|---|
| **Product Notification NIS2700S/04 May 2014** |  |  | The Passing-Bablok regression between the IDS-iSYS (y) and the RMP ID-LC-MS/MS (x) is:<br>IDS-iSYS = 1.04 x (RMP) - 4.0 nmol/L<br>95 % CI. slope: 0.95 to 1.13<br>95 % CI. intercept: -10.5 to 1.4 nmol/L<br>Pearson corr. coeff. r: 0.967 (0.948 to 0.980), P<0.0001<br>Mean %bias: -2.0%<br>The linear regression equation is:<br>IDS-iSYS = 1.00 x (RMP) – 2.0 nmol/L<br>95 % CI. slope: 0.94 to 1.07<br>95 % CI. intercept: -7.6 to 3.5 nmol/L |
| **Alignment verification September 2014** |  |  | Although the Passing-Bablok regression yields a slope >1.05, the slope of linear regression is 0.99.<br>The Passing-Bablok regression is:<br>IDS-iSYS = 1.06 x (RMP) +2.6 nmol/L<br>95 % CI. slope: 0.95 to 1.17<br>95 % CI. intercept: -5.4 to 11.5 nmol/L<br>Pearson corr. coeff. r: 0.954 (0.932 to 0.970), P<0.0001<br>Mean %bias: 12.0%<br>The linear regression equation is:<br>IDS-iSYS = 0.99 x (RMP) + 8.2 nmol/L<br>95 % CI. slope: 0.91 to 1.07<br>95 % CI. intercept: 1.5 to 15.0 nmol/L |
| **Corrected - October 2014** |  |  | After the correction, the Passing-Bablok regression yields a slope of 1.02 and the linear regression slope is 0.95. The Passing-Bablok regression is:<br>IDS-iSYS = 1.02 x (RMP) - 0.0 nmol/L<br>95 % CI. slope: 0.91 to 1.11<br>95 % CI. intercept: -7.6 to 8.8 nmol/L<br>Pearson corr. coeff. r: 0.954 (0.932 to 0.970), P<0.0001<br>Mean %bias: 3.1%<br>The linear regression equation is as follow:<br>IDS-iSYS = 0.95 x (RMP) + 2.1 nmol/L<br>95 % CI. slope: 0.87 to 1.02<br>95 % CI. intercept: -0.5 to 4.7 nmol/L |



## eTable 1. Child Anthropometric Characteristics at Follow-up Visits

| | All | $Group_{400}$ | $Group_{1200}$ |
|---|---|---|---|
| **6-month follow-up** | | | |
| Number of subjects | 892 | 447 | 445 |
| Weight (kg) | 8.0 (0.9) | 8.0 (0.9) | 8.0 (0.9) |
| Length-adjusted weight (%) | 2.5 (9.2) | 2.7 (9.2) | 2.4 (9.2) |
| Length (cm) | 67.5 (2.2) | 67.5 (2.2) | 67.4 (2.1) |
| Length (SDS) | -0.5 (1.0) | -0.5 (1.0) | -0.5 (1.0) |
| | | | |
| **12-month follow-up** | | | |
| Number of subjects | 865 | 434 | 431 |
| Weight (kg)[a] | 9.8 (1.1) | 9.8 (1.2) | 9.8 (1.1) |
| Length-adjusted weight (%) | 1.2 (8.4) | 1.2 (8.5) | 1.1 (8.3) |
| Length (cm) | 75.3 (2.5) | 75.4 (2.6) | 75.2 (2.5) |
| Length (SDS) | -0.5 (1.0) | -0.5 (1.0) | -0.6 (1.0) |
| | | | |
| **24-month follow-up** | | | |
| Number of subjects | 823 | 408 | 415 |
| Weight (kg) | 12.6 (1.4) | 12.5 (1.4) | 12.6 (1.4) |
| Length-adjusted weight (%) | 0.2 (7.5) | -0.1 (7.4) | 0.5 (7.6) |
| Length (cm) | 87.7 (3.1) | 87.7 (3.2) | 87.7 (3.0) |
| Length (SDS) | -0.2 (1.0) | -0.2 (1.0) | -0.3 (1.0) |

$Group_{400}$ represents infants randomized to daily 400 IU vitamin $D_3$ and $Group_{1200}$ to daily 1200 IU vitamin $D_3$. All values are means with standard deviation (SD). SDS denotes standard deviation score.
Data on weight and length at 12 months available for 864; data on weight at 24 months for 820, and data on length at 24 months for 821.

## eTable 2. Compliance With Vitamin D Supplementation During the 24-Month Study

| | **Group$_{400}$** | **Group$_{1200}$** |
|---|---|---|
| **0-6 months** | | |
| Compliance % (mean, 95% CI) | 88.6 (87.4 to 89.8) | 88.1 (86.9 to 89.4) |
| Compliance ≥ 80% (%) | 84.5 | 84.2 |
| **0-12 months** | | |
| Compliance % (mean, 95% CI) | 89.3 (88.2 to 90.4) | 89.0 (87.9 to 90.1) |
| Compliance ≥ 80% (%) | 86.0 | 83.3 |
| **0-24 months** | | |
| Compliance % (mean, 95% CI) | 88.5 (87.4 to 89.7) | 87.2 (85.9 to 88.6) |
| Compliance ≥ 80% (%) | 85.4 | 81.6 |

Data available at 6 months for 889, at 12 months for 847 and at 24 months for 794.

**eTable 3. Serum 25-Hydroxyvitamin D (nmol/L), Plasma Ionized Calcium (mmol/L), and Serum Intact Parathyroid Hormone (ng/L) Concentrations During Follow-up by Intervention Group**

| | $Group_{400}$ | | $Group_{1200}$ | | |
|---|---|---|---|---|---|
| | **n** | **Mean (SD)** | **n** | **Mean (SD)** | **P-value[a]** |
| **25(OH)D in cord blood** | 480 | 81.7 (27.8) | 475 | 81.3 (24.0) | 0.825 |
| **25(OH)D at 12 months** | 401 | 82.7 (19.8) | 404 | 115.0 (27.7) | <0.001 |
| **25(OH)D at 24 months** | 404 | 86.6 (19.6) | 410 | 117.7 (26.1) | <0.001 |
| | | | | | |
| **Ca-ion at 6 months** | 446 | 1.38 (0.04) | 442 | 1.38 (0.04) | 0.548 |
| **Ca-ion at 12 months** | 427 | 1.33 (0.03) | 427 | 1.33 (0.03) | 0.078 |
| **Ca-ion at 24 months** | 362 | 1.31 (0.03) | 364 | 1.31 (0.03) | 0.488 |
| | | | | | |
| **PTH at 12 months** | 387 | 27.6 (13.9) | 388 | 24.7 (14.9) | <0.001 |
| **PTH at 24 months** | 404 | 19.0 (10.3) | 410 | 16.5 (7.9) | 0.004 |

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; Ca-ion, plasma ionized calcium; PTH, intact parathyroid hormone. To convert serum 25(OH)D from nmol/L to ng/mL, divide by 2.496.
[a] Independent samples t-test.

## eTable 4. Vitamin D Status During Follow-up by Intervention Group

| Time-point | 25(OH)D (nmol/L) | Total n (%) | $Group_{400}$ n (%) | $Group_{1200}$ n (%) | P-value[a] |
|---|---|---|---|---|---|
| | | | | | |
| **Cord blood** | <50 | 41 (4.3) | 15 (3.1) | 26 (5.5) | 0.058 |
| | 50.0-75.0 | 378 (39.6) | 206 (42.9) | 172 (36.2) | |
| | 75.1-125.0 | 494 (51.7) | 236 (49.2) | 258 (54.3) | |
| | ≥125.1 | 42 (4.4) | 23 (4.8) | 19 (4.0) | |
| | | | | | |
| **12 months** | <50 | 10 (1.2) | 9 (2.2) | 1 (0.2) | <0.001 |
| | 50.0-75.0 | 163 (20.2) | 142 (35.4) | 21 (5.2) | |
| | 75.1-125.0 | 496 (61.6) | 244 (60.8) | 252 (62.4) | |
| | ≥125.1 | 136 (16.9) | 6 (1.5) | 130 (32.2) | |
| | | | | | |
| **24 months** | <50 | 5 (0.6) | 5 (1.2) | 0 (0.0) | <0.001 |
| | 50.0-75.0 | 133 (16.3) | 114 (28.2) | 19 (4.6) | |
| | 75.1-125.0 | 504 (61.9) | 272 (67.3) | 232 (56.6) | |
| | ≥125.1 | 172 (21.1) | 13 (3.2) | 159 (38.8) | |

Abbreviations: 25(OH)D, 25-hydroxyvitamin D. To convert serum 25(OH)D from nmol/L to ng/mL, divide by 2.496.
[a] Pearson Chi-square.

## eTable 5. Calcium Status During Follow-up by Intervention Group

| | **Group$_{400}$** | **Group$_{1200}$** |
|---|---|---|
| **At 6 months** | **n (%)** | **n (%)** |
| Normocalcemia | 325 (73) | 318 (72) |
| Hypercalcemia | 121 (27) | 124 (28) |
| | | |
| **At 12 months** | | |
| Normocalcemia | 421 (99) | 417 (98) |
| Hypercalcemia | 6 (1) | 10 (2) |
| | | |
| **At 24 months** | | |
| Normocalcemia | 335 (93) | 332 (91) |
| Hypercalcemia | 27 (7) | 32 (9) |

Normocalcemia defined as plasma ionized calcium at 6 and 12 months between 1.16-1.39 mmol/L and at 24 months between 1.17-1.35 mmol/L.
Hypercalcemia defined as plasma ionized calcium at 6 and 12 months > 1.39 mmol/L and at 24 months >1.35 mmol/L.
No participant presented with hypocalcemia during follow-up visits at 6, 12, or 24 months.

## eTable 6. Effect of Vitamin D Supplementation on Incidence of Infections at 24 Months, With Infections in Seven Subtypes According to Parentally Reported Symptoms or Diagnosis

| | $Group_{400}$ | | $Group_{1200}$ | | |
|---|---|---|---|---|---|
| **Outcome measures** | **Number of events** | **Incidence rate[a]** | **Number of events** | **Incidence rate[b]** | **IRR[c] (95% CI)** |
| Upper respiratory tract infections | 2733 | 0.27 | 2619 | 0.26 | 0.96 (0.89 to 1.05) |
| Acute otitis media | 561 | 0.05 | 656 | 0.06 | 1.16 (0.97 to 1.40) |
| Pneumonia | 5 | 0.00 | 8 | 0.00 | 1.60 (0.49 to 5.26) |
| Conjuctivitis | 129 | 0.01 | 146 | 0.01 | 1.13 (0.85 to 1.51) |
| Gastroenteritis | 379 | 0.04 | 349 | 0.03 | 0.92 (0.79 to 1.08) |
| Other viral infections | 367 | 0.04 | 366 | 0.04 | 1.00 (0.86 to 1.17) |
| Other bacterial infections | 48 | 0.00 | 50 | 0.00 | 1.04 (0.68 to 1.60) |

Data on infections available for 449 subjects in $Group_{400}$ and 448 in $Group_{1200}$.
[a] Incidence rate from number of events divided by person-months (=10,237), except for duration per infection episode and number of days infected, divided by person-days (=309,657).
[b] Incidence rate from number of events divided by person-months (=10,204), except for duration per infection episode and dumber of days infected, divided by person-days (=308,675).
[c] IRR denotes incidence rate ratio with 95% confidence interval from negative binomial regression.

## eTable 7. Characteristics of Parent-Reported Infections per Child During 24-Month Follow-up

| | $Group_{400}$ | | | $Group_{1200}$ | | |
|---|---|---|---|---|---|---|
| | n | mean | SD | n | mean | SD |
| Number of infection episodes | | | | | | |
| 0-12 months | 451 | 4.04 | 2.34 | 450 | 3.92 | 2.48 |
| 0-24 months | 449 | 9.18 | 4.83 | 448 | 9.14 | 4.92 |
| Upper respiratory tract infections | 449 | 5.9 | 3.78 | 448 | 5.69 | 3.8 |
| Acute otitis media | 449 | 1.22 | 1.72 | 448 | 1.42 | 1.87 |
| Pneumonia | 449 | 0.01 | 0.12 | 448 | 0.02 | 0.13 |
| Conjuctivitis | 449 | 0.28 | 0.64 | 448 | 0.31 | 0.68 |
| Gastroenteritis | 449 | 0.81 | 0.96 | 448 | 0.75 | 1.01 |
| Other viral infections | 449 | 0.8 | 0.98 | 448 | 0.79 | 0.95 |
| Other bacterial infections | 449 | 0.11 | 0.34 | 448 | 0.11 | 0.37 |
| Antibiotic treatments | 441 | 1.76 | 2.07 | 435 | 2.06 | 2.27 |
| Physician visits | 443 | 3.15 | 2.95 | 435 | 3.38 | 3.17 |
| Hospitalizations | 443 | 0.07 | 0.29 | 435 | 0.09 | 0.3 |
| Number of days infected | 449 | 57.40 | 42.77 | 448 | 55.73 | 44.45 |
| Duration per episode (days) | 443 | 6.18 | 3.60 | 434 | 5.68 | 2.74 |

Abbreviations: SD, standard deviation.

## eReference

1. Saari A, Sankilampi U, Hannila ML, Kiviniemi V, Kesseli K, Dunkel L. New Finnish growth references for children and adolescents aged 0 to 20 years: Length/height-for-age, weight-for-length/height, and body mass index-for-age. *Ann Med.* 2011;43:235-248.