Vitamin D Deficiency in Children in Jerusalem: the Need for Updating the Recommendation for Supplementation

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ABSTRACT: **Background:** Hypovitaminosis D is common worldwide, even in sunny regions.

Objectives: To assess the prevalence and determinants of vitamin D deficiency in toddlers.

Methods: A cross-sectional prospective study was conducted in healthy Jewish children aged 1.5–6 years at five primary care pediatric clinics in the Jerusalem area during the period October 2009 to November 2010. Parents were interviewed regarding personal and demographic data and sun exposure. Blood samples were obtained for serum 25-hydroxyvitamin D [25-OHD] level. Vitamin D deficiency and insufficiency were defined as 25-OHD < 20 ng/ml and < 30 ng/ml, respectively.

Results: Of 247 children studied, 188 (76%) were ultra-Orthodox and 59 (24%) were Orthodox, traditional or secular. Mean (± SD) 25-OHD level was 25.7 ± 10 ng/ml. Only 73 children (29.6%) had sufficient 25-OHD levels, 104 (42.1%) had insufficiency, and 70 (28.3%) had 25-OHD deficiency. The difference between ultra-Orthodox and others was insignificant (25 ± 10 vs. 27.8 ± 10.5 ng/ml respectively, $P = 0.062$). Children aged 1.5–3 years had higher 25-OHD levels than those aged 3–6 years (28.6 ± 10.7 and 24 ± 9.2 ng/ml respectively, $P < 0.001$). Vitamin D deficiency was more common in winter (53%) and autumn (36%) than in summer (19%) and spring (16%). Toddlers attending long-day kindergartens had higher 25-OHD level than those staying at home or at short-day kindergartens (28.8 ± 11.5 and 24.7 ± 9.6 ng/ml respectively, $P < 0.05$).

Conclusions: A high prevalence of vitamin D deficiency was found in toddlers in our study, mainly in older children and in the winter and autumn. We recommend routine supplementation of vitamin D for children beyond the age of one year.

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KEY WORDS: vitamin D, 25-hydroxyvitamin D (25-OHD), hypovitaminosis, deficiency, children, supplementation

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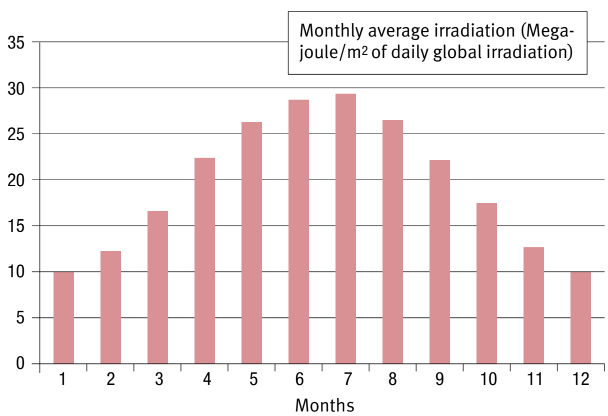
Over the past decade research on the importance of vitamin D has grown steadily, with numerous reports on hypovitaminosis D in adults [1-3] and children [4,5] in both high latitudes and sunny regions. The prevalence of vitamin D deficiency in children has been investigated in several sunny countries such as the southern United States, Australia, Africa, India, and the United Arab Emirates [6-9]. Israel is located in a mostly sunny region, and Jerusalem is situated at a latitude of 31.8°, with marked seasonal variations in solar irradiation. The range of the mean daily solar irradiation varies between 9.9 and 29.3 mega joule/m² in January and July, respectively [Figure 1]. Exposure to sunlight represents the main source of vitamin D. Only about 5%–10% of the total vitamin D comes from dietary intake. In Israel only a negligible amount of foods intended for children consumption are fortified with vitamin D.

In 2003, the American Academy of Pediatrics issued guidelines for rickets prophylaxis, recommending an intake of 200 IU/day vitamin D in the first year of life. This recommendation was both for exclusively breast-fed infants and for those whose milk formula consumption was under 500

Figure 1. Mega joule per square of daily global radiation (from Israel Central Bureau of Statistics), multi-annual monthly average (1990–2010)



ml/day, based on the fact that these formulas contain about 400 IU vitamin D per liter [10]. The Ministry of Health in Israel has also issued guidelines that are in line with those recommendations.

In August 2008, the AAP established a new guideline of 400 IU/day vitamin D3 for all infants, children and adolescents [11,12]. In September 2008 the Israel Ministry of Health adopted a similar recommendation for a uniform dose of vitamin D 400 IU/day for all infants during their first year of life. There are no recommendations for vitamin D supplementations beyond 1 year. Several studies on vitamin D status in Israel were recently published [13-15].

The aim of the present study was to assess vitamin D status in healthy children in the Jerusalem area in Israel, and to investigate risk factors for vitamin D deficiency in order to evaluate the need for vitamin D supplementation in children beyond 1 year. For this purpose, the age group of 1.5–6 year old children was chosen. Preliminary data have shown that 25-hydroxyvitamin D levels in infants up to 1 year old are sufficient but decrease gradually with age [9,16].

SUBJECTS AND METHODS

A cross-sectional prospective study was conducted during the period October 2009 to November 2010 to reflect all four seasons. The study population comprised 1.5–6 year old children attending five primary care pediatric clinics of the Meuhedet Health Services: four in the Jewish sector in Jerusalem and one in Beitar Illit, a city in the Jerusalem hills whose population of about 40,000 is ultra-Orthodox. All children visited the clinics for primary health care. Children with chronic diseases or prematurity were excluded.

The study was approved by the Helsinki Committee of the Hadassah Medical Organization, Jerusalem. The parents were informed about the research and were asked to enroll their children with a written consent. The compliance rate at the five clinics was about 50%. Refusal by the parents was mostly due to the requirement for blood samples. There were no marked differences in refusal among the five clinics. Parents were interviewed by means of a structured questionnaire containing personal and demographic details, medical history, sun exposure (time spent outdoors, and clothing), and a short qualitative Food Frequency Questionnaire.

Blood samples were obtained from each participant for a complete blood count, ferritin and serum 25-OHD levels. 25-OHD levels were determined by a commercially available kit, Liaison 25-OHD (Diasorin, Italy). The assay consists of a direct competitive chemiluminescence immunoassay for quantitative determination of total 25-OHD in human serum. In this paper we report the results of 25-OHD levels; the results of the complete blood count and ferritin are reported elsewhere [17].

AAP = American Academy of Pediatrics
25-OHD = 25-hydroxyvitamin D

To date there is no consensus on the recommended reference range of 25-OHD level. In 2007, the 13th workshop consensus for vitamin D nutritional guidelines, that convened academic authorities in this field, estimated that "all adults should have a much higher blood vitamin D3 of approximately 75 nmol/ml (30 ng/ml)" [18]. However, in November 2010, the United States Institute of Medicine estimated that "a level of 20 ng/ml (50 nmol/ml) is optimal for bone health, and there is no evidence base to establish the optimal level at about 30 ng/ml for the extra-skeletal diseases" [19]. In 2008 new reference ranges for children were recommended by the AAP, namely: "On the basis of the available evidence, serum 25 (OH)D concentrations in infants and children should be ≥ 50 nmol/L (20 ng/ml) [12].

STATISTICAL ANALYSIS

All responses from the questionnaires and laboratory results were grouped in a Microsoft EXCEL table. These data were then transferred to the SPSS statistical program (Version 18). Correlation between variables was computed using the Pearson coefficient. Relationships between ordinal variables were assessed using the Spearman rank correlation coefficient. Differences between the means of two independent samples were tested by the *t*-test, and the chi-square test was used to examine categorical variables. The level of statistical significance was set at $P < 0.05$. The dependent variable chosen was serum 25-OHD level (ng/ml), and the non-dependent variables were age, gender, daycare setting, religious group (ultra-Orthodox and Orthodox/secular), maternal education (number of years), season of the year at the time of the blood test (winter, spring, summer, fall), number of siblings, and sun exposure (duration, clothing, sunscreen use).

RESULTS

Serum 25-OHD levels were obtained from 247 children aged 1.5–6 years, 144 males (58%) and 103 females (42%). The mean ± SD age was 42 ± 17 months. There were 188 children (76%) from ultra-Orthodox Jewish families and 59 (24%) from Orthodox or secular. Parents of 230 children (93%) completed the questionnaires. We collected only demographic data from the remaining 17 who did not complete the questionnaire.

SERUM 25 (OH)D LEVELS

The mean ± SD 25-OHD level was 25.7 ± 10 ng/ml. 25-OHD was sufficient (> 30 ng/ml) in only 73 children (29.6%), insufficient (20–30 ng/ml) in 104 (42.1%), and deficient (< 20 ng/ml) in 70 (28.3%) . The distribution of serum 25-OHD levels among the various ages with the ranges of sufficiency, insufficiency and deficiency is shown in Figure 2.

Figure 2. Distribution of 25-OHD levels in all subjects. The lower horizontal line denotes the boundary between the level defined as deficiency (‹ 20 ng/ml) and insufficiency. The upper line denotes the optimal level recommended, 30 ng/ml

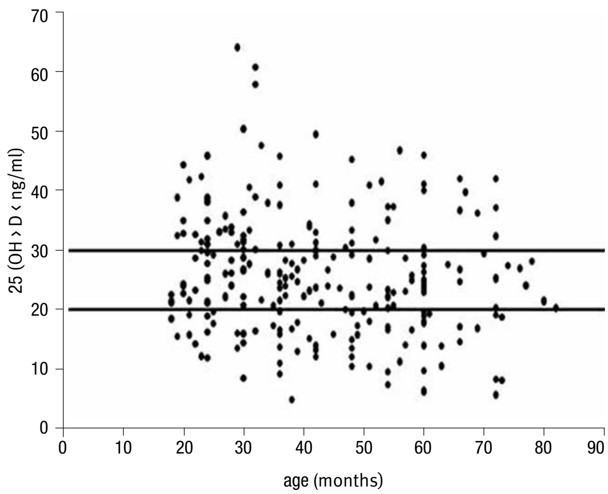
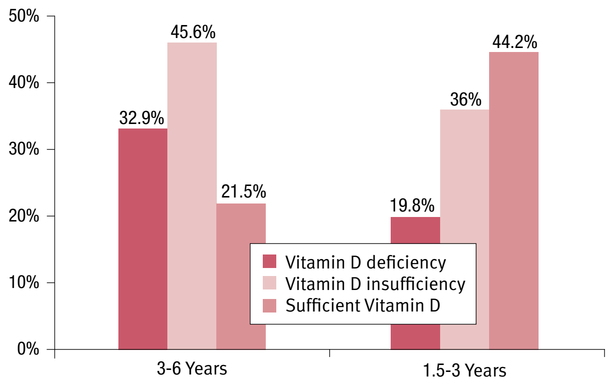


Figure 3. Distribution of 25-OHD levels in the two age groups

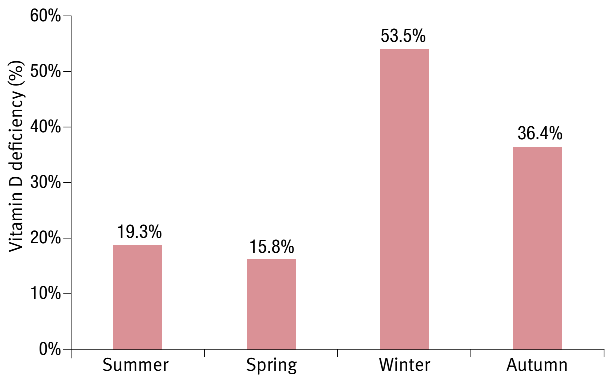


AGE AND VITAMIN D LEVELS

To assess whether there is a relationship between children's age and vitamin D level, Spearman's rank correlation was used, which showed a clear negative relationship between the variables [r (244) = -0.157, $P < 0.05$]. As the age of the child increased, the level of vitamin D decreased ($P = 0.014$).

The mean ± SD 25-OHD level in the age group 1.5–3 years (28.6 ± 10.7 ng/ml) was significantly higher than that of 3–6 year old children [24 ± 9.2 ng/ml, t (242) = 3.527, $P < 0.001$]. The prevalence of vitamin D insufficiency was more common in 3–6 year old children (45.6%) than in those aged 1.5–3 years (36%), as was the prevalence of vitamin D deficiency (32.9% and 19.8% in the age group 3–6 years and 1.5–3 years, respectively) [Figure 3].

Figure 4. Percentage of children with vitamin D deficiency during the four seasons of the year



SEASONS AND VITAMIN D LEVELS

The prevalence of vitamin D deficiency in the four seasons is illustrated in Figure 4. Vitamin D deficiency was more common in winter (53.3%) and autumn (36.4%) than in summer (19.3%) and spring (15.8%). There was a statistically significant association between the prevalence of vitamin D deficiency and season: $\chi^2 = 26.71$, $P < 0.001$.

DURATION OF SUN EXPOSURE, USE OF SUNSCREEN AND VITAMIN D LEVELS

There was no statistically significant association between serum vitamin D level and the duration of sun exposure (hours/day) of the children ($P = 0.215$). To determine whether there is a link between regular use of sunscreen and vitamin D levels, Spearman's rank correlation was used, which showed a statistically significant negative relationship: [r (84) = -0.361, $P < 0.01$], indicating that serum vitamin D levels were lower in children who used sunscreen regularly.

VITAMIN D DEFICIENCY IN THE VARIOUS RELIGIOUS GROUPS

Serum 25-OHD levels were slightly lower in children from ultra-Orthodox families compared with others, but this difference was not statistically significant (25 ± 10 ng/ml and 27.8 ± 10.5 ng/ml, respectively, $P = 0.062$). The prevalence of vitamin D deficiency was higher in children from ultra-Orthodox families compared with others, but this difference was not statistically significant (30.7% and 23.7%, respectively, $P = 0.504$).

CHILDREN'S DAYCARE SETTING AND VITAMIN D LEVELS

Serum 25-OHD levels of children attending long-day kindergartens were significantly higher compared with those of children attending short-day kindergartens or those staying at home [28.8 ± 11.5 ng/ml and 24.7 ± 9.6 ng/ml, respectively, t (211) = -2.379, $P = 0.018$].

NUMBER OF SIBLINGS AND VITAMIN D LEVELS

The relationship between the number of siblings of the index child and the level of vitamin D was tested using the Spearman rank correlation, which showed a marginally significant negative relationship between the variables: r (208) = -0.133, P = 0.055. Thus the level of 25-OHD decreased as the number of siblings increased.

MATERNAL EDUCATIONAL AND VITAMIN D LEVELS

No relationship was found between the number of school years of the mothers of the children and serum 25-OHD levels (P = 0.954).

GENDER AND VITAMIN D LEVELS

Serum 25-OHD levels were very similar in boys (25.9 ± 10.17 ng/ml) and girls (25.4 ± 10 ng/ml) (P = 0.722).

DISCUSSION

The present study provides new data on the high prevalence of vitamin D deficiency among healthy preschool children in Israel as well as the risk factors. Our study population was from the Jewish sector in the Jerusalem area and consisted of predominantly ultra-Orthodox and a small representation of Orthodox and secular families. An important point of this study was that the analysis included one year to determine the effect of season.

Since over 90% of the vitamin D body requirements derive from its synthesis under the influence of solar iradiation, variations in solar iradiation have a major influence on the bioavailability and serum levels of vitamin D. Figure 1 shows the multi-annual monthly average solar radiation in Jerusalem for the years 1990–2010. Indeed, the marked seasonal variations in vitamin D deficiency in our study population correspond to this pattern.

The present study points out the high prevalence of vitamin D deficiency in 1.5–6 year old children: 28.3% had a serum 25-OHD level less than 20 ng/ml, and in 42.1% the level was 20–30 ng/ml. The mean level was 25.7 ng/ml, and only 29.6% had a level higher than 30 ng/ml, which represents the optimal value currently recommended [18]. Another point was the age of the children, which was a significant predictor of vitamin D deficiency as the prevalence of vitamin D insufficiency and deficiency were higher in the 3–6 year old group compared with the 1.5–3 year old group (32.9% and 19.8%, respectively). An increase in sun exposure with increasing age and outdoor activity is expected in children. However, in the ultra-Orthodox population, children over the age of 4 years are taught in *cheder* (Torah classes) and have few outdoor activities, and girls wear longer skirts or dresses due to religious modesty codes. Thus, sun exposure might be reduced with increasing age.

Several studies have reported vitamin D deficiency in adults in Israel [13,14,20], including pregnant women [21]. However, only two studies have been performed in children [16,20]. Two of the present authors (G.K. and L.K.) previously conducted a study over a 1 year period (April 2008–March 2009) in Jerusalem, in two of the five clinics that participated in the present study, one in an ultra-Orthodox and the other in a mixed population. Blood tests from 569 children and adolescents aged 3 months to 19 years were examined. The mean 25-OHD level was 21.8 ± 10.4 ng/ml, which was lower in the ultra-Orthodox (18.5 ± 8.33 ng/ml) than in the mixed population (27.4 ± 11.01 ng/ml), with a highly significant difference (P < 0.0001). A 25-OHD serum level lower than 15 ng/ml was found in 28.1%, 15–20 ng/ml in 22.3%, and 20–30 ng/ml in 30.7%. In total 81% of children had a level < 30 ng/ml, and in 50.4% the level was lower than 20 ng/ml. The mean 25-OHD serum level in infants (< 1 year) was 44.8 ng/ml, and it decreased with age: 31.9 ng/ml in the 1–2 year old group, down to 17.3 ng/ml in the 10–19 year old age group [16].

The increasing prevalence of vitamin D deficiency with age was previously reported by Mansbach et al. [22] in a study of 4558 children in the United States: vitamin D deficiency was found in 15% of children aged 1–5 years compared with 21% of children aged 6–11 years.

Also, a recent study by Madden and co-researchers [22] showed that among children admitted to medical-surgical pediatric intensive care units in Boston (USA), older children had lower 25-OHD levels. In Israel, Oren et al. [20] found that in 195 subjects, of whom 55 were < 20 years old, severe vitamin D deficiency (< 15 ng/ml) was more frequent in children and adolescents aged 5–20 (26.5%) compared with children under 5 years (19%).

High levels of 25-OHD in the first year of life, as found in our previous study [16], could be explained by the fact that daily 400 IU vitamin D3 supplements were routinely given in the first year, as recommended by the Israel Ministry of Health. Another explanation for the decline in 25-OHD level before adolescence is the high demand for vitamin D required for the rapid growth during childhood, which is not met by the daily vitamin D supply. In Israel the dietary intake of vitamin D in children is low. In addition, the use of sunscreen is higher due to the fear of skin cancer and older children are less exposed to the sun due to more hours of indoor activities.

Serum 25-OHD levels were lower in winter (53.3%) and autumn (36.4%) than in summer (19.3%) and spring (15.8%). Since Israel is a very sunny country, the fact that 19.3% of children had vitamin D deficiency in summer is surprising. A similar observation was found in a study from Georgia, USA, located in latitude close to that of Israel (33°), where vitamin D levels were lower in winter than in other seasons [24].

An interesting point not previously reported in the literature concerns the fact that serum 25-OHD levels were higher in children who attended long-day kindergarten (28.8 ng/ml) compared with children staying at home or at short-day kindergarten (24.7 ng/ml). We assume that in these "out of home" daycare settings where playtimes in the yard are more regular, children are more exposed to the sun than children remaining at home. Similarly, in families with numerous siblings a higher prevalence of vitamin D deficiency was found. We assume that mothers in large families do not have enough time to take their children outside to play in open spaces or parks and they are therefore less exposed to the sun.

The prevalence of vitamin D deficiency was not statistically higher in ultra-Orthodox (30.7%) than in the other groups (23.7%) ($P = 0.50$); however, serum 25-OHD levels were marginally lower in ultra-Orthodox (25 ± 10 ng/ml) compared with others (27.8 ± 10.5 ng/ml). We expected the 25-OHD levels to be lower in the ultra-Orthodox subjects because the dress code in this population mandates that they be fully covered. This is in agreement with the study by Mukamel et al. [21] where the 25-OHD level in ultra-Orthodox postpartum women was 13.5 ng/ml compared to 18.6 ng/ml in non-Orthodox postpartum women.

We previously reported that 38% of ultra-Orthodox children had a 25-OHD level lower than 15 ng/ml as compared to 11.7% among others [16]. The ultra-Orthodox Jewish population represents about 10% of the entire population of Israel and is characterized by a larger number of children; the average number of children per ultra-Orthodox family is 7.7 as compared to 2.6 for a non-Orthodox family. A prominent characteristic of this population is their dress, which does not allow exposure of any body part except for the hands and face. This prevents extended sun exposure and thereby strongly diminishes the cutaneous production of vitamin D. However, this manner of dress is less relevant in young children.

The high prevalence of vitamin D deficiency found in 1.5–6 year old children in the present study in addition to similar findings in two previous studies in Israel [16,20] is a call for action. Based on these findings we suggest that the recommendation of the Israel Ministry of Health for routine vitamin D supplementation to children be updated, by extending the age beyond one year, especially during winter. Further research is needed to explore the deficit in other parts of the country among Jews and Arabs, and during all seasons.

Of note, several medical authorities in the United States, among them the Institute of Medicine, have updated their recommendations for vitamin D supplementation of 600 IU/day for children aged 1 to 18 years [25].

LIMITATIONS

The subjects in this study were from the Jerusalem region only and are therefore not representative of the whole country. Moreover, it was limited to a Jewish population that was predominantly ultra-Orthodox (76%) and therefore does not represent other Jewish sectors or Arabs. The uneven distribution between ultra-Orthodox and others reduces the statistical power of the comparison of some variables between the groups. In addition, the study sample represents children attending the clinics whose parents had agreed to participate. Thus they may come from families with a high health awareness and our data may under-represent the severity of vitamin D deficiency in the population.

CONCLUSIONS

We report a high prevalence of vitamin D deficiency in a group of 247 children aged 1.5–6 years mainly from ultra-Orthodox families in the Jerusalem region. Vitamin D deficiency or insufficiency was detected in 70% of children living in a very sunny region, with minor differences between ultra-Orthodox and others. Risk factors were the cold seasons and higher age. These data should lead to the updating of national guidelines for preventing vitamin D deficiency, as well as to further research in older children and adolescents to explore which age groups, seasons and population sectors require vitamin D supplementations in Israel.

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Capsule

Genetic variation in the serotonin receptor gene affects immune responses in rheumatoid arthritis

Many genetic variants associate with the risk of developing rheumatoid arthritis (RA); however, their functional roles are largely unknown. Snir and colleagues investigated whether the RA-associated serotonin receptor 2A (*HTR2A*) haplotype affects T cell and monocyte functions. Patients with established RA (n=379) were genotyped for two single-nucleotide polymorphisms in the *HTR2A* locus, rs6314 and rs1328674, to define the presence of the risk haplotype for each individual. Patients with and without the RA-associated TC haplotype were selected and T cell and monocyte function was monitored following in vitro stimulations with staphylococcal enterotoxin B and lipopolysaccharide using multiparameter flow cytometry. Within the cohort, 44 patients were heterozygous for the TC haplotype (11.6%) while none were homozygous. Upon stimulation, T cells from TC-carrier patients produced more pro-inflammatory cytokines, namely tumor necrosis factor-alpha (TNFα), interleukin-17 and interferon gamma, and monocytes produced higher levels of TNFα compared with patients carrying the non-TC haplotype ($P < 0.05$ and 0.01, respectively). Such cytokine production could be inhibited in the presence of the selective 5-HT2 receptor agonist (2,5-dimethoxy-4-iodoamphetamine, DOI); interestingly, this effect was more pronounced in TC carriers. Our data demonstrate that association of RA with a distinct serotonin receptor haplotype has functional impact by affecting the immunological phenotype of T cells and monocytes.

Genes Immunity 2013; 14: 83

Eitan Israeli

Capsule

The origin of the plague

The Justinian Plague, which resurfaced regularly between the 6th and 8th centuries, is thought to have assisted the decline of the Roman Empire, but it has, until now, only been speculatively diagnosed as bubonic plague caused by the bacterium *Yersinia pestis*. Using stringent ancient DNA anti-contamination protocols, Harbeck et al. have genotyped new material from the early medieval graveyard at Aschheim, Bavaria, dating from the 6th century. This graveyard contained 438 individuals, often in multiple burials – a sign of crisis. The amount of bacterial material available was scant, but *Y. pestis* was identified from one individual using five key single-nucleotide polymorphisms identified in recent phylogenies. Genotyping confirmed this isolate as basal to isolates from the 14th century Black Death and the modern (19th century) third pandemic and that, like the other pandemics, it originated in China or Mongolia.

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