

UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

MOM Enterprises, LLC,  
Petitioner,

v.

ELAINE AND REINHOLD W. VIETH,  
Patent Owner,

---

Case IPR 2023-00726  
Patent 9,066,958

---

DECLARATION OF CHRIS TEMOVSKY

I, Chris Temovsky, declare and state as follows under penalty of perjury:

1. I am the Co-president Ddrops Company (“Ddrops”).
2. I attach as Exhibit A to this declaration, the Declaration of Chris Tomovsky that I signed and that was filed in connection with prior litigation in Ddrops

Company, *et al.* v. iHerb Inc., *et al.*, Civil No. 16-4278-JNE-TNL, submitted to the US District Court for the District of Minnesota on March 8, 2017.

3. I attach as Exhibit B to this declaration, the Third Declaration of Chris Temovsky, that I signed and that was filed in connection with prior litigation in Ddrops Company, *et al.* v. iHerb Inc., *et al.*, Civil No. 16-4278-JNE-TNL, submitted to the US District Court for the District of Minnesota on May 26, 2017.

4. Ddrops sells vitamin D supplements, including vitamin D supplements for infants, to be used according to the method(s) disclosed in one or more claims of the '958 Patent in the United States (the "Patented Product"). Ddrops sells the Patented Product under the registered U.S. trademark "Baby Ddrops®". Ddrops has sold the Patented Product in Minnesota since at least June 2011. Ddrops also sells Kids Ddrops®, Ddrops® Booster, Ddrops® for Adults, and Vegan Ddrops®, all of which are vitamin D supplements.

5. The Patented Product, "Baby Ddrops®", has a composition according to the ingredients listed on the box and has always been sold with instructions. The ingredients are Vitamin D3 (Cholecalciferol) 400 IU Per Drop and Fractionated coconut oil. Temovsky Exhibit A, page 21 (Doc. 39-2 page 5 of 10). One drop of the Patented Product provides a nutritional or therapeutic amount of vitamin D to a human being and is a composition consisting of a nutritional or therapeutic effective amount of 9 to 9000 mcg/ml vitamin D in a liquid triglyceride of 6 to 12

carbon chain length. The Directions on the exterior of the box and on the bottle state, “Infants less than 1 year old: Place 1 drop daily onto mother’s nipple or on a clean surface, such as a washed finger or a pacifier, and allow baby to suck for at least 30 seconds. Or mix one drop daily with milk, juice or other food.” One drop of the Patented Product adheres to the surface of mother’s nipple or a clean surface, such as a washed finger or a pacifier. In addition, the one drop consists of from 150 to 450 mcg/ml vitamin D in a liquid triglyceride of 6 to 12 carbon chain length and also the triglyceride has at least 95% triglycerides having a carbon-chain length selected from 8 to 10.

6. The Patented Product has received several prestigious awards, including: the Mom’s Choice Gold Award; a Parent tested – Parent approved<sup>TM</sup> award; the Bounty Mums Love “Commended” Award; the 2015 Well.ca Green Choice Award Winner; the 2016 National Parenting Product Awards Winner; and the 2015 Cribsie Awards New Arrival “Academy Star” Award. Attached as Exhibit C is a true and correct copy of the industry awards that have been awarded to the Baby Ddrops method and product as of May 26, 2017.

7. Ddrops’ Patented Product has been featured on “The Price Is Right” television program during the “It’s In The Bag” pricing game.

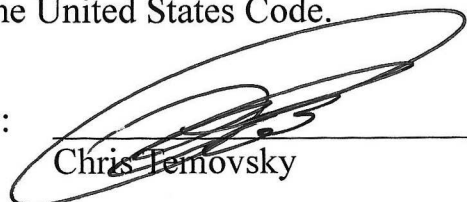
8. Baby Ddrops method and product and has received acclaim from scholarly publications, and researchers. Ddrops’ product and method has been the subject of

several clinical and institutional studies, which have confirmed its efficacy, with the results published in peer-reviewed journals such as Pediatrics and the Journal of Nutrition Studies. Attached as Exhibit D is a true and correct copy of a collection of journal articles published as of May 26, 2017.

9. I declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: June 28, 2023

By:



Chris Temovsky

# Temovsky Exhibit A

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF MINNESOTA

DDROPS COMPANY, REINHOLD VIETH,  
and ELAINE VIETH

Plaintiffs,

v.

iHERB, INC., and MADRE LABS, INC.  
d/b/a CALIFORNIA GOLD NUTRITION,

Defendants.

Civil No. 16-4278-JNE-TNL

**DECLARATION OF CHRIS  
TEMOVSKY**

I, Chris Temovsky, declare and state as follows under penalty of perjury:

1. I am the co-president of Plaintiff Ddrops Company (“Ddrops”). This declaration is based upon personal knowledge and my review of relevant company documents, unless otherwise indicated.

2. I have been co-president Ddrops since July 2008. My key areas of responsibility include overseeing sales, marketing, and distribution of our products. Those areas have remained essentially the same since I became co-president. As co-president, I have access to the books and records of Ddrops.

3. Ddrops is a partnership registered under the laws of Ontario, Canada, with its principal offices located in Woodbridge, Canada. I am one of the partners of Ddrops.

4. Reinhold and Elaine Vieth (“the Vieths”) are individuals who are citizens of Canada and reside in Toronto, Canada. I know them personally.

5. The Vieths are inventors and owners of certain inventions relating to vitamin D compositions and methods of administering such compositions to human beings (the “Inventions”).

6. The Vieths have received numerous patents world-wide on the Inventions, including, but not limited to, Canadian Patent No. 2,578,881 (the “Canadian Patent”), entitled “Vitamin D Compositions and Method of Administration to a Human Being,” which issued on November 4, 2008.

7. On June 30, 2015, the United States Patent and Trademark Office (USPTO) issued U.S. Patent No. 9,066,958 (“the ‘958 Patent”), entitled “Vitamin D Compositions and Method of Administration to a Human Being,” to the Vieths. The Vieths are the owners of the ‘958 Patent. A true and correct copy of the ‘958 Patent is attached as Exhibit A.

8. As of January 1, 2007, the Vieths granted an exclusive, world-wide license under all patents or patent applications relating to the Inventions to The Ddrops Company Inc., a Canadian corporation, including the right to enforce the patent against infringers and to collect damages (“the License”).

9. As of July 24, 2008, The Ddrops Company, Inc., with the consent of the Vieths, transferred and assigned its rights and obligations under the License to Ddrops. Since the time of the assignment, The Ddrops Company, Inc. has not engaged in business operations.

10. Ddrops pays an annual license fee and royalty to the Vieths on all sales of products covered by any of the patents included within the scope of the License, including the ‘958 Patent.

11. Ddrops sells vitamin D supplements, including vitamin D supplements for infants to be used according to the method(s) disclosed in one or more claims of the ‘958 Patent in the United States, including in the state of Minnesota (the “Patented Product”). Ddrops sells the Patent Product under the registered U.S. trademark “Baby Ddrops®”. Ddrops has sold the Patented Product in Minnesota since at least June 2011. Ddrops also sells Kids Ddrops®, Ddrops® Booster, Ddrops® for Adults, and Vegan Ddrops®, all of which are vitamin D supplements.

12. Since sales of the Patented Product began in the United States, Ddrops has marked the product packaging with the words “patent pending.” Since issuance of the ‘958 Patent, Ddrops has marked the product packaging with the notice, “U.S. Patent 9066958.” In or about October 2015, Ddrops began shipping the Patented Product with the ‘958 Patent number into the United States. True and correct photographs of the packaging with the ‘958 Patent number as sold into the United States are attached as Exhibit B.

13. The Patented Product has been the subject of several clinical studies, which confirmed its efficacy in providing vitamin D to infants. The results of these studies have been published in peer-reviewed journals, including in *Pediatrics* and the *Journal of Nutrition*. The Patented Product has also received several prestigious awards, including a Mom’s Choice Gold Award and a Parent tested – Parent approved™ award.

14. I believe that the sale of the Patented Products to parents and caregivers of infants provides an important introduction for long-term sales of vitamin supplements for older children and adults. Ddrops also sells vitamin D supplements for children as they grow older.

15. Since 2009, Ddrops's market share for the Patented Product in Canada has increased to approximately 60% through the end of 2016.

16. From 2013 to 2016, sales of the Patented Product increased 464% in the United States.

17. Since November 4, 2008, Ddrops and the Vieths have successfully enforced the Canadian Patent against various infringers in Canada. The various defendants in those actions have stipulated that the Canadian Patent is valid, enforceable, and infringed, and the infringers against whom actions were commenced in Canada stipulated to injunctions and have ceased sales of their infringing products in Canada.

18. In late 2015, Ddrops and the Vieths commenced a patent infringement action in this District and successfully enforced the '958 Patent against two infringers. Ddrops has continued to vigorously defend its patent rights for the '958 Patent in the United States.

19. In or about August 2013, Defendant iHerb began purchasing the Patented Product from Ddrops and began offering the Patented Product for sale throughout the United States, including in the state of Minnesota on its website iHerb.com. Between August 2013 and September 2016, sales to iHerb from Ddrops totaled over US\$8.64 million.

20. In 2014, Ddrops invested over US\$675,000 in marketing and advertising of the Patented Product in the United States. Year-to-date in 2016, Ddrops has invested nearly US\$2.25 million in marketing and advertising the Patented Product in the United States.

21. On October 5, 2015, Ddrops launched a nation-wide advertising and marketing campaign for the Patented Product in the United States. This campaign features advertising on the television program “Good Morning America,” which ran for the first time on October 5. The cost of this nation-wide advertising and marketing campaign in the United States is in excess of US\$1 million. Examples of the advertising Ddrops has run on “Good Morning, America” are attached as Exhibit C.

22. On or about August 11, 2016, I learned that iHerb was offering for sale and selling an identical product to the Patented Product in the United States. iHerb was offering this identical product for sale under the California Gold Nutrition (“CGN”) brand called “California Gold Nutrition Baby D<sub>3</sub> Liquid Vitamin D<sub>3</sub> for Babies 400 IU” (“the Infringing Product”). True and correct copies of photographs of the packaging for the Infringing Product and the Infringing Product bottle are attached as Exhibit D.

23. In August 2016, I also learned that iHerb’s purchases of the Patented Product from Ddrops had suddenly decreased significantly.

24. In August 2016, I learned that iHerb was using and had placed on its website a product comparison chart (the “Comparison Chart”), comparing the Patented Product and the Infringing Product. The Comparison Chart on iHerb’s website is shown

below.



| Product Comparison                                                       |  | BabyD3   | Ddrops®  |
|--------------------------------------------------------------------------|--|----------|----------|
| Vitamin D3 (as Cholecalciferol)                                          |  | ✓        | ✓        |
| 400 IU D3 Per Drop                                                       |  | ✓        | ✓        |
| Other Ingredient: Fractionated Coconut Oil                               |  | ✓        | ✓        |
| Servings Per Container                                                   |  | 300      | 90       |
| Manufactured & Processed in the U.S.A. in a NSF® GMP Registered Facility |  | ✓        | ?        |
| Triple Quality Tested                                                    |  | ✓        | ?        |
| 100% Guarantee                                                           |  | ✓        | ?        |
| Price                                                                    |  | \$17.50* | \$17.50* |

Ddrops® is a registered trademark of Ddrops Company. \*Prices may vary.

A true and correct copy of the Comparison Chart available on iHerb's website comparing the Patented Product and Infringing Product is attached as Exhibit E.

25. I consider the Comparison Chart false, misleading, and deceptive regarding its assertions relating to the Patented Product. For example, the Comparison Chart misleadingly uses “?” to cast doubt or questions regarding the quality and integrity of the Patented Product when compared to the Infringing Product. Ddrops tests its products for quality assurance, including the Patented Product. Ddrops is licensed with Health Canada, compliant with the Food and Drug Administration (“FDA”), and is a Public Health and Safety Organization (“NSF”) registered facility. A true and correct copy of licenses and compliance certificates with this information is attached as Exhibit F.

26. On or about September 30, 2016, iHerb stopped carrying and selling the Patented Product. True and correct copies of screenshots showing that the Patented Product is not currently available on iHerb's website are attached as Exhibit G.

27. In October 2016, Ddrops heard rumors that iHerb was falsely telling customers that Ddrops had gone out of business. On October 10, 2016, a customer wrote Ddrops via Facebook stating, “I usually purchase ddrops from iherb in the USA. And several days ago I got email from iherb that ddrops shut down the company in the US. May I know what’s going on? Anything to do with safety issue?” [*Sic*]. A true and correct copy of the Facebook message, dated October 10, 2016, is attached as Exhibit H.

28. Although it is no longer selling the Patented Product, iHerb is still using its Comparison Chart on iHerb.com to compare the Infringing Product to the Patented Product. *See* Exhibit E.

29. iHerb is targeting and marketing the Infringing Product directly against the Patented Product. Ddrops has never authorized iHerb’s current use of its marketing materials, trademarks, or any comparison of any Ddrops’ products, pricing, ingredients, or any advertisements regarding its company or the Patented Product.

30. By targeting and marketing the Infringing Product directly against the Patented Product, I believe that iHerb is seeking to capitalize on the significant marketing campaign, advertising, and reputation of Ddrops and its Patented Product to steal customers and sales from Ddrops, including sales of vitamins to older children and adults.

31. In September 2016, Ddrops purchased samples of the Infringing Product that were being sold in the United States through iHerb.com. On September 23, 2016, Ddrops sent samples of the Infringing Product to two testing laboratories in Canada, specifically Chemi Pharmaceutical Inc. (“Chemi”). Chemi completed the testing on the

Infringing Product and provided testing results and certificates of analysis to Ddrops.

The lab requisition form sent by Ddrops for this testing is attached as Exhibit I.

32. On November 1, 2016, Ddrops requested that Chemi conduct additional testing on the Infringing Product. Chemi completed the testing on the Infringing Product and provided testing results and certificates of analysis to Ddrops on November 17, 2016.

The lab requisition form sent by Ddrops for this testing is attached as Exhibit J.

Signed under penalty of perjury pursuant to 28 U.S.C. §1746.

Dated: December 14, 2016.

s/Chris Temovsky  
Chris Temovsky

# Exhibit A



US009066958B2

(12) **United States Patent**  
**Vieth et al.**

(10) **Patent No.:** **US 9,066,958 B2**  
(45) **Date of Patent:** **Jun. 30, 2015**

(54) **VITAMIN D COMPOSITIONS AND METHOD OF ADMINISTRATION TO A HUMAN BEING**

CA 2558202 A1 11/2006  
CA 2578881 A1 7/2007  
WO 0054838 A1 9/2000

(76) Inventors: **Reinhold W. Vieth**, Toronto (CA);  
**Elaine Vieth**, Toronto (CA)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1815 days.

(21) Appl. No.: **11/674,234**

(22) Filed: **Feb. 13, 2007**

(65) **Prior Publication Data**

US 2008/0069925 A1 Mar. 20, 2008

(30) **Foreign Application Priority Data**

Sep. 14, 2006 (CA) ..... 2558202

(51) **Int. Cl.**  
**A61K 31/59** (2006.01)

(52) **U.S. Cl.**  
CPC ..... **A61K 31/59** (2013.01)

(58) **Field of Classification Search**  
None  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

3,149,037 A \* 9/1964 Bauernfeind et al. .... 514/167  
4,248,867 A 2/1981 Ikushima  
5,532,229 A 7/1996 Vieth  
5,601,605 A \* 2/1997 Crowe et al. .... 606/236  
5,620,462 A 4/1997 Valenti  
6,638,978 B1 \* 10/2003 Kabara ..... 514/550  
2003/0099747 A1 5/2003 Eini  
2003/0104078 A1 6/2003 Barrett-Reis  
2003/0191093 A1 10/2003 Chen

**FOREIGN PATENT DOCUMENTS**

CA 2111271 A1 6/1994  
CA 2315224 A1 6/1999  
CA 2393357 A1 2/2003  
CA 2122431 10/2006

**OTHER PUBLICATIONS**

Fliszar et al. (J Pharma Biomed Anal, 40: 896-900, 2006).  
Vieth (<http://www.direct-ms.org/pdf/VitDVieth/Vieth%20Anthropology%20vit%20D.pdf>, Jan. 2006).  
Blass et al., Pain, 83: 611-623, 1999.\*  
Schleithoff et al., "Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized placebo-controlled trial", *Am J Clin Nutr*, 2006, pp. 754-759, vol. 8.  
Holmberg et al., "Absorption of a Pharmacological Dose of Vitamin D<sub>3</sub> From Two Different Lipid Vehicles in Man: Comparison of Peanut Oil and a Medium Chain Triglyceride", *Biopharmaceutics & Drug Disposition*, 1990, pp. 807-815, vol. 11.  
Supplementary European Search Report for corresponding European application (completed Jan. 12, 2012).  
Greer et al., Effects of Increased Calcium, Phosphorus, and Vitamin D Intake on Bone Mineralization in Very Low-Birth-Weight Infants Fed Formulas with Polycose and Medium-Chain Triglycerides, *The Journal of Pediatrics*, vol. 100, No. 6, Dec. 31, 1982, pp. 951-955.  
Scanlon, Vitamin D Expert Panel Meeting—Final Report, CDC Expert Panel Meeting, Oct. 11, 2001, retrieved from the Internet at URL [http://www.cdc.gov/nccdphp/dnpa/nutrition/pdf/Vitamin\\_D\\_Expert\\_Panel\\_Meeting.pdf](http://www.cdc.gov/nccdphp/dnpa/nutrition/pdf/Vitamin_D_Expert_Panel_Meeting.pdf), p. 21 (retrieved on Dec. 13, 2011).  
European Pharmacopoeia 4.0, Dec. 31, 2001, Directorate for the Quality of Medicines of the Council of Europe, pp. 2071-2072.  
Hart et al., Final Report of the Color Additive Scientific Review Panel, Risk Analysis, vol. 6, No. 2, 1986, p. 117-154.  
Wikipedia "Hypervitaminosis D", URL [http://en.wikipedia.org/wiki/Hypervitaminosis\\_D](http://en.wikipedia.org/wiki/Hypervitaminosis_D), p. 1-8, (2010).

\* cited by examiner

*Primary Examiner* — Bong-Sook Baek

(74) *Attorney, Agent, or Firm* — Jeffrey S. Melcher; Manelli Selter PLLC

(57) **ABSTRACT**

Composition of vitamin D in medium-chain triglycerides and use thereof in delivering a nutritional or therapeutic amount of vitamin D to a human being, particularly, an infant. The compositions are applied to an object, such as skin or in the case of an infant to a woman's nipple or pacifier from which the infant sucks off the composition. The method provides a more suitable, safer and efficient way of providing the human being with vitamin D. The compositions further comprise a free fatty acid and/or monoglyceride, oxidant preservative and, optionally, other vitamins.

**12 Claims, No Drawings**

US 9,066,958 B2

1

## VITAMIN D COMPOSITIONS AND METHOD OF ADMINISTRATION TO A HUMAN BEING

This application claims foreign priority under 35 U.S.C. 119 to Canadian Patent Application Serial No. 2,558,202, filed 14 Sep. 2006.

### FIELD OF THE INVENTION

This invention relates to compositions comprising vitamin D in a medium-chain triglyceride medium and use thereof for human beings, particularly, breast-feeding infants.

### BACKGROUND TO THE INVENTION

A balanced level of vitamin D has long been recognized as essential to health. Vitamin D appears to increase the efficiency of the intestines to absorb calcium and also mobilizes calcium from bone tissue when required. A deficiency in vitamin D leads to rickets, a debilitating bone disease while excessive intakes of vitamin D are toxic.

The skin is the major site of cholesterol production and humans acquire vitamin D through the natural action of ultraviolet light on the skin. 7-Dehydrocholesterol, which is unstable to ultraviolet light, is normally a precursor to cholesterol. However, ultraviolet light breaks open the B-ring of the 7-dehydrocholesterol molecule to generate previtamin D<sub>3</sub>, which spontaneously isomerizes over hours and days into vitamin D<sub>3</sub>, which is also known as cholecalciferol. An unknown proportion of the vitamin D from the skin is absorbed into the circulation. Vitamin D<sub>3</sub> is not soluble in water, and in the circulation, there is a protein that specifically binds to and carries vitamin D and its metabolites. The advantage of ultraviolet exposure is that it is natural, and has no vitamin D toxicity associated with it. The disadvantage is that the availability of ultraviolet light is unreliable, and too much of it causes sunburn or skin cancer. At northern latitudes there is often not enough ultraviolet light intensity outdoors to generate previtamin D.

For biological activity, vitamin D must go through two metabolic steps. Vitamin D is metabolized by the liver to 25-hydroxyvitamin D [25(OH)D], which is measured in serum to reflect vitamin D nutritional status. 25-hydroxyvitamin D per se has little biological activity. The kidney metabolizes 25-hydroxyvitamin D into the active hormone, 1, 25-dihydroxyvitamin D, which affects calcium transport across cell membranes. The body, according to its mineral requirements, carefully regulates production and breakdown of 1,25-dihydroxyvitamin D to regulate plasma calcium concentrations. Very few foods naturally contain vitamin D. Melanby, J Physiol (London) volume 52:1iii (1919), instituted the idea that an artificial supplement, cod-liver oil, contained an agent that prevented rickets; the agent became known as vitamin D. Most of the vitamin D in our food is supplementary, synthetic material, which is either in the form of vitamin D<sub>3</sub>, the form naturally produced in animals, or it can be vitamin D<sub>2</sub>, which is derived from a plant steroid. The term, vitamin D, refers to either the vitamin D<sub>2</sub> or vitamin D<sub>3</sub> forms.

Pediatric associations in Canada and the United States now strongly encourage starting vitamin D supplementation from birth onwards (Health Canada, Vitamin D supplementation for breastfed infants). Breast-feeding results in fewer infections and allergies during the first year of life compared to babies fed formula. Breast milk provides nearly optimal nutrition for newborns; however, it provides little vitamin D. Vitamin D has well-recognized effects on bone, but beyond

2

that, better vitamin D nutrition during infancy is associated with less risk of other diseases that develop later in life. These disease reductions include less risk of juvenile diabetes, and schizophrenia (Hypponen, E., Laara, E., Reunanen, A., Jarvelin, M. R., and Virtanen, S. M. (2001) *Lancet* 358, 1500-1503) (McGrath, J., Saari, K., Hakko, H., Jokelainen, J., Jones, P., Jarvelin, M. R., Chant, D., and Isohanni, M. (2004) *Schizophr. Res.* 67, 237-245). However, because it is normally obtained through sun exposure instead of orally, vitamin D is the one nutrient that is most often deficient in breast milk (Centers for Disease Control, Vitamin D Expert Panel Meeting, Oct. 11-12, 2001 Atlanta, Ga. Final Report).

In 2005, the American Academy of Pediatrics issued a new policy statement concerning breast-feeding (American Academy Of Pediatrics Policy Statement 2005; *Pediatrics* 115; 496-506). One major change was that all breast-fed infants should receive 200 IU (5 mcg) of oral vitamin D drops daily, beginning during the first 2 months of life. The older recommendation had been that vitamin D supplementation should start at around 2 months of life. The latest American Academy of Pediatrics recommendation follows what Health Canada has been advising, that vitamin D supplementation should be from birth, with 400 IU (10 mcg) of vitamin D per day (*Pediatrics* 2005; 115; 496-506). Moreover, Health Canada recommends that infants in the north be given 800 IU (20 mcg) of vitamin D per day.

The need to provide vitamin D at an earlier age makes the problem of providing vitamin D nutrition more complicated. Smaller infants are more difficult to handle. Furthermore, breast-feeding mothers may not want to give their infants foreign liquids or compounds that are not natural for them to be taking. What makes the problem worse, is that the recommendations from pediatric societies and government bodies provide no detail or any method for exactly how to give vitamin D to the breast-feeding infant. They simply advise that parents should be giving vitamin D.

Existing products, approved in Canada and the United States for the purpose of infant vitamin D nutrition require the use of one-half to one mL of a detergent-solubilized aqueous liquid emulsion. The liquid is either given directly into the mouth, or mixed into milk or to other food consumed by the infant. Instructions for administering vitamin D drops typically involve inserting the dropper containing the liquid product directly into the baby's mouth.

Parents of infants express great frustration about existing products and methods for providing infants with vitamin D, especially about the taste and the fact that infants often spit out at least some of the liquid. Direct administration of liquid vitamin D preparations is commonly done with an eyedropper, and with the infant lying on its back. One risk associated with direct administration of vitamin D solutions into the mouth is that infants can gag on, or inhale some of the liquid.

Vitamin D liquid drops usually contain other vitamins as well. One milliliter of these products contains 400 IU (10 mcg) of vitamin D. The aqueous vitamin D drops have only a 50-day shelf-life once the bottle is opened. They contain ingredients foreign to infant nutrition, and there are many complaints about the taste. One major problem is that infants spit out the 1 mL liquid vitamin drops. This creates a mess and the dose delivered to the infant is unreliable. For any therapeutic protocol, inconvenience, risk, and difficulty with administration result in lower compliance rates. Poor compliance results in under-dosing, and ineffective treatment. These factors also diminish nutrient supplementation with vitamin D. There are vitamin D drops available in oil, at 400 IU per drop in the United States (naturalhealthsupply.com). The vitamin D for this is dissolved in olive oil and/or corn oil

US 9,066,958 B2

3

and/or sesame or flax-seed oil. The problem with these is that the oils are comprised of long-chain unsaturated fatty-acid triglycerides that will become rancid with repeated opening of the container, they carry a flavor, and they have a greasy feel on a pacifier. Moreover, no product like this is advised for, nor advocated, nor used in any way for nutrition of the breast-feeding infant.

One prescription product contains vitamin D in an unspecified oil, (20,000 IU (500 mcg) per mL of oil). The method for use involves mixing two drops into to two drops in milk or mash. This is not a practical way to provide vitamin D for breast-fed infants younger than two months of age, because it presumes that nutrition is provided by some means other than the breast. Furthermore, this method is no different from what is done in North America with the 1-mL per day liquid vitamin drops that are administered to infants by mixing into milk or food by the same method.

U.S. Pat. No. 5,532,229, issued Jul. 2, 1996 to Vieth, Reinhold W., and Canadian Patent No. 2,122,431, issued Oct. 10, 2006 to Vieth, Reinhold W., describe a method of delivering vitamin D to the blood of a mammal by topically administering to the skin of the mammal, vitamin D in a solution. In principle, this method could be used to provide vitamin D to infants, via the skin, which is a safe and natural route of entry for this nutrient. For example, a skin lotion that contains vitamin D can be absorbed over time through the skin of the infant. For example, medium-chain triglycerides are useful as a skin lotion, and at the same time they can function as a solvent to deliver vitamin D. However, the efficacy of vitamin D delivery is problematic with this approach, because vitamin D could be wiped easily off the skin before it could be absorbed into the body.

U.S. Pat. No. 4,248,867, issued to Ikushima et al on Feb. 3, 1981 describes a method for manufacturing an oily preparation which comprises irradiating a triglyceride of saturated middle chain fatty acid(s) with light longer than 290 nm. This process alters the oil to be a solvent in which a selection of 1-alpha-hydroxy-vitamin Ds in the treated triglyceride can be dissolved and remain stable. These 1-hydroxy vitamin D's are either diol or triol compounds which are fundamentally different from vitamin D<sub>2</sub> and vitamin D<sub>3</sub>.

Notwithstanding the above teachings of the prior art, there remains a need for a safe, convenient and efficacious method of administering nutritional or therapeutic amounts of vitamin D to a human being, particularly, a suckling infant. There is also a utility for adults to be able to deliver a dose of vitamin D efficiently by sucking a vitamin supplement from a surface, instead of directly placing the supplement directly into the mouth.

#### SUMMARY OF THE INVENTION

In this specification and claims, the compound "vitamin D" means (5Z-7E)-(3S)-9,10-seco-5,7,10(19)-cholestatrien-3-ol also having the trivial names cholecalciferol or calciol (D3); and ergocalciferol (D2).

It is an object of the present invention to provide an improved, suitable, safer and efficient method of providing a nutritional or therapeutic effect amount of Vitamin D to a human being, particularly, a suckling infant.

It is a further object is to provide Vitamin D compositions for use in said method.

A composition and method has been developed which involves the application of a vitamin D composition to a human being from the surface of an object that is a suitable and efficient method of administration of a desired amount of vitamin D to the human being.

4

The human being may be an adult or an infant. The term "infant" in this specification includes babies and small children, and the term "adult" includes non-small children.

In the case of administration of the compositions according to the invention to an infant, the method comprises the application of, preferably, one drop of a solution of vitamin D in a suitable, biologically-acceptable oil carrier in the case of an infant onto a mother's nipple or onto a pacifier, and placing it into the mouth of an infant for, preferably, at least 30 seconds, to suck the vitamin D composition off the nipple or pacifier, to thereby consume the vitamin D. In the case of an adult, one or more drops may be applied to the skin of an arm or a knuckle of the hand of the adult who then licks or sucks the composition from the skin.

We have found that the difficulties with the aforesaid previous ways of providing vitamin D to an infant can be overcome by the process of application of vitamin D in a one-drop (about 33 microliter) volume of medium-chain triglyceride oil onto a pacifier or nipple and into the mouth of a suckling infant. This process of nipple or pacifier application eliminates the need to risk over-exposure of the infant to ultraviolet light in order to acquire in vivo vitamin D. Furthermore, the process of nipple or pacifier application eliminates the need to administer vitamin D directly into the mouth with a dropper, or in a larger volume that infants commonly spit out or gag on, or have to take with food.

The process of the present invention can improve compliance by parents to government and medical recommendations to supplement their infants with vitamin D. Implementation of the invention to improve vitamin D supplementation may lower risk of disease for the infant, which, on a broader scale, should benefit public health.

It is highly desirable, though not an essential consideration, that the medium-chain triglyceride is a natural constituent of breast milk since such oil use does not introduce a compound foreign to breastfeeding. Furthermore, medium-chain triglycerides are naturally present in milk fat and are hydrolyzed by lipase present in the saliva of the infant. The medium-chain free fatty acids and monoglycerides released by the action of lipase in the saliva of the infant provide the additional benefit of an antimicrobial action, and play a role in resistance to infectious diseases (M. K. M. Nair 2005 J. Dairy Sci. 88:3488-3495)(CQ Sun 2002 Chemico-Biological Interactions 140: 185-198)(AC Pedersen, A Bardow, SB Jensen, B Nauntofte 2002. Oral Diseases 8:117-129).

Thus, in a preferred aspect, the compositions of the present invention may further comprise said free fatty acids, particularly C<sub>6</sub>-C<sub>12</sub> carbon-chain compounds, to provide an antimicrobial effect.

We have found that the inventive method of indirect application of vitamin D to a pacifier or nipple, or knuckle can provide vitamin D nutrition to a human with an efficiency of vitamin D delivery by sucking that is in the range acceptable for accuracy of a supplement product labeled dose, with about 4% loss as residual vitamin D remaining on the nipple or pacifier, compared to direct placement of vitamin D into the mouth.

The vitamin D compositions of use in the invention may further comprise an antioxidant to serve as a preservative for the vitamin D, or to provide additional nutrition. Examples of such fat-soluble nutrients are vitamin E, vitamin A, vitamin K, or carotene.

The amount of vitamin D in the composition of use in the practice of the invention may be readily selected to be that amount which provides suitable effects on the circulating concentration of 25-hydroxyvitamin D. For example, a daily single dose on a nipple or pacifier may contain from 2-300

US 9,066,958 B2

5

mcg per drop (equivalent to 60 mcg/mL to 9,000 mcg/mL of oil), preferably 5 to 20 mcg per drop (150 mcg/mL to 600 mcg per mL). The stronger compositions are useful for pediatricians who could use them to provide vitamin D as a single-drop dose at each monthly neonatal visit. Thereby, the mother, herself, would not have to deal with vitamin D application.

Accordingly, in one aspect the invention provides a composition comprising vitamin D in liquid, triglycerides of 6 to 12 carbon chain lengths medium for use in delivering a nutritional or therapeutic amount of said vitamin D to a human being from the surface of an object having said composition on said surface to be sucked from said surface by said human being.

Preferably, the composition comprises 9 to 9,000 mcg/ml vitamin D and, more preferably, 150 to 450 mcg/ml vitamin D.

The medium chain triglycerides of use in the practice of the invention have carbon-chain lengths of 6-12 and, preferably, the composition medium comprises at least 95% triglycerides having a carbon-chain length selected from 8-10.

Medium-chain triglycerides are obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. or from the dried endosperm of *Elaeis guineensis* Jacq. They consist of a mixture of triglycerides of saturated fatty acids, mainly of caprylic acid ( $C_8H_{16}O_2$ ) and of capric acid ( $C_{10}H_{20}O_2$ ). They contain not less than 95 percent of saturated fatty acids having 8 to 10 carbon atoms. The substance is a clear solution.

In a most important embodiment, the invention provides a composition as hereinabove defined for use in delivering a nutritional or therapeutic amount of said vitamin D directly into the mouth of an infant from the surface of an object having said composition on said surface to be sucked from said surface by said infant.

Fatty acid composition—The fatty acid fraction of medium-chain triglycerides exhibits the following composition, as determined in the section *Fatty Acid Composition*. Any peak with an area less than 0.05% of the total area, was disregarded.

| Carbon-Chain Length | Number of Double Bonds | Percentage (%) |
|---------------------|------------------------|----------------|
| 6                   | 0                      | ≤2.0           |
| 8                   | 0                      | 50.0-8.0       |
| 10                  | 0                      | 20.0-50.0      |
| 12                  | 0                      | ≤3.0           |
| 14                  | 0                      | ≤1.0           |

To be useful in the practice of the present invention, the vitamin D containing medium, needs to meet many of the aforesaid criteria. Surprisingly we have discovered that the medium-chain triglycerides satisfy these criteria.

In preferred embodiments, the invention provides a composition as hereinabove defined further comprising a compound selected from the group consisting of a free fatty acid

6

and a monoglyceride, preferably, a composition wherein the compound is selected from the group consisting of caprylic acid, caprylic monoglyceride and monocaprylin, at a concentration selected from 0.1 to 20 w/w % medium, preferably, 1 to 10% w/w % medium.

In further preferred embodiments, the invention provides an oxidant preservative, and/or a nutritionally effective amount of a fat-soluble vitamin selected from the group consisting of alpha-tocopherol (vitamin E), vitamin A, vitamin K and B-carotene.

In a further aspect, the invention provides use of a composition as hereinabove defined for the use in delivering a nutritional or therapeutic amount of vitamin D directly from the surface of an object having the composition thereon to be licked or sucked therefrom by a human being, particularly, an infant.

In a particular aspect, the invention provides a method of using a composition as hereinabove defined comprising (i) applying said composition to a surface of an object; and (ii) inserting said object into the mouth of an infant as to allow said infant to suck said composition from said object surface.

Most preferably, in the case of an infant, the object is a woman's nipple or a pacifier

#### DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

In order that the invention may be better understood, preferred embodiments will now be described by way of example only.

#### EXAMPLE 1

The medium-chain triglycerides of use in this invention are liquids that are sufficiently viscous so that one drop does not immediately drip or roll away from the part of the nipple or pacifier that enters the mouth of an infant. The liquid does not coat or adhere to the pacifier so as to prevent efficient removal of the vitamin D from the nipple or pacifier through sucking. The liquid has minimal sensory effects i.e. it has minimal smell, taste, or texture i.e. no oily feel. The liquid is biologically natural in the context of breast-feeding, and is safe for infant consumption. The liquid per se is not subject to rancidity or oxidation over the shelf-life of the composition. Further, it is a medium in which vitamin D does not degrade and, thus, allows of a long shelf life for vitamin D.

This experiment involved the study of a number of liquids to determine their efficiency in the practice of the invention.

One drop of each liquid was applied onto a nipple to determine whether it would adhere well enough so that no portion of it would drip off in a timeframe of 10 seconds. The results of these experimental observations are presented in Table 1 along with further considerations regarding the parameters desired for this invention.

TABLE 1

| Experimental observation of potential liquids for suitability for nipple vitamin D |                                                 |                    |                         |                    |                                   |                                                |                        |
|------------------------------------------------------------------------------------|-------------------------------------------------|--------------------|-------------------------|--------------------|-----------------------------------|------------------------------------------------|------------------------|
| Vehicle for vitamin D                                                              | Experiment drop behavior on nipple <sup>#</sup> | Taste <sup>#</sup> | mouth-feel <sup>#</sup> | taste <sup>#</sup> | Stability of vitamin D in vehicle | Stability of solvent with storage <sup>#</sup> | present in breast milk |
| Water                                                                              | drips off                                       | None               | none                    | none               | Poor <sup>#</sup>                 | Stable                                         | Yes                    |
| water-based emulsion (D-vi-sol)                                                    | drips off                                       | Yes                | no feel                 | strong taste       | 50-days on opening*               | Stable                                         | No                     |

US 9,066,958 B2

7

8

TABLE 1-continued

| Experimental observation of potential liquids for suitability for nipple vitamin D |                                                 |                    |                         |                    |                                    |                                                |                        |
|------------------------------------------------------------------------------------|-------------------------------------------------|--------------------|-------------------------|--------------------|------------------------------------|------------------------------------------------|------------------------|
| Vehicle for vitamin D                                                              | Experiment drop behavior on nipple <sup>#</sup> | Taste <sup>#</sup> | mouth-feel <sup>#</sup> | taste <sup>#</sup> | Stability of vitamin D in vehicle  | Stability of solvent with storage <sup>#</sup> | present in breast milk |
| Ethanol                                                                            | drips off                                       | Yes                | no feel                 | strong taste       | Solvent concentration <sup>#</sup> | Evaporates                                     | No                     |
| Canola oil                                                                         | Adheres                                         | Mild               | Oily                    | mild               | Stable                             | Oxidizes/rancidity                             | No                     |
| Olive oil                                                                          | Adheres                                         | Yes                | Oily                    | mild               | Stable                             | Oxidizes/rancidity                             | No                     |
| Sesame oil                                                                         | Adheres                                         | Yes                | Oily                    | strong taste       | Stable                             | Oxidizes/rancidity                             | no                     |
| Eitamin E acetate oil                                                              | Adheres                                         | None               | Oily                    | none               | Uncertain                          | Stable                                         | no                     |
| Medium-chain triglyceride                                                          | Adheres                                         | None               | slightly oily           | none               | stable >3 yr <sup>#</sup>          | Stable                                         | yes                    |

<sup>#</sup>Direct experimental observation.<sup>\*</sup>Mead-Johnson published stability statement for D-vi-sol.

Water based preparations and alcohol did not adhere to the nipple. The oil vehicles all adhered to the nipple well enough to make them suitable for handling during breastfeeding or for use of a pacifier. However, residual oily feel on the pacifier was interpreted as a sign of incomplete uptake of the drop with its dose from the pacifier. We found that medium-chain triglyceride oil was particularly desirable.

## EXAMPLE 2

This experiment was to determine the efficacy of the uptake of vitamin D in the composition and method through the mouth by sucking and into the body.

A further problem that needed to be addressed was the matter of whether vitamin D dissolved in a liquid vehicle would be removed by sucking and enter the body of the human in an efficacious manner. For this, vitamin D in a solution of medium-chain triglyceride was applied, according to the invention, to pacifiers. One drop of an approximate volume of 33 microliters was applied onto pacifiers, Gerber Nuk™ sizes 1 (small, for newborns) and 3 (for older infants). As the measure of 100% recovery, 33 microliters of vitamin D in medium-chain triglyceride (60,000 IU/33 microliters) was added to 50 mL ethanol directly, or placed onto a pacifier, which was placed in ethanol. To estimate efficiency of removal of the vitamin D, pacifiers were sucked by humans for 30 seconds, and the pacifier was then placed entirely into an 80-mL beaker containing 50 mL ethanol to extract remaining vitamin D. It is important to note that the extraction of remaining vitamin D from the pacifier into ethanol was not immediate. The pacifiers were extracted for 30 min, otherwise measurement of the remaining vitamin D would have been underestimated, with overestimation of efficiency of delivery into the mouth. High-pressure liquid chromatography with absorbance detection at 265 nm of 100 microliters of the ethanol extracts from each of seven such experiments showed that vitamin D remaining on the pacifier comprised a mean of 4%+/-2% SD of the vitamin D applied to the pacifier. Therefore, delivery of the vitamin D applied to a pacifier or to a nipple and taken up into the mouth within half a minute is sufficiently reproducible and complete so as to permit a dose printed on the label of a vitamin supplement product to be claimed as being accurate. Government regulations mandate that vitamin supplements for humans must provide between 90% and 120% of the labeled doses. The dosage loss with the method according to the invention, is accommodated inside

that acceptable range, so that the dose that the label states to be present in one drop of product is an appropriate measure of the dose delivered into a human.

## EXAMPLE 3

This experiment shows that if the invention truly functioned as intended, the serum 25-hydroxyvitamin D [25(OH)D] should increase in response to the intake of vitamin D according to this invention.

Vitamin D<sub>3</sub> was added to medium-chain triglyceride oil to a concentration of 0.4 g per 10 mL. One drop of this had a volume of 33 microliter, and contained 1500 mcg of vitamin D<sub>3</sub>. This is a relatively high dose which was used to elicit a rapid 25(OH)D response that could not be attributed to other factors. Three humans, who had not taken vitamin D supplements during the previous month each sucked on a pacifier for 30 sec, Gerber Nuk™-brand pacifiers, to which one drop of the vitamin D<sub>3</sub> solution in medium-chain triglyceride oil had been applied. Blood samples had been drawn prior to the experiment, and 48 h after taking the dose of vitamin D according to the present invention. Without vitamin D, there could have been no detectable change in serum 25(OH)D concentration in the short timeframe of 48 h. We found that the serum 25(OH)D increased in each human. In the three humans, the mean increase from baseline was 12 nmol/L (the individual increases in serum 25(OH)D were 5, 10 and 20 nmol/L). The results were consistent with the uptake of the vitamin D from the pacifier into the human body. This experiment confirmed the efficacy of the method of the present invention.

## EXAMPLE 4

Crystalline vitamin D<sub>3</sub> (cholecalciferol, United States Pharmacopeia grade) was dissolved into oil of medium chain triglyceride (United States Pharmacopeia grade), to make a solution, according to the invention, containing 300 mcg vitamin D per one mL of oil. This composition was bottled in a glass container closed with a Eurodropper cap, with an opening designed to dispense 30 drops per one mL of oil. A breast-feeding mother applied one drop of the solution to the nipple just before offering her breast to her infant to suckle. To ensure complete delivery of the dose, the infant sucked for 30 seconds.

## US 9,066,958 B2

## 9

## EXAMPLE 5

Crystalline vitamin D3 (cholecalciferol, United States Pharmacopea grade) was dissolved into oil of medium chain triglyceride (United States Pharmacopea grade), to make a solution, according to the invention, containing 300 mcg vitamin D per one mL of oil. This composition was bottled in a plastic container with a dropper opening to dispense one drop of oil. A mother applied one drop of the solution to a pacifier or the nipple of a baby bottle just before putting it into the mouth of her infant to suck. To ensure complete delivery of the dose, the infant sucked for 30 seconds.

## EXAMPLE 6

Crystalline vitamin D3 (cholecalciferol, United States Pharmacopea grade) was dissolved into an oil of medium chain triglycerides (United States Pharmacopea grade), to make a solution containing 300 mcg vitamin D per one mL of oil. This was bottled in a glass container closed with a Euro-dropper cap, with an opening designed to dispense 30 drops per one mL of oil. The human being applied one drop of the solution to a knuckle of a hand from which the vitamin D was sucked into the mouth. To ensure complete delivery of the dose, the human sucked for 30 seconds.

Although this disclosure has described and illustrated certain preferred embodiments of the invention, it is to be understood that the invention is not restricted to those particular embodiments. Rather, the invention includes all embodiments which are functional or mechanical equivalents of the specific embodiments and features that have been described and illustrated.

The invention claimed is:

1. A method of delivering a nutritional or therapeutic amount of vitamin D to a human being, said method comprising:

- (i) applying one drop of a composition consisting of a nutritional or therapeutic effective amount of 9 to 9000 mcg/ml vitamin D in a liquid triglyceride of 6 to 12 carbon chain length, to an exterior surface of an object, wherein said drop adheres to the surface of said object; and
- (ii) having said human being suck or lick said composition directly from said object.

2. A method as claimed in claim 1, wherein said human being is an adult and said object is the skin of an arm or hand of said adult.

3. A method as claimed in claim 1, wherein said human being is an infant and said object is a woman's nipple or the external surface of a pacifier.

## 10

4. A method according to claim 1, wherein the composition consists of from 150 to 450 mcg/ml vitamin D in a liquid triglyceride of 6 to 12 carbon chain length.

5. A method according to claim 1, wherein said triglyceride comprises at least 95% triglycerides having a carbon-chain length selected from 8 to 10.

6. A method of delivering a nutritional or therapeutic amount of vitamin D to a human being, said method comprising:

- (i) applying one drop of a composition consisting of a nutritional or therapeutic effective amount of 9 to 9000 mcg/ml vitamin D, and a compound selected from the group consisting of a free fatty acid, a monoglyceride and an anti-oxidant preservative, in a liquid triglyceride of 6 to 12 carbon chain lengths, to an exterior surface of an object, wherein said drop adheres to the surface of said object; and
- (ii) having said human being suck or lick said composition directly from said object.

7. A method according to claim 6, wherein said compound is selected from the group consisting of caprylic acid, caprylic monoglyceride and monocaprylin.

8. A method according to claim 6, wherein said compound is at a concentration selected from 0.1% to 20% w/w of total weight of the composition.

9. A method according to claim 6, wherein said compound is at a concentration selected from 1% to 10% w/w of total weight of the composition.

10. A method of delivering a nutritional or therapeutic amount of vitamin D to a human being, said method comprising:

- (i) applying one drop of a composition consisting of a nutritional or therapeutic effective amount of 9 to 9000 mcg/ml vitamin D, and a nutritionally effective amount of a fat-soluble vitamin, in a liquid triglyceride of 6 to 12 carbon chain lengths, to an exterior surface of an object, wherein said drop adheres to the surface of said object; and
- (ii) having said human being suck or lick said composition directly from said object.

11. A method as claimed in claim 10 wherein said fat-soluble vitamin is selected from the group consisting of alpha-tocopherol (vitamin E), vitamin A, vitamin K and  $\beta$ -carotene.

12. A method according to claim 1, wherein the composition consists of 300 mcg/ml vitamin D in a liquid triglyceride of 6 to 12 carbon chain length.

\* \* \* \* \*

# Exhibit B

Baby



**Ddrops<sup>®</sup>**  
BRAND

The sunshine vitamin  
in just one drop<sup>®</sup>



Liquid  
**vitaminD<sub>3</sub>**  
Dietary supplement  
90 drops for 90 days



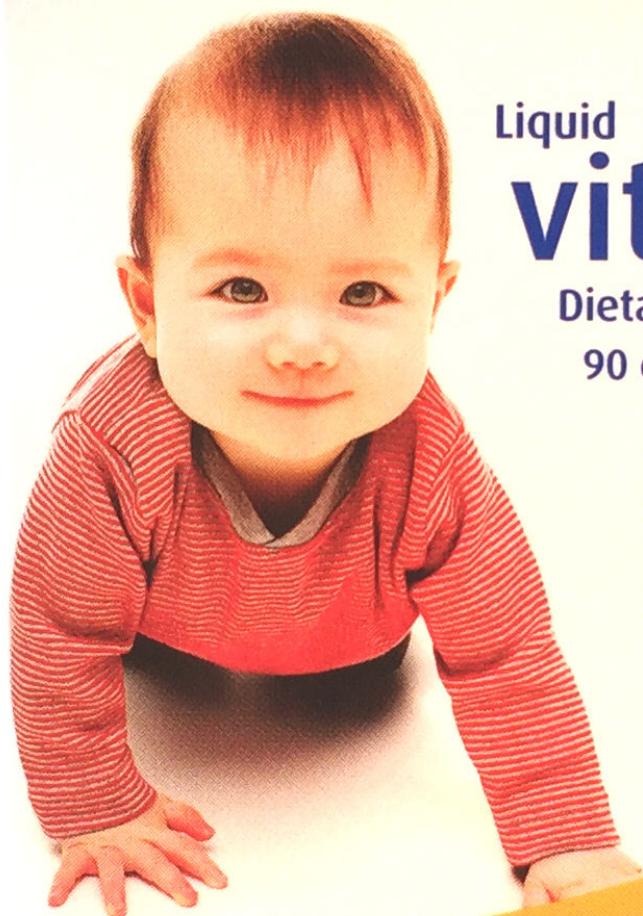
Babies need  
vitamin D for healthy  
growth and development.

Contains no preservatives,  
no artificial flavors,  
no coloring.

**400 IU**  
per drop

**90 drops** 2.5 mL (0.08 fl. oz.)

Baby  
**Ddrops**<sup>®</sup>  
The sunshine vitamin  
in just one drop<sup>®</sup>



Liquid  
**vitaminD<sub>3</sub>**  
Dietary supplement  
90 drops for 90 days



**400 IU**  
per drop

Babies need  
vitamin D for healthy  
growth and development.  
Contains no preservatives,  
no artificial flavors,  
no coloring.

**90 drops** 2.5 mL (0.08 fl. oz.)

Baby  **Ddrops<sup>®</sup>** BRAND  
The sunshine vitamin<sup>®</sup>  
in just one drop

**DO NOT USE IF SEAL ON BOTTLE IS BROKEN. READ INSTRUCTIONS BEFORE USING.**

## Supplement Facts

Serving Size: 1 drop (0.028 mL or 0.001 fl. oz.)

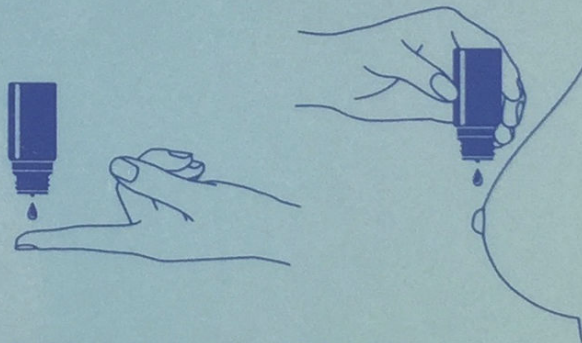
|                                 | Amount Per Drop | % Daily Value |
|---------------------------------|-----------------|---------------|
| Vitamin D3<br>(Cholecalciferol) | 400 IU          | 100%          |

### Other ingredients:

Fractionated coconut oil.

Baby Ddrops® **does not contain** corn, casein, dairy, egg, fish, gluten, lactose, peanuts, shellfish, soy, starch, sugar, sulphites, wheat, yeast, preservatives, coloring or artificial flavors.

**Directions:** Infants less than 1 year old: Place 1 drop daily onto mother's nipple or on a clean surface, such as a washed finger or a pacifier, and allow baby to suck for at least 30 seconds. Or mix one drop daily with milk, juice or other food.



SPECIFICALLY DESIGNED FOR  
BREAST-FED BABIES.

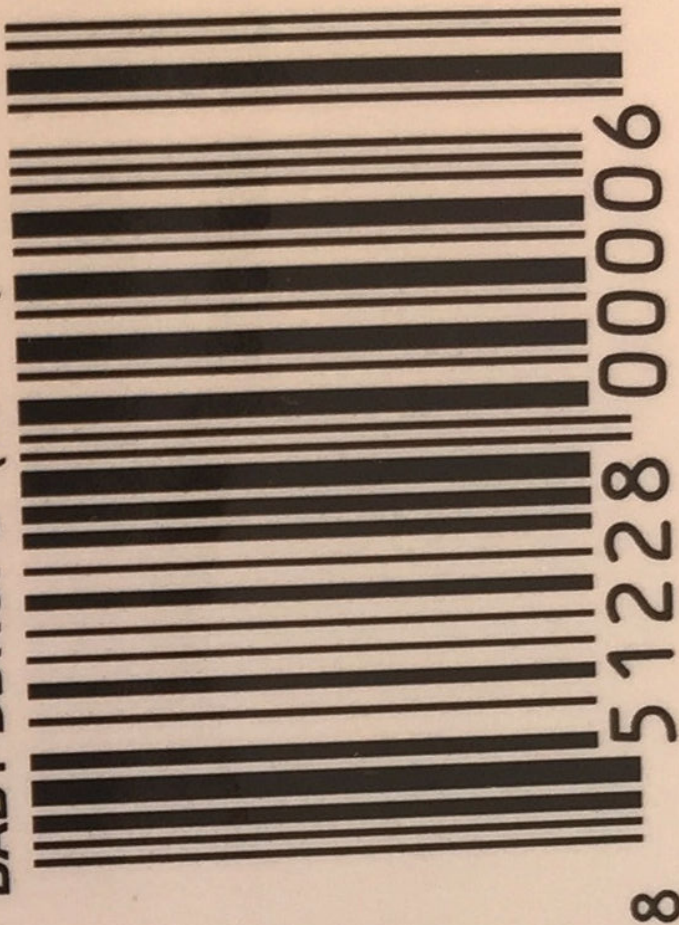
**See insert for more information.**

**STORE BOTTLE UPRIGHT AND BETWEEN  
40°F & 85°F. KEEP OUT OF REACH OF  
CHILDREN.**

**FOR SALE IN USA ONLY**

0200005 EX 09-2009  
U.S. PATENT 9066959

BABY DDROPS® (400 IU) 90 DROPS



Vitamin D is important for healthy growth and development in infancy and childhood especially for normal bone growth and muscle strength.\*

The American Academy of Pediatrics recommends that infants who are breast-fed or partially breast-fed should be supplemented with 400 IU of vitamin D daily.\*

Ddrops Company  
Woodbridge, ON L4L 5Z4 Canada  
**[www.DdropsCompany.com](http://www.DdropsCompany.com)**

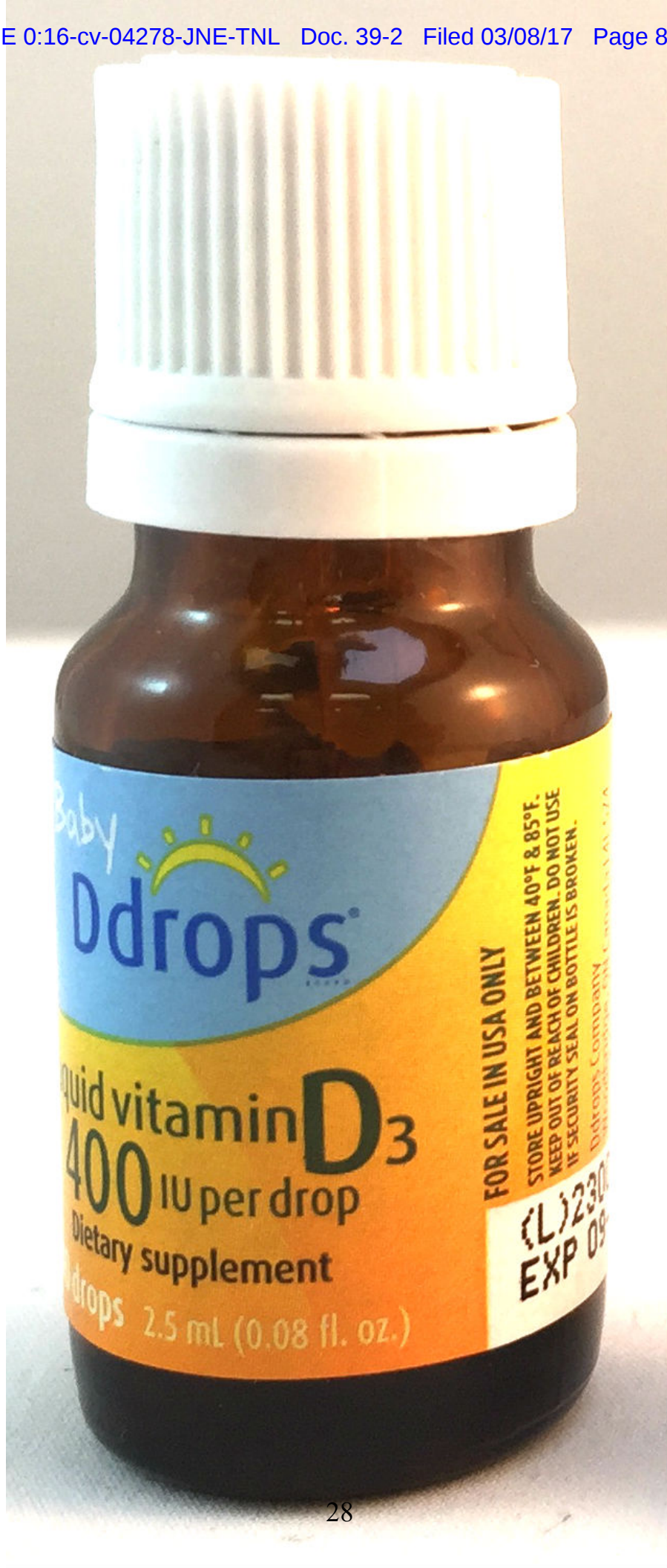
Registered TM of Ddrops Company

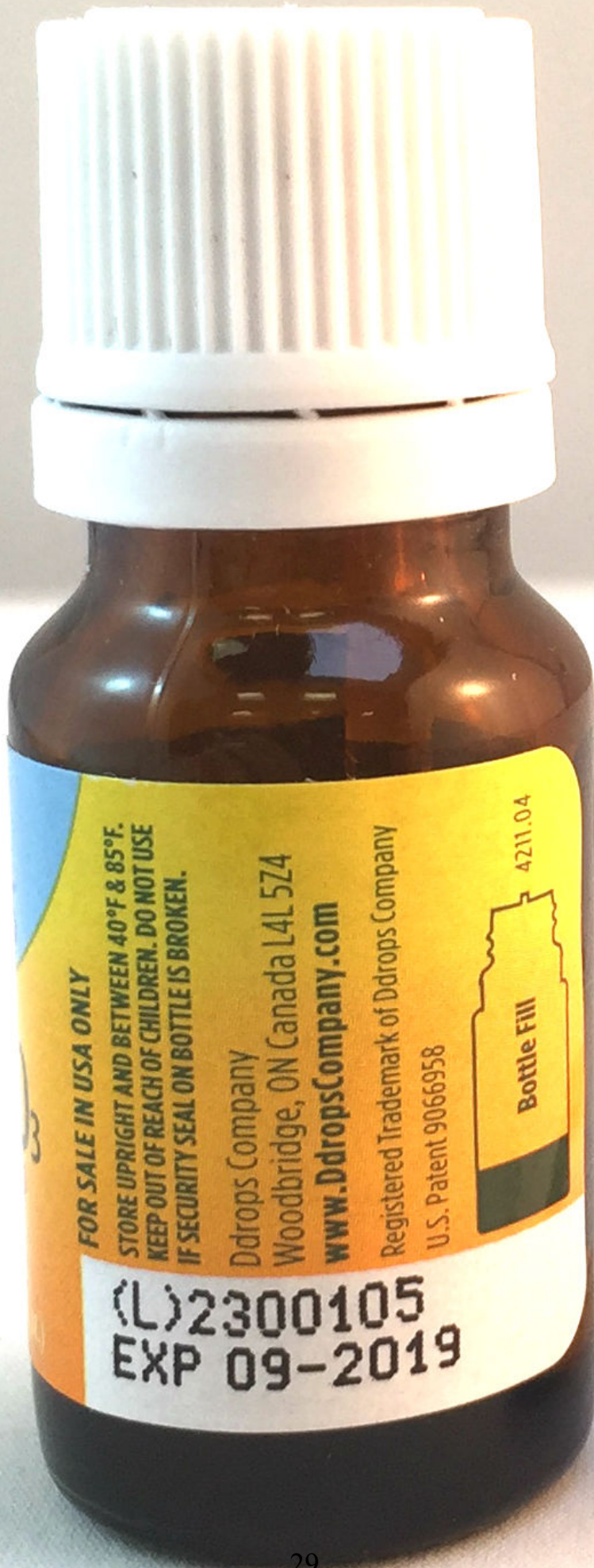
Patent Pending

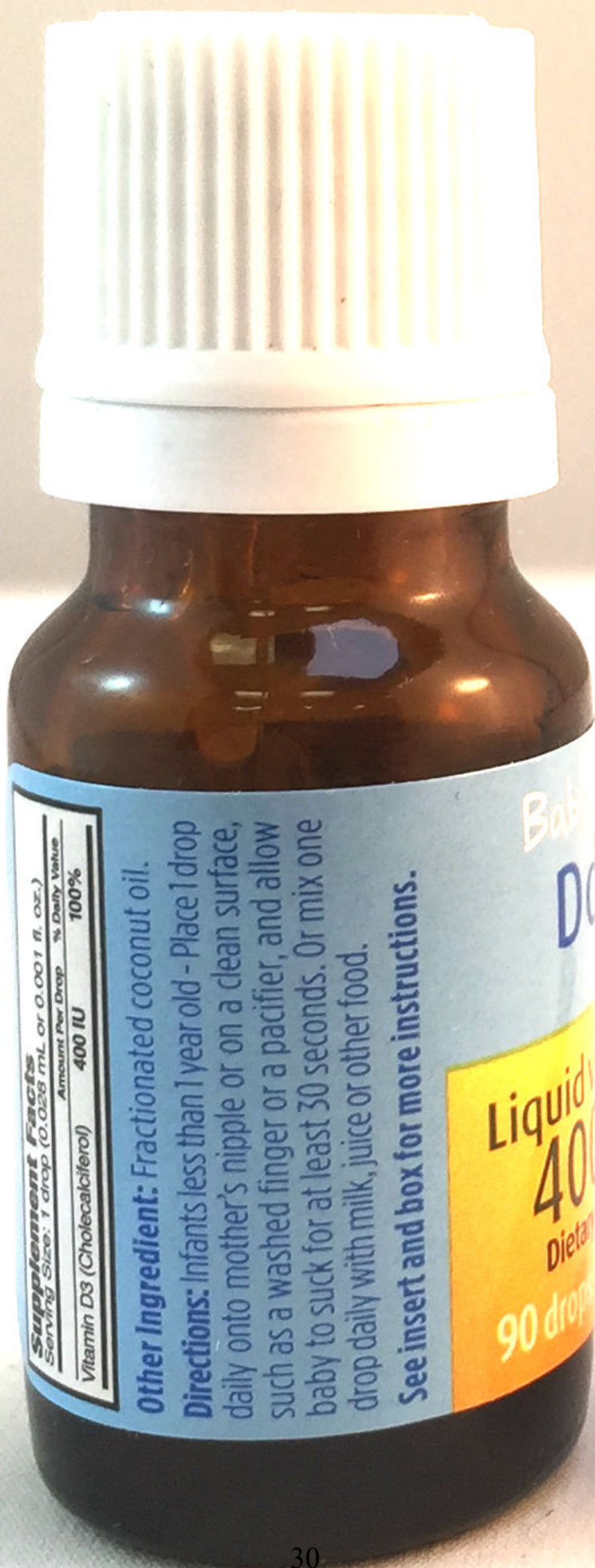
The Mom's Choice Awards Honoring Excellence logo is a trademark of the Mom's Choice Awards.



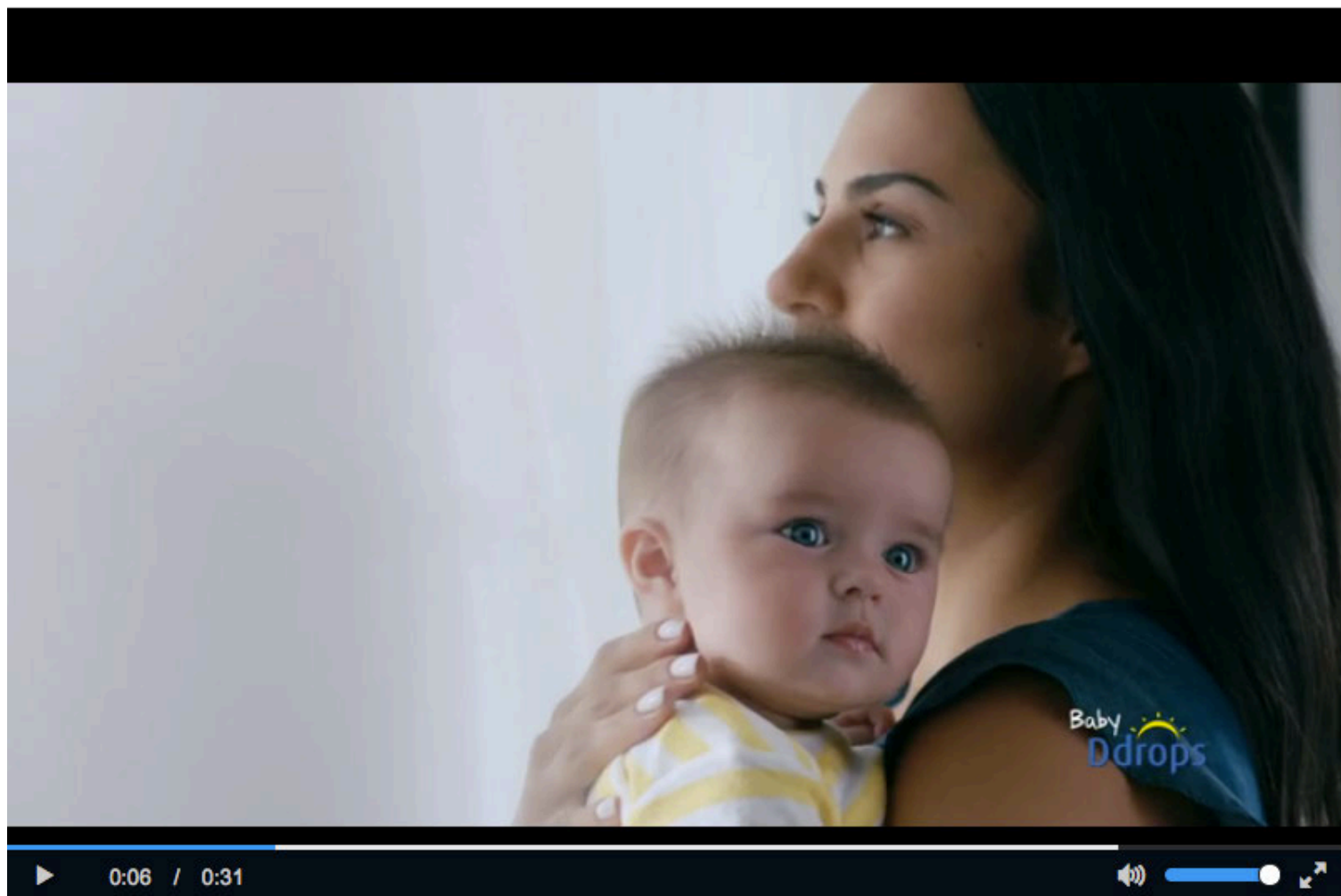
\* These statements have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent any disease.







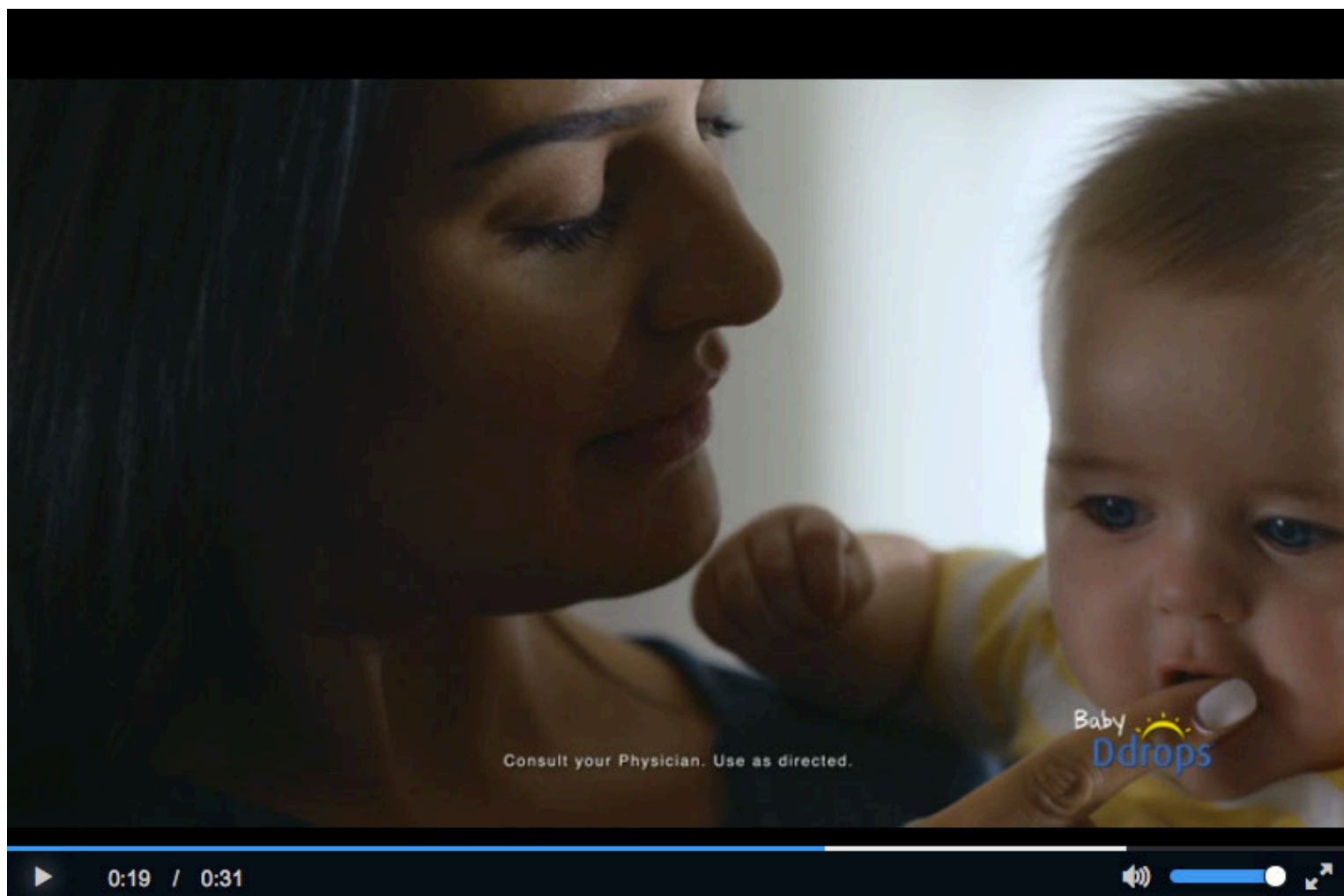
# Exhibit C













**Baby Ddrops**  
The sunshine vitamin in just one drop<sup>®</sup>

**Baby Ddrops**  
Liquid vitamin D<sub>3</sub>  
400 IU per drop  
60 drops

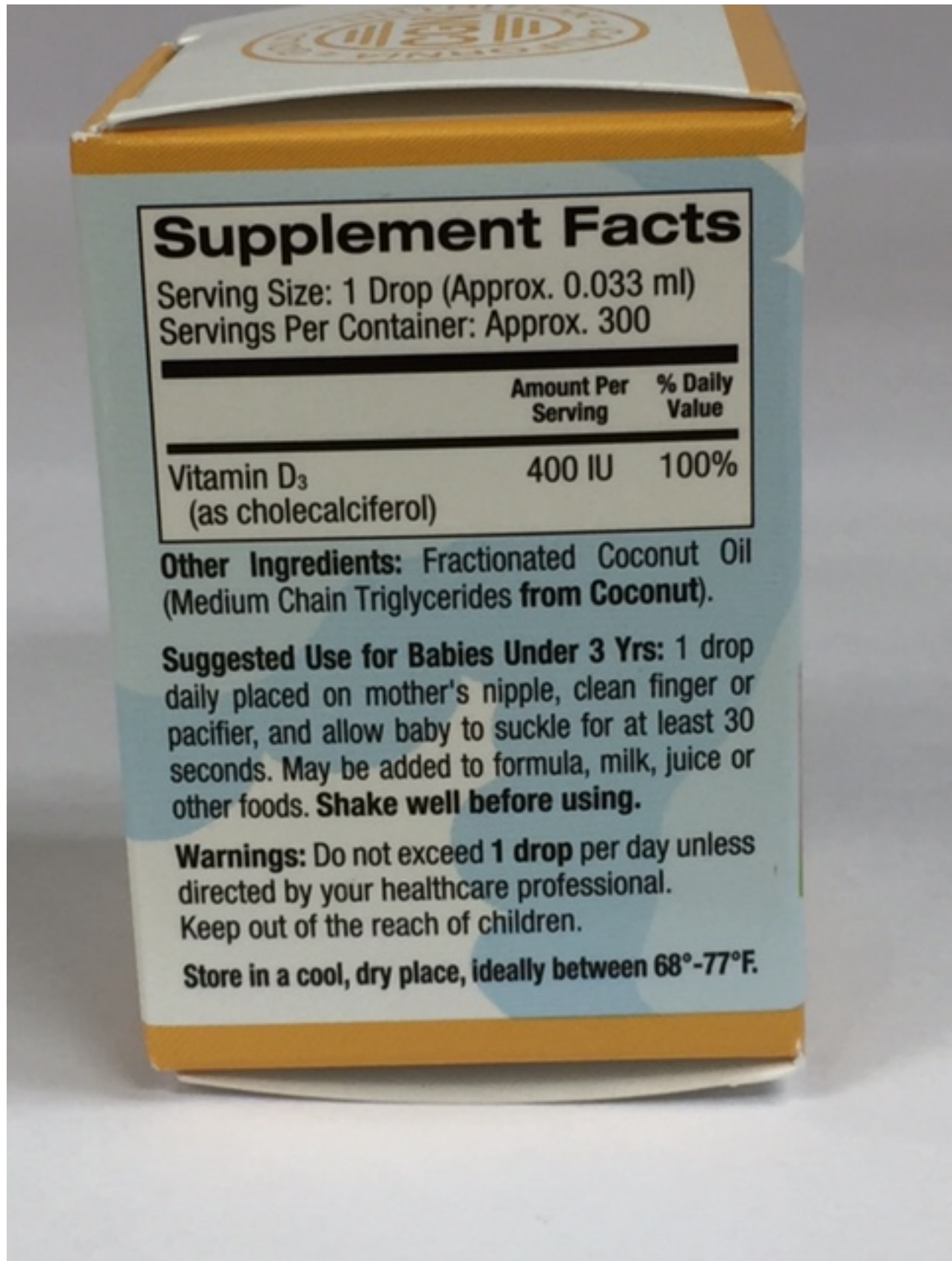
**vitaminDdrops.com**

These statements have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent any disease. U.S. Patent 9066958.  
TM ©2015 Ddrops Company. All Rights Reserved. Ddrops is a registered trademark of Ddrops Company. The Mom's Choice Awards Honoring Excellence logo is a trademark of the Mom's Choice Awards.

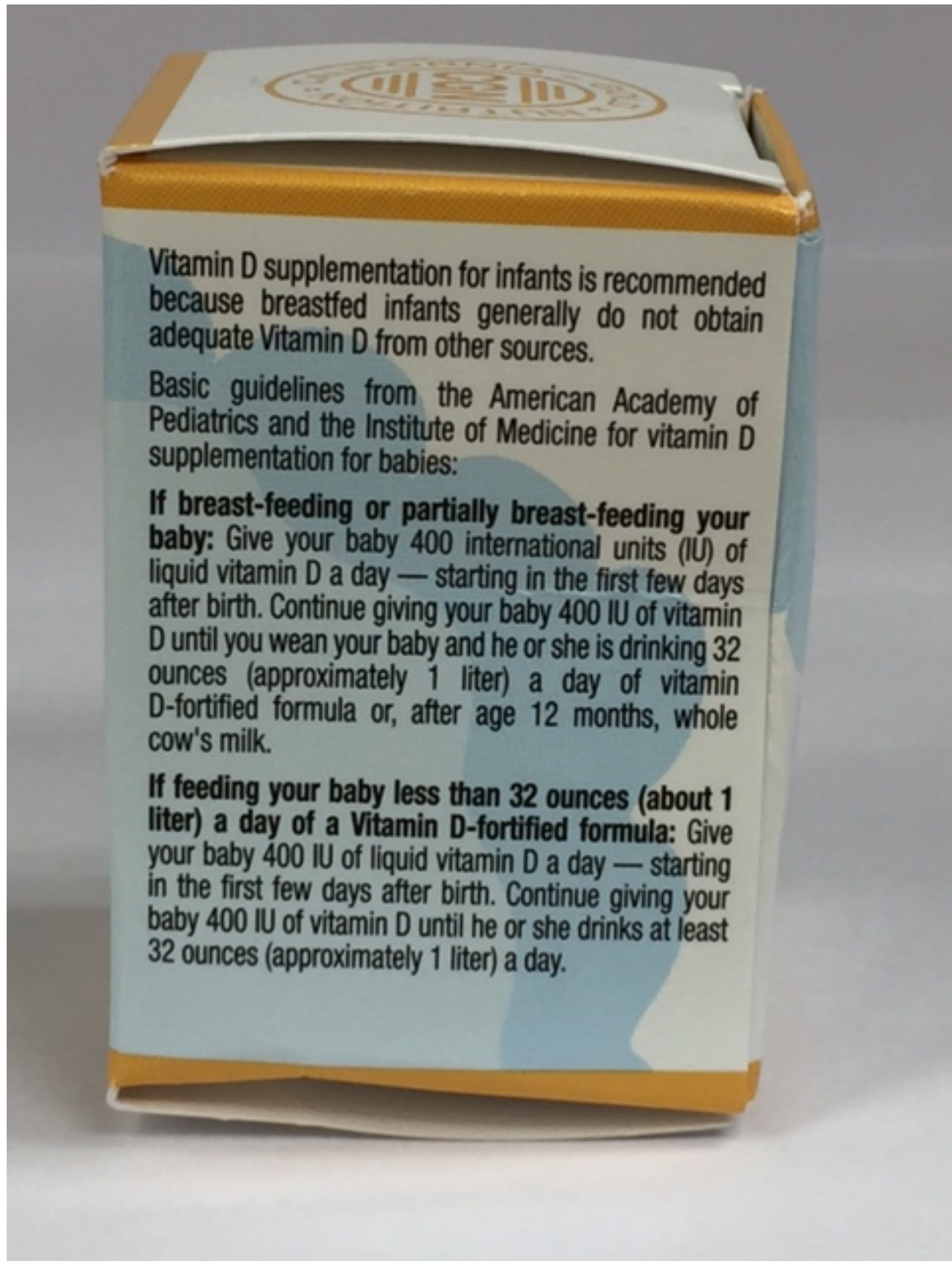
0:29 / 0:31

# Exhibit D









Vitamin D supplementation for infants is recommended because breastfed infants generally do not obtain adequate Vitamin D from other sources.

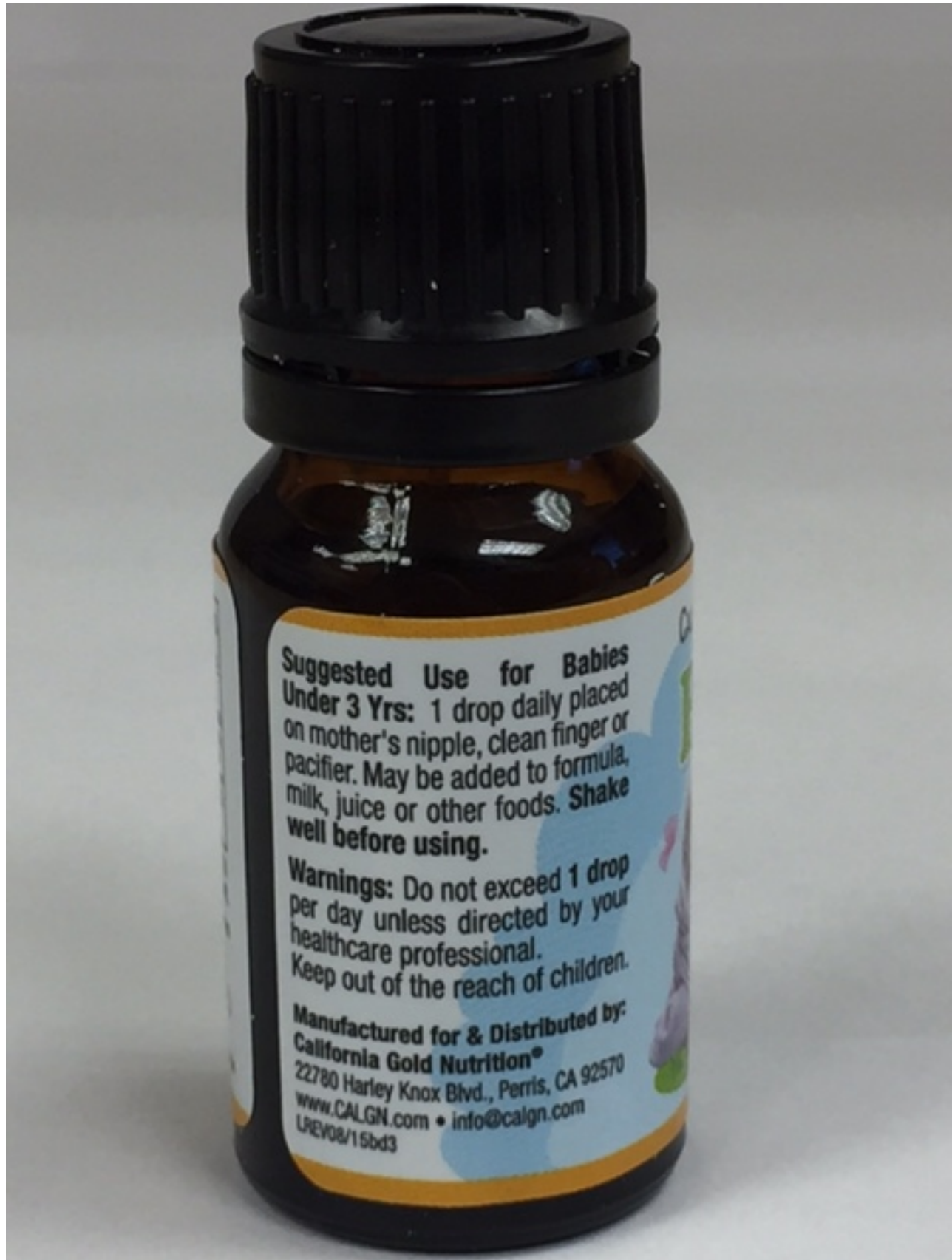
Basic guidelines from the American Academy of Pediatrics and the Institute of Medicine for vitamin D supplementation for babies:

**If breast-feeding or partially breast-feeding your baby:** Give your baby 400 international units (IU) of liquid vitamin D a day — starting in the first few days after birth. Continue giving your baby 400 IU of vitamin D until you wean your baby and he or she is drinking 32 ounces (approximately 1 liter) a day of vitamin D-fortified formula or, after age 12 months, whole cow's milk.

**If feeding your baby less than 32 ounces (about 1 liter) a day of a Vitamin D-fortified formula:** Give your baby 400 IU of liquid vitamin D a day — starting in the first few days after birth. Continue giving your baby 400 IU of vitamin D until he or she drinks at least 32 ounces (approximately 1 liter) a day.











# Exhibit E

New Products | Best Sellers | Gift Giving Ideas | Daily & Weekly Specials | Try & Save

EN USD

iHerb®

Search from over 35,000 products

0

Supplements | Herbs | Bath | Beauty | Grocery | Baby | Sports | More | Conditions

Categories > Vitamins > Vitamin D3 > Vitamin D3, Liquid > California Gold Nutrition, Infant Vitamin D3

### California Gold Nutrition, Infant Vitamin D3



Product Comparison

|                                                                          |          |          |
|--------------------------------------------------------------------------|----------|----------|
| Vitamin D3 (as Cholecalciferol)                                          | ✓        | ✓        |
| 400 IU D3 Per Drop                                                       | ✓        | ✓        |
| Other Ingredient: Fractionated Coconut Oil                               | ✓        | ✓        |
| Servings Per Container                                                   | 300      | 90       |
| Manufactured & Processed in the U.S.A. in a NSF® GMP Registered Facility | ✓        | ?        |
| Triple Quality Tested                                                    | ✓        | ?        |
| 100% Guarantee                                                           | ✓        | ?        |
| Price                                                                    | \$17.50* | \$17.50* |

CALIFORNIA GOLD NUTRITION®

BabyD3

Ddrops

Ddrops® is a registered trademark of Ddrops Company.\*Prices may vary

Ratings

★ ★ ★ ★ ★ (0)

★ ★ ★ ★ ☆ (1)

★ ★ ★ ★ ☆ (0)

★ ★ ★ ☆ ☆ (0)

★ ★ ☆ ☆ ☆ (0)

Price

Min

Max

>

0 - \$5 (0)

0 - \$10 (0)

0 - \$20 (1)

0 - \$50 (0)

0+ (0)

1-1 of 1

Exclude Discontinued

Search Within

Search

Sort By

Best Sellin



California Gold Nutrition, Baby Vitamin D3, 400 IU, .34 fl oz (10 ml)

★★★★★ 58

50

Shipping Weight ▲

☐ 0 - 0.1 lb (0)

☐ 1 - 0.2 lb (1)

☐ 2 - 0.3 lb (0)

☐ 3 - 0.4 lb (0)

☐ 4 lb + (0)

\$17.50

SHOP. SHARE. EARN.

Become an iHerb customer and earn unlimited Rewards by sharing your favorite iHerb products with others.

Get Rewarded Now ▶

CONNECT WITH US



STAY IN THE LOOP

Sign up to our Email list and receive exclusive offers.

Email Address

▶

HAVE A QUESTION?

Find answers from knowledge base.

Get Help Now »



ABOUT IHERB

About Us

Why shop at iHerb?

We Give Back

Eco Friendly Initiatives

Careers

Suppliers

IHERB RESOURCES

iHerb Blog

iHerb Library

My iHerb Page

Healthy Links

MOBILE APPS





CUSTOMER SERVICE

Contact Us

Privacy Policy

Terms of Use

Supply Chains Act

Tuesday, Nov 29, 2016, 11:38 AM PST

iHerb.com © Copyright 1997-2016 iHerb Inc. All rights reserved. iHerb® is a registered trademark of iHerb, Inc. Trusted Brands. Healthy Rewards. and the iHerb.com Trusted Brands. Healthy Rewards. Logo are trademarks of iHerb, Inc. \*Disclaimer: Statements made, or products sold through this website, have not been evaluated by the United States

Food and Drug Administration. They are not intended to diagnose, treat, cure or prevent any disease. [Read More »](#)



# Exhibit F



The Public Health and Safety Organization

**NSF Product and Service Listings**

These NSF Official Listings are current as of **Tuesday, December 20, 2016** at 12:15 a.m. Eastern Time. Please contact NSF International to confirm the status of any Listing, report errors, or make suggestions.

Alert: NSF is concerned about fraudulent downloading and manipulation of website text. Always confirm this information by clicking on the below link for the most accurate information: <http://info.nsf.org/Certified/GMP/Listings.asp?CertName=ddrops&>

---

**Good Manufacturing Practices Registration  
Dietary Supplements**

This is a Registration by NSF International that this company is in compliance with Good Manufacturing Practices (GMP) as set forth in NSF/ANSI 173-2013, Dietary Supplements, Section 8. These requirements are consistent with the published GMP regulation for dietary supplements as defined in 21 CFR § 111, which was published by the FDA in June 2007.

---

**Ddrops Company**  
126 Trowers Road  
Woodbridge, ON L4L 5Z4  
Canada  
905-851-8898

**Manufacturing Facility**

Ddrops Company  
126 Trowers Road  
Woodbridge, Ontario L4L 5Z4  
Canada

---

Number of matching manufacturers is 1  
Processing time was 1 seconds

# Exhibit G

New Products Best Sellers **Gift Giving Ideas** Daily & Weekly Specials Try & Save

EN USD ▼



Search from over 35,000 products



Supplements

Herbs

Bath

Beauty

Grocery

Baby

Sports

More

Conditions



We are sorry. The Web address you entered is not a functioning page on our site.

Please Visit iHerb's [Home Page](#).

**SHOP. SHARE. EARN.**

Become an iHerb customer and earn unlimited Rewards by sharing your favorite iHerb products with others.

[Get Rewarded Now ▶](#)

#### CONNECT WITH US



#### STAY IN THE LOOP

Sign up to our Email list and receive exclusive offers.

Email Address



#### HAVE A QUESTION?

Find answers from knowledge base.

[Get Help Now](#)



#### ABOUT IHERB

[About Us](#)

[Why shop at iHerb?](#)

[We Give Back](#)

#### IHERB RESOURCES

[iHerb Blog](#)

[iHerb Library](#)

[My iHerb Page](#)

#### MOBILE APPS



[Eco Friendly initiatives](#)[Careers](#)[Suppliers](#)[Healthy Links](#)**CUSTOMER SERVICE**[Contact Us](#)[Privacy Policy](#)[Terms of Use](#)[Supply Chains Act](#)

---

Tuesday, Nov 29, 2016, 11:47 AM PST

iHerb.com © Copyright 1997-2016 iHerb, Inc. All rights reserved. iHerb® is a registered trademark of iHerb, Inc. Trusted Brands. Healthy Rewards. and the iHerb.com Trusted Brands. Healthy Rewards. Logo are trademarks of iHerb, Inc. \*Disclaimer: Statements made, or products sold through this website, have not been evaluated by the United States Food and Drug Administration. They are not intended to diagnose, treat, cure or prevent any disease. [Read More](#)



# Exhibit H



**Phoebe Pan**

[View Profile](#)

Actions ▼

---

OCT 10TH, 11:56PM

Hi, I usually purchase ddrops  
From iherb in the USA. And several  
days ago I got email from iherb that  
ddrops shut down the company in the  
US. May I know what's going on?  
Anything to do with safety issue?  
Your website couldn't open the US  
region.



# Exhibit I



The sunshine vitamin in just one drop

Ddrops Company

# Lab Requisition

Date: Nov 30, 2016

**Ship to:**

Chemi Pharmaceutical Inc.  
1435 Bonhill Road #38  
Mississauga ON  
L5T 1V2

**Bill to:**

Ddrops Company  
126 Trowers Road  
Woodbridge ON L4L 5Z4  
905-851-8898

Sample to be Tested

Active Ingredient

|                |                        |                 |
|----------------|------------------------|-----------------|
| <b>Baby D3</b> | <b>Lot # 201519793</b> | Cholecalciferol |
|----------------|------------------------|-----------------|

| Test Item # | Test Description                           | Specifications | Test Requested |
|-------------|--------------------------------------------|----------------|----------------|
| 1           | Description                                |                | X              |
| 2           | Identification for Cholecalciferol, Test C |                | X              |
| 3           | Assay                                      |                | X              |
| 4           | Fatty Acid Composition                     |                |                |
|             | 4.1 C-Chain 6                              |                | X              |
|             | 4.2 C-Chain 8                              |                | X              |
|             | 4.3 C-Chain 10                             |                | X              |
|             | 4.4 C-Chain 12                             |                | X              |
|             | 4.5 C-Chain 14                             |                | X              |
|             |                                            |                |                |
|             |                                            |                |                |
|             |                                            |                |                |
|             |                                            |                |                |
|             |                                            |                |                |
|             |                                            |                |                |

Authorized by: Yen Ho

Date:

Please contact Ddrops at 905-851-8898 with any questions or concerns.

# Exhibit J

The sunshine vitamin in just one drop  
Ddrops Company

Date: Nov 30, 2016

Ship to:

Chemi Pharmaceutical Inc.  
1435 Bonhill Road #38  
Mississauga ON  
L5T 1V2

**Bill to:**

Ddrops Company  
126 Trowers Road  
Woodbridge ON L4L 5Z4  
905-851-8898

Sample to be Tested

Active Ingredient

|         |                 |                 |
|---------|-----------------|-----------------|
| Baby D3 | Lot # 201519793 | Cholecalciferol |
|---------|-----------------|-----------------|

[illegible]

Authorized by: Yen Ho

Date:

# Temovsky Exhibit B

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF MINNESOTA

DDROPS COMPANY, REINHOLD VIETH,  
and ELAINE VIETH

Plaintiffs,

v.

iHERB, INC. and MADRE LABS, INC.,  
d/b/a CALIFORNIA GOLD NUTRITION,

Defendants.

Civil Action No. 16-4278-JNE-  
TNL

**THIRD DECLARATION OF  
CHRIS TEMOVSKY**

I, Chris Temovsky, declare and state as follows under penalty of perjury:

1. I am the co-president of Plaintiff Ddrops Company (“Ddrops”). This declaration is based upon personal knowledge, my review of relevant company documents, and my review of the Defendants’ Response in Opposition to Plaintiffs’ Renewed Motion for a Preliminary Injunction, including the Defendants’ accompanying declarations and exhibits for their opposition (Docs. 66-71), unless otherwise indicated.

2. For years prior to 2006, and even after Ddrops entered the market, vitamin D supplements for infants generally consisted of one-half to one mL of a detergent-solubilized aqueous liquid emulsion. This concentration was typically given directly into the mouth or mixed into milk or other food for consumption by the infant. Instructions for administering these vitamin D drops typically involved inserting a plastic or glass dropper containing the liquid product directly into an infant’s mouth for delivery.

3. The previous products often had a bad taste and infants often spit out at least some of the products in reaction. Additionally, one of the risks associated with such

administration methods was that of the infant gagging on, or inhaling, of some of the liquid, which could cause harm or even death to the infant. Many products used oils comprised of unsaturated fatty-acid triglycerides that became rancid over time, carried an unpleasant or displeasing flavor, and had a greasy feel.

4. In or about 2006, in health food channels, and from 2008 onwards in the food/mass/drug channels, vitamin D supplements for infants were dominated by 1 mL products. The market leader was DI-VI-SOL, produced by Mead Johnson and various private label forms of that product.

5. Vitamin D is an essential vitamin for human development and is especially important in infants and young children. A deficiency in vitamin D can lead to rickets, a debilitating bone disease. In addition, excessive intake of vitamin D is toxic. Many companies in the medical, pharmaceutical and nutrition industries had long worked to develop a product that would provide an effective and safe amount of vitamin D for infants.

6. The Vieths understood that for many years, if not decades, a long-felt, but unmet need had existed to administer a therapeutically effective amount of vitamin D<sub>3</sub>, especially in infants, in a safe and easy manner.

7. The Vieths discovered a solution to the problems that previous products had. They invented a novel and unexpectedly successful method of administering an improved, suitable, safer and efficient nutritional or therapeutic amount of vitamin D to infants. The introduction of the Ddrops product in Canada was revolutionary.

8. The Ddrops patented method and product represented a radical departure from the “1 mL products” with the introduction of a “1 drop” administration concept. This new format allowed for far simpler delivery of a superior product in terms of its pharmaceutical elegance and simplicity. Ddrops’ “one-drop” administration concept was a radical departure from the “one mL” products, such as the previous market leader, DI-VI-SOL.

9. The Ddrops patented method and product innovatively introduced a safe and simple way of delivering a metered dose of vitamin D exactly where a baby feeds while reducing the risk of miss-delivery or aspiration. This risk is illustrated by a recent incident in France in early 2017, which resulted in the death of an infant following administration of a “1 mL product”, which in turn led to a suspension of sales of that product in France. Initially, Ddrops had great difficulty getting stores to stock its products due to their skepticism and reluctance to take on such a revolutionary product.

10. When Ddrops first began marketing its Baby Ddrops® product in earnest in 2008, the product had zero market share. After introduction of Baby Ddrops®, the market leader (Mead Johnson) essentially dismissed Ddrops as a small and inconsequential competitor.

11. As a result of the commercial success of the Ddrops patented method and product, Ddrops now has the largest market share in Canada of over 60%, and leading market shares in other countries in which it sells its product. In the U.S., Ddrops’ market share increased 222.5% from 2013 to 2014. From 2013 through 2016, sales of the Baby Ddrops® increased 464% in the U.S.

12. The Crocker, *et al.* article in the peer-reviewed journal *BMC Public Health* concluded: “Interestingly 80% of care-givers reported giving their infants D-Drops® versus only 16% who supplemented with D-Vi-Sol. ... The reason for the popularity of D-Drops® may be their ease of administration requiring only a single drop that can be placed on the mother’s breast prior to nursing, versus the need to use a dropper to administer D-Vi-Sol®.” This conclusion shows that the Ddrops patented method has directly influenced and is related to, the successful world-wide sales of the Baby Ddrops product. Attached as Exhibit A is a true and correct copy of this article.

13. Aside from publications and many awards, numerous “actual” or “potential” competitors have copied the Ddrops patented method and product. None of these entities (over one dozen), when demanded to cease and desist from infringement, or when sued for patent infringement, have maintained a meritorious invalidity defense. Such entities and defendants have included companies such as: Jamp Pharma, Innotech Nutrition, Nutralab-Wal-Mart, Swiss Herbal, Drugstore.com, and Walgreens. Indeed, in all such cases, the defendants have agreed to remove their infringing product and packaging from the market, have consented to entry of an injunction against further infringement, and/or have paid damages to the Plaintiffs, thus evidencing acquiescence by competitors.

14. In early 2014, iHerb became Ddrops’ largest buyer for its Baby Ddrops® product for international sales. From August 2013 through September 2016 iHerb sales totaled over US\$8.64 million in the U.S. *See* Doc. 39, ¶19. Ddrops therefore began to promote iHerb and its website as an “authorized” seller of the Baby Ddrops® product.

Ddrops also began to promote iHerb and its website as an “authorized” seller of the Baby Ddrops® product on social media platforms, and in direct communications with customers, physicians, and potential purchasers.

15. I have worked in the pharmacy, health, wellness, and vitamin supplement industry for nearly 30 years. I have often been tasked to understand purchasing and consumption behaviors of consumers regarding products and supplements. I use this information to make quality, marketing, and advertising decisions, as well as considerations for future business development and distribution.

16. At trade shows, meetings, advertisement campaigns, and health conferences, I often speak with customers, repeat customers, consumers, parents, and physicians about the Baby Ddrops® product. Individuals often tell me success stories regarding the efficacy and ease of use of the Ddrops patented method and product. Parents routinely tell me that because they loved Baby Ddrops® with their first child, they continued to use it for their subsequent children.

17. In my experience and observation of consumer behaviors, first time users of any new product read and follow directions. Users of any product typically read the instructions, ingredients, directions, and label information prior to the first-time use. For example, an adult administering a product to a vulnerable individual, like an infant, would likely read the label and directions of a product thoroughly, perhaps even multiple times, prior to first time administration.

18. However, users usually will not re-read directions or instructions after first or second time use of a new product. Consumers are typically “creatures of habit”,

meaning most consumers follow an unvarying routine. In other words, if a consumer routinely uses a product in a certain way, he or she will likely use the product according to the way he or she has in the past, which would likely be in accordance with the original instructions read prior to first use. This is especially true for products that instruct a “daily” or frequent use.

19. This same routine is also true for consumers who (after first time use) continue to subsequently repurchase and generally “subscribe” to a product. For example, an adult re-administering a product to an infant, who has frequently repurchased the product, would administer the product the way he or she had done previously. With repetitive and continued product use and purchases over a span of days, months, or years, it would be highly unlikely that an adult would re-read labels and directions before subsequent administrations. Instead, it is more likely that an adult will continue to use the product according to the way he or she has in the past.

20. The above behaviors would also be true for those who administer the Ddrops’ patented method and product. These behaviors would also be true for those who administer the “California Gold Nutrition Baby D3 Liquid Vitamin D3 for Babies 400 IU” (“the iHerb Product”).

21. For example, following the first review of directions and first administration, a single bottle purchaser of the iHerb Product will likely continue to practice the directions for the life of the bottle. The iHerb Product customer could routinely administer the product from a single bottle purchase for over one calendar year, with over 300 servings contained in one bottle of the iHerb Product.

22. Not only would current iHerb Product customers likely administer the contents of one bottle for over a year, but, customers who buy multiple bottles, or who continue to repeatedly purchase the product, would administer the product according to the originally read directions for several years. Even if the iHerb Product label and directions changed *today*, it is likely that customers who had previously used the iHerb Product (even once), would continue to follow the product's previous instructions.

23. This is especially harmful to the Plaintiffs and the Ddrops patented method and product because one bottle of the iHerb Product (300 servings) is over three times the serving size per bottle of the Ddrops patented method and product (90 servings). Thus, every sale by iHerb or CGN of one of the iHerb Products represents nearly four lost unit sales to Ddrops. Furthermore, with far more doses in a bottle, a customer would need to replace the iHerb Product less frequently than Baby Ddrops®. This also means that the infringing iHerb Product directions could sit in commerce, and on consumer shelves, for years.

24. Even after the start of this litigation, and deceptive representations regarding their "intent" to sell the iHerb Product in the future, the Defendants' conduct in the market has continued to harm the Plaintiffs. Not only were the Defendants' previous promises on their future "intent" meaningless, but also their actions in the market display their actual intent, where they have played fast and loose by manipulation of the market and their prices. These games are to the direct, on-going detriment to the Plaintiffs, and to the Baby Ddrops® product.

25. When this litigation commenced in December 2016, the Defendants apparently sold the iHerb Product for their advertised “full manufacturer's suggested retail price” (“MSRP”) on iHerb.com. In my experience, an advertised full MSRP price means that the purchaser will pay the full asking price of the product.

26. In January 2017, the Defendants significantly reduced the price and advertised “26% off MSRP”. A 26% discount off MSRP is a significant savings for a potential purchaser, and typically drives purchasing because of the sale. In my experience, retailers will offer a discounted sale item for a limited time, and then return the item to full MSRP or asking price. Limited discounts are used as promotions, and can drive sales.

27. Although promotions or infrequent discounts off MSRP are not unusual, I found it particularly troubling that iHerb continued this significant 26% discount for the iHerb Product for *over four months*. From January 2017 through April 2017, iHerb advertised 26% off MSRP for the iHerb Product world-wide.

28. A prolonged or essentially permanent discount on products can negatively impact entire markets, including the health, wellness, vitamin, and supplementation industries. In my experience, when a competitor prolongs or permanently lowers its prices of a product, the entire market for the product can shift due to competition and need for profits. Therefore, competitors to the permanently reduced product will be forced to lower their prices in order to maintain sales. This conduct essentially can “reset” and lower the value for products in that market. Such conduct erodes the prices of others in the market and prevents them from being able to return to original prices.

29. Notwithstanding the prolonged and significant 26% discount, in May 2017, iHerb slashed the advertised price for the iHerb Product by offering a 77% automatic discount off MSRP world-wide.

30. When a product price is significantly slashed, especially after an already prolonged discount, price erosion occurs. Sellers are forced to lower prices on their products as a result of a competitor's deeply discounted priced product in order to try to maintain sales. This can also have tremendously negative impact in an entire markets, particularly the health, wellness, vitamin, and supplementation industries.

31. iHerb's prolonged 26% discount off MSRP followed by a 77% discount off MSRP was, is, and will continue to be, immensely harmful to the Plaintiffs and the Baby Ddrops® product. First, iHerb's 77% discount on the iHerb Product is so deep, that potential purchasers may buy several units at far less of a price than the original advertised MSRP price for a single unit offered prior to January 2017.

32. iHerb's price slashing will also erode the prices in the market, especially for Baby Ddrops®. This is especially true because iHerb previously directly compared quality, ingredients, and integrity of the iHerb Product head-to-head with Baby Ddrops®.

33. Furthermore, it would economically impractical, if not impossible, for Ddrops to competitively market Baby Ddrops® against a product that instructs end-users to use the patented method, which is priced with steep discounts, and which contains over three times the number of doses of Baby Ddrops® per bottle. iHerb's actions will pressure Ddrops to lower the price of Baby Ddrops® – an economically unfeasible act – or accept long-term sales losses.

34. In addition to usurping Ddrops' significant advertising and marketing for the Ddrops patented method and product by free-riding on Ddrops' significant advertising and marketing expenditures and efforts (which has developed and grown the market for the Baby Ddrops® product, the Defendants are destroying Ddrops' years of efforts with their pricing games. Ddrops has made tremendous expenditures in money, time, and relationships to promote Baby Ddrops®. iHerb's price games will cause actual purchasers, potential customers, physicians, advertisers, and the industry to question the price and quality of Baby Ddrops®. Consumers will view the vast price discrepancies between the two products and will lose confidence in the Ddrops patented method and product, and in Ddrops as a company. Ddrops' sterling reputation will be tarnished and harmed.

35. Advertising and marketing efforts will be wasted, if not rejected, for a "questionable" product. Overall confidence in Baby Ddrops® and the Ddrops brand will be reduced. iHerb's gamesmanship, if allowed to continue, will cripple the global reputation and efforts of Ddrops' patented method and product.

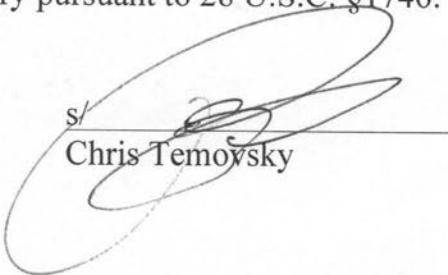
36. The Plaintiffs have suffered, and continue to suffer, substantial harm to the Ddrops brand, reputation in the industry, consumer confidence, advertising, and to the Ddrops method and patented product – all as a result of the Defendants' actions – which are ongoing

Signed under penalty of perjury pursuant to 28 U.S.C. §1746.

Dated: May 26, 2016.

s/

Chris Temovsky

A handwritten signature in black ink, appearing to read "Chris Temovsky", is written over a horizontal line. The signature is stylized with loops and a large flourish at the end.

# Exhibit A

## RESEARCH ARTICLE

## Open Access

# Very high vitamin D supplementation rates among infants aged 2 months in Vancouver and Richmond, British Columbia, Canada

Barbara Crocker<sup>1</sup>, Tim J Green<sup>2\*</sup>, Susan I Barr<sup>2</sup>, Bridgid Beckingham<sup>1</sup>, Radhika Bhagat<sup>1</sup>, Beata Dabrowska<sup>1</sup>, Rachel Douthwaite<sup>1</sup>, Carmen Evanson<sup>1</sup>, Russell Friesen<sup>2</sup>, Kathy Hydamaka<sup>3</sup>, Wangyang Li<sup>2</sup>, Kelly Simmons<sup>1</sup> and Lillian Tse<sup>1</sup>

## Abstract

**Background:** Vitamin D deficiency during infancy may lead to rickets and possibly other poor health outcomes. The World Health Organization recommends exclusive breastfeeding for the first 6 months. Breast milk is the best food for infants but does not contain adequate vitamin D. Health Canada recommends all breastfed infants receive a daily vitamin D supplement of 400 IU; however, there appears to be limited current Canadian data as to whether parents or caregivers are following this advice. The aim of this study was to determine the rates of vitamin D supplementation among 2 month old infants in Vancouver and Richmond, British Columbia, Canada.

**Methods:** Mothers of all healthy infants born between April and May 2010 were approached to participate. Telephone surveys were conducted with 577 mothers (response rate 56%) when their infants turned 2 months.

**Results:** Over half of the infants received only breast milk in the week prior to the survey. One third received a mixture of breast milk and infant formula and 10% received only formula. About 80% of the infants were supplemented with vitamin D at 2 months. Infants who received only breast milk were most likely to be supplemented with vitamin D (91%). Over 60% of the infants had a total vitamin D intake of 300 < 500 IU/d from supplements and formula and only 5% did not receive any vitamin D. Most parents were advised to give vitamin D supplement by health professionals, such as public health nurses, midwives, and doctors.

**Conclusions:** About 90% of the infants received breast milk at 2 months of age. The vitamin D supplementation rate was 80%. Future studies are needed to monitor breastfeeding duration and vitamin D supplementation rates as infants get older.

## Background

Worldwide public health authorities recommend exclusive breastfeeding for the first 6 months of life for healthy term infants [1-3]. Breast milk is the best food for optimal growth of the infant and breastfeeding has been associated with improved health outcomes for mother and infant [1]. While breast milk is the ideal food for infant, it does not generally supply adequate amounts of vitamin D [4]. As such, breastfed infants are at risk of vitamin D deficiency [5]. In its most serious

form vitamin D deficiency in infancy leads to rickets, a condition characterized by weakened bones, resulting from poor mineralization of newly formed bone tissue [6]. Additionally, there is emerging evidence that lack of vitamin D during infancy, is associated with altered calcium metabolism [7], early childhood tooth decay [8], and increased risk of Type 1 Diabetes [9], and asthma later on [10].

While infant formula is fortified with vitamin D, breastfed infants are reliant on skin synthesis of vitamin D through the action of sunlight or supplemental vitamin D. Due to the risk of skin cancer it is generally recommended that infants under 1 year be kept out of direct sunlight [11]. Owing to concerns about vitamin D

\* Correspondence: [tim.green@ubc.ca](mailto:tim.green@ubc.ca)

<sup>2</sup>Food, Nutrition and Health, University of British Columbia, 2205 East Mall, Vancouver V6T 1Z4, Canada

Full list of author information is available at the end of the article



© 2011 Crocker et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

deficiency, Health Canada [4], the American Academy of Pediatrics [3], as well as several European countries [12-14] recommend that breastfed infants receive a daily vitamin D supplement, usually 400 IU. In Canada this recommendation has been in place since 1967 [4], yet, other than in the province of Quebec [15,16], there are few data as to whether parents or caregivers are following this advice. As part of the Canadian Community Health Survey 2007-2008 [17], Statistics Canada reported that among women who had given birth in the past 5 years and exclusively breastfed their infant, 67% provided a vitamin D supplement to the infant. However, this survey did not consider the frequency, dose, or form of supplement, nor were supplementation practices assessed among women who fed their infants a combination of breast milk and formula. Further, this survey included women who gave birth as early as 2002 and there may now be greater awareness about the importance of vitamin D. Indeed, Gallo et al. [18] reported that in one Montreal hospital 98% of exclusively breastfeeding mothers who gave birth in 2007-2008 supplemented their infants at some point prior to 6 months of age.

As part of British Columbia's (BC) publicly funded medical system, public health nurses provide breastfeeding support including advice on vitamin D supplementation within the first few days postpartum. To assess the effectiveness of this health promotion strategy, we conducted a survey in 2010 to determine the rates of breastfeeding and vitamin D supplementation among 2-month old infants in Vancouver and Richmond, BC. We also wanted to determine the type and dose of vitamin D supplementation given, examine the association of socio-demographic factors and vitamin D supplementation and determine barriers to infant vitamin D supplementation.

## Methods

### Sampling frame

Ethical approval to conduct the study was obtained from the University of British Columbia Behavioural Research Ethics Board. The survey was conducted in Richmond and five of six Community Health Areas in Vancouver. Vancouver (population 578,041; 2006) and Richmond (population 174,461; 2006) are the largest and fourth largest cities, respectively, in BC, Canada. All parents or caregivers whose infant was born between April and May of 2010 were invited to participate in the survey. Parents or caregivers were ineligible: if they moved out of the catchment area or were involved in a program that provided care to high-risk mothers (i.e. substance-abuse); or if their infant was adopted, in foster-care, or under the care of a neonatal intensive care unit. An infant age of 2 months was chosen because we wanted

to survey women who had established breastfeeding and before the breastfeeding rates decline. Initial recruitment took place through public health nurses who asked the parent at an early postpartum contact whether they would be willing to participate in a short telephone interview. At an infant age of 2 months (range = 7-10 weeks) a research assistant phoned the parent to complete the survey after again obtaining verbal consent to participate.

### Survey

The survey questionnaire was designed to obtain information on infant feeding practices; vitamin D supplementation including the form, frequency, and dose; who recommended that the infant be supplemented and (if appropriate) the reasons for not supplementing; and basic socio-demographic questions. The questionnaire was initially developed by the study investigators through face-to-face meetings and through consultation and focus testing with relevant stakeholders. We piloted the questionnaire with ten new parents and revised it accordingly. The questionnaire was administered in English or when required in Mandarin, Cantonese, Punjabi, Vietnamese, or Spanish.

### Data analysis

In our study, we defined "All breast milk" as infants who had received only breast milk (vitamins, minerals, and medicines permitted) in the week prior to the survey [2]. "Mixed breast milk and formula" was used to define infants who had received a mixture of breast milk and infant formula in the week prior to the survey. "Infant formula" was used to define infants who had received only formula in the week prior to the survey. Based on data indicating that 2-month old infants are fed an average of 8 times per day [3], we further divided the "mixed breast milk and formula" group into: ">75% of breast milk" defined as  $\leq 2$  feedings of other liquids/food per day; "50- < 75% breast milk" as 3-4 feedings of other liquids/food per day; and "< 50% breast milk" as > 4 feedings of other liquids/food per day. Average daily formula intake was calculated by multiplying frequency of consumption in 24 hours by the amount of formula received in each bottle feed. The amount of vitamin D provided by formula was calculated assuming infant formula contains 40 IU vitamin D/100 ml, and the average intake of vitamin D provided by supplements was calculated based on the amount per dose and the frequency of administration. These two sources were summed to determine daily vitamin D intake. Descriptive statistics were used to describe breastfeeding and vitamin D supplementation rates (proportion with 95% confidence interval). Chi Square tests were used to determine differences in vitamin D supplementation by feeding practice.

Rates were also stratified by socio-demographic variables such as ethnicity. The proportion of infants receiving a total vitamin D intake of  $< 300$  IU from supplements and/or formula was also examined by feeding practice using Chi-square. A cut-point of 300 IU was selected because in order to achieve 400 IU per day a caregiver of breastfed infant would need to be 100% compliant with daily supplementation during the week surveyed. Further, the evidence base for infant requirements is poor [19] and recent trials suggest that 400 IU vitamin D exceeds requirements [20]. Multiple logistic regression was used to determine significant predictors (from among age, ethnicity, parity, income, and education) of receiving vitamin D supplements in two separate models; one in women whose infants had only received breast milk in the week prior to the survey and the other in those providing at least 50% of feeds from breast milk.

### Results

Of the 1028 women eligible to participate, 577 completed the survey giving a response rate of 56% (Figure 1). Participant characteristics are given in Table 1. The majority of the mothers were over 31 y. One third of the infants were of European ethnicity and another one

third was Chinese. Among those who responded to the annual family income question ( $n = 454$ ), almost half had an income greater than \$80,000. Participants were generally well educated with 87% having completed some post-secondary education.

The breastfeeding initiation rate was 99% ( $n = 570$ ) and by 2 months of age over 40% of women were exclusively breastfeeding, using the WHO definition (2). Table 2 displays feeding practices and vitamin D supplementation practices at 2 months of age. Nearly 90% of infants were still receiving some breast milk. Over half received only breast milk in the past week; about one third received a mixture of breast milk and formula ranging from  $\leq 2$  to  $> 4$  feedings of other liquids/food per day; and about 10% received only infant formula. Of the 577 infants, about 80% were supplemented with vitamin D at the time mothers were surveyed. Rates of vitamin D supplementation were significantly higher in those receiving only breast milk in the past week than those who received both breast milk and formula, which in turn were higher than exclusively formula fed babies. Within the mixed breast milk and formula group, infants receiving  $< 50\%$  breast milk were less likely to be supplemented with vitamin D than those receiving 50% or more breast milk ( $P < 0.001$ ). The proportion of

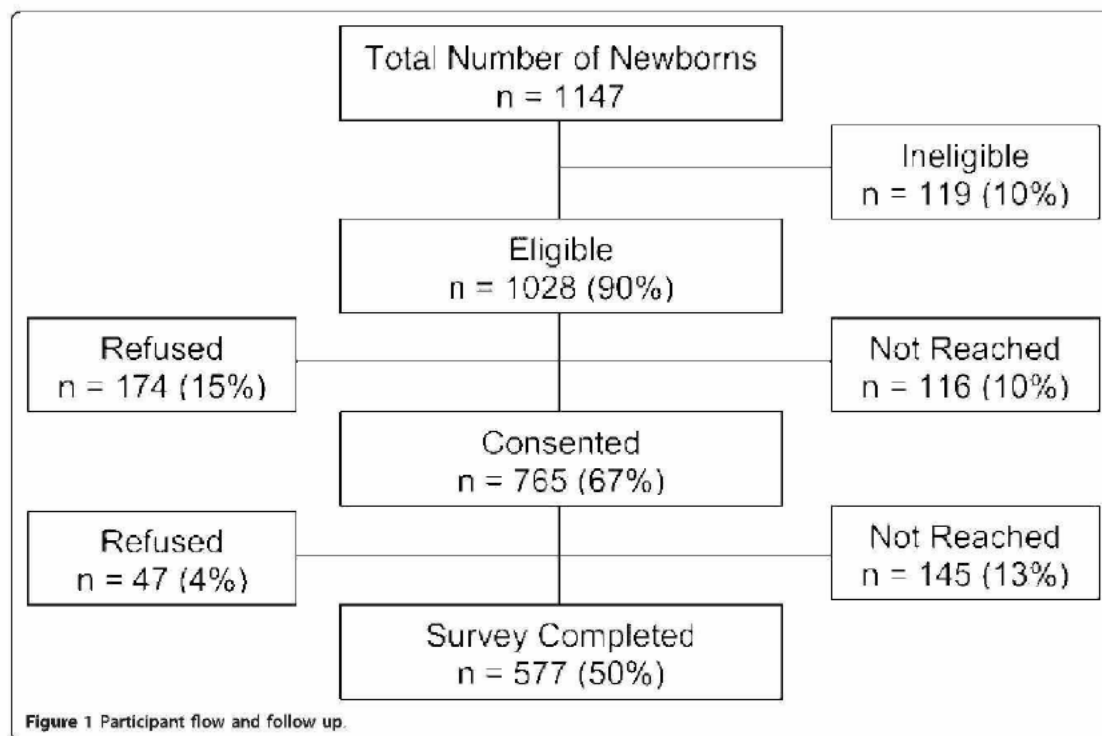


**Table 1 Participant characteristics**

| Characteristic                                             | % (n)         |
|------------------------------------------------------------|---------------|
| Maternal Age                                               |               |
| < 31                                                       | 33.3<br>(192) |
| ≥ 31                                                       | 66.7<br>(385) |
| Baby's ethnicity                                           |               |
| European                                                   | 36.7<br>(212) |
| Chinese                                                    | 31.2<br>(180) |
| Other <sup>1</sup>                                         | 32.1<br>(185) |
| Annual family income                                       |               |
| <\$40,000                                                  | 19.6<br>(113) |
| \$40,000-59,000                                            | 11.3 (65)     |
| \$60,000-80,000                                            | 10.4 (60)     |
| >\$80,000                                                  | 37.4<br>(216) |
| Unknown <sup>2</sup>                                       | 21.3<br>(123) |
| Education                                                  |               |
| < High school                                              | 0.3 (2)       |
| Some and completed high school                             | 12.5 (72)     |
| Some trade/vocational training and college/university      | 8.8 (51)      |
| Completed trade/vocational training and college/university | 78.3<br>(452) |
| Parity                                                     |               |
| Primipara                                                  | 52.0<br>(300) |
| Multipara                                                  | 48.0<br>(277) |
| Baby's gender                                              |               |
| Male                                                       | 50.6<br>(292) |
| Female                                                     | 49.4<br>(285) |
| Marital status                                             |               |
| Single                                                     | 4.9 (28)      |
| Married                                                    | 85.6<br>(494) |
| Common law                                                 | 8.5 (49)      |
| Other                                                      | 1.0 (6)       |

<sup>1</sup>South Asian 42.0% (63), South East Asian 42.7% (64), Korean 6.0% (9), Japanese 9.3% (14), Aboriginal 25.7% (9), Black 22.9% (8), Middle Eastern 42.9% (15), Iranian 2.9% (1), Afghan 2.9% (1), Turkish 2.9% (1)

<sup>2</sup>Do not know and do not want to say

infants receiving less than 300 IU vitamin D per day (supplement and/or formula) was higher among infants receiving only breast milk than among those fed mixed breast milk and formula. However, within this group

there was no difference in the percentage of infants receiving less than 300 IU per day.

About 5% of the infants did not receive any vitamin D from supplements and/or infant formula and 61% had a total vitamin D intake of 300- < 500 IU/d (Figure 2). Approximately 10% received 500 IU or more per day with the highest intake being 1130 IU/d (1000 IU from the supplement). Of those infants who were given vitamin D supplements, 80% received D-Drops<sup>®</sup> (a concentrated formula that provides 400 IU in a single drop) and 16% received D-Vi-Sol<sup>®</sup> (a formula that provides 400 IU per 1 mL). As shown in Table 3, over 90% of participants recalled receiving one or more recommendations to give their infant a vitamin D supplement. Public health nurses and physicians were the most frequent sources of this recommendation. Women who did use a supplement were asked to respond to an open question on why they chose to do so. The most common reasons were related to the inadequate amounts of vitamin D in breast milk, that a supplement had been recommended, that vitamin D had health benefits for the infant, and that lack of sunlight exposure meant supplementation was needed. Women who did not provide a supplement were asked to choose from a list on why they did not. Among those providing a response, the most common reasons were that the infant was being given formula, or that they did not think supplementation was necessary.

In multiple regression analysis of infants receiving only breast milk in the week prior to the survey ( $n = 331$ ), only parity was associated with vitamin D supplementation. Primiparas were more likely to supplement their infants than multiparas (95% versus 84%;  $P = 0.03$ ). Table 4 shows the results of the logistic regression of selected variables associated with vitamin D supplementation in infants who received greater than 50% of their feeds from breast milk ( $n = 517$ ). None of the variables studied was significantly associated with supplementation, although there was a tendency for a higher rate of vitamin D supplementation in infants from families in the two higher income categories than those in the lowest income category.

## Discussion

In this study we build on previous Canadian observations indicating high rates of breastfeeding and vitamin D supplementation, and provide new information regarding the dose of vitamin D provided, and mothers' reasons for choosing to supplement or not supplement. Almost 60% of infants had received only breast milk in the week prior to the survey and of these greater than 90% had received vitamin D supplements. This is much higher than the 67% vitamin D supplementation rate reported in a 2007-2008 survey for Canadian women

**Table 2 Feeding practices and vitamin D supplementation of infants aged two months**

| Feeding practice                  | Feeding Practice | Vitamin D Supplement    | < 300 IU/d Vitamin D <sup>5</sup> |
|-----------------------------------|------------------|-------------------------|-----------------------------------|
|                                   | % (n)            | % yes (n)               | % (n)                             |
| Total                             | 100.0 (577)      | 79.9 (461)              | 28.9 (167)                        |
| All breast milk <sup>1</sup>      | 57.4 (331)       | 91.2 (302)**            | 33.5 (111) <sup>a</sup>           |
| Mixed breast milk and formula     | 32.2 (186)       | 79.0 (147) <sup>b</sup> | 22.0 (41) <sup>b</sup>            |
| ≥75% breast milk <sup>2</sup>     | 53.8 (100)       | 86.0 (86)               | 21.0 (21)                         |
| 50 < 75% breast milk <sup>3</sup> | 20.4 (38)        | 84.2 (32)               | 26.3 (10)                         |
| < 50% breast milk <sup>4</sup>    | 25.8 (48)        | 60.4 (29)               | 20.8 (10)                         |
| Infant formula                    | 10.4 (60)        | 20.0 (12) <sup>c</sup>  | 25.9 (15) <sup>ab</sup>           |

<sup>1</sup>Only breast milk in the past week<sup>2</sup>≤2 feedings of other liquids/food per day<sup>3</sup>3-4 feedings of other liquids/food per day<sup>4</sup>> 4 feedings of other liquids/food per day<sup>5</sup>Total daily vitamin D intake from supplement and formula\*Rows showing different superscripts are significantly different from each other;  $\chi^2 P < 0.001$ 

who had exclusively breastfed an infant in the past 5 years [17]. In that study, the supplementation rate in BC was marginally higher than the national average (70%), but still well below the rate in our study. Our rates of vitamin D supplementation are comparable to those reported more recently in one Montreal hospital where 98% of exclusively breastfed (WHO definition) infants had been supplemented with vitamin D at some point during the first 6 months [18]. Data from the Infant Feeding Practices Study II (2005-2007) suggest that US vitamin D supplementation rates are markedly lower than in Canada; 43% of infants were breastfed at 2 months and of these only 10% were receiving vitamin D [21]. However, the American Academy of Pediatrics only began recommending infant supplementation in November 2008, whereas the Canadian recommendation has been present in some form since 1967. Further, breastfeeding rates have been historically higher in

Canada than in the US and Canada's higher latitude may have created a greater impetus for infant supplementation in this country. As expected infant supplementation at 2 months was lower amongst those receiving mixed feeds (79%) and lower still in infants receiving only infant formula (20%). In Montreal, an apparently higher 88% of mixed feeders had received supplemental vitamin D; however, this was anytime during the first 6 months [18]. In the US study, amongst mixed feeders, only 5% were receiving vitamin D supplements at 2 months of age [21]. Despite a high proportion of breastfed infants receiving vitamin D supplements, one third were not receiving at least 300 IU/d; mainly because of less than daily supplement administration. Although we report less frequent vitamin D supplementation rates among infants who were receiving mixed breast milk and formula in the week before the survey than among those fed only breast milk

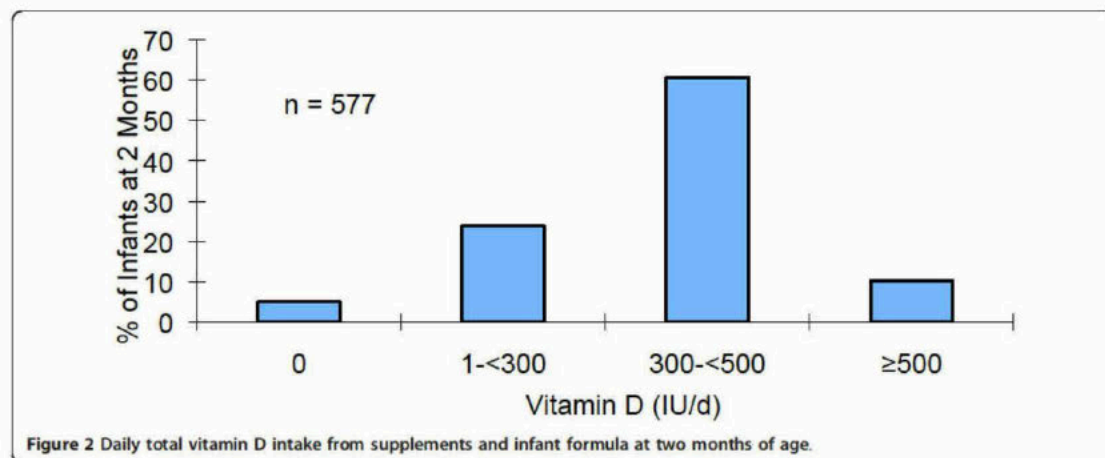


**Table 3 Advice and decisions on vitamin D supplementation**

|                                                                     | % (n)      |
|---------------------------------------------------------------------|------------|
| Did anyone ever recommend a vitamin D supplement?                   |            |
| Yes                                                                 | 92.2 (532) |
| No                                                                  | 7.8 (45)   |
| Who recommended the supplement? (n = 532) <sup>a</sup>              |            |
| Public health nurse                                                 | 80.2 (426) |
| Doctor                                                              | 69.7 (370) |
| Midwife                                                             | 9.6 (51)   |
| Dietitian/pharmacist                                                | 5.1 (27)   |
| Family member or friend                                             | 19.4 (103) |
| Other <sup>1</sup>                                                  | 7.7 (46)   |
| Reasons for providing a vitamin D supplement (n = 452) <sup>a</sup> |            |
| Not in breast milk/I am breastfeeding                               | 43.6 (197) |
| It was recommended                                                  | 30.3 (137) |
| Health benefits for infant                                          | 28.3 (128) |
| Lack of sunlight/northern climate                                   | 21.0 (95)  |
| Other <sup>2</sup>                                                  | 13.1 (59)  |
| Reasons for not supplementing vitamin D (n = 116) <sup>a</sup>      |            |
| Baby is being fed formula                                           | 35.3 (41)  |
| I didn't know to give                                               | 10.3 (12)  |
| I don't think the baby needs it                                     | 19.0 (22)  |
| Forgot to give                                                      | 3.4 (4)    |
| Baby did not tolerate (vomited/spit up)                             | 0.9 (1)    |
| Other <sup>3</sup>                                                  | 5.2 (6)    |
| No response                                                         | 28.4 (33)  |

<sup>a</sup>Multiple responses possible<sup>1</sup>Reading, television, internet, South Community Birth Program, Baby's Best Chance, prenatal class, lactation clinic, natural path, doula, specialist, from first child<sup>2</sup>Knew from first baby, read about it, did not know why, it is important<sup>3</sup>Confused with the recommended dose, will purchase later, will ask doctor, first baby did not tolerate, had not started yet

(79% versus 91%), fewer of the infants receiving mixed feeding had vitamin D intakes below 300 IU/d vitamin D (22%, versus 33.5% in the fully breastfed group). Further, within the group receiving mixed feeds, as the amount of formula increased infant supplementation dropped; however, the percentage of those receiving less than 300 IU/d remained constant at around 20%. This was not unexpected as formula is fortified with vitamin D and it would take about 700 ml of formula to achieve an intake of 300 IU/d. Consuming less than 700 ml/d also explains why 25% of formula fed infants failed to achieve this intake. Using a stricter cut-point of 400 IU/d, the Montreal researchers reported that 74% of exclusively breastfed infants and 51% receiving mixed feeds achieved an intake of 400 IU/d at 6 months [18].

Up to a third of infants not achieving 300 IU/d vitamin D and even less achieving the recommendation of

400 IU/d may appear high. However, only 5% of infants were receiving no vitamin D. Further, it is acknowledged that the evidence base used to derive the infant recommendation is limited. Serum 25-hydroxyvitamin D (25OHD) concentration is the best indicator of vitamin D status. Although controversial the US Institute of Medicine recently affirmed a 25OHD of 50 nmol/L as desirable in all age groups including infants [19]. Greer et al. [22] showed that breastfed infants (n = 9) receiving 400 IU had mean 25-hydroxyvitamin D concentrations of 95 nmol/L after 12 weeks. More recently, infants randomized to 250 or 500 IU per day (n = 20 per group) at birth achieved mean (95% CI) 25OHD concentrations of 139 (114-164) and 151 (126-176) nmol/L, respectively after 6 weeks [20]. Thus, it appears that the recommended intake of 400 IU exceeds the requirements of almost all infants, perhaps by a considerable margin. There have been reports of infant overdosing with vitamin D in the US resulting in the Food and Drug Administration issuing a warning of the potential risk of overdosing infants with liquid vitamin D [23]. In our study only one infant was receiving greater than the upper limit for vitamin D of 1000 IU suggesting this was not a problem.

Among caregivers there was generally good awareness of the need to supplement and why it was important. For example, caregivers indicated that they used a supplement because vitamin D was not present in adequate amounts in breast milk and/or that sunlight exposure was limited or not recommended; and many women who used formula appeared to be aware that supplementation wasn't required. Over 90% of caregivers recalled receiving advice primarily from public health nurses and doctors to supplement with vitamin D, which may explain the high rates of supplementation. In a Seattle study [24], parents who reported that their child's pediatrician recommended vitamin D were 8 times more likely to provide the supplementation than parents whose child's pediatrician did not. However, only a third of parents recalled receiving any recommendation and of these under half supplemented with vitamin D. In contrast to our study, where < 5% of caregivers thought supplementation was unnecessary, 67% of parents in the Seattle study believed that supplementation was unnecessary because breast milk has all needed nutrition.

Multivariate regression revealed little in the way of predictors of supplement use. There was a non-significant tendency for family incomes less than \$40,000 to be associated with lower rates of supplementation. However, vitamin D supplements cost less than \$40 for 6 months and cost of the supplements was not given as a reason for not supplementing. Interestingly 80% of caregivers reported giving their infants D-Drops<sup>®</sup> versus

**Table 4 Percentages and multivariate adjusted odds ratio (and 95% CIs) for infant vitamin D supplementation in infants receiving greater than 50% of feeds from breast milk by select characteristics (n = 420)**

| Characteristic                                                       | % (n)      | OR (95% CI)       | p value |
|----------------------------------------------------------------------|------------|-------------------|---------|
| <b>Maternal Age</b>                                                  |            |                   |         |
| < 31 y                                                               | 87.6 (134) | 1.00              |         |
| ≥ 31 y                                                               | 89.9 (286) | 1.28 (0.65, 2.50) | 0.479   |
| <b>Baby's ethnicity</b>                                              |            |                   |         |
| European                                                             | 88.9 (160) | 1.00              |         |
| Chinese                                                              | 89.6 (129) | 1.34 (0.62, 2.86) | 0.456   |
| Other                                                                | 89.1 (131) | 1.32 (0.62, 2.80) | 0.469   |
| <b>Annual family income</b>                                          |            |                   |         |
| <\$40,000                                                            | 83.1 (74)  | 1.00              |         |
| \$40,000-80,000                                                      | 92.2 (95)  | 2.51 (0.98, 6.41) | 0.054   |
| >\$80,000                                                            | 91.4 (170) | 2.24 (0.94, 5.30) | 0.068   |
| Non responder <sup>1</sup>                                           | 87.1 (81)  | 1.35 (0.58, 3.14) | 0.488   |
| <b>Education</b>                                                     |            |                   |         |
| Less than completed trade/vocational training and college/university | 87.0 (87)  | 1.00              |         |
| Completed trade/vocational training and college/university           | 89.8 (333) | 0.99 (0.48, 2.04) | 0.984   |
| <b>Parity</b>                                                        |            |                   |         |
| Primipara                                                            | 90.5 (219) | 1.00              |         |
| Multipara                                                            | 87.8 (201) | 0.69 (0.37, 1.29) | 0.244   |

Note: CI confidence interval, OR multivariate adjusted odds ratio

<sup>1</sup>Do not know and do not want to say

only 16% who supplemented with D-Vi-Sol<sup>®</sup>. The reason for the popularity of D-Drops<sup>®</sup> may be their ease of administration requiring only a single drop that can be placed on the mother's breast prior to nursing, versus the need to use a dropper to administer D-Vi-Sol<sup>®</sup> [25].

A strength of our study was that we had access to a database that contained the names of nearly all infants born in Vancouver and Richmond over the study period. Also, we sampled an ethnically diverse population where breastfeeding rates are high relative to the rest of North America. Finally, data were collected prospectively at 2 months rather than relying on recall of up to 5 years in one study. In studies of this type, selection bias is always an important consideration. For example, people who choose to participate versus those who do not, may be more educated and of higher socioeconomic status and thus more likely to breastfeed and supplement with vitamin D. Thus a limitation of our study is that we had only a moderate response rate of 56%. Unfortunately, we do not have any data on our non-responders and there are no representative data on pregnant women in Vancouver and Richmond to compare our results with. However, with respect to ethnicity [26], education [27] and family income [28] our sample compares well with 2006 census data for women from Vancouver and Richmond. Further, only half of the non-responders refused participation, while the other half could not be contacted initially or at follow-up.

Because the survey was conducted in the summer months it appeared that many women were away on vacations or staying with family outside the area. We acknowledge that our findings cannot be extrapolated to the rest of Canada or even BC. Breastfeeding rates are higher in BC than elsewhere and Vancouver and Richmond have a unique ethnic mix not present in the rest of the province or Canada. Second, we only sampled at 2 months; this was an intentional decision but more data are needed on older infants. In the US, supplementation rates remained relatively constant out to 12 months; however, in this study both breastfeeding rates and infant supplementation were much lower than ours [21]. In Montreal, of all supplemented breastfed infants around a third had stopped taking the supplement by 6 months [18]. More data are needed on older infants especially around the time of introduction of solids and as breastfeeding rates drop with age.

### Conclusions

Breastfeeding rate was high among this group of mothers. About 90% of the infants received breast milk and 57% were exclusively breastfed at 2 months. Over 60% of the infants had a total vitamin D intake of 300- < 500 IU/d from supplements and formula. The vitamin D supplementation rate was 80%. There was good awareness of the need to supplement with vitamin D and the reasons why. Most parents were advised to give their infants vitamin D

supplement by public health nurses and doctors. Overall it appears that the level of knowledge translation about the importance of vitamin D is high. This points to the success of Vancouver Coastal Health's system of universal contact by public health nurses, especially for providing breast feeding support and also for providing key public health messages such as the use of vitamin D. Future studies are needed to monitor vitamin D supplement rates of older infants and toddlers.

#### Acknowledgements

We are grateful to all public health nurses who recruited participants. We thank research assistants Kathy Ho and Anita Rashidi for their roles in completing surveys and data management. We are also grateful to the participants in this study. This study was supported with a grant from the Vancouver Coastal Health Research Institute.

#### Author details

<sup>1</sup>Infant, Child and Youth Program, Vancouver Coastal Health, 1669 East Broadway, Vancouver V5N 1V9, Canada. <sup>2</sup>Food, Nutrition and Health, University of British Columbia, 2205 East Mall, Vancouver V6T 1Z4, Canada. <sup>3</sup>Healthy Babies and Families Program, Vancouver Coastal Health, 8100 Granville Avenue, Richmond V6Y 3T6, Canada.

#### Authors' contributions

BC and TG were responsible for the conception of the study and obtaining funds. All authors had a role in the design, acquisition of data, analysis and interpretation of data. BC, TG, SB, and WL drafted the initial manuscript. All authors read and approved the final manuscript.

#### Competing interests

The authors declare that they have no competing interests.

Received: 12 July 2011 Accepted: 7 December 2011  
 Published: 7 December 2011

#### References

- Health Canada: *Exclusive breastfeeding duration - 2004 Health Canada recommendation*. Ottawa; 2004.
- World Health Organization: *Global strategy for infant and young child feeding, the optimal duration of exclusive breastfeeding*. Geneva, Switzerland: World Health Organization; 2001. Retrieved March 16, 2011, from [http://apps.who.int/gb/archive/pdf\\_files/WHASS/ea5515.pdf](http://apps.who.int/gb/archive/pdf_files/WHASS/ea5515.pdf).
- American Academy of Pediatrics Section on Breastfeeding: *Breastfeeding and the use of human milk*. *Pediatrics* 2005, **115**:496-506.
- Health Canada: *Vitamin D Supplementation for Breastfed Infants: 2004 Health Canada Recommendation*. Ottawa, ON: Health Canada; 2004.
- Ward LM, Gabourey J, Ladhani M, Zlotkin S: *Vitamin D deficiency rickets among children in Canada*. *Can Med Assoc J* 2007, **177**:161-166.
- Holick MF: *Resurrection of vitamin D deficiency and rickets*. *J Clin Invest* 2006, **116**:2062-2072.
- Brooke OG, Brown IR, Bone CD, Carter ND, Cleeve HJ, Maxwell JD, Robinson VP, Winder SM: *Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth*. *Br Med J* 1980, **280**:751-754.
- Schroth R, Lavelle C, Moffatt M: *Influence of maternal vitamin D status on infant oral health [abstract]*. *J Dent Res* 2008, **87**:1646.
- Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM: *Intake of vitamin D and risk of type 1 diabetes: a birth cohort study*. *Lancet* 2001, **358**:1500-1503.
- Camargo CA, Rifas Shiman SL, Litonjua AA, Rich Edwards JW, Weiss ST, Gold DR, Kleinman K, Gillman MW: *Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age*. *Am J Clin Nutr* 2007, **85**:788-795.
- Health Canada: *A parent's guide to sun protection*. Ottawa, ON: Health Canada; 2004.
- Norwegian Food Safety Authority: *Matportalen (The Food Portal)*; 2006. Personal Communication.
- Swedish National Food Administration; 2006. Personal Communication.
- Healthy Start: *Reform of the welfare food scheme*. England, UK: Healthy Start; 2006. Retrieved October 3, 2011, from <http://www.healthystart.nhs.uk>.
- Dubois L, Bédard B, Girard M, Beauchesne É: *Étude longitudinale du développement des enfants du Québec (ELDEQ 1998 2002). Les nourissons de 5 mois*. Québec, Québec: Institut de la statistique du Québec; 2000.
- Lepage MC, Moisan J, Gaudet M: *What do Québec children eat during their first six months?* *Can J Diet Pract Res* 2004, **65**:106-113.
- Millar WJ, Madean H: *Breastfeeding practices*. *Health Rep (Statistics Canada Catalogue 82-003)* 2005, **16**:23-31.
- Gallo S, Jean-Philippe S, Rodd C, Weiler HA: *Vitamin D supplementation of Canadian infants: practices of Montreal mothers*. *Appl Physiol Nutr Metab* 2010, **35**:303-309.
- Institute of Medicine: *Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academy Press; 2010.
- Siafankas A, Piazana H, Feister U, Bubara MK, Meffert H, Hesse V: *Randomized controlled trial analyzing supplementation with 250 versus 500 units of vitamin D3, sun exposure and surrounding factors in breastfed infants*. *Arch Dis Child* 2011, **96**:91-95.
- Perrine CG, Shama AJ, Jeffers MED, Sordula MK, Scanlon KS: *Adherence to vitamin D recommendations among US infants*. *Pediatrics* 2010, **125**:627-632.
- Greer FR, Searcy JE, Levin RS, Steichen JJ, Asch PS, Tsang RC: *Bone mineral content and serum 25 hydroxyvitamin D concentration in breastfed infants with and without supplemental vitamin D*. *J Pediatr* 1981, **98**:696-701.
- Food and Drug Administration: *Consumer Health Information: Infant overdose risk with liquid vitamin D*. Silver Spring, US: Food and Drug Administration; 2010. Retrieved June 10, 2011, from <http://www.fda.gov/consumer>.
- Taylor JA, Geyer LJ, Feldman KW: *Use of supplemental vitamin D among infants breastfed for prolonged periods*. *Pediatrics* 2010, **125**:105-111.
- Rodd C, Jean-Philippe S, Vanstone C, Weiler H: *Comparison of 2 vitamin D supplementation modalities in newborns: adherence and preference*. *Appl Physiol Nutr Metab* 2011, **36**:414-418.
- Statistics Canada: *2006 Census of Canada highlight tables, ethnocultural portrait of Canada tables: Visible minority groups, 2006 counts, for Canada, provinces and territories, and census metropolitan areas and census agglomerations*. Ottawa, Canada: Statistics Canada; 2006. Retrieved June 6, 2011, from [http://www12.statcan.ca/census-recensement/2006/dp/pd/hlt/97-562/pages/page.cfm?Lang=E&Geo=CMA&Code=59&Table=1&Data\\_Count&Sex=1&StartRec=1&Sort=2&Display=Page&CSDFilter=5000](http://www12.statcan.ca/census-recensement/2006/dp/pd/hlt/97-562/pages/page.cfm?Lang=E&Geo=CMA&Code=59&Table=1&Data_Count&Sex=1&StartRec=1&Sort=2&Display=Page&CSDFilter=5000).
- Statistics Canada: *2006 Census of Canada highlight tables, education tables: Highest level of educational attainment for the population aged 25 to 64, 2006 counts for both sexes, for Canada, provinces and territories, and census metropolitan areas and census agglomerations*. Ottawa, Canada: Statistics Canada; 2006. Retrieved June 6, 2011, from [http://www12.statcan.ca/census-recensement/2006/dp/pd/hlt/97-560/pages/page.cfm?Lang=E&Geo=CMA&Code=59&Table=1&Data\\_Count&Sex=1&StartRec=1&Sort=2&Display=Page&CSDFilter=5000](http://www12.statcan.ca/census-recensement/2006/dp/pd/hlt/97-560/pages/page.cfm?Lang=E&Geo=CMA&Code=59&Table=1&Data_Count&Sex=1&StartRec=1&Sort=2&Display=Page&CSDFilter=5000).
- Statistics Canada: *2006 Census of Canada highlight tables, income and earnings tables: Median earnings and employment for full year, full time earners, all occupations, both sexes, for Canada, provinces and territories, and census metropolitan areas and census agglomerations with 5,000 plus population*. Ottawa, Canada: Statistics Canada; 2006. Retrieved June 6, 2011, from <http://www12.statcan.ca/census-recensement/2006/dp/pd/hlt/97-563/T801-eng.cfm?Lang=E&T=801&GH=6&GF=59&GS=1&SC=1&S=1&O=A>.

#### Pre publication history

The pre publication history for this paper can be accessed here:  
<http://www.biomedcentral.com/1471-2458/11/905/prepub>

doi:10.1186/1471-2458-11-905

Cite this article as: Crocker et al.: Very high vitamin D supplementation rates among infants aged 2 months in Vancouver and Richmond, British Columbia, Canada. *BMC Public Health* 2011 **11**:905.

# Temovsky Exhibit C



## **Mom's Choice Award GOLD Seal**

- The Mom's Choice Awards® (MCA) evaluates products and services created for children, families and educators. The program is globally recognized for establishing the benchmark of excellence in family-friendly media, products and services. The organization is based in the United States and has reviewed thousands of items from more than 55 countries.
- Around the world, parents, educators, retailers and members of the media look for the MCA mother-and-child Honoring Excellence seal of approval when selecting quality products and services for children and families.
- An esteemed panel of evaluators includes education, media and other experts as well as parents, children, librarians, performing artists, producers, medical and business professionals, authors, scientists and others.
- MCA evaluators volunteer their time and are bound by a strict code of ethics which ensures expert and objective analysis free from any manufacturer association.
- The evaluation process uses a proprietary methodology in which items are scored on a number of elements including production quality, design, educational value, entertainment value, originality, appeal and cost. Each item is judged on its own merit.
- MCA evaluators are especially interested in items that help families grow emotionally, physically and spiritually; are morally sound and promote good will; and are inspirational and uplifting.



## **Parent Tested Parent Approved Winner**

- In a competitive market, we are all looking for an advantage and the PTPA Seal of Approval is just that.
- Parent Tested Parent Approved is about putting your product in the hands of real parents, listening to their honest opinions and letting your new brand advocates spread the word about how awesome your product is for families!
- With a built-in community of over 70,000 families across North America, we have immediate access to just the right testers to evaluate your product. When our community loves your product, you'll earn the PTPA Seal of Approval and so much more.
- Your product will stand out from the competition because real parents voted that it meets their needs and earned their approval.
- Recently, we have entered into a new partnership with Toys"R"Us where PTPA award winning products stand out even more in their many locations across Canada, and online!
  - o If you are a Toys"R"Us vendor, your winning product will be highlighted in-store, on print flyers and online at [toysrus.ca](http://toysrus.ca) and [babiesrus.ca](http://babiesrus.ca).
  - o Say hello to getting endorsed by an authentic audience – we'll make sure they shout from the rooftops about your product – on social media through Twitter Parties and Facebook Events, on top blogs, national TV, in magazines and much more.

- When families see the PTPA Seal of Approval on a product or service, they can trust that it has gone through testing in a real-life environment with a family just like theirs. After all, who better to recommend a product to parents than parents themselves? Consider our seal the equivalent of shopping with your best friend.



## **2014 Bounty Mums Love "Commended"**

- Our mums have voted in their thousands for their fave brands, from the first set of wheels to the products that keep those cute chubby baby bottoms clean and dry.
- As a highly-commended product you will automatically benefit from the following activity that will drive to the BML page on Bounty.com:
  - o Ongoing social media (FB & Twitter) shout outs
  - o Inclusion in weekly newsletters (pre & post-natal) driving to the relevant Bounty MUMS LOVE sections
  - o All winners / commended hosted on Bounty.com by category



## **2015 Well.ca Green Choice Award Winner**

- In recognition of Earth Month, we launched our **First Annual Green Choice Awards**, allowing our customers (that's you!) to vote on what their most loved and trusted green and natural brands were.
- There were 88 products in contention for the Green Choice Awards in 14 categories plus a Well.ca Staff Pick, allowing staff to choose their favourite from all of our Green and Natural brands.
- Earth Month is an important time for everyone to take stock and see what each one of us can do to help improve our planet. If we each made one small change, the earth would reap the rewards. This Earth Month, we encourage all Canadians to try a new, environmentally friendly product. Then come back and vote in the annual Green Choice Awards next year!



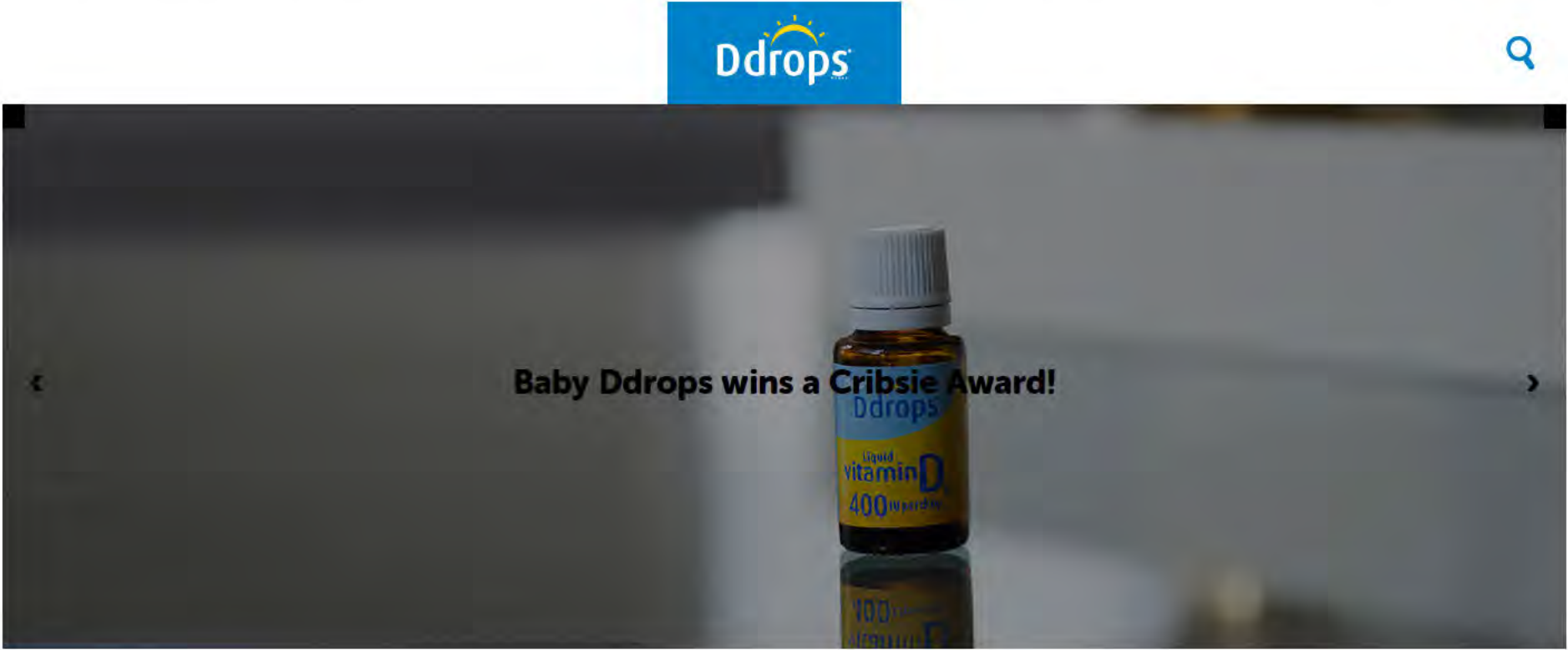
## **2015 Cribsie Awards New Arrival “Academy Star”**

- Founded in 2010 and hosted by StrollerTraffic.com, the Cribsie Awards recognize the best products, services, and websites for babies and tots. The Cribsies offer a secure voting platform that limits users to one unique vote per email address, meaning the Cribsies are a true, untainted measure of the public’s opinion on the top parenting brands.
- With hundreds of thousands of votes cast and a reach in the millions, the Cribsies have quickly become the definitive awards for parents.
- You nominate. We select. Parents vote.



## **2016 National Parenting Product Awards Winner**

- The National Parenting Product Awards (NAPPA) is one of the longest running and most respected awards programs in the country. With 25 years of experience in the industry, we have been continuously celebrated as the "go-to" source for parents and professionals seeking the best products for their children and families.
- NAPPA enlists a team of independent expert judges and family testers to review each submission thoroughly. Together, they select the most entertaining, appealing, safe, educational, age-appropriate and enduring products as NAPPA winners. A NAPPA recognition is more than just a seal of approval. It signifies that a product has been rigorously evaluated against stringent criteria and that it stands out among hundreds of similar products from around the world. Products that receive the prestigious NAPPA award are quality products that parents and professionals can trust.
- All Ddrops products have been awarded Gold: Baby, Booster, Adult (1000 IU and 2000 IU) and Vegan Ddrops by Ddrops Company.



We’re excited to announce that Baby Ddrops® has been selected as one of the Best New Arrival Products of The Year for 2015, along with an Academy Star recognition! This means that the Cribbie Academy has rated Baby Ddrops® with at least a 3.5 out of 5 across four judging criteria (innovation, style/design, marketability, and utility).

Hosted by StrollerTraffic.com, the annual Cribbie Awards were founded in 2011 to create a secure forum for opinionated moms to elect their favorite brands and services from a curated list of best-of-the-best finalists, across six different categories. The Cribbies are currently the definitive awards for the baby industry to help recognize the best brands, products, services, and websites for babies, tots, and of course the parents who adore them.

The Cribbie New Arrivals honor the best new brands and products of last year. These products are judged by the Cribbie Academy, a prestigious panel of industry leaders, experts and celebrities. There are over 50 brands and products with votes from more than 200,000 public votes.



Search Site

 (mailto:NAPPA@NAPPAawards.com)

 <https://www.facebook.com/nappaawards>

- [Home](#)
- [About](#)
- [Find Award-winning Products](#)
- [Recent Winners](#)
- [Contact Us](#)
- [Shop Talk](#)
- [Submit Your Product](#)

## Baby Ddrops® by Ddrops Company



Ddrops® products were specifically designed in response to the need for a simply better way to provide the one most often deficient vitamin – Vitamin D. Ddrops® were specifically designed to be checked off any clean surface such as the back of a washed hand or a spoon making it as easy as one and that's it. Ddrops® are free from preservatives, artificial flavors/colors and are wheat free, gluten free, soy free, corn free, sugar free, milk free and peanut free.

Why we like it: Convenient way to get the added Vitamin D in baby's diet. Easy to administer and absolutely flavorless. Especially made for breastfed babies.

Ages: Babies less than 1 year  
Price: \$12.99  
[www.vitaminDdrops.com](http://www.vitaminDdrops.com)  
PURCHASE



0 Comments

Sort by Oldest

Add a comment

Facebook Comments Plugin



We are excited to announce that Ddrops Company has received 2 levels of NSF International certification – NSF GMP Facility Certification, as well as NSF Product Certification!

The Ddrops® production facility has now been registered as an NSF GMP facility. The NSF GMPs were developed in accordance with the U.S. Food and Drug Administration’s (FDA) 21 CFR part 111 regulations on dietary supplement packaging and distribution. In addition, Ddrops® 400 IU, 600 IU and 1000 IU have received NSF Product Certification (NSF/ANSI 173). This identifies the quality of ingredients, verifies that Ddrops® products do not contain unacceptable levels of contaminants, as well as acknowledges that our manufacturing facility conforms to currently recommended industry GMPs for dietary supplements.

Baby Ddrops® is the only infant vitamin in the world to receive this level of certification!

**What is NSF International?**

NSF International is an internationally recognized third-party independent, not-for-profit organization that writes standards, tests and certifies products and facilities across many industries. NSF International is not mandated by any regulatory agency or governmental body, which proves that Ddrops Company has a strong commitment to going above and beyond industry standards to support our customers’ health and well-being. NSF GMP and Product Certifications are a consistent commitment and an on-going process. Both entail regular semi-annual or annual audits and tests.

**Why is this such exiting news?**

NSF GMP and Product Certification provides consumers with another tool when it comes to choosing which supplements to purchase for their family. NSF values trust, independence and expertise. Having our Ddrops® products certified by NSF provides our customers peace of mind and shows that we are committed to the excellence of our products.

Ddrops® is a pioneer and leader in the development of high quality and effective vitamin D supplements for the entire family. NSF GMP and Product Certification adds to the Health Canada government site license (301515), FDA Food Facility Licence (13805251458) and a list of many awards, patents and recognitions already held and received by Ddrops Company. We continue to work to make Ddrops® *next level!*

**Want to learn more?**

You can read more about the many safety features incorporated into Ddrops® products [here](#). You can also view our listing on the NSF website directory [here](#) and [here](#).

[f](#) [t](#) [g+](#) [p](#) SHARE

By Sydney | May 2, 2017

[Ddrops awards](#), [GMP](#), [NSF](#), [NSF certification](#), [NSF international](#), [Safety](#)

**Baby Ddrops® now in Target stores – Find them and enter to win!**

[← Read More](#)



Shop for products, brands or categories...

CHECKOUT (HTTPS://WELL.CA/CHECKOUT\_SHIPPING.HTML)

0 (/shopping\_cart.html)

THE WELL BLOG (HTTPS://WELL.CA/BLOG?UTM\_SOURCE=WELL.CA&UTM\_MEDIUM=MENU&UTM\_CAMPAIGN=SERIALINK) SUNSCREEN\_299.HTML)

[Go Back](#)

9 ways to go green

(/well.ca/earthmonth/)

-- Sort By --

-- Select a Category --

-- Select a Brand --

-- Product Flags --

# Green Choice Awards

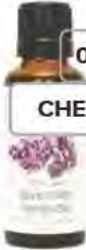
97

FREE SHIPPING ON ORDERS \$35+\*  
(/shipping-and-returns)



REFER A FRIEND: GIVE \$10 OFF & GET \$10 OFF!\* (/referralprogram)





[0 \(/shopping\\_cart.html\)](/shopping_cart.html)

[CHECKOUT \(https://well.ca/checkout\\_shipping.html\)](https://well.ca/checkout_shipping.html)

|                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <a href="https://well.ca/index.php?main_page=landing_page&amp;id=268&amp;action=buy_now&amp;products_id=7336">Add to Cart +<br/>(https://well.ca/index.php?main_page=landing_page&amp;id=268&amp;action=buy_now&amp;products_id=7336)</a> | <a href="https://well.ca/index.php?main_page=landing_page&amp;id=268&amp;action=buy_now&amp;products_id=11625">Add to Cart +<br/>(https://well.ca/index.php?main_page=landing_page&amp;id=268&amp;action=buy_now&amp;products_id=11625)</a> | <a href="https://well.ca/index.php?main_page=landing_page&amp;id=268&amp;action=buy_now&amp;products_id=19588">Add to Cart +<br/>(https://well.ca/index.php?main_page=landing_page&amp;id=268&amp;action=buy_now&amp;products_id=19588)</a> | <a href="https://well.ca/index.php?main_page=landing_page&amp;id=268&amp;action=buy_now&amp;products_id=11627">Add to Cart +<br/>(https://well.ca/index.php?main_page=landing_page&amp;id=268&amp;action=buy_now&amp;products_id=11627)</a> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Baby Ddrops Liquid  
Vitamin D3  
400 IU per drop  
90 Drops / 2.5 mL

  
\$15.99



Green Beaver Frosty  
Mint Toothpaste  
75 mL

  
~~\$5.79~~ \$4.63



NOW Essential Oils  
Lavender Oil  
100% Pure  
30 mL

  
~~\$44.29~~ \$10.00



Green Beaver Green  
Apple Toothpaste  
Safe for Children  
75 mL

  
~~\$5.79~~ \$4.63



Select Colour  
([https://well.ca/products/burts-bees-lip-shimmer\\_3803.html](https://well.ca/products/burts-bees-lip-shimmer_3803.html))

Burt's Bees Lip Shimmer  
2.6 g



[Add to Cart +  
\(https://well.ca/index.php?main\\_page=landing\\_page&id=268&action=buy\\_now&products\\_id=17701\)](https://well.ca/index.php?main_page=landing_page&id=268&action=buy_now&products_id=17701)

Annie's Homegrown  
Organic Cheddar  
Bunnies



[Add to Cart +  
\(https://well.ca/index.php?main\\_page=landing\\_page&id=268&action=buy\\_now&products\\_id=51902\)](https://well.ca/index.php?main_page=landing_page&id=268&action=buy_now&products_id=51902)

Green Beaver Natural  
Mineral Sunscreen  
Spray for Kids



[Add to Cart +  
\(https://well.ca/index.php?main\\_page=landing\\_page&id=268&action=buy\\_now&products\\_id=9461\)](https://well.ca/index.php?main_page=landing_page&id=268&action=buy_now&products_id=9461)

Green Beaver Green  
Tea Facial Moisturizer  
120 mL





Receive **FREE** Products, Share Your Feedback, **WIN** Great Prizes!

**JOIN OUR COMMUNITY!**

Baby Ddrops



\$16.99

3 CUSTOMER REVIEWS: ★★★★★

(HTTP //WWW GOP N COM/T/QZ9HRUV P0NDRUPHS 9HRUV ?URL HTTP%3A%2F %2FWWW TOYSRUS CA%2FENTRY PO NT%3FENTRY%3D46398096%26SOURCE%3DP DF%3A46398096%3ATR %3D%7BSUB D%7D%26CL CK D%3D%7BCL D%7D%26AFF L ATECUSTOM D%3D%7BS D%7D/)

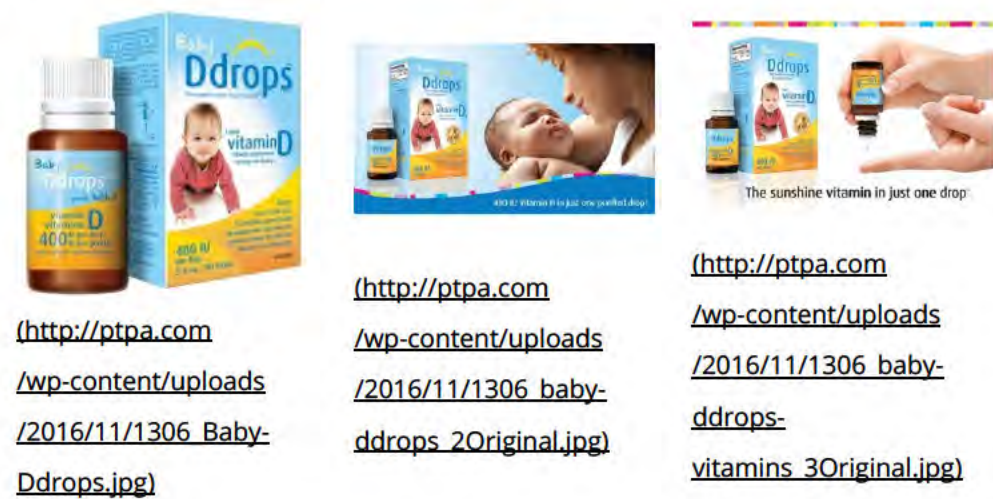
Buy now on (HTTP //WWW AMAZON CA/DP/B00CORNHKW?TAG PARETESTPAREA 20)

V S T WEBS TE (HTTP //WWW DDROPS CA/DDROPS BABY PHP) LEAVE YOUR REV EW



What parent testers (/testing-opportunities/) had to say:

*This is a great product primarily because your child will not be able to complain that they don't like the taste as there really is no taste. One drop from a tiny glass bottle and it's done. Easy to dispense and nothing to complain about. That makes it a great product in my books!*



(http://ptpa.com/wp-content/uploads/2016/11/1306 Baby-Ddrops.jpg)

(http://ptpa.com/wp-content/uploads/2016/11/1306 baby-ddrops\_2Original.jpg)

(http://ptpa.com/wp-content/uploads/2016/11/1306 baby-vitamins\_3Original.jpg)

|             |             |
|-------------|-------------|
| Description | Reviews (3) |
|-------------|-------------|

### 3 reviews for Baby Ddrops

★★★★★

Jessica November 28, 2016

Easy to give, since you need just a drop- they don't even taste it! Ingredients are simple, no extra junk- an easy way to get the recommended DV of vitamin D in a breastfed baby, to protect them from deficiency. With minor exceptions due to lack of availability, I've almost exclusively used this brand for all 3 of my kids. Easy to find, and not too expensive.

★★★★★100

Cassandra

December 14, 2016

Great for breastfed babies. Very easy to give as it's only one drop. Says you can place it on your clean finger or nipple to administer to baby. (I have even placed it on my daughters soother). Baby doesn't even taste it, at least mine doesn't seem to. I have noticed however, it does take some time for the drop to come out of the container. Even when tipped upside down, you have to wait a few seconds for the drop to come out. And once it does you have to immediately turn upright or else multiple drops come out. Other than that, great product and a must for any breast fed baby.

★★★★★

Anonymous

Apr 17, 2017

Great product, I've been using it daily for my breastfed daughter and it's so easy to use.

Add a review

Your email address will not be published. Required fields are marked \*

YOUR RATING



YOUR REVIEW \*

NAME \*

EMAIL \*

Mom's Choice Awards Home



# The Mom's Choice Awards® Shop

a webstore featuring our award-winning products

Search all Mom's Choice Award Winners

All Categories

Search here...

## Categories

- Adult Books
- Apps & Software
- Arts, Crafts & Hobbies
- Audio Experiences
- Children's Picture Books
- Educational Products
- Gear & Accessories
- Juvenile Books (Level 1 - Ages 5 to 8)



## Baby Ddrops

|                    |                                                                                                                                                                                                                                                                               |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Description:       | Baby Ddrops® is a natural-sourced vitamin D supplement. Baby Ddrops® are tasteless, odorless and contain no preservatives, no artificial flavours and no added colours. Baby Ddrops® are wheat-free, gluten-free, soy-free, corn-free, sugar-free, milk-free and peanut-free. |
| Audience:          | Baby, Infants, Toddler, Mom, Dad, Caregiver                                                                                                                                                                                                                                   |
| Type:              | Personal Use                                                                                                                                                                                                                                                                  |
| Retail Price:      | \$ 15.99                                                                                                                                                                                                                                                                      |
| Website:           | <a href="http://www.ddropscompany.com/ca/baby-ddrops/">http://www.ddropscompany.com/ca/baby-ddrops/</a>                                                                                                                                                                       |
| Social Media:      | <a href="#"></a> <a href="#"></a> <a href="#"></a> <a href="#"></a> <a href="#"></a> <a href="#"></a>                                                                                                                                                                         |
| Purchasing Options |                                                                                                                                                                                                                                                                               |

ABOUT WELL.CA(HTTPS://WELL.CA/BLOG/CATEGORY/ABOUT WELL CA/) / APRIL 2, 2015

# 2015 GREEN CHOICE AWARD WINNERS!



**Y**ou voted. We counted...and now we can finally tell you who the winners are! In case you missed it, in recognition of Earth Month we launched our First Annual *Green Choice Awards*, allowing our customers (that s you!) to vote on what their most loved and trusted green and natural brands were.

There were 88 products in contention for the Green Choice Awards in 14 categories plus a Well.ca Staff Pick, allowing staff to choose their favourite from all of our Green and Natural brands.

Earth Month is an important time for everyone to take stock and see what each one of us can do to help improve our planet. If we each made one small change, the earth would reap the rewards. This Earth Month, we encourage all Canadians to try a new, environmentally friendly product. Then come back and vote in the annual Green Choice Awards next year!

And without further ado, here are the winners from the 2015 awards:



([https://we .ca/brand/burts bees.htm ?utm\\_source=socia &utm\\_medium=soc b og&utm\\_campaign=3apr15](https://we .ca/brand/burts bees.htm ?utm_source=socia &utm_medium=soc b og&utm_campaign=3apr15))

Natural Skin Care Award:

What you put onto your skin is as important as what you put into your body and according to you, Burt s Bees(<https://we .ca/bran>



([https://we .ca/products/green beaver natura minera 101553.htm ?utm\\_source=socia &utm\\_medium=soc b og&utm\\_campaign=3apr15](https://we .ca/products/green beaver natura minera 101553.htm ?utm_source=socia &utm_medium=soc b og&utm_campaign=3apr15))

Natural Sun Care Award:

We know sun care is important and so do you...your go-to product is Green Beaver s Natural Mineral Sunscreen(<https://we .ca/p>



([https://we .ca/brand/bobs red mi .htm ?utm\\_source=socia &utm\\_medium=soc b og&utm\\_campaign=3apr15](https://we .ca/brand/bobs red mi .htm ?utm_source=socia &utm_medium=soc b og&utm_campaign=3apr15))

Green Foodie Award:

We sell lots of great green edibles...but your ultimate brand is Bob s Red Mill([https://we .ca/brand/bobs red mi .htm ?utm\\_source socia .](https://we .ca/brand/bobs red mi .htm ?utm_source socia .)



([https://we .ca/brand/annies homegrown.htm ?utm\\_source=socia &utm\\_medium=soc b og&utm\\_campaign=3apr15](https://we .ca/brand/annies homegrown.htm ?utm_source=socia &utm_medium=soc b og&utm_campaign=3apr15))

On-the-go Healthy Snack Award:

Delicious, healthy snacks are not hard to find with Annie s Homegrown([https://we .ca/brand/annies homegrown.htm ?utm\\_source socia S](https://we .ca/brand/annies homegrown.htm ?utm_source socia S)



([https://we .ca/brand/seventh generation.htm ?utm\\_source=socia &utm\\_medium=soc b og&utm\\_campaign=3apr15](https://we .ca/brand/seventh generation.htm ?utm_source=socia &utm_medium=soc b og&utm_campaign=3apr15))

Green Your Home Cleaning Award:

What brand makes your home shine and shimmer without making the earth wither? Seventh Generation(<https://we .ca/brand/seventh ge>



[https://well.ca/brand/pure-anada.htm?utm\\_source=social&utm\\_medium=social&utm\\_campaign=3apr15](https://well.ca/brand/pure-anada.htm?utm_source=social&utm_medium=social&utm_campaign=3apr15)  
Green Beauty Award:  
The brand that easily makes your beauty routine go green is Pure Anada[https://well.ca/brand/pure-anada.htm?utm\\_source=social&utm\\_medium=social&utm\\_campaign=3apr15](https://well.ca/brand/pure-anada.htm?utm_source=social&utm_medium=social&utm_campaign=3apr15)



[https://well.ca/brand/live-clean.htm?utm\\_source=social&utm\\_medium=social&utm\\_campaign=3apr15](https://well.ca/brand/live-clean.htm?utm_source=social&utm_medium=social&utm_campaign=3apr15)  
Green Your Personal Care Routine Award:  
The brand you look for when you want to green your personal care routine is Live Clean[https://well.ca/brand/live-clean.htm?utm\\_source=social&utm\\_medium=social&utm\\_campaign=3apr15](https://well.ca/brand/live-clean.htm?utm_source=social&utm_medium=social&utm_campaign=3apr15)



[https://well.ca/brand/now-foods.htm?utm\\_source=social&utm\\_medium=social&utm\\_campaign=3apr15](https://well.ca/brand/now-foods.htm?utm_source=social&utm_medium=social&utm_campaign=3apr15)  
Natural Remedy Award:  
When you are in need of a boost, or feeling a bit under-the-weather, the brand you are most likely to turn to is Now Foods[https://well.ca/brand/now-foods.htm?utm\\_source=social&utm\\_medium=social&utm\\_campaign=3apr15](https://well.ca/brand/now-foods.htm?utm_source=social&utm_medium=social&utm_campaign=3apr15)



[https://well.ca/products/baby-ddrops-liquid-vitamin-d3-7336.htm?utm\\_source=social&utm\\_medium=social&utm\\_campaign=3apr15](https://well.ca/products/baby-ddrops-liquid-vitamin-d3-7336.htm?utm_source=social&utm_medium=social&utm_campaign=3apr15)  
Healthy Baby Award:  
When your wee one gets sick or you want to keep them healthy, the product you reach for first is Baby Ddrops Liquid Vitamin[https://well.ca/products/baby-ddrops-liquid-vitamin-d3-7336.htm?utm\\_source=social&utm\\_medium=social&utm\\_campaign=3apr15](https://well.ca/products/baby-ddrops-liquid-vitamin-d3-7336.htm?utm_source=social&utm_medium=social&utm_campaign=3apr15)



Every once and awhile, it's fun to look at your accomplishments and do a little "humble bragging." Ddrops products just turned 8 years old, so let's take a look back at some highlights from the past 8 years:

- Baby Ddrops® is the number one selling infant vitamin in Canada with over 100 million doses sold in Canada alone.
- Ddrops social media accounts have over 25,000 fans/followers. Are you [following us yet?](#)
- Baby Ddrops® is also used in several Canadian hospitals in the Neonatal ICU, as it has no effect on osmolality (liquid composition of infant feeding) and the single drop is an advantage in this setting.
- Ddrops® products are often used as study drug in clinical trials all over the world. The Health Canada license, product integrity and stability as well as ease of use makes Ddrops® an option for study and research purposes. There are currently two published, independent, peer-reviewed clinical trials and several underway. Note that these studies have been done with infants and one study also includes

pregnant women.

- Ddrops® are available in many major online and brick and mortar [retailers](#) across the United States, Canada and even the UK! (Have you seen us on [Target.com?](#))
- Baby Ddrops® have been featured on The Price Is Right during the “It’s In The Bag” pricing game.
- Big Brother Canada contestants were reminded by their Mom to [take their Ddrops](#) !
- Baby Ddrops® has received awards including Gold from Mom’s Choice, Parent-Tested-Parent Approved, Bounty Mum’s Luv and Green Choice from Well.ca

[f](#) [t](#) [g+](#) [p](#) SHARE

By Susan | August 16, 2016

[Accomplishments](#), [awards](#), [Ddrops](#), [Ddrops household name](#), [Price is Right](#), [Retailers](#), [vitamin D](#)

**Do Ddrops products have a taste? See what doctors have to say**

[← Read More](#)

**Vitamin D deficiency: How common is it and what can I do about it?**

[Read More →](#)

Claims made have not been evaluated by government agencies, such as the FDA in the

United States. This product is not intended to diagnose, treat, cure or prevent any disease.

The contents of these blog posts are for informational purposes and are not intended to offer personal medical advice. You should seek the advice of your physician or other qualified health provider with any questions you may have regarding a medical condition. Never disregard professional medical advice or delay in seeking it because of something you have read on this blog.



©2016 Ddrops Company. All Rights Reserved.

# TEMOVSKY

## Exhibit D



# The Change in Plasma 25-Hydroxyvitamin D Did Not Differ between Breast-Fed Infants That Received a Daily Supplement of Ergocalciferol or Cholecalciferol for 3 Months<sup>1-4</sup>

Sina Gallo,<sup>5</sup> Anna Phan,<sup>5</sup> Catherine A. Vanstone,<sup>5</sup> Celia Rodd,<sup>5-7</sup> and Hope A. Weiler<sup>5,7\*</sup>

<sup>5</sup>School of Dietetics and Human Nutrition, McGill University, Montréal, Québec, Canada; and <sup>6</sup>Montréal Children's Hospital, McGill University Health Centre, Montréal, Québec, Canada

## Abstract

The biological equivalency of ergocalciferol (D2) and cholecalciferol (D3) has been debated; several comparisons have appeared in the adult literature but are scarce in pediatrics. The objective of this study was to compare increases in plasma 25 hydroxyvitamin D [25(OH)D] concentrations and attainment of 50 and 75 nmol/L status cutoffs following 3 mo of daily supplementation with D2 compared with D3. Healthy, breast fed, 1 mo old infants ( $n = 52$ ) received 10  $\mu\text{g}$  (400 IU) of either D2 or D3 daily. At 1 and 4 mo of age, plasma 25 hydroxyergocalciferol and 25 hydroxycholecalciferol concentrations were determined by liquid chromatography tandem MS (LC MS/MS) and total 25(OH)D by chemiluminescent immunoassay (DiaSorin Liaison). Data were analyzed using  $t$  tests and  $\chi^2$  by intent to treat. A total of 23% of infants were deficient ( $\leq 24.9$  nmol/L) at baseline and 2% at follow up on the basis of LC MS/MS. At 4 mo, 96% were breastfed and there were no differences in compliance, breastfeeding rates, or sun exposure among groups. The change in total 25(OH)D measured by LC MS/MS did not differ between the D2 ( $17.6 \pm 26.7$  nmol/L) and D3 ( $22.2 \pm 20.2$  nmol/L) groups. In the combined groups, the baseline plasma 25(OH)D concentration was inversely related to the change in total 25(OH)D ( $r = -0.52$ ;  $P < 0.001$ ). Overall, 86% of infants met the 50 nmol/L cutoff at follow up; however, fewer infants in the D2 group (75%) met this level compared with the D3 group (96%) ( $P < 0.05$ ). Similar results were obtained by immunoassay. In conclusion, the increase in the 25(OH)D concentration among the D2 and D3 groups did not differ, suggesting daily intake of either isoform is acceptable for infants  $< 4$  mo. J. Nutr. 143: 148–153, 2013.

## Introduction

Most countries around the world recommend supplementing breast fed infants with 10  $\mu\text{g}$  (400 IU) of vitamin D daily (1–6). This dosage is thought to maintain circulating 25 hydroxyvitamin D [25(OH)D]<sup>8</sup> concentrations of 40–50 nmol/L as suggested by the Institute of Medicine (IOM) for bone health (3); however,

other organizations advise using a higher cutoff of 75 nmol/L (7). Standard infant preparations in Canada are mammalian cholecalciferol (D3), but most research studies tested plant derived ergocalciferol (D2) (8–10). These isomers differ in side chain structure and were originally thought to exhibit identical biological responses (3,11,12). There is controversy in the adult literature regarding the equivalency of the 2 isoforms. A single dose of 1250  $\mu\text{g}$  D3 increased 25(OH)D based on AUC during 28 d with 3–10 times greater efficacy than D2 (13). Further more, 100  $\mu\text{g}/\text{d}$  D3 resulted in a 75% greater change in 25(OH)D compared with D2 for 14 d (14). In a study that followed adults for a longer period of 11 wk, a daily intake of 25  $\mu\text{g}$  of either isoform maintained equivalent 25(OH)D status (15). Similar results were observed in elderly women taking supplements containing either D2 or D3 ( $< 12.5$   $\mu\text{g}/\text{d}$ ) for an average 5–6 y (16). It appears that dosage and sustained supplementation may explain the differences observed in these adult studies.

A recent meta analysis concluded that D2 is less effective than D3 at raising the 25(OH)D concentration (17) and highlighted that too few studies exist to verify if this is the

<sup>1</sup> Supported by a grant from the Canadian Foundation for Dietetic Research and the Ddrops Company provided vitamin D supplements in kind. H.A.W. is a Canada Research Chair with infrastructure funding from the Canadian Foundation for Innovation.

<sup>2</sup> Author disclosures: S. Gallo, A. Phan, C. A. Vanstone, C. Rodd, and H. A. Weiler, no conflicts of interest.

<sup>3</sup> This trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as NCT01190137.

<sup>4</sup> Online Supporting Material: Supplemental Table 1 and Figure 1 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at <http://jn.nutrition.org>.

<sup>5</sup> Senior authors.

<sup>8</sup> Abbreviations used: D2, ergocalciferol; D3, cholecalciferol; ITA, individual typological angle; IOM, Institute of Medicine; LC MS/MS, liquid chromatography tandem MS; 25(OH)D, 25 hydroxyvitamin D; 25(OH)D3, 25 hydroxycholecalciferol; 25(OH)D2, 25 hydroxyergocalciferol.

\* To whom correspondence should be addressed. E-mail: [hope.weiler@mcgill.ca](mailto:hope.weiler@mcgill.ca).

situation in children (18,19). In neonates, there are additional physiological differences in intestinal absorption (19) and vitamin D metabolism (20) from adults. Whether differences in the absorption and binding to the vitamin D binding protein between isoforms affect plasma 25(OH)D concentrations in infants is yet undetermined. A study was designed with the objective to compare the effectiveness of 10  $\mu\text{g}/\text{d}$  of D2 compared with D3 to increase or maintain circulating 25(OH)D concentrations during a 3 mo period in healthy, breast fed newborns. Our secondary objective was to compare the proportion of infants able to meet the 50 (3,6) or 75 (7) nmol/L cutoffs at follow up.

## Participants and Methods

**Trial design.** Infants were randomly assigned to receive a 10  $\mu\text{g}/\text{d}$  oral dose of either D2 or D3 in a 1:1 ratio stratified by sex. Both the D3 (NPN no. 80001869) and D2 (NPN no. 80003406) based products are commercially available (Ddrops Company), eliminating the need for Health Canada approval as a phase IV trial. There were no differences in appearance and both products were tasteless and odorless. These products are oil based (coconut and palm) and dosages were delivered in 1 drop volumes (0.03 mL) using a standardized Eurodropper. Compliance was assessed by weighing unused portions in bottles and parent self report. Compliance was calculated as the number of dosages taken divided by the days since last visit and "compliant" was defined as 80–100% of doses taken. The study was approved by the Institutional Review Board of McGill University. Parents gave written informed consent.

**Participants.** Newborns were referred from a primary care hospital and birthing center located in greater Montréal between May 2010 and September 2011. To avoid oversampling in any one season, we aimed to recruit 50% of participants in the vitamin D synthesizing period (April–October) for Montréal located at latitude 45°N (21). Infants were eligible to begin the study at 1 mo of age if they were healthy, singleton,

term infants born the appropriate size for gestational age as assessed according to the WHO growth charts (between 5th and 95th percentile) and to healthy, breastfeeding women (consuming >80% of total feeds from breast milk). Exclusion criteria included infants of mothers with a history of gestational diabetes or hypertension in pregnancy, malabsorption syndromes (celiac and Crohn's disease), or taking medications that interfere with vitamin D metabolism (anticonvulsants and corticosteroids). Mothers taking  $\geq 50 \mu\text{g}/\text{d}$  of vitamin D from supplementation were not included, because this value is above the current nutrition recommendations (22). Demographic information, including race, education, and income (in Canadian dollars), was reported by the mother. At baseline and follow up visits, weight, length, and head circumference were measured. Data are expressed in absolute units and Z scores using data from the 2006 WHO growth charts (23) at each time point.

**Dietary and endogenous vitamin D sources.** Information on infant breastfeeding status (feeds/day) and formula feeds (amount, frequency, brand) was collected at each visit. Skin pigmentation was measured on the constitutive upper underarm and facultative forehead, forearm, and outer lower leg using a portable computerized spectrophotometer (CM 600D, Konica Minolta). Based on the Commission Internationale de l'Eclairage colorimetry system ( $L^*a^*b^*$ ), the individual typological angle (ITA) ( $\text{ITA}^\circ = [\arctan(L^* - 50)/b^*] \cdot 180/3.14159$ ) was calculated (24). Infants were classified into 5 skin phototypes: dark ( $\leq 10^\circ$ ), olive ( $10-28^\circ$ ), medium ( $28-41^\circ$ ), fair ( $41-55^\circ$ ), and very fair ( $>55^\circ$ ). The ITA difference between the exposed (forearm) and unexposed (inner arm) skin sites was used to assess exposure to sun during the trial.

**Plasma 25(OH)D.** Capillary blood samples were collected from infants by heel or finger lance and mother's fasted blood was collected by venipuncture (between 0800 and 1200 h). Samples were centrifuged ( $2235 \times g$  for 20 min at  $4^\circ\text{C}$ ) and stored frozen at  $-80^\circ\text{C}$  for batch analysis. Plasma samples were analyzed using a sensitive (limit of quantification: 12 nmol/L) liquid chromatography tandem MS (LC MS/MS) developed by Warnex Bioanalytical Services. This method uses derivatization of vitamin D metabolites with substituted triazolinediones in a Diels Alder cycloaddition with chromatographic separation of

**TABLE 1** Infant and mother baseline characteristics<sup>1</sup>

| Variable                                                              | Treatments      |                 |
|-----------------------------------------------------------------------|-----------------|-----------------|
|                                                                       | D2              | D3              |
| <b>Mothers</b>                                                        |                 |                 |
| Plasma 25(OH)D <sub>3</sub> , <sup>2</sup> nmol/L                     | 68.3 $\pm$ 21.4 | 69.5 $\pm$ 21.7 |
| Age at delivery, y                                                    | 31.0 $\pm$ 4.5  | 32.6 $\pm$ 4.2  |
| Income $\geq$ 75,000 Canadian \$, n (%)                               | 16 (61.5)       | 13 (50.0)       |
| Education, $\geq$ university, n (%)                                   | 20 (76.9)       | 17 (65.4)       |
| <b>Infants</b>                                                        |                 |                 |
| Male, n (%)                                                           | 12 (46.2)       | 13 (50.0)       |
| Born during vitamin D synthesizing period (April 1–October 31), n (%) | 15 (57.7)       | 15 (57.7)       |
| Taking a vitamin D supplement at baseline, n (%)                      | 17 (65.4)       | 21 (80.8)       |
| Age started vitamin D supplement, d                                   | 4 (3, 7)        | 5 (3, 10)       |
| White, self identified, <sup>3</sup> n (%)                            | 14 (58.3)       | 21 (80.8)       |
| Skin color (based on ITA <sup>4</sup> ), <sup>4</sup> n (%)           |                 |                 |
| Very fair                                                             | 2 (7.7)         | 3 (11.5)        |
| Fair                                                                  | 12 (46.2)       | 12 (46.2)       |
| Medium                                                                | 7 (26.9)        | 11 (42.3)       |
| Olive                                                                 | 3 (11.5)        | 0 (0.0)         |
| Dark                                                                  | 2 (7.7)         | 0 (0.0)         |

<sup>1</sup> Values are frequency and percent or mean  $\pm$  SD, n = 26. Non normally distributed data presented as median (25th, 75th percentile). D2, ergocalciferol; D3, cholecalciferol; ITA, individual typological angle; LC MS/MS, liquid chromatography tandem MS; 25(OH)D, 25 hydroxyvitamin D.

<sup>2</sup> Results were tested by LC MS/MS. The results were similar to LC MS/MS when tested by immunoassay: D2: 74.0  $\pm$  21.7 vs. D3: 79.6  $\pm$  27.4; P = 0.42.

<sup>3</sup> Based on mother's and father's race.

<sup>4</sup> ITA<sup>4</sup> =  $[\arctan(L^* - 50)/b^*] \cdot 180/3.14159$ , classified in 5 skin phototypes: dark ( $\leq 10^\circ$ ), olive ( $10-28^\circ$ ), medium ( $28-41^\circ$ ), fair ( $41-55^\circ$ ), and very fair ( $>55^\circ$ ). 1  $\mu\text{g}$  vitamin D = 40 IU.

epimers (25). The concentrations of 25 hydroxycholecalciferol [25(OH)D3] and 25 hydroxyergocalciferol [25(OH)D2] were calculated using Watson LIMS software, version 7.1.0.01. Pooled serum samples from the Vitamin D External Quality Assessment Scheme were used as quality control samples for 25(OH)D3. Deuterium labeled 25(OH)D3 was used as internal standard. The intra assay and inter assay percent CVs for 25(OH)D2 and 25(OH)D3 were <6.2% and <10.1%, respectively, for all controls. The analytical ranges were 12.5–250.0 nmol/L (5–100 µg/L) for 25(OH)D3 and 25(OH)D2. At baseline, no subjects had detectable concentrations of 25(OH)D2. At follow up, no subjects in the D3 group had detectable 25(OH)D2; therefore, the change in 25(OH)D for the D3 group was based only on 25(OH)D3 concentrations. For the D2 group, the sum of 25(OH)D2 and 25(OH)D3 at follow up was subtracted from baseline 25(OH)D2 to calculate the change in 25(OH)D. Values below the quantification limit of the assay were replaced by zero (26,27). Plasma 25(OH)D concentrations were categorized by different thresholds: ≤24.9 (deficiency), 25–49.9, 50–74.9, and ≥75 nmol/L.

To make this data usable by others using immunoassays, we also measured the total 25(OH)D concentration using an automated chemiluminescent immunoassay system (Liaison, DiaSorin). This assay measures total 25(OH)D in plasma and has a sensitivity of 10.0 nmol/L. The range of the assay was 10–375 nmol/L (4–150 µg/L). The intra assay and inter assay percent CVs were <4.9% and <10.7%, respectively, for the all controls. All analyses were completed in a laboratory meeting the performance targets set by the Vitamin D External Quality Assessment Scheme.

**Sample size.** A previous study in infants (<6 wk old) that gave 10 µg of D2 daily found a  $\Delta 35.7 \pm 20.2$  nmol/L during a 3 mo period (28). With a sample size of 26 participants/group,  $\alpha = 0.05$  and  $\beta = 0.20$  (power  $1 - \beta = 0.8$ ) would allow the detection of a difference of 45% between treatments in the change in 25(OH)D during the 3 mo period. This translates to an effect size of 16 nmol/L, representing ~1 SD in the change in the 25(OH)D concentration (28).

**Statistical methods.** Subject characteristics were tested for baseline differences among treatments using a *t* test for continuous variables and  $\chi^2$  (with Fisher's exact tests for small sample sizes) for categorical variables. Baseline characteristics with differences were included as covariates in the ANOVA model. The intent to treat principle was applied for all outcomes. The associations between mother's and infant's vitamin D status as well as the change in infant 25(OH)D concentrations and infant baseline vitamin D status were both tested using Pearson correlation. Plasma 25(OH)D concentrations at each time point as well as the mean change in 25(OH)D from baseline during the trial were compared between treatments using unpaired *t* tests. Differences in the change in 25(OH)D by treatment were also tested as a mixed model ANOVA accounting for any baseline differences among the groups. To compare the proportion of infants above or below the 50 and 75 nmol/L cutoffs among treatment groups, sample proportions were evaluated by  $\chi^2$  test (Fischer's Exact for small sample size). To evaluate the effect of baseline status on the change in 25(OH)D, the change in 25(OH)D was plotted (mean  $\pm$  SD) by baseline 25(OH)D category and analyzed by ANOVA. Tukey's adjustment for multiple comparisons was used to detect significant differences among categories for the D2 and D3 groups separately and over time. Data were checked for normality and equal variances using Shapiro Wilks and Levene's tests; appropriate nonparametric tests were used if assumptions were violated. Significance was set at  $P \leq 0.05$ ; all tests presented are 2 tailed. Data were analyzed using SAS version 9.2 (SAS Institute).

## Results

A total of 52 healthy infants were enrolled and 73% were taking a vitamin D supplement at baseline. There was a trend ( $P = 0.08$ ) for differences in race among the groups (Table 1); however, skin color did not differ ( $P = 0.23$ ). Two infants in the D2 group were lost to follow up (Fig. 1). Infants were growing; the mean weight for age and length for age Z scores were within 1 SD from the WHO standard. However, the D3 group had a

significantly higher length for age Z score than the D2 group at baseline and follow up (Supplemental Table 1). The supplementation period tended ( $P = 0.09$ ) to be 10% longer in the D3 group than in the D2 group. There were no differences in compliance among groups as assessed by both bottle weighing (median 89, range 32–100% of doses taken) and reported intake (95, 31–100% of doses taken). Maternal vitamin D status at baseline was associated with neonatal values at both baseline ( $r = 0.41$ ;  $P = 0.003$ ) and follow up ( $r = 0.31$ ;  $P = 0.03$ ) as measured using LC MS/MS; similar results were obtained by immunoassay (data not shown).

Overall, based on LC MS/MS measurements, both supplements significantly increased the plasma 25(OH)D concentration during the 3 mo period, with a mean increase of 20.0 nmol/L (95% CI: 13.3–26.6 nmol/L) (Fig. 2). The mean difference between the increases (D2–D3) was 4.5 nmol/L (95% CI: 17.9 to 8.9 nmol/L;  $P = 0.5$ ). The difference between the slopes of the line [ $\Delta$  in plasma 25(OH)D/ $\Delta$  in time] of the 2 groups was not significant (D2:  $24.4 \pm 6.6$  nmol/L; D3:  $18.8 \pm 6.2$  nmol/L;  $P = 0.54$ ). However, a higher ( $P = 0.05$ ) proportion of infants in the D3 group (96.2%) than in the D2 group (75.0%) achieved the 50 nmol/L cutoff at follow up (Table 2). No differences were noted among groups in the proportion that achieved the 75 nmol/L cutoff at follow up. A larger proportion of infants in the D2 group ( $n = 8$ ; 33%) had decreases in 25(OH)D concentration during the 3 mo period compared with infants in the D3 group ( $n = 2$ ; 8%) (Fischer's Exact test,  $P = 0.02$ ). Similar results were observed using the immunoassay (Fig. 2; Table 2).

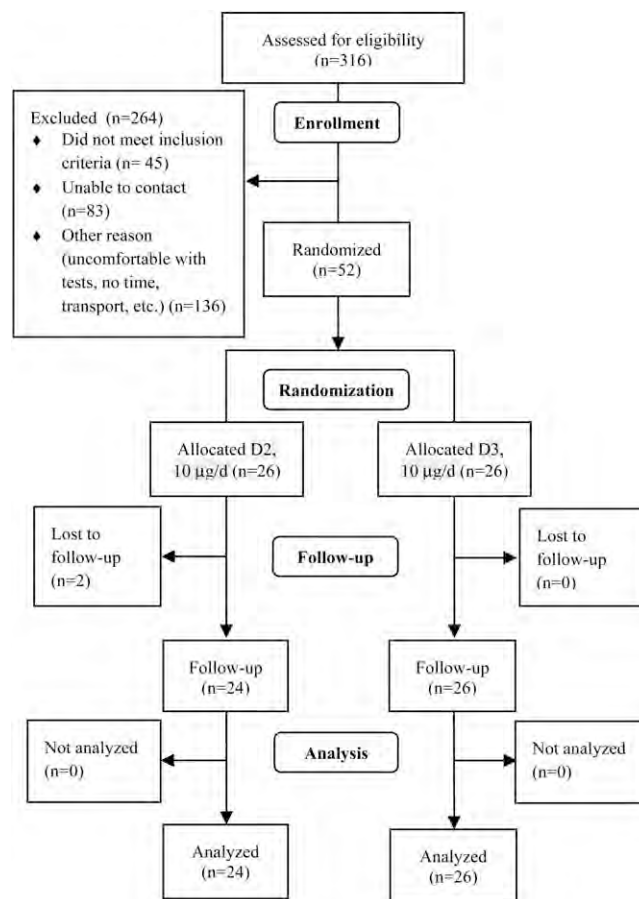


**FIGURE 1** Consort diagram. 1 µg vitamin D = 40 IU. D2, ergocalciferol; D3, cholecalciferol.

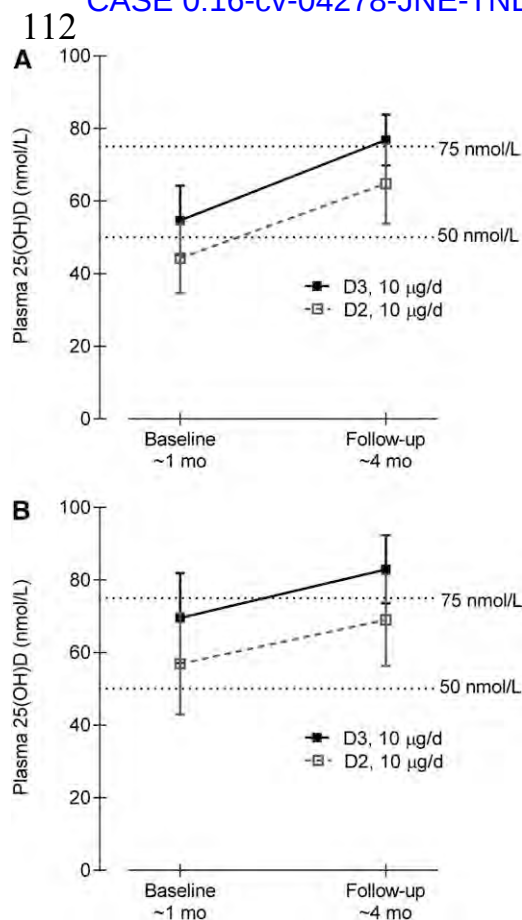


**FIGURE 2** Plasma 25(OH)D concentrations at baseline (~1 mo) and follow up (~4 mo) in infants that received 10 µg/d D2 or D3 as assessed by LC MS/MS (A) and immunoassay (B). Values are means and 95% CI,  $n = 24$ –26. 25(OH)D, 25 hydroxyvitamin D; D2, ergocalciferol; D3, cholecalciferol; LC MS/MS, liquid chromatography tandem <S.

The baseline plasma 25(OH)D concentration based on the LC MS/MS assay was inversely related to the change in 25(OH)D ( $r = 0.52$ ;  $P < 0.001$ ) (Fig. 3). The change in 25(OH)D concentrations did not significantly differ between groups when infants were categorized by baseline plasma 25(OH)D status (Fig. 3). The baseline 25(OH)D concentration, length for age Z score, and supplementation period were included as covariates in the mixed model ANCOVA. There were no differences in the change in plasma 25(OH)D between groups ( $P = 0.21$ ). Similar results were observed using the immunoassay (data not shown).

As assessed by Bland Altman analysis, the LC MS/MS and immunoassay plasma 25(OH)D concentration limits of agreement ranged from  $-40$  to  $+26\%$  (Supplemental Fig. 1). The  $\kappa$  coefficient between methods was 0.57 when infants were categorized according to plasma 25(OH)D concentrations at follow up.

## Discussion

Daily supplementation of either vitamin D isoform at 10 µg/d elevated the plasma 25(OH)D concentration from 1 to 4 mo of age in healthy, breast fed infants. This was important to know, because both D3 and D2 are common in the North American marketplace. These results are in accordance with the IOM's Dietary Reference Intakes for vitamin D (3), which state "the two isoforms appear to be equivalent and adequate for almost all infants." However, a significantly higher proportion of

infants in the D3 group achieved the 50 nmol/L cutoff of plasma 25(OH)D by 3 mo compared with infants in the D2 group. Possible explanations include the fact that infants in the D2 group commenced the study with lower plasma 25(OH)D concentrations ( $P = 0.06$ ) and the supplementation period was slightly shorter ( $P = 0.09$ ). Our results were similar when 25(OH)D concentrations were measured by immunoassay or LC MS/MS. We observed a significantly larger proportion of infants in the D2 group with decreases in 25(OH)D concentrations during the 3 mo period compared with infants in the D3 group. However, the mean decrease for 8 of the 24 infants in the D2 group was  $<10$  nmol/L and compliance was questionable in 4 of these infants, who consumed  $<60\%$  of doses (assessed either as reported or loss from bottle). Overall, the majority of infants (86%) achieved the 50 nmol/L cutoff at follow up as suggested by the IOM for achievement of bone health (3). The results presented in this report complement the work of Gordon et al. (18), who found no differences in 25(OH)D concentrations after 6 wk of supplementation of 50 µg/d D2 compared with D3 for the treatment of low vitamin D status [25(OH)D  $\leq 50$  nmol/L] in older infants and toddlers. The increase in 25(OH)D after supplementation is largely dependent on the baseline 25(OH)D concentration and our sample consisted of 44% of infants with 25(OH)D  $\leq 50$  nmol/L at baseline. The observation that baseline 25(OH)D is a predictor of the change in 25(OH)D over time has been previously observed in adults (29,30). This study shows that baseline status is an important factor in determining the

**TABLE 2** Plasma 25(OH)D concentrations and number (%) meeting 25(OH)D cutoffs of  $\geq 50$  and  $\geq 75$  nmol/L in infants that received 10 µg/d of D2 or D3 as assessed by immunoassay and LC-MS/MS<sup>1</sup>

|                                                            | Treatments  |          |             |          |
|------------------------------------------------------------|-------------|----------|-------------|----------|
|                                                            | D2          | <i>n</i> | D3          | <i>n</i> |
| Immunoassay                                                |             |          |             |          |
| Baseline 25(OH)D, nmol/L                                   | 56.9 ± 33.7 | 25       | 69.5 ± 30.6 | 26       |
| Follow up 25(OH)D, nmol/L                                  | 69.0 ± 30.0 | 24       | 82.9 ± 23.1 | 26       |
| Δ Total 25(OH)D, nmol/L                                    | 7.1 ± 36.7  | 23       | 13.4 ± 19.6 | 26       |
| (95% CI)                                                   | -8.8 22.9   |          | 5.5 21.4    |          |
| LC MS/MS <sup>2</sup>                                      |             |          |             |          |
| Baseline 25(OH)D3, nmol/L                                  | 44.2 ± 23.8 | 26       | 54.6 ± 23.7 | 26       |
| Baseline 25(OH)D3, <i>n</i> (%)                            |             |          |             |          |
| ≤24.9 nmol/L                                               | 8 (30.8)    |          | 4 (15.4)    |          |
| 25 49.9 nmol/L                                             | 5 (19.2)    |          | 6 (23.1)    |          |
| 50 74.9 nmol/L                                             | 12 (46.2)   |          | 13 (50.0)   |          |
| ≥75 nmol/L                                                 | 1 (3.9)     |          | 3 (11.5)    |          |
| Follow up                                                  |             |          |             |          |
| Total 25(OH)D, nmol/L                                      | 64.8 ± 26.2 | 24       | 76.8 ± 17.4 | 26       |
| Follow up 25(OH)D2, nmol/L                                 | 45.1 ± 30.7 |          | na          |          |
| Follow up 25(OH)D3, nmol/L                                 | 19.6 ± 20.2 |          | 76.8 ± 17.4 |          |
| Δ Total 25(OH)D, <sup>2</sup> nmol/L                       | 17.6 ± 26.7 | 24       | 22.2 ± 20.2 | 26       |
| (95% CI)                                                   | 6.4 28.9    |          | 14.0 30.3   |          |
| 25(OH)D ≥50 nmol/L at follow up, <sup>3</sup> <i>n</i> (%) | 18 (75.0)   |          | 25 (96.2)*  |          |
| 25(OH)D ≥75 nmol/L at follow up, <sup>3</sup> <i>n</i> (%) | 9 (37.5)    |          | 14 (53.8)   |          |

<sup>1</sup> Values are frequency and percent or mean ± SD. \*Different from D2 group,  $P \leq 0.05$ . D2, ergocalciferol; D3, cholecalciferol; LC MS/MS: liquid chromatography tandem MS; 25(OH)D, 25 hydroxyvitamin D; 25(OH)D3, 25 hydroxycholecalciferol; 25(OH)D2, 25 hydroxyergocalciferol.

<sup>2</sup> D2 group: total 25(OH)D = 25(OH)D2 + 25(OH)D3; D3 group: 25(OH)D3.

<sup>3</sup> Results were similar to LC MS/MS when tested by immunoassay: proportion of infants  $\geq 50$  nmol (D2: 79.2% vs. D3: 100%) or  $\geq 75$  nmol (D2: 37.5% vs. D3: 57.7%) cutoffs. 1 µg vitamin D = 40 iu.

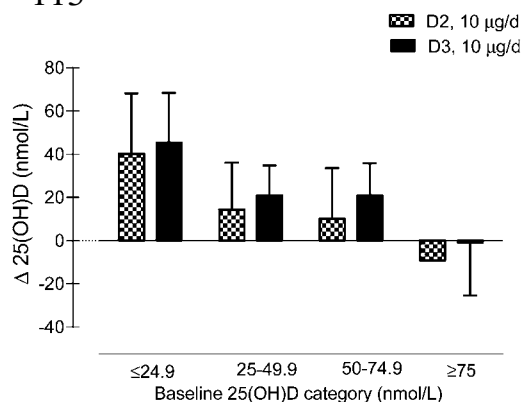


**FIGURE 3** Plasma 25(OH)D concentration by LC MS/MS from 1 to 4 mo of age in infants that received 10 µg/d D2 or D3 by baseline 25(OH)D category. Data are mean change ± SD. 25(OH)D, 25 hydroxyvitamin D; D2, ergocalciferol; D3, cholecalciferol; LC MS/MS, liquid chromatog raphy tandem MS.

response to supplementation in healthy infants. When infants were categorized by baseline status, there were no differences in the change in 25(OH)D concentration between treatment groups.

Previous studies in adults established a magnitude difference of 1.7 fold in the change in 25(OH)D concentration among groups taking D2 compared with D3; however, this was based on administration of an equivalent dosage of 100 µg/d (14). A lower dosage of 10 µg/d might result in more modest differences among groups. A similar pattern was observed in this dataset compared with Trang et al. (14) [30% higher change in 25(OH)D concentration in the D3 vs. D2 group]; however, the present study was perhaps underpowered for this analysis. A larger sample size would have provided more confidence to detect a smaller difference between treatments. Although most equivalence studies testing D2 compared with D3 had a similar number of subjects [Armas et al. (13),  $n = 30$ ; Holick et al. (15),  $n = 68$ ; Trang et al. (14),  $n = 72$ ], future studies testing daily low dose vitamin D (10 µg) should aim for an effect size in the range of 10–20% between the groups.

One of the challenges in assessing vitamin D status in infants includes the potential for a large proportion of 25(OH)D being in the C 3  $\alpha$  epimer form (31). To circumvent this issue and to quantify both 25(OH)D isoforms, 2 assays were used: one to quantify the isoforms and epimers individually (LC MS/MS) and one that measured the total 25(OH)D without cross reactivity to the epimer (chemiluminescence). Although moderate agreement was found between methods (limits of agreement, 40 to +26%), this is in line with other studies in adults (32) (limits of agreement, 57 to +48). In addition, replacing values below the level of quantification with zero or one half the quantification level (26,27) followed the same pattern. Furthermore, because both assays resulted in similar interpretations, either would be suitable for routine monitoring of vitamin D status in infants.

In our study, the infants were of healthy weight at birth and grew well according to the WHO standards. However, the generalizability of our vitamin D status results may pertain to only young infants (<4 mo), because vitamin D metabolism may change during the first year of life secondary to increases in growth, bone accretion, and maturation of enzymes and organs (3). This dataset was limited in sample size; thus, it would be important to conduct future, larger studies of longer duration to help establish whether older infants respond in a similar manner as well as to evaluate functional outcomes such as bone mass or calcium homeostasis.

In conclusion, this study provides novel findings regarding daily low dose supplementation of the 2 vitamin D isoforms in breast fed newborns. The increases in 25(OH)D concentration between the D2 and D3 groups did not differ, suggesting a sustained daily intake of either isoform is acceptable for infants 4 mo of age and younger.

### Acknowledgments

The authors thank Dr. Line Duchesne, Manon Fabi, Louise LaCroix, and Christiane Leonard for their help with recruitment. S.G., C.R., and H.A.W. designed the research project; S.G., A.P., and C.A.V. conducted the research (collected data and conducted biochemistry); S.G. with the consultation of H.A.W. and C.R. performed all statistical analyses and wrote the paper; and C.A.V. and A.P. provided revisions. All authors read and approved the final manuscript.

### Literature Cited

1. European Commission. Opinion on the Scientific Committee on Food on the tolerable upper intake level of vitamin D. Brussels: European Commission; 2003.
2. Vitamin D supplementation for breastfed infants; 2004. Health Canada Recommendations [cited 2012 Aug 14]. Available from: [http://www.hc.gc.ca/fn/alt\\_formats/hpfb/dgpsa/pdf/nutrition/vita\\_d\\_supp\\_e.pdf](http://www.hc.gc.ca/fn/alt_formats/hpfb/dgpsa/pdf/nutrition/vita_d_supp_e.pdf).
3. Institute of Medicine. Dietary Reference Intakes for calcium and vitamin D. Washington, DC: National Academy Press; 2011.
4. Munns C, Zacharin MR, Rodda CP, Batch JA, Morley R, Cranswick NE, Craig ME, Cutfield WS, Hofman PL, Taylor BJ, et al. Prevention and treatment of infant and childhood vitamin D deficiency in Australia and New Zealand: a consensus statement. *Med J Aust.* 2006;185: 268–72.
5. Mutlu GY, Kusdal Y, Ozsu E, Cizmecioglu FM, Hatun S. Prevention of vitamin D deficiency in infancy: daily 400 IU vitamin D is sufficient. *Int J Pediatr Endocrinol.* 2011;4.
6. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics.* 2008;122:1142–52.
7. Vitamin D supplementation: recommendations for Canadian mothers and infants. *Paediatr Child Health (Oxford).* 2007;12:583–9.
8. Greer FR, Searcy JE, Levin RS, Steichen JJ, Steichen Asche PS, Tsang RC. Bone mineral content and serum 25 hydroxyvitamin D concentrations in breast fed infants with and without supplemental vitamin D: one year follow up. *J Pediatr.* 1982;100:919–22.
9. Specker BL, Ho ML, Oestreich A, Yin TA, Shui QM, Chen XC, Tsang RC. Prospective study of vitamin D supplementation and rickets in China. *J Pediatr.* 1992;120:733–9.
10. Zeghoud F, Vervel C, Guillozo H, Walrant Debray O, Boutignon H, Garabedian M. Subclinical vitamin D deficiency in neonates: definition and response to vitamin D supplements. *Am J Clin Nutr.* 1997;65: 771–8.
11. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest.* 2006;116:2062–72.
12. Jones G, Strugnelli SA, DeLuca HF. Current understanding of the molecular actions of vitamin D. *Physiol Rev.* 1998;78:1193–231.
13. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab.* 2004;89: 5387–91.
14. Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R. Evidence that vitamin D3 increases serum 25 hydroxyvitamin D more efficiently than does vitamin D2. *Am J Clin Nutr.* 1998;68:854–8.
15. Holick MF, Biancuzzo RM, Chen TC, Klein EK, Young A, Bibuld D, Reitz R, Salameh W, Ameri A, Tannenbaum AD. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25 hydroxyvitamin D. *J Clin Endocrinol Metab.* 2008;93:677–81.
16. Rapuri PB, Gallagher JC, Haynatzki G. Effect of vitamins D2 and D3 supplement use on serum 25OHD concentration in elderly women in summer and winter. *Calcif Tissue Int.* 2004;74:150–6.
17. Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, Chope G, Hypponen E, Berry J, Vieth R, et al. Comparison of vitamin D2 and

- vitamin D3 supplementation in raising serum 25 hydroxyvitamin D status: a systematic review and meta analysis. *Am J Clin Nutr.* 2012;95:1357-64.
18. Gordon CM, Williams AL, Feldman HA, May J, Sinclair L, Vasquez A, Cox JE. Treatment of hypovitaminosis D in infants and toddlers. *J Clin Endocrinol Metab.* 2008;93:2716-21.
  19. Hollis BW, Lowery JW, Pittard WB III, Guy DG, Hansen JW. Effect of age on the intestinal absorption of vitamin D3 palmitate and nonesterified vitamin D2 in the term human infant. *J Clin Endocrinol Metab.* 1996;81:1385-8.
  20. Fujisawa Y, Kida K, Matsuda H. Role of change in vitamin D metabolism with age in calcium and phosphorus metabolism in normal human subjects. *J Clin Endocrinol Metab.* 1984;59:719-26.
  21. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J Clin Endocrinol Metab.* 1988;67:373-8.
  22. Wren TA, Kim PS, Janicka A, Sanchez M, Gilsanz V. Timing of peak bone mass: discrepancies between CT and DXA. *J Clin Endocrinol Metab.* 2007;92:938-41.
  23. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: growth velocity based on weight, length and head circumference: methods and development. Geneva: WHO; 2009.
  24. Del Bino S, Sok J, Bessac E, Bernerd F. Relationship between skin response to ultraviolet exposure and skin color type. *Pigment Cell Res.* 2006;19:606-14.
  25. Aronov PA, Hall LM, Dettmer K, Stephensen CB, Hammock BD. Metabolic profiling of major vitamin D metabolites using Diels Alder derivatization and ultra performance liquid chromatography tandem mass spectrometry. *Anal Bioanal Chem.* 2008;391:1917-30.
  26. Cole SR, Chu H, Nie L, Schisterman EF. Estimating the odds ratio when exposure has a limit of detection. *Int J Epidemiol.* 2009;38:1674-80.
  27. Langlois K, Greene Finestone L, Little J, Hidioglou N, Whiting S. Vitamin D status of Canadians as measured in the 2007 to 2009 Canadian Health Measures Survey. *Health Rep.* 2010;21:47-55.
  28. Saadi HF, Dawodu A, Afandi B, Zayed R, Benedict S, Nagelkerke N, Hollis BW. Effect of combined maternal and infant vitamin D supplementation on vitamin D status of exclusively breastfed infants. *Matern Child Nutr.* 2009;5:25-32.
  29. Kluczynski MA, Wactawski Wende J, Platek ME, Denyschen CA, Hovey KM, Millen AE. Changes in vitamin D supplement use and baseline plasma 25 hydroxyvitamin D concentration predict 5 y change in concentration in postmenopausal women. *J Nutr.* 2012;142:1705-12.
  30. Zhao LJ, Zhou Y, Bu F, Travers Gustafson D, Ye A, Xu X, Hamm L, Gorsage DM, Fang X, Deng HW, et al. Factors predicting vitamin D response variation in non Hispanic white postmenopausal women. *J Clin Endocrinol Metab.* 2012;97:2699-705.
  31. Singh RJ, Taylor RL, Reddy GS, Grebe SK. C 3 epimers can account for a significant proportion of total circulating 25 hydroxyvitamin D in infants, complicating accurate measurement and interpretation of vitamin D status. *J Clin Endocrinol Metab.* 2006;91:3055-61.
  32. Roth HJ, Schmidt Gayk H, Weber H, Niederau C. Accuracy and clinical implications of seven 25 hydroxyvitamin D methods compared with liquid chromatography tandem mass spectrometry as a reference. *Ann Clin Biochem.* 2008;45:153-9.

## RESEARCH ARTICLE

## Open Access

# Very high vitamin D supplementation rates among infants aged 2 months in Vancouver and Richmond, British Columbia, Canada

Barbara Crocker<sup>1</sup>, Tim J Green<sup>2\*</sup>, Susan I Barr<sup>2</sup>, Bridgid Beckingham<sup>1</sup>, Radhika Bhagat<sup>1</sup>, Beata Dabrowska<sup>1</sup>, Rachel Douthwaite<sup>1</sup>, Carmen Evanson<sup>1</sup>, Russell Friesen<sup>2</sup>, Kathy Hydamaka<sup>3</sup>, Wangyang Li<sup>2</sup>, Kelly Simmons<sup>1</sup> and Lillian Tse<sup>1</sup>

## Abstract

**Background:** Vitamin D deficiency during infancy may lead to rickets and possibly other poor health outcomes. The World Health Organization recommends exclusive breastfeeding for the first 6 months. Breast milk is the best food for infants but does not contain adequate vitamin D. Health Canada recommends all breastfed infants receive a daily vitamin D supplement of 400 IU; however, there appears to be limited current Canadian data as to whether parents or caregivers are following this advice. The aim of this study was to determine the rates of vitamin D supplementation among 2 month old infants in Vancouver and Richmond, British Columbia, Canada.

**Methods:** Mothers of all healthy infants born between April and May 2010 were approached to participate. Telephone surveys were conducted with 577 mothers (response rate 56%) when their infants turned 2 months.

**Results:** Over half of the infants received only breast milk in the week prior to the survey. One third received a mixture of breast milk and infant formula and 10% received only formula. About 80% of the infants were supplemented with vitamin D at 2 months. Infants who received only breast milk were most likely to be supplemented with vitamin D (91%). Over 60% of the infants had a total vitamin D intake of 300 < 500 IU/d from supplements and formula and only 5% did not receive any vitamin D. Most parents were advised to give vitamin D supplement by health professionals, such as public health nurses, midwives, and doctors.

**Conclusions:** About 90% of the infants received breast milk at 2 months of age. The vitamin D supplementation rate was 80%. Future studies are needed to monitor breastfeeding duration and vitamin D supplementation rates as infants get older.

## Background

Worldwide public health authorities recommend exclusive breastfeeding for the first 6 months of life for healthy term infants [1-3]. Breast milk is the best food for optimal growth of the infant and breastfeeding has been associated with improved health outcomes for mother and infant [1]. While breast milk is the ideal food for infant, it does not generally supply adequate amounts of vitamin D [4]. As such, breastfed infants are at risk of vitamin D deficiency [5]. In its most serious

form vitamin D deficiency in infancy leads to rickets, a condition characterized by weakened bones, resulting from poor mineralization of newly formed bone tissue [6]. Additionally, there is emerging evidence that lack of vitamin D during infancy, is associated with altered calcium metabolism [7], early childhood tooth decay [8], and increased risk of Type 1 Diabetes [9], and asthma later on [10].

While infant formula is fortified with vitamin D, breastfed infants are reliant on skin synthesis of vitamin D through the action of sunlight or supplemental vitamin D. Due to the risk of skin cancer it is generally recommended that infants under 1 year be kept out of direct sunlight [11]. Owing to concerns about vitamin D

\* Correspondence: tim.green@ubc.ca

<sup>2</sup>Food, Nutrition and Health, University of British Columbia, 2205 East Mall, Vancouver V6T 1Z4, Canada

Full list of author information is available at the end of the article

deficiency, Health Canada [4], the American Academy of Pediatrics [3], as well as several European countries [12-14] recommend that breastfed infants receive a daily vitamin D supplement, usually 400 IU. In Canada this recommendation has been in place since 1967 [4], yet, other than in the province of Quebec [15,16], there are few data as to whether parents or caregivers are following this advice. As part of the Canadian Community Health Survey 2007-2008 [17], Statistics Canada reported that among women who had given birth in the past 5 years and exclusively breastfed their infant, 67% provided a vitamin D supplement to the infant. However, this survey did not consider the frequency, dose, or form of supplement, nor were supplementation practices assessed among women who fed their infants a combination of breast milk and formula. Further, this survey included women who gave birth as early as 2002 and there may now be greater awareness about the importance of vitamin D. Indeed, Gallo et al. [18] reported that in one Montreal hospital 98% of exclusively breastfeeding mothers who gave birth in 2007-2008 supplemented their infants at some point prior to 6 months of age.

As part of British Columbia's (BC) publicly funded medical system, public health nurses provide breastfeeding support including advice on vitamin D supplementation within the first few days postpartum. To assess the effectiveness of this health promotion strategy, we conducted a survey in 2010 to determine the rates of breastfeeding and vitamin D supplementation among 2-month old infants in Vancouver and Richmond, BC. We also wanted to determine the type and dose of vitamin D supplementation given, examine the association of socio-demographic factors and vitamin D supplementation and determine barriers to infant vitamin D supplementation.

## Methods

### Sampling frame

Ethical approval to conduct the study was obtained from the University of British Columbia Behavioural Research Ethics Board. The survey was conducted in Richmond and five of six Community Health Areas in Vancouver. Vancouver (population 578,041; 2006) and Richmond (population 174,461; 2006) are the largest and fourth largest cities, respectively, in BC, Canada. All parents or caregivers whose infant was born between April and May of 2010 were invited to participate in the survey. Parents or caregivers were ineligible: if they moved out of the catchment area or were involved in a program that provided care to high-risk mothers (i.e. substance-abuse); or if their infant was adopted, in foster-care, or under the care of a neonatal intensive care unit. An infant age of 2 months was chosen because we wanted

to survey women who had established breastfeeding and before the breastfeeding rates decline. Initial recruitment took place through public health nurses who asked the parent at an early postpartum contact whether they would be willing to participate in a short telephone interview. At an infant age of 2 months (range = 7-10 weeks) a research assistant phoned the parent to complete the survey after again obtaining verbal consent to participate.

### Survey

The survey questionnaire was designed to obtain information on infant feeding practices; vitamin D supplementation including the form, frequency, and dose; who recommended that the infant be supplemented and (if appropriate) the reasons for not supplementing; and basic socio-demographic questions. The questionnaire was initially developed by the study investigators through face-to-face meetings and through consultation and focus testing with relevant stakeholders. We piloted the questionnaire with ten new parents and revised it accordingly. The questionnaire was administered in English or when required in Mandarin, Cantonese, Punjabi, Vietnamese, or Spanish.

### Data analysis

In our study, we defined "All breast milk" as infants who had received only breast milk (vitamins, minerals, and medicines permitted) in the week prior to the survey [2]. "Mixed breast milk and formula" was used to define infants who had received a mixture of breast milk and infant formula in the week prior to the survey. "Infant formula" was used to define infants who had received only formula in the week prior to the survey. Based on data indicating that 2-month old infants are fed an average of 8 times per day [3], we further divided the "mixed breast milk and formula" group into: "≥75% of breast milk" defined as ≤2 feedings of other liquids/food per day; "50- < 75% breast milk" as 3-4 feedings of other liquids/food per day; and "< 50% breast milk" as > 4 feedings of other liquids/food per day. Average daily formula intake was calculated by multiplying frequency of consumption in 24 hours by the amount of formula received in each bottle feed. The amount of vitamin D provided by formula was calculated assuming infant formula contains 40 IU vitamin D/100 ml, and the average intake of vitamin D provided by supplements was calculated based on the amount per dose and the frequency of administration. These two sources were summed to determine daily vitamin D intake. Descriptive statistics were used to describe breastfeeding and vitamin D supplementation rates (proportion with 95% confidence interval). Chi Square tests were used to determine differences in vitamin D supplementation by feeding practice.

Rates were also stratified by socio-demographic variables such as ethnicity. The proportion of infants receiving a total vitamin D intake of < 300 IU from supplements and/or formula was also examined by feeding practice using Chi-square. A cut-point of 300 IU was selected because in order to achieve 400 IU per day a caregiver of breastfed infant would need to be 100% compliant with daily supplementation during the week surveyed. Further, the evidence base for infant requirements is poor [19] and recent trials suggest that 400 IU vitamin D exceeds requirements [20]. Multiple logistic regression was used to determine significant predictors (from among age, ethnicity, parity, income, and education) of receiving vitamin D supplements in two separate models; one in women whose infants had only received breast milk in the week prior to the survey and the other in those providing at least 50% of feeds from breast milk.

### Results

Of the 1028 women eligible to participate, 577 completed the survey giving a response rate of 56% (Figure 1). Participant characteristics are given in Table 1. The majority of the mothers were over 31 y. One third of the infants were of European ethnicity and another one

third was Chinese. Among those who responded to the annual family income question ( $n = 454$ ), almost half had an income greater than \$80,000. Participants were generally well educated with 87% having completed some post-secondary education.

The breastfeeding initiation rate was 99% ( $n = 570$ ) and by 2 months of age over 40% of women were exclusively breastfeeding, using the WHO definition (2). Table 2 displays feeding practices and vitamin D supplementation practices at 2 months of age. Nearly 90% of infants were still receiving some breast milk. Over half received only breast milk in the past week; about one third received a mixture of breast milk and formula ranging from  $\leq 2$  to  $> 4$  feedings of other liquids/food per day; and about 10% received only infant formula. Of the 577 infants, about 80% were supplemented with vitamin D at the time mothers were surveyed. Rates of vitamin D supplementation were significantly higher in those receiving only breast milk in the past week than those who received both breast milk and formula, which in turn were higher than exclusively formula fed babies. Within the mixed breast milk and formula group, infants receiving < 50% breast milk were less likely to be supplemented with vitamin D than those receiving 50% or more breast milk ( $P < 0.001$ ). The proportion of

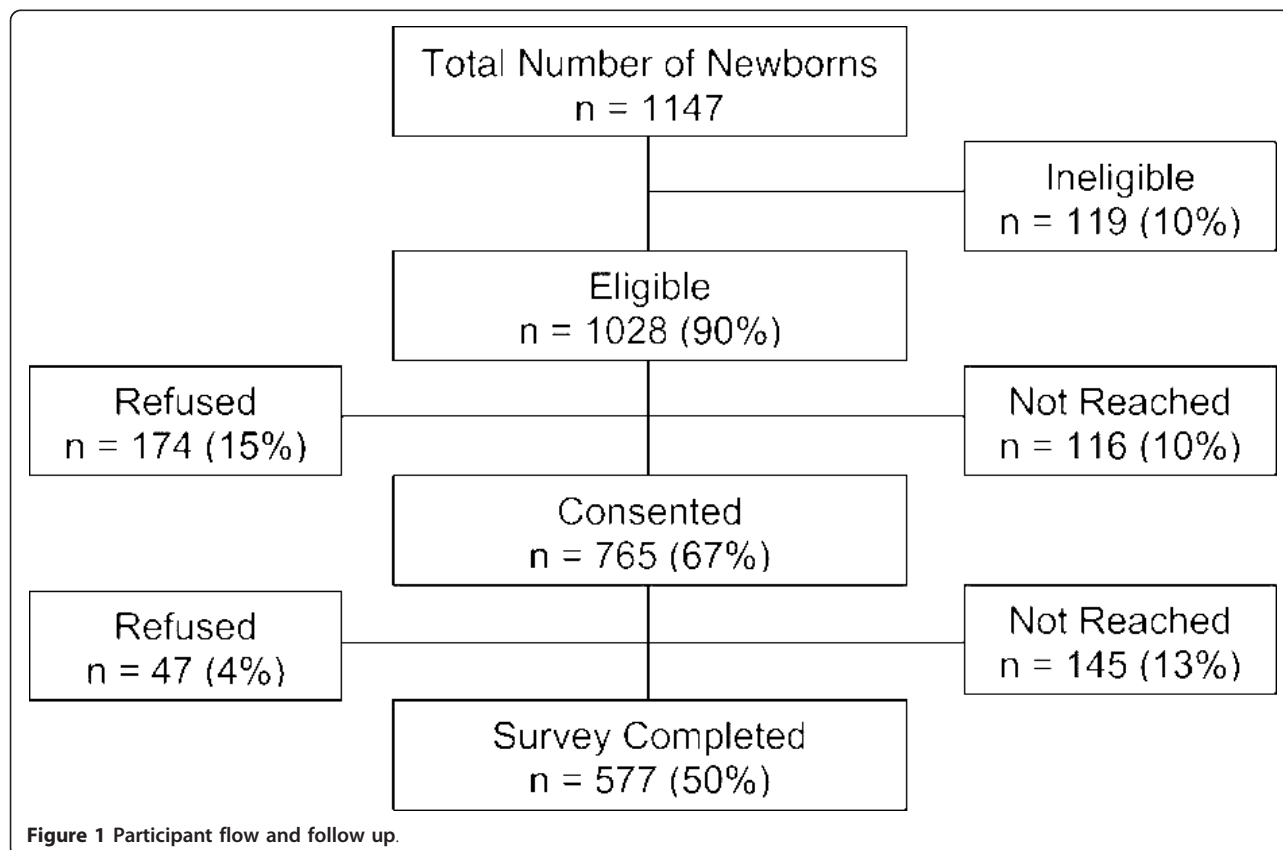


**Table 1 Participant characteristics**

| Characteristic                                             | % (n)         |
|------------------------------------------------------------|---------------|
| Maternal Age                                               |               |
| < 31                                                       | 33.3<br>(192) |
| ≥31                                                        | 66.7<br>(385) |
| Baby's ethnicity                                           |               |
| European                                                   | 36.7<br>(212) |
| Chinese                                                    | 31.2<br>(180) |
| Other <sup>1</sup>                                         | 32.1<br>(185) |
| Annual family income                                       |               |
| <\$40,000                                                  | 19.6<br>(113) |
| \$40,000 59,000                                            | 11.3 (65)     |
| \$60,000 80,000                                            | 10.4 (60)     |
| >\$80,000                                                  | 37.4<br>(216) |
| Unknown <sup>2</sup>                                       | 21.3<br>(123) |
| Education                                                  |               |
| < High school                                              | 0.3 (2)       |
| Some and completed high school                             | 12.5 (72)     |
| Some trade/vocational training and college/university      | 8.8 (51)      |
| Completed trade/vocational training and college/university | 78.3<br>(452) |
| Parity                                                     |               |
| Primipara                                                  | 52.0<br>(300) |
| Multipara                                                  | 48.0<br>(277) |
| Baby's gender                                              |               |
| Male                                                       | 50.6<br>(292) |
| Female                                                     | 49.4<br>(285) |
| Marital status                                             |               |
| Single                                                     | 4.9 (28)      |
| Married                                                    | 85.6<br>(494) |
| Common law                                                 | 8.5 (49)      |
| Other                                                      | 1.0 (6)       |

<sup>1</sup>South Asian 42.0% (63), South East Asian 42.7% (64), Korean 6.0% (9), Japanese 9.3% (14), Aboriginal 25.7% (9), Black 22.9% (8), Middle Eastern 42.9% (15), Iranian 2.9% (1), Afghan 2.9% (1), Turkish 2.9% (1)

<sup>2</sup>Do not know and do not want to say

infants receiving less than 300 IU vitamin D per day (supplement and/or formula) was higher among infants receiving only breast milk than among those fed mixed breast milk and formula. However, within this group

there was no difference in the percentage of infants receiving less than 300 IU per day.

About 5% of the infants did not receive any vitamin D from supplements and/or infant formula and 61% had a total vitamin D intake of 300- < 500 IU/d (Figure 2). Approximately 10% received 500 IU or more per day with the highest intake being 1130 IU/d (1000 IU from the supplement). Of those infants who were given vitamin D supplements, 80% received D-Drops<sup>®</sup> (a concentrated formula that provides 400 IU in a single drop) and 16% received D-Vi-Sol<sup>®</sup> (a formula that provides 400 IU per 1 mL). As shown in Table 3, over 90% of participants recalled receiving one or more recommendations to give their infant a vitamin D supplement. Public health nurses and physicians were the most frequent sources of this recommendation. Women who did use a supplement were asked to respond to an open question on why they chose to do so. The most common reasons were related to the inadequate amounts of vitamin D in breast milk, that a supplement had been recommended, that vitamin D had health benefits for the infant, and that lack of sunlight exposure meant supplementation was needed. Women who did not provide a supplement were asked to choose from a list on why they did not. Among those providing a response, the most common reasons were that the infant was being given formula, or that they did not think supplementation was necessary.

In multiple regression analysis of infants receiving only breast milk in the week prior to the survey ( $n = 331$ ), only parity was associated with vitamin D supplementation. Primiparas were more likely to supplement their infants than multiparas (95% versus 84%;  $P = 0.03$ ). Table 4 shows the results of the logistic regression of selected variables associated with vitamin D supplementation in infants who received greater than 50% of their feeds from breast milk ( $n = 517$ ). None of the variables studied was significantly associated with supplementation, although there was a tendency for a higher rate of vitamin D supplementation in infants from families in the two higher income categories than those in the lowest income category.

## Discussion

In this study we build on previous Canadian observations indicating high rates of breastfeeding and vitamin D supplementation, and provide new information regarding the dose of vitamin D provided, and mothers' reasons for choosing to supplement or not supplement. Almost 60% of infants had received only breast milk in the week prior to the survey and of these greater than 90% had received vitamin D supplements. This is much higher than the 67% vitamin D supplementation rate reported in a 2007-2008 survey for Canadian women

**Table 2 Feeding practices and vitamin D supplementation of infants aged two months**

| Feeding practice                  | Feeding Practice | Vitamin D Supplement     | < 300 IU/d Vitamin D <sup>5</sup> |
|-----------------------------------|------------------|--------------------------|-----------------------------------|
|                                   | % (n)            | % yes (n)                | % (n)                             |
| Total                             | 100.0 (577)      | 79.9 (461)               | 28.9 (167)                        |
| All breast milk <sup>1</sup>      | 57.4 (331)       | 91.2 (302) <sup>a*</sup> | 33.5 (111) <sup>a</sup>           |
| Mixed breast milk and formula     | 32.2 (186)       | 79.0 (147) <sup>b</sup>  | 22.0 (41) <sup>b</sup>            |
| ≥75% breast milk <sup>2</sup>     | 53.8 (100)       | 86.0 (86)                | 21.0 (21)                         |
| 50 < 75% breast milk <sup>3</sup> | 20.4 (38)        | 84.2 (32)                | 26.3 (10)                         |
| < 50% breast milk <sup>4</sup>    | 25.8 (48)        | 60.4 (29)                | 20.8 (10)                         |
| Infant formula                    | 10.4 (60)        | 20.0 (12) <sup>c</sup>   | 25.9 (15) <sup>ab</sup>           |

<sup>1</sup>Only breast milk in the past week<sup>2</sup>≤2 feedings of other liquids/food per day<sup>3</sup>3-4 feedings of other liquids/food per day<sup>4</sup>> 4 feedings of other liquids/food per day<sup>5</sup>Total daily vitamin D intake from supplement and formula\*Rows showing different superscripts are significantly different from each other;  $\chi^2 P < 0.001$ 

who had exclusively breastfed an infant in the past 5 years [17]. In that study, the supplementation rate in BC was marginally higher than the national average (70%), but still well below the rate in our study. Our rates of vitamin D supplementation are comparable to those reported more recently in one Montreal hospital where 98% of exclusively breastfed (WHO definition) infants had been supplemented with vitamin D at some point during the first 6 months [18]. Data from the Infant Feeding Practices Study II (2005-2007) suggest that US vitamin D supplementation rates are markedly lower than in Canada; 43% of infants were breastfed at 2 months and of these only 10% were receiving vitamin D [21]. However, the American Academy of Pediatrics only began recommending infant supplementation in November 2008, whereas the Canadian recommendation has been present in some form since 1967. Further, breastfeeding rates have been historically higher in

Canada than in the US and Canada's higher latitude may have created a greater impetus for infant supplementation in this country. As expected infant supplementation at 2 months was lower amongst those receiving mixed feeds (79%) and lower still in infants receiving only infant formula (20%). In Montreal, an apparently higher 88% of mixed feeders had received supplemental vitamin D; however, this was anytime during the first 6 months [18]. In the US study, amongst mixed feeders, only 5% were receiving vitamin D supplements at 2 months of age [21]. Despite a high proportion of breastfed infants receiving vitamin D supplements, one third were not receiving at least 300 IU/d; mainly because of less than daily supplement administration. Although we report less frequent vitamin D supplementation rates among infants who were receiving mixed breast milk and formula in the week before the survey than among those fed only breast milk

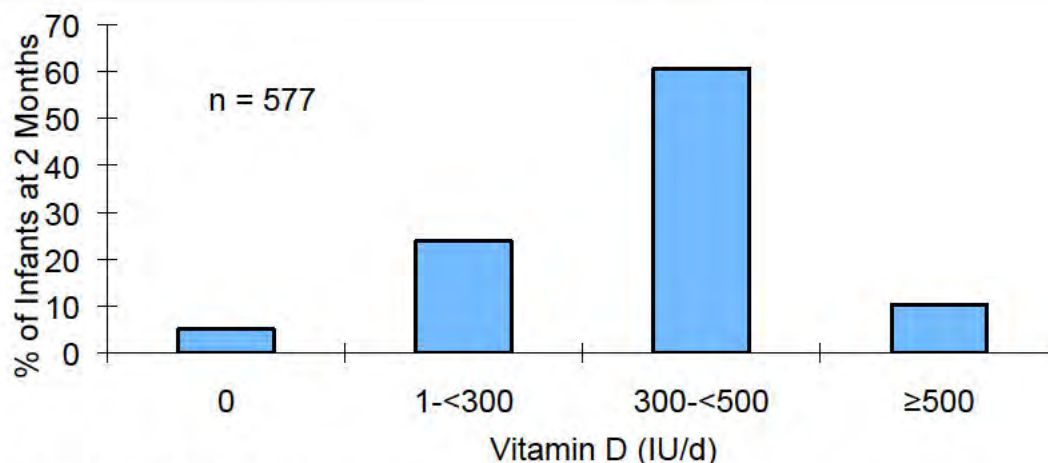
**Figure 2** Daily total vitamin D intake from supplements and infant formula at two months of age.

**Table 3 Advice and decisions on vitamin D supplementation**

|                                                                     | % (n)      |
|---------------------------------------------------------------------|------------|
| Did anyone ever recommend a vitamin D supplement?                   |            |
| Yes                                                                 | 92.2 (532) |
| No                                                                  | 7.8 (45)   |
| Who recommended the supplement? (n = 532) <sup>a</sup>              |            |
| Public health nurse                                                 | 80.2 (426) |
| Doctor                                                              | 69.7 (370) |
| Midwife                                                             | 9.6 (51)   |
| Dietitian/pharmacist                                                | 5.1 (27)   |
| Family member or friend                                             | 19.4 (103) |
| Other <sup>1</sup>                                                  | 7.7 (46)   |
| Reasons for providing a vitamin D supplement (n = 452) <sup>a</sup> |            |
| Not in breast milk/I am breastfeeding                               | 43.6 (197) |
| It was recommended                                                  | 30.3 (137) |
| Health benefits for infant                                          | 28.3 (128) |
| Lack of sunlight/northern climate                                   | 21.0 (95)  |
| Other <sup>2</sup>                                                  | 13.1 (59)  |
| Reasons for not supplementing vitamin D (n = 116) <sup>a</sup>      |            |
| Baby is being fed formula                                           | 35.3 (41)  |
| I didn't know to give                                               | 10.3 (12)  |
| I don't think the baby needs it                                     | 19.0 (22)  |
| Forgot to give                                                      | 3.4 (4)    |
| Baby did not tolerate (vomit/spit up)                               | 0.9 (1)    |
| Other <sup>3</sup>                                                  | 5.2 (6)    |
| No response                                                         | 28.4 (33)  |

<sup>a</sup>Multiple responses possible<sup>1</sup>Reading, television, internet, South Community Birth Program, Baby's Best Chance, prenatal class, lactation clinic, natural path, doula, specialist, from first child<sup>2</sup>Knew from first baby, read about it, did not know why, it is important<sup>3</sup>Confused with the recommended dose, will purchase later, will ask doctor, first baby did not tolerate, had not started yet

(79% versus 91%), fewer of the infants receiving mixed feeding had vitamin D intakes below 300 IU/d vitamin D (22%, versus 33.5% in the fully breastfed group). Further, within the group receiving mixed feeds, as the amount of formula increased infant supplementation dropped; however, the percentage of those receiving less than 300 IU/d remained constant at around 20%. This was not unexpected as formula is fortified with vitamin D and it would take about 700 ml of formula to achieve an intake of 300 IU/d. Consuming less than 700 ml/d also explains why 25% of formula fed infants failed to achieve this intake. Using a stricter cut-point of 400 IU/d, the Montreal researchers reported that 74% of exclusively breastfed infants and 51% receiving mixed feeds achieved an intake of 400 IU/d at 6 months [18].

Up to a third of infants not achieving 300 IU/d vitamin D and even less achieving the recommendation of

400 IU/d may appear high. However, only 5% of infants were receiving no vitamin D. Further, it is acknowledged that the evidence base used to derive the infant recommendation is limited. Serum 25-hydroxyvitamin D (25OHD) concentration is the best indicator of vitamin D status. Although controversial the US Institute of Medicine recently affirmed a 25OHD of 50 nmol/L as desirable in all age groups including infants [19]. Greer et al. [22] showed that breastfed infants (n = 9) receiving 400 IU had mean 25-hydroxyvitamin D concentrations of 95 nmol/L after 12 weeks. More recently, infants randomized to 250 or 500 IU per day (n = 20 per group) at birth achieved mean (95% CI) 25OHD concentrations of 139 (114-164) and 151 (126-176) nmol/L, respectively after 6 weeks [20]. Thus, it appears that the recommended intake of 400 IU exceeds the requirements of almost all infants, perhaps by a considerable margin. There have been reports of infant overdosing with vitamin D in the US resulting in the Food and Drug Administration issuing a warning of the potential risk of overdosing infants with liquid vitamin D [23]. In our study only one infant was receiving greater than the upper limit for vitamin D of 1000 IU suggesting this was not a problem.

Among caregivers there was generally good awareness of the need to supplement and why it was important. For example, caregivers indicated that they used a supplement because vitamin D was not present in adequate amounts in breast milk and/or that sunlight exposure was limited or not recommended; and many women who used formula appeared to be aware that supplementation wasn't required. Over 90% of caregivers recalled receiving advice primarily from public health nurses and doctors to supplement with vitamin D, which may explain the high rates of supplementation. In a Seattle study [24], parents who reported that their child's pediatrician recommended vitamin D were 8 times more likely to provide the supplementation than parents whose child's pediatrician did not. However, only a third of parents recalled receiving any recommendation and of these under half supplemented with vitamin D. In contrast to our study, where < 5% of caregivers thought supplementation was unnecessary, 67% of parents in the Seattle study believed that supplementation was unnecessary because breast milk has all needed nutrition.

Multivariate regression revealed little in the way of predictors of supplement use. There was a non-significant tendency for family incomes less than \$40,000 to be associated with lower rates of supplementation. However, vitamin D supplements cost less than \$40 for 6 months and cost of the supplements was not given as a reason for not supplementing. Interestingly 80% of caregivers reported giving their infants D-Drops<sup>®</sup> versus

**Table 4 Percentages and multivariate adjusted odds ratio (and 95% CIs) for infant vitamin D supplementation in infants receiving greater than 50% of feeds from breast milk by select characteristics (n = 420)**

| Characteristic                                                       | % (n)      | OR (95% CI)       | p value |
|----------------------------------------------------------------------|------------|-------------------|---------|
| Maternal Age                                                         |            |                   |         |
| < 31 y                                                               | 87.6 (134) | 1.00              |         |
| ≥31 y                                                                | 89.9 (286) | 1.28 (0.65, 2.50) | 0.479   |
| Baby's ethnicity                                                     |            |                   |         |
| European                                                             | 88.9 (160) | 1.00              |         |
| Chinese                                                              | 89.6 (129) | 1.34 (0.62, 2.86) | 0.456   |
| Other                                                                | 89.1 (131) | 1.32 (0.62, 2.80) | 0.469   |
| Annual family income                                                 |            |                   |         |
| <\$40,000                                                            | 83.1 (74)  | 1.00              |         |
| \$40,000 80,000                                                      | 92.2 (95)  | 2.51 (0.98, 6.41) | 0.054   |
| >\$80,000                                                            | 91.4 (170) | 2.24 (0.94, 5.30) | 0.068   |
| Non responder <sup>1</sup>                                           | 87.1 (81)  | 1.35 (0.58, 3.14) | 0.488   |
| Education                                                            |            |                   |         |
| Less than completed trade/vocational training and college/university | 87.0 (87)  | 1.00              |         |
| Completed trade/vocational training and college/university           | 89.8 (333) | 0.99 (0.48, 2.04) | 0.984   |
| Parity                                                               |            |                   |         |
| Primipara                                                            | 90.5 (219) | 1.00              |         |
| Multipara                                                            | 87.8 (201) | 0.69 (0.37, 1.29) | 0.244   |

Note: CI confidence interval, OR multivariate adjusted odds ratio

<sup>1</sup>Do not know and do not want to say

only 16% who supplemented with D-Vi-Sol<sup>®</sup>. The reason for the popularity of D-Drops<sup>®</sup> may be their ease of administration requiring only a single drop that can be placed on the mother's breast prior to nursing, versus the need to use a dropper to administer D-Vi-Sol<sup>®</sup> [25].

A strength of our study was that we had access to a database that contained the names of nearly all infants born in Vancouver and Richmond over the study period. Also, we sampled an ethnically diverse population where breastfeeding rates are high relative to the rest of North America. Finally, data were collected prospectively at 2 months rather than relying on recall of up to 5 years in one study. In studies of this type, selection bias is always an important consideration. For example, people who choose to participate versus those who do not, may be more educated and of higher socioeconomic status and thus more likely to breastfeed and supplement with vitamin D. Thus a limitation of our study is that we had only a moderate response rate of 56%. Unfortunately, we do not have any data on our non-responders and there are no representative data on pregnant women in Vancouver and Richmond to compare our results with. However, with respect to ethnicity [26], education [27] and family income [28] our sample compares well with 2006 census data for women from Vancouver and Richmond. Further, only half of the non-responders refused participation, while the other half could not be contacted initially or at follow-up.

Because the survey was conducted in the summer months it appeared that many women were away on vacations or staying with family outside the area. We acknowledge that our findings cannot be extrapolated to the rest of Canada or even BC. Breastfeeding rates are higher in BC than elsewhere and Vancouver and Richmond have a unique ethnic mix not present in the rest of the province or Canada. Second, we only sampled at 2 months; this was an intentional decision but more data are needed on older infants. In the US, supplementation rates remained relatively constant out to 12 months; however, in this study both breastfeeding rates and infant supplementation were much lower than ours [21]. In Montreal, of all supplemented breastfed infants around a third had stopped taking the supplement by 6 months [18]. More data are needed on older infants especially around the time of introduction of solids and as breastfeeding rates drop with age.

## Conclusions

Breastfeeding rate was high among this group of mothers. About 90% of the infants received breast milk and 57% were exclusively breastfed at 2 months. Over 60% of the infants had a total vitamin D intake of 300- < 500 IU/d from supplements and formula. The vitamin D supplementation rate was 80%. There was good awareness of the need to supplement with vitamin D and the reasons why. Most parents were advised to give their infants vitamin D

supplement by public health nurses and doctors. Overall it appears that the level of knowledge translation about the importance of vitamin D is high. This points to the success of Vancouver Coastal Health's system of universal contact by public health nurses, especially for providing breast feeding support and also for providing key public health messages such as the use of vitamin D. Future studies are needed to monitor vitamin D supplement rates of older infants and toddlers.

#### Acknowledgements

We are grateful to all public health nurses who recruited participants. We thank research assistants: Kathy Ho and Anita Rashidi for their roles in completing surveys and data management. We are also grateful to the participants in this study. This study was supported with a grant from the Vancouver Coastal Health Research Institute.

#### Author details

<sup>1</sup>Infant, Child and Youth Program, Vancouver Coastal Health, 1669 East Broadway, Vancouver V5N 1V9, Canada. <sup>2</sup>Food, Nutrition and Health, University of British Columbia, 2205 East Mall, Vancouver V6T 1Z4, Canada. <sup>3</sup>Healthy Babies and Families Program, Vancouver Coastal Health, 8100 Granville Avenue, Richmond V6Y 3T6, Canada.

#### Authors' contributions

BC and TG were responsible for the conception of the study and obtaining funds. All authors had a role in the design, acquisition of data, analysis and interpretation of data. BC, TG, SB, and WL drafted the initial manuscript. All authors read and approved the final manuscript.

#### Competing interests

The authors declare that they have no competing interests.

Received: 12 July 2011 Accepted: 7 December 2011

Published: 7 December 2011

#### References

- Health Canada: *Exclusive breastfeeding duration 2004 Health Canada recommendation* Ottawa; 2004.
- World Health Organization: *Global strategy for infant and young child feeding, the optimal duration of exclusive breastfeeding*. Geneva, Switzerland: World Health Organization; 2001, Retrieved March 16, 2011, from [http://apps.who.int/gb/archive/pdf\\_files/WHA55/ea5515.pdf](http://apps.who.int/gb/archive/pdf_files/WHA55/ea5515.pdf).
- American Academy of Pediatrics Section on Breastfeeding: *Breastfeeding and the use of human milk*. *Pediatrics* 2005, **115**:496-506.
- Health Canada: *Vitamin D Supplementation for Breastfed Infants: 2004 Health Canada Recommendation*. Ottawa, ON: Health Canada; 2004.
- Ward LM, Gaboury I, Ladhani M, Zlotkin S: *Vitamin D deficiency rickets among children in Canada*. *Can Med Assoc J* 2007, **177**:161-166.
- Holick MF: *Resurrection of vitamin D deficiency and rickets*. *J Clin Invest* 2006, **116**:2062-2072.
- Brooke OG, Brown IR, Bone CD, Carter ND, Cleeve HJ, Maxwell JD, Robinson VP, Winder SM: *Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth*. *Br Med J* 1980, **280**:751-754.
- Schroth R, Lavelle C, Moffatt M: *Influence of maternal vitamin D status on infant oral health [abstract]*. *J Dent Res* 2008, **87**:1646.
- Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM: *Intake of vitamin D and risk of type 1 diabetes: a birth cohort study*. *Lancet* 2001, **358**:1500-1503.
- Camargo CA, Rifas Shiman SL, Litonjua AA, Rich Edwards JW, Weiss ST, Gold DR, Kleinman K, Gillman MW: *Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age*. *Am J Clin Nutr* 2007, **85**:788-795.
- Health Canada: *A parent's guide to sun protection*. Ottawa, ON: Health Canada; 2004.
- Norwegian Food Safety Authority Matportalen (The Food Portal): 2006, Personal Communication.
- Swedish National Food Administration: 2006, Personal Communication.
- Healthy Start: *Reform of the welfare food scheme*. England, UK: Healthy Start; 2006, Retrieved October 3, 2011, from <http://www.healthystart.nhs.uk>.
- Dubois L, Bédard B, Girard M, Beaudesne É: *Étude longitudinale du développement des enfants du Québec (ÉLDEQ 1998 2002). Les nourrissons de 5 mois*. Québec, Québec: Institut de la statistique du Québec 2000.
- Lepage MC, Moisan J, Gaudet M: *What do Québec children eat during their first six months?* *Can J Diet Pract Res* 2004, **65**:106-113.
- Millar WJ, Maclean H: *Breastfeeding practices*. *Health Rep (Statistics Canada, Catalogue 82 003)* 2005, **16**:23-31.
- Gallo S, Jean Philippe S, Rodd C, Weiler HA: *Vitamin D supplementation of Canadian infants: practices of Montreal mothers*. *Appl Physiol Nutr Metab* 2010, **35**:303-309.
- Institute of Medicine: *Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academy Press; 2010.
- Siafrikas A, Piazena H, Feister U, Bulsara MK, Meffert H, Hesse V: *Randomized controlled trial analyzing supplementation with 250 versus 500 units of vitamin D3, sun exposure and surrounding factors in breastfed infants*. *Arch Dis Child* 2011, **96**:91-95.
- Perrine CG, Sharma AJ, Jefferds MED, Serdula MK, Scanlon KS: *Adherence to vitamin D recommendations among US infants*. *Pediatrics* 2010, **125**:627-632.
- Greer FR, Searcy JE, Levin RS, Steichen JJ, Asch PS, Tsang RC: *Bone mineral content and serum 25 hydroxyvitamin D concentration in breastfed infants with and without supplemental vitamin D*. *J Pediatr* 1981, **98**:696-701.
- Food and Drug Administration Consumer Health Information: *Infant overdose risk with liquid vitamin D*. Silver Spring, US: Food and Drug Administration; 2010, Retrieved June 10, 2011, from: <http://www.fda.gov/consumer>.
- Taylor JA, Geyer LJ, Feldman KW: *Use of supplemental vitamin D among infants breastfed for prolonged periods*. *Pediatrics* 2010, **125**:105-111.
- Rodd C, Jean Philippe S, Vanstone C, Weiler H: *Comparison of 2 vitamin D supplementation modalities in newborns: adherence and preference*. *Appl Physiol Nutr Metab* 2011, **36**:414-418.
- Statistics Canada: *2006 Census of Canada highlight tables, ethnocultural portrait of Canada tables: Visible minority groups, 2006 counts, for Canada, provinces and territories, and census metropolitan areas and census agglomerations*. Ottawa, Canada: Statistics Canada; 2006, Retrieved June 6, 2011, from <http://www12.statcan.ca/census-recensement/2006/dp/pd/hlt/97-562/pages/page.cfm?Lang=E&Geo=CMA&Code=59&Table=1&DataCount&Sex=1&StartRec=1&Sort=2&Display=Page&CSDFilter=5000>.
- Statistics Canada: *2006 Census of Canada highlight tables, education tables: Highest level of educational attainment for the population aged 25 to 64, 2006 counts for both sexes, for Canada, provinces and territories, and census metropolitan areas and census agglomerations*. Ottawa, Canada: Statistics Canada; 2006, Retrieved June 6, 2011, from <http://www12.statcan.ca/census-recensement/2006/dp/pd/hlt/97-560/pages/page.cfm?Lang=E&Geo=CMA&Code=59&Table=1&DataCount&Sex=1&StartRec=1&Sort=2&Display=Page&CSDFilter=5000>.
- Statistics Canada: *2006 Census of Canada highlight tables, income and earnings tables: Median earnings and employment for full year, full time earners, all occupations, both sexes, for Canada, provinces and territories, and census metropolitan areas and census agglomerations with 5,000 plus population*. Ottawa, Canada: Statistics Canada; 2006, Retrieved June 6, 2011, from <http://www12.statcan.ca/census-recensement/2006/dp/pd/hlt/97-563/T801-eng.cfm?Lang=E&T=801&GH=6&GF=59&G5=1&SC=1&S=1&O=A>.

#### Pre publication history

The pre publication history for this paper can be accessed here:  
<http://www.biomedcentral.com/1471-2458/11/905/prepub>

doi:10.1186/1471-2458-11-905

**Cite this article as:** Crocker et al.: Very high vitamin D supplementation rates among infants aged 2 months in Vancouver and Richmond, British Columbia, Canada. *BMC Public Health* 2011 **11**:905.

**CONCLUSION:** This is the first descriptive study demonstrating the discrepancy within and between institutions in the calculation of TFI for preterm infants. The significant difference in weight gain on day 14 as well as the potential impact of the relative change in TFI on this result warrants further investigation.

#### 46

##### FEED MIXTURES OFTEN EXCEED OSMOLALITY RECOMMENDATIONS IN PRETERM INFANTS

\*A Nash, S Doctor, S Merko, C Findlater, H Joshi, D Iaboni  
Sunnybrook Health Sciences Centre, Toronto, Ontario

**BACKGROUND:** Hyperosmolar feeds have been associated with necrotizing enterocolitis. For preterm infants, a feed osmolality of less than 425mOsm/kg H<sub>2</sub>O has been recommended. Although preterm formula and fortified breastmilk have an osmolality below this cut-off, medications and vitamins with high osmolality are routinely mixed into milk prior to feeding. The extent to which these additions increase total osmolality is largely unknown.

**OBJECTIVE:** Determine the osmolality of feeds after the addition of commonly prescribed medications, vitamins and minerals and compare them to recommendations.

**DESIGN/METHODS:** To mimic a clinical situation, a 1000g infant feeding 160mL/kg/d (13mL q 2) was used as a reference. Commonly prescribed medications and vitamins at typical doses were mixed into 13mL of either Enfamil 24kcal/oz preterm formula or breastmilk with Enfamil human milk fortifier (1 package:25mL). Osmolality was determined by freezing point depression using the Advanced Micro-Osmometer Model 3300.

**RESULTS:** The majority of medications and/or other additives mixed with feeds resulted in an osmolality that exceeded recommendations (Table). Addition of vitamin preparations or Phenobarbital produced the greatest osmotic load.

| Osmolality of feeds combined with common additives                       |                           |                 |                         |
|--------------------------------------------------------------------------|---------------------------|-----------------|-------------------------|
| Additive, volume                                                         | Breastmilk with fortifier | Preterm formula | Exceeds recommendations |
| None                                                                     | 362±14*                   | 310±5           | No                      |
| Tri-Vi-Sol® (400IU Vitamin D, Vitamin A 1500IU, Vitamin C 30mg/1mL) 1 mL | 962±9                     | 930±13          | Yes                     |
| Iron (15mg elemental iron/mL) 0.13mL                                     | 442±8                     | 387±6           | Yes/No                  |
| D-Vi-Sol® (400IU Vitamin D) 1 mL                                         | 891±7                     | 867±9           | Yes                     |
| D drops® (400IU Vitamin D) 0.03mL                                        | 376±5                     | 323±5           | No                      |
| Caffeine (10mg/mL) 1mL                                                   | 345±3                     | 310±2           | No                      |
| NaCl (2.5mmol Na/mL) 0.27mL                                              | 451±5                     | 435±4           | Yes                     |
| NaCl (2.5mmol Na/mL) 0.4mL                                               | 505±3                     | 476±2           | Yes                     |
| Phenobarbital (5mg/mL) 1mL                                               | 1176±7                    | 1235±9          | Yes                     |
| Poly-Vi-Sol® (fat and water soluble multivitamin) 1mL                    | 1034±16                   | 1000±6          | Yes                     |
| Lasix (10mg/mL) 0.1mL                                                    | 399±8                     | 368±4           | No                      |
| Poly-Vi-Sol® 1mL + NaCl 0.4mL + Fe 2mg                                   | 1219±3                    | 1201±11         | Yes                     |

\*expressed in mOsm/kg H<sub>2</sub>O (mean±SD)

**CONCLUSIONS:** Hyperosmolar feed mixtures are commonly fed to preterm infants. To increase safety, efforts should be made to minimize feed osmolality.

#### 47

##### DOES HISTOLOGICAL CHORIOAMNIONITIS HAVE AN IMPACT ON THE DEVELOPMENT OF BRONCHOPULMONARY DYSPLASIA IN PRETERM INFANTS?

\*N Plakkal, A S Soraisham, C Trevenen, R Sauve  
University of Calgary, Calgary, Alberta

**INTRODUCTION:** The relationship between histological chorioamnionitis (HCA) and bronchopulmonary dysplasia (BPD) in preterm infants is controversial. Published studies on the association between HCA and BPD have yielded mixed results. Previous studies that showed an increase in BPD with chorioamnionitis were done before the use of surfactant and antenatal steroids became widespread, and adjustment for gestational age was not done.

**OBJECTIVES:** To examine the effects of HCA on the development of BPD in infants born at <29 weeks of gestation.

**METHODS:** We conducted a retrospective cohort study. All infants born at <29 weeks' gestation and admitted to the regional tertiary care NICU during 2000-2003 were eligible. Infants with major congenital anomalies or chromosomal abnormalities and those without placental histology were excluded. BPD was defined as requiring supplemental oxygen or assisted ventilation at 36 weeks corrected gestational age. We compared the BPD rates between infants exposed to and not exposed to HCA. Multivariate logistic regression analysis was carried out to analyze for the effects of HCA after controlling for potential confounding variables.

**RESULTS:** Of the 289 eligible infants, 136 (47%) were exposed to HCA. The mean gestational age (SD) of infants with HCA was significantly lower than those without chorioamnionitis [25.5 (1.6 wks) vs 26.3 (1.5 wks),  $p < 0.001$ ]. Infants in the HCA group were more likely to be born vaginally and receive a complete course of antenatal steroids. There were no significant differences in the incidence of respiratory distress syndrome, culture proven sepsis or postnatal steroid therapy between the two groups. The risk of BPD was significantly decreased in infants exposed to HCA (RR 0.86; 95% CI 0.76-0.98). The mortality rate was similar between the two groups (19.1% vs 19.6%). Infants exposed to chorioamnionitis had a decreased risk of the combined outcome of BPD/death (RR 0.89; 95% CI 0.80-0.98). After adjusting for confounding variables (gestational age, antenatal steroids, PDA and sepsis), HCA was independently associated with a decreased risk of BPD (adjusted OR 0.27; 95% CI 0.11-0.62) and BPD/death (adjusted OR 0.27; 95% CI 0.12-0.63).

**CONCLUSIONS:** In preterm infants born at less than 29 weeks of gestation, exposure to HCA is associated with a significant decrease in the risk of both BPD and the combined outcome of BPD/death.

#### 48

##### BRADYCARDIAS AND/OR APNEAS: THEIR RELATIONSHIP TO NECROTIZING ENTEROCOLITIS IN THE VERY LOW BIRTH WEIGHT INFANT

\*SET Samar El Tarazi, RM Romain Mandel, NA Nabeel Ali,  
BB Bensouda Brahmi  
McGill Health Centre, Montréal, Québec

**BACKGROUND:** Bradycardias and/or Apneas (B/A) in preterm infants may cause mesenteric hypo-perfusion and intestinal ischemia and thus be a trigger for NEC.

**OBJECTIVE:** To see if there is an increase in the number of B/A the five days prior to the development of NEC, making them possible risk factors for NEC.

**DESIGN/METHODS:** We performed a case-control study among preterm infants with a gestational age (GA) < 30 weeks who were admitted to the NICU at the Royal Victoria Hospital in Montreal, between 2001 and 2007. 38 infants had NEC stage II or greater as defined by Bell (excluding spontaneous perforation). These infants were matched with 76 control infants by GA, birth weight and gender. The day of NEC diagnosis was recorded as day 0 in the NEC group, and the corresponding age (in post-natal days) was noted. Using the nursing notes in the charts, we manually reported the number of B/A for the five days preceding day 0. An apnea was defined as a respiratory pause lasting more than 15 seconds. A bradycardia was defined as a heart rate of less than 85 beats per minute. NEC risk factors were also evaluated.

**RESULTS:** The characteristics of the NEC and control groups are summarized in table 1.

# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **Vitamin D During Pregnancy and Infancy and Infant Serum 25-Hydroxyvitamin D Concentration**

Cameron C. Grant, Alistair W. Stewart, Robert Scragg, Tania Milne, Judy Rowden, Alec Ekeroma, Clare Wall, Edwin A. Mitchell, Sue Crengle, Adrian Trenholme, Julian Crane and Carlos A. Camargo Jr

*Pediatrics*; originally published online December 16, 2013;  
DOI: 10.1542/peds.2013-2602

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/early/2013/12/10/peds.2013-2602>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# Vitamin D During Pregnancy and Infancy and Infant Serum 25-Hydroxyvitamin D Concentration

**AUTHORS:** Cameron C. Grant, MBChB, PhD,<sup>a</sup> Alistair W. Stewart, BSc,<sup>b</sup> Robert Scragg, MBBS, PhD,<sup>b</sup> Tania Milne,<sup>a</sup> Judy Rowden,<sup>a</sup> Alec Ekeroma, MBBS,<sup>c</sup> Clare Wall, PhD,<sup>d</sup> Edwin A. Mitchell, MBBS, DSc,<sup>a</sup> Sue Crengle, MBChB, PhD,<sup>e</sup> Adrian Trenholme, MB, BChir,<sup>f</sup> Julian Crane, MBBS,<sup>g</sup> and Carlos A. Camargo Jr, MD, DrPH<sup>h</sup>

<sup>a</sup>Paediatrics: Child and Youth Health, <sup>b</sup>Epidemiology and Biostatistics, <sup>c</sup>Obstetrics and Gynaecology, <sup>d</sup>Nutrition, and <sup>e</sup>Te Kupenga Hauora Maori, University of Auckland, Auckland, New Zealand; <sup>f</sup>Women and Children's Health, Middlemore Hospital, Auckland, New Zealand; <sup>g</sup>Medicine, University of Otago, Wellington, New Zealand; and <sup>h</sup>Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

## KEY WORDS

vitamin D, 25 hydroxyvitamin D, pregnancy, infancy, supplementation

## ABBREVIATIONS

25(OH)D 25 hydroxyvitamin D

NZ New Zealand

RDI recommended dietary intake

Dr Grant conceived and designed the study, developed the data collection instruments, analyzed and interpreted the data, and completed the first and final drafts of the manuscript; Mr Stewart conceived and designed the study, analyzed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Robert Scragg conceived and designed the study, developed the data collection instruments, critically reviewed the manuscript, and approved the final manuscript as submitted; Ms Milne and Ms Rowden developed the recruitment and retention strategy for the study, designed the data collection instruments, coordinated the collection of the data, and approved the final manuscript as submitted; Dr Ekeroma conceived and designed the study, developed the data collection instruments, and approved the final manuscript as submitted; Drs Wall and Crengle developed the data collection instruments, critically reviewed the manuscript, and approved the final manuscript as submitted; Dr Mitchell conceived and designed the study, developed the data collection instruments, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Trenholme supervised the collection of safety data, critically reviewed the manuscript, and approved the final manuscript as submitted; Dr Crane developed the data collection instruments, reviewed and revised the manuscript, and approved the final manuscript as submitted; and Dr Camargo conceived and designed the study, developed the data collection instruments, analyzed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

(Continued on last page)



**WHAT'S KNOWN ON THIS SUBJECT:** A serum 25-hydroxyvitamin D (25(OH)D) concentration of 20 ng/mL meets the requirements of at least 97.5% of the population older than 1 year. A recommended dietary intake to achieve this serum 25(OH)D concentration has not been established during infancy.



**WHAT THIS STUDY ADDS:** Daily maternal (during pregnancy) and then infant vitamin supplementation with 1000/400 IU or 2000/800 IU increases the proportion of infants with 25(OH)D  $\geq$ 20 ng/mL during infancy with the higher dose sustaining this increase for longer.

## abstract



**OBJECTIVE:** To determine the vitamin D dose necessary to achieve serum 25 hydroxyvitamin D (25(OH)D) concentration  $\geq$ 20 ng/mL during infancy.

**METHODS:** A randomized, double blind, placebo controlled trial in New Zealand. Pregnant mothers, from 27 weeks' gestation to birth, and then their infants, from birth to age 6 months, were randomly assigned to 1 of 3 mother/infant groups: placebo/placebo, vitamin D<sub>3</sub> 1000/400 IU, or vitamin D<sub>3</sub> 2000/800 IU. Serum 25(OH)D and calcium concentrations were measured at enrollment, 36 weeks' gestation, in cord blood, and in infants at 2, 4, and 6 months of age.

**RESULTS:** Two hundred and sixty pregnant women were randomized. At enrollment, the proportions with serum 25(OH)D  $\geq$ 20 ng/mL for placebo, lower dose, and higher dose groups were 54%, 64%, and 55%, respectively. The proportion with 25(OH)D  $\geq$ 20 ng/mL was larger in both intervention groups at 36 weeks' gestation (50%, 91%, 89%,  $P < .001$ ). In comparison with placebo, the proportion of infants with 25(OH)D  $\geq$ 20 ng/mL was larger in both intervention groups to age 4 months: cord blood (22%, 72%, 71%,  $P < .001$ ), 2 months (50%, 82%, 92%,  $P < .001$ ), and 4 months (66%, 87%, 87%,  $P = .004$ ), but only in the higher dose group at age 6 months (74%, 82%, 89%,  $P = .07$ ; higher dose versus placebo  $P = .03$ , lower dose versus placebo  $P = .21$ ).

**CONCLUSIONS:** Daily vitamin D supplementation during pregnancy and then infancy with 1000/400 IU or 2000/800 IU increases the proportion of infants with 25(OH)D  $\geq$ 20 ng/mL, with the higher dose sustaining this increase for longer. *Pediatrics* 2014;133:e143 e153

The Institute of Medicine, in 2011, determined that serum 25 hydroxyvitamin D (25(OH)D) concentrations  $\geq 20$  ng/mL meet the requirements of at least 97.5% of the population  $>1$  year old.<sup>1</sup> The recommended dietary intake (RDI) during pregnancy was defined as 600 IU per day, but data were insufficient to allow an RDI to be defined for infants. Instead, an adequate intake of 400 IU per day was established, with this considered sufficient to maintain serum 25 (OH)D in the range of 16 to 20 ng/mL.<sup>1</sup>

Vitamin D status at birth and during early infancy, when breast milk is the predominant source of nutrition, is determined by maternal vitamin D status.<sup>2,3</sup> Contemporary population and primary care based studies of pregnant women have shown a high prevalence of serum 25(OH)D  $<20$  ng/mL in Asia (70%–96%),<sup>4–6</sup> Australia (10%–47%),<sup>7–10</sup> Europe (15%–44%),<sup>11,12</sup> the United Kingdom (49%–75%),<sup>13–15</sup> India (74%),<sup>16</sup> and the United States (37%).<sup>17</sup> Although less completely studied at the population level, in primary care based studies from the United States, serum 25(OH)D  $<20$  ng/mL is present in 11% to 12% of infants.<sup>18,19</sup>

It is difficult to meet the vitamin D RDI from dietary sources alone. For this reason, in some countries, including the United States, vitamin D is added to an increasing range of food products.<sup>1,20</sup> Determining the vitamin D intake that achieves a desired serum 25(OH)D concentration in this setting is difficult. In many countries though, vitamin D fortification of foods is not mandated, dietary sources of vitamin D are few, and routine vitamin D supplementation is not recommended.<sup>21</sup> Such countries, for example New Zealand (NZ), provide an opportunity to determine the relationship between vitamin D intake and serum 25(OH)D concentration.<sup>22,23</sup> In 2010, we commenced enrollment of pregnant women in NZ into a randomized trial of vitamin D supplementation during pregnancy and infancy. We aimed to

determine the vitamin D dose during late pregnancy and early infancy that safely and effectively increases serum 25(OH)D concentrations to  $\geq 20$  ng/mL in the first 6 months of infancy.

## METHODS

### Trial Design

We performed a randomized, double blind, placebo controlled multiarm parallel study. Pregnant mothers, from enrollment at 27 weeks' gestation to birth, and then their infants, from birth to age 6 months, were randomly and equally assigned, to 1 of 3 groups: placebo, or lower dose or higher dose vitamin D<sub>3</sub>. Woman/infant pairs received a once daily oral dose of placebo/placebo, vitamin D<sub>3</sub> 1000 IU/400 IU, or vitamin D<sub>3</sub> 2000 IU/800 IU.

Ethical approval was obtained from the regional NZ Ministry of Health ethics committee and written informed consent from all participating women. Registration was with the Australian NZ Clinical Trials Registry (ACTRN12610000483055).

### Participants

Women were recruited from a community based primary care maternity clinic in Auckland (latitude 36°S) from April 2010 to July 2011. Women were eligible if their estimated gestation was 26 to 30 weeks and they had a singleton pregnancy. We excluded women taking vitamin D supplementation  $>200$  IU per day, those with a history of renal stones or hypercalcemia, or any serious pregnancy complication at enrollment.

### Interventions

Each participant was instructed to take 1 drop per day of study medicine. For pregnant women, 1 drop contained placebo or 1000 IU or 2000 IU of vitamin D<sub>3</sub>; for infants, 1 drop contained placebo or 400 IU or 800 IU of vitamin D<sub>3</sub>. Pregnant women took 1 drop per day of study medicine from enrollment until

childbirth. They were instructed to then stop taking their study medicine and to start giving their infant 1 drop per day of the infant study medicine until the infant was 6 months old.

Infants admitted to the NICU did not start study medicine until they had discontinued prescribed vitamin D supplements. For those born prematurely, vitamin D supplement was prescribed during their NICU stay and for 3 months after hospital discharge. Infants in the NICU received 160 IU per day while receiving parenteral nutrition and 464 IU per day once orally fed.

### Outcomes

The primary end points at study initiation were the proportion of infants achieving a serum 25(OH)D concentration  $\geq 30$  ng/mL during the first 6 months of infancy and the number of mothers and infants with hypercalcemia at any measurement point. The 25(OH)D cutoff of 30 ng/mL was chosen because at the time of study initiation this was considered to represent optimal vitamin D status.<sup>24,25</sup> Urinary calcium was not used as a safety measure because physiologic hypercalciuria occurs normally during pregnancy,<sup>26</sup> and urinary calcium excretion during infancy is widely variable.<sup>27</sup>

### Sample Size

Sample size calculations were based on the primary study protocol objective of achieving a serum 25(OH)D concentration of 30 ng/mL. In healthy adults, serum 25(OH)D increases by approximately 0.7 ng/mL for every 100 IU per day of vitamin D<sub>3</sub> ingested.<sup>28</sup>

In NZ, the mean 25(OH)D concentration in women of childbearing age and in newborns is approximately 20 ng/mL (interquartile range: women 14–27 ng/mL; newborns 12–31 ng/mL).<sup>23,29</sup> Vitamin D 1000 IU per day was expected to increase average maternal 25(OH)D from 20 to 27 ng/mL and 2000 IU per day to increase 25(OH)D from 20 to

33 ng/mL. We anticipated that the actual increase could be smaller because of the vitamin D demands of the fetus.<sup>25</sup> We estimated that a difference in 25 (OH)D concentration of 3 ng/mL between placebo and lower dose vitamin D and 6 ng/mL between placebo and higher dose vitamin D could be detected (80% power,  $\alpha = 0.05$ ) with 70 in each group. We aimed to enroll 260 to have 210 infants complete the study.

### Randomization and Blinding

Allocation to the 3 study arms was by restricted randomization within blocks of variable size using a computer generated randomization list. The allocation sequence was concealed from research staff involved in recruitment. The study statistician randomly allocated a treatment to each participant and labeled identical study medicine bottles such that study staff and participants were unaware of the treatment status.

Study medicine bottles were sequentially numbered with an identical numbering code used for each mother-infant pair. Bottles of study medicine were prepared by the Ddrops Company (Woodbridge, Ontario, Canada) with the study medicine bottles for the 3 groups being identical in color, shape, and volume and the study medicine identical in color, consistency, and taste.

### Data Collection

Face to face interviews were completed with women at enrollment; at 36 weeks' gestation; and when their infant was 2, 4, and 6 months old. Data collected described demographics, adherence, supplement use, and infant feeding. Mothers were phoned at 2 weekly intervals to check adherence.

Venous (women and umbilical cord) and capillary (infant) blood samples were collected. Serum calcium concentration was measured and then samples were stored at  $-80^{\circ}\text{C}$  until study completion.

Serum 25(OH)D concentration was measured using isotope dilution liquid chromatography tandem mass spectrometry in a Vitamin D External Quality Assurance Scheme certified laboratory.<sup>30,31</sup> Total serum calcium was measured using a colorimetric assay on an Abbott Diagnostic Architect instrument (Abbott Park, IL). Hypercalcemia was defined as an adjusted serum calcium concentration  $>10.4$  mg/dL (women),  $>11.6$  mg/dL (cord blood), and  $>11.2$  mg/dL (infants).<sup>32,33</sup>

### Statistical Methods

Analyses were performed on an intention to treat basis. The  $\chi^2$  test,  $t$  test, and analysis of variance were used for between group comparisons. The treatment effect at 36 weeks in the mothers was assessed using linear regression in a model that included enrollment 25(OH)D concentration. The treatment effect in the infants was assessed using a linear mixed model with stage (cord [birth], and 2, 4, and 6 months of age) as a repeated measure using an unstructured covariance matrix. Interaction between stage and treatment was assessed first and on finding an interaction, each stage was analyzed separately using linear regression. The 3 treatment groups were compared using the 2 hypothesized, orthogonal contrasts: placebo versus vitamin D supplementation and 400 IU versus 800 IU supplementation.

All comparisons used 2 sided tests at a .05 level of significance. The null hypothesis for all analyses was that there is no difference between the study groups.

### RESULTS

Of 404 pregnant women assessed, 260 were randomized to placebo ( $n = 87$ ), lower dose vitamin D<sub>3</sub> ( $n = 87$ ), or higher dose vitamin D<sub>3</sub> ( $n = 86$ ) (Fig 1). Serum 25(OH)D concentration was measured on 259 women at enrollment; 228 (88%) women at 36 weeks'

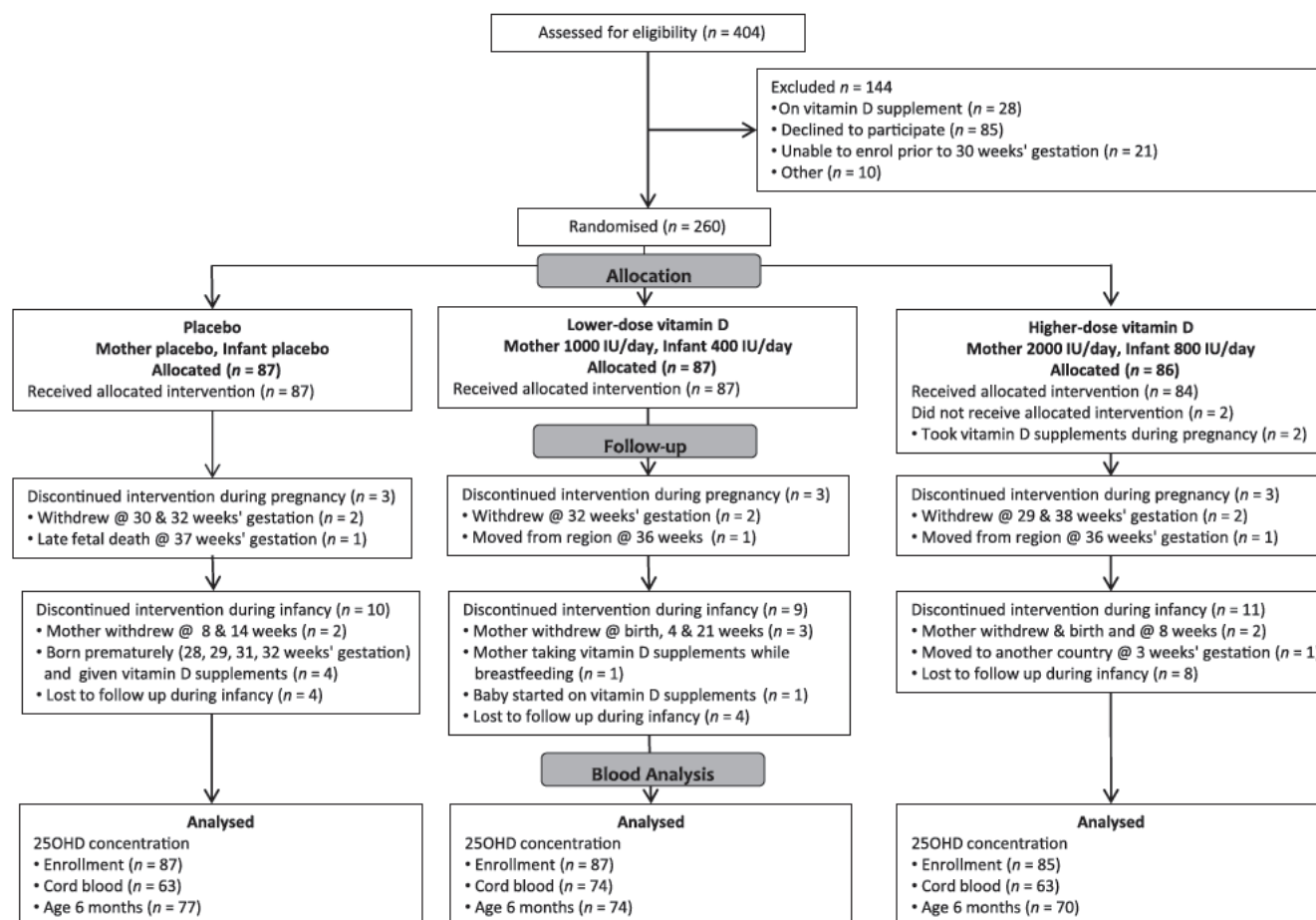
gestation; 200 (77%) cord blood samples; and 198 (76%), 189 (73%), and 221 (85%) infants at 2, 4, and 6 months of age, respectively.

Table 1 shows the characteristics of enrolled women. The proportions enrolled during summer, fall, winter, and spring were 0.23, 0.27, 0.26, and 0.24 respectively. At enrollment, 57% of the women were obese ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ).<sup>34</sup> At 36 weeks' gestation, 11 (5%) of the women were taking vitamin D supplements containing between 100 and 500 IU per dose.

Table 2 shows the characteristics of enrolled infants. Ninety five percent were breastfed, with 26 (12%) exclusively breastfed at age 6 months. The proportion of infants receiving milk formula increased from age 2 to 6 months ( $P = .002$ ), as did the median daily volume consumed (600 mL to 750 mL,  $P = .001$ ). Formula milk volume consumed did not differ between study groups at age 2 ( $P = .25$ ), 4 ( $P = .30$ ), or 6 months ( $P = .34$ ). Six infants, 5 of whom were born prematurely, received supplementary vitamin D.

The hours per day each infant spent outdoors increased from age 2 to 6 months (median 0.23 vs 0.40 hours,  $P = .001$ ) but did not differ between study groups at age 2 ( $P = .18$ ), 4 ( $P = .39$ ), or 6 months ( $P = .55$ ).

Reported compliance did not differ between groups (Table 3). The proportion of infants given 1 drop of study medicine each day decreased during infancy (2 months 90%, 4 months 90%, 6 months 78%, 2 vs 6 months,  $P < .001$ ). Maternal serum 25(OH)D concentrations increased from enrollment to 36 weeks' gestation to a similar extent in the 1000 IU and 2000 IU groups while remaining unchanged in the placebo group (Fig 2). In a regression of cord blood 25(OH)D concentration on maternal 36 week gestation 25(OH)D concentration, adjusted for treatment group, the model  $R^2$  was 0.79 ( $P < .001$ ) (Supplementary Fig 4).

**FIGURE 1**

Flow diagram of enrollment, randomization, attrition, and data collection.

Median 25(OH)D concentrations at age 2 months in all 3 groups were higher than the cord blood 25(OH)D concentrations. The 25(OH)D concentrations in the 3 groups converged with increasing infant age with 25(OH)D concentrations increasing in the placebo group and decreasing in the higher dose intervention group (Fig 2).

Maternal 25(OH)D concentrations at 36 weeks in the 3 treatment groups differed ( $P < .001$ , Table 4). Using the linear mixed model, there was an interaction between age (cord, 2, 4, and 6 months) and treatment group ( $P < .001$ ). At all ages, the order of the estimates was the same, with the higher dose group having the highest levels and the placebo group the lowest levels. Each stage showed a significant

difference across treatment groups ( $P < .01$ ). Table 4 shows estimated differences between groups and their 95% confidence intervals for the 2 hypothesized contrasts.

The proportion of women with 25(OH)D  $\geq 30$  ng/mL or  $\geq 20$  ng/mL differed among the 3 groups at all postenrollment measurement points (Table 5). In the placebo group, the proportion of infants with 25(OH)D  $\geq 30$  ng/mL increased from 33% at age 2 months to 57% at age 6 months ( $P = .006$ ). The proportion of infants with 25(OH)D  $\geq 30$  ng/mL did not differ from age 2 to 6 months in the 400 IU (64% 74%,  $P = .19$ ) or the 800 IU group (79% 73%,  $P = .44$ ). In the placebo group, the proportion of infants with 25(OH)D  $\geq 20$  ng/mL increased from 50% at age 2

months to 74% at age 6 months ( $P = .003$ ). The proportion of infants with 25(OH)D  $\geq 20$  ng/mL did not differ from age 2 to 6 months in the 400 IU (82% 82%,  $P = .96$ ) or the 800 IU group (92% 89%,  $P = .54$ ). Exclusion of women with gestational diabetes ( $n = 13$ ), who took vitamin D supplements ( $n = 11$ ) or whose infants took vitamin D supplements ( $n = 7$ ) made no difference to these comparisons with the exception that the proportion with 25(OH)D  $\geq 20$  ng/mL did not differ between groups at age 6 months (Supplementary Table 6). Based upon the 25(OH)D concentrations at 6 months of age, seasonal variation in vitamin D status was evident with seasonal variation being comparable in all 3 groups (Fig 3). After adjustment for season, the 25(OH)D concentration in

**TABLE 1** Demographics and Clinical Characteristics of Enrolled Pregnant Women

| Variable                                                                                                             | Study Group                                 |                                                                                 |                                                                     |
|----------------------------------------------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------|
|                                                                                                                      | Placebo (Mother Placebo/<br>Infant Placebo) | Lower Dose Vitamin D <sub>3</sub> (Mother 1000 IU<br>Daily/Infant 400 IU Daily) | Higher Dose Vitamin D (Mother 2000 IU<br>Daily/Infant 800 IU Daily) |
|                                                                                                                      | <i>n</i> <sub>1</sub> = 87                  | <i>n</i> <sub>2</sub> = 87                                                      | <i>n</i> <sub>3</sub> = 86                                          |
| Season of enrollment, <sup>a</sup> <i>n</i> (%)                                                                      |                                             |                                                                                 |                                                                     |
| Summer                                                                                                               | 20 (23)                                     | 21 (24)                                                                         | 18 (21)                                                             |
| Fall                                                                                                                 | 25 (29)                                     | 22 (25)                                                                         | 24 (27)                                                             |
| Winter                                                                                                               | 23 (26)                                     | 23 (27)                                                                         | 22 (26)                                                             |
| Spring                                                                                                               | 19 (22)                                     | 21 (24)                                                                         | 22 (26)                                                             |
| Maternal demographics                                                                                                |                                             |                                                                                 |                                                                     |
| Age, y, mean ± SD                                                                                                    | 28 ± 6                                      | 27 ± 6                                                                          | 26 ± 7                                                              |
| Gestation at enrolment, in weeks<br>(median, 25th, 75th centiles)                                                    | 27 (26, 29)                                 | 28 (26, 29)                                                                     | 27 (26, 29)                                                         |
| BMI at enrolment, in kg/m <sup>2</sup> (mean ± SD)                                                                   | 32 (7)                                      | 33 (8)                                                                          | 32 (7)                                                              |
| Ethnic group, <sup>b</sup> <i>n</i> (%)                                                                              |                                             |                                                                                 |                                                                     |
| European                                                                                                             | 33 (38)                                     | 27 (31)                                                                         | 28 (33)                                                             |
| Māori                                                                                                                | 21 (24)                                     | 23 (26)                                                                         | 19 (22)                                                             |
| Pacific                                                                                                              | 40 (46)                                     | 44 (51)                                                                         | 43 (50)                                                             |
| Other                                                                                                                | 22 (25)                                     | 20 (23)                                                                         | 23 (27)                                                             |
| Took vitamin D supplements during<br>pregnancy, <i>n</i> (%)                                                         |                                             |                                                                                 |                                                                     |
| Yes                                                                                                                  | 2 (2)                                       | 6 (7)                                                                           | 3 (4)                                                               |
| No                                                                                                                   | 78 (98)                                     | 75 (93)                                                                         | 68 (96)                                                             |
| Cigarette smoker during current<br>pregnancy, <i>n</i> (%)                                                           |                                             |                                                                                 |                                                                     |
| Yes                                                                                                                  | 18 (21)                                     | 17 (20)                                                                         | 14 (16)                                                             |
| No                                                                                                                   | 69 (79)                                     | 70 (80)                                                                         | 72 (84)                                                             |
| Education, <i>n</i> (%)                                                                                              |                                             |                                                                                 |                                                                     |
| Primary                                                                                                              | 10 (12)                                     | 17 (20)                                                                         | 12 (14)                                                             |
| Secondary                                                                                                            | 23 (26)                                     | 28 (32)                                                                         | 23 (27)                                                             |
| Tertiary                                                                                                             | 54 (62)                                     | 42 (48)                                                                         | 51 (59)                                                             |
| Maternal pregnancy history and health                                                                                |                                             |                                                                                 |                                                                     |
| Previous pregnancies, <i>n</i> (%)                                                                                   |                                             |                                                                                 |                                                                     |
| Yes                                                                                                                  | 67 (77)                                     | 66 (76)                                                                         | 58 (67)                                                             |
| No                                                                                                                   | 20 (33)                                     | 21 (24)                                                                         | 28 (33)                                                             |
| Gestational diabetes during current<br>pregnancy, <sup>c</sup> <i>n</i> (%)                                          |                                             |                                                                                 |                                                                     |
| Yes                                                                                                                  | 4 (5)                                       | 7 (9)                                                                           | 2 (3)                                                               |
| No                                                                                                                   | 79 (95)                                     | 73 (91)                                                                         | 75 (97)                                                             |
| Maternal sunlight exposure and<br>sunlight related behavior                                                          |                                             |                                                                                 |                                                                     |
| Use sunscreen with an SPF15 or stronger<br>when outside in summer, <i>n</i> (%)                                      |                                             |                                                                                 |                                                                     |
| Yes                                                                                                                  | 32 (37)                                     | 36 (41)                                                                         | 40 (47)                                                             |
| No                                                                                                                   | 55 (63)                                     | 51 (59)                                                                         | 45 (53)                                                             |
| Avoid direct sun exposure between 10 AM<br>and 4 PM, <sup>d</sup> <i>n</i> (%)                                       |                                             |                                                                                 |                                                                     |
| Yes                                                                                                                  | 51 (59)                                     | 53 (61)                                                                         | 61 (71)                                                             |
| No                                                                                                                   | 35 (41)                                     | 34 (39)                                                                         | 25 (29)                                                             |
| Reaction of skin to sun exposure, <i>n</i> (%)                                                                       |                                             |                                                                                 |                                                                     |
| Always burn, never tan                                                                                               | 3 (3)                                       | 2 (2)                                                                           | 5 (6)                                                               |
| Usually burn, tan with difficulty                                                                                    | 10 (12)                                     | 4 (5)                                                                           | 15 (17)                                                             |
| Sometimes mild burn                                                                                                  | 30 (35)                                     | 41 (47)                                                                         | 23 (27)                                                             |
| Rarely burn, tan with ease                                                                                           | 23 (26)                                     | 19 (22)                                                                         | 22 (26)                                                             |
| Not stated                                                                                                           | 21 (24)                                     | 21 (24)                                                                         | 21 (24)                                                             |
| Time per spent outdoors on average<br>during month previous to enrollment,<br>in hours, median (25th, 75th centiles) | 0.5 (0.3, 1.6)                              | 1.0 (0.5, 2.0)                                                                  | 1.0 (0.5, 1.8)                                                      |
| Headwear worn when outside, <i>n</i> (%)                                                                             |                                             |                                                                                 |                                                                     |
| Veiled                                                                                                               | 2 (2)                                       | 0 (0)                                                                           | 0 (0)                                                               |

TABLE 1 Continued

| Variable         | Study Group                                 |                                                                                 |                                                                     |
|------------------|---------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------|
|                  | Placebo (Mother Placebo/<br>Infant Placebo) | Lower Dose Vitamin D <sub>3</sub> (Mother 1000 IU<br>Daily/Infant 400 IU Daily) | Higher Dose Vitamin D (Mother 2000 IU<br>Daily/Infant 800 IU Daily) |
|                  | <i>n</i> <sub>1</sub> = 87                  | <i>n</i> <sub>2</sub> = 87                                                      | <i>n</i> <sub>3</sub> = 86                                          |
| Hat              | 9 (11)                                      | 12 (14)                                                                         | 13 (15)                                                             |
| No head covering | 55 (63)                                     | 53 (61)                                                                         | 51 (59)                                                             |
| Not stated       | 21 (24)                                     | 22 (25)                                                                         | 22 (26)                                                             |

<sup>a</sup> Summer (December to February), Fall (March to May), Winter (June to August), Spring (September to November)

<sup>b</sup> Ethnic groups are those used for the national census. Māori is New Zealand's indigenous population. Ethnicity was defined by the participants. More than 1 ethnic group could be identified; therefore, percentages do not add to 100.

<sup>c</sup> At either enrollment or 36 week gestation interview *n*<sub>1</sub> = 83, *n*<sub>2</sub> = 80, *n*<sub>3</sub> = 77

<sup>d</sup> Includes using protective clothing and/or remaining under a shade cover (not stated by 1 mother)

the placebo group at age 6 months was lower than that in the intervention groups ( $P = .025$ ) but did not differ between intervention groups ( $P = .40$ ). Serum calcium was not elevated in any participant, nor did mean serum calcium concentration differ between study groups at any measurement point (Supplementary Table 7). At age 2 months, 1 infant in the 400 IU group (130 ng/mL) and 4 infants in the 800 IU group (104, 128, 130, 134 ng/mL)

TABLE 2 Demographics and Clinical Characteristics of Enrolled Infants

| Variable                                                                               | Study Group                                 |                                                                                 |                                                                     |
|----------------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------|
|                                                                                        | Placebo (Mother Placebo/<br>Infant Placebo) | Lower Dose Vitamin D <sub>3</sub> (Mother 1000 IU<br>Daily/Infant 400 IU Daily) | Higher Dose Vitamin D (Mother 2000 IU<br>Daily/Infant 800 IU Daily) |
|                                                                                        | <i>n</i> <sub>1</sub> = 85                  | <i>n</i> <sub>2</sub> = 83                                                      | <i>n</i> <sub>3</sub> = 81                                          |
| Male gender, <i>n</i> (%)                                                              | 44 (52)                                     | 41 (49)                                                                         | 36 (44)                                                             |
| Gestation, wk, median (25th, 75th centile)                                             | 39 (38, 40)                                 | 40 (39, 40)                                                                     | 40 (39, 40)                                                         |
| Birth weight, g, median (25th, 75th centile)                                           | 3465 (3160, 3780)                           | 3480 (3140, 3870)                                                               | 3540 (3230, 3900)                                                   |
| Breastfed, <i>n</i> (%)                                                                |                                             |                                                                                 |                                                                     |
| Any                                                                                    |                                             |                                                                                 |                                                                     |
| Yes                                                                                    | 74 (94)                                     | 70 (92)                                                                         | 69 (99)                                                             |
| No                                                                                     | 5 (6)                                       | 6 (8)                                                                           | 1 (1)                                                               |
| Exclusively at age 6 mo                                                                |                                             |                                                                                 |                                                                     |
| Yes                                                                                    | 10 (13)                                     | 5 (7)                                                                           | 11 (16)                                                             |
| No                                                                                     | 68 (87)                                     | 71 (93)                                                                         | 59 (84)                                                             |
| Received infant formula, <i>n</i> (%)                                                  |                                             |                                                                                 |                                                                     |
| At age 2 mo                                                                            |                                             |                                                                                 |                                                                     |
| Yes                                                                                    | 42 (57)                                     | 45 (63)                                                                         | 38 (58)                                                             |
| No                                                                                     | 32 (43)                                     | 27 (37)                                                                         | 28 (42)                                                             |
| At age 4 mo                                                                            |                                             |                                                                                 |                                                                     |
| Yes                                                                                    | 44 (62)                                     | 44 (66)                                                                         | 42 (68)                                                             |
| No                                                                                     | 27 (38)                                     | 23 (34)                                                                         | 20 (32)                                                             |
| At age 6 mo                                                                            |                                             |                                                                                 |                                                                     |
| Yes                                                                                    | 56 (71)                                     | 55 (74)                                                                         | 50 (74)                                                             |
| No                                                                                     | 28 (29)                                     | 19 (26)                                                                         | 18 (26)                                                             |
| Average daily volume of infant milk formula consumed, mL, median (25th, 75th centile)  |                                             |                                                                                 |                                                                     |
| At age 2 mo                                                                            | 400 (150, 800)                              | 550 (170, 750)                                                                  | 662 (200, 900)                                                      |
| At age 4 mo                                                                            | 500 (150, 1000)                             | 890 (310, 1000)                                                                 | 805 (300, 1000)                                                     |
| At age 6 mo                                                                            | 720 (120, 1000)                             | 900 (250, 1000)                                                                 | 750 (300, 1000)                                                     |
| Used multivitamin that contains vitamin D, <sup>a</sup> <i>n</i> (%)                   |                                             |                                                                                 |                                                                     |
| Yes                                                                                    | 3 (4)                                       | 1 (1)                                                                           | 2 (3)                                                               |
| No                                                                                     | 77 (96)                                     | 76 (99)                                                                         | 68 (97)                                                             |
| Time per day spent outdoors on average over past 2 mo, h, median (25th, 75th centiles) |                                             |                                                                                 |                                                                     |
| At age 2 mo                                                                            | 0.21 (0.08, 0.65)                           | 0.17 (0.06, 0.48)                                                               | 0.27 (0.08, 0.65)                                                   |
| At age 4 mo                                                                            | 0.25 (0.08, 0.62)                           | 0.33 (0.08, 0.52)                                                               | 0.26 (0.08, 0.65)                                                   |
| At age 6 mo                                                                            | 0.40 (0.12, 0.90)                           | 0.33 (0.13, 0.75)                                                               | 0.50 (0.17, 0.68)                                                   |

<sup>a</sup> Vitadrol C (Nutricia; NZ Limited, Auckland, NZ), which contains 466 IU of vitamin D per daily recommended dose

**TABLE 3** Reported Compliance With Study Medicine<sup>a</sup>

| Variable                             | Study Group                             |                                                                              |                                                                  | P Value |
|--------------------------------------|-----------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------|---------|
|                                      | Placebo (Mother Placebo/Infant Placebo) | Lower Dose Vitamin D <sub>3</sub> (Mother 1000 IU Daily/Infant 400 IU Daily) | Higher Dose Vitamin D (Mother 2000 IU Daily/Infant 800 IU Daily) |         |
|                                      | n <sub>1</sub> = 87                     | n <sub>2</sub> = 87                                                          | n <sub>3</sub> = 86                                              |         |
|                                      | n (%)                                   | n (%)                                                                        | n (%)                                                            |         |
| Took 1 drop daily at 36 wk gestation |                                         |                                                                              |                                                                  | .66     |
| Yes                                  | 77 (96)                                 | 77 (95)                                                                      | 66 (93)                                                          |         |
| No                                   | 3 (4)                                   | 4 (5)                                                                        | 5 (7)                                                            |         |
| Gave 1 drop daily to infant          |                                         |                                                                              |                                                                  |         |
| Age 2 mo                             |                                         |                                                                              |                                                                  | .84     |
| Yes                                  | 67 (92)                                 | 64 (89)                                                                      | 58 (91)                                                          |         |
| No                                   | 6 (8)                                   | 8 (11)                                                                       | 6 (9)                                                            |         |
| Age 4 mo                             |                                         |                                                                              |                                                                  | .25     |
| Yes                                  | 67 (94)                                 | 58 (87)                                                                      | 54 (87)                                                          |         |
| No                                   | 4 (6)                                   | 9 (13)                                                                       | 8 (13)                                                           |         |
| Age 6 mo                             |                                         |                                                                              |                                                                  | .33     |
| Yes                                  | 65 (83)                                 | 57 (75)                                                                      | 52 (74)                                                          |         |
| No                                   | 13 (17)                                 | 19 (25)                                                                      | 18 (26)                                                          |         |

<sup>a</sup> Reported by 220 (95%) of 232 of the women at 36 weeks' gestation and by them for 189 (90%) of 209, 179 (90%) of 200, and 174 (78%) of 224 of the infants at 2, 4, and 6 months of age, respectively

had a serum 25(OH)D concentration  $\geq 100$  ng/mL.

## DISCUSSION

Vitamin D supplementation of pregnant women, from 27 weeks' gestation until

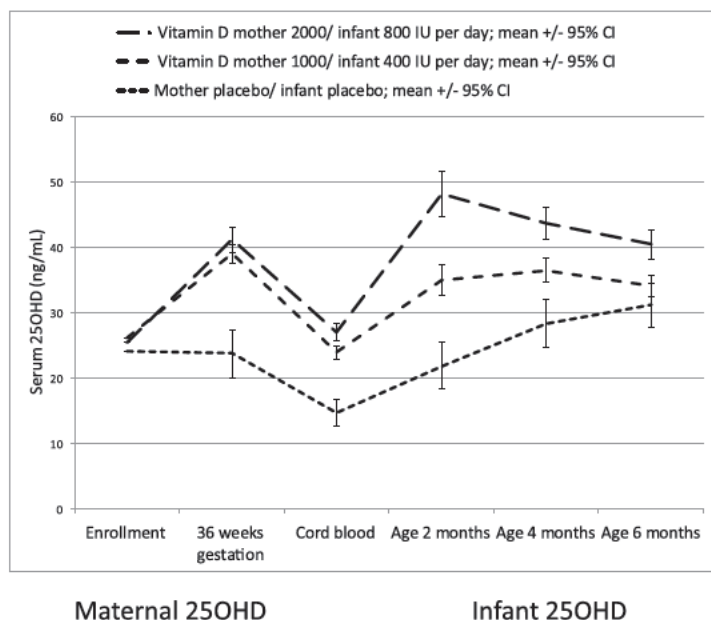
childbirth, and then their infants, from birth until age 6 months, results in 71% to 79% of women, at 36 weeks' gestation, and 73% to 74% of infants at age 6 months achieving serum 25(OH)D concentrations  $\geq 30$  ng/mL when a woman/infant dosing regimen of either vitamin

D<sub>3</sub> 1000 IU/400 IU, or vitamin D<sub>3</sub> 2000 IU/800 IU is used. Ninety percent of women, at 36 weeks' gestation, and 82% to 92% of infants, to age 6 months, achieve serum 25(OH)D concentrations  $\geq 20$  ng/mL when either of these dosing regimens are used. In comparison with placebo, the proportion of infants achieving a serum 25(OH)D concentration  $\geq 20$  ng/mL was greater for the higher dose group to age 6 months and for the lower dose group to age 4 months.

Neither vitamin D dosing regimen caused hypercalcemia. In particular, hypercalcemia did not occur in the 5 infants who at age 2 months had serum 25(OH)D concentrations  $\geq 100$  ng/mL. These findings are consistent with data from other contemporary pregnancy and infancy studies of vitamin D supplementation. Separate studies have shown that vitamin D 4000 IU per day during pregnancy and 1200 IU per day during infancy does not cause hypercalcemia.<sup>35,36</sup> Vitamin D 1600 IU per day from age 2 weeks to 3 months does not cause hypercalcemia despite resulting in serum 25(OH)D concentrations up to 92 ng/mL.<sup>37</sup>

Serum 25(OH)D concentrations at enrollment (4–80 ng/mL) spanned the expected range seen in populations without supplementation.<sup>38</sup> Recruitment was evenly distributed across seasons and the recruited sample included a diversity of skin pigmentation types. Only 5% of the women and 3% of the infants took vitamin D supplements during the study; these few were distributed evenly across the study arms.

Our intervention ceased at age 6 months. Therefore, we cannot comment on the vitamin D dose required during later infancy. With increasing intake of infant formula, dietary intake of vitamin D is likely to increase and, hence, requirement for vitamin D supplementation may be less critical than earlier in infancy.

**FIGURE 2**

Serum 25(OH)D concentration for mother/infant pairs who were randomly assigned to placebo, lower dose, or higher dose vitamin D supplementation.

TABLE 4 Maternal and infant 25(OH)D Concentrations by Study Group Assignment

| Stage                             | Study Group                                                |                                                                                        | Comparisons Between Study Groups                                                        |                                          |                                                                          |                 |
|-----------------------------------|------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|------------------------------------------|--------------------------------------------------------------------------|-----------------|
|                                   | P placebo (Mother P placebo/infant P placebo) <sup>a</sup> | Lower-Dose Vitamin D (Mother 1000 U Da y/ <sup>b</sup> infant 400 U Da y) <sup>b</sup> | Higher-Dose Vitamin D (Mother 2000 U Da y/ <sup>c</sup> infant 800 U Da y) <sup>c</sup> | Difference Between Vitamin D and Placebo | Difference Between Higher-Dose Vitamin D and Lower-Dose Vitamin D Groups | Overall P Value |
|                                   |                                                            | Serum 25(OH)D Concentration, ng/mL Median (25th, 75th Percentile)                      |                                                                                         | Estimate (95% CI)                        | Estimate (95% CI)                                                        |                 |
| Maternal at enrollment            | 22 (13, 32)                                                | 23 (16, 36)                                                                            | 22 (13, 35)                                                                             |                                          |                                                                          |                 |
| Maternal at 36 weeks gestation    | 20 (12, 30)                                                | 39 (32, 46)                                                                            | 41 (29, 50)                                                                             | 14 (11–17)                               | 2 (–1–6)                                                                 | < .001          |
| Cord blood infant at age 2 months | 13 (9, 18)                                                 | 24 (18, 30)                                                                            | 26 (18, 35)                                                                             | 11 (8–14)                                | 3 (0–6)                                                                  | < .001          |
| Cord blood infant at age 4 months | 20 (7, 35)                                                 | 34 (24, 46)                                                                            | 43 (36, 54)                                                                             | 20 (14–26)                               | 13 (6–21)                                                                | < .001          |
| Cord blood infant at age 6 months | 30 (14, 41)                                                | 38 (29, 45)                                                                            | 45 (35, 54)                                                                             | 12 (7–17)                                | 7 (1–13)                                                                 | < .001          |
|                                   | 31 (19, 40)                                                | 34 (29, 44)                                                                            | 38 (28, 51)                                                                             | 6 (2–10)                                 | 6 (0–11)                                                                 | .004            |

CI, confidence interval.

<sup>a</sup> For enrollment, 36 weeks, cord, 2, 4, and 6 months  $n = 87, 78, 63, 70, 68$ , and  $77$ , respectively.<sup>b</sup> For enrollment, 36 weeks, cord, 2, 4, and 6 months  $n = 87, 78, 74, 67, 61$ , and  $74$ , respectively.<sup>c</sup> For enrollment, 36 weeks, cord, 2, 4, and 6 months  $n = 85, 72, 63, 61, 60$ , and  $70$ , respectively.

Serum 25(OH)D concentration increased during infancy in our placebo group. This was also observed in a study of exclusively breastfed infants born during winter in Ioannina, Greece (39°N).<sup>39</sup> In our sample, the increased serum 25(OH)D concentration during infancy was probably multifactorial, but we suspect was largely due to increased intake of vitamin D from milk formula. In NZ, infant formula is fortified with 360 IU/L of vitamin D.<sup>40</sup> Therefore by age 6 months, infants randomized to the placebo group were, on average, receiving 260 IU per day of vitamin D.

Serum 25(OH)D concentrations decreased during infancy in the 800 IU per day group. Although decreasing compliance may have contributed to this, it is likely also due to the vitamin D dose per kilogram of body weight decreasing.<sup>41</sup> A similar pattern has been observed in other infant supplementation trials and suggests that a vitamin D dose per kilogram may be necessary in this age group.<sup>36,42,43</sup>

Our study is the first randomized controlled trial of vitamin D supplementation during infancy that commenced supplementation before birth. By doing so, ~90% of the pregnant women randomized to vitamin D achieved a serum 25(OH)D concentration  $\geq 20$  ng/mL. Consistent with other reports, there was a linear positive association between the cord 25(OH)D and maternal 36 week gestation 25(OH)D concentration.<sup>10,35,44</sup> In our study, the cord 25(OH)D concentration was, on average, 13.8 ng/mL lower than the maternal concentration. Although this also has been observed previously,<sup>44</sup> cord blood 25(OH)D concentrations in other populations have been similar to<sup>45</sup> or higher than maternal late pregnancy serum 25(OH)D concentrations.<sup>10</sup> For neonates to be born with adequate vitamin D status requires their mothers to be vitamin D sufficient during pregnancy.<sup>46</sup>

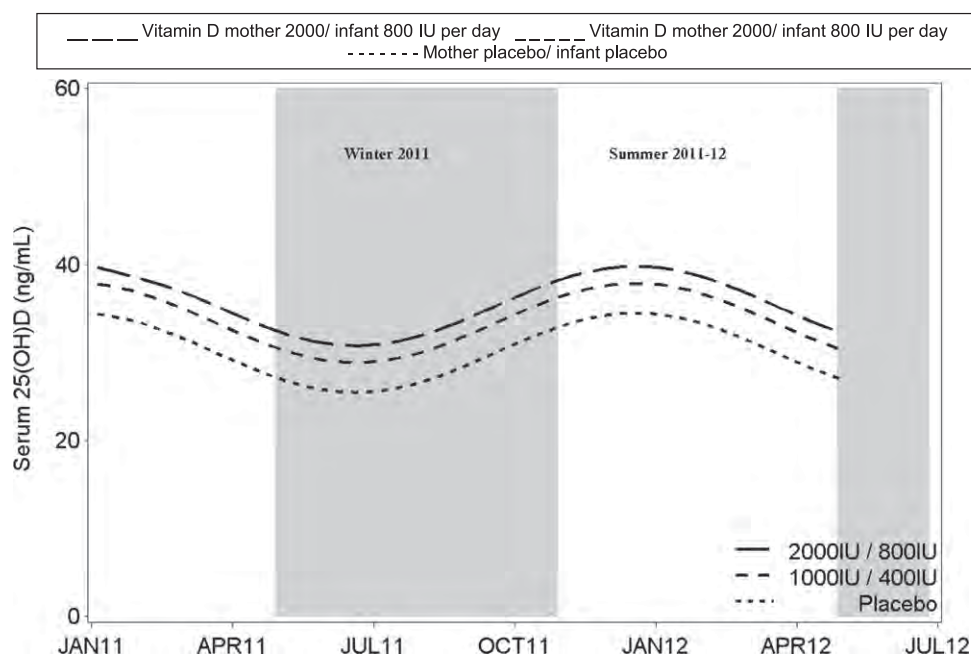
**TABLE 5** Maternal and Infant 25(OH)D Concentrations by Study Group Assignment and Proportion With 25(OH)D  $\geq 20$  ng/mL and  $\geq 30$  ng/mL

|                                                           | Study Group                                                   |                                                                                     |                                                                                      | Comparisons Between Study Groups |                                                     |                                                      |                                                            |
|-----------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------|-----------------------------------------------------|------------------------------------------------------|------------------------------------------------------------|
|                                                           | Placebo<br>(Mother<br>Placebo/Infant<br>Placebo) <sup>a</sup> | Lower Dose Vitamin D<br>(Mother 1000 IU Daily/<br>Infant 400 IU Daily) <sup>b</sup> | Higher Dose Vitamin D<br>(Mother 2000 IU Daily/<br>Infant 800 IU Daily) <sup>c</sup> | P Value<br>(All 3<br>Groups)     | P Value (Lower<br>Dose Vitamin D<br>Versus Placebo) | P Value (Higher<br>Dose Vitamin D<br>Versus Placebo) | P Value (Higher Dose<br>Vitamin D Lower<br>Dose Vitamin D) |
| Serum 25(OH)D concentration $\geq 20$ ng/mL, <i>n</i> (%) |                                                               |                                                                                     |                                                                                      |                                  |                                                     |                                                      |                                                            |
| Maternal at enrollment                                    | 47 (54)                                                       | 56 (64)                                                                             | 47 (55)                                                                              |                                  |                                                     |                                                      |                                                            |
| Maternal at 36 wk gestation                               | 39 (50)                                                       | 71 (91)                                                                             | 64 (89)                                                                              | < .001                           | < .001                                              | < .001                                               | .66                                                        |
| Cord blood                                                | 14 (22)                                                       | 53 (72)                                                                             | 45 (71)                                                                              | < .001                           | < .001                                              | < .001                                               | .98                                                        |
| Infant at age 2 mo                                        | 35 (50)                                                       | 55 (82)                                                                             | 56 (92)                                                                              | < .001                           | < .001                                              | < .001                                               | .11                                                        |
| Infant at age 4 mo                                        | 45 (66)                                                       | 53 (87)                                                                             | 52 (87)                                                                              | .004                             | .006                                                | .007                                                 | .97                                                        |
| Infant at age 6 mo                                        | 57 (74)                                                       | 61 (82)                                                                             | 62 (89)                                                                              | .07                              | .21                                                 | .03                                                  | .30                                                        |
| Serum 25(OH)D concentration $\geq 30$ ng/mL, <i>n</i> (%) |                                                               |                                                                                     |                                                                                      |                                  |                                                     |                                                      |                                                            |
| Maternal at enrollment                                    | 26 (30)                                                       | 32 (37)                                                                             | 31 (36)                                                                              |                                  |                                                     |                                                      |                                                            |
| Maternal at 36 wk gestation                               | 21 (27)                                                       | 62 (79)                                                                             | 51 (71)                                                                              | < .001                           | < .001                                              | < .001                                               | .22                                                        |
| Cord blood                                                | 3 (5)                                                         | 18 (24)                                                                             | 25 (40)                                                                              | < .001                           | .002                                                | < .001                                               | .05                                                        |
| Infant at age 2 mo                                        | 24 (33)                                                       | 43 (64)                                                                             | 48 (79)                                                                              | < .001                           | < .001                                              | < .001                                               | .07                                                        |
| Infant at age 4 mo                                        | 34 (50)                                                       | 43 (70)                                                                             | 48 (80)                                                                              | .001                             | .02                                                 | < .001                                               | .23                                                        |
| Infant at age 6 mo                                        | 44 (57)                                                       | 55 (74)                                                                             | 51 (73)                                                                              | .04                              | .03                                                 | .05                                                  | .84                                                        |

<sup>a</sup> For enrollment, 36 weeks, cord, 2, 4, and 6 months *n* 87, 78, 63, 70, 68, and 77, respectively

<sup>b</sup> For enrollment, 36 weeks, cord, 2, 4, and 6 months *n* 87, 78, 74, 67, 61, and 74, respectively

<sup>c</sup> For enrollment, 36 weeks, cord, 2, 4, and 6 months *n* 85, 72, 63, 61, 60, and 70, respectively

**FIGURE 3**

Seasonal patterns of 25(OH)D concentration for infants at age 6 months who were randomly assigned to placebo (mother placebo/infant placebo), lower dose (mother 1000/infant 400 IU per day) or higher dose (mother 2000/infant 800 IU per day) vitamin D supplementation.

Among infants randomized to 400 IU per day, the median serum 25(OH)D concentration at age 2 (33.5 ng/mL) and 6 months (34.4 ng/mL) approximated that achieved in the 3 other clinical trials reporting comparable data for infants receiving 400 IU per day from the first weeks of life. These trials enrolled infants in Cincinnati, Ohio (39°N) (25[OH]D 2 months 37 ng/mL, 6 months 33 ng/mL),<sup>47</sup> Madison, Wisconsin (43°N) (2 months 30 ng/mL, 6 months 24 ng/mL),<sup>43</sup> and Montreal, Quebec (46°N) (3 months, 31 ng/mL).<sup>36</sup>

At age 2 months, serum 25(OH)D concentrations  $\geq 20$  ng/mL were achieved in 82% of infants in the 400 IU per day group and 92% in the 800 IU per day group. In comparison, 97% of breastfed infants living in Montreal and randomized at age 1 month to vitamin D 400, 800, 1200, or 1600 IU per day had

a serum 25(OH)D concentration at age 3 months  $\geq 20$  ng/mL, as did almost all infants in Finland randomized at age 2 weeks to 400, 1200, or 1600 IU per day.<sup>36,37</sup> The lower percentages in our study are possibly due to differences in the enrolled populations. In the Canadian study  $>85\%$  of mothers had completed tertiary education. The mothers of the Finnish infants were considered more health orientated than the general population.<sup>36,37</sup> In comparison, our sample of mothers was less well educated (57% tertiary education) and comparable demographically to the region from which they were recruited.<sup>48</sup>

## CONCLUSIONS

If the objective of vitamin D supplementation is to achieve a serum 25(OH)D concentration  $\geq 20$  ng/mL in 97.5% of infants, then it seems likely that this

requires both maternal vitamin D supplementation during pregnancy and high compliance with daily dosing regimens. For serum 25(OH)D concentration to be maintained throughout infancy, it is likely to also require dose adjustment to meet the demands created by rapid growth during infancy. Given the global variation in serum 25(OH)D concentration during pregnancy, recommended infant vitamin D supplementation in different countries will need to take into account maternal pregnancy vitamin D status in each country.

## ACKNOWLEDGMENTS

The authors acknowledge the contributions made to the Pregnancy and Infancy Vitamin D trial by Debbie Raroa and Carol Taylor, by the staff at Lead Maternity Carer Services, and by Dr Jocelyn Neutze at Kidz First Children's Hospital.

## REFERENCES

1. Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press; 2011
2. Dawodu A, Wagner CL. Mother child vitamin D deficiency: an international perspective. *Arch Dis Child*. 2007;92(9):737-740
3. Seth A, Marwaha RK, Singla B, et al. Vitamin D nutritional status of exclusively breast fed infants and their mothers. *J Pediatr Endocrinol Metab*. 2009;22(3):241-246
4. Jiang L, Xu J, Pan S, Xie E, Hu Z, Shen H. High prevalence of hypovitaminosis D among pregnant women in southeast China. *Acta Paediatr*. 2012;101(4):e192-e194
5. Tao M, Shao H, Gu J, Zhen Z. Vitamin D status of pregnant women in Shanghai, China. *J Matern Fetal Neonatal Med*. 2012;25(3):237-239
6. Shibata M, Suzuki A, Sekiya T, et al. High prevalence of hypovitaminosis D in pregnant Japanese women with threatened premature delivery. *J Bone Miner Metab*. 2011;29(5):615-620
7. McLeod DS, Scott KA, Lust KM, McIntyre HD. Routine screening for vitamin D deficiency in early pregnancy. *Med J Aust*. 2011;195(7):384-385
8. Perampalam S, Ganda K, Chow KA, et al. Vitamin D status and its predictive factors in pregnancy in 2 Australian populations. *Aust N Z J Obstet Gynaecol*. 2011;51(4):353-359
9. Teale GR, Cunningham CE. Vitamin D deficiency is common among pregnant women in rural Victoria. *Aust N Z J Obstet Gynaecol*. 2010;50(3):259-261
10. Bowyer L, Catling Paul C, Diamond T, Homer C, Davis G, Craig ME. Vitamin D, PTH and calcium levels in pregnant women and their neonates. *Clin Endocrinol (Oxf)*. 2009;70(3):372-377
11. Sääf M, Fernell E, Kristiansson F, Barnevik Olsson M, Gustafsson SA, Bågenholm G. Severe vitamin D deficiency in pregnant women of Somali origin living in Sweden. *Acta Paediatr*. 2011;100(4):612-614
12. Leffelaar ER, Vrijkotte TG, van Eijdsden M. Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi ethnic Amsterdam Born Children and their Development cohort. *Br J Nutr*. 2010;104(1):108-117
13. O'Riordan MN, Kiely M, Higgins JR, Cashman KD. Prevalence of suboptimal vitamin D status during pregnancy. *Ir Med J*. 2008;101(8):240, 242-243
14. Holmes VA, Barnes MS, Alexander HD, McFaul P, Wallace JM. Vitamin D deficiency and insufficiency in pregnant women: a longitudinal study. *Br J Nutr*. 2009;102(6):876-881
15. Gale CR, Robinson SM, Harvey NC, et al; Princess Anne Hospital Study Group. Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr*. 2008;62(1):68-77
16. Das V, Agarwal A, Bhatia V, et al. Evaluation of vitamin D status and need for supplementation in pregnant women of a rural area of North India. *Int J Gynaecol Obstet*. 2009;107(suppl 2):S151
17. Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, Sempos CT. Vitamin D status: United States, 2001-2006. *NCHS Data Brief*. 2011(59):1-8
18. Gordon CM, Feldman HA, Sinclair L, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. *Arch Pediatr Adolesc Med*. 2008;162(6):505-512
19. Liang L, Chantry C, Styne DM, Stephensen CB. Prevalence and risk factors for vitamin D deficiency among healthy infants and young children in Sacramento, California. *Eur J Pediatr*. 2010;169(11):1337-1344
20. Yetley EA. Assessing the vitamin D status of the US population. *Am J Clin Nutr*. 2008;88(2):558S-564S
21. Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. *J Nutr*. 2005;135(2):310-316
22. Ministry of Health and Cancer Society of New Zealand. *Consensus Statement on Vitamin D and Sun Exposure in New Zealand*. Wellington: Ministry of Health; 2012

23. Camargo CA Jr, Ingham T, Wickens K, et al; New Zealand Asthma and Allergy Cohort Study Group. Vitamin D status of newborns in New Zealand. *Br J Nutr*. 2010;104(7):1051–1057.
24. Bischoff Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson Hughes B. Estimation of optimal serum concentrations of 25 hydroxyvitamin D for multiple health outcomes [published correction appears in *Am J Clin Nutr*. 2006;84(5):1253]. *Am J Clin Nutr*. 2006;84(1):18–28.
25. First Nations Inuit and Métis Health Committee Canadian Paediatric Society (CPS). Vitamin D supplementation: recommendations for Canadian mothers and infants. *Paediatr Child Health (Oxford)*. 2007;12(7):583–598.
26. Gertner JM, Coustan DR, Kliger AS, Mallette LE, Ravin N, Broadus AE. Pregnancy as state of physiologic absorptive hypercalciuria. *Am J Med*. 1986;81(3):451–456.
27. Matos V, van Melle G, Boulat O, Markert M, Bachmann C, Guignard JP. Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. *J Pediatr*. 1997;131(2):252–257.
28. Heaney RP, Davies KM, Chen TC, Holick MF, Barger Lux MJ. Human serum 25 hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr*. 2003;77(1):204–210.
29. Rockell JE, Skeaff CM, Williams SM, Green TJ. Serum 25 hydroxyvitamin D concentrations of New Zealanders aged 15 years and older. *Osteoporos Int*. 2006;17(9):1382–1389.
30. Maunsell Z, Wright DJ, Rainbow SJ. Routine isotope dilution liquid chromatography tandem mass spectrometry assay for simultaneous measurement of the 25 hydroxy metabolites of vitamins D2 and D3. *Clin Chem*. 2005;51(9):1683–1690.
31. Lewis JG, Elder PA. Serum 25 OH vitamin D2 and D3 are stable under exaggerated conditions. *Clin Chem*. 2008;54(11):1931–1932.
32. Kovacs CS, Kronenberg HM. Maternal fetal calcium and bone metabolism during pregnancy, puerperium, and lactation. *Endocr Rev*. 1997;18(6):832–872.
33. Loughhead JL, Mimouni F, Tsang RC. Serum ionized calcium concentrations in normal neonates. *Am J Dis Child*. 1988;142(5):516–518.
34. World Health Organization. *Global Database on Body Mass Index*. Geneva: World Health Organization; 2007.
35. Dawodu A, Saadi HF, Bekdache G, Javed Y, Altaye M, Hollis BW. Randomized controlled trial (RCT) of vitamin D supplementation in pregnancy in a population with endemic vitamin D deficiency. *J Clin Endocrinol Metab*. 2013;98(6):2337–2346.
36. Gallo S, Comeau K, Vanstone C, et al. Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants: a randomized trial. *JAMA*. 2013;309(17):1785–1792.
37. Holmlund Suila E, Viljakainen H, Hytinen T, Lamberg Allardt C, Andersson S, Mäkitie O. High dose vitamin D intervention in infants effects on vitamin D status, calcium homeostasis, and bone strength. *J Clin Endocrinol Metab*. 2012;97(11):4139–4147.
38. Jones G. Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr*. 2008;88(2):582S–586S.
39. Challa A, Ntourtoui A, Cholevas V, Bitsori M, Galanakis E, Andronikou S. Breastfeeding and vitamin D status in Greece during the first 6 months of life. *Eur J Pediatr*. 2005;164(12):724–729.
40. Ministry of Health. *Companion Statement on Vitamin D and Sun Exposure in Pregnancy and Infancy in New Zealand*. Wellington, NZ: Ministry of Health; 2013.
41. Pludowski P, Socha P, Karczmarewicz E, et al. Vitamin D supplementation and status in infants: a prospective cohort observational study. *J Pediatr Gastroenterol Nutr*. 2011;53(1):93–99.
42. Greer FR, Ho M, Dodson D, Tsang RC. Lack of 25 hydroxyvitamin D and 1,25 dihydroxyvitamin D in human milk. *J Pediatr*. 1981;99(2):233–235.
43. Greer FR, Marshall S. Bone mineral content, serum vitamin D metabolite concentrations, and ultraviolet B light exposure in infants fed human milk with and without vitamin D2 supplements. *J Pediatr*. 1989;114(2):204–212.
44. Wieland P, Fischer JA, Trechsel U, et al. Perinatal parathyroid hormone, vitamin D metabolites, and calcitonin in man. *Am J Physiol*. 1980;239(5):E385–E390.
45. Novakovic B, Galati JC, Chen A, Morley R, Craig JM, Saffery R. Maternal vitamin D predominates over genetic factors in determining neonatal circulating vitamin D concentrations. *Am J Clin Nutr*. 2012;96(1):188–195.
46. Kovacs CS. Vitamin D in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies. *Am J Clin Nutr*. 2008;88(2):520S–528S.
47. Greer FR, Searcy JE, Levin RS, Steichen JJ, Asch PS, Tsang RC. Bone mineral content and serum 25 hydroxyvitamin D concentration in breastfed infants with and without supplemental vitamin D. *J Pediatr*. 1981;98(5):696–701.
48. Craig E, Anderson P, Jackson C. *The Health Status of Children and Young People in Counties Manukau*. Dunedin, NZ: New Zealand Child and Youth Epidemiology Service; 2008.

(Continued from first page)

Dr Grant and Mr Stewart had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. This trial has been registered with the Australian New Zealand Clinical Trials Registry, identifier ACTRN12610000483055.

[www.pediatrics.org/cgi/doi/10.1542/peds.2013.2602](http://www.pediatrics.org/cgi/doi/10.1542/peds.2013.2602)

doi:10.1542/peds.2013.2602

Accepted for publication Oct 29, 2013

Address correspondence to Cameron Grant, MBChB, PhD, Department of Paediatrics: Child and Youth Health, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Wellesley St, Auckland 1142, New Zealand. E mail: [cc.grant@auckland.ac.nz](mailto:cc.grant@auckland.ac.nz)

PEDIATRICS (ISSN Numbers: Print, 0031 4005; Online, 1098 4275).

Copyright © 2014 by the American Academy of Pediatrics

**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** The pregnancy and infancy vitamin study was funded by the Health Research Council of New Zealand, grant number 09/215R. Dr Mitchell is supported by Cure Kids. The funder played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Study medicine was prepared by the Ddrops Company (Woodbridge, Ontario, Canada).

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

# **Vitamin D During Pregnancy and Infancy and Infant Serum 25-Hydroxyvitamin D Concentration**

Cameron C. Grant, Alistair W. Stewart, Robert Scragg, Tania Milne, Judy Rowden, Alec Ekeroma, Clare Wall, Edwin A. Mitchell, Sue Crengle, Adrian Trenholme, Julian Crane and Carlos A. Camargo Jr

*Pediatrics*; originally published online December 16, 2013;

DOI: 10.1542/peds.2013-2602

## **Updated Information & Services**

including high resolution figures, can be found at:  
<http://pediatrics.aappublications.org/content/early/2013/12/10/peds.2013-2602>

## **Supplementary Material**

Supplementary material can be found at:  
<http://pediatrics.aappublications.org/content/suppl/2013/12/11/peds.2013-2602.DCSupplemental.html>

## **Permissions & Licensing**

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
<http://pediatrics.aappublications.org/site/misc/Permissions.xhtml>

## **Reprints**

Information about ordering reprints can be found online:  
<http://pediatrics.aappublications.org/site/misc/reprints.xhtml>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# Baby Ddrops® 400 IU/drop - Institutional



Package of 10 x 15 dose bottles



Baby Ddrops® 400 IU – Institutional was developed to support the need for vitamin D for inpatients within the institutional setting. Just one purified drop (0.028mL) of Baby Ddrops® provides 400 IU of vitamin D3, without chemicals or additives. Healthcare professionals have requested Baby Ddrops® for patients as an option that enables easy administration with minimal impact on the patient. This special format is designed for individual patient use or can be used as ward stock. Each bottle contains 15 drops or 0.5mL and is packaged in a box of 10 units. Also included within the package are detailed administration instructions as well as dose cards for quick references for institution staff.

Please Note: This product is only offered for sale to hospitals in Canada.

## Product Specifics

| PRODUCT (Unit = Pack of 10 bottles)                 | ITEM NUMBERS | NPN      | UNIT UPC -SKU- | UNIT WEIGHT | UNIT DIMENSIONS (CM)         |
|-----------------------------------------------------|--------------|----------|----------------|-------------|------------------------------|
| Baby Ddrops® 400 IU/drop Institutional - Pack of 10 | DD0030       | 80001869 | 851228000309   | 0.35kg      | 12.75"x5"x8.25"<br>L x W x H |

| PRODUCT (Case of 3 x 10)                            | CASE UPC -SKU- | CASE WEIGHT | CASE DIMENSIONS (CM)         |
|-----------------------------------------------------|----------------|-------------|------------------------------|
| Baby Ddrops® 400 IU/drop Institutional - Case of 30 | 20851228000303 | 1.05kg      | 14"x19.5"x10.5"<br>L x W x H |

## Wholesaler Item Numbers

 AmerisourceBergen® 10 00030

 McKesson 028389

 Ddrops.ca