



**Should Vitamin B12 Tablets be Included in More Drug Formularies? An Economic Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular Vitamin B12 for Alberta Seniors**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004501
Article Type:	Research
Date Submitted by the Author:	19-Nov-2013
Complete List of Authors:	Houle, Sherilyn; University of Alberta, Medicine Kolber, Michael; University of Alberta, Family Medicine Chuck, Anderson; Institute of Health Economics,
<b>Primary Subject Heading</b>:	General practice / Family practice
Secondary Subject Heading:	General practice / Family practice, Health economics, Evidence based practice
Keywords:	HEALTH ECONOMICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

SCHOLARONE™  
Manuscripts

1  
2  
3 Should Vitamin B<sub>12</sub> Tablets be Included in More Drug Formularies? An Economic Model of the  
4  
5 Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular Vitamin B<sub>12</sub> for  
6  
7  
8 Alberta Seniors  
9

10  
11  
12 Sherilyn KD Houle, Michael R Kolber, Anderson W Chuck  
13

14 **Authors:**

15  
16 Sherilyn KD Houle (corresponding author)

17  
18 EPICORE Centre

19  
20 3<sup>rd</sup> Floor, Brain and Aging Research Building

21  
22 University of Alberta

23  
24 Edmonton AB, Canada

25  
26 T6G 2M8  
27  
28  
29  
30

31 Michael R Kolber

32  
33 Department of Family Medicine

34  
35 University of Alberta

36  
37 Edmonton AB, Canada  
38  
39  
40  
41

42 Anderson W Chuck

43  
44 Institute of Health Economics

45  
46 Edmonton AB, Canada  
47  
48  
49  
50

51 **Keywords:** Cost analysis, healthcare costs, vitamin B<sub>12</sub> deficiency  
52

53  
54  
55 **Word Count:** 2521  
56  
57  
58  
59  
60

**ABSTRACT:**

**Objectives:** The aim of this study is to estimate the cost-savings attainable if all patients aged  $\geq 65$  in Alberta and currently on intramuscular therapy were switched to oral therapy, from the perspective of a provincial ministry of health.

**Setting:** Primary care setting in Alberta, Canada.

**Participants:** Seniors age 65 and older currently receiving intramuscular vitamin B<sub>12</sub> therapy.

**Intervention:** Oral vitamin B<sub>12</sub> therapy at 1000 mcg per day versus intramuscular therapy at 1000 mcg per month.

**Primary and Secondary Outcome Measures:** Cost-saving from oral therapy over intramuscular therapy, from the perspective of the Alberta Ministry of Health, including drug costs, dispensing fees, injection administration fees, additional laboratory monitoring, and physician visit fees.

**Results:** Over 5 years, if all Albertans age 65 and older who currently receive intramuscular B<sub>12</sub> are switched to oral therapy, our model found that CAD \$13,975,883 can be saved. Even if no additional physician visits are billed for among patients receiving IM therapy, \$8,444,346 could be saved from reduced administration costs alone.

**Conclusions:** Oral B<sub>12</sub> therapy has been shown to be an effective therapeutic option for patients with vitamin B<sub>12</sub> deficiency, yet only three provinces and the Non-Insured Health Benefits program include oral tablets on their formulary rather than the parenteral preparation.

To ensure judicious use of limited health resources, clinicians and formulary committees are encouraged to adopt oral B<sub>12</sub> therapy as a clinically- and cost-effective first line therapy for vitamin B<sub>12</sub> deficiency.

#### **STRENGTHS AND LIMITATIONS OF THIS STUDY:**

- Minimal assumptions built into the model, as exact costs and the exact number of eligible residents comprising the population were available
- Three randomized controlled trials and two prospective case series support our use of a cost-minimization analysis approach
- Comprehensive sensitivity analyses employed using Monte Carlo simulation to incorporate multiple variables
- Study is from the perspective of the provincial ministry of health (the payer) and does not adopt a societal perspective since much of the additional information required for that is not available
- Despite being set in one Canadian province, the use of intramuscular B<sub>12</sub> therapy is prevalent worldwide. Therefore, these results, while not directly generalizable to other jurisdictions, point to an economic argument for greater uptake of oral B<sub>12</sub> therapy which is likely consistent across other jurisdictions

#### **BACKGROUND:**

For over twenty years, oral vitamin B<sub>12</sub> has been referred to as “medicine’s best kept secret” [1]. Despite evidence of the effectiveness of oral B<sub>12</sub> therapy [2-7], intramuscular (IM) administration remains the most commonly prescribed route in North America [8].

1  
2  
3 Approximately 5% of Canadians are B<sub>12</sub> deficient [9], with Framingham data suggesting that B<sub>12</sub>  
4 deficiency in community-dwelling adults age 67 and older may be as high as 12% [10].  
5

6  
7 Deficiency can occur as a result of gastric atrophy or previous gastric or intestinal surgery, use  
8 of antacids and other medications (metformin), inadequate animal product intake, and a  
9 deficiency in intrinsic factor required for the absorption of cobalamin from the gut [11-12]. While  
10 the absorbability of oral B<sub>12</sub> has been questioned, a number of studies have reported successful  
11 results with oral therapy including treatment in patients with pernicious anemia or bowel  
12 resection [4, 5, 13]. Since 1% of orally-ingested B<sub>12</sub> is absorbed via passive diffusion  
13 independent of the presence of intrinsic factor [7], daily oral doses of 1000 mcg or more are  
14 considered sufficient to meet daily requirements [14] even in patients with insufficient intrinsic  
15 factor.  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28

29 While oral tablets often cost more to acquire than B<sub>12</sub> injection solution, the costs associated  
30 with administering the injections in the form of health professionals' time and resources can be  
31 significant. A 2001 cost study estimated that between \$2.9-17.6 million could be saved over 5  
32 years in the province of Ontario if elderly patients on IM B<sub>12</sub> were switched to oral therapy [15].  
33 In addition, a British study estimated that 2000 nursing hours are required to provide one year of  
34 injections to 492 patients in their homes [16]. Across Canada, only Nova Scotia, Northwest  
35 Territories, Yukon, and the Non-Insured Health Benefits program for First Nations and Inuit  
36 consider oral B<sub>12</sub> tablets to be a benefit in their provincial drug formularies, while all provinces  
37 and territories cover the injectable product.  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50

51 The objective of this study is to estimate the cost savings of treatment using daily oral vitamin  
52 B<sub>12</sub> supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular  
53 injections in Alberta seniors over the age of 65 who are currently using B<sub>12</sub> injection. Such a  
54 study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to  
55  
56  
57  
58  
59  
60

1  
2  
3 renew discussion about the best allocation of limited healthcare resources and whether oral B<sub>12</sub>  
4 should be covered by all Canadian provincial formularies.  
5  
6  
7  
8

## 9 10 **METHODS:**

11  
12  
13  
14 **Study Type:** A cost-minimization analysis (CMA) was performed wherein alternatives compared  
15 are considered to be equivalent in terms of factors that are relevant to the decision such as  
16 efficacy and tolerability, so the lowest cost alternative is selected [17]. While a major  
17 assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75  
18 patients on IM therapy) [2-4] and two prospective case series of 87 patients switching from IM to  
19 oral therapy [5, 7] have concluded that the oral route is as clinically effective as the  
20 intramuscular route. Across both case series, no patients switched from IM to oral therapy  
21 required a switch back to IM replacement as a result of therapeutic failure. Costs were modeled  
22 over a period of five years, and the perspective of the Alberta Ministry of Health was adopted for  
23 this study.  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

38 **Setting / Patients:** The study population consists of individuals aged 65 or older with an Alberta  
39 Health Care number receiving IM B<sub>12</sub> therapy. The number of Alberta seniors dispensed  
40 injectable B<sub>12</sub> over a 1-year period (January-December 2012) was determined from prescription  
41 dispensing records collected by IMS Brogan [18].  
42  
43  
44  
45  
46  
47  
48

49 **Primary Outcome:** Cost-savings achievable by the province of Alberta if patients aged ≥65 and  
50 currently receiving IM B<sub>12</sub> therapy are switched to oral therapy. Cost savings are estimated in  
51 Canadian currency.  
52  
53  
54  
55  
56

57 **Cost Determination:**  
58  
59  
60

1  
2  
3 Cost of B<sub>12</sub> Tablets: The suggested retail price of Swiss Naturals<sup>®</sup>, Jamieson<sup>®</sup>, and Nature's  
4 Bounty<sup>®</sup> brands of 1000 mcg B<sub>12</sub> tablets were obtained from the manufacturers and averaged to  
5 obtain the cost per tablet. In Alberta, the maximum professional fee allowed for dispensing  
6 products with an acquisition cost of ≤\$74.99 is \$11.93 (consists of \$10.22 professional fee and  
7 \$1.71 inventory allowance) [19].  
8  
9

10  
11  
12 Quantity of B<sub>12</sub> Tablets and Professional Fees: It was assumed that patients would receive a  
13 three-month supply with each fill, therefore amassing four professional fees annually and 365  
14 tablets. Albertans age 65 and older are automatically enrolled into a 'Coverage for Seniors'  
15 program, where the patient co-pay is 30% of the cost to a maximum of \$25 [20]. Since this study  
16 assumes the perspective of the provincial Ministry of Health, the payer is assumed to cover 70%  
17 of the total drug cost. Despite being a non-prescription product, sales tax was not applied since  
18 such tablets would be dispensed through the pharmacy as a tax-free product similar to a  
19 prescription drug.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32

33  
34  
35 Cost of B<sub>12</sub> Injection: Parenteral B<sub>12</sub> in Alberta is available in 10 mL multi-dose vials at a  
36 concentration of 1000 mcg/mL. The cost per mL for the two products currently available in  
37 Alberta (DIN 00521515 and DIN 01987003) were determined from the Alberta Health Drug  
38 Benefit List [21]. In Alberta, the total charge allowable for injectable drugs other than insulin is  
39 5/3 of the product's acquisition cost [19]. Therefore, with an acquisition cost of \$4.50 per vial of  
40 parenteral B<sub>12</sub>, the total charge allowed – including the drug and professional fee – cannot  
41 exceed \$7.50, or \$0.75 per dose.  
42  
43  
44  
45  
46  
47  
48  
49  
50

51  
52 Quantity of B<sub>12</sub> injection: At the usual dosage of 1000 mcg/month, one vial contains a ten-month  
53 supply of drug. Therefore, 1.2 vials would be required for a one-year supply.  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Cost of Additional Laboratory Monitoring: Costs for the laboratory analyses were obtained from  
4 Alberta Health Services, laboratory technicians' time to draw and analyze the blood samples  
5 were estimated by consulting with practicing laboratory technicians, and laboratory technician  
6 wages were obtained from a Government of Alberta occupational survey [22] with a 20% fringe  
7 benefit applied.  
8  
9

10  
11  
12  
13  
14  
15  
16 Quantity of Additional Laboratory Monitoring: To ensure adequate response to therapy, we  
17 assumed that patients to be switched from IM to oral B<sub>12</sub> would receive a baseline complete  
18 blood count and serum B<sub>12</sub> prior to the switch, repeated once after the switch to confirm  
19 effectiveness. It was assumed that this additional monitoring would occur only upon switch from  
20 IM to oral therapy, with long-term monitoring occurring at the same rate as if the patient had  
21 remained on IM injections, therefore representing no additional cost of oral therapy over IM  
22 therapy following the initial switch.  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32

33  
34 Cost of Injection Administration: Currently, physicians, nurses, and pharmacists are authorized  
35 to administer B<sub>12</sub> by intramuscular injection in Alberta. Fees for physician office administration of  
36 injections and pharmacist administration of injections are provided in Table 1.  
37  
38  
39  
40  
41

42 Quantity of Injection Administrations: It is unknown the proportion of patients on IM B<sub>12</sub> therapy  
43 receiving their monthly injections from their physician's office or their pharmacy. For the purpose  
44 of the study, based on the experience of the authors including a practicing pharmacist and  
45 family physician, it was assumed that 25% of all B<sub>12</sub> injections are administered in a community  
46 pharmacy with the remainder administered in a medical clinic.  
47  
48  
49  
50  
51  
52  
53  
54

55 Cost of Additional Physician Visits: The current cost for a standard family physician consultation  
56 visit in Alberta of \$35.91 was utilized in the model.  
57  
58  
59  
60



1  
2  
3  
4  
5 Quantity of Additional Physician Visits: Based on available administrative data, we were unable  
6  
7 to determine the number of additional physician visits received by and billed for patients on IM  
8  
9 versus oral B<sub>12</sub> supplementation apart from simply the administration of the injection in the  
10  
11 medical clinic. For the base case scenario, we assumed that 10% of injections administered in a  
12  
13 physician's office also included a billed physician consultation which would not have occurred if  
14  
15 the patient were not on IM B<sub>12</sub>, and have explored other scenarios in sensitivity analyses as  
16  
17 described below.  
18  
19

### 20 21 22 **Model Assumptions:**

23  
24  
25 A number of assumptions were made with the model in addition to those previously described. It  
26  
27 was assumed that patients on oral B<sub>12</sub> therapy were able to self-administer the medication, and  
28  
29 if assistance was required, it was assumed that they already required this assistance for other  
30  
31 medications rather than solely for B<sub>12</sub> tablets. Since B<sub>12</sub> tablets can be taken concurrently with  
32  
33 other medications, it was not assumed that additional assistance would be needed if oral B<sub>12</sub>  
34  
35 were added to their medication regimen. The cost of supplies to administer the intramuscular  
36  
37 injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded  
38  
39 from the model as these are relatively inexpensive and were not felt to significantly contribute to  
40  
41 the overall cost of the injectable product.  
42  
43  
44  
45

### 46 47 **Discounting:**

48  
49  
50 Consistent with CADTH guidelines for the economic evaluation of health technologies [23], a  
51  
52 discount rate of 5% for outcomes occurring after one year was applied to the reference case,  
53  
54 with sensitivity analyses performed around this value as described below.  
55  
56  
57  
58  
59  
60

## Sensitivity Analyses:

Multi-way sensitivity analysis was performed in the form of 10,000 Monte Carlo simulation iterations, adjusting for a number of variables. Model inputs and the probabilistic distributions used in the sensitivity analyses are presented in Table 1. The base case scenario was calculated using the expected value for each variable and assumed a 10% rate of additional physician consultations for patients on intramuscular versus oral therapy.

**Table 1. Expected Values and Distribution Parameters for the Deterministic Model and Probabilistic Sensitivity Analyses**

Parameter	Expected Value $\pm$ SE	Distribution
Study population	28,252 $\pm$ 10%	Gamma
Cost per B <sub>12</sub> tablet	\$0.16 $\pm$ 0.008	Gamma
Professional Fee for Dispensing Tablets [19]	\$11.93	--
Cost per B <sub>12</sub> injectable dose [19-21]	\$0.75	--
Cost for CBC and serum B <sub>12</sub> analyses*	\$6.50	--
Laboratory technician time for blood sample draw and analyses (hours)*	0.75 (range 0.25-1)	Triangular
Laboratory technician wage and benefits [22]*	\$44.60 (range \$35.82-\$51.41)	Triangular
Fee for administration of intramuscular injection in a physician's office [24]	\$10.30	--
Cost for physician consultation visit [24]	\$35.91	--
Fee for administration of intramuscular injection in a pharmacy [25]	\$20.00	--

- SE=Standard Error; CBC=Complete blood count
- \* indicates parameter only included in year 1 of the model
- Normal distribution samples values probabilistically from a normal curve with specified mean (expected value) and standard error. Triangular distribution samples values probabilistically within the range specified, with increasing probability as values near the expected value.

Sensitivity analysis was also performed for different proportions of additional physician office visits including a billed consultation. While the base scenario assumed a 10% rate of office

consultations during injection visits, the analyses were repeated for rates of 0% and 25%.

Discounting rates of 0% and 3% were also tested in sensitivity analysis.

## RESULTS:

Estimated five-year cost savings associated with switching all Alberta seniors currently receiving injectable B<sub>12</sub> to oral therapy is \$13,975,883. Base scenario and sensitivity analysis results are presented in Table 2. Our model found that even if no additional physician visits were billed for among patients receiving IM therapy, over \$8 million could be saved from reduced administration costs alone.

**Table 2. Model Results Over 5 Years**

Proportion In-Office Injections Including a Fee for a Physician Visit	Discounting Rate for Years 2-5	Mean Cost Saving For Payer	Mean Cost Saving per Patient
<b>Reference Case</b>			
10%	5%	\$13,975,883	\$494.69
<b>Sensitivity Analyses</b>			
0%	0%	\$9,564,224	\$338.53
0%	3%	\$8,878,728	\$314.27
0%	5%	\$8,444,346	\$298.89
10%	0%	\$15,677,500	\$554.92
10%	3%	\$14,635,912	\$518.05
25%	0%	\$24,784,224	\$877.26
25%	3%	\$23,212,469	\$821.62
25%	5%	\$22,216,488	\$786.37

Due to the additional laboratory monitoring performed in the year of the change from IM to oral therapy, the model found the switch to be moderately cost-effective in the first year, with larger

1  
2  
3 savings realized in years 2-5. For the base scenario, cost savings in year 1 were estimated at  
4  
5 \$48.34 (SD \$8.58) per patient, increasing to \$126.55 (SD \$2.04) in year 2. Over 5 years,  
6  
7 average cost-savings per patient was estimated at \$494.69.  
8  
9

## 11 **DISCUSSION:**

12  
13  
14  
15  
16 Over five years, the province of Alberta can be expected to free nearly \$14 million in healthcare  
17  
18 costs if all seniors over the age of 65 currently receiving IM B<sub>12</sub> are switched to oral tablets.  
19  
20 Despite evidence confirming that sufficient B<sub>12</sub> is absorbed by passive diffusion at a dose of  
21  
22 1000 mcg daily to be effective even in patients lacking intrinsic factor or with gastrointestinal  
23  
24 disease [12], the intramuscular route continues to be commonly prescribed. With high health  
25  
26 professional workloads and increasingly restricted healthcare budgets, a switch from IM to oral  
27  
28 therapy will not only free health professional resources to see patients at greater need, but can  
29  
30 also result in cost-savings for reinvestment into other needed services.  
31  
32  
33

34  
35  
36 The option of oral supplementation is well received by patients. A Canadian study by Kwong *et*  
37  
38 *al.* found that 73% of patients receiving B<sub>12</sub> injections were willing to try oral B<sub>12</sub>, and of those  
39  
40 who tried the oral therapy, 71% wished to permanently remain on oral therapy [7]. Travel  
41  
42 inconveniences were the most common reason for preferring the oral route. The authors  
43  
44 concluded that oral therapy would decrease physician burden, increase patient control over  
45  
46 therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding  
47  
48 injections is unknown in adult patients, previous research has suggested that patients with  
49  
50 diabetes value a reduced injection burden as much as they value disease control [26].  
51  
52

53 Therefore, if a societal perspective including utility were considered, it is likely that the benefit of  
54  
55 switching patients from IM to oral therapy would be even greater.  
56  
57  
58  
59  
60

1  
2  
3 A number of assumptions employed in the model have the potential to alter the results in either  
4 direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy  
5 rather than monthly refills, which would be expected to underestimate the cost-saving potential  
6 of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have  
7 also occurred as a result of calculating tablet cost based on non-generic products at higher  
8 costs per tablet. Home care costs for the administration of B<sub>12</sub> injections in home-bound patients  
9 was not included since the proportion of patients receiving in-home injections was unknown,  
10 and it was assumed that these injections would be administered in conjunction with a regular  
11 visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits  
12 are indeed being performed for B<sub>12</sub> injections, then the savings of switching to oral B<sub>12</sub> would  
13 obviously be greater. Importantly, the model also assumed that all patients making the switch to  
14 oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore  
15 representing maximum saving potential. This assumption is consistent with previously published  
16 randomized controlled trials and case series reporting treatment success across all patients  
17 studied [2-7].  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

38 Direct comparison between our model and the results of the 2001 cost-saving paper cannot be  
39 performed due to differing model assumptions and available data. Overall, both models report  
40 significant cost-saving potential of the switch from the perspective of a government payer over  
41 five years. However, due to higher current professional fees for injection administration, our  
42 model found overall cost-savings even if no additional physician visits occurred for patients  
43 receiving B<sub>12</sub> injections, whereas the previous study found a break-even point when 16.3% of  
44 additional physician visits were avoided.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 The use of cost-minimization analysis is controversial as it assumes equal efficacy and  
56 tolerability between the two options being compared; however, we feel this assumption is  
57  
58  
59  
60

1  
2  
3 justifiable based on published data comparing the oral and intramuscular routes [2-7]. However,  
4  
5 the total number of patients studied in the randomized trials (total n=141 across 3 studies) and  
6  
7 case series (n=87) remains relatively small and doses employed across each study differed.  
8  
9  
10 Further research on a larger population, comparing standard-dose IM therapy to standard-dose  
11  
12 oral therapy is therefore recommended and is currently being planned. Additionally, payers  
13  
14 considering adding oral B<sub>12</sub> tablets to their formularies should consider allowing for the coverage  
15  
16 of intramuscular therapy in the event of documented treatment failure on oral supplementation,  
17  
18 until larger-scale studies confirming equivalence are conducted. Indeed, a planned randomized  
19  
20 controlled trial of 320 patients age ≥65 in Spain will be directly comparing oral to IM B<sub>12</sub> and is  
21  
22 expected to examine non-inferiority of oral therapy over one year (clinicaltrials.gov  
23  
24 NCT01476007).  
25  
26  
27  
28

29  
30 Overall, our model estimates that \$8-24 million in cost-savings can be realized over five years if  
31  
32 all Alberta seniors currently receiving IM vitamin B<sub>12</sub> are switched to oral therapy. Within closed  
33  
34 systems like universal healthcare, this is unlikely to represent true cost savings, but rather room  
35  
36 for re-allocation of resources to other health system needs. With an aging population and  
37  
38 increasing rates of chronic disease, switching of patients from IM to oral vitamin B<sub>12</sub>  
39  
40 replacement appears to be not only clinically efficacious, but also an effective use of limited  
41  
42 healthcare resources.  
43  
44  
45  
46

47 **Competing Interests:** The authors declare no conflicts of interest related to the above work.  
48  
49  
50

51 **Funding Statement:** No funding was received for completion of this study. Ms. Houle is funded  
52  
53 for her graduate studies by the Canadian Institutes of Health Research, Hypertension Canada,  
54  
55 and the Interdisciplinary Chronic Disease Collaboration (funded by Alberta Innovates – Health  
56  
57 Solutions).  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

1. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret. *JAMA* 1991;**265**:94-5.
2. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998;**92**(4):1191-1198.
3. Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective, randomized, open-label study. *Clin Ther* 2003;**25**(12):3124-3134.
4. Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, et al. Comparing the Efficacy and Tolerability of a New Daily Oral Vitamin B12 Formulation and Intermittent Intramuscular Vitamin B12 in Normalizing Low Cobalamin Levels: A Randomized, Open-Label, Parallel-Group Study. *Clin Ther* 2011;**33**(3):358-71.
5. Nyholm E, Turpin P, Swain D, Cunningham B, Daly S, Nightingale P, et al. Oral vitamin B12 can change our practice. *Postgrad Med J* 2003;**79**:218-220.
6. Vidal-Alaball J, Butler C, Cannings-John R, Goringe A, Hood K, McCaddon A, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.:CD004655. DOI:10..1002/14651858.CD004655.pub2.
7. Kwong JC, Carr D, Dhalla IA, Tom-Kun D, Upshur REG. Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. *BMC Fam Pract* 2005;**6**:8.
8. Graham ID, Jette N, Tetroe J, Robinson N, Milne S, Mitchell SL. Oral cobalamin remains medicine's best kept secret. *Archives of Gerontology and Geriatrics* 2007;**44**(1):49–59.



- 1  
2  
3 9. MacFarlane AJ, Greene-Finestone LS, Shi Y. Vitamin B-12 and homocysteine status in a  
4 folate-replete population: results from the Canadian Health Measures Survey. *Am J Clin*  
5  
6  
7  
8  
9  
10 Nutr 2011;**94**:1079-87.
- 11 10. Lindenbaum J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH. Prevalence of cobalamin  
12 deficiency in the Framingham elderly population. *Am J Clin Nutr* 1994;**60**:2-11.
- 13 11. de Jager J, Kooy A, Lehert P, Wulffele MG, van der Kolk J, Bets D, et al. Long term  
14 treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency:  
15 randomized placebo controlled trial. *Br Med J* 2010;**340**:c2181.
- 16 12. Andrès E, Vidal-Alaball J, Federici L, Henoun Loukili N, Zimmer J, Kaltenbach G. Clinical  
17 aspects of cobalamin deficiency in elderly patients. Epidemiology, causes, clinical  
18 manifestations, and treatment with special focus on oral cobalamin therapy. *Eur J Int Med*  
19 2007;**18**:456-62.
- 21 13. Andrès E, Federici L, Affenberger S, Vidal-Alaball J, Henoun Loukili N, et al. B12 deficiency:  
22 A look beyond pernicious anemia. *J Fam Pract* 2007;**56**(7):537-42.
- 23 14. Health Canada. Dietary Reference Intakes: Reference Values for Vitamins. Accessed 17  
24 May 2012 at <[http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref\\_vitam\\_tbl-eng.php](http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref_vitam_tbl-eng.php)>.
- 25 15. van Walraven CG, Austin P, Naylor CD. Vitamin B12 injections versus oral supplements:  
26 How much money could be saved by switching from injections to pills? *Can Med Assoc J*  
27 2001;**47**:79-86.
- 28 16. Middleton J, Wells W. Vitamin B12 injections: considerable source of work for the district  
29 nurse. *BMJ* 1985;**270**:1254-1255.
- 30 17. Drummond MF, Sculpher MJ, Torrance G, O'Brien B, Stoddart G. *Methods for the Economic*  
31 *Evaluation of Health Care Programmes*. 3<sup>rd</sup> ed. New York: Oxford University Press; 2005.
- 32 18. IMS Brogan LRx database, January 2013 and Compuscript audit, January 2013.
- 33 19. Alberta Health. Pharmacy fee reimbursement. Retrieved from:  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60 <http://www.health.alberta.ca/services/pharmacy-fee-reimbursement.html>

- 1  
2  
3 20. Alberta Health. Coverage for Seniors. Retrieved from:  
4  
5 <http://www.health.alberta.ca/services/drugs-seniors.html>  
6  
7  
8 21. Alberta Health. Interactive Drug Benefit List. Retrieved from:  
9  
10 <https://idbl.ab.bluecross.ca/idbl/load.do>  
11  
12 22. Government of Alberta. 2011 Alberta Wage and Salary Data – Medical Laboratory  
13  
14 Technologist. Retrieved from:  
15  
16 [http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro\\_id=71003140](http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140)  
17  
18  
19  
20 23. *Guidelines for the economic evaluation of health technologies: Canada* [3rd Edition].  
21  
22 Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.  
23  
24 24. Alberta Health Care Insurance Plan. Medical Price List as of 01 April 2012. Retrieved from:  
25  
26 <http://www.health.alberta.ca/documents/SOMB-Medical-Prices-2012-04.pdf>  
27  
28  
29 25. Alberta Health. Compensation for Pharmacy Services, July 2012. Retrieved from:  
30  
31 <http://www.health.alberta.ca/documents/Pharmacy-Services-Compensation-2012.pdf>  
32  
33  
34 26. Hauber AB, Johnson FR, Sauriol L, Lescrauwaet B. Risking health to avoid injections:  
35  
36 Preferences of Canadians with type 2 diabetes. *Diabetes Care* 2005;28(9):2243-5.  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## EVEREST Statement

	Study section	Additional remarks
<b>Study design</b>		
(1) The research question is stated	Background	
(2) The economic importance of the research question is stated	Background	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods (Study Type); Discussion	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Background; Methods	
(5) The alternatives being compared are clearly described	Methods (Cost Determination)	
(6) The form of economic evaluation used is stated	Methods (Study Type)	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Methods; Discussion	
<b>Data collection</b>		
(8) The source(s) of effectiveness estimates used are stated	Methods (Study Type)	
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A (based on multiple studies)	3 randomized controlled trials and 2 prospective case series
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods (Primary Outcome)	
(12) Methods to value health states and other benefits are stated	N/A	
(13) Details of the subjects from whom valuations were obtained are given	Methods (Setting/Patients)	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods (Cost Determination)	
(17) Methods for the estimation of quantities and unit costs are described	Methods (Cost Determination)	
(18) Currency and price data are recorded	Methods (Primary Outcome)	
(19) Details of currency of price adjustments for inflation or currency conversion are given	N/A	

(20) Details of any model used are given	Methods (Model Assumptions, Discounting, Sensitivity Analyses)	
(21) The choice of model used and the key parameters on which it is based are justified	Methods (Study Type); Discussion	
<b>Analysis and interpretation of results</b>		
(22) Time horizon of costs and benefits is stated	Methods (Study Type)	
(23) The discount rate(s) is stated	Methods (Discounting)	
(24) The choice of rate(s) is justified	Methods (Discounting)	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods (Sensitivity Analyses)	
(28) The choice of variables for sensitivity analysis is justified	Methods (Sensitivity Analyses)	
(29) The ranges over which the variables are varied are stated	Table 1	
(30) Relevant alternatives are compared	Introduction	
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	N/A	
(33) The answer to the study question is given	Results; Discussion	
(34) Conclusions follow from the data reported	Discussion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	



**Should Vitamin B12 Tablets be Included in More Canadian Drug Formularies? An Economic Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular Vitamin B12 Maintenance Therapy for Alberta Seniors**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004501.R1
Article Type:	Research
Date Submitted by the Author:	24-Jan-2014
Complete List of Authors:	Houle, Sherilyn; University of Alberta, Medicine Kolber, Michael; University of Alberta, Family Medicine Chuck, Anderson; Institute of Health Economics,
<b>Primary Subject Heading</b>:	General practice / Family practice
Secondary Subject Heading:	General practice / Family practice, Health economics, Evidence based practice
Keywords:	HEALTH ECONOMICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

SCHOLARONE™  
Manuscripts

1  
2  
3 Should Vitamin B<sub>12</sub> Tablets be Included in More Canadian Drug Formularies? An Economic  
4  
5 Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular  
6  
7 Vitamin B<sub>12</sub> Maintenance Therapy for Alberta Seniors  
8  
9

10  
11  
12 **Authors:**

13  
14 Sherilyn KD Houle (corresponding author)

15  
16 EPICORE Centre

17  
18 3<sup>rd</sup> Floor, Brain and Aging Research Building

19  
20 University of Alberta

21  
22 Edmonton AB, Canada

23  
24 T6G 2M8  
25  
26  
27  
28

29 Michael R Kolber

30  
31 Department of Family Medicine

32  
33 University of Alberta

34  
35 Edmonton AB, Canada  
36  
37  
38  
39

40 Anderson W Chuck

41  
42 Institute of Health Economics

43  
44 Edmonton AB, Canada  
45  
46  
47  
48

49 **Keywords:** Cost analysis, healthcare costs, vitamin B<sub>12</sub> deficiency  
50  
51

52  
53 **Word Count:** 2881  
54  
55  
56  
57  
58  
59  
60

**ABSTRACT:**

**Objectives:** The aim of this study is to estimate the cost-savings attainable if all patients aged  $\geq 65$  in Alberta, Canada, currently on intramuscular therapy were switched to oral therapy, from the perspective of a provincial ministry of health.

**Setting:** Primary care setting in Alberta, Canada.

**Participants:** Seniors age 65 and older currently receiving intramuscular vitamin B<sub>12</sub> therapy.

**Intervention:** Oral vitamin B<sub>12</sub> therapy at 1000 mcg per day versus intramuscular therapy at 1000 mcg per month.

**Primary and Secondary Outcome Measures:** Cost-saving from oral therapy over intramuscular therapy, from the perspective of the Alberta Ministry of Health, including drug costs, dispensing fees, injection administration fees, additional laboratory monitoring, and physician visit fees.

**Results:** Over 5 years, if all Albertans age 65 and older who currently receive intramuscular B<sub>12</sub> are switched to oral therapy, our model found that CAD \$13,975,883 can be saved. Even if no additional physician visits are billed for among patients receiving IM therapy, \$8,444,346 could be saved from reduced administration costs alone.

**Conclusions:** Oral B<sub>12</sub> therapy has been shown to be an effective therapeutic option for patients with vitamin B<sub>12</sub> deficiency, yet only three provinces and the Non-Insured Health Benefits program include oral tablets on their formulary rather than the parenteral preparation.

To ensure judicious use of limited health resources, clinicians and formulary committees are encouraged to adopt oral B<sub>12</sub> therapy as a clinically- and cost-effective first line therapy for vitamin B<sub>12</sub> deficiency.

#### **STRENGTHS AND LIMITATIONS OF THIS STUDY:**

- Minimal assumptions built into the model, as exact costs and the exact number of eligible residents comprising the population were available
- Three randomized controlled trials and two prospective case series support our use of a cost-minimization analysis approach
- Comprehensive sensitivity analyses employed using Monte Carlo simulation to incorporate multiple variables
- Study is from the perspective of the provincial ministry of health (the payer) and does not adopt a societal perspective since much of the additional information required for that is not available
- Despite being set in one Canadian province, the use of intramuscular B<sub>12</sub> therapy is prevalent worldwide. Therefore, these results, while not directly generalizable to other jurisdictions, point to an economic argument for greater uptake of oral B<sub>12</sub> therapy which is likely consistent across other jurisdictions



**BACKGROUND:**

For over twenty years, oral vitamin B<sub>12</sub> has been referred to as “medicine’s best kept secret” [1]. Despite evidence of the effectiveness of oral B<sub>12</sub> therapy [2-8], intramuscular (IM) administration remains the most commonly prescribed route in North America [9].

Approximately 5% of Canadians are B<sub>12</sub> deficient [10], with Framingham data suggesting that B<sub>12</sub> deficiency in community-dwelling adults age 67 and older may be as high as 12% [11]. Deficiency can occur as a result of gastric atrophy or previous gastric or intestinal surgery, use of antacids and other medications (metformin), inadequate animal product intake, and a deficiency in intrinsic factor required for the absorption of cobalamin from the gut [12-13]. While the absorbability of oral B<sub>12</sub> has been questioned, a number of studies have reported successful results with oral therapy including treatment in patients with pernicious anemia or bowel resection [4, 5, 8, 14]. Since 1% of orally-ingested B<sub>12</sub> is absorbed via passive diffusion independent of the presence of intrinsic factor [7], daily oral doses of 1000 mcg or more are considered sufficient to meet daily requirements [15] even in patients with insufficient intrinsic factor.

While oral tablets often cost more to acquire than B<sub>12</sub> injection solution, the costs associated with administering the injections in the form of health professionals’ time and resources can be significant. A 2001 cost study estimated that between \$2.9-17.6 million could be saved over 5 years in the province of Ontario if elderly patients on IM B<sub>12</sub> were switched to oral therapy [16]. In addition, a British study estimated that 2000 nursing hours are required to provide one year of injections to 492 patients in their homes [17]. Across Canada, only Nova Scotia, Northwest Territories, Yukon, and the Non-Insured Health Benefits program for First Nations and Inuit

1  
2  
3 consider oral B<sub>12</sub> tablets to be a benefit in their provincial drug formularies, while all provinces  
4  
5 and territories cover the injectable product.  
6  
7  
8

9  
10 The objective of this study is to estimate the cost savings of treatment using daily oral vitamin  
11  
12 B<sub>12</sub> supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular  
13  
14 injections in Alberta seniors over the age of 65 who are currently using B<sub>12</sub> injection. Such a  
15  
16 study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to  
17  
18 renew discussion about the best allocation of limited healthcare resources and whether oral B<sub>12</sub>  
19  
20 should be covered by all Canadian provincial formularies.  
21  
22  
23

## 24 25 **METHODS:** 26 27 28

29 **Study Type:** A cost-minimization analysis (CMA) was performed wherein alternatives compared  
30  
31 are considered to be equivalent in terms of factors that are relevant to the decision such as  
32  
33 efficacy and tolerability, so the lowest cost alternative is selected [18]. While a major  
34  
35 assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75  
36  
37 patients on IM therapy) [2-4] and three prospective case series of 151 patients switching from  
38  
39 IM to oral therapy [5, 7, 8] have concluded that the oral route is as clinically effective as the  
40  
41 intramuscular route. Across all case series, no patients switched from IM to oral therapy  
42  
43 required a switch back to IM replacement as a result of therapeutic failure. Costs were modeled  
44  
45 over a period of five years, and the perspective of the Alberta Ministry of Health was adopted for  
46  
47 this study.  
48  
49  
50

51  
52  
53 **Setting / Patients:** The study population consists of individuals aged 65 or older with an Alberta  
54  
55 Health Care number receiving IM B<sub>12</sub> therapy. The number of Alberta seniors dispensed  
56  
57  
58  
59  
60

1  
2  
3 injectable B<sub>12</sub> over a 1-year period (January-December 2012) was determined from prescription  
4  
5  
6 dispensing records collected by IMS Brogan [19].  
7  
8  
9

10 **Primary Outcome:** Cost-savings achievable by the province of Alberta if patients aged ≥65 and  
11  
12 currently receiving IM B<sub>12</sub> therapy are switched to oral therapy. Cost savings are estimated in  
13  
14 Canadian currency.  
15

16  
17  
18 **Cost Determination:**  
19

20 All costs are reported in Canadian dollars.  
21  
22

23  
24  
25 Cost of B<sub>12</sub> Tablets: The suggested retail price of Swiss Naturals<sup>®</sup>, Jamieson<sup>®</sup>, and Nature's  
26  
27 Bounty<sup>®</sup> brands of 1000 mcg B<sub>12</sub> tablets were obtained from the manufacturers and averaged to  
28  
29 obtain the cost per tablet. In Alberta, the maximum professional fee allowed for dispensing  
30  
31 products with an acquisition cost of ≤\$74.99 is \$11.93 (consists of \$10.22 professional fee and  
32  
33 \$1.71 inventory allowance) [20].  
34  
35

36  
37  
38 Quantity of B<sub>12</sub> Tablets and Professional Fees: It was assumed that patients would receive a  
39  
40 three-month supply with each fill, therefore amassing four professional fees annually and 365  
41  
42 tablets. Albertans age 65 and older are automatically enrolled into a 'Coverage for Seniors'  
43  
44 program, where the patient co-pay is 30% of the cost to a maximum of \$25 [21]. Since this study  
45  
46 assumes the perspective of the provincial Ministry of Health, the payer is assumed to cover 70%  
47  
48 of the total drug cost. Despite being a non-prescription product, sales tax was not applied since  
49  
50 such tablets would be dispensed through the pharmacy as a tax-free product similar to a  
51  
52 prescription drug.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Cost of B<sub>12</sub> Injection: Parenteral B<sub>12</sub> in Alberta is available in 10 mL multi-dose vials at a  
4 concentration of 1000 mcg/mL. The cost per mL for the two products currently available in  
5 Alberta (DIN 00521515 and DIN 01987003) were determined from the Alberta Health Drug  
6 Benefit List [22]. In Alberta, the total charge allowable for injectable drugs other than insulin is  
7 5/3 of the product's acquisition cost [20]. Therefore, with an acquisition cost of \$4.50 per vial of  
8 parenteral B<sub>12</sub>, the total charge allowed – including the drug and professional fee – cannot  
9 exceed \$7.50, or \$0.75 per dose.  
10  
11

12 Quantity of B<sub>12</sub> injection: At the usual dosage of 1000 mcg/month, one vial contains a ten-month  
13 supply of drug. Therefore, 1.2 vials would be required for a one-year supply.  
14  
15  
16  
17  
18  
19

20 Cost of Additional Laboratory Monitoring: Costs for the laboratory analyses were obtained from  
21 Alberta Health Services, laboratory technicians' time to draw and analyze the blood samples  
22 were estimated by consulting with practicing laboratory technicians, and laboratory technician  
23 wages were obtained from a Government of Alberta occupational survey [23] with a 20% fringe  
24 benefit applied.  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

38 Quantity of Additional Laboratory Monitoring: To ensure adequate response to therapy, we  
39 assumed that patients to be switched from IM to oral B<sub>12</sub> would receive a baseline complete  
40 blood count and serum B<sub>12</sub> prior to the switch, repeated once after the switch to confirm  
41 effectiveness. It was assumed that this additional monitoring would occur only upon switch from  
42 IM to oral therapy, with long-term monitoring occurring at the same rate as if the patient had  
43 remained on IM injections, therefore representing no additional cost of oral therapy over IM  
44 therapy following the initial switch.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Cost of Injection Administration: Currently, physicians, nurses, and pharmacists are authorized  
4 to administer B<sub>12</sub> by intramuscular injection in Alberta. Fees for physician office administration of  
5 injections and pharmacist administration of injections are provided in Table 1.  
6  
7  
8  
9

10  
11 Quantity of Injection Administrations: It is unknown the proportion of patients on IM B<sub>12</sub> therapy  
12 receiving their monthly injections from their physician's office or their pharmacy. For the purpose  
13 of the study, based on the experience of the authors including a practicing pharmacist and  
14 family physician, it was assumed that 25% of all B<sub>12</sub> injections are administered in a community  
15 pharmacy with the remainder administered in a medical clinic.  
16  
17  
18  
19  
20  
21  
22  
23

24  
25 Cost of Additional Physician Visits: The current cost for a standard family physician consultation  
26 visit in Alberta of \$35.91 was utilized in the model.  
27  
28  
29  
30

31 Quantity of Additional Physician Visits: Based on available administrative data, we were unable  
32 to determine the number of additional physician visits received by and billed for patients on IM  
33 versus oral B<sub>12</sub> supplementation apart from simply the administration of the injection in the  
34 medical clinic. For the base case scenario, we assumed that 10% of injections administered in a  
35 physician's office also included a billed physician consultation which would not have occurred if  
36 the patient were not on IM B<sub>12</sub>, and have explored other scenarios in sensitivity analyses as  
37 described below.  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48

#### 49 **Model Assumptions:**

50  
51 A number of assumptions were made with the model in addition to those previously described. It  
52 was assumed that patients on oral B<sub>12</sub> therapy were able to self-administer the medication, and  
53 if assistance was required, it was assumed that they already required this assistance for other  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 medications rather than solely for B<sub>12</sub> tablets. Since B<sub>12</sub> tablets can be taken concurrently with  
4  
5 other medications, it was not assumed that additional assistance would be needed if oral B<sub>12</sub>  
6  
7 were added to their medication regimen. The cost of supplies to administer the intramuscular  
8  
9 injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded  
10  
11 from the model as these are relatively inexpensive and were not felt to significantly contribute to  
12  
13 the overall cost of the injectable product.  
14  
15

### 16 17 18 **Discounting:** 19

20  
21  
22 Consistent with CADTH guidelines for the economic evaluation of health technologies [24], a  
23  
24 discount rate of 5% for outcomes occurring after one year was applied to the reference case,  
25  
26 with sensitivity analyses performed around this value as described below.  
27  
28  
29

### 30 31 **Sensitivity Analyses:** 32

33  
34  
35 Multi-way sensitivity analysis was performed in the form of 10,000 Monte Carlo simulation  
36  
37 iterations, adjusting for a number of variables. Model inputs and the probabilistic distributions  
38  
39 used in the sensitivity analyses are presented in Table 1. The base case scenario was  
40  
41 calculated using the expected value for each variable and assumed a 10% rate of additional  
42  
43 physician consultations for patients on intramuscular versus oral therapy.  
44  
45  
46  
47  
48

49 **Table 1. Expected Values and Distribution Parameters for the Deterministic Model and**  
50 **Probabilistic Sensitivity Analyses**  
51

52 <b>Parameter</b>	53 <b>Expected Value ± SE</b>	54 <b>Distribution</b>
55 Study population	28,252 ± 10%	Gamma
56 Cost per B <sub>12</sub> tablet	\$0.16 ± 0.008	Gamma
57 Professional Fee for Dispensing Tablets [20]	\$11.93	--

Cost per B <sub>12</sub> injectable dose [20-22]	\$0.75	--
Cost for CBC and serum B <sub>12</sub> analyses*	\$6.50	--
Laboratory technician time for blood sample draw and analyses (hours)*	0.75 (range 0.25-1)	Triangular
Laboratory technician wage and benefits [23]*	\$44.60 (range \$35.82-\$51.41)	Triangular
Fee for administration of intramuscular injection in a physician's office [25]	\$10.30	--
Cost for physician consultation visit [25]	\$35.91	--
Fee for administration of intramuscular injection in a pharmacy [26]	\$20.00	--

- SE=Standard Error; CBC=Complete blood count
- \* indicates parameter only included in year 1 of the model
- Normal distribution samples values probabilistically from a normal curve with specified mean (expected value) and standard error. Triangular distribution samples values probabilistically within the range specified, with increasing probability as values near the expected value.

Sensitivity analysis was also performed for different proportions of additional physician office visits including a billed consultation. While the base scenario assumed a 10% rate of office consultations during injection visits, the analyses were repeated for rates of 0% and 25%. Discounting rates of 0% and 3% were also tested in sensitivity analysis.

## RESULTS:

Estimated five-year cost savings associated with switching all Alberta seniors currently receiving injectable B<sub>12</sub> to oral therapy is \$13,975,883. Base scenario and sensitivity analysis results are presented in Table 2. Our model found that even if no additional physician visits were billed for among patients receiving IM therapy, over \$8 million could be saved from reduced administration costs alone.

**Table 2. Model Results Over 5 Years**

Proportion In-Office Injections Including a Fee for	Discounting Rate for Years 2-5	Mean Cost Saving For Payer	Mean Cost Saving per Patient
---	--------------------------------	----------------------------	------------------------------



<b>a Physician Visit</b>			
<b>Reference Case</b>			
10%	5%	\$13,975,883	\$494.69
<b>Sensitivity Analyses</b>			
0%	0%	\$9,564,224	\$338.53
0%	3%	\$8,878,728	\$314.27
0%	5%	\$8,444,346	\$298.89
10%	0%	\$15,677,500	\$554.92
10%	3%	\$14,635,912	\$518.05
25%	0%	\$24,784,224	\$877.26
25%	3%	\$23,212,469	\$821.62
25%	5%	\$22,216,488	\$786.37

Due to the additional laboratory monitoring performed in the year of the change from IM to oral therapy, the model found the switch to be moderately cost-effective in the first year, with larger savings realized in years 2-5. For the base scenario, cost savings in year 1 were estimated at \$48.34 (SD \$8.58) per patient, increasing to \$126.55 (SD \$2.04) in year 2. Over 5 years, average cost-savings per patient was estimated at \$494.69.

## DISCUSSION:

Over five years, the province of Alberta can be expected to free nearly \$14 million in healthcare costs if all seniors over the age of 65 currently receiving IM B<sub>12</sub> are switched to oral tablets.

Despite evidence confirming that sufficient B<sub>12</sub> is absorbed by passive diffusion at a dose of 1000 mcg daily to be effective even in patients lacking intrinsic factor or with gastrointestinal disease [13], the intramuscular route continues to be commonly prescribed. With high health professional workloads and increasingly restricted healthcare budgets, a switch from IM to oral therapy will not only free health professional resources to see patients at greater need, but can also result in cost-savings for reinvestment into other needed services.



1  
2  
3  
4  
5 The option of oral supplementation is well received by patients. A Canadian study by Kwong *et*  
6 *al.* found that 73% of patients receiving B<sub>12</sub> injections were willing to try oral B<sub>12</sub>, and of those  
7 who tried the oral therapy, 71% wished to permanently remain on oral therapy [7]. Travel  
8 inconveniences were the most common reason for preferring the oral route. The authors  
9 concluded that oral therapy would decrease physician burden, increase patient control over  
10 therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding  
11 injections is unknown in adult patients, previous research has suggested that patients with  
12 diabetes value a reduced injection burden as much as they value disease control [27].

13  
14 Therefore, if a societal perspective including utility were considered, it is likely that the benefit of  
15 switching patients from IM to oral therapy would be even greater. Furthermore, the elimination  
16 of risk for injection site reactions following a switch to oral therapy represents another potential  
17 benefit from the patient perspective.  
18  
19  
20  
21  
22

23  
24 A number of assumptions employed in the model have the potential to alter the results in either  
25 direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy  
26 rather than monthly refills, which would be expected to underestimate the cost-saving potential  
27 of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have  
28 also occurred as a result of calculating tablet cost based on non-generic products at higher  
29 costs per tablet. Home care costs for the administration of B<sub>12</sub> injections in home-bound patients  
30 was not included since the proportion of patients receiving in-home injections was unknown,  
31 and it was assumed that these injections would be administered in conjunction with a regular  
32 visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits  
33 are indeed being performed for B<sub>12</sub> injections, then the savings of switching to oral B<sub>12</sub> would  
34 obviously be greater. Importantly, the model also assumed that all patients making the switch to  
35 oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 representing maximum saving potential. This assumption is consistent with previously published  
4  
5 randomized controlled trials and case series reporting treatment success across all patients  
6  
7 studied [2-8]. Additionally, we assumed in the base scenario that additional laboratory  
8  
9 monitoring is only required for the first year following the switch to oral therapy, with monitoring  
10  
11 as usual for the remaining years. Considering that adherence to self-administered oral therapy  
12  
13 may be lower than a healthcare professional-administered injection, even if an additional set of  
14  
15 laboratory tests were performed each year for the 5-year term of the model, estimated cost  
16  
17 savings would still amount to \$12 million.  
18  
19

20  
21  
22 Direct comparison between our model and the results of the 2001 cost-saving paper cannot be  
23  
24 performed due to differing model assumptions and available data. Overall, both models report  
25  
26 significant cost-saving potential of the switch from the perspective of a government payer over  
27  
28 five years. However, due to higher current professional fees for injection administration, our  
29  
30 model found overall cost-savings even if no additional physician visits occurred for patients  
31  
32 receiving B<sub>12</sub> injections, whereas the previous study found a break-even point when 16.3% of  
33  
34 additional physician visits were avoided.  
35  
36

37  
38  
39 The use of cost-minimization analysis is controversial as it assumes equal efficacy and  
40  
41 tolerability between the two options being compared; however, we feel this assumption is  
42  
43 justifiable based on published data comparing the oral and intramuscular routes [2-8]. However,  
44  
45 the total number of patients studied in the randomized trials (total n=141 across 3 studies) and  
46  
47 case series (n=151) remains relatively small and doses employed across each study differed.  
48  
49 Further research on a larger population, comparing standard-dose IM therapy to standard-dose  
50  
51 oral therapy is therefore recommended and is currently being planned. Additionally, payers  
52  
53 considering adding oral B<sub>12</sub> tablets to their formularies should consider allowing for the coverage  
54  
55 of intramuscular therapy in the event of documented treatment failure on oral supplementation,  
56  
57  
58  
59  
60

1  
2  
3 until larger-scale studies confirming equivalence are conducted, or allowing for short-term IM  
4 therapy for patients with neurologic symptoms followed by oral maintenance therapy. Indeed, a  
5  
6 planned randomized controlled trial of 320 patients age  $\geq 65$  in Spain will be directly comparing  
7  
8 oral to IM B<sub>12</sub> and is expected to examine non-inferiority of oral therapy over one year  
9  
10  
11  
12 (clinicaltrials.gov NCT01476007).  
13

14  
15  
16 Overall, our model estimates that \$8-24 million in cost-savings can be realized over five years if  
17  
18 all Alberta seniors currently receiving IM vitamin B<sub>12</sub> are switched to oral therapy. Within closed  
19  
20 systems like universal healthcare, this is unlikely to represent true cost savings, but rather room  
21  
22 for re-allocation of resources to other health system needs. With an aging population and  
23  
24 increasing rates of chronic disease, switching of patients from IM to oral vitamin B<sub>12</sub>  
25  
26 replacement appears to be not only clinically efficacious, but also an effective use of limited  
27  
28 healthcare resources.  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **Funding Statement:** No funding was received for completion of this study. Ms. Houle was  
4 funded for her graduate studies by the Canadian Institutes of Health Research, Hypertension  
5 Canada, and the Interdisciplinary Chronic Disease Collaboration (funded by Alberta Innovates –  
6 Health Solutions).  
7  
8  
9  
10

11  
12  
13  
14 **Contributorship Statement:** All authors (Dr. Houle, Dr. Kolber, and Dr. Chuck) contributed to  
15 the design and analysis/interpretation of data, drafting of the article, and approval of the final  
16 version.  
17  
18  
19

20 **Competing Interests:** The authors declare no conflicts of interest related to the above work.  
21  
22  
23

24 **Data Sharing Statement:** There is no additional unpublished data related to this study.  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

1. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret. *JAMA* 1991;**265**:94-5.
2. Kuzminski AM, Del Giacco EJ, Allen RH, et al. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998;**92**(4):1191-1198.
3. Bolaman Z, Kadikoylu G, Yukselen V, et al. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective, randomized, open-label study. *Clin Ther* 2003;**25**(12):3124-3134.
4. Castelli MC, Friedman K, Sherry J, et al. Comparing the Efficacy and Tolerability of a New Daily Oral Vitamin B12 Formulation and Intermittent Intramuscular Vitamin B12 in Normalizing Low Cobalamin Levels: A Randomized, Open-Label, Parallel-Group Study. *Clin Ther* 2011;**33**(3):358-71.
5. Nyholm E, Turpin P, Swain D, et al. Oral vitamin B12 can change our practice. *Postgrad Med J* 2003;**79**:218-220.
6. Vidal-Alaball J, Butler C, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.:CD004655. DOI:10.1002/14651858.CD004655.pub2.
7. Kwong JC, Carr D, Dhalla IA, et al. Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. *BMC Fam Pract* 2005;**6**:8.
8. Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. *Acta Med Scand* 1968;**184**:247-58.
9. Graham ID, Jette N, Tetroe J, et al. Oral cobalamin remains medicine's best kept secret. *Archives of Gerontology and Geriatrics* 2007;**44**(1):49-59.

10. MacFarlane AJ, Greene-Finestone LS, Shi Y. Vitamin B-12 and homocysteine status in a folate-replete population: results from the Canadian Health Measures Survey. *Am J Clin Nutr* 2011;**94**:1079-87.
11. Lindenbaum J, Rosenberg IH, Wilson PW, et al. Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr* 1994;**60**:2-11.
12. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomized placebo controlled trial. *Br Med J* 2010;**340**:c2181.
13. Andrès E, Vidal-Alaball J, Federici L, et al. Clinical aspects of cobalamin deficiency in elderly patients. Epidemiology, causes, clinical manifestations, and treatment with special focus on oral cobalamin therapy. *Eur J Int Med* 2007;**18**:456-62.
14. Andrès E, Federici L, Affenberger S, et al. B12 deficiency: A look beyond pernicious anemia. *J Fam Pract* 2007;**56**(7):537-42.
15. Health Canada. Dietary Reference Intakes: Reference Values for Vitamins. Accessed 17 May 2012 at <[http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref\\_vitam\\_tbl-eng.php](http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref_vitam_tbl-eng.php)>.
16. van Walraven CG, Austin P, Naylor CD. Vitamin B12 injections versus oral supplements: How much money could be saved by switching from injections to pills? *Can Med Assoc J* 2001;**47**:79-86.
17. Middleton J, Wells W. Vitamin B12 injections: considerable source of work for the district nurse. *BMJ* 1985;**270**:1254-1255.
18. Drummond MF, Sculpher MJ, Torrance G, O'Brien B, et al. *Methods for the Economic Evaluation of Health Care Programmes*. 3<sup>rd</sup> ed. New York: Oxford University Press; 2005.
19. IMS Brogan LRx database, January 2013 and Compuscript audit, January 2013.
20. Alberta Health. Pharmacy fee reimbursement. Retrieved from:  
<http://www.health.alberta.ca/services/pharmacy-fee-reimbursement.html>

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
21. Alberta Health. Coverage for Seniors. Retrieved from:  
<http://www.health.alberta.ca/services/drugs-seniors.html>
  22. Alberta Health. Interactive Drug Benefit List. Retrieved from:  
<https://idbl.ab.bluecross.ca/idbl/load.do>
  23. Government of Alberta. 2011 Alberta Wage and Salary Data – Medical Laboratory Technologist. Retrieved from:  
[http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro\\_id=71003140](http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140)
  24. *Guidelines for the economic evaluation of health technologies: Canada* [3rd Edition]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.
  25. Alberta Health Care Insurance Plan. Medical Price List as of 01 April 2012. Retrieved from:  
<http://www.health.alberta.ca/documents/SOMB-Medical-Prices-2012-04.pdf>
  26. Alberta Health. Compensation for Pharmacy Services, July 2012. Retrieved from:  
<http://www.health.alberta.ca/documents/Pharmacy-Services-Compensation-2012.pdf>
  27. Hauber AB, Johnson FR, Sauriol L, et al. Risking health to avoid injections: Preferences of Canadians with type 2 diabetes. *Diabetes Care* 2005;28(9):2243-5.

Should Vitamin B<sub>12</sub> Tablets be Included in More Canadian Drug Formularies? An Economic Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular Vitamin B<sub>12</sub> Maintenance Therapy for Alberta Seniors

**Authors:**

Sherilyn KD Houle (corresponding author)

EPICORE Centre

3<sup>rd</sup> Floor, Brain and Aging Research Building

University of Alberta

Edmonton AB, Canada

T6G 2M8

Michael R Kolber

Department of Family Medicine

University of Alberta

Edmonton AB, Canada

Anderson W Chuck

Institute of Health Economics

Edmonton AB, Canada

**Keywords:** Cost analysis, healthcare costs, vitamin B<sub>12</sub> deficiency

**Word Count:** 28812524



**ABSTRACT:**

**Objectives:** The aim of this study is to estimate the cost-savings attainable if all patients aged  $\geq 65$  in Alberta, ~~Canada, and~~ currently on intramuscular therapy were switched to oral therapy, from the perspective of a provincial ministry of health.

**Setting:** Primary care setting in Alberta, Canada.

**Participants:** Seniors age 65 and older currently receiving intramuscular vitamin B<sub>12</sub> therapy.

**Intervention:** Oral vitamin B<sub>12</sub> therapy at 1000 mcg per day versus intramuscular therapy at 1000 mcg per month.

**Primary and Secondary Outcome Measures:** Cost-saving from oral therapy over intramuscular therapy, from the perspective of the Alberta Ministry of Health, including drug costs, dispensing fees, injection administration fees, additional laboratory monitoring, and physician visit fees.

**Results:** Over 5 years, if all Albertans age 65 and older who currently receive intramuscular B<sub>12</sub> are switched to oral therapy, our model found that CAD \$13,975,883 can be saved. Even if no additional physician visits are billed for among patients receiving IM therapy, \$8,444,346 could be saved from reduced administration costs alone.

**Conclusions:** Oral B<sub>12</sub> therapy has been shown to be an effective therapeutic option for patients with vitamin B<sub>12</sub> deficiency, yet only three provinces and the Non-Insured Health Benefits program include oral tablets on their formulary rather than the parenteral preparation.

To ensure judicious use of limited health resources, clinicians and formulary committees are encouraged to adopt oral B<sub>12</sub> therapy as a clinically- and cost-effective first line therapy for vitamin B<sub>12</sub> deficiency.

#### STRENGTHS AND LIMITATIONS OF THIS STUDY:

- Minimal assumptions built into the model, as exact costs and the exact number of eligible residents comprising the population were available
- Three randomized controlled trials and two prospective case series support our use of a cost-minimization analysis approach
- Comprehensive sensitivity analyses employed using Monte Carlo simulation to incorporate multiple variables
- Study is from the perspective of the provincial ministry of health (the payer) and does not adopt a societal perspective since much of the additional information required for that is not available
- Despite being set in one Canadian province, the use of intramuscular B<sub>12</sub> therapy is prevalent worldwide. Therefore, these results, while not directly generalizable to other jurisdictions, point to an economic argument for greater uptake of oral B<sub>12</sub> therapy which is likely consistent across other jurisdictions

#### BACKGROUND:

For over twenty years, oral vitamin B<sub>12</sub> has been referred to as “medicine’s best kept secret” [1].

Despite evidence of the effectiveness of oral B<sub>12</sub> therapy [2-78], intramuscular (IM) administration remains the most commonly prescribed route in North America [98].

1  
2  
3 Approximately 5% of Canadians are B<sub>12</sub> deficient [910], with Framingham data suggesting that  
4 B<sub>12</sub> deficiency in community-dwelling adults age 67 and older may be as high as 12% [4011].  
5  
6 Deficiency can occur as a result of gastric atrophy or previous gastric or intestinal surgery, use  
7 of antacids and other medications (metformin), inadequate animal product intake, and a  
8  
9 deficiency in intrinsic factor required for the absorption of cobalamin from the gut [4412-132].  
10  
11 While the absorbability of oral B<sub>12</sub> has been questioned, a number of studies have reported  
12  
13 successful results with oral therapy including treatment in patients with pernicious anemia or  
14  
15 bowel resection [4, 5, 8, 1314]. Since 1% of orally-ingested B<sub>12</sub> is absorbed via passive diffusion  
16  
17 independent of the presence of intrinsic factor [7], daily oral doses of 1000 mcg or more are  
18  
19 considered sufficient to meet daily requirements [4415] even in patients with insufficient intrinsic  
20  
21 factor.  
22  
23  
24  
25  
26  
27  
28

29 While oral tablets often cost more to acquire than B<sub>12</sub> injection solution, the costs associated  
30  
31 with administering the injections in the form of health professionals' time and resources can be  
32  
33 significant. A 2001 cost study estimated that between \$2.9-17.6 million could be saved over 5  
34  
35 years in the province of Ontario if elderly patients on IM B<sub>12</sub> were switched to oral therapy  
36  
37 [4516]. In addition, a British study estimated that 2000 nursing hours are required to provide one  
38  
39 year of injections to 492 patients in their homes [4617]. Across Canada, only Nova Scotia,  
40  
41 Northwest Territories, Yukon, and the Non-Insured Health Benefits program for First Nations  
42  
43 and Inuit consider oral B<sub>12</sub> tablets to be a benefit in their provincial drug formularies, while all  
44  
45 provinces and territories cover the injectable product.  
46  
47  
48  
49  
50

51 The objective of this study is to estimate the cost savings of treatment using daily oral vitamin  
52  
53 B<sub>12</sub> supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular  
54  
55 injections in Alberta seniors over the age of 65 who are currently using B<sub>12</sub> injection. Such a  
56  
57 study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to  
58  
59  
60

renew discussion about the best allocation of limited healthcare resources and whether oral B<sub>12</sub> should be covered by all Canadian provincial formularies.

## METHODS:

**Study Type:** A cost-minimization analysis (CMA) was performed wherein alternatives compared are considered to be equivalent in terms of factors that are relevant to the decision such as efficacy and tolerability, so the lowest cost alternative is selected [4718]. While a major assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75 patients on IM therapy) [2-4] and threetwo prospective case series of 15187 patients switching from IM to oral therapy [5, 7, 8] have concluded that the oral route is as clinically effective as the intramuscular route. Across allboth case series, no patients switched from IM to oral therapy required a switch back to IM replacement as a result of therapeutic failure. Costs were modeled over a period of five years, and the perspective of the Alberta Ministry of Health was adopted for this study.

**Setting / Patients:** The study population consists of individuals aged 65 or older with an Alberta Health Care number receiving IM B<sub>12</sub> therapy. The number of Alberta seniors dispensed injectable B<sub>12</sub> over a 1-year period (January-December 2012) was determined from prescription dispensing records collected by IMS Brogan [4819].

**Primary Outcome:** Cost-savings achievable by the province of Alberta if patients aged ≥65 and currently receiving IM B<sub>12</sub> therapy are switched to oral therapy. Cost savings are estimated in Canadian currency.

**Cost Determination:**

All costs are reported in Canadian dollars.

Cost of B<sub>12</sub> Tablets: The suggested retail price of Swiss Naturals<sup>®</sup>, Jamieson<sup>®</sup>, and Nature's Bounty<sup>®</sup> brands of 1000 mcg B<sub>12</sub> tablets were obtained from the manufacturers and averaged to obtain the cost per tablet. In Alberta, the maximum professional fee allowed for dispensing products with an acquisition cost of ≤\$74.99 is \$11.93 (consists of \$10.22 professional fee and \$1.71 inventory allowance) [2049].

Quantity of B<sub>12</sub> Tablets and Professional Fees: It was assumed that patients would receive a three-month supply with each fill, therefore amassing four professional fees annually and 365 tablets. Albertans age 65 and older are automatically enrolled into a 'Coverage for Seniors' program, where the patient co-pay is 30% of the cost to a maximum of \$25 [210]. Since this study assumes the perspective of the provincial Ministry of Health, the payer is assumed to cover 70% of the total drug cost. Despite being a non-prescription product, sales tax was not applied since such tablets would be dispensed through the pharmacy as a tax-free product similar to a prescription drug.

Cost of B<sub>12</sub> Injection: Parenteral B<sub>12</sub> in Alberta is available in 10 mL multi-dose vials at a concentration of 1000 mcg/mL. The cost per mL for the two products currently available in Alberta (DIN 00521515 and DIN 01987003) were determined from the Alberta Health Drug Benefit List [224]. In Alberta, the total charge allowable for injectable drugs other than insulin is 5/3 of the product's acquisition cost [2049]. Therefore, with an acquisition cost of \$4.50 per vial of parenteral B<sub>12</sub>, the total charge allowed – including the drug and professional fee – cannot exceed \$7.50, or \$0.75 per dose.

1  
2  
3 Quantity of B<sub>12</sub> injection: At the usual dosage of 1000 mcg/month, one vial contains a ten-month  
4 supply of drug. Therefore, 1.2 vials would be required for a one-year supply.  
5  
6  
7

8  
9  
10 Cost of Additional Laboratory Monitoring: Costs for the laboratory analyses were obtained from  
11 Alberta Health Services, laboratory technicians' time to draw and analyze the blood samples  
12 were estimated by consulting with practicing laboratory technicians, and laboratory technician  
13 wages were obtained from a Government of Alberta occupational survey [232] with a 20% fringe  
14 benefit applied.  
15  
16  
17  
18  
19

20  
21  
22 Quantity of Additional Laboratory Monitoring: To ensure adequate response to therapy, we  
23 assumed that patients to be switched from IM to oral B<sub>12</sub> would receive a baseline complete  
24 blood count and serum B<sub>12</sub> prior to the switch, repeated once after the switch to confirm  
25 effectiveness. It was assumed that this additional monitoring would occur only upon switch from  
26 IM to oral therapy, with long-term monitoring occurring at the same rate as if the patient had  
27 remained on IM injections, therefore representing no additional cost of oral therapy over IM  
28 therapy following the initial switch.  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39

40 Cost of Injection Administration: Currently, physicians, nurses, and pharmacists are authorized  
41 to administer B<sub>12</sub> by intramuscular injection in Alberta. Fees for physician office administration of  
42 injections and pharmacist administration of injections are provided in Table 1.  
43  
44  
45  
46  
47  
48

49 Quantity of Injection Administrations: It is unknown the proportion of patients on IM B<sub>12</sub> therapy  
50 receiving their monthly injections from their physician's office or their pharmacy. For the purpose  
51 of the study, based on the experience of the authors including a practicing pharmacist and  
52 family physician, it was assumed that 25% of all B<sub>12</sub> injections are administered in a community  
53 pharmacy with the remainder administered in a medical clinic.  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 Cost of Additional Physician Visits: The current cost for a standard family physician consultation  
7 visit in Alberta of \$35.91 was utilized in the model.  
8  
9

10  
11 Quantity of Additional Physician Visits: Based on available administrative data, we were unable  
12 to determine the number of additional physician visits received by and billed for patients on IM  
13 versus oral B<sub>12</sub> supplementation apart from simply the administration of the injection in the  
14 medical clinic. For the base case scenario, we assumed that 10% of injections administered in a  
15 physician's office also included a billed physician consultation which would not have occurred if  
16 the patient were not on IM B<sub>12</sub>, and have explored other scenarios in sensitivity analyses as  
17 described below.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28

### 29 **Model Assumptions:**

30  
31  
32 A number of assumptions were made with the model in addition to those previously described. It  
33 was assumed that patients on oral B<sub>12</sub> therapy were able to self-administer the medication, and  
34 if assistance was required, it was assumed that they already required this assistance for other  
35 medications rather than solely for B<sub>12</sub> tablets. Since B<sub>12</sub> tablets can be taken concurrently with  
36 other medications, it was not assumed that additional assistance would be needed if oral B<sub>12</sub>  
37 were added to their medication regimen. The cost of supplies to administer the intramuscular  
38 injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded  
39 from the model as these are relatively inexpensive and were not felt to significantly contribute to  
40 the overall cost of the injectable product.  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51

### 52 **Discounting:**

53  
54  
55  
56  
57  
58  
59  
60



Consistent with CADTH guidelines for the economic evaluation of health technologies [243], a discount rate of 5% for outcomes occurring after one year was applied to the reference case, with sensitivity analyses performed around this value as described below.

### Sensitivity Analyses:

Multi-way sensitivity analysis was performed in the form of 10,000 Monte Carlo simulation iterations, adjusting for a number of variables. Model inputs and the probabilistic distributions used in the sensitivity analyses are presented in Table 1. The base case scenario was calculated using the expected value for each variable and assumed a 10% rate of additional physician consultations for patients on intramuscular versus oral therapy.

**Table 1. Expected Values and Distribution Parameters for the Deterministic Model and Probabilistic Sensitivity Analyses**

Parameter	Expected Value $\pm$ SE	Distribution
Study population	28,252 $\pm$ 10%	Gamma
Cost per B <sub>12</sub> tablet	\$0.16 $\pm$ 0.008	Gamma
Professional Fee for Dispensing Tablets [2019]	\$11.93	--
Cost per B <sub>12</sub> injectable dose [2019-224]	\$0.75	--
Cost for CBC and serum B <sub>12</sub> analyses*	\$6.50	--
Laboratory technician time for blood sample draw and analyses (hours)*	0.75 (range 0.25-1)	Triangular
Laboratory technician wage and benefits [232]*	\$44.60 (range \$35.82-\$51.41)	Triangular
Fee for administration of intramuscular injection in a physician's office [254]	\$10.30	--
Cost for physician consultation visit [254]	\$35.91	--
Fee for administration of intramuscular injection in a pharmacy [265]	\$20.00	--

- SE=Standard Error; CBC=Complete blood count
- \* indicates parameter only included in year 1 of the model
- Normal distribution samples values probabilistically from a normal curve with specified mean (expected value) and standard error. Triangular distribution samples values probabilistically within the range specified, with increasing probability as values near the expected value.



Sensitivity analysis was also performed for different proportions of additional physician office visits including a billed consultation. While the base scenario assumed a 10% rate of office consultations during injection visits, the analyses were repeated for rates of 0% and 25%. Discounting rates of 0% and 3% were also tested in sensitivity analysis.

## RESULTS:

Estimated five-year cost savings associated with switching all Alberta seniors currently receiving injectable B<sub>12</sub> to oral therapy is \$13,975,883. Base scenario and sensitivity analysis results are presented in Table 2. Our model found that even if no additional physician visits were billed for among patients receiving IM therapy, over \$8 million could be saved from reduced administration costs alone.

**Table 2. Model Results Over 5 Years**

Proportion In-Office Injections Including a Fee for a Physician Visit	Discounting Rate for Years 2-5	Mean Cost Saving For Payer	Mean Cost Saving per Patient
<b>Reference Case</b>			
10%	5%	\$13,975,883	\$494.69
<b>Sensitivity Analyses</b>			
0%	0%	\$9,564,224	\$338.53
0%	3%	\$8,878,728	\$314.27
0%	5%	\$8,444,346	\$298.89
10%	0%	\$15,677,500	\$554.92
10%	3%	\$14,635,912	\$518.05
25%	0%	\$24,784,224	\$877.26
25%	3%	\$23,212,469	\$821.62
25%	5%	\$22,216,488	\$786.37

1  
2  
3 Due to the additional laboratory monitoring performed in the year of the change from IM to oral  
4 therapy, the model found the switch to be moderately cost-effective in the first year, with larger  
5 savings realized in years 2-5. For the base scenario, cost savings in year 1 were estimated at  
6 \$48.34 (SD \$8.58) per patient, increasing to \$126.55 (SD \$2.04) in year 2. Over 5 years,  
7 average cost-savings per patient was estimated at \$494.69.  
8  
9  
10  
11  
12  
13

## 14 15 16 **DISCUSSION:** 17

18  
19  
20 Over five years, the province of Alberta can be expected to free nearly \$14 million in healthcare  
21 costs if all seniors over the age of 65 currently receiving IM B<sub>12</sub> are switched to oral tablets.  
22

23 Despite evidence confirming that sufficient B<sub>12</sub> is absorbed by passive diffusion at a dose of  
24 1000 mcg daily to be effective even in patients lacking intrinsic factor or with gastrointestinal  
25 disease [132], the intramuscular route continues to be commonly prescribed. With high health  
26 professional workloads and increasingly restricted healthcare budgets, a switch from IM to oral  
27 therapy will not only free health professional resources to see patients at greater need, but can  
28 also result in cost-savings for reinvestment into other needed services.  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39

40 The option of oral supplementation is well received by patients. A Canadian study by Kwong *et*  
41 *al.* found that 73% of patients receiving B<sub>12</sub> injections were willing to try oral B<sub>12</sub>, and of those  
42 who tried the oral therapy, 71% wished to permanently remain on oral therapy [7]. Travel  
43 inconveniences were the most common reason for preferring the oral route. The authors  
44 concluded that oral therapy would decrease physician burden, increase patient control over  
45 therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding  
46 injections is unknown in adult patients, previous research has suggested that patients with  
47 diabetes value a reduced injection burden as much as they value disease control [276].  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57

58 Therefore, if a societal perspective including utility were considered, it is likely that the benefit of  
59  
60

1  
2  
3 switching patients from IM to oral therapy would be even greater. Furthermore, the elimination  
4 of risk for injection site reactions following a switch to oral therapy represents another potential  
5 benefit from the patient perspective.  
6  
7  
8  
9

10  
11 A number of assumptions employed in the model have the potential to alter the results in either  
12 direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy  
13 rather than monthly refills, which would be expected to underestimate the cost-saving potential  
14 of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have  
15 also occurred as a result of calculating tablet cost based on non-generic products at higher  
16 costs per tablet. Home care costs for the administration of B<sub>12</sub> injections in home-bound patients  
17 was not included since the proportion of patients receiving in-home injections was unknown,  
18 and it was assumed that these injections would be administered in conjunction with a regular  
19 visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits  
20 are indeed being performed for B<sub>12</sub> injections, then the savings of switching to oral B<sub>12</sub> would  
21 obviously be greater. Importantly, the model also assumed that all patients making the switch to  
22 oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore  
23 representing maximum saving potential. This assumption is consistent with previously published  
24 randomized controlled trials and case series reporting treatment success across all patients  
25 studied [2-87]. Additionally, we assumed in the base scenario that additional laboratory  
26 monitoring is only required for the first year following the switch to oral therapy, with monitoring  
27 as usual for the remaining years. Considering that adherence to self-administered oral therapy  
28 may be lower than a healthcare professional-administered injection, even if an additional set of  
29 laboratory tests were performed each year for the 5-year term of the model, estimated cost  
30 savings would still amount to \$12 million.  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Direct comparison between our model and the results of the 2001 cost-saving paper cannot be  
4 performed due to differing model assumptions and available data. Overall, both models report  
5 significant cost-saving potential of the switch from the perspective of a government payer over  
6 five years. However, due to higher current professional fees for injection administration, our  
7 model found overall cost-savings even if no additional physician visits occurred for patients  
8 receiving B<sub>12</sub> injections, whereas the previous study found a break-even point when 16.3% of  
9 additional physician visits were avoided.  
10  
11

12  
13  
14  
15  
16  
17  
18  
19  
20  
21 The use of cost-minimization analysis is controversial as it assumes equal efficacy and  
22 tolerability between the two options being compared; however, we feel this assumption is  
23 justifiable based on published data comparing the oral and intramuscular routes [2-87].  
24

25  
26  
27 However, the total number of patients studied in the randomized trials (total n=141 across 3  
28 studies) and case series (n=15187) remains relatively small and doses employed across each  
29 study differed. Further research on a larger population, comparing standard-dose IM therapy to  
30 standard-dose oral therapy is therefore recommended and is currently being planned.  
31  
32

33  
34  
35 Additionally, payers considering adding oral B<sub>12</sub> tablets to their formularies should consider  
36 allowing for the coverage of intramuscular therapy in the event of documented treatment failure  
37 on oral supplementation, until larger-scale studies confirming equivalence are conducted, or  
38 allowing for short-term IM therapy for patients with neurologic symptoms followed by oral  
39 maintenance therapy. Indeed, a planned randomized controlled trial of 320 patients age ≥65 in  
40 Spain will be directly comparing oral to IM B<sub>12</sub> and is expected to examine non-inferiority of oral  
41 therapy over one year (clinicaltrials.gov NCT01476007).  
42  
43  
44  
45  
46  
47  
48  
49  
50

51  
52  
53 Overall, our model estimates that \$8-24 million in cost-savings can be realized over five years if  
54 all Alberta seniors currently receiving IM vitamin B<sub>12</sub> are switched to oral therapy. Within closed  
55 systems like universal healthcare, this is unlikely to represent true cost savings, but rather room  
56  
57  
58  
59  
60

1  
2  
3 for re-allocation of resources to other health system needs. With an aging population and  
4  
5 increasing rates of chronic disease, switching of patients from IM to oral vitamin B<sub>12</sub>  
6  
7 replacement appears to be not only clinically efficacious, but also an effective use of limited  
8  
9 healthcare resources.  
10

11  
12  
13  
14 **Competing Interests:** The authors declare no conflicts of interest related to the above work.  
15

16  
17  
18 **Funding Statement:** No funding was received for completion of this study. Ms. Houle wasis  
19  
20 funded for her graduate studies by the Canadian Institutes of Health Research, Hypertension  
21  
22 Canada, and the Interdisciplinary Chronic Disease Collaboration (funded by Alberta Innovates –  
23  
24 Health Solutions).  
25  
26

## 27 REFERENCES

- 28  
29  
30  
31 1. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret. JAMA  
32  
33 1991;**265**:94-5.  
34  
35 2. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of  
36  
37 cobalamin deficiency with oral cobalamin. Blood 1998;**92**(4):1191-1198.  
38  
39 3. Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T. Oral versus  
40  
41 intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective,  
42  
43 randomized, open-label study. Clin Ther 2003;**25**(12):3124-3134.  
44  
45 4. Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, et al. Comparing the  
46  
47 Efficacy and Tolerability of a New Daily Oral Vitamin B12 Formulation and Intermittent  
48  
49 Intramuscular Vitamin B12 in Normalizing Low Cobalamin Levels: A Randomized, Open-  
50  
51 Label, Parallel-Group Study. Clin Ther 2011;**33**(3):358-71.  
52  
53 5. Nyholm E, Turpin P, Swain D, Cunningham B, Daly S, Nightingale P, et al. Oral vitamin B12  
54  
55 can change our practice. Postgrad Med J 2003;**79**:218-220.  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
6. Vidal-Alaball J, Butler C, Cannings-John R, Goringe A, Hood K, McCaddon A, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.:CD004655. DOI:10.1002/14651858.CD004655.pub2.
  7. Kwong JC, Carr D, Dhalla IA, Tom-Kun D, Upshur REG. Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. *BMC Fam Pract* 2005;**6**:8.
  8. [Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. \*Acta Med Scand\* 1968;\*\*184\*\*:247-58.](#)
  - ~~8-9.~~ Graham ID, Jette N, Tetroe J, Robinson N, Milne S, Mitchell SL. Oral cobalamin remains medicine's best kept secret. *Archives of Gerontology and Geriatrics* 2007;**44**(1):49–59.
  - ~~9-10.~~ MacFarlane AJ, Greene-Finestone LS, Shi Y. Vitamin B-12 and homocysteine status in a folate-replete population: results from the Canadian Health Measures Survey. *Am J Clin Nutr* 2011;**94**:1079-87.
  - ~~10-11.~~ Lindenbaum J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH. Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr* 1994;**60**:2-11.
  - ~~11-12.~~ de Jager J, Kooy A, Lehert P, Wulffele MG, van der Kolk J, Bets D, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomized placebo controlled trial. *Br Med J* 2010;**340**:c2181.
  - ~~12-13.~~ Andrès E, Vidal-Alaball J, Federici L, Henoun Loukili N, Zimmer J, Kaltenbach G. Clinical aspects of cobalamin deficiency in elderly patients. Epidemiology, causes, clinical manifestations, and treatment with special focus on oral cobalamin therapy. *Eur J Int Med* 2007;**18**:456-62.
  - ~~13-14.~~ Andrès E, Federici L, Affenberger S, Vidal-Alaball J, Henoun Loukili N, et al. B12 deficiency: A look beyond pernicious anemia. *J Fam Pract* 2007;**56**(7):537-42.

- 1  
2  
3 | 14-15. Health Canada. Dietary Reference Intakes: Reference Values for Vitamins. Accessed 17  
4 | May 2012 at <[http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref\\_vitam\\_tbl-eng.php](http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref_vitam_tbl-eng.php)>.  
5  
6  
7 | 15-16. van Walraven CG, Austin P, Naylor CD. Vitamin B12 injections versus oral supplements:  
8 | How much money could be saved by switching from injections to pills? Can Med Assoc J  
9 | 2001;**47**:79-86.  
10  
11 | 16-17. Middleton J, Wells W. Vitamin B12 injections: considerable source of work for the district  
12 | nurse. BMJ 1985;**270**:1254-1255.  
13  
14 | 17-18. Drummond MF, Sculpher MJ, Torrance G, O'Brien B, Stoddart G. Methods for the  
15 | Economic Evaluation of Health Care Programmes. 3<sup>rd</sup> ed. New York: Oxford University  
16 | Press; 2005.  
17  
18 | 18-19. IMS Brogan LRx database, January 2013 and Compuscript audit, January 2013.  
19  
20 | 19-20. Alberta Health. Pharmacy fee reimbursement. Retrieved from:  
21 | <http://www.health.alberta.ca/services/pharmacy-fee-reimbursement.html>  
22 |  
23 | 20-21. Alberta Health. Coverage for Seniors. Retrieved from:  
24 | <http://www.health.alberta.ca/services/drugs-seniors.html>  
25 |  
26 | 21-22. Alberta Health. Interactive Drug Benefit List. Retrieved from:  
27 | <https://idbl.ab.bluecross.ca/idbl/load.do>  
28 |  
29 | 22-23. Government of Alberta. 2011 Alberta Wage and Salary Data – Medical Laboratory  
30 | Technologist. Retrieved from:  
31 | [http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro\\_id=71003140](http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140)  
32 |  
33 | 23-24. *Guidelines for the economic evaluation of health technologies: Canada* [3rd Edition].  
34 | Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.  
35 |  
36 | 24-25. Alberta Health Care Insurance Plan. Medical Price List as of 01 April 2012. Retrieved  
37 | from: <http://www.health.alberta.ca/documents/SOMB-Medical-Prices-2012-04.pdf>  
38 |  
39 |  
40 |  
41 |  
42 |  
43 |  
44 |  
45 |  
46 |  
47 |  
48 |  
49 |  
50 |  
51 |  
52 |  
53 |  
54 |  
55 |  
56 |  
57 |  
58 |  
59 |  
60 |

1  
2  
3 | 25-26. Alberta Health. Compensation for Pharmacy Services, July 2012. Retrieved from:  
4 | <http://www.health.alberta.ca/documents/Pharmacy-Services-Compensation-2012.pdf>  
5  
6

7 | 26-27. Hauber AB, Johnson FR, Sauriol L, Lescauwat B. Risking health to avoid injections:  
8 | Preferences of Canadians with type 2 diabetes. Diabetes Care 2005;28(9):2243-5.  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



## EVEREST Statement

	Study section	Additional remarks
<b>Study design</b>		
(1) The research question is stated	Background	
(2) The economic importance of the research question is stated	Background	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods (Study Type); Discussion	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Background; Methods	
(5) The alternatives being compared are clearly described	Methods (Cost Determination)	
(6) The form of economic evaluation used is stated	Methods (Study Type)	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Methods; Discussion	
<b>Data collection</b>		
(8) The source(s) of effectiveness estimates used are stated	Methods (Study Type)	
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A (based on multiple studies)	3 randomized controlled trials and 2 prospective case series
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods (Primary Outcome)	
(12) Methods to value health states and other benefits are stated	N/A	
(13) Details of the subjects from whom valuations were obtained are given	Methods (Setting/Patients)	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods (Cost Determination)	
(17) Methods for the estimation of quantities and unit costs are described	Methods (Cost Determination)	
(18) Currency and price data are recorded	Methods (Primary Outcome)	
(19) Details of currency of price adjustments for inflation or currency conversion are given	N/A	

(20) Details of any model used are given	Methods (Model Assumptions, Discounting, Sensitivity Analyses)	
(21) The choice of model used and the key parameters on which it is based are justified	Methods (Study Type); Discussion	
<b>Analysis and interpretation of results</b>		
(22) Time horizon of costs and benefits is stated	Methods (Study Type)	
(23) The discount rate(s) is stated	Methods (Discounting)	
(24) The choice of rate(s) is justified	Methods (Discounting)	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods (Sensitivity Analyses)	
(28) The choice of variables for sensitivity analysis is justified	Methods (Sensitivity Analyses)	
(29) The ranges over which the variables are varied are stated	Table 1	
(30) Relevant alternatives are compared	Introduction	
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	N/A	
(33) The answer to the study question is given	Results; Discussion	
(34) Conclusions follow from the data reported	Discussion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	



**Should Vitamin B12 Tablets be Included in More Canadian Drug Formularies? An Economic Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular Vitamin B12 Maintenance Therapy for Alberta Seniors**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004501.R2
Article Type:	Research
Date Submitted by the Author:	19-Feb-2014
Complete List of Authors:	Houle, Sherilyn; University of Alberta, Medicine Kolber, Michael; University of Alberta, Family Medicine Chuck, Anderson; Institute of Health Economics,
<b>Primary Subject Heading</b>:	General practice / Family practice
Secondary Subject Heading:	Pharmacology and therapeutics, Health economics, Evidence based practice, Nutrition and metabolism, Geriatric medicine
Keywords:	HEALTH ECONOMICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

SCHOLARONE™  
Manuscripts

1  
2  
3 Should Vitamin B<sub>12</sub> Tablets be Included in More Canadian Drug Formularies? An Economic  
4  
5 Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular  
6  
7 Vitamin B<sub>12</sub> Maintenance Therapy for Alberta Seniors  
8  
9  
10

11  
12 **Authors:**

13  
14 Sherilyn KD Houle (corresponding author)

15  
16 EPICORE Centre

17  
18 3<sup>rd</sup> Floor, Brain and Aging Research Building

19  
20 University of Alberta

21  
22 Edmonton AB, Canada

23  
24 T6G 2M8  
25  
26  
27  
28

29  
30 Michael R Kolber

31  
32 Department of Family Medicine

33  
34 University of Alberta

35  
36 Edmonton AB, Canada  
37  
38  
39

40  
41 Anderson W Chuck

42  
43 Institute of Health Economics

44  
45 Edmonton AB, Canada  
46  
47  
48

49 **Keywords:** Cost analysis, healthcare costs, vitamin B<sub>12</sub> deficiency  
50  
51

52  
53 **Word Count:** 2911  
54  
55  
56  
57  
58  
59  
60

**ABSTRACT:**

**Objectives:** The aim of this study is to estimate the cost-savings attainable if all patients aged  $\geq 65$  in Alberta, Canada, currently on intramuscular therapy were switched to oral therapy, from the perspective of a provincial ministry of health.

**Setting:** Primary care setting in Alberta, Canada.

**Participants:** Seniors age 65 and older currently receiving intramuscular vitamin B<sub>12</sub> therapy.

**Intervention:** Oral vitamin B<sub>12</sub> therapy at 1000 mcg per day versus intramuscular therapy at 1000 mcg per month.

**Primary and Secondary Outcome Measures:** Cost-saving from oral therapy over intramuscular therapy, from the perspective of the Alberta Ministry of Health, including drug costs, dispensing fees, injection administration fees, additional laboratory monitoring, and physician visit fees.

**Results:** Over 5 years, if all Albertans age 65 and older who currently receive intramuscular B<sub>12</sub> are switched to oral therapy, our model found that CAD \$13,975,883 can be saved. Even if no additional physician visits are billed for among patients receiving IM therapy, \$8,444,346 could be saved from reduced administration costs alone.

**Conclusions:** Oral B<sub>12</sub> therapy has been shown to be an effective therapeutic option for patients with vitamin B<sub>12</sub> deficiency, yet only three provinces and the Non-Insured Health Benefits program include oral tablets on their formulary rather than the parenteral preparation.

To ensure judicious use of limited health resources, clinicians and formulary committees are encouraged to adopt oral B<sub>12</sub> therapy as a clinically- and cost-effective first line therapy for vitamin B<sub>12</sub> deficiency.

#### **STRENGTHS AND LIMITATIONS OF THIS STUDY:**

- Minimal assumptions built into the model, as exact costs and the exact number of eligible residents comprising the population were available
- Three randomized controlled trials and two prospective case series support our use of a cost-minimization analysis approach
- Comprehensive sensitivity analyses employed using Monte Carlo simulation to incorporate multiple variables
- Study is from the perspective of the provincial ministry of health (the payer) and does not adopt a societal perspective since much of the additional information required for that is not available
- Despite being set in one Canadian province, the use of intramuscular B<sub>12</sub> therapy is prevalent worldwide. Therefore, these results, while not directly generalizable to other jurisdictions, point to an economic argument for greater uptake of oral B<sub>12</sub> therapy which is likely consistent across other jurisdictions

#### **BACKGROUND:**

For over twenty years, oral vitamin B<sub>12</sub> has been referred to as “medicine’s best kept secret” [1]. Hesitation by clinicians to treat B<sub>12</sub> deficiency with oral preparations dates back to a 1959 report by the U.S.P. Anti-Anemia Preparations Advisory Board suggesting inadequate absorption of oral dosage forms. [2] Despite evidence of the effectiveness of oral B<sub>12</sub> therapy since [3-9],

1  
2  
3 intramuscular (IM) administration remains the most commonly prescribed route in North  
4  
5 America [10].  
6  
7  
8

9  
10 Approximately 5% of Canadians are B<sub>12</sub> deficient [11], with Framingham data suggesting that  
11  
12 B<sub>12</sub> deficiency in community-dwelling adults age 67 and older may be as high as 12% [12].  
13  
14 Deficiency can occur as a result of gastric atrophy or previous gastric or intestinal surgery, use  
15  
16 of antacids and other medications (metformin), inadequate animal product intake, and a  
17  
18 deficiency in intrinsic factor required for the absorption of cobalamin from the gut [13-14]. While  
19  
20 the absorbability of oral B<sub>12</sub> has been questioned, a number of studies have reported successful  
21  
22 results with oral therapy including treatment in patients with pernicious anemia or bowel  
23  
24 resection [5, 6, 9, 15]. Since 1% of orally-ingested B<sub>12</sub> is absorbed via passive diffusion  
25  
26 independent of the presence of intrinsic factor [8], daily oral doses of 1000 mcg or more are  
27  
28 considered sufficient to meet daily requirements [16] even in patients with insufficient intrinsic  
29  
30 factor.  
31  
32  
33

34  
35  
36 While oral tablets often cost more to acquire than B<sub>12</sub> injection solution, the costs associated  
37  
38 with administering the injections in the form of health professionals' time and resources can be  
39  
40 significant. A 2001 cost study estimated that between \$2.9-17.6 million could be saved over 5  
41  
42 years in the province of Ontario if elderly patients on IM B<sub>12</sub> were switched to oral therapy [17].  
43  
44 In addition, a British study estimated that 2000 nursing hours are required to provide one year of  
45  
46 injections to 492 patients in their homes [18]. Across Canada, only Nova Scotia, Northwest  
47  
48 Territories, Yukon, and the Non-Insured Health Benefits program for First Nations and Inuit  
49  
50 consider oral B<sub>12</sub> tablets to be a benefit in their provincial drug formularies, while all provinces  
51  
52 and territories cover the injectable product.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 The objective of this study is to estimate the cost savings of treatment using daily oral vitamin  
4  
5 B<sub>12</sub> supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular  
6  
7 injections in Alberta seniors over the age of 65 who are currently using B<sub>12</sub> injection. Such a  
8  
9 study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to  
10  
11 renew discussion about the best allocation of limited healthcare resources and whether oral B<sub>12</sub>  
12  
13 should be covered by all Canadian provincial formularies.  
14  
15

## 16 17 18 **METHODS:** 19

20  
21  
22 **Study Type:** A cost-minimization analysis (CMA) was performed wherein alternatives compared  
23  
24 are considered to be equivalent in terms of factors that are relevant to the decision such as  
25  
26 efficacy and tolerability, so the lowest cost alternative is selected [19]. While a major  
27  
28 assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75  
29  
30 patients on IM therapy) [3-5] and three prospective case series of 151 patients switching from  
31  
32 IM to oral therapy [6, 8, 9] have concluded that the oral route is as clinically effective as the  
33  
34 intramuscular route. Across all case series, no patients switched from IM to oral therapy  
35  
36 required a switch back to IM replacement as a result of therapeutic failure. Costs were modeled  
37  
38 over a period of five years, and the perspective of the Alberta Ministry of Health was adopted for  
39  
40 this study.  
41  
42  
43  
44  
45

46  
47 **Setting / Patients:** The study population consists of individuals aged 65 or older with an Alberta  
48  
49 Health Care number receiving IM B<sub>12</sub> therapy. The number of Alberta seniors dispensed  
50  
51 injectable B<sub>12</sub> over a 1-year period (January-December 2012) was determined from prescription  
52  
53 dispensing records collected by IMS Brogan [20].  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 **Primary Outcome:** Cost-savings achievable by the province of Alberta if patients aged  $\geq 65$  and  
4 currently receiving IM B<sub>12</sub> therapy are switched to oral therapy. Cost savings are estimated in  
5 Canadian currency.  
6  
7  
8  
9

10  
11 **Cost Determination:**

12 All costs are reported in Canadian dollars.  
13

14  
15  
16  
17  
18 Cost of B<sub>12</sub> Tablets: The suggested retail price of Swiss Naturals<sup>®</sup>, Jamieson<sup>®</sup>, and Nature's  
19 Bounty<sup>®</sup> brands of 1000 mcg B<sub>12</sub> tablets were obtained from the manufacturers and averaged to  
20 obtain the cost per tablet. In Alberta, the maximum professional fee allowed for dispensing  
21 products with an acquisition cost of  $\leq \$74.99$  is \$11.93 (consists of \$10.22 professional fee and  
22 \$1.71 inventory allowance) [21].  
23  
24  
25  
26  
27  
28

29  
30  
31 Quantity of B<sub>12</sub> Tablets and Professional Fees: It was assumed that patients would receive a  
32 three-month supply with each fill, therefore amassing four professional fees annually and 365  
33 tablets. Albertans age 65 and older are automatically enrolled into a 'Coverage for Seniors'  
34 program, where the patient co-pay is 30% of the cost to a maximum of \$25 [22]. Since this study  
35 assumes the perspective of the provincial Ministry of Health, the payer is assumed to cover 70%  
36 of the total drug cost. Despite being a non-prescription product, sales tax was not applied since  
37 such tablets would be dispensed through the pharmacy as a tax-free product similar to a  
38 prescription drug.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48

49  
50  
51 Cost of B<sub>12</sub> Injection: Parenteral B<sub>12</sub> in Alberta is available in 10 mL multi-dose vials at a  
52 concentration of 1000 mcg/mL. The cost per mL for the two products currently available in  
53 Alberta (DIN 00521515 and DIN 01987003) were determined from the Alberta Health Drug  
54 Benefit List [23]. In Alberta, the total charge allowable for injectable drugs other than insulin is  
55  
56  
57  
58  
59  
60

1  
2  
3 5/3 of the product's acquisition cost [21]. Therefore, with an acquisition cost of \$4.50 per vial of  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

5/3 of the product's acquisition cost [21]. Therefore, with an acquisition cost of \$4.50 per vial of parenteral B<sub>12</sub>, the total charge allowed – including the drug and professional fee – cannot exceed \$7.50, or \$0.75 per dose.

Quantity of B<sub>12</sub> injection: At the usual dosage of 1000 mcg/month, one vial contains a ten-month supply of drug. Therefore, 1.2 vials would be required for a one-year supply.

Cost of Additional Laboratory Monitoring: Costs for the laboratory analyses were obtained from Alberta Health Services, laboratory technicians' time to draw and analyze the blood samples were estimated by consulting with practicing laboratory technicians, and laboratory technician wages were obtained from a Government of Alberta occupational survey [24] with a 20% fringe benefit applied.

Quantity of Additional Laboratory Monitoring: To ensure adequate response to therapy, we assumed that patients to be switched from IM to oral B<sub>12</sub> would receive a baseline complete blood count and serum B<sub>12</sub> prior to the switch, repeated once after the switch to confirm effectiveness. It was assumed that this additional monitoring would occur only upon switch from IM to oral therapy, with long-term monitoring occurring at the same rate as if the patient had remained on IM injections, therefore representing no additional cost of oral therapy over IM therapy following the initial switch.

Cost of Injection Administration: Currently, physicians, nurses, and pharmacists are authorized to administer B<sub>12</sub> by intramuscular injection in Alberta. Fees for physician office administration of injections and pharmacist administration of injections are provided in Table 1.

1  
2  
3 Quantity of Injection Administrations: It is unknown the proportion of patients on IM B<sub>12</sub> therapy  
4 receiving their monthly injections from their physician's office or their pharmacy. For the purpose  
5 of the study, based on the experience of the authors including a practicing pharmacist and  
6 family physician, it was assumed that 25% of all B<sub>12</sub> injections are administered in a community  
7 pharmacy with the remainder administered in a medical clinic.  
8  
9

10  
11  
12 Cost of Additional Physician Visits: The current cost for a standard family physician consultation  
13 visit in Alberta of \$35.91 was utilized in the model.  
14  
15

16  
17  
18 Quantity of Additional Physician Visits: Based on available administrative data, we were unable  
19 to determine the number of additional physician visits received by and billed for patients on IM  
20 versus oral B<sub>12</sub> supplementation apart from simply the administration of the injection in the  
21 medical clinic. For the base case scenario, we assumed that 10% of injections administered in a  
22 physician's office also included a billed physician consultation which would not have occurred if  
23 the patient were not on IM B<sub>12</sub>, and have explored other scenarios in sensitivity analyses as  
24 described below.  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

### 38 **Model Assumptions:**

39  
40  
41 A number of assumptions were made with the model in addition to those previously described. It  
42 was assumed that patients on oral B<sub>12</sub> therapy were able to self-administer the medication, and  
43 if assistance was required, it was assumed that they already required this assistance for other  
44 medications rather than solely for B<sub>12</sub> tablets. Since B<sub>12</sub> tablets can be taken concurrently with  
45 other medications, it was not assumed that additional assistance would be needed if oral B<sub>12</sub>  
46 were added to their medication regimen. The cost of supplies to administer the intramuscular  
47 injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

from the model as these are relatively inexpensive and were not felt to significantly contribute to the overall cost of the injectable product.

### Discounting:

Consistent with CADTH guidelines for the economic evaluation of health technologies [24], a discount rate of 5% for outcomes occurring after one year was applied to the reference case, with sensitivity analyses performed around this value as described below.

### Sensitivity Analyses:

Multi-way sensitivity analysis was performed in the form of 10,000 Monte Carlo simulation iterations, adjusting for a number of variables. Model inputs and the probabilistic distributions used in the sensitivity analyses are presented in Table 1. The base case scenario was calculated using the expected value for each variable and assumed a 10% rate of additional physician consultations for patients on intramuscular versus oral therapy.

**Table 1. Expected Values and Distribution Parameters for the Deterministic Model and Probabilistic Sensitivity Analyses**

Parameter	Expected Value $\pm$ SE	Distribution
Study population	28,252 $\pm$ 10%	Gamma
Cost per B <sub>12</sub> tablet	\$0.16 $\pm$ 0.008	Gamma
Professional Fee for Dispensing Tablets [20]	\$11.93	--
Cost per B <sub>12</sub> injectable dose [20-22]	\$0.75	--
Cost for CBC and serum B <sub>12</sub> analyses*	\$6.50	--
Laboratory technician time for blood sample draw and analyses (hours)*	0.75 (range 0.25-1)	Triangular
Laboratory technician wage and benefits [23]*	\$44.60 (range \$35.82-\$51.41)	Triangular
Fee for administration of intramuscular injection in a physician's office [25]	\$10.30	--

Cost for physician consultation visit [25]	\$35.91	--
Fee for administration of intramuscular injection in a pharmacy [26]	\$20.00	--

- SE=Standard Error; CBC=Complete blood count
- \* indicates parameter only included in year 1 of the model
- Normal distribution samples values probabilistically from a normal curve with specified mean (expected value) and standard error. Triangular distribution samples values probabilistically within the range specified, with increasing probability as values near the expected value.

Sensitivity analysis was also performed for different proportions of additional physician office visits including a billed consultation. While the base scenario assumed a 10% rate of office consultations during injection visits, the analyses were repeated for rates of 0% and 25%. Discounting rates of 0% and 3% were also tested in sensitivity analysis.

## RESULTS:

Estimated five-year cost savings associated with switching all Alberta seniors currently receiving injectable B<sub>12</sub> to oral therapy is \$13,975,883. Base scenario and sensitivity analysis results are presented in Table 2. Our model found that even if no additional physician visits were billed for among patients receiving IM therapy, over \$8 million could be saved from reduced administration costs alone.

**Table 2. Model Results Over 5 Years**

Proportion In-Office Injections Including a Fee for a Physician Visit	Discounting Rate for Years 2-5	Mean Cost Saving For Payer	Mean Cost Saving per Patient
<b>Reference Case</b>			
10%	5%	\$13,975,883	\$494.69
<b>Sensitivity Analyses</b>			
0%	0%	\$9,564,224	\$338.53
0%	3%	\$8,878,728	\$314.27

0%	5%	\$8,444,346	\$298.89
10%	0%	\$15,677,500	\$554.92
10%	3%	\$14,635,912	\$518.05
25%	0%	\$24,784,224	\$877.26
25%	3%	\$23,212,469	\$821.62
25%	5%	\$22,216,488	\$786.37

Due to the additional laboratory monitoring performed in the year of the change from IM to oral therapy, the model found the switch to be moderately cost-effective in the first year, with larger savings realized in years 2-5. For the base scenario, cost savings in year 1 were estimated at \$48.34 (SD \$8.58) per patient, increasing to \$126.55 (SD \$2.04) in year 2. Over 5 years, average cost-savings per patient was estimated at \$494.69.

## DISCUSSION:

Over five years, the province of Alberta can be expected to free nearly \$14 million in healthcare costs if all seniors over the age of 65 currently receiving IM B<sub>12</sub> are switched to oral tablets. Despite evidence confirming that sufficient B<sub>12</sub> is absorbed by passive diffusion at a dose of 1000 mcg daily to be effective even in patients lacking intrinsic factor or with gastrointestinal disease [14], the intramuscular route continues to be commonly prescribed. With high health professional workloads and increasingly restricted healthcare budgets, a switch from IM to oral therapy will not only free health professional resources to see patients at greater need, but can also result in cost-savings for reinvestment into other needed services.

The option of oral supplementation is well received by patients. A Canadian study by Kwong *et al.* found that 73% of patients receiving B<sub>12</sub> injections were willing to try oral B<sub>12</sub>, and of those who tried the oral therapy, 71% wished to permanently remain on oral therapy [8]. Travel

1  
2  
3 inconveniences were the most common reason for preferring the oral route. The authors  
4  
5 concluded that oral therapy would decrease physician burden, increase patient control over  
6  
7 therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding  
8  
9 injections is unknown in adult patients, previous research has suggested that patients with  
10  
11 diabetes value a reduced injection burden as much as they value disease control [28].

12  
13  
14 Therefore, if a societal perspective including utility were considered, it is likely that the benefit of  
15  
16 switching patients from IM to oral therapy would be even greater. Furthermore, the elimination  
17  
18 of risk for injection site reactions following a switch to oral therapy represents another potential  
19  
20 benefit from the patient perspective.  
21  
22

23  
24  
25 A number of assumptions employed in the model have the potential to alter the results in either  
26  
27 direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy  
28  
29 rather than monthly refills, which would be expected to underestimate the cost-saving potential  
30  
31 of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have  
32  
33 also occurred as a result of calculating tablet cost based on non-generic products at higher  
34  
35 costs per tablet. Home care costs for the administration of B<sub>12</sub> injections in home-bound patients  
36  
37 was not included since the proportion of patients receiving in-home injections was unknown,  
38  
39 and it was assumed that these injections would be administered in conjunction with a regular  
40  
41 visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits  
42  
43 are indeed being performed for B<sub>12</sub> injections, then the savings of switching to oral B<sub>12</sub> would  
44  
45 obviously be greater. Importantly, the model also assumed that all patients making the switch to  
46  
47 oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore  
48  
49 representing maximum saving potential. This assumption is consistent with previously published  
50  
51 randomized controlled trials and case series reporting treatment success across all patients  
52  
53 studied [3-9]. Additionally, we assumed in the base scenario that additional laboratory  
54  
55 monitoring is only required for the first year following the switch to oral therapy, with monitoring  
56  
57  
58  
59  
60



1  
2  
3 as usual for the remaining years. Considering that adherence to self-administered oral therapy  
4 may be lower than a healthcare professional-administered injection, even if an additional set of  
5 laboratory tests were performed each year for the 5-year term of the model, estimated cost  
6 savings would still amount to \$12 million.  
7  
8  
9  
10

11  
12  
13  
14 Direct comparison between our model and the results of the 2001 cost-saving paper cannot be  
15 performed due to differing model assumptions and available data. Overall, both models report  
16 significant cost-saving potential of the switch from the perspective of a government payer over  
17 five years. However, due to higher current professional fees for injection administration, our  
18 model found overall cost-savings even if no additional physician visits occurred for patients  
19 receiving B<sub>12</sub> injections, whereas the previous study found a break-even point when 16.3% of  
20 additional physician visits were avoided.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

31 The use of cost-minimization analysis is controversial as it assumes equal efficacy and  
32 tolerability between the two options being compared; however, we feel this assumption is  
33 justifiable based on published data comparing the oral and intramuscular routes [3-9]. However,  
34 the total number of patients studied in the randomized trials (total n=141 across 3 studies) and  
35 case series (n=151) remains relatively small and doses employed across each study differed.  
36 Further research on a larger population, comparing standard-dose IM therapy to standard-dose  
37 oral therapy is therefore recommended and is currently being planned. Additionally, payers  
38 considering adding oral B<sub>12</sub> tablets to their formularies should consider allowing for the coverage  
39 of intramuscular therapy in the event of documented treatment failure on oral supplementation,  
40 until larger-scale studies confirming equivalence are conducted, or allowing for short-term IM  
41 therapy for patients with neurologic symptoms followed by oral maintenance therapy. Indeed, a  
42 planned randomized controlled trial of 320 patients age ≥65 in Spain will be directly comparing  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 oral to IM B<sub>12</sub> and is expected to examine non-inferiority of oral therapy over one year  
4  
5 (clinicaltrials.gov NCT01476007).  
6  
7  
8

9  
10 Overall, our model estimates that \$8-24 million in cost-savings can be realized over five years if  
11 all Alberta seniors currently receiving IM vitamin B<sub>12</sub> are switched to oral therapy. Within closed  
12 systems like universal healthcare, this is unlikely to represent true cost savings, but rather room  
13 for re-allocation of resources to other health system needs. With an aging population and  
14 increasing rates of chronic disease, switching of patients from IM to oral vitamin B<sub>12</sub>  
15 replacement appears to be not only clinically efficacious, but also an effective use of limited  
16 healthcare resources.  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **Funding Statement:** No funding was received for completion of this study. Ms. Houle was  
4 funded for her graduate studies by the Canadian Institutes of Health Research, Hypertension  
5 Canada, and the Interdisciplinary Chronic Disease Collaboration (funded by Alberta Innovates –  
6 Health Solutions).  
7  
8  
9

10  
11 **Contributorship Statement:** All authors (Dr. Houle, Dr. Kolber, and Dr. Chuck) contributed to  
12 the design and analysis/interpretation of data, drafting of the article, and approval of the final  
13 version.  
14  
15  
16

17 **Competing Interests:** The authors declare no conflicts of interest related to the above work.  
18  
19

20 **Data Sharing Statement:** There is no additional unpublished data related to this study.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

1. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret. J Am Med Assoc 1991;**265**:94-5.
2. Bethell FH, Castle WB, Conley CL. Present status of treatment of pernicious anemia: Ninth announcement of the U.S.P. Anti-Anemia Preparations Advisory Board. J Am Med Assoc 1959;171(15):2092-4.
3. Kuzminski AM, Del Giacco EJ, Allen RH, et al. Effective treatment of cobalamin deficiency with oral cobalamin. Blood 1998;**92**(4):1191-1198.
4. Bolaman Z, Kadikoylu G, Yukselen V, et al. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective, randomized, open-label study. Clin Ther 2003;**25**(12):3124-3134.
5. Castelli MC, Friedman K, Sherry J, et al. Comparing the Efficacy and Tolerability of a New Daily Oral Vitamin B12 Formulation and Intermittent Intramuscular Vitamin B12 in Normalizing Low Cobalamin Levels: A Randomized, Open-Label, Parallel-Group Study. Clin Ther 2011;**33**(3):358-71.
6. Nyholm E, Turpin P, Swain D, et al. Oral vitamin B12 can change our practice. Postgrad Med J 2003;**79**:218-220.
7. Vidal-Alaball J, Butler C, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.:CD004655. DOI:10.1002/14651858.CD004655.pub2.
8. Kwong JC, Carr D, Dhalla IA, et al. Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. BMC Fam Pract 2005;**6**:8.
9. Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. Acta Med Scand 1968;**184**:247-58.

- 1  
2  
3 10. Graham ID, Jette N, Tetroe J, et al. Oral cobalamin remains medicine's best kept secret.  
4  
5 Archives of Gerontology and Geriatrics 2007;**44**(1):49–59.  
6
- 7  
8 11. MacFarlane AJ, Greene-Finestone LS, Shi Y. Vitamin B-12 and homocysteine status in a  
9  
10 folate-replete population: results from the Canadian Health Measures Survey. Am J Clin  
11  
12 Nutr 2011;**94**:1079-87.  
13
- 14  
15 12. Lindenbaum J, Rosenberg IH, Wilson PW, et al. Prevalence of cobalamin deficiency in the  
16  
17 Framingham elderly population. Am J Clin Nutr 1994;**60**:2-11.  
18
- 19  
20 13. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type  
21  
22 2 diabetes and risk of vitamin B-12 deficiency: randomized placebo controlled trial. Br Med J  
23  
24 2010;**340**:c2181.  
25
- 26  
27 14. Andrès E, Vidal-Alaball J, Federici L, et al. Clinical aspects of cobalamin deficiency in elderly  
28  
29 patients. Epidemiology, causes, clinical manifestations, and treatment with special focus on  
30  
31 oral cobalamin therapy. Eur J Int Med 2007;**18**:456-62.  
32
- 33  
34 15. Andrès E, Federici L, Affenberger S, et al. B12 deficiency: A look beyond pernicious anemia.  
35  
36 J Fam Pract 2007;**56**(7):537-42.  
37
- 38  
39 16. Health Canada. Dietary Reference Intakes: Reference Values for Vitamins. Accessed 17  
40  
41 May 2012 at <[http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref\\_vitam\\_tbl-eng.php](http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref_vitam_tbl-eng.php)>.  
42
- 43  
44 17. van Walraven CG, Austin P, Naylor CD. Vitamin B12 injections versus oral supplements:  
45  
46 How much money could be saved by switching from injections to pills? Can Med Assoc J  
47  
48 2001;**47**:79-86.  
49
- 50  
51 18. Middleton J, Wells W. Vitamin B12 injections: considerable source of work for the district  
52  
53 nurse. BMJ 1985;**270**:1254-1255.  
54
- 55  
56 19. Drummond MF, Sculpher MJ, Torrance G, et al. Methods for the Economic Evaluation of  
57  
58 Health Care Programmes. 3<sup>rd</sup> ed. New York: Oxford University Press; 2005.  
59
- 60  
60 20. IMS Brogan LRx database, January 2013 and Compuscript audit, January 2013.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
21. Alberta Health. Pharmacy fee reimbursement. Retrieved from:  
<http://www.health.alberta.ca/services/pharmacy-fee-reimbursement.html>
  22. Alberta Health. Coverage for Seniors. Retrieved from:  
<http://www.health.alberta.ca/services/drugs-seniors.html>
  23. Alberta Health. Interactive Drug Benefit List. Retrieved from:  
<https://idbl.ab.bluecross.ca/idbl/load.do>
  24. Government of Alberta. 2011 Alberta Wage and Salary Data – Medical Laboratory Technologist. Retrieved from:  
[http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro\\_id=71003140](http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140)
  25. *Guidelines for the economic evaluation of health technologies: Canada* [3rd Edition]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.
  26. Alberta Health Care Insurance Plan. Medical Price List as of 01 April 2012. Retrieved from:  
<http://www.health.alberta.ca/documents/SOMB-Medical-Prices-2012-04.pdf>
  27. Alberta Health. Compensation for Pharmacy Services, July 2012. Retrieved from:  
<http://www.health.alberta.ca/documents/Pharmacy-Services-Compensation-2012.pdf>
  28. Hauber AB, Johnson FR, Sauriol L, et al. Risking health to avoid injections: Preferences of Canadians with type 2 diabetes. *Diabetes Care* 2005;28(9):2243-5.

1  
2  
3 Should Vitamin B<sub>12</sub> Tablets be Included in More Canadian Drug Formularies? An Economic  
4  
5 Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular  
6  
7 Vitamin B<sub>12</sub> Maintenance Therapy for Alberta Seniors  
8  
9

10  
11  
12 **Authors:**

13  
14 Sherilyn KD Houle (corresponding author)

15  
16 EPICORE Centre

17  
18 3<sup>rd</sup> Floor, Brain and Aging Research Building

19  
20 University of Alberta

21  
22 Edmonton AB, Canada

23  
24 T6G 2M8  
25  
26  
27  
28

29  
30 Michael R Kolber

31  
32 Department of Family Medicine

33  
34 University of Alberta

35  
36 Edmonton AB, Canada  
37  
38  
39

40  
41 Anderson W Chuck

42  
43 Institute of Health Economics

44  
45 Edmonton AB, Canada  
46  
47  
48

49 **Keywords:** Cost analysis, healthcare costs, vitamin B<sub>12</sub> deficiency  
50  
51

52  
53 **Word Count:** ~~29112884~~  
54  
55  
56  
57  
58  
59  
60

**ABSTRACT:**

**Objectives:** The aim of this study is to estimate the cost-savings attainable if all patients aged  $\geq 65$  in Alberta, Canada, currently on intramuscular therapy were switched to oral therapy, from the perspective of a provincial ministry of health.

**Setting:** Primary care setting in Alberta, Canada.

**Participants:** Seniors age 65 and older currently receiving intramuscular vitamin B<sub>12</sub> therapy.

**Intervention:** Oral vitamin B<sub>12</sub> therapy at 1000 mcg per day versus intramuscular therapy at 1000 mcg per month.

**Primary and Secondary Outcome Measures:** Cost-saving from oral therapy over intramuscular therapy, from the perspective of the Alberta Ministry of Health, including drug costs, dispensing fees, injection administration fees, additional laboratory monitoring, and physician visit fees.

**Results:** Over 5 years, if all Albertans age 65 and older who currently receive intramuscular B<sub>12</sub> are switched to oral therapy, our model found that CAD \$13,975,883 can be saved. Even if no additional physician visits are billed for among patients receiving IM therapy, \$8,444,346 could be saved from reduced administration costs alone.

**Conclusions:** Oral B<sub>12</sub> therapy has been shown to be an effective therapeutic option for patients with vitamin B<sub>12</sub> deficiency, yet only three provinces and the Non-Insured Health Benefits program include oral tablets on their formulary rather than the parenteral preparation.

To ensure judicious use of limited health resources, clinicians and formulary committees are encouraged to adopt oral B<sub>12</sub> therapy as a clinically- and cost-effective first line therapy for vitamin B<sub>12</sub> deficiency.

#### STRENGTHS AND LIMITATIONS OF THIS STUDY:

- Minimal assumptions built into the model, as exact costs and the exact number of eligible residents comprising the population were available
- Three randomized controlled trials and two prospective case series support our use of a cost-minimization analysis approach
- Comprehensive sensitivity analyses employed using Monte Carlo simulation to incorporate multiple variables
- Study is from the perspective of the provincial ministry of health (the payer) and does not adopt a societal perspective since much of the additional information required for that is not available
- Despite being set in one Canadian province, the use of intramuscular B<sub>12</sub> therapy is prevalent worldwide. Therefore, these results, while not directly generalizable to other jurisdictions, point to an economic argument for greater uptake of oral B<sub>12</sub> therapy which is likely consistent across other jurisdictions

#### BACKGROUND:

For over twenty years, oral vitamin B<sub>12</sub> has been referred to as “medicine’s best kept secret” [1].

[Hesitation by clinicians to treat B<sub>12</sub> deficiency with oral preparations dates back to a 1959 report by the U.S.P. Anti-Anemia Preparations Advisory Board suggesting inadequate absorption of oral dosage forms. \[2\]](#) Despite evidence of the effectiveness of oral B<sub>12</sub> therapy [since \[32-98\]](#),



1  
2  
3 intramuscular (IM) administration remains the most commonly prescribed route in North  
4  
5 America [109].  
6  
7

8  
9  
10 Approximately 5% of Canadians are B<sub>12</sub> deficient [110], with Framingham data suggesting that  
11  
12 B<sub>12</sub> deficiency in community-dwelling adults age 67 and older may be as high as 12% [124].  
13

14 Deficiency can occur as a result of gastric atrophy or previous gastric or intestinal surgery, use  
15  
16 of antacids and other medications (metformin), inadequate animal product intake, and a  
17  
18 deficiency in intrinsic factor required for the absorption of cobalamin from the gut [132-143].  
19

20 While the absorbability of oral B<sub>12</sub> has been questioned, a number of studies have reported  
21  
22 successful results with oral therapy including treatment in patients with pernicious anemia or  
23  
24 bowel resection [54, 65, 98, 154]. Since 1% of orally-ingested B<sub>12</sub> is absorbed via passive  
25  
26 diffusion independent of the presence of intrinsic factor [87], daily oral doses of 1000 mcg or  
27  
28 more are considered sufficient to meet daily requirements [165] even in patients with insufficient  
29  
30 intrinsic factor.  
31  
32

33  
34  
35 While oral tablets often cost more to acquire than B<sub>12</sub> injection solution, the costs associated  
36  
37 with administering the injections in the form of health professionals' time and resources can be  
38  
39 significant. A 2001 cost study estimated that between \$2.9-17.6 million could be saved over 5  
40  
41 years in the province of Ontario if elderly patients on IM B<sub>12</sub> were switched to oral therapy  
42  
43 [4617]. In addition, a British study estimated that 2000 nursing hours are required to provide one  
44  
45 year of injections to 492 patients in their homes [187]. Across Canada, only Nova Scotia,  
46  
47 Northwest Territories, Yukon, and the Non-Insured Health Benefits program for First Nations  
48  
49 and Inuit consider oral B<sub>12</sub> tablets to be a benefit in their provincial drug formularies, while all  
50  
51 provinces and territories cover the injectable product.  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 The objective of this study is to estimate the cost savings of treatment using daily oral vitamin  
4  
5 B<sub>12</sub> supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular  
6  
7 injections in Alberta seniors over the age of 65 who are currently using B<sub>12</sub> injection. Such a  
8  
9 study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to  
10  
11 renew discussion about the best allocation of limited healthcare resources and whether oral B<sub>12</sub>  
12  
13 should be covered by all Canadian provincial formularies.  
14  
15

## 16 17 18 **METHODS:** 19

20  
21  
22 **Study Type:** A cost-minimization analysis (CMA) was performed wherein alternatives compared  
23  
24 are considered to be equivalent in terms of factors that are relevant to the decision such as  
25  
26 efficacy and tolerability, so the lowest cost alternative is selected [198]. While a major  
27  
28 assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75  
29  
30 patients on IM therapy) [32-54] and three prospective case series of 151 patients switching from  
31  
32 IM to oral therapy [65, 87, 98] have concluded that the oral route is as clinically effective as the  
33  
34 intramuscular route. Across all case series, no patients switched from IM to oral therapy  
35  
36 required a switch back to IM replacement as a result of therapeutic failure. Costs were modeled  
37  
38 over a period of five years, and the perspective of the Alberta Ministry of Health was adopted for  
39  
40 this study.  
41  
42  
43  
44  
45

46  
47 **Setting / Patients:** The study population consists of individuals aged 65 or older with an Alberta  
48  
49 Health Care number receiving IM B<sub>12</sub> therapy. The number of Alberta seniors dispensed  
50  
51 injectable B<sub>12</sub> over a 1-year period (January-December 2012) was determined from prescription  
52  
53 dispensing records collected by IMS Brogan [2019].  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **Primary Outcome:** Cost-savings achievable by the province of Alberta if patients aged  $\geq 65$  and  
4 currently receiving IM B<sub>12</sub> therapy are switched to oral therapy. Cost savings are estimated in  
5 Canadian currency.  
6  
7  
8  
9

10  
11  
12 **Cost Determination:**

13  
14 All costs are reported in Canadian dollars.  
15

16  
17  
18 Cost of B<sub>12</sub> Tablets: The suggested retail price of Swiss Naturals<sup>®</sup>, Jamieson<sup>®</sup>, and Nature's  
19 Bounty<sup>®</sup> brands of 1000 mcg B<sub>12</sub> tablets were obtained from the manufacturers and averaged to  
20 obtain the cost per tablet. In Alberta, the maximum professional fee allowed for dispensing  
21 products with an acquisition cost of  $\leq \$74.99$  is \$11.93 (consists of \$10.22 professional fee and  
22 \$1.71 inventory allowance) [219].  
23  
24  
25  
26  
27  
28  
29

30  
31 Quantity of B<sub>12</sub> Tablets and Professional Fees: It was assumed that patients would receive a  
32 three-month supply with each fill, therefore amassing four professional fees annually and 365  
33 tablets. Albertans age 65 and older are automatically enrolled into a 'Coverage for Seniors'  
34 program, where the patient co-pay is 30% of the cost to a maximum of \$25 [224]. Since this  
35 study assumes the perspective of the provincial Ministry of Health, the payer is assumed to  
36 cover 70% of the total drug cost. Despite being a non-prescription product, sales tax was not  
37 applied since such tablets would be dispensed through the pharmacy as a tax-free product  
38 similar to a prescription drug.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48

49  
50 Cost of B<sub>12</sub> Injection: Parenteral B<sub>12</sub> in Alberta is available in 10 mL multi-dose vials at a  
51 concentration of 1000 mcg/mL. The cost per mL for the two products currently available in  
52 Alberta (DIN 00521515 and DIN 01987003) were determined from the Alberta Health Drug  
53 Benefit List [232]. In Alberta, the total charge allowable for injectable drugs other than insulin is  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 5/3 of the product's acquisition cost [210]. Therefore, with an acquisition cost of \$4.50 per vial of  
4  
5 parenteral B<sub>12</sub>, the total charge allowed – including the drug and professional fee – cannot  
6  
7 exceed \$7.50, or \$0.75 per dose.  
8  
9

10  
11 Quantity of B<sub>12</sub> injection: At the usual dosage of 1000 mcg/month, one vial contains a ten-month  
12  
13 supply of drug. Therefore, 1.2 vials would be required for a one-year supply.  
14  
15

16  
17 Cost of Additional Laboratory Monitoring: Costs for the laboratory analyses were obtained from  
18  
19 Alberta Health Services, laboratory technicians' time to draw and analyze the blood samples  
20  
21 were estimated by consulting with practicing laboratory technicians, and laboratory technician  
22  
23 wages were obtained from a Government of Alberta occupational survey [243] with a 20% fringe  
24  
25 benefit applied.  
26  
27  
28  
29  
30

31  
32 Quantity of Additional Laboratory Monitoring: To ensure adequate response to therapy, we  
33  
34 assumed that patients to be switched from IM to oral B<sub>12</sub> would receive a baseline complete  
35  
36 blood count and serum B<sub>12</sub> prior to the switch, repeated once after the switch to confirm  
37  
38 effectiveness. It was assumed that this additional monitoring would occur only upon switch from  
39  
40 IM to oral therapy, with long-term monitoring occurring at the same rate as if the patient had  
41  
42 remained on IM injections, therefore representing no additional cost of oral therapy over IM  
43  
44 therapy following the initial switch.  
45  
46  
47  
48

49  
50 Cost of Injection Administration: Currently, physicians, nurses, and pharmacists are authorized  
51  
52 to administer B<sub>12</sub> by intramuscular injection in Alberta. Fees for physician office administration of  
53  
54 injections and pharmacist administration of injections are provided in Table 1.  
55  
56  
57  
58  
59  
60

1  
2  
3 Quantity of Injection Administrations: It is unknown the proportion of patients on IM B<sub>12</sub> therapy  
4 receiving their monthly injections from their physician's office or their pharmacy. For the purpose  
5 of the study, based on the experience of the authors including a practicing pharmacist and  
6 family physician, it was assumed that 25% of all B<sub>12</sub> injections are administered in a community  
7 pharmacy with the remainder administered in a medical clinic.  
8  
9

10  
11  
12 Cost of Additional Physician Visits: The current cost for a standard family physician consultation  
13 visit in Alberta of \$35.91 was utilized in the model.  
14  
15

16  
17  
18 Quantity of Additional Physician Visits: Based on available administrative data, we were unable  
19 to determine the number of additional physician visits received by and billed for patients on IM  
20 versus oral B<sub>12</sub> supplementation apart from simply the administration of the injection in the  
21 medical clinic. For the base case scenario, we assumed that 10% of injections administered in a  
22 physician's office also included a billed physician consultation which would not have occurred if  
23 the patient were not on IM B<sub>12</sub>, and have explored other scenarios in sensitivity analyses as  
24 described below.  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39

#### 40 **Model Assumptions:**

41  
42  
43 A number of assumptions were made with the model in addition to those previously described. It  
44 was assumed that patients on oral B<sub>12</sub> therapy were able to self-administer the medication, and  
45 if assistance was required, it was assumed that they already required this assistance for other  
46 medications rather than solely for B<sub>12</sub> tablets. Since B<sub>12</sub> tablets can be taken concurrently with  
47 other medications, it was not assumed that additional assistance would be needed if oral B<sub>12</sub>  
48 were added to their medication regimen. The cost of supplies to administer the intramuscular  
49 injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

from the model as these are relatively inexpensive and were not felt to significantly contribute to the overall cost of the injectable product.

### Discounting:

Consistent with CADTH guidelines for the economic evaluation of health technologies [24], a discount rate of 5% for outcomes occurring after one year was applied to the reference case, with sensitivity analyses performed around this value as described below.

### Sensitivity Analyses:

Multi-way sensitivity analysis was performed in the form of 10,000 Monte Carlo simulation iterations, adjusting for a number of variables. Model inputs and the probabilistic distributions used in the sensitivity analyses are presented in Table 1. The base case scenario was calculated using the expected value for each variable and assumed a 10% rate of additional physician consultations for patients on intramuscular versus oral therapy.

**Table 1. Expected Values and Distribution Parameters for the Deterministic Model and Probabilistic Sensitivity Analyses**

Parameter	Expected Value $\pm$ SE	Distribution
Study population	28,252 $\pm$ 10%	Gamma
Cost per B <sub>12</sub> tablet	\$0.16 $\pm$ 0.008	Gamma
Professional Fee for Dispensing Tablets [20]	\$11.93	--
Cost per B <sub>12</sub> injectable dose [20-22]	\$0.75	--
Cost for CBC and serum B <sub>12</sub> analyses*	\$6.50	--
Laboratory technician time for blood sample draw and analyses (hours)*	0.75 (range 0.25-1)	Triangular
Laboratory technician wage and benefits [23]*	\$44.60 (range \$35.82-\$51.41)	Triangular
Fee for administration of intramuscular injection in a physician's office [25]	\$10.30	--

Cost for physician consultation visit [25]	\$35.91	--
Fee for administration of intramuscular injection in a pharmacy [26]	\$20.00	--

- SE=Standard Error; CBC=Complete blood count
- \* indicates parameter only included in year 1 of the model
- Normal distribution samples values probabilistically from a normal curve with specified mean (expected value) and standard error. Triangular distribution samples values probabilistically within the range specified, with increasing probability as values near the expected value.

Sensitivity analysis was also performed for different proportions of additional physician office visits including a billed consultation. While the base scenario assumed a 10% rate of office consultations during injection visits, the analyses were repeated for rates of 0% and 25%. Discounting rates of 0% and 3% were also tested in sensitivity analysis.

## RESULTS:

Estimated five-year cost savings associated with switching all Alberta seniors currently receiving injectable B<sub>12</sub> to oral therapy is \$13,975,883. Base scenario and sensitivity analysis results are presented in Table 2. Our model found that even if no additional physician visits were billed for among patients receiving IM therapy, over \$8 million could be saved from reduced administration costs alone.

**Table 2. Model Results Over 5 Years**

Proportion In-Office Injections Including a Fee for a Physician Visit	Discounting Rate for Years 2-5	Mean Cost Saving For Payer	Mean Cost Saving per Patient
<b>Reference Case</b>			
10%	5%	\$13,975,883	\$494.69
<b>Sensitivity Analyses</b>			
0%	0%	\$9,564,224	\$338.53
0%	3%	\$8,878,728	\$314.27



0%	5%	\$8,444,346	\$298.89
10%	0%	\$15,677,500	\$554.92
10%	3%	\$14,635,912	\$518.05
25%	0%	\$24,784,224	\$877.26
25%	3%	\$23,212,469	\$821.62
25%	5%	\$22,216,488	\$786.37

Due to the additional laboratory monitoring performed in the year of the change from IM to oral therapy, the model found the switch to be moderately cost-effective in the first year, with larger savings realized in years 2-5. For the base scenario, cost savings in year 1 were estimated at \$48.34 (SD \$8.58) per patient, increasing to \$126.55 (SD \$2.04) in year 2. Over 5 years, average cost-savings per patient was estimated at \$494.69.

## DISCUSSION:

Over five years, the province of Alberta can be expected to free nearly \$14 million in healthcare costs if all seniors over the age of 65 currently receiving IM B<sub>12</sub> are switched to oral tablets.

Despite evidence confirming that sufficient B<sub>12</sub> is absorbed by passive diffusion at a dose of 1000 mcg daily to be effective even in patients lacking intrinsic factor or with gastrointestinal disease [143], the intramuscular route continues to be commonly prescribed. With high health professional workloads and increasingly restricted healthcare budgets, a switch from IM to oral therapy will not only free health professional resources to see patients at greater need, but can also result in cost-savings for reinvestment into other needed services.

The option of oral supplementation is well received by patients. A Canadian study by Kwong *et al.* found that 73% of patients receiving B<sub>12</sub> injections were willing to try oral B<sub>12</sub>, and of those who tried the oral therapy, 71% wished to permanently remain on oral therapy [87]. Travel



1  
2  
3 inconveniences were the most common reason for preferring the oral route. The authors  
4  
5 concluded that oral therapy would decrease physician burden, increase patient control over  
6  
7 therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding  
8  
9 injections is unknown in adult patients, previous research has suggested that patients with  
10  
11 diabetes value a reduced injection burden as much as they value disease control [287].  
12  
13

14 Therefore, if a societal perspective including utility were considered, it is likely that the benefit of  
15  
16 switching patients from IM to oral therapy would be even greater. Furthermore, the elimination  
17  
18 of risk for injection site reactions following a switch to oral therapy represents another potential  
19  
20 benefit from the patient perspective.  
21  
22

23  
24  
25 A number of assumptions employed in the model have the potential to alter the results in either  
26  
27 direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy  
28  
29 rather than monthly refills, which would be expected to underestimate the cost-saving potential  
30  
31 of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have  
32  
33 also occurred as a result of calculating tablet cost based on non-generic products at higher  
34  
35 costs per tablet. Home care costs for the administration of B<sub>12</sub> injections in home-bound patients  
36  
37 was not included since the proportion of patients receiving in-home injections was unknown,  
38  
39 and it was assumed that these injections would be administered in conjunction with a regular  
40  
41 visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits  
42  
43 are indeed being performed for B<sub>12</sub> injections, then the savings of switching to oral B<sub>12</sub> would  
44  
45 obviously be greater. Importantly, the model also assumed that all patients making the switch to  
46  
47 oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore  
48  
49 representing maximum saving potential. This assumption is consistent with previously published  
50  
51 randomized controlled trials and case series reporting treatment success across all patients  
52  
53 studied [32-98]. Additionally, we assumed in the base scenario that additional laboratory  
54  
55 monitoring is only required for the first year following the switch to oral therapy, with monitoring  
56  
57  
58  
59  
60

1  
2  
3 as usual for the remaining years. Considering that adherence to self-administered oral therapy  
4 may be lower than a healthcare professional-administered injection, even if an additional set of  
5 laboratory tests were performed each year for the 5-year term of the model, estimated cost  
6 savings would still amount to \$12 million.  
7  
8  
9  
10

11  
12  
13  
14 Direct comparison between our model and the results of the 2001 cost-saving paper cannot be  
15 performed due to differing model assumptions and available data. Overall, both models report  
16 significant cost-saving potential of the switch from the perspective of a government payer over  
17 five years. However, due to higher current professional fees for injection administration, our  
18 model found overall cost-savings even if no additional physician visits occurred for patients  
19 receiving B<sub>12</sub> injections, whereas the previous study found a break-even point when 16.3% of  
20 additional physician visits were avoided.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

31 The use of cost-minimization analysis is controversial as it assumes equal efficacy and  
32 tolerability between the two options being compared; however, we feel this assumption is  
33 justifiable based on published data comparing the oral and intramuscular routes [32-98].  
34  
35

36  
37 However, the total number of patients studied in the randomized trials (total n=141 across 3  
38 studies) and case series (n=151) remains relatively small and doses employed across each  
39 study differed. Further research on a larger population, comparing standard-dose IM therapy to  
40 standard-dose oral therapy is therefore recommended and is currently being planned.  
41  
42  
43  
44  
45

46 Additionally, payers considering adding oral B<sub>12</sub> tablets to their formularies should consider  
47 allowing for the coverage of intramuscular therapy in the event of documented treatment failure  
48 on oral supplementation, until larger-scale studies confirming equivalence are conducted, or  
49 allowing for short-term IM therapy for patients with neurologic symptoms followed by oral  
50 maintenance therapy. Indeed, a planned randomized controlled trial of 320 patients age ≥65 in  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Spain will be directly comparing oral to IM B<sub>12</sub> and is expected to examine non-inferiority of oral therapy over one year (clinicaltrials.gov NCT01476007).

Overall, our model estimates that \$8-24 million in cost-savings can be realized over five years if all Alberta seniors currently receiving IM vitamin B<sub>12</sub> are switched to oral therapy. Within closed systems like universal healthcare, this is unlikely to represent true cost savings, but rather room for re-allocation of resources to other health system needs. With an aging population and increasing rates of chronic disease, switching of patients from IM to oral vitamin B<sub>12</sub> replacement appears to be not only clinically efficacious, but also an effective use of limited healthcare resources.

**Competing Interests:** The authors declare no conflicts of interest related to the above work.

**Funding Statement:** No funding was received for completion of this study. Ms. Houle was funded for her graduate studies by the Canadian Institutes of Health Research, Hypertension Canada, and the Interdisciplinary Chronic Disease Collaboration (funded by Alberta Innovates – Health Solutions).

## REFERENCES

1. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret. J Am Med Assoc 1991;**265**:94-5.
2. Bethell FH, Castle WB, Conley CL. Present status of treatment of pernicious anemia: Ninth announcement of the U.S.P. Anti-Anemia Preparations Advisory Board. J Am Med Assoc 1959;171(15):2092-4.
- 2.3. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. Blood 1998;**92**(4):1191-1198.

- 1  
2  
3 | ~~3~~.4. Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T. Oral versus  
4 | intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective,  
5 | randomized, open-label study. *Clin Ther* 2003;**25**(12):3124-3134.  
6  
7  
8  
9  
10 | ~~4~~.5. Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, et al. Comparing  
11 | the Efficacy and Tolerability of a New Daily Oral Vitamin B12 Formulation and Intermittent  
12 | Intramuscular Vitamin B12 in Normalizing Low Cobalamin Levels: A Randomized, Open-  
13 | Label, Parallel-Group Study. *Clin Ther* 2011;**33**(3):358-71.  
14  
15  
16  
17  
18 | ~~5~~.6. Nyholm E, Turpin P, Swain D, Cunningham B, Daly S, Nightingale P, et al. Oral vitamin  
19 | B12 can change our practice. *Postgrad Med J* 2003;**79**:218-220.  
20  
21  
22  
23 | ~~6~~.7. Vidal-Alaball J, Butler C, Cannings-John R, Goringe A, Hood K, McCaddon A, et al. Oral  
24 | vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane*  
25 | *Database of Systematic Reviews* 2005, Issue 3. Art. No.:CD004655.  
26 | DOI:10.1002/14651858.CD004655.pub2.  
27  
28  
29  
30  
31 | ~~7~~.8. Kwong JC, Carr D, Dhalla IA, Tom-Kun D, Upshur REG. Oral vitamin B12 therapy in the  
32 | primary care setting: a qualitative and quantitative study of patient perspectives. *BMC Fam*  
33 | *Pract* 2005;**6**:8.  
34  
35  
36  
37  
38 | ~~8~~.9. Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of  
39 | vitamin B12 without intrinsic factor. *Acta Med Scand* 1968;**184**:247-58.  
40  
41  
42 | ~~9~~.10. Graham ID, Jette N, Tetroe J, Robinson N, Milne S, Mitchell SL. Oral cobalamin remains  
43 | medicine's best kept secret. *Archives of Gerontology and Geriatrics* 2007;**44**(1):49-59.  
44  
45  
46 | ~~10~~.11. MacFarlane AJ, Greene-Finestone LS, Shi Y. Vitamin B-12 and homocysteine status in  
47 | a folate-replete population: results from the Canadian Health Measures Survey. *Am J Clin*  
48 | *Nutr* 2011;**94**:1079-87.  
49  
50  
51 | ~~11~~.12. Lindenbaum J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH. Prevalence of  
52 | cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr* 1994;**60**:2-11.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 | ~~12-13.~~ de Jager J, Kooy A, Lehert P, Wulffele MG, van der Kolk J, Bets D, et al. Long term  
4 | treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency:  
5 | randomized placebo controlled trial. Br Med J 2010;**340**:c2181.  
6  
7  
8  
9  
10 | ~~13-14.~~ Andrès E, Vidal-Alaball J, Federici L, Henoun Loukili N, Zimmer J, Kaltenbach G. Clinical  
11 | aspects of cobalamin deficiency in elderly patients. Epidemiology, causes, clinical  
12 | manifestations, and treatment with special focus on oral cobalamin therapy. Eur J Int Med  
13 | 2007;**18**:456-62.  
14  
15  
16  
17  
18 | ~~14-15.~~ Andrès E, Federici L, Affenberger S, Vidal-Alaball J, Henoun Loukili N, et al. B12  
19 | deficiency: A look beyond pernicious anemia. J Fam Pract 2007;**56**(7):537-42.  
20  
21  
22  
23 | ~~15-16.~~ Health Canada. Dietary Reference Intakes: Reference Values for Vitamins. Accessed 17  
24 | May 2012 at <[http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref\\_vitam\\_tbl-eng.php](http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref_vitam_tbl-eng.php)>.  
25  
26  
27  
28 | ~~16-17.~~ van Walraven CG, Austin P, Naylor CD. Vitamin B12 injections versus oral supplements:  
29 | How much money could be saved by switching from injections to pills? Can Med Assoc J  
30 | 2001;**47**:79-86.  
31  
32  
33  
34 | ~~17-18.~~ Middleton J, Wells W. Vitamin B12 injections: considerable source of work for the district  
35 | nurse. BMJ 1985;**270**:1254-1255.  
36  
37  
38  
39 | ~~18-19.~~ Drummond MF, Sculpher MJ, Torrance G, O'Brien B, Stoddart G. Methods for the  
40 | Economic Evaluation of Health Care Programmes. 3<sup>rd</sup> ed. New York: Oxford University  
41 | Press; 2005.  
42  
43  
44  
45 | ~~19-20.~~ IMS Brogan LRx database, January 2013 and Compuscript audit, January 2013.  
46  
47 | ~~20-21.~~ Alberta Health. Pharmacy fee reimbursement. Retrieved from:  
48 | <http://www.health.alberta.ca/services/pharmacy-fee-reimbursement.html>  
49  
50  
51 | ~~21-22.~~ Alberta Health. Coverage for Seniors. Retrieved from:  
52 | <http://www.health.alberta.ca/services/drugs-seniors.html>  
53  
54  
55 | ~~22-23.~~ Alberta Health. Interactive Drug Benefit List. Retrieved from:  
56 | <https://idbl.ab.bluecross.ca/idbl/load.do>  
57  
58  
59  
60

- 1  
2  
3 | 23-24. Government of Alberta. 2011 Alberta Wage and Salary Data – Medical Laboratory  
4 |  
5 |     Technologist. Retrieved from:  
6 |  
7 |     [http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=ht](http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140)  
8 |     [ml&occpro\\_id=71003140](http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140)  
9 |  
10 |  
11 |  
12 | | 24-25. *Guidelines for the economic evaluation of health technologies: Canada* [3rd Edition].  
13 |  
14 |     Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.  
15 |  
16 | | 25-26. Alberta Health Care Insurance Plan. Medical Price List as of 01 April 2012. Retrieved  
17 |  
18 |     from: <http://www.health.alberta.ca/documents/SOMB-Medical-Prices-2012-04.pdf>  
19 |  
20 |  
21 | | 26-27. Alberta Health. Compensation for Pharmacy Services, July 2012. Retrieved from:  
22 |  
23 |     <http://www.health.alberta.ca/documents/Pharmacy-Services-Compensation-2012.pdf>  
24 |  
25 | | 27-28. Hauber AB, Johnson FR, Sauriol L, Lescrauwaet B. Risking health to avoid injections:  
26 |  
27 |     Preferences of Canadians with type 2 diabetes. *Diabetes Care* 2005;28(9):2243-5.  
28 |  
29 |  
30 |  
31 |  
32 |  
33 |  
34 |  
35 |  
36 |  
37 |  
38 |  
39 |  
40 |  
41 |  
42 |  
43 |  
44 |  
45 |  
46 |  
47 |  
48 |  
49 |  
50 |  
51 |  
52 |  
53 |  
54 |  
55 |  
56 |  
57 |  
58 |  
59 |  
60 |

## EVEREST Statement

	Study section	Additional remarks
<b>Study design</b>		
(1) The research question is stated	Background	
(2) The economic importance of the research question is stated	Background	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods (Study Type); Discussion	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Background; Methods	
(5) The alternatives being compared are clearly described	Methods (Cost Determination)	
(6) The form of economic evaluation used is stated	Methods (Study Type)	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Methods; Discussion	
<b>Data collection</b>		
(8) The source(s) of effectiveness estimates used are stated	Methods (Study Type)	
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A (based on multiple studies)	3 randomized controlled trials and 2 prospective case series
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods (Primary Outcome)	
(12) Methods to value health states and other benefits are stated	N/A	
(13) Details of the subjects from whom valuations were obtained are given	Methods (Setting/Patients)	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods (Cost Determination)	
(17) Methods for the estimation of quantities and unit costs are described	Methods (Cost Determination)	
(18) Currency and price data are recorded	Methods (Primary Outcome)	
(19) Details of currency of price adjustments for inflation or currency conversion are given	N/A	



(20) Details of any model used are given	Methods (Model Assumptions, Discounting, Sensitivity Analyses)	
(21) The choice of model used and the key parameters on which it is based are justified	Methods (Study Type); Discussion	
<b>Analysis and interpretation of results</b>		
(22) Time horizon of costs and benefits is stated	Methods (Study Type)	
(23) The discount rate(s) is stated	Methods (Discounting)	
(24) The choice of rate(s) is justified	Methods (Discounting)	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods (Sensitivity Analyses)	
(28) The choice of variables for sensitivity analysis is justified	Methods (Sensitivity Analyses)	
(29) The ranges over which the variables are varied are stated	Table 1	
(30) Relevant alternatives are compared	Introduction	
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	N/A	
(33) The answer to the study question is given	Results; Discussion	
(34) Conclusions follow from the data reported	Discussion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	