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

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ABSTRACT:

Objectives: The aim of this study is to estimate the cost-savings attainable if all patients aged ≥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_{12} therapy.

Intervention: Oral vitamin B_{12} 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_{12} 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_{12} therapy has been shown to be an effective therapeutic option for patients with vitamin B_{12} 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_{12} therapy as a clinically- and cost-effective first line therapy for vitamin B_{12} 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_{12} 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_{12} therapy which is likely consistent across other jurisdictions

BACKGROUND:

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

Approximately 5% of Canadians are B_{12} deficient [9], with Framingham data suggesting that B_{12} deficiency in community-dwelling adults age 67 and older may be as high as 12% [10]. 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 [11-12]. While the absorbability of oral B_{12} 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, 13]. Since 1% of orally-ingested B_{12} 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 [14] even in patients with insufficient intrinsic factor.

While oral tablets often cost more to acquire than B_{12} 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_{12} were switched to oral therapy [15]. In addition, a British study estimated that 2000 nursing hours are required to provide one year of injections to 492 patients in their homes [16]. Across Canada, only Nova Scotia, Northwest Territories, Yukon, and the Non-Insured Health Benefits program for First Nations and Inuit consider oral B_{12} tablets to be a benefit in their provincial drug formularies, while all provinces and territories cover the injectable product.

The objective of this study is to estimate the cost savings of treatment using daily oral vitamin B_{12} supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular injections in Alberta seniors over the age of 65 who are currently using B_{12} injection. Such a study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to renew discussion about the best allocation of limited healthcare resources and whether oral B_{12} 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 [17]. 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 two prospective case series of 87 patients switching from IM to oral therapy [5, 7] have concluded that the oral route is as clinically effective as the intramuscular route. Across both 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_{12} therapy. The number of Alberta seniors dispensed injectable B_{12} over a 1-year period (January-December 2012) was determined from prescription dispensing records collected by IMS Brogan [18].

Primary Outcome: Cost-savings achievable by the province of Alberta if patients aged ≥65 and currently receiving IM B_{12} therapy are switched to oral therapy. Cost savings are estimated in Canadian currency.

Cost Determination:

Cost of B_{12} Tablets: The suggested retail price of Swiss Naturals®, Jamieson®, and Nature's Bounty® brands of 1000 mcg B_{12} 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) [19].

Quantity of B_{12} 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 [20]. 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_{12} Injection: Parenteral B_{12} 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 [21]. In Alberta, the total charge allowable for injectable drugs other than insulin is 5/3 of the product's acquisition cost [19]. Therefore, with an acquisition cost of $4.50 per vial of parenteral B_{12}, the total charge allowed – including the drug and professional fee – cannot exceed $7.50, or $0.75 per dose.

Quantity of B_{12} 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 [22] 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_{12} would receive a baseline complete blood count and serum B_{12} 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_{12} by intramuscular injection in Alberta. Fees for physician office administration of injections and pharmacist administration of injections are provided in Table 1.

Quantity of Injection Administrations: It is unknown the proportion of patients on IM B_{12} therapy receiving their monthly injections from their physician's office or their pharmacy. For the purpose of the study, based on the experience of the authors including a practicing pharmacist and family physician, it was assumed that 25% of all B_{12} injections are administered in a community pharmacy with the remainder administered in a medical clinic.

Cost of Additional Physician Visits: The current cost for a standard family physician consultation visit in Alberta of $35.91 was utilized in the model.

Quantity of Additional Physician Visits: Based on available administrative data, we were unable to determine the number of additional physician visits received by and billed for patients on IM versus oral B_{12} supplementation apart from simply the administration of the injection in the medical clinic. For the base case scenario, we assumed that 10% of injections administered in a physician's office also included a billed physician consultation which would not have occurred if the patient were not on IM B_{12}, and have explored other scenarios in sensitivity analyses as described below.

Model Assumptions:

A number of assumptions were made with the model in addition to those previously described. It was assumed that patients on oral B_{12} therapy were able to self-administer the medication, and if assistance was required, it was assumed that they already required this assistance for other medications rather than solely for B_{12} tablets. Since B_{12} tablets can be taken concurrently with other medications, it was not assumed that additional assistance would be needed if oral B_{12} were added to their medication regimen. The cost of supplies to administer the intramuscular injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded 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 [23], 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 ± SE	Distribution
Study population	28,252 ± 10%	Gamma
Cost per B_{12} tablet	$0.16 ± 0.008	Gamma
Professional Fee for Dispensing Tablets [19]	$11.93	--
Cost per B_{12} injectable dose [19-21]	$0.75	--
Cost for CBC and serum B_{12} 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_{12} 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
Reference Case			
10%	5%	$13,975,883	$494.69
Sensitivity Analyses			
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_{12} are switched to oral tablets. Despite evidence confirming that sufficient B_{12} 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 [12], 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_{12} injections were willing to try oral B_{12}, and of those who tried the oral therapy, 71% wished to permanently remain on oral therapy [7]. Travel inconveniences were the most common reason for preferring the oral route. The authors concluded that oral therapy would decrease physician burden, increase patient control over therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding injections is unknown in adult patients, previous research has suggested that patients with diabetes value a reduced injection burden as much as they value disease control [26]. Therefore, if a societal perspective including utility were considered, it is likely that the benefit of switching patients from IM to oral therapy would be even greater.

A number of assumptions employed in the model have the potential to alter the results in either direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy rather than monthly refills, which would be expected to underestimate the cost-saving potential of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have also occurred as a result of calculating tablet cost based on non-generic products at higher costs per tablet. Home care costs for the administration of B_{12} injections in home-bound patients was not included since the proportion of patients receiving in-home injections was unknown, and it was assumed that these injections would be administered in conjunction with a regular visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits are indeed being performed for B_{12} injections, then the savings of switching to oral B_{12} would obviously be greater. Importantly, the model also assumed that all patients making the switch to oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore representing maximum saving potential. This assumption is consistent with previously published randomized controlled trials and case series reporting treatment success across all patients studied [2-7].

Direct comparison between our model and the results of the 2001 cost-saving paper cannot be performed due to differing model assumptions and available data. Overall, both models report significant cost-saving potential of the switch from the perspective of a government payer over five years. However, due to higher current professional fees for injection administration, our model found overall cost-savings even if no additional physician visits occurred for patients receiving B_{12} injections, whereas the previous study found a break-even point when 16.3% of additional physician visits were avoided.

The use of cost-minimization analysis is controversial as it assumes equal efficacy and tolerability between the two options being compared; however, we feel this assumption is justifiable based on published data comparing the oral and intramuscular routes [2-7]. However, the total number of patients studied in the randomized trials (total n=141 across 3 studies) and case series (n=87) remains relatively small and doses employed across each study differed. Further research on a larger population, comparing standard-dose IM therapy to standard-dose oral therapy is therefore recommended and is currently being planned. Additionally, payers considering adding oral B_{12} tablets to their formularies should consider allowing for the coverage of intramuscular therapy in the event of documented treatment failure on oral supplementation, until larger-scale studies confirming equivalence are conducted. Indeed, a planned randomized controlled trial of 320 patients age ≥65 in Spain will be directly comparing oral to IM B_{12} 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_{12} 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_{12} 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.

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EVEREST Statement

	Study section	Additional remarks
Study design		
(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	
Data collection		
(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	
Analysis and interpretation of results		
(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	

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Approximately 5% of Canadians are B_{12} deficient [10], with Framingham data suggesting that B_{12} 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_{12} 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_{12} 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_{12} 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_{12} 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 consider oral B_{12} tablets to be a benefit in their provincial drug formularies, while all provinces and territories cover the injectable product.

The objective of this study is to estimate the cost savings of treatment using daily oral vitamin B_{12} supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular injections in Alberta seniors over the age of 65 who are currently using B_{12} injection. Such a study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to renew discussion about the best allocation of limited healthcare resources and whether oral B_{12} 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 [18]. 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 three prospective case series of 151 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 all 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_{12} therapy. The number of Alberta seniors dispensed injectable B_{12} over a 1-year period (January-December 2012) was determined from prescription dispensing records collected by IMS Brogan [19].

Primary Outcome: Cost-savings achievable by the province of Alberta if patients aged ≥65 and currently receiving IM B_{12} therapy are switched to oral therapy. Cost savings are estimated in Canadian currency.

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All costs are reported in Canadian dollars.

Cost of B_{12} Tablets: The suggested retail price of Swiss Naturals®, Jamieson®, and Nature's Bounty® brands of 1000 mcg B_{12} 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) [20].

Quantity of B_{12} 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 [21]. 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.

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Quantity of Additional Laboratory Monitoring: To ensure adequate response to therapy, we assumed that patients to be switched from IM to oral B_{12} would receive a baseline complete blood count and serum B_{12} 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.

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

<u>Quantity of Injection Administrations:</u> It is unknown the proportion of patients on IM B_{12} therapy receiving their monthly injections from their physician's office or their pharmacy. For the purpose of the study, based on the experience of the authors including a practicing pharmacist and family physician, it was assumed that 25% of all B_{12} injections are administered in a community pharmacy with the remainder administered in a medical clinic.

<u>Cost of Additional Physician Visits:</u> The current cost for a standard family physician consultation visit in Alberta of $35.91 was utilized in the model.

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Model Assumptions:

A number of assumptions were made with the model in addition to those previously described. It was assumed that patients on oral B_{12} therapy were able to self-administer the medication, and if assistance was required, it was assumed that they already required this assistance for other medications rather than solely for B_{12} tablets. Since B_{12} tablets can be taken concurrently with other medications, it was not assumed that additional assistance would be needed if oral B_{12} were added to their medication regimen. The cost of supplies to administer the intramuscular injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded 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 ± SE	Distribution
Study population	28,252 ± 10%	Gamma
Cost per B_{12} tablet	$0.16 ± 0.008	Gamma
Professional Fee for Dispensing Tablets [20]	$11.93	--

Cost per B_{12} injectable dose [20-22]	$0.75	--
Cost for CBC and serum B_{12} 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_{12} 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

a Physician Visit			
Reference Case			
10%	5%	$13,975,883	$494.69
Sensitivity Analyses			
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_{12} are switched to oral tablets. Despite evidence confirming that sufficient B_{12} 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.

The option of oral supplementation is well received by patients. A Canadian study by Kwong *et al.* found that 73% of patients receiving B_{12} injections were willing to try oral B_{12}, and of those who tried the oral therapy, 71% wished to permanently remain on oral therapy [7]. Travel inconveniences were the most common reason for preferring the oral route. The authors concluded that oral therapy would decrease physician burden, increase patient control over therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding injections is unknown in adult patients, previous research has suggested that patients with diabetes value a reduced injection burden as much as they value disease control [27]. Therefore, if a societal perspective including utility were considered, it is likely that the benefit of switching patients from IM to oral therapy would be even greater. Furthermore, the elimination of risk for injection site reactions following a switch to oral therapy represents another potential benefit from the patient perspective.

A number of assumptions employed in the model have the potential to alter the results in either direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy rather than monthly refills, which would be expected to underestimate the cost-saving potential of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have also occurred as a result of calculating tablet cost based on non-generic products at higher costs per tablet. Home care costs for the administration of B_{12} injections in home-bound patients was not included since the proportion of patients receiving in-home injections was unknown, and it was assumed that these injections would be administered in conjunction with a regular visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits are indeed being performed for B_{12} injections, then the savings of switching to oral B_{12} would obviously be greater. Importantly, the model also assumed that all patients making the switch to oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore representing maximum saving potential. This assumption is consistent with previously published randomized controlled trials and case series reporting treatment success across all patients studied [2-8]. Additionally, we assumed in the base scenario that additional laboratory monitoring is only required for the first year following the switch to oral therapy, with monitoring as usual for the remaining years. Considering that adherence to self-administered oral therapy may be lower than a healthcare professional-administered injection, even if an additional set of laboratory tests were performed each year for the 5-year term of the model, estimated cost savings would still amount to $12 million.

Direct comparison between our model and the results of the 2001 cost-saving paper cannot be performed due to differing model assumptions and available data. Overall, both models report significant cost-saving potential of the switch from the perspective of a government payer over five years. However, due to higher current professional fees for injection administration, our model found overall cost-savings even if no additional physician visits occurred for patients receiving B_{12} injections, whereas the previous study found a break-even point when 16.3% of additional physician visits were avoided.

The use of cost-minimization analysis is controversial as it assumes equal efficacy and tolerability between the two options being compared; however, we feel this assumption is justifiable based on published data comparing the oral and intramuscular routes [2-8]. However, the total number of patients studied in the randomized trials (total n=141 across 3 studies) and case series (n=151) remains relatively small and doses employed across each study differed. Further research on a larger population, comparing standard-dose IM therapy to standard-dose oral therapy is therefore recommended and is currently being planned. Additionally, payers considering adding oral B_{12} tablets to their formularies should consider allowing for the coverage of intramuscular therapy in the event of documented treatment failure on oral supplementation, until larger-scale studies confirming equivalence are conducted, or allowing for short-term IM therapy for patients with neurologic symptoms followed by oral maintenance therapy. Indeed, a planned randomized controlled trial of 320 patients age ≥65 in Spain will be directly comparing oral to IM B_{12} 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_{12} 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_{12} replacement appears to be not only clinically efficacious, but also an effective use of limited healthcare resources.

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Contributorship Statement: All authors (Dr. Houle, Dr. Kolber, and Dr. Chuck) contributed to the design and analysis/interpretation of data, drafting of the article, and approval of the final version.

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

Data Sharing Statement: There is no additional unpublished data related to this study.

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Should Vitamin B_{12} 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_{12} Maintenance Therapy for Alberta Seniors

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Keywords: Cost analysis, healthcare costs, vitamin B_{12} deficiency

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ABSTRACT:

Objectives: The aim of this study is to estimate the cost-savings attainable if all patients aged ≥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_{12} therapy.

Intervention: Oral vitamin B_{12} 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_{12} 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_{12} therapy has been shown to be an effective therapeutic option for patients with vitamin B_{12} 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_{12} therapy as a clinically- and cost-effective first line therapy for vitamin B_{12} 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_{12} 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_{12} therapy which is likely consistent across other jurisdictions

BACKGROUND:

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Quantity of Additional Physician Visits: Based on available administrative data, we were unable to determine the number of additional physician visits received by and billed for patients on IM versus oral B_{12} supplementation apart from simply the administration of the injection in the medical clinic. For the base case scenario, we assumed that 10% of injections administered in a physician's office also included a billed physician consultation which would not have occurred if the patient were not on IM B_{12}, and have explored other scenarios in sensitivity analyses as described below.

Model Assumptions:

A number of assumptions were made with the model in addition to those previously described. It was assumed that patients on oral B_{12} therapy were able to self-administer the medication, and if assistance was required, it was assumed that they already required this assistance for other medications rather than solely for B_{12} tablets. Since B_{12} tablets can be taken concurrently with other medications, it was not assumed that additional assistance would be needed if oral B_{12} were added to their medication regimen. The cost of supplies to administer the intramuscular injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded 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 [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 ± SE	Distribution
Study population	28,252 ± 10%	Gamma
Cost per B_{12} tablet	$0.16 ± 0.008	Gamma
Professional Fee for Dispensing Tablets [2019]	$11.93	--
Cost per B_{12} injectable dose [2019-221]	$0.75	--
Cost for CBC and serum B_{12} 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_{12} 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
Reference Case			
10%	5%	$13,975,883	$494.69
Sensitivity Analyses			
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_{12} are switched to oral tablets. Despite evidence confirming that sufficient B_{12} 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~~2~~], 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_{12} injections were willing to try oral B_{12}, and of those who tried the oral therapy, 71% wished to permanently remain on oral therapy [7]. Travel inconveniences were the most common reason for preferring the oral route. The authors concluded that oral therapy would decrease physician burden, increase patient control over therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding injections is unknown in adult patients, previous research has suggested that patients with diabetes value a reduced injection burden as much as they value disease control [27~~6~~]. Therefore, if a societal perspective including utility were considered, it is likely that the benefit of switching patients from IM to oral therapy would be even greater. Furthermore, the elimination of risk for injection site reactions following a switch to oral therapy represents another potential benefit from the patient perspective.

A number of assumptions employed in the model have the potential to alter the results in either direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy rather than monthly refills, which would be expected to underestimate the cost-saving potential of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have also occurred as a result of calculating tablet cost based on non-generic products at higher costs per tablet. Home care costs for the administration of B_{12} injections in home-bound patients was not included since the proportion of patients receiving in-home injections was unknown, and it was assumed that these injections would be administered in conjunction with a regular visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits are indeed being performed for B_{12} injections, then the savings of switching to oral B_{12} would obviously be greater. Importantly, the model also assumed that all patients making the switch to oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore representing maximum saving potential. This assumption is consistent with previously published randomized controlled trials and case series reporting treatment success across all patients studied [2-8~~7~~]. Additionally, we assumed in the base scenario that additional laboratory monitoring is only required for the first year following the switch to oral therapy, with monitoring as usual for the remaining years. Considering that adherence to self-administered oral therapy may be lower than a healthcare professional-administered injection, even if an additional set of laboratory tests were performed each year for the 5-year term of the model, estimated cost savings would still amount to $12 million.

Direct comparison between our model and the results of the 2001 cost-saving paper cannot be performed due to differing model assumptions and available data. Overall, both models report significant cost-saving potential of the switch from the perspective of a government payer over five years. However, due to higher current professional fees for injection administration, our model found overall cost-savings even if no additional physician visits occurred for patients receiving B_{12} injections, whereas the previous study found a break-even point when 16.3% of additional physician visits were avoided.

The use of cost-minimization analysis is controversial as it assumes equal efficacy and tolerability between the two options being compared; however, we feel this assumption is justifiable based on published data comparing the oral and intramuscular routes [2-87]. However, the total number of patients studied in the randomized trials (total n=141 across 3 studies) and case series (n=15187) remains relatively small and doses employed across each study differed. Further research on a larger population, comparing standard-dose IM therapy to standard-dose oral therapy is therefore recommended and is currently being planned. Additionally, payers considering adding oral B_{12} tablets to their formularies should consider allowing for the coverage of intramuscular therapy in the event of documented treatment failure on oral supplementation, until larger-scale studies confirming equivalence are conducted, or allowing for short-term IM therapy for patients with neurologic symptoms followed by oral maintenance therapy. Indeed, a planned randomized controlled trial of 320 patients age ≥65 in Spain will be directly comparing oral to IM B_{12} 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_{12} 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_{12} 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.

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EVEREST Statement

	Study section	Additional remarks
Study design		
(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	
Data collection		
(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	
Analysis and interpretation of results		
(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	

BMJ open

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

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Should Vitamin B_{12} 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_{12} Maintenance Therapy for Alberta Seniors

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Keywords: Cost analysis, healthcare costs, vitamin B_{12} deficiency

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ABSTRACT:

Objectives: The aim of this study is to estimate the cost-savings attainable if all patients aged ≥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_{12} therapy.

Intervention: Oral vitamin B_{12} 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_{12} 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_{12} therapy has been shown to be an effective therapeutic option for patients with vitamin B_{12} 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_{12} therapy as a clinically- and cost-effective first line therapy for vitamin B_{12} 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_{12} 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_{12} therapy which is likely consistent across other jurisdictions

BACKGROUND:

For over twenty years, oral vitamin B_{12} has been referred to as "medicine's best kept secret" [1]. Hesitation by clinicians to treat B_{12} 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_{12} therapy since [3-9], intramuscular (IM) administration remains the most commonly prescribed route in North America [10].

Approximately 5% of Canadians are B_{12} deficient [11], with Framingham data suggesting that B_{12} deficiency in community-dwelling adults age 67 and older may be as high as 12% [12]. 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 [13-14]. While the absorbability of oral B_{12} has been questioned, a number of studies have reported successful results with oral therapy including treatment in patients with pernicious anemia or bowel resection [5, 6, 9, 15]. Since 1% of orally-ingested B_{12} is absorbed via passive diffusion independent of the presence of intrinsic factor [8], daily oral doses of 1000 mcg or more are considered sufficient to meet daily requirements [16] even in patients with insufficient intrinsic factor.

While oral tablets often cost more to acquire than B_{12} 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_{12} were switched to oral therapy [17]. In addition, a British study estimated that 2000 nursing hours are required to provide one year of injections to 492 patients in their homes [18]. Across Canada, only Nova Scotia, Northwest Territories, Yukon, and the Non-Insured Health Benefits program for First Nations and Inuit consider oral B_{12} tablets to be a benefit in their provincial drug formularies, while all provinces and territories cover the injectable product.

The objective of this study is to estimate the cost savings of treatment using daily oral vitamin B_{12} supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular injections in Alberta seniors over the age of 65 who are currently using B_{12} injection. Such a study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to renew discussion about the best allocation of limited healthcare resources and whether oral B_{12} 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 [19]. While a major assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75 patients on IM therapy) [3-5] and three prospective case series of 151 patients switching from IM to oral therapy [6, 8, 9] have concluded that the oral route is as clinically effective as the intramuscular route. Across all 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_{12} therapy. The number of Alberta seniors dispensed injectable B_{12} over a 1-year period (January-December 2012) was determined from prescription dispensing records collected by IMS Brogan [20].

Primary Outcome: Cost-savings achievable by the province of Alberta if patients aged ≥65 and currently receiving IM B_{12} 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_{12} Tablets: The suggested retail price of Swiss Naturals®, Jamieson®, and Nature's Bounty® brands of 1000 mcg B_{12} 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) [21].

Quantity of B_{12} 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 [22]. 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_{12} Injection: Parenteral B_{12} 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 [23]. In Alberta, the total charge allowable for injectable drugs other than insulin is

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

Quantity of B_{12} 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_{12} would receive a baseline complete blood count and serum B_{12} 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_{12} by intramuscular injection in Alberta. Fees for physician office administration of injections and pharmacist administration of injections are provided in Table 1.

Quantity of Injection Administrations: It is unknown the proportion of patients on IM B_{12} therapy receiving their monthly injections from their physician's office or their pharmacy. For the purpose of the study, based on the experience of the authors including a practicing pharmacist and family physician, it was assumed that 25% of all B_{12} injections are administered in a community pharmacy with the remainder administered in a medical clinic.

Cost of Additional Physician Visits: The current cost for a standard family physician consultation visit in Alberta of $35.91 was utilized in the model.

Quantity of Additional Physician Visits: Based on available administrative data, we were unable to determine the number of additional physician visits received by and billed for patients on IM versus oral B_{12} supplementation apart from simply the administration of the injection in the medical clinic. For the base case scenario, we assumed that 10% of injections administered in a physician's office also included a billed physician consultation which would not have occurred if the patient were not on IM B_{12}, and have explored other scenarios in sensitivity analyses as described below.

Model Assumptions:

A number of assumptions were made with the model in addition to those previously described. It was assumed that patients on oral B_{12} therapy were able to self-administer the medication, and if assistance was required, it was assumed that they already required this assistance for other medications rather than solely for B_{12} tablets. Since B_{12} tablets can be taken concurrently with other medications, it was not assumed that additional assistance would be needed if oral B_{12} were added to their medication regimen. The cost of supplies to administer the intramuscular injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded 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 ± SE	Distribution
Study population	28,252 ± 10%	Gamma
Cost per B_{12} tablet	$0.16 ± 0.008	Gamma
Professional Fee for Dispensing Tablets [20]	$11.93	--
Cost per B_{12} injectable dose [20-22]	$0.75	--
Cost for CBC and serum B_{12} 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
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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_{12} 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
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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_{12} are switched to oral tablets. Despite evidence confirming that sufficient B_{12} 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_{12} injections were willing to try oral B_{12}, and of those who tried the oral therapy, 71% wished to permanently remain on oral therapy [8]. Travel inconveniences were the most common reason for preferring the oral route. The authors concluded that oral therapy would decrease physician burden, increase patient control over therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding injections is unknown in adult patients, previous research has suggested that patients with diabetes value a reduced injection burden as much as they value disease control [28]. Therefore, if a societal perspective including utility were considered, it is likely that the benefit of switching patients from IM to oral therapy would be even greater. Furthermore, the elimination of risk for injection site reactions following a switch to oral therapy represents another potential benefit from the patient perspective.

A number of assumptions employed in the model have the potential to alter the results in either direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy rather than monthly refills, which would be expected to underestimate the cost-saving potential of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have also occurred as a result of calculating tablet cost based on non-generic products at higher costs per tablet. Home care costs for the administration of B_{12} injections in home-bound patients was not included since the proportion of patients receiving in-home injections was unknown, and it was assumed that these injections would be administered in conjunction with a regular visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits are indeed being performed for B_{12} injections, then the savings of switching to oral B_{12} would obviously be greater. Importantly, the model also assumed that all patients making the switch to oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore representing maximum saving potential. This assumption is consistent with previously published randomized controlled trials and case series reporting treatment success across all patients studied [3-9]. Additionally, we assumed in the base scenario that additional laboratory monitoring is only required for the first year following the switch to oral therapy, with monitoring as usual for the remaining years. Considering that adherence to self-administered oral therapy may be lower than a healthcare professional-administered injection, even if an additional set of laboratory tests were performed each year for the 5-year term of the model, estimated cost savings would still amount to $12 million.

Direct comparison between our model and the results of the 2001 cost-saving paper cannot be performed due to differing model assumptions and available data. Overall, both models report significant cost-saving potential of the switch from the perspective of a government payer over five years. However, due to higher current professional fees for injection administration, our model found overall cost-savings even if no additional physician visits occurred for patients receiving B_{12} injections, whereas the previous study found a break-even point when 16.3% of additional physician visits were avoided.

The use of cost-minimization analysis is controversial as it assumes equal efficacy and tolerability between the two options being compared; however, we feel this assumption is justifiable based on published data comparing the oral and intramuscular routes [3-9]. However, the total number of patients studied in the randomized trials (total n=141 across 3 studies) and case series (n=151) remains relatively small and doses employed across each study differed. Further research on a larger population, comparing standard-dose IM therapy to standard-dose oral therapy is therefore recommended and is currently being planned. Additionally, payers considering adding oral B_{12} tablets to their formularies should consider allowing for the coverage of intramuscular therapy in the event of documented treatment failure on oral supplementation, until larger-scale studies confirming equivalence are conducted, or allowing for short-term IM therapy for patients with neurologic symptoms followed by oral maintenance therapy. Indeed, a planned randomized controlled trial of 320 patients age ≥65 in Spain will be directly comparing oral to IM B_{12} 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_{12} 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_{12} replacement appears to be not only clinically efficacious, but also an effective use of limited healthcare resources.

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Contributorship Statement: All authors (Dr. Houle, Dr. Kolber, and Dr. Chuck) contributed to the design and analysis/interpretation of data, drafting of the article, and approval of the final version.

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

Data Sharing Statement: There is no additional unpublished data related to this study.

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Should Vitamin B_{12} 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_{12} Maintenance Therapy for Alberta Seniors

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Keywords: Cost analysis, healthcare costs, vitamin B_{12} deficiency

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ABSTRACT:

Objectives: The aim of this study is to estimate the cost-savings attainable if all patients aged ≥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_{12} therapy.

Intervention: Oral vitamin B_{12} 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_{12} 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_{12} therapy has been shown to be an effective therapeutic option for patients with vitamin B_{12} 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_{12} therapy as a clinically- and cost-effective first line therapy for vitamin B_{12} 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_{12} 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_{12} therapy which is likely consistent across other jurisdictions

BACKGROUND:

For over twenty years, oral vitamin B_{12} has been referred to as “medicine’s best kept secret” [1]. Hesitation by clinicians to treat B_{12} 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_{12} therapy since [3~~2~~-9~~8~~], intramuscular (IM) administration remains the most commonly prescribed route in North America [109].

Approximately 5% of Canadians are B_{12} deficient [110], with Framingham data suggesting that B_{12} deficiency in community-dwelling adults age 67 and older may be as high as 12% [121]. 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 [132-143]. While the absorbability of oral B_{12} has been questioned, a number of studies have reported successful results with oral therapy including treatment in patients with pernicious anemia or bowel resection [54, 65, 98, 154]. Since 1% of orally-ingested B_{12} is absorbed via passive diffusion independent of the presence of intrinsic factor [87], daily oral doses of 1000 mcg or more are considered sufficient to meet daily requirements [165] even in patients with insufficient intrinsic factor.

While oral tablets often cost more to acquire than B_{12} 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_{12} were switched to oral therapy [1617]. In addition, a British study estimated that 2000 nursing hours are required to provide one year of injections to 492 patients in their homes [187]. Across Canada, only Nova Scotia, Northwest Territories, Yukon, and the Non-Insured Health Benefits program for First Nations and Inuit consider oral B_{12} tablets to be a benefit in their provincial drug formularies, while all provinces and territories cover the injectable product.

The objective of this study is to estimate the cost savings of treatment using daily oral vitamin B_{12} supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular injections in Alberta seniors over the age of 65 who are currently using B_{12} injection. Such a study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to renew discussion about the best allocation of limited healthcare resources and whether oral B_{12} 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 [19~~8~~]. While a major assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75 patients on IM therapy) [3~~2~~-5~~4~~] and three prospective case series of 151 patients switching from IM to oral therapy [6~~5~~, 8~~7~~, 9~~8~~] have concluded that the oral route is as clinically effective as the intramuscular route. Across all 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_{12} therapy. The number of Alberta seniors dispensed injectable B_{12} over a 1-year period (January-December 2012) was determined from prescription dispensing records collected by IMS Brogan [20~~19~~].

Primary Outcome: Cost-savings achievable by the province of Alberta if patients aged ≥65 and currently receiving IM B_{12} 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_{12} Tablets: The suggested retail price of Swiss Naturals®, Jamieson®, and Nature's Bounty® brands of 1000 mcg B_{12} 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) [2~~1~~0].

Quantity of B_{12} 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 [2~~2~~1]. 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_{12} Injection: Parenteral B_{12} 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 [2~~3~~2]. In Alberta, the total charge allowable for injectable drugs other than insulin is

5/3 of the product's acquisition cost [21~~0~~]. Therefore, with an acquisition cost of $4.50 per vial of parenteral B_{12}, the total charge allowed – including the drug and professional fee – cannot exceed $7.50, or $0.75 per dose.

<u>Quantity of B_{12} injection:</u> 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.

<u>Cost of Additional Laboratory Monitoring:</u> 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~~3~~] with a 20% fringe benefit applied.

<u>Quantity of Additional Laboratory Monitoring:</u> To ensure adequate response to therapy, we assumed that patients to be switched from IM to oral B_{12} would receive a baseline complete blood count and serum B_{12} 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.

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

Quantity of Injection Administrations: It is unknown the proportion of patients on IM B_{12} therapy receiving their monthly injections from their physician's office or their pharmacy. For the purpose of the study, based on the experience of the authors including a practicing pharmacist and family physician, it was assumed that 25% of all B_{12} injections are administered in a community pharmacy with the remainder administered in a medical clinic.

Cost of Additional Physician Visits: The current cost for a standard family physician consultation visit in Alberta of $35.91 was utilized in the model.

Quantity of Additional Physician Visits: Based on available administrative data, we were unable to determine the number of additional physician visits received by and billed for patients on IM versus oral B_{12} supplementation apart from simply the administration of the injection in the medical clinic. For the base case scenario, we assumed that 10% of injections administered in a physician's office also included a billed physician consultation which would not have occurred if the patient were not on IM B_{12}, and have explored other scenarios in sensitivity analyses as described below.

Model Assumptions:

A number of assumptions were made with the model in addition to those previously described. It was assumed that patients on oral B_{12} therapy were able to self-administer the medication, and if assistance was required, it was assumed that they already required this assistance for other medications rather than solely for B_{12} tablets. Since B_{12} tablets can be taken concurrently with other medications, it was not assumed that additional assistance would be needed if oral B_{12} were added to their medication regimen. The cost of supplies to administer the intramuscular injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded 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 ± SE	Distribution
Study population	28,252 ± 10%	Gamma
Cost per B_{12} tablet	$0.16 ± 0.008	Gamma
Professional Fee for Dispensing Tablets [20]	$11.93	--
Cost per B_{12} injectable dose [20-22]	$0.75	--
Cost for CBC and serum B_{12} 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.

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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_{12} are switched to oral tablets. Despite evidence confirming that sufficient B_{12} 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.

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The use of cost-minimization analysis is controversial as it assumes equal efficacy and tolerability between the two options being compared; however, we feel this assumption is justifiable based on published data comparing the oral and intramuscular routes [32-98]. However, the total number of patients studied in the randomized trials (total n=141 across 3 studies) and case series (n=151) remains relatively small and doses employed across each study differed. Further research on a larger population, comparing standard-dose IM therapy to standard-dose oral therapy is therefore recommended and is currently being planned. Additionally, payers considering adding oral B_{12} tablets to their formularies should consider allowing for the coverage of intramuscular therapy in the event of documented treatment failure on oral supplementation, until larger-scale studies confirming equivalence are conducted, or allowing for short-term IM therapy for patients with neurologic symptoms followed by oral maintenance therapy. Indeed, a planned randomized controlled trial of 320 patients age ≥65 in

Spain will be directly comparing oral to IM B_{12} 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_{12} 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_{12} 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.

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EVEREST Statement

	Study section	Additional remarks
Study design		
(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	
Data collection		
(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	
Analysis and interpretation of results		
(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	