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Model-based cost-impact analysis of a diagnostic test for patients with community-acquired pneumonia in Canada

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Abstract

Background Antibiotics are broadly prescribed for community-acquired pneumonia (CAP) despite being only effective for bacterial infections. LIAISON® MeMed BV® (LMMBV) is a novel diagnostic test that can support clinicians in differentiating bacterial from viral infections and guide diagnostic-driven antibiotic prescribing.

Methods We developed a cost-impact model to compare the clinical and economic outcomes of using LMMBV with the current standard of care (SOC) versus SOC alone among a hypothetical cohort of 1,000 CAP patients presenting to the emergency department. The analysis was conducted from a Canadian public health payer's perspective. Outcomes of interest included antibiotic use (number of patients and days saved), hospital admission (admissions avoided and days saved), intensive care unit admission, adverse events, and clostridium difficile infection. One-way sensitivity analyses were conducted to explore parameter uncertainty. Scenario analyses were conducted according to age group, province, and impact of LMMBV on hospitalization.

Results In the base case, LMMBV plus SOC reduced the number of patients prescribed antibiotic treatment (429 patients avoided) and the total number of antibiotic treatment days (1,020 days avoided). The per-patient cost savings were $504.96 compared to SOC alone. These findings were consistent across all sensitivity and scenario analyses. Assuming full adoption of LMMBV, the per patient cost savings are projected to result in more than $163 million in total savings annually in Canada based on population estimates and published incidence data.

Conclusion Considering the burden of CAP and antimicrobial resistance to the health care system, the use of LMMBV with SOC can offer both clinical and economic benefits to Canadian public payers.

Keywords Community-acquired pneumonia, Cost-impact, Diagnostic testing

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Introduction

Community-acquired pneumonia (CAP) is a common respiratory condition that disproportionately affects older adults (aged 65 + years) and children (aged 0–17 years) [1]. CAP varies in severity, with symptoms ranging from mild fever and cough to severe pneumonia requiring hospitalization [2, 3]. Despite being considered an acute condition, patients with CAP face long-term risks, such as higher mortality and exacerbation of underlying health conditions [4, 5]. In 2016, the overall incidence of CAP in Canada was estimated as 347/100,000, with an increased risk among individuals aged less than 4 years and older than 65 years (i.e., 611 and 1,537/100,000, respectively) [6]. As a result, CAP constitutes a significant clinical and economic burden for patients and the healthcare system. The annual costs attributable to CAP in Canada vary by province. In Ontario, the annual cost has been estimated at $261 million for inpatient care and $417 million for outpatient care [1]. It's anticipated that the clinical and financial burden will increase amid an aging population [7, 8].

Antibiotics are a common strategy for treating CAP [9, 10]. Despite being only effective for bacterial CAP, they are often inappropriately prescribed for viral infections [11, 12]. There is no gold standard for distinguishing between bacterial and viral infections [13]. The etiology of CAP is unidentified in 62% of patients and physicians have stated they prefer to err on the side of caution and prescribe antibiotics to most CAP-presenting patients because of diagnostic uncertainty, time pressure, and/or patient preferences [14]. This has been observed to result in substantial inappropriate overprescribing [15]. Indiscriminate antibiotic use increases the risk of side effects, such as adverse events and Clostridium difficile infections (CDI) [16]. It also contributes to antimicrobial resistance (AMR), thereby escalating healthcare costs [17]. In Canada, the current standard of care (SOC) involves a combination of clinical judgement, chest x-rays, and laboratory testing [18]. A diagnostic test that could help differentiate between bacterial and viral CAP would be invaluable to front-line clinicians.

The LIAISON® MeMed BV® (LMMBV) test is an immune-based assay that analyzes three host proteins (TRAIL, IP-10, and CRP) and integrates them into a single score to distinguish between bacterial and viral infection under one hour. Scores from 65 to 100 are suggestive of bacterial infection; scores from 0 to 35 are suggestive of viral infection; and scores from 35 to 65 are equivocal. Studies indicate that, compared to SOC diagnostics, LMMBV offers quicker results and improved specificity and sensitivity [19–21]. This could reduce diagnostic uncertainty and ultimately support more diagnostic-driven antibiotic prescribing.

The widespread adoption of diagnostic testing in Canada hinges on supporting evidence from randomized controlled trials and economic evaluations [22]. Therefore, our objective was to conduct a cost-impact analysis to compare the clinical and economic outcomes of using SOC combined with LMMBV versus SOC alone in diagnosing bacterial versus viral infection among CAP patients. This analysis was conducted from a Canadian public payer perspective.

Methods

Model structure

We developed a decision tree model in Microsoft Excel for a hypothetical cohort of 1,000 patients (aged 18–64) with suspected CAP presenting to the emergency department (ED) in Canada's publicly funded healthcare system. This model was a simulation based on published (not patient-level) data. Patients either received SOC or a combined approach of SOC plus LMMBV (LMMBV + SOC) for diagnosis of bacterial or viral infection. SOC was defined as X-ray, complete blood count, and viral PCR testing [11, 23]. For patients receiving LMMBV+SOC, diagnosis was based on the LMMBV score, such that patients with scores from 0–35 would not be given antibiotics, patients with scores from 65–100 would be given antibiotics, and those with equivocal scores (35–65) would be managed as per SOC.

The model structure is presented in Fig. 1. Post-diagnosis pathways included hospital admission or treatment in the ED, with outcomes categorized as true positive (TP, bacterial diagnosis), false positive (FP, misclassified viral etiology), true negative (TN, viral diagnosis), or false negative (FN, misclassified bacterial etiology). Hospitalized patients faced the possibility of intensive care unit (ICU) admission. For those patients prescribed antibiotics, there was a risk of experiencing antibiotic-related adverse events or CDI. Both types of events were assumed to be treated in hospital based on evidence from published literature [24, 25]. This model structure was adapted from a previous cost-impact analysis conducted in the United States [26]. Clinical trial number: not applicable.

Clinical inputs

The clinical inputs and sources used for the base case analysis are presented in Table 1. These inputs were identified via a targeted literature search and supplemented with Canadian clinical expert opinion, when necessary. Two infectious disease specialists located in Ontario, Canada were consulted at multiple time points throughout the project. Their feedback was used to refine the model development and input selection, confirm the face validity of the model outputs, and support the interpretation of results.

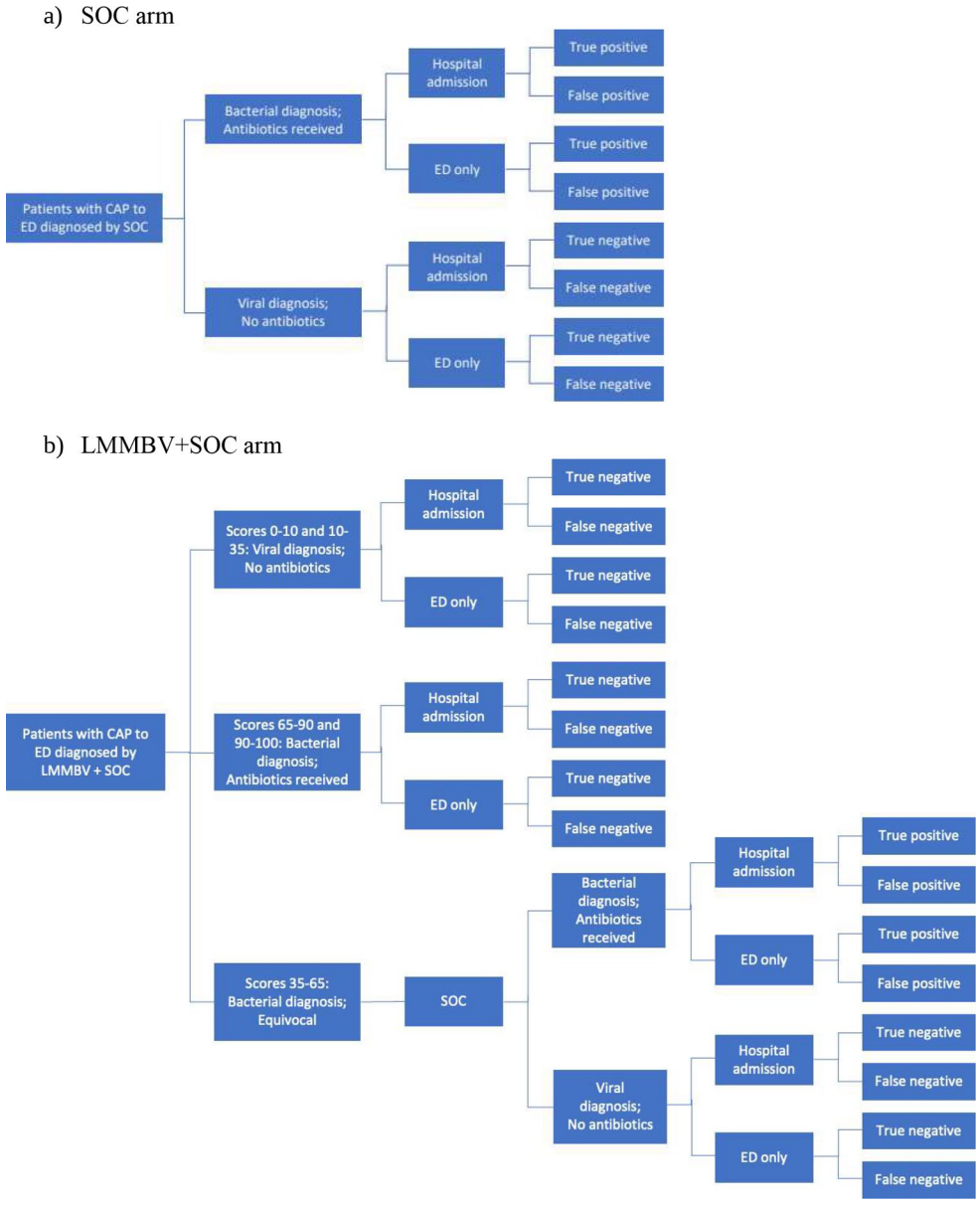


Fig. 1 Decision tree illustrating the model structure according to diagnostic arms. (**a**) SOC arm. (**b**) LMMBV + SOC arm. Abbreviations. LMMBV, LIAISON MeMed BV; SOC, standard of care; ED, emergency department. Adapted from: Houshmand, H.; Porta, C.; Pradelli, L.; Pinciroli, M.; Sotgiu, G. Cost-Impact Analysis of a Novel Diagnostic Test to Assess Community-Acquired Pneumonia Etiology in the Emergency Department Setting: A Multi-Country European Study. Int. J. Environ. Res. Public Health 2023, 20, 3853. https://doi.org/10.3390/ijerph20053853

In the model, the decision to prescribe antibiotics depends on both bacterial/viral etiology. The etiology of patients was obtained from a US population-based surveillance study, where etiology was calculated as the ratio of viral and bacterial pathogens (assuming that reported coinfections are treated as bacterial) among adults with CAP [27]. The sensitivity (i.e., the percentage of patients receiving a true positive test result) and specificity (i.e., the percentage of patients receiving true negative test result) for SOC diagnostic testing was based on another US study [26]. In the absence of Canadian-specific data, Canadian clinical experts indicated that prescribing practices more closely align with the US than other jurisdictions (e.g., Europe). This US study reported that viral pneumonia patients received antibiotics 21.7% of the time (FP), while non-viral (assumed bacterial) patients were given antibiotics in 66.6% of cases (TP) [28]. This equates to a sensitivity of 66.6% and specificity of 78.3% (where a false positive test result is equal to 1– specificity) for SOC [26]. Sensitivity and specificity of LMMBV were taken from published cost-impact models, which based their estimates on a recent study of 1,016 patients

Table 1 Clinical inputs for base case analysis

	Value		Source	
	SOC	**LMMBV + SOC**	**SOC**	**LMMBV + SOC**
Clinical inputs				
Bacterial infection rate	37.8%		[27]	
Viral infection rate	62.2%		[27]	
Sensitivity	66.6%	96.7%	[42, 43]	(19–21, 44, 45)
Specificity	78.3%	89.8%	[42, 43]	(19–21, 44, 45)
Test equivocal rate	NA	8.3%	NA	(19–21, 44, 45)
Baseline cohort PSI level severity distributions				
PSI 1 or 2	55.0%		[30]	
PSI 3	14.0%		[30]	
PSI 4	21.0%		[30]	
PSI 5	10.0%		[30]	
Probability of pre-diagnostic antibiotics				
PSI 1 or 2	75.0%		(a)	
PSI 3	90.0%		(a)	
PSI 4	100.0%		(a)	
PSI 5	100.0%		(a)	
Probability of diagnosis-driven antibiotic decisions				
PSI 1 or 2	100.0%		(a)	
PSI 3	80.0%		(a)	
PSI 4	50.0%		(a)	
PSI 5	0.0%		(a)	
Probability of hospital admission				
PSI 1 or 2	33.5%		[30]	
PSI 3	78.0%		[30]	
PSI 4	92.0%		[30]	
PSI 5	100.0%		[30]	
Probability of ICU admission among hospitalized patients				
PSI 1 or 2	7.5%		[33]	
PSI 3	9.4%		[33]	
PSI 4	17.0%		[33]	
PSI 5	17.0%		[33]	
Rate of antibiotic adverse events per person-day	0.2%		[39]	
Probability of CDI	3.2%		[40]	
Bacterial LOS				
PSI 1 or 2	5.18		[34]	
PSI 3	5.74		[34]	
PSI 4	6.63		[34]	
PSI 5	8.94		[34]	
Difference in LOS between bacterial and viral infection	31.0%		[41]	
ICU LOS	4.63		[46]	
Duration of antibiotic treatment	5.00		[18]	
Duration of antibiotic treatment for FN	7.50		(a)	
Pre-diagnostic days of treatment	1.50		(a)	
Hospital-onset CDI-attributable LOS	7.80		[25]	
Community-onset CDI-attributable LOS	5.70		[25]	
Adverse event related LOS	1.30		[28]	

Abbreviations. PSI, Pneumonia Severity Index; LMMBV, LIAISON MeMed BV; SOC, standard of care; ED, emergency department; FN, false negative; LOS, length of stay; CDI, Clostridium difficile infection; ICU, intensive care unit; PCR, polymerase chain reaction. (a) Assumption

with an acute infection, where an expert panel developed the reference standard for bacterial/viral etiologies [26, 29]. Specifically, LMMBV sensitivity was 96.7% and specificity 89.8%.

In addition to the diagnostic test result, antibiotic prescribing also depends on disease severity in the model. Pneumonia severity index (PSI) is a validated scoring system to assess disease severity in adults with

pneumonia [30]. A score under 90 means patients have a low risk. Scores between 91 and 130 suggest a moderate risk, and scores higher than 130 to a high risk [31]. This tool is recommended in both Ontario and North American CAP guidelines [18, 32]. In the model, a higher PSI score increases the likelihood of antibiotic prescribing. Specifically, the diagnostic test result from SOC or LMMBV + SOC was assumed to account for 100%, 80%, 50%, and 0% of the antibiotic prescribing decisions for PSI levels 1 or 2, 3, 4, and 5, respectively [26]. This means that for patients with a PSI level of 1 (i.e., low risk), physicians would follow the diagnostic test results completely when deciding whether to prescribe antibiotics to the patient. A bacterial diagnosis would result in antibiotic treatment while a viral diagnosis would result in no antibiotics. In contrast, patients with a PSI of 5 would receive antibiotics regardless of the diagnostic test result as they are classified high risk. Based on published literature, the probability of hospitalization, hospital length of stay (LOS), and ICU admission rates also depend on PSI [30, 33, 34]. Any inputs that are not stratified by PSI are assumed to be the same across all PSI levels.

With regard to antibiotic use, patients in the SOC arm received pre-diagnostic antibiotics for an average of 1.5 days [26]. Pre-diagnostic treatment was defined as antibiotic prescription before microbiological confirmation by culture. According to published literature and clinical expert opinion, obtaining blood culture results often takes between 24 and 48 h [26, 35, 36]. Because of the faster diagnostic turnaround (under 1 h), it was assumed that patients in the LMMBV + SOC arm did not need pre-diagnostic antibiotics. On average, TP and FP patients received antibiotics for 5 days [18]. FN patients are assumed to have a 50% longer duration of antibiotic treatment due to disease progression resulting from delayed antibiotic treatment. This assumption is supported by published literature [37, 38] and was used in the original model [26]. The probabilities of developing antibiotic-related adverse events and CDI were linked to treatment duration, at 0.2% and 3.2%, respectively [39, 40]. A hazard ratio of 1.09 for CDI was applied for each additional day of antibiotic use based on the results of a prospective, observational, cohort study, which found that CDI was significantly associated with longer duration of antibiotic therapy among CAP patients [40].

The impact of LMMBV was considered on both hospital admission and LOS. Not all patients presenting to the ED were hospitalized. Probability of hospital admission among SOC patients was based on PSI level and sourced from literature [30]. For LMMBV + SOC patients only, hospital admission decisions were further adjusted by the diagnostic test result. Specifically, 20% (PSI 1 and 2), 40% (PSI 3), 30% (PSI 4), and 0% (PSI 5) of hospital admission decisions were assumed to be determined by test outcomes, with bacterial diagnoses associated with hospital admission and viral diagnoses with discharge [26]. An additional risk of hospitalization for FN diagnoses in both arms was considered as patients who were initially discharged from the ED would need to return to receive the appropriate treatment [26]. A change in LOS was associated with an expected reduction in bacterial-diagnosed and FN hospital admissions, characterized by longer hospital stays. Bacterial-diagnosed hospital stays (TP or FP) were assumed to be equal to baseline LOS values. The LOS for TN was assumed to be 31% shorter. For FN, it was assumed to be 50% longer. This is attributed to delayed antibiotic treatment and subsequent increase in severity of disease [26, 41]. Among hospitalized patients, a certain percentage were admitted to the ICU based on their PSI level [33]. In the absence of published literature, there was no differentiation in ICU admissions or LOS between those receiving LMMBV + SOC versus SOC alone.

Table 2 Economic inputs for base case analysis

	Value		Source	
	SOC	LMMBV + SOC	SOC	LMMBV + SOC
Diagnostic test				
X-ray	$24.90		[51]	
Complete blood count	$3.98		[52]	
Viral PCR	$120.00		(a)	
LMMBV	$85.00		(a)	
Antibiotic treatment				
Inpatient antibiotic treatment per day	$31.82		[18, 49]	
ED visit	$352.67		[53]	
Hospital cost per day	$1,845.76		[48]	
ICU cost per day	$2,488.00		[46]	

Abbreviations. PSI, Pneumonia Severity Index; LMMBV, LIAISON MeMed BV; SOC, standard of care; ED, emergency department; FN, false negative; ICU, intensive care unit; PCR, polymerase chain reaction. (a) Assumption

Economic inputs

The economic inputs and sources used for the base case analysis are presented in Table 2. Economic inputs were sourced from Canadian databases and published literature.

The cost for SOC was calculated by combining the costs for chest X-ray, complete blood count, and viral PCR testing. As there is no gold standard for diagnostic testing and many options are available [47], the selection of SOC components was based on published North American literature and clinical expert opinion [18, 32] to ensure that it reflects the Canadian context. It was assumed that LMMBV would be provided as an additional cost to SOC. For LMMBV, a price of $85 was used at the base case analysis.

Hospital and ED costs were obtained from the Canadian Institute for Health Information (CIHI) [48]. For ED visits, a one-time cost was applied. Hospital costs were estimated by multiplying cost per day by LOS. For those hospitalized patients who were ultimately admitted to the ICU, an additional cost per day was applied for the duration of stay in the ICU [46]. The cost of AEs and CDI was accounted for as additional hospital days based on published literature [25]. The cost of inpatient antibiotic treatment was calculated by combining information on the antibiotics and dosage, as recommended by clinical guidelines provided by the American Thoracic Society and Infectious Diseases Society of America [18], with unit prices obtained from the Ontario Drug Benefit Formulary [49]. All costs are presented in 2023 Canadian dollars. Unit costs were adjusted for inflation using the Bank of Canada inflation calculator [50], when necessary.

Analyses

Base case analysis

The base case analysis assesses both the clinical and economic impact of LMMBV + SOC. Clinical outcomes of interest include antibiotic use, adverse events, CDI as well as hospital and ICU admissions, which are reported in terms of the number of days and events avoided. Economic outcomes of interest include the individual costs for each clinical outcome as well as the total cost according to the diagnostic strategy. The differences in clinical outcomes between SOC and LMMBV + SOC were calculated at the per cohort (1,000 patients) level, while differences in costs were calculated both at the patient level and for the entire cohort.

Sensitivity analyses

We conducted one-way sensitivity analyses to evaluate the impact of parameter uncertainty, assuming LMMBV list price ranges from $65 to $95, and varying all other parameters by ± 20%. We then conducted five additional analyses where alternative parameters were identified during our literature search and/or consultations with Canadian clinical experts. For example, clinical experts indicate that Canadian clinicians prefer to prescribe antibiotics for CAP, regardless of the diagnostic test result. This is reflected in high levels of antibiotic overprescribing in Canada [54]. As a result, we conducted a sensitivity analysis where the probability of pre-diagnostic antibiotic use was set to 100% (see Analysis 2, Table 3). For full details on each analysis, refer to Table 3.

Scenario analyses

We also conducted scenario analyses to explore differences in clinical and economic outcomes according to different age groups, perspectives, and clinical scenarios.

In Canada, there are differences in diagnostics tests, treatments regimens, public insurance coverage, and the clinical events experienced by patients depending on their age. As a result, we conducted two scenario analyses focusing on pediatric (aged < 18 years) and older patients (aged 65 + years) to explore expected clinical and economic outcomes when using LMMBV + SOC compared

Table 3 Summary of sensitivity analyses

Analysis	Parameter	Value Used in Base Case	Value Used in Sensitivity Analysis	Description
Analysis 1	Bacterial infection	37.8%	33.0%	According to a Canadian publication by Nascreen et al., 2022, 33.0% of CAP are bacterial [55].
Analysis 2	Probability of pre-diagnosis AB use	75.0% for PSI 1&2, 90.0% for PSI 3, 100.0% for PSI 4&5	100.0% for all PSI levels	According to KOLs and published literature, Canadian clinicians prefer to prescribe antibiotics 100.0% of the time, regardless of the test result [56].
Analysis 3	Viral PCR cost	$120.00	$0.00	According to KOLs, diagnostic testing is not a common practice in Canada. As a result, the cost of viral PCR was excluded from SOC.
Analysis 4	Hospital cost per day	$1,845.76	$1,580.97	Cost for bacterial pneumonia (CMG 136) used for base case as it is one of the most common forms [57]. Cost for viral or unspecified pneumonia (CMG 138) used for sensitivity analysis [48].
Analysis 5	Adverse event related LOS	1.30	0.65	For the base case, we used resource utilization consistent with a previous model [26] and published literature [24, 25]. For the sensitivity analysis, this was reduced by 50% based on clinical expert opinion that not all antibiotic-related AEs or CDI would require hospitalization.
	Hospital-onset CDI-attributable LOS	7.80	3.90	
	Community-onset CDI-attributable LOS	5.70	2.85	
Analysis 6	LMMBV sensitivity	96.7%	90.0%	For the base case, we used inputs consistent with a previous model. For the sensitivity analysis, we used recent data published from the APOLLO study [58, 59].
	LMMBV specificity	89.8%	92.8%	

Abbreviations. CAP, community-acquired pneumonia; AB, antibiotic; PSI, Pneumonia Severity Index; PCR, polymerase chain reaction; KOL, key opinion leader; CMG, Case Mix Group; SOC, standard of care; LOS, length of stay; AE, adverse event; CDI, Clostridium difficile infection; LMMBV, LIAISON MeMed BV

Table 4 Scenario analyses inputs for pediatric and older patients

	Base case values	Scenario analysis values	Source
Scenario: Pediatric patients			
SOC diagnostic cost	$148.88	$80.69	(a)
Rate of antibiotic adverse events per person-day	0.2%	0.00	[57]
Probability of CDI	3.2%	0.00	[57]
Outpatient antibiotic cost per day	$0.00	$0.39	[49]
Inpatient antibiotic cost per day	$31.82	$0.39	[49]
Hospital cost per day	$1,845.76	$1,559.32	[48]
Scenario: Older patients			
% admitted to ICU PSI1&2	0.08	0.04	(a)
% admitted to ICU PSI3	0.09	0.06	
% admitted to ICU PSI4	0.17	0.10	
% admitted to ICU PSI5	0.17	0.10	
Outpatient antibiotic treatment cost per day	$0.00	$2.92	[49]
ICU Stay	$4.63	$4.21	[46]
Hospital cost per day	$1,845.76	$1,438.05	[48]
ICU cost per day	$2,488.00	$2,010.15	[46]

Abbreviations. PSI, Pneumonia Severity Index; CDI, Clostridium difficile infection; ICU, intensive care unit; SOC, standard of care. (a) Calculated as a weighted average

to SOC alone. A summary of each scenario analysis by age group is presented in Table 4.

For pediatric patients, only patients with severe disease would receive CBC and viral PCR testing as part of SOC based on clinical expert opinion and published guidance from the Canadian Paediatric Society [23]. We also extended insurance coverage to include outpatient antibiotics in line with provincial drug programs [60, 61]. The type of antibiotic prescribed (i.e., monotherapy) as well as the costs for antibiotics and hospital stays were updated based on clinical expert feedback and published data [48]. In addition, clinical inputs were revised because the rates of antibiotic-related adverse events and CDI are markedly lower among pediatric patients [57].

For older patients, insurance coverage was also extended to the outpatient setting. Antibiotic, hospitalization, and ICU costs were also updated. A key difference for this patient population is that the percent of hospitalized CAP patients who are admitted to ICU decreases with age (e.g., 28.5% among patients aged 50–64 years, 22.5% aged 65–74, and 16.2% aged 75–84) [46]. This may be attributed to the existence of other healthcare supports (e.g., long term care) or personal choice (e.g., people reach an age where they choose not to have ICU care).

With regard to perspective, the provincial and territorial governments are responsible for delivering health services in Canada [62]. As a result, there are differences in drug prices, service fees, and hospital costs across jurisdictions [63]. To account for these differences, we conducted scenario analyses according to the perspective of five different provincial payers (i.e., Ontario, British Columbia, Alberta, Saskatchewan, and Quebec). Across each scenario, clinical inputs remained the same. Full details on the province-specific cost inputs are available in the Appendix.

Finally, we conducted one additional scenario analysis that did not consider the impact of LMMBV + SOC on hospitalization. In the base case, incorrect diagnoses and delay of treatment were assumed to lead to worsening of a patient's condition and, subsequently, their admission to hospital. However, available data on LMMBV and hospital admission rates and LOS are limited. As a result, this scenario analysis considered the impact LMMBV on antibiotic stewardship and related AEs only.

Table 5 Clinical outcomes per cohort– LMMBV + SOC vs. SOC

	Cohort (1,000 patients)
Antibiotic patients avoided	-429
Antibiotic days saved	-1020
Hospital admissions avoided	-8
Hospital days saved	-298
Probability of adverse events	-2
Probability of CDI	-6
ICU admission avoided	-1

Abbreviations. CDI, Clostridium difficile infection; ICU, intensive care unit

Results

Base case

The base case results for clinical outcomes of interest are presented in Table 5. For every 1,000 patients, LMMBV + SOC shows significant savings in terms of the number of patients who avoid antibiotic treatment (429 patients) and the total number of antibiotic treatment days avoided (1,020 days). The impact on hospital and ICU admissions, as well as antibiotic-related AEs and CDI events, was limited.

The base case results for economic outcomes are presented in Table 6. Despite the increase in costs for diagnostic testing, LMMBV + SOC results in a total cost savings of $504.96 compared to SOC alone. The majority of these savings are attributed to reduced hospitalization costs ($465.96 per person).

Sensitivity analyses

Results from the one-way sensitivity analyses indicate that the specificity of LMMBV, daily hospital cost, and the specificity of SOC are the top three model drivers. That is, the parameters with the greatest impact on expected cost savings. A summary of the results for other inputs is presented in the Appendix. In all the one-way analyses, LMMBV + SOC remained a cost-saving strategy.

Table 6 Cost savings per patient– SOC + LMMBV vs. SOC

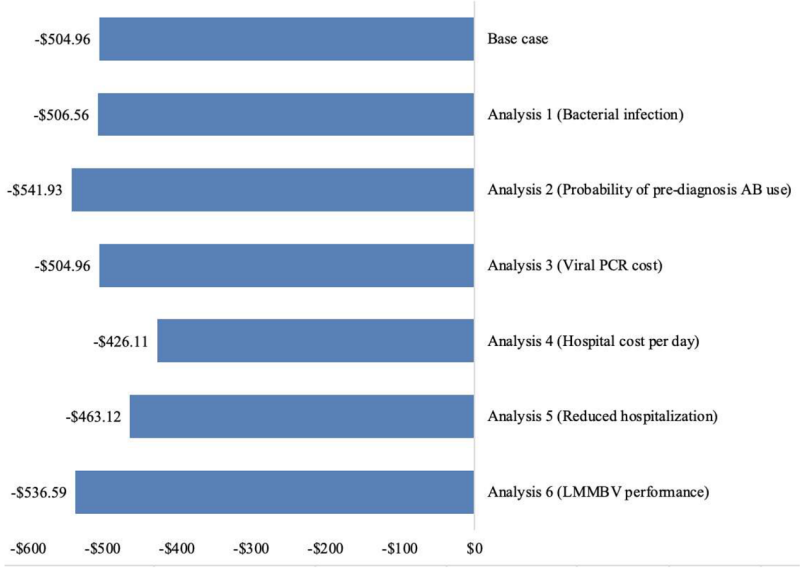
	Per patient	Cohort (1,000 patients)
Diagnostic testing	$85.00	$85,000
ED visit	$0.00	$0
Inpatient days of AB treatment	-$34.23	-$34,226
Outpatient days of AB treatment	$0.00	$0
Adverse events	-$2.39	-$2,389
Inpatient CDI	-$41.66	-$41,657
Outpatient CDI	-$39.62	-$39,619
Baseline Hospital Stay	-$465.96	-$465,959
ICU Stay	-$6.11	-$6,106
Total	**-$504.96**	**-$504,956**

Abbreviations. ED, emergency department; AB, antibiotic; CDI, Clostridium difficile infection; ICU, intensive care unit

The results of the six additional analyses are presented in Fig. 2. Removing the cost of viral PCR (Analysis 3) had no impact on the cost difference between LMMBV + SOC and SOC arms. This is because the cost of viral PCR was removed from both arms (from $120 to $0). Total per patient costs decreased (from $8,990.26 to $8,870.26 for SOC arm, and from $8,485.30 to $8,365.30 for LMMBV + SOC arm), but the absolute difference remained the same. The cost savings from LMMBV + SOC increased when using a different source of data for the rate of bacterial infection (Analysis 1) and LMMBV performance (Analysis 6) as well as adjusting the likelihood of pre-diagnostic antibiotic use (Analysis 2). Using the daily hospital cost for viral or unspecified pneumonia instead of bacterial pneumonia (Analysis 4), and reducing the resource utilization associated with treatment of antibiotic-related AEs and CDI (Analysis 5) resulted in lesser savings.

Scenario analyses

Results for each scenario analysis are presented in Table 7. The cost difference between LMMBV + SOC and SOC alone was smaller in the two scenarios according to age group compared to the base case. For pediatric patients, this is primarily due to the lower incidence of antibiotic-related adverse events and CDI. For older



Abbreviations. AB, antibiotic; PCR, polymerase chain reaction; LMMBV, LIAISON MeMed BV

Legend

Analysis 1: Rate of bacterial infection reduced to 33.0%
Analysis 2: Probability of pre-diagnostic antibiotic use increased to 100% for all PSI levels
Analysis 3: Viral PCR excluded from SOC
Analysis 4: Hospital cost per day reduced to $1,580.97
Analysis 5: Hospital LOS reduced by 50%
Analysis 6: LMMBV sensitivity 90.0% and specificity 92.8%

Fig. 2 Results of sensitivity analyses– LMMBV + SOC versus SOC
Abbreviations. AB, antibiotic; PCR, polymerase chain reaction; LMMBV, LIAISON MeMed BV. Analysis 1: Rate of bacterial infection reduced to 33.0%. Analysis 2: Probability of pre-diagnostic antibiotic use increased to 100% for all PSI levels. Analysis 3: Viral PCR excluded from SOC. Analysis 4: Hospital cost per day reduced to $1,580.97. Analysis 5: Hospital LOS reduced by 50%. Analysis 6: LMMBV sensitivity 90.0% and specificity 92.8%

Table 7 Per patient results for scenario analyses

	SOC	LMMBV + SOC	LMMBV + SOC vs. SOC
Base case			
Adult patients	$8,990.26	$8,485.30	-$504.96
Scenario analysis			
Pediatric patients	$7,336.27	$7,021.11	-$315.15
Older patients	$6,837.83	$6,457.90	-$379.93

Abbreviations. LMMBV, LIAISON MeMed BV; SOC, standard of care

patients, it is due to the reduction in daily hospital costs and ICU admissions. A full breakdown of costs for each scenario is presented in the Appendix (see Table S2 for details).

Discussion

This cost-impact analysis, which was based on simulated data, found both clinical and economic benefits of using LMMBV among patients presenting to the ED with CAP. Notably, LMMBV results in a decrease in antibiotic use, days of therapy, and the length of stay among patients and in cost savings for Canadian public payers. The estimated per patient costs savings from LMMBV + SOC were $504.96 compared to SOC alone.

We conducted separate analyses for pediatric and older patient populations because of the heterogeneity in diagnosis, treatment practices, and insurance coverage for CAP patients in Canada. In both scenarios, LMMBV + SOC resulted in cost savings, albeit reduced compared to the base case. These results should be considered exploratory in nature as the PSI is not validated among pediatric patients and certain inputs are not specific to these populations, which constitute key limitations of these scenario analyses. For example, viral infection rates are often higher among children, which would increase the cost savings attributable to LMMBV + SOC. Even within the age groups considered, there could be variations in expected costs and outcomes. A population-based retrospective study conducted in Canada found that the incidence rates of CAP are significantly higher among the very young and very old (i.e., 0–4 years and ≥ 85 years) compared to other age groups [55]. Although this variability in incidence will not affect the base case results because the analysis is conducted on a per-patient level, it will impact the projected cost-savings. To account for this, we used the best available peer-reviewed evidence and conducted subgroup analyses to consider each population separately. Similarly, CIHI data indicate a decrease in the average hospital cost for bacterial pneumonia with age ($11,722 among 60–79 years versus $9,397 among 80 + years) [48]. This decrease in inpatient costs for older CAP patients has been observed in other studies [1]. This is an important consideration for the base case analysis as hospital costs are a key driver in our model. A decrease in hospital costs for older patients would reduce the cost savings attributable to LMMBV. Due to data availability, we did not conduct further analyses in these subgroups. Further research is required to confirm these findings, with particular attention paid to clinical and economic outcomes that are important to these populations (e.g., long-term care costs or indirect costs due to work absences among parents of pediatric patients) [64, 65].

While the base case analysis was from a Canadian public payer perspective, additional scenarios were conducted from the perspective of provincial payers. In all instances, LMMBV + SOC was confirmed as a cost-saving strategy, with results ranging from $457.54 (Ontario) to $606.93 (Alberta). These scenarios were conducted to account for differences in costs across jurisdictions [63]. It is possible that variations in clinical inputs may further exacerbate the differences between provinces. For example, the incidence of bacterial CAP has been shown to vary significantly between Ontario (111.0/100,000) and British Columbia (749.3/100,000) [55]. Antibiotic prescribing practices also vary between provinces and even locally depending on factors, such as provider experience, patient characteristics (age, disease severity, comorbidities, allergies, previous antibiotic use), and the practice setting (hospital or community) [66].

The cost savings associated with LMBBV across Canada (and among individual provinces) were lower compared to those estimated in a cost-impact analysis conducted in the United States (per person cost savings of $808.65 USD) [26]. This difference is primarily attributed to the higher healthcare costs in the United States, which are reflected in the cost inputs in the model (e.g., $765 USD for viral PCR, $1,217 USD for ED visit, $2,209 USD per day for hospital stays). These higher costs elevate the overall cost savings for LMMBV. A cost-impact analysis conducted in Europe also found costs savings due to LMMBV. In Italy and Germany, per patient cost savings were up to €364 and €328 for hospitals and €91 and €59 for payers, respectively [29]. In Spain, cost saving due to LMMBV for both hospitals and payers were €165 [29]. Differences with the Canadian results can be attributed to healthcare financing (i.e., public payer perspective versus separate hospital and third-party payers in Europe), the inclusion of ICU and LMMBV costs in the Canadian analysis as well as higher hospitalization costs in Canada.

Given the high incidence of CAP in Canada, there could be considerable overall savings for the healthcare system [55]. Based on Statistics Canada population estimates [67] and published incidence data (i.e., 12.9/1,000 person-years) [1], the per patient cost savings may result in more than $163 million in savings annually in Canada assuming full adoption of LMMBV. Projected cost savings

by subgroup and province are available in the Appendix. The findings from these cost-impact analyses highlight the potential economic benefit of using LMMBV for diagnostic testing in CAP, however, real-world studies are required to understand the use of LMMBV in clinical practice (e.g., expected one hour turnaround time, impact on prescribing and hospital admission decisions) and its true impact across different patient groups (e.g., pediatrics, older individuals) and jurisdictions (e.g., provinces and territories). A previous cost-impact analysis that did not take the impact of LMMBV on hospital admission decisions into account found a decrease in savings for payers [26]. In addition, these analyses only consider a portion of the costs attributable to CAP. Patients with CAP face long term risks, including higher mortality and exacerbation of underlying health conditions, which can incur additional medical expenses after the acute phase [4, 5]. In a population-based cohort study, O'Reilly and colleagues estimated the healthcare costs of 692,090 CAP patients over a three-year period. They found that 55% of the healthcare costs for inpatient episodes occurred after the initial 30-day period [1].

This cost-impact analysis has several limitations. One limitation is that, in the model, the decision to prescribe antibiotics depends on both bacterial and viral etiology. There exist substantial diagnostic challenges in CAP [15] and, as a result, significant heterogeneity of microbiologic data. A systematic review on the etiology of CAP found that, regardless of the technique used (e.g., cultures, PCR), no etiologic agent could be identified in more than 50% of cases [68]. It is also possible that some patients with a viral etiology could have a bacterial co-infection [69]; co-infections are particularly common in children [70]. This challenge has been exacerbated by SARS-CoV-2, where the immune response can often lead to a misclassification as bacterial. To estimate etiology, we used the method of a previous model to facilitate comparisons across jurisdictions [26]. Data were obtained from a study conducted in the United States [27]. Compared to the United States, sophisticated diagnostic techniques (e.g., multiplex PCR, procalcitonin [PCT] testing) are less frequently used in Canada because of the high costs of the tests, resource constraints (e.g., for labs and staffing), and a lack of published data on reliability and efficacy. Moreover, while these tests may facilitate reductions in antibiotic prescriptions [47], there is little evidence to suggest any impact of rapid sample-to-answer multiplex PCR testing on ED LOS or the rate of hospital admission from ED (which are key model drivers) [36]. Other data were also either dated or not specific to a Canadian setting, including percentage of patients by PSI, probability of hospital admission by PSI, hospital LOS by PSI, and the rates of antibiotic-related AEs [30, 34, 41, 42]. This may have introduced uncertainty into the model via several clinical parameters. Finally, based on a recent review [58], we may have over-estimated LMMBV performance given the exclusion of equivocal scores. To address these limitations of clinical inputs, we conducted extensive one-way sensitivity analyses and found that results were robust to variations of +/- 20% for all inputs. That is, LMMBV remained cost saving. Additional scenarios confirmed these findings across different patient groups (pediatric, older patients) and provinces (Ontario, British Columbia, Alberta, Saskatchewan, and Quebec).

Another limitation is that the model structure did not encompass the full spectrum of clinical and economic outcomes relevant to the use of LMMBV. Our findings suggest that LMMBV improves the accuracy of antibiotic prescribing and reduces their overuse, which has been consistently recognized as a key driver of the emergence of AMR [72]. AMR, in turn, is a significant threat to human health [73]. However, the model did not capture the expected benefit in AMR prevention from reducing inappropriate antibiotic use. AMR significantly increases healthcare costs due to expensive treatments and increased resource use. Patients with resistant infections often require longer hospitalizations, more ICU time, and isolation beds, as standard treatments may be ineffective in controlling their infections [74]. In 2018, AMR was linked to approximately 5,400 deaths in Canada, and it was expected to cause an expenditure of $1.4 billion in healthcare system [75]. Given these considerations, it is very possible that we underestimated the true benefit of LMMBV.

Conclusion

This cost-impact analysis, which was based on simulated data, found that using LMMBV in combination with SOC for CAP patients presenting to the ED could reduce antibiotic prescribing, days of therapy, hospital LOS, and costs for Canadian public payers. Sensitivity and scenario analyses indicated that these results are robust to variations in the parameters and assumptions used in the base case analysis. Considering the burden of CAP to the Canadian healthcare system, the use of LMMBV offers both clinical and economic benefits. Future research is required to confirm these findings among different subgroups of patients, and to explore the full clinical and economic benefits associated with diagnostic testing in CAP in a real-world Canadian setting.

Supplementary Information

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Supplementary Material 1

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Author contributions
F.X., B.H., and Y.S. developed the protocol, J.P. reviewed the protocol, Y.S. and B.H. adapted the model, all authors contributed to data analysis and interpretation, Y.S. and B.H. drafted the manuscript, all authors reviewed and approved the manuscript.

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Data availability
All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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