

Encouraging the Development of New Antibiotics: Are Financial Incentives the Right Way Forward? A Systematic Review and Case Study

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Abstract: Antibiotic resistance is an urgent public health threat that has received substantial attention from the world's leading health agencies and national governmental bodies alike. However, despite increasing rates of antibiotic resistance, pharmaceutical companies are reluctant to develop new antibiotics due to scientific, regulatory, and financial barriers. Nonetheless, only a handful of countries have addressed this by implementing or proposing financial incentive models to promote antibiotic innovation. This study is comprised of a systematic review that aimed to understand which antibiotic incentive strategies are most recommended within the literature and subsequently analyzed these incentives to determine which are most likely to sustainably revitalize the antibiotic pipeline. Through a case study of Canada, we apply our incentive analysis to the Canadian landscape to provide decision-makers with a possible path forward. Based on our findings, we propose that Canada support the ongoing efforts of other countries by implementing a fully delinked subscription-based market entry reward. This paper seeks to spark action in Canada by shifting the national paradigm to one where antibiotic research and development is prioritized as a key element to addressing antibiotic resistance.

Keywords: antimicrobial resistance, antibiotics, health policy, financial incentives, Canada

Introduction

Antibiotics – drugs that target bacterial infections – have revolutionized modern medicine by allowing us to treat previously lethal communicable diseases. This has resulted in higher life expectancies worldwide, as people are living approximately 30 years longer than they were in the early 20th century.^{1,2} A century ago, communicable diseases were the leading cause of death; however, the incidence of death in this category has been on a downward trend since the commercialization of antibiotics in the 1940s. Communicable diseases have been replaced by non-communicable diseases, such as heart disease and cancer, as top causes of death in recent decades.³ In addition to provoking a shift in mortality causes, the widespread use of antibiotics has also significantly lowered the risks associated with many medical procedures, including organ transplants, childbirth, and chemotherapy.⁴⁻⁶ However, the effectiveness of many antibiotics is diminishing at a concerning rate, as bacteria are becoming increasingly more resistant to the existing supply of antibiotics as a result of natural evolution, certainly, but also largely due to almost 80 years of inappropriate use.⁷ Inappropriate use has been prevalent from commercialization onwards, with most recent studies reporting that between 45% to 66% of

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antibiotics prescribed at the primary care level are unnecessary and that the indicated drug, dosage, or treatment duration are unsuitable in approximately 50% of prescriptions.^{5,8–10} The effects of antibiotic resistance (ABR) have already been devastating, with at least 700,000 deaths from drug-resistant infections occurring worldwide every year and experts estimating that this number will surpass 10 million deaths per year by 2050.⁶ In Canada, 14,000 deaths from drug-resistant infections occurred in 2018 and 400,000 Canadians are expected to die from drug-resistant infections by 2050.⁹ Notably, diminishing antibiotic effectiveness is leading to the resurgence of existing communicable disease threats and the emergence of novel ones, as illustrated by increasing prevalence of hard-to-treat multi-drug infections¹¹ and by the ongoing COVID-19 pandemic which has motivated superfluous antibiotic prescriptions in patients hospitalized with suspected COVID-19.¹²

Although this problem has received significant attention in recent years, with influential agencies like the World Health Organization (WHO), the World Bank, and national governments investing significant resources into the development of action plans and surveillance systems to address ABR, little has been done in the area of encouraging the development of new antibiotic drugs in countries such as Canada.^{13,14} Worldwide, the antibiotic development pipeline has all but dried up, demonstrated by the fact that few antibiotics that provide a significant clinical benefit over existing drugs have been approved in the last 30 years.^{15–17} Rather, for many antibiotics, there are limited, if any, replacement products in development, with only 12 of 50 antibiotics in the development pipeline targeting priority Gram-negative pathogens, although these pose a great risk to humans.^{16,18,19} To exacerbate matters, many pharmaceutical companies are abandoning their antibiotic research and development (R&D) programmes altogether, as seen by the exiting of 15 of the 18 largest global pharmaceutical firms from this space in the last 30 years.^{9,20} This concerning shift in pharmaceutical companies' ventures is due to multiple scientific, regulatory, and economic barriers associated with the development and marketing of new antibiotics.

The purpose of this article is two-fold: (1) to analyze the existing and proposed antibiotic financial incentive strategies from around the world through a systematic literature review and (2) to present a case study of Canada to propose which – if any – financial incentives could be feasibly implemented in this country to support

the global effort for inducing antibiotic innovation. These objectives were realized by critically analyzing the strategies recommended by articles meeting our inclusion criteria and assessing each recommended incentive strategy for their ability to productively foster R&D. Through a case study of Canada, we provide decision-makers with a possible path forward that could benefit the Canadian landscape based on our financial incentive analysis.

Background

While scientific barriers, which consider the challenges associated with the discovery of new antibiotic molecules of clinical value, and regulatory barriers, such as the innate difficulties of meeting regulatory expectations for clinical trials involving antibiotics, are certainly significant, it has been argued that economic barriers present the biggest hurdle to antibiotic development, as this deters drug developers from investing in antibiotics at every point of the R&D process.²¹

The production of new antibiotics is greatly hindered by profitability challenges which uniquely affect antibiotics. Antibiotic infections generally occur over a short period of time and then the patient is no longer in need of the drug – contrary to chronic diseases that tend to generate revenue over the span of the patient's life post-diagnosis.^{9,22,23} However, while other existing short-course pharmaceuticals (ie, vaccines) are nonetheless profitable, the threat of ABR requires increased antibiotic stewardship, meaning that any new antibiotics that would be introduced into the market would be reserved for infections caused by multi-drug resistant bacterial strains for which no other effective drugs exist, thereby keeping profits low.^{21,22,24} Alternatively, if new antibiotics are active against multidrug-resistant bacteria for which few, if any, effective treatments exist, it is predicted that these drugs will become ineffective relatively quickly upon use as a result of ABR. Furthermore, since antibiotics of the same class typically have the same mechanism of action, resistance may develop towards a shelved product that belongs to the same class as a different drug that has higher volume sales, thereby rendering it less effective despite it being preserved.²⁵ This problem has no easy solution, due to the fact that increasing antibiotic drug prices to combat decreased pharmaceutical profitability would only serve to exacerbate the problem, as lower-income countries – which are disproportionately affected by ABR^{26,27} – require access to affordable drugs to prevent deaths due to treatable infections.^{6,28} Also, the prices

of new antibiotics are generally kept low by the existence of a wide variety of inexpensive generic products that have similar clinical indications as branded products and which continue to have clinical utility.^{6,17,21,22,29}

Given these multi-layered challenges and the lack of significant progress – despite strategies to address antibiotic resistance at other levels (ie, stewardship programs, awareness campaigns, surveillance, etc.) – action is needed to stimulate the R&D of new antibiotics. In order to address ABR, we need a steady supply of new and clinically important antibiotics; therefore, a handful of antibiotics should be in development at any given time, rather than there being extremes where multiple antibiotic developments occur and then many years where they do not.³⁰ Around the world, incentives have been implemented and numerous more are being suggested as possible options to sustainably revitalize the antibiotic pipeline to tackle the presented issues. Financial incentives that motivate investment in antibiotics by drug companies can be classified into either push or pull mechanisms, whereby push mechanisms focus on decreasing antibiotic development costs and pull mechanisms aim to increase or ensure adequate market revenue for newly approved antibiotics (further discussed in the results section).^{18,19,29,31,32}

Methods

This research consists of two distinct methodological approaches: first we conducted a systematic literature review and secondly, building upon those results, we applied an incentive analysis to draw out our conclusions. The literature review was performed to answer the following question: should drug developers be given financial incentives to encourage the development of novel antibiotics to address the global health threat of ABR, and if so, which incentives would be most productive when applied to a Canadian case study? This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.³³ On April 6, 2020 an electronic search of the following five databases was performed: Medline (Ovid), Pubmed, Embase, Web of Science (Science & Social Science Citation Indexes), and Scopus. The medical subject headers (MeSH) used in the search were “drug resistance, microbial” and “drug industry” and the key words used were “incentive”, “award”, “reward”, “antibiotic”, “antimicrobial”, “research”, and “development”. Appropriate variations were used to account for word variations and plurals.

In order to be included, studies had to:

- Be published in English;
- Be published after January 2010, to correspond with rising ABR awareness in the last decade;
- Focus on the analysis or review of one or more financial incentive strategies for encouraging antibiotic R&D;
- Be peer-reviewed or commentaries published in peer-review journals.

The literature search retrieved 2227 records. After duplicates were removed, 1098 titles and abstracts were screened, and 986 records were excluded for not conforming to the inclusion criteria. Studies were further excluded if they:

- Comprised of records consisting of letters to the editor, correspondence, or conference papers and abstracts;
- Did not specifically focus on financial incentives to promote new antibiotics or which only broadly addressed financial incentives, without offering an in-depth insight into any models or offering any incentive suggestions;
- Focused on incentives to reduce inappropriate prescriptions, improve antibiotic stewardship, improve multi-country availability of antibiotics, or promote fewer antibiotic emissions into the environment;
- Focused on the topic of scientific and/or regulatory incentives;
- Focused on financial incentives but not specifically for antibiotic agents, as ideas from other sectors have been largely considered and applied to the antibiotics landscape.

The full texts of the remaining 112 articles were assessed for eligibility by the authors, of which 70 were deemed outside the inclusion criteria. The review encompasses 42 records which were included in the final analysis (Figure 1). Notably, most of the included studies were either perspective, commentary, or review articles (88%), which was expected for two reasons: (1) since this research question is at the policy level and cannot be tested for safety and efficacy through observation or interventional trials at the individual level, original research is scarce, and (2) the scope of this paper is to determine a recommendation for a Canadian case study based on analyzing the recommendations from existing literature pertaining to this topic; therefore, opinion articles and review articles are particularly useful. Commentaries were included because they are

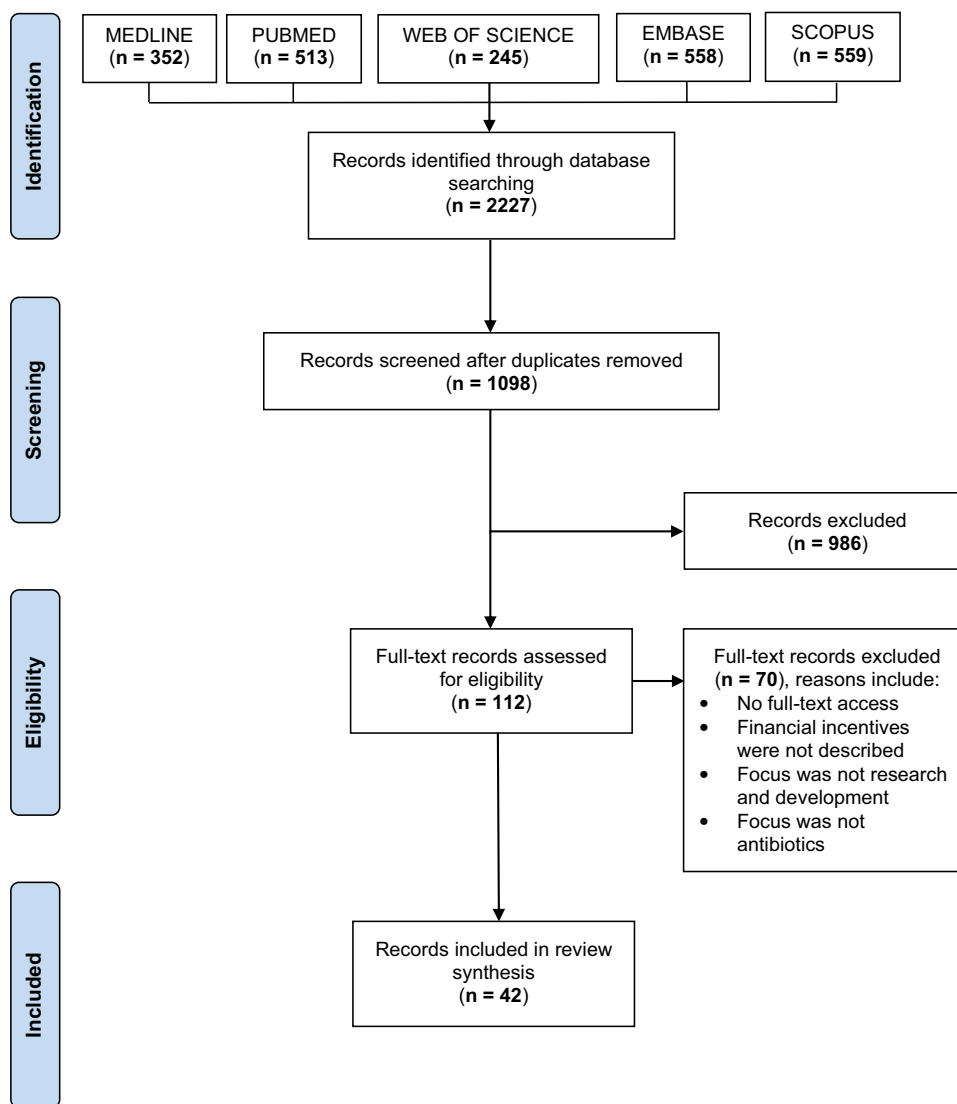


Figure 1 Study flowchart according to the PRISMA recommendations.

Notes: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*. 2009;62(10). Creative Commons.³³

taken up in the public domain by policy experts, and are therefore valuable for understanding current international trends in this subject area. All included articles were given equal weighting as perspective and reviews represent the current academic perspective whilst commentaries are readily applicable at the policy-level. Next, the recommendations provided by the articles included in this review were critically assessed to determine which incentive strategies could be effectively implemented within a Canadian context. To this effect, article-recommended incentives were analyzed using a modified version of the assessment framework developed by Renwick et al.¹⁸ Renwick's framework

consists of four market criteria for selecting an optimal incentive model:

1. Does the incentive improve the net present value (i.e., the profitability metric) for antibiotic projects?
2. Does the incentive promote small to medium-sized enterprise (SME) participation?
3. Does the incentive promote large pharmaceutical company participation?
4. Does the incentive promote cooperation and synergy among key players (i.e., industry, academia, government)?

Besides these market criteria, Renwick's framework also evaluates whether the incentive model aligns with public health objectives, namely:

1. Does the incentive promote antibiotic stewardship?
2. Does the incentive improve patient access to antibiotics?

However, given the pull incentive pilot schemes that have been recently launched in the United Kingdom and Sweden, we modified Renwick's framework to ensure that these schemes were being taken into consideration as part of the incentive feasibility assessment. Additionally, while paying special attention to Canada as the setting for the proposed incentives, we opted to further modify Renwick's framework to add new but related assessment criteria that preserve Renwick's categories (ie, market attractiveness, public health objectives, and implementation feasibility) while providing more context, insight, and specificity to these categories. Our modified framework also assesses the following items:

1. Is the incentive strategy forecasted to entail large structural changes to the current business model in Canada?
2. Has the incentive strategy already been piloted or implemented in other countries?
3. Does the incentive strategy involve delinking the developer's return from sales volume and price?
4. Does the incentive strategy involve conditional payments based on antibiotic performance?
5. Does the incentive strategy promote or reward innovation in antibiotic R&D projects?

To account for the heterogeneity between included articles, all article-recommended incentive strategies were subjected to the same criteria-based assessment and assigned a score between 0 and 11, with a greater score indicating a higher probability that the incentive strategy would productively increase the market value for antibiotics, be feasible to implement, and contribute to antibiotic conservation efforts. Each incentive strategy was given either a score of 1 if it met the respective criteria or a score of 0 if it did not. The total score was then calculated for each incentive strategy. While every effort was made to ensure the framework criteria and derived scores were as non-biased as possible, there is nonetheless a level of subjectiveness within the aforementioned assessment

process. Bias was controlled to the extent possible by reaching consensus between authors on all scoring.

This modified framework was utilized to assign each incentive strategy recommended by the articles included in this review an individual score by which we were able to quantify the advantages and notable shortcomings each. These scores were taken into account within our wider discussion pertaining to the Canadian context and assisted us in coming up with recommendations for how Canada can work with the global community to sustainably improve the antibiotic market.

Results

Tables 1 and 2 demonstrate the characteristics of the 42 articles included in this analysis. These articles were published between 2010 and 2020 with most of the records being published in 2018 (26%). Table 2 indicates that interest in the topic of financial incentives rose significantly in 2016, evidenced by the increase in annual publications from that year onwards compared to the years before. Interestingly, recommendation trends have remained consistent over the decade – despite changes in particular implementation models, as discussed later – with market entry reward (MER)-based incentives representing the most recommended strategy type (Table 2).

Within the 42 articles, numerous types of push and pull incentive models were identified, with many being referenced in only one to three articles, whilst others, such as grants or MERs, being referenced in most of the articles. Despite this, there are broad categories of push and pull mechanisms that these articles identified (Table 3). Pertaining to push mechanisms, research grants, subsidies from public-private partnerships, and tax incentives (ie, tax credits or tax cuts) that can be offered for any stage of the R&D process represent the three broad categories of described mechanisms.^{18,34–36} Moreover, pull strategies were identified as (1) patent extensions, which delay generic drugs from entering the market; (2) MERs, which reward drugs for entering the market and fully or partially delink the product from the amount sold; and (3) tradeable vouchers, which would be given to drug companies after regulatory approval of a new high-priority drug, and can be used by the drug company to fast-track the review process, extend the patent life of another one of their compounds, or sell it to another company.^{1,18,29,34,37,38} Table 3 provides a simplified overview of each of these

Table 1 Characteristics of the Included Articles

Authors, Year	Type of Article	Comparative?	Pro Push Incentives?	Pro Pull Incentives?	Recommendation?	Enforced/ Managed by?
Årdal et al ²⁸ 2017	Perspective	Yes	Yes	Yes	MER (partially delinked model); market-price model	N/D
Årdal et al ⁴⁹ 2018	Pilot study	Yes	N/D	Yes	MER (partially delinked model)	Government
Baraldi et al ³⁴ 2016	Qualitative study (interviews)	Yes	N/D	N/D	N/D	N/D
Batista et al ¹⁹ 2019	Review	Yes	Yes	Yes	N/D	Multi-national (EU)
Bhatti et al ⁵¹ 2018	Perspective	No	Yes	Yes	Mix/hybrid; tax credits, MER	Government
Brogan et al ²² 2013	Perspective	No	Yes	Yes	Mix/hybrid; OMA model	NGO Government Multi-national (EU)
Brogan et al ³⁶ 2016	Perspective	No	Yes	Yes	Mix/hybrid; OMA model	NGO Government Multi-national
Brogan et al ⁵² 2016	Commentary	No	Yes	Yes	Mix/hybrid; early-stage push funding, OMA model	Multi-national (G20)
Ciabuschi et al ³¹ 2019	Simulation study	Yes	Yes	Yes	Mix/hybrid; grants for SMEs, MERs for large pharmaceutical companies	N/D
Daniel et al ⁵⁰ 2017	Perspective	Yes	Yes	Yes	MER (PAVE award)	PPPs
Daniel et al ³⁹ 2018	Perspective	Yes	N/D	Yes	MER (PAVE award)	PPPs (PAVE award is paid by insurance companies)
Darrow et al ²³ 2018	Review	Yes	Yes	Yes	Mix/hybrid; grants in early stages of research, advance market commitments	NGO PPPs Global coordination
Hojgard ⁴⁰ 2012	Review	Yes	Yes	N/D	Subsidise R&D costs, levied fee on antibiotic use	Multi-national (WHO) Government
Hollis et al ²⁵ 2015	Perspective	No	N/D	Yes	MER (de-linkage models), Pigouvian tax on non-human antibiotic use	Global coordination Governments
James ⁶² 2018	Perspective	No	No	No	Does not support financial incentives	Global infrastructure to address antibiotic resistance
Kesselheim et al ⁴¹ 2010	Perspective	Yes	Yes	Yes	Conservation-based market exclusivity	N/D

(Continued)

Table 1 (Continued).

Authors, Year	Type of Article	Comparative?	Pro Push Incentives?	Pro Pull Incentives?	Recommendation?	Enforced/ Managed by?
Kesselheim et al ⁴² 2011	Review	Yes	Yes	Yes	Mix/hybrid ACE program; MER, value-based reimbursements (eg, advance market commitments), conservation-based market exclusivity, grants	PPPs Government
Laxminarayan et al ⁴³ 2011	Perspective	Yes	No	Yes	Conservation-based market exclusivity	PPPs
Livermore ⁵³ 2018	Perspective	No	Yes	No	Push incentives: reducing developmental costs and barriers to market-entry	Government/ regulatory bodies
Luepke et al ²⁹ 2017	Review	Yes	Yes	Yes	Mix/hybrid	Global coordination
Lum et al ⁵⁴ 2018	Perspective	No	N/D	Yes	Diagnosis confirmation model for the hospital setting, value-based reimbursements, MER	Government PPPs
Mckellar et al ⁴⁴ 2014	Perspective	Yes	No	Yes	Increase antibiotic prices	N/D
Morel et al ³⁸ 2018	Commentary	Yes	N/D	Yes	MER (fully delinked approach)	Global coordination
Okhravi et al ⁴⁵ 2018	Simulation study	Yes	N/D	Yes	MER	N/D
Outterson et al ¹⁷ 2015	Review	No	N/D	Yes	MER	Multi-national
Outterson et al ⁵⁵ 2020	Review	No	N/D	Yes	MER	Multi-national PPPs (specifically, public benefit corporations)
Renwick et al ¹⁸ 2016	Review	Yes	Yes	Yes	Mix/hybrid; 1–2 push incentives and 1 large pull incentive	Government
Renwick et al ²¹ 2018	Perspective	No	Yes	Yes	Mix/hybrid; expand late-stage push funding of clinical trials, implement a global pull mechanism (MER or OMA)	Multi-national Government NGOs
Rex et al ⁵⁶ 2016	Perspective	No	N/D	Yes	MER (fully delinked approach based on benchmarked payments)	Multi-national
Rome et al ⁶¹ 2019	Simulation study	No	N/D	N/D	N/D	N/D

(Continued)

Table I (Continued).

Authors, Year	Type of Article	Comparative?	Pro Push Incentives?	Pro Pull Incentives?	Recommendation?	Enforced/ Managed by?
Savic et al ³⁵ 2018	Review	No	Yes	N/D	Grants that are more targeted and effective	Pipeline coordinator
Sciarretta et al ³⁷ 2016	Review	Yes	Yes	Yes	Mix/hybrid; MER (de-linkage models)	Global pull mechanism
Simpkin et al ⁴⁶ 2017	Review	Yes	Yes	Yes	Mix/hybrid; late-stage push funding, tax incentives, value-based reimbursements, advanced market commitments, MER (with bonuses for meeting clinical goals)	Multi-national Government
Singer et al ⁵⁷ 2019	Perspective	No	Yes	Yes	Mix/hybrid; open-source drug development	Multi-national PPPs
Sinha et al ¹ 2016	Review	No	Yes	No	Early-stage push funding	N/D
So et al ³² 2014	Review	No	Yes	Yes	Mix/hybrid; OSDD initiative (Indian pilot business model; shared resources, with drug leads tested in publicly funded clinical trials and marketed as generic drugs)	PPPs
Spellberg ⁵⁸ 2014	Review	No	Yes	No	Grants	PPPs
Talbot et al ²⁰ 2019	Review	No	Yes	Yes	Mix/hybrid	N/D
Theuretzbacher et al ⁵⁹ 2017	Review	No	N/D	Yes	MER (based on clinical value)	Global collaboration
Towse et al ⁴⁸ 2011	Review	Yes	Yes	Yes	Pull incentives: MER, higher antibiotic prices	N/D
Towse et al ⁴⁷ 2017	Perspective	Yes	N/D	Yes	MER (partially delinked model) - insurance model	Healthcare system
Vågsholm et al ⁶⁰ 2010	Perspective	No	N/D	N/D	Pigouvian tax	Multi-national

Abbreviations: MER, market entry reward; OMA, options market award; NGO, non-governmental organizations; PAVE, priority antimicrobial value and entry; PPPs, public-private partnerships; ACE, antibiotic conservation and effectiveness; OSDD, open-source drug discovery.

incentive strategies as well as their associated advantages and disadvantages, reflecting our literature findings. Importantly, this table describes incentives based on the general characteristics of the type of incentive strategy, which inherently overlooks differences between the characteristics of actual policies representing a strategy type that have been implemented.

Of the 42 articles included for analysis, 21 compared two or more incentive models to determine which one(s) were superior to the others.^{18,19,23,28,29,31,34,37–50} Thirty-

eight articles recommended a particular push incentive, pull incentive, or a push-pull hybrid model.^{1,17,18,20–23,25,28,29,31,32,35–60} In terms of the four that did not make a recommendation, two of the studies simply reviewed different incentives and outlined possible benefits and disadvantages of each without offering a final recommendation,^{19,34} one focused on analyzing the disadvantages associated with exclusivity extension pull strategies,⁶¹ and the last paper did not support any push or pull financial incentives.⁶²

Table 2 Trends Pertaining to Financial Incentive Models for Antibiotic Innovation in the Literature Between 2010 and 2020

Publication Year	Number of Publications	Most Popular Recommendation
2010	2	X
2011	3	Pull incentives
2012	1	Pull incentives
2013	1	Mix/hybrid
2014	3	X
2015	2	MER
2016	7	Mix/hybrid
2017	6	MER
2018	11	MER
2019	5	Mix/hybrid
2020	1	MER

Note: X = No majority in respective year.

Abbreviation: MER, market entry reward.

Mix/Hybrid Models

The incentive strategy that was the most recommended among the included articles was a mix/hybrid model, suggested by 15 articles.^{18,20–23,29,31,32,36,37,42,46,51,52,57} However, there was no consensus among authors on what a hybrid model should or could look like. The specific push and pull components varied from one article to the next, with many of the articles not specifying which particular push or pull incentives they would suggest for the model (Table 1). Nonetheless, the most recommended hybrid model among these articles was the Options Market Award (OMA) model, with four studies suggesting it as the optimal approach.^{21,22,36,52} The OMA model uniquely combines aspects of both push and pull mechanisms into one model, whereby interested stakeholders may purchase an “option” to buy a set volume of an antibiotic at a discounted price to be redeemed if and when the antibiotic drug is marketed.²² The earlier the options are purchased, the lower its price but the greater the risk of the antibiotic not making it to market.²² Another hybrid model, known as the Antibiotic Conservativeness and Effectiveness (ACE) model, was described by Kesselheim and Outtersen,⁴² whereby the value of MER payments is determined by the level of success that the antibiotic has in meeting conservation targets. A distinctive feature of the ACE model is that it is proposed as a voluntary program that antibiotic manufacturers or sponsors can choose to opt-out of after market approval.⁴² Interestingly, five of the 15 articles suggesting a mix/hybrid model included an

MER as one of the components for their suggested model.^{31,37,42,46,51,52}

Other components of recommended mix/hybrid models consisted of research grants,^{21,23,31,42,46,52} advance market commitments,^{23,42,46} tax credits,⁵¹ conservation-based market exclusivity,⁴² and open-source drug development.^{32,57} Three articles did not elaborate on the characteristics of their proposed mix/hybrid models, focusing instead on advocating for the strengths of concurrently implementing multiple mechanisms as opposed to just one on a general level.^{18,20,29}

Market Entry Award Models

The second most popular suggestion among the articles was an MER, with 14 articles recommending this pull mechanism.^{17,25,28,38,39,45,47–50,54–56,59} Articles outlining how the MER should be implemented, awarded, and distributed varied widely in their proposed approaches, with model differences being observed between the eligibility criteria for marketed antibiotics, the value of award payments, the extent of disruptiveness to existing market systems, and whether or not they are concerned with promoting antibiotic stewardship.

Five articles suggested a partially delinked MER model, whereby conventional volume-sale revenues are topped up through annual payments.^{28,39,47,49,50} These articles posited that a partially delinked MER model has the advantage of being minimally disruptive, since it would be implementable within current systems and would avoid the need for law changes associated with other proposed models.^{28,49} Årdal et al⁴⁹ suggested that the value of the MER should be established on a case-by-case basis, according to a predefined criteria for antibiotics. Daniel et al^{39,50} took this one step further, by advocating that financial awards should only be given for novel antibiotics that target the highest-priority pathogens, an idea that has been previously suggested in reports such as the Chatham House Report⁶³ and O’Neill’s Review on Antimicrobial Resistance.⁶ In addition, Daniel et al^{39,50} argued that the MER model needs to encourage antibiotic stewardship, therefore suggesting that MER payments should require drug manufacturers to negotiate value-based contracts (ie, where payments are dependent on the “value” of the antibiotic to society) with insurers. In this model, known as the Priority Antimicrobial Value and Entry (PAVE) award model, the MER would provide drug manufacturers with the majority of the annual revenue in the first year

Table 3 Characterizing the Advantages and Disadvantages of Financial Incentives for Antibiotic R&D

Incentive Strategy	Policy Examples	Advantages	Disadvantages
Push Incentives			
Grants	JPIAMR CARB-X ND4BB BARDA NIH MRC	<ul style="list-style-type: none"> - Lowers cost for R&D which will promote antibiotic innovation⁵² - Funds projects which SMEs may lack the capital reserve to otherwise pursue - Create temporary jobs for scientists³⁵ 	<ul style="list-style-type: none"> - Risk of funding a project that ultimately will fail¹⁸ - SMEs may not be motivated to apply due to the belief that they will not get them³⁴
Subsidies	–	<ul style="list-style-type: none"> - Lowers company cost for R&D which will promote antibiotic innovation⁵² 	<ul style="list-style-type: none"> - Large amounts of public funding given to pharmaceutical companies may produce negative public opinion³⁴ - Only companies that already have potential candidates would be attracted by subsidies; if no candidates exist, they are not likely to start R&D from scratch³⁴
Tax incentives	READI Act	<ul style="list-style-type: none"> - Easily implemented by the government¹⁸ - Market dictates which investments are profitable¹⁸ 	<ul style="list-style-type: none"> - If only tax credits, not useful for SMEs because they do not help cash flow³⁴ - Negative public opinion on tax breaks for pharmaceutical companies³⁴
Pull Incentives			
Advance market commitments	–	<ul style="list-style-type: none"> - Only rewards successful antibiotics¹⁸ - Lowers manufacturing risk¹⁸ - Do not require major regulatory or law changes¹⁸ 	<ul style="list-style-type: none"> - Difficult to pre-determine drug specifications¹⁸ - Require upfront commitment from investors⁴⁸ - Incentive to maximize sales remains¹⁸
Exclusivity/patent extensions	GAIN	<ul style="list-style-type: none"> - Drug companies will have a longer time to recuperate R&D costs post-market¹⁸ - Higher drug cost may discourage overuse¹⁸ 	<ul style="list-style-type: none"> - Resistance to the antibiotic could occur during period of patent extension which would decrease incentive value³⁷ - Do not reduce level of risk of investment in early R
&D phases ³⁴ - Reduced access to drugs due to high drug prices ¹⁹ Market entry reward (fully delinked)	UK Pilot	<ul style="list-style-type: none"> - Only rewards successful antibiotics¹⁸ - Drug conservation is ensured since the product will not be sold by the developing company³⁷ - Guaranteed revenue³⁷ 	<ul style="list-style-type: none"> - Requires a substantial amount of funding to generate sustainable impact³⁷ - Challenging to implement³⁷ - Global coordination needed to ensure access to the drug and to conserve use³⁷ - Implementation needs to be tailored to national circumstances
Market entry reward (partially delinked)	Swedish Pilot	<ul style="list-style-type: none"> - Only rewards successful antibiotics¹⁸ - More feasible to implement than a fully delinked market entry reward model³⁷ 	<ul style="list-style-type: none"> - Requires a substantial amount of funding to generate sustainable impact³⁷ - Some incentive to maximize sales remains³⁸
Tradeable vouchers	REVAMP Act	<ul style="list-style-type: none"> - Only rewards successful antibiotics⁶ - Do not require direct funding from the government, which may make implementation easier⁶ - Commercial value of the voucher incentivizes the development of antibiotics¹ 	<ul style="list-style-type: none"> - Does not effectively incentivize early-stage antibiotic development¹ - Implementation will differ in each country³⁷ - High cost on health system in the future due to generic drugs being prohibited for longer (for wildcard vouchers)

Abbreviations: JPIAMR, Joint Programming Initiative on Antimicrobial Resistance (global); CARB-X, Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (global); ND4BB, New Drugs for Bad Bugs (European Union); BARDA, Biomedical Advanced Research and Development Authority (U.S.); NIH, National Institutes of Health (U.S.); MRC, Medical Research Council (U.K.); READI Act, Reinvigorating Antibiotic and Diagnostic Innovation Act (U.S.); GAIN, Generating Antibiotic Incentives Now (U.S.); REVAMP Act, Re-Valuing Anti-Microbial Products Act (U.S.); R&D, research and development; SMEs, small-medium enterprises.

post-market approval and this revenue would subsequently decline over the remaining years of the five-year PAVE award period.^{39,50} Lastly, Towse et al⁴⁷ offered another take on a partially delinked model, suggesting that the payment should be based on an insurance model whereby the government or healthcare system pays an annual fee to access and use the antibiotic.

On the other hand, two articles disagreed that a partially delinked option represents the optimal MER model, advocating for a fully delinked MER incentive instead.^{38,56} These articles argued that the advantages of fully delinked models pertaining to ensuring long-term sustainable use trump the benefits of partially delinked models, as the former ensure that manufacturers no longer have incentive to increase unit prices to maximize sales whereas the latter do not.³⁸ Although Morel and Edwards³⁸ did not provide suggestions pertaining to how such models should be implemented, Rex and Outterson⁵⁶ recommended that these awards should be paid out to manufacturers annually for a period of five years, with payment values being higher for antibiotics meeting one or more of the following criteria: a novel mechanism of action, addressing unmet clinical needs, targeting high-priority pathogens, and/or providing a cost-advantage over existing agents.

The remaining seven articles did not elaborate on the characteristics of their proposed MER models, endorsing delinkage models on a general level instead.^{17,25,45,48,54,55,59} The general consensus among these articles seemed to be that there is a need for studies that pilot different MER models to determine which types hold the most promise.⁴⁵

Other Incentive Models

Finally, 10 articles recommended other push or pull mechanisms, including targeted research grants or R&D subsidies,^{1,35,53,58} taxing antibiotic use,^{25,40,60} reimbursement reforms,⁴¹ conservation-based market exclusivity,^{41,43} and antibiotic price increases.⁴⁴

It is worth noting that while other incentive mechanisms beyond the ones mentioned above exist and may have promising qualities, the aim of this review was to ascertain which financial incentives for antibiotics are currently being recommended within the literature and to subsequently determine their usefulness according to set criteria. Therefore, incentives not recommended by any of the included articles fell outside the scope of this review.

Global versus National Managing Body

Regardless of which types of financial incentive mechanisms are implemented, a managing body that determines eligibility criteria for new antibiotics and distributes these incentives to manufacturers must be determined. However, akin to the diversity among articles concerning incentive model recommendations, the included articles also varied widely in their suggestions of how and by whom proposed incentives should be enforced and managed. Some articles had completely opposing views, with 11 articles^{17,19,29,37,38,52,55–57,59,60} arguing that incentives must be globally coordinated and enforced by a multi-national body, while six articles^{18,47,49,51,53,54} suggested that appropriate incentives need to be determined at a national level and enforced by domestic governments. In contrast, seven articles^{21–23,25,36,40,46} recommended that multiple systems should be involved in the implementation of financial incentives. For example, Brogan and Mossialos³⁶ recommended their OMA model, envisioning it to be open to non-governmental organizations, government, or multi-national investors to purchase options for antibiotics in clinical development; therefore, this model would engage different systems in administering financial incentive payments to manufacturing and pharmaceutical companies. Alternatively, Renwick and Mossialos²¹ suggested that a global governing body should be established to mobilize and coordinate action and that this should be coupled with national investment from governments to fund antibiotic R&D. Relatedly, five articles were less concerned with whether incentives will be managed nationally or multi-nationally, advocating instead for the need to engage both the industry and the state and thereby recommending public-private partnerships (PPPs).^{32,39,43,50,58} Ten articles did not provide any information, perspective, or suggestions pertaining to how a financial incentive for antibiotics should be administered.^{1,20,28,31,34,41,44,45,48,61}

Incentive Analysis

For all incentive strategies recommended by one or more of the articles, Table 4 depicts our incentive assessment based on market attractiveness, public health objectives, and feasibility of incentive implementation. In total, we ranked three push incentive strategies (open-source drug discovery, grants, and tax incentives), seven pull incentive strategies (conservation-based market exclusivity, diagnosis confirmation model, antibiotic use fees, increased antibiotic prices, fully delinked MER, partially delinked MER, and value-based reimbursement) and two hybrid models

(OMA and ACE). Importantly, this table is not comprehensive as other incentive models exist or have been proposed; however, this analysis is focused on the recommended incentives from articles meeting our search inclusion criteria. Applying the modified Renwick framework¹⁸ coupled with our scoring strategy, the fully delinked MER incentive strategy scored 6, the highest among all incentives, with partially delinked MERs, value-based reimbursements, the OMA model, and the ACE model all tied in second place with a score of 5. The majority of the remaining incentive strategies had a score of 4, including all three push incentives, as well as the conservation-based market exclusivity pull strategy and the increasing antibiotic prices strategy. The lowest-scoring incentive strategies were the fee on antibiotic use, with 3 points, and the diagnosis confirmation model, with only 1 point.

The criterium that was unmet by most of the incentive strategies included in this assessment was the “promotes cooperation and synergy among key players” criterium, with only one incentive strategy (open-source drug discovery) scoring in this area. Other criteria with limited uptake on the assessment included the antibiotic conservation criteria (ie, “involves delinking” criterium and “conditional grants/payments” criterium), with only two incentives meeting each individual criterium within this category.

Discussion

The topic of financial incentives for antibiotic development has only recently become of interest to researchers and policymakers, as evidenced by the low number of records published on this topic between 2010 to 2015, with interest rising from 2016 onwards (Table 2), likely due to the publication of the World Health Organization’s Global Action Plan for addressing antimicrobial resistance in 2015. In this systematic review, it was found that there is consensus within the literature regarding the gravity of the problem of antibiotic resistance, with articles on the topic of antibiotic financial incentives agreeing that ABR rates are rising faster than the rate of production of clinically important antibiotic drugs. Included articles also generally agreed that although push incentives are necessary, a substantial pull incentive or hybrid model will be needed to tackle this complex issue. However, when it comes to what the optimal pull or incentive model should look like, there is no consensus in the literature, with diverging opinions on whether a national or international incentive strategy would be more effective in motivating

the development of new antibiotics. Generally, the recommendations from the articles varied widely, as even the articles which recommended the same incentive mechanism (ie, push, pull, or a hybrid push-pull mechanism) still differed in regard to the suggested implementation approach, the managing body, the types of antibiotics which would qualify for the incentive, and whether the incentive would be a one-time payment or split-payments administered over a number of years.

There were 38 articles that supported financial incentives as promising for addressing the lack of new antibiotics being approved for use on a global scale. These articles agreed that while scientific and regulatory barriers to antibiotic innovation contribute to the lack of progress in new treatment options for hard-to-treat bacterial infections, the unattractive antibiotic market is the true hindrance for drug developers. Specifically, the fact that generic antibiotics that are capable of treating most common infections remain widely available coupled with the development of resistance occurring as soon as new antibiotics are clinically used unfortunately renders most antibiotics unprofitable. In order to stimulate impactful progress to ensure that future alternative treatments exist for even the most resistant pathogens – even if ABR rates keep rising – financial incentives must be implemented.

However, not all included articles endorsed financial incentives as promising solutions to the ABR problem. In particular, James⁶² did not agree that a financial incentive of any kind was an appropriate way of combating ABR, arguing that any publicly-financed incentives will only encourage the development of marginally improved antibiotics, rather than truly innovative products. As a result, publicly financed incentives would have little overall clinical benefit to tackling antibiotic resistance. James⁶² argues that since the public sector has limited resources, those resources would be better spent in creating a new international coordinating body that operates through public-private partnerships to overcome the antibiotic resistance challenges. James⁶² also argues that the market works best when it is left to operate freely, possibly implying that pharmaceutical companies will respond to the need of new anti-bacterial therapies when there is truly an immediate need for more solutions. However, while James’⁶² proposal for a global coordinating infrastructure to oversee the management of antibiotic resistance – regarding both R&D and antibiotic stewardship – is a valid recommendation, other parts of this argument overlook matters that consequently weaken the author’s position. For instance,

the antibiotic market cannot operate freely due to the need to restrict the use of marketed antibiotics to preserve their effectiveness; therefore, the regulations imposed on antibiotic development and distribution inherently distort the market.²¹ Also, as it takes between 10 to 15 years for a new antibiotic to progress through the antimicrobial development pipeline,^{6,31} there will be a significant lag in response time from when existing antibiotics will entirely lose their effectiveness to when new, effective anti-bacterial therapies will be introduced into the market. This lag time will result in hundreds of thousands of deaths, which could be prevented by acting now – through incentives, if need be – rather than waiting for the market to necessitate action. In addition, while it is certainly true that the public sector works within a budget and that there are other causes that require public funding, it is relevant to point out that governments in developed countries tend to have more money than many corporations – however, governmental budgets are constrained due to other priorities.^{64,65} Nonetheless, the percentage of public-financing of R&D incentives could vary depending on the nation, with higher percentages of funds coming from private sources through public-private partnerships in certain countries.

Besides James,⁶² three other articles did not recommend any particular financial incentive model. Instead, one article solely focused on potential obstacles to implementation pertaining to different incentive mechanisms, identifying which mechanisms would be attractive or unattractive to not-for-profit research institutes, SMEs, or large pharmaceutical companies.³⁴ Another article exclusively focused on the potential negative economic effects of market exclusivity extensions, noting that such incentive strategies are quite costly and are not evidenced to particularly reward drug innovativeness or clinical value.⁶¹ Similarly, Batista et al¹⁹ concentrated on intellectual property-based incentives, providing a thorough analysis of the theoretical advantages (eg, longer exclusivities could encourage patent-holders to preserve the effectiveness of their antibiotic drugs for longer) and empirical challenges or disadvantages (eg, the extra cost associated with transferable exclusivity incentives would be unfairly borne by patients) pertaining to such mechanisms. In these articles, the reason behind the lack of final financial incentive recommendation is unclear; however, it is possible that this was simply outside the scope of their analyses. Alternatively, it should be considered that these articles may have refrained from recommending a model because

they do not believe that any particular financial incentive strategy would be useful in motivating the development of clinically beneficial antibiotics. We argue, however, that if this were the case, this perspective would be indicated and discussed within the articles; yet, neither of these three articles contain such arguments.

Our incentive analysis revealed that while different push incentive strategies each have their own specific set of strengths and weaknesses, they all appear to be moderately productive in motivating change, as all were tied with a total score of 4 points each. The strengths of push incentives lie in their tendency to be more readily implementable than pull or hybrid incentive models coupled with their ability to encourage the participation of SMEs.^{18,21,66} As push incentives of various types and sizes have already been implemented to motivate antibiotic R&D in many countries, they are relatively familiar, politically palatable, and cost-effective compared to many pull incentives, thereby facilitating implementation.^{21,66} In addition, push incentives benefit SMEs by providing them with the funding they need for investing in new antibiotic projects or completing expensive later-stage clinical trials.^{18,48,67} However, such incentives are less likely to motivate large pharmaceutical firms to resume R&D in antibiotics if they have already abandoned this field. Additionally, push incentives do little in supporting public health goals such as antibiotic conservation, rewarding innovation, or improving patient access to antibiotics, as they are typically not tied to any post-approval conditions.⁶⁷ Therefore, we support the consensus in the literature that push incentives alone are not sufficient for addressing the antibiotic innovation problem; however, they are nonetheless a good place to start. Overall, our literature findings and assessments suggest that push incentives will be most productive when applied in conjunction with one or more pull incentives.

Interestingly, a much wider scoring variability was observed for pull incentive strategies, with both the lowest score and the highest score being awarded to strategies within this category. A commonality between all the pull incentives evaluated in this review was that none would be particularly helpful in encouraging the participation of SMEs; however, the majority of pull strategies are forecasted to encourage the participation of large pharmaceutical companies with access to R&D capital reserves instead.^{18,63} Moreover, most pull incentives are projected to have challenges pertaining to their implementation feasibility, as the majority would require significant change to

the current business model and many have not yet been implemented in other countries. However, this could be subject to change given that a couple pilot projects are currently underway that may soon redefine how we view the implementation feasibility of pull incentives, if they are successful.

In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) and the National Health Service (NHS) of England have begun to implement a pilot project that plans to use a hybrid subscription model to reimburse pharmaceutical companies for antimicrobial drug development.^{68,69} This subscription model combines a value-based reimbursement with a fully-delinked MER, with antibiotics being subjected to a health technology assessment that is to be conducted by NICE to determine the clinical value of the antibiotic in question.⁶⁹ Suppliers of antibiotics which pass this assessment will be reimbursed on the basis of a multi-year contract paid in yearly installments, with the antibiotic's performance over time affecting the actual annual fee paid to suppliers.⁶⁹

In Sweden, another subscription model is being piloted by the Swedish Public Health Agency.⁷⁰ Similar to the UK model, this model will also pay suppliers of qualifying clinically-important antibiotics a value-based annual fee in exchange for access to the antibiotic.⁷¹ Unlike the UK model, however, the Swedish pilot represents a partially-delinked MER whereby participating suppliers are able to perform volume-based sales while also being guaranteed a minimum annual revenue for qualifying antibiotics, as defined in the subscription contract between the Swedish Public Health Agency and the supplier.⁷⁰⁻⁷²

Both these models represent novel methods of reimbursement for antibiotics. By combining the MER strategy with a value-based component for reimbursement, these pilot projects may be better equipped than any other implemented incentive to begin addressing the antibiotic pipeline problem. While it is too early to tell how effective these projects will be as data are not yet available, the existence of these projects is certainly an extraordinary step in the right direction.

Lastly, the two hybrid incentives we analyzed both scored 5 points in our assessment, meeting several important framework criteria. The OMA model is unique in that it is the only assessed incentive that would be expected to encourage participation of pharmaceutical companies of all sizes, as it allows funders to share some of the venture risk with the pharmaceutical firm by investing in a drug

regardless of where it is in the development pipeline.¹⁸ However, the OMA model does not promote antibiotic conservation. On the other hand, the ACE model has antibiotic conservation as its primary goal, using conditional performance-based payments to reward innovative antibiotics and drug stewardship in post-market use.¹⁸ Unfortunately, being a pull-centered incentive strategy, the drawback is that this model would appeal to large pharmaceutical firms much more than to SMEs.¹⁸

In the next section, a case study using Canada as a country-based example will assess which of the recommended incentive strategies from the articles included in this review could best benefit the Canadian landscape.

Applying Incentives in the Canadian Landscape: A Case Study

The Canadian Landscape

In Canada, the health care system, best known as Medicare, is a universal publicly funded system regulated by the federal government and delivered through Canada's 13 provinces and territories.⁷³ At present, Canada is the only country with a universal health care system that lacks a national pharmacare program, with prescription drug coverage varying considerably among provinces, resulting in one in five Canadians struggling to afford prescription medicines.⁷⁴ However, a plan to implement a cost-saving national pharmacare program has recently been announced by the Canadian government.⁷⁴ In brief, this plan recommends the creation of a drug agency responsible for assigning and approving drugs to a national formulary (ie, the drugs which will be covered under pharmacare), with the initial list of national formulary drugs set to be available on January 1, 2022.⁷⁴ Over the next five years, the national formulary will expand to include drugs beyond essential medicines, including expensive drugs for rare diseases, with the goal of having a full, comprehensive formulary in place by 2027.⁷⁴

When it comes to addressing antibiotic resistance, proposed solutions lack focus on antibiotic innovation, with possible drug development financial incentive models or suggestions remaining largely unexplored. In fact, most reports, awareness platforms, or action plans in Canada^{14,75-77} have largely refrained from suggesting solutions that specifically address the lack of new antibiotics as one of the challenges contributing to the overall threat of antibiotic resistance, although treating drug-resistant bacterial infections in the future will become

increasingly difficult without new antibiotics. So far, the only way that this problem has been addressed in Canada has been by the recent implementation of an expedited regulatory review process for antibiotic drugs that target pathogens from Health Canada's "Pathogen of Interest" list, published in 2018, which contains a list of the pathogens responsible for the most hard-to-treat infections in Canada.⁷⁸

A Path Forward?

When translating antibiotic incentive recommendations from the literature into the context of a Canadian perspective, there are a couple criteria that are relevant to consider. First, it is likely that the implementation of a financial incentive model in Canada may involve a slow uptake due to the fact that the revitalizing of the antibiotic pipeline is not currently seen as a pressing issue within the national strategy for combatting antibiotic resistance.¹⁴ Thus, the feasibility of implementation will be of particular importance in deciding an appropriate incentive strategy for implementation in Canada. Furthermore, the composition of Canada's pharmaceutical industry must also be considered when assessing the suitability of different antibiotic incentive strategies for Canada. While some local pharmaceutical companies exist, foreign multinational companies with subsidiaries in Canada represent the majority of Canadian drug sales and R&D investment.⁷⁹ Despite this, interest in R&D investment in Canada by multinational companies is relatively low on the global priority list, with Canadian SMEs and contract research organizations carrying out an increasingly large proportion of Canadian R&D activities.^{79,80} In terms of antibiotic R&D, Canada is not a major global player, as evidenced by the fact that Canadian companies are only developing two of the 32 antibiotics targeting WHO priority pathogens which are currently in clinical development.¹⁶

Based on our incentive analysis, we recommend that Canada follow in the footsteps of the UK and Sweden by implementing a subscription-based MER which would be accessible to both local and multinational drug developers selling into the Canadian market. While there may be some resistance to the implementation of such an incentive in Canada due to the high associated cost, we argue that investing in this field now will ultimately end up saving taxpayer money which would otherwise be spent on the health burden due to ABR if the status quo is maintained.^{6,81} As per our assessment (Table 4), MERs

were highly ranked among analyzed incentive strategies, with fully delinked incentives receiving the highest score and partly delinked incentives being one of the four strategies awarded the next highest score. However, by combining a basic MER strategy with a value-based reimbursement strategy, the subscription-based model addresses the two major weaknesses of a basic MER strategy: an inherent disregard for the antibiotic's level of innovativeness and its performance over time. The value-based reimbursement component of both the UK and Swedish subscription-based models ensures that only antibiotics of sufficient clinical importance receive the reward and calls for the value of the antibiotic's annual subscription fee to be adjusted according to the antibiotic's performance. The UK and Swedish pilot schemes could be used as models to inspire the creation of a similar pull MER incentive strategy in Canada, whereby the government will pay an annual subscription fee to suppliers of qualifying antibiotics. Referring to the details surrounding the implementation of these pilot schemes in other countries will facilitate the design and implementation of a subscription-based MER in Canada that complements, supports, and builds upon existing pull incentive pilot projects. Conversely, most other pull incentive strategies and both hybrid incentive strategies analyzed in this review have not yet been successfully implemented in other countries (Table 4), which may consequently render implementation in Canada more challenging. Beyond feasibility challenges, implementing an incentive that has not yet been implemented anywhere else in the world would result in a less positive effect than the translation of an existing incentive to the Canadian landscape. As ABR is an issue affecting all countries, a solution that contributes to a multi-national approach by supporting the work being done in other countries is needed; therefore, a subscription-based MER following an existing model is well-suited.

In terms of whether the UK's fully delinked or Sweden's partially delinked subscription model would be more effective, we posit that Canada would benefit from following the UK's lead in order to implement a similar fully delinked subscription-based MER optimized for the Canadian landscape. Given Canada's early stage of development for its new national pharmacare program, the integration of a similar program could be easier to achieve. A fully delinked MER model is distinguished from a partially delinked model as the former requires the drug developer to agree to not sell or promote the use of their product, with the developer's main revenue stream consisting of the MER, whereas the latter allows the developer to continue selling their product for

Table 4 Criteria-Based Assessment of Recommended Incentive Strategy Using Modified Renwick et al.¹⁸ Framework

Incentive Strategy + Total Score	Improves NPV	Enables SME Participation	Enables Big Pharma Participation	Promotes Cooperation/Synergy Among Key Players	Feasible Within Current Business Model	Piloted in Other Countries	Involves Delinking	Conditional Grants/Payments	Promotes Antibiotic Stewardship	Rewards Innovation	Improves Patient Access
Push Incentives											
Open-source drug discovery (4)	✓	✓	X	✓	X	✓	X	X	X	X	X
Grants (4)	✓	✓	X	X	✓	✓	X	X	X	X	X
Tax incentives/ Credits (4)	✓	X	✓	X	✓	✓	X	X	X	X	X
Pull Incentives											
Conservation-based market exclusivity (4)	✓	X	✓	X	✓	X	X	X	✓	X	X
Diagnosis confirmation model (1)	✓	X	X	X	X	X	X	X	X	X	X
Fee on antibiotic use (3)	✓	X	X	X	✓	X	X	X	✓	X	X
Increase antibiotic prices (4)	✓	X	✓	X	✓	X	X	X	✓	X	X
MER (fully delinked) (6)	✓	X	✓	X	X	✓	✓	X	✓	X	✓
MER (partially delinked) (5)	✓	X	✓	X	X	✓	✓	X	X	X	✓
Value-based reimbursement (5)	✓	X	✓	X	X	✓	X	✓	X	✓	X
Hybrid Incentives											
OMA (5)	✓	✓	✓	X	X	X	X	X	X	✓	✓
ACE (5)	✓	X	✓	X	X	X	X	✓	✓	✓	X

Notes: Adapted with permission from Renwick M, Brogan DM, Mossialos E. A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. *J Antibiot (Tokyo)*. 2016;69(2):73–88. Copyright 2016 Springer Nature.¹⁸

Abbreviations: NPV, net present value; SME, small-medium enterprise; MER, market entry reward; OMA, options market award; ACE, antibiotic conservation and effectiveness.

profit and also awards the developer with an MER.³⁷ The main advantage of the fully delinked model compared to the partial model is that it completely removes the motivation to maximize unit sales, aligning with antibiotic conservation and stewardship efforts. Additionally, given that more implementation design information and details are publicly available for the UK model at present, it will be easier to apply this pilot incentive model over the Swedish model to the Canadian landscape.

Alternatively, if the Canadian government does not have the political traction or appropriate resources to commit to a pull incentive strategy at this point in time, targeted grants for financing clinical development may also be productive given the considerations of the Canadian landscape. Despite being undervalued by our included articles, with only 10 articles (24%) suggesting grants as a component of their proposed mix/hybrid incentive model or as a standalone mechanism, we posit that this mechanism is an appropriate way forward in Canada. One advantage of grants is that they have been used as incentives to promote antibiotic research in other countries, such as the Biomedical Advanced Research and Development Authority (BARDA) in the United States (US), among others, which demonstrates that this is a feasible approach to implement in Canada.³⁵ The fact that such an incentive could be funded either by the government or by an NGO is also an attractive component, as it gives some flexibility regarding its implementation. Furthermore, this incentive would not radically change the market or pharmaceutical business model; instead, it would simply function to lower R&D cost for both small and large pharmaceutical companies, thereby encouraging them to develop new antibiotics. While it is true that grants mainly encourage the participation of SMEs over large pharmaceutical firms,¹⁸ this type of incentive may be particularly well-suited in Canada, where R&D is being increasingly carried out by Canadian SMEs and contract organizations.⁷⁹ As access to capital is the biggest hurdle to drug commercialization for these Canadian SMEs,⁷⁹ implementing a grant incentive strategy may serve as an important motivator for driving projects forward. These targeted grants should only finance the development of antibiotics for high-priority pathogens for which limited treatment options currently exist, thereby allowing the managing body to control which antibiotics will enter the market, ensuring that future Canadians have access to alternative treatments for high-threat bacterial infections.

Importantly, given the Canadian government's recent commitment to the implementation of a national pharmacare program, we must consider whether pharmacare would impact the suitability or success level of certain financial incentive mechanisms in motivating antibiotic innovativeness. We posit that a possible negative effect of introducing pharmacare could be that systemic changes to the pricing and reimbursement environment may result in drug manufacturing companies becoming even more demotivated to produce innovative antibiotics; however, there is much that is still unknown about how pharmacare will be implemented in Canada and its downstream effects.⁸² If drastically reduced prices are enforced, this would provide Canada with all the more reason to invest in financial incentives as a mitigation measure. The introduction of a national pharmacare program in Canada would render the fully delinked subscription model developed as per the UK's pilot as a particularly suitable mechanism to stimulate substantial innovation, as it will motivate drug manufacturers to develop clinically beneficial antibiotics whilst guaranteeing qualifying manufacturers revenue from successfully marketing such antibiotics. Additionally, it is possible that national pharmacare may bring new challenges pertaining to antibiotic stewardship at the community level, as it would eliminate cost-related barriers to antibiotic access and use; however, implementing an incentive similar to the UK subscription model – which fully unlinks product sales from revenue and also considers how well the antibiotic performs as a factor in determining a supplier's actual payment – will significantly counteract this issue.

Conclusion

As more and more people become infected with hard-to-treat, multi-drug resistant infections, having reliable and effective antibiotic drugs will become more important than ever. However, multiple barriers exist that render antibiotic investment an unattractive business endeavor for pharmaceutical companies and novel solutions need to be explored by policymakers to urgently address this lack of innovation.

This systematic review identified 42 articles containing recommendations for solutions for revitalizing the antibiotic pipeline, with the majority advocating for the implementation of mix/hybrid financial incentive models. The lack of consensus regarding the specific design and size of a financial incentive model suggests that there is no one-size-fits-all solution; rather, it seems that some incentive schemes may be more useful for some countries than for others.

When applying the results of this literature review to a case study of Canada that considers Canada's specific needs, we propose that Canada support ongoing efforts in other countries by implementing a fully delinked subscription-based MER similar to the pilot model that was recently launched in the UK. Following the model laid out by the UK provides Canada with a reference for facilitating implementation, despite the feasibility challenges otherwise associated with fully delinked incentives. Further, the fully delinked model removes the drug manufacturer's desire to maximize revenue from unit sales and the annually adjusted subscription fee ensures that the payment reflects the antibiotic's performance over time. On the other hand, if Canada is unwilling to implement a pull incentive, we also suggest an alternative and less disruptive incentive strategy: grants targeting high-priority pathogens for which there are limited treatment options. Implementing a financial incentive model suited to the Canadian context will be an overdue and crucial step forward for controlling antibiotic resistance and lowering the incidence of death due to drug-resistant infections in Canada as well as around the world.

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