



Australian Government
Department of Health
and Aged Care

Antimicrobial Resistance Pricing and Reimbursement Scoping Study

Final Report

August 2022

Report to the Australian Government Department of Health and Aged Care

ACIL ALLEN



Copyright

© 2024 Commonwealth of Australia as represented by the Department of Health and Aged Care

Disclaimer

This publication is provided for general information only.

The opinions, comments, recommendations, and/or analysis expressed in this publication are those of the author(s) and relevant third parties and do not necessarily reflect the views of the Australian Government, including the Department of Health and Aged Care, and cannot be taken in any way as an endorsement or a commitment to a particular course of action, including any future development or implementation.

The Department of Health and Aged Care, its employees and advisers disclaim all liability, including liability for negligence and for any loss, damage, injury, expense or cost incurred by any person as a result of accessing, using or relying on any of the information or data in this publication to the maximum extent permitted by law.

The report should be considered as a foundation for further development and not as Government policy endorsement.

Creative Commons Licence



This publication is licensed under the Creative Commons Attribution 4.0 International Public License available from <https://creativecommons.org/licenses/by/4.0/legalcode> ("Licence"). You must read and understand the Licence before using any material from this publication.

Restrictions

The Licence may not give you all the permissions necessary for your intended use. For example, other rights (such as publicity, privacy and moral rights) may limit how you use the material found in this publication.

The Licence does not cover, and there is no permission given for, use of any of the following material found in this publication:

- the Commonwealth Coat of Arms. (by way of information, the terms under which the Coat of Arms may be used can be found on the Department of Prime Minister and Cabinet website <http://www.dpmc.gov.au/government/commonwealth-coat-arms>);
- any logos and trademarks;
- any photographs and images;
- any signatures; and
- any material belonging to third parties.

Attribution

- Without limiting your obligations under the Licence, the Department of Health requests that you attribute this publication in your work. Any reasonable form of words may be used provided that you:
- include a reference to this publication and where, practicable, the relevant page numbers;
- make it clear that you have permission to use the material under the Creative Commons Attribution 4.0 International Public License;
- make it clear whether or not you have changed the material used from this publication;

- include a copyright notice in relation to the material used. In the case of no change to the material, the words “© Commonwealth of Australia (Department of Health and Aged Care) 2024” may be used. In the case where the material has been changed or adapted, the words: “Based on Commonwealth of Australia (Department of Health and Aged Care) material” may be used; and
- do not suggest that the Department of Health endorses you or your use of the material.

Enquiries

Enquiries regarding any other use of this publication should be addressed to the Branch Manager, Communication Branch, Department of Health and Aged Care, GPO Box 9848, Canberra ACT 2601, or via e-mail to copyright@health.gov.au

Authors

This report was commissioned by the Australian Government Department of Health and Aged Care and delivered under contract by ACIL Allen Consulting.

Preferred citation

ACIL Allen. Antimicrobial Resistance Pricing and Reimbursement Scoping Study: Final Report. Canberra: Australian Government Department of Health and Aged Care; 2024.

Contents

Key Findings	i
Project Purpose	i
Economic Assessment Approach	i
Priority Mechanisms	i
Economic Assessment Results	ii
Recommendations	iii
1 Project Background	1
1.1 This Project	1
1.2 Problem statement	1
1.3 Antibiotic Development	2
1.3.1 Stages of the antibiotic’s development pipeline	2
1.3.2 Mechanisms to incentivise antibiotic development	3
1.4 Priority Mechanisms	4
1.4.1 Literature Review	4
1.4.2 Stakeholder Consultation	4
2 Impact Identification	7
2.1 Overview	7
2.2 Approach	7
2.2.1 Meetings	7
2.2.2 Resources	7
2.2.3 Stakeholders	8
2.3 Findings	9
2.3.1 Frame of reference	9
2.3.2 Identified impacts	9
3 Options	11
3.1 Service availability premiums, subscriptions and licenses (SSL)	11
3.1.1 Overview of the mechanism	11
3.1.2 How the mechanism shifts antibiotic funding from a cost focus to a focus on societal value 11	
3.1.3 How the mechanism can be implemented in Australia	13
3.1.4 Risk to Government, barriers to implementation and mitigation strategies	14
3.2 Accelerated assessment and approval (AAA)	15
3.2.1 Overview of the mechanism	15

3.2.2	How the mechanism shifts antibiotic funding from a cost focus to a focus on societal value	15
3.2.3	How the mechanism can be implemented in Australia	16
3.2.4	Risk to Government, barriers to implementation and mitigation strategies.....	17
3.3	Advance Market Commitments (AMC).....	18
3.3.1	Overview of the mechanism	18
3.3.2	How the mechanism shifts antibiotic funding from a cost focus to a focus on societal value	18
3.3.3	How the mechanism can be implemented in Australia	19
3.3.4	Risk to Government, barriers to implementation and mitigation strategies.....	20
3.4	Strategic Antibiotic Reserve (SAR)	21
3.4.1	Overview of the mechanism	21
3.4.2	How the mechanism shifts antibiotic funding from a cost focus to a focus on societal value	22
3.4.3	How the mechanism can be implemented in Australia	22
3.4.4	Risk to Government, barriers to implementation and mitigation strategies.....	23
3.5	Value-based pricing/reimbursement and pay-for-performance (VBP).....	24
3.5.1	Overview of the mechanism	24
3.5.2	How the mechanism shifts antibiotic funding from a cost focus to a focus on societal value	24
3.5.3	How the mechanism can be implemented in Australia	26
3.5.4	Risk to Government, barriers to implementation and mitigation strategies.....	27
4	Assessment of costs.....	29
4.1	Overview	29
4.2	Key considerations.....	29
4.3	Cost 1: Mechanism implementation	30
4.3.1	Guaranteed revenue models	31
4.3.2	Accelerated review models.....	32
4.3.3	Value models.....	33
4.4	Cost 2: Cost to conduct regulatory approval for each antibiotic	34
5	Assessment of benefits	36
5.1	Overview	36
5.2	Key considerations.....	36
5.3	Base Case.....	37
5.4	Benefit 1: Avoided mortality due to AMR.....	39
5.4.1	Likelihood of mechanisms addressing the problem.....	39
5.4.2	Duration until antibiotics are available	43

5.4.3	Pathogen of focus for novel antibiotic.....	45
5.4.4	Infections by pathogen.....	45
5.4.5	Growth in infections by pathogen	46
5.4.6	Resistance rates by pathogen	46
5.4.7	Mortality rates by pathogen	46
5.4.8	Antibiotic effectiveness discount.....	46
5.4.9	Value of a Statistical Life (VSL)	47
5.4.10	Calculation.....	47
5.5	Benefit 2: Avoided morbidity due to AMR.....	48
5.5.1	Hospitalised days.....	48
5.5.2	Disability weights	48
5.5.3	Value of a Statistical Life Year (VSLY)	48
5.6	Benefit 3: Avoided hospitalisation costs due to AMR.....	49
5.6.1	Cost per hospital bed day	49
6	Findings and results	50
6.1	CBA Results.....	50
6.2	Avoided mortality and hospitalisation days	50
6.3	Incremental costs and benefits	51
6.3.1	Guaranteed revenue models	51
6.3.2	Accelerated review models.....	53
6.3.3	Value models.....	53
7	Sensitivity Analysis.....	54
7.1	Overview	54
7.2	Sensitivity tests	54
7.2.1	Sensitivity test 1: New antibiotic effectiveness rate	54
7.2.2	Sensitivity test 2: Timing of availability of novel antibiotic.....	55
7.2.3	Sensitivity test 3: Likelihood of mechanisms addressing the problem	55
7.2.4	Sensitivity test 4: Discount rate.....	56
7.2.5	Sensitivity test 5: Assessment period	56
7.2.6	Sensitivity test 6: Mechanism cost.....	57
7.2.7	Sensitivity test 7 – Infection rates	57
7.2.8	Sensitivity test 8 – Mortality rates	58
7.2.9	Sensitivity test 9 – Resistance rates	58
8	Qualitative Impacts and Distributional Analysis	60
8.1	Overview	60

8.2	Qualitative Benefits	60
8.3	Qualitative Costs	61
9	Validation	62
9.1	Overview	62
9.2	Process	62
9.3	Limitations of this study and areas for future research.....	62
10	Prioritisation	65
10.1	Overall Assessment	65
11	Conclusion and recommendations.....	66
11.1	Overview	66
11.2	Recommendations	66
11.2.1	Recommendation 1: AMR Taskforce	66
11.2.2	Recommendation 2: Mechanism Funding	66
11.2.3	Recommendation 3: Manufacturing capacity and capability.....	66
11.2.4	Recommendation 4: Mechanism and contract design	67
11.2.5	Recommendation 5: Mechanism and contract management.....	67
11.2.6	Recommendation 6: Mechanism and contract evaluation	68
	Appendices.....	69
A	Reference List.....	A-1
B	Mechanism Prioritisation.....	B-1

Key Findings

This section provides a brief summary of the key findings from the Final Report of the Antimicrobial Resistance Pricing and Reimbursement Scoping Study.

Project Purpose

The Australian Government Department of Health and Aged Care (the Department) engaged ACIL Allen to develop the evidence base on mechanisms that may be used to incentivise the discovery of novel antibiotics for human health and bring them to market in Australia (the mechanisms), and recommend suitable models for the Australian context.

This project has involved three phases, including a literature review, stakeholder consultation and economic assessment.

This report presents the findings of economic assessment, which was informed by the preceding two phases.

Economic Assessment Approach

ACIL Allen undertook a cost benefit analysis to estimate the overall direct and indirect costs and impacts on implementing each mechanism, accounting for all the effects on the community and economy of Australia.

ACIL Allen identified five quantitative and seven qualitative impacts, as presented below.

Quantitative impacts

- Avoided mortality associated with AMR
- Avoided morbidity associated with AMR
- Avoided hospitalisation costs
- Cost to implement the mechanism
- Cost to conduct regulatory approval for each antibiotic

Qualitative impacts

- Enablement value of antibiotics
- Contribution to a global solution
- Build capacity and responsiveness
- Synergistic effects of antibiotics
- Use of antibiotics during clinical trials
- Agreement risk
- Diversion of development focus

Priority Mechanisms

ACIL Allen has adopted a staged approach to identify and prioritise mechanisms with the potential to incentivise the development of antibiotics. This process identified five mechanisms that have been assessed in this report and are presented below in order of prioritisation:

1. **Rank 1: Accelerated assessment and approval (AAA):** Provides fast tracking and priority reviews through regulatory processes for antibiotics. This reduces the length of drug registration and market approval for antibiotics that meet certain specifications.

The accelerated assessment can be provided as a priority review voucher following approval of an antibiotic, which can be sold or transferred.

2. **Rank 2: Advance Market Commitments (AMC):** Contracts between researchers and/or manufacturers and a funder (typically a government or financial entity) to guarantee a viable market for a product once it is developed. The AMC sets out an agreement where the funder heavily subsidises the future purchase of a set amount of antibiotics at a pre-specified price upon successful development. The transfer of funding occurs after the product reaches the market.
3. **Rank 3: Service availability premiums, subscriptions and licenses (SSL):** Financial rewards, paid on an ongoing basis, to a manufacturer for guaranteed availability of and access to an antibiotic. They involve agreements between funders (typically government(s) and not-for-profit(s)) and antibiotic manufacturers.
4. **Rank 4: Strategic Antibiotic Reserve (SAR):** A single or group of governments buy or license the patent for an important first-in-class antibiotic to hold it in reserve for the future, or urgent and serious infection cases. SARs involve contractual arrangements between governments and manufacturers where value-based payments are made to manufacturers who agree to place antibiotics in a SAR in lieu of their right to freely market and sell the antibiotic.
5. **Rank 5: Value-based pricing and pay-for-performance (VBP):** Pricing mechanisms designed to support pricing of antibiotics in line with the public health value that antibiotics contribute by setting a guaranteed price for certain antibiotics. It de-links the reimbursement of the antibiotic from its sale price and volume.

Each mechanism is analysed in terms of:

- How the mechanism shifts antibiotic funding from a cost focus to a focus on societal value
- How the mechanism can be implemented in Australia
- Risk to Government, barriers to implementation and mitigation strategies

Economic Assessment Results

Table ES 1 provides a summary of the net benefits and costs associated with implementing the mechanisms, relative to the absence of implementation (the base case scenario).

Table ES 1 Cost benefit analysis results, \$2021

Present value (\$, 10 years @7%)	SSL	AAA	AMC	SAR	VBP
1. Avoided mortality	\$208,506,696	\$215,952,850	\$195,677,971	\$185,277,518	\$158,260,232
2. Avoided morbidity	\$221,184	\$228,284	\$207,479	\$195,945	\$167,819
3. Avoided hospitalisation costs	\$5,796,448	\$5,982,512	\$5,437,298	\$5,135,041	\$4,397,946
Total benefits	\$214,524,328	\$222,163,646	\$201,322,748	\$190,608,504	\$162,825,998
1. Mechanism cost	\$58,623,559	\$37,853,872	\$54,788,373	\$54,788,373	\$162,825,998
2. Regulatory approval cost	\$111,847	\$128,053	\$104,530	\$104,530	\$79,745
Total costs	\$58,735,406	\$37,981,925	\$54,892,903	\$54,892,903	\$162,825,998
NPV of Benefits minus Costs	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
BCR	3.65	5.85	3.67	3.47	1.00

Source: ACIL Allen, 2022

Recommendations

Recommendation 1: AMR Taskforce

The Australian Government should establish a taskforce to be responsible for implementing a mechanism to incentivise the development and availability of novel antibiotics in Australia. The taskforce should include representation of members with suitable skills and experience to progress these initiatives, including in the fields of infectious diseases, medical R&D and commercialisation, research and procurement of antibiotics. The Taskforce should consider the findings and directions in this scoping study and look to progress implementation, including consideration of the following recommendations.

Recommendation 2: Mechanism Funding

As outlined in this study, a number of initiatives have been trialled in other countries in an effort to incentivise the development of novel antibiotics. Furthermore, with the growing awareness of the threat AMR poses, an increasing number of countries are also considering how best to contribute to a solution. The Australian Government, through the AMR Taskforce, should explore opportunities to partner with other countries and / or funding organisations (e.g., not-for-profit organisations) to fund the implementation of a mechanism. Possible partnerships may be based around geographical proximity (e.g., Asia Pacific region) and / or around existing diplomatic relations.

Recommendation 3: Manufacturing capacity and capability

The Australian Government, through the AMR Taskforce, should commence a market sounding exercise to gauge the manufacturing capacity and capability of potential suppliers to engage with under the mechanism (i.e., antibiotics manufactures). In the first instance, this should include industry consultation with pharmaceutical companies, particularly those already participating in similar trial in other counties (e.g., the NICE trials involving Pfizer and Shionogi). This consultation should focus on identifying interest, capacity and the conditions under which suppliers would be willing to engage.

Recommendation 4: Mechanism and contract design

The Australian Government, through the AMR Taskforce, should commence the design of a contract to implement the mechanism. While this scoping study indicates that AAA is the highest priority mechanism, this should be further considered by the Taskforce and through industry consultation (i.e., recommendation 3). Some aspects to consider further include:

- Mechanism value
- Number of suppliers
- Target antibiotic
- Contract specification

Based on the contract design, a suitable set of selection criteria should also be developed, and the AMR Taskforce should oversee the evaluation of supplier submissions.

Recommendation 5: Mechanism and contract management

The Australian Government, through the AMR Taskforce, should design a contract management framework to support the delivery of services under the mechanism. This should include reporting requirements, such as contract operations and risks. This may include antibiotic volumes, contract payments and reporting of adverse patient events. The

framework may also consider unintended risks, such as the impact of the mechanism on the existing medical supplies (including those produced by manufacturers who are involved in the mechanism contract). The contract management should also account for review points between government and the supplier, to enable terms to be re-negotiated based on key parameters to ensure the mutually beneficial ongoing operation of the mechanism.

Recommendation 6: Mechanism and contract evaluation

The Australian Government should direct the Taskforce to develop a monitoring and evaluation framework and undertake periodic evaluations to determine the achievement of process and outcome measures.

The AMR Taskforce should commission periodic evaluations to both monitor the ongoing operation of the mechanisms to inform improvement opportunities and at the conclusion of the contract to assess the overall performance of the contract.

1 Project Background

1.1 This Project

The Australian Government Department of Health and Aged Care (the Department) engaged ACIL Allen to develop the evidence base on mechanisms that may be used to incentivise the discovery of novel antibiotics for human health and bring them to market in Australia (the mechanisms), and recommend suitable models for the Australian context.

This project has involved three phases:

- A Literature Review
- Stakeholder Consultation
- Economic Assessment

This report presents the findings of economic assessment, which was informed by the preceding two phases.

1.2 Problem statement

Antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi and parasites adapt over time and no longer respond to existing medicines (Larsson and Flach, 2022). As a result, antibiotics and other antimicrobial agents become ineffective and infections become increasingly difficult or impossible to treat (Larsson and Flach, 2022). Especially concerning is the emergence and global spread of multi-, extensively- and pan-resistant bacteria that cause infections that are not treatable with existing antibiotics (Magiorakos et al., 2012). Antibiotic resistance (ABR) is a subset of AMR, that applies specifically to bacteria that become resistant to antibiotics.

Developing new, particularly novel, antibiotics is a well-recognised, global challenge (World Health Organization, 2017, Wellcome Trust, 2020, Morice et al., 2020, Williams and Wyner, 2019, United Nations Interagency Coordination Group on Antimicrobial Resistance, 2019). The development pipeline has stalled. It is not financially viable for researchers and manufacturers to invest in the research and development (R&D) needed to identify novel antibiotics and bring these to market, particularly given the low financial return from antibiotics sales and the need to conserve the use of antibiotics to maintain their effectiveness (Jackson et al., 2018, Kmietowicz, 2017).

Given these challenges, no novel classes of antibiotics have been brought to market since 1987, and few novel classes are in the development pipeline (Eisenstein et al., 2010, Miller et al., 2016). Further, existing antibiotics are not always easily available or accessible when and where they are needed (The Pew Charitable Trusts, 2021).

Various international bodies (the United Nations (UN), World Health Organization (WHO), G20 Leaders) have called for urgent global and national efforts to identify practical market incentive options that can reinvigorate the antibiotic R&D pipeline (World Health Organization, 2017, Wellcome Trust, 2020, Wellcome Trust, Williams and Wyner, 2019, United Nations Interagency Coordination Group on Antimicrobial Resistance, 2019). These incentive options should consider antibiotics as a public good, that is, that public value is

generated by the availability and accessibility of effective antibiotics when they are needed (Gotham et al., 2021).

Significant work has begun on identifying and implementing incentives to address challenges to developing antibiotics across the development pipeline (Vogler et al., 2021). Broadly, these incentives are classified as push and pull mechanisms and aim to support development at the early and late stages of the development pipeline respectively (Renwick et al., 2016, Ciabuschi et al., 2020, Luepke et al., 2017). Push mechanisms focus on promoting collaboration and on decreasing early antibiotic development costs and pull mechanisms aim to increase or ensure adequate market revenue for newly approved antibiotics (Renwick et al., 2016, Ciabuschi et al., 2020, Luepke et al., 2017).

Australia faces a range of challenges and opportunities in supporting global efforts to develop novel antibiotics (AusBiotech et al., 2019, MTPConnect, 2020a, Ciabuschi et al., 2020).

Australia maintains a strong and well-funded research sector, and has many advantages as a place to conduct clinical trials, owing to the country's high quality researchers and health professionals, world-class research infrastructure, a stable socio-political environment, and high standards that ensure confidence in the scientific conclusions reached by clinical trials (MTPConnect, 2020a, Australian Clinical Trials).

On the other hand, Australia has a federated health and hospital system with siloed funding arrangements leading to duplication, including funding from the Australian Government, state and territory government funding, non-government funding (including philanthropy, private sector investment, and self-financing), and government co-investment (Australian Department of Education Skills and Employment, 2015, Industry Innovation and Science Australia (IISA), 2021, Australian Department of Education Skills and Employment, 2021).

Relative to the aggregate global market, Australia has a small human antibiotic market size and low volume of usage of antibiotics accordingly (Browne et al., 2021, Australian Government Antimicrobial Resistance, 2017, Australian Commission on Safety and Quality in Health Care (ACSQHC), 2019). These factors contribute to Australia being a less attractive market for firms to enter given registration costs and low sales price, which in turn reduces availability and accessibility of effective antibiotics when they are needed.

In the context of antimicrobial development, Australia also faces barriers in terms of accessing people with sufficient capacity and deep skills in commercialisation, access to research infrastructure and access to manufacturing capability (AusBiotech et al., 2019, MTPConnect, 2020a).

1.3 Antibiotic Development

1.3.1 Stages of the antibiotic's development pipeline

Antibiotic development can take many years and go through appropriate regulatory bodies and approvals to ensure that they are safe and effective when they reach the public. The antibiotic development pipeline can be divided into 5 key stages, summarised below.

- **Stage 1: Discovery and translational research:** The discovery and translational research for a new antibiotic begins in research laboratories at research institutions and universities, which are primarily funded by government funding agencies. This

- stage includes pre-clinical development, including activities and testing that links drug discovery in the laboratory to initiation of human clinical trials (Miethke et al., 2021).
- **Stage 2: Clinical research and trials:** Clinical research can be divided into three distinct clinical trial phases (Phase I, II and III). In the early trial phases, the new antibiotic is tested in a small number of participants to assess safety and effectiveness. Antibiotics showing promising results may move to later phases of testing in larger participation samples to collect more information on effectiveness and possible side effects (Australian Clinical Trials, 2015).
 - **Stage 3: Market approval:** During this stage regulatory bodies examine the submitted clinical research and trials data of the new antibiotic and decide whether to approve or not for human use (Somers, 2021, Therapeutic Goods Administration, 2018).
 - **Stage 4: Pricing and reimbursement:** Pricing and reimbursement policy frameworks for antibiotics are set by reimbursement policy makers, which determine how manufacturers price their new antibiotic and the approaches for procurements and reimbursement (Australian Government Department of Health, 2017).
 - **Stage 5: Production, distribution and marketing:** At this stage, manufacturers scale up production of the approved antibiotic, engage in marketing, sales and distribution to purchasers / procurers. In addition, regulatory bodies and the manufacturer monitor all antibiotic safety once antibiotics are available for use by the public. Additional Phase IV clinical trial studies may be performed after the antibiotic is approved (Australian Clinical Trials, 2015).

Figure 1.1 Antibiotic development pipeline



Source: ACIL Allen, 2022. Adapted from Global AMR R&D Hub, Incentives for antibacterial R&D Dynamic Dashboard

The Global AMR R&D Hub pipeline is segmented into 8 stages, which are condensed in the above pipeline to 5 stages.

Market approval (stage 3) is a combination of two stages: ‘1st national filing’ and ‘global filing & label expansion’.

Production, distribution and marketing (stage 5) is a combination of three stages: ‘manufacture and supply’, ‘distribution’ and ‘marketing’

In addition, a range of participants are involved in the antibiotic development pipeline, including early-stage researchers, late-stage researchers, manufacturers, priority-setting policy makers, funders / purchasers, regulators and reimbursement policy makers.

1.3.2 Mechanisms to incentivise antibiotic development

Mechanisms can be classified into either push or pull mechanisms, whereby push mechanisms focus on promoting collaboration and on decreasing early antibiotic development costs and pull mechanisms aim to increase or ensure adequate market revenue to development or sponsor companies for newly approved antibiotics (Renwick et al., 2016, Ciabuschi et al., 2020, Luepke et al., 2017).

Push and pull mechanisms also address the key point of failure in the antibiotic development pipeline, colloquially referred to as the “valleys of death”. These occurs between “lab research and clinical trials” or stage 1 and stage 2 in the above diagram (International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), 2020) and after market approval (Access to Medicines Foundation 2021).

To date the most commonly used strategies to incentivise antibiotic development have been push incentives, mostly in the form of R&D grants and funding (Simpkin et al., 2017). The focus on push incentives has led to an increase in international funding for antibiotic R&D in recent years (AMR Industry Alliance, 2017, Ardal et al., 2017, Wellcome Trust, 2020). As noted by the AMR Preparedness Index report, “most countries have made measurable progress implementing push incentives” (Global Coalition on Aging, 2021). However, to date these have been insufficient in reviving the antibiotic pipeline (Cama et al., 2021, Interagency Coordination Group on Antimicrobial Resistance, 2018). This is widely believed to be a result of market failures, specifically around ineffective market conditions and unprofitable antibiotic markets (Cama et al., 2021, Ardal et al., 2020, G7 Finance Ministers, 2021). This is because the commercial success of an antibiotic is subject to a unique set of challenges on sales volume and price that are not incurred by many other drugs (Cama et al., 2021).

1.4 Priority Mechanisms

ACIL Allen adopted a staged approach to identify and prioritise mechanisms with the potential to incentivise the development of novel antibiotics. This approach and findings of each phase are detailed in separate reports and are described briefly below.

1.4.1 Literature Review

ACIL Allen conducted a comprehensive literature review to identify options for funding models, pricing and reimbursement mechanisms, incentives for novel antibiotic R&D and market access across all aspects of the development pipeline, including actual and theoretical models used or otherwise discussed internationally and in Australia.

ACIL Allen identified 15 discrete mechanisms with the potential to incentivise the development of antibiotics, 5 push mechanisms and 10 pull mechanisms.

Given the recent focus and insufficient success of push mechanism in reviving the antibiotic pipeline, ACIL Allen prioritised the 10 pull mechanisms identified from the review.

Furthermore, pull mechanisms aim to send a clear signal to market that approved antibiotics are commercially viable. While directly focussing on late stage development activities, pull mechanisms may also contribute to more effort at the early stages of the pipeline.

1.4.2 Stakeholder Consultation

ACIL Allen engaged with relevant stakeholders via a survey and interviews to collect perceptions on the 5 mechanisms with the greatest potential to incentivise the development and availability of novel antibiotics in Australia.

The results of both phases of the project and the prioritisation of mechanisms are presented below and a comparison of how the prioritisation changed across each stage of the project is presented in **Appendix B**.

Table 1.1 Priority mechanisms

Mechanisms
Priority Pull mechanisms
Service availability premiums, subscriptions and licenses (SSL): Financial rewards, paid on an ongoing basis, to a manufacturer for guaranteed availability of and access to an antibiotic. They involve agreements between funders (typically government(s) and not-for-profit(s)) and antibiotic manufacturers.
Accelerated assessment and approval (AAA): Provides fast tracking and priority reviews through regulatory processes for antibiotics. This reduces the length of drug registration and market approval for antibiotics that meet certain specifications. The accelerated assessment can be provided as a priority review voucher following approval of an antibiotic, which can be sold or transferred.
Advance Market Commitments (AMC): Contracts between researchers and/or manufacturers and a funder (typically a government or financial entity) to guarantee a viable market for a product once it is developed. The AMC sets out an agreement where the funder heavily subsidises the future purchase of a set amount of antibiotics at a pre-specified price upon successful development. The transfer of funding occurs after the product reaches the market.
Strategic Antibiotic Reserve (SAR): A single or group of governments buy or license the patent for an important first-in-class antibiotic to hold it in reserve for the future, or urgent and serious infection cases. SARs involve contractual arrangements between governments and manufacturers where value-based payments are made to manufacturers who agree to place antibiotics in a SAR in lieu of their right to freely market and sell the antibiotic.
Value-based pricing and pay-for-performance (VBP): Pricing mechanisms designed to support pricing of antibiotics in line with the public health value that antibiotics contribute by setting a guaranteed price for certain antibiotics. It de-links the reimbursement of the antibiotic from its sale price and volume.
Other Pull mechanisms
Patent buyout: Large end prizes given in exchange for the national IP rights to a successfully developed antibiotic once it has received national marketing approval. This can be part of an AMC or as a stand-alone purchase. The buyout gives the buyer control over the product price (and thus patient access) once released to market.
Extended market exclusivity: Where a manufacturer can market their product for an extended period of time, free from competition (the IP is protected for longer). This aims to increase returns to the manufacturer. This exclusivity can also be made available in the form of a voucher, which can be sold to other pharmaceutical companies for the purpose of extending market exclusivity of an existing drug or transferred to other drugs in a portfolio in the form of transferable IP rights.
Market entry reward (MER): Rewards paid to researchers and/or manufacturers by funders upon reaching product development milestones. This includes lump sum and milestone monetary prizes and research tournaments that award competitive milestone prizes to developer researchers and/or manufacturers reaching specified checkpoints. MERs are an example of milestone payments, with payments made upon market entry.
Tax incentives: Tax incentives in the form of credits, allowances or deferrals can reduce a company's tax liability. Tax credits can also be redeemed for cash in lieu of reducing a company's current tax liability.
Anti-trust waivers: Relaxation of anti-trust laws allows manufacturers to cooperate with and sell antibiotics to a competing pharmaceutical company with a competing antibiotic.
Push mechanisms
Product development partnerships (PDPs): Not-for-profit public-private partnerships typically formed between research/academia, government, private sector and industry. PDPs are collaborative agreements to share R&D risks and rewards and raise the level of funding available for R&D, using a needs-based approach for underserved areas of health research. Funding is pooled from multiple partners, which allows each partner to contribute a portion of the cost of the R&D (and share the investment risk) while generating sufficient capital to fund the R&D.

Mechanisms

Social Impact Investing (SII): SII combines capital and expertise from the public, private and not-for-profit sectors to finance social services and infrastructure to achieve social objectives. Crowdfunding is a prominent example of SII.

Open access to research: Sharing and providing access to intellectual property (IP) and resources, for example, journal articles, good practice approaches, resources and infrastructure, scientific databases, molecule libraries and outcome registries. Open access extends the reach of research beyond its immediate academic circle.

Conditional loans: Payment arrangements between a researcher and a lender to support the costs of R&D. Loans can be for a set period, or repayment can be contingent on the R&D reaching set milestones.

R&D grants and funding: Cash, subsidies or loans, which can be targeted to specific issues/areas and dependent on conditions.

Source: ACIL Allen

2 Impact Identification

This chapter outlines the process undertaken to identify and estimate the costs and benefits associated with each mechanism, including key meetings, resources, and stakeholders.

2.1 Overview

An initial task in the economic assessment was to identify the impacts (i.e., costs and benefits) associated with each mechanism. Three benefits (including avoided mortality associated with AMR, avoided morbidity associated with AMR and avoided hospitalisation costs) and two costs (including cost to implement the mechanism and cost to conduct regulatory approval for each antibiotic) were identified, and are described in this section, as well as other impacts that were considered but not assessed in this report.

2.2 Approach

The approach to identifying impacts involved three processes, each of which is described below.

2.2.1 Meetings

Between 3 November 2021 and 22 June 2022, ACIL Allen met with the Department project sponsors 17 times to provide project control updates. Meetings were initially conducted on a fortnightly basis and then revised to a weekly basis from 5 May 2022 as the project neared completion, with these sessions also including experienced health economists from the Department.

The objective of the meetings was to provide an overall project update, as well as share recent findings and agree on key project decisions.

ACIL Allen also engaged a number of subject matter experts to assist in developing the modelling approach and assumptions. Experts included Nadine Hillock (Australia), Sir Professor John Tooke (United Kingdom), Professor Deenan Pillay (United Kingdom) and Professor Peter Taylor (United Kingdom).

These experts were consulted periodically and engagement included email correspondences and video conferences to review and verify the project approach.

Lastly, the ACIL Allen core team met regularly during the engagement to progress project deliverables.

2.2.2 Resources

ACIL Allen conducted an extensive review of the current literature to identify an appropriate methodology to estimate the overall direct and indirect costs and impacts of five mechanisms to incentivise the development of novel antibiotics. Key sources relied on for the modelling are referenced in this report, however, three papers were particularly important for developing the modelling approach:

- The global economic impact of anti-microbial resistance (*KPMG LLP, 2014*)

- Estimating the economic costs of antimicrobial resistance (*RAND Europe, 2014*)
- Antibiotic Resistance: Modelling the Impact on Mortality and Morbidity (*Institute and Faculty of Actuaries, 2019*)

These documents provide information on the type of costs and benefits typically observed in a similar cost-benefit analysis, and help identify additional publicly-available data which could be used in this project. In an Australian context, there are several publicly available datasets that have been used as inputs in the cost-benefit analysis. These inputs, and a description of how they have been used, are described below.

The Antimicrobial Use and Resistance in Australia (AURA) reports

The AURA reports provide valuable surveillance and information on antimicrobial resistance rates across a spectrum of priority pathogens at a national level. Data on resistance rates are reported nationally for each priority pathogen, with the latest published in August 2021.

ACIL Allen has collated data between 2015 and 2019 to observe trends and capture any fluctuations in resistance rates over time.

Australian Group on Antimicrobial Resistance (AGAR): Sepsis Outcome Program reports

The Sepsis Outcome Program reports are released on an annual basis and provides valuable data on 30-day all-cause mortality rates (including the number of infections and deaths) across a range of gram-negative species. The reports also include data on hospitalisations.

Given that the available data only includes blood-stream infections, we have limited our analysis to specific pathogens where data exists on resistance rates to bloodstream infections from the AURA reports. Mortality data, at a pathogen level, is available between 2017 to 2020.

Other publicly available data sources

ACIL Allen has collected, and used other publicly available data sources as key inputs in the cost-benefit analysis. This includes:

- Projected population data between 2017 to the latest available calendar year, 2066. Data was collated from the Australian Bureau of Statistics (Australian Bureau of Statistics, 2018).
- Valuation of a Statistical Life (VSL) and Valuation of a Statistical Life Year (VSLY) from the Office of Best Practice Regulation (OBPR)

Compound annual growth rates have been used to forecast the total number of infections over time. To monetise benefits of reduced mortality (due to the five mechanisms), the Value of a Statistical Life (VSL) was sourced from the Office of Best Practice Regulation (OBPR).

2.2.3 Stakeholders

As part of the stakeholder consultation process, ACIL Allen invited 70 stakeholders to complete a brief survey on priority mechanisms to incentivise the development of novel antibiotics.

Those invited represented a broad range of stakeholder groups, including

- Health System Procurement / Jurisdictional Purchasers
- Pharmaceutical Research & Development
- Health Economics
- Health Technology Assessment and Regulation
- Pharmaceutical Pricing and Reimbursement Authorities
- Researchers / Academia; and
- Professional Bodies.

In total, 23 stakeholders responded to the survey, of whom 11 agreed to an interview to further explore the subject.

The findings of this process have been documented in a stakeholder consultation report and were a critical input to supporting the identification of impacts and discussing the veracity of modelling assumptions.

2.3 Findings

2.3.1 Frame of reference

The frame of reference refers to the perspective from which cost and benefits are considered.

It was agreed with the Department that given the terms of reference for this study, the assessment would assume the perspective of the Australian community.

The implication of this frame of reference is that any impacts beyond the Australian community are not accounted for in this assessment.

ACIL Allen acknowledges the widely held view that AMR represents a global threat, which requires a coordinated global response. However, this project is focussed on the response the Australian Government might pursue to support the development of novel antibiotics and therefore the assessment has been conducted under this constraint.

2.3.2 Identified impacts

ACIL Allen identified a range of impacts that may be generated following the implementation of a mechanism to incentivise the development of novel antibiotics and bring them to market in Australia. Impacts are described according to how they were treated in the analysis (included as quantitative impacts, included as qualitative impacts, excluded from the analysis).

Quantitative impacts

Five impacts were analysed quantitatively in the assessment:

- Avoided mortality associated with AMR
- Avoided morbidity associated with AMR
- Avoided hospitalisation costs
- Cost to implement the mechanism
- Cost to conduct regulatory approval for each antibiotic.

The approach to quantifying these impacts is detailed in chapter 4 (costs) and chapter 5 (benefits).

Qualitative impacts

Seven impacts were analysed qualitatively in the assessment:

- Enablement value of antibiotics
- Contribution to a global solution
- Build capacity and responsiveness
- Synergistic effects of antibiotics
- Use of antibiotics during clinical trials (impact has potential to impose costs or generate benefits)
- Agreement risk
- Diversion of development focus.

Impacts excluded from the assessment

An additional four impacts were identified but not captured quantitatively or qualitatively in the assessment. Impacts were excluded after further examination determined they were unlikely to be associated with the implementation of the mechanisms or were likely to be generated outside Australia. These include:

- **Indirect innovations from base scientific endeavours:** This impact relates to the value of innovations that are discovered as a result of base scientific activities related to novel antimicrobial development (other than the development of an antibiotic). This impact was deemed as having limited relevance to the assessment, given the mechanisms reviewed related to late stage antibiotic development and were therefore less likely to stimulate base scientific activities.
- **Reduction in food security threat posed by AMR:** This impact relates to the protective factor new antibiotics may have in terms of mitigating the risk of a resistant pathogen disrupting food production. This impact was deemed as having limited relevance to the assessment, given that the focus of the mechanisms was to stimulate the development of novel antibiotics for human health, and would not be used on animals.
- **Commercial returns generated by the mechanism:** This impact relates to the value manufactures generate from developing, manufacturing and selling novel antibiotics. It was determined that the majority of the activity associated with the development of novel antibiotics will occur outside Australia (given the infrastructure, technology, skills and manufacturing constraints Australia faces for pharmaceutical R&D) and therefore would not be a benefit that accrues to the Australian community. This is due to the frame of reference adopted in the study (i.e., any impacts that arise outside of Australian are not accounted for in this assessment).
- **Employment and income generated by the mechanism:** This impact relates to the jobs and income generated from developing, manufacturing and selling novel antibiotics that are developed from the mechanism. As with the commercial returns impact, it was determined that this impact would likely be realised outside of Australia and for this reason was excluded from the analysis.

3 Options

This chapter provides an overview of the top five mechanisms assessed in this report. The mechanisms are described below, with discussion on how the mechanism shifts antibiotic funding from a cost focus to a focus on societal value, the risk to Government, barriers to implementation and mitigation strategies, and how the mechanism can be implemented in Australia.

3.1 Service availability premiums, subscriptions and licenses (SSL)

3.1.1 Overview of the mechanism

Service availability premiums, subscriptions and licenses (SSL) provide financial rewards, paid on an ongoing basis, to an antibiotic manufacturer for guaranteed availability of and access to an antibiotic (Gotham et al., 2021). It involves a contractual agreement between funders (typically government(s) and not-for-profit(s)) and antibiotic manufacturers. This guarantees funding certainty for the manufacturer and payment certainty for the funder (Liu, 2020).

SSL address a key challenge by ensuring a guaranteed market/revenue stream for antibiotics, however, rather than supporting development directly, they support access to developed antibiotics.

Governance arrangements are established between the manufacturer and funder, which may provision for performance, reporting and quality requirements. The arrangements vary based on the nature of the agreement, and can involve the funder implementing competitive procurement processes (Public Health Agency of Sweden, n.d., Public Health Agency of Sweden, 2020a). This mechanism may incorporate elements of antibiotic value and stewardship, which would require changes to the current Health Technology Assessment (HTA) processes and enable the economic and social/health value of the antibiotic to be captured in this assessment (for example, see **Box 3.2**).

3.1.2 How the mechanism shifts antibiotic funding from a cost focus to a focus on societal value

SSL can focus on areas of need or societal value (Moon and Erickson, 2019, Public Health Agency of Sweden, n.d., Public Health Agency of Sweden, 2020a). In implementing a SSL, organisations (i.e., researchers, policy makers, industry and governments) would identify areas of antibiotic need through research, reporting and strategy development. These needs would need to be recognised by the funder (i.e., the funder would need to agree to fund SSL in an area of need proposed by the priority setting and reimbursement policy makers). As an example, the Public Health Agency of Sweden (PHAS) is delivering a pilot study of a SSL focused on the World Health Organisation's (WHO) priority pathogens (see **Box 3.1**). The United Kingdom National Institute for Health and Care Excellence (NICE) and the National Health Service (NHS) are also implementing a pilot project that uses a hybrid of a subscription-based payment model and fully-de-linked market entry reward (see **Box 3.2**) (Dutescu and Hillier, 2021, Crabb et al., 2020, MTPConnect, 2020a, Gotham et al., 2021).

Box 3.1 Case study: Public Health Agency of Sweden pilot study

The PHAS is delivering a pilot study for a new service availability and reimbursement model. It is funded by PHAS and the Vinnova, the Swedish innovation agency. PHAS has partnered with four pharmaceutical companies and set a minimum guaranteed annual revenue per product for selected antibiotics, in exchange for a guaranteed volume of and timely access to supplies through warehousing arrangements (Public Health Agency of Sweden, n.d., Public Health Agency of Sweden, 2020a). The agreement does not change the prescription or payment of antibiotics by health care workers and users. The pilot focuses on the WHO's critical priority pathogens and is set to conclude in 2022.

An evaluation of the pilot will be conducted, focusing on antibiotic availability before and after implementation of the pilot, economic consequences of the pilot, the procurement process and the interest of the pharmaceutical companies.

Source: ACIL Allen, various sources (as referenced)

SSL are typically funded by entities such as governments and not-for-profit donors who are interested in supporting novel antibiotics to reach the market. SSL set a pre-agreed amount for payment to manufacturers in a timeframe (Renwick et al., 2016, Moon and Erickson, 2019, Public Health Agency of Sweden, n.d., Public Health Agency of Sweden, 2020a). This agreement achieves the primary aims of creating financial certainty for i) funders, as they will know in advance the amount they will pay for accessing the antibiotic (Liu, 2020), as well as for ii) the antibiotic manufacturers, with a minimum guaranteed annual revenue at pre-agreed prices and payments linked to the manufacturer meeting agreed antibiotic performance and conservation criteria.

As such, this aims to increase the market value of antibiotics, by supporting a shift from focus on the cost of the antibiotic toward the societal value produced by the antibiotic.

By creating this funding certainty, through reducing the funder's financial liability for incentivising novel antibiotic production, this aims to incentivise funders to finance novel antibiotics. Further, manufacturers are not incentivised to sell antibiotics at scale because their revenue is not linked to sales and does not increase with increasing sales volume. This partial de-linkage reduces a manufacturer's dependence on sales volume, and aims to incentivise drug development and ongoing availability by guaranteeing an income stream.

If SSL are linked to conservation conditions, manufacturers are actively disincentivised to increase their sales volume, as doing so would risk delivering poorer antibiotic performance and conservation outcomes, failing to meet the antibiotic performance and conservation criteria, and thereby forfeiting the subscription revenue. This mechanism encourages manufacturers to act in a way that improves antibiotic conservation.

Box 3.2 Case study: National Institute for Health and Care Excellence and the National Health Service pilot

The NICE and the NHS are implementing a pilot project that uses a hybrid of a subscription-based payment model and fully-de-linked MERs (Dutescu and Hillier, 2021, Crabb et al., 2020, MTPConnect, 2020a, Gotham et al., 2021). Antibiotics undergo a HTA to determine their clinical value and the value of a multi-year contract, paid in yearly instalments. The annual payments are subject to the antibiotic's performance over time, including supply, stewardship, manufacturing and environmental practices, monitoring and reporting and antimicrobial surveillance (Dutescu and Hillier, 2021, Crabb et al., 2020, MTPConnect, 2020a).

The Pilot project completed product selection in 2020, HTA in 2021 and commercial negotiations are set to be concluded in 2022. The proposed model would cap the maximum annual contract value at £10 million on a 3–10-year contract. If the United Kingdom's contribution was matched by G20 countries, this could value this incentive at up to £3.3 billion (Crabb et al., 2020). Lessons could be learned from the pilot on how to appropriately consider the unpredictability of resistance, which is not adequately factored into Australian HTAs (Hillock, 2021, MTPConnect, 2020b). As the Pilot has not matured, the outcomes are unknown (Crabb et al., 2020, Gotham et al., 2021).

Source: ACIL Allen, various sources (as referenced)

3.1.3 How the mechanism can be implemented in Australia

SSL is a pull (outcome based) mechanism that targets the antibiotic pipeline at Stage 5: Production, distribution and marketing.

SSL would allow the Australian Government to guarantee revenue for an antibiotic manufacturer, and secure timely access. This mechanism would also provide greater return on investment to antibiotic manufacturers. Australia can determine the subscription value based on the value of the antibiotic, and other factors such as exclusivity of access or stewardship arrangements. This could be undertaken in collaboration with other countries (under the same agreement or similar agreements) or pursued without collaboration.

The implementation of this mechanism in Australia is described below.

The Australian Government implemented a subscription model in 2015 to procure treatment for 104,000 Hepatitis C patients over five years (Moon and Erickson, 2019, MTPConnect, 2020a, Liu, 2020). This involved price negotiation between reimbursement policy makers and manufacturers that guaranteed an income for the manufacturer. Approximately \$1 billion was spent over five years in exchange for an unlimited volume of direct-acting antivirals from several manufacturers.

In implementing the Australian Hepatitis C program, the Australian Government pays manufacturers for the prescribed medicines on a monthly basis from the Pharmaceutical Benefits Scheme (PBS) budget. A portion of any excess in funding that exceeds the agreed annual limit is returned by manufacturers to the Australian Government's general revenue as a rebate (not the PBS budget) (Grebely et al., 2018).

Manufacturers and other stakeholders involved in the Australian Hepatitis C program received a range of benefits: lower per-patient prices for the drug, those that need medicines can access them due to more competitive pricing, funders received greater payment certainty about the overall cost (and use of public funds), manufacturers receive a "considerable financial reward for innovation and face reduced risk thanks to guaranteed revenue over 5 years" (Moon and Erickson, 2019). The program was economically feasible because the cost of drug manufacture is small relative to the drug price (Moon and Erickson, 2019).

The program resulted in a significant, 10fold increase in the number of people treated per year compared to the previous decade (Moon and Erickson, 2019). The model was considered highly successful and adaptable to other medical products (Moon and Erickson, 2019).

A similar approach could be applied to novel antibiotics. The Australian Government could negotiate with priority-setting policy makers and reimbursement policy makers to identify areas of need and suitable antibiotics for inclusion in the SSL. The Australian Government could tender for antibiotic manufacturers to identify suitable antibiotics, prices (as informed by a HTA performed by the Pharmaceutical Benefits Advisory Committee (PBAC)), volume and access arrangements. The antibiotics could then be paid for from the PBS budget.

3.1.4 Risk to Government, barriers to implementation and mitigation strategies

In implementing a mechanism, consideration should be made of the risk to Government, the ways in which the mechanism will be implemented, any barriers likely to be encountered and potential mitigation strategies.

Through ACIL Allen's review of relevant general literature, there are a number of risks in delivering the SSL which are shared between the manufacturer and funder and are described below.

There are governance and control risks for Government in implementing the mechanism. These exist for all procurement activities that involve government and include the effectiveness, safety, supply, quality and use of the antibiotic. Each of these factors may be heightened given the longer-term nature of the SSL arrangement (when compared to short-term procurement activities).

There are financial (and reputational) risks to both the manufacturer and funder of incorrectly estimating the volume of antibiotics required, or other factors involved in calculating the fixed payment (Liu, 2020). This risk may be managed through shorter-term arrangement and / or clauses that enable periodic negotiation / review of key contract parameters.

Where agreements are non-compulsory, such as the Australian Hepatitis C model (see section 3.1.3), the model must be beneficial for the funder and manufacturer for the agreement to be attractive. As noted by Moon and Erickson (2019), "if the lump-sum amount was too low, firms could simply have refused to supply the Australian market. The agreement's existence suggests that firms found it more attractive than the best alternative" (Moon and Erickson, 2019).

In implementing this mechanism, the Government would need to balance the funding amount to ensure it was achieving value for money and sufficiently incentivising the manufacturers to take part in the agreement. The agreement would also need to consider the need to adjust payment amounts, in the instance that there are changes in the volume of antibiotics required or other factors involved in calculating the fixed payment.

SSL require successful development of an antibiotic in order for the manufacturer to access the income stream and recuperate costs for R&D (Renwick et al., 2016, Moon and Erickson, 2019, Public Health Agency of Sweden, n.d., Public Health Agency of Sweden, 2020a). ACIL Allen's consideration of relevant general literature finds that making SSL dependent on successful development creates a risk that manufacturers will not be compensated for their effort. This is a risk for the manufacturers and is mitigated by

sustaining investment in the develop an antibiotic to improve the likelihood an antibiotic will be successfully developed.

Barriers to implementation include designing an appropriate funding agreement, raising awareness of the mechanism and securing sufficient numbers of high quality and competitive tenders from manufacturers (given Australia's limited current pharmaceutical manufacturing capacity). There may also need to be amendments to the HTA process to appropriately consider the unpredictability of resistance. Australia has the opportunity to learn from the current trials – the NICE Pilot Study is currently ongoing and the PHAS will be evaluated following the conclusion of the pilot in 2022 (Public Health Agency of Sweden, n.d.).

3.2 Accelerated assessment and approval (AAA)

3.2.1 Overview of the mechanism

Accelerated assessment and approval (AAA) provides fast-tracking and priority reviews for antibiotics. This reduces the length of drug registration and market approval for antibiotics that meet certain specifications. The accelerated assessment can also be provided in the form of a priority review voucher following approval of an antibiotic. This can then be sold or transferred to other products within the manufacturer's portfolio.

This mechanism aims to address the barrier of long and onerous review and approval processes and get antibiotics to market faster. AAA target stages that require approval, including clinical trials, registration and market approval. It also aims to promote cooperation between manufacturers and government approval agencies.

3.2.2 How the mechanism shifts antibiotic funding from a cost focus to a focus on societal value

The primary aim of the mechanism is to address regulatory hurdles to bringing drugs to market while maintaining high quality and safety (Sansom et al., 2017). In doing so, it aims to directly streamline administrative burden and reduce duration of and requirements for approval for antibiotics. It does not directly incentivise investment in R&D or the development of novel antibiotics, rather to coordinate assessment and approval once an antibiotic has been developed.

However, AAA may reduce the timeframe that late-stage researchers and/or manufacturers need to wait between the development of an antibiotic and the antibiotic's release to the market and may reduce the administrative burden and other costs and requirements for approval for antibiotics (Renwick et al., 2016). Although approvals may still be rejected these will likely happen sooner than under previous arrangements and potentially at lower cost to the applicant (Mossialos et al., 2010). This may allow for additional funding to be invested in R&D, which may lead to more value for society (i.e., from improved quality or diversity of antibiotics available).

For manufacturers, the antibiotic's market entry is when they can begin to generate revenue through sales (assuming they are not participating in some other mechanism that impacts the timing of manufacturers' receipt of revenue). AAA work by reducing the time between development and market approval, thereby reducing the time required before the manufacturer can generate revenue through sales. As such, manufacturers are indirectly incentivised to attract and sustain funding to complete development of antibiotics to receive

the benefits of the mechanism and generate sale revenue earlier / reduce their financial risk.

The mechanism does not focus on the cost of antibiotic development, the cost of antibiotics once on the market, nor the societal value of the antibiotics. However, by implementing the mechanism and investing in streamlining the regulatory processes, there is an implicit recognition (which applies to all mechanisms identified in this study) that antibiotics contribute value to society and there is benefit in improving the accessibility of antibiotics.

An example of implementation of this mechanism is provided in **Error! Reference source not found.** The U.S. Food and Drug Administration’s Limited Population Antibacterial Drug (LPAD) Approval pathway targets antibacterial and antifungal drugs that are used to treat serious or life-threatening infections in limited populations of patients with unmet needs. As such, this may improve society’s access to high-value drugs (U.S. Food and Drug Administration, 2020).

Box 3.3 Case study: the U.S. FDA Limited Population Antibacterial Drug Approval pathway

An example of this mechanism is the U.S. FDA Limited Population Antibacterial Drug (LPAD) Approval pathway (U.S. Food and Drug Administration, 2020). This is a streamlined clinical assessment process that allows antibiotics’ safety and efficacy to be studied using smaller, faster, and less expensive clinical trials than typically required. This allows patients without appropriate treatments to receive early access to promising new antibiotics.

To be eligible, antibiotics need to target rare and deadly pathogens and approval would be restricted to use in specific pathogens and cohorts. It is designed to be used in limited populations with unmet needs. Drugs approved under this pathway must be clearly labelled and advertised with the statement “Limited Population”, to designate that they have been approved using limited population clinical trials (U.S. Food and Drug Administration, 2020).

The LPAD was added to the *Federal Food, Drug, and Cosmetic (FD&C) Act* through section 3042 of the *21st Century Cures Act (section 506(h) of the FD&C Act)* (U.S. Food and Drug Administration, 2020).

FDA approved the first drug under the LPAD pathway in 2018, Arikayce, which provides for the treatment of a bacterial-induced lung disease in patients that cannot be treated using conventional therapies (U.S. Food and Drug Administration, 2020).

Such a mechanisms could be applied in Australia for antibiotics that have not yet been granted market approval, but for which there may be benefit to patients for which no other treatment options exists.

Source: ACIL Allen, various sources (as referenced)

3.2.3 How the mechanism can be implemented in Australia

AAA is a pull (regulatory based) mechanism that targets the antibiotic pipeline at Stage 3: Market approval.

Priority-setting policy makers in the Australian Government have a role in identifying whether there is a need for AAA and how this can be incorporated into Australia’s regulatory system. This would consider factors such as the burden of the existing processes, regulatory processes that could be accelerated (i.e., clinical safety, clinical effectiveness and / or market access) need to shorten time to access new medications, the relative costs and benefits of reviewing, designing and implementing new processes, and any risk associated with shorter timeframes.

The 2015 *Expert Review of Medicines and Medical Devices Regulation* examined Australia's medicines and medical devices regulatory framework and processes with a focus on identifying opportunities to remove or streamline unnecessary, duplicative, or ineffective regulation (without impacts on safety or quality) and to enhance the regulatory framework to be able to respond well to global development, manufacture, marketing and regulation trends (Sansom et al., 2017).

In Australia, the TGA is responsible for conducting assessment and approval processes and would be responsible for making any changes to processes. The acceleration process would need to be carefully designed to ensure its fitness for purpose and operation are sound.

For example, should an accelerated process be adopted, they would need to specify the criteria that need to be satisfied for the process to be triggered. Regulators may also need to consider how many antibiotics are granted an accelerated process at any one time to prevent potential delays. By extension, a cap on the number of antibiotics being accelerated would promote the integrity of an accelerated process rather than risking the 'accelerated' process being slowed down to what is currently standard.

Following the 2015 *Expert Review of Medicines and Medical Devices Regulation*, the TGA implemented a number of changes to existing approval processes including a new provisional approval pathway to streamline approval (by up to 2 years) for promising new medicines with major therapeutic benefit, creation of a priority review pathway for prescription medicines (up to 3 months shorter), introduction of a notification process for minor changes to low risk drugs and to allow for better use of assessments made by comparable international regulators (Therapeutic Goods Administration, 2018). This aims to remove or streamline unnecessary, duplicative, or ineffective regulation and to enhance the regulatory framework.

These efforts may yield some benefit to the prospects of novel antibiotic development in Australia. Most of these reforms have been implemented, but their impact has not been evaluated. MTPConnect's industry consultation report on AMR, *Fighting Superbugs*, highlights a number of regulatory pathways and recommends accelerating the Pharmaceutical Benefits Advisory Committee review processes (Therapeutic Goods Administration, 2020, MTPConnect, 2020a).

Pursuing related initiatives may result in duplicated effort and therefore these reforms should be evaluated before further changes are considered.

3.2.4 Risk to Government, barriers to implementation and mitigation strategies

In implementing a mechanism, consideration should be made of the risk to Government, the ways in which the mechanism will be implemented, any barriers likely to be encountered and potential mitigation strategies.

There is a reputational risk to the Australian Government with implementing any changes to accelerate the assessment and approval process. Public communication of any reforms to regulatory pathways would need to manage perceptions of changes to quality and safety and promote awareness of the value in speeding up access to antibiotics (Renwick et al., 2016, U.S. Food and Drug Administration, 2020, Therapeutic Goods Administration, 2018, Somer, 2021).

Further, some research indicates that AAA may increase the costs incurred by the public for expedited review and funding of antibiotics, particularly where more resources are

dedicated to undertaking the review when compared to standard review processes (Renwick et al., 2016). Renwick et al. (2016) also noted that any compromise in the safety and efficacy of the process, may increase the cost to the Government and public. AAA of antibiotics could also increase the time taken to approve non-antibiotic drugs that are not being prioritised according to the date of application for approval (Renwick et al., 2016). These factors would need to be considered by Government during the design phases and communication activities with the public (given the heightened public health risk) in order to understand and mitigate any potential financial and reputational risk.

3.3 Advance Market Commitments (AMC)

3.3.1 Overview of the mechanism

Advanced Market Commitments (AMCs) are pre-market, legally binding contracts between an antibiotic researcher and/or manufacturer and a funder (typically a government or financial entity) to guarantee a viable market for a product once it is developed (Leoni, 2019). The AMC sets out an agreement where the funder agrees to the future purchase of a set amount of drug that meets prespecified criteria at a pre-specified price upon successful development of the drug (Ardal et al., 2018). The transfer of funding occurs after the product reaches the market (Leoni, 2019).

AMCs aim to reimburse a manufacturer for the value of the antibiotic at pre-agreed prices, while providing the antibiotic at a subsidised price to end users to facilitate equity of access (Ardal et al., 2018, World Bank and GAVI Alliance, 2012, Leoni, 2019).

Governance arrangements are established between the antibiotic manufacturer and funder. The arrangements vary based on the nature of the agreement, and could include a contract-based arrangement between the stakeholders and an independent scientific committee to assess whether the antibiotic products qualify for financial rewards (Ferraro et al., 2017a). Arrangements could also cover the effectiveness, safety, supply, quality and use of the antibiotic.

AMCs implemented to date have sought to increase uptake of the drug (i.e., increase usage of vaccines). As such, if AMCs were to be used to incentivise antibiotic development, this would need to consider antibiotic consumption and stewardship (Simpkin et al., 2017).

AMCs are often used in combination with direct payment mechanisms, such as R&D grants and funding.

3.3.2 How the mechanism shifts antibiotic funding from a cost focus to a focus on societal value

A core feature of AMCs is their role in improving the market value of antibiotics (i.e., the sales price), and fundamentally shifting the focus of antibiotic funding from a cost focus to the value antibiotics contribute to society. AMCs aim to reimburse a manufacturer for the value of the antibiotic (at pre-agreed prices), but provide the antibiotic at a subsidised price to end users (to facilitate equity of access) (World Bank and GAVI Alliance, 2012, Leoni, 2019). AMCs support the process of bringing antibiotics to market and ongoing availability by guaranteeing an income stream to ensure the ongoing availability of antibiotics.

AMCs have been used to address high-priority areas “based on essential requirements rather than actual results” with the potential to provide more societal value, including

pneumonia and COVID19 (Cernuschi et al., 2011, GAVI, 2021b, Federal Reserve Bank of San Francisco & Nonprofit Finance Feed, 2018).

AMCs have been successfully used to incentivise development of pneumococcal and COVID-19 vaccines (see **Box 3.4**) yet are only theoretical for antibiotics.

Box 3.4 Global applications of AMCs

Gavi, the Vaccine Alliance (GAVI) is a public-private partnership focused on immunisation in low- and middle-income countries. It received US\$1.5 billion funding to fund a pilot AMC for pneumococcal vaccine from the governments of Italy, the United Kingdom, Canada, the Russian Federation, Norway and the Bill & Melinda Gates Foundation. The pilot AMC aimed to incentivise researchers and manufacturers to make pre-existing vaccines already available in high income countries available in low and middle income countries (Cernuschi et al., 2011).

This example differs from antibiotic development as the aim of the AMC is to increase usage of vaccines rather than establish access but maintain stewardship of antibiotics. However, the example highlights the potential role of AMCs in creating markets for medical products. Researchers noted the need for AMCs to have a robust contract, an appropriate value of precommitted funding, and the need for an independent scientific committee to assess whether a vaccine qualified and the range of rewards available to various market entrants (Ferraro et al., 2017a).

Another recent example of AMCs is the COVAX Facility arrangement operated by GAVI. More than 180 countries and economies supported the COVAX AMC in order to provide a global response to the COVID-19 pandemic based on rapid, fair and equitable access to vaccines (GAVI, 2021a). In June 2021, US\$9.6 billion was secured for vaccine procurement, allowing the COVAX AMC to purchase 1.8 billion fully subsidised doses (GAVI, 2021a). However, the conditions for this AMC vary from antibiotic development as, for the COVID-19 vaccine, there was a huge immediate and medium-term market potential for successful vaccines, significant urgency and an almost unlimited volume of vaccines required. Australia contributed \$123 million to the COVAX Facility (Dalzell, 2020).

Source: ACIL Allen, various sources (as referenced)

3.3.3 How the mechanism can be implemented in Australia

AMCs is a pull (outcome based) mechanism that targets the antibiotic pipeline at Stage 1: Discovery and translational research, Stage 2: Clinical research and trials (including testing of antibiotic candidates), Stage 4: Pricing and reimbursement, and Stage 5: Production, distribution and marketing (final stages of regulatory approval and where manufacturing capacity is being established).

Priority-setting policy makers in Australia and internationally would identify priorities for AMCs through research, reporting and strategy development. This would need to be recognised by the funder (i.e., the funder would need to agree to fund an AMC in an area of need proposed by the priority-setting policy makers).

AMCs are typically funded by entities such as governments and not-for-profit donors, who are interested in supporting R&D to achieve social and health outcomes. As such, they are prepared to pay more than the market price for any resulting antibiotic reaching the market, to “compensate companies for capital-intensive R&D, regulatory approval, and manufacturing capacity” (Federal Reserve Bank of San Francisco & Nonprofit Finance Feed, 2018). AMCs set a pre-agreed amount for the subsidy they will pay manufacturers. This subsidy agreement creates financial certainty for funders, as they will know in advance the amount they will pay for the antibiotic. This limits the funder’s financial liability for subsidising antibiotic development and aims to incentivise their investment in R&D. In

Australia, the funder could be a combination of the Australian Government, industry and not-for-profit donors.

AMCs are used where the costs of R&D are higher than the potential return once the product reaches the market. In such cases, there is no commercial incentive to develop a product without an advanced commitment to purchase the product. The guaranteed revenue stream alleviates researchers' financial risk that their antibiotics will not generate adequate revenue upon market entry. This reduced risk aims to stimulate antibiotic R&D, incentivise early- and late-stage researchers to participate in R&D, attract and sustain funding to develop an antibiotic and ensure antibiotics reach the market.

AMCs provide financial certainty to early- and late-stage researchers, and protect against low market returns to manufacturers through a guaranteed revenue stream for successful antibiotic development. This guaranteed market/revenue stream is currently lacking in Australia. This is a major current challenge for the development of new antibiotics which could be directly addressed by offering a greater return on investment to small and established pharmaceutical companies and other funders compared with alternate use of resources. Australia has prominent national funding bodies (e.g. the National Health and Medical Research Council, Medical Research Future Fund, Cooperative Research Centres) and a well-defined regulatory landscape which could be leveraged to facilitate this mechanism.

Even if manufacturers did not receive any of the AMC subsidy (i.e., where manufacturers manufacture the antibiotic but did not develop the antibiotic nor participate in the AMC), they would still benefit through being able to produce and sell a new product. Being able to manufacture a new antibiotic provides an additional revenue stream for manufacturers. Manufacturers may also be entitled to patent rights, which would ensure exclusivity over production for an agreed period. Through providing manufacturers with more opportunities to sell novel antibiotics, AMCs incentivise manufacturers to produce novel antibiotics (Ferraro et al., 2017a).

The Australian Government could collaborate with international governments to leverage processes and insights on AMCs, and procure antibiotics for the Australian market.

3.3.4 Risk to Government, barriers to implementation and mitigation strategies

This section considers the risk to Government in implementing a mechanism, any barriers likely to be encountered and potential mitigation strategies.

In the instance where the Australian Government funded an AMC, reputational risk would be shared between the Australian Government and the manufacturer. The Australian Government would vet manufacturers prior to agreements being made and establish governance arrangements with the antibiotic manufacturer. This has the potential to mitigate the financial and reputational risks to Government from implementing the AMC.

AMCs also lower the financial risk for researchers/manufacturers by guaranteeing an ongoing revenue stream (Renwick et al., 2016).

Renwick et al. (2016) note that AMCs do not require significant changes in regulatory statutes or laws in order to be implemented (Renwick et al., 2016). While a detailed assessment would need to be undertaken in an Australian context to confirm these findings, this has the potential to reduce the regulatory burden on the Australian Government from implementing an AMC.

ACIL Allen's assessment of the literature has identified some risks to implementing AMCs some of which would impact Government.

For example, the 2018 Drive-AB report notes that AMCs have the potential to make antibiotic development a more attractive business, through purchasing commitments (Ardal et al., 2018). As such, "either the price per unit has to be extremely high or excessive quantities will be produced" (Ardal et al., 2018). The authors argue that Market Entry Rewards are "a stronger incentive since it is not tied to units [i.e. unit price of the developed antibiotic]" (Ardal et al., 2018). However, AMCs may also maintain artificially high prices for antibiotics in some countries, which could restrict patient access to antibiotics (Renwick et al., 2016). This issue may be less relevant in Australia, particularly if the mechanism is not funded from patient fees (i.e., government funding).

There is also a potential for significant financial risk for early- and late-stage researchers as AMCs require successful development to access the income stream and recuperate costs for R&D (Renwick et al., 2016).

Further, if AMCs are not tied to volume of antibiotics sold, then manufacturers are incentivised to increase sales volume, which could contribute to ABR (Renwick et al., 2016). As such, in designing any governance arrangements, Government would need to consider the value of additional controls to manage how and when antibiotics are used. This would incorporate elements of antibiotic stewardship. For example, as noted in **Box 3.4**, the aim of the pneumococcal vaccine AMC is to increase usage of vaccines. An antibiotic AMC would need to consider approaches to maintaining stewardship of antibiotics.

These factors would need to be considered in designing and implementing an AMC to mitigate the reputational risk to Government.

3.4 Strategic Antibiotic Reserve (SAR)

This mechanism is poorly described and predominantly referenced in earlier journal papers due to limited recently published descriptions of its operation. Clear instances of the use of Strategic Antibiotic Reserves (SARs) could not be identified.

3.4.1 Overview of the mechanism

An SAR involves a contractual arrangement between governments and manufacturers where a single or group of governments buy or license the patent for an important first-in-class antibiotic to hold it in reserve for the future, or for instances of the most urgent and serious infection cases (Otterson, 2009, Kesselheim and Otterson, 2011). The manufacturer forgoes their right to freely market and sell the antibiotic in return for the payment.

Having multiple antibiotics on the market at the same time increases the chance that resistance will develop across the antibiotics, leaving patients without treatment options. A specific benefit of SAR is that antibiotics are kept in reserve, which helps to delay the emergence of resistant strains (Fair and Tor, 2014).

SAR payments need to be comparable to the potential revenue that could be generated through standard sales (Renwick et al., 2016).

3.4.2 How the mechanism shifts antibiotic funding from a cost focus to a focus on societal value

A key feature of SARs is that they aim to provide value-based payments once antibiotics are developed and ensure an ongoing market/revenue stream for manufacturers and ongoing availability of antibiotics. In that way, they are similar to AMCs in seeking to support the market access and ongoing availability of antibiotics. They address the major barrier of financial viability for manufacturers by increasing the revenue manufacturers can earn (when compared to traditional sales arrangements), and therefore support the development of novel antibiotics.

SARs keep antibiotics in reserve and therefore aim to help to delay the emergence of resistant strains (Fair and Tor, 2014). By targeting future antibiotic needs and the most urgent and serious infection cases (Outterson, 2009), SARs aim to focus on areas of highest societal need, where the largest value can be generated. SARs also de-link the antibiotic's revenue from market sales, with payment made to the researcher or manufacturer based on the value the antibiotic contributes. This aims to foster more effective antibiotic stewardship (Ardal et al., 2017).

SARs require successful development of an antibiotic in order for the manufacturer to access the income stream and recuperate costs of R&D, and thereby aim to stimulate R&D that results in successful development of an antibiotic with a high societal value (Renwick et al., 2016).

Clear instances of the use of SARs could not be identified. However, the vancomycin was often referred to as a case study of an unintentional SAR. This is overviewed in **Box 3.5**.

Box 3.5 Case study: unintentional use of a SAR with vancomycin

Vancomycin, an antibiotic used to treat penicillin resistant infections, was initially conserved following its introduction in 1958 (Outterson, 2009). It was first thought to cause toxicities and its use was restricted in the 1960s and 1970s.

This unintentional conservation prolonged the efficacy of the antibiotic in treating resistant infections. Some researchers have identified this as a signal of the potential success of using SARs where multiple antibiotics are developed for the same infection (Outterson, 2009).

Source: ACIL Allen, various sources (as referenced)

3.4.3 How the mechanism can be implemented in Australia

SAR is a pull (outcome based) mechanism that targets the antibiotic pipeline at Stage 4: Pricing and reimbursement and Stage 5: Production, distribution and marketing.

A SAR would allow the Australian Government to control access to a first-in-class antibiotic once it is developed, ensuring accessibility. However, noting the likely cost of SARs, the Australian Government may be best placed contributing to international efforts to hold antibiotics in reserve (i.e., stockpiled), rather than implementing a SAR individually. Therefore, this mechanism is likely best viewed as having the potential for Australia to assist with an international initiative only.

SARs could be used by priority-setting policy makers to identify high priority molecules (i.e., components of antibiotics) to hold in reserve (Outterson et al.). These priorities would be identified by organisations (i.e., policy makers, researchers and governments) through research, reporting and strategy development, as recognised by the funder (i.e., the funder

would need to agree to fund the SAR in an area of need proposed by the prioritysetting policy makers).

Funders would secure control over the antibiotic price through negotiation with the manufacturer (Renwick et al., 2016). This would be based on the assessed value of the antibiotic.

A key implementation initiative would require the Australian Government to contribute to the identification of high priority molecules and support funding arrangements and price negotiations to secure the antibiotics in reserve.

SARs withhold developed novel antibiotics from entering the market. While this negatively impacts manufacturers' ability to generate revenue from the antibiotic, the SAR provides a value-based payment to the manufacturer. This compensation for the manufacturer's prohibition from introducing the antibiotic to the market should be high enough to mitigate the forgone revenue (Renwick et al., 2016).

The effect of the SAR depends on how much is paid to the manufacturer. If the SAR payment is greater than the expected sales revenue the manufacturer would have received, then the manufacturer is financially incentivised to participate in the mechanism. Conversely, if the SAR payment is less than the expected sales revenue, the SAR does not directly incentivise manufacturers to withhold antibiotics from the market, and instead removes a direct disincentive for manufacturers to produce but not sell them.

As noted above, these factors are likely to prohibit the Australian Government from operating such a mechanism independently.

3.4.4 Risk to Government, barriers to implementation and mitigation strategies

In implementing a mechanism, Government needs to consider any risks and barriers likely to be encountered, and potential mitigation strategies.

SARs provide value-based payments to manufacturers. While this does require successful development to access the income stream and recuperate costs for R&D, ACIL Allen's assessment of relevant general literature suggests that as SARs would be implemented following successful product development, there would be a lower risk that the funding did not achieve the intended outcomes. This helps mitigate the financial and reputational risk incurred by Government in supporting only successfully developed antibiotics. In contrast, this could also create unacceptable financial risks for the researcher, which could limit their involvement in the R&D.

ACIL Allen's assessment of relevant general literature notes that reputational risk would be shared between the manufacturer and funder (e.g. Government), with the manufacturer vetted by funders prior to agreements being made. This also provides the opportunity for Government to define the governance arrangements to best mitigate risks to success of the SAR.

SARs require large amounts of public funds to buy the first-in-class antibiotic, which may not be feasible for governments and/or not-for-profit donors. Funding agreements would be difficult to negotiate (Outterson et al.). As a result, the Australian Government would likely need to support, rather than independently operate and fund, a SAR (see section 3.3.4).

There is a risk that resistance develops during the period that the antibiotic is being held in reserve, which reduces the effectiveness of the antibiotic and the value for money from the

mechanism (Renwick et al., 2016). This financial risk would be better distributed across multiple funding bodies.

Furthermore, SARs may raise ethical issues (and reputational risk), in the event where an antibiotic treatment is available but only reserved for Australian use (if the arrangement was implemented to impose this condition). Overcoming this requires international collaboration to determine eligibility of access and to determine an equitable funding arrangement.

SARs' requirement for manufacturers not to release antibiotics to the market may appear irregular to competition regulators. While manufacturers may be following the conditions of a SAR they have made with government, regulators may interpret their behaviour as anti-competitive. For example, this suspicion may arise because withholding supply of a product may take place where either one or few suppliers agree to set artificially high prices (collusion). To address this risk, regulators (such as the Australian Competition & Consumer Commission) need to be informed of the SAR and to consider any relevant manufacturers' actions in that context.

3.5 Value-based pricing/reimbursement and pay-for-performance (VBP)

3.5.1 Overview of the mechanism

Value-based pricing, value-based reimbursement and pay-for-performance (VBP) are pricing mechanisms designed to support pricing of antibiotics in line with the public health value that antibiotics contribute by setting a guaranteed price for certain antibiotics across set countries (Lum et al., 2018). VBP is a cooperative agreement across government regulators and health authorities and antibiotic manufacturers.

The value of antibiotics may be determined based on a country's HTA of the drug's value to society and the ongoing utility of the antibiotic, considering appropriate antibiotic stewardship. VBP increase the price of the antibiotic, thereby reducing imperative for sales volume. It delinks the reimbursement of the antibiotic from its sale price and volume (Renwick et al., 2016, Vogler et al., 2021).

Governance and procurement arrangements are established between the antibiotic manufacturer and funder. The arrangements vary based on the nature of the agreement, and typically involve competitive procurement processes and ongoing performance and reporting requirements.

3.5.2 How the mechanism shifts antibiotic funding from a cost focus to a focus on societal value

VBP offer a new reimbursement and procurement model that redefines the value of antibiotics to better incentivise researchers and/or manufacturers to attract and sustain funding in order to develop an antibiotic and bring it to market. It provides a dedicated income stream for researchers and/or manufacturers. This income or reimbursement of the antibiotic is de-linked from its sale price and volume. As such, this directly aims to improve the pricing of antibiotics to better reflect the public health value they contribute to society (Renwick et al., 2016). Pricing is determined through a HTA that allows for better reflection of the benefits delivered beyond the field of antibiotics. This will include determining an appropriate modelling methodology to capture the public health value of antibiotics that can be applied to augment current HTA valuations. Such efforts should include a review of the

current NICE trial, as this involved adaptation to the HTA process to better capture the public health value of antibiotics.

Higher antibiotic prices can incentivise innovation in areas of larger market potential (e.g., broad spectrum rather than narrow spectrum antibiotics), reduce the use of antibiotics and improve antibiotic stewardship (Renwick et al., 2016). VBP can also lead to higher antibiotic prices, which can incentivise innovation in areas of larger market potential (e.g., broad spectrum rather than narrow spectrum antibiotics) and thereby reduce the use of antibiotics and improve antibiotic stewardship. These all have the potential to deliver higher value to society.

VBP also promote cooperation across researchers, government regulators and health authorities and antibiotic manufacturers. This has the potential lead to better alignment of priorities and outcomes for society (i.e. through targeting of high-priority pathogens and antibiotics).

VBP was recently identified by the G7 Finance Ministers as a key approach to revitalising the antibiotic development pipeline. National and/or regional plans for antimicrobial valuation, procurement, payment and/or reimbursement were deemed necessary to “help secure a sustainable supply of high-quality, effective, and clinically necessary new and existing antimicrobials for human medicine” (G7 United Kingdom Department of Health & Social Care, 2021). The AMR Industry Alliance also commits to “progress incentives, such as lump-sum payments, insurance models and novel IP mechanisms that reflect the societal value of new antibiotics and vaccines and will attract further investment in R&D” (Allergan, 2016).

Other countries also operate VBP models, for example, the United States (see **Box 3.6**) and United Kingdom. In the United Kingdom, the NICE and NHS Pilot project (see **Box 3.2**) uses value-based pricing, with antibiotics undergoing a HTA to determine their clinical value and the value of a multi-year contract. The annual payments are subject to the antibiotic’s performance over time, including supply, stewardship, manufacturing and environmental practices, monitoring and reporting and antimicrobial surveillance (Dutescu and Hillier, 2021, Crabb et al., 2020, MTPConnect, 2020a).

Box 3.6 U.S. new technology add-on payments

New technology add-on payments (NTAP) is a U.S. hospital reimbursement plan that allows manufacturers to apply for special NTAP designations for new drugs. This allows for additional government-funded payments to be made to hospitals when using drugs that are not yet included in Diagnosis Related Group (DRG) rates, which set the amount that Medicare pays hospitals for products and services provided (Fetter and Freeman, 1986, Manz et al., 2020). This provides incentives for hospitals to adopt new antibiotics and allows for newly approved antibiotics to be appropriately reimbursed. This is critical as DRGs can take 2-3 years to be revised and incorporate new drugs and devices. The payment is based on the newness of the antibiotic, clinical benefit and cost. NTAP reimburses up to 65 per cent of the cost of NTAP-approved drugs (Manz et al., 2020).

Source: ACIL Allen, various sources (as referenced)

Box 3.7 outlines a proposed global effort to deliver a reimbursement mechanism.

Box 3.7 Antibiotic Health Impact Fund

The Antibiotic Health Impact Fund (AHIF) is a proposal to provide rewards/reimbursements for researchers or manufacturers retrospectively based on the calculated health benefits delivered by the antibiotic (Morel, 2011, Outterson et al., Hollis and Pogge, 2008, Fukuda-Parr and Ariana, 2011, Renwick et al., 2016). Antibiotics are sold at or near cost, ensuring access to low- and middle-income people and countries. While the lower cost has the potential to lead to higher consumption, unnecessary use of the antibiotic would be monitored, and the value of the reward/reimbursement would be proportionally reduced if unnecessary use occurs.

The reward would be financed by governments and other donors (i.e., not-for-profits) and the size of the reward would be determined by the market, where all registered products share in the Quality Adjusted Life Years (QALYs) saved by the antibiotic. For example, if a total of 10 million QALYs are saved, and one product/manufacturer contributed to 10 per cent of those QALYs, then they would be rewarded with 10 per cent of the payment. If the payments are high, more manufacturers will register products to share in the payments (Hollis and Pogge, 2008).

Source: ACIL Allen, various sources (as referenced)

3.5.3 How the mechanism can be implemented in Australia

VBP is a pull (outcome based) mechanism that targets the antibiotic pipeline at Stage 5: Production, distribution and marketing.

In implementing this mechanism in Australia, Australian and international priority-setting and reimbursement policy makers (e.g. government and not-for-profit organisations) would play a role in identifying gaps and opportunities in current policies and services and identifying solutions to address these gaps.

In line with this, the recent House of Representatives Standing Committee on Health, Aged Care and Sport review into approval processes for new drugs and novel medical technologies in Australia recommended that the Australian Government should “In partnership with the states and territories, develop and implement a pilot scheme for value-based payments for new antimicrobial drugs. This pilot should apply the lessons learned from the Australian Government’s pilot scheme for payment for Hepatitis C drugs, as well as from overseas antimicrobial drug schemes” (Recommendation 29) (House of Representatives Standing Committee on Health Aged Care and Sport, 2021). This should include a review of the HTA process to ensure there are appropriate pathways for antimicrobials and similar treatments to progress through the system (Recommendation 29) (House of Representatives Standing Committee on Health Aged Care and Sport, 2021).

Funders are government and not-for-profit organisations that, under this mechanism, are responsible for pricing antibiotics and making payments to manufacturers. In Australia, this is the Australian Government, through schemes such as the PBS.

Funders seek to secure antibiotic supply and price. A mechanism that focuses on the value of antibiotics to societal health can increase the per unit cost of antibiotics (as the cost of the antibiotic is linked to its assessed societal value rather than cost of production). This improves the viability of antibiotic manufacturing, which encourages manufacturers to produce antibiotics. This increase in the number of antibiotic manufacturers reduces the risk of supply issues arising from having too few manufacturers. In this way, VBP addresses profitability barriers to production while promoting antibiotic supply security (Ardal et al., 2021).

Research commissioned by the Global AMR R&D Hub across ten G20 countries (including Australia) showed that all ten countries conduct reimbursements linked to HTAs. However,

there is a need for countries to adapt their value assessment frameworks to better capture the public health value of AMR health technologies (Vogler et al., 2021). This is also the case for Australia, with HTA processes currently lacking the capacity to capture the public health value of AMR health technologies. Australia's HTA processes would therefore need to be developed to calculate payments to support the implementation of this mechanism. This may require the Australian Government to refine the HTA process to better incorporate elements of the public health value antibiotics contribute to society, a measure which would deliver benefits beyond the field of antibiotics.

VBP requires coordination across government regulators and health authorities (to administer and monitor the mechanism) and antibiotic manufacturers. It also requires the development of good practice guidelines on the economic evaluation of antibiotics and their broader impact on society, disease transmission and resistance development, for incorporation into HTAs (Simoens and Spriet, 2020). Regulators play an important role in this mechanism, specifically in HTAs.

3.5.4 Risk to Government, barriers to implementation and mitigation strategies

Risks to Government are considered in this section, as well as other barriers to implementation and mitigation strategies.

ACIL Allen's assessment of relevant general literature notes that reputational risk is shared between the researcher/manufacturer and funder, with researcher/manufacturer vetted by funders prior to agreements being made. The arrangements vary based on the nature of the agreement, and typically involve competitive procurement processes. This provides the opportunity for the funder (in this case, the Australian Government) to select suitable researcher/manufacturer candidates (based on appropriate criteria, such as staffing, infrastructure and financial capacity) to design appropriate governance arrangements to ensure the effective and efficient operation of the mechanism. This has the potential to reduce the financial and reputational risk to Government.

VBP requires successful development of an antibiotic in order for the manufacturer to access the income stream and recuperate costs for R&D (Renwick et al., 2016). Making VBP dependent on successful development creates a risk that researchers or manufacturers will not be compensated for their effort. The presence of that risk incentivises researchers or manufacturers to attract and sustain funding to develop an antibiotic and receive the benefits of the mechanism. This also reduces the risk to Government, by ensuring that, through the mechanism, Government only pays for successful antibiotic development.

Raising the cost of antibiotics through VBP requires the funder to have the capacity to pay for higher reimbursement rates (Renwick et al., 2016). Further, with higher prices, manufacturers may be incentivised to overmarket and promote antibiotics (Renwick et al., 2016). These risks need to be carefully considered in designing the mechanisms to help mitigate the financial risk to Government and the risk of developing ABR. This risk might be mitigated by establishing criteria to restrict the conditions under which antibiotics are prescribed (i.e., only in a hospital setting for patients with infections caused by certain priority pathogens).

Higher antibiotic prices can restrict access, particularly for low- and middle-income patients and countries (Ardal et al., 2017). While this risk may be less applicable in Australia, particularly if the mechanism was fully funded by the Australian Government, this risk would need to be considered as part of Australia's broader international engagement on ABR and antibiotic development and access.

Renwick et al (2016) also note that VBP does not directly provide small to medium enterprises with the capital needed to address barriers to R&D (Renwick et al., 2016). As such, there is a financial risk to Government that there is an ongoing need to fund early stage research, as well as implement this mechanism.

4 Assessment of costs

This section outlines the assumptions and estimated value of costs associated with each mechanism

4.1 Overview

In determining the assessment of costs, ACIL Allen has considered the mechanism's purpose, development costs for novel antibiotics, the alignment of proposed mechanisms to existing schemes, the relative difference in cost between each mechanism and the cost borne by different stakeholders.

These considerations are described below, and the estimated costs are presented in the following section.

4.2 Key considerations

A number of factors were considered in the development of cost estimates for each mechanism. These are described below.

- Mechanism purpose: The cost of each mechanism will largely depend on the purpose each is designed to achieve. It was determined that four of the mechanisms (SSL, AMC, SAR and VBP) fundamentally operate by offering a financial incentive for late stage researchers and manufacturers to develop and manufacture novel antibiotics. Therefore, the cost of these mechanisms needs to be sufficient to reimburse these activities to the extent that existing arrangements are insufficient. Alternatively, AAA work by reducing the cost / increasing the efficiencies of antibiotic development. Therefore, the cost of this is related to the changes to assessment and approval processes, which need to be sufficiently low to incentivise development. Importantly, the mechanism does not need to cover the full cost of antibiotic R&D, but rather the costs that are not currently adequately addressed.
- Novel antibiotic development costs: The literature on the cost to develop novel antibiotics provides a broad range of cost estimates. Cost estimates are most directly influenced by two factors – the development stage and likelihood of successful development. Other factors include where and when development occurs and required investment returns. A recent report found that incentives using a cost-based approach fall into a range from about US\$1 billion to about US\$5 billion per novel antibiotic (A\$1.5 billion to A\$7.2 billion) and that the best estimate was about US\$3.1 billion (A\$4.5 billion) (Boluarte and Schulze, 2022). These figures relate to the total cost of development and other research found that the combined operational costs of Phase I to III clinical trials of an antibiotic are estimated to be upwards of US\$130 million (A\$190 million), with post-approval follow-on trials costing an additional US\$150 million (A\$220 million) (Renwick and Mossialos, 2018). Similar levels of variation were reported across the stages of the development cycle. A comparison of development cost found that as a share of total capitalised antibiotic R&D costs (Ferraro et al., 2017b), there were variations at each stage including preclinical (1% - 18%), clinical trials phase (18% – 28%) and total R&D costs, excluding capitalised costs (21% -

50%). Such variation may reflect the uncertain nature of R&D and different accounting methodologies.

- Alignment to existing mechanisms: It was determined that in addition to the absolute size of incentive for each mechanism, the relative size of the mechanism compared to existing mechanisms was also an important consideration. If existing mechanisms had been successful in attracting manufacturers to attempt to develop novel antibiotics, this would suggest the value of the mechanism was sufficient. In this way the value of the mechanisms doesn't need to cover the entire cost of development and manufacturing, but simply be enough to address the perceived shortfall developers currently face.
- Relativity of mechanism cost: In order for the assessment to present a reasonable comparison of the mechanisms, it was determined that the relative value of each mechanism should be broadly aligned where the functions were similar. Put simply, the higher the value of the incentive, the more likely it will be to attract developers to undertake novel antibiotic development. Therefore, the way the mechanism works (i.e., how it impacts novel antibiotic development by stimulating development and address existing development barriers) is not reflected in the cost of the mechanism, but in the expected effectiveness of the mechanism. The matter of effectiveness is addressed in the benefit calculation.
- Cost borne by different stakeholders: An important element of cost benefit analyses is determining the costs borne by stakeholders included in the frame of reference. This includes the cost of novel antibiotic development and procurement. It is assumed that for the four mechanisms designed to provide a financial incentive for developers (i.e., SAP, AMC, SAR and VBP), the development of novel antibiotics will occur outside of Australia, given the infrastructure, technology, skills and manufacturing constraints Australia faces for pharmaceutical R&D. Given this cost will be incurred in other jurisdictions and by non-Australian companies, the direct cost of development has not been included in this analysis for these mechanisms. On the other hand, the cost incurred by the Australian Government to implement these mechanisms (which serve as financial incentives to developers) has been captured in this analysis and has been assumed to be sufficient to incentivise development. The remaining mechanism (AAA) relates to assessment and approval and is a cost directly borne by the developers. The cost of this development is assumed to occur within Australia (as the mechanism operates by accelerating Australian assessment and approval) and therefore this cost is captured in the analysis.

4.3 Cost 1: Mechanism implementation

In order to develop estimates for the cost to implement each mechanism, ACIL Allen conducted a review of existing schemes that have involved the implementation of related mechanisms. From this scan, three types of mechanisms were identified:

- Guaranteed revenue models: Case studies within this group broadly involved an agreement between a funder and manufacturer to make antibiotics available. This model was deemed to be relevant to SSL, AMC and SAR.
- Accelerated review models: Case studies within this group involved adapting processes and priorities to enable faster reviews of antibiotics seeking approval. This model was deemed to be relevant to AAA models.
- Value models: Case studies within this group involved revising health technology assessment methodologies that more fully reflect the value antibiotics deliver to society. This model was deemed to be relevant to VBP.

Each mechanism type is described below.

4.3.1 Guaranteed revenue models

By participating in this mechanism, antibiotic manufacturers are seeking to hedge against the downside risk of low sales revenue and to facilitate the recovery of their development costs. In practice, this results in the development of antibiotics that otherwise will not be manufactured, since the government is essentially guaranteeing a minimum target return for manufacturers.

To estimate the implementation cost, ACIL Allen conducted two case studies on this mechanism: 1) the PHAS pilot study and 2) NHS pilot study (Public Health Agency of Sweden, 2020b, Dall, 2022). While both pilot studies rely on the same incentive mechanism, the amount compensated by government can be either fixed or variable.

For the PHAS pilot study, the amount compensated by the government declines with sales revenue. Specifically, if sales revenue falls below A\$560,000 (or SEK 4M), the government covers the difference to ensure that manufacturers earn at least A\$560,000 per annum. However, should revenue exceed that threshold, the manufacturer is still entitled to receive 10% of the subscription cap (A\$56,000 or SEK 400,000) from the government.

This compares with the NHS pilot study, where the manufacturer's compensation is not linked to actual sales revenue. Instead, it is fixed at a pre-determined fee. Currently, there are two manufacturers approved under this study, namely Pfizer (for its existing antimicrobial, ceftazidime-avibactam) and Shionogi (for its new antimicrobial, cefiderocol).

At this stage, the NHS has negotiated a three-year contract with each manufacturer, and has the option to extend it for a total of 10 years. Barring any significant development, each manufacturer may stand to receive up to A\$17.5M (or GBP 10M) per annum, from 2022 to 2031. This is irrespective of the number of antibiotics sold. It follows guidance from NICE, which determined that the benefits of the drugs were in excess of the fixed fee.

Cost estimate

For the benefit-cost assessment, ACIL Allen adopted cost estimates as outlined by the NHS pilot study. This assumes that manufacturers will anchor their expectations on compensation, based on the largest historical transaction. Specifically, this is equivalent to an annual payment of A\$17.5M for the duration of the agreement (as per the NHS pilot study, and converted to \$AUD using the current prevailing exchange rate). These costs are assumed to span the course of the agreement, which has also been based on the NHS pilot study (i.e., 10 years). The costs are assumed to start once antibiotics are available, and therefore account for the timing assumptions outlined in **Table 5.2** below. As such, costs are assumed to be incurred for the following periods for each mechanism:

- SSL: 2034 – 2043
- AMC: 2035 – 2044
- SAR: 2035 – 2044

Recognising that research and development is constrained due to a finite budget, manufacturers will typically prioritise initiatives that offer the largest compensation since it is usually associated with product scalability and consequently, greater profitability. Given the scheme in the UK has successfully attracted two developers to enter an agreement with the NHS, the value of this agreement has been applied in this assessment.

4.3.2 Accelerated review models

Accelerated review models are intended fast-track assessment processes for therapeutic products, and may be applied to clinical and regulatory approval processes. Such models are typically applied to ensure that patients with serious or life-threatening diseases are able to access the necessary treatment in a timely manner. This mechanism relies on regulators establishing pathways which enable rapid decision-making on whether the drug is safe and fit for its intended purpose. Importantly, accelerated review models are the only mechanism for which the cost of clinical trials are captured in this analysis. This is because for other mechanisms, it is assumed these costs will be incurred in jurisdictions outside of Australia (given limited activity currently occurring domestically) and therefore not within reference for this study (given the scope is limited to costs and benefits within Australia). Additionally, this mechanism works by accelerating the assessment within the reference jurisdiction, and so will incentivise this activity within Australia.

To represent the implementation cost, ACIL Allen conducted a case study into the Limited Population Antibacterial Drug (LPAD) approval pathway, an expedited approval pathway in the US for antibacterial or antifungal drugs used to treat life-threatening indications in small patient populations with unmet needs. Under the pathway, a drug's safety and effectiveness is studied in substantially smaller clinical trials, over shorter durations. Given this pathway is strictly limited to drugs treating highly resistant bacterial and/or fungal infections, it is not feasible to conduct large-scale trials due to the limited incidences of serious infections.

These constraints mean that LPADs are narrowly indicated for use in small, well-defined populations of patients for whom the drug's benefits are proven to outweigh their risks. However, these products may not be used to treat the more common infections or where there are alternative treatments available.

To date, only two drugs have been approved the LPAD pathway in the US, namely liposomal amikacin (Arikayce) to treat *Mycobacterium avium* complex lung infections where conventional treatment was unsuccessful, and Pretomanid, a combination product or bedaquiline and linezolid to treat highly drug-resistant tuberculosis. Importantly, data available to the FDA at time of assessment is limited to Phase 2 clinical trial evidence, as conventionally defined (European Medicines Agency, 2020, Center for Drug Evaluation and Research, 2019).

In Australia, the TGA has a similar expedited pathway, known as the Orphan Drug program. Consistent with LPAD, applications are limited to drugs targeting rare and very serious medical conditions. The eligibility criteria for orphan drug status is challenging for anti-infective drugs though, as one of the criteria¹ is "it is not medically plausible that the medicine could effectively treat" ... "another class of patients" ..

Cost estimate

For the benefit-cost assessment, ACIL Allen has used the both the LPAD and Orphan Drug program as benchmarks, to develop cost estimates for this mechanism.

To substantiate their applications, manufacturers are required to perform clinical trials on the efficacy and safety of the newly development drugs. In line with LPAD drugs, these trials are assumed to be conducted up until Phase 2. Based on the existing literature, these

¹ <https://www.tga.gov.au/publication/orphan-drug-designation-eligibility-criteria>

costs typically amount to roughly A\$66M (or USD 47M) across eight years (Patel and Fadaei, 2016).

It is assumed this cost will be borne by antibiotic developers conducting clinical trials in Australia. Furthermore, the cost of manufacturing and selling antibiotics under this mechanism is not captured in the analysis as it is assumed buyers will simply substitute away from current and ineffective antibiotics in the base case to the new and effective antibiotics made available under the mechanism scenario. It is assumed the cost to substitute between the antibiotics available in the base case and those available under the assessment case is broadly similar.

The underlying cost profile is summarised in **Table 4.1** showing how the assessment cost is distributed over time.

Table 4.1 Cost of implementation

Year	Cost of clinical trials (\$A)
2025 to 2029	\$13.6M
2030	\$8.4M
2031	\$25.5M
2032	\$18.4M

4.3.3 Value models

Value models work by establishing compensation arrangements and economic incentives that better align the societal value (including public health needs) from the discovery of new drugs to the price setting process. Such models work by increasing the revenue manufacturer stand to earn by making novel antibiotics available, thereby stimulating innovation and research and development as successful development of a novel antibiotic carries a greater financial reward.

To understand the cost of implementing value models, ACIL Allen reviewed two examples of this mechanism: 1) the US New Technology Add-on Payment (NTAP) and 2) Antibiotic Health Impact Fund (AHIF) payment. Even though both initiatives share similar mechanisms, the key distinction lies with the segment of the value chain, where it seeks to better reflect economic value.

For the NTAP, the intent is to bridge the potential shortfall in hospital reimbursements that is prevalent during the initial adoption of newly available drugs / medical devices. Currently, the Centre for Medicare & Medicaid Services (CMS) in the US pays hospitals for the provision of acute care, with reimbursements largely dictated by the cost of medical treatment.

These costs are estimated based on historical claims data; hence, it does not accurately capture the cost of new treatments. This may result in a reimbursement gap since the payment recalibration may take up to three years to accurately reflect revised costs.

Addressing this shortfall is particularly important since the inability to recover costs may constrain the widespread adoption of new treatments in hospitals. Therefore, CMS may pay up to an additional 65 per cent of the cost of the approved new technology, on top of the base payment rate. By facilitating payments in excess of costs, CMS is essentially incentivising greater treatment uptake since it is satisfied with the resultant societal benefits.

In FY22, 42 technologies were eligible for add-on payments, amounting to roughly A\$2.1B (or USD 1.5B) in Medicare spending.² This is equivalent to an annual payment of \$50M per technology. These payments are typically available for up to three years, mirroring the payment recalibration cycle.

On the other hand, AHIF payments seek to revamp the existing revenue model of antibiotic manufacturers. By registering with AHIF, manufacturers agree to supply new drugs at or below cost. Instead, manufacturers will be compensated based on AHIF's assessment of health benefits.

Importantly, these benefits are derived from greater accessibility to drugs, particularly in low- and middle-income countries. Depending on the accrued benefits, AHIF then pays manufacturers to enable them to make a return on investment.

Since AHIF is still in its conceptualisation, actual cost estimates are not available. However, proponents estimated that the minimum efficient scale for a proposed pilot study is roughly \$8.4B (or USD 6B) per annum. This payment is assumed to be evenly distributed across 20 new drugs, implying an average payment of \$420M per drug. Notably, this does not reflect the potential benefits accruing to a single country, since it is designed to improve the accessibility of drugs globally.

While the above case studies provide some indication of how a value model mechanism may be implemented in Australia, significant work will need to be undertaken to ensure the model is relevant in the Australian context. In particular, this work should examine the current HTA processes, which do not holistically capture the societal value of drugs, including antibiotics. This work should focus on identifying approaches to capturing the elements of societal value, which include preventing transmission of infections to other patients and slowing the development of resistance.

Cost estimate

For the benefit-cost assessment, ACIL Allen assumed that the cost of implementing this mechanism wholly reflects the societal benefits (as measured in this assessment) from the introduction of new antibiotics.

As such, the mechanism cost is equivalent to the estimated benefits, and span 2039 – 2048.

4.4 Cost 2: Cost to conduct regulatory approval for each antibiotic

The regulatory cost is assumed to apply to all antibiotics that are submitted for approval in Australia. This cost is incurred by the TGA as the regulating body responsible for assessing and approving drugs to be used in Australia.

This cost estimate has been based on the current application cost for a prescription medicine of \$251,900 (Therapeutic Goods Administration, 2021).

This cost is assumed to be incurred by the TGA for all mechanisms prior to the antibiotic being available in Australia.

² <https://www.cms.gov/newsroom/fact-sheets/fiscal-year-fy-2022-medicare-hospital-inpatient-prospective-payment-system-ipp-and-long-term-care-0>

The basis for how long it will take before antibiotics are available under each mechanism are explained in section 5.4.2, and take into consideration the complexity to implement the mechanism and pace at which antibiotic will be developed under each mechanism.

Table 4.2 presents the assumptions around the timing of regulatory costs.

Table 4.2 Year regulatory costs incurred

Criteria	SSL	AAA	AMC	SAR	VBP
Year regulatory costs incurred	2034	2032	2035	2035	2039

Source: ACIL Allen, 2022

5 Assessment of benefits

This section outlines the assumptions and estimated value of benefits associated with each mechanism and to whom they accrue.

5.1 Overview

As noted in Chapter 2, three quantitative benefits have been included in this assessment, including:

- Avoided mortality due to AMR
- Avoided morbidity due to AMR
- Avoided hospitalisation costs due to AMR

The assumptions and approach adopted to estimate each benefit are presented below. We also discuss some of the key consideration that arose during the estimation of benefits.

5.2 Key considerations

A number of factors were considered in the development of benefit estimates for each mechanism. These are described below.

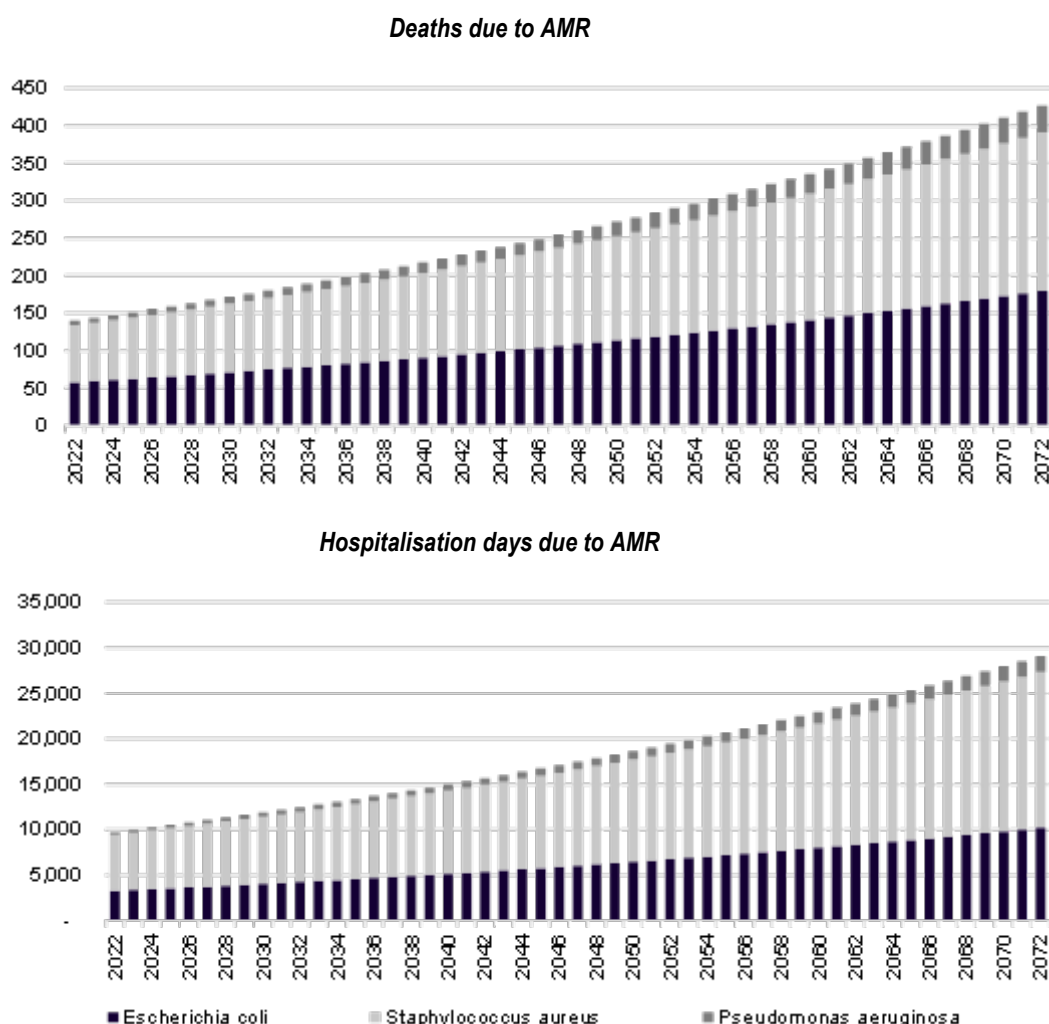
- Antibiotic use: The way in which novel antibiotics are used has an impact on the nature and magnitude of benefits that might be realised. Firstly, a narrow spectrum antibiotic that is only used to treat a single pathogen will have fewer application, may be more effective and less exposed to the risk of resistance. Alternatively, broad spectrum antibiotic will have greater application given the range of pathogens it may treat but may also be at a greater risk of resistance. Another factor related to use is the stewardship protocols that apply to the antibiotic. Such protocols govern how the antibiotic is used, including any restrictions on who is authorised to prescribe the antibiotic, the eligible patient indicators / infections and the setting in which the antibiotic can be used. Those with higher stewardship standards will be better protected against resistance. The analysis assumes the novel antibiotic will be used to target a single pathogen (narrow spectrum) and be subject to strong stewardship protocols under each mechanism.
- Uncertain future threat of resistance: The threat AMR poses in the future is highly uncertain. The rate at which resistance develops is not linear and may accelerate with little warning. A number of antibiotics are providing last line of defence protection against a range of pathogens, and if resistance emerges, the public health threat will increase. Related to this uncertainty is how Australia (and other countries) would react to a rapid acceleration in AMR (although the response to the COVID-19 pandemic may provide some indication). Given the level of uncertainty, and myriad of possible scenarios that may arise in the absence of mechanism implementation, the analysis has applied conservative assumptions to assume the threat increase at a gradual and steady rate, in order to avoid over estimating the value of potential benefits emerging from the implementation of a mechanism.

5.3 Base Case

The base case represents the ‘no intervention’ scenario which assumes that the proposed mechanisms are not implemented in Australia. Without the implementation of a mechanism to incentivise the development of novel antibiotics, no new antibiotics will be developed or become available in the Australian market during the assessment period. The key assumption made under the base case is that resistance rates for pathogen antibiotic combinations will increase over time.

Figure 5.1 illustrates the impacts of increasing resistance rates for *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* under the base case from 2022 to 2072. The estimated number of deaths due to AMR is illustrated in the top pane and estimated number of hospitalisation days due to AMR is illustrated in the bottom pane. It shows that the number of deaths and hospitalisation days due to AMR increases over time as the resistance rates of pathogen antibiotic combinations increase over time.

Figure 5.1 Mortality and hospitalisation days



Source: ACIL Allen, 2022

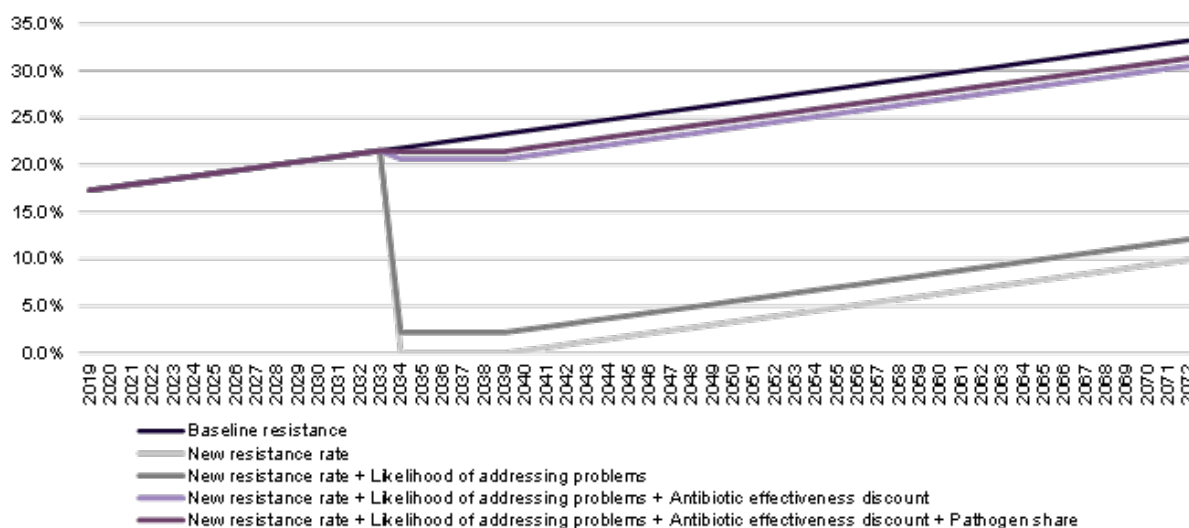
With the implementation of the mechanisms to incentivise the development of novel antibiotics, it is assumed that projected resistance rates for each pathogen antibiotic combination will change. To illustrate, **Figure 5.2** shows how the resistance curve for

Escherichia coli evolves over time if SSL was implemented. The key factors that impact resistance rates projections include:

- **Likelihood of mechanisms addressing the problem:** This assumption relates to the likelihood that the mechanism will be effective in the development and availability of a novel antibiotic. A highly effective mechanism will lower the resistance rates.
- **Antibiotic effectiveness discount:** This assumption aims to account for the extent to which a novel antibiotic will be effective at addressing the mortality threat posed by pathogens.
- **Duration until antibiotics are available:** This assumption relates to the estimated time until antibiotics are likely to be available under each mechanism. Two key activities are required to take place before antibiotics are available – time for the mechanism to be implemented and time for manufacturers to respond to the mechanism.
 - Introducing novel antibiotics into the Australian market will drive resistance rates to zero for a period of time until resistance to those new antibiotics will emerge. Across all mechanisms, it is assumed that the duration until resistance occurs is 7 years, which represents average time to resistance from antibiotics introduced historically (Boluarte and Schulze, 2022).

The changes to projected resistance rates relative to the base case will subsequently have impacts on the estimated number of deaths and hospitalisation days. Differences in the estimated number of deaths and hospitalisation days between the base case and mechanism represent avoided deaths and avoided hospitalisation days respectively. Note that the assumptions described above differ between all five mechanisms, with further detail provided in the sections below.

Figure 5.2 Projected resistance rates for *Escherichia coli*, under the SSL mechanism



Source: ACIL Allen, 2022

5.4 Benefit 1: Avoided mortality due to AMR

This benefit is an estimate of the avoided mortality (loss of human life) as a result of having a novel antibiotic available following the implementation of each mechanism. The approach and assumptions applied to quantifying this benefit are described below.

5.4.1 Likelihood of mechanisms addressing the problem

This assumption relates to the likelihood that each mechanism will be effective in resulting in the development and availability of a novel antibiotic.

This assumption differentiates the effectiveness of each mechanism based on the extent to which each mechanism might overcome the current challenges restricting the development of antibiotics.

The approach to determining estimates for this assumption are necessarily subjective and therefore require some judgement based on the project team's understanding of each mechanism, the key challenges currently facing antibiotic development, and the extent to which mechanisms may address each challenge.

To develop a basis for these assumptions, ACIL Allen developed an Multicriteria Assessment (MCA) where each mechanism is scored against four weighted criteria. As noted, the criteria aligns to the barriers currently impeding antibiotic development, with weighting applied to reflect the relative importance of each barrier. The criteria include:

- **Addresses financial return:** This criterion relates to the extent to which the mechanism provides a sufficient financial incentive to encourage development and manufacturing of novel antibiotics. This is a key barrier limiting antibiotic development, as the limited financial incentives fail to attract sufficient investment and attention from developers, particularly at the late stages of development. As such, this criterion was assigned a weight of 50%. Scoring of 1 – 5 were based on:
 - 1 - Does not address the problem regarding financial return
 - 2 - Weakly addresses the problem regarding financial return
 - 3 - Somewhat addresses the problem regarding financial return
 - 4 - Strongly addresses the problem regarding financial return
 - 5 - Very strongly addresses the problem regarding financial return
- **Simplifies process:** This criterion relates to the extent to which the mechanism simplifies the process to develop and / or manufacture of novel antibiotics. This criterion reflects the process complexity barriers facing those attempting to bring antibiotics through the development pipeline, in particular the regulatory and pricing processes. While important, this barrier was assigned a weight of 15%, which reflects the importance of this barrier relative to others identified. Scoring of 1 – 5 were based on:
 - 1 - Does not simplify development process
 - 2 - Weak contribution to simplify development process
 - 3 - Mild contribution to simplify development process
 - 4 - Good contribution to simplify development process
 - 5 - Strong contribution to simplify development process

- **Encourages partnerships:** This criterion relates to the extent to which the mechanism encourages partnerships to perform key functions along the development pipeline (i.e., late-stage research, assessment and approval, manufacturing, etc.) to drive the development and manufacturing of novel antibiotics. While it is desirable that the development pipeline functions are encouraged to form partnerships, this criterion was deemed to be the lowest priority of the four criteria applied in the analysis and therefore assigned a weighting of 10%. Scoring of 1 – 5 were based on:
 - 1 - Does not encourage a partnership
 - 2 - Provides weak support for a partnership
 - 3 - Provides support for a partnership
 - 4 - Provides strong support for a partnership
 - 5 - Provide strong support for 2 or more partnerships

- **Feasibility:** This criterion relates to the extent to which the mechanism is deemed to be a feasible solution to stimulating the development and manufacturing of novel antibiotics – either through existing example or from a theoretical basis. This criterion was assigned a weight of 25%, reflecting the relative importance in ensuring the mechanism could be based on some case study (and therefore leverage the process and findings for this mechanism) or thoroughly defined theoretical model. Scoring of 1 – 5 were based on:
 - 1 - No evidence and / or not theoretically feasible
 - 2 - Weak evidence and / or weak theoretical basis for feasibility
 - 3 - Some evidence and / or somewhat theoretically feasible
 - 4 - Good evidence and / or likely to be theoretically feasible
 - 5 - Strong evidence and / or very likely to be theoretically feasible

Table 5.1 Likelihood of mechanisms addressing the problem

Criteria	Mechanism	Score	Rationale
Addresses financial return (50%)	SSL	5	A key feature of SSL is to provide an ongoing payment to address the current barrier to sufficient financial returns. Manufacturers are paid a contracted amount to make the antibiotic available and the payment is set at a level that is sufficient to provide a financial return.
	AAA	2	AAA do not ensure a direct financial return for the developers or manufactures, but instead focus on reducing approval times and costs, thereby reducing the financial return required to make development financially viable (i.e., indirectly addresses financial return).
	AMC	5	AMC are an agreement to ensure a financial return to developed in exchange for drug availability and directly address this barrier. In a similar way to SSL, AMC aim to provide financial assurances for developers to make antibiotics available.
	SAR	4	SAR aim to provide some assurance on financial return via an agreement for the reserve and funding for antibiotics, but may impose conditions on the availability and use of antibiotics which may impact financial return for manufacturers, depending on how the mechanism is implemented.
	VBP	5	A key feature of VBP is to reimburse manufactures based on the social value on antibiotics. While there remains some uncertainty as to how the societal value is calculated, it is highly likely the calculation will lead to a significant increase in financial returns for manufacturers.
Simplifies process (15%)	SSL	3	SSL are based on establishing clear parameters for the purpose and use of an antibiotic developed under this arrangement, which may simplify the development process. The arrangement with Government under the mechanism may also lead greater assistance from other government agencies / functions into a progressing the antibiotic. However, agreement to the mechanisms may also impose some additional process complexity for manufacturers.
	AAA	5	A key feature of AAA is to reduce the time and cost of antibiotic development. As such, developers seeking approval under a AAA will likely face a simplified development process.
	AMC	3	AMC are assumed to face similar factors outlined under SSL above and have therefore been assigned the same score.
	SAR	3	SAR are assumed to face similar factors outlined under SSL above and have therefore been assigned the same score.
	VBP	3	VBP are assumed to face similar factors outlined under SSL above and have therefore been assigned the same score.
Encourages partnerships (10%)	SSL	3	SSL establish a partnership between at least two functions - the funder and manufacturer. However, this partnership may only be maintained over the term of the contract / mechanism duration.
	AAA	5	AAA establish strong partnerships between at least three functions - the late stage research, manufacturing and regulatory functions. These partnerships are likely to provide strong support to antibiotic development.

Criteria	Mechanism	Score	Rationale
	AMC	4	AMC establish a strong partnership between at least 2 functions - the funder and manufacturer. These partnerships are likely to involve strong foundational negotiations to ensure appropriate product development and availability and therefore support a longer-term arrangement
	SAR	4	SAR establish a strong partnership between at least two functions - the funder and manufacturer. This mechanism will require detailed consideration of the conditions of the antibiotic reserve (i.e., manufacturing, volumes, quality assurance, distribution) and are likely to support a longer-term arrangement.
	VBP	4	VBP establish a strong partnership between at least two functions - the funder and manufacturer. This mechanism will require detailed consideration of the value-based payment and both the consideration of this and the value of the payment are likely to support a longer-term arrangement.
Feasibility (25%)	SSL	5	There are existing examples of the design and implementation of SSL. Similar models have been implemented for antibiotics in various forms, including trials in the UK and Sweden, and these models and those involved could be used to support an Australian model.
	AAA	5	There are existing examples of the design and implementation of AAA. Similar models have been implemented, including a trial in the U.S, and this model and those involved could be used to support an Australian model.
	AMC	4	There are existing examples of the design and implementation of AMC. While similar models have been implemented globally (i.e., GAVI and COVAX), these models have been applied to a difference drug (vaccines) to be used at higher volumes. Some lessons could be utilised for an Australian model.
	SAR	3	SAR are currently only a hypothetical model, however the development and use of Vancomycin may provide a model on which to base an Australian model. This situation could be studied in detail to guide the implementation of a model in Australia.
	VBP	4	There are existing examples of the design and implementation of VBF. Similar models have been implemented in the US and in low and middle income countries (AIHF). These examples did not apply to antibiotic and may therefore need to be adapted to be compatible in Australia.
Weighted total score	SSL = 0.90	AAA = 0.70	AMC = 0.87 SAR = 0.72 VBP = 0.87

Source: ACIL Allen, 2022

5.4.2 Duration until antibiotics are available

The analysis also accounts for the estimated time until antibiotics are likely to be available under each mechanism. Two key activities are required to take place before antibiotics are available – time for the mechanism to be implemented and time for manufacturers to respond to the mechanism.

Based on the literature review and stakeholder consultation, each mechanism was assigned a score of 1 – 5 scale for each activity, as described below:

- **Time to implement mechanisms:** This activity relates to the complexity, risk and degree of novelty of the mechanism and how long it will take for government to implement the associated scheme. The range of timeframes are assumed to be broadly representative of government policy of this nature.
 - 1 - Very high complexity to implement (7 years)
 - 2 - High complexity to implement (5 years)
 - 3 - Moderate complexity to implement (3 years)
 - 4 - Low complexity to implement (2 years)
 - 5 - Very low complexity to implement (1 year)
- **Time until novel antibiotics are developed:** This activity relates to how responsive manufacturers are likely to be in developing an antibiotic after the introduction of the mechanism. The range of timeframes are assumed to be broadly representative of the time to undertake drug development.
 - 1 - Very long period to deliver novel antibiotic (15 years)
 - 2 - Long period to deliver novel antibiotic (12 years)
 - 3 - Average period to deliver novel antibiotic (10 years)
 - 4 - Short period to deliver novel antibiotic (7 years)
 - 5 - Very short period to deliver novel antibiotic (4 years)

The scoring and rationale for each mechanism across each activity are presented in **Table 5.2** below.

Table 5.2 Duration until antibiotics are available - assumptions

Criteria	Mechanism	Score	Rationale
Time to implement mechanisms	SSL	4 (2 YRS)	SSL are deemed to be relatively low risk and complexity to implement and there are also similar models in UK and Sweden, which could be adapted, with input from experts involved in these models, to suit an Australian context.
	AAA	3 (3 YRS)	AAA are deemed to be moderately risky and complex to implement given the importance in ensuring any relaxation in approval requirements do not expose substantial risks for patients. Similar models exist, particularly the LPAD, which could be adapted, with input from experts involved in this model, to suit an Australian context.
	AMC	3 (3 YRS)	AMC are deemed to be moderately risky and complex to implement given the requirement to commit to purchasing an antibiotic before it has been developed. Furthermore, examples of AMC have to-date focussed on vaccines, with no similar models for antibiotics from which to draw expertise.
	SAR	3 (3 YRS)	SAR are deemed to be relatively low risk and moderately complex to implement given the requirement to specify how antibiotics would be reserved (volumes, storage, duration and quality assurance) and policies on how antibiotics are accessed and who is eligible. There are also no direct examples of SAR from which to draw expertise.
	VBP	2 (5 YRS)	VBP are considered to be relatively low risk but highly complex to implement given the requirement to determine a pricing methodology the appropriately reflects the value to society and also mitigate the risk of excessive costs to government. While some similar mechanisms exist (see NTAP and AIHF) the expertise required would need to be augmented with experts with a strong understanding of the Australia health system to ensure the mechanism implemented in Australia was compatible.
Time until novel antibiotics are developed	SSL	3 (10 YRS)	SSL deemed to result in an average period to deliver novel antibiotic as agreement will likely outline the specification for an eligible antibiotic
	AAA	4 (7 YRS)	AAA deemed to result in a short period to deliver novel antibiotic as mechanism seeks to reduce development time.
	AMC	3 (10 YRS)	AMC deemed to result in an average period to deliver novel antibiotic as agreement will likely outline the specification for an eligible antibiotic
	SAR	3 (10 YRS)	SAR deemed to result in an average period to deliver novel antibiotic as agreement will likely outline the specification for an eligible antibiotic
	VBP	2 (12 YRS)	VBP deemed to result in long period to deliver novel antibiotic as agreement and value payment will likely restrict the types of eligible antibiotics
Commencement year	SSL = 2034	AAA = 2032	AMC = 2035 SAR = 2035 VBP = 2039

Source: ACIL Allen, 2022

5.4.3 Pathogen of focus for novel antibiotic

This assumption is based on outlining the pathogens the novel antibiotic will likely target.

According to the WHO’s 2021 report on Antibacterial agents in clinical and preclinical development, of the 45 traditional antibiotics in the clinical pipeline, six are considered innovative compounds that are expected to target either one or a combination of Enterobacteriales, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Neisseria gonorrhoeae*.

ACIL Allen sought to include all pathogens that are likely to be addressed by these six antibiotics in the cost benefit analysis. However, given that mortality data is unavailable for *Neisseria gonorrhoeae*, this pathogen was excluded from the modelling framework. Zoliflodacin, one of the six novel antibiotics, was subsequently excluded.

Table 5.3 shows that each of the five novel antibiotics are under different phases of clinical trial. It is assumed that novel antibiotics are more likely to be developed if they’ve passed the initial stages of clinical trials. It is also assumed that there is a 70 per cent probability that the novel antibiotic will be developed if it’s under a Phase 3 development phase, 20 per cent if under Phase 2 and 10 per cent if under Phase 1. A weighted score and probability of developing a novel antibiotic is subsequently computed for each pathogen.

Overall, there is a 32 per cent probability that the novel antibiotics will be developed for *Escherichia coli*, 28 per cent probability for *Pseudomonas aeruginosa* and an 40 per cent probability for *Staphylococcus aureus*.

Table 5.3 Novel antibiotics by phase of clinical trial

Antibiotic	Development phase	Pathogens that antibiotic addresses		
		<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus aureus</i>
TXA709	Phase 1	No	No	Yes
VNRX-7145 + ceftibuten	Phase 1	Yes	No	No
Afabicin (Debio-1450)	Phase 2	No	No	Yes
Taniborbactam + cefepime	Phase 3	Yes	Yes	No
Gepotidacin	Phase 3	No	No	Yes

Source: World Health Organisation, 2021 Antibacterial Agents in Clinical and Preclinical development: an overview and analysis

5.4.4 Infections by pathogen

This assumption is a measure of the reported number of human bacteraemia (blood stream infections) in Australia, by pathogen. Note, these estimates are not inclusive of infections or mortality not associated with bacteraemia.

Data on total bacteraemia infections are available between 2017 and 2020 (Australian Group on Antimicrobial Resistance (AGAR), 2017, Australian Group on Antimicrobial Resistance, 2018, Resistance, 2019, Resistance, 2020). This data shows bacteraemia infections by pathogen can increase and decrease over time. To minimise the impact of a high or low year, the analysis takes an average of 2017 to 2020 infection and applies this as the starting infection count for 2020. In 2020, AGAR data included bacteraemia infections reported from 49 public and private Australian hospitals and their communities and is not inclusive of all incidences of bacteraemia in Australia.

The count of blood stream infections is assumed to be the same under each mechanism – i.e., infection count is not impacted by the availability or absence of the novel antibiotic.

There is some degree of uncertainty with this assumption, and therefore this sensitivity has been subject to sensitivity testing in chapter 7.

5.4.5 Growth in infections by pathogen

The incidence of bacteraemia infections are assumed to grow in line (linear correlation) with population growth.

The Australian Bureau of Statistics provides age and gender stratified population growth projections in Australia. The latest data on population projections cover a time-period between 2017 to 2066 (Australian Bureau of Statistics, 2018). A compounded average growth rate (CAGR) of 1.1 per cent, derived across all ages and all persons, was used project the number of infections from 2020 to 2072.

5.4.6 Resistance rates by pathogen

Data on resistance rates for a range of pathogen-antibiotic combinations are available from 2015 to 2019 (Australian Commission on Safety and Quality in Health Care, 2021). Historical data on resistance rates was smoothed by a 3-year average to minimise fluctuations in resistance rates. Projections therefore begin from 2019.

It is assumed that the resistance for each pathogen antibiotic pairs will increase by a constant annual growth rate of 0.3 per cent from 2019 onwards. This growth rate is based on OECD estimates where resistance rates for eight pathogen antibiotic pairs increased from 7 per cent in 2005 to 10 per cent by 2015.

There is some degree of uncertainty with this assumption, and therefore this sensitivity has been subject to sensitivity testing in chapter 7.

5.4.7 Mortality rates by pathogen

Australian data on sepsis mortality rates by pathogen are available from the Antimicrobial Use and Resistance in Australia (AURA) surveillance program, and data on blood culture isolates from 2017 to 2020 were used for the base case modelling in this report. As with the infection and resistance rates, the mortality rate was averaged between this time-period for each pathogen to reduce variability.

It is assumed that the average mortality rate is constant across all projected years to derive the total number of deaths under the base case, and across the five mechanisms.

There is some degree of uncertainty with this assumption, and therefore this sensitivity has been subject to sensitivity testing in chapter 7.

5.4.8 Antibiotic effectiveness discount

This assumption aims to account for the extent to which a novel antibiotic will be effective at addressing the mortality threat posed by pathogens.

There are a number of factors that may mean the availability of a novel antibiotic may not prevent the loss of human life. One factor is access – the antibiotic may not be administered in time to prevent mortality based on where the person in need is (i.e., remote location) and how advanced the infection is. Another factor is the co-morbidities the person in need is experiencing, and the patient may succumb to other factors even if the infection is susceptible to treatment. Furthermore, antibiotics are typically restricted to being used only when certain indications are identified based on the microbiological diagnosis – the

person may not have an eligible indication or may not have the diagnosis conducted in time.

This assumption is essentially an estimate of the proportion of people that survive with the availability of a novel antibiotic under each mechanism scenario, but would die under the base case.

Based on a recent study that quantified the effect of new antibiotics targeting *Enterobacteriaceae*, of 1,000 admissions, approximately 6 deaths are prevented at an importation rate of 10 per cent (Toth. et al, 2021). ACIL Allen has inferred that at an importation rate of 100 per cent, 6 per cent of deaths will be prevented from new antibiotics.

Based on the abovementioned factors that limit the potential effectiveness of a novel antibiotic and as a conservative measure, ACIL Allen has assumed an effectiveness rate of 6 per cent.

There is some degree of uncertainty with this assumption, and therefore this sensitivity has been subject to sensitivity testing in chapter 7.

5.4.9 Value of a Statistical Life (VSL)

Under each mechanism, the VSL is used to monetise reduced mortality. A more precise approach would be to determine the statistical life years preserved by each mechanism. However, through consultation with the project's subject matter expert reviewer, it was suggested that antibiotic resistance is the greatest threat to the very young and elderly and therefore an average estimate (such as is provided by the VSL) is an appropriate measure for this assumption.

The Office of Best Practice Regulation suggests that the appropriate valuation of a Statistical Life is \$5,100,000 in 2021 dollars.

5.4.10 Calculation

The calculation incorporates each of the above assumptions (including target pathogens and timing of novel antibiotic availability) to derive an estimate of the avoided mortality due to AMR.

$$\text{Mortality (Baseline)} = \text{Infections} \times \text{resistance rate} \times \text{mortality rate (1)}$$

$$\text{Mortality (Mechanisms)} = \text{Infections} \times \text{resistance rate reduction} \times \text{mortality rate (2)}$$

$$\text{Avoided mortality} = \text{Difference in mortality [(1) - (2)]} \times \text{value of a statistical life}$$

Where:

$$\text{Resistance rate reduction} = \text{Baseline resistance rate} - (\text{Baseline resistance rate} \times \text{antibiotic effectiveness discount} \times \text{likelihood of mechanisms addressing the problem})$$

Age related risk factors for mortality associated with bacteraemia have not been incorporated into this analysis. Age is the strongest predictor of all-case and infection-related mortality for bacteraemia, and therefore as the population ages, there could potentially be an age-related increase in mortality.

5.5 Benefit 2: Avoided morbidity due to AMR

This benefit relates to the reduction in morbidity (human pain and suffering) associated with AMR.

This benefit draws on a number of the assumptions developed under benefit 1 and includes additional assumptions for the number of bed days for patients with a resistant form of infection, disability weights and value of a statistical life year.

5.5.1 Hospitalised days

AURA data on the total number of patients by length of hospital stay was available at the pathogen level for reported bacteraemia episodes. The length of stay was categorised by various intervals (i.e., less than 7 days, between 7 and 14 days, 15 to 30 days and greater than 30 days). Given this categorisation, the average length of stay was computed (e.g., 10.5 days for the 7 to 14-day interval). It is assumed that patients stay in the hospital for a maximum number of 60 days. The total number of hospitalised days for patients was subsequently computed.

In a previous study, patients with a resistant form of *Escherichia coli* stayed in hospital for a mean of 12 days relative to 10 days for those with an *E.coli* isolate susceptible to currently available antibiotics (de Kraker et al., 2011). It is assumed that 55 per cent of total hospitalised days is attributable to patients with a resistant infection. The average number of hospitalised days for patients with a resistant infection was subsequently computed. Note that hospitalised days are projected by applying these averages to the projected number of people with a resistant infection (refer to Section 5.5.3 below for this calculation).

5.5.2 Disability weights

Disability weights are obtained from the Australian Institute of Health and Welfare's (AIHW) Burden of Disease Study 2013.

Disability weights range from zero (representing perfect health) to one (representing death). It is assumed that patients can experience any of the infectious diseases.

Given that the model is based on bacteraemia, ACIL Allen used a disability weight of 0.133 for 'Infectious disease – Acute episode, severe'.

5.5.3 Value of a Statistical Life Year (VSLY)

The VSLY is a valuation of a year of perfect health. It is an estimate of the value society places on reducing the risk of premature death, expressed in terms of saving a statistical life year.

The Office of Best Practice Regulation suggests that the appropriate valuation of a Statistical Life Year is \$220,000 in 2021 dollars.

Calculation

The calculation incorporates each of the above assumptions to derive an estimate of the avoided morbidity due to AMR.

Hospitalisation days (Baseline) = Average hospitalised days for patients with a resistant infection x Infections x resistance rate (3)

Hospitalisation days (Mechanisms) = Average hospitalised days for patients with a resistant infection x Infections x reduced resistance rate (4)

Avoided morbidity days = Difference in hospitalisation days (annualised) [(3) – (4)] x value of a statistical life year x disability weight

Where:

Resistance rate reduction = Baseline resistance rate – (Baseline resistance rate x antibiotic effectiveness discount x likelihood of mechanisms addressing the problem)

5.6 Benefit 3: Avoided hospitalisation costs due to AMR

This benefit is a measure of the avoided hospitalisation costs associated with AMR. This benefit also uses assumptions developed for benefits 1 and 2, with the addition of cost per hospital bed day.

5.6.1 Cost per hospital bed day

This assumption is an estimate of the cost of care for a person hospitalised with a resistant pathogen.

It is likely a patient will receive care in both a medical ward and progress to an intensive care unit (ICU) if suffering from a resistant pathogen.

As a conservative measure, ACIL Allen has adopted the lower cost care setting based on the national average cost per bed day of \$1,901 in 2015 dollars (Independent Hospital Pricing Authority, 2016), which is \$2,101 in 2021 dollars after applying the ABS consumer price index for all groups.

Calculation

Avoided hospitalisation costs due to AMR = Difference in hospitalisation days [(3) – (4)] x average cost per hospital bed day

6 Findings and results

This section presents the key CBA outputs (NPV and BCR) and summary tables.

6.1 CBA Results

The key results of the baseline analysis for each mechanism are presented below in **Table 6.1**. The NPV is calculated by subtracting the present value of costs from the present value of benefits, while BCR is obtained by dividing the present value of benefits by the present value of costs.

Under a 7 per cent real discount rate, the NPV for Accelerated assessment and approval (AAA) mechanism is estimated at \$184,181,721, with a corresponding BCR of 5.85. In contrast to the subscription-based and value-based models, the AAA mechanism has the highest NPV and BCR.

The NPV and BCR estimates for SSL, AMC and SAR are similar but differ due to the timing of implementation and the timing that novel antibiotics are developed. Meanwhile, the NPV and BCR estimate for VCP is \$0 and 1 respectively as the estimated implementation costs are assumed to be equivalent to the estimated benefits, which span from 2039 to 2048.

Table 6.1 Cost benefit analysis results at 7 per cent discount rate, \$2021

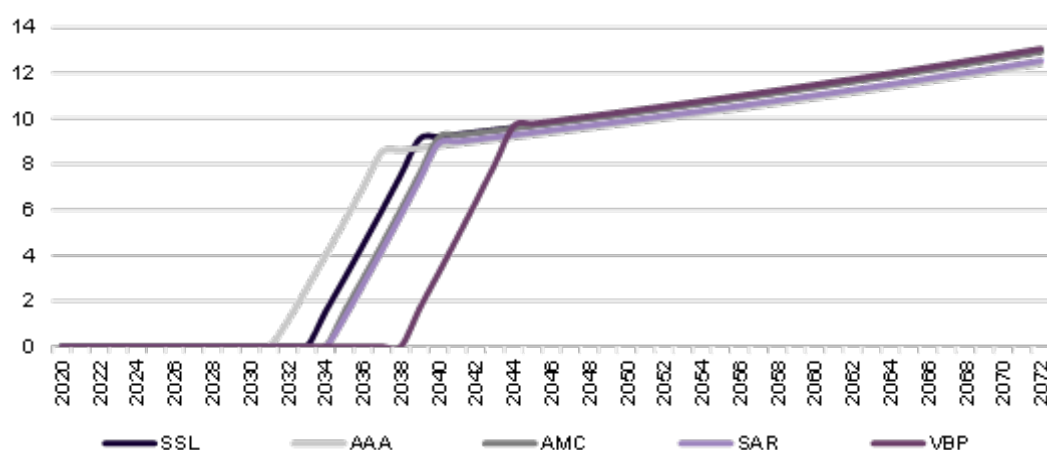
Present value (\$, 10 years @7%)	SSL	AAA	AMC	SAR	VBP
Benefits					
1. Avoided mortality	\$208,506,696	\$215,952,850	\$195,677,971	\$185,277,518	\$158,260,232
2. Avoided morbidity	\$221,184	\$228,284	\$207,479	\$195,945	\$167,819
3. Avoided hospitalisation costs	\$5,796,448	\$5,982,512	\$5,437,298	\$5,135,041	\$4,397,946
Total benefits	\$214,524,328	\$222,163,646	\$201,322,748	\$190,608,504	\$162,825,998
Costs					
1. Mechanism cost	\$58,623,559	\$37,853,872	\$54,788,373	\$54,788,373	\$162,825,998
2. Regulatory approval cost	\$111,847	\$128,053	\$104,530	\$104,530	\$79,745
Total costs	\$58,735,406	\$37,981,925	\$54,892,903	\$54,892,903	\$162,825,998
Outputs					
NPV of Benefits minus Costs	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
BCR	3.65	5.85	3.67	3.47	1.00

Source: ACIL Allen, 2022

6.2 Avoided mortality and hospitalisation days

Avoided mortality by mechanism is shown below in **Figure 6.1**. The main differentiating factor across all mechanisms is the estimated time until antibiotics are available. For all mechanisms, there are no lives saved until the novel antibiotics are available in the first decade from 2022 onwards. The number of lives saved each year gradually increases over time following the implementation of each mechanism and once novel antibiotics are developed.

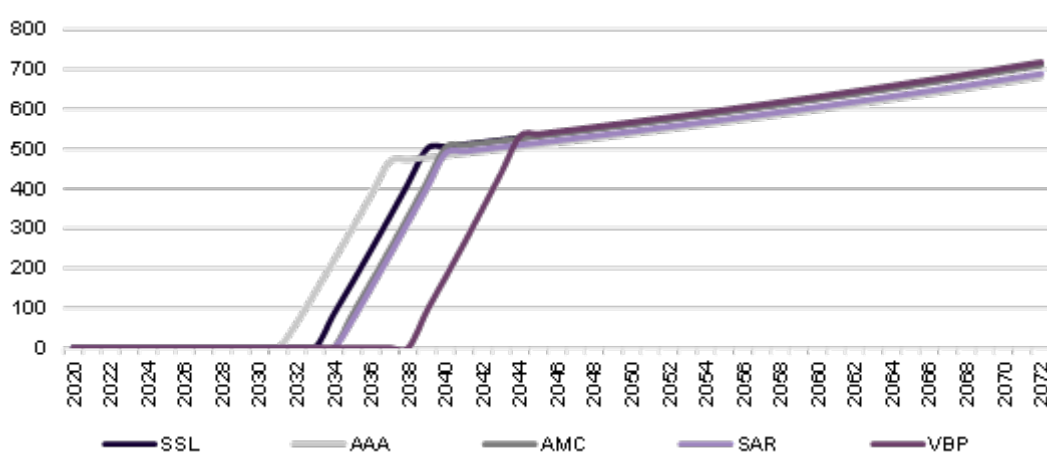
Figure 6.1 Avoided mortality (annual deaths avoided each year), by mechanism



Source: ACIL Allen, 2022

Avoided hospitalisation days by mechanism is shown below in **Figure 6.2**. Similar to avoided mortality, the number of avoided hospitalised days increases rapidly following the implementation of each mechanism and once novel antibiotics are developed.

Figure 6.2 Avoided hospitalisation (annual hospitalisation days avoided each year) by mechanism



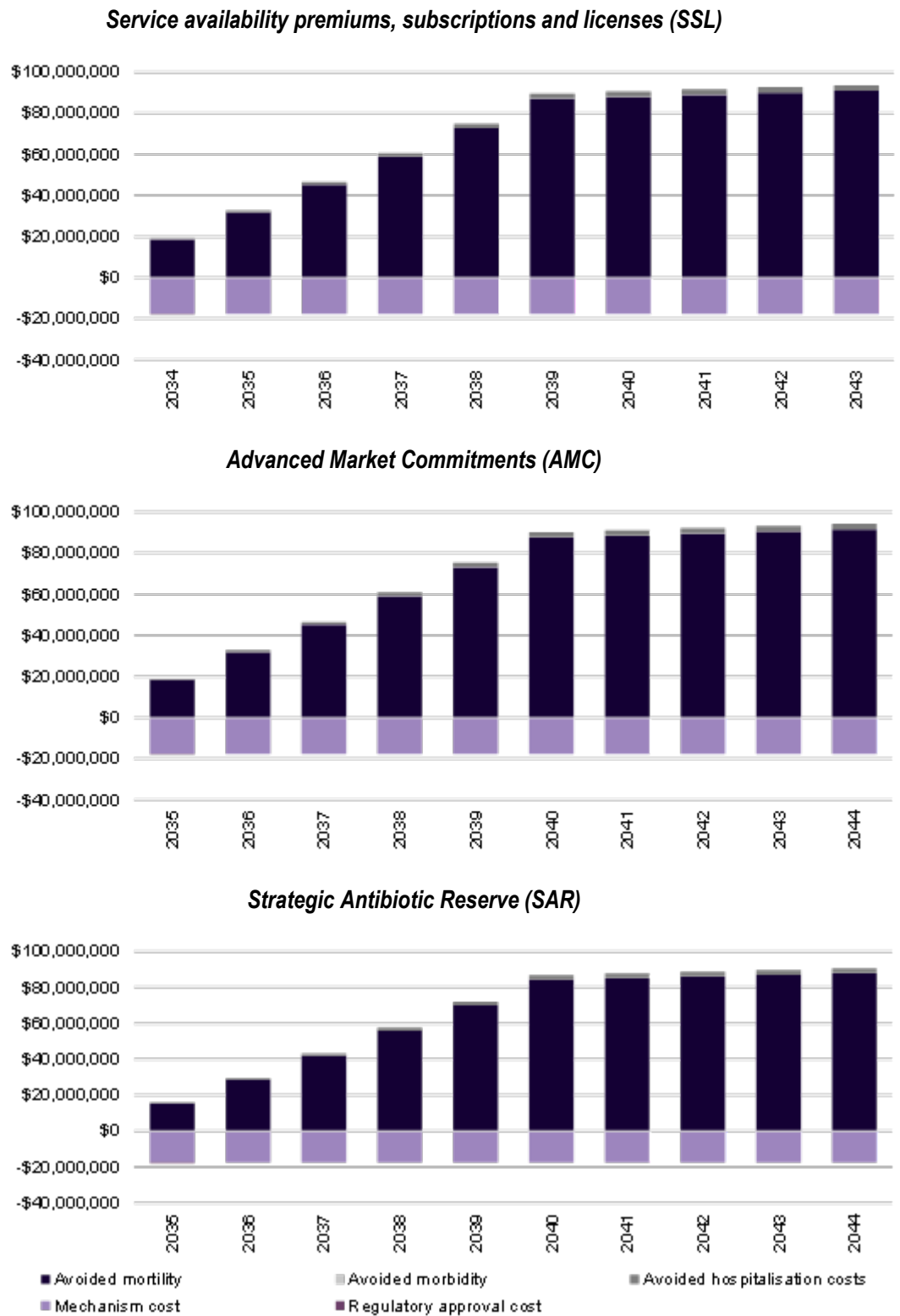
Source: ACIL Allen, 2022

6.3 Incremental costs and benefits

6.3.1 Guaranteed revenue models

The year-by-year incremental costs and benefits associated with the five mechanisms are shown below in **Figure 6.3**. For visual clarity, model and regulatory approval costs are shown as negative values. It shows that the benefits incurred from avoided mortality account for the majority of total benefits. Annual payment of A\$17.5M are incurred in various periods of time, based on the time each mechanism is implemented and once novel antibiotics become available. Regulatory approval costs represent a small proportion of total costs.

Figure 6.3 Guaranteed revenue models – incremental benefits and costs

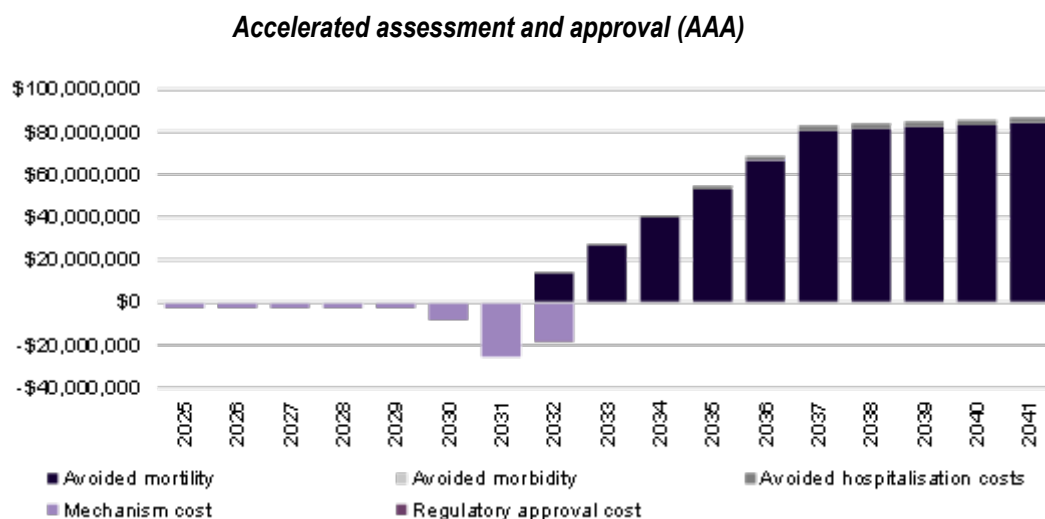


Source: ACIL Allen, 2022

6.3.2 Accelerated review models

The year-by-year incremental costs and benefits for the Accelerated Assessment Approval (AAA) mechanism is shown below in **Figure 6.4**. In contrast to the guaranteed revenue models, the cost profile differs substantially as it considers the cost of clinical trials which varies across different time periods, as outlined in **Table 4.1**.

Figure 6.4 Accelerated review models – incremental benefits and costs

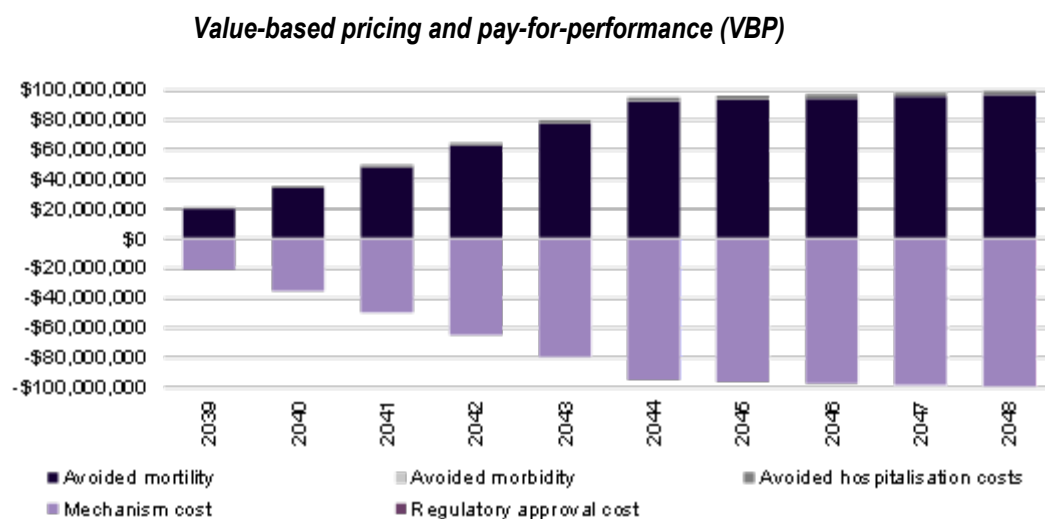


Source: ACIL Allen, 2022

6.3.3 Value models

The year-by-year incremental costs and benefits for the Value-based pricing and pay-for-performance (VBP) mechanism is shown below in **Figure 6.5**. In contrast to the subscription-based and accelerated review model, the costs of implementing the mechanism wholly reflects the estimated benefits from 2039 to 2048.

Figure 6.5 Value models – incremental benefits and costs



Source: ACIL Allen, 2022

7 Sensitivity Analysis

This section presents the results of the sensitivity tests performed on key assumptions in the assessment.

7.1 Overview

- Sensitivity Test 1: New antibiotic effectiveness rate (3 per cent and 12 per cent)
- Sensitivity Test 2: Timing of availability of novel antibiotics (-3 years and +3 years)
- Sensitivity Test 3: Likelihood of mechanisms addressing the problem (score of 1 and score of 5 across all criteria)
- Sensitivity Test 4: Discount rate (3 per cent and 10 per cent)
- Sensitivity Test 5: Assessment period (20 and 35 years)
- Sensitivity Test 6: Mechanism cost (+20 per cent and -20 per cent)
- Sensitivity Test 7: Infection rates (+2.5 per cent and +5 per cent annually)
- Sensitivity Test 8: Mortality rates (+2.5 per cent and +5 per cent annually)
- Sensitivity Test 9: Resistance rates (double and triple growth rate)

Conservative assumptions in tests 3 and 6 lead to the greatest reduction in BCRs across each mechanism, while more optimistic assumptions in tests 7 and 9 lead to the greatest increase in BCRs across each mechanism. Another notable observation from the sensitivity testing is the responsiveness of AAA to test 5, in which the BCR increases markedly with an assessment period of 35 years (i.e., baseline of 5.85 to 14.01). This is because the costs for this mechanism are incurred prior to market access and benefits are assumed to continue to accrue over the assessment period.

7.2 Sensitivity tests

7.2.1 Sensitivity test 1: New antibiotic effectiveness rate

As discussed in Section 5.4.8, there are a number of factors that impact the effectiveness of an antibiotic in addressing the mortality threat, including the accessibility and the potentially restrictive-use of the antibiotic, as well as the co-morbidities the person in need is experiencing.

In response to a high degree of uncertainty around the antibiotic effectiveness rate, a sensitivity analysis based on new rates are shown in **Table 7.1**. Doubling the antibiotic effectiveness rate from 6 per cent to 12 per cent has a considerable impact on the BCR under each mechanism. This is primarily driven by the significant benefits that are estimated from a higher number of lives saved (avoided mortality) over time.

Table 7.1 Sensitivity Test 1 – new antibiotic effectiveness rate

	SSL	AAA	AMC	SAR	VBP
BCR					
3 per cent	3.08	5.10	3.10	3.00	1.00
6 per cent (no change)	3.65	5.85	3.67	3.47	1.00
12 per cent	4.80	7.35	4.80	4.41	1.00
NPV					
3 per cent	\$122,194,117	\$155,652,504	\$115,358,539	\$110,001,417	\$0
6 per cent (no change)	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
12 per cent	\$222,978,532	\$241,240,156	\$208,572,458	\$187,143,971	\$0

Source: ACIL Allen, 2022

7.2.2 Sensitivity test 2: Timing of availability of novel antibiotic

The changes in NPV and BCR estimates based on the timing of available antibiotics are shown in **Table 7.2**. A change in timing (3 years earlier/ 3 years later) has a minor impact on the BCR under each mechanism.

Table 7.2 Sensitivity Test 2 – timing of availability of novel antibiotic

	SSL	AAA	AMC	SAR	VBP
BCR					
3 years earlier	3.49	5.61	3.51	3.33	1.00
No timing change	3.65	5.85	3.67	3.47	1.00
3 years later	3.82	6.10	3.83	3.62	1.00
NPV					
3 years earlier	\$179,461,442	\$214,341,729	\$168,774,528	\$156,547,721	\$0
No timing change	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
3 years later	\$135,074,614	\$158,175,374	\$126,893,221	\$117,517,992	\$0

Source: ACIL Allen, 2022

7.2.3 Sensitivity test 3: Likelihood of mechanisms addressing the problem

The changes in NPV and BCR estimates based on changes in the likelihood of antibiotic development are shown in **Table 7.3**. As this assumption was developed under a subjective assessment of the strengths of each mechanism across defined criteria (see 5.4.1) this test demonstrates the relative importance of this assumption on the overall results for each mechanism. A change in the likelihood of antibiotics development (score of 1 or 5 across all criteria) has a minor impact on the BCR under each mechanism.

Table 7.3 Sensitivity Test 3 – likelihood of antibiotics development

	SSL	AAA	AMC	SAR	VBP
BCR					
Score of 1 for all criteria	2.76	4.78	2.80	2.80	1.00
No score change	3.65	5.85	3.67	3.47	1.00
Score of 5 for all criteria	3.78	6.49	3.84	3.84	1.00

	SSL	AAA	AMC	SAR	VBP
NPV					
Score of 1 for all criteria	\$103,530,337	\$143,425,696	\$98,572,891	\$98,572,891	\$0
No score change	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
Score of 5 for all criteria	\$163,254,434	\$208,635,336	\$155,715,523	\$155,715,523	\$0

Source: ACIL Allen, 2022

7.2.4 Sensitivity test 4: Discount rate

The changes in NPV and BCR estimates based on changes in the discount rate shown in **Table 7.4**. A change to the discount rate (3 per cent / 10 per cent) results in a larger change to the BCR estimate for the AAA mechanism, but minor changes for the remaining four mechanisms. This is primarily driven by the significant benefits that are estimated in the period between 2035 and 2044 for AAA – the benefits are discounted less with a low discount rate and discounted more with a higher discount rate.

Table 7.4 Sensitivity Test 4 – discount rate

	SSL	AAA	AMC	SAR	VBP
BCR					
3 per cent	3.81	7.68	3.83	3.63	1.00
7 per cent (no change)	3.65	5.85	3.67	3.47	1.00
10 per cent	3.54	4.81	3.55	3.36	1.00
NPV					
3 per cent	\$304,871,926	\$346,077,234	\$297,760,529	\$277,136,681	\$0
7 per cent (no change)	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
10 per cent	\$96,164,398	\$115,941,698	\$87,904,077	\$81,193,562	\$0

Source: ACIL Allen, 2022

7.2.5 Sensitivity test 5: Assessment period

The assessment period used for the cost benefit analysis is 10 years from when the novel antibiotics are first available under each mechanism. Across all mechanisms, benefits are incurred during the 10-year assessment period. In response to the uncertainty of how long the novel antibiotics will be used for, a sensitivity analysis based on various assessment periods are shown in **Table 7.5**.

A change in the assessment period from 10 years to 20 or 35 years has a significant impact on the NPV and BCR values for the AAA mechanism, but minor changes to the remaining four mechanisms. For accelerated review models, it is assumed that the cost of clinical trials are incurred between 2025 to 2032 (i.e., prior to mechanism implementation or the assessment period). This indicates that the costs of implementation will be discounted at different points of time, as opposed to the benefits of implementing the AAA mechanism. Increasing the assessment period from 10 to 20 and 35 years will account for an additional stream of benefits, thus increasing the NPV and BCR.

Table 7.5 Sensitivity Test 5 – assessment period

	SSL	AAA	AMC	SAR	VBP
BCR					
20 Years	4.31	10.52	4.33	4.13	1.00
10 Years (no change)	3.65	5.85	3.67	3.47	1.00
35 Years	4.69	14.01	4.71	4.50	1.00
NPV					
20 Years	\$293,349,106	\$361,410,301	\$275,925,020	\$259,147,839	\$0
10 Years (no change)	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
35 Years	\$398,994,386	\$494,087,572	\$375,358,331	\$354,042,300	\$0

Source: ACIL Allen, 2022

7.2.6 Sensitivity test 6: Mechanism cost

The changes in NPV and BCR estimates based on changes in the mechanism cost are shown in **Table 7.6** below. As anticipated, The NPV and BCR decrease as the mechanism cost increases from -20 per cent to +20 per cent. There are minor impacts in the NPV and BCR estimates.

Table 7.6 Sensitivity Test 6 – mechanism cost

	SSL	AAA	AMC	SAR	VBP
BCR					
+20 per cent	3.04	4.88	3.06	2.89	1.00
No cost change	3.65	5.85	3.67	3.47	1.00
-20 per cent	4.56	7.31	4.58	4.34	1.00
NPV					
+20 per cent	\$144,064,210	\$176,610,947	\$135,472,170	\$124,757,927	\$0
No cost change	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
-20 per cent	\$167,513,634	\$191,752,495	\$157,387,520	\$146,673,276	\$0

Source: ACIL Allen, 2022

7.2.7 Sensitivity test 7 – Infection rates

The rate at which the population contracts an infectious disease is also projected with uncertainty. While the current modelling approach assumes that the number of infections increases proportionally to the expected population growth rate, it may be plausible to assume that infection rates will increase over time.

Given the high degree of certainty relating to the infection rate projections, a sensitivity analysis around increases in the rate of infections are shown in **Table 7.7**. To allow for comparisons to the current modelling approach, the number of infections also increase proportionally to the expected population growth rate for both scenarios.

Increasing the rate of infection annually by either 2.5 and 5 per cent has a significant impact on the NPV and BCR across all mechanisms. This indicates that the analysis is more sensitive to the assumptions used to project infection rates.

Table 7.7 Sensitivity Test 7 – infection rates

	SSL	AAA	AMC	SAR	VBP
BCR					
+2.5 per cent (annual)	5.86	8.96	6.04	5.72	1.00
No annual increase (no change)	3.65	5.85	3.67	3.47	1.00
+5 per cent (annual)	9.34	13.62	9.85	9.35	1.00
NPV					
+2.5 per cent (annual)	\$285,644,914	\$302,180,036	\$276,429,495	\$259,244,639	\$0
No annual increase (no change)	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
+5 per cent (annual)	\$489,922,131	\$479,430,930	\$485,917,819	\$458,534,901	\$0

Source: ACIL Allen, 2022

7.2.8 Sensitivity test 8 – Mortality rates

The current modelling approach assumes a constant mortality rate specified by pathogen and based on historic data. It is plausible that mortality rates may increase over time as resistance increases and current available drugs are less effective.

The changes in NPV and BCR estimates based on changes in the annual mortality rate are shown in **Table 7.8**. Increasing mortality rates annually by 2.5 and 5 per cent has a minor impact on the BCR values across all mechanisms.

Table 7.8 Sensitivity Test 8 – mortality rates

	SSL	AAA	AMC	SAR	VBP
BCR					
+2.5 per cent (annual)	3.74	5.99	3.76	3.56	1.00
No annual increase (no change)	3.65	5.85	3.67	3.47	1.00
+5 per cent (annual)	3.83	6.13	3.85	3.64	1.00
NPV					
+2.5 per cent (annual)	\$161,001,590	\$189,580,542	\$151,321,794	\$140,347,539	\$0
No annual increase (no change)	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
+5 per cent (annual)	\$166,214,257	\$194,979,364	\$156,213,744	\$144,979,477	\$0

Source: ACIL Allen, 2022

7.2.9 Sensitivity test 9 – Resistance rates

Resistance rates are highly unpredictable. For the purposes of this analysis, it is assumed that resistance rates increase by a constant annual growth rate of 0.3 per cent. Given the uncertainty around this assumption, a sensitivity analysis with a doubling or tripling resistance growth rate was conducted. As shown in **Table 7.9**, increasing growth rate in resistance by two or three times has a significant impact on the BCR under each mechanism.

Table 7.9 Sensitivity Test 9 – resistance rates

	SSL	AAA	AMC	SAR	VBP
BCR					
Double growth rate	6.38	10.46	6.44	6.20	1.00
No change	3.65	5.85	3.67	3.47	1.00
Triple growth rate	8.87	14.88	8.85	8.58	1.00
NPV					
Double growth rate	\$316,221,092	\$359,199,294	\$298,357,568	\$285,445,464	\$0
No change	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
Triple growth rate	\$462,145,782	\$527,365,092	\$431,179,919	\$416,069,956	\$0

Source: ACIL Allen, 2022

8 Qualitative Impacts and Distributional Analysis

This section presents an analysis of the qualitative cost and benefits identified as well as distributional or equity issues relevant to each mechanism.

8.1 Overview

A number of qualitative benefits and costs also apply to this assessment and are described below. These costs and benefits are represented qualitatively, due to data or methodological constraints.

8.2 Qualitative Benefits

The following qualitative benefits relate to the development and availability of a novel antibiotics:

- Enablement value of antibiotics: Antibiotics are used prophylactically to minimise the risk of infection due to health interventions that compromise the immune system or otherwise increase the risk of infection. For example, most surgical procedures and chemotherapy increase the risk of infection and require prophylactic antimicrobials. As antibiotics become less effective, people may either avoid necessary interventions and / or become ill with resistant infections following the intervention. This is referred to as the enablement value of antibiotics and is deemed to be undervalued in current HTA evaluation methods. The enablement value of antibiotics has not been included in the quantitative analysis but as the threat of AMR grows, the enablement value of available novel antibiotics will increase.
- Contribution to a global solution: AMR is widely accepted to be a global problem, requiring a global solution. The frame of reference adopted in this analysis did not allow the issue to be analysed through a global lens, however given the threat of AMR is more acute in low and middle income countries, it is likely even higher benefits will be achieved by developing and making antibiotics available in these jurisdictions. By investing in the implementation of a mechanism, Australia would be seen as another global leader working to tackle the challenge of AMR. This may also build support and encourage other countries to assist, but may also enable Australia to have better access to antibiotics that are developed in the future and encourage new antibiotics to address threats Australia may face.
- Build capacity and responsiveness: By investing in a mechanism, Australia would also be investing in capability and capacity to develop novel antibiotics. As well as potentially delivering a novel antibiotic, the mechanism would increase the chances that novel antibiotics are developed in the future, by upskilling and encouraging antibiotic development. This may deliver additional benefits, particularly if the threat of AMR suddenly accelerates and the world experiences a highly transmissible strain.
- Synergistic effects of antibiotics: New antibiotics may deliver synergistic effects with existing antibiotics, which increases the efficacy of the existing antibiotics when used in

combination with the new antibiotic. With an undeveloped drug, it is unclear whether these synergistic effects will arise, and for which combinations.

- Use of antibiotics during clinical trials. Antibiotics may deliver therapeutic value to recipients during the clinical trials phase. Antibiotics that are effective and safe start delivering benefits to patients as soon as they are used, however all antibiotics are required to undergo testing until these outcomes can be assured. On the other hand, unsafe antibiotics can impose greater harm on patients and contribute to poorer health outcomes and in severe cases can result in death, particularly if the toxicity of the antibiotic is too great. Given the uncertainty of the direction of this potential impact, it has been treated qualitatively.

8.3 Qualitative Costs

The following qualitative benefits relate to the development and availability of a novel antibiotics in Australia:

- Agreement risk: Each mechanism will require the Australian Government to enter into an agreement with prospective antibiotic developers. While these agreements should involve carefully considered agreement conditions, there is a risk that an agreement does not generate the intended outcomes or results in unforeseen outcomes. While these outcomes are a feature of any agreement, given the innovative nature of each mechanism, these risks may be greater, and impose higher costs, when compared to standard agreements.
- Use of antibiotics during clinical trials. As noted in Section 8.2, antibiotics with unknown safety profiles given to humans during the clinical trials process may result in greater harm to patients and contribute to poorer health outcomes and, in severe cases, can result in death, due to unexpected toxicity or ineffective resolution of the infection. Alternatively, safe and effective antibiotics administered during clinical trials are highly beneficial to recipients. Given the uncertainty of the direction of this potential impact, it has been treated qualitatively. This cost is likely to relate to AAA, given this mechanism is focussed on fast tracking approval processes.
- Diversion of development focus: The implementation of any mechanisms may divert the attention of developers away from maintaining supplies of existing drugs and antimicrobials. The cost of this impact would be the lost benefit provided by these products. The risk of this impact may be greater if the incentive is so attractive that the developer reorients their focus to supply antibiotics under the mechanism, and subsequently fails to maintain supplies of other antimicrobials they market.

9 Validation

This section presents an overview of the process and findings from the validation phase.

9.1 Overview

This report presents an economic assessment of costs and benefits associated with five mechanisms to incentivise novel antibiotic development in Australia. While ACIL Allen has consulted broadly with a range of experts and drawn on contemporary research into antimicrobial resistance, the magnitude of the issue is challenging to forecast with a high degree of precision. This complexity means that any projection of costs and benefits attributable to each mechanism is necessarily based on subjective estimates.

The approach to validating this project, and key findings from the validation process are described below.

9.2 Process

ACIL Allen conducted the following processes to validate the modelling approach:

- **Subject Matter Expert Review:** The primary external reviewer for this project has been Nadine Hillock. Nadine has provided expert input during the development of the modelling approach and also reviewed the modelling output.
- **Project Management Review:** ACIL Allen's project leadership, including Annabel Brebner and Jerome Fahrer, have provided guidance and input into the modelling approach. The management team have also reviewed modelling outputs.
- **Modelling Quality Assurance:** The cost benefit analysis model (developed in excel) has been reviewed by Michael Clark to verify the accuracy of calculations and assumptions.
- **Deliverable Review:** ACIL Allen has worked closely with the Project Sponsor from the Department, (i.e., Health Economics and Modelling Branch of the Health Economics and Research Division, Department of Health and Aged Care). The Project Sponsor has provided input into the design and development of the modelling approach.

The above validation processes identified a number of limitations with this work, which may represent areas for future research.

9.3 Limitations of this study and areas for future research

The key limitations of the modelling approach include the following:

- **Accuracy of current estimates:** Limitations with current estimates of AMR-associated deaths in Australia are primarily due to reporting definitions and data capture. The modelling approach used resistance data reported to the AURA surveillance system and is limited to bacteraemia isolates from some (but not all) public and private healthcare facilities in Australia. Mortality estimates vary based on whether they include deaths due to infections susceptible to available antibiotics as well as the

marginal increase in deaths due to resistant infections. Deaths associated with other infections caused by resistant bacteria that are not included in the modelling include (but may not be limited to) lower respiratory tract infections (hospital or community acquired pneumonias etc) where there was no simultaneous bacteraemia, and other bacterial infections not associated with bacteraemia are not included. The validation process indicated that most current estimates are likely an under count due to the above factors. Some deaths attributable to AMR may also not be reported if the pathogen wasn't detected via a timely diagnosis in the person.

- *The modelling approach has adopted data from AURA, which is understood to be the best available estimate of bacteraemia deaths due to AMR in Australia, however, do not include deaths attributable to pneumonia (which may be attributable to AMR, particularly if acquired in hospital)*
- **Resistance rate projections:** The rate of antimicrobial resistance is highly unpredictable over time and subject to a number of factors. Pathogen interactions can result in the transfer of resistance between pathogens, which can accelerate resistance at a much faster rate than a linear progression. Furthermore, it is suggested that resistance increases in a non-linear fashion, not accelerating until usage rates reach a certain threshold, referred to as the 'threshold model'.
 - *To adopt a conservative approach and to limit fluctuations in resistance rates, the modelling approach smooths historical resistance rates from available surveillance data from AURA. In addition, it is assumed that the future resistance rates will increase by a constant annual growth rate of 0.3 per cent. This growth rate is based on OECD estimates where resistance rates for eight pathogen antibiotic pairs increased from 7 per cent in 2005 to 10 per cent by 2015. However, it is unlikely that the relationship between antimicrobial use and future resistant rates will be linear. A non-linear relationship may be more likely, however further research into the correlation between use and resistance is required to inform such predicted resistance rates.*
- **Infection rate projections:** The rate at which the population contracts an infectious disease is also highly uncertain. The rate of infections may grow if the pathogens evolve and become more virulent. Alternatively, better public health measures, including infection control strategies, may also reduce the rate of rate of infection, including drug-resistant infections, particularly in the hospital setting.
 - *The current modelling approach assumes that the number of infections will increase proportionately to the expected population growth rate.*
- **Mortality rate projection:** The mortality rate refers to the death rate associated with infections with a resistant pathogen. That is, the incremental deaths over the expected deaths to drug-susceptible pathogens. It is likely that the incremental mortality rate will increase as resistance increases and currently available drugs are less effective.
 - *Given the uncertainty regarding possible changes in mortality rate, the modelling has conservatively assumed a constant mortality rate, specified by pathogens and based on historical mortality data.*
- **Antibiotic development:** The modelling assumes that in the absence of the implementation of a mechanism to incentivise the development of novel antibiotics (the base case scenario), no new antibiotics will enter the Australian market during the assessment period. Given the increasing global attention on the issue of AMR, and numerous initiatives attempting to address the growing threat, it is possible a novel antibiotic will be developed and become available in Australia.

- *The approach adopted in this report assumes the under the base case, no new antibiotics will be developed or become available in Australia. This is an appropriate approach for a conventional CBA, where the costs and benefits of this impact have not been recognised under the ‘no intervention’ scenario.*
- **Antibiotic availability:** The analysis implicitly assumes the novel antibiotic will continue to be made available for the duration of the assessment period. If the manufacturer is unable, or unwilling to maintain supply of the antibiotic, the associated benefits will also cease for the corresponding time period. This limitation is perhaps less applicable to the guaranteed revenue and value models (i.e., SSL, AMC, SAR and VBP), as the mechanism continues to reward the manufacturer with an ongoing payment for each year the antibiotics is made available. However, this may be a limitation for the AAA mechanism, where the manufacturer benefits from an accelerated assessment process, after which point are assumed to continue to make the antibiotic available. As such, this requirement should be considered as part of implementation, where any manufacturer granted accelerated approval is also required to make the antibiotic available for a minimum period of time.
- **Populations vulnerabilities:** Certain individuals are at a greater risk of mortality, morbidity and hospitalisation due to AMR. For instance, those that have previously undergone antimicrobial treatment, or had a previous drug-resistant infection, have a higher risk of developing drug resistant infections in the future. Furthermore, people with allergies are unable to take certain antibiotics (for example, penicillins), limiting the effective treatment options available and may also impact the benefits of mechanisms if a newly developed drug has a high allergy rate. These characteristics will impact the outcomes people experience under both the base case and mechanism implementation scenarios and have not been accounted for in the modelling. These factors may result in an under-estimate of the benefit values (for example, if a new antibiotic enabled someone to receive treatment when they otherwise would have been allergic to the available antibiotic) or over-estimate benefit values (if the individual is allergic to the new antibiotic).
 - *The mortality rates also do not incorporate age as a risk factor. Increasing age is a known predictor of the risk of death due to bacteraemia, and as the population ages, the death rate due to bacteraemia may proportionately increase.*
 - *The approach adopted in this report does not differentiate between the vulnerability of sub-populations, which may lead to an over- or under-estimate of benefits. The effectiveness discount applied to the mechanism scenarios reflects an attempt to ensure benefit values are not an over estimate.*

While ACIL Allen has attempted to conduct a comprehensive assessment of mechanisms to incentivise the development and availability of novel antibiotics in Australia, the above limitations represent critical constraints on the analysis and are important caveats for those interpreting the results of this report.

10 Prioritisation

This section presents the prioritised ranking of the models and rationale for prioritisation.

10.1 Overall Assessment

This assessment has considered five mechanisms that may be used to incentivise the discovery of novel antibiotics for human health and bring them to market in Australia.

The cost benefit analysis indicate that Accelerate Assessment and Approval (AAA) mechanisms returned the highest BCR and NPV, and under each sensitivity test.

Table 10.1 Cost benefit analysis results at 7 per cent discount rate, \$2021

	SSL	AAA	AMC	SAR	VBP
NPV of Benefits minus Costs	\$155,788,922	\$184,181,721	\$146,429,845	\$135,715,602	\$0
Mechanisms Rank (NPV)	2	1	3	4	5
BCR	3.65	5.85	3.67	3.47	1.00
Mechanisms Rank (BCR)	3	1	2	4	5

Source: ACIL Allen, 2022

For the AAA mechanism, the relatively low upfront cost that is incurred by manufacturers, is offset by a strong stream of benefits that is primarily driven by the economic benefits derived from avoided mortality, but less so on avoided morbidity and avoided hospitalisation costs.

In contrast to the guaranteed revenue models (SSL, AMC and SAR) and the value model (VBP), the AAA mechanism also only includes the cost of clinical trials, while the other mechanisms rely on an ongoing annual payment to enable manufacturers to recovery development costs.

The mechanisms have been prioritised based on their BCR result – the only case of misalignment between the BCA and NPV results is for AMCs and SSL (i.e., AMCs rank 3 according to NPV and rank 2 for BCR and vice-versa for SSL). BCR has been chosen as the prioritisation metric as it provides an estimate of the benefits for every dollar invested and is a strong indicator of efficiency, however either indicator could be chosen. The mechanisms score very similarly for both BCR (0.02 difference) and NPV (6% net benefit difference) and as such the assessment finds both are almost equally prioritised.

AAA is at a slightly higher risk (relative to other mechanisms assessed) of causing harm on patients given the expedited review process of antibiotics made available under AAA. This risk should be monitored if this mechanism is progressed.

The next chapter provide some direction on implementation steps.

11 Conclusion and recommendations

This section provides direction on the preferred mechanism assessed as having the greatest potential to stimulate R&D for novel antibiotics and promote product availability in Australia, accounting for the quantitative and qualitative analysis performed as part of the CBA.

11.1 Overview

As noted in the preceding chapter, the Accelerate Assessment and Approval (AAA) mechanism is shown to deliver the highest NPV benefit to Australia and generates the highest BCR.

This scoping study has highlighted a number of important considerations to be explored further as part of future implementation efforts. The following recommendations outline directions to support the implementation of a mechanism that may be used to incentivise the discovery of novel antibiotics for human health and bring them to market in Australia.

11.2 Recommendations

ACIL Allen makes the following recommendation in order to provide guidance to progress the implementation of the mechanism.

11.2.1 Recommendation 1: AMR Taskforce

The Australian Government should establish an AMR Taskforce to be responsible for implementing a mechanism to incentivise the development and availability of novel antibiotics in Australia. The AMR Taskforce should include representation of members with suitable skills and experience to progress these initiatives, including in the fields of infectious diseases, public health, medical R&D and commercialisation, research and procurement of antibiotics. The AMR Taskforce should consider the findings and directions in this scoping study and look to progress implementation, including consideration of the following recommendations.

11.2.2 Recommendation 2: Mechanism Funding

As outlined in this study, a number of initiatives have been trialled in other countries in an effort to incentivise the development of novel antibiotics. Furthermore, with the growing awareness of the threat AMR poses, an increasing number of countries are also considering how best to contribute to a solution. The Australian Government, through the AMR Taskforce, should explore opportunities to partner with other countries and / or funding organisations (e.g., not-for-profit organisations) to fund the implementation of a mechanism. Possible partnerships may be based around geographical proximity (e.g., Asia Pacific region) and / or around established diplomatic relationships.

11.2.3 Recommendation 3: Manufacturing capacity and capability

The Australian Government, through the AMR Taskforce, should commence a market sounding exercise to gauge the manufacturing capacity and capability of potential suppliers to engage with under the mechanism (i.e., antibiotics manufactures). In the first instance,

this should include industry consultation with pharmaceutical companies, particularly those already participating in similar trials in other countries (e.g., the NICE trials involving Pfizer and Shionogi). This consultation should focus on identifying interest, capacity and the conditions under which suppliers would be willing to engage.

11.2.4 Recommendation 4: Mechanism and contract design

The Australian Government, through the AMR Taskforce, should commence the design of a contract to implement the mechanism. While this scoping study indicates that AAA is the highest priority mechanism, this should be further considered by the Taskforce and through industry consultation (i.e., recommendation 3). Some aspects to consider further include:

- **Mechanism value:** The value of the mechanism should be determined based on the fair and sufficient amount to incentivise development (in the case of guaranteed revenue and value mechanisms) and address existing barriers (in the case of accelerate assessment mechanisms). This should also consider commercial arrangement such as minimum / maximum payment thresholds, if applicable.
- **Number of Suppliers:** The mechanism may be implemented with one or more suppliers. A single supplier will likely be lower cost and risk for government, however engaging multiple suppliers may increase the likelihood of successful development and provide an opportunity to trial numerous mechanism configurations. This may include a hybrid of push and pull mechanisms or a combination of two or more pull mechanisms.
- **Target Antibiotic:** The target antibiotic should be carefully considered. As indicated in this study, a novel antibiotic targeting a priority pathogen and currently advancing through clinical trials would likely represent a feasible candidate for a pull mechanism. Some other aspects that might be considered include degree of current unmet need for the antibiotic and degree of novelty.
- **Contract specification:** The contract should be carefully designed to provision for the financial, supply and government components of the mechanism and to mitigate risks for government. This should include consideration of antibiotic production volumes, storage location, limitation on use and stewardship and post contract arrangements to ensure an option to extend supply / transition of IP, if the trial has been successful. The AMR Taskforce should engage with governments involved in similar trials to understand how these contracts were established and to benefit from any potential lessons.

Based on the contract design, a suitable set of selection criteria should also be developed, and the AMR Taskforce should oversee the evaluation of supplier submissions.

11.2.5 Recommendation 5: Mechanism and contract management

The Australian Government, through the AMR Taskforce, should design a contract management framework to support the delivery of services under the mechanism. This should include reporting requirements, such as contract operations and risks. This may include antibiotic volumes, contract payments and reporting of adverse patient events. The framework may also consider unintended risks, such as the impact of the mechanism on the existing medical supplies (including those produced by manufacturers who are involved in the mechanism contract). The contract management should also account for review points between government and the supplier, to enable terms to be re-negotiated based on key parameters to ensure the mutually beneficial ongoing operation of the mechanism.

11.2.6 Recommendation 6: Mechanism and contract evaluation

The Australian Government should direct the Taskforce to develop a monitoring and evaluation framework and undertake periodic evaluations to determine the achievement of process and outcome measures.

The AMR Taskforce should commission periodic evaluations to both monitor the ongoing operation of the mechanism to inform improvement opportunities and at the conclusion of the mechanism to assess its overall performance.

Appendices

A Reference List

- ALLERGAN, A., CIPLA, DSM SINOCEM PHARMACEUTICALS, F. HOFFMAN-LA ROCHE LTD., SWITZERLAND, GSK, JOHNSON & JOHNSON, MERCK & CO., INC., KENILWORTH, NEW JERSEY, U.S.A., NOVARTIS, PFIZER, SANOFI, SHIONOGI & CO., LTD., WOCKHARDT. 2016. Industry Roadmap for Progress on Combating Antimicrobial Resistance – September 2016. Available: <https://www.ifpma.org/resource-centre/industry-roadmap-for-progress-on-combating-antimicrobial-resistance/>.
- AMR INDUSTRY ALLIANCE. 2017. *AMR industry declaration* [Online]. Available: <https://www.amrindustryalliance.org/amr-industry-alliance-declaration/> [Accessed 4 January 2022].
- ARDAL, C., FINDLAY, D., SAVIC, M., CARMELI, Y., GYSSENS, I., LAXMINARAYAN, R., OUTTERSON, K. & REX, J. H. 2018. DRIVE-AB report: revitalizing the antibiotic pipeline: Stimulating innovation while driving sustainable use and global access. Available: <http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf>.
- ARDAL, C., LACOTTE, Y., EDWARDS, S., PLOY, M. C., ON BEHALF OF THE EUROPEAN UNION JOINT ACTION ON ANTIMICROBIAL, R. & HEALTHCARE-ASSOCIATED INFECTIONS, E.-J. 2021. National Facilitators and Barriers to the Implementation of Incentives for Antibiotic Access and Innovation. *Antibiotics (Basel)*, 10, 749. DOI: <https://doi.org/10.3390/antibiotics10060749>
- ARDAL, C., LACOTTE, Y. & PLOY, M. C. 2020. Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe. *Clin Infect Dis*, 71, 1994-1999. DOI: <https://doi.org/10.1093/cid/ciaa153>
- ARDAL, C., ROTTINGEN, J. A., OPALSKA, A., VAN HENGEL, A. J. & LARSEN, J. 2017. Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance. *Clin Infect Dis*, 65, 1378-1382. DOI: <https://doi.org/10.1093/cid/cix526>
- AUSBIOTECH, PFIZER, MSD, CSIRO, AUSTRALIA, M. & BIOINTELECT. 2019. Antimicrobial resistance (AMR) Industry Position Paper September 2019. Available: <https://www.ausbiotech.org/documents/item/628>.
- AUSTRALIAN BUREAU OF STATISTICS. 2018. 3222.0 - Population Projections, Australia, 2017 (base) - 2066. Table B9. Population projections, By Age and sex, Australia – Series B. Available: <https://www.abs.gov.au/statistics/people/population/population-projections-australia/latest-release> [Accessed 28 June 2022].
- AUSTRALIAN CLINICAL TRIALS. Why conduct a clinical trial in Australia. Available: <https://www.australianclinicaltrials.gov.au/why-conduct-clinical-trial-australia> [Accessed 10 January 2022].
- AUSTRALIAN CLINICAL TRIALS. 2015. Phases of clinical trials. Available: <https://www.australianclinicaltrials.gov.au/what-clinical-trial/phases-clinical-trials> [Accessed 15 January 2022].

- AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE. 2021. AURA 2021: Fourth Australian report on antimicrobial use and resistance in human health. Available: <https://www.safetyandquality.gov.au/our-work/antimicrobial-resistance/antimicrobial-use-and-resistance-australia-surveillance-system/aura-2021#:~:text=The%20Commission%20released%20its%20Fourth,of%20AMR%20and%20improvement%20of> [Accessed 28 June 2022].
- AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE (ACSQHC) 2019. AURA 2019: third Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC.
- AUSTRALIAN DEPARTMENT OF EDUCATION SKILLS AND EMPLOYMENT 2015. Review of Research Policy and Funding Arrangements.
- AUSTRALIAN DEPARTMENT OF EDUCATION SKILLS AND EMPLOYMENT. 2021. NCRIS Factsheet. Available: <https://www.dese.gov.au/national-research-infrastructure/resources/ncris-factsheet> [Accessed 10 January 2022].
- AUSTRALIAN GOVERNMENT. 2022. Pharmaceutical Benefits Advisory Committee. Available: <https://www.directory.gov.au/portfolios/health/department-health/pharmaceutical-benefits-advisory-committee> [Accessed 8 February 2022].
- AUSTRALIAN GOVERNMENT ANTIMICROBIAL RESISTANCE. 2017. AMR and human health in Australia. Available: <https://www.amr.gov.au/about-amr/what-current-amr-situation/amr-internationally#:~:text=In%202015%2C%20Australia%20had%20the.The%20Netherlands%2C%20Sweden%20and%20Austria.> [Accessed 10 January 2022].
- AUSTRALIAN GOVERNMENT DEPARTMENT OF HEALTH. 2017. HTA for reimbursement. Available: <https://www1.health.gov.au/internet/hta/publishing.nsf/Content/reimbursement-1> [Accessed 10 January 2022].
- AUSTRALIAN GOVERNMENT DEPARTMENT OF PRIME MINISTER AND CABINET OFFICE OF BEST PRACTICE REGULATION 2020. Best Practice Regulation Guidance Note: Value of statistical life
- AUSTRALIAN GROUP ON ANTIMICROBIAL RESISTANCE. 2017. AGAR Sepsis Outcome Programs 2017 report. Available: <https://www.safetyandquality.gov.au/publications-and-resources/resource-library/agar-sepsis-outcome-programs-2017-report> [Accessed 28 June 2022].
- AUSTRALIAN GROUP ON ANTIMICROBIAL RESISTANCE. 2018. AGAR Sepsis Outcome Programs 2018 Report. Available: <https://www.safetyandquality.gov.au/publications-and-resources/resource-library/agar-sepsis-outcome-programs-2018-report> [Accessed 28 June 2022].
- BOLUARTE, T. & SCHULZE, U. 2022. The Case for a Subscription Model to Tackle Antimicrobial Resistance. Available: <https://www.bcg.com/publications/2022/model-for-tackling-antimicrobial-resistance> [Accessed 28 June 2022].
- BROWNE, A. J., CHIPETA, M. G., HAINES-WOODHOUSE, G., KUMARAN, E. P. A., HAMADANI, B. H. K., ZARAA, S., HENRY, N. J., DESHPANDE, A., REINER, R. C., JR., DAY, N. P. J., LOPEZ, A. D., DUNACHIE, S., MOORE, C. E., STERGACHIS, A., HAY, S. I. & DOLECEK, C. 2021. Global antibiotic consumption and usage in humans, 2000-18: a spatial modelling study. *Lancet Planet Health*, 5, e893-e904. DOI: [https://doi.org/10.1016/S2542-5196\(21\)00280-1](https://doi.org/10.1016/S2542-5196(21)00280-1)

- CAMA, J., LESZCZYNSKI, R., TANG, P., KHALID, A., LOK, V., DOWSON, C. & EBATA, A. 2021. To Push or To Pull? In a Post-COVID World, Supporting and Incentivizing Antimicrobial Drug Development Must Become a Governmental Priority. *ACS Infectious Diseases*. DOI: <https://doi.org/10.1021/acsinfectdis.0c00681>
- CENTER FOR DRUG EVALUATION AND RESEARCH. 2019. Application Number: 212862 Orig1s000. Available: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212862Orig1s000Lbl.pdf [Accessed 28 June 2022].
- CERNUSCHI, T., FURRER, E., SCHWALBE, N., JONES, A., BERNDT, E. R. & MCADAMS, S. 2011. Advance market commitment for pneumococcal vaccines: putting theory into practice. *Bulletin of the World Health Organization*, 89, 913-918. DOI: <https://doi.org/10.2471/BLT.11.087700>
- CIABUSCHI, F., BARALDI, E., LINDAHL, O. & CALLEGARI, S. 2020. Supporting innovation against the threat of antibiotic resistance: exploring the impact of public incentives on firm performance and entrepreneurial orientation. *Journal of Business Research*, 112, 271-280. DOI: <https://doi.org/10.1016/j.jbusres.2019.12.021>
- COMMONWEALTH OF AUSTRALIA 2021. The New Frontier - Delivering better health for all Australians. Canberra.
- CRABB, N., LEONARD, C., JENNINGS, G., PERKINS, M. & GLOVER, D. 2020. Developing and testing innovative models for the evaluation and purchase of antimicrobials: subscription-based payment model. National Institute for Health and Care Excellence, National Health Service and Department of Health and Social Care.
- DALL, C. 2022. UK moves closer to experimental payment model for antibiotics. Available: <https://www.cidrap.umn.edu/news-perspective/2022/04/uk-moves-closer-experimental-payment-model-antibiotics> [Accessed 28 June 2022].
- DALZELL, S. 2020. *Australia joins global COVAX pool, opening door to more coronavirus vaccine options* [Online]. Australian Broadcasting Corporation Available: <https://www.abc.net.au/news/2020-09-22/australia-joins-covax-coronavirus-vaccine-options/12690702> [Accessed 14 January 2022].
- DE KRAKER, M. E., WOLKEWITZ, M., DAVEY, P. G., KOLLER, W., BERGER, J., NAGLER, J., ICKET, C., KALENIC, S., HORVATIC, J., SEIFERT, H., KAASCH, A., PANIARA, O., ARGYROPOULOU, A., BOMPOLA, M., SMYTH, E., SKALLY, M., RAGLIO, A., DUMPIS, U., MELBARDE KELMERE, A., BORG, M., XUEREB, D., GHITA, M. C., NOBLE, M., KOLMAN, J., GRABLJEVEC, S., TURNER, D., LANSBURY, L. & GRUNDMANN, H. 2011. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to *Escherichia coli* resistant to third-generation cephalosporins. *J Antimicrob Chemother*, 66, 398-407. DOI: <https://doi.org/10.1093/jac/dkq412>
- DUTESCU, I. A. & HILLIER, S. A. 2021. Encouraging the Development of New Antibiotics: Are Financial Incentives the Right Way Forward? A Systematic Review and Case Study. *Infect Drug Resist*, 14, 415-434. DOI: <https://doi.org/10.2147/IDR.S287792>
- EISENSTEIN, B. I., OLESON, F. B., JR. & BALTZ, R. H. 2010. Daptomycin: from the mountain to the clinic, with essential help from Francis Tally, MD. *Clin Infect Dis*, 50 Suppl 1, S10-5. DOI: <https://doi.org/10.1086/647938>
- EUROPEAN MEDICINES AGENCY. 2020. Assessment report: Arikayce liposomal Available: https://www.ema.europa.eu/en/documents/assessment-report/arikayce-liposomal-epar-public-assessment-report_en.pdf [Accessed 28 June 2022].

- FAIR, R. J. & TOR, Y. 2014. Antibiotics and bacterial resistance in the 21st century. *Perspect Medicin Chem*, 6, 25-64. DOI: <https://doi.org/10.4137/PMC.S14459>
- FEDERAL RESERVE BANK OF SAN FRANCISCO & NONPROFIT FINANCE FEED 2018.
- FERRARO, J., TOWSE, A. & MESTRE-FERRANDIZ, J. 2017a. Incentives for new drugs to tackle anti-microbial resistance. Office of Health Economics.
- FERRARO, J., TOWSE, A. & MESTRE-FERRANDIZ, J. 2017b. Incentives for New Drugs to Tackle Anti-Microbial Resistance Briefing Available: <https://www.ohe.org/publications/incentives-new-drugs-tackle-anti-microbial-resistance> [Accessed 28 June 2022].
- FETTER, R. B. & FREEMAN, J. L. 1986. Diagnosis related groups: product line management within hospitals. *Academy of management Review*, 11, 41-54. DOI: <https://doi.org/10.5465/amr.1986.4282622>
- FUKUDA-PARR, S. & ARIANA, P. 2011. Health Impact Fund–Raising Issues of Distribution, IP Rights and Alliances. *Intellectual Property Watch*. DOI: <https://doi.org/10.1186/s12992-021-00744-x>
- G7 FINANCE MINISTERS 2021. G7 Finance Ministers statement on supporting antibiotic development. United Kingdom G7 United Kingdom 2021.
- G7 UNITED KINGDOM DEPARTMENT OF HEALTH & SOCIAL CARE 2021. G7 Shared Principles for the Valuation of Antimicrobial Therapeutics. United Kingdom G7 United Kingdom 2021.
- GAVI. 2021a. *The Gavi COVAX AMC Explained* [Online]. GAVI. Available: <https://www.gavi.org/vaccineswork/gavi-covax-amc-explained> [Accessed 6 January 2022].
- GAVI. 2021b. *World leaders unite to commit to global equitable access for COVID-19 vaccines* [Online]. GAVI. Available: <https://www.gavi.org/news/media-room/world-leaders-unite-commit-global-equitable-access-covid-19-vaccines> [Accessed 6 January 2022].
- GLOBAL COALITION ON AGING, I. D. S. O. A. 2021 2021 AMR Preparedness Index. Global Coalition on Aging and Infectious Diseases Society of America.
- GOTHAM, D., MOJA, L., VAN DER HEIJDEN, M., PAULIN, S., SMITH, I. & BEYER, P. 2021. Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. *Health Policy*, 125, 296-306. DOI: <https://doi.org/10.1016/j.healthpol.2020.11.015>
- GREBELY, J., DALGARD, O., CONWAY, B., CUNNINGHAM, E. B., BRUGGMANN, P., HAJARIZADEH, B., AMIN, J., BRUNEAU, J., HELLARD, M., LITWIN, A. H., MARKS, P., QUIENE, S., SIRIRAGAVAN, S., APPELEGATE, T. L., SWAN, T., BYRNE, J., LACALAMITA, M., DUNLOP, A., MATTHEWS, G. V., POWIS, J., SHAW, D., THURNHEER, M. C., WELTMAN, M., KRONBORG, I., COOPER, C., FELD, J. J., FRASER, C., DILLON, J. F., READ, P., GANE, E., DORE, G. J. & GROUP, S. S. 2018. Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial. *Lancet Gastroenterol Hepatol*, 3, 153-161. DOI: [https://doi.org/10.1016/S2468-1253\(17\)30404-1](https://doi.org/10.1016/S2468-1253(17)30404-1)
- HILLOCK, N. 3 December 2021 2021. *RE: Personal communication*.
- HOLLIS, A. & POGGE, T. 2008. The Health Impact Fund Making New Medicines Accessible for All. Incentives for Global Health.

- HOUSE OF REPRESENTATIVES STANDING COMMITTEE ON HEALTH AGED CARE AND SPORT 2021. The New Frontier - Delivering better health for all Australians: Inquiry into approval processes for new drugs and novel medical technologies in Australia. Canberra: Parliament of the Commonwealth of Australia.
- INDEPENDENT HOSPITAL PRICING AUTHORITY. 2016. National Hospital Cost Data Collection Cost Report: Round 19 financial year 2014-15 Available: <https://www.iHPA.gov.au/publications/national-hospital-cost-data-collection-public-hospitals-cost-report-round-19-financial> [Accessed 28 June 2022].
- INDUSTRY INNOVATION AND SCIENCE AUSTRALIA (IISA) 2021. Driving effective Government investment in innovation, science and research. Canberra.
- INSTITUTE AND FACULTY OF ACTUARIES 2018. Antibiotic Resistance: Modelling the Impact on Mortality and Morbidity: A report by the Antibiotic Resistance Working Party
- INTERAGENCY COORDINATION GROUP ON ANTIMICROBIAL RESISTANCE 2018. Future Global Governance for Antimicrobial Resistance IACG Discussion Paper Interagency Coordination Group on Antimicrobial Resistance.
- INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS & ASSOCIATIONS (IFPMA). 2020. New AMR Action Fund steps in to save collapsing antibiotic pipeline with pharmaceutical industry investment of US\$1 billion. Available: <https://www.ifpma.org/resource-centre/new-amr-action-fund-steps-in-to-save-collapsing-antibiotic-pipeline/> [Accessed 10 January 2022].
- JACKSON, N., CZAPLEWSKI, L. & PIDDOCK, L. J. V. 2018. Discovery and development of new antibacterial drugs: learning from experience? *J Antimicrob Chemother*, 73, 1452-1459. DOI: <https://doi.org/10.1093/jac/dky019>
- KESSELHEIM, A. S. & OUTTERSON, K. 2011. Improving antibiotic markets for long-term sustainability. *Yale J Health Policy Law Ethics*, 11, 101-67. DOI: <https://doi.org/10.1016/j.cmi.2017.08.002>
- KIM, H., BYRNES, J., GOODALL, S. & COMMITTEE, I. A. C. E. 2021. Health Technology Assessment in Australia: The Pharmaceutical Benefits Advisory Committee and Medical Services Advisory Committee. *Value Health Reg Issues*, 24, 6-11. DOI: <https://doi.org/10.1016/j.vhri.2020.09.001>
- KMIETOWICZ, Z. 2017. Few novel antibiotics in the pipeline, WHO warns. *BMJ*, 358, j4339. DOI: <https://doi.org/10.1136/bmj.j4339>
- KPMG 2014. The global economic impact of antimicrobial resistance.
- LARSSON, D. G. J. & FLACH, C. F. 2022. Antibiotic resistance in the environment. *Nat Rev Microbiol*, 20, 257-269. DOI: <https://doi.org/10.1038/s41579-021-00649-x>
- LEONI, P. 2019. Advance Market Commitment: Some Issues and a Remedy. *Revue d'economie politique*, 129, 1-9. DOI: <https://doi.org/10.3917/redp.291.0001>
- LIU, H. H., MULCAHY, A.W., ROSE, A.J. 2020. Subscription Models for Prescription Drugs The Motivation, Potential, and Limitations of a New Payment Model. Santa Monica, California: RAND Corporation.
- LUEPKE, K. H., SUDA, K. J., BOUCHER, H., RUSSO, R. L., BONNEY, M. W., HUNT, T. D. & MOHR, J. F., 3RD 2017. Past, Present, and Future of Antibacterial Economics: Increasing Bacterial Resistance, Limited Antibiotic Pipeline, and Societal Implications. *Pharmacotherapy*, 37, 71-84. DOI: <https://doi.org/10.1002/phar.1868>
- LUM, K., BHATTI, T., HOLLAND, S., GUTHRIE, M. & SASSMAN, S. 2018. Diagnosis Confirmation Model: A Value-Based Pricing Model for Inpatient Novel Antibiotics. *J Law Med Ethics*, 46, 66-74. DOI: <https://doi.org/10.1177/1073110518782917>

- MAGIORAKOS, A. P., SRINIVASAN, A., CAREY, R. B., CARMELI, Y., FALAGAS, M. E., GISKE, C. G., HARBARTH, S., HINDLER, J. F., KAHLMETER, G., OLSSON-LILJEQUIST, B., PATERSON, D. L., RICE, L. B., STELLING, J., STRUELENS, M. J., VATOPOULOS, A., WEBER, J. T. & MONNET, D. L. 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*, 18, 268-81. DOI: <https://doi.org/10.1111/j.1469-0691.2011.03570.x>
- MANZ, C. R., BEKELMAN, J. E. & DOSHI, J. A. 2020. The Changing Characteristics of Technologies Covered by Medicare's New Technology Add-on Payment Program. *JAMA network open*, 3, e2012569-e2012569. DOI: <https://doi.org/10.1001/jamanetworkopen.2020.12569>
- MIETHKE, M., PIERONI, M., WEBER, T., BRONSTRUP, M., HAMMANN, P., HALBY, L., ARIMONDO, P. B., GLASER, P., AIGLE, B., BODE, H. B., MOREIRA, R., LI, Y., LUZHETSKYY, A., MEDEMA, M. H., PERNODET, J. L., STADLER, M., TORMO, J. R., GENILLOU, O., TRUMAN, A. W., WEISSMAN, K. J., TAKANO, E., SABATINI, S., STEGMANN, E., BROTZ-OESTERHELT, H., WOHLLEBEN, W., SEEMANN, M., EMPTING, M., HIRSCH, A. K. H., LORETZ, B., LEHR, C. M., TITZ, A., HERRMANN, J., JAEGER, T., ALT, S., HESTERKAMP, T., WINTERHALTER, M., SCHIEFER, A., PFARR, K., HOERAUF, A., GRAZ, H., GRAZ, M., LINDVALL, M., RAMURTHY, S., KARLEN, A., VAN DONGEN, M., PETKOVIC, H., KELLER, A., PEYRANE, F., DONADIO, S., FRAISSE, L., PIDDOCK, L. J. V., GILBERT, I. H., MOSER, H. E. & MULLER, R. 2021. Towards the sustainable discovery and development of new antibiotics. *Nat Rev Chem*, 5, 726-749. DOI: <https://doi.org/10.1038/s41570-021-00313-1>
- MILLER, W. R., BAYER, A. S. & ARIAS, C. A. 2016. Mechanism of Action and Resistance to Daptomycin in *Staphylococcus aureus* and Enterococci. *Cold Spring Harb Perspect Med*, 6. DOI: <https://doi.org/10.1101/cshperspect.a026997>
- MOON, S. & ERICKSON, E. 2019. Universal medicine access through lump-sum remuneration—Australia's approach to hepatitis C. *New England Journal of Medicine*, 380, 607-610. DOI: <https://doi.org/10.1056/NEJMp1813728>
- MOREL, C. M. 2011. Exploring responses to the need for new antibiotics: how do different incentives compare? Available: <http://eprints.lse.ac.uk/id/eprint/60157>.
- MOREL, C. M., LINDAHL, O., HARBARTH, S., DE KRAKER, M. E. A., EDWARDS, S. & HOLLIS, A. 2020. Industry incentives and antibiotic resistance: an introduction to the antibiotic susceptibility bonus. *J Antibiot (Tokyo)*, 73, 421-428. DOI: <https://doi.org/10.1038/s41429-020-0300-y>
- MORICE, A. H., MILLQVIST, E., BIEKSIENE, K., BIRRING, S. S., DICPINIGAITIS, P., DOMINGO RIBAS, C., HILTON BOON, M., KANTAR, A., LAI, K., MCGARVEY, L., RIGAU, D., SATIA, I., SMITH, J., SONG, W. J., TONIA, T., VAN DEN BERG, J. W. K., VAN MANEN, M. J. G. & ZACHARASIEWICZ, A. 2020. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J*, 55. DOI: <https://doi.org/10.1183/13993003.01136-2019>
- MOSSIALOS, E., MOREL, C. M., EDWARDS, S., BERENSON, J., GEMMILL-TOYAMA, M., BROGAN, D. & ORGANIZATION, W. H. 2010. *Policies and incentives for promoting innovation in antibiotic research*, World Health Organization. Regional Office for Europe.
- MTPCONNECT. 2020a. *Australian Antimicrobial Resistance Network - AAMRNet* [Online]. Available: https://www.mtpconnect.org.au/Category?Action=View&Category_id=266 [Accessed 5 January 2022].

- MTPCONNECT 2020b. Fighting Superbugs: A Report on the Inaugural Meeting of Australia's Antimicrobial Resistance Stakeholders.
- OUTTERSON, K. 2009. The legal ecology of resistance: the role of antibiotic resistance in pharmaceutical innovation. *Cardozo L. Rev.* [Online], 31. Available: https://scholarship.law.bu.edu/cgi/viewcontent.cgi?article=1768&context=faculty_scholarship.
- OUTTERSON, K., POGGE, T. & HOLLIS, A. The "Antibiotic Health Impact Fund": A Proposal.
- PATEL, J. & FADAEI, R. 2016. Cost of Antibiotics in Society and Economic Approach. *IOSR Journal of Economics and Finance*, 7, 2321-5933. DOI: <https://doi.org/10.9790/5933-0706031720>
- PUBLIC HEALTH AGENCY OF SWEDEN. 2020a. *Questions and answers- Agreements signed for a pilot study of a new reimbursement model* [Online]. Available: https://www.folkhalsomyndigheten.se/contentassets/c09fd6d5d42243e097be216767686c08/questions_answers_agreements_signed_pilot_study_new_reimbursement_model.pdf [Accessed 6 January 2022].
- PUBLIC HEALTH AGENCY OF SWEDEN. 2020b. *Questions and answers: Agreements signed for a pilot study of a new reimbursement model*. Available: https://www.folkhalsomyndigheten.se/contentassets/c09fd6d5d42243e097be216767686c08/questions_answers_agreements_signed_pilot_study_new_reimbursement_model.pdf [Accessed 28 June 2022].
- PUBLIC HEALTH AGENCY OF SWEDEN. n.d. *Availability of antibiotics* [Online]. Available: <https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/antibiotics-and-antimicrobial-resistance/availability-of-antibiotics/> [Accessed 6 January 2022].
- RENWICK, M. & MOSSIALOS, E. 2018. What are the economic barriers of antibiotic R&D and how can we overcome them? *Expert Opin Drug Discov*, 13, 889-892. DOI: <https://doi.org/10.1080/17460441.2018.1515908>
- RENWICK, M. J., BROGAN, D. M. & MOSSIALOS, E. 2016. A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. *J Antibiot (Tokyo)*, 69, 73-88. DOI: <https://doi.org/10.1038/ja.2015.98>
- RESISTANCE, A. G. O. A. 2019. AGAR Sepsis Outcome Programs 2019 Report. Available: <https://www.safetyandquality.gov.au/publications-and-resources/resource-library/agar-sepsis-outcome-programs-2019-report> [Accessed 28 June 2022].
- RESISTANCE, A. G. O. A. 2020. AGAR Sepsis Outcome Programs 2020 Report. Available: <https://www.safetyandquality.gov.au/publications-and-resources/resource-library/agar-sepsis-outcome-programs-2020-report> [Accessed 28 June 2022].
- SANSOM, L., DELAAT, W. & HORVATH, J. 2017. *Expert Review of Medicines and Medical Devices Regulation* [Online]. Canberra: Australian Government Department of Health. Available: <https://www1.health.gov.au/internet/main/publishing.nsf/Content/Expert-Review-of-Medicines-and-Medical-Devices-Regulation#review> [Accessed 14 January 2022].
- SIMOENS, S. & SPRIET, I. 2020. Guidance for Demonstrating the Societal Value of new Antibiotics. *Front Pharmacol*, 11, 618238. DOI: <https://doi.org/10.3389/fphar.2020.618238>
- SIMPKIN, V. L., RENWICK, M. J., KELLY, R. & MOSSIALOS, E. 2017. Incentivising innovation in antibiotic drug discovery and development: progress, challenges and next steps. *J Antibiot (Tokyo)*, 70, 1087-1096. DOI: <https://doi.org/10.1038/ja.2017.124>

- SOMER, E. D. 2021. RE: Submission from Medicines Australia: TGA Consultation on Repurposing of Prescription Medicines. Type to SKERRITT, J.
- THE PEW CHARITABLE TRUSTS 2021. Antibiotic Development Needs Economic Incentives. Pennsylvania, United States.
- THERAPEUTIC GOODS ADMINISTRATION. 2018. *MMDR: Prescription medicines regulatory reforms* [Online]. Australian Government Department of Health. Available: <https://www.tga.gov.au/hubs/mmdr/mmdr-prescription-medicines-regulatory-reforms> [Accessed 14 January 2022].
- THERAPEUTIC GOODS ADMINISTRATION. 2020. *Overview of program status for the MMDR reforms* [Online]. Australian Government Department of Health. Available: <https://www.tga.gov.au/hubs/mmdr/overview-program-status-mmdr-reforms> [Accessed 14 January 2022].
- THERAPEUTIC GOODS ADMINISTRATION. 2021. Fees and charges: summary. Available: <https://www.tga.gov.au/sites/default/files/fees-and-charges-summary-1-december-2021.pdf> [Accessed 28 June 2022].
- U.S. FOOD AND DRUG ADMINISTRATION. 2020. *Limited Population Pathway for Antibacterial and Antifungal Drugs – the LPAD Pathway* [Online]. Available: <https://www.fda.gov/drugs/development-resources/limited-population-pathway-antibacterial-and-antifungal-drugs-lpad-pathway> [Accessed 7 January 2022].
- UNITED NATIONS INTERAGENCY COORDINATION GROUP ON ANTIMICROBIAL RESISTANCE 2019. No Time to Wait: Securing the future from drug-resistant infections. *Report to the Secretary-General of the United Nations*. Geneva.
- VOGLER, S., HABIMANA, K., FISCHER, S. & HAASIS, M. A. 2021. Novel policy options for reimbursement, pricing and procurement of AMR health technologies.
- WELLCOME TRUST. Director's update: G20 leaders' pledges on global health. Available: <https://wellcome.org/news/directors-update-g20-leaders-pledges-global-health> [Accessed 21 December 2021].
- WELLCOME TRUST 2020. The Global Response to AMR Momentum, success, and critical gaps. Longon: Wellcome Trust.
- WILLIAMS, M. A. & WYNER, S. N. 2019. Antimicrobial Resistance: Facing the Rise of a Global Threat. *American Journal of Public Health*, 109, 521-522. DOI: <https://doi.org/10.2105/ajph.2019.304981>
- WORLD BANK & GAVI ALLIANCE 2012. Brief 17: Innovative Financing - Advance Market Commitments (AMCs). *Immunization Financing Toolkit*.
- WORLD HEALTH ORGANIZATION. 2017. The world is running out of antibiotics, WHO report confirms. Available: <https://www.who.int/news/item/20-09-2017-the-world-is-running-out-of-antibiotics-who-report-confirms> [Accessed 26 November 2021].
- WRIGHT, G. D. 2014. Something old, something new: revisiting natural products in antibiotic drug discovery. *Can J Microbiol*, 60, 147-54. DOI: <https://doi.org/10.1139/cjm-2014-0063>

B Mechanism Prioritisation

Table B.1 shows the comparison of prioritisation of mechanisms between the three phases of the project (Literature Review, Stakeholder Consultation and Economic Assessment).

Difference in priority ranking can be explained by:

- Differences in ranking methodology (see the project reports the literature review and stakeholder consultation for an overview of the prioritisation methodology); and
- Differences in understanding and perspectives on the issue between ACIL Allen (who determined the prioritisation for the literature review and then subsequently undertook the economic assessment) and those invited to complete the survey for the stakeholder consultation phase.

Table B.1 Comparison of mechanism ranking, by project phase

Heading	Literature Review Rank	Stakeholder Consultation Rank	Economic Assessment Rank
Accelerated assessment and approval (AAA)	12	2	1
Advance Market Commitments (AMC)	6	3	2
Service availability premiums, subscriptions and licenses (SSL)	3	1	3
Strategic Antibiotic Reserve (SAR)	2	4	4
Value-based pricing and pay-for-performance (VBP)	4	5	5
Market entry reward (MER)	8	6	-
R&D grants and funding	15	7	-
Extended market exclusivity	7	8	-
Product development partnerships (PDPs)	1	9	-
Tax incentives	13	10	-
Open access to research	10	11	-
Patent buyout	5	12	-
Conditional loans	11	13	-
Anti-trust waivers	14	14	-
Social Impact Investing (SII)	9	15	-

Source: ACIL Allen