Antimicrobial resistance (AMR)

Industry Position Paper

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“Antimicrobial resistance is a global public health concern. Australia has specific strengths and capabilities in science and research related to immunity and infectious diseases, as well as some unique pathogens of concern to Australia and the neighbours in our region. However, the limited number of industry players actively engaged in antimicrobial product development makes it difficult to create momentum or secure resources for this topic in the context of so many competing priorities. There is therefore an urgent need for the industry sector to come together and align on key issues and priorities to ensure industry perspectives, capability and contribution are communicated in the development of the next National AMR strategy.”

Executive Summary

Table 1. Current challenges and key industry recommendations for antimicrobial R&D, AMR international engagement and regulatory and reimbursement framework in Australia.

TOPIC	CHALLENGE	RECOMMENDATION
Antimicrobial Research & Development, Translation and Commercialisation	There's a lack of a coordinated national research agenda to comprehensively address the growing threat of AMR in Australia.	Conduct a national audit and AMR R&D activity in Australia and prioritise activities in the context of priority pathogens.
	The true rates of resistant infections nationally are yet to be confirmed.	Invest in comprehensive surveillance systems including point of care, rapid diagnostics.
	Current R&D funding is largely directed at research institutes and academic institutions.	Australia's 20-year vision for AMR should include industry-specific 'push' and 'pull' incentives to help accelerate development of new antimicrobials.
International Partnerships and Collaborations	Australia is not a member of the many international AMR alliances, and may be missing out on opportunities to learn, collaborate and contribute.	Review existing international AMR alliances and join those where there are the greatest synergies.
	There is no single point of contact for consulting with industry in Australia on the topic of AMR.	Form an Australian AMR industry alliance that can provide a strong coordinate voice for industry on key issues.
Regulation of Antimicrobials and Regulatory Incentives	Current TGA regulatory pathways are not tailored for novel antimicrobials.	Develop a fit-for-purpose regulatory framework for registration of novel antimicrobials for priority organisms of high AMR importance.
	There are minimal pull incentives for novel antimicrobials in Australia.	Review regulatory incentives available internationally and determine which could be applied in Australia.
Pricing & Reimbursement Policy Framework	The market for novel antimicrobials is broken – innovative new valuation and funding models are required.	Review the UK's new HTA and funding model for novel antimicrobials and evaluate the potential for implementing a similar model in Australia.
		Review all potential funding pools (National Medicines Stockpile, Medical Benefits Scheme, Pharmaceutical Benefits Scheme etc.) and assess their applicability to novel antimicrobials.
	There is no national system for antimicrobial reimbursement, most antimicrobials are procured and funded through states via hospitals.	In reviewing HTA, funding models and pools, also consider the opportunity to Implement a national, COAG-led reimbursement system for novel antimicrobials.

Antimicrobial resistance: **The clock is ticking**

Antimicrobial resistance (AMR) represents a significant unmet need and an urgent threat that needs to be addressed, both globally and here in Australia. Infections caused by the AMR pathogens are estimated to cause approximately 700,000 deaths worldwide annually, and if the crisis is not tackled, the annual toll could climb to 10 million deaths in the next three decades, exceeding even the projected number of cancer-caused deaths.[1] The biopharmaceutical industry, spanning pharmaceutical companies, early biotechnology and medical technology companies, together with researchers, regulators and reimbursers, plays an essential role in developing and bringing innovative medicines to patients. Whilst these new antimicrobials are urgently needed, over the past two decades, there has been substantial decline in the number of companies undertaking antimicrobial R&D. Consequently, the current pipeline of antimicrobials is unlikely to be sufficient to successfully keep up with the pace of AMR development globally. This is mainly due to challenges posed by the of development of new antimicrobial, spanning scientific research and discovery, regulatory and economic/market entry challenges as described in Figure 1:[2,3,4]

Figure 1

Challenges in development of new antimicrobials result in a weak pipeline of effective treatments

Challenges in scientific research/discovery

Constantly evolving microorganisms with difficult to predict resistance pathways.

Novel preclinical models required.

Novel targets need to be identified.

Regulatory challenges

Need to adapt regulatory pathways.

Clinical trials complexity.

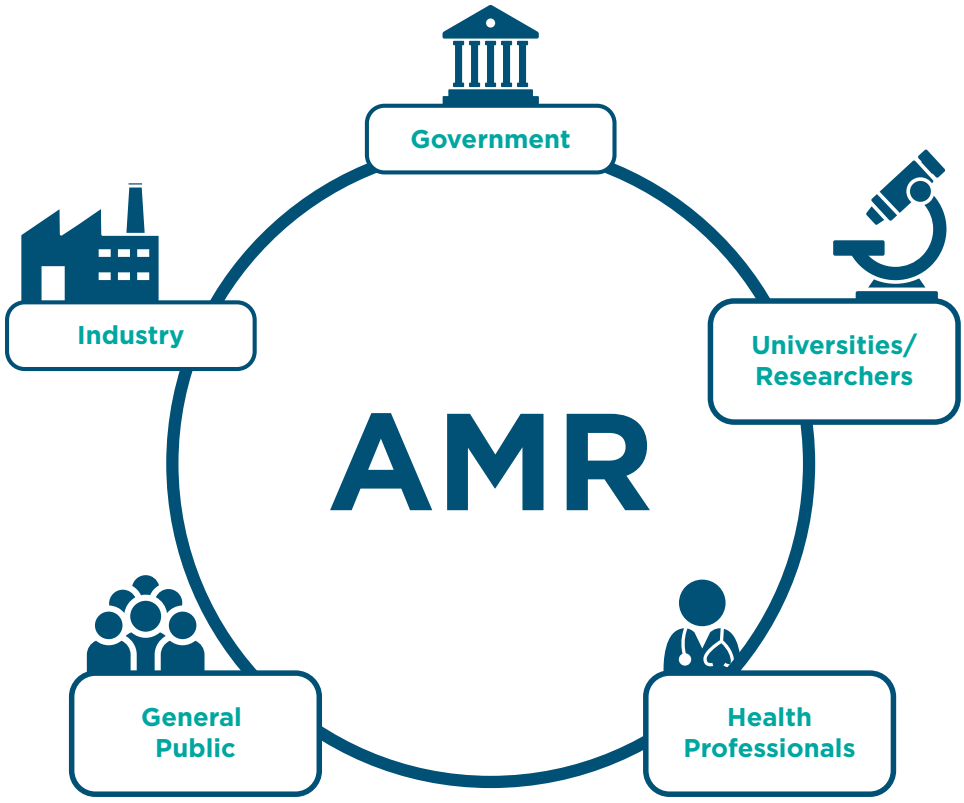
Harmonisation of regulatory guidelines.

Economic/market challenges

The market for novel antimicrobials is broken, as new antibiotics are typically held in reserve, which limits their usage, so it is difficult to recoup R&D costs.

Currently available data through Australian surveillance programs suggest that increased rates of resistance have been indeed observed to many frequently used antibiotics.[5] Reports also indicate that some specific pathogens are either resistant or emerging as resistant in Australia to first- and second-line antibiotics. For example, *Enterococcus* resistance to vancomycin, methicillin or penicillins is among the highest in the world.[6] Other high-priority organisms include *Neisseria gonorrhoeae* and *Streptococcus pneumoniae*.[7] Two highly resistant cases of Neisseria gonorrhoea were reported in Australia last year.[8]

Australia has specific strengths and capabilities in science and research related to immunity and infectious diseases, as well as some unique pathogens of concern to Australia and the neighbours in our region. Australia also has a National AMR Strategy. To combat AMR successfully, the whole life science "eco-system" should be aligned and work together on a coordinated national AMR research program. The ecosystem includes universities, medical research institutes and researchers, industry, government, health professionals and general public (Figure 2).



The Commonwealth Government's first National AMR strategy 2015-2019 was released in 2015. Work is commencing on the new National AMR strategy and the Department of Health have previously communicated that this will be finalised by the end of 2019. There has been limited consultation with the MTP sector this far and there are a number of issues that the sector is keen to engage on.

The limited number of industry players actively engaged in antimicrobial product development makes it difficult to create momentum or secure resources for this topic in the context of so many competing priorities. There is therefore an urgent need for the sector to come together, align on key issues, key priorities, and to ensure industry perspectives, capability and contribution are communicated in the development of the next National AMR strategy.

The AMR industry workshop was held on the 20 August 2019 in Sydney with the aim of bringing together key industry stakeholders to discuss opportunities and challenges associated with research, development and commercialisation of novel antimicrobial therapies and related technologies in human health. A secondary objective was to raise awareness of the AMR challenges, develop a sector position and foster relationships and ongoing collaboration towards longer term industry engagement with a credible, stronger, whole of sector approach. Participants were as follows: representatives from Medicine Australia, AusBiotech, Commonwealth Scientific and Industrial Research Organisation (CSIRO), and individual pharmaceutical and biotech/medtech companies with a specific interest in this area. Discussion centred on the following challenges and key recommended actions for industry.

Antimicrobial Research & Development, Translation and Commercialisation

The R&D related to AMR and novel antimicrobials in Australia is siloed and true extent of this research is not known and requires detailed mapping and audit. More importantly, research is not driven by a national AMR research agenda, which would ensure that resources are directed to research priorities across drug development, diagnostics and surveillance. **There is therefore a need for a detailed mapping and national audit of AMR R&D in Australia**. Collaboration between Australian universities and research institutes, the industry sector and international groups would accelerate the projects underway and facilitate new product development. Whilst AMR is noted as a priority for research funding, funds are largely directed at research institutes and academic institutions. For example, the number one priority for the MRFF is: "Support stronger partnerships between researchers, healthcare professionals, governments and the community. This will help position Australia as a leader in significant global research, such as tackling antimicrobial resistance." However, the challenges for product development and commercialisation are not well understood by these groups. The industry sector has the expertise and resources to bring new products to market, but unfortunately is not currently recognised as an important stakeholder in addressing AMR. Australian industry is already involved in international public health initiatives in AMR. **Industry should actively advocate for more industry led "push" and "pull" incentives to accelerate development of novel antimicrobials**.

Conversely, there still appears to be "lack of urgency to tackle AMR resistance in Australia", mainly due to apparent lower resistance rates locally compared to other regions and countries. However, the true rates of drug-resistant infections are yet to be nationally confirmed, as current surveillance systems need enhancement in collecting and reporting data in a more routine, rapid and real-time manner. To support better surveillance, **industry should therefore advocate for allocation of resources for development of innovative rapid diagnostics, allowing better tracking of inappropriate use of antimicrobials and AMR pathogen rates**.

International Partnerships and Collaborations

There are a number of important global and regional AMR related initiatives involving the biotech, pharmaceutical and medical technology sector in partnership with government and not-for profit organisations. Some of them are listed in Table 2.

Table 2. Examples of AMR-related initiatives and alliances

Initiative/ alliance	Region	Description/ Output to date
amr INDUSTRY ALLIANCE	**Global (over 20 countries)**	Private Sector coalition set up to provide sustainable solutions to curb antimicrobial resistance, with over 100 biotech, diagnostics, generics and research-based pharmaceutical companies and associations joining forces. At least USD 2 billion in R&D dedicated to AMR-related products in 2016: covering R&D-related costs for early-stage R&D exploring new product classes, 10 antibiotics in late-stage clinical development, 13 clinical bacterial vaccine candidates, and 18 AMR-relevant diagnostic products, as well as other preventive therapies; 1/3 of the Alliance companies that produce antibiotics currently have a strategy, policy or plan in place to address the issue of the release of antibiotics in their own manufacturing effluent that may contribute to AMR.[9]
BEAM Alliance	**Europe**	BEAM (Biotech companies in Europe combating AntiMicrobial Resistance) Alliance is a strong Network of approx. 65 small and medium-sized European companies involved in developing innovative products and kits to tackle antimicrobial resistance (AMR). In numbers, members of the BEAM Alliance together contribute over 120 potential new antibiotic compounds or curative and preventive technologies to this pipeline (majority target critical pathogens as mentioned by the WHO priority list).[10]
CARB-X Combating Antibiotic Resistant Bacteria	**Global**	Global non-profit partnership, led by Boston University, dedicated to accelerating antibacterial research to tackle the global rising threat of drug-resistant bacteria. Funded by BARDA, Wellcome Trust, the UK Government's Global Antimicrobial Resistance Innovation Fund (GAMRIF), and the Bill & Melinda Gates Foundation, with in-kind support from NIAID, CARB-X is investing more than $500 million between 2016-2021 in antibacterial R&D to accelerate the development of new antibiotics, rapid diagnostics, vaccines and other life-saving products.[11]
imi innovative medicines initiative ND4BB TRANSLOCATION DRIVE AB RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE	**Europe**	IMI is an EU public-private partnership funding health research and innovation (not unique to AMR). The IMI initiative ND4BB (New Drugs for Bad Bugs) represents an unprecedented partnership between industry, academia and biotech organisations to combat antimicrobial resistance in Europe. DRIVE-AB is a subsidiary program within the ND4BB which develops concrete recommendations for new economic models that would provide industry with an incentive to invest in this area while reconciling this with the need to use new antibiotics wisely.[12]
GARDP Global Antibiotic Research & Development Partnership	**Global**	The Global Antibiotic Research and Development Partnership (GARDP) is a joint initiative of the World Health organisation (WHO) and the Drugs for Neglected Disease initiative (DNDi). GARDP is a not-for-profit research and development (R&D) organization that addresses global public health needs by developing and delivering new or improved antibiotic treatments, while endeavouring to ensure their sustainable access.[13]
jpiamr	**Global**	In 2011, the European Commission established the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), together with 11 European member countries. Today, JPIAMR is a global collaborative platform and has engaged 27 nations to curb antibiotic resistance (AMR) with a One Health approach. The initiative coordinates national funding to support transnational research and activities within the six priority areas of the shared JPIAMR Strategic Research and Innovation Agenda – therapeutics, diagnostics, surveillance, transmission, environment and interventions.[14]

While some of these initiatives are research or industry alliances, others have been able to generate funding for specific "push" initiatives, focused on stimulating research and development of novel antimicrobial products. It is notable that the local industry sector in Australia is engaged in these initiatives however the Australia "National Strategy" does not seem to be aligned optimally with these international movements. There is an opportunity to consult with the industry sector to understand the work already being done against internationally recognised priority pathogens and existing products in development, including vaccines and diagnostics, and to explore how Australia could complement or contribute to international initiatives, or/and optimise and create its own national incentives. An overarching key recommendation was to **form an Australian industry alliance with goal to: provide a single point of contact for government to engage with industry on the subject of AMR; review international and regional initiatives and develop an Australian specific plan AMR industry agenda; put forward some specific requests (e.g. Australian CARB-X accelerator); and to develop a platform to advocate for industry's place in the ecosystem as a key stakeholder**.

Regulation of Antimicrobials and Regulatory Incentives

The Therapeutic Goods Administration (TGA) has the essential role in ensuring that the medicines available in Australia are safe and efficacious. However, ensuring access to new antimicrobials will require the introduction of better defined and more streamlined regulatory approaches and guidelines by TGA, which may allow faster development, expedited review and earlier access for patients. The harmonisation of clinical trial requirements is also urgently required to further support faster access to new antimicrobials (e.g. clinical trial design, patient enrolment, levels of data to support approvals and indications) (Figure 3).

Figure 3. Regulatory barriers vs. the threat of antimicrobial resistance

The standard practice of conducting trials of novel antimicrobials as non-inferiority studies also has implications for recognising the full societal value of these products when it comes to seeking reimbursement, as superiority has not been clinically demonstrated. There are already certain TGA regulatory pathways in place which can facilitate and/or accelerate patient access to prescription medicines. Orphan designation, by virtue of the fee waiver is intended to provide an incentive to registration of medicines for small populations, and in the case of some novel antimicrobials this is an appropriate incentive. The provisional and priority review pathways, however, are not tailored for novel antimicrobials, particularly as they require demonstrated superior efficacy in clinical trials.

Even if superior efficacy could be demonstrated for a subset of the trial population, this would lead to a determination for a very narrow population which is not only commercially unviable, but not consistent with good antimicrobial stewardship i.e. resulting in new agents being registered for use as last-line therapies instead of using them when most clinically appropriate. Given the nature and **urgency of drug-resistant infections, TGA guidelines for priority review/provisional registration could be reviewed and language could be refined to accommodate registration of novel antimicrobials for priority organisms of high AMR importance (e.g. AMR specific provisional pathway)**. Additionally, alternate mechanisms for prioritising registrations of antimicrobials for priority organisms/infections, similar to the QIDP process in the US, could be considered. The registration pathway for novel antimicrobials should enable registration on the basis of different types of data throughout clinical development for registration process, including PK/PD data, in vitro susceptibility data, real world data etc., similar to the adaptive pathways model in the EU.

In addition to aligning the incentives for appropriate antibiotic use and action plans to improve current surveillance of resistant infections in Australia, a variety of financial and regulatory incentives are needed to address the lack of development of products and undervaluation of existing products to combat antibiotic resistance. "Pull" initiatives include regulatory and market incentives which indirectly facilitate higher market returns for companies that launch a new antibiotic (e.g. The Generating Antibiotics Incentives Now (GAIN) act and priority review vouchers, orphan drug designations). These strategies reward only successful research and thereby maximise R&D efficiency and motivation. **Industry should engage with the TGA to review international incentives to assist the TGA to make informed decisions on what would work best within the Australian context**.

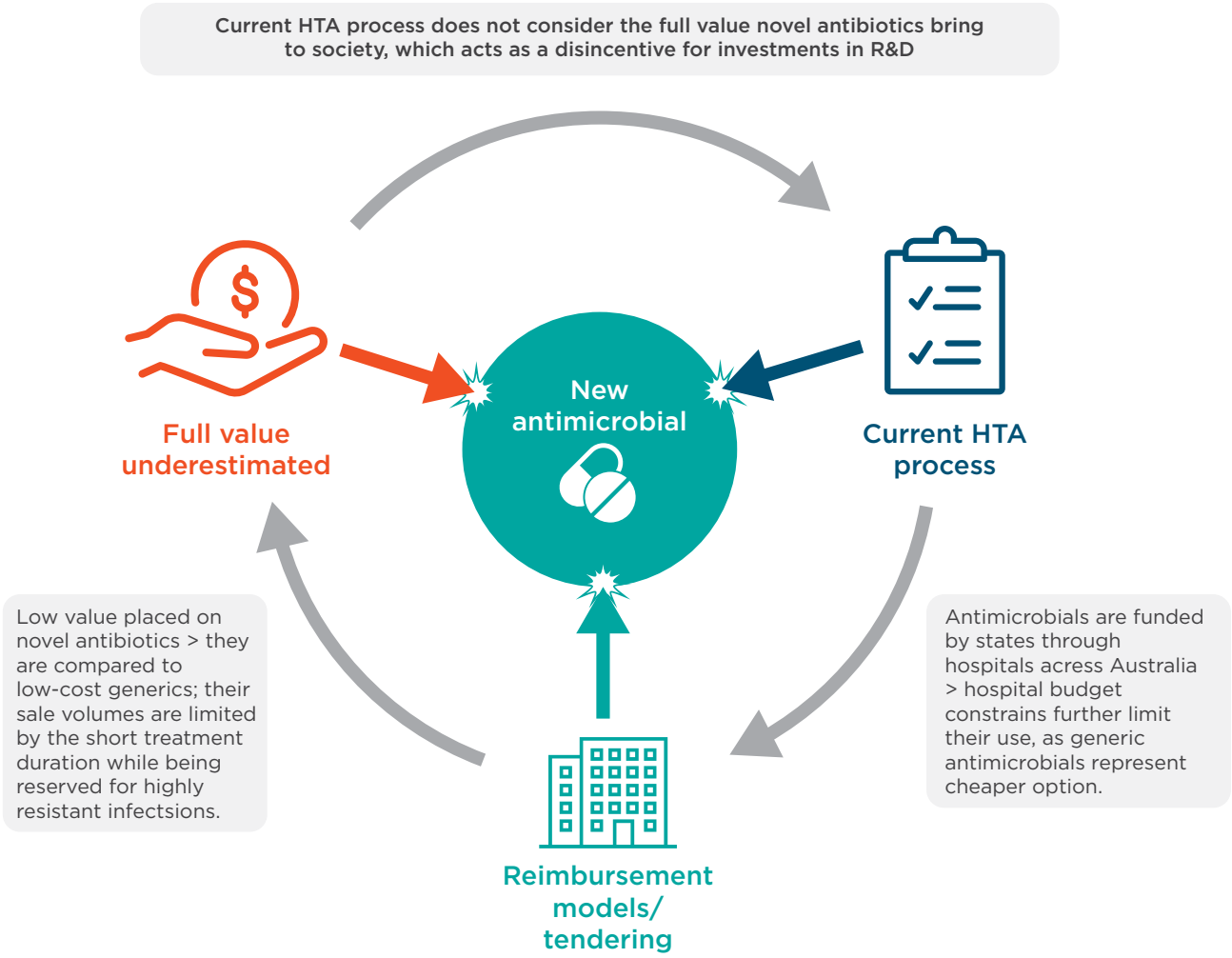
Table 3. Examples of "pull incentives" offered by the regulatory agencies

"Pull" Incentive	Description
The Generating Antibiotics Incentives Now (GAIN) Act[15]	A US bill ratified in 2012, which provides: - Five years of additional market exclusivity for those new antibiotics designated under the law as a "qualified infectious disease product," defined as "an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections." - Priority review and fast track approval - The FDA guidance for antibiotic development (including clinical trials guidance)
Priority review vouchers[16]	US legislation enacted in 2007 aimed to provide an incentive to develop drugs for neglected tropical diseases by allowing the FDA to grant companies that obtain approval for a drug for a tropical disease a one-time, transferable priority review voucher for an unrelated future drug. These vouchers could facilitate faster patient access to antibiotics and the possibility for voucher application to blockbuster drugs draws large cap companies to antibiotic market.
Orphan drug designations[16,17]	Special drug designation status offered by FDA, EMA and TGA – historically effective at stimulating R&D of drugs with poor reimbursement prospects. Benefits include extended market exclusivity, subsidies towards the cost of clinical trials and assistance to manufacturers navigating through regulatory requirements more easily. Note that Orphan drug designation available through TGA only offers "fee waiver" (no registration and PBAC submission fees), which is designed to remove a potential financial disincentive for companies to pursue registration and reimbursement for medicines that treat small numbers of patients.
Limited Population Antibacterial Drug Approval[18]	The FDA LPAD pathway will facilitate development and approval of certain antibacterial and antifungal drugs to treat serious or life-threatening infections in limited populations of patients with unmet needs. The development programs for drugs eligible for approval under the LPAD pathway follow streamlined approaches to clinical development. This may involve smaller, shorter or fewer clinical trials.

Pricing & Reimbursement Policy Framework

Secure and sustainable supply of essential anti-infective products, as well as access to novel therapies, is crucial to address the growing threat of AMR, however the market conditions remain challenging. Existing HTA, pricing and procurement policies for pharmaceuticals are not optimal for all AMR products. Novel antimicrobials are usually undervalued by current HTA and pricing approaches and this acts as disincentive for companies doing antimicrobial R&D (Figure 4).

Figure 4. Reimbursement challenges for novel antimicrobials



Novel therapies are likely to be compared to low-cost generics within the HTA process and their sale volumes are limited by the short treatment duration and / or are reserved for highly resistant infections.[4] Given that antimicrobials are funded by states through hospitals across Australia, hospital budget constraints further limit their use, as generic antimicrobials represent a cheaper therapeutic option. New ways of purchasing antimicrobials are needed in order to provide incentives for continued investment in antimicrobial R&D. Without these incentives, the burden of developing new antimicrobial therapies falls on governments, who have neither the ability nor the resource to undertake this currently. **Industry sector should actively engage with payers to do a detailed review of all existing funding pools (including PBS, Medical Benefits Schedule (MBS/MSAC), National Medicines Stockpile (NMS), alternative payers etc) to help create more flexible reimbursement pathways, allowing more appropriate payment for and access to these much-needed drugs.** Furthermore, there should be an **active advocacy for The Council of Australia Governments (COAG) to consider a national system for antimicrobial reimbursement.** On the other hand, a more

holistic government approach is needed across the full antimicrobial value chain, to ensure secure and sustainable supply of old and access to new antimicrobials. **Advocacy is needed to ensure the value is also being placed on the supply of antimicrobials, through recognition and industry rewards for sustainable supply.** Finally, new HTA, pricing and reimbursement models are required for novel antimicrobials in Australia that better acknowledge the societal value as well as having the flexibility to pay for stockpile or 'reserve' status, as opposed to the current PBS reimbursement per prescription. As part of this, **industry should request that the UK National Institute for Health and Care Excellence (NICE) and National Health Service (NHS) "subscription" style funding model for antibiotics is closely monitored and evaluated for potential implementation in Australia**.[19] Many countries will likely set up similar pilot models, and Australia has a real opportunity here to show global leadership in AMR policy.

Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act has been recently presented to the US Senate and should also be considered. This legislation, if passed, will set up a new reimbursement policy in US, which eliminates the incentive for hospitals to choose lower-cost generics, removing price as a factor in a hospital's decision to stock or use new, potentially more expensive antibiotics for highly resistant infections. The legislation would also require implementation of meaningful antibiotic stewardship programs.[20]

Antimicrobial stewardship promotes optimal antimicrobial prescribing and the Australian Commission on Safety and Quality in Healthcare works hard to collect data on usage and survey drug-resistant infections in Australia. However, it is evident that significant gaps remain in identifying how hospitals prescribe antimicrobials and how these medicines are being used in the wider community. By nature, industry might have a broader access to data sets allowing more comprehensive information on antimicrobial usage, and should therefore, offer participation in initiatives related to antimicrobial stewardship and promotion of optimal antimicrobial prescribing in Australia.

Conclusion

Industry plays an essential role in developing and bringing innovative medicines to patients and in order to meet the goal of the National AMR Strategy: "Minimise the development and spread of antimicrobial resistance and ensure the continued availability of effective antimicrobials", industry will need to be included as a key stakeholder in consultations to tailor strategies to combat AMR, together with other stakeholders. This workshop was not intended to 'solve' the wider AMR problem, which obviously requires much broader stakeholder engagement (e.g. including animal health, agriculture etc). In this context, the AMR industry workshop and future establishment of AMR Industry Alliance can be seen as one of many activities that will ultimately be required to successfully address the AMR challenge in Australia.

References 1. O'Neill J. (2014): Review on Antimicrobial Resistance Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. London: Review on Antimicrobial Resistance. **2.** The PEW charitable trusts report: A Scientific Roadmap for Antibiotic Discovery (2016). https://www.pewtrusts.org/-/media/assets/2016/05/ascientificroadmapforantibioticdiscovery.pdf. **3.** Schaffer S.K. *et al.* (2017): Assessing the value of new antibiotics: Additional elements of value for health technology assessment decisions. OHE. https://www.ohe.org/system/files/private/publications/OHE%20AIM%20Assessing%20The%20Value%20of%20New%20Antibiotics%20May%202017.pdf. **4.** Renwick M. & Mossialos E. (2018): What are the economic barriers of antibiotic R&D and how can we overcome them? Expert Opinion on Drug Discovery, 13:10, 889-892, DOI: 10.1080/17460441.2018.1515908 **5.** NPS Medicinewise: Antibiotic resistance in Australia: here and now https://www.nps.org.au/news/antibiotic-resistance-in-australia-here-and-now#r6. **6.** Williamson, D.A. Howden, B.P, Paterson, D.L. The Risk of Resistance: what are the major antimicrobial resistance threats facing Australia, Medical Journal of Australia 211(3) 5 August 2019, DOI: 10.5694/mja2.50249 **7.** AURA 2016: First Australian Report on Antimicrobial Use and Resistance in Human Health - Full Report https://www.safetyandquality.gov.au/sites/default/files/migrated/AURA-2016-First-Australian-Report-on-Antimicrobial-use-and-resistance-in-human-health.pdf. **8.** https://www.brisbanetimes.com.au/national/queensland/super-gonorrhoea-resistant-to-all-routine-antibiotics-found-in-australia-20180417-p4za4s.html. **9.** https://www.amrindustryalliance.org/ accessed August 2019. **10.** https://beam-alliance.eu/ accessed August 2019. **10.** CARB-X annual report 2017-2018: Progress against superbugs https://carb-x.org/wp-content/uploads/2018/09/CARB-X_AR-2017-18.pdf. **12.** https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb accessed August 2019. **12.** https://www.gardp.org/about/ accessed August 2019. **14.** https://www.jpiamr.eu/ accessed August 2019. **15.** PEW report: GAIN: How a New Law is Stimulating the Development of Antibiotics (2013) https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics. **16.** Renwick M.J. *et al.* (2016): A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics; *The Journal of antibiotics* 69, 73-88, doi:10.1038/ja.2015.98. **17.** Department of Health, Therapeutic Goods Administration: Orphan drug designation – A step-by-step guide for prescription medicines https://www.tga.gov.au/publication/orphan-drug-designation accessed August 2019. **18.** US Food and Drug Administration (FDA): Limited Population Pathway for Antibacterial and Antifungal Drugs – the LPAD Pathway https://www.fda.gov/drugs/development-resources/limited-population-pathway-antibacterial-and-antifungal-drugs-lpad-pathway accessed August 2019. 1**9.** https://www.gov.uk/government/news/development-of-new-antibiotics-encouraged-with-new-pharmaceutical-payment-system accessed August 2019. **20.** https://www.pewtrusts.org/en/research-and-analysis/speeches-and testimony/2019/06/18/pew-thanks-senators-for-introducing-bill-to-spur-antibiotic-development.