The cost-effectiveness of azithromycin in reducing exacerbations in uncontrolled asthma

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Add-on AZM in the treatment of poorly controlled persistent asthma is cost-effective. It is associated with a positive net monetary benefit when costs including those associated with antimicrobial resistance are considered. https://bit.ly/31aZ3fi

Cite this article as: O'Neill C, Gibson PG, Heaney LG, *et al*. The cost-effectiveness of azithromycin in reducing exacerbations in uncontrolled asthma. *Eur Respir J* 2021; 57: 2002436 [https://doi.org/10.1183/13993003.02436-2020].

ABSTRACT Add-on azithromycin (AZM) results in a significant reduction in exacerbations among adults with persistent uncontrolled asthma. The aim of this study was to assess the cost-effectiveness of add-on AZM in terms of healthcare and societal costs.

The AMAZES trial randomly assigned 420 participants to AZM or placebo. Healthcare use and asthma exacerbations were measured during the treatment period. Healthcare use included all prescribed medicine and healthcare contacts. Costs of antimicrobial resistance (AMR) were estimated based on overall consumption and published estimates of costs. The value of an avoided exacerbation was based on published references. Differences in cost between the two groups were related to differences in exacerbations in a series of net monetary benefit estimates. Societal costs included lost productivity, over the counter medicines, steroid induced morbidity and AMR costs.

Add-on AZM resulted in a reduction in healthcare costs (mean (95% CI)) including nights in hospital (AUD 433.70 (AUD 48.59–818.81) or EUR 260.22 (EUR 29.15–491.29)), unplanned healthcare visits (AUD 20.25 (AUD 5.23–35.27) or EUR 12.15 (EUR 3.14–21.16)), antibiotic costs (AUD 14.88 (AUD 7.55–22.21) or EUR 8.93 (EUR 4.53–13.33)) and oral corticosteroid costs (AUD 4.73 (AUD 0.82–8.64) or EUR 2.84 (EUR 0.49–5.18)); all $p<0.05$. Overall healthcare and societal costs were lower (AUD 77.30 (EUR 46.38) and AUD 256.22 (EUR 153.73) respectively) albeit not statistically significant. The net monetary benefit of add-on AZM was estimated to be AUD 2072.30 (95% CI AUD 1348.55–2805.23) or EUR 1243.38 (EUR 809.13–1683.14) assuming a willingness to pay per exacerbation avoided of AUD 2651 (EUR 1590.60). Irrespective of the sensitivity analysis applied, the net monetary benefit for total, moderate and severe exacerbations remained positive and significant.

Add-on AZM therapy in poorly controlled asthma was a cost-effective therapy. Costs associated with AMR did not influence estimated cost-effectiveness.

This article has supplementary material available from erj.ersjournals.com

This study is registered at the Australian and New Zealand Clinical Trials Registry (ANZCTR), number 12609000197235.

Received: 21 June 2020 | Accepted: 13 Aug 2020

Introduction

Asthma is a highly prevalent disease affecting over 300 million people worldwide [1]. It is associated with a significant economic burden [2, 3], a burden shown across a variety of healthcare systems to be concentrated among those with severe disease [4–7]. Patients with severe asthma are known to be at increased risk of exacerbations [8, 9] and patients with severe asthma who experience exacerbations have been shown to incur approximately twice the asthma-related costs of patients with controlled severe disease as well as increased risks of morbidity and mortality [9, 10]. Given the major impact of exacerbations on patients, there remains a global imperative to prevent asthma exacerbations.

Treatments used in this respect have included tiotropium [11, 12], type 2-directed monoclonal antibody therapies [13–15] and oral corticosteroid therapy [16]. While these have been shown to be effective, issues, such as cost in the case of monoclonal antibody therapies [17] and toxicity in the case of oral corticosteroid therapy [18] have called into question their potential for widespread use. In addition, while studies of cost-effectiveness with respect to tiotropium as an add-on to standard therapy suggest its cost-effectiveness, these have been based on modelling exercises rather than trials and remain to be fully explored [19, 20].

Recent studies have explored the prophylactic use of macrolide antibiotics in the avoidance of exacerbations where asthma is severe or not completely controlled [21–23]. The most recent study randomised patients to 500 mg of oral azithromycin (AZM), taken three times per week for 48 weeks as an add on to standard therapy and compared to placebo in terms of the number of exacerbations (severe and moderate), time to first exacerbation and asthma-related quality of life over the course of a year. It found that the azithromycin group had significantly fewer exacerbations (1.07 per patient-year (95% CI 0.85–1.29)) compared with placebo (1.86 per patient-year (1.54–2.18)), better asthma-related quality of life compared with the placebo group (adjusted mean difference 0.36 (95% CI 0.21–0.52); p=0.001) and a longer interval before experiencing a first exacerbation than the placebo group. Based on the study results, the authors concluded that azithromycin might be a useful add-on therapy in persistent asthma.

The aim of this study was to estimate the cost-effectiveness of add-on azithromycin based on the AMAZES study [23] accounting for healthcare and other costs including estimated costs for potential antibiotic resistance associated with prophylactic use of AZM and other antibiotics prescribed during the study.

Methods

Study design

Full details of the AMAZES trial are reported elsewhere including recruitment, exclusions, outcome measures and adverse events [23]. Briefly, the trial was powered to detect a difference in the number of exacerbations between the AZM and placebo groups which was evaluated in 420 adults with symptomatic asthma despite current use of inhaled corticosteroid and long-acting bronchodilators: 213 and 207 to the AZM and placebo groups respectively. Differences in the primary and secondary outcomes were assessed on an intention-to-treat basis after 48 weeks treatment with oral AZM, 500 mg, three times per week, or matching placebo. Adverse events observed over the course of the study and measures of antibiotic resistance were taken at the end of the study. In the original study, exacerbations were expressed in terms of per person-year; here, we explore them simply in terms of the trial end point: *i.e.* after 48 weeks.

Methods and analyses

In the cost-effectiveness analysis, data on healthcare use collected alongside outcomes were aggregated, monetised and related to outcomes in a series of incremental cost-effectiveness analyses from both a

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healthcare system and societal perspective. Resource use included the number of general practitioner visits, emergency room visits, hospital inpatient nights and drug use, including both prescribed and those bought over the counter (OTC). Each aspect of cost was monetised using standard references for Australia and full details are provided in the online supplementary methods and table S1. To take account of broader costs that may arise due to therapy, costs related to antimicrobial resistance (AMR) were estimated as were the costs related to corticosteroid induced morbidity and those related to productivity losses. Here, recourse was made to the literature, with adjustments for purchasing power parity as detailed in the supplementary material.

Descriptive statistics for each element of resource, together with its associated cost were estimated for the AZM and placebo groups separately. Differences of means in cost and outcomes were estimated between the groups. The ratio of the difference in mean cost to mean effect (all exacerbations, severe and moderate exacerbations only) between groups were estimated as the incremental cost-effectiveness ratio between the AZM and placebo groups. To take account of the potential joint distribution of cost and effects a non-parametric approach was used to estimate incremental cost effectiveness ratios (ICER). The process was repeated for each outcome, total exacerbations (severe and moderate) as well as severe and moderate exacerbations only, separately and with respect to each cost measure, healthcare costs (excluding steroid induced morbidity, antimicrobial resistance, OTC and lost productivity costs) and societal costs (that is including steroid induced morbidity, antimicrobial resistance, OTC and lost productivity costs). Net monetary benefit estimates for moderate, severe and total exacerbations with respect to healthcare and societal costs based on an assumed willingness to pay per exacerbation avoided of AUD 2651 using an estimate by Lloyd *et al.* [24] adjusted for purchasing power parity and updated for inflation were calculated. A cost-effectiveness acceptability curve with respect to societal costs and total exacerbations was estimated to capture uncertainty with respect to the willingness to pay for an avoided exacerbation. The probability of cost effectiveness assuming a willingness to pay per avoided exacerbation ranging from 0 to $3000 was examined.

A series of sensitivity analyses were undertaken as detailed in the supplementary methods. Societal costs were winsorised at the 99th centile for each group and net monetary benefits re-estimated**.** Winsorising data limits the effect of extreme values that might give rise to potentially spurious conclusions. Antimicrobial resistance costs were estimated at twice the upper bound of the range for cost per course provided in the literature to assess its potential impact on net monetary benefit estimates [5] relative to the base case analysis. Decrements in health-related quality of life associated with an exacerbation were estimated using the literature and monetised using a threshold willingness to pay of AUD 64 000 per quality-adjusted life-year (QALY)**.** Estimates allowed for the severity of the exacerbation experienced. The net monetary benefit and the probability of the intervention being deemed cost effective was re-estimated based on the difference in estimated QALY gain. Net monetary benefit was re-estimated for complete cases only, that is, where any censored observations were removed. As costs and outcomes were confined to 48 weeks discounting was not necessary.

Results

Demographics of the participants are reported elsewhere. Briefly, they were older adults with a median age of 60 years, predominantly (76%) atopic who had longstanding asthma (median of 32 years) [23]. The descriptive statistics for healthcare use, medication costs and estimated antimicrobial resistance are shown in table 1, all values are expressed in Australian dollars (AUD). Costs for general practitioner and emergency room visits as well as inpatient nights were lower in the AZM group. Similarly, cost of antibiotics and OCS prescriptions are around half that of the placebo costs for those treated with add-on AZM. Estimated costs for antimicrobial resistance was six-times higher in the AZM group, while costs for OTC therapies and asthma therapies were similar between the groups.

The difference between the groups subtracting AZM costs from placebo are presented in table 2. Those who received AZM had significantly reduced costs for visits with a physician and inpatient nights as well as antibiotic requirements other than the intervention and OCS treatment (table 2). They also had lower total healthcare costs, though these failed to achieve statistical significance. The cost of the AZM and estimated costs for antimicrobial resistance were significantly higher in the AZM group. Mean societal costs were lower in the AZM group than in the placebo group; however, the difference was not statistically significant. This suggests add-on AZM is not more expensive relative to usual care but attains significantly better outcomes. The net reduction in societal costs due to AZM is greater than the saving in healthcare costs; with the inclusion of antimicrobial resistance costs being counterbalanced by the inclusion of corticosteroid-induced morbidity and lost productivity costs.

The net monetary benefit which assesses the net value of the intervention was positive for total exacerbations (table 3), that is, at an assumed willingness-to-pay of AUD 2651 per exacerbation [24] or

TABLE 1 Descriptive statistics and healthcare costs according to treatment group

	Azithromycin (n=213)		Placebo (n=207)	
	Visits/nights/units	Cost	Visits/nights/units	Cost
GP visits	0.29±0.05	22.70±4.25	0.55±0.08	42.96±6.40
ER visits	0.07±0.02	29.51±8.21	0.11±0.03	47.72±11.44
Inpatient nights	0.04±0.03	71.40±54.93	0.27±0.10	505.10±190.54
Antibiotic costs#	7.83±1.55	14.20±2.04	11.94±1.61	29.08±3.14
Oral corticosteroid dose mg	250.80±43.20	5.02±0.86	487.38±90.66	9.75±1.81
Antimicrobial resistance		172.82±4.62		31.97±3.03
Combination therapy		16.40±5.46		15.86±3.41
Inhaled steroids		18.86±5.67		17.81±3.53
Other prescribed medicines		9.36±2.18		9.08±1.91
OTC cost		15.06±2.92		17.34±2.86
Overall costs				
Intervention cost		413.14±9.51		0
Healthcare cost		584.19±60.64		661.49±199.80
Societal cost		1256.47±107.25		1512.69±275.04
Exacerbations				
Moderate exacerbations	0.39±0.05	0.71±0.08		
Severe exacerbations	0.48±0.06	0.85±0.10		
Total exacerbations	0.87±0.09	1.56±0.13		

Data are presented as mean±SEM; all figures reported to 2 decimal places. #: other than intervention costs. GP: general practitioner; ER: emergency room; OTC: over the counter. All monetary values quoted in AUD.

EUR 1590.60 (based on an exchange rate of AUD 1=EUR 0.6 current at the time of writing), add-on AZM has a positive net monetary value for both healthcare and societal costs. This is also the case for moderate and severe exacerbations when considered individually, both were positive and, when added together, the gain is the greatest. Healthcare and societal costs are lower, and exacerbations avoided higher in the AZM group, confirming AZM as an add-on therapy is less expensive and more effective. This is seen in figure 1 showing the cost-effectiveness plane for costs *versus* total exacerbations, where both healthcare (figure 1a)

TABLE 2 Differences in mean costs (placebo minus azithromycin group)

	Visits/nights/units	Cost
GP visits	0.26** (0.07–0.45)	20.25** (5.23–35.27)
ER visits	0.04 (−0.02–0.10)	18.21 (−9.34–45.75)
Inpatient nights	0.23* (0.03–0.43)	433.70* (48.59–818.81)
Antibiotic costs#	4.10 (−0.29–8.50)	14.88** (7.55–22.21)
Oral corticosteroid dose mg	236.58* (40.92–432.23)	4.73* (0.82–8.64)
Antimicrobial resistance		−140.83** (−151.76–−129.90)
Combination therapy		−0.54 (−13.28–12.20)
Inhaled steroids		−1.05 (−14.27–12.17)
Other prescribed medicines		−0.27 (−5.99–5.44)
OTC cost		2.28 (−5.76–10.33)
Overall costs		
Intervention cost		−413.14
Healthcare cost		77.30 (−328.29–482.90)
Societal cost		256.22 (−318.04–830.48)
Exacerbations		
Moderate exacerbations	0.32** (0.13–0.52)	
Severe exacerbations	0.37** (0.14–0.59)	
Total exacerbations	0.69** (0.38–1.00)	

Data are presented as mean difference (95% CI) or mean difference. GP: general practitioner; ER: emergency room; OTC: over the counter. #: other than intervention costs. *: p<0.05; **: p<0.01. All figures reported to 2 decimal places. All monetary values quoted in AUD.

TABLE 3 Net monetary benefit estimates for exacerbations

	Healthcare costs	Societal costs
Moderate exacerbations	935.49 (531.46–1343.16)	1110.64 (628.30–1584.63)
Severe exacerbations	1051.77 (568.63–1571.91)	1206.85 (538.68–1808.61)
Total exacerbations	1910.70 (1327.72–2525.64)	2072.30 (1348.55–2805.23)

Data are mean (95% CI), All figures reported to two decimal places. All monetary values quoted in AUD.

and societal costs (figure 1b) are both in the south-west quadrant of the plane signifying fewer exacerbations at a lower cost.

The probability of add-on AZM being deemed to be cost-effective was further explored using a cost effectiveness acceptability curve for total exacerbations and societal costs, shown in figure 2. The probability of AZM being cost-effective exceeded 0.95 at a willingness to pay to avoid an exacerbation of AUD 100, approaching 1 at higher values.

Irrespective of the sensitivity analysis applied, the net monetary benefit for total, moderate and severe exacerbations remained positive and significant (table 4). This process allowed examination of whether the results were robust to the role of outliers in the sample, the inflation of antimicrobial resistance costs or removal of censored observations.

Discussion

Asthma is a highly prevalent condition and among those with persistent asthma, exacerbations contribute significantly to its burden [9, 10]. Various efforts have been made to reduce the burden associated with exacerbations [11–16] though issues of toxicity, cost and the robustness of evidence exist [17–20]. Prophylactic use of AZM has been shown to be effective in reducing the total number of asthma exacerbations as well as the number of severe exacerbations while having no significant effect on serious adverse events and similar results in terms of prevalence of AZM-resistant organisms [23]. This study has shown that AZM as an add-on therapy is associated with a reduction in healthcare and societal cost, though the reduction is not statistically significant, while resulting in significant reductions in exacerbations. The increased cost of AZM was counterbalanced by the reductions in cost associated with fewer healthcare contacts and, in particular, those associated with inpatient stays and general practitioner visits.

Evidence of the cost effectiveness is provided by the estimated net monetary benefit and sensitivity analyses. The net monetary benefit at a willingness to pay of AUD 2651 per exacerbation was positive (AUD 1910.70 (EUR 1146.42) from a healthcare perspective) and statistically significant. Incorporating the estimated cost associated with antimicrobial resistance along with other societal costs/savings into the analysis did not materially affect the results (the net monetary benefit rising to AUD 2072.30 (EUR 1243.38)). In addition, when we performed sensitivity analyses in which antimicrobial costs were inflated to the twice the upper bound of reported range per course, the net monetary benefit remained positive and statistically significant (AUD 1700.68 (EUR 1020.41)). The probability of AZM being considered cost-effective

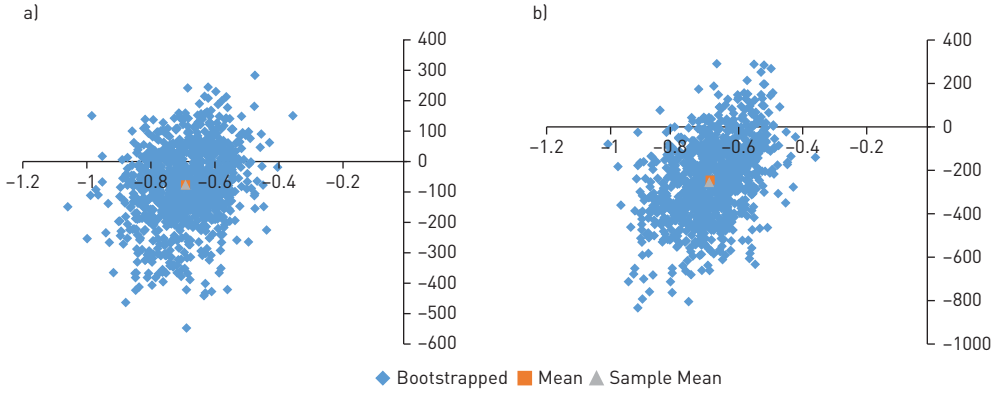

FIGURE 1 Cost-effectiveness plane: a) incremental healthcare costs/incremental total exacerbations, b) incremental societal costs/incremental total exacerbations.

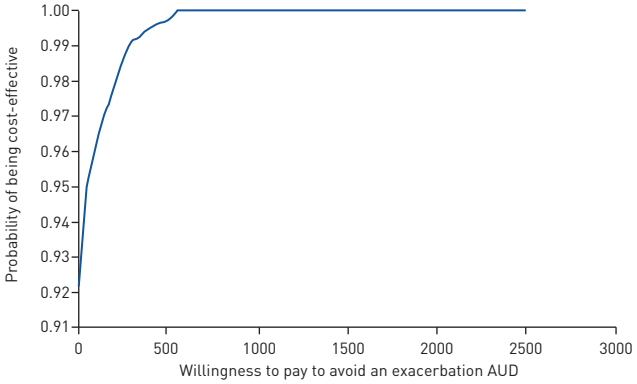

FIGURE 2 Cost-effectiveness acceptability curve.

approached 1 at a willingness to pay to avoid an exacerbation of AUD 100; far lower than that used in the base case analysis (AUD 2651). The net monetary benefit remained positive and significant when based on an estimated value of QALY gain. When productivity losses were confined to those aged 65 years and under, NMB estimates remained virtually unchanged (results not shown). Overall, these results provide reassurance as to the robustness of the cost effectiveness of AZM as an add-on therapy to usual care.

While no significant difference was found in the prevalence of AZM-resistant organisms in the main study [23], the impact of inappropriate use of antibiotics on antimicrobial resistance is of concern given its potential health and economic impact globally [25]. Our treatment of antimicrobial resistance costs were based on the use of the midpoint of the estimated cost per course range, the use of 48 weeks of AZM which would disadvantage the intervention in terms of cost and make the cost effectiveness estimates conservative. That the World Health Organization (WHO) continues to classify AZM as a key access antibiotic (designating it among those that should be widely available, affordable and quality assured) [26] notwithstanding, it remains among its Watch group *i.e.* those who stewardship should be prioritised. More generally, a cautious approach to use of any antibiotic, given its potential to increase antimicrobial resistance risks and costs, is prudent and has been reflected in the approach we use. How high we should raise antimicrobial resistance costs to reflect such prudence lies beyond the scope of this paper. As noted, however, estimates of a positive net monetary benefit remained robust to a variety of assumptions regarding cost and the value of outcomes including the assumption that antimicrobial resistance costs were twice the upper bound estimate of the cost per course reported in the literature.

Strengths and limitations

Strengths of the study include the detailed recording of healthcare use that allowed drug use to be estimated based on actual prescriptions, including dose and frequency rather than simply cost per course of an assumed standard prescription. Our ability to include antimicrobial resistance, OCS and productivity losses are added strengths of the paper.

Limitations of the paper are also evident. The accuracy of antimicrobial resistance costs per course reported in the literature is open to challenge. That our results remain robust to the inflation of antimicrobial resistance to twice the upper bound of the reported cost range may offer some reassurance in this regard as may our other conservative treatments of antimicrobial resistance costs. It remains important to acknowledge the uncertainty that exists around this figure, however. Similarly, while we relied on average earnings to estimate productivity losses, we were conservative in our approach to their

TABLE 4 Sensitivity analyses showing net monetary benefit for moderate, severe and total exacerbations

Analysis method	A	B	C	D
Exacerbation				
Moderate	1051.17 (621.34–1509.39)	724.90 (251.26–1220.27)	855.02 (433.42–1261.45)	1166.22 (675.48–1663.27)
Severe	1173.83 (563.49–1769.42)	839.36 (195.49–1451.85)	923.81 (392.95–1426.40)	1107.01 (454.97–1748.75)
All	2031.77 (1353.49–2748.34)	1700.68 (990.78–2441.65)	1523.32 (941.44–2068.36)	2094.77 (1361.48–2852.22)

Data are mean (95%CI). All monetary values quoted in AUD. A: Winsorised costs; B: antimicrobial resistance at twice upper bound cost per course; C: utility decrement experienced over 8 weeks, and societal willingness to pay per quality-adjusted life-year of AUD 64 000; D: exclusion of censored observations.

inclusion, assuming only days spent in hospital were lost to work rather than total sick days. The paucity of estimates regarding the willingness to pay to avoid an exacerbation is a further limitation. As shown by the cost effectiveness acceptability curve though, the probability that add-on azithromycin was cost effective continued to exceed 0.95 at willingness to pay of around AUD 100. The net monetary benefit also remained positive using alternative valuation approaches based on extrapolations.

The cost-effectiveness of the intervention is likely to vary across healthcare systems based on factors, such as the price of healthcare and earnings. In the USA, for example, where the price of services are generally higher than those in Australia [27], the reduction is use of general practitioner and hospital services reported in this study may translate to greater nominal savings in healthcare costs even allowing for higher antibiotic costs for example. As with any evaluation there will be a need to adjust for local circumstances.

Conclusion

The study has shown that add-on oral AZM therapy is a cost-effective treatment for adults with persistent asthma and poor control being associated with lower healthcare costs and significantly fewer exacerbations. While due caution is warranted in the use of any antibiotic, the estimated net monetary benefit remained positive and significant even when the costs of antimicrobial resistance were inflated to twice the upper bound of the ranges used for their costs. Based on these analyses the prophylactic use of 500 mg AZM taken three times per week to reduce exacerbations would appear to be cost-effective even allowing for a cautious approach to the use of antibiotics.

Acknowledgements: We wish to acknowledge the comments of Paddy Gillespie and Grainne Crealey, NUI Galway, and Luke Barry, Queen's University Belfast, on an earlier draft of this paper, and Nga Nguyen for advice on the analyses of prescribed medicine. We also wish to acknowledge the AMAZES research group for undertaking the study, as well as the AMAZES study participants.

Conflict of interest: C. O'Neill reports grants for education activities from Roche, AbbVie, Novartis and Pfizer, outside the submitted work. P.G. Gibson reports personal fees for lectures from AstraZeneca, GlaxoSmithKline and Novartis, grants from AstraZeneca and GlaxoSmithKline, outside the submitted work. L.G. Heaney reports sponsorship for meeting attendance from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline and Napp Pharmaceutical, personal fees for advisory board work and lectures from Novartis, Hoffman la Roche/Genentech Inc, Sanofi, GlaxoSmithKline, AstraZeneca, Teva, Theravance and Circassia, grants from Medimmune, Novartis UK, Roche/Genentech Inc. and GlaxoSmithKline, and Amgen, outside the submitted work; and is Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma, which involves industrial partnerships with Genentech/Hoffman la Roche, AstraZeneca, Medimmune, GlaxoSmithKline, Aerocrine and Vitalograph. J.W. Upham reports grants from NHMRC, during the conduct of the study. I.A. Yang reports grants from NHMRC, during the conduct of the study. P.N. Reynolds reports grants from NHMRC, during the conduct of the study. S. Hodge reports grants from NHMRC, during the conduct of the study. C.R. Jenkins reports grants from NHMRC, during the conduct of the study. M. Peters reports grants from NHMRC, during the conduct of the study. G.B. Marks reports grants from NHMRC, during the conduct of the study; grants and advisory board work from AstraZeneca, grants from GSK, outside the submitted work. A.L. James reports grants from NHMRC, during the conduct of the study. J.L. Simpson reports grants from NHMRC, during the conduct of the study.

Support statement: This work was supported by the National Health and Medical Research Council. Funding information for this article has been deposited with the Crossref Funder Registry.

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