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Early View

Original article

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

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Take home message

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 were considered.

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 ($48.59 – $818.81) or €260.22(€29.15 - €491.29)), unplanned healthcare visits (AUD$20.25 ($5.23-$35.27) or €12.15 (€3.14-€21.16)), antibiotic costs (AUD$14.88 ($7.55 – $22.21) or €8.93(€4.53-€13.33)) and oral corticosteroid costs (AUD$4.73 ($0.82-$8.64) or €2.84(€0.49 - €5.18)), all $p<0.05$. Overall healthcare and societal costs were lower (AUD$77.30 (€46.38) and AUD$256.22 (€153.73) respectively) albeit not statistically significant. The net monetary benefit of add-on AZM was estimated to be AUD$2072.30 (95% CI $1348.55-$2805.23) or (€1243.38 (€809.13-€1683.14) assuming a willingness to pay per exacerbation avoided of AUD$2651 (€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.

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), T2-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 500mg 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 to 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, 500mg, 3 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 healthcare system and societal perspective. Resource use included the number of general practitioner (GP) visits, emergency room (ER) 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 supplement.

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 $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 $3,000 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 $64,000 (AUD) 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%) topic 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 6 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 €1590.60 based on an exchange rate of AUD$1 = €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) 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 (€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 (€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 (€1020.41)). The probability of AZM being considered cost-effective 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 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 conservative the cost effectiveness estimates. That the 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 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 WTPs 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 US, for example, where the price of services are generally higher than those in Australia (27), the reduction is use of GP

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 500mg 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.

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References

1. Global Asthma Network. The Global Asthma Report. Auckland, New Zealand; 2014.
2. Mukherjee M, Stoddart A, Gupta RP, Nwaru BI, Farr A, Heaven M, Fitzsimmons D, Bandyopadhyay A, Aftab C, Simpson CR. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC medicine* 2016; 14: 113.
3. Barnett SBL, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. *Journal of Allergy and Clinical Immunology* 2011; 127: 145-152.
4. Chastek B, Korrer S, Nagar SP, Albers F, Yancey S, Ortega H, Forshag M, Dalal AA. Economic Burden of Illness Among Patients with Severe Asthma in a Managed Care Setting. J Manag Care Spec Pharm. 2016 Jul;22(7):848-61.
5. Flórez-Tanus Á, Parra D, Zakzuk J, Caraballo L, Alvis-Guzmán N Health care costs and resource utilization for different asthma severity stages in Colombia : a claims data analyis. World Allergy Organ J. 2018 Nov 12;11(1):26.
6. Lee YJ, Kwon SH, Hong SH, Nam JH, Song HJ, Lee JS, Lee EK, Shin JY. Health Care Utilization and Direct Costs in Mild, Moderate, and Severe Adult Asthma: A Descriptive Study Using the 2014 South Korean Health Insurance Database. Clin Ther. 2017 Mar;39(3):527-536
7. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. BMC Pulm Med. 2017 Apr 27;17(1):74.
8. Calhoun WJ, Haselkorn T, Mink DR, Miller DP, Dorenbaum A, Zeiger RS. Clinical burden and predictors of asthma exacerbations in patients on guideline-based steps 4-6 asthma therapy in the TENOR cohort. *J Allergy Clin Immunol Pract. 2*014;2(2):193-200.
9. Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K. Effect of asthma exacerbations on health care costs amongasthmatic patients with moderate and severe persistent asthma. *J Allergy Clin Immunol.* 2012;129(5):1229-35.

10 Sullivan SD, Rasouliyan L, Russo PA, Kamath T, Chipps BE, Group TS. Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma. *Allergy*. 2007;62(2):126-33.

11 Kerstjens et al (see Randonovch) Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012;367(13):1198–207.

12 Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Meredes BT, et al. Tiotropium bromide step up therapy for adults with uncontrolled asthma. N Engl J Med. 2010;363:1715–26.

13 Busse WW. Biological treatments for severe asthma: A major advance in asthma Care. Allergology International 68 (2019) 158-166.

14 Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev. 2017 Sep 21;9:CD010834.

15 McDowell PJ, Heaney LG. Different endotypes and phenotypes drive the heterogeneity in severe asthma. Allergy. 2020;75(2): 302-310.doi: 10.1111/all.13966

16 Wark PA, McDonald VM, Gibson PG. Adjusting prednisone using blood eosinophils reduces exacerbations and improves asthma control in difficult patients with asthma. Respirology. 2015 Nov;20(8):1282-4

17 Zafari Z Sadatsafavi M, Fitzgerald JM and for the Canadain Respiratory Research Network. Cost‐effectiveness of tiotropium versus omalizumab for uncontrolled allergic asthma in US. Cost Eff Resour Alloc. 2018 Jan 30;16:3

18 Barry LE, O'Neill C, Patterson C, Sweeney J, Price D, Heaney LG. Age and Sex Associations with Systemic Corticosteroid-Induced Morbidity in Asthma. J Allergy Clin Immunol Pract. 2018 Nov - Dec;6(6):2014-2023.e2.

19 Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D. Cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled gluco

corticosteroids and long-acting β-agonists. Appl Health Econ Health Policy. 2014 Aug;12(4):447-59.

20 Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D. Erratum to: Cost Effectiveness of Tiotropium in Patients with Asthma Poorly Controlled on Inhaled Glucocorticosteroids and Long-Acting β-Agonists. Appl Health Econ Health Policy. 2016 Feb;14(1):119-25.

21 Simpson J, Powell H, Boyle M, Scott R, Gibson P. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. *Am J Respir Crit Care Med* 2008; **177:** 148–55.

22 Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax* 2013; **68:** 322–29.

23 Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet. 2017 Aug 12;390(10095):659-668

24 Lloyd A, McIntosh E, Rabe KF, Williams A. Patient preferences for asthma therapy: a discrete choice experiment. *Primary Care Respiratory Journal* (2007); 16(4): 241-248

25 O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. The review on antimicrobial resistance. 2016. https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf. Accessed December 2016.

26 The World Health Organizations Model List of Essential Medicines. March 2017. http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed December 2019.

27 International comparisons of health care prices from the 2017 iFHP survey. https://healthcostinstitute.org/in-the-news/international-comparisons-of-health-care-prices-2017-ifhp-survey. Accessed August 2020.

Table 1: Descriptive statistics and healthcare costs according to treatment group

	Azithromycin		Placebo	
N	213		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 corticosteroids 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)	

Mean (SE), all figures reported to 2 decimal places. # other than intervention costs

All monetary values quoted in AUD$

Table 2: Differences in mean costs (Placebo minus Azithromycin group)

	Mean difference	95% Confidence interval

	Visits/nights/units	Cost	Visits/nights/units	Cost
GP visits	0.26**	20.25**	0.07 – 0.45	5.23 – 35.27
ER visits	0.04	18.21	-0.02 – 0.10	-9.34 - 45.75
Inpatient nights	0.23*	433.70*	0.03 – 0.43	48.59 – 818.81
Antibiotic costs	4.10	14.88**	-0.29 – 8.50	7.55 – 22.21
Oral corticosteroids dose (mg)	236.58*	4.73*	40.92 - 432.23	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	

** $p<0.01$, * $p<0.05$. All figures reported to 2 decimal places. # other than intervention costs

All monetary values quoted in AUD$

Table 3: Net monetary benefit estimates for exacerbations

NMB	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 2 decimal places

All monetary values quoted in AUD$

Table 4: Sensitivity analyses showing net monetary benefit for moderate, severe and total exacerbations based on A) Winsorised costs B) AMR at twice upper bound cost per course, C). Utility decrement experienced over 8 weeks, and societal WTP per QALY of $64,000. D) Exclusion of censored observations. Data are mean (95%CI).

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)

All monetary values quoted in AUD$

Figure 1A

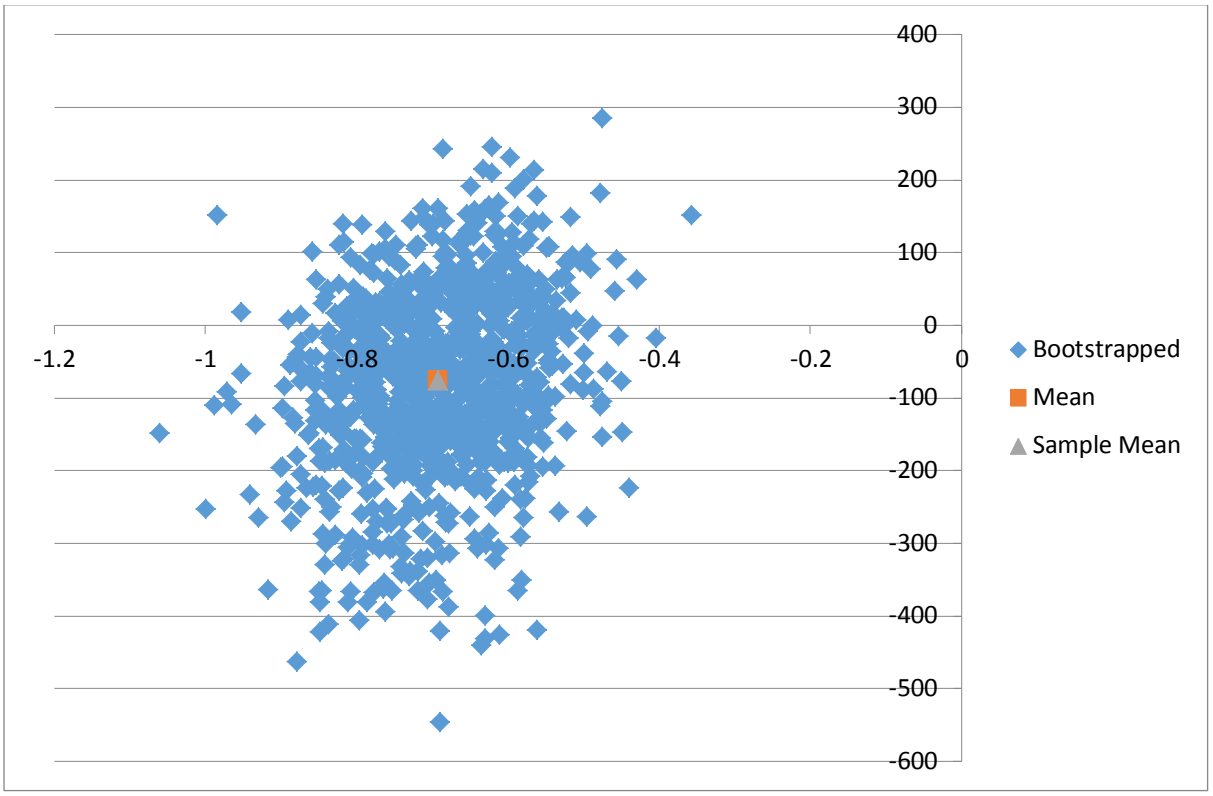

Figure 1B

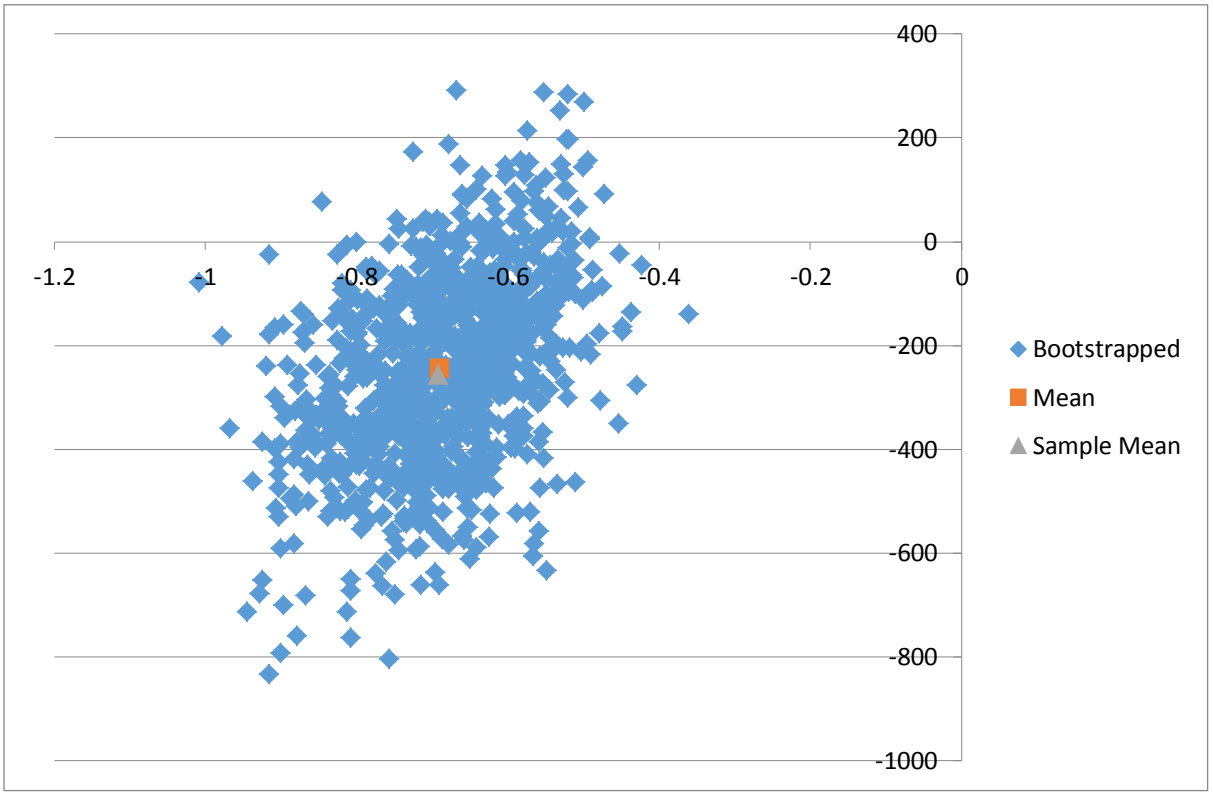

Figure 2

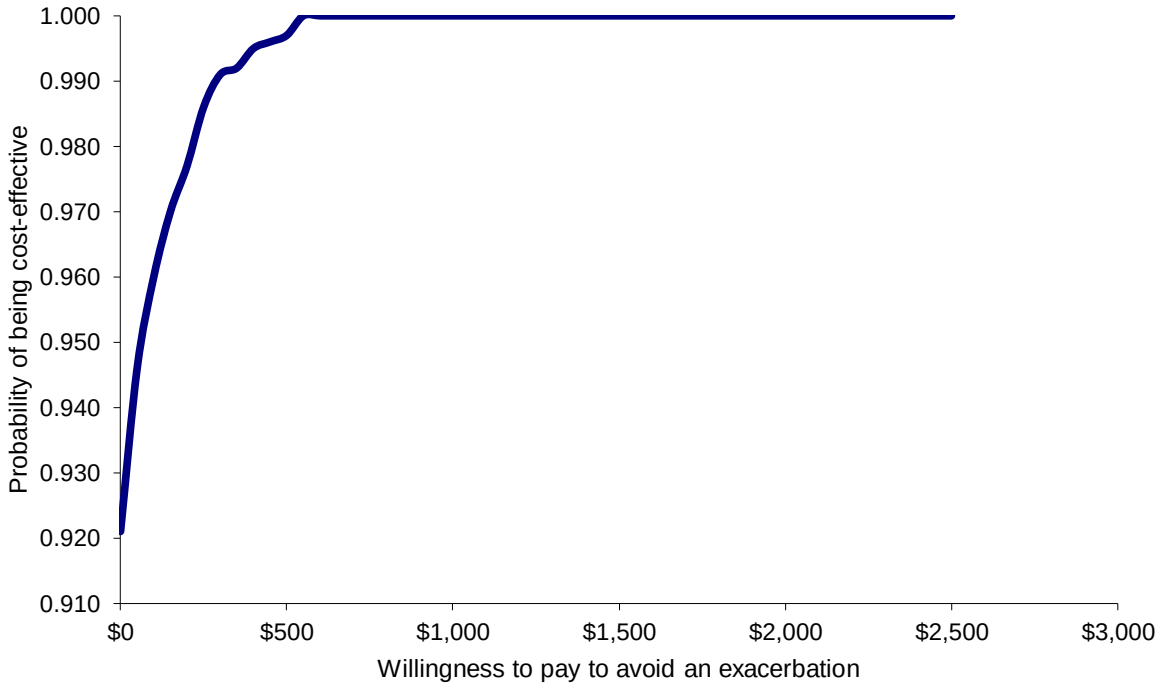

Figure legend

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

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

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Methods

Cost estimates

The National Hospital Cost Data Collection Report, Average separation cost, Table 1 Round 19 (1) was used for hospital costs. The Australian Medical Association estimated costs of GP visits in 2016 (2) were used for GP services and the Pharmaceutical Benefits Scheme Schedule at March 2016 (3) was used for prescribed medicines where each drug by dose was matched by name with that appearing in the Schedule of Pharmaceutical Benefits. Over the counter (OTC) therapies were monetised using 2018 market price data (4), the time point at which the economic analyses were initiated and at which price data were available. No adjustment for inflation. Each drug was priced based on its name, dose and frequency of use as recorded by the research staff with the exception of oral corticosteroid (OCS) use. For OCS, to take account of titration over the course of an OCS prescription, OCS cumulative consumption was first calculated. The cumulative milligram (mg) was then valued at $0.02AUD, the cost per mg based on a pack of 30, 25mg tablets in March 2016. When OCS use was titrated, cost was based an assumed equal distribution of consumption across the doses recorded. Other antibiotics were valued at the mid-point of combined range in base case analysis ($23.21), and highest of combined range in sensitivity analyses (AUD79.61 for 95% upper bound confidence interval and AUD159.22 for twice the upper bound estimate.

As use of antibiotics may present an externality to society from higher healthcare costs and lost productivity arising from higher mortality (5) these were included in analyses as an example of indirect healthcare costs. Similarly, with respect to corticosteroid induced morbidity (6) the cost of treating morbidities induced based on exposure were incorporated into analyses as a further example of indirect morbidity costs. Healthcare costs were estimated based on all healthcare use except for OTC costs, antimicrobial resistance (AMR) costs and induced morbidity costs– the first was treated as having fallen on the individual

rather than the healthcare system and the second as an externality borne by society. As it is not possible with certainty to ascertain where induced morbidity costs would be borne across differing healthcare systems, they were assigned conservatively as being borne ultimately by society, rather than assigned to healthcare.

Antimicrobial Resistance costs

AMR costs were estimated per antibiotic course consumed at the midpoint of the range for cost per course associated with various types of antibiotics prescribed as previously described (5). Figures were converted to AUD to adjust for purchasing power parity at USD1 = AUD1.49. The midpoint of the range in each instance exceeded the mean cost per course and served to increase AMR cost estimates to the detriment of the intervention group. For the intervention group the AMR costs of 48 additional prescriptions associated with the use of azithromycin as a trial intervention were added to this. This exceeds the actual number taken by the intervention group. This further served to overestimate AMR costs to the disadvantage of the AZM treatment group and serve to reflect concerns around AMR costs biasing downward the intervention's cost-effectiveness and serving to make estimates of its relative value conservative.

The cost of AMR was estimated using US data from 2008 to 2014 on the relationship between antibiotic consumption by humans and instances of antimicrobial resistance to first line treatment across five pathogens (*Staphylococcus aureus* (*S. aureus*); *Escherichia coli* (*E. coli*); *Klebsiella pneumoniae (K. pneumonia); Acinetobacter baumanii (A. ; baumanii)* and; *Pseudomonas aeruginosa (P. aeruginosa)*. In brief for a given class of antibiotic the correlation between human use and instances antimicrobial resistance along with their associated 95% confidence intervals were calculated using data from 2008 to 2014 for each pathogen. These were multiplied by the incremental cost of treating patients with resistant infections as compared with sensitive ones combined with the indirect productivity losses due to excess mortality attributable to resistant infections. The former was estimated based on the Medical Panel Expenditure Survey and the latter based on a human capital

approach applied to estimated instances of premature death due to antimicrobial resistance multiplied by per capita GDP and assumptions regarding years of productive life lost with adjustment for discounting and productivity growth.

Estimates were initially based on a “standard unit (SU) of consumption” – namely the smallest identifiable dose given to a patient. The resulting economic costs per SU of antibiotic consumed in each pathogen were then aggregated for each pathogen in which that antibiotic class was implicated to calculate the cumulative economic cost per antibiotic consumed for each drug class. For example, as quinolones are assumed to drive resistance in all 5 pathogens the cost of resistance per standard unit of quinolones would be the sum of the estimated cost of resistance across for all 5 pathogens. Cost estimates per standard unit were subsequently multiplied by the number of standard units that would constitute a course of treatment for an adult based on estimates from the British National Formulary.

Upper and lower bound estimates of cost per course were based on the 95% confidence intervals for correlation coefficients used to estimate instances of resistant infection across the five pathogens and a range of 5–20 productive life years assigned to each excess death to calculate the indirect cost. Full details are reported in Shrestha et al 2018.”

Corticosteroid induced morbidity

Estimates of the additional annual healthcare costs associated with various levels of systemic steroid exposure in the UK were used (6). Based on these and the levels of OCS exposure observed in the data, it was possible to estimate an annual corticosteroid induced morbidity cost for both control and intervention groups. Estimated costs were adjusted for purchasing power parity to Australian dollars at £1 = AUD 2.07.

Productivity losses

The average adult fulltime weekly earnings of AUD$1575.4 (7) were used were used to estimate a per day cost assuming a 40-hour working week of AUD$315.08. Assuming each day/night in hospital resulted in one lost day of work, these were combined with observed length of hospital stay to estimate lost production costs using a human capital approach.

Willingness to pay (WTP) to avoid an exacerbation

The WTP to avoid an exacerbationwas estimated using previous data [8]. This estimates the WTP per month to avoid an exacerbation that involves a trip to the doctor of ER of €109. This implies a WTP per year to avoid an exacerbation of approximately €1312 prices (12 times €109 allowing for rounding) in 2007 prices. This was converted to AUD$2113 based on an exchange rates of €1 = AUD1.61, adjusted for inflation to 2016 at 25% (sourced from https://knoema.com/atlas/Australia/Inflation-rate). The cost of AZM was estimated using published sources [12].

Sensitivity Analyses

To facilitate interpretation a simple linear regression was used in each instance with the ratio of the estimated coefficients on treatment group with respect to cost and outcome providing an estimate of the incremental cost effectiveness ratio (ICER). ICERs were re-estimated when the distribution of societal costs was winsorized (i.e. extreme values replaced by the values of the distribution observed at the 99th percentile) to assess the effect on results of outliers. The lowest and highest 1 percentile of societal costs was used for this purpose.

Given the role of antibiotics in AMR is an issue of concern, further focus was given to AMR costs. Twice the upper bound estimate of the AMR cost per course for each type of antibiotic were used to assess the impact of uncertainty regarding the cost of AMR on estimated cost-effectiveness. Twice the upper bound estimate was chosen arbitrarily from the same

published source used to estimate the mid-point of the AMR range used in the base case analysis (5).

Further, there is also uncertainty around the willingness to pay (WTP) to avoid an exacerbation. The cost-effectiveness of the intervention was subsequently re-assessed based on the estimated health-related quality of life difference and QALY gain between the two groups. The health related quality of life decrement associated with an exacerbation was estimated as the drop in utility from 0.89 (9) to 0.65 for a moderate exacerbation (10), 0.53 (9) for a severe exacerbation that did not involve a hospital stay and 0.33 (9) for a severe exacerbation that did involve a hospital stay based on data from published references (9,10). The decrement was estimated to last 8 weeks out of 52 based on published references (11). Data on differences in the number of admissions, moderate and severe exacerbations for the two group were used to calculate the utility decrement associated with each type of exacerbation which was weighted by estimated duration per year (8/52 = 0.1538) of an exacerbation and multiplied by $64,000, the threshold WTP for a QALY in Australia (12).

In the base case analysis individuals on whom there was incomplete data were treated as missing at random; costs and outcomes were assumed complete at the point where they were lost to follow-up (44 intervention group; 37 control group). A sensitivity analysis was undertaken in which data on these observations were removed from the analysis and complete cases only used. There was no significant difference in months of data lost between the two groups or in NMBs when re-estimated.

Results

Table S1: Resource use and service costs

Service	Cost (AUD)	Source
GP visit	$78	[2]

ER visit	$449	[1]
Inpatient night	$1901	[1]
Anti-microbial cost (per course)	Macrolides (0.3 – 7.45) Quinolone (3.13 – 76.29) Co-amoxiclav (3.28 – 81.80) Amioglycoside (0.6 – 13.56) Cephalosporins (1.49– 38.14) Phenoxymethlypenicillin (1.64 – 40.83)	[5]
Steroid induced morbidity per course	$921.85 - $6,796.85	[6]
Lost productivity per day	$315.08	[7]
Oral steroid cost	$0.02 per mg	[3]
Other prescribed drug costs	As per prescribed amount	[3]
Over the counter drug costs	As per purchase	https://www.chemistwarehouse.com.au/
Willingness to pay to avoid an exacerbation	$2651	[8]
AZM	$10	[12]

References

1 Independent Hospital Pricing Authority. National hospital cost data collection, Public Hospitals Costs Report, Round 19 (Financial Year 2014-15) from https://www.ihpa.gov.au/publications/national-hospital-cost-data-collection-public-hospitals-cost-report-round-19-financial. Accessed December

2019.https://ama.com.au/ausmed/health-costs-rise-rebate-freeze-bitesAustralian Government Department of Health, Schedule of Pharmaceutical Benefits. Effective 1 March 2016 – 31 March 2016.

2 Australian medical association fee recommendation 2016 http://www.pbs.gov.au/publication/schedule/2016/03/2016-03-01-general-schedule.pdf. Accessed December 2019.

3 Shrestha P, Cooper BS, Coast J, Oppong R, Do Thi Thuy N, et al. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to info rm the evaluation of interventions affecting their use. Antimicrob Resist Infect Control. 2018; 7:98.

4 Voorham J, Xu X, Price DB, Golam S, Davis J, Zhi Jie Ling J, Kerkhof M, Ow M, Tran TN. Healthcare resource utilization and costs associated with incremental systemic corticoster oid exposure in asthma. Allergy. 2019; 74:273-283.

5 Australian Bureau of Statistics, Average weekly fulltime earnings in Australia, May 2016. https://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/6302.0Main+Features1May%202016?OpenDocument. Accessed December 2019.

6 Lloyd A, McIntosh E, Rabe KF, Williams A. Patient preferences for asthma therapy: a discrete choice experiment. *Primary Care Respiratory Journal.* 2007; 16: 241-248

7 Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. Prim. Care Respir. J. 2007; 16: 22-7.

8 Zafari Z, Sadatsafavi M, FitzGerald JM, and for the Canadian Respiratory Research Network. Cost-effectiveness of tiotropium versus omalizumab for uncontrolled allergic asthma in US. Cost Eff Resource Alloc. 2018; 6:3. doi: 10.1186/s12962-018-0089-8.

9 Crossman-Barnes CJ, Sach T, Wilson A, Barton G. Estimating loss in quality of life associated with asthma-related crisis events (EQUARE): a cohort, observational study. Health Qual Life Outcomes. 2019; 17: 58 doi: 10.1186/s12955-019-1138-5.

10 Jean A. McDougall, Wesley E. Furnback, Bruce C. M. Wang & Jörg Mahlich. Understanding the global measurement of willingness to pay in health. J Mark Access Health Policy. 2020;8:1717030, doi: 10.1080/20016689.2020.1717030