Beyond expectations : post-implementation data shows rotavirus vaccination is likely cost-saving in Australia

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Supplementary material captions:

Supplementary File 1: Detailed description of health outcomes and estimation of rates

Supplementary File 2: Sensitivity analyses: one-way SA and PSA

Supplementary File 3: Future benefits and cost-effectiveness over time

ABSTRACT

Background Universal vaccination against rotavirus was included in the funded Australian National Immunisation Program in July 2007. Predictive cost-effectiveness models assessed the program before introduction.

Methods We conducted a retrospective economic evaluation of the Australian rotavirus program using national level post-implementation data on vaccine uptake, before-after measures of program impact and published estimates of excess intussusception cases. These data were used as inputs into a multi-cohort compartmental model which assigned cost and quality of life estimates to relevant health states, adopting a healthcare payer perspective. The primary outcome was discounted cost per quality adjusted life year gained, including or excluding unspecified acute gastroenteritis (AGE) hospitalisations.

Results Relative to the baseline period (1997-2006), over the 6 years (2007-2012) after implementation of the rotavirus program, we estimated that ~77,000 hospitalisations (17,000 coded rotavirus and 60,000 unspecified AGE) and ~3 deaths were prevented, compared with an estimated excess of 78 cases of intussusception. Approximately 90% of hospitalisations prevented were in children <5 years, with evidence of herd protection in older age groups. The program was cost-saving when observed changes (declines) in both hospitalisations coded as rotavirus and as unspecified AGE were attributed to the rotavirus vaccine program. The adverse impact of estimated excess cases of intussusception was far outweighed by the benefits of the program.

Conclusion

The inclusion of herd impact and declines in unspecified AGE hospitalisations resulted in the value for money achieved by the Australian rotavirus immunisation program being substantially greater than predicted by pre-implementation models, despite the potential increased cases of intussusception. This Australian experience is likely to be relevant to high-income countries yet to implement rotavirus vaccination programs.

INTRODUCTION

Rotavirus is the most frequent cause of severe dehydrating diarrhoea in young children worldwide [1], resulting in substantial health care utilisation, quality of life impact, and productivity loss in caregivers. The introduction of rotavirus vaccination in many high-income settings led to an almost immediate impact on the burden of rotavirus disease, especially in preventing substantial numbers of hospitalisations in young children [2-5].

Prior to introduction of universal vaccination against rotavirus for infants to the Australian National Immunisation Program (NIP) in July 2007, there were an estimated ~19,000 annual hospitalisations for acute gastroenteritis (AGE) in children less than 5 years of which ~10,000 were attributable to rotavirus infection [6]. Since program implementation, marked declines in both rotavirus and all-cause AGE hospitalisations [7-13] as well as presentations to an emergency department (ED) [14] were observed for children less than 5 years, in both vaccinated cohorts and in other young children [10]. Assessment of risk of intussusception (IS) following rotavirus vaccination in Australia [15-17] found evidence of a small increased risk of IS in the first 1-21 days after receipt of doses 1 and 2 for both vaccines [15, 16].

Public funding of vaccines in Australia requires confidential economic evaluations by the respective vaccine manufacturers submitted to the Pharmaceutical Benefits Advisory Committee (PBAC) [18, 19]. For rotavirus vaccination in Australia, there was also an academic-led cost-effectiveness analysis [20, 21] suggesting borderline cost-effectiveness of the program at the manufacturer-listed price. Since this time, Australian surveillance data captured effects across a broad range of rotavirus disease indicators and provided evidence of herd immunity effects not anticipated in earlier evaluations [5, 11, 22, 23].

We have previously outlined the value of retrospective cost-effectiveness analyses for vaccination programs, through methodological advice and an evaluation of the 7-valent pneumococcal conjugate vaccine in Australia [24, 25]. In this study, we expand on our previous research to

evaluate the value for money achieved by the Australian rotavirus vaccination program using post-implementation data on vaccine coverage, program impact, and adverse events following immunisation.

METHODS

Study design and model

We designed an age-specific static multi-cohort compartmental model to examine the impact of the Australian rotavirus program. While the program was implemented (in July 2007 for children born from 1 May 2007) using two different vaccine brands, we examined the vaccination program as a whole, not as individual brands of the vaccine. We adopted a healthcare payer perspective with costs and benefits discounted at 5% per annum as recommended in Australian PBAC guidelines [26]. We calculated the incremental cost-effectiveness ratio (ICER) for different scenarios (see below Program impact) and report results from the base case model and use the median when reporting results from the probabilistic sensitivity analyses.

Data sources and rates of health outcomes

We included potential rotavirus-associated AGE health outcomes, including hospitalisations, deaths, ED presentations, general practitioner (GP) consultations, rotavirus infections not requiring medical care, and intussusception cases. Rates of health outcomes were estimated using observational data over the years 1997 to 2012, where available. For each of these outcomes, we converted the data to annual age-specific rates using population data from the Australian Bureau of Statistics (ABS) [27]. Specific details are reported in Supplementary File 1. Where possible, we considered the following age stratifications: 0-<6 months, 6-<12 months, 1-<2 years, 2-<3 years, 3-<4 years, 4-<5 years, 5-<10 years and 10-<15 years. The available observational data was divided into two main categories: either '***coded' rotavirus (coded-RV)*** using rotavirus-specific diagnostic codes or '***unspecified' acute gastroenteritis (unspecified AGE)***. Studies prior to vaccination have shown that a high proportion of unspecified AGE in young children was due to rotavirus infection [6]. The coded-RV data was determined using rotavirus-specific diagnostic codes. Any change in this category is likely to underestimate the program impact since not all cases of AGE due to rotavirus are coded as such (e.g. due to a lack of laboratory testing [13]). For coded-RV hospitalisations we used ICD-10-AM A08.0 (Rotaviral enteritis), while for unspecified

AGE hospitalisations we combined ICD-10-AM A08.4 (Viral intestinal infection, unspecified) and A09 (Infectious gastroenteritis and colitis, unspecified) as used previously [6]. For GP consultations and non-admitted ED presentations, we focused on syndromic AGE presentations since rotavirus is rarely tested for in these settings. Details of the calculation of annual rates and changes in non-medical care as well as intussusception cases as are provided in Supplementary File 1. The annual rates used in the model are illustrated in Figures S1.1 and S1.2.

Program impact

We established two different scenarios on the period 2007-12: the “with vaccine” scenario which was based on the observed data, and the hypothetical “no vaccine” scenario which was estimated based on an average of the pre-implementation rates in the data available prior to 2007 (see Supplementary File 1) in each of the outcomes. The impact of the vaccination program was calculated by taking the difference between estimates for the numbers of cases from the “with vaccine” scenario and those from the “no vaccine” scenario. For projections of the “with vaccine” scenario beyond the observed data, we applied the average rate in the last 3 years of available post-implementation data (see Supplementary File 3, Future benefits).

We considered two main scenarios for the impact on hospitalisations, including either changes in ***coded-RV*** hospitalisations only or in both ***coded-RV + unspecified AGE*** hospitalisations. Impacts using observed changes were presented separately in order of increasing uncertainty (in hospitalisations, deaths, ED presentations, GP consultations and excess IS cases in infants <1 year old) in children i) <5 years, ii) <15 years, and iii) <15 years with the addition of non-medical care. We excluded impacts on persons aged 15 years and above due to a lack of supportive evidence of effect.

Costs and quality of life

Costs and QALY losses used in the model are shown in Table 1 and details of their estimation are provided in Supplementary File 1. Hospitalisation costs in Australia were estimated using

Australian Refined Diagnosis-Related Groups (AR-DRG) codes associated with corresponding ICD-10-AM hospitalisation codes [28, 29]. Costs of ED presentations were calculated in the same way using the ED component of this data [28, 29]. GP consultation costs were estimated as in Newall et al. 2007 [20], using costs of consultation and bulk-billing service fee in 2007 [30]. No costs were included for non-medical care.

While the negotiated price for rotavirus vaccines in Australia is confidential, an estimated program cost was listed in Australian budget papers [31] in 2008. We used this to estimate a cost per completed schedule set to the same value for each vaccine based on the PBAC recommendations [18, 19]. The total cost of program implementation between 2007 and 2012 was calculated using annual data on vaccine uptake from the Australian Childhood Immunisation Register (ACIR) (see Supplementary File1). Vaccine administration costs were applied as in Newall et al. 2007 [20].

QALY loss estimates were taken from Brisson et al. [32] and are assumed to be the same for all cases with medical care. The QALY loss for non-medical care was assumed to be half that associated with medical care as assumed by Bilcke et al. [33]. As inclusion of QALY loss for caregivers (not ill from rotavirus) remains controversial, it was only included in additional scenario analyses.

Sensitivity analyses

One-way (varying each parameter by +/-25% from base case) sensitivity analyses were conducted to explore which parameters were most influential in the model. Probabilistic sensitivity analyses (PSA) were conducted to assess the impact of parameter value uncertainty (with ranges derived from data, where possible) on the cost-effectiveness results. The PSA involved 10,000 parameter sets selected using Latin Hypercube sampling from parameter distributions detailed in Table S2.1. Separate sensitivity analyses were conducted on important inputs including the cost of a completed vaccination schedule and the IS burden.

RESULTS

Epidemiological impacts of the national childhood rotavirus program are shown by age group for each outcome in Figure 1 (aggregated age groups shown for illustration purposes with more detailed data as used in the model shown in Figure S1.1). As expected, the declines in coded-RV hospitalisations in children less than 5 years (2007-2012 compared to 1998-2006) were higher than those in unspecified AGE hospitalisations (76% against 49%, respectively), also found true in declines on 2013-22 compared to 2007-12 for children less than 5 years. Declines in ED presentations for AGE were lower than for other health outcomes at 9% for children <5 years in the period 2007-14 compared to 1997-2006, while rates in ED presentations among children 5-14 years increased in the post-vaccination data period compared to “no vaccine” rates based on pre-implementation data.

In the initial years of the program (2007-12), we estimated that the program prevented the following outcomes (Table 2) among children <5 years (prevented cases among infants <1 year): 3 RV deaths, 17,000 (5,000) coded-RV hospitalisations, an additional 60,000 (14,000) unspecified AGE hospitalisations, 26,000 (6,000) ED presentations, 318,000 (37,000) GP consultations and 240,000 (167,000) cases without medical care. Among children 5-14 years, except for an increased 21,000 ED presentations, numbers prevented were lower compared to the younger <5 year age group. The estimated prevented outcomes for the continued ten-year program duration (2013-22) are shown in Table S3.1.

Program cost was estimated at A$120 million in 2007-12 (Table 3). In the most inclusive scenario (with all health outcomes), total healthcare cost savings were A$65 million in excess of the cost of the program (Figure 2). The largest cost savings were from prevented unspecified AGE hospitalisations (A$123 million in children <5 years; A$11 million in children 5-14 years), followed by coded-RV hospitalisations (A$34 million in children <5 years; A$780,000 in children 5-14 years) and GP consultations (A$12 million for children <5 years; $3 million for children 5-14 years). Savings from prevented ED presentations were A$10 million for children <5 years (with an

increased cost of A$8 million for children 5-14 years). Total QALYs gained when only quality of life changes in children were included (i.e. no caregivers) were 1,240. Most QALYs gained were from GP consultations (610 QALYs gained in children <5 years; 150 QALYs gained in children 5-14 years), followed by cases without medical care (230 QALYs gained in children <5 years; 40 QALYs gained in children 5-14 years), and unspecified AGE hospitalisations (115 QALYs gained in children <5 years; 10 QALYs gained in children 5-14 years). There were 40 QALYs gained from deaths and 30 QALYs gained from coded-RV hospitalisations.

In the scenario including coded-RV + unspecified AGE hospitalisations, the program was cost-saving in all scenarios (Table 3). In the conservative scenario using only coded-RV hospitalisation, we estimated an ICER of A$88,000 per QALY gained (median A$85,000; 95%CI A$70,000-A$170,000) when only quality of life measures in children were included. The ICER improved to A$62,000 per QALY gained (median A$65,000; 95%CI A$ 53,000-A$134,000) when cases without medical care were included. ICER point estimates were below threshold (A$50,000) in scenarios where quality of life impact from (one or two) caregivers are included. Results were similar when modelling a continuation of the program for a further 10 years (Table S3.1) and the estimated value for money was relatively constant over alternative implementation periods (Figure S3.2).

Changes to the estimated completed cost of vaccination were highly influential under all scenarios (Supplementary Figure S2.1). The cost of hospitalisation was also very influential especially when both coded-RV and unspecified AGE hospitalisations were included. Other influential parameters included quality of life loss from a sick child and the cost of a GP consultation. Parameters related to the estimation of changes in cases without medical care (proportion of rotavirus disease, rate of waning of vaccine efficacy against any severity of rotavirus infection) and the quality of life loss attached to these cases became influential when included. In the scenario that includes all outcomes but QALY impacts only for children (excluding caregivers), the program was cost-effective at a willingness-to-pay (WTP) threshold of A$50,000 per QALY if the price of a completed schedule was less than A$190 and cost-saving if a completed schedule was less than A$150

(Figure 3). When unspecified AGE hospitalisations were excluded, the program was cost-effective (<A$50,000 per QALY) if the completed schedule price was less than A$80 and cost-saving when less than A$50.

In the most inclusive scenario, and when both coded-RV and unspecified AGE hospitalisations were included with QALY impacts only for children, the probabilities of the rotavirus program being cost-effective over the period 2007-12 at a willingness-to-pay (WTP) threshold of A$50,000 per QALY gained was 99.9% and cost-saving at 99.3% respectively (Figure 4). When only coded-RV hospitalisations were included, the probability of cost-effectiveness at this WTP threshold was only 3.83% (increasing to 9.09% and 17.7% respectively when QALY impacts from one or two caregivers were included, respectively).

We estimated that 78 excess IS hospitalisations among infants <1 year would occur in 2007-12, associated with a QALY loss of 0.3, with QALY gains from the program more than 1,000 times higher even in the most conservative scenario. In the supplementary analysis where we assumed an IS case fatality rate (CFR) of 1 death per 2,738 cases [34], the program QALY gains from vaccination were 340 times higher .

DISCUSSION

We found that the Australian childhood rotavirus program was likely to have been cost-saving. This finding is in contrast to the initial industry-funded cost-effectiveness analysis that estimated an ICER range of between A$15,000-A$45,000 [19] and an independent pre-implementation economic analysis that found that the program may be cost-effective but was not cost-saving [20]. The main reason for the differences was the larger number of prevented hospitalisations (coded-RV and unspecified AGE) found in our analysis compared to previous studies [20]. This may be due to previous studies underestimating the pre-implementation hospitalisation burden [6, 20] and the larger than expected herd effects from the vaccination program. In addition, hospitalisation costs were 20% higher at the time of vaccination implementation compared to estimates available at the time of the previous study [20]. Together, these factors resulted in a doubling of the hospitalisation costs prevented in comparison to the published pre-implementation analysis [20]. The use of higher market-listed prices for vaccines also impact results in the academic-led study [20].

Our findings focused on impacts on changes in both coded-RV and unspecified AGE hospitalisations, as we believe these are more likely to show the full impact of the rotavirus vaccination program. The wider vaccine impact on all AGE hospitalisations from any cause is supported by clinical trial data [35, 36] which likely reflects the presence of both diagnosed and undiagnosed rotavirus cases amongst this broad disease category. Our observed decline of ~50% in unspecified AGE hospitalisations (which includes undiagnosed rotavirus illness) for children <5 years was of similar magnitude to declines observed in all-cause AGE admissions in the United Kingdom [37] and the United States [38-42].

Pre-implementation assessments in Australia did not include herd impacts on unvaccinated individuals, as this was thought to be unlikely at the time. However, post-implementation data has shown evidence of herd protection in Australia [10] and in other countries [43-46]. Substantial herd

effects on children aged 5-14 years and unvaccinated children <5 years were estimated using observational data. Furthermore, this impact was immediate, with large reductions in morbidity and associated costs in unvaccinated 1-4 year olds occurring within a year of vaccine introduction.

Unlike hospitalisations, impacts on other healthcare outcomes appeared less substantial than predicted before implementation which may indicate a possible shift in the severity of burden from severe to less severe outcomes. However, it should be noted that data sources used to inform the impact on ED presentations and GP consultations were not national databases. This study is the first to present data on declines in GP consultations in Australia coincidental with the vaccination program. While the pre-implementation analysis predicted that 77,000 GP consultations would be prevented in a single cohort (followed for 5 years) [20], we estimated ~50,000 GP consultations prevented each year in all children less than 5 years old. We also estimated only 4,000 ED presentations prevented each year in children less than 5 years old, as opposed to 16,000 ED presentations prevented in pre-implementation analysis [20]. Indeed, we observed higher rates of ED presentations due to AGE among children 5-14 years old after vaccination when compared to the estimated "no vaccine" rates (Figure S1.1). Possible explanations include increased use of ED facilities for care unrelated to vaccination [47, 48] and a shift in the burden of infection from younger children to older age groups [49].

Our analysis has a number of limitations primarily related to the data accessible. Access to weekly or monthly data would have allowed use of time-series methods to estimate changes in proportion of AGE due to rotavirus [6, 14, 50]. However, we found a strong correlation between annual rates of coded-RV and unspecified AGE hospitalisations over the period of analysis, with similar sharp declines in both series following the introduction of vaccination in 2007 (Supplementary Figure S3.1). All hospitalisation data was based on primary diagnosis codes, which may have had an impact on the estimated overall burden and the inclusion of nosocomial infections. Deaths due to rotavirus are rare and due to privacy implications limited data could be provided. This led us to use a fixed rate of death for hospitalised cases inferring changes in mortality from changes in

hospitalisations. Finally, the potential for death due to IS was uncertain, as only a single IS death was reported in the Australian portion of a meta-analysis on IS mortality in infants [34] prior to vaccination.

This is one of the first published cost-effectiveness studies using data obtained after implementation of a rotavirus vaccination program. We found that the program is cost-saving in Australia, which differs from the pre-implementation predictions. As of 1 May 2016, 18 high-income countries have introduced rotavirus into their national immunisation programs [51]. We believe our methods and findings will be of interest to high-income countries that either have yet to recommend implementation of rotavirus vaccination or have not yet assessed costs and benefits post-introduction. Our findings also suggest that the benefits of the program are likely to far outweigh potential increases in IS cases, which may provide further reassurance to policymakers.

Footnotes

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Contributors: ATN conceived of the project. JR led the project, parameterisation, reviewed the literature, designed and implemented technical aspects of the model, performed analyses, prepared figures and tables, and drafted the manuscript. ATN and JW designed the broad structure of the model, were involved in the methodological decisions, reviewed the literature and edited the manuscript. PM, KM, RM, NM and PB were involved in the parameterisation decisions, and reviewed the manuscript. All authors approved the final manuscript.

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Table 1 Key parameters

	Base value	Lower	Upper	Distribution (for PSA)	Source
Health care costs					
Hospitalisation (rotavirus)	$2,350.60	$1,762.95	$2,938.25	Gamma	Data from National Hospital Cost data collection, Round 12 (2007-2008) (see Supplementary File); Range: +/-25%
ED[1] presentation	$435.68	$326.76	$544.60	Gamma	
GP[2] consultation	$42.50	$31.88	$53.13	Gamma	Includes service fee type B, co-payment and bulk-billing fee (see Supplementary File); Range**:** +/-25%
Hospitalisation (IS[3])	$3,637.2	$2,727.90	$4,546.50	Gamma	Data from National Hospital Cost data collection, Round 12 (2007-2008) (see Supplementary File); Range**:** +/-25%
Vaccine price, per dose					
RotaTeq	$33.17	-	-	-	From top-down estimate of completed schedule taken from Australian Budget papers $99.52/3 doses = $33.17.
Rotarix	49.76	-	-	-	From top-down estimate of completed schedule taken from Australian Budget papers $99.52/2 doses = $49.76.
Administration costs per dose					
RotaTeq	$2	$0	$10.9	Gamma	As assumed in Newall et al 2007
Rotarix	$2.67	$0	$10.9	Gamma	As assumed in Newall et al 2007
QALYs[4] lost					
Hospitalisation, ED or GP visit, child	0.0022	0.0017	0.0071	Beta	Brisson et al 2010
Hospitalisation, ED or GP visit, intussusception, caregiver	0.0018	0.001	0.0031	Beta	Brisson et al 2010
Intussusception, child	0.0037	0.0029	0.0045	Beta	Bucher et al 2011
No medical care, child	0.0011	0.0008	0.0035	Beta	As assumed in Bilcke et al 2007
No medical care, caregiver	0.0009	0.0005	0.0015	Beta	As assumed in Bilcke et al 2007
Vaccine efficacy (used only for estimation of no medical care)					
Against rotavirus, any severity	74%	67%	80%	Lognormal	Vesikari et al 2006
Annual probability of symptomatic rotavirus infections					
Age 0-<2 years	0.24	0.17	0.34	Beta	Bilcke et al 2009
Age 2-<3 years	0.06	0.01	0.16	Beta	Bilcke et al 2008
Age 3-<5 years	0.03	0.002	0.11	Beta	Bilcke et al 2008
Age 5-<15 years	0.02	0.001	0.04	Beta	As assumed in Bilcke et al 2007 and Bilcke et al 2008

[1]ED = Emergency Department; [2]GP = General Practitioner; [3]IS = intussusception; [4]QALY = quality-adjusted life-year

Table 2 Epidemiological results

	Total cases (no program)	Total cases (with program)	Total prevented cases	% prevented cases	Rate per 100,000 (no program)	Rate per 100,000 (with program)	Rate prevented per 100,000
2007-2012 (program period)							
0-4 year olds							
Deaths (coded RV)	3.45	0.83	2.62	75.90%			
Hospitalisations (coded RV)	21,799	5,250	16,549	75.90%	254	61	193
Hospitalisations (unspecified AGE)	116,436	56,498	59,938	51.50%	1,357	661	696
ED presentations	259,412	233,388	26,024	10.00%	2,996	2,731	265
GP consultations	1,737,016	1,419,173	317,843	18.30%	20,412	16,605	3,807
No medical care*			236,134				
IS (excess cases)[#]	-	-78	-78				
5-14 year olds (additional benefit)							
Hospitalisations (coded RV)	1,468	1,132	336	22.90%	9	7	2
Hospitalisations (unspecified AGE)	29,757	24,605	5,152	17.30%	180	149	31
ED presentations	80,544	102,029	-21,485	-26.70%	489	619	-130
GP consultations	1,127,150	1,044,283	82,867	7.40%	6,835	6,332	502
No medical care*			33,952				
2013-2022 (continued program)^							
0-4 year olds							
Deaths (coded RV)	6.56	1.11	5.45	83.10%			
Hospitalisations (coded RV)	41,458	7,011	34,447	83.10%	254	43	211
Hospitalisations (unspecified AGE)	221,381	93,241	128,140	57.90%	1,357	572	784
ED presentations	491,153	447,192	43,961	9.00%	2,996	2,745	251
GP consultations	3,321,447	2,754,248	567,199	17.10%	20,412	16,905	3,506
No medical care*			566,684				
IS (excess cases)[#]	-	-161	-161				
5-14 year olds (additional benefit)							
Hospitalisations (coded RV)	2,840	3,110	-270	-9.50%	9	10	-1
Hospitalisations (unspecified AGE)	56,821	49,136	7,684	13.50%	180	158	22
ED presentations	153,624	214,668	-61,044	-39.70%	489	691	-202
GP consultations	2,123,535	1,908,392	215,143	10.10%	6,835	6,142	692
No medical care*			57,374				

*estimated assuming all prevented cases are rotavirus cases, which requires data on the proportion of all rotavirus cases, the efficacy of the vaccine against rotavirus of any severity, the uptake of the vaccine adjusted for waning, and the declines in cases who seek medical care (hospitalisations, ED presentations and GP consultations).

^uptake assumed to be sustained from 2012 levels; declines of rates in the program period 2007-2012 compared to the average of rates based on data available pre-vaccine period (prior to 2007) are applied in the 10-year period 2013-2022, using as baseline the average of rates in the last three years with available data.

[#]IS cases are reported here as excess cases that occur among vaccinated children <1 year old, using the estimate by Carlin et al 2013 [16].

Table 3 Cost-effectiveness results for the period 2007-2012

Scenario 2007-2012		Total costs saved: baseline (median; 95%CI)	Total QALYs gained: baseline (median; 95%CI)	ICER[&]: baseline(median; 95%CI)
		Child only[$]		
Coded RV + unspecified AGE hospitalisations§	**Children <5 years**	$58,437,819 ($60,873,698; $28,362,920 to $71,720,221)	848 (838; 519 - 1,241)	Cost-saving
	+ Children 5-14 years	$65,068,854 ($67,687,488; $30,888,676 to $82,215,984)	972 (958; 520 - 1,494)	Cost-saving
	+ No medical care	$65,068,854 ($67,687,488; $30,888,676 to $82,215,984)	1,241 (1,125; 699 - 1,659)	Cost-saving
Coded RV hospitalisations**	**Children <5 years**	-$64,632,691 (-$61,222,897; $-71,418,992 to -$77,756,318)	733 (724; 414 - 1,113)	88,152 (84,615; 69,880 - 172,523)
	+ Children 5-14 years	-$68,891,940 (-$65,510,985; $-77,592,432 to -$80,310,683)	847 (834; 403 - 1,361)	81,334 (78,578; 58,989 - 192,617)
	+ No medical care	-$68,891,940 (-$65,510,985; $-77,592,432 to -$80,310,683)	1,115 (1,000; 579 - 1,524)	61,773 (65,499; 52,694 - 133,938)
		Child + 1 caregiver^		
Coded RV + unspecified AGE hospitalisations§	**Children <5 years**	$58,437,819 ($60,873,698; $28,362,920 to $71,720,221)	1,509 (1,497; 920 - 2,283)	Cost-saving
	+ Children 5-14 years	$65,068,854 ($67,687,488; $30,888,676 to $82,215,984)	1,734 (1,714; 928 - 2,750)	Cost-saving
	+ No medical care	$65,068,854 ($67,687,488; $30,888,676 to $82,215,984)	2,222 (2,021; 1,242 - 3,066)	Cost-saving
Coded RV hospitalisations**	**Children <5 years**	-$64,632,691 (-$61,222,897; -$71,418,992 to -$77,756,318)	1,300 (1,286; 732 - 2,036)	49,734 (47,594; 38,187 - 97,586)
	+ Children 5-14 years	-$68,891,940 (-$65,510,985; -$77,592,432 to -$80,310,683)	1,507 (1,487; 710 - 2,497)	45,729 (44,057; 32,159 - 109,338)
	+ No medical care	-$68,891,940 (-$65,510,985; -$77,592,432 to -$80,310,683)	1,994 (1,795; 1,026 - 2,801)	34,546 (36,496; 28,674 - 75,641)
		Child + 2 caregivers[#]		
Coded RV + unspecified AGE hospitalisations§	**Children <5 years**	$58,437,819 ($60,873,698; $28,362,920 to $71,720,221)	2,170 (2,145; 1,271 - 3,430)	Cost-saving
	+ Children 5-14 years	$65,068,854 ($67,687,488; $30,888,676 to $82,215,984)	2,497 (2,457; 1,292 - 4,130)	Cost-saving
	+ No medical care	$65,068,854 ($67,687,488; $30,888,676 to $82,215,984)	3,204 (2,907; 1,750 - 4,581)	Cost-saving
Coded RV hospitalisations**	**Children <5 years**	-$64,632,691 (-$61,222,897; -$71,418,992 to -$77,756,318)	1,866 (1,841; 1,013 - 3,054)	34,638 (33,253; 25,462 - 70,498)
	+ Children 5-14 years	-$68,891,940 (-$65,510,985; -$77,592,432 to -$80,310,683)	2,166 (2,128; 999 - 3,728)	31,806 (30,790; 21,544 - 77,648)
	+ No medical care	-$68,891,940 (-$65,510,985; -$77,592,432 to -$80,310,683)	2,873 (2,580; 1,449 - 4,172)	23,978 (25,396; 19,249 - 53,549)

*Program costs are estimated at $120 million over the period 2007-2012.

**Coded RV scenario includes coded RV hospitalisations, coded RV deaths, ED presentations coded as unspecified AGE and GP consultations coded as unspecified AGE

[§]Coded RV + unspecified AGE scenario includes coded RV and unspecified AGE hospitalisations, coded RV, ED presentations coded as unspecified AGE and GP consultations coded as unspecified AGE

[$]Child only scenario considers costs and QALYs from cases of sick children in the outcomes included

^Child + 1 caregiver scenario considers costs and QALYs from cases of sick children as well as QALYs from one caregiver for each sick child in the outcomes included

[#]Child + 2 caregivers scenario considers costs and QALYs from cases of sick children as well as QALYs from two caregivers for each sick child in the outcomes included

[&]The ICER is estimated using the costs and QALYs of the “with vaccine scenario” against the hypothetical “no vaccine” scenario.

Abbreviations: QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; AGE = acute gastroenteritis

Figure captions

Figure 1 Estimates of the rates per 100,000 of each outcome. The rows show, from top to bottom, observed and estimated rates for hospitalisations (coded RV and unspecified AGE), ED presentations and GP consultations, with disaggregation into <5 years in the left column and 5-14 years in the right column. Estimated average rates are shown only over the period in which they are applied in the model (2007-22 for “no-program” and 2013-22 for “program” projections). Vertical lines establish the start of vaccination (2007) and the end of the observed data period (2012). Estimated % declines are shown for two periods: pre/post in 2007-2012, where data is available for all outcomes and post/future in the period 2013-2022. Horizontal dashed lines represent estimated rates for “no vaccine” scenario, while horizontal dotted lines represent estimated rates for “with vaccine” scenario for 2012-2022.

Figure 2 Healthcare costs saved and QALYs gained in the period 2007-2012. The panels show cost savings (top) and QALYs gained (bottom) for three scenarios (0-4 years only, <15 years and <15 years including QALY change from non-medically attended cases). The cost savings and QALYs gained are disaggregated by category of health care outcome as shown in the legend. Changes due to adverse events (intussusception) are imperceptible at this scale and are reported in the main text.

Figure 3 Sensitivity analysis based on varying the cost of completed schedule. ICERs for scenarios including only children <5 years old (no caregivers), and all outcomes except no medical care, where hospitalisations include only coded RV (solid line) and when also including unspecified AGE hospitalisations (dashed line). These are compared with pre-implementation estimates for Rotarix (square) and RotaTeq (triangle) from the academic led analysis and the current base case results (asterisks, see Table 3). Horizontal dotted lines corresponding to ICERs A$0 and A$50,000 per QALY gained are shown for reference, while vertical dashed line corresponds to the estimated vaccination completed schedule cost. Negative ICERs correspond to cost-saving scenarios.

Figure 4 Cost-effectiveness acceptability curves (CEAC). The impact of parametric uncertainty on willingness to pay is shown using CEACs for scenarios representing QALY gains excluding effects on unspecific AGE hospitalisations (stratified by inclusion of QALY gains for 0, 1 or 2 caregivers) vs that for coded-RV + unspecified AGE where caregiver effects are excluded. In each scenario, the proportion of simulations that are cost-effective is shown against increasing willingness-to-pay thresholds.

Figure 1

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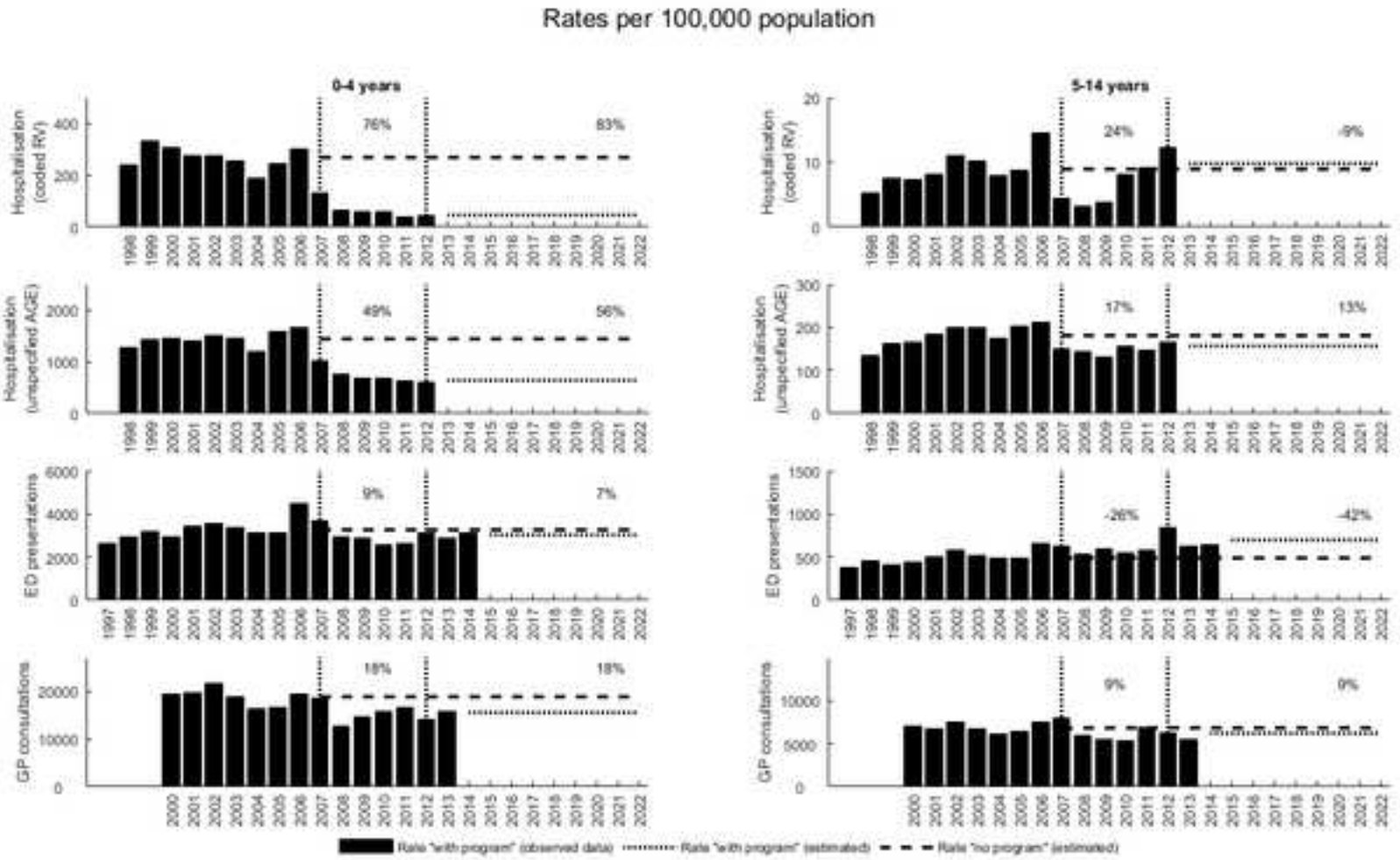

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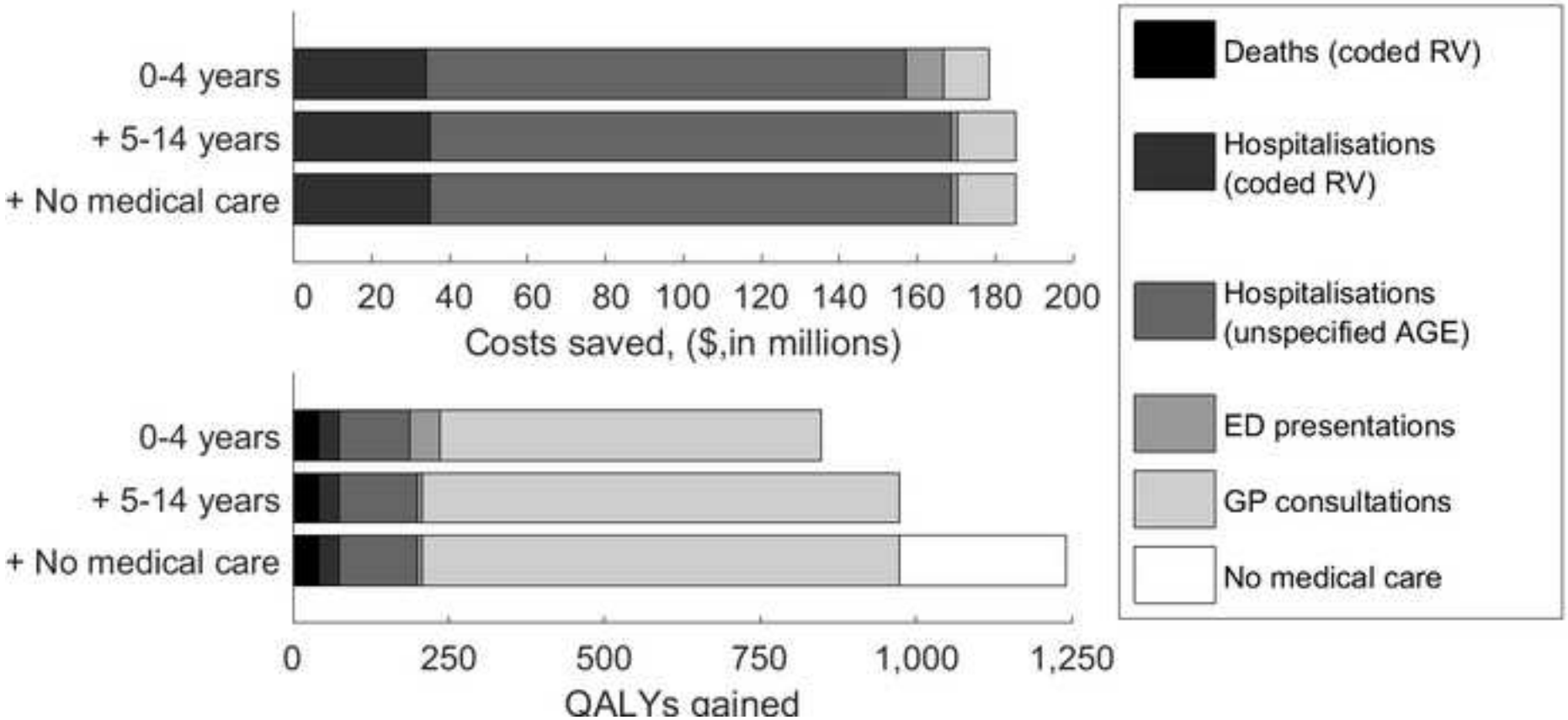

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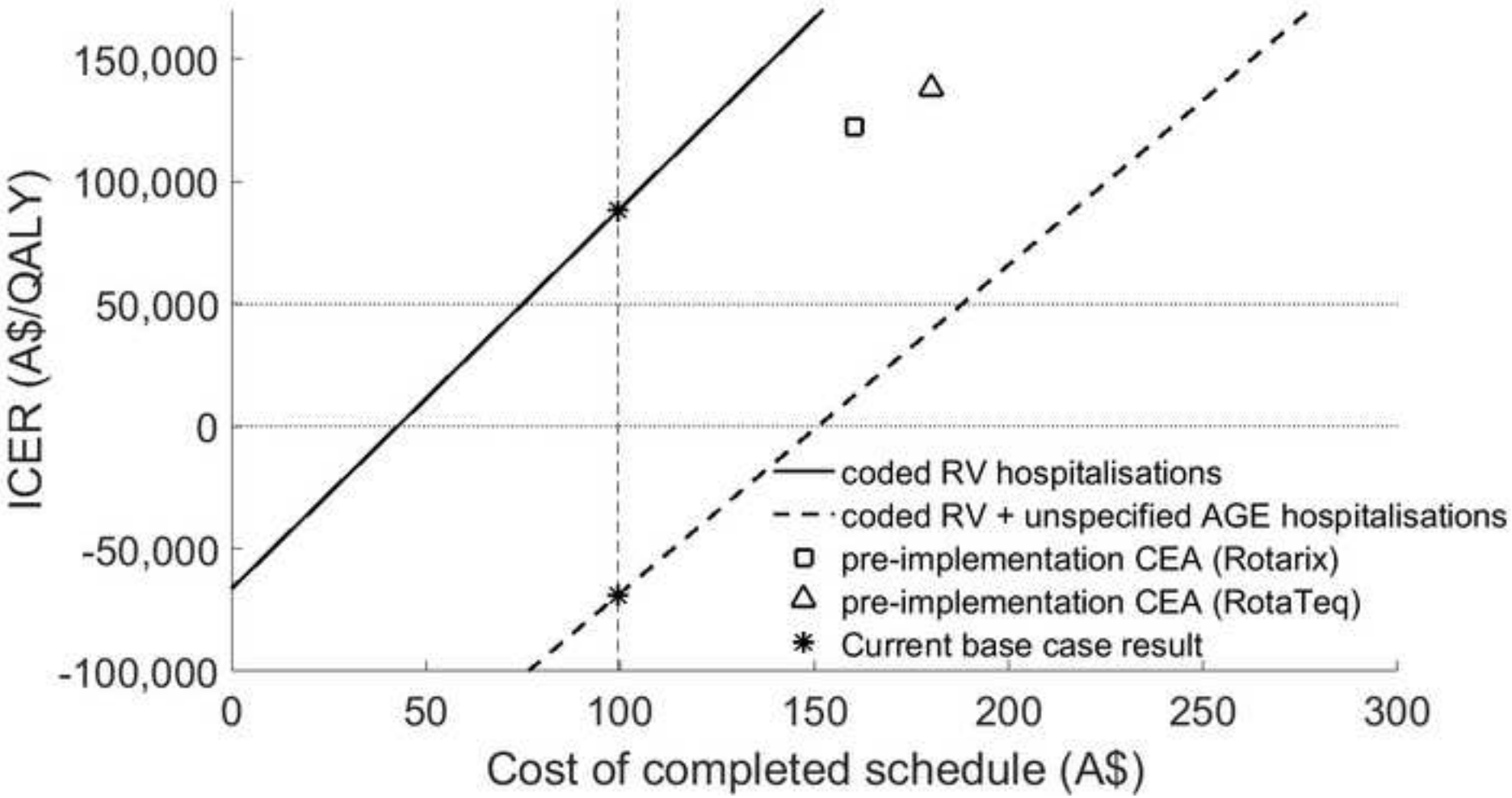

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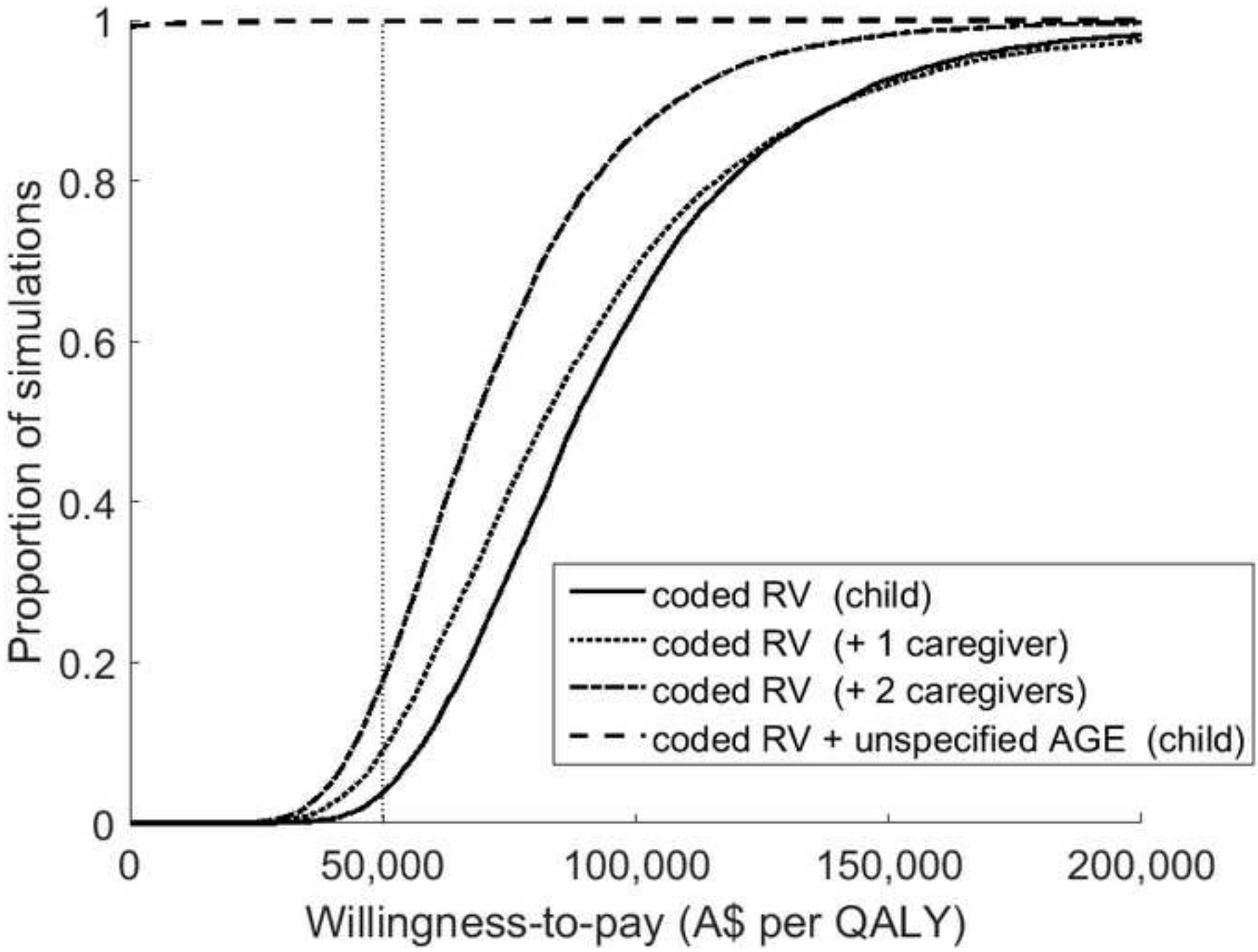

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