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Control of varicella in the post-vaccination era in Australia: a model-based assessment of catch-up and infant vaccination strategies for the future

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SUMMARY

In Australia, varicella vaccine was universally funded in late 2005 as a single dose at 18 months. A school-based catch-up programme for children aged 10–13 years without a history of infection or vaccination was funded until 2015, when those eligible for universal infant vaccination would have reached the age of high school entry. This study projects the impact of discontinuing catch-up vaccination on varicella and zoster incidence and morbidity using a transmission dynamic model, in comparison with alternative policy options, including two-dose strategies. At current vaccine coverage (83% at 2 years and 90% at 5 years), ceasing the adolescent catch-up programme in 2015 was projected to increase varicella-associated morbidity between 2035 and 2050 by 39%. Although two-dose infant programmes had the lowest estimated varicella morbidity, the incremental benefit from the second dose fell by 70% if first dose coverage increased from 83% to 95% by age 24 months. Overall zoster morbidity was predicted to rise after vaccination, but differences between strategies were small. Our results suggest that feasibility of one-dose coverage approaching 95% is an important consideration in estimating incremental benefit from a second dose of varicella vaccine.

Key words: Infectious disease epidemiology, modelling, vaccination (immunization), varicella zoster.

INTRODUCTION

Varicella vaccination programmes have been introduced in several developed nations, with subsequent marked declines in the incidence of chicken pox (primary varicella infection) [1–4]. In Australia, a single dose of varicella vaccine has been funded under the National Immunization Programme (NIP) since November 2005 for all children at age 18 months, with a catch-up dose funded until 2015 for children aged 10–13 years without a history of infection or vaccination [1]. The most recent analysis [1] using routinely collected data suggests declines of principal diagnosis varicella-zoster virus (VZV) hospitalization rates of 75% in children aged 18–59 months and 50% in all ages when comparing pre-vaccine and funded vaccination periods in Australia.

Despite these reported health benefits [1–4], many developed countries, particularly in Europe, have not introduced varicella vaccination due to three main concerns [5]: first, that vaccination would increase the average age of infection and therefore

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have the potential to increase morbidity due to rising severity with age; second, that effectiveness after a single dose is lower than desired [6–8]; and finally, and most significantly, modelling studies have predicted a rise in the incidence of zoster in the medium term following universal varicella vaccination, due to reduced exposure to varicella cases [9–11]. With respect to the latter, several modelling studies have suggested the projected rise in zoster would outweigh the benefits from reductions in primary varicella disease in the short to medium term [12, 13]. However, while an increase has been observed, a recent US study [14] provides evidence of a marked upward trend in zoster rates several years prior to vaccination.

A separate question is whether a two-dose primary schedule is required, with modelling studies predicting that a two-dose schedule would, in particular, reduce the rate of breakthrough infection [9, 10, 12, 15]. For example, Brisson *et al.* [9], predicted a two-dose infant schedule would further reduce varicella incidence by an average of 22% (sensitivity range 0–82%) over the first 80 years of the programme, mainly through the prevention of breakthrough cases. The rationale for the introduction of a two-dose schedule in the USA was the burden of breakthrough varicella and continued outbreaks in schools and child-care with a one-dose schedule [16]. Recent data from active surveillance sites in the USA suggest a strong impact on both incidence and outbreak risks in the first 5 years of the two-dose programme [17]. However, the impact of a two-dose programme on the incidence and morbidity from zoster is subject to the same concerns as one-dose programmes, with similar potential for incremental increases in short- to medium-term zoster-related morbidity [12, 13].

In Australia, the end of the supplementary adolescent catch-up programme is approaching. In addition, recent changes to the NIP whereby varicella vaccine will be combined with measles-mumps-rubella (MMR) vaccine from July 2013 are expected to lead to improved varicella vaccination coverage by age 2 years (coverage with MMR assessed at 24 months is ~94% in Australia). Therefore, it is an opportune time to consider policy options for varicella vaccination both in the Australian and broader international contexts. In this paper, we use predictive models to estimate the relative future impact of one-dose and two-dose schedules with and without a continued adolescent catch-up programme, with a focus on the effect of increased coverage with the first dose of vaccine.

METHODS

Model description

VZV dynamics were simulated in this study using an age-structured deterministic model governed by a set of ordinary differential equations. The model possesses 101 age cohorts (0, 1, 2, …, >100) and 17 distinct VZV epidemiological states (see Supplementary Fig. S1). The population distribution in the model was based on the characteristics of the 2010 Australian population using data from the Australian Bureau of Statistics (ABS). The model assumes that following primary or breakthrough infection, there is lifelong immunity to primary varicella disease and a risk of developing zoster disease. Lifelong immunity to zoster is assumed to occur following a zoster (reactivation) episode, and in addition, exposure to a varicella case boosts immunity to zoster. Vaccine efficacy (VE) is governed by several parameters (see Supplementary Table S2), including waning immunity (see Supplementary Fig. S2).

As this model is an extension of previously published work [9, 10] we focus here on key differences to these studies. In this study, we explicitly separated one-dose vaccinees from two-dose vaccinees, in terms of their modified susceptibilty to infection. In addition, the model now allows for development of zoster following breakthrough infection, with rates of reactivation assumed to be identical to those following natural infection. The probability of being boosted following exposure to VZV is now assumed to decrease with age and is based on the age-dependent vaccine efficacies estimated in the Shingles Prevention Study [18] (as also used in Brisson *et al.* [9]), although the duration of immunity following a successful boost was age-independent (24·4 years in base case). However, we also compare the effect of this with our previous assumptions in a sensitivity analysis (see Supplementary material section S7). Age-dependent transmission rates are assumed to be directly proportional to rates of social contact as measured in the UK as part of the POLYMOD project [19]. The model equations and structure are provided in Supplementary material section S1, while a complete list of model parameters is given in Supplementary Table S1. Numerical results, figures and model programmes were generated with Matlab R2010b (www.mathworks.com).

Data sources, calibration and validation

Vaccine coverage assumptions were informed by varicella immunization coverage data sourced from the

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Table 1. *Vaccination strategies and coverage*

Strategy	Programme	Year	Target age	Coverage		Reference
				Base case	Projected	
Strategy 1 (S1)	Infant dose	2005–2050	18 months	83%/90%*	95%	ACIR [20, 21]
	Catch-up	2005–2015	12 years	35%†	35%†	ATAGI [22]
Strategy 2 (S2)	Infant dose	2005–2050	18 months	83%/90%*	95%	ACIR [20, 21]
	Catch-up	2005–2050	12 years	35%/19%‡	35%/15%‡	ATAGI [22]
Strategy 3 (S3)	1st dose	2005–2050	18 months	83%/90%*	95%	ACIR [20, 21]
	2nd dose	2015–2050	12 years	70%	80%	DOHA
Strategy 4 (S4)	1st dose	2015–2050	12 months	90%	95%	ACIR [20, 21]
	2nd dose	2005–2050	18 months	83%/90%*	95%	ACIR [20, 21]

ACIR, Australian Childhood Immunisation Register; ATAGI, Australian Technical Advisory Group on Immunization; DOHA, Australian Government Department of Health and Ageing website (http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv).

* Coverage of the 18-month dose assessed at 2 years (applied from 18 months) and 5 years (data from ACIR 2005–2010).

† Coverage of age cohort. Susceptible coverage ~50% (see Supplementary material section S3 for details).

‡ Before 2015/after 2020, the value is linearly decreasing between 2015 and 2020.

Australian Childhood Immunization Register (ACIR) [20, 21] and school-based immunization programmes, with age-cohort coverage in the state of New South Wales publicly reported [22]. To estimate coverage for susceptible adolescents we used reported coverage for the age cohort and values for the specificity and sensitivity of parental report of their child's varicella infection [23, 24] and vaccination history [25] (see Supplementary material section S3 for more details of coverage calculations and wastage).

Age-specific pre-vaccination transmission rates were calibrated to force-of-infection estimates from the national serosurvey conducted in 1997–1999 [26], under the assumption of endemic equilibrium. Case-hospitalization rates were calibrated to national age-stratified hospitalization data for which varicella or zoster was the principal diagnosis, sourced from the Australian Institute for Health and Welfare (AIHW). Pre-vaccination hospitalization rates were calibrated to the average age-specific rates of hospitalization for varicella and zoster between July 1996 and June 1999. To validate the model we compared the predicted varicella morbidity (total annual age-specific in-patient days) with observed hospitalization data from 2000 to 2010.

Varicella vaccination strategies

Four strategies relevant to future policy considerations (Table 1) were considered and compared by predicting trends in varicella and zoster incidence and morbidity between 2015 and 2050. Strategy 1 is the current one-dose infant programme including planned discontinuation of adolescent catch-up in 2015. Strategy 2 is identical to strategy 1 but with adolescent catch-up continued through to 2050. Under strategies 3 and 4, the adolescent catch-up programme is replaced in 2015 with a universal second dose. In strategy 3, the first dose continues to be given at 18 months with a universal second dose at 12 years, while in strategy 4 the first dose is given earlier, at 12 months, and the second dose at 18 months.

The current uptake for the 18-month dose was estimated using ACIR coverage assessments at age 2 years (83%, applied from 18 months) and age 5 years (90%) [20, 21] (Table 1). There is potential for first dose coverage to increase to ~95%, as varicella vaccine will be combined with the second dose of MMR vaccine from July 2013. National MMR dose 1 coverage, given at age 12 months, reached 94% at age 24 months in 2009 [20]. Therefore, we examined 'projected' scenarios for each strategy, where coverage for doses at either 12 and 18 months (strategy 4) or 18 months only (strategies 1–3) increased to 95% after 2015. Base-case coverage (70%) of the second dose of varicella vaccine at 12 years (strategy 3) was informed by school-based human papilloma virus (HPV) vaccine coverage in girls aged 12–13 years in 2011 but was raised to 80% under the 'projected' scenario [22]. Base-case coverage (90%) for varicella vaccine at 12 months (strategy 4) was informed by the percentage of children fully immunized at age 12 months in 2009 [20].

Varicella and zoster morbidity

Total annual in-patient days, calculated as the product of the annual age-specific incidence, case-hospitalization

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Table 2. *Estimated annual varicella and zoster pre-vaccination incidence and percent hospitalized, and actual annual hospitalization rates and mean length of stay in hospital by age group for Australia*

	Age group (years)							
	0–4	5–14	15–24	25–34	35–49	50–79	⩾80	Total
Varicella								
Incidence (per million)*	105 045	37 660	3680	3185	1162	249	60	13 292
Hospitalization rate (per million)†	314	65	45	51	17	9	10	52
% Hospitalized‡	0·3	0·2	1·2	1·6	1·5	3·6	16·7	0·4
Mean length of stay in hospital (days)	2·5	3·2	3·3	3·7	4·2	7·2	9·3	3·4
Zoster								
Incidence (per million)*	216	1262	3004	3818	3956	4967	5360	3546
Hospitalization rate (per million)†	14	19	14	21	34	212	1 026	97
% Hospitalized‡	6·5	1·5	0·5	0·6	0·9	4·3	19·1	2·7
Mean length of stay in hospital (days)	3·9	3·5	4·2	4·1	5·1	6·9	10·3	7·5

* Incidence estimated from the model where vaccination coverage = 0%.
† Principal diagnosis of varicella (ICD-10-AM code B01) or zoster (ICD-10-AM code B02) for financial years 1996/1997 to 1998/1999. [Source: Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity database.]
‡ Percent hospitalized = (hospitalization rate/incidence) × 100.

proportion and length of stay in hospital [30], were used to measure varicella and zoster morbidity. Hospitalization from breakthrough infections was assumed to occur one tenth as frequently as from natural infection [27], but with no change in the length of hospital stay. Modelled estimates of varicella and zoster pre-vaccination incidence, and actual hospitalization rates and mean length of stay in hospital by age group for Australia are listed in Table 2.

Sensitivity analysis

One-way sensitivity analyses were conducted for 15 key model parameters including vaccine coverage and efficacy (see Supplementary material, Table S2, section S1). To assess the impact of changes to these parameters, mean annual morbidity from hospitalized varicella (in-patient days) during 2035–2050 was calculated for the base-case parameter value as well as expected minimum and maximum estimates under the four vaccination strategies. To assess the potential impact of multivariate uncertainty, we took best- or worst-case values for the five VE parameters simultaneously and examined the effect on differences in morbidity induced by changing strategy.

RESULTS

Model validation

There was a good agreement between model-generated estimates of varicella hospitalized cases and observed data from 2000 to 2010 in Australia, with the lowest level of hospitalization in the 12–19 years age group (Fig. 1*a*). The estimated pre-vaccination immunity (solid curve) is also a reasonable fit to the 1997–1999 Australian national serosurvey data (Fig. 1*b*). The force of infection (Fig. 1*b*) was estimated to be highest in the 5–9 years age group, and the basic reproductive number (R_0) was estimated to be 4·2 for varicella in Australia.

Varicella incidence

Regardless of the 18-month coverage, the two-dose infant vaccination programme (strategy 4) produced the lowest incidence while current practice (strategy 1) produced the highest incidence (Fig. 2*a–c*). However, both relative and absolute differences in incidence between strategies are reduced as dose 1 coverage increased, with the absolute difference in varicella incidence between strategies 1 and 4 being 66% lower in 2050 at projected (95%) coverage compared to the base-case scenario (83%) (Fig. 2*c*).

Zoster incidence

All strategies, regardless of coverage, predict an initial rise in zoster incidence before declining to levels lower than in 2015 by 2050 (Fig. 2*d–f*). However, differences between strategies and as a result of increased coverage are small compared to the changes in varicella incidence.

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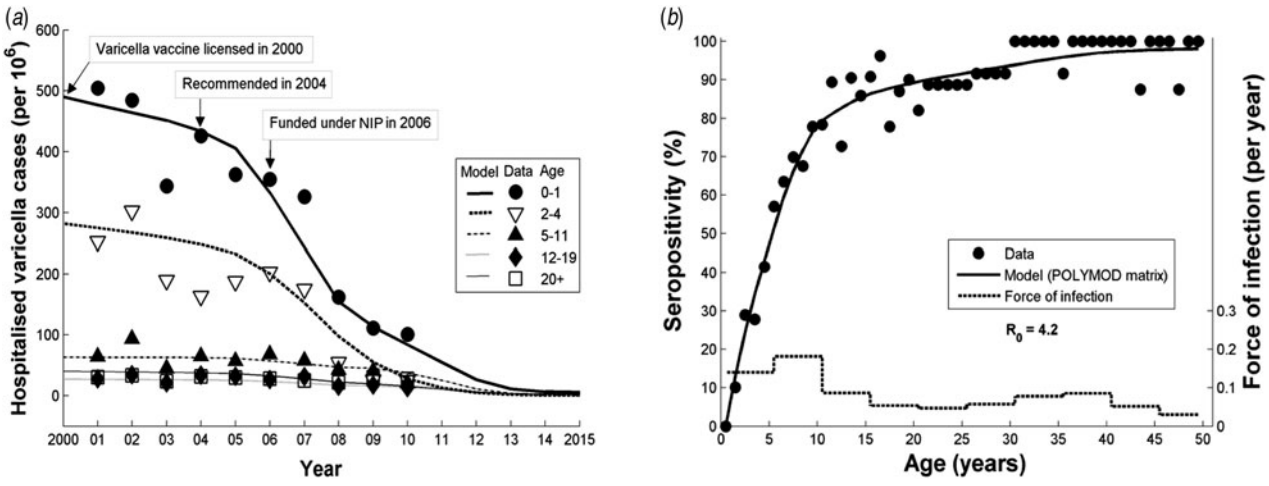

Fig. 1. (*a*) Model predicted age-specific varicella hospitalized cases *vs.* observed varicella hospitalized cases based on age-specific hospitalization data from 2000 to 2010 in Australia. (*b*) Model generated seropositivity (solid curve) *vs.* observed seropositivity (black dots) from the Australian national serosurvey (1997–1999), and estimated force of infection by age group.

Natural and breakthrough varicella infections

Figure 3 shows the age distribution of predicted natural and breakthrough varicella cases in 2015, 2025 and 2050. Compared to strategy 1, voluntary adolescent catch-up (strategy 2) achieves a greater impact on primary than on breakthrough infection, while the two-dose strategies achieve large reductions for both infection types. All strategies are projected to lead to an increasing proportion of cases in older age groups, with this being more pronounced for natural than breakthrough infections.

Under both coverage scenarios two-dose strategies would keep cases of primary varicella infection below the 2015 levels over the follow-up period, while containing the rise in breakthrough infection. The addition of a universal adolescent dose (strategy 3) is most protective against rises in adult cases. Under the projected scenario, both single-dose strategies are sufficient to keep primary infections in 2050 below those in 2015 but see a rise in breakthrough disease over the same period.

The differential impact on natural and breakthrough infections results from vaccine coverage being high in younger cohorts and absent in older cohorts at the beginning of simulated period. Strategy 1 is predicted to result in higher infection rates than alternative strategies for both natural and breakthrough varicella infections in 2025 and 2050 but under the projected coverage scenarios differences between strategies in these outcomes are much reduced. Two-dose strategies produce the lowest rates of breakthrough varicella infections, with the benefits increasing with time (Fig. 3).

Varicella and zoster morbidity

Impacts on varicella and zoster morbidity were assessed for the periods 2015–2024, 2025–2034 and 2035–2050 using differences in the mean annual varicella and zoster morbidity (in-patient days) introduced by switching from strategy 1 to the other strategies (Fig. 4*a–d*) in 2015. For these periods, strategy 1 (base-case coverage) produces the highest varicella morbidity (11, 22 and 67 in-patient days per million population per year, respectively) and the lowest zoster morbidity (617, 691 and 697 in-patient days per million population per year, respectively). For projected coverage (95%), the varicella morbidity under strategy 1 reduces to 10, 16 and 31 in-patient days per million population per year in 2015–2024, 2025–2034 and 2035–2050, a reduction of 9%, 27% and 54%, respectively. In contrast, zoster morbidity under strategy 1 is almost unchanged at 617, 692 and 701 in-patient days per million per year respectively. For comparison, the pre-vaccination morbidity from varicella and zoster was estimated to be 184 and 525 in-patient days per million per year, respectively.

Compared to the current programme (strategy 1), continuing the adolescent catch-up programme after 2015 (strategy 2) would prevent 26 (39%) varicella in-patient days per million population per year in 2035–2050, with two-dose strategies providing greater impacts, including prevention of 49 in-patient days per

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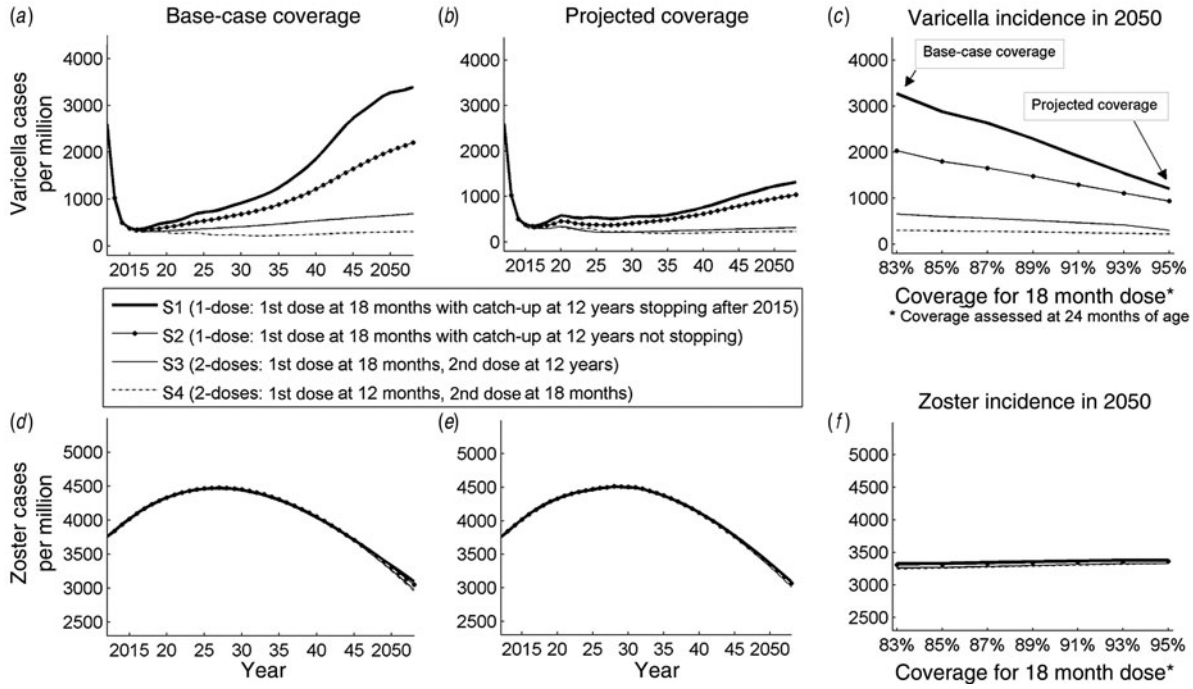

Fig. 2. (*a, b*) Varicella incidence (natural plus breakthrough) and (*d, e*) zoster incidence for four strategies after 2015 under base-case coverage and projected coverage scenarios. Estimated varicella (*c*) and zoster (*f*) incidence in 2050 by coverage for 18-month dose from base-case coverage (83%) to projected coverage (95%). Coverage for dose 1 at 12 months in strategy 4 also increases from 90% to 95% over the same time-frame.

million population per year in 2035–2050 (a 74% reduction) under strategy 4. However, under the 'projected' coverage scenario these benefits are much reduced, with corresponding reductions of just 7 and 15 in-patient days per million per year for varicella morbidity in 2035–2050 for strategies 2 and 4, respectively. In relative terms these figures represent reductions of 23% and 48% for strategies 2 and 4, respectively, but in absolute terms they represent only 26% and 30% of the benefits of switching strategies at base-case coverage values. While zoster contributes most to overall morbidity, differences in zoster morbidity induced by changes in strategy or coverage were small in comparison to changes in varicella morbidity.

Sensitivity analysis

Varicella mean annual morbidity during 2035–2050 is most sensitive to coverage for the 18-month dose (C_1) for all strategies (Fig. 4*e*). In terms of the second-dose parameters, the largest impact comes through varying the rate at which immunity wanes (w_2), although strategy 4 is relatively insensitive to all parameters. When considering the multivariate impact of the first dose vaccine efficacy parameters, our worst/best case scenarios for one dose efficacy indicated that morbidity benefits from two-dose strategies would be 100–200% greater/smaller than in base case (see Supplementary material Figs S7 and S8, section S6).

DISCUSSION

Our study of potential strategies for varicella control in Australia suggests that considerable reductions in severe varicella morbidity are obtainable using one-dose vaccine strategies with high vaccination coverage. The two-dose programme in the USA has demonstrated additional advantages in preventing breakthrough disease and reducing outbreaks in schools and day-care centres [28] but this may not be a high priority in all settings. Based on current one-dose vaccine coverage in Australia, the addition of a second dose in infancy is projected to reduce morbidity by about 74% in the period 2035–2050. However, if 95% coverage with the first dose was achieved, both absolute and relative reductions in severe morbidity from adding a second dose would decline considerably, making two-dose strategies less efficient and likely to be less cost-effective. For

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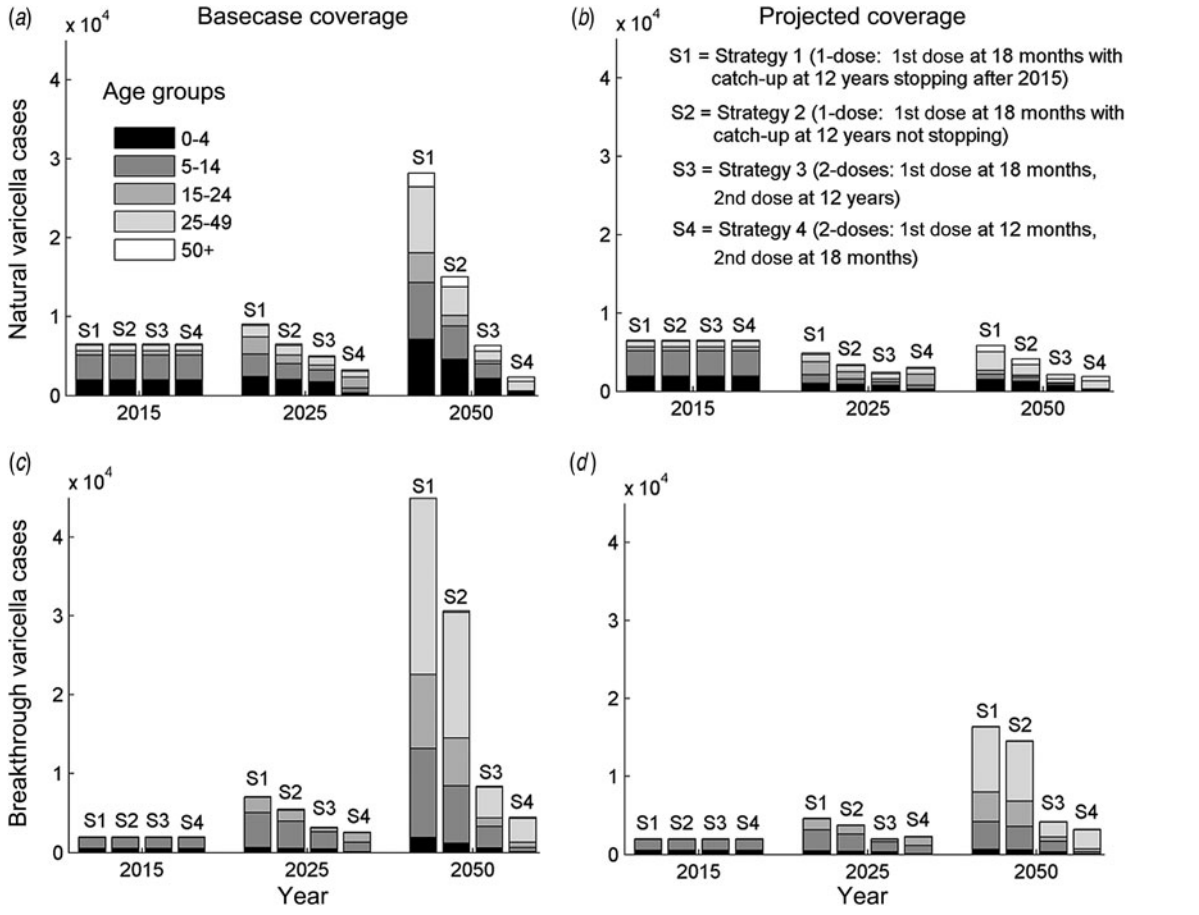

Fig. 3. Model predicted numbers of natural varicella infections (*a, b*) and breakthrough infections (*c, d*) in 2015, 2025 and 2050 in Australia under base-case coverage and projected coverage scenarios. Note that simulated population size and distribution remain constant in time, so case numbers at different time points are directly comparable.

one-dose coverage between these extremes, we found an almost linear decline in varicella incidence, suggesting that incremental improvements in first dose coverage are also valuable. We note, however, that if one-dose efficacy is similar to our 'worst-case' scenario, adding a second dose would prevent 100–200% more varicella in-patient days than under base-case assumptions. A recent blinded RCT comparing two-dose measles-mumps-rubella-varicella (MMRV) with a single varicella dose and MMR vaccine alone in Europe [29], found substantially higher efficacy for the two-dose programme (95% *vs.* 65%) against any varicella but a smaller absolute difference in effect against moderate to severe varicella (99·5% *vs.* 91%). These latter efficacies are of more relevance to the analysis in this study, given the focus on hospitalized cases.

Part of the impetus for this study was to assess the benefits from the voluntary catch-up programme operating in Australian high schools which is planned to cease in 2015. Under current coverage conditions, continuation of this programme beyond 2015 is predicted to become more valuable with time as it progressively reduces the pool of naive teenagers and adults. In the base-case analysis, continuation is predicted to lead to a decrease in morbidity compared to current policy of 39% of expected varicella in-patient days over the period 2035–2050. The absence of prior immune status for catch-up vaccine recipients hinders more precise estimates of programme impact. However, if infant coverage were to improve from the current level of 83% to 95% starting in 2015, varicella morbidity under current policy is predicted to fall by 54% in comparison to the base-case predictions in 2035–2050. Vaccine wastage would also increase from 80% in base case to around 90% (Supplementary Fig. S4), although wastage could be prevented if schools were able to access immunization register records prior to offering vaccination. Reduced morbidity benefits from alternative strategies would

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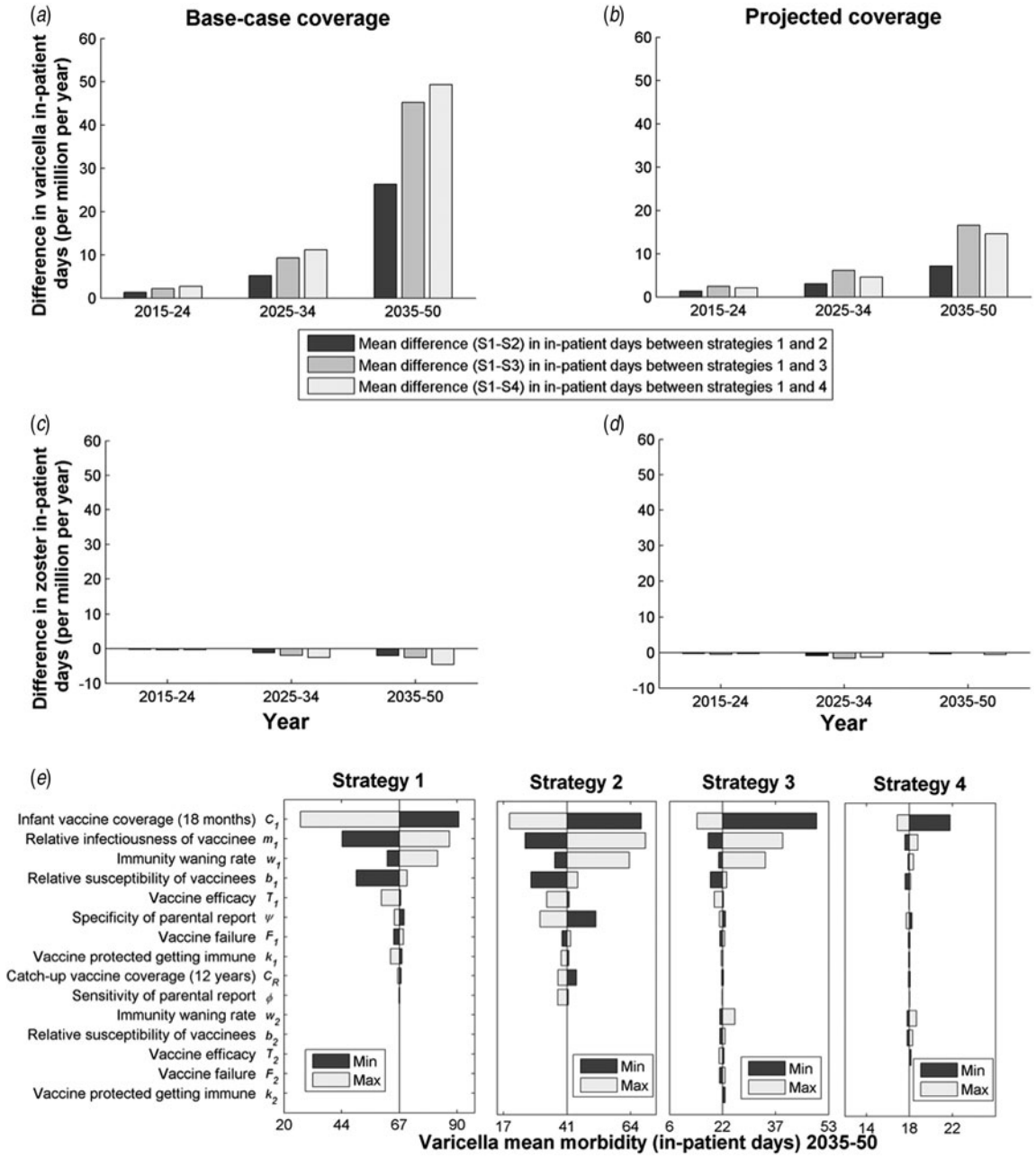

Fig. 4. (*a, b*) Mean annual difference in varicella morbidity (in-patient days) and (*c, d*) zoster morbidity between strategy 1 (S1) and alternative strategies (S2, S3, S4) in the periods: 2015–2024, 2025–2034 and 2035–2050 under base-case coverage (infant dose coverage 83%) and projected coverage (infant dose coverage 95%) scenarios. (*e*) Sensitivity analysis for 15 key parameters in terms of mean annual varicella morbidity (in-patient days) during 2035–2050.

also occur, with relative reductions in morbidity of 23% and 48% for strategies 2 and 4 which equate to only 26% and 30% of the absolute morbidity reductions from switching to these strategies at base-case (83%) coverage levels. While the feasibility of achieving 95% coverage is not certain, programme changes in the Australian context increase its plausibility. From July 2013, the second dose of MMR vaccine has been given as a combined MMRV vaccine and incentives paid to parents with 'fully vaccinated' children will be contingent on receipt of varicella vaccination. It seems reasonable to expect that these changes to lead to coverage of more than 90%, given that other infant programmes required for the incentive payments typically reach 92–95% coverage by age 2 years [20, 21].

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In contrast to our findings for varicella, we found that the impact on severe zoster morbidity was relatively insensitive to the alternative strategies proposed here. This appears to be primarily because the predicted rise in zoster depends on the relative decrease in boosting associated with introduction of vaccination. The majority of this reduction in boosting will be induced by the first 10 years of the current programme, so that alternative strategies are introduced once incidence of boosting has already greatly decreased, leading to minimal further changes in zoster incidence and morbidity.

Our predictions are sensitive to several key assumptions regarding varicella epidemiology and vaccination programmes. We assumed that receipt of the second dose was independent of the first which may lead to over-estimates of coverage with $\geqslant 1$ dose of vaccine and hence impacts of two-dose programmes. Other important assumptions include setting the severity of breakthrough cases to be lower than wild-type infections (contributing one tenth as much in morbidity calculations), based loosely on post-implementation data collected in the USA [27]. Other modelling analyses have also assumed low morbidity due to breakthrough infections [15] but data to establish the severity of breakthrough disease and whether the subsequent risk of zoster is identical to that following wild-type infection remain limited and will need to be revisited as vaccine programmes mature. Most modelling studies, including ours, assume lifelong immunity against varicella re-infection following natural infection [9, 12, 15] but the validity of this in the absence of frequent exposure remains to be evaluated. The absence of lifelong immunity would influence estimates of the reproductive number and also the projected impacts of vaccination.

Our simulations apply the Hope-Simpson hypothesis [31] regarding protection against zoster from varicella exposure, which is supported by data from several other observational studies [32–34]. The Shingles Prevention Study [18] offers definitive evidence that boosting with a high-dose vaccine reduces the risk of zoster, but the effect of reduced exposure to varicella on zoster incidence at the population level is still uncertain, with both the incidence and duration of boosting unclear. A recent review of observational studies of boosting [35] suggests that immunological correlates of boosting show little evidence of an effect beyond 2 years post-exposure, indicating that endogenous boosting may be more important in sustained zoster protection than assumed in models. Validation of zoster trends also remains difficult due to limitations in the design and duration of current surveillance programmes. A recent retrospective study of Medicare claims conducted by Hales *et al*. [14] suggests a continuous rise in age-standardized zoster incidence in the over-65 s in the USA from the early 1990s, predating VZV immunization. Despite these uncertainties, we note that the zoster predictions in this study were insensitive to coverage and strategy changes. Minor limitations include the reliance on estimates from studies in other settings [23–25] regarding parental recall of their child's varicella infection and vaccination history and limited data [9, 36] underpinning estimates of vaccine efficacy parameters, particularly for the second dose.

In conclusion, our study suggests that an increase in one-dose vaccine coverage, particularly in infancy, would substantially reduce future incidence, particularly of severe disease, potentially avoiding the need for additional doses in the childhood schedule. Even moderate increases in one-dose coverage to levels consistent with other vaccines included in the Australian NIP are predicted to be highly beneficial.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268814002222.

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DECLARATION OF INTEREST

None.

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