Predicting and comparing long-term measles antibody profiles of different immunization policies

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Objective Measles outbreaks are infrequent and localized in areas with high coverage of measles vaccine. The need is to assess long-term effectiveness of coverage. Since 1991, no measles epidemic affecting the whole island has occurred in Taiwan, China. Epidemiological models are developed to predict the long-term measles antibody profiles and compare the merits of different immunization policies on the island.

Methods The current measles immunization policy in Taiwan, China, is 1 dose of measles vaccine at 9 months of age and 1 dose of measles, mumps and rubella (MMR) vaccine at 15 months of age, plus a 'mop-up' of MMR-unvaccinated schoolchildren at 6 years of age. Refinements involve a change to a two-dose strategy. Five scenarios based on different vaccination strategies are compared. The models are analysed using Microsoft Excel.

Findings First, making the assumption that measles vaccine-induced immunity will not wane, the predicted measles IgG seroprevalences in preschool children range from 81% (lower bound) to 94% (upper bound) and in schoolchildren reach 97–98% in all strategy scenarios. Results are dependent on the association of vaccine coverage between the first and second dose of vaccine. Second, if it is assumed that vaccine-induced antibody titres decay, the long-term measles seroprevalence will depend on the initial titres post vaccination, decay rates of antibody titres and cut-off of seropositivity.

Conclusion If MMR coverage at 12 months of age can reach >90%, it would be worth changing the current policy to 2 doses at 12 months and 6 years of age to induce higher antibody titres. These epidemiological models could be applied wherever a similar stage of measles elimination has been reached.

Keywords Measles/immunology; IgG/immunology; Measles vaccine/administration and dosage/immunology; Forecasting/methods; Child; Child, Preschool; Immunization programs; Health policy; Seroepidemiologic studies; Models, Theoretical; Taiwan, China (*source: MeSH*).

Mots clés Rougeole/immunologie;IgG/immunologie Vaccin antimorbilleux/administration et posologie/immunologie; Prévision/méthodes; Enfant; Enfant âge pré-scolaire; Programmes de vaccination; Politique sanitaire; Etude séro-épidémiologique; Modèle théorique; Taïwan, Chine (*source: INSERM*).

Palabras clave Sarampión/inmunología; IgG/inmunología; Vacuna antisarampión/administración y dosificación/inmunología; Predicción/métodos; Niño; Infante; Programas de inmunización; Política de salud; Estudios seroepidemiológicos; Modelos teóricos; Taiwán, China (*source: BIREME*).

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Voir page 622 le résumé en français. En la página 622 figura un resumen en español.

Introduction

Before the introduction of the mass immunization programme in 1978, measles was endemic with a 2-year epidemic cycle in Taiwan, China (*1*). The most recent outbreak affecting the whole island occurred in 1988–89 (*1–2*). After that outbreak, a goal for measles elimination by 2000 was established in 1991. Towards achieving this, an MMR (measles, mumps and rubella combined vaccine) campaign targeting primary and secondary schoolchildren (6–15 years old) was conducted in 1991–94 and reached 90% of the target population (*3*). Meanwhile, a 2-dose policy with 1 dose of measles vaccine at 9 months of age and 1 dose of MMR at 15 months of age has been implemented since 1991. Based on the vaccine coverage survey conducted among children aged 13–24 months in 1993–94, the mean coverage was 84% (range: 77–96%) for one dose of measles vaccine and 69% (range: 60–83%) for one dose of MMR vaccine (*3*). Recent health statistics showed that the MMR coverage in 2-year-old children in 1995 was about 80–85% (*4*). In addition, immunization requirements have been implemented by screening vaccination records and immunizing unvaccinated individuals among newcomers (6 years of age) to primary school since 1991 ('mop-up'). This policy has

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been extended to kindergarten since 1994. Under the strategy of 'mop-up', the overall vaccine coverage with at least 1 dose of MMR vaccine in primary schoolchildren was 96% in 1995 (*4*).

In addition to improving measles vaccine coverage, since 1992 measles surveillance has also been strengthened by incorporating active case investigation and laboratory diagnosis. Except for a small-scale outbreak with 33 confirmed cases in the northern part of the island in 1994, only sporadic confirmed cases were identified in 1992 (7 cases) and 1993 (2 cases). No confirmed cases were detected in 1995 and 1996. However, 7 confirmed cases, including 2 imported cases, were identified in 1997, and a small-scale outbreak with 9 confirmed cases occurred in the southern part of the island in 1998 (*3–6*). Seroepidemiological studies conducted in Taiwan, China, in 1993–97 showed that measles IgG seroprevalences were 85–92% in preschool and kindergarten children (2–5 years old) and reached 92–98% in schoolchildren (6–15 years old) and young adults over 16 years old (*6–9*).

In this study we investigate the probable long-term measles antibody profiles and evaluate the need for policy refinement with or without the assumption of waning vaccine-induced immunity. Using vaccine coverage rates, empirical seroconversion rates and assumed antibody titre decay rates, epidemiological models are developed by which to compare the merits of different vaccination strategies on the island. This will assist in formulating measles elimination strategies there and in other parts of the world where a similar stage in measles elimination has been reached.

Materials and methods

Predicting measles IgG seroprevalence

It is assumed that the measles IgG seroprevalence in preschool children will be only from vaccination. Initially, it is also assumed that measles vaccine-induced immunity will not wane once seroconversion after vaccination occurs. The current measles vaccination policy is one dose of measles vaccine at 9 months of age and one dose of MMR vaccine at 15 months of age, with an additional an 'mop-up' strategy. Kindergarten education is voluntary on the island and the proportion of children attending is not known. Primary education starting from 6 years of age is mandatory and the proportion in attendance is over 99%. Therefore, the possible effect of MMR 'mop-up' among newcomers to primary school but not newcomers to kindergarten will be considered. Health statistics on vaccine coverage are classified broadly as coverage for 1 dose of measles vaccine and coverage for 1 dose of MMR. Inclusive data are not available on the proportion receiving 1 dose of measles vaccine and no MMR, or 1 dose of MMR and no measles vaccine, or the proportion receiving 2 doses of vaccination (measles and MMR). Therefore, 3 scenarios based on current policy are proposed to estimate the possible coverage resulting from 4 different combinations of measles and MMR vaccination in individuals (no vaccination, 1 dose of measles, 1 dose of MMR, and 2 doses) (Table 1). In addition, 1 scenario with 2 doses of MMR at 1 and 6 years of age and 1 scenario with 2 doses of MMR at 15 months and 6 years of age are proposed to compare with current policy (Table 1). Based on empirical data in 3 communities in 1997, children receiving the measles vaccine are more likely to have MMR vaccination than children without measles vaccination (*9*). Therefore, the true level of vaccine coverage should be between scenario 1 (upper bound) and 2 (lower bound) and the vaccine coverage of the first dose in scenario 4 and 5 are assumed to be the mean of cumulative coverage in scenario 1 and 2 (Table 2).

Based on the assumptions in 5 scenarios, the vaccine coverage of 4 different combinations can be calculated and the measles seroprevalence in preschool and primary school children can be also determined after incorporating the seroconversion rates of measles vaccination at different ages (Table 2). Based on the vaccine coverage survey made in 1993–94, the measles vaccine coverage at 9 months of age and MMR vaccine coverage at 15 months of age were 84% and 69%, respectively (*3*). Based on the experience of the MMR campaign in schoolchildren in 1991–94, the MMR coverage for 6-year-old schoolchildren in the 'mop-up' or universal vaccination is set to 90% and assumed to be independent of the previous vaccination (*3*). Based on an empirical study done in 1987 on the island, and studies done in other parts of the world, the seroconversion rates of measles or MMR vaccination at 9, 12, 15 and 72 months of age are set to 85%, 90%, 95% and 97%, respectively (Table 2) (*10–11*).

Predicting the long-term antibody profiles

Although measles vaccine-induced immunity is believed to be durable, there is evidence to show that vaccine-induced antibody titres decrease with time post vaccination, and secondary vaccine failure is possible (*12–13*). Here it is assumed that no wild measles virus is circulating to boost antibody titres in vaccinees and individuals with primary vaccination failure are excluded. Measles vaccine-induced antibody titres are assumed to follow a normal distribution after natural log transformation, and experience a constant exponential decay with time post vaccination. Mathematically these assumptions can be expressed as equation 1 (*14*):

$$A_t = A_i \exp^{-\delta(t-i)},\ t>i, \qquad \text{eq. (1)}$$

where A_i is the geometric mean titre (GMT) at time i post vaccination, A_t is the GMT at time t post vaccination, and δ is the decay rate of antibody titres. Under the assumption of normal distribution, 4 parameters — the initial GMT post vaccination, the standard deviation (SD, denoted as s) of the distribution of antibody titres, the decay rates of antibody titres, and the cut-off of seropositivity

(denoted as A_t) — are crucial for estimating the seroprevalence in different time points post vaccination, which can be expressed as equation 2:

$$P(t) = \int_0^{\ln A_t} (1/\sqrt{\pi}s) \exp [-(x - \ln A_t)^2/2s^2] \, dx, \quad \text{eq. (2)}$$

where $P(t)$ is the proportion seronegative at time t post vaccination and is calculated using the Microsoft Excel built-in normal distribution function.

Longitudinal studies show that measles antibody levels reach the peak at 1–2 months post vaccination then decrease 4–8fold within 1 year post vaccination and continue to decline with a half-life of about 2–4 years during 1–10 years post vaccination (*12, 13, 15*). Therefore, it is assumed that the antibody titres decline with a constant decay rate at 1–10 years post vaccination. Three decay rates, corresponding to a half-life of antibody titres of 2 (decay rate = 0.347 per year), 3 (decay rate = 0.231 per year) and 4 years (decay rate = 0.173 per year), are used to compare their effects on measles antibody profiles at 1–10 years post vaccination.

The initial titres post vaccination vary with the vaccine potency, doses and age of vaccination, time post vaccination of blood collection and serological tests (Table 3). This study tries to compare the policies of giving vaccines at 9, 12 and 15 months of age. Therefore, only the studies which give the vaccine at 9–24 months of age and present standardized antibody titres (mIU/ml) were included in the comparison (*15–22*, see Table 3). No empirical information about antibody titres post vaccination on the island is available, and the measles or MMR vaccines used are apparently imported from different manufacturers in different years. Therefore, it is reasonable to assume the initial antibody titres at 1 year post vaccination to be between 500 and 1000 mIU/ml (Table 3). None of the studies in Table 3 showed the standard deviation (SD) of antibody titres in the original papers so the SD are calculated when the GMT and their 95% confidence intervals are available. The SD of measles antibody titres varies from 0.07 to 1.0 in different studies (Table 3). Therefore, 3 reasonable SDs, 0.3, 0.4 and 0.5 are used to compare their effects on antibody titres distribution (Table 3) (*14*). To calculate the proportion seronegative under different decay rates, 3 cut-offs of seropositivity, 50, 100 and 250 mIU/ml are compared. The 50 mIU/ml is to be the detection limit of neutralization tests (*24*) and the 100 mIU/ml is to be the detection limit of enzyme immunoassay (EIA) (*25*). The 250 mIU/ml may be related to the protection against typical symptomatic infection (*23, 26*). The putative mean protective duration (T_p) of vaccine-induced antibody is defined as the duration when the initial GMT (1 year post vaccination) decline to the level of protective titres and is calculated as equation 3:

$$T_p = [-Ln(A_p/A_1)/\delta] + 1, \quad \text{eq. (3)}$$

where A_1 is the GMT at 1 year post vaccination, A_p is the putative protective titre, and δ is the decay rate of antibody titres.

Table 1. **Description of vaccination strategies and assumptions investigated**

Scenario	Doses (age)[a]	Description
1	2 (9 and 15 m)	One dose of measles vaccine at 9 months and one dose of MMR at 15 months. Whether or not children receive the first dose does not affect the possibility of the second dose. Checking vaccine record at 6 years of age and immunizing the children without MMR vaccination ('mop-up').
2	2 (9 and 15 m)	As for scenario 1 except the assumption that children receiving the 1st dose are more likely to get the 2nd dose vaccination.
3	2 (9 and 15 m)	As for scenario 1 except the assumption that children not receiving the 1st dose are more likely to get the 2nd dose vaccination.
4	2 (12 m and 6 y)	Two doses of MMR vaccine at 1 and 6 years of age. The vaccine coverage (VC) of the first dose is equal to the mean cumulative VC of scenarios 1 and 2.
5	2 (15 m and 6 y)	Two doses of MMR vaccine at 15 months and 6 years of age. The VC of the first dose is equal to the mean cumulative VC of scenarios 1 and 2.

[a] m = months, y = years.

Results

Seroprevalence without antibody waning

Based on the data from the vaccine coverage survey of 1993–94 and the assumption without measles infection and antibody waning, the measles IgG seroprevalence in preschool children (2–5 years old) in the 5 scenarios are estimated to vary from 81% in scenario 2 and 4 to 94% in scenario 3 (Table 2). The predicted measles IgG seroprevalence in schoolchildren in the 5 scenarios are very similar and range from 97% to 98% (Table 2). To assess the impact of MMR coverage on measles IgG seroprevalence in preschool children, the measles vaccine coverage at 9 months of age is set to 84%. Under this condition, scenario 3 always has the highest seroprevalence but the difference in seroprevalence between scenarios 3 and 1 decreases with an increase of MMR coverage (Fig. 1). However, scenario 3 is unrealistic for the situation in Taiwan, China. Scenario 1 has higher seroprevalence than scenario 2. The difference in seroprevalence between scenario 1 and 2 increases with the increase of MMR coverage when MMR coverage is less then measles coverage (84%) but the difference decreases with the increases of MMR coverage when MMR coverage is greater than measles coverage (Fig. 1). The differences in seroprevalence between scenarios 1 and 4 or scenarios 1 and 5 both increase with the increase of MMR coverage when MMR coverage is less than measles coverage but both decrease with the increase of MMR coverage when MMR coverage is greater than measles coverage (Fig. 1). The differences in seroprevalence are 11% between scenario 1 and 4 and 6% between scenario 1 and 5 when MMR coverage is 90% (Fig. 1).

Table 2. **Parameters for predicting the measles IgG seroprevalence in preschool (2–5 years old) and school children (⩾ 6 years old)**

Scenario	Vaccine coverage[a]	SR[b]	Doses category[c]	Cumulative Coverage at 15m proportion in category	Seroprevalence at age 2–5 years ($P_{2\text{-}5}$)	Seroprevalence at age 6 years after mop-up or revaccination
1	V_9=0.84 V_{15}=0.69 V_{72}=0.90	S_9=0.85 S_{15}=0.95 S_{72}=0.98	0 1m 1mmr 2	$(1\text{-}V_9)(1\text{-}V_{15})$=0.05 $(1\text{-}V_{15})V_9$=0.26 $(1\text{-}V_9)V_{15}$=0.11 (V_9V_{15})=0.58	$\{0.26(S_9)+0.11$ $(S_{15})+0.58[(1\text{-}S_9)$ $(1\text{-}S_{15})]\}$ =0.90	$[P_{2\text{-}5}+(1\text{-}V_9)(1\text{-}V_{15})$ $V_{72}S_{72}+(1\text{-}V_{15})$ $V_9(1\text{-}S_9)\ V_{72}S_{72}]$ =0.98
2[d]	V_9=0.84 V_{15}=0.69 V_{72}=0.90	S_9=0.85 S_{15}=0.95 S_{72}=0.98	0 1m 1mmr 2	$(1\text{-}V_9)$=0.16 $(V_9\text{-}V_{15})$=0.15 0 when $V_9 \geqslant V_{15}$ V_{15}=0.69	$\{0.15(S_9)+0(S_{15})$ $+0.69[(1\text{-}S_9)$ $(1\text{-}S_{15})]\}$=0.81	$[P_{2\text{-}5}+(1\text{-}V_9)V_{72}S_{72}$ $+(V_9\text{-}V_{15})(1\text{-}S_9)$ $V_{72}S_{72}]$=0.97
3[e]	V_9=0.84 V_{15}=0.69 V_{72}=0.90	S_9=0.85 S_{15}=0.95 S_{72}=0.98	0 1m 1mmr 2	0 when $V_9+V_{15} \geqslant 1$ $1\text{-}V_{15}$=0.31 $1\text{-}V_9$=0.16 $V_9+V_{15}\text{-}1$=0.53	$\{0.31(S_9)+0.16$ $(S_{15})+0.53[1\text{-}(1\text{-}S_9)$ $(1\text{-}S_{15})]\}$=0.94	$[P_{2\text{-}5}+(1\text{-}V_{15})(1\text{-}S_9)$ $V_{72}S_{72}]$=0.98
4	V_{12}=0.90 V_{72}=0.90	S_{12}=0.90 S_{72}=0.98	0 1	0.10=(0.05+0.16)/2 0.90=(0.95+0.84)/2	$0.90(S_{12})$=0.81	$[P_{2\text{-}5}+(1\text{-}P_{2\text{-}5})$ $V_{72}S_{72}]$=0.98
5	V_{15}=0.90 V_{72}=0.90	S_{15}=0.95 S_{72}=0.98	0 1	0.10=(0.05+0.16)/2 0.90=(0.95+0.84)/2	$0.90(S_{15})$=0.86	$[P_{2\text{-}5}+(1\text{-}P_{2\text{-}5})$ $V_{72}S_{72}]$=0.98

[a] V_9, V_{12}, V_{15} and V_{72} are the vaccine coverage at 9, 12, 15 and 72 months of age, respectively.

[b] SR = seroconversion rates. S_9, S_{12}, S_{15} and S_{72} are the seroconversion rates at 9, 12, 15 and 72 months of age, respectively.

[c] 1m = 1 dose of measles vaccine, 1mmr = 1 dose of MMR, 2 = 1 dose of measles and 1 dose of MMR.

[d] When $V_9 < V_{15}$, the cumulative coverage are 0 dose = $1\text{-}V_{15}$, 1m = 0, 1mmr = $V_{15}\text{-}V_9$, 2 doses = V_9.

[e] When $V_9+V_{15}<1$, the cumulative coverage are 0 dose = 0, 1m = $1\text{-}V_{15}$, 1mmr = $1\text{-}V_9$, 2 doses = $V_9+V_{15}\text{-}1$.

Table 3. **Measles vaccine-induced antibody geometric mean titres (GMT) after one dose of vaccination given at 9–24 months of age in different studies**

Reference (Country)	Age[a]	Brand ($TCID_{50}$)[b]	Time post vaccination *n*	Assay[c]	GMT, mIU/ml (95% confidence interval)	SD[e] (*n*)
15 (Canada)	12 m	MSD-MMR (3162)	1 month	PRNT	1802 (no data)[d]	no data (27)
16 (USA)	9 m	MSD-M (1000)	12 weeks	PRNT	402 (138–1170)[d]	0.55 (20)
	12 m	MSD-MMR	12 weeks		1944 (1338–2830)[d]	0.19 (22)
17 (Guinea Bissau)	9 m	Schwarz-M (5000 PFU)	9 months	HI	2439 (2082–2856)	0.08 (119)
18 (Ghana)	9 m	Schwarz-M (5011 PFU)	3 months 6 months	HI	690 (580–821) 691 (572–835)	0.09 (114) 0.10 (111)
19 (South Africa)	9 m	Schwarz (19498 PFU)	3 months	PRNT	1367 (no data)	no data (14)
20 (UK)	12–18 m	MMR (no data)	3–5 years	PRNT	382 (no data)	no data (475)
21 (Canada)	12–24 m	MSD-MMR (1000)	5–6 years	PRNT	644 (560–734)[d]	0.07 (241)
		TrivirixMMR	5–6 years		976 (844–1120)[d]	0.07 (247)
22 (Sweden)	18–36 m	MSD-MMR (4000-8000)	8–10 years	PRNT	624 (87–4466)[d]	1.0 (314)

[a] Age at vaccination, m = months.

[b] MSD = Merck, Sharp, Dohme Inc. M = measles, MMR = measles, mumps and rubella, TCID = tissue culture infectious dose, PFU = plaque forming unit.

[c] PRNT = plaque reduction neutralization test, HI = haemagglutination inhibition.

[d] The PRNT titre is adjusted from dilution fold into mIU/ml based on the fact that 1:120 approximates to 250 mIU/ml (*24*).

[e] SD = standard deviation of antibody titres with natural log transformation, *n* = sample size.

Measles antibody profiles with antibody waning

When the effect of antibody waning is taken into consideration, seroprevalence will change with the initial titre (1 year post vaccination), the SD of antibody titres distribution, the half-life of antibody titres and the cut-off of seropositivity. Setting the initial titre at 500mIU/ml and the cut-off of seropositivity at 50 mIU/ml, the differences in seronegative proportions 1–10 years post vaccination are all less than 5% when comparing the prediction from medium SD (0.4) with the predictions from low SD (0.3) and high SD (0.5) for different half-lives of antibody titres (Fig 2). Therefore, the SD of antibody titres distribution is set to 0.4 in later analysis.

If the initial titre is set at 500 mIU/ml and the half-life of antibody titres is set to 4 years, the proportion of antibody titres under 50, 100 and 250 mIU/ml increases with time post vaccination and reaches 3.2%, 45% and 98.5% at 10 years post vaccination, respectively (Fig 3a). When the half-life of antibody titres is set to 3 years, the proportion of antibody titres under 50, 100 and 250 mIU/ml are 0.03%, 4.3% and 71.8% at 5 years post vaccination and 28.8%, 88% and 100% at 10 years post vaccination (Fig 3b). Reducing the half-life of antibody titres to 2 years, the proportions of antibody titres under 50, 100 and 250 mIU/ml are 1.1%, 28.8% and 95.8% at 5 years post vaccination and all reach >97% at 10 years post vaccination (Fig 3c). If the initial titre is set at 1000 mIU/ml and the half-life of antibody titres is set at 4 years, the proportions of antibody titres under 50, 100 and 250 mIU/ml are 0.2%, 3.2% and 66.8% at 10 years post vaccination, respectively (Fig. 4a). When the half-life of antibody titres is set at 3 years, the proportions of antibody titres under 50, 100 and 250 mIU/ml are 1.1%, 28.8% and 95.8% at 10 years post vaccination, respectively (Fig 4b). Reducing the half-life of antibody titres to 2 years, the proportions of antibody titres under 50, 100 and 250 mIU/ml are 62.1%, 97.9% and 100% at 10 years post vaccination, respectively (Fig 4c).

If the initial titre in the 1-dose policy at 9 months of age (policy 1) is assumed to be 500 mIU/ml and the half-life of antibody titres is assumed to be 4 years, the mean protective duration of antibody under this policy is 14, 10 or 5 years, corresponding to 3 different putative protective titres (50, 100 and 250 mIU/ml), respectively (Table 4). When the half-life of antibody titres is reduced to 3 years, the mean protective duration of policy 1 is 11, 8 or 4 years, corresponding to 3 different protective titres, respectively (Table 4). If the initial titre in the 1-dose-policy at 12 months of age (policy 2) is assumed to be 1000 mIU/ml and the half-life of antibody titre is set to 4 years, the mean protective duration of policy 2 is 18, 14 or 9 years, corresponding to 3 different protective titres, respectively (Table 4). When the half-life of antibody titres is reduced to 3 years, the mean protective duration of policy 2 is 14, 11 or 7 years, corresponding to 3 different protective titres, respectively (Table 4).

Fig. 1. **Predicted measles seroprevalence in preschool children. The parameters are set as follows: V_9=0.84, S_9=0.85, S_{12}=0.90 and S_{15}=0.95.** See Table 2 for full details

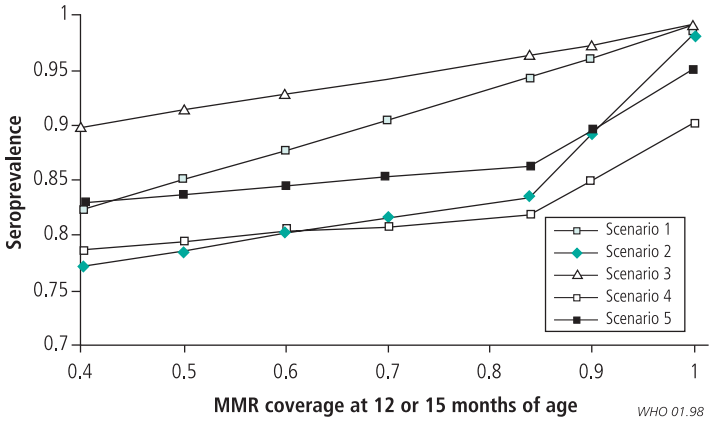


Fig. 2. **Differences in the proportion seronegative for different SD (standard deviation) and half-lives of antibody titres. The cut-off of seropositivity is 50 mIU/ml and the initial titre is 500 mIU/ml**

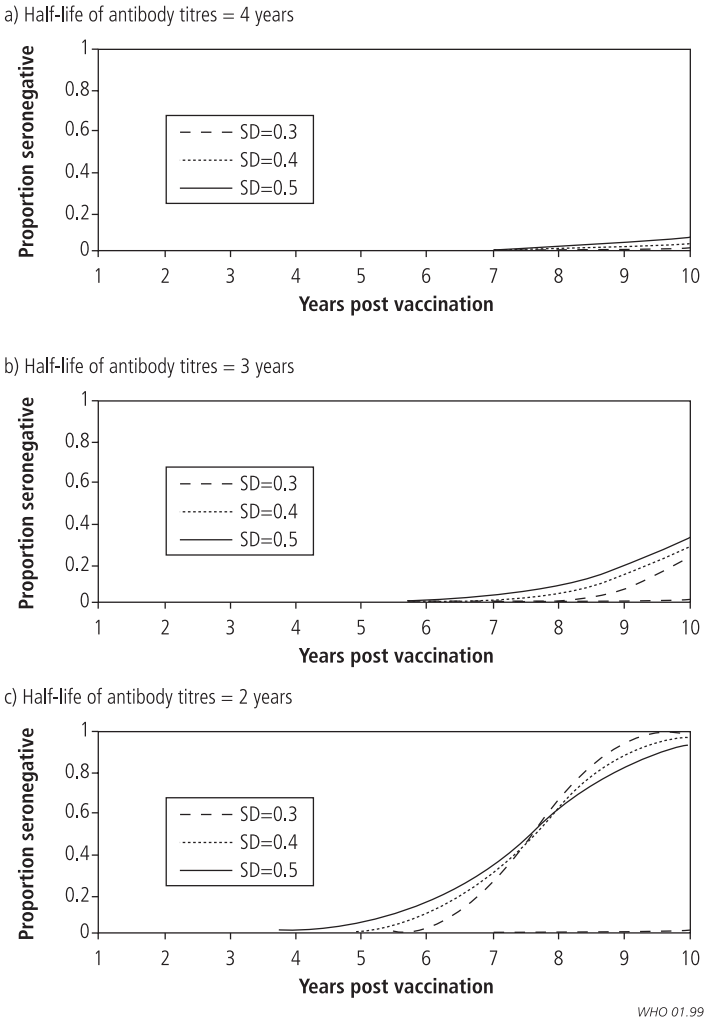
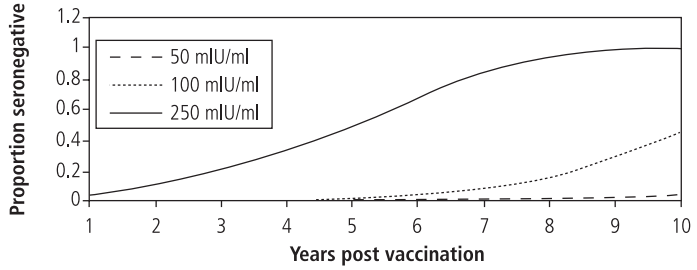
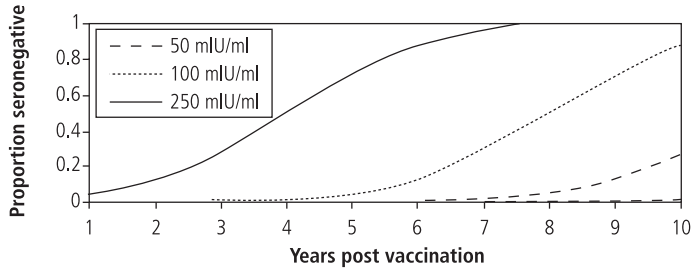


Fig. 3. **Predicting the proportion seronegative for different cut-offs of seropositivity and half-lives of antibody titres. The SD of antibody titres distribution is set to 0.4 and initial titres is 500 mIU/ml**

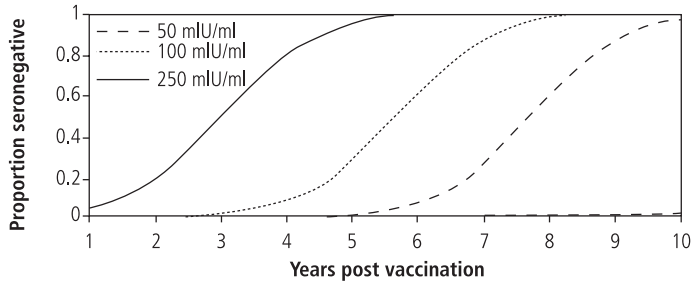
a) Half-life = 4 years, initial titre = 500 mIU/ml



b) Half-life = 3 years, initial titre = 500 mIU/ml



c) Half-life = 2 years, initial titre = 500 mIU/ml



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Discussion

Based on the island-wide vaccine coverage survey in 1993–94 and empirical seroconversion studies, this study estimates that the probable measles immunity prevalence is between 81% and 90% in preschool children and between 97% and 98% in the school population under the current 2-dose and 'mop-up' policy. This is consistent with the serological surveys conducted in 1993–97 (*6–9*). If the kindergarten can effectively implement the 'mop-up' strategy and reach the same vaccine coverage as through the primary school, measles immunity prevalence in kindergarten children will be similar to primary school children. The most important factor affecting measles immunity prevalence in preschool children is the association between vaccine uptake by individuals at the time of the first and second doses. Several studies in different countries have found that individuals receiving the first dose are more likely to have the second dose compared with individuals missing the first dose (*9, 27, 28*). Under such conditions, the second dose is more likely to revaccinate vaccine failures than to reach unvaccinated susceptibles and will not greatly improve the overall vaccine coverage, which may explain why the 2-dose policy (9 and 15 months of age with coverage of about 80% and 50%, respectively) in 1985–87 did not prevent children <5 years old from contracting measles infections during the outbreak in 1988–89 (*1*). In addition, 55% of reported cases occurred in the preschool children (1–6 years of age) during a local outbreak in the northern part of the island in 1994, where the measles and MMR coverage were 82% and 63%, respectively (*6*).

After the MMR campaign in 1991–94, measles has been temporarily eliminated on the island, so the risk of measles infection in infants is very low. Therefore, it has been suggested that the current policy can be changed from 9 and 15 months of age to 2 doses of MMR at 12 months and 6 years of age to reduce the risk of primary vaccination failure and induce higher antibody titres in preschool children (*6*). However, it is estimated in this study that if the vaccine coverage at 12 months of age cannot reach over 90%, the population immunity in preschool children will be under 81%, which may not be high enough to block measles transmission in preschool children. Compared with the 1970s, the basic reproduction number of measles transmission in the 1990s and beyond may change as the birth rate and proportion of young children decrease. Practically, this is impossible to quantify when measles infection is no longer endemic (*29*). The fact that infants <1 year old had the highest attack rate during the 1988–89 outbreak shows that the unimmunized infants will be the high risk group when an outbreak occurs (*1*). This may also imply that the basic reproduction number of measles transmission in preschool children in 1988–89 was still high.

In addition to reducing the risk of primary vaccination failure, measles vaccination at 12 months of age also induces higher antibody titres than vaccination at 9 months of age (Table 3) (*16, 30*). As the boosting effect of revaccination on antibody titres is short-term, the long-term antibody titres induced by 2-dose vaccination at 9 and 15 months may not be as high as that induced by 1-dose vaccination at 12 months of age (*11, 30*). Another alternative schedule, 2 doses of MMR at 15 months and 6 years of age, has lower risk of primary vaccination failure than 2 doses at 12 months and 6 years of age. Considering the effect of delayed vaccination and the high basic reproduction number of measles infection, this schedule may not be suitable for the island, although it has been successful in northern Europe.

It is well-documented that measles vaccine-induced antibody titres will decrease with time post vaccination when no wild measles virus circulates to boost the antibody titres (*12–13*). However, the dynamics of antibody decay have not been studied thoroughly. Based on the haemagglutination inhibition (HI) assay, two studies found that the half-life of measles vaccine-induced HI titres is about

4–6 months and 2–4 years at the first and 2–14 years post vaccination, respectively (*12–13*). However, Stetler et al. found that the decay rates of measles HI titres were different from that of neutralizing (NT) antibody titres at the first year post vaccination (*30*). The HI assay measures the antibody which can bind to haemagglutinin protein in the surface of the measles virus, and the NT assay measures the functional antibodies which can inhibit virus growth in cell cultures. Neither of these two methods measure the antibody involved in antibody-dependent cell-mediated immunity (*31*). Therefore, different antibodies may have different decay rates at different time points. Through a simplified model, this study tries to compare the effect of different antibody decay rates on the antibody profiles by assuming that the antibody titres decay constantly at 1–10 years post vaccination. Even if the decay rates are not constant, which we need more empirical studies to clarify, the method used in this study can still be applied by changing the decay rates at different time points post vaccination.

Assuming no natural booster, a low decay rate (half-life = 4 years) and different cut-off of protective titres, this study estimates that the mean protective duration varies from 5 to14 years for 1 dose of vaccine at 9 months of age and from 9 to 18 years for 1 dose at 12 months of age. However, there is evidence showing that vaccinees with undetectable or low antibody titres may be susceptible to inapparent measles infection but not symptomatic measles infection (*12, 13, 32–34*). Therefore, antibody assays may not be able to define the threshold of measles immunity accurately. It may be necessary to combine antibody detection with immune memory detection, for instance through the lymphocyte proliferation assay, to develop a more reliable indicator for measles immunity (*35*). In addition, the other important issue regarding the duration of vaccine-induced immunity is the long-term effect of revaccination (*11, 32, 35*). When the

Fig. 4. **Predicting the proportion seronegative for different cut-offs of seropositivity and half-lives of antibody titres. The SD of antibody titres distribution is set to 0.4 and initial titres is 1000 mIU/ml**

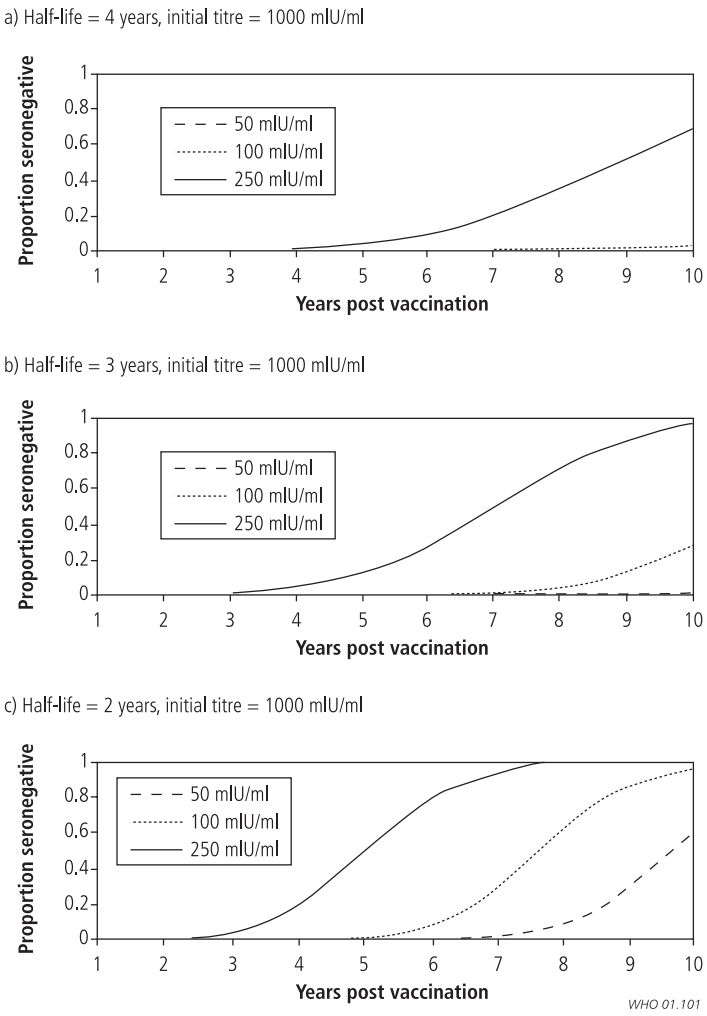

Table 4. **Mean protective duration of measles vaccine-induced antibody in different vaccination policies, half-life of antibody titres and putative protective titres**

Policy	Vaccine doses (age)	Antibody titre at 1 year post vaccination (mIU/ml)	Half-life of antibody titre (years)	Putative protective titres (mIU/ml)	Protective duration (years)
1	1 (9 months)	500	4	50	14
				100	10
				250	5
1	1 (9 months)	500	3	50	11
				100	8
				250	4
2	1 (12 months)	1000	4	50	18
				100	14
				250	9
2	1 (12 months)	1000	3	50	14
				100	11
				250	7

dynamics of antibody titres after revaccination at different ages (15 months, 6 or 12 years) are defined more clearly, the method used in this study could also be employed to predict the long-term antibody profiles after revaccination.

Two longitudinal studies have detected 5% (9/175) and 1.2% (4/333) of secondary vaccination failure (VF) during a follow-up of 10 years in Canada (*36*) and 12 years in Zhejiang Province, China (*12*). In addition, Chen et al. (*26*) serologically documented 7 clinical cases of secondary VF in the USA, and Hirose et al. (*37*) documented 8 in Japan. Moreover, two other studies also posited the existence of secondary VF based on the observation of an IgM response in 77.4% and 84.3% of measles cases in vaccinees, respectively (*38–39*). Although secondary VF may cause mild symptoms and not appear to be a major impediment to measles control at the moment, it needs to be continuously monitored until measles has been globally eradicated (*40–41*). ■

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Résumé

Prévision et comparaison des profils d'anticorps antirougeoleux à long terme pour différentes politiques vaccinales

Objectif Les flambées de rougeole, rares, sont localisées dans des régions où la couverture vaccinale antirougeoleuse est bonne. Il est donc nécessaire d'évaluer l'efficacité à long terme de cette couverture. Depuis 1991, aucune épidémie de rougeole touchant la totalité de l'île n'a sévi à Taïwan (Chine). Des modèles épidémiologiques ont été développés pour prévoir les profils d'anticorps antirougeoleux à long terme et comparer les avantages respectifs de différentes politiques vaccinales.

Méthodes La politique actuelle de vaccination antirougeoleuse à Taïwan (Chine) consiste en l'administration d'une dose de vaccin antirougeoleux à l'âge de 9 mois et une dose de vaccin ROR (contre la rougeole, les oreillons et la rubéole) à l'âge de 15 mois, plus un rattrapage chez les écoliers de 6 ans non vaccinés par le ROR. Ce schéma pourrait être perfectionné en une stratégie à deux doses. Cinq scénarios basés sur différentes stratégies ont été comparés. Nous avons utilisé Microsoft Excel pour l'analyse des modèles.

Résultats Si l'on suppose que l'immunité induite par le vaccin antirougeoleux ne diminue pas, la séroprévalence prévue des IgG antirougeoleuses chez les enfants d'âge préscolaire va de 81 % (limite inférieure) à 94 % (limite supérieure), et atteint 97 à 98 % chez les enfants d'âge scolaire dans tous les scénarios. Les résultats dépendent des valeurs respectives de la couverture antirougeoleuse et de la couverture par le ROR entre la première et la deuxième dose de vaccin. Si l'on suppose au contraire que les titres d'anticorps induits par la vaccination diminuent, la séroprévalence des IgG antirougeoleuses à long terme dépendra du titre initial après la vaccination, de la vitesse de diminution des titres d'anticorps et du seuil retenu pour définir la séropositivité.

Conclusion S'il est possible d'obtenir une couverture de plus de 90 % par le vaccin ROR chez les enfants de 12 mois, il peut être utile de remplacer la politique actuelle par un schéma en deux doses, l'une à 12 mois et l'autre à six ans, afin d'induire des titres d'anticorps plus élevés. Les modèles épidémiologiques étudiés pourraient être appliqués partout où l'élimination de la rougeole a atteint un stade équivalent.

Resumen

Predicción y comparación de los perfiles de anticuerpos contra el sarampión a largo plazo conseguidos mediante distintas políticas de inmunización

Objetivo Los brotes de sarampión son infrecuentes y se declaran en zonas de alta cobertura de vacunación antisarampionosa. Es necesario evaluar la eficacia a largo plazo de la cobertura. Desde 1991 no se ha declarado en Taiwán (China) ninguna epidemia de sarampión que afectara a la totalidad de la isla. Se han elaborado modelos epidemiológicos para predecir los perfiles de anticuerpos contra el sarampión a largo plazo y comparar las ventajas de distintas políticas de inmunización en la isla.

Métodos La política de inmunización contra el sarampión aplicada actualmente en Taiwán (China) consiste en administrar una dosis de vacuna antisarampionosa a los 9 meses de edad y una dosis de la vacuna contra el sarampión, la parotiditis y la rubéola (MMR) a los 15 meses de edad, a lo que se añade una vacunación de barrido de los escolares no vacunados con MMR a los 6 años de edad. Otras alternativas mejoradas emplean una estrategia de dos dosis. Se comparan cinco escenarios basados en distintas estrategias de vacunación. Los modelos han sido analizados con el programa Excel de Microsoft.

Resultados En primer lugar, si se supone que la inmunidad inducida por la vacuna contra el sarampión no decaerá, se puede predecir que la seroprevalencia de IgG contra el sarampión entre los niños en edad preescolar se situará entre el 81% (límite inferior) y el 94% (límite superior), y que alcanzará el 97%–98% entre los

escolares en todos los escenarios considerados. Los resultados dependen de los valores respectivos de la cobertura antisarampionosa y la cobertura con MMR entre la primera y la segunda dosis de vacuna. En segundo lugar, si se supone que los títulos de anticuerpos inducidos por la vacuna decaen, la seroprevalencia a largo plazo dependerá de los títulos iniciales tras la vacunación, de la velocidad de la disminución de los títulos de anticuerpo y del punto crítico de seropositividad.

Conclusión Si la cobertura con MMR a los 12 meses de edad puede superar el 90%, conviene reemplazar la actual política por la administración de dos dosis a los 12 meses y los 6 años, para inducir mayores títulos de anticuerpo. Estos modelos epidemiológicos pueden aplicarse siempre que se haya alcanzado una fase similar de eliminación del sarampión.

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