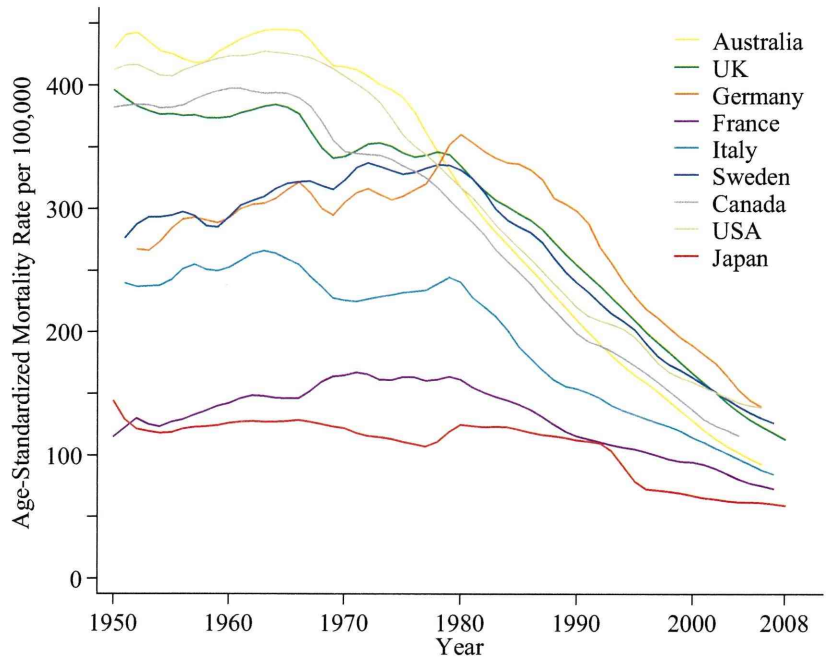
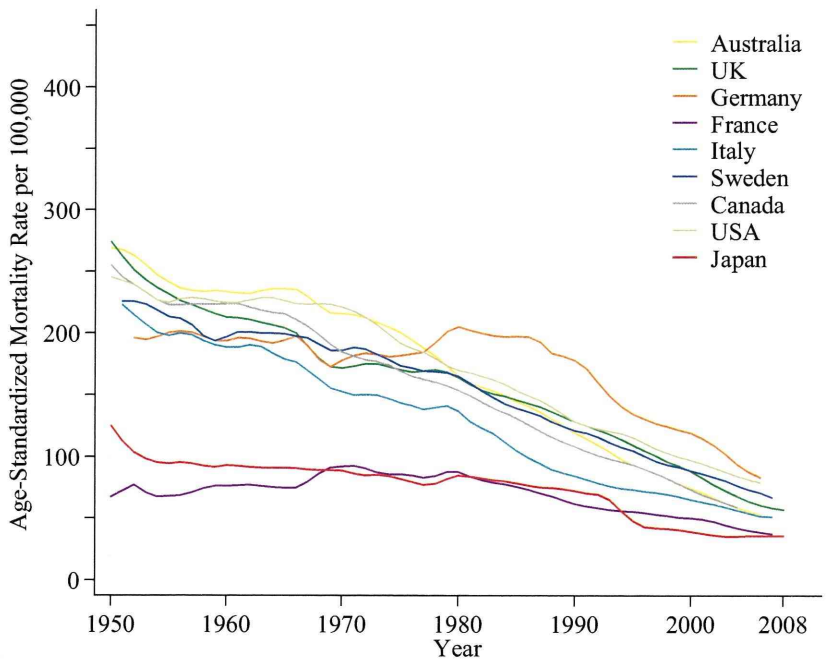
B）虚血性心疾患

男性

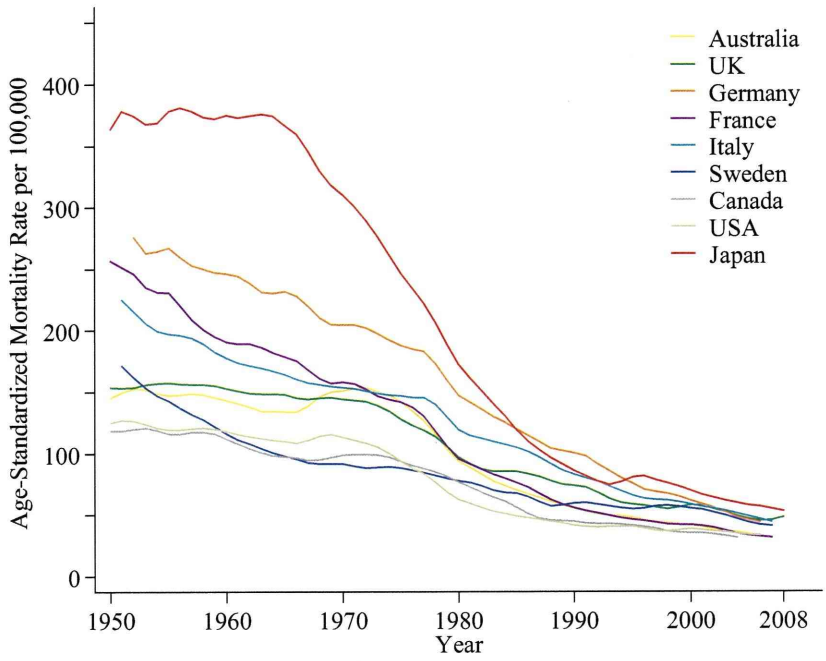


女性



C）脳血管疾患

男性


Age-Standardized Mortality Rate per 100,000
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100
200
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1960
1970
1980
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Year
Australia
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Germany
France
Italy
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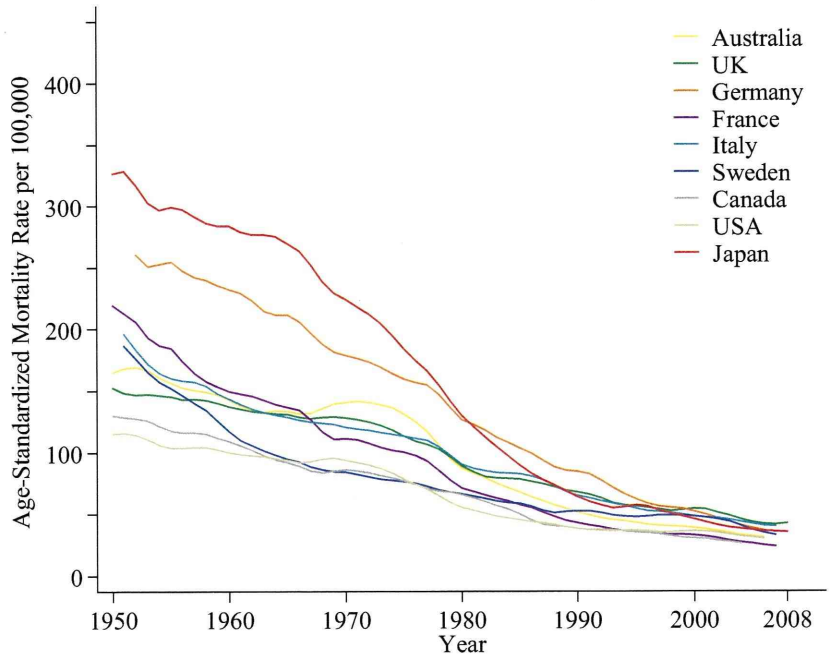
Canada
USA
Japan

女性


Age-Standardized Mortality Rate per 100,000
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Germany
France
Italy
Sweden
Canada
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Japan

図 7. 30～59 歳日本人男性における全死因による職業別年齢調整死亡率の推移

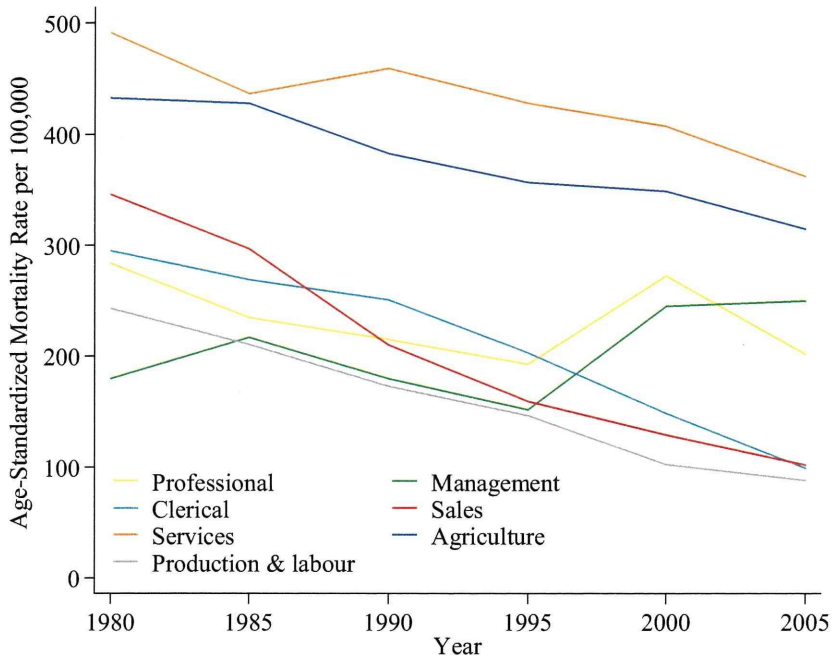
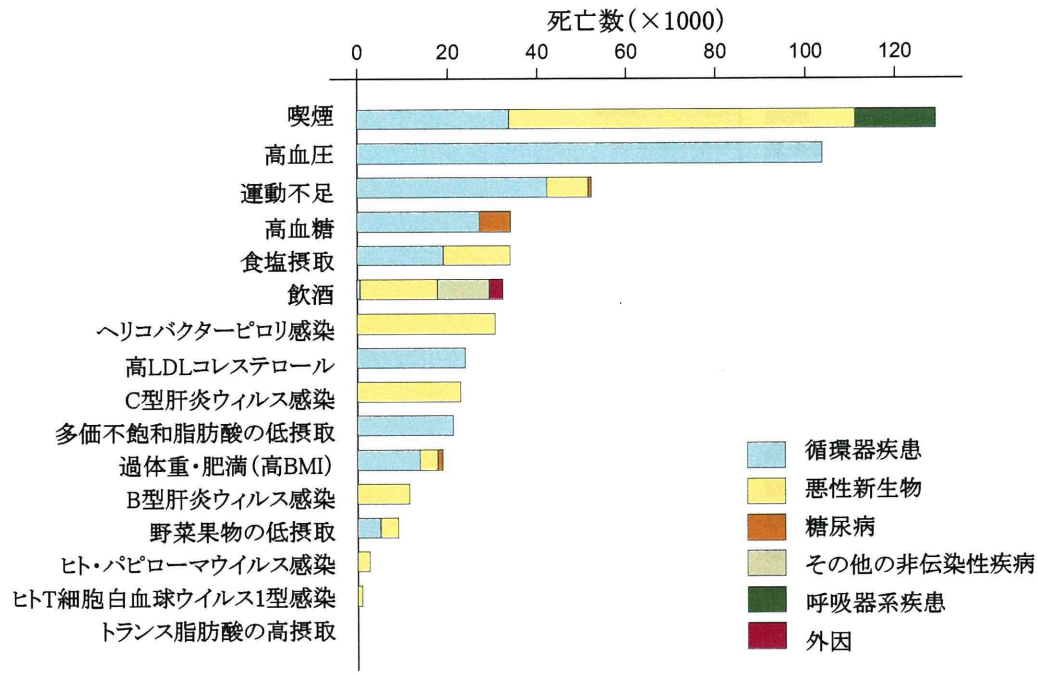
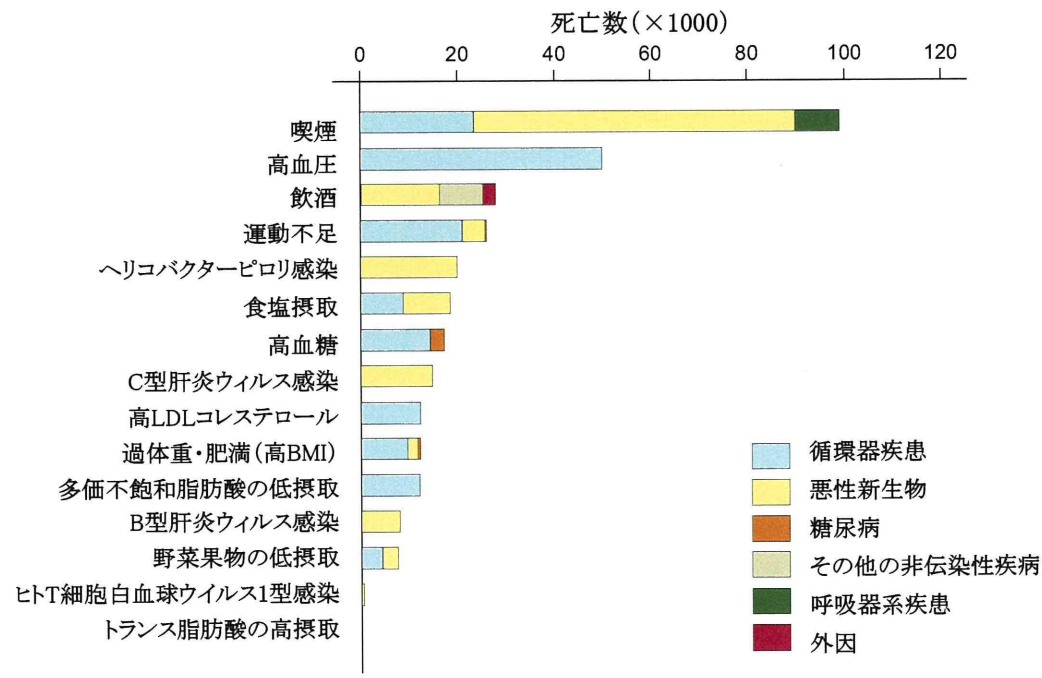


図 8. 2007 年の我が国における危険因子に関連する非伝染性疾病と外因による死亡数

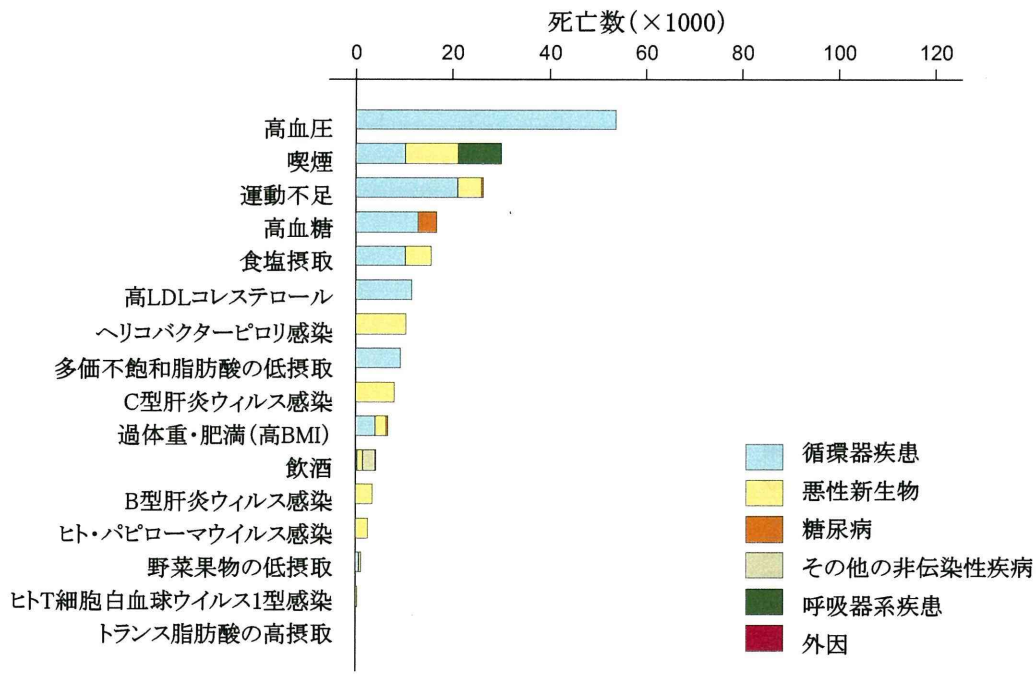
A）男女計



B）男性



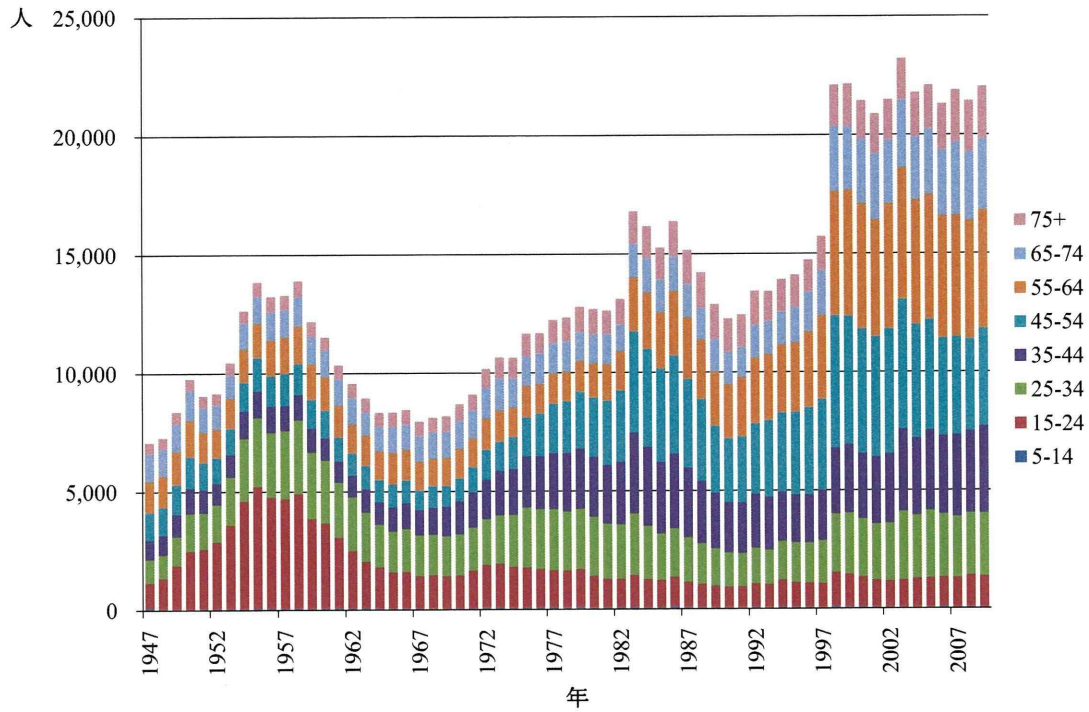
C）女性



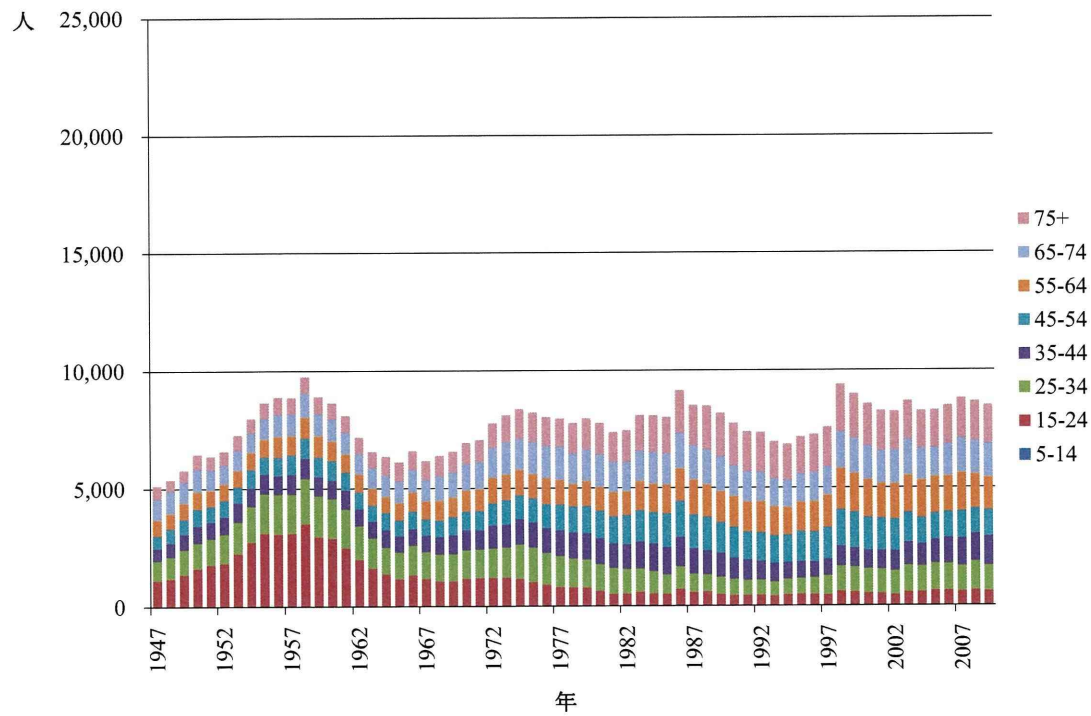
資料：渋谷健司（37）より作成

図 9. 1947～2009 年の我が国の年齢階級別自殺死亡者数

A）男性



B）女性



資料：厚生労働省（62）より作成

Ⅳ章
研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

(2011年4月1日～2012年3月31日迄)

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Zhang X, Shirayama Y, Zhang Y, Ba W, Ikeda N, Mori R, Shibuya K.	Duration of maternally derived antibody against measles: A seroepidemiological study of infants aged under 8 months in Qinghai, China.	Vaccine	30(4)	752-7	2011
Reich MR, Ikegami N, Shibuya K, Takemi K	50 years of pursuing a healthy society in Japan	Lancet	378(9796)	1051-3	2011
Kario K, Nishizawa M, Satoshi Hoshide, Shimpo M, Ishibashi Y, Kunii O, Shibuya K	Development of a disaster cardiovascular prevention network	Lancet	378(9797)	1125-7	2011
Ikeda N, Saito E, Kondo N, Inoue M, Ikeda S, Satoh T, Wada K, Stickley A, Katanoda K, Mizoue T, Noda M, Iso H, Fujino Y, Sobue T, Tsugane S, N	What has made the population of Japan healthy?	Lancet	378(9796)	1094-105	2011
Ikegami N, Yoo BK, Hashimoto H, Matsumoto M, Ogata H, Babazono A, Watanabe R, Shibuya K, Yang BM, Reich MR, Kobayashi Y	Japanese universal health coverage: evolution, achievements, and challenges	Lancet	378(9796)	1106-15	2011
Mori R, Takemi K, Fineberg HV	Science and consensus for health policy making in Japan	Lancet	379(9810)	12-2	2012

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Inoue M, Sawada N, Matsuda T, Iwasaki M, Sasazuki S, Shimazu T, Shibuya K, Tsugane S.	Attributable causes of cancer in Japan in 2005--systematic assessment to estimate current burden of cancer attributable to known preventable risk factors in Japan.	Annals of Oncology.	23(5)	1362-9	2012
Hosoda M, Inoue H, Miyazawa Y, Kusumi E, Shibuya K	Vaccine-associated paralytic poliomyelitis in Japan. (Correspondence)	Lancet	379(9815)	520	2012
Hirayama F, Koyanagi A, Mori R, Zhang J, Souza J P, Gülmezoglu A M.	Prevalence and risk factors for 3rd and 4th degree perineal laceration during vaginal delivery: A multi-country study.	BJOG	119(3)	340-7	2012
Takemoto N, Koyanagi A, Yamamoto H.	Comparison between endoscope-assisted partial mastectomy with filling of dead space using absorbable mesh and conventional conservative method on cosmetic outcome in patients with stage I or II breast cancer.	Surg Laparosc Endosc Percutan Tech	22(1)	68-72	2012

Ⅴ章.
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Duration of maternally derived antibody against measles: A seroepidemiological study of infants aged under 8 months in Qinghai, China

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ABSTRACT

To estimate the sero-prevalence of protective maternal measles antibodies among young infants and examine patterns of waning immunity in one of the poorest provinces in China, infants aged under 8 months and their mothers were randomly selected by multi-stage probabilistic sampling and blood samples were collected. Measles-specific IgG antibodies were measured in all serum samples by enzyme-linked immunosorbent assay. We determined measles-specific antibody titres for 477 pairs of infants and their mothers. After excluding 44 sub-clinical measles infection in infants, the measles antibody titres were ≧1:200, ≧1:800, and ≧1:3200 in 79.2%, 46.9%, and 17.8% of the 433 infants, respectively. The proportion of infants with titre ≧1:800 declined with age from 90.2% in newborns to 45.5% and 14.9% in the fourth and eighth month, respectively. Among the 433 mothers, measles antibody titres were ≧1:800 in 94.0%. Multivariate regression analysis showed that residence, mother's antibody levels and infant's age were significantly associated with infants' having a measles antibody titre ≧1:800. The relatively rapid decay of protective antibody in infants suggests that an earlier administration of the first dose of measles vaccination should be considered in China and a high quality interventional study is needed to decide the optimal schedule of measles immunization.

1. Introduction

Measles remains a leading cause of vaccine-preventable deaths globally, particularly in low-income countries. In 2005, more than 20 million cases occurred, and 345,000 people died from measles worldwide, most of whom were children under five years of age [1–3]. These deaths account for 50–60% of the estimated 1.6 million childhood deaths from vaccine-preventable diseases annually [4].

Primary protection against measles at birth is provided by passively acquired maternal antibodies obtained through the placenta and lactation. These measles-specific maternal antibodies decline gradually during the first year of life with the development of the infants' own immune system. Maternal antibodies may neutralize the vaccine antigen before the development of an immune response, if the measles vaccine is administered to infants who still have maternal antibodies. The timing of the vaccination should be, therefore, carefully determined, and the interval between vaccination and the loss of maternally derived antibodies should be minimized to protect children from infection with measles.

In the early 1980s, the World Health Organization (WHO) established a policy for measles immunization which recommended the administration of a single dose of measles vaccine at 9 months of age [5,6]. This recommendation was based on the finding that infants born to naturally infected mothers have a high antibody titre against measles and do not lose protection from maternal antibodies until 7–9 months of age [7]. Thanks to an increase in vaccine coverage in developing countries over the past 20–25 years, there are now more mothers than ever who have not contracted measles but were vaccinated against measles in their childhood. Previous studies show that infants born to those mothers who have been vaccinated can lose protective antibody before 7–9 months of age [5,8–11]. The changes in the epidemiology of and the immunity against measles require a reconsideration of the vaccination policy against measles in developing countries.

Measles vaccination policy and delivery strategies vary considerably among countries. In the early years of the Expanded Program on Immunization (EPI), most countries followed the recommendation from WHO to administer only one dose of measles vaccine. However, since primary vaccination failure occurs in up to 10–15% of infants vaccinated at age 9 months, this strategy has been proven insufficient to prevent measles outbreaks [12]. WHO now recommends a 2 dose measles vaccine program with a 2nd opportunity for measles vaccine being offered during childhood through

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routine services or periodically through mass campaigns targeted at defined age groups.

Measles vaccination was first introduced into China in 1965. It was not until the launch of the national EPI in 1978, however, that the measles vaccination was routinely administered to children. In 1986, the Chinese Government established a nation-wide two-dose regimen which recommended the administration of the first and second dose of measles vaccine to children at 8 months and 7 years of age, respectively [13]. From 2006, the second dose of measles vaccine was advanced to 18–24 months and all measles vaccinations are free of charge. Following the expansion of measles vaccination and the launch of the EPI, the reported cases of measles in China decreased substantially from 3–4 million cases in the 1960s to less than 74,000 in 2000 and mortality from measles has also subsequently declined from 3000–5000 deaths per year in the 1980s to less than 200 in 2000s [14].

Despite such a dramatic reduction in measles mortality in China, measles cases have significantly increased during recent years and periodic outbreaks of measles continue to occur, particularly alarming is the increase of measles cases among infants who are less than 9 months of age [15–17]. Study shows that the reported total cases rose from 74,813 in 2003 to 100,267 in 2006, with the incidence of 7.67 per 100,000 population [18]. Moreover, the age distribution of measles has changed markedly. In 1990s, 1.74% of reported cases occurred among children less than 8 months of age [19]; however, of cases reported during 2003 and 2004, 4.31% and 2.25% occurred among children less than 8 months of age respectively, and during 2005 and 2006, the proportion of cases occurring in children less than 8 months old increased to 7.62% and 10.98% respectively [18]. In a hospital in Shanghai, nearly 60% of 503 hospitalized children with measles in 2005 were younger than 9 months old [20]. These data demonstrate that young infants in China have increased susceptibility to measles virus. This is problematic given the WHO's target of eliminating measles from the Western Pacific Region by 2012.

The present study is the first sero-epidemiological assessment of measles antibodies in women and infants in Qinghai, one of the poorest provinces in China, where measles has remained endemic since the establishment of EPI with quadrennial epidemic cycles. The average incidence of measles during the 1990s was 33 cases per 100,000 in Qinghai, compared with 0.2 per 100,000 in the developed provinces in eastern China [14]. A review of surveillance data from Qinghai Provincial Center for Disease Control and Prevention (CDC) suggests that measles cases among infants (0–12 months old) have been increasing since 2004, without obvious improvement of surveillance quality. In 2007, reported total measles cases were 86 in Qinghai Province, infant cases accounted for 30% (26/86), and cases among infants aged 0–8 months old accounted for 20% of total cases and 65% of infant cases.

The objectives of this study were three-fold: (1) to estimate the sero-prevalence of protection with passively transferred maternal measles antibodies among unvaccinated infants aged less than 8 months and examine the patterns of waning of their maternal antibodies; (2) to identify factors that affect the level of maternally derived measles antibodies in infants; and (3) to provide evidence for public health policies on the optimal age for measles vaccination.

2. Materials and methods

2.1. Study design

A cross-sectional survey was carried out in Xining, the capital of Qinghai Province from January to May 2009. Xining City covers seven counties and has 2.2 million inhabitants, accounting for 40% of the population of Qinghai Province, which has the highest measles incidence in the country. Two-stage probabilistic sampling was employed to select infants aged 0–8 months and their mothers. In the first stage, three counties were randomly selected out of seven, and one rural township which had the largest population was selected from each sampled county. During the study period, there was no measles outbreak in the townships that participated in the study. In the second stage, newborns and infants aged 1 month or older were sampled separately. A sample of newborn children was obtained by recruiting 15–20 consecutive babies born at each county central hospital. For infants aged 1–8 months, immunization records kept in township health centers were used as a sampling frame to randomly select 15–20 children for each month-age group from each township to ensure the representativeness of the sample. Children were recruited into the study if they had never been vaccinated against measles, they had never had clinical measles, and they did not have any severe illness or an acute illness with a rash at the time of the survey. Interviewers visited the home of each sampled child.

A standardized questionnaire was used to interview mothers. The questionnaire included modules on socio-demographic characteristics (e.g. age, ethnicity, educational background, the number of household members, and household income), the mother's history of infection with measles and vaccination (measles vaccine Hu 191 strain was used in Qinghai), and the birth history of children aged 8 months or younger including questions on the place of delivery, birth order, birth weight, breastfeeding habits, and gestational age. Due to the lack of objective records, the questionnaire asked mothers to self-report whether they had vaccinated against measles or had clinical measles during childhood, and if they could not remember, their mothers were contacted to provide this information. We also examined the mother's knowledge regarding measles and its vaccination program. This study was approved by Qinghai Provincial CDC Institutional Review Board, and all mothers gave informed consent for themselves and their infants before surveyed.

2.2. Serological analyses

Blood samples were collected by finger prick from children aged 1 month or older and their mothers. Neonatal blood samples were obtained from the umbilical cord immediately after delivery, and mothers' blood samples were taken by venopuncture. A sterile technique was followed to obtain all blood specimens. The blood specimens were taken to the Qinghai CDC Laboratory and centrifuged at 3000 rpm for 10–15 min. The sera were then pipetted into a sterile tube labelled with a unique identification code and stored at −20 °C until the analysis was completed. Measles specific IgG antibodies were measured in all serum samples by enzyme-linked immunosorbent assay (ELISA). The ELISA kits were obtained from National Laboratory for Measles, Institute of Viral Disease Control and Prevention, China CDC. The semi-quantitative ELISA method defines measles antibody titres as negative, 1:200, 1:800, 1:3200 and 1:12,800. Sub-clinical measles infection in infants was defined as the infants with a four-fold or greater rise in measles antibody titre when the infant's titre is compared with the corresponding maternal antibody titre.

2.3. Statistical analyses

Antibody titres were log-transformed, and the Geometric Mean Titres (GMTs) were calculated in order to compare the differences between groups. Only antibody titres over the limit of detection (≥1:200) were used for the calculation of GMTs. IgG antibody against measles was considered to be seropositive or detectable (assumed to be immune) at 1:200 or greater, protective at 1:800 or greater, and high at 1:3200 or greater [21,22]. Youwang et al.

[21] tested the titre of ELISA IgG measles antibody among 145 persons exposed to measles virus in 3 measles outbreak villages and observed the occurrence of clinical measles cases. They found all clinical measles infection occurred among those with titre ≤1:200, and no clinical measles infection among those with titre ≥1:800, which demonstrated that a measles IgG titre of 1:800 was associated with protection against clinical measles infection. In this paper, the cut-off was chosen based on the assumption that 1:800 correlates with protection against clinical infection in vaccinated individuals and acknowledge that although it is known that passively acquired antibody protects against measles infection, a precise serological correlate has not yet been defined for this situation.

The proportions of children who had detectable and protective measles antibody titres were estimated by single-month age group. The analysis of variance (ANOVA) and *t*-test were used for comparisons of GMTs between groups. The Pearson Chi-square test and the Fisher exact test were used to compare the proportions in each cohort who had detectable and protective measles antibodies.

A logistic regression analysis was performed to examine the change in infants' measles antibodies with age and to investigate the impact of differing factors on infants' antibody decay. A dichotomous dependent variable was created for the infant's antibody levels to indicate whether they were ≧1:800 or not. The impact of age among the infants was examined for each month, using zero month (newborns) as the reference group. The age of the mothers was used as a proxy for their immunization status in childhood, on the assumption that mothers aged 31 or younger (born in 1978 or later) had vaccine induced immunity and were immunized under the EPI program.

3. Results

Of the 503 pairs of infants and their mothers recruited for this study, 26 were excluded from the analysis because the blood specimens of either the mother or infant were inadequate to run serologic tests. 44 (9.2%) were excluded because of sub-clinical measles infection in infants. The final study population included 433 pairs and blood samples were processed for all of them.

The infant female to male ratio was 1:1.1. The mean gestational age was 279.0 (SD 11.5) days. The mean birth weight was 3272.3 (SD 687.3) g, and 5.7% of the children had a low birth weight (<2500 g). None of these low birth weight infants were premature. Three quarters of the 433 interviewed mothers (75.5%) were born after 1978, the year when China's EPI was established and with it, the launching of the routine administration of measles vaccine to all infants. The mean parity was 1.3 (SD 0.5), and 68.6% of the mothers were primiparas.

None of mothers had records of their vaccination status or history of measles infection. The majority of the 433 mothers (65.3%) could not recall whether or not they had been vaccinated against measles during childhood, whereas 68 (15.7%) reported that they had been vaccinated against measles during childhood and 46 (10.6%) confirmed that they had suffered a natural infection of measles.

The measles antibody titre was seropositive, protective, and high in 79.2%, 46.9%, and 17.8% of the 433 infants, respectively. The proportion of infants with detectable (seropositive) measles antibodies decreased with age from 98.0% in newborns to 77.3% at age 4 months and 53.2% at age 8 months. The proportion of infants with protective antibody levels declined with age from 90.2% in newborns to 45.5% and 14.9% in the fourth and eighth month, respectively (Table 1).

The GMTs of detectable measles antibodies in newborns were not statistically different from that of their mothers (newborns

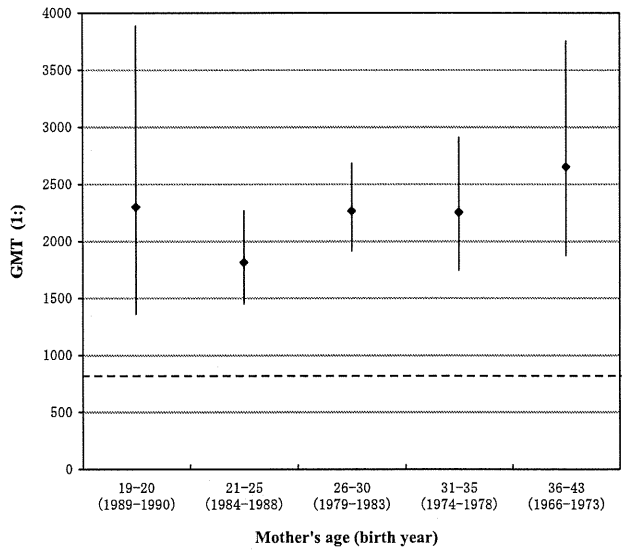

Fig. 1. Distribution of GMTs of measles antibodies in infants 0–8 months in Qinghai, China, 2009. *Note*: Measles antibody titre of 1:800 or greater, defined as protective, is indicated by the dashed line. The points are mean GMTs, and bars are 95% CI.

2294.3 vs. mothers 2870.3, $P = 0.20$). The GMTs in infants decreased dramatically between newborns and infants aged 1 month old. The GMTs fell below the protective antibody level in infants at 3 months of age (GMTs of 1:570.1, 95% CI: 413.1–786.7) (Fig. 1). There were no statistical differences in GMTs between 106 infants whose mothers were born before 1978 and 327 infants born to younger mothers (623.5 vs. 682.9, $P = 0.55$).

Among the 433 mothers, measles antibody titres were equal to or higher than 1:800 in 94.0% (95% CI: 91.3–95.9%) and detectable levels in 99.8% (95% CI: 98.4–100.0%). More than half of the mothers had measles antibody titre ≧1:3200 (59.1%, 95% CI: 54.4–63.7%). The mean antibody titres in mothers did not differ significantly between age groups ($P = 0.87$) (Fig. 2). The mothers of infants with antibody titres ≧1:800 had significantly higher GMT than did mothers of infants with antibody titres lower than 1:800 (3009.2 vs. 1624.4, $P < 0.01$). 26 (6%) mothers had measles antibody titres <1:200.

Table 2 presents the results of logistic regression analysis. After controlling for all other covariates, infants were less likely to have measles antibody titre of ≧1:800 than newborns (<1 month old)

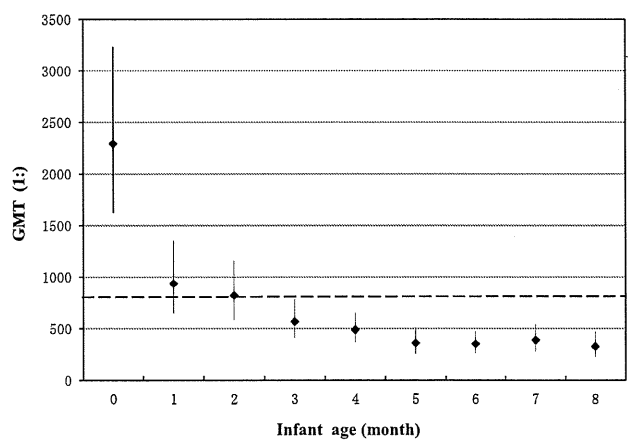

Fig. 2. Distribution of GMTs of measles antibodies in mothers by age in Qinghai, China, 2009. *Note*: Measles antibody titre of 1:800 or greater, defined as protective, is indicated by the dashed line. The points are mean GMTs, and bars are 95% CI.

Table 1
Distribution of measles-specific antibodies among infants aged 0–8 months by age in Xining City, Qinghai Province, China, 2009.

Age (months)	Total	Positive antibody (≥1:200)			Protective antibody (≥1:800)			High antibody (≥1:3200)		
		No.	%	95% CI	No.	%	95% CI	No.	%	95% CI
0	51	50	98.0	(87.4–99.7)	46	90.2	(78.5–95.9)	32	62.7	(48.8–74.8)
1	54	52	96.3	(86.4–99.1)	37	68.5	(55.1–79.4)	16	29.6	(19.0–43.0)
2	49	46	93.9	(82.7–98.0)	33	67.3	(53.2–78.9)	12	24.5	(14.5–38.3)
3	49	45	91.8	(80.2–96.9)	26	53.1	(39.2–66.5)	7	14.3	(7.0–27.1)
4	44	34	77.3	(62.7–87.3)	20	45.5	(31.5–60.1)	2	4.5	(1.1–16.4)
5	40	28	70.0	(54.3–82.1)	10	25.0	(14.0–40.5)	2	5.0	(1.3–17.9)
6	50	34	68.0	(54.0–79.4)	12	24.0	(14.2–37.7)	2	4.0	(1.0–14.6)
7	49	29	59.2	(45.1–71.9)	12	24.5	(14.5–38.3)	2	4.1	(1.0–14.9)
8	47	25	53.2	(39.1–66.8)	7	14.9	(7.3–28.1)	2	4.3	(1.1–15.5)
Total	433	343	79.2	(75.1–82.8)	203	46.9	(42.2–51.6)	77	17.8	(14.5–21.7)

Abbreviation: CI, confidence interval.

by 93% at age 3 months (odds ratio, OR: 0.07, 95% CI: 0.02–0.28, $P<0.001$), 97% at 5 months old (OR: 0.03, 95% CI: 0.01–0.14, $P<0.001$), and 99% at 7 months old (OR: 0.01, 95% CI: 0.00–0.04, $P<0.001$). Infants were more likely to have measles antibody titre of ≧1:800, if they lived in rural areas (OR: 24.62, 95% CI: 8.43–71.94, $P<0.001$) or if their mother had measles antibody titre equal to or greater than 1:3200 (OR: 7.13, 95% CI: 3.67–13.82, $P<0.001$). The likelihood of being protected was higher on average in infants born to mothers who had been born before 1978 (assumed to be naturally infected) than those born to younger mothers, although this difference was not statistically significant (OR: 1.27, 95% CI: 0.64–2.54, $P=0.49$).

Table 2
Odds ratios for the protective levels of passively transferred maternal measles antibodies in infants aged 0–8 months in Xining City, Qinghai Province, China, 2009.

	Not protective (<1:800)	Protective (≥1:800)	OR	95% CI
Residence				
Urban	203	121	1	
Rural	27	82	24.62	8.43–71.94**
Monthly income (log-transformed)			0.85	0.28–2.58
Family member				
>3	121	136	1	
3	108	63	1.37	0.66–2.86
Mother's age (year)				
≤31	179	148	1	
>31	51	55	1.27	0.64–2.54
Mother's antibody				
≤1:800	117	60	1	
≥1:3200	113	143	7.13	3.67–13.82**
Mother's ethnicity				
Han	137	141	1	
Minority	93	62	1.28	0.65–2.52
Mother's education (year)				
≥6	197	168	1	
<6	33	35	1.08	0.47–2.49
Infant's age (month)				
0	5	46	1	
1	17	37	0.32	0.09–1.16
2	16	33	0.26	0.07–0.97*
3	23	26	0.07	0.02–0.28**
4	24	20	0.06	0.02–0.24**
5	30	10	0.03	0.01–0.14**
6	38	12	0.01	0.00–0.05**
7	37	12	0.01	0.00–0.04**
8	40	7	0.01	0.00–0.04**
Gender				
Female	107	98	1	
Male	123	105	0.82	0.46–1.45
Birth weight (g)				
≥2500	213	187	1	
<2500	12	12	0.55	0.16–1.90
Birth order				
First	160	125	1	
2–4	69	75	1.40	0.67–2.92
Gestation age (day)				
≥280	155	138	1	
<280	67	63	1.03	0.54–1.98

Abbreviations: OR, odds ratio; CI, confidence interval.
* $P<0.05$.
** $P<0.001$

4. Discussion

The first cross-sectional study in the capital of one of the poorest provinces in China showed that passively acquired maternal measles antibodies rapidly decreased with age among infants aged 8 months or younger. The measles antibody titres of the majority of the infants had already lower than 1:800 a few months before the 8th month of life, the age for the first dose of measles vaccine under the current policy in China.

The seroprevalence of measles antibodies both in mothers and infants in Qinghai Province is higher than that in other parts of China. Previous serosurveys of mothers and infants aged 8 months or younger in other areas of China reported measles seropositive rates in the range of 84.3–88.5% and 28.9–55.2%, respectively [23–25]. Qinghai Province is located in the north-eastern part of the Qinghai-Tibet Plateau in western China, covering an area of 720,000 km^2. By the end of 2008, the population of Qinghai was 5.38 million, and 70% of inhabitants live in the rural or mountainous areas. Most mothers in this study were unlikely to have been vaccinated, since it is extremely difficult for the providers of health services to reach these rural and mountainous locations. A review of the provincial data by the author found that the measles vaccination coverage was very low at the time when EPI was initially established (data not shown). Mothers were likely to have had a natural measles infection during their lifetime, especially in rural and mountainous areas. Mothers' antibody levels were thus continually boosted due to the high transmission and periodic outbreak of measles in the study area. The association between the higher antibody levels in the infants and rural residence would also suggest that perhaps in the rural areas there are pockets of unvaccinated mothers and more of the mothers had natural disease.

In this study, we found that the concentration of maternally derived measles antibodies in infants was significantly associated with age and the concentration of maternal antibody. This result is consistent with previous study [26]. We did not find a significant difference in average maternal antibody levels between infants born to mothers who reported that they had natural measles infection and those born to mothers who reported that they had vaccination against measles, although several studies have suggested that measles antibody titres induced by vaccination are lower [27–29] and decline earlier in maternal derived antibodies [10,11,27,30–34] than those induced by natural infection. The possible explanation is that mother's history of vaccination and measles natural infection was obtained only through her own recall, without the confirmation of individual health records, moreover, the majority of mothers could not remember clearly whether they had been vaccinated against measles or had natural measles infection during childhood, thus subject to recall bias.

We used a traditional semi-quantitative ELISA method to measure the measles IgG antibodies in infants and their mothers. This method has been widely used in China for many years. In order to compare this traditional method with quantitative measles IgG ELISA assay, Mao et al. [35] retested 92 serum samples from healthy adults that had been tested using the CDC-China assay using the German Vrion/Serion test kit. They found an excellent correlation between the results obtained using each method (Spearman correlation coefficient of 0.963 ($P < 0.000$)). It indicated that the results of measles antibody in our study are reliable.

Measles vaccination has proven to be an extremely successful public health intervention and has already resulted in the remarkable decline of measles in many developing countries. However, the success of measles immunization depends on a number of factors, including the presence of maternal antibodies at the time of vaccination. Maternal antibody is transferred via the placenta during the last trimester of pregnancy and gradually declines during the first year of life when the infant's own immune system develops [36]. Interference by maternal antibodies has been generally thought to be an important issue in the seroconversion following early measles vaccination. The administration of measles vaccine at early age may not be effective because maternal antibodies neutralize the vaccine antigens before the development of a specific immune response [28]. On the other hand, any delay in vaccination may increase the risk of disease complications in infants. It is critical to identify an optimal age for measles vaccination to balance the risk of an early loss of maternal antibodies in the majority of infants with the risk of primary vaccine failure as a result of the presence of maternal antibodies [8].

One of the criteria to determine the optimal age for measles vaccination is the age at which the largest percentage of children lose measles antibodies and at which most respond to vaccine. Our results showed that passively transferred maternal antibodies decline rapidly among infants aged 8 months and younger, and that the mean titres were below 1:800 at 3 months of age. At the same time, 76.0% of infants aged 6 months of age have measles antibody lower than 1:800. In contrast with the developed provinces on the east coast of China, the risk of contracting measles prior to the stipulated age of the first dose of measles vaccine is substantially high in Qinghai Province due to the high incidence and periodic outbreaks of measles. This risk may further increase, once cohorts of vaccinated mothers enter reproductive age.

Although the majority of infants in our study had detectable level of maternal antibodies, previous studies suggest both humoral and cellular immune responses contribute to protection against measles following early vaccination with the currently available vaccine. A study carried out in China from 1991 to 1998 showed that vaccination at the age of 6 months with live attenuated measles vaccine induced a positive immune response in 91.7% of the vaccinated infants [22]. A study on seroconversion rates after administration of the standard Edmonston-Zagreb measles vaccination in infants aged 4.5 months also concluded that, although 28% of infants tested at 4.5 months of age had protective levels of maternal antibodies, 92% had measles antibodies at 9 months of age after early vaccination against measles [5]. Because of the uncertainty about using 1:800 as a serological correlate of protection for passively acquired antibody and because the level of antibody that inhibits vaccine take has not been defined, further studies are needed to understand the dynamics of maternal measles antibody. However, our results suggest that an earlier administration of the first dose of measles vaccine might be considered and that trials of seroconversion of measles vaccine administered before eight months of age may be warranted in China.

This study is one of the few studies that provides solid evidence on the seroprevalence of measles antibodies in a lowly developed area in China with periodic measles outbreaks. Since the majority of infants younger than 8 months had detectible maternal antibody against measles in the study area, more comprehensive trials examining seroconversion following measles vaccination at an early age are needed before lowering the recommended age for the first dose. Immunization programs in China could continue with the current policy of the first measles vaccination at eight months of age and a second opportunity for measles immunization for all children until further results are available.

Measles in young infants usually indicates poor measles control in general. Strategies to give a first dose earlier than 8 months of age during measles outbreak or mass campaign activities, to vaccinate women of childbearing age with measles vaccine will be the another optional ways to resolve the problem of measles cases in infants too young to be vaccinated. In this study, 6% (26/433) mothers had measles antibody titres <1:200. The non-immune mothers may contribute to recurrent epidemics in children and young infants born to these women in Qinghai Province. Achieving an immunization coverage rate of at least 95% with two doses

for all birth cohorts remains the most effective strategy to accelerate and sustain the reduction of mortality from measles and for the elimination of the disease in developing countries.

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50 years of pursuing a healthy society in Japan

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In this Series in *The Lancet*, we review the past 50 years of Japan's universal health coverage, identify the major challenges of today, and propose paths for the future, within the context of long-term population ageing and the devastating crises triggered by the March 11 earthquake. Japan is recognised internationally for its outstanding achievements during the second half of the 20th century, in both improving the population's health status and developing a strong health system. At the end of World War 2, in Japan, life expectancy at birth was 50 years for men and 54 years for women; by the late 1970s, Japan overtook Sweden as the world's leader for longest life expectancy at birth.[1] Japanese women have remained in the number one slot for 25 years, reaching a life expectancy of 86·4 years in 2009 (while Japanese men slipped to fifth longest living that year, at 79·6 years).[2,3]

In 2011, Japan celebrates 50 years of *kaihoken*: health insurance for all. Universal health insurance was achieved in 1961, assuring access to a wide array of health services for the whole population. Since then, benefits have become more egalitarian while health expenditures have remained comparatively low: 8·5% of the gross domestic product and 20th out of countries in the Organisation for Economic Co-operation and Development in 2008.[4] This achievement is all the more remarkable because the percentage of the population aged 65 years or older has increased nearly four-fold (from 6% to 23%) over the past 50 years.[5]

What produced Japan's impressive performance over the past half century? This question is not easily answered, because many factors contributed, including public health policies, high literacy rates and educational levels, the traditional diet and exercise, economic growth, and a stable political environment. Further, buried in the successes of the past 50 years are the roots of Japan's health-care challenges today. This Series examines not only specific factors that have contributed to improved health status but also challenges and opportunities faced today. Here we explore the broader context in which these changes have evolved—and in which Japan's emerging challenges are situated.

With the inauguration of Emperor Meiji in 1868, the Japanese Government embarked on a policy of rapid westernisation throughout society. In health care, the government over time succeeded in changing the basis of medical practice from Chinese to western medicine. Unlike other Asian countries, independent schools or formal qualifications in Chinese medicine were not allowed to co-exist with those teaching western medicine. Moreover, this transition was achieved with minimum cost and limited social disruption.[6]

However, for hospitals, Japan needed to adopt a new method of delivering care, because there were virtually no public or religious institutions that could serve this role. Japan developed hospitals for specific purposes, including teaching and research hospitals, army and navy hospitals, public hospitals for quarantining patients with communicable and venereal diseases, and—the most numerous—private hospitals expanded from clinics. In all four cases, the hospital was regarded as the doctor's workplace, and a doctor served as director with clinical and administrative responsibilities. The medical staff of these

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new hospitals was typically controlled by the professors of prestigious medical schools, notably the University of Tokyo. Physicians were rotated, at the decision of the professor, within the closed network of the university clinical department and its affiliated hospitals.

The most successful of the private hospitals established by physicians continued to expand until they rivalled the large hospitals in the public sector. Thus there was not much distinction between physicians' offices and hospitals, with even large medical centres maintaining outpatient departments, which patients could visit without referrals. There was also not much distinction between specialists and general practitioners. Those who went into private practice continued to regard themselves as specialists, but they mostly provided primary care because they did not have access to hospital facilities. This basic structure continues today.

In 1945, at the end of the war, Japan was confronted with widespread devastation: major cities had been destroyed and two cities were completely wiped out; an estimated 3·2 million people had died; and deep poverty and malnutrition scarred the entire country. Japan's surrender, in August, 1945, was followed by 7 years of US occupation that sought to restructure the health-care system as part of its goal of democratising the fabric of society.

These endeavours had mixed results. On the one hand, to address the population's health problems, the occupying forces strengthened community health institutions, which advanced the control of infectious diseases. Astounding gains in health status occurred in the immediate post-war years. Between 1947 and 1955, average life expectancy increased by nearly 14 years.[7]

These achievements have been attributed to public health policies that were started before the war, facilitated during the occupation along with social reconstruction efforts, and expanded by the Japanese Government after regaining sovereignty in 1952. Importantly, these early post-war health gains occurred before Japan's period of rapid economic growth, but while Japan was expanding employee-based health insurance and community health insurance, both of which already covered over 70% of the population during the war (in 1943). There was also continuity in medical education: the hierarchical structure, with the University of Tokyo at the top, remained intact.

In addition to its impressive health gains, Japan achieved unprecedented economic growth starting in the 1960s. But Japan also saw major setbacks to health in some population groups. Disastrous pollution problems erupted in the 1960s, with serious health consequences for locally affected populations.[8] The lessons learnt led to Japan taking a lead in environmental health. Since the late 1970s, Japan's health gains have captivated the attention of researchers from various disciplines who sought to explain how the country achieved the world's longest life expectancy.

Japan is currently undergoing several sociocultural changes that are challenging the formation of contemporary society. These changes include the rise of part-time and temporary employment for young workers, a growing number of young women who postpone marriage and child-bearing, the ever-expanding number of people who are elderly, an increasing sense of widening inequality in income, and diversity in values that weaken the national myth of homogeneity.[9] One manifestation of these changes is Japan's low fertility rate. Total fertility has declined in Japan to 1·37 livebirths per woman—about the same rates as in Italy and Germany, slightly greater than those in Singapore and South Korea, and much less than the replacement rate.[10] Japan's low fertility combines with low mortality to drive the rapid ageing of the population. People aged 65 years and older made up 20% of the population in 2005, and this group is expected to increase to 40% by 2050. This changing demographic structure has profound implications for many social institutions, including the health-care system, the financing of health care, and how to care for older people.

Japan is now confronting major challenges to its health system in the midst of major political and economic stagnation. The country has slogged through 20 years of economic non-growth, accumulating a huge national debt. Japan's percentage of global gross domestic product rose steadily from 3·9% in 1960, to 18·0% in 1994, but since has declined to 8·3% in 2008.[11] The time of Japan as number one—the 1960s and 1970s—is long over.[12] Unemployment is rising, and income inequality has increased since the late 1980s. The conservative Liberal Democratic Party, the country's dominant political party that held power almost continuously for 54 years, lost heavily in the 2009 Lower House elections and is now the opposition party. This political economy context complicates Japan's efforts to reform its health system today. But the fluid

political situation might also open new opportunities for structural change in how Japan operates, and expands the potential for policy innovation in the health system.

Over the past 50 years, Japan has transformed its health-care system through incremental changes that have been largely successful in expanding universal coverage and containing costs, while increasing fairness, and reducing inequities across different health plans. The basic premise of egalitarian and community-based health care has led to the construct of human security, which is now the core of Japanese diplomacy.[13] But during this time Japan also postponed certain structural changes in its health-insurance plans; these accumulated problems have become harder to avoid, along with the continued expansion of the elderly population and the public debt.

This Series addresses major achievements and challenges now confronting Japan's health system. Nayu Ikeda and colleagues[14] analyse Japan's success in extending life expectancy and the sources of its mortality reductions. Naoki Ikegami and colleagues[15] explain how Japan achieved universal coverage and reduced inequities in different health plans, to remove the risk of financial impoverishment from health-care costs. Hideki Hashimoto and colleagues[16] examine how the health-care system has been able to contain costs while still maintaining standards of quality of care. Nanako Tamiya and colleagues[17] explore Japan's main policy to address its rapidly ageing population: the public long-term-care insurance programme established in 2000. Rayden Llano and colleagues,[18] examine Japan's efforts to expand its role in global health, to provide policy guidance and not just funding. Finally, Kenji Shibuya and colleagues[19] pull together the main lessons for Japan and other countries.

This Series contributes analysis and recommendations to five crucial health-policy debates in Japan. The country's current political circumstances offer opportunities for a bipartisan reform of the health-care system. Japan's concept of human security might provide the key values for confronting both domestic and global conundrums in health policy. We are confident that Japan—the first non-western country to achieve economic development and universal health coverage—has the capacity to resolve these problems in ways that will provide lessons for the world.

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lower than in other high-income countries.[5] Given poor measures on quality of care, further reduction in mortality may require that Japan revamp its health-care system. Economic stagnation and rising income inequality could also be part of the explanation of recent trends.

What lessons can be drawn from the experience of Japan? Drawing from Ikeda and colleagues' analysis, I make four observations. First, strong government action at relatively low national income per capita (Japan in the 1950s) in a comparatively educated population can result in implementation of effective infectious disease control programmes. The critical necessity for high levels of educational attainment[6] should not be underestimated. Second, the main effects of the health-care system in explaining accelerated mortality decline were probably through public health action and primary care management of key risks such as blood pressure. These make up a small fraction of health expenditure in any nation. Low health expenditure as a fraction of GDP in Japan associated with excellent health outcomes could be because most health expenditure in other nations contributes little to improved population health outcomes. Third, Japan has benefited enormously from favourable risk factors for ischaemic heart disease and some cancers. Japan already had lower death rates from ischaemic heart disease than the other eight nations in the 1950s. Favourable risk factor endowment must be taken into consideration when undertaking any type of assessment of health system performance. Fourth, in an era of economic stagnation, political turmoil, ageing populations, and inadequate tobacco control, Japan does not seem to be effective in addressing its new set of health challenges. It will take more than universal access to a low-spending, high-volume health system to tackle these challenges. Without concerted action, Japan, like the USA[7] is likely to continue dropping in the global mortality league tables. Although the relative decline will not be as severe as we are witnessing in the USA, it is a cautionary tale that success in the past does not guarantee top performance in the future.

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Development of a disaster cardiovascular prevention network

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The magnitude 9·0 Great East Japan Earthquake that hit Tohoku in the northeast region of the main island, Honshu, on March 11, 2011, was followed by a devastating tsunami that has killed 15 538 people to date and left 7060 missing. Japan's Disaster Medical Assistance Team, which was developed on the experience of the 1995 Great Hanshin-Awaji (Kobe) Earthquake, went into action immediately. However, the unique nature of the 2011 disaster made it more challenging than its predecessors, as witnessed by the fact that the process of recovery has been far from satisfactory and is expected to be extensive.[1,2] The experience of similar events in the past suggests that survivors will have acute injuries and infections and will be at an increased risk of chronic illness, such as cardiovascular disease or mental ill health.[3]

Major cardiovascular events, such as stroke and myocardial infarction, occur more frequently in survivors of disasters and the effect can last months after the event. An increased incidence of cardiac events (myocardial infarction and sudden death within 24 h of onset) and stroke was reported in communities around the epicentre of the Great Hanshin-Awaji Earthquake in the 3 months after the event.[4,5] Moreover, the frequency of cardiovascular disease in every community was positively correlated with the magnitude of