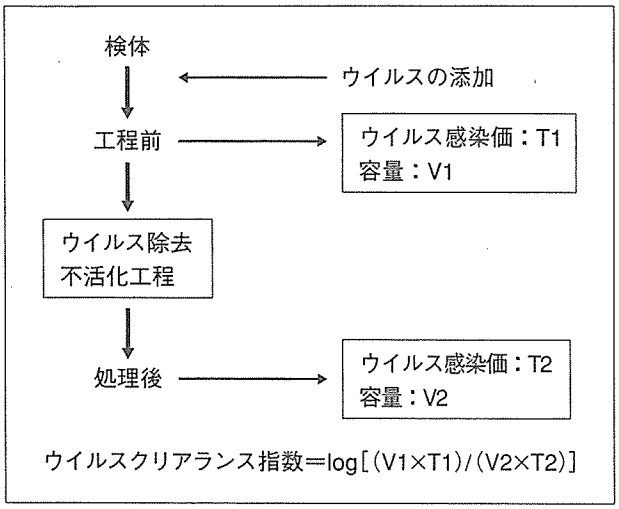

図 3　ウイルスの除去・不活化工程の評価法

入してウイルスの除去・不活化効率を評価することは現実的には不可能なので，工程のスケールを忠実に実験室レベルまで縮小した評価が実施されている．この試験をウイルスプロセスバリデーション試験という[1]．用いるウイルスや試験法によって結果の数値が大きく変動する可能性があるため，用いるウイルスの種類や試験法を定めたガイドラインが作成され，それに沿って除去・不活化の評価がされている[1]．

評価の概要を簡単に説明すると，評価する工程の処理前の検体に処理量の 10%以下の容量のウイルス液を添加し，十分攪拌後，処理前の検体としてサンプリングする．その際に全体の容量を測定する．つぎに工程を忠実に再現したウイルスの除去・不活化を実施し，処理後の容量を測定し，検体をサンプリングする．処理前後のウイルス量(実際の評価では感染価を測定する)を測定し，処理前後の容量をかけることによってそれぞれのウイルス総量を求め，評価した工程での除去・不活化された値をウイルスクリアランス指数として求める(図 3)(「サイドメモ」参照)．

ウイルスの除去・不活化が期待できるおもな工程においてそれぞれウイルスクリアランス指数を評価し，これらの工程では評価されたウイルス量を独立的に除去・不活化することができるので，それぞれウイルスクリアランス指数をかけ合わせた値が製剤の全工程における除去・不活化できるウイルス量になる．評価するウイルスの種類は DNA ウイルスと RNA ウイルスにつきそれぞれエンベロープのあり・なしの 4 つのウイルスについて，すくなくとも実施する必要がある．さらに，レトロウイルスも実施しているところが多い．評価に用いるウイルスは実際に原料血漿に混入する可能性のあるウイルスを用いるべきであるが，HBV や HCV は一般的に利用できる培養系が開発されていない．さらに，原料血漿に存在する抗体によってウイルスクリアランス指数が影響を受ける可能性もあるため，培養できないウイルスに関しては，動物由来の培養できるウイルスを“モデルウイルス”として評価に用いている．“モデルウイルス”は評価の対象となるヒト由来ウイルスとウイルス学的に近縁なウイルス，または同じ特性を有するウイルスを用いることになっている(表 1)[1]．

ウイルスクリアランス指数の解釈として，同じ工程を繰り返してもウイルスクリアランス指数に加算されない．なぜならば，その工程の除去・不

サイドメモ　ウイルスクリアランス指数とウイルスリダクション指数

製造工程で実施されているウイルス除去・不活化工程の機能を評価する際に，ウイルスクリアランス指数とウイルスリダクション指数が用いられており，一部では混乱している．評価のためのウイルス液を検体に添加するが，当然，添加するウイルスの感染価は事前に測定されているので，添加容量から添加した総ウイルス量は計算できる．これをウイルス除去・不活化実施後の総ウイルス量で割った数値がウイルスクリアランス指数とよばれている．一方，添加されたウイルスは添加された溶液の性状などによって一部は不活化されることがある．そのため，添加されたウイルスが溶液に十分攪拌された状態で測定されたウイルス感染価から工程前の総ウイルス量を計算し，工程後の総ウイルス量で割った値が，より実際の値を反映しているものと考えられ，ウイルスリダクション指数(virus reduction factor)とよばれている．しかし，本来ならばウイルスリダクション指数とよばなければならないはずなのに，日本においては習慣的にウイルスクリアランス指数とよばれている．図 3 もそれに従ったが，日本において，ウイルスクリアランス指数はウイルスリダクション指数を意味することに注意しなければならない．

表 1　ウイルスプロセスバリデーションに用いられるモデルウイルス

ウイルス	略号	ゲノム	envelope	サイズ	耐性
HIV-1		RNA	+	100 nm	低
ウシ下痢ウイルス	BVDV	RNA	+	50～70 nm	低
仮性狂犬病ウイルス	PRV	DNA	+	120 nm	中
脳心筋炎ウイルス	EMC	RNA	−	25～30 nm	中
A 型肝炎ウイルス	HAV	RNA	−	25～30 nm	高
ブタ Parbo ウイルス	PPV	DNA	−	18～24 nm	非常に高い

活化法に抵抗性を示すウイルスは同じ除去・不活化法を実施しても除去・不活化できない，との考えからである．また，1log 以上のウイルスクリアランスがなければ，ウイルスクリアランス指数として加算できないことになっている．

また，1 つのウイルスの除去・不活化工程だけではウイルスの種類や量に対して限界があるので，原理が異なる 2 つ以上の除去・不活化工程を製造に組み込むことが求められている[1]．これらによって血漿分画製剤のウイルスに対する安全性は飛躍的に向上した．

ところで，どれくらいのウイルスクリアランス指数が求められているのか，または必要なのであろうか．ウイルスの混入する頻度や種類によって一般的に言うことは困難であるが，わが国では 2003 年より HBV，HCV，HIV に関して，9log 以上のウイルスクリアランス指数が求められている[2]．原料血漿のスクリーニングとして NAT が導入されているが，ミニプール(当時は 50 人の献血をプールして試験を実施していたため，ウイルス濃度は 50 倍に希釈される)での検査は陰性であっても個別の NAT では陽性を示す血液が原料血漿に混入する場合があり，混入した原料血漿から製造された血漿分画製剤は回収となっていた．しかし，NAT や除去・不活化法の整備によって混入したウイルスが製造工程で十分に除去・不活化されれば安全性の確保は可能との考えから，検出感度から混入するウイルス量を計算し，除去・不活化工程によって十分なセーフティマージンの確保可能なウイルスクリアランス指数として 9log 以上となった．

4. 感染症定期報告制度

血漿分画製剤の使用によるものと疑われる感染症が発生した場合，薬事法第 77 条の 4 の 2 の規定に基づき，製造業者らは厚生労働大臣に報告する義務がある．さらに，安全性を向上させるために，2002 年の薬事法および採血および供血あっせん業取締法の改正によって，2003 年から生物由来製品の原料あるいは材料に関した感染症の最新の論文，およびその他により得られた知見に基づいて，該当する生物由来製品を評価し，その成果を感染症定期報告として定期的に報告制度ができた[3]．これによって最終製品の投与による感染症発生だけでなく，原料となる血液を介する感染症の情報を集め，評価することが製造業者らに求められている．

5. 特定生物由来製品としての指定

2002 年の薬事法および採血および供血あっせん業取締法の改正によって血漿分画製剤は“特定生物由来製品”に指定され，他の医薬品と比べてとくに注意を要する製剤となった．そのため，“特定生物由来製品”とわかるように白地に黒枠，黒字をもって“特生物”と明記すること，投与に際して使用する必要性の説明やリスクを完全には排除できないなどの説明が求められている．また，患者の氏名，住所，製造番号，投与日などを医療機関は記録として 20 年間保存しなければならなくなった[4]．これによって使用する医療側も適正使用が求められることになった．

血漿分画製剤に対するさらなる感染症対策を

薬事法の改正によって，前述したような原料血漿や製造工程だけでなく，より幅広く感染症の情報を解析することによって，血漿分画製剤の安全性の確保と仮に感染症が発生した場合に被害の拡大を防ぐ処置がとられている．しかし，血漿分画製剤では，より安全性の高い製剤の製造が期待さ

れていることには変わりがない．また，感染症がグローバル化し，海外で問題となっている新興・再興感染症が短期間に国内に侵入・発生する危険性もあることから，ウイルスに対してより有効な除去・不活化が可能な新しい方法の開発(とくにエンベロープをもたないウイルスに対して)や，異常プリオンを除去する方法の開発が今後必要と考えられる．

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Shifting Seroepidemiology of Hepatitis A in Japan, 1973–2003

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Abstract: *Background.* **Hepatitis A infection is caused by hepatitis A virus (HAV) contracted through fecal-oral transmission. Life-long immunity is conferred after infection. Improved sanitary conditions have generally resulted in a significant decline in the incidence of hepatitis A. However, a low incidence of infection results in increased HAV susceptibility. The present study investigates the prevalence of anti-HAV antibody and clarifies the current HAV status and HAV susceptibility in Japan at 2003.** *Methods.* **A total of 2,430 serum specimens collected during 2003 from Japanese individuals ranging in age from 0–92 years, were tested for anti-HAV antibody using an inhibition enzyme linked immunosorbent assay. All specimens were obtained from the WHO and the National Serum Reference Bank/National Institute of Infectious Diseases, Tokyo, Japan.** *Results.* **The overall seroprevalence was 12.2%. Anti-HAV antibodies were rarely detected in individuals between 0–44 years of age. Starting from the age of 45–49 years, seropositivity gradually increased through age 65 years and above. Seroprevalence was not affected by gender, and geographic distribution did not affect age-specific seroprevalence until the age of 60 years.** *Conclusions.* **HAV susceptibility in Japan is increasing annually. Particularly, the prevalence of anti-HAV antibody in individuals older than 50 years in 2003 was 50.3%, which is significantly lower than that of corresponding studies in 1994 (74.3%), 1984 (96.9%) and 1973 (96.9%). The growing susceptible population of advanced age results in more frequent HAV infection among them. The surveillance of anti-HAV antibody prevalence is useful for implementing preventive measures and for controlling the spread of HAV.**

Key words: **Hepatitis A, Seroepidemiology, Anti-HAV antibody**

Hepatitis A virus (HAV) is a pathogen of human acute hepatitis and is considered to be one of epidemiologically important viruses. It is a positive-strand RNA virus belonging to the Family *Picornaviridae*, genus *hepatovirus* (17).

Most HAV infections occur through fecal-oral transmission, either by direct contact with an infected person or by ingestion of food or water contaminated with HAV (5). Improved sanitary conditions and hygiene practices have reduced the incidence of hepatitis A infection. Children who become infected are usually asymptomatic or develop mild symptoms, whereas adults infected with hepatitis A develop fever, fatigue, malaise and jaundice that lasts between 4 and 10 weeks. Regardless of symptoms, seroconversion occurs after infection and convalescent individuals develop permanent immunity (13).

Hepatitis A virus has only one known serotype and anti-HAV antibody (anti-HAV) induced by infection or vaccination protects individuals against infection with any HAV strains (14). Both immunoglobulin M (IgM) and immunoglobulin G (IgG) types of anti-HAV antibodies are detectable during the early stages of illness. Levels of IgM antibody usually diminish within 2 or 3 months after infection, but IgG antibody confers life-long immunity. Individuals without anti-HAV antibodies are susceptible to HAV infection.

Improved socioeconomic status, urbanization, ethnic origin, and access to clean water and sanitation have

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Abbreviations: anti-HAV, anti-hepatitis A virus antibody; ELISA, enzyme linked immunosorbent assay; GMT, geometric mean titer; HAV, hepatitis A virus; IgG, immunoglobulin G; IgM, immunoglobulin M; OD, optical density.

changed hepatitis A epidemiology. The distribution of anti-HAV seroprevalence by age group might reflect current hepatitis A status in various countries and regions (7, 11).

In highly endemic areas, people become infected with HAV during early childhood and acquire anti-HAV antibodies before 10 years of age. As infections in early childhood are either asymptomatic or mild, hepatitis A is not a clinical problem and the virus is recognizable only by serological studies or the occurrence of infection among visitors.

In intermediate or transition areas, HAV circulation has been reduced by improving hygiene conditions and socioeconomic status. Those who become infected are older in such areas than in highly endemic areas. The incidence of symptomatic hepatitis A is higher in adolescents and young adults. Frequent outbreaks of hepatitis A are recognized as serious public health problems (21).

In low endemic areas, rare incidence results in the accumulation of non-immune populations. Susceptible adults who are exposed to HAV infection and symptomatic hepatitis A are mostly high risk groups such as child care providers, hospital workers or family members with direct patient contact, travelers to endemic areas, drug abusers and men who have sex with men.

The incidence of hepatitis A has decreased in Japan mainly due to improved sanitary conditions and hygiene practices (Fig. 1) (15) and thus an HAV-susceptible population has developed.

This study examines the current seroprevalence of hepatitis A in Japan, and describes the seroepidemiological shift over the past three decades. The results should provide useful epidemiological information upon which to base decisions that will prevent and control the spread of hepatitis A.

Materials and Methods

Serum specimens. A total of 2,430 serum specimens (1,242 and 1,188 from males and females, respectively, aged between 0 and 92 years) were collected from 12 Japanese prefectures during 2003 and tested for anti-HAV. All specimens were obtained through the WHO and National Serum Reference Bank/National Institute of Infectious Diseases, Tokyo, Japan and stored at −20 C. The specimens were separated into groups based on age, gender and geographic location for further analysis.

Anti-HAV screening. Total anti-HAV antibody was determined for all specimens using an inhibition enzyme linked immunosorbent assay (ELISA) as described (12). Briefly, purified inactivated HAV (KRM003 strain, genotype IIIB) was bound to microtiter plates (Nunc, F96 CERT.MAXISOAP, Denmark) coated with anti-HAV rabbit serum (HAV-plates). Non HAV-binding wells prepared on each HAV-plate comprised positive controls (100% inhibition). Negative controls comprised several HAV-binding wells. Diluted test specimens (1:32) were added to appropriate wells. Equal volumes of diluents (phosphate-buffered saline (pH 7.2) containing 0.5% skim milk and 0.05% Tween 20) were added to both positive and negative control wells. Plates were incubated overnight at 4 C and then the wells were emptied. Diluted horseradish peroxidase (HRPO)-conjugated anti-HAV rabbit IgG was added to the wells and incubated at 37 C for 2 hr in

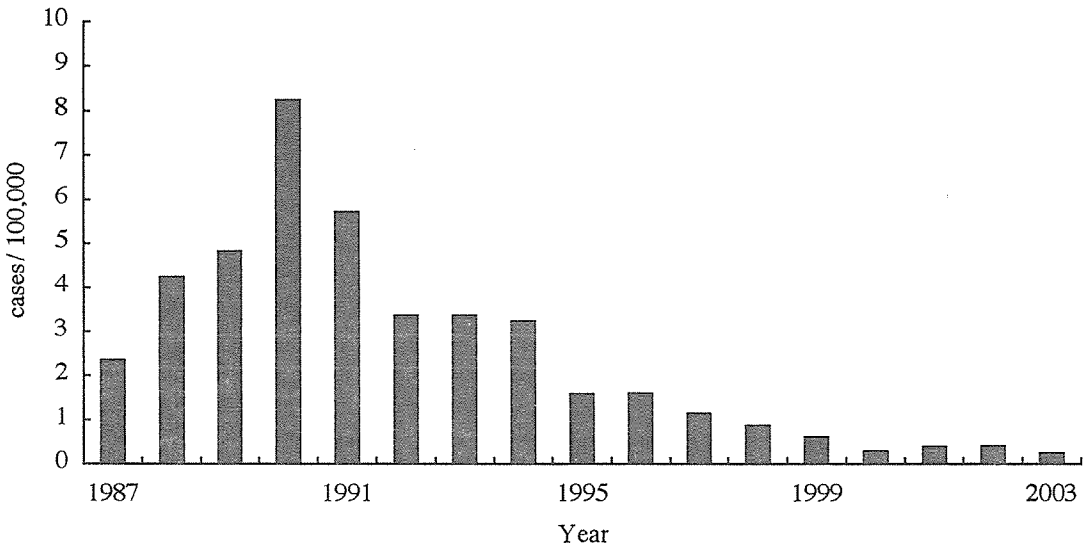

Fig. 1. Reported incidence of hepatitis A, Japan, 1987–2003. Data are cited from Ref. 15.

a humidified atmosphere. Plates were washed and 100 μl of substrate *o*-phenylenediamine (Tokyo Chemical Industry Co., Ltd., Japan) was applied to each well. Thirty minutes later, reactions were stopped by adding 100 μl of 2 N H_2SO_4 and the optimal density (OD) was measured at 492 nm in an ELISA plate reader (Corona, Japan). The inhibition rate was measured using the following formula:

Inhibition rate (%)=$(N-S)/(N-P)\times 100$ where N= mean OD_{492} value of negative controls, P=mean OD_{492} value of positive controls and S=mean OD_{492} value of specimens. Specimens with non-specific responses detected in the same manner using the non HAV-binding plates were excluded from this study.

Titration of anti-HAV positive specimens. Titers of anti-HAV were determined in all positive specimens and are expressed as mIU/ml using the parallel line assay (19) with a national human anti-HAV reference calibrated with a WHO standardized preparation. All positive sera were separated into five age categories as follows: 0–49 years (n=32), 50–59 years (n=103), 60–69 years (n=71), 70–79 years (n=60) and 80–92 years (n=31). The geometric mean titer (GMT) of anti-HAV in each age group was determined.

Data analysis. All data were statistically assessed by the χ^2-test or one-factor ANOVA using Statcel software (version 1; OMS, Japan, 1998). $P<0.05$ was accepted as the minimal level of significance.

Results

Prevalence of Anti-HAV

Figure 2 shows that all specimens plotted by inhibition rate were divided into two groups. Specimens with inhibition rates above 80% were regarded as anti-HAV positive. The cutoff inhibition rate of 80% was equivalent to 352.3 mIU/ml. Of the 2,340 serum specimens, 297 were anti-HAV positive (Table 1). Anti-HAV prevalence remained very low until the age of 45–49 years. Most individuals below or equal to 49 years of age were HAV susceptible. Seroprevalence gradually increased among persons above 50 years of age. The highest seroprevalence was 86.5% in the oldest age group (≥65 years). Seroprevalence between males (158/1,242) and females (139/1,188) did not significantly differ (P=0.59).

Geographic differences in anti-HAV seroprevalence in the Tohoku (north area), Kanto (central east area), Kansai (central west area) and Kyushu-Yamaguchi (south area) regions of Japan were analyzed over the age groups 0–9, 10–19, 20–29, 30–39, 40–49, 50–59 and over 60 years old (Fig. 3). Age-specific seroprevalence was very similar in populations under 59 years of age in each area. Statistical differences were evident in individuals over 60 years of age between Tohoku and Kansai (P=0.0066), and between Kansai and Kyushu-

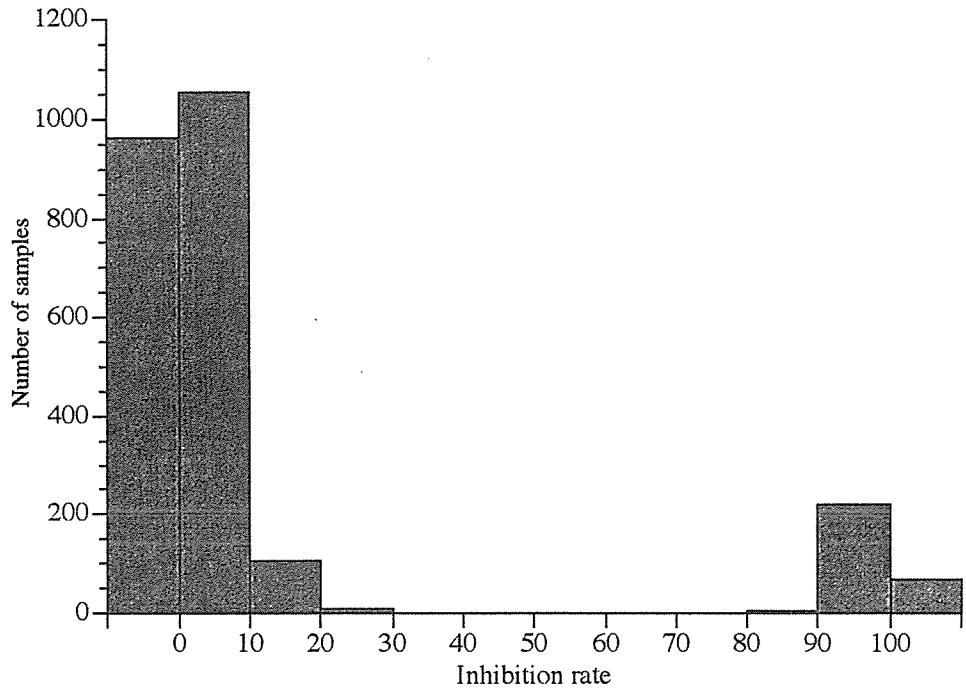

Fig. 2. Distribution of inhibition rates. Sera were divided into two groups by inhibition rate. Sera over 80% inhibition corresponding to 352.3 mIU/ml of anti-HAV antibody were identified as anti-HAV positive.

Yamaguchi (P=0.012).

Titration of Anti-HAV Positive Specimens

The GMT values of anti-HAV were 7,486 (95% confidence interval, 4,437–12,629), 7,397 (6,061–9,027), 6,210 (4,742–8,132), 7,944 (5,917–10,666), and 5,007 (3,351–7,481) mIU/ml for the age groups 0–49, 50–59, 60–69, 70–79 and 80–92 years old, respectively (no significant difference, P=0.34).

Discussion

In 2003, the overall anti-HAV prevalence in Japan was 12.2% (Table 1) and gender did not affect this value. The GMT of anti-HAV in five age groups remained high and did not change with age (P=0.34). This confirmed that individuals who acquired anti-HAV immunity would retain high titers of anti-HAV and life-long immunity. Fifty percent of individuals over 50 years of age had anti-HAV whereas only 1.68% of people younger than 50 years of age had immunity. Because of the low incidence of hepatitis A, fewer younger people would acquire HAV-immunity, whereas anti-HAV positive individuals who mostly belong to older age groups have retained anti-HAV from past exposure. Seroprevalence also remained very low in individuals under the age of 40–44 years who were born around 1960. This finding implies that the incidence of hepatitis A in Japan has been rare since 1960. The seroprevalence of the oldest age group (over 65

Table 1. Age-specific prevalence of anti-HAV in Japan, 2003

Area	Tohoku								Kanto					
Prefecture	Akita		Yamagata		Miyagi		Fukushima		Niigata		Ibaraki		Nagano	
Age (years)	Tested	Positive	Tested	Positive	Tested	Positive	Tested	Positive	Tested	Positive	Tested	Positive	Tested	Positive
0–4	13	0	NA		NA		16	0	NA		19	0	9	0
5–9	23	0	NA		NA		11	0	NA		21	0	23	0
10–14	8	0	NA		2	0	14	0	NA		15	0	NA	
15–19	17	0	NA		27	0	17	0	NA		7	0	4	0
20–24	4	0	1	0	14	0	2	0	NA		9	0	43	1
25–29	14	0	NA		11	0	23	0	1	0	14	0	12	0
30–34	9	0	NA		7	0	17	0	32	1	14	0	21	0
35–39	11	2	NA		1	0	8	0	29	3	11	0	14	1
40–44	15	0	NA		9	1	21	0	26	1	6	0	24	0
45–49	9	2	19	0	8	0	4	0	19	3	10	2	27	0
50–54	14	5	13	2	14	2	11	3	26	6	9	1	19	3
55–59	11	6	12	7	6	1	14	5	20	11	9	2	14	8
60–64	4	4	6	3	1	1	5	4	2	1	5	3	8	7
65–	23	23	19	19	NA		18	14	NA		NA		14	13
Total	175	42	70	31	100	5	181	26	155	26	149	8	232	33

Area	Kansai				Kyushu-Yamaguchi						Total		
Prefecture	Fukui		Kyoto		Yamaguchi		Fukuoka		Saga				
Age (years)	Tested	Positive	Tested	Positive	Tested	Positive	Tested	Positive	Tested	Positive	Tested	Positive	%
0–4	NA		25	0	34	2	16	0	24	0	156	2	1.3
5–9	NA		34	0	35	0	46	0	26	0	219	0	0
10–14	NA		24	0	71	0	35	0	18	0	187	0	0
15–19	NA		19	0	44	0	45	0	18	0	198	0	0
20–24	1	0	24	0	42	1	43	0	12	0	195	2	1
25–29	2	0	27	0	46	3	38	1	15	1	203	5	2.5
30–34	NA		19	0	41	0	37	0	14	0	211	1	0.5
35–39	NA		24	0	42	0	34	1	12	0	186	7	3.8
40–44	13	0	32	0	17	1	12	0	13	0	188	3	1.6
45–49	5	1	23	3	11	0	13	1	12	0	160	12	7.5
50–54	15	5	32	4	17	5	8	0	15	6	193	42	21.8
55–59	4	2	26	12	11	3	3	2	7	2	137	61	44.5
60–64	NA		9	5	2	2	1	1	6	3	49	34	69.4
65–	NA		26	19	26	23	NA		22	17	148	128	86.5
Total	40	8	344	43	439	40	331	6	214	29	2,430	297	12.2

NA: not available.

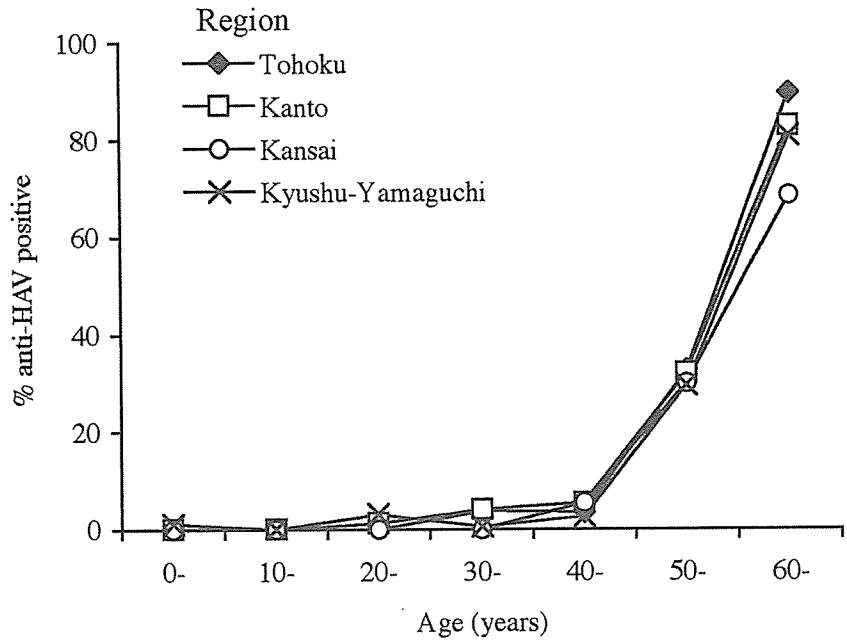

Fig. 3. Geographic distribution of anti-HAV antibody. Geographic distribution does not significantly differ among 4 areas of Japan until the population reaches 60 years of age. Seroprevalence in individuals over 60 years old significantly differs between Kansai and Tohoku (P=0.0066), and between Kansai and Kyushu-Yamaguchi (P=0.0121).

years old) is the highest at 86.5%. Individuals within this population, born before 1940, presumably acquired immunity during an era when hepatitis A was endemic in Japan. Between 1940 and 1960, risk of HAV-exposure was decreased by rapid infrastructural improvement, including hygiene conditions particularly after World War II.

Interestingly, regional differences in seroprevalence were evident only in individuals over 60 years of age (Fig. 3). We surmise that when HAV was endemic over 60 years ago, the frequency of hepatitis A endemicity varied across locations. However, regional features might have no impact on current hepatitis A status.

Figure 4 shows the shift in anti-HAV seroprevalence in Japan during the past three decades. The shapes of seroprevalence curves derived from studies reported in 1973, 1984, 1994 (12) and 2003 have remained similarly sigmoidal, and shift towards older groups in 10-year increments. Numbers of HAV-susceptible individuals have accumulated not only among younger generations, but also among older age groups. The seroprevalence of anti-HAV in individuals older than 50 years in 2003 was 50.3%, which is significantly lower than that of corresponding studies in 1994 (74.3%), 1984 (96.9%) and 1973 (96.9%). This has led to a shift in hepatitis A patients towards older age groups, in which clinical illness is more frequent and severe (Fig. 5) (8, 13).

Hepatitis A is one of the major vaccine preventable diseases. Hepatitis A vaccine is an inactivated preparation of cell-culture adapted HAV, and has been used in many parts of the world (20). Several hepatitis A mass vaccination programs have been started since 1997 in regions of intermediate endemicity. A universal vaccination program in the United States of America resulted in a 76% decline in the overall incidence of hepatitis A to 2.6 per 100,000 reported in 2003, compared with 10.7 per 100,000 during the baseline period of 1990–1997 (18). A study in Israel found that a toddler-only universal vaccination program effectively reduced the incidence of hepatitis A by 95% (4). In that study, the annual pre-vaccination incidence of 50.4 per 100,000 declined post-vaccination to 2.2–2.5 per 100,000. The authors of these reports suggested that this decline was not solely a result of the universal vaccination program but was also associated with improved environmental and hygiene conditions. However, both studies suggest that the implementation of a universal hepatitis A vaccination program for children provides a significant degree of immunity for individuals who live in intermediate epidemic regions. Determining the impact of hepatitis A on current health care resources and defining the benefit and cost of hepatitis A vaccination will greatly influence the decision as to whether to implement such programs in particular countries and population groups (1, 3). The recent incidence of hepatitis A of 0.34 per 100,000 in Japan is lower than the post-vac-

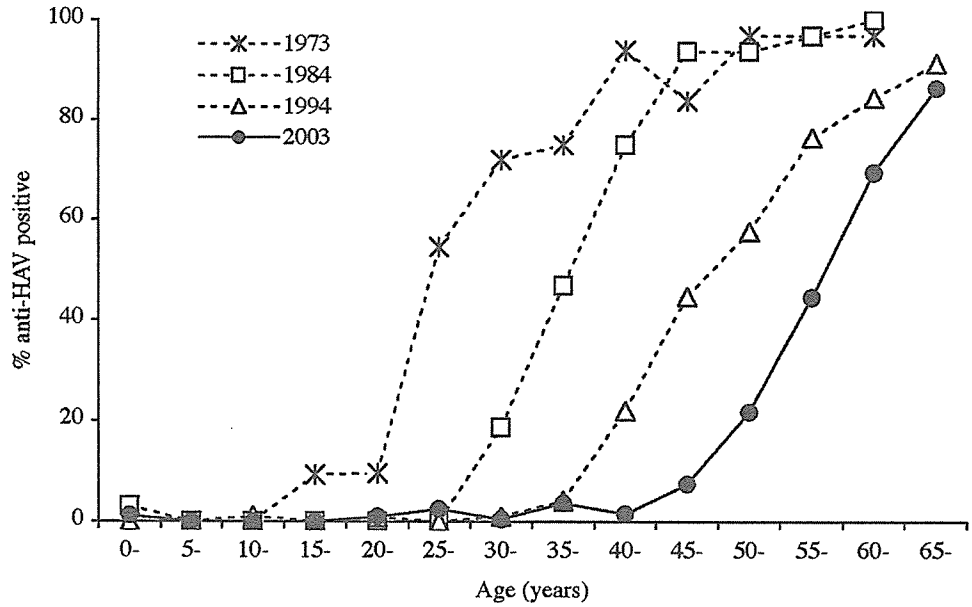

Fig. 4. Age-specific seroprevalence of anti-HAV from 1973 to 2003 in Japan. Data for 1973, 1984 and 1994 are cited from Ref. 12.

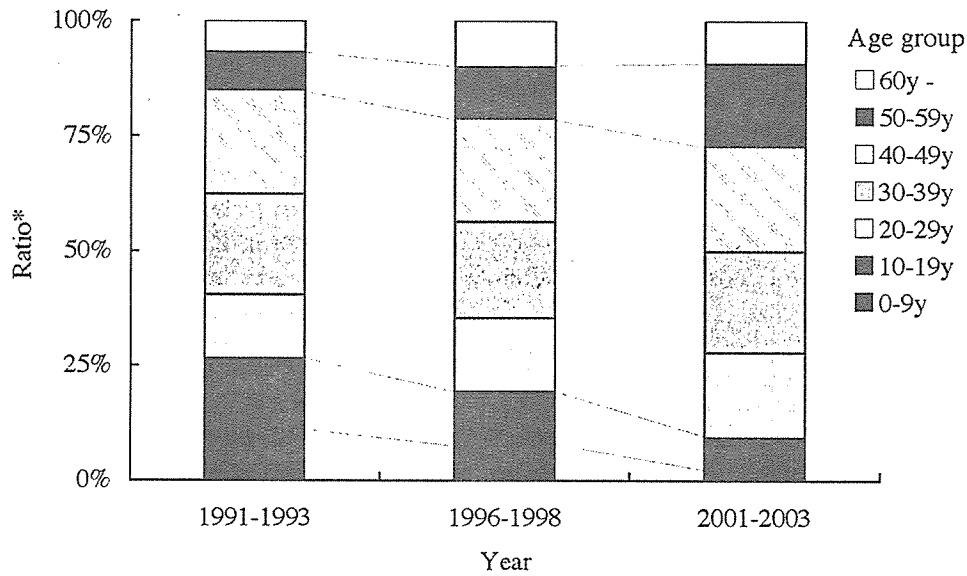

Fig. 5. Age-distribution of hepatitis A reported cases in Japan from 1991 to 2003. Data are cited from Ref. 15. Ratio of reported cases aged 50–59 increased during the period 1989 to 2003. Simultaneously, ratio of the 0–9 and 10–19 age groups decreased. * Ratio=Number of reported cases per age group in each study period/all reported cases in each study period (%). Study period was separated into 3-year intervals.

cination incidence in studies reported from the United States and Israel, namely 2.6 and 2.2–2.5 per 100,000, respectively. The current incidence of hepatitis A in Japan might be too low to warrant the introduction of a universal vaccination policy.

Hepatitis A infection might not be considered as a disease of great importance in Japan due to its low frequency and low mortality rate. However, our study suggests that susceptibility to hepatitis A among Japanese is increasing. As in other low HAV-endemic areas of the world, the major risk factors for hepatitis A in Japan have been travel to endemic areas (16), consumption of contaminated food including that imported from HAV endemic areas (6), patients medicated with clotting factors (9) and men who have sex with men (2). In addition, immunization of food handlers would seem

worthwhile, to prevent the possibility of food-borne, common-source outbreaks of hepatitis A. Furthermore, people with chronic liver disease are not more likely to be infected with hepatitis A virus, but they are more likely to develop fulminant hepatitis and die if infected (10).

In conclusion, the timely release of information regarding the current status of hepatitis A together with a vaccination program for high-risk groups, food handlers and persons with chronic liver disease in Japan would be suitable for the control of this virus at present.

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