Acknowledgments

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Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for Injecting Drug Users

On June 12, 2013, the Thailand Ministry of Health and CDC published results from a randomized controlled trial of a daily oral dose of 300 mg of tenofovir disoproxil fumarate (TDF) that showed efficacy in reducing the acquisition of human immunodeficiency virus (HIV) infection among injecting drug users (IDUs) (*1*). Based on these findings, CDC recommends that preexposure prophylaxis (PrEP) be considered as one of several prevention options for persons at very high risk for HIV acquisition through the injection of illicit drugs.

Background

Among the approximately 50,000 new HIV infections acquired each year in the United States, 8% were attributed to injection-drug use in 2010 (*2*). The National HIV Behavioral Surveillance System, surveying IDUs in 20 U.S. cities in 2009, found high frequencies of both injection-drug use and sexual practices that are associated with HIV acquisition (*3*). Among IDUs without HIV infection, 34% reported having shared syringes in the preceding 12 months, and 58% reported having shared injection equipment; 69% reported having unprotected vaginal sex and 23% reported having unprotected male-female anal sex. Among HIV-uninfected male IDUs, 7% reported previous male-male anal sex, and 5% reported unprotected male-male anal sex. However, only 19% of male and female IDUs reported participating in an intervention to reduce risk behaviors. These findings underscore a need to provide effective interventions to further reduce HIV infections among IDUs in the United States.

Several clinical trials have demonstrated safety and efficacy of daily oral antiretroviral PrEP for the prevention of HIV acquisition among men who have sex with men (MSM) (*4*) and heterosexually active men and women (*5,6*), although two trials were unable to show efficacy, likely because of low adherence (*7,8*) (Table). CDC previously has issued interim guidance for PrEP use with MSM (*9*) and heterosexually active adults (*10*) and now provides interim guidance for PrEP use in IDUs.

During 2009–2013, CDC convened workgroup meetings and consulted with external subject matter experts, including clinicians, epidemiologists, academic researchers, health department policy and program staff members, community representatives, and HIV and substance abuse subject matter experts at federal health agencies, to 1) review the results of PrEP trials and other data as they became available and 2) deliberate and recommend content for interim guidance and comprehensive U.S. Public Health Service guidelines for PrEP use in the United States. The expert opinions from the IDU workgroup and other workgroups were used to develop this interim guidance on PrEP use with IDUs.

Rationale and Evidence

The Bangkok Tenofovir Study enrolled HIV-uninfected persons who reported injecting illicit drugs in the prior year into a phase-III randomized, double-blind, placebo-controlled trial to determine the safety and efficacy of daily oral TDF to reduce the risk for HIV acquisition. In all, 2,413 eligible, consenting men and women aged 20–60 years were randomized to receive either daily oral doses of 300 mg of TDF (n = 1,204) or a placebo tablet (n = 1,209). Participants could elect to receive tablets daily by directly observed therapy or receive a 28-day supply of daily doses to take home; they could switch medication supply method at their monthly follow-up visits. At follow-up visits every 28 days, individualized adherence and risk-reduction counseling, HIV testing, pregnancy testing for women, and assessment for adverse events were conducted. An audio computer-assisted self-interview was conducted every 3 months to assess risk behaviors. Blood was collected at enrollment; months 1, 2, and 3; and then every 3 months for laboratory testing to screen for adverse reactions to the medication. At study clinics (operated by the Bangkok Metropolitan Administration), social services, primary medical care, methadone, condoms, and bleach (for cleaning injection equipment) were provided free of charge.

The study was conducted during 2005–2012, with a mean follow-up time of 4.6 years (maximum: 6.9 years) and a 24% loss to follow-up or voluntary withdrawal in the TDF group and a 23% loss in the placebo group. Participants took their study drug an average of 83.8% of days and were on directly observed therapy 86.9% of the time.

After enrollment, 50 patients acquired HIV infection: 17 in the TDF group and 33 in the placebo group. In the modified "intent-to-treat" analysis (excluding two participants later found to have been HIV-infected at enrollment), HIV incidence was 0.35 per 100 person-years in the TDF group and 0.68 per 100 person-years in the placebo group, representing a 48.9% reduction in HIV incidence (95% confidence interval [CI] = 9.6%–72.2%). Among those in an unmatched case-control study that included the 50 persons with incident HIV infection (case-patients) and 282 HIV-uninfected participants from four clinics (controls), detection of tenofovir in plasma was associated with a 70% reduction in the risk for HIV infection (CI = 2.3%–90.6%).

TABLE. Results from randomized, placebo-controlled, clinical trials of the efficacy of daily oral antiretroviral preexposure prophylaxis (PrEP) for preventing human immunodeficiency virus (HIV) infection

Clinical trial	Participants	Type of medication	mITT efficacy*		Adherence-adjusted efficacy based on TDF detection in blood	
			%	(95% CI)	%	(95% CI)
Bangkok Tenofovir Study	Injecting drug users	TDF	49	(10–72)	70	(2–91)
Partners PrEP	HIV discordant couples	TDF	67	(44–81)	86	(67–94)
		TDF/FTC	75	(55–87)	90	(58–98)
TDF2	Heterosexually active men and women	TDF/FTC	62	(22–83)	84	NS
iPrEx	Men who have sex with men	TDF/FTC	42	(18–60)	92	(40–99)
Fem-PrEP	Heterosexually active women	TDF/FTC	NS	—	NA	—
VOICE	Heterosexually active women	TDF	NS	—	NA	—
		TDF/FTC	NS	—	NA	—

Abbreviations: mITT = modified intent to treat analysis, excluding persons determined to have had HIV infection at enrollment; CI = confidence interval; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; NS = not statistically significant; NA = data not available.
* % reduction in acquisition of HIV infection.

The rates of adverse events, serious adverse events, deaths, grade 3–4 laboratory abnormalities, and elevated serum creatinine did not differ significantly between the two groups. Reports of nausea and vomiting were higher in the TDF group than the placebo group in the first 2 months of medication use but not thereafter. No HIV infections with mutations associated with TDF resistance were identified among HIV-infected participants.

Comparing rates at enrollment with rates at 12 months of follow-up, risk behaviors decreased significantly for injecting drugs (from 62.7% to 22.7%), sharing needles (18.1% to 2.3%), and reporting multiple sexual partners (21.7% to 11.0%), and these risk behaviors remained below baseline throughout the entire period of the trial (all three comparisons, $p<0.001$). Rates were similar in the TDF and placebo groups.

PrEP Recommendation for IDUs

On July 16, 2012, based on the results of trials in MSM and heterosexually active women and men, the Food and Drug Administration approved a label indication for the use of the fixed dose combination of TDF 300 mg and emtricitabine (FTC) 200 mg (Truvada) as PrEP against sexual HIV acquisition by MSM and heterosexually active women and men (*11*). These trials did not evaluate safety and efficacy among injecting-drug users.

CDC recommends that daily TDF/FTC be the preferred PrEP regimen for IDUs for the following reasons: 1) TDF/FTC contains the same dose of TDF (300 mg) proven effective for IDUs, 2) TDF/FTC showed no additional toxicities compared with TDF alone in PrEP trials that have provided both regimens, 3) IDUs also are at risk for sexual HIV acquisition for which TDF/FTC is indicated, and 4) TDF/FTC has an approved label indication for PrEP to prevent sexual HIV acquisition in the United States. Its use to prevent parenteral HIV acquisition in those without sexual acquisition risk is currently an "off-label" use. Reported injection practices that place persons at very high risk for HIV acquisition include sharing of injection equipment, injecting one or more times a day, and injection of cocaine or methamphetamine. CDC recommends that prevention services provided for IDUs receiving PrEP include those targeting both injection and sexual risk behaviors (12).

In all populations, PrEP use 1) is contraindicated in persons with unknown or positive HIV status or with an estimated creatinine clearance <60 mL/min, 2) should be targeted to adults at very high risk for HIV acquisition, 3) should be delivered as part of a comprehensive set of prevention services, and 4) should be accompanied by quarterly monitoring of HIV status, pregnancy status, side effects, medication adherence, and risk behaviors, as outlined in previous interim guidance (*9,10*). Adherence to daily PrEP is critical to reduce the risk for HIV acquisition, and achieving high adherence was difficult for many participants in PrEP clinical trials (Table).

Comment

Providing PrEP to IDUs at very high risk for HIV acquisition could contribute to the reduction of HIV incidence in the United States. In addition, if PrEP delivery is integrated with prevention and clinical care for the additional health concerns faced by IDUs (e.g., hepatitis B and C infection, abscesses, and overdose), substance abuse treatment and behavioral health care, and social services, PrEP will contribute additional benefits to a population with multiple life-threatening physical, mental, and social health challenges (*12,13*). CDC, in collaboration with other federal agencies, is preparing comprehensive U.S. Public Health Service guidelines on the use of PrEP with MSM, heterosexually active men and women, and IDUs, currently scheduled for release in 2013.

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Mass Drug Administration for the Elimination of Lymphatic Filariasis — Port-au-Prince, Haiti, 2011–2012

Lymphatic filariasis (LF), also known as elephantiasis, results from mosquito-borne infection with filarial worm parasites, predominantly *Wuchereria bancrofti*, and can lead to severe disfigurement from lymphedema and hydrocele. The World Health Organization (WHO) has called for the elimination of LF using the strategy of annual mass drug administration (MDA). WHO defines adequate MDA coverage (the percentage of all residents of an endemic area who swallow the drugs) as ≥65%. By late 2011, all areas in Haiti where LF is endemic had received MDA, except Port-au-Prince, which was considered the most challenging area. The first MDA in Port-au-Prince was conducted from November 2011 through February 2012. To evaluate coverage, a stratified, three-stage cluster-sample survey was conducted. In all, 71% (95% confidence interval = 69%–74%) of persons swallowed the MDA tablets, according to their own or a proxy respondent's recall. Coverage was highest (77%) among internally displaced persons (IDPs) in camps, and <65% in two of the remaining six survey strata (urban communes). Among the 1,976 adults asked additional questions, 88% said they heard about the MDA before it happened, 74% that they were given tablets, and 71% that they swallowed the tablets. Only 50% of those who did not hear about the MDA in advance swallowed the tablets. The MDA was a large step toward the elimination of LF in Haiti but must be followed by MDA rounds that maintain adequate coverage.

In 2010, WHO estimated that 120 million persons were infected with LF globally (*1*). In the Americas, Haiti is one of four countries where LF is still endemic, accounting for 78.7% of 12.4 million persons at risk in this region (*2*). In 2000, WHO called for the elimination of LF by 2020, based on a strategy of annual MDA with drugs that clear microfilaria, the circulating stage of the parasite in humans (*3*). LF elimination guidelines are based on the expectation that five consecutive annual MDA rounds, each achieving ≥65% coverage in the total population, will result in interruption of transmission (*3*). By late 2011, at least one round of MDA using albendazole and diethylcarbamazine had been conducted throughout all endemic areas of Haiti except the capital, Port-au-Prince. Port-au-Prince includes the communes of Cité Soleil, Carrefour, Delmas, Pétion-Ville, Port-au-Prince, and Tabarre, and is considered the most challenging area in which to conduct an MDA (*4*). During November 2011–February 2012, an MDA was conducted for the first time in these communes. Based on reports of doses administered divided by the estimated population of this area, the National Program for the Elimination of Lymphatic Filariasis estimated that 92% coverage had been achieved, varying from 79% to 160% by commune. After the MDA, a household survey was conducted by the Ministry of Public Health and Population and partners as an independent means of assessing coverage and to identify ways of increasing coverage and improving coverage evaluation of MDAs in subsequent years.

A stratified, three-stage cluster sample design was used to select households in seven strata: the IDP camps located within the six communes (one stratum) and non-IDP camp households in each of the six communes (six strata). The first-stage sampling frame for the IDP camps was a list of camps and their sizes in households from administrative records updated every 2–3 months. For non-IDP camp households, the sampling frame was a list of census enumeration areas (sections démographiques d'énumeration [SDEs]), with SDE sizes in households taken from a 2011 update (without enumeration) of the 2003 national census. In all, 35 IDP camps and 30 SDEs in each of the remaining strata were selected, with probability proportional to estimated camp and SDE size. Each selected SDE and camp was divided into two or more segments of approximately equal size in households based on natural lines of division. A single segment was randomly chosen within each selected SDE and camp and survey teams then selected a systematic sample of households within the segment using a sampling interval calculated so that all households in the same stratum had the same overall probability of selection and provided the target sample size.

Within each selected household, a parent or guardian provided responses for children aged <10 years, and this person or another adult provided responses for older children and adults who were absent. Persons asked about swallowing the tablets were first shown the tablets. A knowledge, attitudes, and practices (KAP) questionnaire was administered to persons aged ≥18 years who were present at the time of the survey visit. Coverage and KAP survey data were collected using questionnaires on smart phones and were cleaned and analyzed using statistical software. Children aged <2 years, pregnant women, and severely ill persons were ineligible for treatment during the MDA. However, coverage was defined as the percentage of all persons who swallowed the tablets (*3*). Coverage estimates for the Port-au-Prince population as a whole (all seven strata) were calculated using sampling weights derived from the overall selection probabilities of households.

A total of 2,102 households were selected for the survey sample during the survey fieldwork, which took place during May 3–21, 2012. In 78% of these households, with a total of 6,345

household members, an adult member was present and agreed to participate in the survey. In all, 63% of persons aged ≥10 years answered the question about swallowing the MDA tablets themselves; for the remaining 37%, the question was answered by a proxy adult household member. In a weighted analysis of all seven strata, the answer to the question about swallowing the MDA drugs was "yes" for 71% (95% confidence interval = 69%–74%), "no" for 23%, and "don't know" for 6% (Table) of household members in the sample. In all, 97% of "don't know" answers were from proxy respondents for household members who were absent. "Yes" answers, by stratum, ranged from 60% in Tabarre Commune to 77% in the IDP camps. By this measure, two of the strata, Tabarre and Pétion-Ville Communes, did not achieve adequate (≥65%) coverage. Coverage by sex was nearly the same (71% among females, 72% among males.) Among persons aged ≥2 years, coverage was lowest (55%) among children aged 2–4 years and highest (83%) among children aged 5–14 years, declining gradually in older age groups to 62% overall among persons aged ≥65 years. The coverage-by-age group curve for non-IDP camp residents was slightly lower, but generally paralleled the curve for IDP camp residents, except for the oldest age group, for which non-IDP coverage declined and IDP-camp resident coverage increased (Figure).

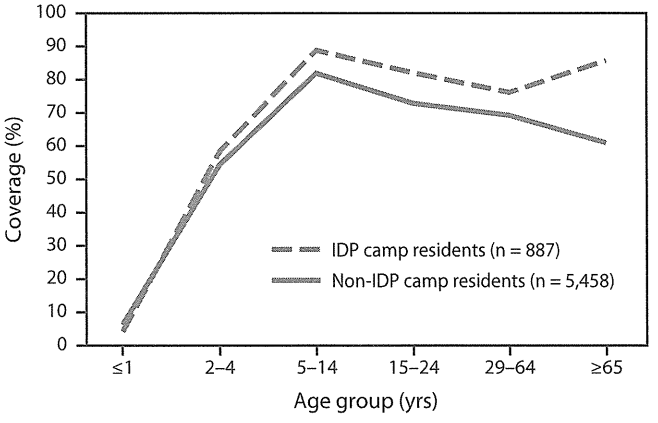
A total of 1,976 adults were interviewed with the KAP questionnaire. Because 70% of the respondents were women, who were more often at home than men, the following results were weighted according to selection probabilities and nonresponse rates by gender. In all, 88% of respondents said they heard about the MDA before it began; 74% said they were given tablets during the MDA, and 71% said they swallowed the tablets. Only 50% of those who did not hear about the MDA in advance swallowed the tablets, compared with 74% among those who heard about the MDA in advance. The most commonly mentioned preferred means of communication for those who did not hear about the MDA in advance were television (30%), radio (28%), community resource persons (17%), and a vehicle with loudspeaker (15%).

Most respondents who received tablets got them at a distribution post (85%); less common sites were home (8%) and school (4%). When asked about the distance to the nearest distribution point from their home, 77% of those who did not receive tablets answered that they did not know or were not aware of a distribution point, as compared with 6% of those who received tablets. The most common reason for not swallowing tablets that were received was concern about safety or becoming ill (61%). Among all persons given tablets at a distribution post, 76% swallowed them at the post; 13% reported that no water was available at the post (because of the threat of cholera, the program sought to offer a source of safe drinking water at distribution posts by purchasing water in small plastic bags from commercial sources; persons seeking treatment were given the tablets to swallow at home when distributors ran out of the plastic bags of water). Among all those who swallowed the drugs, 34% reported having adverse events within a day, most often nausea or vomiting (62%), and fatigue (42%).

TABLE. Estimated treatment coverage resulting from mass drug administration for lymphatic filariasis during December 2011–February 2012 — household survey, Port-au-Prince, Haiti, May 2012

Survey stratum	"Did you [or name of person for whom respondent answered] swallow tablets for lymphatic filariasis during the last mass drug distribution?" (%)			Sample size
	Yes	No	Do not know	
Carrefour Commune	75	20	5	1,111
Cité Soleil Commune	75	20	4	855
Delmas Commune	71	23	6	829
Pétion-Ville Commune	62	31	7	911
Port-au-Prince Commune	72	22	6	827
Tabarre Commune	60	29	11	925
Internally displaced person camps within the six communes	77	19	4	887
All strata (weighted averages and total)	71	23	6	6,345

FIGURE. Estimated treatment coverage resulting from mass drug administration for lymphatic filariasis, December 2011–February 2012, by age group and residence in internally displaced person (IDP) camps — household survey, Port-au-Prince, Haiti, May 2012



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What is already known on this topic?

Haiti is one of four countries in the Americas where lymphatic filariasis is still endemic. Approximately 9.7 million persons are at risk for lymphatic filariasis in Haiti. By late 2011, at least one round of mass drug administration (MDA) with albendazole and diethylcarbamazine had been conducted in all endemic parts of the country except the capital, Port-au-Prince.

What is added by this report?

A household survey conducted after the first MDA in Port-au-Prince showed that overall coverage with albendazole and diethylcarbamazine was 71% and that five of the seven populations within Port-au-Prince surveyed (residents of six communes and of camps for internally displaced persons) achieved adequate coverage (≥65%). The survey also showed that informing a greater percentage of adults in advance about the MDA and more effectively addressing concerns about safety and side effects might increase coverage. In addition, it showed that coverage estimates for the Port-au-Prince area based on tallies of the number of persons treated and population estimates were inaccurate.

What are the implications for public health practice?

Haiti's National Program for the Elimination of Lymphatic Filariasis will intensify the dissemination of specific health education messages before subsequent MDAs in Port-au-Prince and rely on household surveys to measure the coverage achieved in the Port-au-Prince area.

Editorial Note

The 71% MDA coverage calculated by the household survey in Port-au-Prince demonstrates that despite substantial obstacles posed by recent natural disasters and public health emergencies, Haiti has taken an important step toward meeting the challenge of LF elimination. Future MDA efforts should incorporate strategies that were identified in this analysis as potentially important to increase coverage and sustain program success.

MDA coverage, as determined by survey results, was inadequate (<65%) among permanent residents of Tabarre Commune (60%) and Pétion-Ville Commune (62%). This classification is conservative because these communes had the highest proportions of "don't know" answers to the coverage question (11% and 7%, respectively), the consequence of accepting adults as proxy respondents for household members not available when the survey team visited. If only persons who responded "yes" or "no" are considered, then the coverage estimates for these communes would be ≥65%. For future MDA coverage surveys in Port-au-Prince, survey teams could reduce the percentage of "don't know" answers by making repeat visits, including in the evening and on subsequent days, if needed, even if doing so within resource constraints requires smaller sample sizes or combining strata.

Although the coverage survey results might have been lowered slightly by "don't know" answers, they likely present a more accurate estimate of coverage than the 92% derived from reports of doses administered and estimated population sizes. Such estimates of coverage (sometimes called "administrative") can be in error because of inaccurate denominators, inaccurate reporting of doses administered, and treatment of persons outside their area of residence. The administrative result of 160% for Tabarre Commune clearly reflects one or more of these problems. At present, administrative coverage appears to be too inaccurate to be of value in Port-au-Prince; additional household surveys are planned to track MDA coverage.

Coverage estimates among adult respondents who stated that they heard about the MDA before it began were higher than among those who had not heard about it, suggesting that broadening the reach of pre-MDA communication, including by the means preferred by those who did not hear about the MDA in advance, might increase coverage. The survey also showed that the majority of respondents who did not receive tablets either were not aware of a distribution point or did not know how far away it was. Guidance on narrowing this knowledge gap might be provided by a follow-up study focused on the reasons for the lack of awareness, in particular, on whether post locations were systematically announced by megaphone throughout each post's catchment area daily during the MDA, as intended. Further efforts to disseminate information on the safety of the drugs also might increase coverage by addressing concerns about safety and becoming ill, which were the most common reasons for not swallowing tablets that had been received. These interventions for increasing coverage might help sustain progress toward national LF elimination. The 2011–2012 MDA in Port-au-Prince demonstrated that Haiti has the capacity to achieve this goal.

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Emergency Department Visits by Patients with Mental Health Disorders — North Carolina, 2008–2010

Patients with mental health disorders (MHDs) use the emergency department (ED) for acute psychiatric emergencies, for injuries and illnesses complicated by or related to their MHD, or when psychiatric or primary-care options are inaccessible or unavailable (*1,2*). An estimated 5% of ambulatory-care visits in the United States during 2007–2008 were made by patients with primary mental health diagnoses (*3*). To measure the incidence of ED visits in North Carolina with MHD diagnostic codes (MHD-DCs), the Carolina Center for Health Informatics (University of North Carolina at Chapel Hill) analyzed ED visits occurring during the period 2008–2010 captured by the North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT). This report describes the results of that analysis, which indicated that nearly 10% of ED visits had one or more MHD-DCs assigned to the visit and the rate of MHD-DC-related ED visits increased seven times as much as the overall rate of ED visits in North Carolina during the study period. Those with an MHD-DC were admitted to the hospital from the ED more than twice as often as those without MHD-DCs. Stress, anxiety, and depression were diagnosed in 61% of MHD-DC-related ED visits. The annual rate of MHD-DC-related ED visits for those aged ≥65 years was nearly twice the rate of those aged 25–64 years; half of those aged ≥65 years with MHD-DCs were admitted to the hospital from the ED. Mental health is an important component of public health (*4*). Surveillance is needed to describe trends in ED use for MHDs to develop strategies to prevent hospitalization, improve access to ambulatory care, and develop new ways to provide ED care for the elderly with MHDs.

ED visit data for the period 2008–2010 were extracted from NC DETECT, a population-based, statewide public health surveillance system that contains ED visit data (*5,6*) for 99% of ED visits in North Carolina occurring during the study period. ED visits were characterized by sex and age group, ED disposition, and type of MHD. MHD-DCs were identified from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for mental disorders (290–299); symptoms, signs, and ill-defined conditions (787–789.9); and supplementary codes (V11–79). ICD-9-CM codes for poisoning and overdose, metabolic or structural encephalopathies that are classified as psychiatric diagnostic codes by ICD-9-CM, substance abuse disorders, and tobacco use disorder were excluded. For each ED visit, a mental health ICD-9-CM diagnostic code in any one of up to 11 positions classified that visit as MHD-DC-related. Visit records with more than one MHD-DC were counted as a single MHD-DC-related visit. Using the first-listed MHD-DC for the ED visit, MHDs were subcategorized into 11 groups of clinically similar diagnostic categories for calculating rates. For purposes of regression analyses, all MHD-DCs were classified as present or absent for each ED visit. Data were extracted and stratified for univariate and two-way descriptive analyses, and annual rates were calculated per 10,000 population. Risk ratios were computed using log binomial regression with Poisson robust variances.

From 2008 to 2010, the annual number of ED visits in North Carolina increased by 5.1%, from 4,190,911 to 4,405,676, and MHD-DC-related ED visits increased by 17.7%, from 347,806 to 409,276 (Table 1). By 2010, ED visits with MHD-DCs accounted for 9.3% of all ED visits; 31.1% of ED visits with MHC-DCs resulted in hospital admission, compared with 14.1% of all ED visits.

For each ED visit, up to 11 diagnostic codes are captured by NC DETECT. One quarter of first-listed MHD-DCs were in the first-listed diagnostic code position, 56% of the MHD-DCs were within the first three diagnostic code positions, and 77% were within the first five. "Stress/Anxiety/Depressive disorders" was the MHD-DC category with the highest number of ED visits (Table 2).

Increasing age was associated with an increase in hospital admission, with 14% of children aged <15 years admitted and 51% of adults aged ≥65 years admitted (Table 3). The highest admission proportion was for ED visits associated with dementia (60.5%) (Table 2). Population-based rates of MHD-DC related visits for those aged ≥65 years were very high for any MHD diagnosis compared with all other age groups, driven primarily by higher rates of schizophrenia/delusions/psychoses, dementia, and stress/anxiety/depression (Table 4).

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Editorial Note

The ED is an important link between outpatient and inpatient services for the care of patients with MHDs. ED visits by patients with MHD-DCs are increasing more rapidly than

TABLE 1. Number and percentage of emergency department (ED) visits related to mental health disorders (MHDs) compared with all other ED visits, overall and among those resulting in hospital admission — North Carolina, 2008–2010

	2008			2009			2010		
	ED visits overall			ED visits overall			ED visits overall		
Type of ED visit	No.	(%)	Rate per 10,000 population	No.	(%)	Rate per 10,000 population	No.	(%)	Rate per 10,000 population
MHD-related visits	347,806	(8.3)	376	381,700	(8.7)	407	409,276	(9.3)	430
All other ED visits	4,190,911	(100.0)	4,532	4,382,028	(100.0)	4,670	4,405,676	(100.0)	4,628

	2008		2009		2010	
	ED visits resulting in hospital admission		ED visits resulting in hospital admission		ED visits resulting in hospital admission	
Type of ED visit	No.	(%)	No.	(%)	No.	(%)
MHD-related visits	116,936	(35.7)	123,429	(34.1)	126,808	(31.1)
All other ED visits	580,655	(14.8)	597,177	(14.2)	619,831	(14.1)

TABLE 2. Mental health disorders (MHDs) resulting in emergency department (ED) visits and hospital admissions, by diagnostic category — North Carolina, 2008–2010

		% of MHD-related ED visits in this category†				
Type of MHD*	ICD-9-CM codes	2008	2009	2010	Risk ratio for hospital admission§	Mean % admitted 2008–2010
Stress/Anxiety/Depression	300 (excluding 300.9), 306, 308, 309, 311, 313.1, V11.2, V69.8, V79.0	60.78	61.70	62.33	0.91 (0.90–0.92)	28.89
Schizophrenia/Delusional/Psychosis	294.0, 294.8, 294.9, 295, 297, 298, V11.0	19.89	19.37	19.49	1.08 (1.07–1.09)	42.99
Bipolar	296, V11.1	17.96	18.26	18.32	1.28 (1.27–1.29)	37.32
Suicidal/Homicidal ideation	300.9, V62.84, V62.85	6.69	6.87	6.82	1.44 (1.42–1.45)	40.01
Dementia	290, 294.1, 294.2	5.99	5.53	5.21	1.26 (1.25–1.27)	60.54
Personality/Conduct disorder	301, 312	3.03	2.93	2.05	1.37 (1.35–1.39)	48.38
Miscellaneous/Other¶	302, 307 (excluding 307.1, 307.5, 307.8), V11.8, V11.9, V15.4 (excluding V15.41)	1.61	1.47	1.41	0.81 (0.79–0.83)	24.49
Psychiatric examination	V70.1, V70.2, V71.0	1.02	1.06	1.03	0.49 (0.47–0.52)	13.35
Mental disorders from brain damage	310	0.74	0.69	0.68	0.86 (0.83–0.89)	23.81
Developmental disorders originating in childhood	299	0.64	0.75	0.71	0.96 (0.91–1.01)	15.87
Eating disorders	307.1, 307.5	0.20	0.44	0.16	1.01 (0.95–1.06)	32.36

Abbreviation: ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*.

* Up to 11 ICD-9-CM diagnostic codes were examined to classify presence or absence of categories of MHDs.

† Percentages in each column sum to more than 100% because 16% of MHD-related ED visits during 2008–2010 were counted in more than one MHD category.

§ Risk ratio for the presence of each condition versus its absence, controlling for number of diagnostic codes of any type (classified as either 6–11 codes or 1–5 codes), tobacco use, and presence or absence of nine comorbidities (substance abuse, injury, asthma/chronic obstructive pulmonary disorder, cancer, diabetes/hypoglycemia, heart failure, hepatic failure, renal failure, and obesity). Computed using log binomial regression with Poisson robust variances.

¶ Includes sexual and gender-identity disorders, personal history of other or unspecified mental disorder, personal history of psychiatric trauma, and special symptoms or syndromes not elsewhere classified.

general ED visits (*3,7*). Only minor changes in ICD-9-CM codes have been issued since October 2000 (*8*), so coding procedures for MHD likely did not change greatly during the course of the study. In this study, population-based rates of MHD-DC-related ED visits in North Carolina increased progressively from 2008 to 2010, by 14.4%, whereas the rate of all ED visits increased by only 2.1%. The rate of MHD-DC-related ED visits by patients of all ages is increasing but is especially high for those aged ≥65 years, who have the highest MHD-DC-related ED visit rate of any age group and the highest risk ratio (2.2) for hospital admission. Patients with stress/anxiety/depression accounted for the majority (60.8%) of the MHD-DC related ED visits, an unanticipated finding because such disorders often are more appropriately treated in an office setting. Hospital admissions for ED visits with MHD-DCs decreased from 35.7% in 2008 to 31.1% in 2010. The reasons for this decrease are unclear.

TABLE 3. Risk for hospital admission after emergency department (ED) visits related to mental health disorders (MHDs) versus all ED visits, by age group — North Carolina, 2008–2010

Age group (yrs)	Risk ratio for hospital admission after an MHD-related ED visit*	% of MHD-related ED visits occurring in this age group	% of MHD-related ED visits in this age group resulting in hospital admission	% of all ED visits in this age group resulting in hospital admission
0–14	1.00 (referent)	2.30	14.03	3.73
15–24	1.22 (1.18–1.26)	10.99	17.70	4.70
25–44	1.36 (1.31–1.40)	31.12	22.19	7.84
45–64	1.79 (1.73–1.86)	28.33	36.52	20.01
≥65	2.21 (2.13–2.28)	27.25	51.19	38.76

* Computed using log binomial regression with Poisson robust variances, controlling for other MHDs, tobacco use, and presence or absence of nine comorbidities (substance abuse, injury, asthma/chronic obstructive pulmonary disorder, cancer, diabetes/hypoglycemia, heart failure, hepatic failure, renal failure, and obesity).

TABLE 4. Population-based rates* of emergency department (ED) visits related to mental health disorders (MHDs), by diagnostic category, age group, and year — North Carolina, 2008–2010

		Diagnostic category†										
Age group and year	Any MHD diagnosis (all categories combined)	Stress/ Anxiety/ Depression	Schizophrenia/ Delusional/ Psychosis	Bipolar	Suicidal/ Homicidal ideation	Dementia	Personality/ Conduct disorder	Miscellaneous/ Other	Psychiatric examination	Mental disorders from brain damage	Developmental disorders originating in childhood	Eating disorders
0–14 yrs												
2008	43.7	15.5	1.7	8.3	2.8	0.1	4.1	1.7	1.4	1.0	6.8	0.3
2009	50.2	16.2	1.9	8.4	3.4	0.2	4.2	1.8	1.1	1.1	8.8	3.1
2010	48.1	16.8	1.9	8.8	3.5	0.2	4.4	1.8	1.2	1.3	7.8	0.4
15–24 yrs												
2008	288.3	170.8	18.5	57.0	17.4	0.4	7.7	4.0	4.9	3.5	3.2	0.7
2009	316.6	183.9	18.1	66.6	20.1	0.3	8.2	4.4	5.5	4.0	3.8	1.7
2010	331.3	192.1	20.7	68.3	22.7	0.2	8.8	4.0	5.5	3.9	4.2	0.8
25–44 yrs												
2008	415.4	260.8	32.4	87.4	18.1	0.2	4.9	3.8	4.0	2.6	0.7	0.6
2009	455.4	288.2	31.8	95.2	21.0	0.4	5.5	4.1	4.1	2.8	1.1	1.3
2010	482.0	308.1	34.2	97.5	23.5	0.3	5.6	4.2	4.0	3.0	1.2	0.5
45–64 yrs												
2008	410.8	267.1	48.2	66.6	12.5	3.4	3.8	3.7	3.2	1.9	0.3	0.3
2009	451.0	296.9	50.9	71.2	14.8	3.7	3.9	3.5	3.2	2.0	0.3	0.7
2010	483.0	318.1	52.6	77.1	17.6	4.0	3.8	4.5	3.1	2.0	0.3	0.3
≥65 yrs												
2008	840.4	308.2	321.0	34.0	3.2	158.5	2.2	6.5	1.4	4.6	0.0	0.6
2009	865.3	324.0	336.1	34.1	4.0	152.5	2.2	6.0	1.6	3.7	0.1	1.1
2010	905.8	344.1	355.7	35.4	5.4	150.5	2.3	8.0	1.6	3.8	0.1	0.3

* Per 10,000 population.
† Diagnostic category for each MHD-related ED visit based on the category of the first-listed MHD *International Classification of Diseases, Ninth Revision, Clinical Modification* code.

Good mental health services require a system of care that includes EDs, hospitals, and ambulatory-care clinics that are adequately resourced. If the trends reported in this study continue to escalate, EDs, hospitals, and (most importantly) patients will be further burdened. The high numbers of ED visits and hospital admissions for patients with any type of MHD-DCs, for those aged ≥65 years (especially with dementia), and for those with low-acuity MHDs, indicate a need for system adjustment. Strategies are needed to counteract the effects of inpatient bed shortages and the increased volume of MHD-DC-related visits to EDs. Surveillance is the first step, because identifying trends in ED use by patients with MHDs can guide policies and procedures designed to reduce hospitalization, improve access to ambulatory care services, and develop new ways to care for the elderly with MHDs in the ED.

The findings in this report are subject to at least four limitations. First, ED visit data in NC DETECT are secondary data from hospital administrative and clinical data sources; diagnostic codes typically are extrapolated by hospital coders from the patient record. Second, the percentage of ED visits identified as having associated MHD-DCs probably is an underestimate; other coding studies have reported underestimation of medical disorders when relying solely on diagnostic codes. Third, some types of ED visits by patients with MHDs, such as visits attributed to involuntary commitment or those initiated by law enforcement, likely would not be prevented by better outpatient access. Finally, coder training and experience, clinician documentation, and billing practices affect diagnosis coding for all types of medical conditions (*9*). For this study, MHD-DCs were categorized into clinically coherent groups

What is already known on this topic?

The number of emergency department (ED) visits associated with mental health disorders (MHDs) is increasing in the United States. Patients with mental health disorders (MHDs) use the emergency department (ED) for acute psychiatric emergencies, for injuries and illnesses complicated by or related to their MHD, or when psychiatric or primary-care options are inaccessible or unavailable. EDs are an important part of the overall system providing health care for patients with MHDs.

What is added by this report?

In North Carolina during 2008–2010, 8.8% of ED visits were assigned at least one MHD diagnosis code (MHD-DC) among 11 possible, with a 2010 rate of 430 MHD-DC-related ED visits per 10,000 population. The rate of MHD-DC-related ED visits increased by 14.4%, whereas the rate of all ED visits increased by 2.1%, and the proportion of MHD-DC-related ED visits resulting in hospital admission was 2.3 times greater than that for all ED visits. Persons aged ≥65 years with MHD-DC-related diagnoses had the highest ED visit and admission rate of any age group.

What are the implications for public health practice?

The increasing numbers and rates of ED visits by patients with MHDs, especially the elderly, indicate a growing burden on the health-care delivery system. Standardized surveillance is needed to identify trends in ED use and the impact of any interventions.

by clinicians on the study team. A study reviewing ED visits for MHDs in New South Wales, Australia, using a similar classification methodology, resulted in almost identical ICD-9-CM categorization and frequencies of disorders (*10*).

Additional information about NC DETECT and ED visit data for North Carolina is available at http://www.ncdetect.org.

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Influenza Activity — United States, 2012–13 Season and Composition of the 2013–14 Influenza Vaccine

During the 2012–13 influenza season in the United States, influenza activity* increased through November and December before peaking in late December. Influenza A (H3N2) viruses predominated overall, but influenza B viruses and, to a lesser extent, influenza A (H1N1)pdm09 (pH1N1) viruses also were reported in the United States. This influenza season was moderately severe, with a higher percentage of outpatient visits for influenza-like illness (ILI), higher rates of hospitalization, and more reported deaths attributed to pneumonia and influenza compared with recent years. This report summarizes influenza activity in the United States during the 2012–13 influenza season (September 30, 2012–May 18, 2013) as of June 7, 2013, and reports the recommendations for the components of the 2013–14 Northern Hemisphere influenza vaccine.

Viral Surveillance

During September 30, 2012–May 18, 2013, World Health Organization and National Respiratory and Enteric Virus Surveillance System collaborating laboratories in the United States tested 311,333 specimens for influenza viruses; 73,130 (23%) were positive (Figure 1). Of the positive specimens, 51,675 (71%) were influenza A viruses, and 21,455 (29%) were influenza B viruses. Among the seasonal influenza A viruses, 34,922 (68%) were subtyped; 33,423 (96%) were influenza A (H3N2) viruses, and 1,497 (4%) were pH1N1 viruses. In addition, two variant influenza A (H3N2v) viruses were identified.†

Typically the influenza season is said to begin when certain key indicators remain elevated for a number of consecutive weeks. One of these indicators is the percent of respiratory specimens testing positive for influenza. The proportion of specimens testing positive for influenza during the 2012–13 season first exceeded 10% during the week ending November 10, 2012 (week 45), and peaked at 38% during the week ending December 29, 2012 (week 52).

Since the start of the 2012–13 season, influenza A (H3N2) viruses have predominated nationally, followed by influenza B viruses; pH1N1 viruses have been identified less frequently. The relative proportion of each type and subtype varied by geographic U.S. Department of Health and Human Services region§ and week. Influenza A viruses predominated until the end of February, with influenza B viruses predominating from the week ending February 23, 2013 (week 8) through the week ending May 18, 2013 (week 20).

Regional differences were observed in the timing of influenza activity and the relative proportions of circulating viruses. Using the percentage of specimens testing positive for influenza to determine the peak of influenza activity, Region 4 activity peaked earliest, during the week ending December 8, 2012 (week 49), and Region 9 activity peaked latest, during the week ending January 26, 2013 (week 4). The highest proportion of influenza B viruses was observed in Region 6 (42%) and the lowest proportion of influenza B viruses was detected in Region 1 (15%).

Novel Influenza A Viruses

During the 2012–13 influenza season, one case of human infection with a variant influenza A (H3N2) (H3N2v) virus was reported in each of two states, Minnesota and Iowa. Both infections occurred in children, one with known exposure to swine. Both patients recovered fully.

Antigenic Characterization

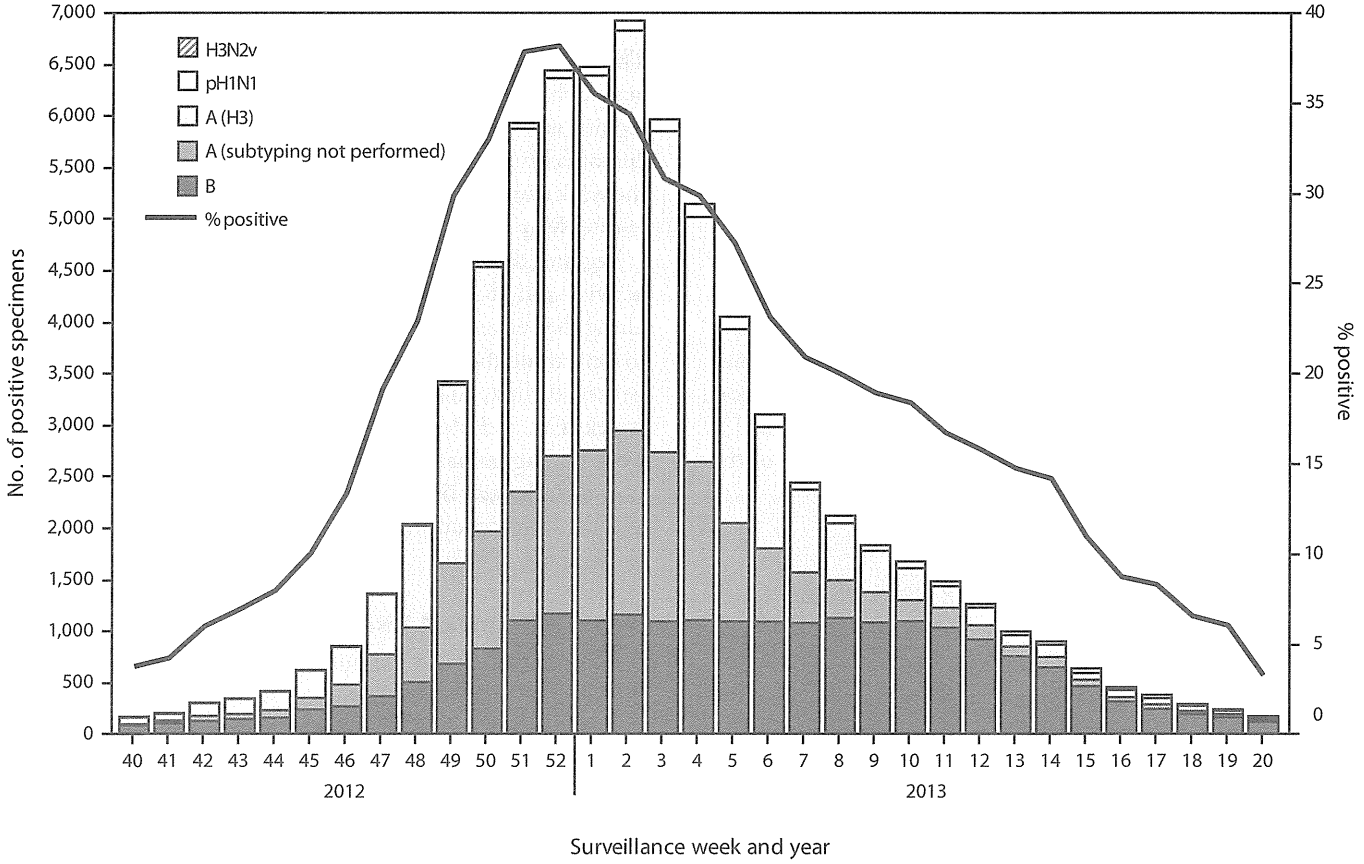
CDC has antigenically characterized 2,452 influenza viruses collected since October 1, 2012, and submitted by U.S. laboratories, including 252 pH1N1 viruses, 1,324 influenza A (H3N2) viruses, and 876 influenza B viruses. Of the 252 pH1N1 viruses tested, 249 (98.8%) were characterized as A/California/7/2009-like, the influenza A(H1N1) component of the 2012–13 influenza vaccine. Three viruses (1.2%) of the 252 tested showed reduced titers with ferret antiserum raised against A/California/7/2009. Of the 1,324 influenza A (H3N2) viruses, 1,319 (99.6%) were antigenically similar to the cell-propagated A/Victoria/361/2011 reference virus; most viruses tested were cell-propagated. The H3N2 vaccine component for the 2012–13 Northern Hemisphere season was egg-propagated A/Victoria/361/2011; the use of egg-propagated vaccine viruses is a current regulatory requirement for vaccine production. Five (0.4%) of the 1,324 tested showed reduced titers with antiserum produced against cell-propagated A/Victoria/361/2011.

* Additional information on influenza surveillance and reporting systems in the United States, methods, and levels of activity is available at http://www.cdc.gov/flu/weekly/overview.htm.

† Influenza viruses that normally circulate in pigs are called "variant" viruses when they are found in humans. Influenza A (H3N2) variant viruses ("H3N2v" viruses) with the matrix (M) gene from the 2009 H1N1 pandemic virus were first detected in humans in July 2011. Since then, 319 cases of H3N2v infection have been confirmed in humans, mostly associated with prolonged exposure to pigs at agricultural fairs.

§ Additional information available at http://www.hhs.gov/about/regionmap.html.

FIGURE 1. Number and percentage of respiratory specimens testing positive for influenza reported to CDC, by type and surveillance week and year — World Health Organization and National Respiratory and Enteric Virus Surveillance System collaborating laboratories, United States, September 30, 2012–May 18, 2013



Of the 876 influenza B viruses tested, 581 (66.3%) belonged to the B/Yamagata lineage, and were characterized as B/Wisconsin/1/2010-like, the influenza B component for the 2012–13 Northern Hemisphere influenza vaccine. A total of 295 (33.7%) viruses tested belonged to the B/Victoria lineage.

Resistance to Antiviral Medications

Since October 1, 2012, a total of 3,626 influenza virus specimens have been tested for antiviral resistance. All 961 influenza B viruses tested were sensitive to both oseltamivir and zanamivir. Among 2,123 influenza A (H3N2) viruses tested, one (0.05%) was found to be resistant to oseltamivir alone and one (0.05%) to both oseltamavir and zanamivir. Among the 542 pH1N1 viruses tested for resistance to oseltamivir, two (0.4%) were resistant, and all of the 258 viruses tested for resistance to zanamivir were sensitive. High levels of resistance to the adamantanes (amantadine and rimantadine) persist among influenza A viruses currently circulating globally (the adamantanes are not effective against influenza B viruses).

Composition of the 2013–14 Influenza Vaccine

The Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee has recommended that the 2013–14 influenza trivalent vaccines used in the United States contain an A/California/7/2009(H1N1) pdm09-like virus, an A(H3N2) virus antigenically like the cell-propagated A/Victoria/361/2011 virus (A/Texas/50/2012), and a B/Massachusetts/2/2012-like (B/Yamagata lineage) virus. A/Texas/50/2012 is an egg-propagated A(H3N2) virus antigenically similar to cell-propagated A/Victoria/361/2011. The committee recommended that A/Texas/50/2012 be used as the H3N2 vaccine component because of antigenic changes in A/Victoria/361/2011 vaccine virus resulting from mutations acquired during growth in eggs. The committee also recommended that quadrivalent vaccines contain a B/Brisbane/60/2008-like (B/Victoria lineage) virus (*1*). These recommendations were based on global influenza virus surveillance data related to epidemiology, antigenic and genetic characteristics, and serological responses to 2012–13 seasonal vaccines, and the availability of candidate strains and reagents.

Outpatient Illness Surveillance

Nationally, the weekly percentage of outpatient visits for ILI[¶] to health-care providers participating in the U.S. Outpatient Influenza-Like Illness Surveillance Network (ILINet) exceeded the national baseline level of 2.2% for 15 weeks during the 2012–13 influenza season (Figure 2). The peak percentage of outpatient visits for ILI was 6.1%, and occurred in the week ending December 29, 2012 (week 52). In contrast, the peak percentage of outpatient visits for ILI during the previous influenza season (2011–12) was 2.4% and occurred in mid-March. During the 2007–08 and 2010–11 influenza seasons, both of which had influenza A (H3N2) virus as the predominant circulating virus, the peak percentage of outpatient visits for ILI was 6.0% and 4.6%, respectively; both peaks occurred in mid-February. During the 2012–13 season, on a regional level, the percentage of visits for ILI exceeded region-specific baselines in all 10 regions. ILINet data are used to produce a weekly state-level measure of ILI activity varying from minimal to high: the number of states experiencing high ILI activity peaked during the week ending December 29, 2012 (week 52) with 35 states.

State-Specific Activity Levels

State and territorial epidemiologists report the geographic distribution of influenza in their states through a weekly influenza activity code. The geographic distribution of influenza activity was most extensive during the week ending January 12, 2013 (week 2), when 48 states reported widespread influenza activity and two states reported regional influenza activity. The week ending May 18, 2013 (week 20) was the first week no state or territory reported regional or widespread influenza activity. The number of states reporting widespread or regional activity during the peak week of activity has ranged from 20 to 50 states during the previous four influenza seasons (Influenza Division, CDC, unpublished data, 2013).

Influenza-Associated Hospitalization

CDC monitors hospitalizations associated with laboratory-confirmed influenza virus infections using the FluSurv-NET** surveillance system. Cumulative hospitalization rates (per 100,000 population) were calculated by age group based on 12,337 total hospitalizations resulting from influenza during October 1, 2012–April 30, 2013. Among 12,293 cases with influenza type specified, 9,767 (79.2%) were associated with influenza A and 2,492 (20.2%) with influenza B; and 34 (0.3%) were associated with influenza A and influenza B co-infections; 44 (0.4%) had no virus type information available. Persons aged ≥65 years accounted for approximately 50% of reported cases. The cumulative incidence[††] for all age groups since October 1, 2012, was 44.3 per 100,000 (Figure 3). The cumulative hospitalization rate (per 100,000 population) by age group for this period was 66.2 (0–4 years), 14.5 (5–17 years), 16.4 (18–49 years), 41.2 (50–64 years), and 191.2 (≥65 years). During the past four influenza seasons, age-specific hospitalization rates ranged from 15.8 to 72.8 (0–4 years), 4.0 to 27.3 (5–17 years), 3.6 to 23.1 (18–49 years), 5.1 to 30.8 (50–64 years), and 13.5 to 65.9 (≥65 years).

What is already known on this topic?

CDC collects, compiles, and analyzes data on influenza activity year-round in the United States. The influenza season generally begins in the fall and continues through the winter and spring months; however, the timing and severity of influenza activity varies by geographic location and season.

What is added by this report?

During the 2012–13 influenza season, influenza A (H3N2), influenza A (H1N1)pdm09, and influenza B viruses cocirculated. In addition, two cases of infection with variant influenza A viruses were reported in the United States. Compared with recent influenza seasons, this season had a higher percentage of outpatient visits for influenza-like illness, higher rates of hospitalizations, and more deaths attributed to pneumonia and influenza.

What are the implications for public health practice?

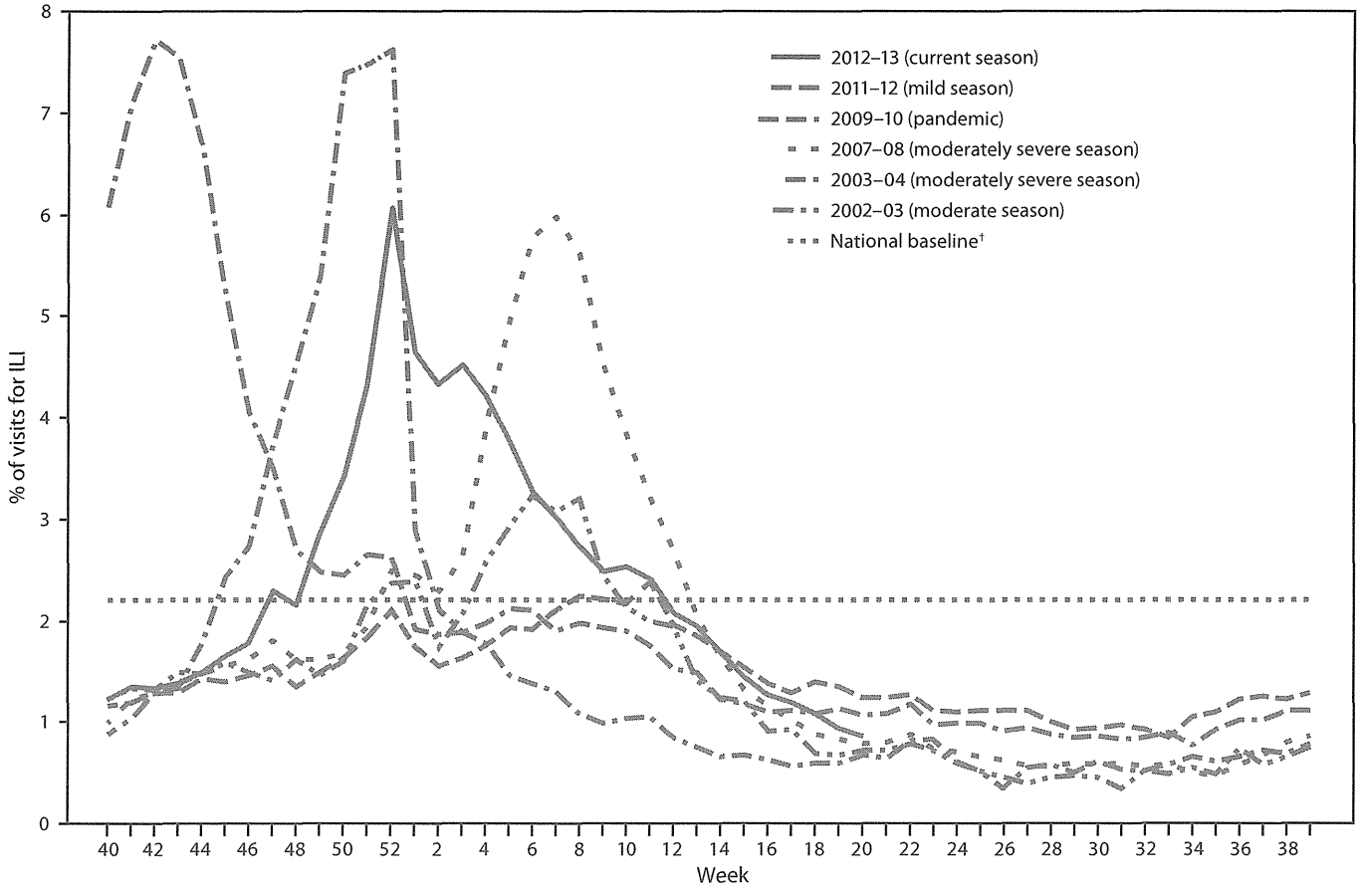
All unvaccinated persons aged ≥6 months should be offered influenza vaccine throughout the influenza season. In addition, timely empiric antiviral treatment is recommended for patients with severe, complicated, or progressive influenza illness; those at higher risk for influenza complications; or those for whom treatment can be started within 48 hours of illness onset. In addition, influenza surveillance, including for novel influenza viruses, should continue through the summer months, and physicians should consider influenza as a cause of respiratory illness outside of the typical season.

[¶] Defined as a temperature of ≥100.0°F (≥37.8°C), oral or equivalent, and cough or sore throat, in the absence of a known cause other than influenza.

** FluSurv-NET covers approximately 80 counties in the 10 Emerging Infections Program states (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee) and additional Influenza Hospitalization Surveillance Project (IHSP) states. IHSP began during the 2009–10 season to enhance surveillance during the 2009 H1N1 pandemic. IHSP sites included Iowa, Idaho, Michigan, Oklahoma, and South Dakota during 2009–10 season; Idaho, Michigan, Ohio, Oklahoma, Rhode Island, and Utah during the 2010–11 season; Michigan, Ohio, Rhode Island, and Utah during the 2011–12 season; and Iowa, Michigan, Ohio, Rhode Island, and Utah during the 2012–13 season.

[††] Incidence rates are calculated using population estimates for the counties included in the surveillance catchment area. Laboratory confirmation is dependent on clinician-ordered influenza testing, and testing for influenza often is underused because of the poor reliability of rapid test results and greater reliance on clinical diagnosis for influenza. As a consequence, cases identified as part of influenza hospitalization surveillance likely are an underestimation of the actual number of persons hospitalized with influenza.

FIGURE 2. Percentage of visits for influenza-like illness (ILI)* reported to CDC, by surveillance week and year — U.S. Outpatient Influenza-Like Illness Surveillance Network, United States, September 30, 2012–May 18, 2013, and selected previous seasons



* Defined as a temperature of ≥100.0°F (≥37.8°C), oral or equivalent, and cough or sore throat, in the absence of a known cause other than influenza.

† The national baseline is the mean percentage of visits for ILI during noninfluenza weeks for the previous three seasons plus two standard deviations. A noninfluenza week is defined as periods of two or more consecutive weeks in which each week accounted for <2% of the season's total number of specimens that tested positive for influenza. Use of the national baseline for regional data is not appropriate.

As of June 1, 2013, among the FluSurv-NET adult patients for whom medical chart data were available, the most frequent underlying conditions were chronic lung disease (27%), cardiovascular disease (45%), and metabolic disorders (39%). Among children hospitalized with laboratory-confirmed influenza and for whom medical chart data were available, 46% did not have any recorded underlying conditions, and 22% had underlying asthma or reactive airway disease. Among the 819 hospitalized women of childbearing age (15–44 years), 233 (28%) were pregnant.

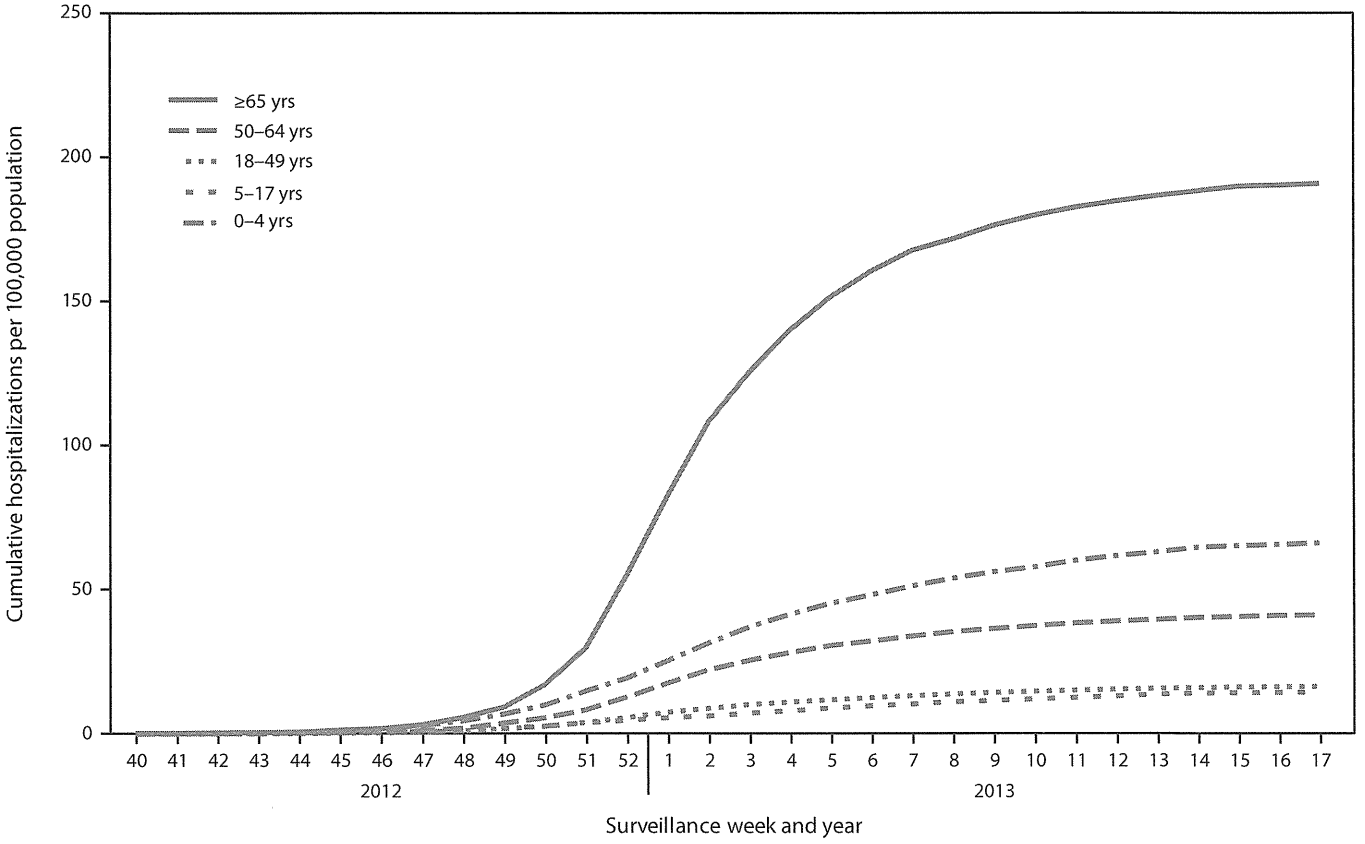
Pneumonia- and Influenza-Related Mortality

During the 2012–13 influenza season, the percentage of deaths attributed to pneumonia and influenza (P&I) exceeded the epidemic threshold for 13 consecutive weeks spanning December 30, 2012 to March 30, 2013 (weeks 1–13). The percentage of deaths attributed to P&I peaked at 9.9% during the week ending January 19, 2013 (week 3) (Figure 4). From the 2008–09 season through the 2011–12 season, the peak percentage of P&I deaths ranged from 7.9% to 9.1%, and the total number of consecutive weeks at or above the epidemic threshold ranged from 1 to 13 (Influenza Division, CDC, unpublished data, 2013).

Influenza-Related Pediatric Mortality

For the 2012–13 influenza season, 149 laboratory-confirmed, influenza-associated pediatric deaths were reported. These deaths were reported from 38 states. The states with the greatest numbers of deaths were Texas (18), New York (14), and Florida (eight). The deaths included 11 children aged <6 months, 20 aged 6–23 months, 20 aged 2–4 years, 52 aged 5–11 years, and 46 aged 12–17 years; mean and median ages were 8.2 years and 8.1 years, respectively. Among the 149 deaths, 79 were associated with influenza B viruses,

FIGURE 3. Cumulative hospitalization rates for laboratory-confirmed influenza, by age group and surveillance week and year — FluSurv-NET* surveillance system, United States, October 1, 2012–April 30, 2013



32 with influenza A (H3) viruses, four with pH1N1 viruses, 31 with an influenza A virus for which the subtype was not determined, one with an influenza virus for which the type was not determined, and two with both an influenza B and influenza A virus.

Since influenza-associated pediatric mortality became a nationally notifiable condition in 2004, the total number of influenza-associated pediatric deaths has previously ranged from 34 to 123 per season; this excludes the 2009 pandemic, when 348 pediatric deaths were reported to CDC during April 15, 2009, through October 2, 2010.

Reported by

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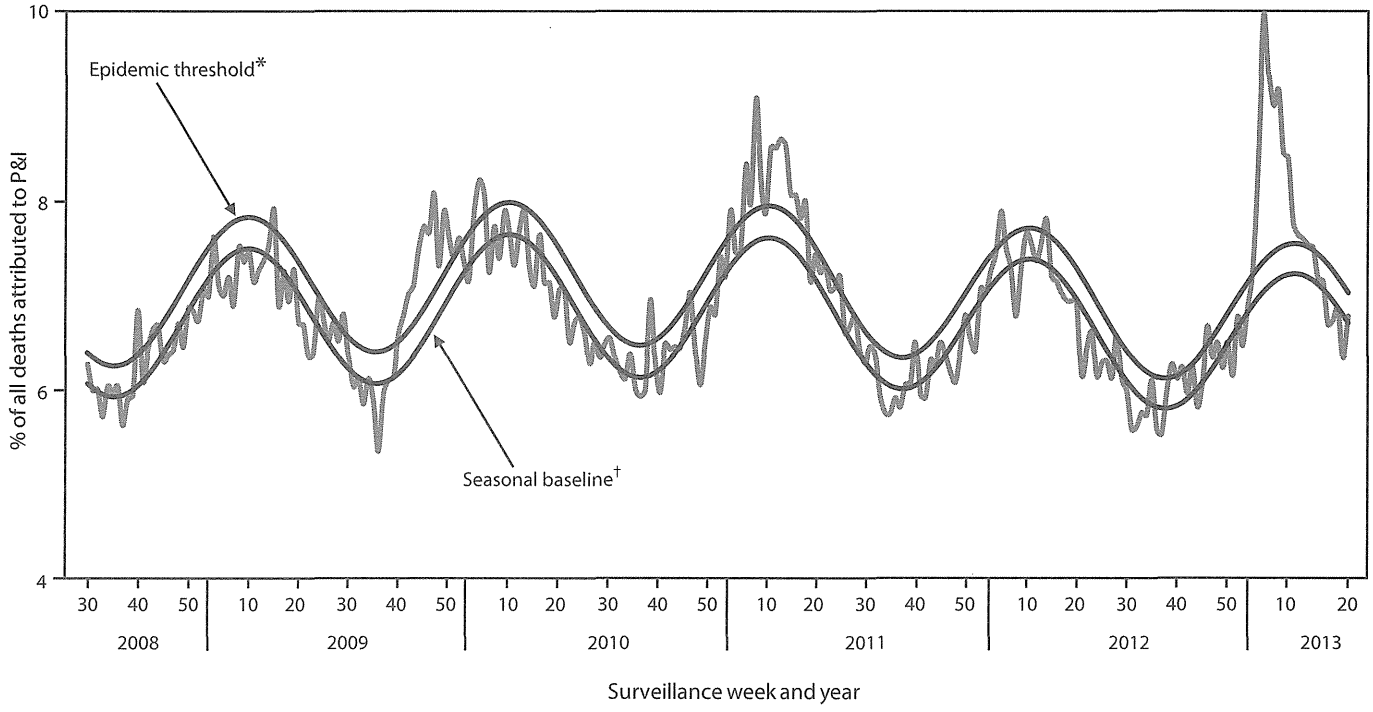
Editorial Note

The 2012–13 influenza season peaked early and was a moderately severe season, with influenza A (H3N2) viruses predominating. Activity peaked in late December, and influenza A (H3N2) viruses were most commonly reported through the week ending February 16, 2013 (week 7). From the week ending February 23, 2013 (week 8), through the end of the season, influenza B viruses were more commonly reported. The majority of all influenza viruses in specimens sent to CDC for further antigenic characterization were similar to the components of the 2012–13 Northern Hemisphere vaccine.

The peak percentage of outpatient visits for ILI (6.1%) was one of the highest reported since the system began in its current format in 1997. For comparison, the peak percentage of visits for ILI during those 15 seasons ranged from 2.4% for the 2011–12 season to 7.7% during the 2009 H1N1 pandemic. The number and rate of influenza-associated hospitalizations

FIGURE 4. Percentage of all deaths attributable to pneumonia and influenza (P&I), by surveillance week and year — 122 Cities Mortality Reporting System, United States, 2008–May 18, 2013



* The epidemic threshold is 1.645 standard deviations above the seasonal baseline.
† The seasonal baseline is projected using a robust regression procedure that applies a periodic regression model to the observed percentage of deaths from P&I during the preceding 5 years.

among adults aged ≥65 years during the 2012–13 influenza season are the highest since systematic data collection on laboratory-confirmed, influenza-associated hospitalization in adults began in the 2005–06 season. Hospitalization rates for those aged ≥65 years were 191 per 100,000 population, two and a half times the highest rate previously reported for this age group. With the exception of the 2009 H1N1 pandemic, the number of influenza-associated pediatric deaths reported to CDC for the 2012–13 season was the highest reported since data collection began in 2004. Reported P&I mortality exceeded the epidemic threshold for 13 consecutive weeks. Based on the percentage of specimens testing positive for influenza, the peak of influenza activity for the 2012–13 season, occurring during the week ending December 29, 2012 (week 52), was similar to the 2003–04 season, which peaked during the week ending November 30, 2003 (week 48), and was the earliest since the 2009 H1N1 pandemic, when activity peaked during the week ending October 24, 2009 (week 42).

On March 31, 2013, Chinese health authorities reported a novel avian influenza A (H7N9) virus causing human infection. As of June 7, 2013, 132 cases have been confirmed; many of the infected people are reported to have had close contact with poultry. The virus has only been seen in mainland China and Taiwan; no cases have been reported in the United States. Unlike the variant influenza A (H3N2)v virus associated with swine exposure in the United States, which generally caused mild illness, the avian influenza A (H7N9) virus has caused severe illness in the majority of cases in humans, and approximately 27% of identified cases have been fatal (*2*).

Testing for seasonal influenza viruses and monitoring for novel influenza A virus infections should continue year-round, as should specimen submission to CDC for further antigenic and genetic analysis and antiviral resistance monitoring. A total of 308 infections with variant influenza viruses (304 H3N2v viruses, three H1N2v viruses, and one H1N1v virus) were reported from 10 states during the summer and fall of 2012, before the start of the 2012–13 influenza season, and two cases of H3N2v were detected during the 2012–13 season. The H3N2v virus circulated in pigs in 2010 and was first detected in humans in 2011, when 12 cases were identified. Most of these infections occurred in children with prolonged exposure to pigs at agricultural fairs. Limited human-to-human spread of this virus was detected, but no sustained community spread of H3N2v was identified (*3*). However, this increase in H3N2v cases in 2012,

and the recent emergence of the novel avian influenza A (H7N9) virus in China, further emphasizes the importance of continuing to monitor for novel influenza A viruses.

Although summer influenza activity in the United States typically is low, cases of influenza and even sporadic outbreaks are detected in the United States throughout the summer. Health-care providers should remain vigilant and consider influenza as a potential cause of summer respiratory illnesses. They also should consider novel influenza viruses in persons with ILI and swine exposure, and those with severe acute respiratory infection after travel to China. Public health laboratories should immediately send to CDC virus specimens that they cannot type or subtype using standard methods and submit all specimens that are otherwise unusual, including all summer specimens, as soon as possible after identification.

Since 2010, CDC has recommended annual influenza vaccination for all persons aged ≥6 months, preferably in the fall before the U.S. influenza season begins (*4*). However, during other times of the year, persons who have not received the vaccine for the current season should be vaccinated before traveling to parts of the world where influenza activity is ongoing. This is particularly important for persons at high risk for influenza-related complications.[§§] This recommendation also applies to persons traveling within the temperate regions of the Southern Hemisphere or as part of large tourist groups (e.g., on cruise ships) that might include persons from other parts of the world where influenza activity is ongoing (*5*). Persons should be vaccinated at least 2 weeks before travel for immunity to develop. Travelers also should be aware that all Northern Hemisphere influenza vaccine manufactured for the 2012–13 season expires by June 30, 2013, after which influenza vaccines will not be available in the United States until the 2013–14 vaccine is available in the fall.

As a supplement to vaccination, influenza antiviral drugs are an important adjunct to reduce the impact of influenza. Based on recommendations of the Advisory Committee on Immunization Practices, antiviral treatment is recommended as soon as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness; who require hospitalization; or who are at higher risk for influenza-related complications (*6*). Antiviral treatment also may be considered for outpatients with confirmed or suspected influenza who do not have known risk factors for severe illness if treatment can be initiated within 48 hours of illness onset. In addition, if a clinician does suspect that a patient might have an infection caused by a novel influenza virus, prompt empiric antiviral therapy is recommended. Recommended antiviral medications include oseltamivir and zanamivir. Recent viral surveillance and resistance data indicate that the majority of currently circulating influenza viruses are sensitive to these medications. Amantadine and rimantadine should not be used because of sustained high levels of resistance to these drugs among circulating influenza A viruses.

[§§] Additional information available at http://www.cdc.gov/flu/about/disease/high_risk.htm.

Acknowledgments

Participating state, city, county, and territorial health departments and public health laboratories; US World Health Organization collaborating laboratories; National Respiratory and Enteric Virus Surveillance System collaborating laboratories; US Outpatient Influenza-Like Illness Surveillance Network; Influenza Hospitalization Surveillance Network; Influenza-Associated Pediatric Mortality Surveillance System; 122 Cities Mortality Reporting System.

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Update: Severe Respiratory Illness Associated with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) — Worldwide, 2012–2013

On June 7, 2013, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

CDC continues to work in consultation with the World Health Organization (WHO) and other partners to better understand the public health risk posed by the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), formerly known as novel coronavirus, which was first reported to cause human infection in September 2012 (*1–4*). The continued reporting of new cases indicates that there is an ongoing risk for transmission to humans in the area of the Arabian Peninsula. New reports of cases outside the region raise concerns about importation to other geographic areas. Nosocomial outbreaks with transmission to health-care personnel highlight the importance of infection control procedures. Recent data suggest that mild respiratory illness might be part of the clinical spectrum of MERS-CoV infection, and presentations might not initially include respiratory symptoms. In addition, patients with comorbidities or immunosuppression might be at increased risk for infection, severe disease, or both. Importantly, the incubation period might be longer than previously estimated. Finally, lower respiratory tract specimens (e.g., sputum, bronchoalveolar lavage, bronchial wash, or tracheal aspirate) should be collected in addition to nasopharyngeal sampling for evaluation of patients under investigation. An Emergency Use Authorization (EUA) was recently issued by the Food and Drug Administration (FDA) to allow for expanded availability of diagnostic testing in the United States.

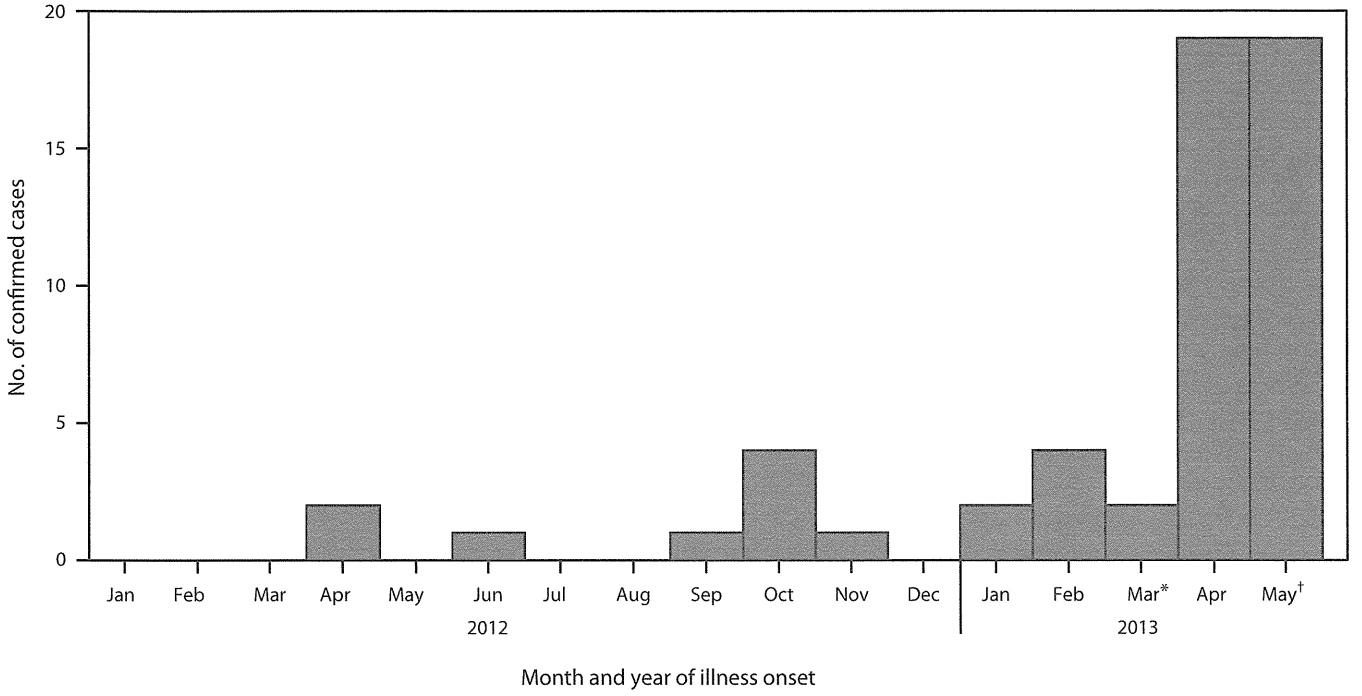
As of June 7, 2013, a total of 55 laboratory-confirmed cases have been reported to WHO. Illness onsets have occurred during April 2012 through May 29, 2013 (Figure 1). All reported cases were directly or indirectly linked to one of four countries: Saudi Arabia, Qatar, Jordan, and the United Arab Emirates (Figure 2). Most cases (40) were reported by Saudi Arabia. Four countries, the United Kingdom (UK), Italy, France, and Tunisia, have reported cases in returning travelers and their close contacts (*5–8*). Ill patients from Qatar and the United Arab Emirates have been transferred to hospitals in the UK and Germany. To date, no cases have been reported in the United States. WHO and CDC have not issued any travel advisories at this time; updated information for travelers to the Arabian Peninsula is available at http://wwwnc.cdc.gov/travel/notices/watch/coronavirus-arabian-peninsula.

The median age of patients is 56 years (range: 2–94 years), with a male-to-female ratio of 2.6 to 1.0. All patients were aged ≥24 years, except for two children, one aged 2 years and one aged 14 years. All patients had respiratory symptoms during their illness, with the majority experiencing severe acute respiratory disease requiring hospitalization. Thirty-one of the 55 patients are reported to have died (case-fatality rate: 56%) (*5–8*). Two cases in Tunisia, in siblings whose father's illness was a probable case, and a case from the UK, were in persons with mild respiratory illnesses who were not hospitalized (*5,9*). Information was not available for all cases; however, several patients had accompanying gastrointestinal symptoms, including abdominal pain and diarrhea, and many cases occurred among persons with chronic underlying medical conditions or immunosuppression, as reported to WHO (*5,9*).

The original source(s), route(s) of transmission to humans, and the mode(s) of human-to-human transmission have not been determined. Eight clusters (42 cases) have been reported by six countries (France, Italy, Jordan, Saudi Arabia, Tunisia, and the UK) (*5*) among close contacts or in health-care settings and provide clear evidence of human-to-human transmission of MERS-CoV. The first documented patient-to-patient nosocomial transmission in Europe was confirmed recently in France (*10*). The first French patient, a man aged 64 years with a history of renal transplantation, became ill on April 22, 2013, within 1 week after returning from Dubai. He presented with fever and diarrhea. Pneumonia was diagnosed incidentally on radiographic imaging, and he subsequently died with severe respiratory disease. The secondary case is in a man aged 51 years on long-term corticosteroids who shared a room with the index patient during April 26–29 and who remains hospitalized on life support. The incubation period for the secondary case was estimated to be 9–12 days; this is longer than the previously estimated 1–9 days (*10*). A larger cluster, consisting of 25 cases including 14 deaths, ongoing since April 2013 in the region of Al-Ahsa in eastern Saudi Arabia, also has included cases linked to a health-care facility (*5*). Cases have included health-care personnel and family contacts. An additional five cases, not linked to the cluster in Al-Ahsa, were reported recently in another region of eastern Saudi Arabia (*5*). Thus far, no evidence of sustained community transmission beyond the clusters has been reported in any country.

In some instances, sampling with nasopharyngeal swabs did not detect MERS-CoV by polymerase chain reaction (PCR); however, MERS-CoV was detected by PCR in lower respiratory tract specimens from these same patients. In the two patients reported by France, nasopharyngeal specimens were weakly positive or inconclusive, whereas bronchoalveolar lavage and induced sputum were positive (*10*).

FIGURE 1. Number of confirmed cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (N = 55) reported as of June 7, 2013, to the World Health Organization, by month of illness onset — worldwide, 2012–2013



* Case count for March assumes that the two cases included in the March 23, 2013 WHO announcement had symptom onset during March 2013.
† Case count for May 2013 assumes that six recently reported cases had symptom onset during May 2013.

CDC Guidance

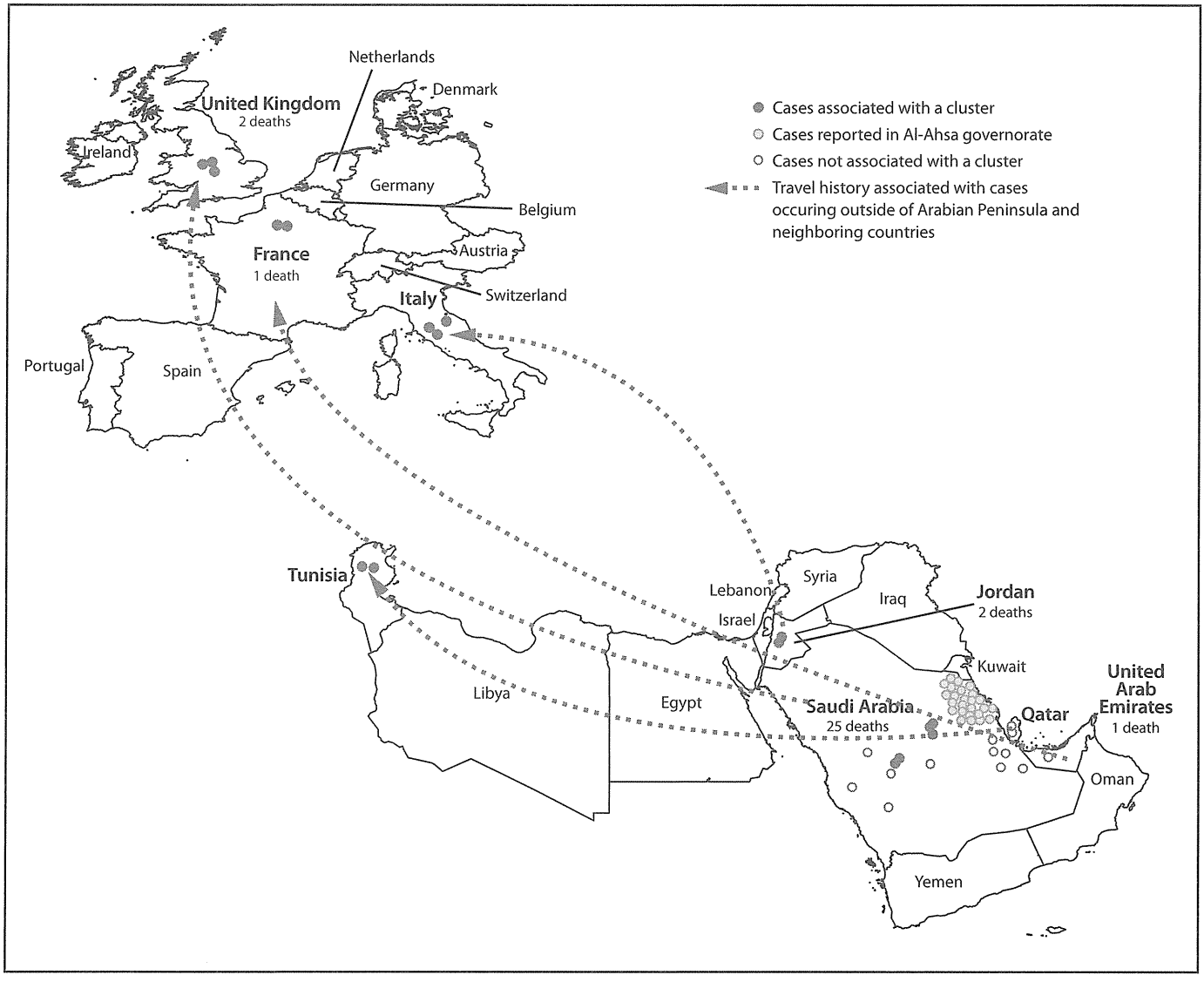
In consultation with WHO, the period for considering evaluation for MERS-CoV infection in persons who develop severe acute lower respiratory illness days after traveling from the Arabian Peninsula or neighboring countries* has been extended from within 10 days to within 14 days of travel. Persons who develop severe acute lower respiratory illness within 14 days after traveling from the Arabian Peninsula or neighboring countries should be evaluated according to current guidelines (available at http://www.cdc.gov/coronavirus/mers/case-def.html). Persons whose respiratory illness remains unexplained and who meet criteria for "patient under investigation" should be reported immediately to CDC through state and local health departments. Persons who develop severe acute lower respiratory illness who are close contacts† of a symptomatic traveler who developed fever and acute respiratory illness within 14 days of traveling from the Arabian Peninsula or neighboring countries may be considered for evaluation for MERS-CoV. In addition, CDC recommends that clusters of severe acute respiratory illness be investigated and, if no obvious etiology is identified, local public health officials be notified and testing for MERS-CoV conducted, if indicated.

To increase the likelihood of detecting MERS-CoV, CDC recommends collection of specimens from different sites (e.g., a nasopharyngeal swab and a lower respiratory tract specimen, such as sputum, bronchoalveolar lavage, bronchial wash, or tracheal aspirate). Specimens should be collected at different times after symptom onset, if possible. Lower respiratory tract specimens should be a priority for collection and PCR testing; stool specimens also may be collected. Specimens should be collected with appropriate infection control precautions (available at http://www.cdc.gov/coronavirus/mers/case-def.html).

Testing of specimens for MERS-CoV currently is being conducted at CDC. FDA issued an EUA on June 5, 2013, to authorize use of CDC's novel coronavirus 2012 real-time reverse transcription–PCR assay (NCV-2-12 rRT-PCR assay) to test for MERS-CoV in clinical respiratory, blood, and stool specimens. This EUA is needed because, at this time, there are no FDA-approved tests that identify MERS-CoV in clinical specimens. This assay will be deployed to Laboratory Response

* Countries considered to be on or neighboring the Arabian Peninsula include Bahrain, Iraq, Iran, Israel, Jordan, Kuwait, Lebanon, Oman, Palestinian Territories, Qatar, Saudi Arabia, Syria, the United Arab Emirates, and Yemen.
† Close contacts are defined as 1) persons who provided care for the patient, including health-care personnel and family members, or who had other similarly close physical contact, or 2) persons who stayed at the same place (e.g., lived with or visited) as the patient while the patient was ill.

FIGURE 2. Confirmed cases* of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (N =55) reported as of June 7, 2013, to the World Health Organization, and history of travel from the Arabian Peninsula or neighboring countries within 14 days of illness onset — worldwide, 2012–2013



* Dots representing the cases are not geographically representative of the exact location of the residence of the patient.

Network (LRN) laboratories in all 50 states over the coming weeks. Updated information about laboratories with the capacity to conduct MERS testing with the NCV-2-12 rRT-PCR assay will be provided on CDC's MERS website (http://www.cdc.gov/coronavirus/mers/case-def.html).

In consultation with WHO, the definition of a probable case of MERS-CoV infection has been updated to also include persons with severe acute respiratory illness with no known etiology with an epidemiologic link to a confirmed case of MERS-CoV infection. Until the transmission characteristics of MERS-CoV are better understood, patients under investigation and probable and confirmed cases should be managed in health-care facilities using standard, contact, and airborne precautions. As information becomes available, these recommendations will be reevaluated and updated as needed.

Recommendations and guidance on case definitions, infection control (including use of personal protective equipment), case investigation, and specimen collection and testing, are available at the CDC MERS website (http://www.cdc.gov/coronavirus/mers/index.html). The MERS website contains the most current information and guidance, which is subject to change. State and local health departments with questions should contact the CDC Emergency Operations Center (770-488-7100).

Reported by

Div of Global Migration and Quarantine, Div of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases; Office for Emergency Preparedness and Response, National Institute of Occupational Safety and Health; Div of Global Health Protection (proposed), Center for Global Health; Div of Viral Diseases, National Center for Immunization and Respiratory Diseases; Paul A. Gastañaduy, MD, EIS Officer, CDC. ***Correspondence:*** *eocreport@cdc.gov, 770-488-7100.*

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Notes from the Field

Outbreak of Poliomyelitis — Somalia and Kenya, May 2013

On May 9, 2013, the Somalia Ministry of Health and the World Health Organization (WHO) reported a confirmed wild poliovirus type 1 (WPV1) case in a girl aged 32 months from Mogadishu (Banadir Region), with onset of acute flaccid paralysis (AFP) on April 18, 2013. Subsequently, eight additional WPV1 cases have been confirmed in Somalia, seven in Banadir Region and one in Bay Region. These are the first reported polio cases in Somalia since March 2007.

On May 16, 2013, the Kenya Ministry of Public Health and Sanitation and WHO reported a confirmed WPV1 case with onset on April 30, 2013, in a girl aged 4 months from the Dadaab refugee camps near the Somalia border. Four additional cases were confirmed in the camps. These are the first reported polio cases in Kenya since July 2011. All data are as of June 11, 2013.

Genetic sequence analysis of isolates from both countries indicates the isolates are closely related, with evidence of a single introduction of virus into the region and subsequent local transmission before detection. These viruses are both closely related to WPV1 currently circulating in West Africa.

In Somalia, a rapid response polio supplementary immunization activity (SIA) was conducted May 14–17 in all 16 districts of Banadir Region. A subsequent SIA was conducted May 26–29 in a larger geographic area of Somalia, and SIAs are planned for June, July, and August. In Kenya, the first SIA in the Dadaab refugee camps and the surrounding three districts was conducted May 27–30. Subsequent SIAs with increasing geographic coverage in Kenya are planned for June, July, and August. Preventive SIAs are being conducted in areas of Ethiopia and Yemen, and surveillance for AFP is being strengthened in all countries in the Horn of Africa.

Poliovirus is spread person-to-person through fecal-oral contact and through contaminated water. For every WPV1 case with paralysis, approximately 200 asymptomatic infected susceptible persons are also shedding poliovirus (*1*). In 2012, only 223 polio cases were reported globally, the fewest ever reported in a calendar year (*2*). As of June 11, a total of 50 polio cases had been reported in 2013 globally, compared with 67 cases reported during the same period in 2012 (*3*).

CDC recommends that all international travelers complete polio vaccination before travel. For travelers to countries with designated polio risk, including Ethiopia, Kenya, and Somalia, CDC recommends an additional polio vaccine booster dose (*4*). CDC has issued guidelines requiring that all refugees from Kenya scheduled for U.S. resettlement receive 3 doses of oral polio vaccine regardless of age before departure for the United States, with a 2-week hold after the third dose. CDC also recommends that all refugees from Kenya who have arrived since the beginning of April 2013 receive 1 inactivated poliovirus vaccine dose regardless of vaccination history.

Reported by

World Health Organization. Div of Global Migration and Quarantine, National Center for Emerging and Zoonotic Infectious Diseases; Div of Viral Diseases, National Center for Immunization and Respiratory Diseases; Global Immunization Div, Center for Global Health, CDC. ***Corresponding contributors:*** *Derek Ehrhardt, dehrhardt@cdc.gov, 404-310-5650; Nina Marano, nmarano@cdc.gov, 404-319-9618.*

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Announcement

Recommendations Regarding Tobacco Use and Secondhand Smoke Exposure from the Community Preventive Services Task Force

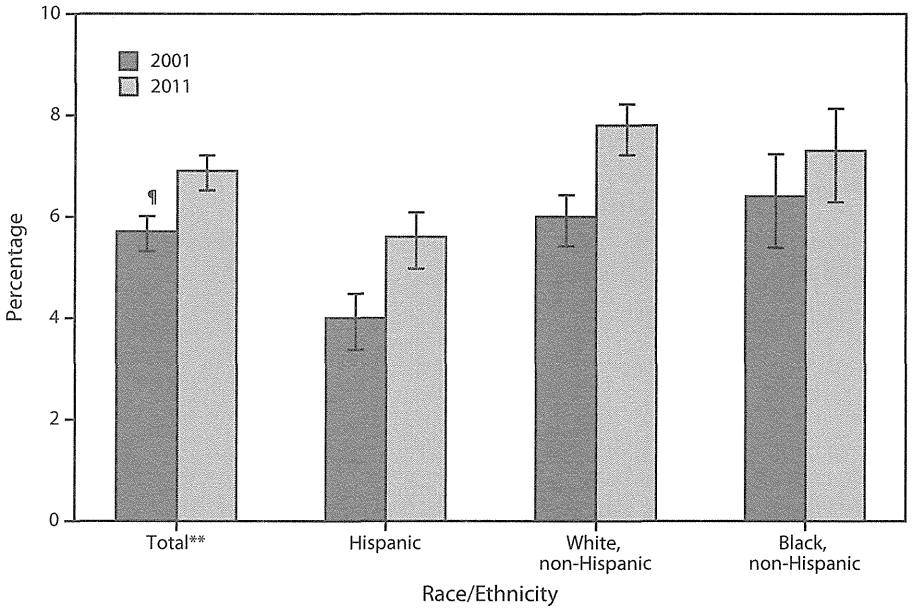
The Community Preventive Services Task Force recently posted new information about two recommendations: 1) "Reducing Tobacco Use and Secondhand Smoke Exposure: Reducing Out-of-Pocket Costs for Evidence-Based Tobacco Cessation Treatments," available at http://www.thecommunityguide.org/tobacco/outofpocketcosts.html, and 2) "Reducing Tobacco Use and Secondhand Smoke Exposure: Quitline Interventions," available at http://www.thecommunityguide.org/tobacco/quitlines.html.

Established in 1996 by the U.S. Department of Health and Human Services, the task force is an independent, nonfederal, unpaid panel of public health and prevention experts whose members are appointed by the Director of CDC. The task force provides information for a wide range of decision makers on programs, services, and policies aimed at improving population health. Although CDC provides administrative, research, and technical support for the task force, the recommendations developed are those of the task force and do not undergo review or approval by CDC.

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Percentage of Persons Aged <18 Years Who Received Special Educational or Early Intervention Services,* by Race/Ethnicity† — National Health Interview Survey, United States, 2001 and 2011§



* Based on response to the question, "Do any of the following [family members aged <18 years] receive special educational or early intervention services?" Special educational and early intervention services are designed to meet the needs of a child with special needs or disabilities and are provided by the state or school system at no cost to the parent. Early intervention services might include, but are not limited to, medical and social services, parental counseling, and therapy.

† Persons of Hispanic ethnicity might be of any race or combination of races.

§ Estimates are based on household interviews of a sample of the civilian noninstitutionalized U.S. population and are derived from the National Health Interview Survey Family Core component.

¶ 95% confidence interval.

** Includes other races not shown separately.

From 2001 to 2011, the percentage of children aged <18 years who were receiving special educational or early intervention services increased overall and among Hispanic and non-Hispanic white children, no change was observed among non-Hispanic black children. In 2001 and 2011, Hispanic children were less likely than non-Hispanic white and non-Hispanic black children to receive these services.

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IASR

渡航歴のない麻疹集団発生からの B3 型麻疹ウイルス検出—愛知県

(IASR Vol. 34 p. 345-346: 2013 年 11 月号)

2013 年8月 23 日～9月 12 日の期間に愛知県内で麻疹と診断された患者のうち、愛知県衛生研究所にて行った麻疹ウイルス遺伝子検査陽性を示した 13 例について、ウイルス検査の概要を報告する。このうち遺伝子型別のできなかった1例を除く 12 例の遺伝子型は B3 型であった。保健所による疫学調査では、13 例とも患者および同居者に患者発症前1か月間の渡航歴はない。なお患者番号は NESID 届け出 ID 順に付番した。

1）8月上旬に同一医療機関来院歴のある者7名

患者2：9歳男児、麻疹含有ワクチン(MCV)接種歴なし、8月 16 日発熱。患者1：9カ月女児、MCV 接種歴なし、8月 18 日発熱。患者 12：26 歳女、MCV 接種2回、8月 18 日発熱。患者8：6歳女児、MCV 接種1回、8月 20 日発熱。患者3：1歳男児、MCV 接種歴なし、8月 21 日発熱。患者4：2か月女児、MCV 接種歴なし、8月 29 日発熱・発疹、患者 12 の家族。患者5：11 歳女児、MCV 接種歴不明、8月 28 日発熱。

2）来院者の同居家族4名

患者9：1歳男児、MCV 接種歴なし、母が受診、8月 30 日発熱。患者7：1歳男児、MCV 接種歴なし、患者8の家族、8月 31 日発熱。患者6：35 歳男、MCV 接種歴不明、患者1の家族、9月2日発熱。患者 10：3か月男児、MCV 接種歴なし、患者 12 の家族、9月7日発熱。

3）上記医療圏を通勤し、患者との接触歴のない患者 2 名

患者 11：39 歳男、MCV 接種歴なし、8月 31 日発熱。患者 13：19 歳男、MCV 接種歴不明、9月6日発熱。

患者1～13 より採取された血液（全血もしくは血清）、尿、咽頭ぬぐい液を検体として、RT-nested PCR 法および Vero/hSLAM 細胞を用いたウイルス分離による実験室診断を試みた。PCR の結果、患者 12 を除く 12 例については、提供された1検体以上より麻疹ウイルス N および H 遺伝子（1st primer の product）が増幅され、N 遺伝子の増幅産物について塩基配列を決定した。患者由来 N 遺伝子の部分塩基配列（456bp）はすべて同一で、系統樹解析の結果、B3 型麻疹ウイルスに分類された（図）。この部分塩基配列は 2013 年福岡市がタイからの帰国者より検出を報告した配列および同年尼崎市から報

告された配列と100%の相同性を示した(図、文献1)。H遺伝子 nested primer による product が生成されなかった(文献1)点も福岡市の事例と同じである。なお患者12については第4病日に採取後冷蔵されていた血清を18日後に検査したところ、H遺伝子のみが増幅された。また、患者5名(1, 3, 4, 6, 10)由来検体より麻疹ウイルスが分離された。

愛知県では、2010年以降毎年輸入麻疹関連症例への対応がなされており、適切な時期に採取された検体が増えて遺伝子検出やウイルス分離率が向上している。2013年は、2月と3月に中国からの輸入各1例より遺伝子型H1を、3月と4月には渡航歴のない患者各1例より遺伝子型D9を検出しており、異なる遺伝子型の麻疹流入が繰り返し検知されている。今回の集団発生は、医療機関以外に接点のない患者5名が8月16～21日の期間に集中して発症しており、感染源は共通と考えられる。また、患者13名中MCV接種歴のあった者は6歳(1回)および26歳(2回)2名のみ、残り11名(うち0歳児3名)のMCV接種歴はなしまたは不明であり、ひとたび麻疹が発生するとMCV未接種者間で速やかな感染拡大がみられる[2-4]ことが改めて認識された。日本における2006～2008年のアウトブレイクの主たる原因ウイルスであり、常在型ウイルスとされている遺伝子型D5の麻疹ウイルスの検出は2010年5月を最後に報告がない。輸入麻疹との関連や感染経路の特定に有用な分子疫学的解析の重要性が、今後ますます高まると思われる。

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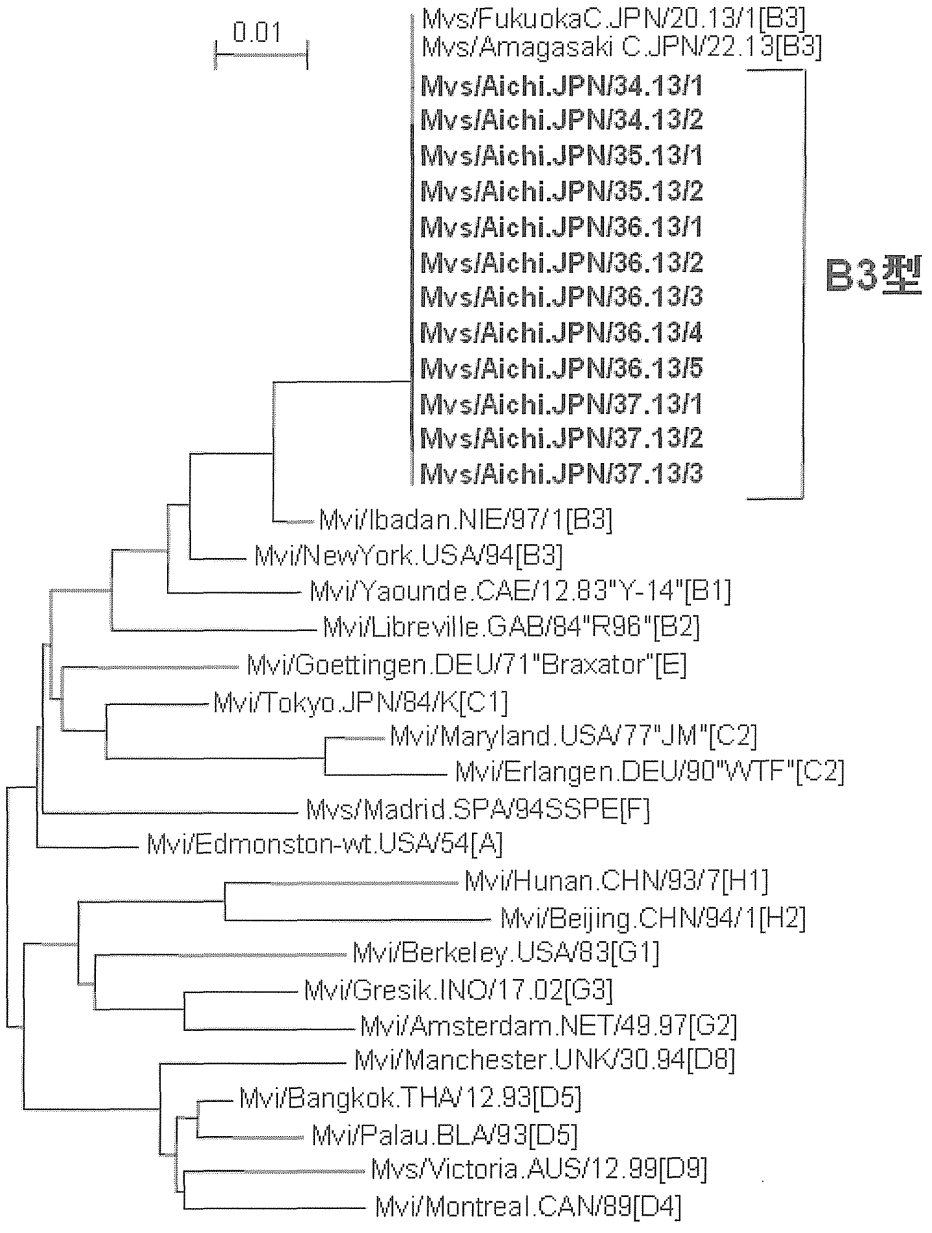

図. 麻疹ウイルスN遺伝子増幅産物(456 塩基)の配列に基づく分子系統樹

CLINICAL COMMUNICATION TO THE EDITOR

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Late Onset of Vaccine-associated Measles in an Adult with Severe Clinical Symptoms: A Case Report

To the Editor:

Measles is a highly contagious disease causing an estimated 2.6 million deaths per year before a vaccine was developed.[1] However, the attenuated measles vaccine has brought the disease under control.[1] Vaccine-associated measles can occur in children and immunocompromised individuals.[2-4] Little is known about the occurrence of vaccine-associated measles in healthy adults because preschool children usually are vaccinated. We describe an adult who presented with vaccine-associated measles and severe clinical symptoms after an atypical incubation period.

A 23-year-old healthy man was given a measles vaccine, not rubella or mumps vaccine at the same time, on March 27, 2013, as part of an occupational health protocol; however, he presented with a high fever (40°C) at 18 days post-vaccination. At 20 days post-vaccination, a rash appeared on his trunk, legs, and arms. Koplik's spots, a runny nose, and red eyes also were noted. Two days after disease onset, blood samples, a throat swab, and a urine sample were collected and tested for measles virus by reverse transcription-polymerase chain reaction. A sequence corresponding to the measles N protein (533 bp) was amplified from the serum, peripheral blood mononuclear cells, and throat swab, and was identical to that of the genotype A virus (DQ345721). The subject had no history of travel before the vaccination or contact with patients with measles. Before vaccination, he tested negative for serum antibodies against the measles virus. Thus, he was diagnosed with vaccine-associated measles.

According to the National Infectious Disease Surveillance Center of Japan, genotype A measles virus was detected in 71 individuals who showed adverse effects after measles vaccination between May 2006 and May 2013 (~0.0004% of vaccinations at most). The age range of the patients was 1 to 14 years (median, 1 year). No adult cases were reported. The most frequently reported clinical signs were fever (91.6%; temperature range, 37-41°C; median, 39.1°C) and a rash (81.7%). Less common clinical signs included upper respiratory tract inflammation (29.6%), lymphadenopathy (15.5%), and lower respiratory tract inflammation (14.1%). The most common symptoms (fever and rash) were observed in the current adult case reported.

The US Centers for Disease Control and Prevention reports that complications after measles infection are more common among children aged less than 5 years and adults aged more than 20 years, consistent with this case.[5] Analyses of 57 of these cases revealed that the average time of disease onset was 8.8 days post-vaccination (median, 9 days; range, 0-18 days). The majority (94.7%) developed clinical signs within 2 weeks post-vaccination. The case reported developed symptoms at 18 days post-vaccination, which is exceptionally long among these cases.

Side effects of measles vaccine, including vaccine-associated measles, are rarely reported in adults because they are usually not vaccinated. The case reported is notable because some adults may be given the measles vaccine during regional outbreaks of mumps, rubella, or measles.[6,7] Clinicians should be aware of the possibility of vaccine-associated measles in both children and adults.

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総合医学会報告

シンポジウム：「職業感染対策」

ワクチンによる医療従事者の麻疹・風疹・ムンプス・水痘・インフルエンザ感染予防対策

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第65回国立病院総合医学会
（平成23年10月８日　於岡山）

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要旨　医療従事者は感染を受けやすい集団であり，また感染を周囲に拡大させるリスクが高い集団であるため，日頃からの感染対策が大切である．麻疹・風疹・ムンプス・水痘は小児期の代表的なワクチン予防可能疾患であるが，近年成人発症例を経験することがある．医療従事者においては，これらの感染症が医療現場で流行したときに行う曝露後対策よりも，採用時に抗体価を測定し，接種が必要な医療従事者にワクチン接種を行う曝露前対策の方が効率的である．国立病院機構三重病院では平成２年から採用者や転勤者の抗体測定を行い，発症予防抗体価よりも低い人にワクチン接種を行っているが，ワクチン接種者，非接種者ともに麻疹・ムンプス・水痘患者との接触機会があっても１例も発症者を認めていない．なお，環境感染学会のワクチン接種基準は感染予防に重きをおいており，当院の接種基準の抗体価よりも高い基準が示されている．

インフルエンザは局所性感染症であり，発症予防のためには高い抗体価が必要である．インフルエンザワクチン後の抗体価は接種後半年を経過すると１/２に低下するため，２シーズン続けて同じワクチン株がワクチンに使用されたとしても，毎年のワクチン接種が必要である．また，インフルエンザワクチンでは集団免疫効果が認められており，施設でのインフルエンザ流行を予防するためには，医療従事者の高い接種率が必要である．

キーワード　医療従事者，院内感染予防，ワクチン，インフルエンザ，麻疹

はじめに

病院は感染のリスクが高い事業所であり，職員が院内感染を受けない，院内感染を媒介しないことが大切である．院内感染予防対策として手指の衛生を含めた標準予防策が基本であるが，ワクチンで予防できる感染症はワクチンで予防するのが原則である[1]．ワクチンの効果には個人を予防するだけではなく，ヒトからヒトに感染する感染症では，多くの人がワクチンを受けることで流行を抑制する効果がある．この流行を抑制する免疫率が集団免疫率であり，集団免疫率が高い感染症ほど一人の感染者が免

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（平成24年１月30日受付，平成25年３月８日受理）
Measles, Rubella, Mumps, Varicella, and Influenza Vaccines : Control Measures for Health-care Workers
Toshiaki Ihara, NHO Mie National Hospital
Key Words : health-care personnels, prevention of nosocomial infections, vaccine, influenza, measles

表1　代表的な感染症の基本再生産数と集団免疫率

感染症	基本再生産数（R_0）	集団免疫率（%）	感染時間（同室内）
麻疹	16-21	90-95	≧20分間
風疹	7-9	80-85	
ムンプス	11-14	85-90	
ポリオ	5-7	80-86	
天然痘	5-7	80-85	
百日咳	16-21	90-95	
ジフテリア	6-7	85	
インフルエンザ	1.4-2.4	50*	≧24時間†
水痘	8-10	90?	≧60分間†

R_0：基本再生産数，集団免疫率＝（1−1/R_0）×100
＊小学校における集団免疫率
†飛沫が届く範囲（1～1.5m）ならば，インフルエンザでは4時間以上の，水痘では5分以上の接触で感染する．

疫のないヒトに感染させる数（基本再生産数）が高く，短い接触時間でヒトに感染させることが示されている（表1）[2]．また，この集団免疫率が社会で必要とされるワクチン接種率の指標となっている．集団免疫率が一番高い感染症が麻疹と百日咳である．

本稿ではワクチン予防可能疾患のうち，麻疹，風疹，ムンプス，水痘，インフルエンザに対する医療従事者の感染予防対策を概説する．

ウイルス感染症の病態と発症予防・感染予防

ウイルス感染症には，ウイルスが感染した局所で増殖して症状が出現する局所性感染症と，感染したウイルスがウイルス血症により全身の親和性臓器に広がり，そこで増殖して症状が出現する全身性感染症とがある．局所性感染症は潜伏期間が短く，発症予防のためには比較的高い血中抗体価が必要である．発症予防の抗体価と感染予防の抗体価はほぼ同じレベルである．局所性ウイルス感染症の発症予防には粘膜免疫が重要な役割を担っているが，RSウイルス（RSV）のFタンパクに対する中和抗体製剤であるパリビズマブがRSV感染の重症化予防に効果があるように，血中抗体も粘膜に滲み出ることで感染防御に働いている．

全身性ウイルス感染症は潜伏期間が長い感染症で，ウイルスが生体に感染したとしても早期に二次免疫応答が働き，賦活された免疫により感染したウイルスの増殖が抑制され，結果として発症は予防される．全身性ウイルス感染症では，感染予防レベルの抗体価（抗体ブースタがかからない），感染するが発症は予防される抗体価（抗体ブースタがかかる），発症したとしても軽症に経過する抗体価，発症し通常の経過を示す抗体価に分類される．麻疹における感染予防抗体価は750mIU/ml（中和抗体価32倍），発症予防抗体価は120mIU/ml（中和抗体価4倍）であり，中和抗体＜2倍が抗体陰性である[3)4)]．風疹では発症予防抗体価は10IU/mlであり，酵素免疫抗体（EIA）価5.0EIA価に相当し，HI抗体価では8倍と16倍の間に相当する．ムンプス，水痘の発症予防抗体価は確立されていない．

麻疹・風疹・ムンプス・水痘対策

麻疹，風疹，ムンプス，水痘は小児期の代表的なウイルス感染症であるが，近年成人の感染例を経験することがある．医療従事者における麻疹・風疹・ムンプス・水痘対策には，前もって抗体測定を行い，基準値よりも抗体価が低い人にワクチンを接種する曝露前対策と，感染者と接触したときに既往歴やワクチン歴からワクチンを接種する曝露後対策とがある．曝露前対策の方が効率的である[1)]．

国立病院機構三重病院では，平成2年から新規採用者および転勤者のうち抗体検査を希望する職員を対象に，麻疹，風疹，ムンプス，水痘の抗体測定を

表2　医療従事者における麻疹・風疹・ムンプス・水痘ワクチンの接種基準

	測定法	抗体陽性基準	環境感染学会＊	三重病院＊
麻疹	NT	≧2倍	≦4倍	≦2倍
	PA	≧16倍	≦128倍	≦32倍
	EIA	≧4 EIA価	＜16 EIA価	＜4 EIA価
風疹	HI	≧8倍	≦16倍	≦8倍
	EIA	≧4 EIA価	＜8 EIA価	＜4 EIA価
水痘	IAHA	≧2倍	≦4倍	≦2倍
	EIA	≧4 EIA価	＜4 EIA価	＜4 EIA価
ムンプス	EIA	≧4 EIA価	＜4 EIA価	＜4 EIA価

NT：中和法，PA：粒子凝集法，EIA：酵素免疫法，HI：赤血球凝集抑制法，IAHA：免疫付着赤血球凝集法

＊環境感染学会の基準（とくに麻疹と風疹）は感染予防の基準を用いており，三重病院の基準は95%以上の人の発症予防基準を用いている．全身性ウイルス感染症では，免疫記憶細胞や免疫実行細胞が誘導されていると，ウイルスが感染しても早期に二次免疫応答がおこり，結果として感染したウイルスの増殖が抑制されるため発症が予防される．発症予防抗体価は感染予防抗体価よりも低値である．[3]

行い，一定の基準を設けてワクチン接種を行ってきた[3]．当院が行っている接種基準を表2に示した．平成23年度までの22年間この基準で接種を行っているが，ワクチン接種者もワクチン非接種者も，全員麻疹，風疹，ムンプス，水痘の発症が予防されている．当院ではワクチン接種後の抗体測定は行っていないが，今までの疫学的経験から，ワクチン接種後の抗体測定は不要と考えている．なお，表2に示した日本環境感染学会のワクチン接種基準は，日本からの麻疹・風疹排除を目指し，麻疹および風疹ワクチンの2回接種を目標としているため，発症予防を目的としている当院の接種基準よりも高い抗体価が提唱されている．

麻疹・風疹・ムンプス・水痘接触時の対策には，免疫健常者を対象とするワクチン接種と免疫不全者や妊婦を対象とするガンマグロブリン投与とがある．ワクチン緊急接種による予防効果は，ワクチン接種により誘導された免疫により野生株の増殖を抑制するものであり，ワクチン接種による免疫誘導が，自然感染の潜伏期間よりも早い感染症で効果が期待される（表3）．麻疹・水痘では接触後72時間以内にワクチンを接種すると発症予防が，120時間以内ならば軽症化が期待され，風疹では米国小児科学会は理論上緊急接種が有効としている．ムンプスではワクチン後の免疫誘導時期が他の感染症よりも遅いため，緊急接種をしても発症予防効果は期待しにくいが軽症化は期待される．

ガンマグロブリンの投与は，ガンマグロブリン中に含まれる各ウイルスに対する中和抗体により感染したウイルス増殖を抑制するものである．麻疹ではガンマグロブリンの効果は確認されているが，他の感染症においては，効果は十分に確認されていない．

インフルエンザ対策

医療従事者はインフルエンザウイルスの曝露を受け，仕事を休まざるをえない機会が多いため，ワクチン接種が勧められる集団である．また，医療従事者のインフルエンザワクチン接種率が高い高齢者施設や介護施設では，入所している高齢者や要介護者のインフルエンザ発症や肺炎発症が低下するなど，インフルエンザワクチンには集団免疫効果が認められている[5]．

インフルエンザは局所性感染症であり，発症予防のためには高い抗体価が必要である．成人ではHI抗体40倍では50%，HI抗体160倍では90%が発症予防される[4]．インフルエンザワクチン後の抗体価は接種後6カ月を過ぎれば約半分に低下するため，毎年のワクチン接種が勧められる．2010/2011年シーズンと2011/2012年シーズンのインフルエンザワクチンには，3種類ともに同じワクチン株が使用されたが，このような場合でも高い抗体価を誘導するた

表3　生ワクチンの曝露後接種の効果

項目	麻疹	水痘	風疹	ムンプス
潜伏期間（日）	10-14	14-16	16-18	16-18
症状出現前のウイルス排泄	あり	あり	あり	あり
ウイルス血症のピーク（主症状出現との関係）	出現時	出現時	出現時	出現前？
ワクチン後の反応				
副反応出現（日）	7-10	14-	7-14	18-21
CMI出現（日）	7-10	5-13	10-14	14-
曝露後接種*	有効	有効	理論上有効	無効
接種までの期間	72時間以内	72時間以内	72時間以内	当日†

CMI：cell mediated immunity（細胞性免疫）
＊ワクチン接種により誘導された免疫により，先に感染した野生株の増殖を抑制し，発症を予防する．麻疹や水痘では72時間以内ならば発症予防が，120時間以内ならば発症したとしても軽症化が期待される．米国小児科学会は風疹ワクチンも曝露後接種は理論上有効としている．
†家族内曝露当日の有効率は57%．発症したとしても軽症化する．

めに毎年のワクチン接種が必要である．

ま と め

医療従事者は感染を受けやすい集団であり，また感染を周囲に拡大させるリスクが高い集団であるため，日頃からの感染対策が大切である．麻疹・風疹・ムンプス・水痘では，採用時に抗体価を測定し，ワクチン接種が必要な医療従事者に接種を行う曝露前対策が効率的である．インフルエンザワクチンは集団免疫効果も認められており，医療従事者には毎年のインフルエンザワクチン接種が勧められる．

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原　著

MRワクチンと水痘ワクチン同時接種の効果ならびに安全性

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要　旨

【目的】MRワクチンと水痘ワクチンの同時接種の効果と安全性を評価する．

【対象と方法】MRワクチンの第1期接種時に水痘ワクチンの同時接種に同意した82名と，年齢，性別をそろえた水痘ワクチン単独接種43名，およびMRワクチン単独接種51名を対象とした．ワクチン接種前後の水痘，麻疹，風疹の各ウイルス抗体価を測定し，副反応を調査し，同時接種者には水痘抗原に対するELISPOTアッセイを実施した．さらに接種1年後に水痘罹患状況を調査し，未罹患者に水痘ワクチンを追加接種し評価した．また1歳時にMRワクチンと，水痘ワクチンが接種された28名を対象に，MRワクチンの第2期接種時に水痘ワクチンの同時接種を実施し，同様にウイルス抗体価を評価した．

【結果】水痘抗体陽転率，平均抗体価ともに単独接種群と同時接種群間で有意差はなかった．麻疹，風疹も同様に抗体陽転率，接種後平均抗体価に両群間で有意差はなかった．水痘特異的細胞性免疫能の評価では71.4％に細胞性免疫の獲得が示唆された．また，特に問題となる副反応はなかった．ワクチン接種後1年間の水痘罹患は11％であった．接種1年後に水痘ワクチンの追加接種を実施し，明確なブースター効果が確認された．MRワクチン第2期接種時の水痘ワクチン追加接種においても接種前に比べ水痘抗体価の有意な上昇を示した．

【考察】MRワクチンと水痘ワクチンの同時接種は，安全かつ有効であり，また水痘ワクチンの追加接種の有効性が示された．

キーワード：水痘ワクチン，MRワクチン，ワクチンの同時接種，定期接種

はじめに

我が国の小児予防接種を欧米先進国レベルに引き上げるため，現行の定期接種ワクチンに加え任意接種ワクチンを定期接種化し，より多くのワクチンを効率的に接種してゆく必要があり，複数ワクチンの同時接種は極めて有用な手段である．欧米ではワクチン同時接種が一般的に実施されているが，我が国ではその歴史がなく，その効果，安全性に関する基礎的なデータが求められている．

水痘ワクチンは，Takahashiら[1]により開発，実用化された唯一のヒトヘルペスウイルスワクチンである．開発当初，わが国で安全性，有効性についての数多くの知見が蓄積され[2)3)]，それを基盤として1995年米国食品医薬局の承認を受け，翌年から米国でuniversal vaccinationが開始された[4)～6)]．その目覚ましい効果については既に数多くの報告があり，水痘の季節流行パターンが消失しつつあることも明らかになっている[7)]．しかしながら，ワクチン開発国であるわが国では未だ任意接種のため，接種率は約40％程度にとどまっており，毎年春の流行期には数多くの患者が発生し，中には重篤な合併症を来たす症例がみられる．特に免疫不全宿主では極めて重症化し，中には致死的な経過をたどる例がある[8)]．費用対効果分析の結果から，定期接種化のメリットが明らかになっており[9)10)]，わが国においても早急に定期接種化がなされるべき重要なワクチンである．

そこで本研究では，水痘ワクチン定期接種化に際し，現時点で問題となる麻疹風疹混合（MR）ワクチンとの同時接種について，その効果と安全性を評価すること

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室温放置し，洗浄後ストレプトアビシン標識ペルオキシダーゼ添加，45分間室温放置したのち，テトラメチルベンジンを添加して3分間静置後にスポット数測定に使用した．スポットの検出はES ELISPOT system (Carl Zeiss) で行った．

4. 副反応調査

調査項目(37.5℃以上の発熱，発疹，咳嗽，鼻汁，接種部腫脹発赤）が記された調査票に被検児の保護者が記載する方法でワクチン接種日から接種後28日間までの症状を前方視的に調査した．

5. 水痘ワクチン接種後罹患に関する調査

第1期MRワクチンと水痘ワクチン同時接種例82名のうち藤田保健衛生大学病院ならびに豊川市民病院で接種を受けた50名を対象として，ワクチン接種後罹患のアンケート調査を行った．平成23年12月に往復ハガキによる調査を行った．調査項目は水痘罹患の有無，罹患した場合は罹患時期，発疹数，発熱の有無，感染源，抗ウイルス剤治療の有無について確認した．

6. 水痘ワクチン追加接種

上記アンケート調査の中で，水痘未罹患の場合には希望者に水痘ワクチン追加接種することを記載し，水痘ワクチン追加接種の希望者を募集した．応募者9名に水痘ワクチンを接種し，ワクチン接種前と接種後1か月の2回血清を採取し，水痘抗体価を測定した．

7. 統計学的解析

統計解析には「Microsoft エクセル統計2008(SSRI, Tokyo, Japan)」を使用した．ウイルス抗体価の比較はMann Whitney U-testを用い，対象者の年齢，性別，副反応発生頻度の比較はχ^2検定およびt検定で解析した．

結　果

第1期MRワクチンとの同時接種（study 1）

1. 水痘抗体価の推移

MRワクチンと水痘ワクチン同時接種群82例の接種前水痘抗体はIAHA法で判定不能であった1例を除き全例が陰性，接種後水痘平均抗体価は，IAHA法で3.81±2.17(log2で表記)，gp-ELISA法で2.38±0.40(log10で表記）であった（表1A)．各抗体の陽転者数はそれぞれ66例（81.5%)，74例（90.2%）であった．また，水痘ワクチン単独接種群42例の接種前水痘抗体も全例で陰性，接種後抗体価は3.31±2.38(IAHA法)，2.34±0.46（gp-ELISA法）であり，それぞれの抗体陽転例は30例（71.4%）と36例（85.7%）だった．同時接種群と単独接種群間の各抗体価を比較すると，IAHA（$p=0.33$)，gp-ELISA（$p=0.57$）ともに2群間で有意差はなかった．

2. 水痘ELISPOTアッセイ

凍結保存細胞の解凍後にアッセイに必要なPBMCs数（4×10^6cells/mlに調整した浮遊液を1.5ml）が得られた7名について水痘ワクチン接種前後のELISPOTアッセイの結果を解析した(表2)．水痘抗原刺激，PHA刺激および対象の数値は2回実施した平均値を記載した．VZV抗原刺激による反応が陰性コントロールに対し2倍以上の場合を陽性と定義すると，7名中5名(71.4%）が接種後陽性となった．ワクチン接種後もIAHA法とgp-ELISA法の両方法で抗体陽転を認めなかった5名の中で，3名でELISPOTアッセイを実施し，うち2名（No.7, 8）が陽性を示した．

3. 麻疹・風疹抗体価

MRワクチンと水痘ワクチンの同時接種群82名中2名が接種前麻疹抗体陽性であったため，接種前抗体陰性の80名について評価した(表1B)．その結果，接種後麻疹抗体価(log2で表記）は5.41±1.57(NT法)，風疹抗体価(log2で表記）は5.54±1.74(HI法）であった．麻疹NT抗体≧2，風疹HI抗体≧8を陽性と定義すると，各抗体のワクチン接種後陽転者はそれぞれ79例（98.8%)，77例（96.3%）であった．また，MRワクチン単独接種群51名の接種後抗体陽転者は，麻疹51例（100%)，風疹49例（96.1%）であった．接種後平均抗体価は，麻疹5.34±1.29(NT法)，風疹5.63±1.62(HI法）であり，それぞれMRワクチンと水痘ワクチン同時接種群との間に有意差はなかった（麻疹NT抗体；$p=0.40$，風疹HI抗体；$p=0.52$)．

4. 副反応

水痘ワクチン・MRワクチン（第1期）同時接種群(n=50）で副反応について調査した結果，重篤な副反応は認めず，今回の調査対象とした発熱，発疹，咳嗽，鼻汁，接種部発赤や腫脹のみであった．MR単独接種群(n=50）と比較した結果，発熱(同時接種群：26.0%，MR単独接種群：28.0%，$p=0.82$)，発疹(同時接種群：10.0%，MR単独接種群：12.0%，$p=0.75$)，咳嗽(同時接種群：12.0%，MR単独接種群：12.0%，$p=1.00$)，鼻汁(同時接種群：16.0%，MR単独接種群：20.0%，$p=0.60$)，接種部発赤（同時接種群：4.0%，MR単独接種群：6.0%，$p=0.65$)，接種部腫脹(同時接種群：2.0%，MR単独接種群：2.0%，$p=1.00$）と両群間に有意差は認めなかった．

5. 水痘ワクチン接種後1年間の水痘罹患状況

50名中36名（回収率72%）から返信があり，ワクチン接種後罹患者は4例(11.1%）であった．罹患時期は全例接種後7か月以降であり，いずれも発熱はなく，発疹数100個未満と軽症だった．感染源は同胞3例，保育所の友人1例であった．

表3　水痘ワクチン追加接種の効果

MRワクチン第1期と水痘ワクチンの同時接種者への水痘ワクチン追加接種効果.

	初回接種				追加接種				
	接種前		接種後		接種前		接種後		
Case	IAHA	gp-ELISA	IAHA	gp-ELISA	IAHA	gp-ELISA	IAHA	gp-ELISA	接種間隔（月）
1	<2	<50	32	218	<2	211	128	30,954	15
2	<2	<50	<2	<50	<2	250	32	3,182	14
3	<2	<50	8	204	<2	198	64	5,012	16
4	8	<50	32	180	<2	208	128	12,813	13
5	<2	<50	<2	<50	<2	150	32	2,102	17
6	<2	60	64	364	<2	334	128	7,654	15
7	<2	73	<2	414	2	388	≧256	20,948	15
8	<2	<50	64	770	64	5,496	≧256	12,694	15
9	<2	<50	32	148	4	371	128	15,348	15
陽性率（%）			66.7	77.8	33.3	100	100	100	
平均抗体価（Ave. ±SD）			3.3±2.6	2.3±0.4	1.0±2.0	2.5±0.5	6.9±1.4	4.0±0.4	15.0±1.1*

（平均抗体価はIAHA法：log2，gp-ELISA法：log10で表記.）
*平均接種間隔を示す

第2期MRワクチンとの同時接種（study 2）

1. 水痘抗体価の推移（表4A）

第2期MRワクチンと水痘ワクチンの同時接種では，接種前水痘平均抗体価および陽性率はIAHA法で2.96±3.10, 55.6%，gp-ELISA法で3.02±0.92, 89.3%であったが，ワクチン接種後は，IAHA法で6.07±1.38, 100%，gp-ELISA法で3.97±0.56, 100%であり，接種前後で平均抗体価の有意な上昇（それぞれ$p=0.0017$, $p=0.0003$）が認められた.

2. 麻疹・風疹抗体価（表4B）

接種前麻疹平均抗体価および陽性率はNT法で5.71±1.37, 100%であったが，ワクチン接種後は，6.66±0.81, 100%と抗体価の有意上昇を認めた．接種前に比較的低い抗体価を示したのは2.5（1名），3.5（1名），4.0（1名）であり，その他は4.5以上と比較的高い抗体価が維持されていた．接種後抗体価は5.0（1名）と5.5（2名）を除き，6.0以上の抗体価を示した．また，風疹においても接種前平均風疹抗体価および陽性率はHI法で5.93±1.30, 100%であったが，ワクチン接種後は，6.57±0.88, 100%と，抗体価の有意上昇を認めた．接種前最低抗体価は8倍が2名，16倍が2名であり比較的高い抗体価が維持されていたが，接種後抗体価は32倍（3名）を除き，他は64倍以上の抗体価を示した.

3. 副反応

第2期のMRワクチンと水痘ワクチンの同時接種において全身性の有害事象はなかった．17人中接種局所の発赤を2名に，腫脹を2名に認めた程度で特に問題となる副反応はなかった.

考　察

水痘ワクチンのuniversal immunizationの効果は，既に導入後16年が経過した米国からの種々の報告を見れば明らかである[12)13)]．さらに，わが国においての費用対効果研究においても，間接効果を考慮に入れることにより定期接種化が有益なことが示されていることから[9)10)]，一刻も早い水痘ワクチンの定期接種化が望まれている．実際に水痘ワクチンの定期接種化を導入する際，最も現実的なスケジュールは第1期MRワクチンとの同時接種と考えられる．今回の研究の結果，水痘ワクチン単独接種群と水痘ワクチンとMRワクチン同時接種群間でワクチン接種後VZV抗体価に有意差は認められなかったので，水痘ワクチンとMRワクチンの同時接種により，VZVに対する液性免疫誘導に支障のないことが裏付けられた．また，MRワクチン単独接種群と水痘ワクチン，MRワクチン同時接種群間でワクチン接種後の麻疹，風疹抗体価を比較したが，両群間で有意差がなかったことから，同時接種は麻疹ワクチン，風疹ワクチンの抗体誘導能に関しても影響がないことが示された．さらに2期MRワクチンとの同時接種でもVZV抗体価の上昇が確認でき，追加接種の有効性も示唆された．以上の結果から，水痘ワクチンとMRワクチンの同時接種が，両ワクチンの効果に影響を与えないことが示された．これは，対象数は

では十分な免疫誘導ができず接種後罹患を起こすことが問題となっている．したがって，現時点でのわが国での水痘ワクチン接種施策は，米国とは異なり，より早期の追加接種で全体の患者数削減を目指すことが重要と思われる．実際，一部のワクチン接種後水痘未罹患者について1年後のVZV抗体価を調べた結果，IAHA法では9名中6名（67%）の対象者で検出限界以下であった．さらにこれらの患者に水痘ワクチンを追加接種することにより，明確なブースター効果が確認されたことから，今後は適切な追加接種時期を明らかにするために，水痘ワクチン2回接種時期について検討してゆく必要があると思われた．

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原　著

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抗風疹IgG国内標準血清の作製，およびELISA法によるIgG抗体価（国際単位）とHI抗体価の相関性の解析

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風疹罹患歴のある成人ボランティアの血清をプールし，抗風疹IgG国内標準血清候補（JPN'03）とした．民間検査施設等の協力を得てJPN'03の抗体価を抗風疹IgG抗体国際標準品（RUBI-1-94）とともに測定し，平行線定量法で国際標準品に対する相対抗体価を算出，統計処理し，JPN'03の相対抗体価を100国際単位（IU）/mLとした．また，ボランティアから収集したパネル血清候補の国際標準品に対する相対抗体価をELISA法で測定し，国際単位による値付けを行った．並行して風疹HI抗体価を測定し，国際単位に基づいた風疹IgG抗体価とHI抗体価の相関を解析した．IgG抗体価（IU/mL）とHI抗体価には有意な相関が認められ（R^2=0.897），HI抗体価16倍以上においては近似式［Log_{10}（IU）≒ 0.26 Log_2（HI）+ 0.084］による換算が可能と考えられた．

Key words：抗風疹血清，抗風疹国内標準血清，ELISA，HI抗体価，抗風疹IgGパネル

緒言

妊娠初期の女性が風疹に罹患すると出生児に先天性の障害（先天性風疹症候群：CRS）をもたらす可能性がある．CRSの予防には，妊娠前に抗風疹抗体価を測定し，必要に応じてワクチンを接種することが唯一の方法であり，抗風疹抗体価の標準化が求められている．

抗体価等の血清中の生物活性値を測定する場合，不特定な夾雑物が存在する等から，他の医薬品に適用されるような物理化学的な絶対定量による有効成分の含量測定は困難な場合が多く，標準物質に対する相対値として表すのが一般的である．WHOでは血清を含む様々な生物学的製剤の国際標準品を多施設の共同研究により[1]整備しており，現在の抗風疹IgG抗体国際標準品，RUBI-1-94（1,600 international units（IU）/vial）は1996年に作製、承認され，National Institute for Biological Standards and Control（NIBSC, UK）により配布されている．しかし，国際標準品は潤沢ではないため，国際標準品を基準とした国内標準品等の二次標準品の作製，使用をWHOは推奨しているが[2]，これまで我が国では抗風疹IgG抗体の国内標準品は整備されていなかった．

一方，我が国では抗風疹抗体測定法として主に抗風疹赤血球凝集阻止法（HI法）と酵素抗体法（ELISA法）が用いられているが，両法で表示されるHI抗体価と抗風疹IgG抗体価の相関，互換法についての情報が十分でないため，臨床現場において抗体価の評価においてしばしば混乱が生じている．

本研究では，WHO抗風疹IgG抗体国際標準品を基準として国内標準血清候補（JPN'03）の相対抗体価を決定し，国内標準抗風疹血清を作

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製した．さらに，ボランティアより提供されたパネル血清候補をELISA法とHI法で測定し，国際単位による抗体価とHI抗体価の相関を解析し，両者間の近似式による互換法を求めたので報告する．

1．材料と方法

1.1　候補品の作製

国内標準血清候補JPN'03：風疹既往歴のある成人ボランティアから提供された血清をプールし候補品とした．それぞれの血清は事前に抗風疹IgM抗体が陰性であることを確認した．

パネル血清候補：成人ボランティア76人から提供された血清を候補品とした．

本研究は国立感染症研究所，および国立病院機構三重病院の倫理委員会の承認を受け，採血はボランティアからインフォームドコンセントを得て実施した．

1.2　国際標準品

WHO国際標準品(RUBI-1-94, 1600 IU/vial)はNIBSC (UK)より提供を受けた．

1.3　参加施設

風疹抗体価測定を業務としている民間検査会社等7施設で抗体価を測定した．

1.4　測定方法

国際標準品や国内標準品などの二次標準品の抗体価決定で行われている共同研究による標準化[1,2,5]の定法に従い，参加施設が通常の業務で使用している試薬・機器を用い，通常行っている方法で抗体価を測定した．各施設で使用した試薬，機器を表1に示す．国際標準品(RUBI-1-94, 1600 IU / vial)はPBS(-)に溶解し800 IU/mLの溶液を調製後，凍結し各施設に配布した．JPN'03およびパネル血清候補は原液を各施設に配布した．JPN'03および国際標準品は，各

表1　各施設による国際標準品に対する国内標準品候補JPN'03の相対力価の測定結果

Lab	使用キット	製造会社	測定機種	Assay No	IU	95% LL[*1]	95% UL[*2]	Lab GM IU
1	ウイルス抗体EIA「生研」ルベラIgG	デンカ生研株式会社	自社オリジナル	1	100.0	97.7	102.4	96.8
				2	91.0	88.6	93.4	
				3	99.7	98.2	101.3	
2	ウイルス抗体EIA「生研」ルベラIgG	デンカ生研株式会社	シーメンス ベーリング ELISA プロセッサーIII	1	101.6	98.6	104.6	93.6
				2	86.0	83.6	88.5	
				3	93.7	91.9	95.6	
3	ウイルス抗体EIA「生研」ルベラIgG	デンカ生研株式会社	シーメンス ベーリング ELISA プロセッサーIII	1	93.9	90.5	97.3	92.9
				2	97.5	94.6	100.5	
				3	87.6	85.6	89.6	
4	ウイルス抗体EIA「生研」ルベラIgG	デンカ生研株式会社	協和メディックス株式会社 AP-960	1	86.9	80.9	93.3	90.3
				2	93.8	88.1	99.8	
5	ウイルス抗体EIA「生研」ルベラIgG	デンカ生研株式会社	協和メディックス株式会社 AP-960	1	70.8	68.1	73.7	69.4[*3]
				2	59.6[*3]	58.1	61.1	
				3	68.0	65.7	70.3	
6	エンザイグノスト風疹IgG	シーメンスヘルスケアダイアグノスティクス株式会社	シーメンス ベーリングELISA プロセッサーIII	1	122.2	117.4	127.2	135.6
				2	142.2	131.7	153.5	
				3	143.4	135.3	152.0	
7	ランピアラテックスルベラ	極東製薬工業株式会社	日立7170型自動分析装置	1	128.6	126.3	131.0	126.4
				2	128.4	126.7	130.2	
				3	122.2	119.6	124.8	
				GM	100.9[*4]			98.6[*5]

[*1]：LL：95%信頼区間の下限値
[*2]：UL：95%信頼区間の上限値
[*3]：Lab5の2回目の結果を解析から除外した
[*4]：個々の測定値より算出した幾何平均値
[*5]：施設ごとの測定値から算出した幾何平均値

施設においてPBS(-)を用いて2倍段階希釈を行い，国際標準品については8点，国内標準血清候補については7点の希釈列を作製しIgG抗体価の測定に用いた．パネル血清候補については原液を測定に用い，検量範囲を超えたものについてはPBS(-)にて適宜希釈を行って再測定した．検体の測定は，独立した希釈列を日を変えて3回作製し，それぞれの希釈列を，JPN'03では5重測定，パネル血清では3重測定した．一度融解した国際標準品等は再使用しなかった．

パネル血清候補の抗風疹抗体価は，参加施設のうち風疹HI抗体価の測定も業務としている5施設で，ELISA法とHI抗体測定法で測定された．HI抗体価測定は段階希釈した検体とウイルス抗原を反応後，ガチョウ赤血球を添加し，ウイルス抗原と赤血球の凝集反応が抑制される血清の希釈段階を測定する「感染症流行予測調査事業検査術式」[3]に準じ，通常の業務に用いている方法で3回測定した．得られた結果の幾何平均をHI抗体価とした．

1.5 IgG抗体価算出

測定ごとの抗体価は試料の吸光度と濃度の対数変換値から，平行線定量法[4]を用いて国際標準品に対する相対力価として算出した．

1.6 統計処理によるIgG抗体価の決定

候補品の抗体価は，各施設の独立3回の試験結果から国際標準品に対する相対力価としてそれぞれ算定した値の幾何平均値として求めた．

2. 結果

2.1 国内標準品候補JPN'03の国際単位による抗体価

表1に各施設によるJPN'03の測定結果を示す．数値は独立した3回の測定により国際標準品に対する相対力価として得られたJPN'03の抗体価および95%信頼区間，および各施設，試験結果全体の抗体価の幾何平均値を示している．Lab 5の2回目の測定結果は試験結果全体の幾何平均±2SD(標準偏差)を外れるため，解析から除外した．Lab 4は都合により3回目の測定ができなかったため，2回の測定結果を解析に用いた．候補品の抗体価を各測定結果の幾何平均値として算出した場合は100.9 IU / mL，各施設の幾何平均値から算出した場合は98.6 IU/mLであった(表1)．国際標準品RUBI-1-94の抗体価表示が有効数字二桁であることも考慮し，JPN'03の抗体価を100 IU/mLと決定した．

2.2 パネル血清の国際単位による抗体価とHI抗体価との相関

ELISA法による抗体価は各施設の独立した3回の測定により得られた国際標準品に対する相対力価の幾何平均値，HI抗体価は各施設の独立した3回の測定により得られたHI抗体価の幾何平均値を求めた．パネル血清候補の抗体価測定における施設内(intra-lab)の変動係数(Geometric coefficient of variation : GCV)はLab 1で4.1 %，Lab 2，3で6.5 %，Lab 4で16.3 %，およびLab 5で36.1 %であり，再現性が低かったLab 5の結果は解析から除外した．Lab 1～4の施設間(inter-lab)の変動係数は10.3 %であった．HI抗体価8倍の血清候補が含まれなかったため，8倍以下を除外したパネル血清候補のELISA法による抗体価とHI抗体価の対数変換値の相関を解析した．各施設(intra-Lab)の回帰分析の結果を表2に，施設毎に算出した抗体価とHI抗体価の幾何平均値の相関図を図1に示す．施設毎および全施設の分析結果においてともにELISA法による抗体価とHI抗体価の間には有意な相関が認められ(表2)，HI抗体価16倍以上において，[Log_{10} (IU) ≒ 0.26 Log_2 (HI) + 0.084]の近似式が得られた．

3. 考察

WHOの標準品作製の標準的手法である多施設による共同研究により国内標準品候補JPN'03の値付けを行った．測定には7施設中，5施設がデンカ生研のキットを用いていた．測定結果を統計処理したところ，施設間に多少のばらつきはあったものの，おおむねどの施設の結果からも妥当と判断される抗体価が得られ，JPN'03の抗体価は100 IU/mLとした．国内抗風疹標準血清や風疹パネル血清は今後，キットの精度管理や新規診断キットの評価に用いられることが期待される．

表2　パネル血清候補のELISAによる抗体価とHI抗体価の回帰分析

Lab	傾き	y切片	決定係数 (R^2)	P値
1	0.264	0.174	0.798	< 0.001
2	0.218	0.294	0.838	< 0.001
3	0.300	-0.220	0.898	< 0.001
4	0.233	0.337	0.872	< 0.001
All*	0.263	0.084	0.897	< 0.001

*: 全施設の幾何平均値

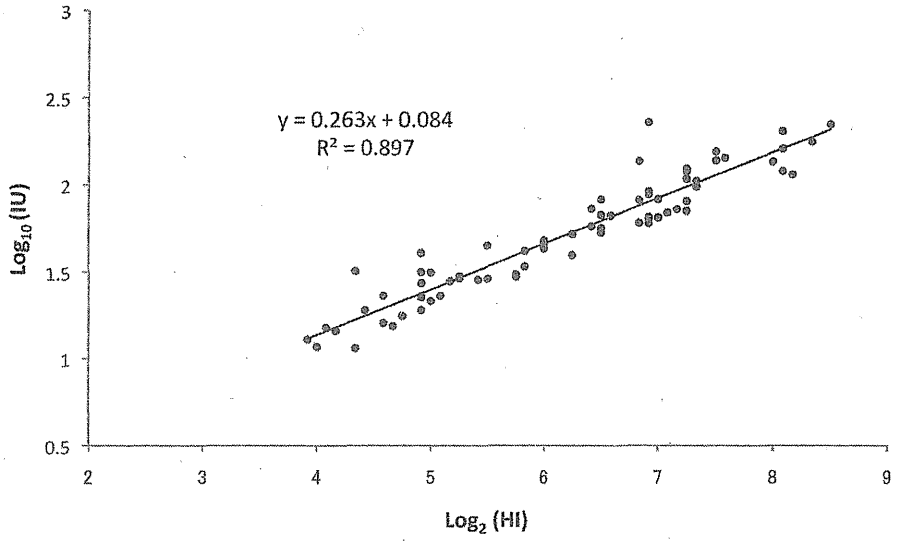

図1　パネル血清候補のELISAによる抗体価とHI抗体価の相関図

日本では長い間，HI法による風疹抗体価表示が行われているため，国際単位での表示が医療現場でわかりにくいという問題があった．今回，パネル血清をELISA法による国際単位に基づく測定とともに，HI抗体価を測定し，両者の相関性を解析したところ，HI抗体価16倍以上においてHI抗体価とELISA法によるIU値に高い正の相関(R^2=0.897)が認められ，近似式[Log_{10} (IU) ≒ 0.26 Log_2 (HI) + 0.084]による両者の換算が可能であると考えられた．近似式よりHI抗体価16倍は13.3 IU/mL，32倍は24.1 IU/mLに相当した．また，8倍の値を外挿してIU値を求めると計算上は7.5 IU/mLと算出された．

現在，日本では定期接種以外にHI抗体価16倍以下の妊娠可能年齢の女性に風疹ワクチン接種を勧めている[6,7]．一方，WHOは一般に感染防御に有効な抗体価を≥10 IU/mLとしている[8,9]．今回得られた近似式から，HI抗体価16倍は約13.3 IU/mLとなり，日本では，WHOが一般に有効とする抗体価(10 IU/mL)よりやや高い抗体価を保有する人にもワクチン接種を推奨していることになるが，HI法の抗体価表示の特性，およびCRS予防の重要さを考慮すれば妥当であると考えられた．今回作製した候補品は国内標準品および国内パネル血清として国立感染症研究所で管理，分与を行う予定である．

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Establishment of the Japanese National standard for anti-rubella IgG human serum and analysis for correlation between HI titer and international units

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Summary

The reference standard is essential for quantification of biological substances. However, the Japanese National standard for anti-rubella immunoglobulin has not been established. In this study, the Japanese National standard for anti-rubella IgG human serum (JPN'03) was established with an assigned titer of 100 IU/mL by calibrating against WHO 1st international standard for anti-rubella immunoglobulin (RUBI-1-94), according to the standard method for development of International standards. In addition, antibody titers of rubella antiserum panel candidates were measured by both ELISA method calibrating by RUBI-1-94 and HI method. Their ELISA titers had good correlation with HI titers (R^2=0.897) above HI titer 16, and the regression equation, [Log_{10} (IU) ≒ 0.26 Log_2 (HI) + 0.084] was obtained.

Key words

rubella anti-sera, Japanese National standard anti rubella serum, enzyme-linked immunoassay, hemagglutination inhibition test, antiserum panel

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改良された抗麻疹IgM抗体検出EIA試薬の評価

庵原俊昭[1)]・要藤裕孝[2)]
堤　裕幸[2)]・吉川哲史[3)]

はじめに

麻疹ウイルス感染症は，厚生労働省を始めわが国の医療関係者が臨床・基礎の分野を問わず，一丸となり2012年の排除（Elimination）に向け全力を挙げて活動してきた。その結果2010年以降，日本における常在性麻疹ウイルス（D5型）は国内で検出されておらず，減少を続けてきた症例はすべて海外由来の麻疹ウイルスであることから，Eliminationはほぼ達成されたものと考えられる[1)]。このように，感染症症例が減少してくると，関連試薬の陽性的中率が減少することは避けられないが，診断学的および疫学的見地より考慮すると，感染症の流行状況にあった性能へと試薬の改良が求められる。

抗麻疹IgM抗体検出試薬においては，近年，他の発疹性疾患（風疹[2)]，伝染性紅斑[3)]，突発性発疹[4)]，テング熱[4)5)]）等においても，抗麻疹IgM抗体陽性例が報告され，one point IgM抗体を用いた麻疹の確定診断に注意が払われるようになった。わが国では2008年より，風疹とともに麻疹が全数報告の対象となり，2010年からは確定診断として3種類（咽頭拭い液，血液，尿）の検体を用いた遺伝子検査（PCR検査）と抗麻疹IgM抗体検出が推奨されている[6)]。これら実験室診断は，主治医からの依頼に基づき，各地方衛生研究所で実施されているが，抗麻疹IgM抗体の偽陽性の懸念から，検出試薬の改良についての要望は大きい。

デンカ生研株式会社（以下デンカ生研と略す）は，この問題に対応するため，改良試薬の開発を行ってきたが，今回，現行抗麻疹IgM抗体検出試薬（ウイルス抗体EIA「生研」麻疹IgM）の改良型試作品（コードNo. DC-12-01，以下試作品と略す）の臨床的有用性を評価する機会を得たので，その結果について報告する。

Ⅰ．材料と方法

1．被験検体

1）麻疹患者検体

日本国内で麻疹患者検体を収集することは不可能であったため，2009年に麻疹流行地であるベトナムにおいて臨床的に麻疹と診断された患者より採集された，ベトナム国立公衆衛生疫学研究所（National Institute of Hygiene and Epidemiology以下NIHEと略す）にて保存されていた110血清を使用した。

1）国立病院機構三重病院 小児科　2）札幌医科大学医学部 小児科学講座　3）藤田保健衛生大学医学部 小児科学
Evaluation of an improved anti-measles virus IgM antibody-detection EIA kit
Toshiaki Ihara et al　*Department of Pediatrics, National Hospital Organization Mie National Hospital*
Key words：抗麻疹IgM抗体，偽陽性，EIA，IgM capture法

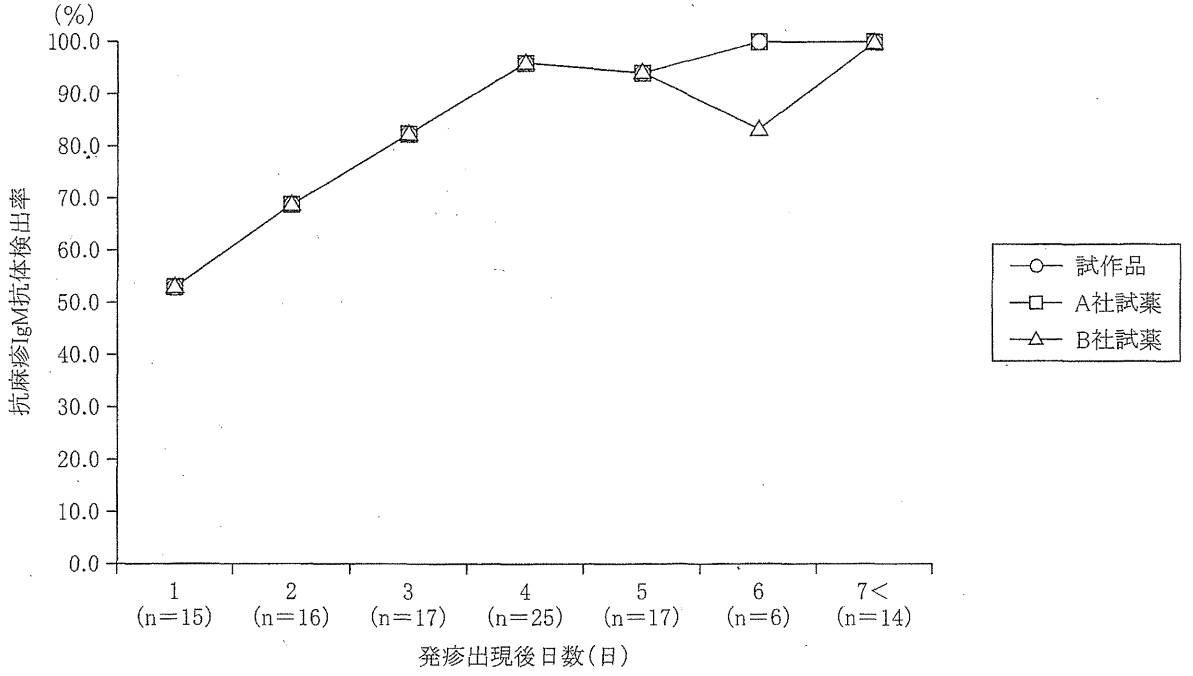

図 1　麻疹患者における発疹出現後の日数と各試薬の抗麻疹 IgM 抗体検出率

2）風疹患者検体

ベトナム NIHE で保存されていた，2009 年に臨床的に風疹と診断され，かつ血清学的に抗風疹ウイルス IgM 抗体が検出された患者より採取された 30 血清を使用した。

3）デングウイルス感染症患者検体

ベトナム NIHE で保存されていた，2011～2012 年に臨床的にデング熱と診断され，かつ血清学的に抗デング IgM 抗体が検出された患者より採取された 20 血清を使用した。

4）突発性発疹患者検体

藤田保健衛生大学小児科で 2005～2012 年に突発性発疹と診断され，かつウイルス学的にヒトヘルペスウイルス 6B（以下 HHV-6B と略す）初感染が証明された突発性発疹患者の有熱期の血清 15 検体を使用した。

5）伝染性紅斑患者検体

札幌医科大学小児科において保存されていた，臨床的に伝染性紅斑と診断され，血清学的に抗ヒトパルボウイルス B19-IgM 抗体が検出された，抗ヒトパルボウイルス B19 初感染例 57 血清を使用した。

6）陰性検体

健常成人から採取した 78 血清を本検討の陰性対照として使用した。

すべての検体にはペア血清は含まれていない。なお，上記検体はすべて，各施設にて事前に使用の同意が得られているものを使用した。また，1)～3）の検体を用いた試験は，すべてベトナム NIHE にて実施した。

2．抗麻疹 IgM 抗体検出法

デンカ生研が，改良を進めている試作品を，デンカ生研の推奨する方法にて実施した。比較対照品としては，体外診断用医薬品として承認・市販されている，A 社および B 社の抗麻疹 IgM 抗体検出 EIA 試薬を，各添付文書に準じて使用した。各 EIA 試薬は，A 社試薬は試作品と同様の「IgM capture 法」であり，B 社試薬は「IgG 吸収法」を反応原理としている。

3．統計解析

統計解析には（有）オーエムエス出版が発行している「Statcel 2」を使用した。

表 1　試作品とA社試薬の判定一致率

		A社試薬			計
		陽性	判定保留	陰性	
試作品	陽性	93	0	0	93
	判定保留	0	0	0	0
	陰性	0	2	93	95
計		93	2	93	188

陽性一致率：93/93＝100.0%
陰性一致率：93/93＝100.0%
全体一致率：(93＋0＋93)/188＝98.9%

表 2　試作品とB社試薬の判定一致率

		B社試薬			計
		陽性	判定保留	陰性	
試作品	陽性	92	1	0	93
	判定保留	0	0	0	0
	陰性	0	2	93	95
計		92	3	93	188

陽性一致率：92/92＝100.0%
陰性一致率：93/93＝100.0%
全体一致率：(92＋0＋93)/188＝98.4%

表 3　他発疹性疾患検体との反応性

	風疹 (n＝30)	デング熱 (n＝20)	突発性発疹 (n＝15)	伝染性紅斑 (n＝57)
試作品	0/30 (0.0%)	0/20 (0.0%)	0/15 (0.0%)	0/57 (0.0%)
A社試薬	1/30 (3.3%)	0/20 (0.0%)	0/15 (0.0%)	18/57 (31.6%)

II. 結　果

1．発疹出現後の日数毎の各試薬の抗麻疹IgM抗体検出率の比較（図1）

試作品，A社試薬，B社試薬で発疹出現後の日数毎の，抗麻疹IgM抗体の検出率を比較した。試作品とA社試薬は今回の検討では全く同じ動向を示した。B社試薬もほぼ同様の検出率で推移したが，6日目に若干低値を示した。

2．試作品と既存品との判定一致率（表1，2）

麻疹患者検体および陰性検体を用いた，試作品と既存品の判定一致率を表1及び表2に示す。A社試薬とは陽性一致率，陰性一致率ともに100.0%，全体一致率98.9%，B社試薬とは陽性一致率，陰性一致率ともに100.0%，全体一致率98.4%と，どちらの試薬とも試作品とは良好な一致率であった。

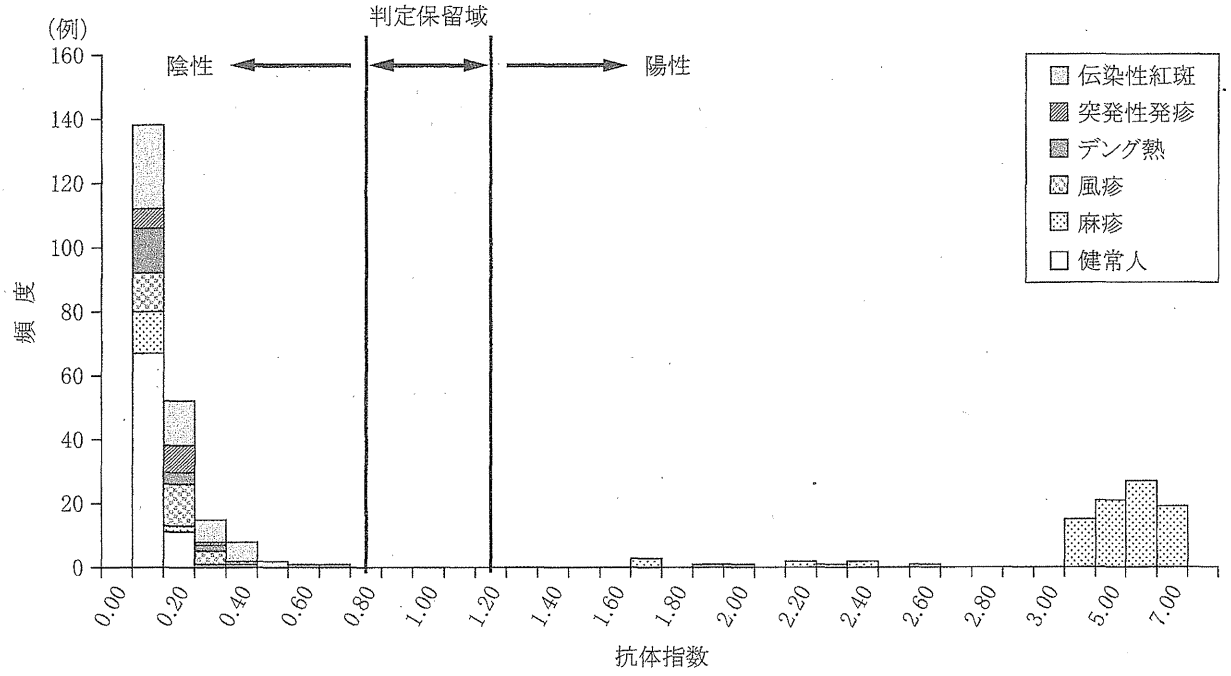

図 2　測定検体の抗体指数分布

3．他の発疹性疾患検体との反応性（表 3）

同じ反応原理である「IgM capture 法」を利用している A 社試薬と試作品の，他発疹性疾患検体における抗麻疹 IgM 抗体陽性率の比較検討を行った。A 社試薬は風疹および伝染性紅斑検体において，それぞれ，3.3%，31.6%と抗麻疹 IgM 抗体陽性と判定された検体が存在したが，試作品においては，陽性と判定されるものは，今回検討した他の発疹性疾患検体で認められなかった。

4．試作品における測定検体の抗体指数分布（図 2）

今回測定したすべての検体の，試作品における抗体指数の分布を図 2 に示す。本試作品の抗体指数 1.0 は，健常人検体の吸光度の平均値＋28 SD に相当し，その上下 20%に判定保留域を設定している。本検討においては，抗麻疹 IgM 抗体陽性と判定された検体はすべて麻疹検体であり，偽陽性反応は認められなかった。また，判定保留となる検体も存在せず，クリアカットな結果が得られた。

5．抗体指数とワクチン接種歴（図 3）

麻疹患者検体には，ワクチン接種歴がはっきりとした検体が存在した。その内訳は，ワクチン未接種 26 検体，接種 1 回 8 検体，接種 2 回 6 検体である。試作品で得られた抗体指数をワクチン接種回数で分類し，ワクチン接種回数と抗麻疹 IgM 抗体指数の関連性を確認するため，Mann-Whitney's U test を実施した。ワクチン接種歴なしと接種歴 1 回，接種歴 1 回と 2 回では有意差を認めなかったが，ワクチン接種歴なしと 2 回の比較では，ワクチン接種歴 2 回の方が有意に低値を示した。また，ワクチン接種歴 2 回で麻疹に罹患した検体はすべて（n＝6）抗麻疹 IgM 抗体が陰性であった。

III．考　　察

今回，デンカ生研が試作した抗麻疹 IgM 抗体検出試薬の性能評価を実施した。評価に当たり ① 検出感度は臨床的にどのように評価できるか？　② 既存試薬との相関性はどうか？ ③ 現在臨床現場で問題となっている他の発疹性疾患での偽陽性反応はどの程度まで改善されたか？　が最も注目される点である。

ベトナムで最も流行している麻疹ウイルスの遺伝子型は H1 型であり[7]，日本国内で 2009～

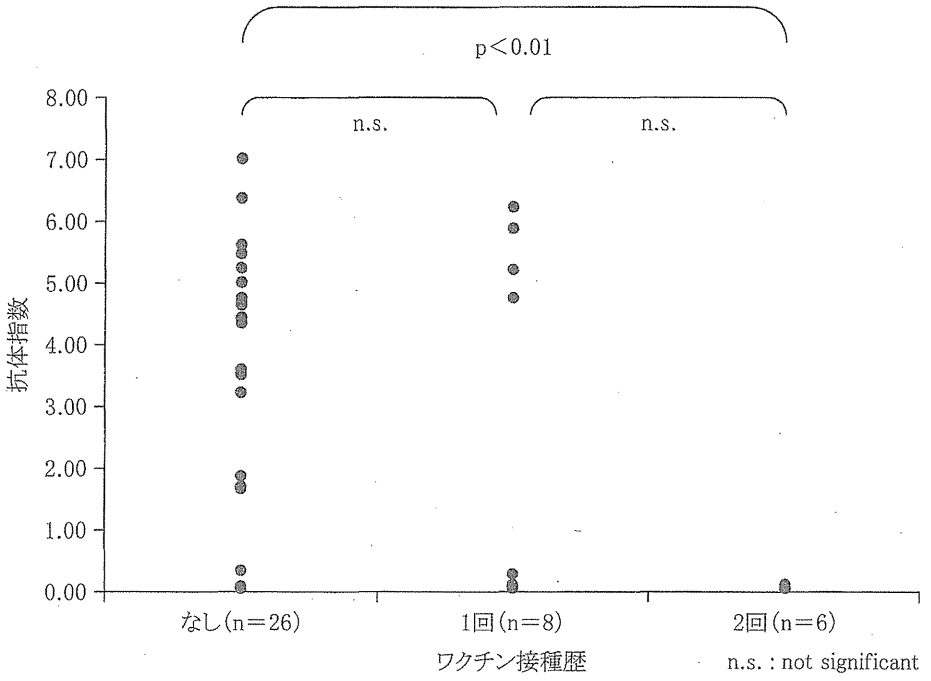

図 3　抗体指数とワクチン接種歴

表 4　麻疹患者における発疹出現後の日数と各試薬の抗麻疹 IgM 抗体検出率の比較

	Early (～3day)	Intermediate (4～14day)	Late (15～28day)
試作品	68.8% (33/48)	96.7% (58/60)	100.0% (2/2)
A 社試薬	68.8% (33/48)	96.7% (58/60)	100.0% (2/2)
B 社試薬	68.8% (33/48)	95.5% (57/60)	100.0% (2/2)

2012 年に分離された土着型の D5 型，輸入例であるさまざまの D 型や G3 型[1]とは異なっている。しかし麻疹ワクチンの研究で，麻疹ウイルスの流行（野生）株とワクチン株の抗原性は同等であり，遺伝子型の違いは抗体惹起に差を与えないことが示されている[8)9)]。したがって，ベトナムで採取された検体を使用することは問題がないと判断し，検討を実施した。

発疹出現後の日数毎の抗麻疹 IgM 抗体検出率についての検討（図 1）では，麻疹流行地（ベトナム）において臨床履歴が明確となっている患者検体を用いた。試作品は既存品 2 種とほぼ同等の陽性率の推移を示した。WHO[10)]によると，麻疹の場合，発疹出現後 3 日目（Early）までの血清中の IgM 抗体陽性率は 60～70%，4～14 日（Intermadiate）では 90～100%，15～28 日（Late）では 100%と報告されている。今回の検討結果は，どの試薬においてもこの報告に合致した（**表 4**）。したがって，本試作品の臨床面より考察した検出感度は妥当であるものと判断される。なお，B 社試薬は発疹出現後 6 日目に陽性率がやや低下しているが，これは判定保留が 1 検体存在したことによる影響である。

新規試薬を使用する場合，同一検体を用い既

存試薬との判定の乖離がどの程度発生するかを，しっかりと理解しておかなければならない。そこで麻疹患者検体および陰性検体を用い，改良品と同様の「IgM capture 法」を反応原理としているA社試薬（表1）および，「IgG 吸収法」を検出原理としているB社試薬（表2）についての比較検討を実施した。試作品は，どちらの試薬とも，陽性一致率・陰性一致率が100％を示した。判定保留検体の存在で全体一致率がそれぞれ98.9％と98.4％と算出されているが，全体的に判断すると，良好な一致率を示したものと判断できる。感染症関連抗体検出試薬における「判定保留域」は，操作誤差や測定誤差による誤判定を防ぐためにカットオフ近辺に設定され，一定時間経過後の再検査を促すために重要な役割を果たしている。本試作品と既存2試薬との判定乖離は判定保留と陽性または陰性との齟齬であり，各検出試薬の微妙な検出感度の差や操作/反応誤差を反映しているものと推測される。また，B社試薬の反応原理である「IgG 吸収法」を用いた試薬は本試作品とほぼ同等の性能であることも示された。

麻疹患者が減少している現在，検査試薬の陽性的中率が麻疹流行時と比較して低下しているのは避けられない現象ではあるが[11]，他の発疹性疾患において抗麻疹IgM抗体が稀に検出されることが臨床現場では問題視されている[2)~5)]。そこで，他の発疹性疾患患者より採取された検体を用い，同一の検出原理である試作品とA社試薬との比較を実施した（表3）。今回の検討では，デング熱（n＝20）と突発性発疹（n＝15）では，どちらの試薬においても，抗麻疹IgM抗体陽性と判定される検体は認められなかった。風疹（n＝30）では，A社試薬では1例（3.3％），伝染性紅斑（n＝57）では18例（31.6％）の抗麻疹IgM抗体陽性例が認められた。これに対し試作品では，今回検討した検体において，抗麻疹IgM抗体陽性例は認められなかった。A社試薬での陽性例については詳細な解析は実施していないが，1例を除きすべて抗麻疹IgMの抗体指数が2.0を下回っていた。試薬の感度の問題であるのか，特異性の問題であるのか，起因ウイルスが宿主に抗麻疹IgM抗体産生を誘導するのか，さまざまのことがこの現象の原因として推測されるが，この解明は，今後の検討課題となる。しかしながら，試作品においては現行試薬での問題点（他の発疹性疾患における抗麻疹IgM抗体の検出）を十分に解決でき，試薬の特異性は劇的に向上したものと考えられる。また，測定検体すべての抗麻疹IgM抗体指数の分布を検討した結果（図2），今回測定した検体については，本試作品で判定保留となる検体はなく，陽性・陰性もはっきりと抗体指数が分離されたものとなった。このことからも，診断に苦慮するような抗体指数低値陽性検体や判定保留検体の減少が予想され，試作品は，より特異性が向上し，使いやすい抗麻疹IgM検出試薬となったものと判断される。

少数例ではあるが，麻疹ワクチン接種歴が明確な検体での麻疹罹患例の検討を実施した。抗体指数をワクチン接種回数ごとにMann-Whitney's U testを用いて解析したところ，ワクチン接種歴なしと1回接種，およびワクチン1回接種と2回接種では，統計的に差は認められなかったが，ワクチン接種歴なしと2回接種では有意にワクチン2回接種の方が抗体指数が低値であった。この6例はワクチン接種より約1年経過した12～14歳の4症例と，最終接種日が不明の27歳と35歳の症例である。抗麻疹IgG抗体価は測定できなかったが，抗麻疹IgM抗体が陰性であったため，何らかのワクチン不全であるものと推測される。試作品は抗体検出試薬ではあるが，このように抗体指数の有意低値が分別されることから，近い将来，定量標準品が設定された場合に，定量試薬として使用できる可能性も示された。

結　論

今回検討した試作品は，現在問題になっている他の発疹性疾患患者での抗麻疹IgM抗体の検出が極力抑えられ，感度的にも既存試薬と同等であることが示された。また，発疹出現後の

日数毎のIgM検出率を指標とした性能（検出感度）もWHOの既報告と合致した。さらに「IgM capture法」を反応原理に使用しているため，単純な操作で結果を得られる好ましい試薬と云えよう。この試作品が「抗麻疹IgM抗体検出試薬」として使用される様になれば，麻疹の確定診断は血清学的検索でもかなりの程度，正確性を持つものと期待される。

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Question

ウイルス感染症に既罹患か否か検査を行うのはCF法，HI法，EIA法のどれがよいですか？

Answer

ウイルスにより，感度と特異度が高い抗体検査方法はそれぞれ異なります．一般的に既罹患を確認する検査にはEIA法が優れており，CF法は不適切です．その他の方法として，麻疹ではNT法，PA法が，風疹ではHI法，LA法が，水痘ではIAHA法が優れています．ムンプスではNTやHIは不適切です．

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CF：complement fixation（補体結合）

NT：neutralizing method（中和）

HI：hemagglutinaton inhibition（赤血球凝集抑制）

PA：particle agglutination（粒子凝集）

IAHA：immune-adherence hemagglutination assay（免疫付着赤血球凝集）

EIA：enzyme immunoassay（酵素免疫）

LA：latex agglutination（ラテックス凝集）

＊1
標準血清がある代表的なウイルス感染症は，麻疹，風疹，水痘，パルボウイルスB19，B型肝炎ウイルス，A型肝炎ウイルスなどである．

＊2
生物学的抗体と物理学的抗体
生物学的抗体とは生体で起こる反応を *in vitro* の系で測定して求められる抗体であり，物理学的抗体とは抗原と反応する抗体量を物理的に測定する方法である．

ウイルス抗体測定方法

抗体測定法の分類

●ウイルス抗体測定方法は測定原理から2種類に分類される[1]．

▶一つは血清2倍段階希釈法で，測定する血清を2倍段階希釈し，ウイルス液またはウイルス抗原と反応させ，残ったウイルス量を測定したり（NT法），残ったウイルス抗原を赤血球と反応させたり（HI法），または反応した抗原抗体複合体を粒子の凝集（PA法）や添加した赤血球で凝集させ（IAHA法），抗体価を測定する方法である．抗体価は最大血清希釈倍数の逆数（倍）で表示される．

▶もう一つの方法は血清一点濃度希釈法で，測定する血清を一定濃度に希釈し，一定量のウイルス抗原と反応させ，反応した抗体量を発色させて吸光度を測定する方法（EIA法），反応した抗原抗体複合体をラテックスの濁度（LA法）で測定する方法である．抗体価は連続した数字で表示される（EIA価，国際単位）．

抗体価の国際単位表示

●測定方法により抗体表示が異なること，異なる方法で測定した抗体価の結果を同じ「倍」で表示しても，方法により含まれる抗体価は異なること（例：麻疹HI抗体8倍は麻疹NT抗体16倍に相当）から，世界保健機関（WHO）は標準血清＊1を作製し，異なった方法で測定しても同じ抗体表示方法で抗体価（国際単位，IU/mL）を表示することを求めている．

生物学的抗体と物理学的抗体＊2

●生物学的抗体と物理学的抗体との間には，生物学的抗体量＝抗体の生物活性×物理学的抗体量の関係がある．ウイルス感染の急性期には，まず抗原とのaffinity（結合力）が弱い抗体が産生されるため，物理学的抗体量よりも生物学的抗体量が低く評価されるが，既感染の抗体を測定するときは，結合力が強い抗体を測定するため，生物学的抗体量と物理学的抗体量はほぼパラレルの関係がある．

●生物学的抗体測定方法としてNT法，HI法などがあり，物理学的抗体測定方法としてEIA法，PA法，LA法などがある＊3．

抗体陽性と発症予防抗体価，感染予防抗体価

- ウイルス抗体は陰性と陽性に分けられる．感度の高い方法を用いると少ない抗体量まで検出できるが，臨床的に意味のある抗体価は発症予防抗体価と感染予防抗体価である[2,3]．麻疹や風疹などの全身性ウイルス感染症では，高い抗体価から低い抗体価に向かって，ウイルスに感染しない抗体価の範囲，ウイルスに感染するが早期に二次免疫応答が始まり，発症が抑制される抗体価の範囲，感染して発症するが軽症に経過する抗体価の範囲(抗体は二次免疫応答)，通常の経過をする抗体価の範囲(陰性)に分けられる．抗体陰性の基準はNT抗体<2倍である．
- 麻疹や風疹では発症予防抗体価と感染予防抗体価は確立しているが，水痘やムンプスの発症予防抗体価は確立していない[2]．便宜上，麻疹や風疹の発症予防抗体価から演繹して発症予防抗体価が提唱されている(❶)．水痘の発症予防抗体価は，IAHA法で4倍以上，EIA法で4.0 EIA価以上であり，ムンプスではEIA法で4.0 EIA価以上である．

III 抗体価の互換性と麻疹，風疹，水痘，ムンプス抗体測定方法(❷)

- ウイルスに対する陽性抗体価は対数をとると正規分布する．2倍段階血清

❶ 主要な感染症の抗体測定方法とワクチン接種基準

感染症	測定法	単位	抗体価			ワクチン接種基準抗体価	
			陽性	発症予防	感染予防	三重病院	環境感染学会
麻疹		mIU/mL		≧120	≧500		
	NT	倍	≧2	≧4	≧32	≦2	≦4
	PA	倍	≧8	≧64	≧512	≦32	≦128
	EIA-D	EIA価	≧4.0	≧4.0	nd	<4.0	<16.0
	EIA-S	mIU/mL	≧300	nd	nd		
	HI	倍	≧8	≧8	≧16		
風疹		IU/mL		≧10	≧15～25		
	HI	倍	≧8	≧16	≧32	≦8	≦16
	EIA-D	EIA価	≧4.0	≧5.0	≧7.5～12.5	<4.0	<8.0
	EIA-S	IU/mL	≧8	≧10	≧15～25		
	LA	IU/mL	≧10	≧10	≧15～25		
水痘	IAHA	倍	≧2	nd		≦2	≦2
	EIA-D	EIA価	≧4.0	nd		<4.0	<4.0
	EIA-S	mIU/mL	≧100	nd		<200	
ムンプス	EIA-D	EIA価	≧4.0	nd		<4.0	<4.0
	EIA-S	倍	≧500	nd			

D：デンカ生研，S：シーメンス，nd：not determined(未決定)，接種基準抗体価の空欄は未決定．

- WHOは抗体の国際標準品を作製し，国際標準品がある感染症では抗体価を国際単位(IU/mL)で表記するよう求めている．
- 麻疹HI法は特異性は高いが，感度はNT，PA，EIAと比較すると低下する．
- 麻疹，風疹の発症予防抗体価，感染予防抗体価は確立されているが，水痘，ムンプスの発症予防抗体価は確立されていない．三重病院では25年にわたり上記の基準で接種し，ワクチン後の発症者を経験していない．
- D社およびS社のEIAともに陽性閾値の1/2の値まで抗体の検出は可能であるが，陽性閾値は添付文書に従い記載した．S社の水痘EIA抗体100 mIU/mLはD社の水痘EIA抗体2.0 EIA価に相当する．

＊3
生体のなかでのウイルス抗体の主たる役割は，感染したウイルスと反応しウイルス増殖を抑制することにある．生体内の抗体の働きを*in vitro*で評価する方法がNT法であり，NT法はウイルス抗体測定の基本である[1]．しかし，NT法を測定するためにはウイルスが効率的に増殖する細胞が必要であり，また手間と時間がかかるため，大量の検体を測定するには不向きである．大量の検体を短時間で測定するために開発されたのがEIA法である．

❷ 測定方法による抗体価(低値～中等値)の互換性

麻疹	NT	4倍＝150 mIU/mL
	NT	4倍＝EIA-D 4.0 EIA価
		＝PA 64倍
	NT	16倍＝HI 8倍
風疹	HI	8倍＝LA 8 IU/mL
		＝EIA-D 4.0 EIA価
水痘	IAHA	4倍＝EIA-D 4.0 EIA価
	EIA-D 4.0 EIA価＝EIA-S 200 mIU/mL	

EIA-D：酵素免疫法(デンカ生研)，EIA-S：酵素免疫法(シーメンス)．
EIA法で測定すると，高い抗体価は低く表示される傾向がある．国際標準血清がある感染症の抗体価は世界的に国際単位で表示される．

希釈して抗体価を測定していた習慣上，NT法，HI法，PA法などは2を底とする対数に変換して統計処理するのが一般的である．EIA法(デンカ生研，シーメンスともに)，LA法の抗体価は実数で表示されるが，NT法やHI法との互換性を検討するときは，2を底とする対数に変換してから比較するのが基本である．

- 互換性を検討するときは，抗体陽性率から一致する抗体価を求める方法と，相関直線から求める方法とがある．
- NT法やHI法とEIA法の互換性では，低い抗体価ではほぼパラレルの関係にあるが，高い抗体価ではNT抗体価やHI抗体価と比較してEIA抗体価は低く表示される傾向がある．
- 麻疹抗体測定方法には，NT法，EIA法，PA法などがあるが，NT抗体4倍は150 mIU/mLに相当し，EIA抗体4.0 EIA価，PA抗体64倍にほぼ相当する[3]．風疹抗体では，HI抗体8倍はLA抗体8.0 IU/mL，EIA抗体4.0 EIA価にほぼ相当する．水痘抗体では，IAHA抗体4倍はデンカEIA抗体4.0 EIA価，シーメンスEIA抗体200 mIU/mLにほぼ相当する．

m ワクチン接種基準

- 麻疹，風疹などの発症予防には，曝露されたウイルス量と曝露された宿主の抗体価とが関係している．すなわち，曝露量が多いと発症予防には高い抗体価が必要であり，曝露量が少ないと低い抗体価で発症予防が期待される[2]．
- ❶に国立病院機構三重病院のワクチン接種の基準抗体価と環境感染学会が示す基準抗体価を示した[3,4]．当院の基準は曝露量が少ない人の基準であり，95%の人の発症予防を期待したものである．この基準は平成元年に設けたものであり，毎年新規採用者や転勤者の抗体価を測定し，25年にわたり該当者にワクチン接種を行ってきたが，ワクチンを受けなかった人も受けた人もいずれも麻疹や水痘などの発症を認めていない．
- 環境感染学会の基準は，麻疹風疹対策を見据え，麻疹ウイルスを含むワク

チン(MCV)と風疹ウイルスを含むワクチン(RCV)の2回接種を目標にしている．MCVおよびRCVの2回接種を受けている人は，環境感染学会の接種基準に該当していたとしても追加接種は不要である*4.

MCV：measles containing vaccine

RCV：rubella containing vaccine

*4
なお，接種基準を満たし当該ワクチンを受けたが，接種後の抗体価が接種基準を超えなかった人は，接種した生ワクチンウイルス株が増殖しなかった人であり，さらなる接種は不要である．

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知恵の実

細菌感染症の起炎菌の変遷

細菌感染症の起炎菌は，時代とともに変遷している．起炎菌の変遷を知ることは，感染症の初期治療において大切なことである．起炎菌の変遷の原因として以下のことが考えられる．

① 抗菌薬の濫用(新種抗菌薬の開発促進，広域抗菌薬の普及)
② 耐性菌の出現(MRSA，多剤耐性菌など)
③ 医療環境の変化(高度医療，集中医療など)
④ 予防接種の普及(肺炎球菌ワクチン，Hibワクチンなど)

小児の細菌感染症のなかでも，新生児は敗血症・髄膜炎など重症感染症が多い．ひとつの施設で新生児敗血症の起炎菌の変遷を長期間追跡した事例で，最もよく知られているのはYale New Haven Hospitalのデータである．1928年より，定期的に施設の起炎菌の種類と数を専門誌に報告している．これに触発されて，私も1973年より沖縄県立中部病院の新生児敗血症の起炎菌をまとめるようになった．約10年ごとにデータをまとめて未熟児新生児学会等で報告した．かつて最多だったGBS(B群溶連菌)は近年，激減している．これは妊婦に対しGBSのスクリーニングを行い，陽性者の分娩時にアンピシリンの予防投与を行うなどの対策をとったためだと思う．

1935年，サルファ剤が感染症の治療に用いられて以来，おびただしい抗菌薬の発見・開発はヒトの救命に貢献し，医学史上最も特筆すべきことと考えられている．しかし，病原微生物と戦う強力な武器を手にした私たちは，未だに細菌感染をコントロールできていない．テキもさるもの，姿を変え，鎧を変え，私たちの挑戦を受けて立つ．

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