5 抗体診断

多くのウイルス感染症や百日咳，マイコプラズマ，クラミジアなどの一部の細菌感染症では，抗体検査が診断に有用である．マイコプラズマでは血中IgM抗体の迅速診断キットが市販され臨床に用いられている[6]．クラミジアではIgA抗体測定が活動性感染の診断に有用である[7]．また，百日咳では百日咳様症状があり，流行株，ワクチン株にかかわらず凝集反応が陽性を示す場合は，百日咳と診断する．

抗体検査でウイルス感染症を診断する方法として，①IgM抗体を検出する，②抗体の有意上昇を確認する，の二種類の方法がある．IgM抗体は主として酵素免疫測定(enzyme immunoassay；EIA)法で測定する．抗体の有意上昇とは，急性期に採取した血清と急性期から2～4週間経過した回復期に採取した血清の抗体価を同じ方法で測定し，測定誤差以上〔赤血球凝集抑制試験(hemagglutination inhibition test；HI test)や中和試験(neutralization test；NT test)では2管(4倍)以上〕の上昇を示すことである．EIA法での測定誤差以上の上昇とはEIA価2倍以上の上昇である．EIA法での有意上昇の定義は確立されていないが，2倍以上の抗体価上昇または，HI testなどと同様に4倍以上の抗体価上昇が用いられている．

ウイルス性髄膜炎や脳炎などの診断には，血清と同時に髄液のウイルス抗体価を測定する．血液髄液関門の破綻による血清IgGの流入を除外するために，抗体インデックス〔=(髄液ウイルス抗体/血清ウイルス抗体価)÷(髄液IgG/血清IgG)〕が用いられる．インデックスが2を超えると，そのウイルスが中枢神経系に感染している根拠となる[8]．

血清抗体測定は，病原体に対する免疫状態を調べるときにも用いられる．このときには補体結合反応検査(complement fixation reaction test；CF test)は用いない．おもなウイルスに対する適切な抗体測定方法を表3に示した[4]．EIA法は他の測定方法に比べ高価である．

血清抗体の最低陽性レベルと感染防御レベルは必ずしも一致しない．感染曝露前後やワクチン接種前後の抗体レベルの変動から，血清抗体レベルには，①感染を受けないレベル，②感染を受けて抗体価は上昇するが発症しないレベル，③感染を受けて発症するが軽症の経過をとり(修飾感染)，抗体価も上昇するレベル，④感染を受けて発症し通常の臨床経過を示し，抗体価が上昇するレベルの4段階がある．通常の臨床症状が発症する抗体レベルは抗体陰性である．麻疹や風疹における各レベルの抗体価を表4に示した[9～11]．麻疹はマイクロ中和試験で，100 %細胞変性効果抑制を示す血清希釈倍数の逆数で表示したときの抗体価である．

インフルエンザにおいてHI抗体40倍では感染防御率は50 %であり，抗体価が上昇するにつれ感染防御率は上昇し，発症したとしても軽症化する．また，パリビズマブの臨床効果から，同じ局所性ウイルス感染症であるRSウイルスにおいても，高い抗体価を有していると軽症化する．

表3　目的に応じて選択するウイルス抗体測定法

感染症	免疫の有無＊	感染の診断	
		シングル血清	シングル血清
麻疹	NT，EIA-IgG	EIA-IgM	HI，NT
VZV	IAHA，EIA-IgG	EIA-IgM	IAHA
ムンプス	EIA-IgG	EIA-IgM	HI，NT
風疹	HI，EIA-IgG	EIA-IgM	HI
EB ウイルス	EBNA，VCA-IgG	EADR，VCA-IgM	VCA-IgG
CMV	FA-IgG	FA-IgM	FA-IgG，CF
インフルエンザ	HI		HI
日本脳炎	HI		HI

VZV：水痘・帯状疱疹ウイルス，CMV：サイトメガロウイルス，
NT：中和法，EIA：酵素免疫法，HI：赤血球凝集抑制試験，IAHA：免疫粘着血液凝集法，
FA：蛍光抗体法，CF：補体結合反応試験
＊：免疫の有無を調べるときにCFは用いない．

表4　目的に応じて選択するウイルス抗体測定法

	抗体価	
	麻疹（mNT）	風疹（HI）
抗体陽性	≧2倍	≧8倍
臨床との関係		
典型発症	＜2倍	＜8倍
軽症発症	≧2倍～＜4倍	不明＊
発症しないが抗体ブースターあり†	≧4倍～＜32倍	≧8倍～＜64倍
抗体ブースターなし‡	≧32倍	≧64倍

mNT：マイクロ中和試験，HI：赤血球凝集抑制試験
＊：風疹HI抗体8倍には時に擬陽性が含まれる．
†：ウイルスは感染して抗体価は上昇するが，保有している免疫により発症は免れる．
‡：抗体の動きからウイルスは体内に侵入していない．

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Review

Current concepts of management for congenital cytomegalovirus infection

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ABSTRACT

Universal screening of congenital cytomegalovirus (CMV) infection without symptoms at birth seems to be necessary to detect late-onset neurodevelopmental sequelae. Congenital CMV infection, as demonstrated by isolation of the virus within the first week of life, was diagnosed in 37 (0.31%) of 11,938 infants born between 1977 and 2002 in the city of Sapporo, Japan, during the 26-year period from January 1977 through December 2002. The characteristics of CMV-specific T-cell immunity was also investigated in pregnant women with primary, latent, or reactivated CMV infection, and in a comparative group of non-pregnant women. The frequency of CMV-specific CD4 T cells in peripheral blood lymphocytes was determined by staining for intracellular cytokines, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α. The frequency of CMV-specific CD4+ T cells in pregnant women associated with CMV reactivation or reinfection was significantly higher than in CMVseropositive normal pregnant and non-pregnant women. The genetic variability of 74 human CMV (HCMV) clinical isolates from 60 Japanese infants and children during 1983 - 2003 was investigated, and the relevance to their clinical course was observed. The hypervariable region of the HCMV genome, that is the a sequence and UL144 region was analyzed using the polymerase chain reaction (PCR) and unrooted phylogenetic trees. HCM glycoprotein B (gB) polymorphism was also investigated. Unrooted phylogenetic trees of a sequence and UL144 allowed the isolates to be grouped to 5 and 3 clades, respectively. Three gB genotypes were also identified. A real-time PCR assay was used to determine vaginal shedding of CMV in 993 healthy pregnant Japanese women and the results were compared with the outcome of pregnancy. HCMV DNA was detected in 76 (7.7%) of the women. The outcome of pregnancy could be determined finally in 848 women, of whom 60 (7.1%) were CMV DNA-positive. These findings suggest that latent genital tract CMV infection predisposes to adverse pregnancy outcomes.

KEYWORDS: cytomegalovirus (CMV), congenital infection, intracranial calcification, chorioretinitis, sensorineural hearing loss

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1. General concept of congenital cytomegalovirus infection

Human cytomegalovirus (HCMV) is a herpes virus and contains approximately 240 Kb DNA and over 200 open reading frames (ORFs) [1, 2, 3]. CMV is the most common cause of congenital and perinatal infections throughout the world [4]. The prevalence of congenital CMV infection varies widely between different populations (0.2-3.0%) [5, 6]. Only less than 5% of the infants with congenital CMV infection have typical

cytomegalic inclusion disease (CID) recognized to cause a fetal abnormality of microcephaly, hydrops, intracranial calcification, chorioretinitis, liver dysfunction, and thrombocytopenia [7, 8, 9]. Another 5% have atypical involvement, and the remainder (90%) are asymptomatic at the time of delivery [10, 11, 12, 13].

The mortality rate of symptomatic fetal CMV infection is as high as 30% and 90 to 95% of survivors left with neurological sequelae [14]. Factors that have been associated with a poor neurodevelopmental prognosis include the presence of microcephaly, chorioretinitis, or neurological abnormalities at birth [15, 16, 17, 18]. Considering the necessity for longterm follow-up of infected infants, it is important to detect intrauterine CMV infection at the fetal stage.

Even asymptomatic at birth, 5% to 17% of infants with fetal HCMV infection patients may present with neurodevelopmental disorders, such as sensorineural hearing loss (SNHL), spastic diplegia or quadriplegia, and mental retardation within the first 4 years of life [19, 20]. It is possible that progression of neurological complications is related to the persistent infection and replication of CMV or host immunological response to infection.

SNHL causes serious impairment in the normal development of the child, especially in the field of communication and learning. We studied the longitudinal prognosis in children with asymptomatic congenital infection according to growth, cognitive function and the presence and progression of SNHL [21]. The causes of SNHL are various, ranging from genetic to infective, both congenitally and postnatally acquired, to pharmacological. However, prediction of which infants will have developmental disabilities remains controversial [22, 23]. Follow-up studies in children with congenital CMV infection have shown that SNHL is the most common consequence of this infection, affecting up to 22% of infected children.

Prior studies have shown prolonged viral excretion with congenital CMV infection, and speculated persistent viral replication was a possible explanation for the development of sequelae. Furthermore recent reports have documented the hearing and vision loss may be progressive or late onset. Although progressive hearing loss in children with asymptomatic congenital CMV infection has been described before, less is known about fluctuating hearing loss after asymptomatic congenital CMV infection [18, 24, 25, 26].

CMV infection occurs in 40 to 100% of individuals in populations worldwide, and the lowest rates are generally found in the developed world [27]. Serum antibodies against CMV are found in approximately 40% to 60% of adults in European countries [28], and caused too be 80% to 90% of Japanese adults [29]. In recent years the CMV infection rate in adult women has been decreasing, raising concerns of an increase in congenital infections secondary to primary maternal infection during pregnancy. Seropositive pregnant women to CMV can be re-infected with different HCMV strains and those re-infections may lead to intrauterine transmission and symptomatic congenital infections [19, 30, 31].

In certain countries parental interest groups have called for screening programs for the general obstetric population in an attempt to reduce the rate of fetal damage with congenital CMV infection. Since annual live births in Japan used to be approximately 1.22 million, four to five thousands infants with congenital CMV infection were presumed to be born each year. Congenital CMV infection is an unsolved public health problem, unlikely to be solved by means other than immune prophylaxis.

A decrease in the prevalence of serum antibodies against CMV has been estimated in recent years in consequence to improvement in the social and economic conditions in Japan in the last 20 years [32, 33, 34]. We have studied the incidence of congenital CMV infection in Japan as reported previously (Numazaki and Chiba, 1996) [21, 35]. Congenital CMV infection was diagnosed in 37 (0.31%) of 11,938 infants born between 1977 and 2002. In the CMV follow-up study; 32 (86.5%) with asymptomatic and 5 (13.5%) with symptomatic infection (Table 1). There were 20 (54.1%) male subjects and 17 (45.9%) were female. A decrease in the total incidence of congenital CMV infection has been seen in recent years. However, the incidences of symptomatic congenital have been slightly increased. The shortest duration of urinary

Table 1. Incidence of congenital CMV infection by era [21].

Era	No. of neonates screened	No. of congenital CMV infection (%)	No. of symptomatic congenital CMV infection (%)
1977-1981	3,084	14 (0.45%)	1 (0.032%)
1982-1985	2,814	10 (0.36%)	1 (0.035%)
1986-1990	2,097	7 (0.33%)	1 (0.048%)
1991-1996	1,898	3 (0.16%)	1 (0.052%)
1997-2002	2,045	3 (0.15%)	1 (0.049%)
1997-2002	11,938	37 (0.31%)	5 (0.042%)

excretion of CMV was 6 months, and the longest duration was 6.5 years.

Of the 21 children evaluated with asymptomatic CMV infection, 18 (85.7%) had an IQ/DQ of >=90, 3 (14.3%) had an IQ/DQ of 70 to 89, and none had a major motor disorder on follow-up. All 21 children with normal findings on head computed tomographic (CT) scan or magnetic resonance imaging (MRI) had a good prognosis. Hearing evaluations were also performed during follow-up of 17 children, and 2 had late-onset SNHL (mild bilateral and moderate unilateral) detected after the newborn period. When children with SNHL detected were compared with the children with normal hearing, no significant differences in cognitive and motor functions were noted (Table 2).

Our findings indicate 2 of 17 (11.8%) infants with asymptomatic congenital CMV infection had late-onset SNHL. Hearing loss at birth would be identified by newborn hearing screening. Because delayed-onset SNHL followed congenital CMV infection, about two thirds of SNHL (>20 dB thresholds) caused by congenital CMV infection would not have been identified by universal screening of newborns for hearing in this population. If the definition of hearing loss for newborn screening were used, approximately one half of SNHL that may impair speech and language development in a child would not have been identified by newborn auditory screening in this CMV-positive population [36].

Table 2. Characteristics of 21 children with asymptomatic congenital CMV infection [21].

Clinical Characteristics	No. of Positive / No. of Tested
Growth Retardation	
Height less than –2 SD	1 / 21
Weight less than –2 SD	1 / 21
Mental Retardation	0 / 21
Sensorineural Hearing Loss	2 / 17
Uilateral (moderate, 46-70 dB)	1 / 17
Bilateral (mild, 21-45 dB)	1 / 17

Congenital CMV infection can be definitively diagnosed only in the newborn period, so many of these infections remain undetected. Of the children with asymptomatic congenital CMV infection, only 8.0% had an auditory screen based on recognition of congenital CMV infection as the risk factor. All the other neonates with asymptomatic congenital CMV infection who had auditory screening were tested because of risk criteria other than CMV infection. Clearly all children with congenital CMV infection should be screened for hearing loss.

Persistent CMV infection, as estimated by presence of urinary viral excretion, was not associated with

a deleterious effect on growth, intellectual function or development in congenitally infected children. This is in contrast to findings in children with congenital HIV or rubella infection, in whom the persistence of infection leads to delayed growth and neurodevelopment. It is possible that a more site-specific or invasive method of detecting and monitoring chronic CMV replication in the central nervous system could have provided more data on the pathogenesis of neurological sequelae.

Infants with symptomatic disorders at birth are more likely to be identified and have appropriate virological testing for congenital CMV infection in the newborn period. These infants will likely have a hearing evaluation completed at the time of diagnosis. However, infants with asymptomatic infection may not be recognized as being at increased risk for late-onset neurodevelopmental disorders.

2. Maternal immunological factors in the pathogenesis of congenital cytomegalovirus infection

CMV infection is controlled effectively by specific cellular immunity without the ultimate clearance of the virus, resulting in a frequent occurrence of latent CMV infection. Generally, natural immunosuppression during pregnancy is thought to play an important role by protecting the fetus from rejection by the maternal immune system [37, 38, 39]. This immunosuppression may cause susceptibility of pregnant women to primary or reactivated CMV infection. However, the changes in CMV-specific T cell immunity during pregnancy have not been fully clarified.

Although the natural history of intrauterine CMV infection is not completely clarified, a proportion of fetuses are damaged before delivery and it is sometimes difficult to get accurate clinical diagnosis. Primary infection during pregnancy is more likely to be transmitted to the fetus (average 40%) [40] with more severe sequelae than reactivated latent infection. However, recently it was reported that reactivated latent infection was also transmitted in approximately 1% of fetus and that infants with symptomatic HCMV infection were born [41].

Macrophages and natural killer (NK) cells are considered the main immunomodulating cells that control activities of infecting cells in primary and latent HCMV infection, and produce IFN-γ and TNF-α to express antiviral activity. CD4+ and CD8+ T cells are also activated by HCMV infection and produce interleukin 2 (IL-2) and IL-12. Asanuma *et al.* [42] measured serum levels of sIL-2R, in infants with liver dysfunction due to perinatal CMV infection and found that serum sIL-2R, one of the indicators of T cell activation, was correlated with the severity of liver dysfunction.

It is presumed that these cytokines are involved not only in the development of persistent CMV infection and reactivation of CMV infection but also in infectious transmission to the fetus. Numazaki *et al.* [43] found that serum levels of soluble IL-2 receptor and IFN-γ were elevated during pregnancy in mothers delivered babies with congenital HCMV infection. Based on their findings, they underlined the possibility of the clinical application for perinatal diagnosis of CMV infection.

Methods for the analysis of T cell responses to specific viral antigens have relied traditionally on the limiting dilution assay or enzyme-linked immunospot (ELISPOT) assay [44]. An assay for detection of virus-specific T cells by staining of intracellular cytokines (ICC) has been developed as an indicator of adaptive immunity [45, 46]. This approach to counting them avoids the errors inherent in limiting dilution estimates of responder cell frequencies that result from apoptosis during longer-term incubation and shows high sensitivity.

The ICC staining to detect CMV-specific CD4+ T cells was also available for the evaluation of immunological conditions in children with symptomatic congenital CMV infection [47]. A high frequency of CMV-specific CD4+ T cells may indicate the presence of stimulation against cellular immunity related to asymptomatic congenital CMV infection. These findings should assist pediatricians, neonatologists, neurologists, developmentalists, and infectious disease specialists in counseling families about the prognosis of newborns with congenital CMV infection.

The methods of screening for CMV infection should be compared with the frequencies of CMV specific CD4+ T cells. A pregnant woman with serum anti-CMV IgM antibody showed higher frequency and the frequency of HCMV-specific CD4+ T cells might be associated to some extent

with virus quantity in the body. As time of pregnancy proceeds, CMV becomes to be reactivated at the cervix of uterus [48]. Low frequency of CMV-specific CD4+ T cells in the cervical DNA-positive specimens suggests the possibility of local virus reactivation of viruses from latent infection.

3. Genetic diversity of cytomegalovirus strains associated with congenital infection

The results of the screening of pregnant women for HCMV infection in Sapporo, 2000 were shown in Table 3 [49]. The positive rate for anti-CMV IgG antibody was 67.6%, and 3 of 173 pregnant women (1.7%) were positive for anti-CMV IgM antibody. HCMV was isolated from urinary samples of 3 out of 642 pregnant women (0.5%) and HCMV the glycoprotein B (gB) DNA was detected by PCR in the cervical swabs from 2 pregnant women.

Molecular epidemiological studies revealed the hypervariability of gB gene among HCMV; however, the correlation between gB genotypes and clinical symptoms remains unclear [50, 51, 52]. Congenital infection of CMV has not been considered from the point of view of viral genetic heterogeneity [53]. CMV is composed of unique long (L) and short (S) sequences containing terminal segments with repeating elements [54, 55].

Recently, the epidemiological relationships between variation of the a sequence gene and HCMV clinical isolates were reported [1, 2, 55, 56]. Hypervariability of UL144 gene sequences has also been reported [57]. UL144 is one of the ORFs and encodes a homolog of the herpes simplex virus entry mediator [58]. UL144 ORF can be categorized into three major groups, however no apparent correlation between UL144 variants and HCMV pathogenesis has been identified.

Table 3. Screening of CMV infection in pregnant women of Sapporo, Japan [49].

Serum anti-CMV IgG (+)	117/173 (67.3%)
Serum anti-CMV IgM (+)	3/173 (1.7%)
Isolation of CMV from urine (+)	3/642 (0.5%)
HCMV gB DNA from cervical swab (+)	2/105 (1.9%)

Bale *et al.* [1] analyzed the genetic variability of a sequences of HCMV strains from healthy children in a day care center and from subjects with a congenital infection. Although they divided wild strains into five groups which primarily corresponded to nosocomial infection within the day care center, hany correlation between our five groups of gB and theirs could not be tested because sequence data on their HCMV strains was unavailable. In the unrooted tree of the UL144 region, our 63 strains could be clearly classified into three major groups (I to III).

Lurain *et al.* [57] analyzed UL144 genotypes of clinical HCMV isolates from immunocompromised patients who had had organ transplantation or HIV infection. These studies divided HCMV strains into three major groups with similar designations (I to III). The patient's clinical details in these three studies were different, and there was considerable geographical and temporal variation. Their HCMV genetic distribution pattern was similar irrespective of the geographical or temporal variation, and of the genetic background of the host, in terms of UL144 genetic variability. In our study of the UL144 gene, almost all strains causing congenital infection were located in group I, in contrast Bale *et al.* [1] found that strains causing congenital infections belonged mainly to group III. This difference cannot be resolved given the small number of cases of congenital infection studied and a much larger study of CMV strains is required to determine the correlation between congenital infection and UL144 genotype. If particular strain genotypes do infect fetuses more readily, such knowledge would be helpful in predicting congenital infections and developing preventative measures.

There have been no similar molecular epidemiologial studies on CMV isolates from an Asian population except for a few studies on gB [58, 59]. CMV clinical strains isolated from Japanese infants and children during the last two decades were studied [60]. Genetic variability in the a sequence, UL144 region, and gB genes, and their association with clinical course was investigated. In addition, the findings were compared with those from other countries.

There was 0% to 27% nucleotide differences HCMV Genetic Variability in Japanese Children 357 among strains located in the same group [60]. They contained strains which were isolated from subjects with variable clinical symptoms. Each cluster includes 1 to 3 isolates from infants with a congenital infection. The dates of isolation of strains belonging to each group were 1984 to 2002, 1990 to 2002, 1989 to 2000, 1988 to 2001, and 1983 to 2001 in groups A, B1, B2, C1, and C2, respectively. Serial isolates from the same patients possessed identical sequences for a sequence region. UL144 Variability Sixty-three (85%) strains (all 48 re-isolated strains and 15 stocked-virus fluid) yielded UL144 gene PCR products which had 737-bp length. The HCMV laboratory strain, that is AD169 lacks 19 ORFs including UL144, thus AD169 did not yield amplicons [1, 57, 61].

However, the sequences of the a sequence region and gB genotypes could not differentiate these two strains, emphasizing the need for plural analysis for differentiation of CMV field strains. gB is a major component of the virion envelope and is transported to the plasma membrane of infected cells [62, 63, 64]. Chou and Dennison [65] classified HCMV strains into four variant groups by PCR-RFLP. The hypervariability of the gB region is well established and the correlation between gB and pathogenicity has been examined without any obvious relationship being found [50, 51, 52, 57].

The gB gene of 67 of 74 (90%) strains (all 48 re-isolated strains and 19 stocked-virus fluid) could be amplified and analyzed by RFLP assay using enzymes, Hinf I and Rsa I [60]. Excepting the 14 strains isolated from the same subjects, 34, 2, and 17 were identified as gB group I, II, and III, respectively (Table 4). None of our strains were classified as group IV. There was no obvious correlation between a certain gB genotype and the type of disease. AD169 was identified as group II. Linkage of a Sequence, UL144 Polymorphism, and gB Strains were compared according to their unrooted phylogenetic dendrogram of a sequence, UL144, and gB genotypes. No apparent linkage of polymorphisms or genotypes was observed. Group A was the dominant genotype in a sequence (39.6% of all isolates), group III in UL144 (46.2% of all isolates), and group I in gB (68.7% of all isolates). But no relationships were apparent between the dominant genotypes.

Table 4. Distribution of human cytomegalovirus glycoprotein B (gB) genotype and type of infections in 53 strains analyzed [60].

Classification	I	II	III	IV
Congeital infection	6	2	1	0
Perinatal, postnatal infection	26	0	15	0
Immunocompromised host	2	0	1	0
Total	34	2	17	0

4. Relationship between CMV infection and complications during pregnancy

Practically, accurate clinical diagnosis of maternal primary CMV infection is sometimes hard because most CMV infection is asymptomatic and goes unnoticed [66, 67]. Serum anti-CMV IgM as a parameter for serological diagnosis of primary infection can be present in 10% of pregnant women with CMV reactivation and continue to increase for about 18 months after onset of primary infection [68, 69]. CMV can be reactivated more frequently in late stage of pregnancy because women are in some kind of immuno-suppressive condition. The urinary excretion rate of CMV increased from 1% in early pregnancy to 13% in late pregnancy, as determined by PCR. Attempts have been made to diagnose primary infection by the avidity index for serum anti-CMV IgG antibodies or by a new CMV IgM immunoblotting [69], but these methods do not yet provide for evaluation of possible prognostic markers in infected pregnant women and intrauterine CMV infection.

Cervical shedding of CMV have been estimated in pregnant or nonpregnant woman with or without underlying conditions such as HIV infection or other sexually transmitted disease (STD) [48, 70, 71, 72, 73, 74]. The existence of CMV in the genital tract is thought to be associated with maternal-fetal transmission of CMV during the perinatal period [75].

In young women genital shedding of CMV may reflect a pelvic inflammatory disease and involves the risk of sexual transmission [73]. CMV infection in the genital tract might be associated with pregnancy wastage [76]; however, the possible causal relationship between CMV and miscarriages or intrauterine fetal death (IUFD) remains controversial. PCR, especially real-time PCR, has higher sensitivity to detect genital CMV shedding than conventional approaches, such as virus isolation by tissue culture or antigen detection by immunohistochemistry. Real-time PCR assay for CMV DNA was assessed in vaginal secretions during the first trimester of pregnancy in 933 healthy pregnant Japanese women. The correlation between CMV DNA shedding and adverse pregnancy outcomes was evaluated.

There were 12 miscarriages (1.4%) in all 848 women, 4 (6.7%) in 60 CMV positive, and 8 (1.2%) in 788 CMV negative women [77]. As a result, the miscarriage rate was significantly higher in CMV positive women than in CMV negative women (relative risk 6.96, 95% CI 2.04-23.84, P<0.01). No other parameter showed statistical difference between CMV-positive and in CMV-negative women (Table 5). Real-time PCR was used to detect CMV DNA in vaginal fluids during the first trimester of pregnancy, and pregnancies were followed to parturition. The positive ratio of 7.7% (76/993) was lower than previous study by Shen *et al.* [48] who reported that cervical CMV excretion rate increased from 13% to 40% as pregnancy proceeded.

A relationship between CMV DNA in vaginal fluid during the first trimester and miscarriage risk was found. No other cause of miscarriage such as other virus infection or amniocentesis was detected. Neither the frequency of premature delivery nor the gestational age at live birth was affected by the presence of CMV [78].

Table 5. Clinical parameters and number of adverse events related to CMV DNA in vagina [77].

	CMV in vagina		
Characteristics	**All pregnancies (n =848)**	**Positive (n=60)**	**Negative (n=788)**
Maternal age (years)	28.9 ± 4.6	29.8 ± 4.9	28.8 ± 4.6
Gestational age (weeks)	38.8 ± 1.7	38.7 ± 1.7	38.7 ± 1.7
Birth weight (g)	3,010 ± 445	3,052 ± 389	3,007 ± 450
Full term delivery	784 (92.4%)	52 (86.7%)	732 (93.0%)
Premature delivery	49 (5.8%)	4 (6.7%)	45 (5.7%)
Threatened miscarriage	20 (2.4%)	0	20 (2.5%)
Threatened premature delivery	49 (5.8%)	4 (6.7%)	45 (5.7%)
Cervical cerclage	19 (2.2%)	1 (1.7%)	18 (2.3%)
Miscarriage *	12 (1.7%)	4 (6.7%)	8 (1.2%)
Intrauterine fetal death	3 (0.4%)	0	3 (0.4%)

Statistical significance/relative risk (95%CI), *P <0.01, mean standard deviation.

Conditions which disrupt the balanced interaction between CMV and NK cells in the decidua may cause NK cell activation and fetal death. An immunocompromised condition during the first trimester may lead to CMV reactivation and facilitate infection by other microorganisms such as *Mycoplasma* species, *Chlamydia trachomatis* and adeno-associated viruses; the latter were found to be related to premature delivery and miscarriage [79]. These might induce inflammatory reaction in the deciduas and fetal death or miscarriage. In conclusion, vaginal CMV detection during pregnancy is important to estimate pregnacy outcomes, and therefore it should be introduced as part of the follow-up of pregnancy [80, 81, 82].

CMV infection may cause excessive immune reactions at the maternal-fetal interface [83]. Activation of the immune system involving decidual NK cells leading to fetal death or miscarriage [84]. CMV upregulates the class I homologue UL18 [85] and CEACAM1 [86] to avoid NK-mediated elimination, and downregulates the NKcell-activating ligand CD155 [87].

5. CONCLUSIONS

The total incidence of congenital CMV infection in 11, 938 children in Sapporo, Japan was 0.31%, between 1977 and 2002. Although a decrease in the total incidence of congenital CMV infection has been seen in recent years, the incidences of symptomatic congenital have been slightly increased. Congenital CMV infection as the probable leading infectious cause of SNHL in childhood [88]. Each year more children will continue to have SNHL caused by congenital CMV infection.

Flow cytometric assay for CMV-specific CD4+ T cells was found to be applicable in pregnant women with some kind of immunosuppressive condition. The flow cytometric assay may be useful as a tool for real-time monitoring of CMV-specific cellular immunity in pregnant women and have the clinical application for maternal immune activity against CMV infection to transmit to the fetus [89].

Three genes of CMV field strains were investigated and great variability in each gene was observed, however there was no correlation between variations. The infection and pathogenesis of an individual HCMV strain may be defined by the combination of multiple variant genes that it encodes. The genomic variability of HCMV is important to efforts to develop a HCMV vaccine [63].

Further large scale CMV infection monitoring during pregnancy would provide more precise information on the influence of CMV in the vagina on the outcome of pregnancy. Entirely new approaches to prevention and treatment of congenital CMV infection are necessary, including antiviral interventions and the development of a vaccine strategy [90].

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特集　わが国の予防接種の現状と今後

ジフテリア・破傷風・百日咳ワクチン

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Ⅰ．患者報告数と現行のDTaPワクチンの効果

DTaP（diphtheria toxoid, tetanus toxoid and acellular pertussis vaccine；ジフテリア・破傷風・無細胞百日咳ワクチン）開始後の国立感染症研究所感染症情報センターによる感染症発生動向調査における定点当たりの百日咳患者報告数を**図1**上に示す．接種率上昇に伴い，百日咳患者報告数は着実に減少し，1982年には2万4,782人だったが，2005年には1,355人と約1/20となっている．しかし，患者年齢に変化が認められる（図1下）．10～14歳は2004年から，15歳以上は2002年から漸増し，2005年は0歳37.9%，1～4歳25.9%，5～9歳13.0%，10～14歳8.6%，15歳以上14.5%となっている．

図2に1989年以降の福岡地区での百日咳患者年齢分布を示す．1989～1997年に比較して，1998年以降は7歳以上，特に11～15歳，21歳以上の患者数が増加している．

図3にDTaPワクチン開始後のジフテリア・破傷風患者報告数を示す．ジフテリア患者は，近年ほとんど報告されていないが，ジフテリア毒素をもつ*Corynebacterium ulcerans*菌感染症が問題となっている．破傷風患者数は1999年以降増加しているが，集計方法の変更の影響も考えられる．2000年以降では毎年100人前後が報告されている．破傷風患者年齢は70歳以上が圧倒的に多く（図3下），現行の小児のみを対象としているDTaP接種方式では破傷風への効果は低いと考えられる．

Ⅱ．副反応の種類と頻度

1．通常の副反応としての局所反応，発熱

予防接種後健康状況調査集計報告書[1]から接種後14日間の接種回数別の局所反応および発熱率を抜粋すると，1期初回1回目の局所反応は16.7%に認められ，接種後0～2日（6.9%）と7～8日（6.7%）に多かった．発熱は2日目に多く1.1%に認められた．2回目以降の局所反応は，1回目と異なり2日以内が大部分で，発現率は2回目25.3%，3回目19.7%，追加（4回目）39.0%，発熱率は2回目1.9%，3回目1.5%，追加（4回目）2.5%であった．局所反応は数日で治まるが，硬結は数か月持続することがある．

2．まれな副反応

肘を超えて腕全体が腫れる異常腫脹は，年間平均96例報告されている[2]．接種後のアナフィラキシーは年間平均4.6件，全身蕁麻疹は7.3件と報告されている．接種者数は約450万人/年と推定され，アナフィラキシーの頻度は100万接種当たり約1例ときわめて少なく，安全なワクチンの1つと考えられている．

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昭和62年九州大学大学院修了．
主研究領域／小児感染症，予防接種，小児呼吸器．

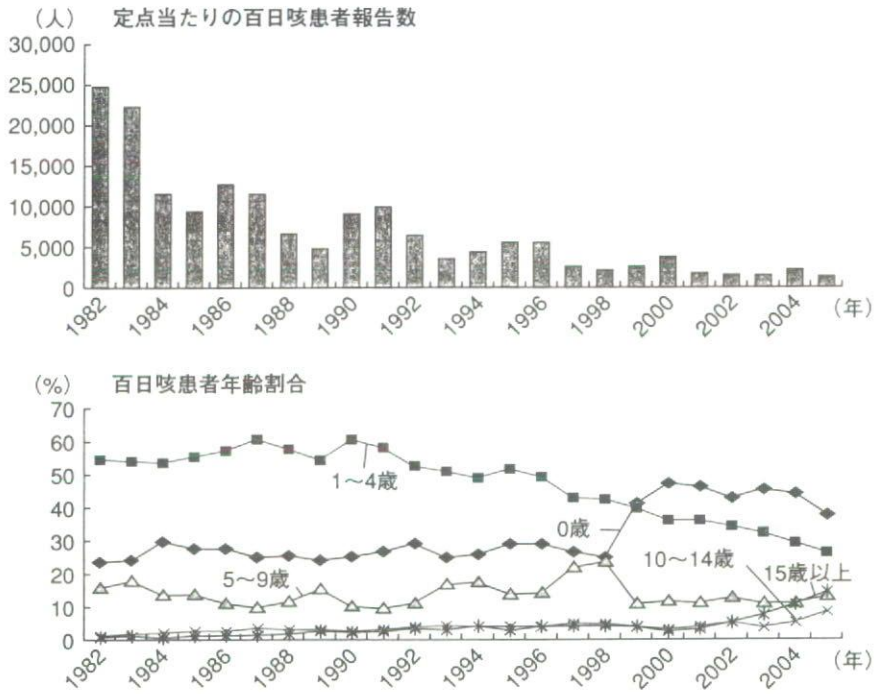


図１　定点当たりの百日咳患者報告数と患者年齢（1982～2005 年）

（国立感染症研究所感染症情報センター：感染症発生動向調査）

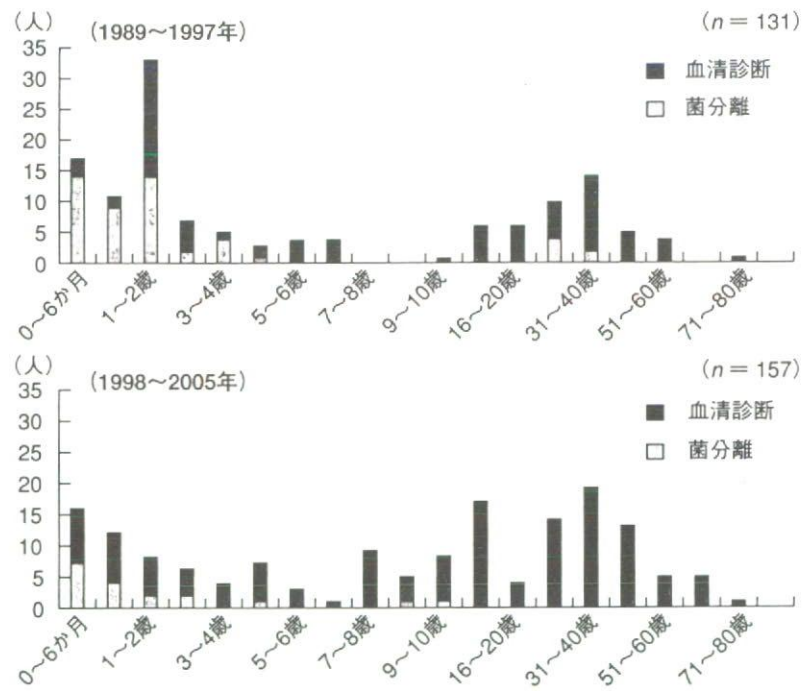
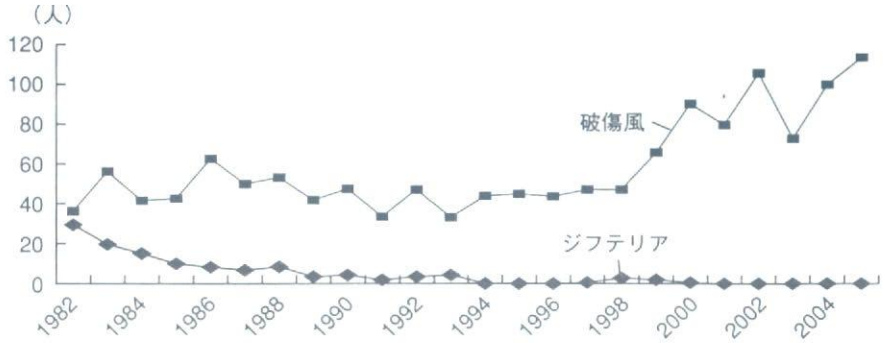


図２　福岡地区における百日咳患者年齢分布（1989～2005 年）

（九州大学・国立病院機構福岡病院）



［厚生省統計情報部：伝染病統計（1999年3月まで）/国立感染症研究所国立感染症情報センター：感染症発生動向調査（1999年4月以降）より作成］

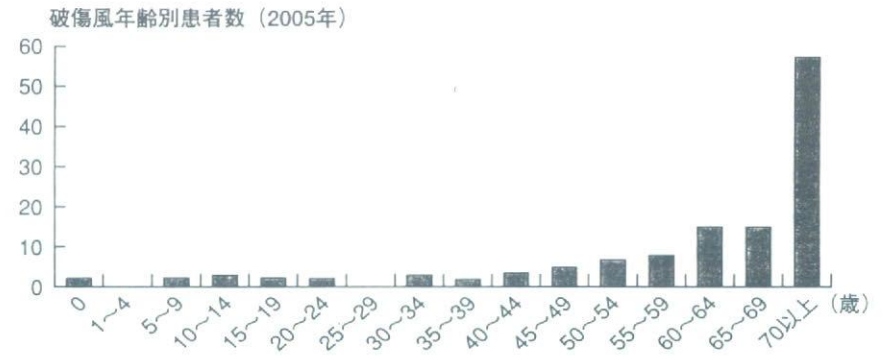


図3　ジフテリア・破傷風患者報告数（1982～2005年）

（国立感染症研究所感染症情報センター：感染症発生動向調査）

Ⅲ．わが国の今後の課題

1．これまでのワクチン接種と成人・高齢者の抗体価[3]

ジフテリア抗毒素抗体価（図4上）は，ジフテリアトキソイド世代（当時48歳以下）が前トキソイド世代（当時49歳以上）より高い傾向にあったが，両群の抗体陽性率は76.3%および75.7%であり，有意差は認められなかった（表1）．

破傷風抗毒素抗体価の分布（図4下）は，破傷風トキソイド前世代（当時29歳以上）とトキソイド世代（当時28歳以下）とでは大きく異なり，前世代がきわめて低い抗体価を示した．抗体陽性率は10.5%および91.7%であり，両群間に有意差が認められた（$p<0.001$）．

百日咳ワクチン前世代（当時47歳以上）とワクチン世代（当時46歳以下）のPT（pertussis toxin；百日咳毒素）抗体陽性率およびFHA（filamentous haemagglutinin；線維状赤血球凝集素）抗体陽性率は，両群間に両抗体共に有意差は認められなかった（表1）．

2．増加する成人百日咳

成人百日咳の症状は典型的でなく，長引く咳が唯一の症状であることが多い[4,5]．6日以上咳が続いた成人の場合，13～32%が百日咳と診断されていた[6]．DTaPワクチン未接種乳幼児の百日咳に特徴的な吸気性笛声（whoop）は8～82%，発作性咳嗽は70～99%，咳込み後の嘔吐は17～50%とされている[7]．

当院呼吸器内科の持続咳嗽患者（4週間以上続く咳）で百日咳と診断できた症例の臨床的特徴は，平均年齢36歳，初診時白血球数3,470～11,820/μl，リンパ球7～58%であった．咳の特

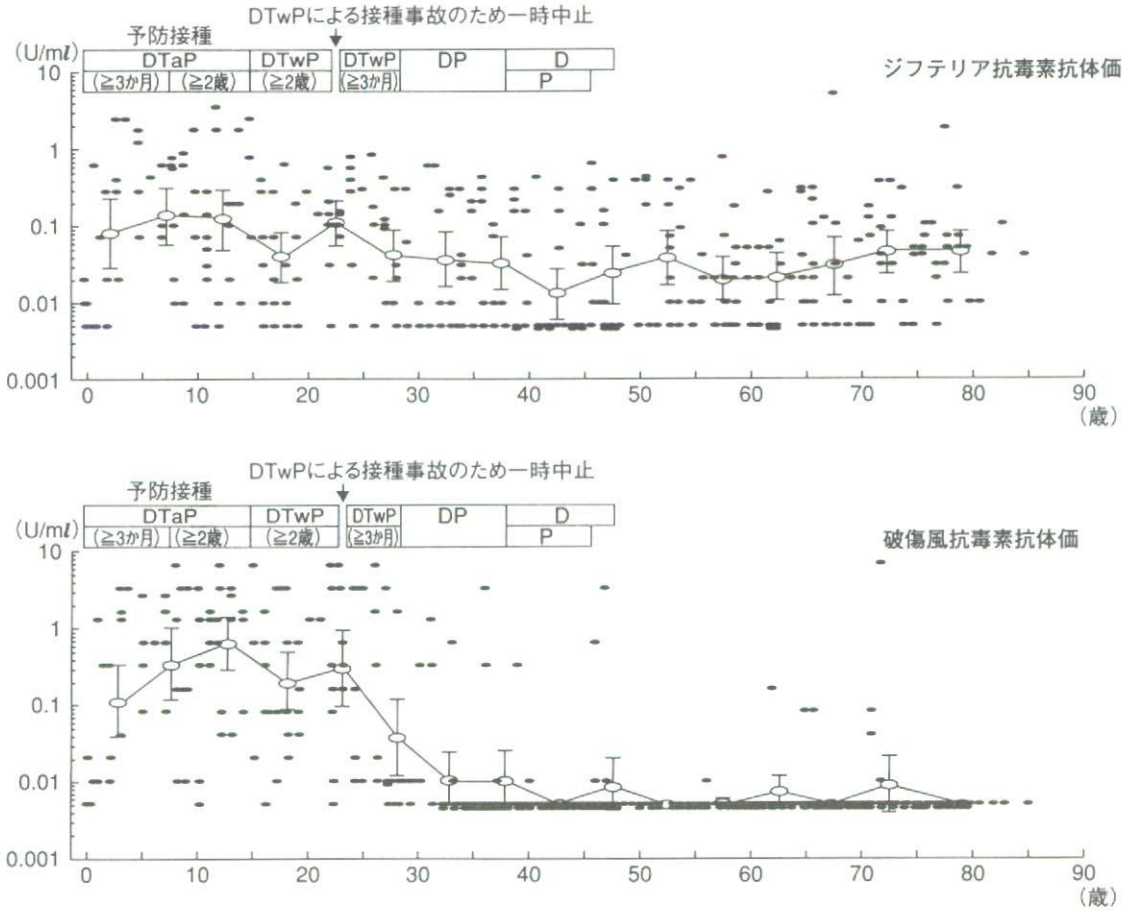


図4　年齢別ジフテリア・破傷風抗毒素抗体価

(Okada K, *et al* : *Jpn J Infect Dis* 2004 ; 57 : 67—71 より引用)

表1　ワクチン世代と前ワクチン世代の百日咳，ジフテリア，破傷風抗体陽性率

	抗体陽性率	
	ワクチン世代 ※1,2,3	前ワクチン世代
百日咳※1	PT　55.0%（99/180）	57.9%（81/140）
	FHA　65.6%（118/180）	79.3%（111/140）
ジフテリア※2	76.3%（122/160）	75.7%（106/140）
破傷風※3	91.7%（110/120）*	10.5%（21/200）

※1 百日咳ワクチン世代：46歳以下
（PT・FHA抗体陽性　10 EU/ml以上）
※2 ジフテリアトキソイド世代：48歳以下
（感染防御レベル　0.01 U/ml以上）
※3 破傷風トキソイド世代：28歳以下
（感染防御レベル　0.01 U/ml以上）

*$p<0.001$

(Okada K, *et al* : *Jpn J Infect Dis* 2004 ; 57 : 67—71 より引用)

徴は，咳込みによる目覚め，発作性の咳込み，咳が止まらず息苦しい，咳込み後の嘔吐などであった．家族内の有症状者が確認できた例が23例(56.1%)あり，うち14例は同居中の児が百日咳で入院または外来治療を受けていた．詳細な家族歴を聴取することが診断の手がかりとなる．

3. 10歳代および成人にDTaPワクチン接種を

わが国で開発された小児へのDTaPワクチンは，高い有効性と安全性で小児の百日咳，ジフテリア，破傷風患者数を低く抑えている．しか

し，最近は図1に示したように百日咳の患者年齢が変化している．思春期・成人の百日咳は症状が典型的でなく，気付かれないことが多いため，乳幼児の感染源になっていることが世界的に問題となっている．対策として，青年・成人への追加接種が提案され，実施されている国々もある（表2）．

欧州やカナダでは10歳代にDTaPワクチンまたはDTaP-IPV（inactivated polio virus vaccine；不活化ポリオワクチン）混合ワクチンが接種されている．

米国では新しく思春期成人用の3種混合Tdap（tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine；破傷風・抗原量減量ジフテリア・無細胞百日咳ワクチン）を，2006年1月から11～13歳児にTdに替えて推奨している[8]．

15～65歳の健康成人約3,000人を対象としたDTaPワクチンの無作為臨床試験では，まだ確定されていないが，有効率は92%であった[9]．費用対効果研究でも，百日咳ワクチンの追加接種が最も有用であるとする報告が多い[10]．日本でも，現在の2期年齢（11～12歳）でDTトキソイドに替わり，百日咳対策としてDTaPが必要な時期にきていると考えられる．

さらに，図3に示したように現行のDTaP接種方式では破傷風制御は難しい．米国では10年ごとに成人への破傷風トキソイド接種が推奨されている．わが国でも成人へのDTaPワクチン接種を考慮する必要がある．

表2　国による百日咳ワクチンの種類と接種時期の違い

国	初回接種の年齢	追加接種の年齢
日本	3～6か月　DTaP 3回	12～18か月　DTaP
ドイツ	2，3，4か月 DTaP-IPV-Hib-HB	11～14か月　DTaP-IPV-Hib-HB 9～17歳　Tdap または Tdap-IPV
フランス	2，3，4か月 DTaP-IPV-Hib または DTwP-IPV-Hib	16～18か月　DTaP-IPV-Hib 11～13歳　DTaP-IPV または Tdap-IPV
カナダ	2，4，6か月 DTaP-IPV-Hib	18か月　DTaP-IPV-Hib 4～6歳　DTaP-IPV 13～16歳　Tdap
米国	2，4，6か月 DTaP	15～18か月　DTaP 4～6歳　DTaP 11～18歳　Tdap

DTaP；ジフテリア・破傷風・無細胞百日咳ワクチン，IPV；不活化ポリオワクチン，Hib；インフルエンザ菌タイプbワクチン，HB；B型肝炎ワクチン，DTwP；ジフテリア・破傷風・全菌体百日咳ワクチン，Tdap；破傷風・抗原量減量ジフテリア・無細胞百日咳ワクチン

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感染症 今月の話題

変貌する百日咳と進む世界の対策

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はじめに

ジフテリア・破傷風・百日咳三種混合ワクチン（DTPワクチン）未接種児の百日咳は，特有な咳と特徴的な検査所見から臨床診断に迷うことは少ない。一方，青年・成人の場合は，特有な咳はないため，百日咳と気付かれないまま，感染源となっていることが問題である。変化する百日咳の疫学，臨床症状，診断およびその対策について概説する。

I．疫　学

百日咳ワクチンのない時代の百日咳罹患率は人口10万あたり157～230と高かった。ワクチン導入後0.5～2.3まで低下したが，流行周期は2～5年と変わっていない[1]。ワクチン導入前は，10歳未満が全体の85%以上を占めたが，ワクチン導入後は10歳未満は半減し(41%)，10歳以上から青年・成人の割合が著増してきた（28%）[1]。青年・成人例は1970年代から報告されている[2][3]。青年・成人百日咳が乳幼児への感染源となっていることは，多くの国々で指摘されている[4][5][6]（PIDJ 2007 を追加[6]）。

R-Book 2006では米国内で通年性に患者発生が少なかった1976年以降，年間報告患者数は年々増加し，2004年には25,827例まで増加した（CDCのMMWR[7] では25倍以上の増加と算定されている）。罹患率は，6カ月未満の乳児で最も高く，10～14歳の世代がこれに次いでいると紹介している[8]。カナダでも患者年齢のピークに変化が認められ，1990年は3歳，1995年は6歳，2000年は9歳となっている[9]。

わが国の状況を感染症発生動向調査事業報告書から1982年から2006年までの百日咳定点患者総数を示す（図1）。1981年からわが国では世界に先駆け，副反応が少なく効果も優れた無菌体百日咳ワクチン（DTaP）を接種している。接種率上昇とともに百日咳患者は著明に減少してきた（図1上）が，年齢割合に変化が認められる（図1下）。1999年以降それまで多かった1～4歳に代わり乳児が増加しはじめ，2003年以降は15歳以上の割合が増加している（図1下）。日本の2004～2006年の患者年齢割合と米国で増加が著しくなってきた1992～1994年の患者年齢割合はほぼ同じとなっている（図2）。米国内は，基本的には百日咳は全数報告されることになっているが，わが国では百日咳は小児科の5類定点把握疾患となっているため，報告されている青年・成人百日咳症例は氷山の一角にすぎない。今後，青少年・成人例を確実には把握・報告されるシステムと対策が必要になる。

II．症状と合併症

DTPワクチン未接種の乳幼児の症状に変