Countermeasures against Congenital Toxoplasmosis and Cytomegalovirus Infection Led by the Research Team* under the Supervision of the Ministry of Health, Labor and Welfare in Japan

Learning objectives:

Describe how academia and the Ministry of Health, Labor and Welfare in Japan have been working on prevention of congenital CMV infection and early intervention in infected children.

When the Japanese government (or specifically, the Ministry of Health, Labor and Welfare [MHLW]) tries to change or establish public health policies, *ad hoc* research groups are organized to discuss the issues and draft the detailed plans.
Changing epidemiology of CMV infection in Japan

cCMV infection in Japan (retrospective studies)

Current countermeasure activities against cCMV infection by the research team led by the Ministry of Health, Labor and Welfare in Japan

Issues to be solved on countermeasures against cCMV infection in Japan
Changing epidemiology of CMV infection in Japan

- cCMV infection in Japan (retrospective studies)
- cCMV infection in Japan (a prospective study)
- Current countermeasure activities against cCMV infection by the research team led by the Ministry of Health, Labor and Welfare in Japan
  - Issues to be solved on countermeasures against cCMV infection in Japan
CMV Ab prevalence among pregnant women in various countries

- Solomon: 100%
- Vietnam: 100%
- India: 98%
- Chile: 92%

Epidemiology of CMV infection is influenced by socioeconomic factors (higher seroprevalence in developing countries)

- UK: 59%
- France: 56%
- USA: 48%

One generation ago, Japan was a developing country

(Yamashita et al, 2006)
CMV Ab prevalence among pregnant women in various countries

- Solomon 100%
- Vietnam 100
- India 98
- Chile 92

Epidemiology of CMV infection is influenced by socioeconomic factors (higher seroprevalence in developing countries)

- UK 59
- France 56
- USA 48

One generation ago, Japan was a developing country

Currently, Japan is on a transition stage between developing and developed countries

(Yamashita et al, 2006)
Changing epidemiology of CMV infection in Japan

Susceptible pregnant women have been increasing: <10% in 1980’s to 30% in 2001-05.

Impact of cCMV will become greater in the near future.

Issues to be solved on countermeasures against cCMV infection in Japan
Changing epidemiology of CMV infection in Japan

**cCMV infection in Japan (retrospective studies)**

Current countermeasure activities against cCMV infection by the research team led by the Ministry of Health, Labor and Welfare in Japan

**Issues to be solved on countermeasures against cCMV infection in Japan**

**cCMV infection in Japan (a prospective study)**
A retrospective survey of congenital infections for the year 2011 (Nationwide questionnaire survey for all obstetric institutes in Japan)

<table>
<thead>
<tr>
<th>Mother-to-child infections</th>
<th>Numbers of reported cases*</th>
<th>Adjusted cases per 100,000 pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>abortion</td>
<td>miscarriage</td>
</tr>
<tr>
<td>Congenital parvovirus B19</td>
<td>3 (1)</td>
<td>35 (13)</td>
</tr>
<tr>
<td>Congenital CMV infection</td>
<td>3 (1)</td>
<td>0 (3)</td>
</tr>
<tr>
<td>Congenital/neonatal herpes</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Congenital rubella</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Congenital toxoplasmosis</td>
<td>0 (2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate cases of confirmed maternal infections without confirmation of fetal/neonatal infection.

**Nationwide epidemic of erythema infectiosum (Fifth disease) was reported in 2011.

Principal investigator: Hideto Yamada (Kobe University)
A retrospective survey for the period from 2006 to 2008 (the Committee of TORCH Complex Survey by Japanese Society for Pediatric Infectious Diseases)

<table>
<thead>
<tr>
<th>Mother-to-child infections</th>
<th>Numbers of reported cases</th>
<th>Adjusted cases per 100,000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2006</td>
<td>2007</td>
</tr>
<tr>
<td>Congenital CMV infection</td>
<td>46</td>
<td>37</td>
</tr>
<tr>
<td>Vertical HBV infection</td>
<td>23</td>
<td>28</td>
</tr>
<tr>
<td>Vertical HCV infection</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Neonatal herpes</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Congenital toxoplasmosis</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Congenital parvovirus B19</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Vertical HTLV-I infection</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Congenital rubella</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Vertical HIV infection</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Changing epidemiology of CMV infection in Japan

### cCMV infection in Japan (retrospective studies)

Current countermeasure activities against cCMV infection by the research team led by the Ministry of Health, Labor and Welfare in Japan

Current symptomatic congenital CMV infections: 0.0043-0.0095% (46-102 babies/year)

Issues to be solved on countermeasures against cCMV infection in Japan

### cCMV infection in Japan (a prospective study)
Changing epidemiology of CMV infection in Japan

CMV infection in Japan (retrospective studies)

CMV infection in Japan (a prospective study)

Current countermeasure activities against CMV infection by the research team led by the Ministry of Health, Labor and Welfare in Japan

Issues to be solved on countermeasures against CMV infection in Japan
Study sites:
Hokkaido, Fukushima, Saitama, Tokyo, Aichi, and Nagasaki

(Nozawa et al., J Clin Microbiol 2007; 45: 1305)
0.31% of all live births (95%CI: 0.24-0.39%)

Two thirds have elder siblings

CMV strains identical to those of their siblings in 21 out of 25

CMV DNA undetectable in 3 out of 12 w/ DBS

Typical clinical manifestations in 15/66 (23%)
Abnormal brain imaging in 10/58
Any of the above in 20/66 (30%)

Koyano et al, BMJ Open 2011;1:000118
43 infants with asymptomatic cCMV

38 with normal development

5 (12%) with late-onset neurological deficits as follows:
1: sensorineural hearing loss (SNHL)
2: speech delay w/o SNHL
1: autism spectrum disorder
1: AD/HD

>2-year follow-up

9 infants with SNHL who were treated with GCV/VGCV

7 (78%): stable
2 (22%): recovered
1: bilateral (R: 90dB, L: 60dB)
1: unilateral (R: 6-dB)

>2-year follow-up

Reconfirmed the importance of follow-up of asymptomatic infants

Reconfirmed the effectiveness of antiviral therapy

Koyano et al, submitted for publication
Changing epidemiology of CMV infection in Japan

C CMV infection in Japan (retrospective studies)

C CMV infection in Japan (a prospective study)

Current countermeasure activities against cCMV infection by the research team led by the Ministry of Health, Labor and Welfare in Japan

Congenital CMV infection: 0.31% (3,300) of all live births (1.07 millions/year)
Symptomatic congenital CMV infections: 0.094% (1000 babies/year)
Prepregnancy CMV Ab prevalence

- Negative (uninfected): 30%*
- Positive (infected): 70%*

Primary infection: 1-4%
Reinfection/Reactivation

Probability of intrauterine infection

- 30-50%
- 0.2-2%

0.31%* of all live births

- Symptomatic at birth (23%*)
- Asymptomatic at birth (77%*)
- Late-onset sequelae (12%*)
- Long-term sequelae (32%* of all infected)

Infantile death (10% of all symptomatic)

0.1%* of all live births
1000 babies annually

*Data in Japan
Congenital CMV infection: 0.31% (3,300) of all live births (1.07 millions/year)

Symptomatic congenital CMV infections: 0.094% (1000 babies/year)

Recognized symptomatic congenital CMV infections: 0.0043-0.0095% (46-102 babies/year)

90-95% of cases have been left undiagnosed
Changing epidemiology of CMV infection in Japan

cCMV infection in Japan (retrospective studies)

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Issues to be solved on countermeasures against cCMV infection in Japan

Current countermeasure activities against cCMV infection by the research team led by the Ministry of Health, Labor and Welfare in Japan
<table>
<thead>
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<th>TORCH</th>
<th>Preventive and therapeutic measures</th>
<th>Cases reported* (estimated)</th>
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<tr>
<td><strong>T: Toxoplasmosis</strong></td>
<td>Caution in daily life; antipROTOZOAL therapy for infected mothers and infants</td>
<td>5<del>6 (100</del>300)*</td>
</tr>
<tr>
<td><strong>Others: Syphilis</strong></td>
<td>Screening → penicillin therapy for mothers and infants with active disease</td>
<td>8~9 On the rise!</td>
</tr>
<tr>
<td><strong>R: Rubella</strong></td>
<td>Screening → rubella-containing vaccine after delivery</td>
<td>1~2 [45 in 2012-14] §</td>
</tr>
<tr>
<td><strong>C: CMV</strong></td>
<td>Caution in daily life; valganciclovir therapy for infected infants</td>
<td>37~57 (1000) ¶</td>
</tr>
<tr>
<td><strong>H: Herpes simplex</strong></td>
<td>Acyclovir therapy and elective cesarean section for mothers with genital herpes; acyclovir therapy for affected infants</td>
<td>12~13 Decreasing</td>
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* According to the nationwide survey by JSPID (2006-2008)

* Estimated on the basis of age-specific serological prevalence.

§ A total of 45 CRS babies were born following the 2012-13 outbreak of rubella.

¶ Estimated on the basis of the prospective study (Koyano et al, 2011)
**TORCH in Japan: Facts and Measures**

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- **No reporting system**
- **No screening test**
- **Poor awareness**
- **Therapeutic agents either unavailable or unapproved**

*According to the nationwide survey by JSPID (2006-2008)

*Estimated on the basis of age-specific serological prevalence.

§ A total of 45 CRS babies were born following the 2012-13 outbreak of rubella.

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A mother and child health handbook

Cervical cancer checkup
Serological test for syphilis
HBs antigen
Hepatitis C antibody
HIV antibody
Rubella antibody
HTLV-1 antibody
*Chlamydia trachomatis*
Group B streptococci

Why has neither *Toxoplasma gondii* Ab nor CMV Ab been added to the list of screening tests for pregnant women?
Pros and Cons about Screening of Pregnant Women for *T. gondii* and CMV

**Pros**

- **T. gondii**
  - Spiramycin therapy can reduce the risk of fetal infection.

- **CMV**
  - Identification of seronegative (susceptible) women leads to effective education, identification of seroconverted cases and early diagnosis of cCMV.

**Cons**

- Positive IgM does not necessarily indicate primary infection.


- Effective prenatal intervention has not been established yet.
A low IgG avidity level indicates recent primary infection.

Positive IgM does not necessarily indicate primary infection.

IgG avidity

Not standardized
Not covered by medical insurance

Persistent IgM

Positive IgM does not necessarily indicate primary infection.
Laboratory diagnosis of congenital CMV infection

- **Virus isolation (cell culture)**
  - Gold standard
  - Available in the limited institutes
  - Slow in getting results

- **Virus antigen detection**
  - Much faster than virus isolation
  - Less sensitive
  - Not covered by medical insurance

- **Specific IgM antibody**
  - Covered by medical insurance
  - Not fast not slow in getting results
  - Less sensitive (50%)

- **PCR**
  - Fast, Sensitive
  - Not standardized
  - Not covered by medical insurance
Very few pregnant women know (or believe to know) CMV

Morioka et al, 2014
Proportion of pregnant women who had knowledge about infection during pregnancy and of methods to prevent maternal infection with four pathogens (n = 343)

<table>
<thead>
<tr>
<th></th>
<th>Rubella virus</th>
<th>Toxoplasma gondii</th>
<th>CMV</th>
<th>Parvovirus B19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission route</td>
<td>179 (52%)</td>
<td>147 (42%)*</td>
<td>28 (8%)**</td>
<td>42 (12%)**</td>
</tr>
<tr>
<td>The most susceptible time of severe fetal infection</td>
<td>137 (40%)</td>
<td>103 (30%)**</td>
<td>39 (11%)**</td>
<td>26 (8%)**</td>
</tr>
<tr>
<td>The maximum frequency of fetal infection</td>
<td>16 (5%)</td>
<td>19 (6%)</td>
<td>10 (3%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Methods to prevent maternal infection</td>
<td>151 (44%)</td>
<td>123 (36%)*</td>
<td>37 (11%)**</td>
<td>23 (7%)**</td>
</tr>
</tbody>
</table>

*P*-values are shown for comparison among the four pathogens.  
* *p* < 0.05, ** *p* < 0.01 compared to that of rubella virus  
* *p* < 0.01 compared to that of *T. gondii*  

Morioka et al, 2014
Proportion of pregnant women who had knowledge about actions that can reduce risks of maternal infection during pregnancy (n = 343)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wash hands after diaper changing</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>Avoid kissing a child on lips and cheeks</td>
<td>16 (5%)</td>
</tr>
<tr>
<td>Do not share foods, drinks, or tableware with children</td>
<td>17 (5%)</td>
</tr>
<tr>
<td>Avoid taking care of children under 2.5 years old if you are working in a day-care center</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Use a condom during sexual intercourse</td>
<td>9 (3%)</td>
</tr>
</tbody>
</table>

Morioka et al, 2014
Proportion of pregnant women who had knowledge about actions that can reduce risks of maternal infection during pregnancy ($n = 343$)

<table>
<thead>
<tr>
<th>Action</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cook meat to a safe temperature</td>
<td>75 (22%)</td>
</tr>
<tr>
<td>Wear gloves during any contact with sand or soil</td>
<td>49 (14%)</td>
</tr>
<tr>
<td>Avoid trips to Europe during pregnancy</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Keep away from cats</td>
<td>87 (25%)</td>
</tr>
</tbody>
</table>

Morioka et al, 2014
<table>
<thead>
<tr>
<th>Tests</th>
<th>All pregnant women (%)</th>
<th>Only those who want</th>
<th>Never</th>
<th>No response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV Ab</td>
<td>90 (4.5%)</td>
<td>15</td>
<td>1,879</td>
<td>6</td>
</tr>
<tr>
<td><em>T. gondii</em> Ab</td>
<td>962 (48.5%)</td>
<td>59</td>
<td>961</td>
<td>8</td>
</tr>
<tr>
<td>Rubella Ab</td>
<td>1,951 (99.2%)</td>
<td>4</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>STS*</td>
<td>1,966 (99.9%)</td>
<td>2</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>HIV Ab</td>
<td>1,962 (99.7%)</td>
<td>2</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>HTLV-I Ab</td>
<td>1,964 (99.8%)</td>
<td>1</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>HBs Ag</td>
<td>1,967 (99.9%)</td>
<td>1</td>
<td>0</td>
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<tr>
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*STS: serological tests for syphilis  
(Nationwide survey in 2011)
The state of implementation of screening of infections for pregnant women

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<table>
<thead>
<tr>
<th>Measures</th>
<th>Number (%)</th>
<th>How many times?</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF Ab</td>
<td>26 (29%)</td>
<td>Once</td>
<td>75 (83%)</td>
</tr>
<tr>
<td>IgG + IgM (EIA)</td>
<td>20 (22%)</td>
<td>Twice</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>IgG (EIA)</td>
<td>20 (22%)</td>
<td>Thrice</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>IgM (EIA)</td>
<td>5 (6%)</td>
<td>No response</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>No response</td>
<td>19 (21%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Very few with positive CMV-IgG/IgM were followed by IgG avidity test.

30% of pregnant women are CMV-IgG negative in Japan, but many of them are not repeatedly checked for seroconversion during pregnancy.
Changing epidemiology of CMV infection in Japan

C CMV infection in Japan (retrospective studies)

Issues to be solved on countermeasures against cCMV infection in Japan

- Poor awareness of cCMV
- *In vitro* diagnostics (IVD) for pregnant women with primary CMV infection and neonates with cCMV have been neither evaluated for reliability nor covered by medical insurance.
- Therapeutic agents are either unavailable or unapproved, and no practical guideline has been established.

C CMV infection in Japan (a prospective study)
“Perhaps, I had heard of [mother-to-child infections] before,
but none told me if we should pay attention to them.”

Tragic diseases I should have prevented if I had known them.

I wish no more patients with congenital infections and no more sad families.

Association for Congenital Toxoplasmosis and CMV Infections

Active approaches to policy makers for developing strategies against congenital infections directly or through mass media.
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Issues to be solved on countermeasures against cCMV infection in Japan

- cCMV infection in Japan (retrospective studies)

- cCMV infection in Japan (a prospective study)
Awareness raising activities

For obstetricians:
“CMV-infected pregnant women management manual”

For pregnant women:
• Educational poster
• Educational brochure

http://cmvtoxo.umin.jp/

Prime Minister of Japan, Shigeru Ishiba

Minister of Health, Labour and Welfare, Masayoshi Takeshita

Minister of Education, Culture, Sports, Science and Technology, Akira Amari

Health Care Promotion Bureau, Ministry of Health, Labour and Welfare
妊娠中のみなさんに知って欲しい

サイトメガロウイルス
母子感染に注意しましょう

妊娠中のお母さんがサイトメガロウイルスに感染すると、赤ちゃんが何らかの障がいを持って生まれてくることがあります。
今の中高生が接種したワクチンがありません。
ですから、お母さんが妊娠中に感染しないことがとても大切です。

「サイトメガロウイルス」ってなに？

発生しやすい状況と症状

サイトメガロウイルスは、世界中のいとこにいる、ありふれたウイルスです。
母乳、唾液や尿や血液を介して主に子供のうちに感染します。その他、性行為を介して感染するなどし、日本では成人女性の70％程度がすでに感染し、抗体（免疫）を持っています。

感染したときの症状はほとんどないか、発熱症状にとどまることが多く、サイトメガロウイルス感染後つくことはまずありません。妊娠中の子供や大人が感染しても全く問題ないのです。しかし妊娠中の子どもが感染した場合は、既存の感染の増強を受けるため、胎児は健常の子供ができないことがよくあります。

感染した子どもは、後遺症、心臓、肺、閉眼塞いなどなど、高率に生まれる可能性があります。

何らかの症状がある先天性サイトメガロウイルス感染症を発症するのは、感染した赤ちゃんの10%～30%程度です。

国立研究開発法人 日本医薬品研究開発機構（AMED）
産業医療研究等総合評価事業
「母子感染の観察・診断及び治療に関する研究」室
「妊娠中」は要注意！

妊娠中の感染に注意しなければならない理由

妊娠中のお母さんがサイトメガロウイルスに感染すると、胎盤や血液を通じて胎児から胎児に感染してしまい、赤ちゃんが何らかの障害を持って生まれることがあります。これをサイトメガロウイルス子感染（または先天性感染）といいます。

特にサイトメガロウイルスの先天性感染症に対して今もとてに国で認めた治療薬、感染を防ぐためのワクチンがあります。ですから、お母さんが妊娠中に感染しないことがとても大切です。

成人女性の70%は既に、サイトメガロウイルスに感染したことがあり、血液中に抗体（免疫）を持っていますが、30%は感染を防ぐための抗体を持っていません。抗体を持っている方でもサイトメガロウイルスに感染することがありますので、抗体を持たない方は、サイトメガロウイルスの感染を受けるやすいので、特に注意が必要です。

妊娠中の感染以外に、分娩時・授乳・輸血・感染者（特に子供）との接触によりサイトメガロウイルスに感染しますが、未熟児を除き、生後に感染した赤ちゃんやお子さんには、ほとんど症状は無く、健康問題は発生しません。

妊娠中の子供のサイトメガロウイルス抗体保護

妊娠中は30%

妊娠中は70%
サイトメガロウイルス Q&A

妊娠中は、感染している人との接触を避けた方が良いのでしょうか？

サイトメガロウイルスは、世間でいただくところにいるウイルスです。感染してもほとんど産後が出ないように言われることが普通です。発症が感染しているかどうかは、わからないので、インフルエンザのように飛沫感染（くしゃみや咳による「ふき上り」によって起こる感染）することなく、感染している人の接觸や密に接する手から感染します。これまで接触の人と接して問題ありません。予防には手洗いをきちんと行うことが重要です。

妊娠中に感染すると全ての胎児に障がいが出るのでしょうか？

過去にサイトメガロウイルスに感染していて、既に抗体（免疫）を持っている妊娠した場合は、赤ちゃんに感染するおそれはまれです。
サイトメガロウイルスに対する抗体を持っているお母さんが、妊娠中に初めて感染した場合、赤ちゃんにまで感染がおよぶ可能性があります。抗体を持たない方が、手洗いなどの感染予防法（p3参照）を守った場合、妊娠中に感染する確率は1%〜2%とされています。そのうち40%に先天性感染がおきます。先天性感染がおいても多くの赤ちゃんは無症状で生まれられます。お母さんが妊娠中に初めて感染しても、大多数の赤ちゃんには症状は見られないので、安心に考えてください。

ウェブサイトでも情報を提供しています
http://cmvtoxo.umin.jp/

「母子感染の実態調査把握及び検査・治療に関する研究」班では、より多くの人にサイトメガロウイルス感染について知ってもらうよう、上記ウェブサイトにてサイトメガロウイルス感染に関する情報を提供を行っています。
Changing epidemiology of CMV infection in Japan

cCMV infection in Japan (retrospective studies)

cCMV infection in Japan (a prospective study)

Issues to be solved on countermeasures against cCMV infection in Japan

- Poor awareness of cCMV
- *in vitro* diagnostics (IVD) for pregnant women with primary CMV infection and neonates with cCMV have been neither evaluated for reliability nor covered by medical insurance.
- *Therapeutic agents* are either unavailable or unapproved, and no practical guideline has been established.
in vitro diagnostics (IVD)
1) evaluation for reliability    2) coverage by medical insurance

- **Toxoplasma gondii IgG avidity test**
  Three commercial companies
  1) in progress    2) in progress

- **CMV IgG avidity test**
  Two commercial companies
  1) in progress    2) in progress

- **Urine-filter-based CMV assay**
  1) done    2) in progress

- **DNA-based CMV assays**
  Commercial companies:
  Shino-Test Corporation, QIAGEN Japan
  1) done    2) in progress (soon coming)

Routine screening of pregnant women

Neonatal mass-screening of cCMV

Early confirmatory diagnosis followed by antiviral therapy
Diagnostic service

Until the aforementioned diagnostic tests are available in clinical sites, a service of real-time PCR for infants suspected of cCMV is provided without charge.

Requirements: A+B
A) A urine sample collected within 3 weeks after birth is available.
B) Any of the following is present:
   1) Abnormal finding(s) in brain imaging
   2) Microcephaly (<-1.5SD)
   3) ALT >100 IU/L and PLT <150K/µL
   4) Abnormal finding(s) in AABR or ABR
Registry → follow-up

Internet-based registry systems of infants with cCMV and congenital toxoplasmosis

The registry system is used for prehension of epidemiological and clinical features of congenital CMV infection and congenital toxoplasmosis and preparation of clinical studies on antiviral or antiprotozoal therapy.

Establishment of follow-up systems for registered patients

Upon registration, doctors in charge will be instructed for standardized patient management. Collaboration with pediatric neurologists and otolaryngologists is critical.
Nationwide consultation network
Inform all obstetric and pediatric institutes of registry system

Provide **consultation and counseling service** for medical professionals and patients/families through nationwide network organization

Not only cover diagnosis and treatment strategies but also **comprehensive care** of mothers, children and families

Will cover not only cCMV and congenital toxoplasmosis but also **other mother-to-child infections** including congenital Zika virus disease
Desired administrative actions

**Designation of cCMV and congenital toxoplasmosis as diseases required to report all cases to the administration**

Currently, all cases of congenital syphilis and congenital rubella syndrome are required to report to the administration. Designation of cCMV and congenital toxoplasmosis as the same category will help understand their impacts.

**Confirmation of cost-effectiveness and feasibility of neonatal cCMV mass-screening systems**

Academia has already demonstrated them (Koyano et al, BMJ Open 2011).
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Issues to be solved on countermeasures against cCMV infection in Japan

- cCMV infection in Japan (a prospective study)
**Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease**


<table>
<thead>
<tr>
<th>Comparison of hearing at baseline and follow-up</th>
<th>6-Wk (n=58)</th>
<th>6-Mo (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved at follow-up</td>
<td>2 (3.5%)</td>
<td>6 (8.6%)</td>
</tr>
<tr>
<td>Normal at baseline and follow-up</td>
<td>35 (60.3%)</td>
<td>48 (68.6%)</td>
</tr>
<tr>
<td>Same degree of HL at baseline and follow-up</td>
<td>16 (27.6%)</td>
<td>8 (11.4%)</td>
</tr>
<tr>
<td>Worsened at follow-up</td>
<td>5 (8.6%)</td>
<td>8 (11.4%)</td>
</tr>
</tbody>
</table>

**Log_{10} Viral Load**

- **Open-Label Valganciclovir**
  - Day 1: P=0.001
  - Day 7: P<0.001
  - Day 14: P<0.001
- **Blinded Valganciclovir vs. Placebo**
  - Day 56: P=0.23
  - Day 70: P=0.20
  - Month 4: P=0.16
  - Month 6: P=0.009

<table>
<thead>
<tr>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved + Kept normal</td>
</tr>
<tr>
<td>Language composite*</td>
</tr>
<tr>
<td>Receptive-communication*</td>
</tr>
</tbody>
</table>

*Bayley-III components
Pharmacokinetic analysis of VGCV

Cmax lower than expected in a minority of cases

Considerable variation in Cmax values among cases

Kimberlin et al. J Infect Dis 2008; 197: 836
PMDA, a Japanese version of FDA will not approve VGCV without Japanese infants’ data.

Drug company’s reluctance to conduct clinical trial.

No liquid form of VGCV available in Japan.

Considerable variation in pharmacokinetics.

6-month valganciclovir therapy is effective and tolerable in infants with symptomatic cCMV.

A clinical trial of valganciclovir (VCGV) led by the research team without involvement of the drug company.

Both cost-effectiveness and long-term safety unknown.
Guideline

Clinical management of infants with cCMV

Examine what?
Blood tests
Auditory tests
Ophthalmological tests
Brain imaging
and so on

Treat how?
Valganciclovir?
Ganciclovir?
6 weeks? 6 months?
Side effects

Follow up how long?

Explain how?
Research plans for comprehensive mother and child health countermeasures against mother-to-child infections

1st stage (2013–2015)

- In vitro diagnostics (for pregnant women)
- In vitro diagnostics (for neonates)
- cCMV diagnosis service
- Congenital toxoplasmosis + cCMV registry
- Consultation system (clinical management, counseling, etc.)

2nd stage (2016–2017)

- Preventive intervention strategies
- Educational tools (brochure, etc.)
- Prospective study to demonstrate effectiveness of preventive strategies
- Preparation of clinical trial for cCMV treatment
- Clinical trial
- Guidelines for clinical management