

2007 FDA/PAC Meeting, USA

***Influenza Surveillance, Influenza Encephalopathy
and Therapy for Influenza, in Japan***

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27 Nov. 2007, Maryland, USA**

Function of NIID, Japan



NIH-like

(basic research and
development)



CDC-like

(disease control and
prevention)

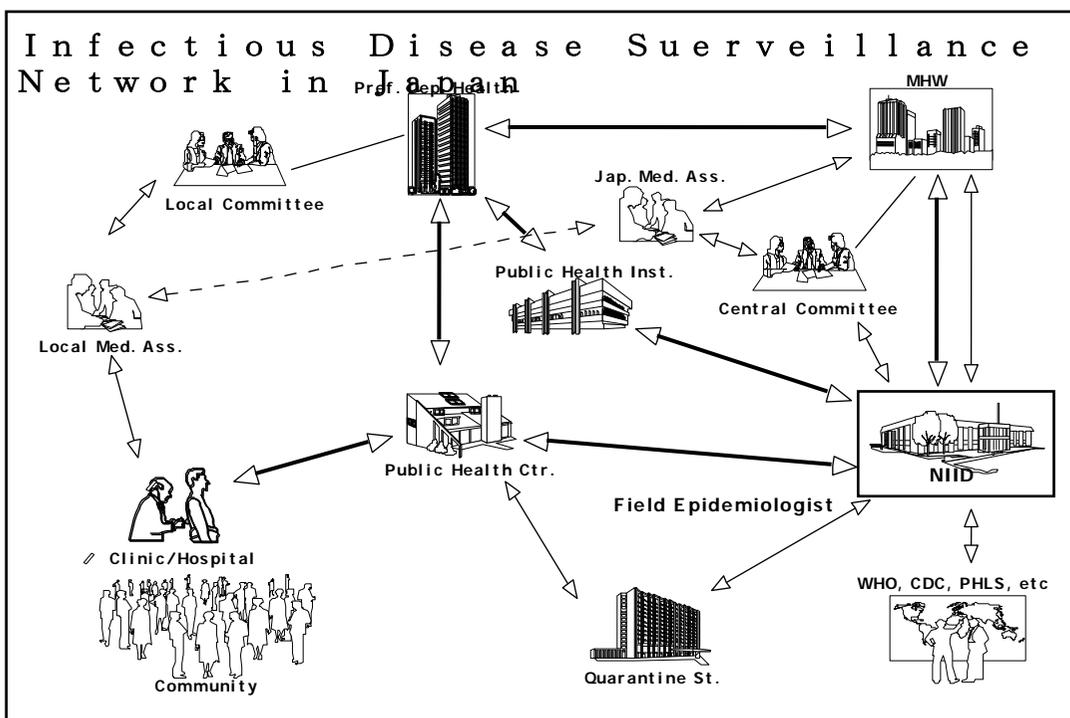


FDA-like

(quality control of
biological product)

Organization of NIID

- OFFICE OF ADMINISTRATION
- PLANNING AND COORDINATION
- DEPARTMENT OF VIROLOGY I
- DEPARTMENT OF VIROLOGY II
- DEPARTMENT OF VIROLOGY III
- DEPARTMENT OF BACTERIOLOGY
- DEPARTMENT OF BACTERIAL PATHOGENESIS AND INFECTION CONTROL
- DEPARTMENT OF PARASITOLOGY
- DEPARTMENT OF PATHOLOGY
- DEPARTMENT OF IMMUNOLOGY
- DEPARTMENT OF BIOACTIVE MOLECULES
- DEPARTMENT OF BIOCHEMISTRY AND CELL BIOLOGY
- DEPARTMENT OF MEDICAL ENTOMOLOGY
- DEPARTMENT OF VETERINARY SCIENCE
- DEPARTMENT OF SAFETY RESEARCH ON BLOOD AND BIOLOGICS
- DIVISION OF INTERNATIONAL COOPERATION
- DIVISION OF MOLECULAR GENETICS
- DIVISION OF GENETIC RESOURCES
- DIVISION OF BIOSAFETY CONTROL AND RESEARCH
- DIVISION OF RADIOLOGICAL PROTECTION AND BIOLOGY
- DIVISION OF EXPERIMENTAL ANIMALS RESEARCH
- AIDS RESEARCH CENTER
- INFECTIOUS DISEASE SURVEILLANCE CENTER
- LEPROSY RESEARCH CENTER



Target Diseases on National Infectious Disease Surveillance

provided and classified by the Infectious Disease Control law

enacted at 1999

revised at 2003 and 2007.

Sentinel-Reporting Diseases -weekly report- Category 5

- **Influenza (5000 sentinels**
– 3000 pediatrics and 2000 internal medicines)
- **Pediatric (3000 sentinels, 13 diseases)**
Erythema infectiosum, Exanthem subitum, Group A streptococcal pharyngitis, Hand-foot-mouth disease, Herpangina, Infectious gastroenteritis, Measles (excluding adult cases), Mumps, Pertussis, Pharyngo-conjunctival fever, RS virus infection, Rubella, Varicella
- **Ophthalmic (600 sentinels, 2 diseases)**
Acute hemorrhagic conjunctivitis, Epidemic keratoconjunctivitis
- **Specially-designated (500 sentinels, 5 diseases)**
aseptic meningitis, bacterial meningitis, Chlamydial pneumonia (excluding psittacosis), Measles in adults (>15ys old), Mycoplasma pneumonia

Notifiable Diseases, Category V (14 diseases)

– Acquired immunodeficiency syndrome, Acute encephalitis (including encephalopathy) , Amebiasis, Congenital rubella syndrome, Creutzfeldt-Jakob disease, Cryptosporidiosis, Giardiasis, Meningococcal meningitis, Severe invasive streptococcal infection, Syphilis, Tetanus, VCM-resistant *Enterococcus* infection, VCM-resistant *Staphylococcus aureus* infection, Viral hepatitis (excluding hepatitis A and E)

- Confirmed cases
- Time of reporting: Within 7 days
- Hospitalization: If necessary, ordinary hospital

Notifiable Diseases, Category IV (41 diseases)

– Anthrax, Avian influenza virus infection, Botulism, Brucellosis, B-virus infection, Coccidioidomycosis, Dengue fever, Eastern equine encephalitis, Echinococcosis, Epidemic louse-borne typhus fever, Glanders, Hantavirus pulmonary syndrome, Hemorrhagic fever with renal syndrome, Hepatitis A, Hepatitis E, Japanese encephalitis, Japanese spotted fever, Kyasanur Forest disease, Legionellosis, Leptospirosis, Lyme disease, Lyssa virus infection (excluding rabies), Malaria, Melioidosis, Monkeypox, Nipah virus infection, Omsk hemorrhagic fever, Psittacosis, Q fever, Rabies, Relapsing fever, Rift Valley fever, Rocky Mountain spotted fever, Scrub typhus, Tick-borne encephalitis, Tularemia, Venezuelan equine encephalitis, Hendra viral disease, West Nile fever (including West Nile encephalitis), Western equine encephalitis, Yellow fever

- Confirmed cases, Asymptomatic cases
- Time of reporting: immediately
- Hospitalization: If necessary, ordinary hospital

- **Human case of H5N1 infectious disease has been classified as a special designated infectious diseases (as category 2 level) since 2006.4.**

Patients should be admitted into class-2 infectious disease hospital until recovered.

National Epidemiological Surveillance for Infectious Diseases (NESID) based on the Law

INFLUENZA sentinels

- **Randomly selected 5,000 sentinels (3,000 pediatric practitioners and 2,000 general practitioner)**
- **Weekly patients number by age group**
- **Based on clinical case definition**
 - Sudden onset, fever over 38°C, URI symptom, and general symptom
- **Weekly reported number per sentinel as index of activity on PHC area, prefecture and national level**

Influenza surveillance system in Japan

- Morbidity surveillance by NESID system
- Microbiological surveillance
 - 10% of flu-sentinels appointed as laboratory diagnose sentinels
- Serological surveillance (antibody prevalence) among healthy populations
- Early warning system based on PHC level
- Daily rapid reporting system
 - 350 sentinels all over the country
 - Daily reporting using web entry system
 - Mostly based on rapid Ag detection kits
- School absentees surveillance
- Excess death

Patient number of influenza per sentinels by week

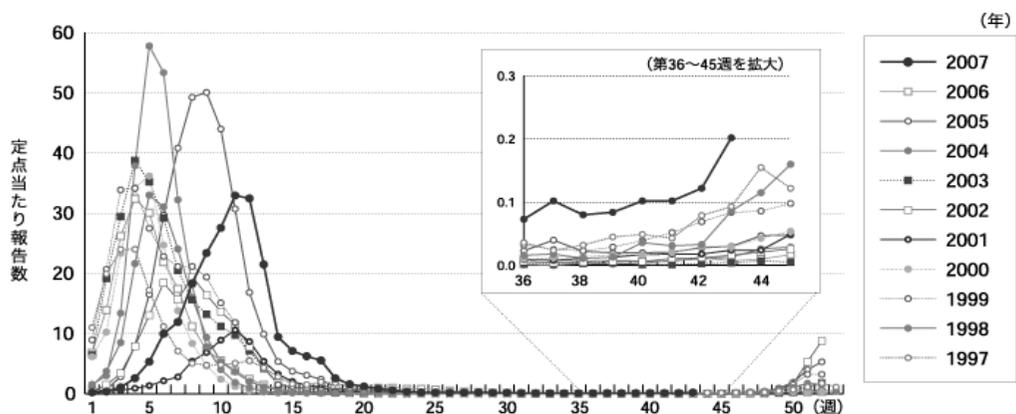
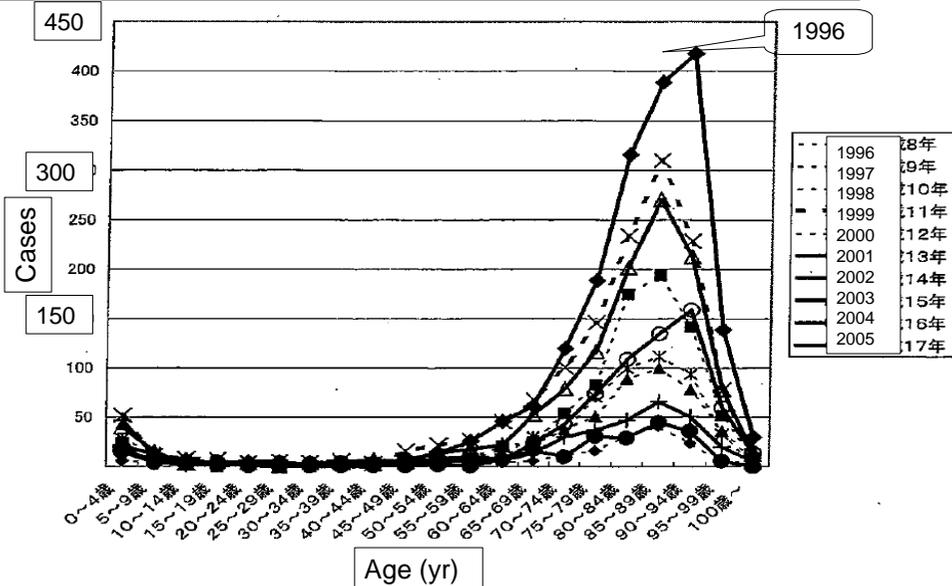


図1. インフルエンザの年別・週別発生状況 (1997年～2007年第43週)

Impact of Seasonal Influenza in Japan

death No.	Reported No.	Estimated No.	Excess
2002/2003	1.180 M	14.850 M	11,000
2003/2004	0.770 M	9.230 M	2,400
2004/2005	1.500 M	17.700 M	15,100
2005/2006	0.960 M	11.160 M	週

Influenza Deaths by Age Groups in Japan



Influenza viruses isolated in the local public health laboratories, 2006/07 season.

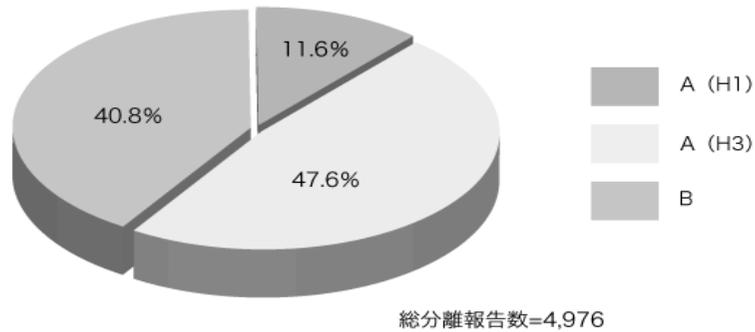


図6. インフルエンザウイルス分離報告割合 (2006年第36週～2007年第29週)

Influenza Encephalopathy in Japan

- In 1995 and 1998, many child death associated flu were reported in Japan.
- In 1999, Japan MHLW has determined to organize the collaborative study group
Chief Investigator: Prof.T.Morishima.
Dr.Okabe
one of the member of the group
- 1999-2002: to investigate epidemiology , virology, clinical feature, pathology in autopsy cases.
- 2003-2007: to investigate pathogenesis, genetic background, and to complete the guide line for the management of IAE.

Annual Reported Cases of Influenza Encephalopathy (1999~2006)

1998/1999: 217 cases
1999/2000: 109 cases
2000/2001: 63 cases
2001/2002: 117 cases
2002/2003: 160 cases
2003/2004: 102 cases
2004/2005: 119 cases
2005/2006: 119 cases

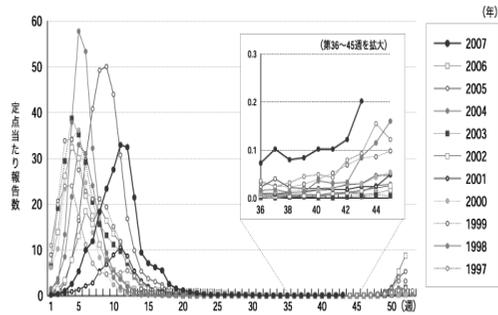
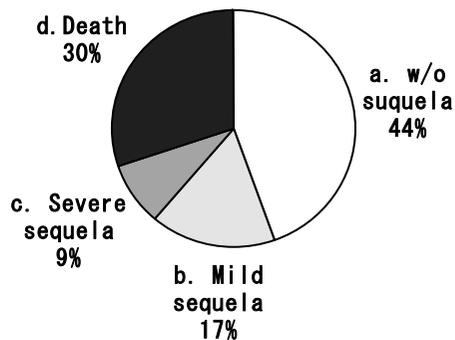


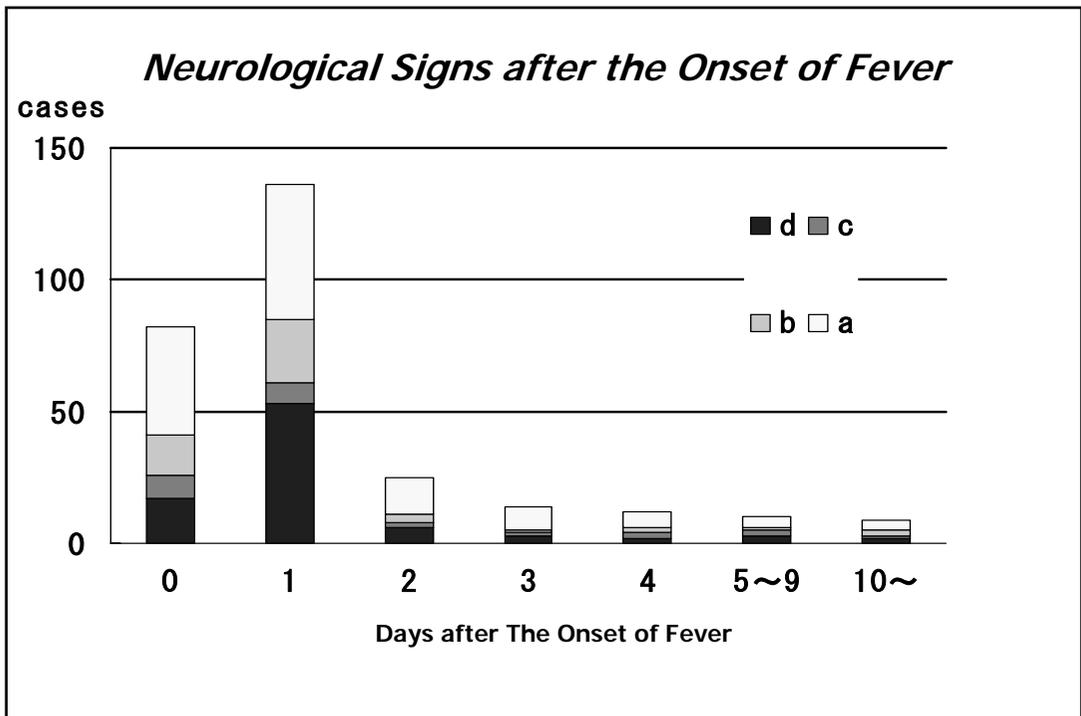
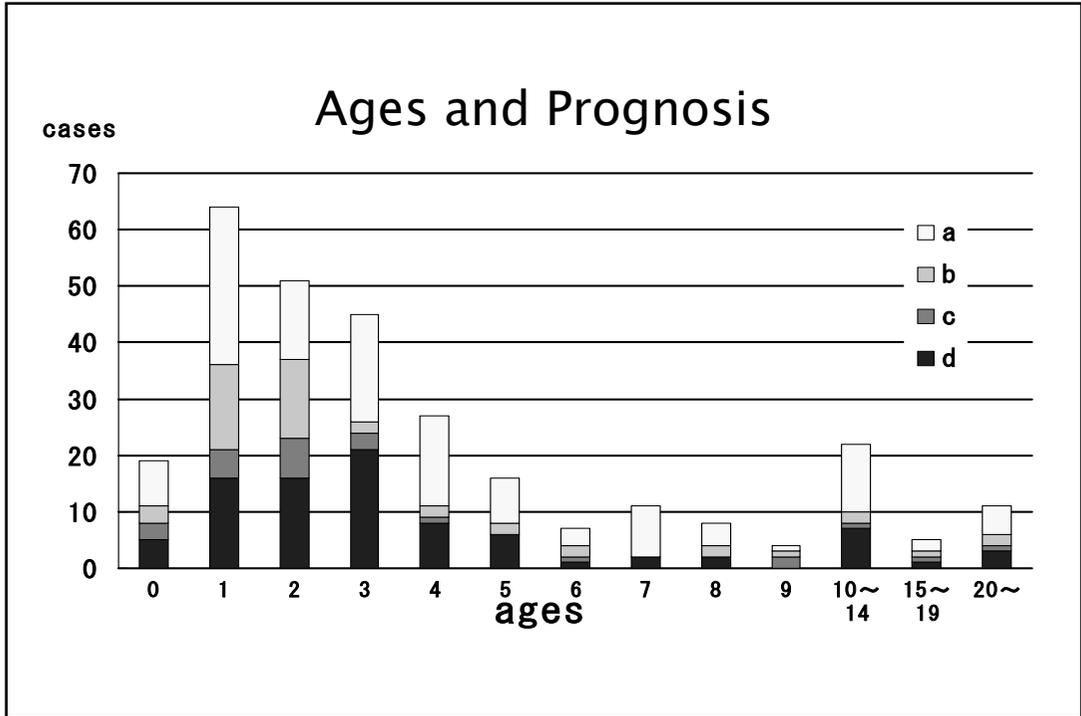
図1. インフルエンザの年別・週別発生状況(1997年~2007年第43週)

100-500 cases / year are estimated in Japan

Prognosis of Influenza Encephalopathy



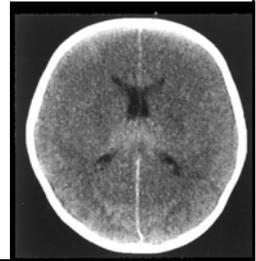
1999~2000



Brain CT Findings (4 categories)

- Severe brain edema *
- Acute necrotizing encephalopathy *
- Intra-cranial hemorrhage with DIC (HSES) *
- Brain atrophy with prolonged seizures

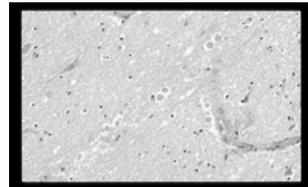
- * extremely severe outcome
- * higher incidence in infants



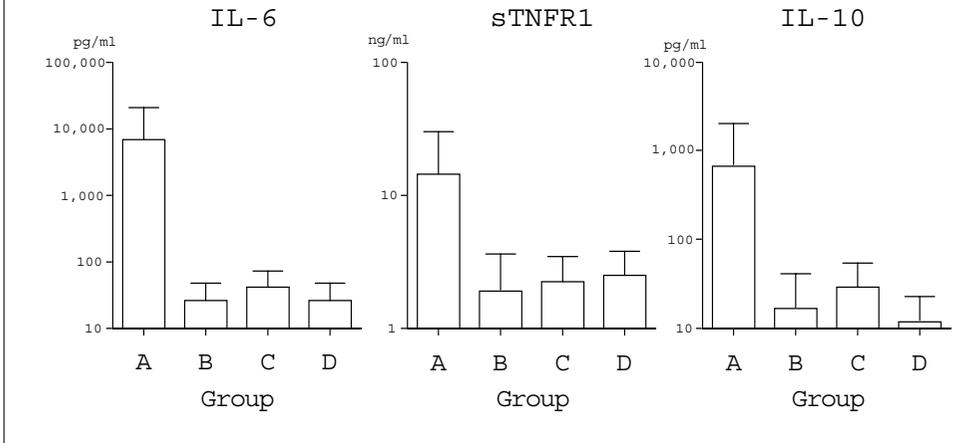
Pathology of Influenza Encephalopathy

(20 autopsy cases)

- (1) severe brain edema w/o inflammatory cells infiltration
- (2) damage of blood vessels/vascular endothelial cells
- (3) mild pathological changes in lower respiratory tract
- (4) virus-associated hemophagocytosis was found in 1/3 patients
- (5) fatty degeneration of the liver similar to Reye's syndrome in some cases
- (6) virus antigens could not be detected in the CNS
- (7) rapidly progressive apoptosis was found in nerve tissues and liver
- (8) activation of astroglia cells was found in the cases including sudden death cases



Cytokines Levels in Sera of IAE Patients



Group A: IE poor prognosis (n=14)

Group B: IE good prognosis (n=14)

Group C: FC (n=13)

Group D: Flu (n=39)

Ichiyama et al. 2003

Influenza

Hyper Cytokinemias

- Apoptosis↑
(cytochrome C↑, mAST↑)
- Hemophagocytosis
- SIRS-like Disease

Vascular Endothelium Damage

- Severe Brain Edema
- Plasma Influx to Brain Tissue
- Acute Necrotizing Encephalopathy
- Others

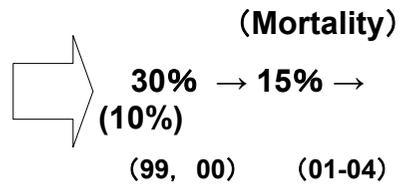
Multiple Organ Failure

(J Infect Dis, 2003 Morishima et al.)

Recommendation on Treatment by IE Study G

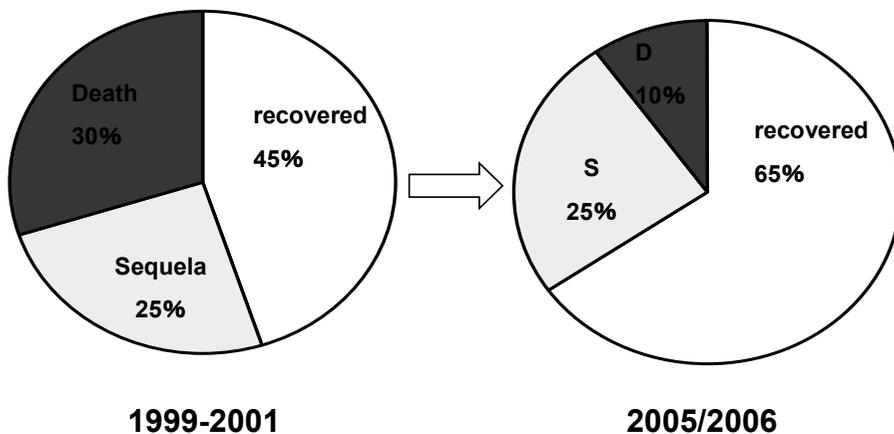
(2001–2004)

- Anti-influenza drugs
- **Steroid Pulse Therapy**
- High-dose Gammaglobulin
- Cyclosporin A
- ATIII Supplement Therapy
- Plasma Exchange
- Others



(Guideline for The Management of IAE 2005)

Outcome of IAE



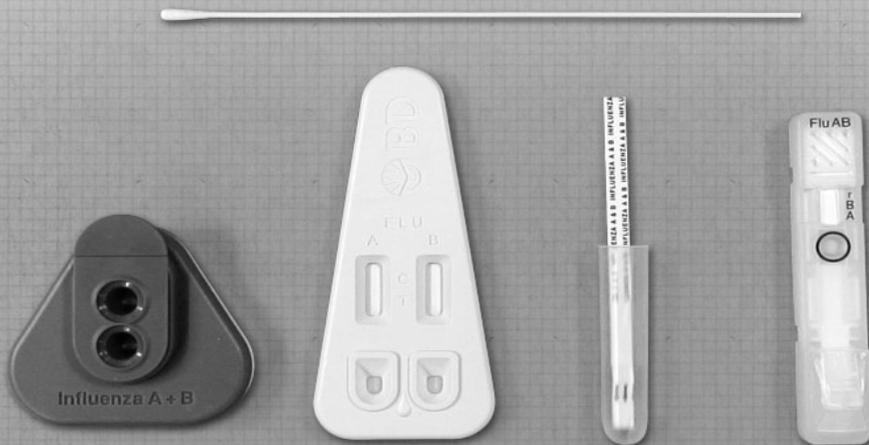
**Please send us any information
on the influenza-associated CNS disorders**

**Chief Investigator of study group
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Co-investigator
Dr.N.Okabe (IDSC/NIID Japan)
okabenob@nih.go.jp**

**Recent progress on Influenza
Influenza immunization to senior population**



インフルエンザ 迅速診断キットの例



Introducing rapid diagnosis kits in Clinics

主なインフルエンザの治療薬

タミフル
(オセルタミビル)

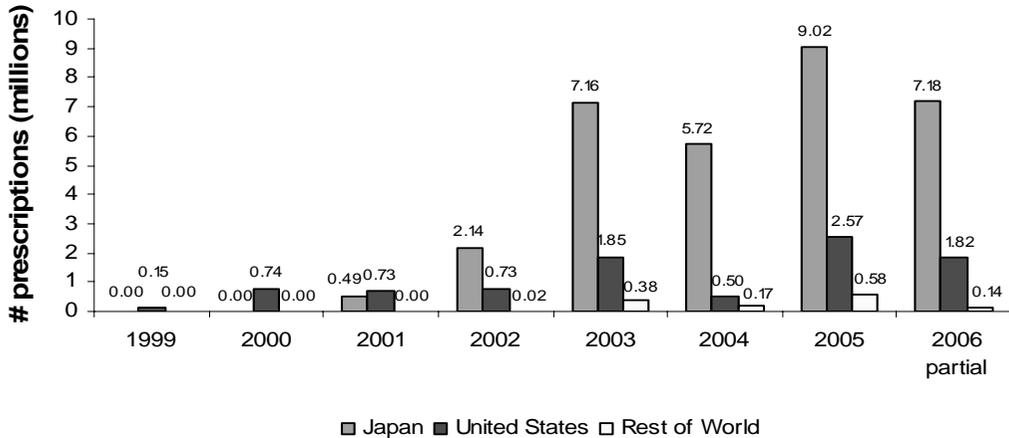


リレンザ
(ザナミビル)



Introducing anti-influenza drugs in clinics and accepted widely

Tamiflu® Prescriptions by Year and Country (all ages)



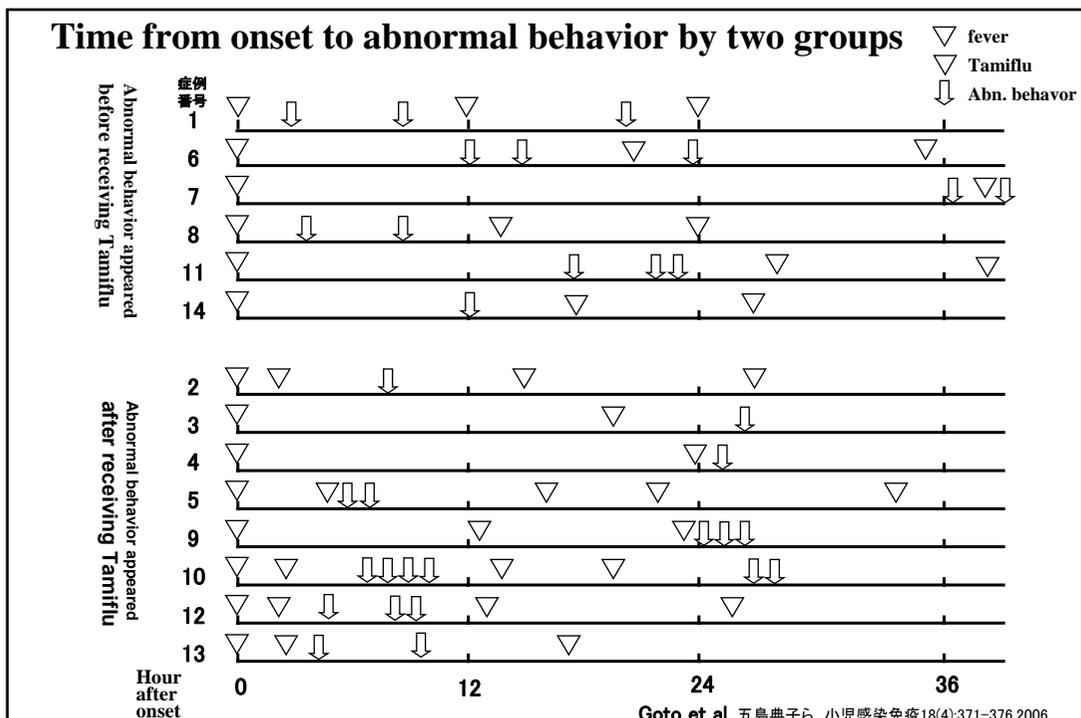
Data courtesy of Hoffmann-La Roche, Inc.
 Japan : IMS Quarterly Rx Data until June 2005, Biannual data until June 2006
 United States : IMS Weekly prescriptions until September 2006
 Rest of World : IMS MIDAS Quarterly Retail data (Germany, France UK, Brazil, Canada, Argentina) until June 2006

Presentation on abnormal behavior with Tamiflu, in 2005 and 2006 Japanese Pediatric Infectious Disease Society Annual Meeting

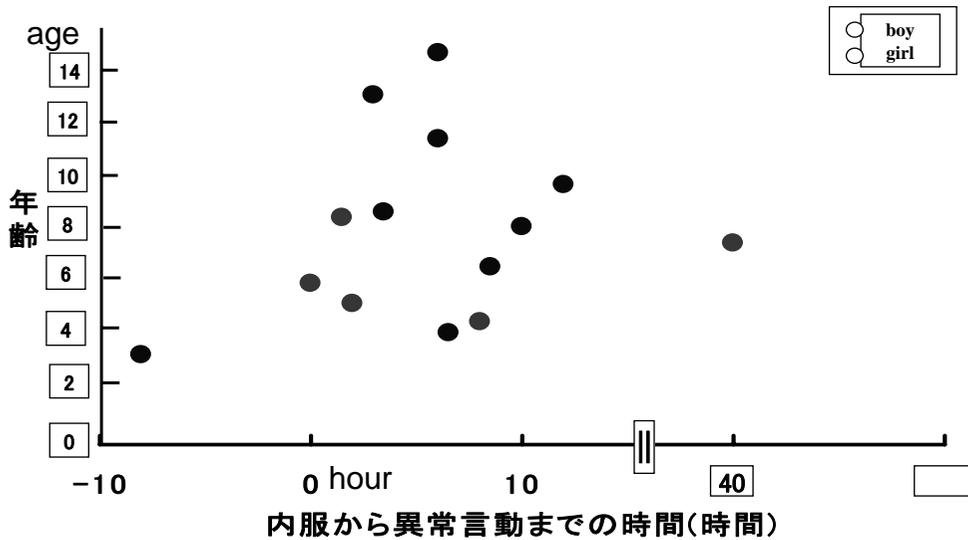
- Hama R (sources: review and personal information)
 - # 5 cases of sudden death during sleeping after taking Tamiflu.
 - # 2 cases of accidental death associated with abnormal behavior after taking Tamiflu.
 - # 3 cases of sudden death after taking Tamiflu.
- Hoshino et al (sources: own experiences)
 - # 2 cases of abnormal behavior after taking Tamiflu
- Hama et al (sources: review and his web information)
 - # 15 delirium without Tamiflu, and 52 delirium with Tamiflu
 - Delirium observed higher among Tamiflu but low fever group (OR:44.0)

Tamiflu ADR Cases Update

- Cases of 1,377 patients reported by May 31, 2007
 - 567 cases reported as Neuropsychiatric event cases
 - 211 cases showed symptoms like abnormal behaviors
 - 27 cases led to falling or jumping off higher buildings, and 6 of them were fatal
 - 71 fatal cases including 12 sudden deaths
- More cases are being reported and scrutinized as of today



Time from receiving Tamiflu to onset of abnormal behavior



五島典子ら, 小児感染免疫18(4):371-376,2006

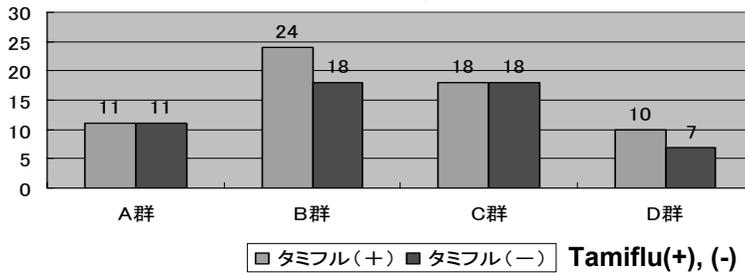
Report from Jpn Pediatric Soc., Kanagawa Branch in Jpn Ped Inf Dis Soc Ann Meeting, 2007

- 130 cases were reported from 12 Hosp. and 38 clinics, (05/06; 12, 06/07; 13)

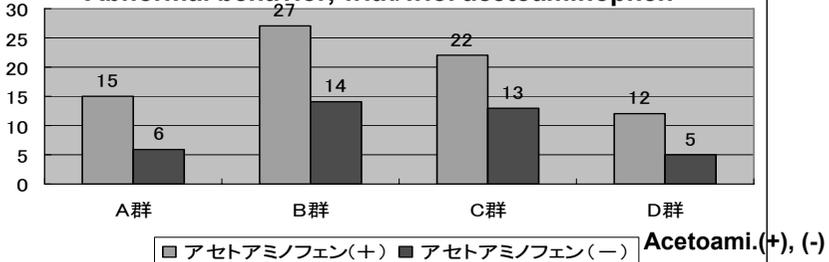
A: Abnormal behavior possible to progress to accident or to harm to others	22 cases
B: illusion, abnormal sense/vision	42
C: talk in delirium, sing songs, meaningless motion	36
D: scare, angry, cry, expressionless,	17

* convulsion 1, aseptic meningitis 1, excitement 5, no details 6

タミフル使用の有無と異常行動
Abnormal behavior, with/w.o. Tamiflu

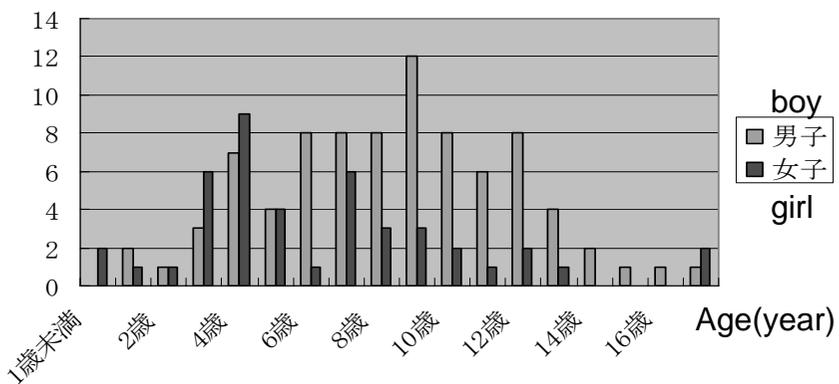


アセトアミノフェン使用の有無と異常行動
Abnormal behavior, with/w.o. acetoaminophen



Age and sex distribution

男女別年齢分布



Mean age boy: 8.5yo girl 6.3 yo (p=0.0011)
Sexual distinction; boy : girl = 8:1

Conclusion of the report from Kanagawa pediatrics group

- 130 cases of abnormal behavior were reported from pediatric clinics and hospitals in Kanagawa Prefecture.
- Almost 2 times higher in boys, and higher in elementary school age group than infant age group.
- Especially, in severe case group, school age and boys were higher.
- No differences were observed among influenza virus type, with/without Tamiflu group, and with/without acetoaminophen group.
- These factors could not be contribute for serious abnormal behaviors.

Issues to be tackled by this flu season*

- **Scrutinize closely the cases of abnormal behaviors and sudden deaths**
 - Psychiatrists in the subcommittee suggested the similarity to “Sleep Disorder” of Abnormal Behavior reported in teenagers
- **Additional studies to be conducted**
 - Sleep Laboratory Study
 - Nonclinical Study
 - Epidemiological Study

* Opinions of the Subcommittee on Safety of Drugs, Council on Drug and Food Safety Sanitation, April 4, 2007.

Epidemiological Study '05/'06

- **Chief Researcher:**
 - Prof. Shumpei Yokota (Graduate School of Medicine, Yokohama City University)
- **Title:**
 - Scientific Study on the Occurrence Status of Influenza-associated Symptoms
- **Study Method:**
 - Prepared the questionnaire survey sheets, distributed them to pediatricians in '05/'06 influenza season in Japan. Physicians are asked to fill them with clinical symptoms, drug used, and individual progresses of influenza. Survey sheets are collected and statistically analyzed.
- **Results:**
 - Relationship between the use of Tamiflu and clinical symptoms was examined in about 2,800 pediatric patients (90.4% of them were less than 10 y/o). There was no significant difference between Tamiflu-unused and -used for occurrence frequency of abnormal behaviors, etc., where the frequencies were 10.6% in unused against 11.9% in used.
 - About 90% of abnormal behaviors and other clinical symptoms expressed on the first and second days of disease.

Epidemiological Study on '06/'07

Improvement of epidemiological study '05/'06

1. Chief Researcher

- Prof. Yokota → Prof. Yoshio Hirota (Graduate School of Medicine, Osaka City University)

2. Survey Scale

- ca. 10,000 cases (ca.700 medical institutions)

3. Scope of the subjects (Age)

- Enhancement of research scope to target influenza patients in teenagers (less than 18y/o)

4. Time relationship

- More precise examination on the time relationship between observed symptoms and drug use

National Survey for Influenza- Associated Abnormal Behaviors

Chief Researcher: Dr. Nobuhiko Okabe (Director, Infectious Disease Surveillance Center, National Institute of Infectious Diseases)

Study Title: National Survey for Influenza-Associated Abnormal Behaviors

Study Purpose: To grasp the number of the abnormal behaviors and their details by gathering case reports from medical institutes.

1) Survey for serious cases: call for all doctors in Japan

Data collection of the cases where the patients have been diagnosed as influenza and shown serious abnormal behaviors. Serious abnormal behaviors are the acts which might lead to fatal endings; e.g. jumping off higher buildings or running abruptly.

– Data Collection Term : Last and Next flu-season

2) Survey for non-serious cases: call for influenza sentinels

Data collection of the cases where the patients have been diagnosed as influenza and shown non-serious abnormal behaviors. Non-serious abnormal behaviors are the acts which might not lead to fatal cases; e.g. fluttering hands with scared to something.

– Data Collection Term : Next flu-season

Thank you very much

doumo arigatou gozai mashita

どうもありがとうございます



NIID, Tokyo, Japan

**Severe Morbidity and Mortality Associated with Influenza
in Children and Young Adults --- Michigan, 2003 (MMWR 2003)**

TABLE. Number and percentage of signs and symptoms and conditions among influenza-positive patients* — Michigan, 2003

Signs and symptoms/Conditions	No.	(%)
Fever	14	(100)
Encephalopathy [†]	8	(57)
Seizures	4	(29)
Nausea/Vomiting	5	(36)
Rhabdomyolysis	2	(14)
Leg pains	3	(21)
Myocarditis	1	(7)
ALT [§] /AST [¶] >3x normal	4/10	(40)

*N = 14.

[†] Defined as altered mental status of any duration, including seizure, and not including simple febrile seizures.

[§] Alanine aminotransferase.

[¶] Aspartate transaminase.

Tamiflu Chronology 1

2000 Dec. Tamiflu Capsule / **2002 Jan.** Dry Syrup approved

2004 May. Revision of the PRECAUTIONS Section to include Neuropsychiatric Events in the labeling

2004 Jul. Prophylactic Use for Capsule approved

7) Psychoneurological symptoms (frequency unknown):

Tentative translation from Japanese original labeling

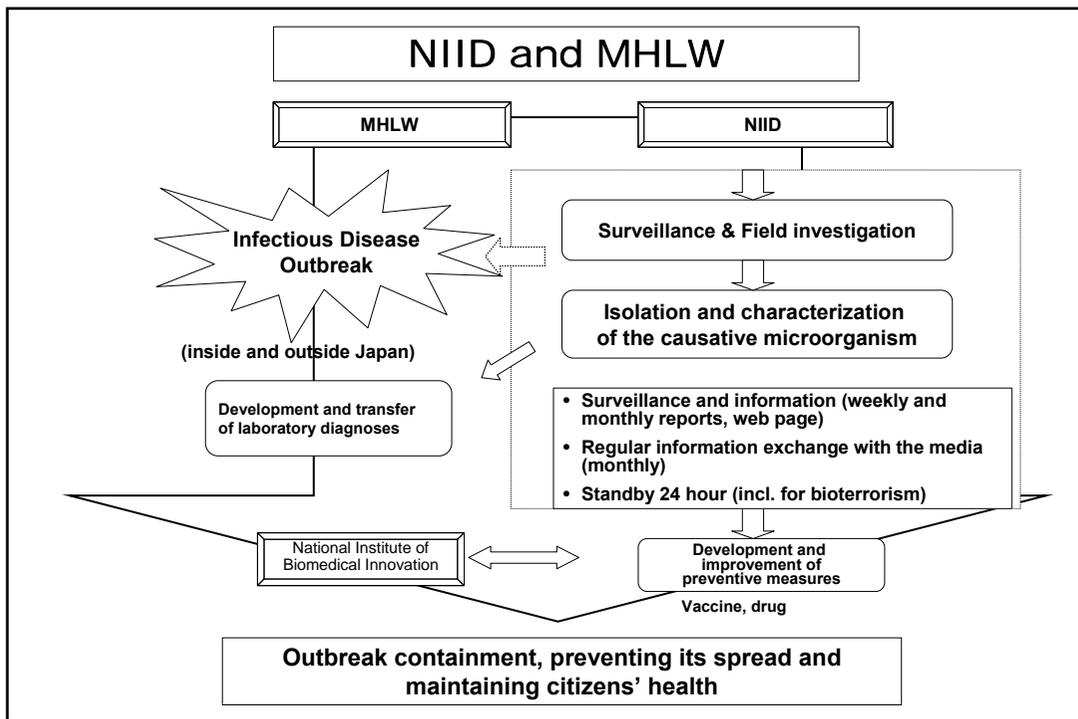
Psychoneurological symptoms (e.g. disturbances in consciousness, abnormal behaviour, delirium, hallucination, delusion, convulsions) may occur. Patients should be carefully monitored. If any abnormality is observed, the administration should be discontinued and appropriate therapeutic measures should be taken according to individual symptoms.

Tamiflu Chronology 2

- 2005 Nov.** US FDA Pediatric Advisory Committee: "The committee stated it did **not**, at this time, think the evidence supported a link between Tamiflu and the deaths and neurologic complications being reported."
- 2005 Nov.** MHLW published Influenza Q&A stating no serious concerns in the safety of Tamiflu at this stage because of the negative link between the drug and the pediatric deaths reported.
- 2005 Nov.** Japan Pediatric Society's Statement: No explicit causal relationship between Tamiflu and Pediatric deaths found
- 2005 Dec.** EMEA Statement as to no changes for Tamiflu safety information needed and to continuous monitoring
- 2006 Oct.** MHLW-sponsored Epidemiological Study (FY2005): "There was no significant difference between Tamiflu-unused and -used for occurrence frequency of Abnormal Behavior."
- 2006 Nov.** US FDA Labeling Change, and Pediatric Advisory Committee
- 2006 Nov.** EMEA Statement as to no changes for Tamiflu safety information

Tamiflu Chronology 3

- 2007 Feb.** MHLW warned Healthcare Professionals after 2 Fatal Cases of Junior High School Student falling from Apartment House Reported
- 2007 Mar.** Chugai issued Urgent Safety Information after 2 More Cases of Falling Reported under the instruction of MHLW
- 2007 Mar.** EMEA Statement on safety of Tamiflu: Update of the product information about neuro-psychiatric side effects
- 2007 Apr.** MHLW Subcommittee for Tamiflu
- 2007 May and June.** Clinical- and Nonclinical-WG twice each
- 2007 Jun.** MHLW Subcommittee for Tamiflu: Public hearing



Infectious Diseases Control Law

become effective on April 1, 1999

Direction of the new law

- **Strengthen the preparedness**
 - Strengthen surveillance system
 - Equip with basic guidelines for comprehensive promotion of infectious disease prevention
 - Formulation of diseases specific control guide line
 - Promotion of international cooperation

O157感染 3791人に



点滴中の児童を見舞う奥田文相—大阪府堺市の市立堺病院で15日午後2時25分、近藤卓真撮影

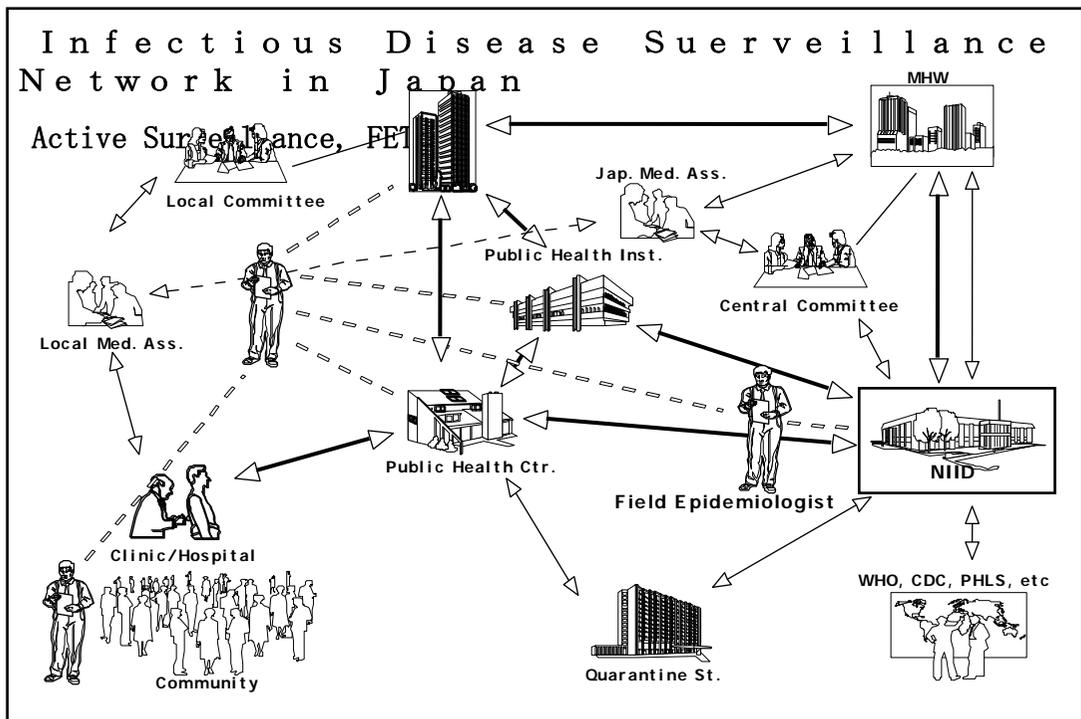
**Sakai
outbreak
July, 1996**

**The
Education
Minister
visited sick
children**

IDSC

Surveillance System in Japan -three components-

- 1. Patient surveillance**
- 2. Infectious agent surveillance**
- 3. Sero-epidemiological surveillance
(for vaccine preventable diseases)**



Infectious Disease Surveillance Center

1. Intelligence and Policy Planning Division
2. Surveillance and Information Division
3. Immunization Program Division
4. Laboratory Diagnosis
(for unknown diseases) Division
5. Division of Bacteriological Laboratory Training
(for local public health laboratories)
6. Division of Virological Laboratory Training
(for local public health laboratories)

Specific Measures by Category

1. **Category I**
Hospitalized in the class I infectious disease hospital.
2. **Category II**
Hospitalized in the class II infectious disease hospital.
3. **Category III**
Restrictions on engagement in certain types of work (ex. Cooking)
4. **Category IV**
Action for disinfection, mosquito/rat control, restriction to import animals. can be taken (ex. for zoonosis, food-borne diseases)
5. **Category V**
Surveillance and notice. (to see trends of the diseases)
6. **Hitherto unknown and serious infectious diseases**
Hospitalized in highest-security Infectious disease hospital
7. **Designated infectious diseases**
Special measures equivalent to those of category I or II infectious diseases, limited within one year

Notifiable Diseases, Category I (7 diseases)

– **Crimean-Congo hemorrhagic fever, Ebola hemorrhagic fever, Lassa fever, Marburg disease, Plague, Smallpox, South American hemorrhagic fever**

- **Confirmed cases, Suspected cases, Asymptomatic cases**
- **Time of reporting: immediately**
- **Hospitalization: Class I Infectious disease Hospital**

**Notifiable Diseases, Category II
(4 diseases)**

Diphtheria, Poliomyelitis, Severe acute respiratory syndrome (SARS), Tuberculosis

- **Confirmed cases, Suspected cases (※), Asymptomatic cases**
※: except Diphtheria and Poliomyelitis
- **Time of reporting: immediately**
- **Hospitalization: if necessary (if symptomatic),
Class II Infectious disease Hospital**

**Notifiable Diseases, Category III
(5 disease)**

– Cholera, Entero-hemorrhagic *Escherichia coli* infection, Paratyphoid fever, Shigellosis, Typhoid fever

- **Confirmed cases, Asymptomatic cases**
- **Time of reporting: immediately**
- **Hospitalization: If necessary, ordinary hospital**

**Sentinel-Reporting Diseases (2) 2007.4~
-monthly report-**

- **Sexually-transmitted diseases (900 sentinels,4 diseases)**
Condyloma acuminatum, Genital chlamydial infection,
Genital herpes, Gonorrhea

- **Specially-designated Hospitals (500 sentinels, 3 diseases)**
MRSA infection, multidrug-resistant *Pseudomonas* infection,
PRSP infection