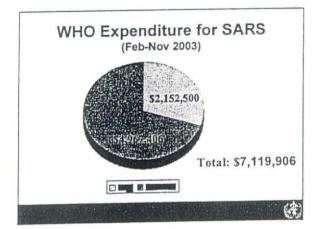
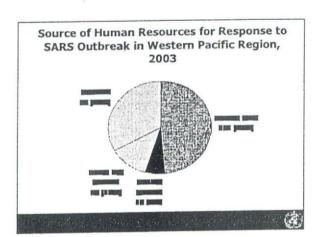
### SARS Laboratory Networks

- · Global Network
  - The network of reference laboratories
  - To identify a causative agent and develop diagnostic tests
- · Regional Network
  - The network of regional reference laboratories and all national laboratories
  - To support countries without adequate lab capacities

### Why regionalization?

- 1) Regional / country needs
- 2) Logistics





## Why regionalization?

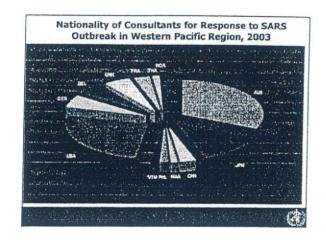
- 1) Regional / country needs
- 2) Logistics
- 3) Coordination

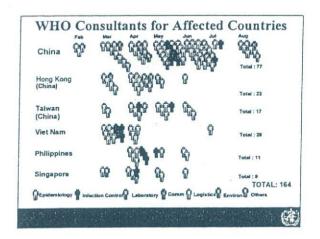
#### Coordination

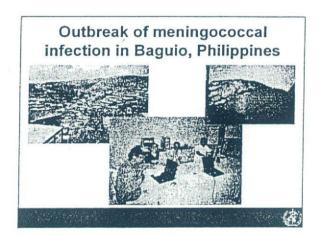
- Coordination with country offices / governments
- · Coordination with regional partners
  - Donors
  - Technical institutes
  - National networks

## Why regionalization?

- 1) Regional / country needs
- 2) Logistics
- 3) Coordination
- 4) Capacity strengthening







## Regional Capacity Strengthening

- Inter-country collaboration within the region
   Networking
- · Utilization of regional expertise
- Field experience



# Developing a Field Epidemiology Training Program in Japan

Seven-Year Challenge of FETP-Japan

Takaaki Ohyama Field Epidemiology Training Program (FETP) National Institute of Infectious Diseases, Japan

### FETP-J: Why now?

- Bitter experience!
   Large-scale EHEC outbreak in Osaka, 1996
   Emerging problems (SARS, Avian Influenza, etc.)
- New regulation ("Infectious Disease Control Law" 1999)
- International network of field epidemiologists
   TEPHINET (Training of Epidemiology for
   Public Health Intervention Network)
   GOARN (Global Outbreak Alert & Response Network)



FETP-Japan

#### FETP-J: Goals

- To establish a core of field epidemiologists on communicable disease control and prevention
- To strengthen "local capacity" and establish a national network in Japan
- To create a strong FETP network in Asia and the world

#### FETP-J: Training strategies

- Two-year "On-The-Job" training on communicable disease control and prevention
- Twelve trainees (9 in 6<sup>th</sup>, and 3 in 6<sup>th</sup>), four trainers (Japanese and a resident advisor), and several short-term consultants
- Following the curriculums developed by EIS (US), EPIET (EU), etc.

## FETP-J: Training components

- 1. Outbreak investigation
- 2. Surveillance activity
- 3. Communication
- 4. Research activity
- 5. Training seminar
- 6. Teaching

# FETP-J: Achievements Outbreak investigation

In Japan

EHEC outbreaks (local & multi-prefectural)
Measles outbreak in school

Nosocomial outbreaks (VRE, Serratia and Chlamydia infection)

Emerging issues (SARS, Avian Influenza, etc.)

International

AFP investigation in China & Philippines Measles surveillance in China SARS in Asia

# FETP-J: Achievements Surveillance activity

- · On-going analysis of surveillance data
- System
- · VRE
- evaluation
- · Pertussis
- Measles
- Tetanus
- Syphilis
- · Tsutsugamushi disease
- Malaria
- · Echinococcosis

# FETP-J: Achievements Communication

- · Dissemination of public health message
- · Scientific meeting
  - Academic meetings (national & international)
  - Other FETP conference
- · Weekly/monthly bulletins
- Communication with decision makers
   (MOH, Local authorities)



# FETP-J: Achievements Research Activity

- Influenza surveillance under "school" system
- Representativeness of STI surveillance in Japan
- Tsutsugamushi disease in Japn (epidemiological perspectives)
- Syndromic surveillance for massgathering events
- And more ......



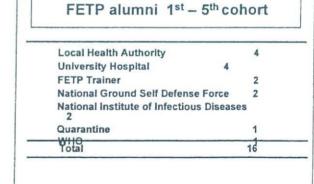
# FETP-J: Achievements Training Seminar

- · Introductory course (four weeks)
- · Short seminar with specific topics
  - Hospital infection
  - Global surveillance system for emerging diseases
  - Food/water-born diseases
  - Bioterrorism preparedness
  - And more .....



# FETP-J: Achievements Teaching

- Short course "Communicable disease control and prevention"
  - Regional/prefecture level
  - Lecture & "case study" exercise
- · Feedback to the sending institute
  - Local authorities, University,
     Quarantine office



# FETP-J: Perspectives

- Improving relationships with local health authorities
- Strengthening regional collaboration in Asia on surveillance and infectious disease control
- · Expanding our field of interest



Improving public health

# Anyway .....

# FETP-Japan

Ready to work with you !!



http://idsc.nih.go.jp/fetpj/index.html

# Influenza Laboratory Network in Asia/Pacific Regions



Masato Tashiro, MD., PhD.
WHO Collaborating Center for Surveillance
and Research on Influenza,
National Institute of Infectious Diseases, Tokyo

#### What is surveillance?

It is more than just collecting data!

Surveillance has been defined as:

"the ongoing systematic collection,
analysis, and interpretation of outcomespecific data for the use in the planning,
implementation, and evaluation of public
health practices".

#### patentina in 1908 il monto in proprio participato de 12 Estados estado

- Support and strengthen influenza surveillance during the interpandemic period to be prepared for a pandemic (Sentinel networks and laboratory capacity)
- Develop surveillance system to monitor morbidity, hospitalization and deaths
- Establish specimens collection, transport, virus detection and isolation systems for early identification of a "new" subtype virus
- Transfer technology and information through training, distribution of reagents

#### Surveillance data is used

- Outbreak defection and control: Data is published weekly and widely circulated (FluNet)
- · Formulation of Vaccine Policy
- Burden of Disease: Advocate for national "Influenza Awareness Programme"
  - Health care professions
  - Public
  - Policy makers
- Vaccine strain selection: Virus isolates forwarded to WHOCC
- Novel subtypes/Pandemic Surveillance

## Influenza surveillance system in Japan

Disease surveillance (ILI)
 Ministry of Health, Labour and Welfare (MHLW)

National Institute of Infectious Diseases (NIID)
Infectious Disease Surveillance Center (IDSC)

Sentinels

3000 Pediatric clinics and hospitals

2000 Internal medicine clinics, hospitals and nursing homes

2. Virus surveillance (laboratory-based surveillance)

National Influenza Center (NIID)

74 Public Health Institutes of Local Governments

2000 Sentinel clinics, hospitals and nursing homes

3. Outbreak surveillance

# Issues about National Influenza Surveillance System in Japan

- · National laboratory network well organized and functioning
- PHLs of local governments actively participating
   Up to 10,000 isolates yearly
- Pathogen surveillance for influenza is not always authorized by the Infectious Disease Law
- All-year-round routine surveillance necessary
- Outbreak surveillance/responses to be improved
- Maintenance and sustainability of experts
   Cutting down and frequent rotation of experts
  - ·Overwhelmed with responsibility for many pathogens
  - · Training and exercise insufficient
  - ·Officially legal and financial supports needed
  - · Collaboration with other sectors needed

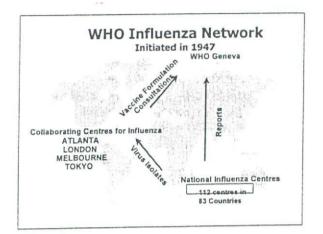
### Knowledge of the Epidemiology of Influenza

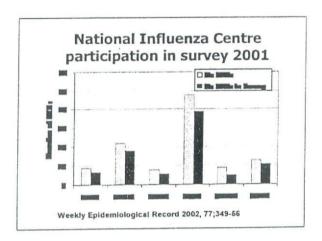
Data from countries with influenza surveillance

- · Virological surveillance -Foundation on which national and international influenza surveillance systems are built
  - 4 WHO Collaborating Centers
  - National Influenza Centres (NICs)
  - Sentinel site surveillance

#### Challenges in establishing surveillance:

- 1. To establish a National Influenza Centre in each country
  - ensure each lab meets NIC WHO Terms of Reference
- 2. To establish Sentinel Site Surveillance in each country
  - ensure objectives appropriate for each country





#### WPRO NIC Network

- New Zealand
  - ESR, Wellington
     Lab+ Auckland
- Australia
- WHOCC Melbourne ICPMR, Sydney VIDRL Melbourne
- Singapore Sing. General Hospital
- Malaysia - IMR, Kuala Lumpur
- Viet Nam
- NIHE, Hanoi
- · South Korea
- KCDC, Seoul

- · China
  - GVU, Hong Kong
  - CCDC, Beiling
- Mongolia
  - NCCD
- · Philippines
  - RIMT, Manila
- Fiji
  - Matalka House
- New Caledonia
  - Institute Pasteur
- Japan
  - WHOCC NIID, Tokyo

# Challenges in establishing surveillance:

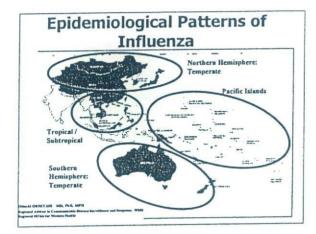
- · Disease burdens of influenza not recognized
- · Many people with ILI do not seek medical
- · Cases of influenza usually not identified by standard laboratory tests - need a clinical virology lab.
- · Reporting of influenza not mandatory
- · Therefore, specific Surveillance System for influenza needs to be established

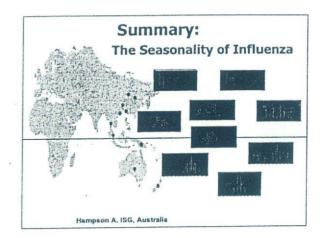
# WHO/NIID/CDC 5-year Plan to establish a national surveillance system for influenza in China

- · First project from 2001 to 2005
- · All Provinces enrolled gradually
- · Epidemiology and virus surveillance combined
- · Seasonality of annual epidemics in different areas
- · National immunization program established
- · Pandemic Preparedness Plan
- · Lessons from SARS and avian flu
- Difficulty in information sharing and sample shipping due to bureaucracies and sectionalism
- · Next 5-year plan to be implicated

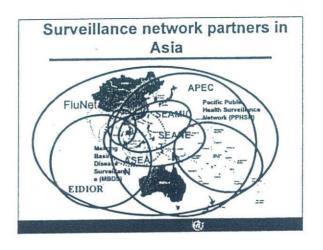
# Challenges in establishing surveillance:

- · Early Warning Systems- reporting of unusual clusters
  - Animal die off
  - Human ILI Surveillance or acute ARI
- · Virological Surveillance
  - Sentinel site surveillance
  - Epidemiological information
    - · Influenza-like-illness
    - · Illness outcome eg. Mortality, Absenteeism
- · Requirement or virus laboratory testing









#### WHO SARS Laboratory Network for Diagnosis and Research

· Established 17 March 2003

To identify the causative agent of SARS To test all clinical materials

- · Based on WHO Influenza Lab Network
- · Agreement to;
  - · Public health purpose as the first priority (not research and publication)
  - · All information and materials to be shared
  - ·Agreement by the network to be required for publication and material transfer to others
- Successfully identification of a new SARS-CoV as the causative agent of SARS within a month
- Further development of diagnostic systems and supply of standard reagents

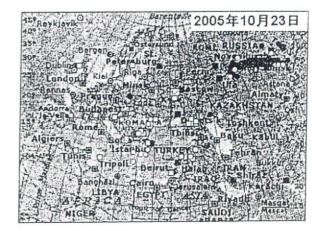
#### WHO SARS Laboratory Network

- · Canada: Natl. Microbiol. Lab., Winnipeg
- · France: Pasteur Institute, Paris
- Germany: Bernard Nocht Inst. of Tropical Med., Hamburg (Frankfurt and Marburg Univ.)
- Hong Kong: GVU, HKU, Chinese UHK
   Japan: NIID, Tokyo
- · Netherlands: Erasmus Univ., Rotterdam
- · Singapore: Virol. Unit, Singapore Gen. Hospital
- UK: PHLS, London
- · USA: CDC, Atlanta
- · China: Chinese CDC, Beijing and Guandong CDC

# Summary of Influenza A(H5N1) outbreaks in poultry in Asia to Europe, 2003-5 Multi-country outbreak

- - Rep of Korea, Japan, Viet Nam, Thailand, China, Lao, PDR, Cambodia, Indonesia

  - Mongolia, Russia, Kazakhstan, Iran
- Turkey, Romania, Croatia and so on · More than 160 million poultry have died or been culled
- Very highly pathogenic virus causing fatal systemic infections in a variety of bird and mammalian species
- · Historically unprecedented outbreak
- Human cases in affected areas with severe systemic infection and high fatality (beyond the general concept of flu)
- · Pandemic threat of a highly pathogenic virus
- · Economical/agricultural issues
- · Insufficient information available





### H5N1 outbreak in Indonesia, July 2005-

- · Chicken epidemic continues since 2003
- Two human clusters since July 2005 High mortality (>75%) Up to 200 suspected cases Only few laboratory-confirmed
- · Poor information and diagnostic systems
- · Clade 2 A/H5N1 HPA1 virus

Different from Vietnam and Thailand

· Emergency declared by the Government International Concerns about a pandemic

#### Human Public Health Risk of H5N1 HPAI

- Severe human cases in affected areas
  - · Increasing number of confirmed cases
  - · Family clusters; human-to-human transmission
  - · Less information to assess public health impact
- Emergence of a new H5 influenza virus with pandemic potential
  - Efficient human to human transmission by gene reassortment and mutations
  - · Vast majority of people with no immunity to H5
  - · Pandemic with huge morbidity and mortality
  - · Great health burden and social/economical impact

#### Pandemic influenza

· LPAI virus-derived

Pandemic influenza in the past

1918 Spanish Flu (H1N1)

1957 Asian Flu (H2N2)

1968 Hong Kong Flu (H3N2)

ILI: infection restricted to respiratory organs

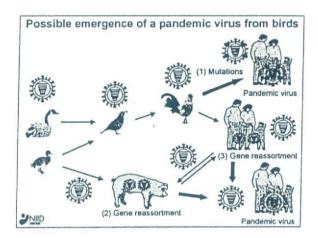
· HPAI virus-derived (?)

No record in the past, but with threat currently

1997 Hong Kong (H5N1)

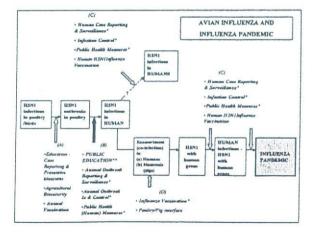
2003 Hong Kong (H5N1), Netherlands (H7N7)

2004-2005 Eastern Asian countries (H5N1) Clinical picture far beyond ILI: ARDS, MOF,



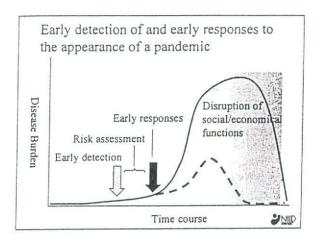
#### Pandemic influenza

- · LPAI virus-derived
  - LPAI virus does not kill birds and will not be recognized until the emergence of pandemic
  - Symptom: ILI & pneumonia
- · HPAI virus-derived (?)
  - HPAI may be recognized beforehand and response actions may be possible
- Clinical picture far beyond ILI: ARDS, MOF, encephalopathy, systemic infection?
- # Early detection and characterization critical!



### Goals of Pandemic Influenza Response

- Decrease the burden of disease
- Minimize social disruption
- Reduce economic impacts



#### WHO H5N1 Reference Laboratory Network

- · Established in January 2004
- · WHO CCs:

Australia; Melbourne Japan; NIID, Tokyo UK; NIMR, London USA; CDC, Atlanta

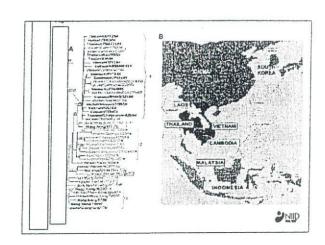
USA; St. Jude, Memphis (animal influenza)

Governmental Virus Unit, HK SAR

HKU, HK SAR Pasteur Inst., Paris

### WHO H5N1 Reference Laboratory Network

- To receive clinical specimens from NICs
- Diagnosis of H5N1 by RT-PCR, virus isolation and micro-neutralization test
- Characterization of viruses for antigenic, genetic, biological, and pathogenic natures as well as anti-viral drug resistance
- Feed-back the results to the originating labs and sharing among the network
- Development and supply of diagnostic reagents and references
- Development of prototype vaccine viruses
- Technical support and assistance to NICs



Antigenic	Al		PERMIT	ulencos
Antigenic	diversity	among	INCH	Alt nzcz

Virus	Ferret serum				Sheep serum			
	HK/480	Draing	ИК/213	NIBRG -12	VNI 1201	30321	НКИ489	HK/213
HKJ489/97	120	120	<10	<10	<10	<10	≥1280	960
Duck/Sing/97	640	160	10	<10	<10	<10	>1280	640
HK/213/03	640	80	640	120	160	<10	640	≥1280
NIBRG-12	320	160	960	120	120	<10	>1280	>1280
VietN/1194/04	<10	<10	<10	<10	160	<10	160	160
VietN/1203/04	<10	<10	40	20	320	20	320	640
VietN/1204/04	<10	<10	<10	<10	160	2	10	160
VietN/JP30321/05	<10	<10	< 10	<10	20	320	<10	
Indonesia/5/05	<10	<10	<10	<10	<10	<10	<1	)

Development of attenuated H5N1 virus by Reverse Genetics Technology

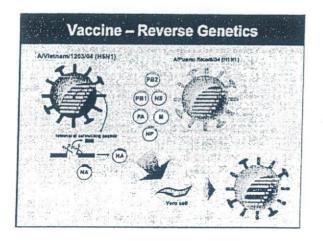
Modification of the cleavage site of HA

HPAI PQRERRKKR/GL LPAI PQ----RETR/GL

NA gene is derived from the original virus

The other 6 genes are derived from human attenuated virus A/PR/8/34





#### Issues in pandemic vaccine policy

- 1. Production of pandemic vaccines
- Urgent development Technology, IPR, safety and efficacy, clinical trials, licenses
- Production capacity Infrastructure, facilities, supply of eggs, incentive
- 2. Access, supply and immunization
- Short of vaccine supply
- Priority of vaccination target groups
- Equitable international supply of limited amount
- Infrastructure and feasibility of immunization program

#### Problems with the WHO H5N1 Reference Laboratory Network

- · Information sharing not so smoothly
- Some labs more interested in research and publication rather than public health
- Some counties hesitating to share information and send specimens
- International regulations on bioterrorism inhibiting rapid exchange of specimens
- Conflict and competition with parallel channels of international assistances
- · Lack of resources in affected countries
- Insufficient leadership by WHO; manpower and resources

### Needs for laboratory experts

- Laboratory diagnosis
  - -Front-line responses
  - -Practical wide knowledge and skills
- -International standards and methods
- -Collaboration with epidemiology
- Public health-orientation rather than research and publication
- Sharing information, clinical specimens and pathogens with Network

### Laboratory experts

- · Main human resources
  - NIID
- Local public health institutes
- Veterans from the above
- · Potential human resources
- Universities, research institutes
- Commercial diagnostic laboratories
   Not always reliable and stable
   External evaluations needed
   Training and exercise required

#### Issues concerning academia

- More research-oriented to publish papers and get grants rather than public health contribution
- · Little practical knowledge, skills and experiences
- · Little training and exercise to young people
- · No international standards and methods
- · No QC and GLP, leading to
  - miss-diagnosis
- miss-interpretation
- loss of external (international) confidence
- Useless when working internationally and in fields

#### Surveillance for potential pandemic viruses

Pre-pandemic Phase (Early detection of a new virus)

- Disease surveillance (All year around)
  - ILI survelllance
    - clusters; ILI, pneumonia, severe cases single case; HPAI-derived, severe cases
- Rapid reporting
- Virologic surveillance
  - animals (chickens, pigs, etc.) and human cases
  - sample collection, transport to diagnostic lab
  - virologic investigation
  - virus isolation and characterization
  - new subtype or un-subtypable viruses
- Shipping viruses and/or clinical specimens to WHO CCs for further characterization and confirmation
- Active surveillance

#### Virologic Surveillance

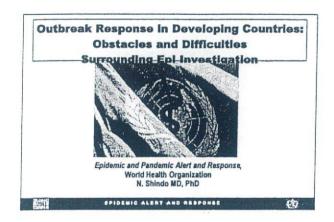
- · Targets; suspect cases and contacts
- . Sampling: timing, procedures
- Transport: procedures, rapid
- · Early detection of a novel virus
- BSL-2 with higher precaution or BSL-3 (HPAI)
- Virus isolation and identification using WHO diagnostic kit
- RT-PCR using WHO recommended primers
- · Information sharing among WHO network
- Novel subtype or un-subtypable viruses to be shipped to WHO CCs or WHO Network labs
- Sharing & feedback of information

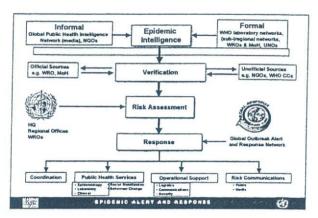
## Characterization of a new virus

- · Subtyping for a "new" subtype
- · Antigenic characterization
- Nucleotide sequencing and phylogenetic analysis
- · Avian or mammalian characteristic?
- . Gene segment reassortment?
- Drug sensitivity?
- Risk assessment and alert
- Implementation of pandemic preparedness measures
- Development and improvement of diagnostics
- · Development of vaccines

#### Pandemic Potential Strain Surveillance

- Depending on annual influenza surveillance activities
  - Establishment of annual surveillance
- Pandemic emerges without seasonality
  - All year around surveillance
- Early detection
  - Sensitive disease surveillance system
- Rapid information sharing nationally & internationally
- Rapid virus isolation and characterization
  - Virus/clinical specimens sharing & exchange timely
- Biosafety and biosecurity concerns
- International collaboration





### Your Terms of Reference are most likely...

To assist national/local health authorities by providing technical support in epidemiologic investigation under WHO coordination.

EPIDENIC ALERT AND RESPONSE

#### Ideally,

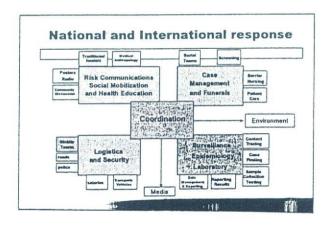
#### You work as an epidemiologist to:

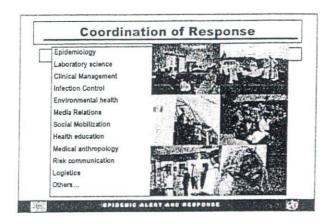
- · Identify source of infection and transmission route to stop the disease spread.
- Characterize outbreak by:
  - Demographic and geographic distribution,
  - Attack rate and case fatality ratio,
  - Incubation period,
  - Infectious period,
  - Clinical presentation, risk factors, efficacy of treatment, etc.

EPIDENIC ALERT AND RESPONSE

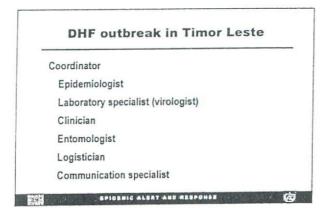
#### Your Role in Reality...

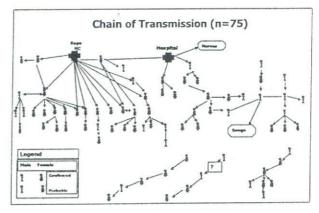
- · Searching for corps in the bush and bury them,
- Taking samples from deceased,
- Site visiting to remote & isolated villages,
- Updating database,
- · Cleaning hospital ward, or sitting in an office in vain...

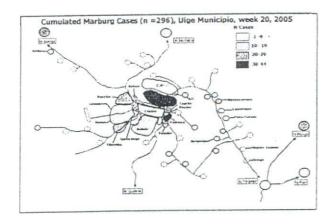


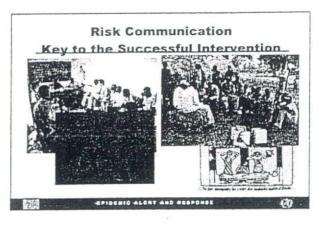


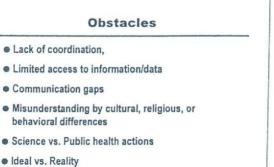




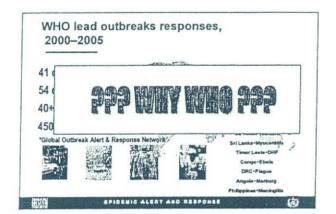




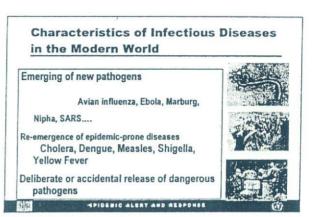








EPIDENIC ALERT AND RESPONSE

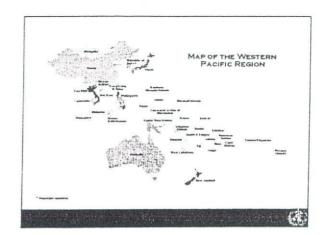




# Present situation of influenza type A/H5 diagnostic capacity in developing countries and their issues

31 Oct 2005

Futoshi Hasebe (ADB Consultant)
WHO Western Pacific Regional Office (WPRO)



# National Influenza Centers (NIC) & National Influenza laboratories (NIL)

· Cambodía : Pasteur institute Phnom Penh

· China : China CDC, Government virus unit (Hong Kong)

Lao-PDR: National Center for Laboratory and Epidemiology (NCLE)

Malaysia: Institute for Medical Research (IMR), University Malaya,

National Public Health Laboratory

Mongolia: National Center for Communicable Diseases (NCCD)

Philippines: Research Institute for Tropical Medicine (RITM)

Viet Nam : National Institute of Hygiene and Epidemiology (NIHE)

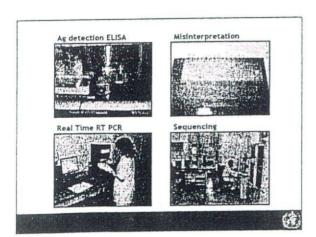
Pasteur Institute of Ho Chi Minh

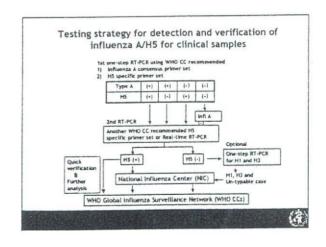
Pacific Islands : Pasteur Institute Noumea (New Caledonia)

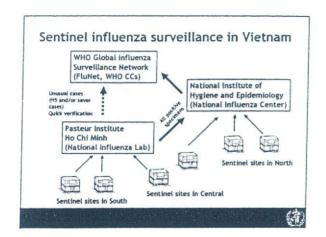
Mataika House Suva (Fiji Islands)

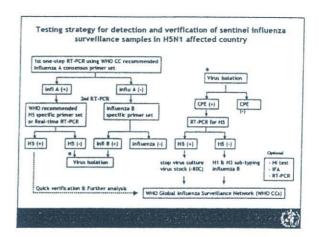
# Present laboratory situations and influenza diagnostic capacity

Country	Virus isolation	RT-PCR	BSL-3
Cambodia	у	у	n
China	У	у	у
Lao-PDR	n	n	n
Malaysia	у	У	у
Mongolia	у	У	n
Philippines	у	У	n
Viet Nam	у	У	У
New Caledonia	у	У	n
Fiji Islands	n	n	n









#### External verification

- · 4 WHO CCs (Japan, Australia, UK and USA)
- 112 NICs in 83 countries



- Problems -
- · No dry ice
- · No CO2 gas or different standard
- No permission from MoH
- · No permission from air company



#### An instance of Lao-PDR case

#### Chronology

- 17 Sept 14 yrs boy admitted hospital
- 19 Sept Severe respiratory symptom
- NGO reported WR/WPRO 23 Sept
  - Sample and information collection (NCLE) WPRO requested NIID for H5 tests
- 28 Sept Arrangement for Shipment (World Courier) 29 Sept
- Sample arrived at NIID 07 Oct
- Feedback the result from NIID 13 Oct



# Increasing number of BSL-3 laboratories

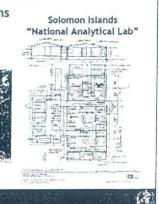








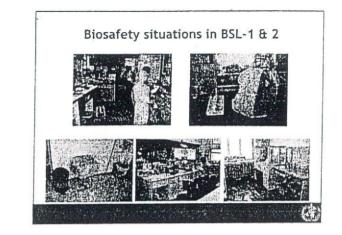
New BSL-3 lab plans Viet Nam "NIHE Annex"



#### Biosafety issues

- Bad practice in laboratory management
- Poor supervision of less experienced professionals
- A lack of accountability for occupational health and safety
- · A lack of biosafety policy
- A lack of biosafety procedures and staff training in biosafety practice





### Other Biosafety issues

- There are many labs that are not under MoH responsibility, e.g. agriculture, military, environment, commercial labs etc.
- No bio-safety practices in hospital labs



#### Influenza lab staff in Vietnam

NIHE influenza lab staff	Responsible work		
Dr. Le Thi Quynh Mei,	Head		
Ms. Nguyen La Khanh Hang	RT-PCR, Sequencing (H5)		
Dr. Dinh Tuan Duc	Vinus isolation		
Ms. Tren Thi Nguyen Hon	Real Time RT-PCR		
Mr. Nguyen Viet Honng	Sample collection		
Ms. Houng Vu Mai Phuong	RT-PCR (seasonal influenza)		
Ms. Tren Thi Thu Huong	Culture cell maintenance		
Ms. Pham Thi Hiss	Serology (HI)		
Mr. Nguyen Kim Tan	Electropheresis		

Plinthenas inb staff	Responsible work		
Dr Phan Van Tu	Head, supervision		
Dr Nguyen Thanh Long	RT-PCR diagnosis		
Mr Tran Ngoc Phuong	RT-PCR diagnosis		
Ma Niguyen The Nigoc	RNA extraction		
Ms Nguyes Thi Mhung	Preparation of master mix		

Need to recruit long term experts. Lack of influenza expert who can diagnose A/H5N1 property.



#### External Quality Assessment Programme for the detection of H5 RNA by RT-PCR

- Pilot study (Vietnam & Cambodia)
- Educational purpose (qualitative & quantitative)
- Serially diluted dried RNA extract (stable & low cost for shipment)
- · Deliver 2 panels / year
- In cooperation with the Public Health Laboratory Centre in Hong Kong



### Problems of bi-lateral program

- · Overlap training programme
- Different methods & materials
- · No information sharing
- Difficult to track specimens and test results







# Requirement for Lab expert

- To assess AI diagnosis capacity and tested results including biosafety situation
- · To perform and guide proper AI diagnosis
- Long term (3 6 month)
- · Proficient in English



