Emerging Viral Diseases in South-East Asia and the Western Pacific: the Importance of Biosecurity and the Dilemma of Dual-Use

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Format of the Presentation

1. A brief introduction of the concept of emerging viral diseases, with examples, and their potential economic consequences.

2. A brief discussion of three recent emerging diseases in South-East Asia and the Western Pacific: Nipah virus, SARS-coronavirus and new LCM-like virus, from different perspectives.

3. Some of the problems exemplified by these viruses, and an introduction of the concept of dual-use, and the need for biosecurity for highly-virulent infectious agents.

4. The importance of surveillance, and the role of WHO.

Emerging diseases: definition

- **New diseases which have not been recognised previously.**
- **Known diseases which are increasing, or threaten to increase, in incidence or in geographic distribution.**

  The diseases of most concern are those that may have international significance – either as a possible global epidemic or pandemic, or because they pose a risk for travellers with high case fatality rates or because they have trade implications.

Emerging viral diseases – the importance of animal reservoirs

- Over 75% of all emerging viruses over the past two decades have been zoonotic (transmitted from an animal source);

- Most of these viruses have come from either bats (particularly fruit bats), rodents or birds – for others, the hosts have yet to be determined;

- Thus the importance of understanding wildlife diseases and the role of wildlife in disease emergence cannot be understated, and there is strong belief that wildlife diseases should be a major component of global surveillance strategies.

EMERGING VIRUSES: RECENT EXAMPLES

2007 - NIPAH VIRUS (Bangladesh, India)
- *LCM-LIKE VIRUS (Australia, ex Balkans)
- *POLYOMA-LIKE RESP. VIRUS (Australia)

2006 - CHIKUNGUNYA (SW Indian Ocean, East Africa, India, Sri Lanka, Indonesia)
- AVIAN INFLUENZA (H5N1) (Egypt, Iraq)
- WEST NILE (Argentina)
- RIFT VALLEY FEVER (Kenya, Somalia, Tanzania)
- *NEW HUMAN RHINOVIRUS (USA)

2005 - AVIAN INFLUENZA (H5N1) (Cambodia, China, Indonesia)
- MARBURG IAngola)

2004: - AVIAN INFLUENZA (H5N1) (Thailand, Vietnam,)
- NIPAH VIRUS (Cambodia)
- *HUMAN CORONAVIRUS NL63

2003: - *SARS CORONAVIRUS

2001: - *HUMAN METAPNEUMOVIRUS
NIPAH VIRUS (Bangladesh, India)

2000 - RIFT VALLEY FEVER (Mid. East)

1999 - *NIPAH VIRUS (Malaysia)
- INFLUENZA H9N2 (HK)
- WEST NILE VIRUS (USA)

1998 - *SEN VIRUS (Italy)
- JAPANESE ENCEPHALITIS VIRUS (Australian Mainland))

1997 - *ALKHURMA VIRUS (Saudi Arabia)
- *MENANGLE VIRUS (Australia)
- INFLUENZA H5N1 (HK)
- *TT VIRUS (Japan)

1996 - *AUST BAT LYSSAVIRUS
- WEST NILE (Romania)

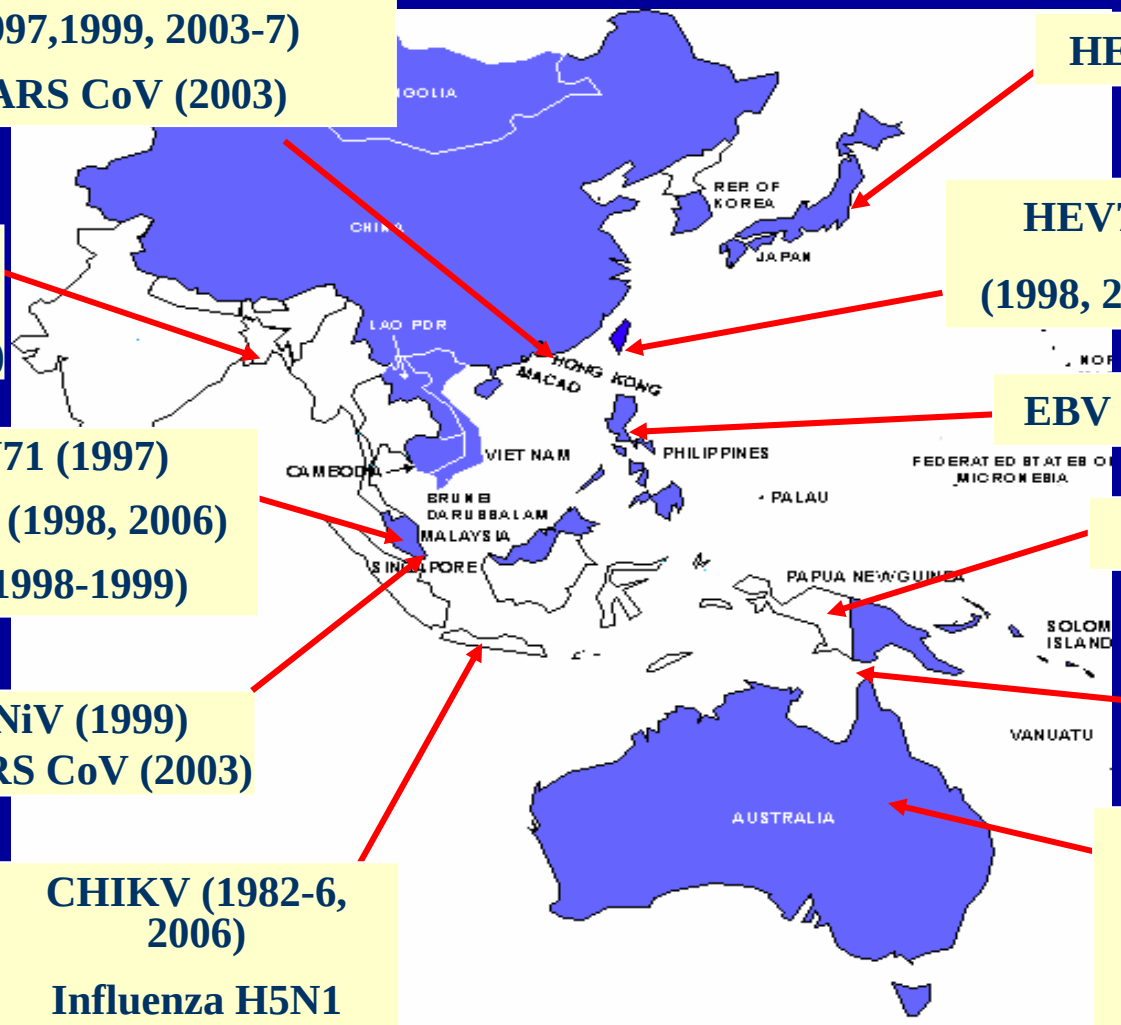
1995: - JAPANESE ENCEPHALITIS VIRUS (Aust. Torres Strait)
- *HUMAN HERPESVIRUS 8
- *HEPATITIS G

1994: - *HENDRA VIRUS (Australia)
- *SABIA VIRUS (Brazil)

1993: - *SIN NOMBRE VIRUS (USA)

White = human, no animal reservoir; yellow = initial zoonotic event; Orange = zoonosis.
* = novel virus which has not been seen previously.

EMERGING DISEASES IN THE ASIA-PACIFIC



Influenza A (H5N1)
(1997,1999, 2003-7)
SARS CoV (2003)

HEV71 (1997)

NiV
(2001, 2003,
2004-5, 2007)

HEV71
(1998, 2000)

EBV Reston (1989)

HEV71 (1997)
CHIKV (1998, 2006)
NiV (1998-1999)

JEV (1997-1998)

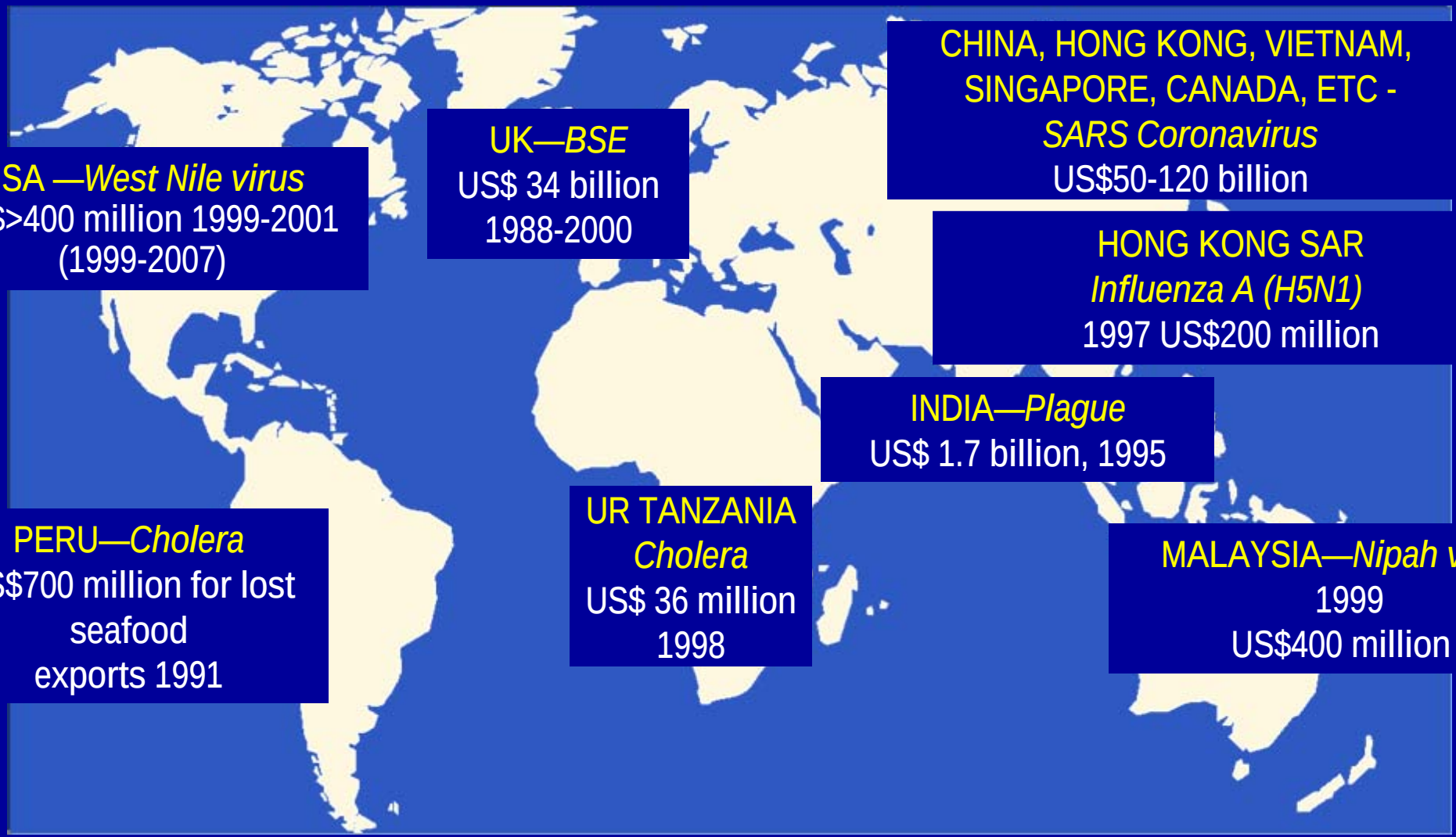
JEV (1995-1998,
2000-2006)

NiV (1999)
SARS CoV (2003)

CHIKV (1982-6,
2006)
Influenza H5N1
(2005-7)

HeV (1994, 1995)
ABLV (1996, 1998)
MENV (1997)
JEV (1998, 2004)
LCM-likeV (2007)

Economic impact, selected infectious disease outbreaks, 1990–2006



CDC, 2005

Three recent examples of novel emerging diseases in South-East Asia and the Western Pacific, but looked at from different viewpoints:

- **Nipah virus – the disease and its implications**
- **SARS-coronavirus – the outbreak, its aftermath, and the importance of biocontainment.**
- **New LCM-like virus causing encephalitis**

Nipah Virus: a Novel Virus from Pteropid Bats

A virus which came to light as the aetiological agent of a highly fatal disease of pigs and humans, Peninsular Malaysia, 1999

New viruses from fruit bats

1994 – Hendra virus (Australia)

1996 – Australian bat lyssavirus (Australia)

1997 – Menangle virus (Australia)

1999 – Nipah virus (Malaysia)

2000 – Tioman virus (Malaysia)

2001 – Nipah-like virus (Bangladesh)

THE NIPAH OUTBREAK

- Early cases of encephalitis in Perak, north of Kuala Lumpur.
- First thought to be Japanese encephalitis (JE), and extensive immunisation was carried out with JE vaccine.
- However, human cases were observed in vaccinated individuals and pigs were dying, not a normal symptom of JE in pigs
- Unfortunately, communication between medical and veterinary authorities was poor.
- Outbreak then exploded in early March 1999 in Negeri Sembilan, an area of intensive small-holding pig farms near to Kuala Lumpur.

IMPACT OF THE OUTBREAK: PEOPLE

Malaysia:	**282 cases**	**105 deaths**
Singapore:	**11 cases**	**1 death**

No new cases occurred after the outbreak, but further deaths were observed in individuals who had recovered but suffered from relapses.

Demographics - Human Cases (N=282)

Median age – 38 (1-75)

Gender: Male 230 (82%)

Ethnicity:

- Chinese 198 (70%)
- Indian 48 (17%)
- Malay 7 (2.5%)
- Nepalese 7 (2.5%)

Occupation:

Pig farmer 221 (78%)
Lorry driver 7 (2.5%)
Abattoir worker 4 (1.4%)
Pig culler 4 (1.4%)
Other 39 (14%)
No pig contact 8 (2.8%)

NB: No human-to-human cases

IMPACT OF THE OUTBREAK: PIG FARMING

- Over 1.1 million pigs culled on 946 farms in the outbreak areas, and during surveillance.
- Value of 1.1 million pigs was in excess of USD 58.3m.
- Loss of capital infrastructure on farms.
- Loss of over 36,000 jobs.
- Total cost of the outbreak, in both direct and indirect costs, estimated to be in excess of USD 450m

Evidence for implicating fruit bats as the wildlife hosts of Nipah virus

Wildlife serology:

- ***Pteropus vampyrus*** **5/29 seropositive**
- ***Pteropus hypomelanus*** **11/35 seropositive**

Virus isolation – Nipah virus was first isolated from urine collected from *P.hypomelanus* on Tioman Island.

Transmission was presumed to be from bats to pigs, and then from pig-to-pig, and pigs to cats, dogs, horses and humans. NO HUMAN-TO-HUMAN TRANSMISSION.

Since the outbreak of Nipah virus in Malaysia, there has been two (and probably more) outbreaks in West Bengal, India, and a series of outbreaks in Bangladesh.

Nipah Virus Outbreaks

Dates	Location	No. cases	No. deaths	CFR(%)
Sep1998-Apr 1999	Malaysia; Singapore	265 11	105 1	40 9
Feb 2001	Siliguri, W. Bengal, India	*66*	*45*	*68*
Apr–May 2001	Meherpur, Bangladesh	13	9	69
Jan 2003	Naogaon, Bangladesh	12	8	67
Jan-Apr 2004	Goalando, Bangladesh Faridpur, Bangladesh	29 36	22 27	76 75
Jan-Mar 2005	Tangail, Bangladesh	12	11	92
Mar-Apr 2007	Kushtia, Bangladesh Nadia, W. Bengal, India	19 5	5 5	26 100

Nipah in Bangladesh, India and Cambodia

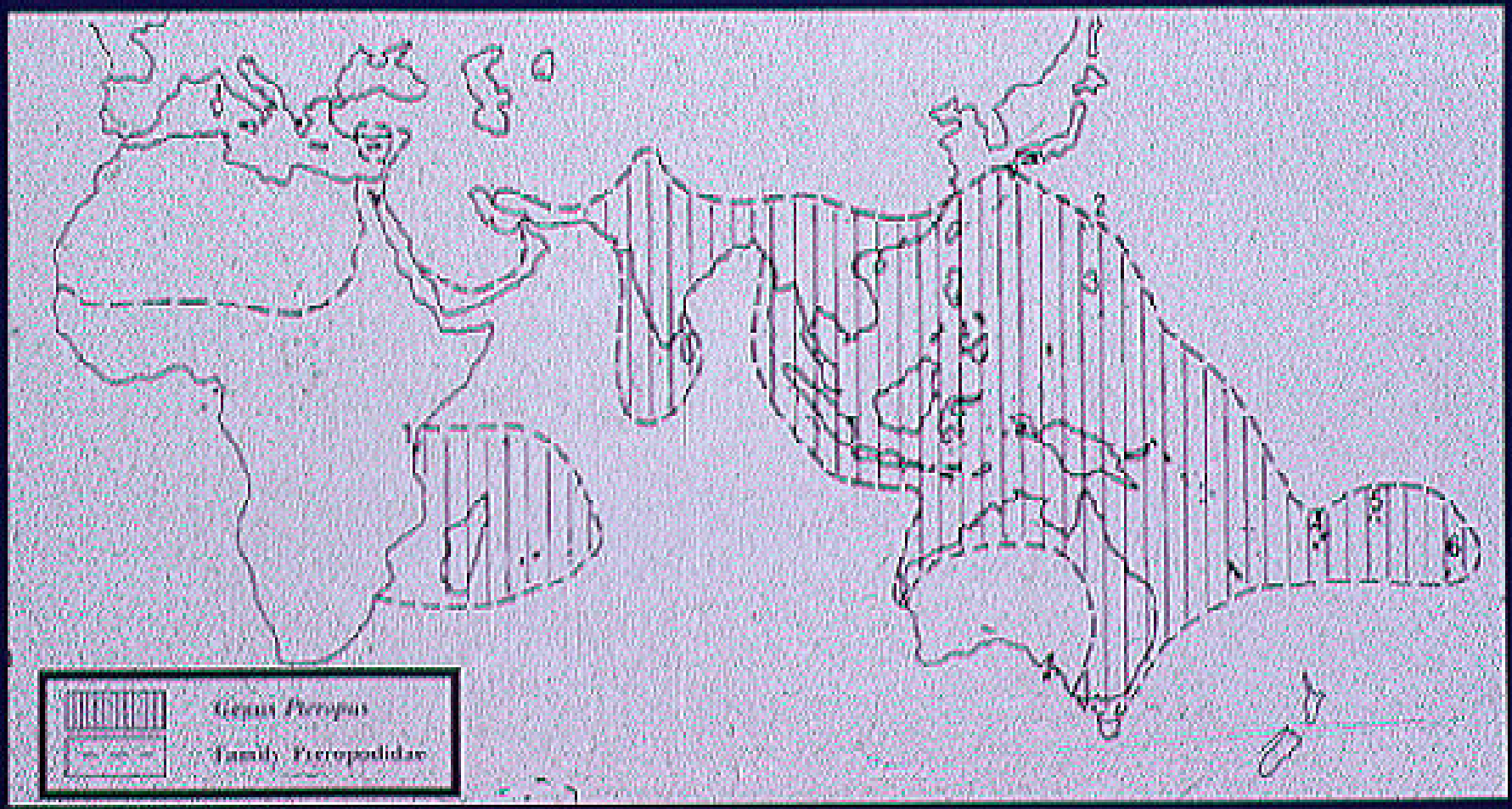
Of international concern:

Good but circumstantial evidence of human-to-human transmission in 2004 and 2005 in Bangladesh, and in 2001 in Siliguri, India. Further evidence of human-to-human transmission in 2007 in Bangladesh.

Does this indicate future pandemic potential??

- **Nipah virus may also been involved with outbreaks of disease in other parts of India.**
- **A Nipah-like virus has recently been isolated from fruit bats in Cambodia, and antibody to a Nipah-like virus has been found in Pteropid bats from Thailand and Timor Leste.**
- **Antibody to a Hendra-like virus in Pteropid bats in Papua New Guinea.**
- **Other possible henipaviruses in the range of Pteropid bats**

World Distribution of the Family Pteropodidae



SARS Coronavirus: the summary of the outbreak, the aftermath, and issues of biocontainment and biosafety.

SARS: a puzzling and new disease

- **SARS was the first severe and readily transmissible new disease to emerge in the 21st century.**
- **Much about the disease even now remains poorly understood, especially major epidemiological aspects such as super-spreading events, source of the animal reservoir, and the curious paucity of milder syndromes during the outbreak.**
- **SARS has shown a clear capacity for spread, and has a high morbidity and a global case fatality rate of 9.5%, with rates over 50% in the elderly.**

Reports of respiratory infection, WHO global surveillance networks, 2002–2003

- **27 November**
  - **Guangdong Province, China: Non-official report of outbreak of respiratory illness with government recommending isolation of anyone with symptoms (GPHIN)**
- **11 February**
  - **Guangdong Province, China: WHO received a report from the Chinese MOH of an outbreak of acute respiratory syndrome with 305 cases and 5 deaths (WHO)**
- **19 February**
  - **Hong Kong, SAR China: Official report of 33-year male and 9 year old son in Hong Kong with Avian influenza (H5N1), source linked to Fujian Province, China (Hong Kong- FluNet)**

Intensified surveillance for pulmonary infections, WHO 2003

- **21 February - Hong Kong: A medical doctor from Guangdong checks into the 9th floor of a hotel in Hong Kong; he had treated patients with atypical pneumonia prior to departure.**
- **He had been infected from contact with his patients, with onset of symptoms on Feb 15. He subsequently died of SARS.**
- **He stayed on the 9th Floor, in Room 911, at Hotel M during Feb 21-22.**
- **All subsequent cases in Singapore, Vietnam, Canada, and most of those in Hong Kong can be traced back to this individual.**
- **As of June 12, 2003, 17 probable/suspect SARS cases associated with hotel M**

Continued Chronology of the Epidemic

- 28 March: Confirmation by the first WHO mission to China that the cases of atypical pneumonia in Guangdong Province were consistent with the case definition of SARS, and data from Guangdong suggestive of an animal/food association.
- 28 April - Viet Nam became the first country to stop local transmission of SARS.
- Mid June - Last cases of SARS reported to WHO.
- 5 July - WHO announced that the last human chain of SARS transmission had been broken.

A global epidemic

- **The last cases were reported to WHO in mid-June 2003.**
- **On 5th July, WHO announced that the last human chain of SARS transmission had been broken, and the outbreak had ended.**
- **Cases were reported by 30 countries in 6 continents based on WHO's surveillance case definition.**
- **Cumulative total 8098 cases and 774 deaths; 21% HCWs.**
- **This almost exceeded the surge capacity of acute care facilities and public health services in several countries.**
- **A number of social, political and economic impacts, including psychosocial impact, were recognised.**
- **The economic cost was estimated to be $US100 billion (Nature); $US48 billion in China alone (Chinese Center for Economic Research);$50-130 billion (Asian Development bank).**

Global SARS Figures*

Country	No. of Cases	HCWs	Deaths (CFR)
China	5,327	19%	349 (7)
Hong Kong	1,755	22%	299 (17)
Taiwan	346	20%	37 (11)
Canada	251	43%	43 (17)
Singapore	238	41%	33 (14)
Other	182	25%	13 (7)
Total	**8,098**	**21%**	**774 (10)**

*Source: WHO, data through Sept. 26, 2003

Routes of transmission and infectious dose

- Contact and droplet spread through close person to person contact
  - Within 1 metre
  - Sustained exposure or short, intense exposure
  - Breaches in infection control
- Aerosol generating procedures
- Fomites (intense environmental contamination in hospitals, Hotel M, Amoy Gardens)
- ?Faecal-oral (Amoy Gardens)
- ?Faecal inhalation (Amoy Gardens)
- ?Aerosolisation rarely (airline transmission)

The role of WHO in the SARS outbreak

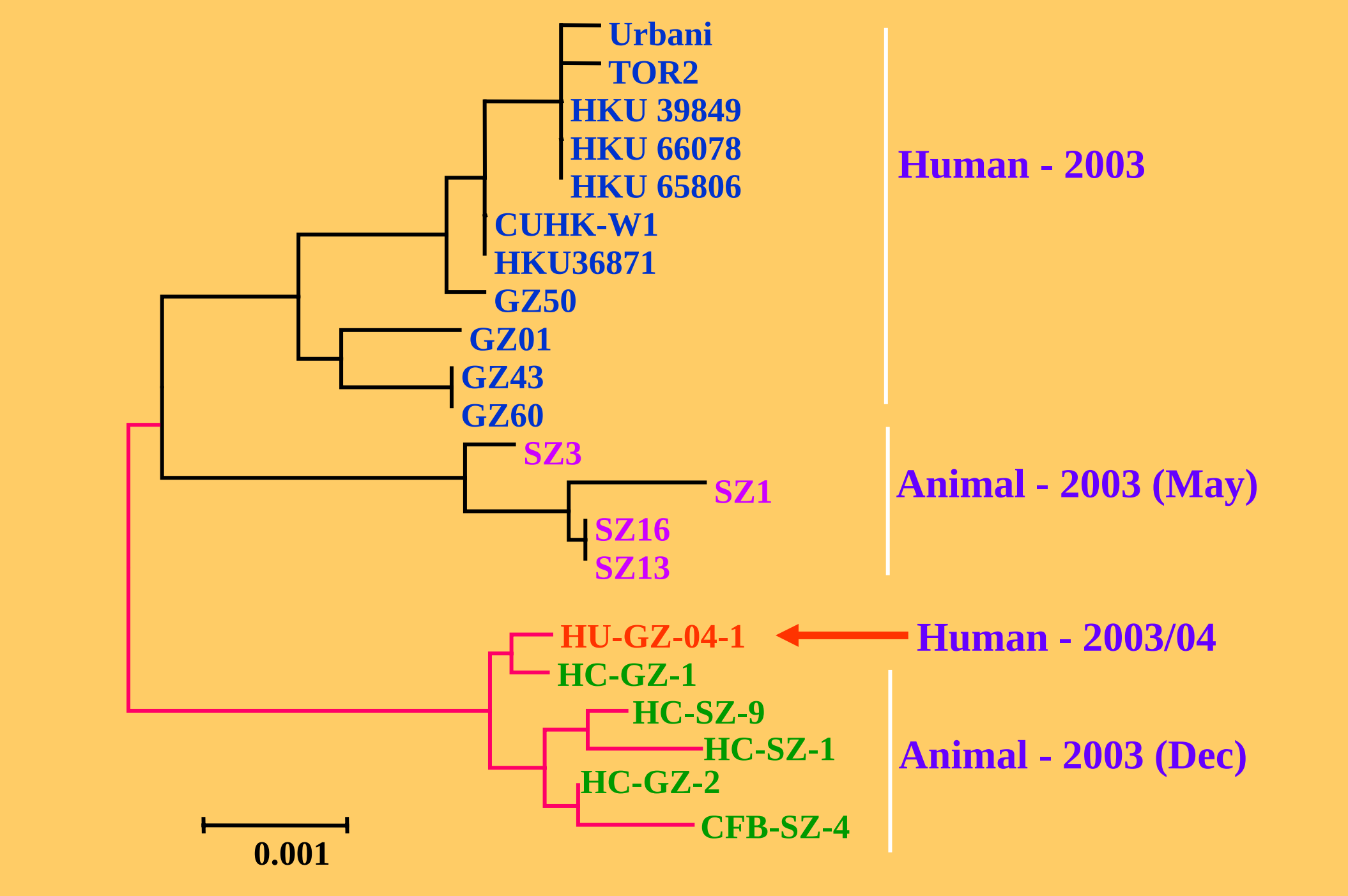
- SARS Global alerts 12 and 15 March, 2003.
- Travel recommendations - to government, industry& the public.
- Global surveillance - case definitions, risk assessment.
- Creation of SARS virtual networks.
- Guidance documents or statements:
  - clinical case description, clinical alert, diagnosis and clinical management of patients and contacts, hospital infection control, discharge policy
  - laboratory sampling and testing of SARS-CoV, laboratory case definitions, virus stability and resistance, virus detection and survival in food and water,
  - food safety, blood safety, biosafety guidelines for handling SARS specimens.

Post epidemic cases of SARS-CoV infection

- Since the end of the SARS epidemic there have been 14 recognised cases of SARS-CoV infection. These have been:
- Four cases of laboratory-acquired infection; one in September in a BL3 laboratory in Singapore, one in December in a BL4 laboratory in Taiwan, and two cases from the Institute of Virology in Beijing;
- The two cases of laboratory-acquired infection in Beijing gave rise to seven further cases and one death, with three generations of cases, in Beijing and Anhui Province; and
- Three confirmed naturally-acquired cases and one possible case in Guangdong, southern China in December 2003-January 2004, all of which were relatively mild, and no further human-to-human transmission occurred.

Chinese cases of post epidemic SARS: Dec 2003-Jan 2004

- The naturally-acquired Chinese cases appeared to be much milder than those during the epidemic.
- There was no evidence of animal exposure, except for the second case which was that of a waitress working in a restaurant serving Himalayan palm civet.
- The third case ate at a nearby restaurant (next door?), but not one serving civet.
- There is no known connection between the 4 cases.
- No other evidence of any prior or onward transmission.
- Sequences from the first case were different from previous human isolates, and more closely aligned to recent civet isolates (next slide).
- It was on the basis of these latter findings that the Chinese government elected to cull of civets in Guangdong.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HC-GZ-2
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Human - 2003
Animal - 2003 (May)
Human - 2003/04
Animal - 2003 (Dec)

Arenaviruses

- All rodent transmitted, and each believed to have evolved with its own specific rodent host species.
- Main members:

  - Lymphocytic choriomeningitis (LCM) virus, found worldwide and associated with *Mus musculus*;

  - Lassa fever virus, found in West Africa;

  - Machupo (Bolivian), Junin (Argentinian), Guanarito (Venezuealan), Sabia (Brazilian) etc – all South American haemorrhagic fever viruses, and most with significant mortalities

A novel LCM-like virus

- A new LCM-like virus recently discovered in Australia.
- Index case had recently returned from southern Europe. Hospitalised and subsequently died in Melbourne.
- He donated liver and kidneys to three recipients, all of whom died from encephalitis, three days apart.
- A new, previously unknown LCM-like virus was detected using new genomic technology (4 5 4 blast search) in the US, and. this virus has now been cultured by the laboratory in Melbourne.

Messages from these three examples

We can take a number of messages from these three examples which relate to biosecurity and biosafety. These include:

- The importance of animal reservoirs in undertaking risk assessments;
- That novel emerging diseases can occur at any time, and thus the need to take adequate precautions in laboratory diagnosis;
- That laboratory accidents can happen at any time if facilities are sub-standard or not maintained, or if training is poor or even absent; and
- The importance of on-going global surveillance in real-time, and to monitor for possible changes in natural transmission patterns.

So where does all this bring us to to-day??

The problems….

- We need to have better and broader surveillance, and for political reasons, this can only be achieved by WHO in collaboration with ALL member countries and working under the aegis of the new International Health Regulations;
- We need to ensure that we have a truly international outbreak response capability at both global and regional levels through WHO, and particularly to avoid any one country dominating the response activities, and to avoid bilateral outbreak response agreements which might prevent sharing of knowledge and strains;
- We need to ensure that there is a widely available forensic detection capability by a system of international sharing of strains and reagents by regional reference laboratories.
- We need to have better understanding of the dual-use dilemma by scientists and clinicians from first year undergraduate level, so it becomes ingrained in their early scientific/clinical life;

…….continuing….

- We need to ensure that potential for dual-use is widely taught in scientific, medical, veterinary, dental, and environmental sciences;
- We need to realise that Increasing numbers of laboratories will have the potential of handling highly infectious agents either unknowingly through their diagnostic responsibilities, or knowingly as part of their research programmes.
- We need to ensure that all countries have legislation about the design of labs to ensure their level of biosafety, of training for the lab workers, of safe work practices, and for the training of all lab workers.
- We need to ask whether all countries comply with an internationally-recognised agent classification list.

Introducing the Dual-Use Dilemma

We all acknowledge the importance of biosecurity and biosafety with respect to handling and storing highly infectious agents, especially the need to avoid accidental laboratory-acquired infections or even worse, the accidental release into the community, **but** we must also recognise that these same agents could be used for harmful purposes by those who wish us (or others) ill through bioterrorism. This represents the dual-use dilemma - that while we wish to work with these agents, we need to be mindful that they can be mis-used and therefore need to be subject to certain levels of secure biocontainment. We also have an ethical expectation to ensure that our colleagues and students are aware of this dilemma.

Biosecurity

- **This can be done by top-down and bottom-up approaches.**
- **The top-down approach is through various avenues, but particularly through the Biological Weapons Convention that most states are party to, and by national legislation to legislate for biocontainment and for adherence to the concept of select agents.**
- **The bottom-up approach is through scientific and health individuals and communities recognising this dilemma and agreeing to an ethical use of pathogenic organisms for the good of humanity.**

International Union of Microbiological Societies (IUMS): Code of Ethics

The following IUMS Code of Ethics for Preventing the Misuse of Scientific Knowledge, Research and Resources was agreed to at the General Assembly of IUMS, San Francisco, 2005:

'There has always been the potential for dual application of scientific knowledge for beneficial or malicious purpose. However, current societal and geopolitical changes have increased the risk of the misuse of this knowledge. The IUMS reaffirms its major goal is to promote research and the open exchange of scientific information for advancement of the health and welfare of humankind and the environment and strongly discourages any uses of knowledge and resources to the contrary. In particular, the IUMS strives to promote ethical conduct of research and training in the areas of biosecurity and biosafety so as to prevent use of microorganisms as biological weapons and therefore to protect the public's health and to promote world peace.'

Select Agent Lists

- There are a number of different ‘select agents’ lists.
- The major ones are the US Homeland Security, the US USDA, and the ‘Australia Group’ list.
- The ‘Australia Group’ list refers to those requiring export controls, whereas the HHS and USDA lists refers to those which are considered serious ‘dual-use’ agents.
- They all differ slightly, but in essence, all BL4 agents and many BL3 agents are listed.
- The following slides provide a compendium of some of the major agents on various lists, but note that NOT all agents fall into all lists.
- Compliance with these lists is legally enforced in some countries, but whether there is punitive legislation or not, it is extremely important that the lists are scientifically creditable if they are to be widely accepted by the scientific community.

Export Control of Viruses with Potential for Dual-Use

Australia Group list

Alphaviruses:	**Chikungunya virus**
	Eastern, Western and Venezuelan equine encephalitis viruses
Flaviviruses:	**Dengue viruses**
	Tick-borne encephalitis viruses (incl. Kyasanur Forest, Louping Ill, Omsk Haemorragic fever, Powassan viruses)
	Japanese encephalitis virus
	Murray Valley encephalitis virus
	Yellow fever virus
	St Louis encephalitis virus
	Rocio virus
Filoviruses:	**Ebola virus (Sudan/Zaire/Cote d'Ivoire/Reston)**
	Marburg virus
Arenaviruses:	**LCM, Lassa, Sabia, Machipo, Junin, Guanarito viruses**
Hantaviruses:	**Hantaan, Seoul, Dobrava, Puumala, and Sin Nombre viruses**
Henipaviruses:	**Nipah virus**
	Hendra virus
Coronaviruses:	**SARS Coronavirus**
Phleboviruses:	**Rift Valley fever virus**
Nairovirus:	**Congo-Crimean haemorrhagic fever virus**
Poxviruses:	**Monkey pox, Variola, Whitepox**

Orange = viruses found in SE Asia and W Pacific

Viruses of Potential Dual-Use Concern: HHS & USDA Select Agent List – as of 23 Feb 2006

Alphaviruses: Eastern and Venezuelan equine encephalitis viruses

Flaviviruses: Japanese encephalitis virus, Classical swine fever
Tick-borne complex (incl. Kyasnur Forest, Omsk, RSSE, etc)

Arenaviruses: Lassa fever, South American Haemorrhagic fever viruses (Junin, Machupo, Sabia, Guanarito, Flexal viruses)

Filoviruses: Ebola viruses (Zaire, Sudan, Cote D'Ivoire, Reston); Marburg

Poxiruses: Camel-, Goat-, Sheep- Monkey-pox, Lumpy skin, (Smallpox)

Henipaviruses: Nipah virus, Hendra virus

Paramyxoviruses: NDV (velogenic), PPR, Rinderpest, Menangle

Myxoviruses: Avian influenza (Highly pathogenic), 1918 reconstructed virus

Bunyaviruses: CCHF, Akabane, Rift Valley fever,

Rhabdoviruses: VSV

Reoviruses: African horse sickness, bluetongue

Herpesviruses: Herpes virus B, Malignant catarrhal virus

Others: FMDV, African swine fever, Swine vesicular disease.

RED = HHS list of human disease viruses (some are on both HHS and

Some Additional Non-Viral Biological Agents of Concern

Rickettsia:	**Coxiella burnetii**
	Ricettsia prowazeki
Bacteria:	**Bacillus anthracis**
	Brucella abortus
	Brucella melitencis
	Clostridium botulinum
	Francisella tularensis
	Burkholderia mallei
	Burkholderia pseudomallei
	Salmonella typhi
	Shigella dysenteriae
	Vibrio cholerae
	Yersinia pestis
	Clostridium perfringens
	Enterohaemorrhagic Escherichia coli, serotype 157 and others

But, surveillance is the key to detect any miss-use of novel, virulent infectious agents – through WHO

- In WHO, this is undertaken by the Alert and Response Operations group within the Division of Communicable Disease Surveillance and Response.
- The rationale in Alert and Response Operations is that the earlier an outbreak can be detected, the sooner it can be controlled;
- Thus speedy identification and rapid verification are essential;
- And once verified, if deemed to be of international significance, there is a need to put in every possible effort for its control.

Responding to the unexpected

WHO Alert and Response Operations

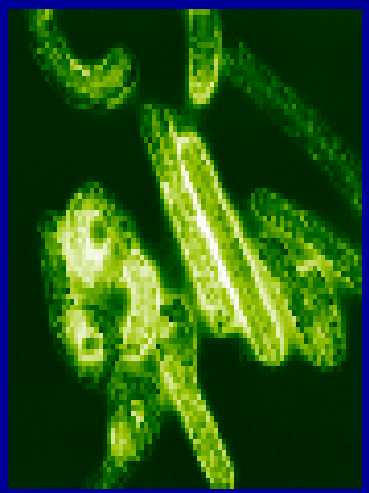
- **24 hours / 7days** a week, on call.
- ~ 200 events of potential importance verified, in each year.
- 350 advices/assistance provided.

- Since 2000, international outbreak response coordinated through the Global Outbreak Alert & Response Network (GOARN).
- GOARN has provided assistance to 106 outbreak events globally, of which 89 were responded to by GOARN in 54 countries
- The process is follows a pathway of detection, verification, intervention/response.

Human-made "bio-risk" increasing

Accidental and deliberate release of infectious agents

- Serious biosafety incidents (e.g. SARS 2003-2004; Ebola 2004)
- WHO presentation at the Convention on Biological and Chemical Weapons, 2004
- Increased concerns during mass gathering events (e.g. Olympics)
- **The need to keep in mind the dual-use nature of many of the highly pathogenic emerging diseases.**

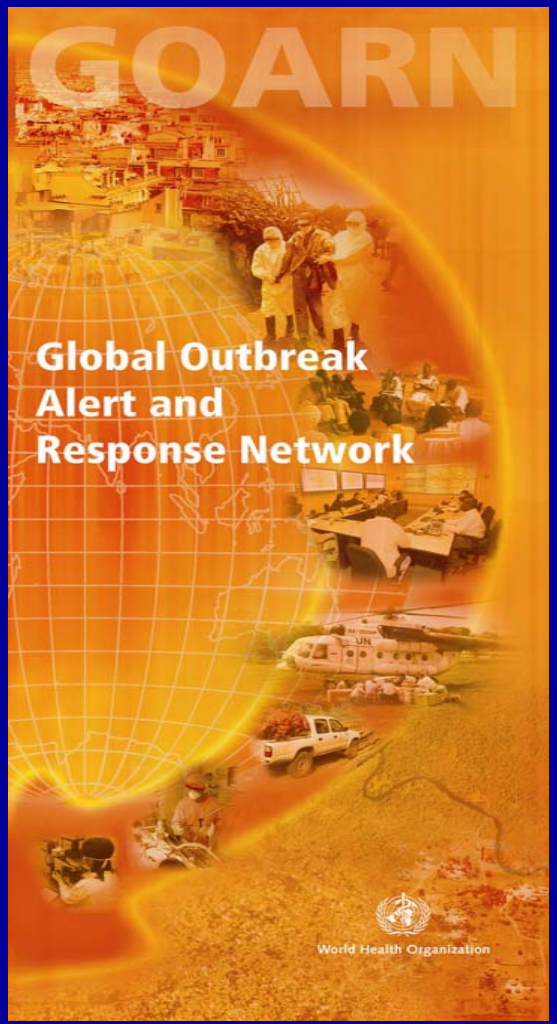


No institution has all the capacity to respond

The Global Outbreak Alert and Response Partnership

- In 2000, to help it fulfil these expectations, WHO developed a global partnership with over 100 other organizations and NGOs in order to provide the personnel and resources for outbreak investigation and control. In so doing, WHO accepted a coordinating role.
- This partnership is the Global Outbreak Alert and Response Network, or GOARN.

GOARN's Primary Aims



- **Assist countries with disease control efforts** by ensuring rapid appropriate technical support to affected populations
- **Investigate and characterize events and assess risks** of rapidly emerging epidemic disease threats
- **Support national outbreak preparedness** by ensuring that responses contribute to sustained containment of epidemic threats

HIGH-LEVEL PLENARY MEETING
OF THE 60TH SESSION OF
THE GENERAL ASSEMBLY
14-16 SEPTEMBER 2005

Para 57 (e)…

Ensure the full implementation of our obligations under the International Health Regulations adopted by the 58th World Health Assembly in May 2005, including the need **to support the Global Outbreak Alert and Response Network** of the World Health Organization

– Secretary-General Kofi Annan

EVERYONE'S
A DELEGATE
Ad campaign