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NTS ALERT

Update on Infectious Diseases

The Emergence of Virtually Untreatable TB Strains: XDR-TB

The incidence of **Extensively Drug Resistant Tuberculosis** (XDR-TB) has been recorded for some years around the world, however previously these cases were relatively isolated. Recent surveys of drug resistance in many countries indicate that XDR-TB cases have been reported in increasing numbers. In March 2006, researchers began to recognize the emergence of highly resistant TB strains as a global threat.

Concerns were heightened last August by a cluster of XDR-TB cases in an area of South Africa with high prevalence of HIV. 52 out of 53 patients died in an average of 25 days after samples were taken for drug resistance tests. This May, researchers have reported two cases of TB in Italy that were resistant to every single drug currently available to treat the disease.

The World Health Organization (WHO) has also found high levels of **multi-drug resistant tuberculosis (MDR-TB)** in Baltic countries, Eastern Europe and Central Asia. MDR-TB usually has to occur before XDR-TB arises. There are an estimated 424 000 new cases of MDR-TB each year, and the disease is most frequent in the countries of the former Soviet Union and in Asia. The cost of treating MDR-TB can be 1000 times more than treating standard TB.

WHO Director-General Dr. Margaret Chan has labelled XDR-TB as 'a threat to the security and stability of global health.' There are an estimated 25 000 to 30 000 new cases of XDR-TB every year and 37 countries have confirmed cases of XDR-TB. The disease is currently virtually untreatable.

In this edition

What is MDR-TB and XDR-TB?

MDR-TB (Multidrug Resistant Tuberculosis) describes strains of tuberculosis that are resistant to two TB drugs - isoniazid and rifampicin, these drugs are the two most important and powerful anti-tubercular drugs used in the standard first line treatment of the disease.

XDR-TB (Extensively Drug Resistant Tuberculosis) is MDR-TB that is resistant to any fluoroquinolone (a family of antibiotics), and at least one of three anti-TB second-line drugs (capreomycin, kanamycin, and amikacin).

There is no difference in the speed of transmission of regular TB and XDR-TB. In several countries with very good TB control programmes, 30% of affected people may be cured. These programmes ensure that physicians have access to laboratories that provide early and accurate diagnosis of the disease, and have all six classes of second-line drugs available for treatment by TB specialists.

Source
Drug and multidrug-resistant tuberculosis, *World Health Organization website*

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How does regular TB become XDR-TB?

One in three people in the world is infected with dormant TB bacteria. These bacteria may become active when a person's immunity is low. HIV patients are thus highly susceptible to becoming infected.

TB can usually be treated with a course of four standard, or first-line, anti-TB drugs. If these drugs are misused or mismanaged, **multidrug-resistant TB (MDR-TB)** can develop. MDR-TB takes longer to treat and requires expensive second-line drugs, which also have more side-effects. XDR-TB can develop when these second-line drugs are misused or mismanaged, rendering these drugs ineffective.

Drugs mismanagement is often manifested through incorrect drug prescribing practices by providers, poor quality or erratic supply of drugs, and patient non-adherence. Drug resistance also arises due to the improper use of antibiotics in chemotherapy of drug-susceptible TB patients.

Sources
Drug and multidrug-resistant tuberculosis, *World Health Organization website*
European Union 'faces 'TB crises', *BBC News*, 10 October 2006
New plan to contain drug-resistant TB, *World Health Organization website*, 22 June 2007

What is DOTS?

DOTS (Directly Observed Treatment, Short-course) is internationally-recommended and identified as the most effective strategy of controlling the worldwide TB epidemic today. The DOTS Strategy combines five specific elements:

- Political commitment with increased and sustained financing
- Case detection through quality-assured bacteriology
- Standardized treatment, with supervision and patient support
- An effective drug supply and management system
- Monitoring and evaluation system, and impact measurement

DOTS remains at the core of the Stop TB Strategy.

Source: DOTS, *World Health Organization* website

Latest Efforts to Control MDR-TB and XDR-TB

Major improvements have been made in the last decade to control the spread of TB, through the successful implementation of the DOTS programme, first implemented in 1994. Through DOTS, 20 million TB patients had been treated and 16 million cured by 2004. Subsequently, the first Global Plan to Stop TB was launched in 2001 and sustained till 2005. It succeeded in steering the actions needed to control TB during that period, and increased political commitment of high-burdened countries in the fight against TB.

In line with the Millennium Development Goal to "have halted by 2015 and begun to reverse the incidence" of TB, the WHO has laid out the **Stop TB Strategy** to sustain existing achievements and more effectively address remaining constraints and challenges of eradicating TB.

The main targets of the strategy:

- By 2015, reduce TB prevalence and death rates by 50% relative to 1990
- By 2050, eliminate TB as a public health problem (<1 case per million population)

The Stop TB Strategy underpins the **Global Plan to Stop TB (2006–2015),** developed by the Stop TB Partnership, a collaborative effort of more than 400 partners worldwide. This plan has to counter rising numbers of MDR-TB and XDR-TB cases all over the world.

Asia in particular, continues to bear two-thirds of the global burden of TB. India and China rank first and second respectively in terms of total number of TB cases. An emerging HIV epidemic in Asia also threatens recent progress in TB control. In some parts of China, MDR-TB is a major problem.

The Global MDR-TB and XDR-TB Response Plan 2007-2008

The WHO and the Stop TB partnership published and launched a two-year response plan, *The Global MDR-TB and XDR-TB Response Plan*

2007-2008 on 22 June. This plan sets out specific measures to prevent, treat and control XDR-TB and MDR-TB, potentially preventing hundreds of thousands of cases of XDR-TB and saving as many as 134 000 lives.

The plan emphasizes the urgent need to boost basic TB control and to target investment in key areas:

- Strengthening programmes to treat drug-resistant TB
- Building capacity in diagnostic laboratories
- Expanding infection control and surveillance
- Funding research into new and improved diagnostics, drugs and vaccines
- Strengthening advocacy, communication and social mobilization for sustained political commitment to eliminating TB
- Pursuing resource mobilization at global, regional and country levels

The plan aims to achieve a ten-fold increase in detection of MDR-TB cases, and in the number of MDR-TB and XDR-TB patients being treated and cured under WHO guidelines.

The total budget for the two-year plan is US$ 2.15 billion, of which 80% is for country-specific needs. US$ 102 million is catered to essential support functions needed to fight TB drug resistance by international partners, at global, regional and national levels.

By reaching a 2015 goal of providing access to drugs and diagnostic tests to all MDR-TB and XDR-TB patients, 1.2 million lives can be saved.

Sources

The Stop TB Strategy, *World Health Organization and Stop TB Partnership*, 2006
The Global MDR-TB and XDR-TB Response Plan 2007-2008, *World Health Organization and Stop TB Partnership*, 2007
New plan to contain drug-resistant TB, *World Health Organization website*, 22 June 2007

MDR-TB and XDR-TB in Asia

The mean prevalence of MDR-TB among newly-detected, smear-positive cases in South East Asia is estimated to be low at an overall 3% and MDR-TB rates among previously untreated patients were reported to be 1.1%, 3.4% and 2.4% for **India, Nepal** and **Thailand** respectively.

The following table lists the Asian countries among the top 25 priority MDR-TB and XDR-TB countries. These numbers show the proportion of MDR-TB among **both** newly-detected and re-treatment cases combined.

Priority MDR-TB and XDR-TB Countries

Country	Estimated total number of MDR-TB cases	Estimated proportion of MDR-TB among combined cases (%)
China	139 894	8.9
India	87 413	4.1
Indonesia	10 024	1.8
Pakistan	9306	3.2
Bangladesh	7216	2.2
Vietnam	5033	3.2
Myanmar	4756	5.2
Philippines	4469	1.8

Sources

The Regional Strategic Plan for TB control 2006- 2015, *World Health Organization, Regional Office for South East Asia,* 2006
The Global MDR-TB and XDR-TB Response Plan 2007-2008, *World Health Organization and Stop TB Partnership*, 2007

An Avian Flu Update

Vietnam

Vietnamese health officials have announced that bird flu killed a 20 year-old man, the first bird flu death in the country since 2005. 43 people have died out of 97 known infections in Vietnam since the virus's re-emergence in 2005. This death however, has yet to be confirmed by the WHO.

5 people have been infected in the country this May, the first human cases of H5N1 in Vietnam in a year and a half. Cases that appear in clusters are cause for concern because it implies that the virus might have been transmitted human to human. Fortunately, these cases remain isolated.

However, incidence of the virus has been detected across the country. Vietnam's agricultural ministry reports that bird flu has spread to ducks and chickens near Vietnam's border with China. 87 ducks and chickens died of the virus on June 11 in Cao Bang province, which lies along a 311km border between Vietnam and China.

The Animal Health Department said that 690 ducks and chickens died over 2 days at eight farms in Bac Giang province, just south of the Vietnam-China border. A central province Ha Tinh was also hit, where 350 out of 2,500 ducks on a farm died from the virus. Remaining birds in both areas were culled after tests confirmed that the dead birds were infected with the H5N1 virus.

Prime Minister Nguyen Tan Dung has approved an order to import another batch of 200 million doses of bird flu vaccine to battle the outbreaks that have struck 18 provinces and two cities. Dung also emphasized the need for tight controls of Vietnam's 70 million ducks.

The Vietnam Administration of Preventive Medicine and the US Centres for Disease Control and Prevention (CDC) initiated a co-operative programme for fighting the avian flu on June 14. This five-year project will be carried out in nine provinces and cities across the country, at an estimated cost of over US $7 million.

The programme which began this April is expected to use $1.15 million in the first year. According to US Ambassador to Vietnam Michael Marine, the US has provided more than US $12 million to the government of Vietnam in support of their efforts to control bird flu.

He also emphasized that this project will create a strong partnership between the US and Vietnamese health organisations, and simultaneously complement other avian flu projects in Vietnam which were supported by the US Agency for International Development and the US Department of Agriculture.

The WHO has highlighted Vietnam's commitment and alertness to curbing the spread of avian flu, but also concedes that implementing effective measures across its 59 provinces will be challenging.

Research Drives for a Bird Flu Vaccine

The National Institute of Hygiene and Epidemiology (NIHE) in Hanoi has announced plans to start its first human trial of a locally-made H5N1 bird flu vaccine using 20 to 30 volunteers. The drug trial will be carried out with US government technical assistance.

The NIHE project is one of Vietnam's three research drives for a bird flu vaccine, along with work at the Pasteur Institute in Ho Chi Minh City and at the national vaccine producer IVAC in Nha Trang.

WHO representative in Vietnam Hans Troedsson has hinted that the UN body was likely to accept a request to grant the IVAC project up to 2.5 million dollars. Vietnam was praised by US Health Attaché Michael Iademarco for launching three different research projects in the search for a human avian influenza vaccine. Each of the three vaccines has a different background in biology.

Iademarco points out that the trials would improve the skills of Vietnamese epidemiologists

A Bird Flu Vaccine Insurance Policy?

The World Health Organization proposed a unique bird flu vaccine insurance policy, where big donors can pool resources to take out private insurance to pay for vaccines in the case of a bird flu pandemic.

WHO Director-General Dr. Margaret Chan said the organisation had been given ample preparation time than it could have hoped for ahead of an influenza pandemic. In this time, the WHO is studying various financing options for poor developing nations to receive vaccines, preventing a pandemic catastrophe that could kill millions of people. Chan points out cost-conscious donors may be against donating to buy vaccines before an outbreak, but it may be more logical for organisations to donate money to pay for an insurance policy premium.

The WHO says a pandemic of some kind of influenza is inevitable, although it is not clear when it would come and which strain of flu would cause it. The H5N1 avian influenza is causing the greatest concern. A vaccine would be the most effective way to contain the disease but they take months to formulate and manufacture. Many developing nations are concerned that drug companies will make vaccines too expensive for poorer countries.

Earlier this year, Indonesia had refused to share samples of H5N1 with the WHO unless it guarantees the samples would not be used commercially. The two sides reached an agreement in March to improve access to safe and effective H5N1 vaccines and other potential pandemic influenza vaccines.

Vaccine procurement aid for developing nations could cost about $6 billion, meeting the needs of half the world's population for a $2 a dose vaccine.

Source
WHO says studying bird flu vaccine insurance policy, *Reuters*, 13 June 2007

and help the country deal with future health threats, including dangerous new strains of the flu. Furthermore, Vietnam's long-term goal is to develop influenza vaccine capacity not only for H5N1, but also other viruses that emerge in the future.

Sources
Vietnam reports first bird flu death since 2005, *Channel News Asia*, 16 June 2007
Bird flu kills hundreds poultry in northern Vietnam, *Thanh Nien Daily*, 16 June 2007
Vietnam finds bird flu near border with China, *China Daily*, 15 June 2007
PM calls for better bird flu control, *Viet Nam News*, 15 June 2007
Vietnam and US co-operate in bird flu control, *Nhan Dan*, 15 June 2007
Vietnam plans human trial of bird flu vaccine, *France 24*, 20 June 2007

Indonesia

Indonesia's health ministry has confirmed that a 29-year-old man who died at a hospital in Pekanbaru, central Sumatra, had the H5N1 strain of bird flu virus. This man had slaughtered chickens carrying the virus, cooked and ate them. This is Indonesia's 100th case of bird flu; the country's current death toll stands at 80.

Indonesia reported its first human bird flu patient 2 years ago and has had the highest number of infections in the world. Forty percent of all human bird flu deaths have occurred in the country. Currently, three variations of the H5N1 virus can be found in Indonesia: the South Sulawesi, Bali and Sumatra strains. These variations are also found on Java.

Millions of birds kept in close proximity with humans through backyard farming, and unsuccessful educational campaigns about the disease, both contribute to the relatively higher infection rate in Indonesia. The country only has enough vaccine supplies for 10% of its backyard fowl and 30% of small chicken farms. It also lacks the logistics for transport and distribution of the vaccines.

Measures to control the spread of H5N1 virus

The National Committee for Avian Influenza Control and Pandemic Preparedness has called for vaccination to be integrated into all poultry

sectors: chicken production, transport and sales. The area and supply-chain approaches will be used to achieve this. With the area approach, regions infected with bird flu consisting of several poultry sectors will be handled together. The supply-chain approach will control the spread of the virus through infected chickens moving from one sector to another.

The Association of Indonesian Veterinarians has drafted a bill on animal health that will become a benchmark on avian influenza prevention for all Indonesian ministries. The bill specifies that the community is responsible for reporting outbreaks of any animal diseases to authorities. It also calls for the formation of a veterinary authority at the regency and municipality levels.

Other measures Indonesia has taken to keep the spread of the virus under control include collaborating with US drug manufacturer Baxter Healthcare Corp to produce and clinically test two million vaccine tablets. While Indonesia intends to use the vaccines to manage future bird flu clusters, the WHO prefers that the vaccines be stockpiled and used only in a pandemic.

Indonesia's Health Minister Siti Fadilah Supari highlights their dilemma: Last year, six out of seven infected people were killed by H5N1 virus in Karo of the North Sumatra province. This is the biggest bird flu cluster worldwide, where initially the mode of transmission (animal-human or human-human) was ambiguous. Although such clusters could be isolated cases of H5N1 virus outbreak, they could also be the potential origins of a pandemic. Using the vaccines in these severe clusters could be significant in helping the authorities put an outbreak under control.

A solution to the dispute is expected to be achieved at the upcoming meeting between the Indonesian health ministry and the WHO in July.

Source

Indonesia wants to use its bird flu vaccine directly, *China View,* 20 June 2007
Indonesia Confirms 100th Bird Flu Infection *Nippon Hōsō Kyōkai online*, 15 June 2007
Vaccines key to curbing bird flu, *The Jakarta Post*, 15 June 2007
Indonesia man becomes 80th bird flu victim-official, *Reuters*, 14 June 2007

Malaysia

67 chickens died over three days from June 2, at Kampung Paya Jaras Hilir, Sungai Buloh, Selangor. However, efforts to cull fowl have ceased as there were no more incidences of the disease. The Malaysian health ministry will apply to the WHO to be declared free from the H5N1 virus if the country does not encounter any more bird flu cases in the next 2 weeks. Up to now, Malaysia has not had any incidences of human bird flu.

The ministry has also warned the public that more than seven million people could die of bird flu if there is a pandemic in the country. Speaking at the Kuala Lumpur-Organization of the Islamic Conference (OIC) Health Ministerial Conference, the ministry's disease control division director, Datuk Dr Hasan Abdul Rahman, said that 40% of the victims would be children, between 2% and 22% of those who seek treatment will need hospitalization, and of those hospitalized, 15% will require intensive care.

Malaysia has set aside a special fund of RM 60.4 million to help fight the disease in the event of a pandemic.

Sources

Malaysia to seek WHO declaration of bird flu, *The New Straits Times*, 15 June 2007
7 million could die if bird flu pandemic hits Malaysia, *The Straits Times*, 15 June 2007

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Erratic Weather to Blame for the Surge in Dengue

In recent weeks, South East Asia has seen a sharp increase in dengue cases. Infectious diseases expert Hong Kong based Lo Wing Lok attributes this to global warming. With rising temperatures, mosquitoes are becoming more active each year, since their geographical reach expands both north and south of the equator.

Malaysia

Malaysia reports between 200 and 300 new confirmed dengue cases weekly. For the past 5 months, 48 people died from dengue, more than twice the 21 deaths for the same period last year. By May 26 this year, a total of 20,658 people in Malaysia had contracted dengue, a surge of 55 per cent over the corresponding 2006 figure. There are currently around 900 and 1,000 suspected cases a week, much higher than the usual levels of 600 suspected cases a week.

Singapore

Dengue cases have hit epidemic levels (more than 378 cases a week) since the previous outbreak in 2005. In 2005, 714 cases were reported in a single week. The country has already recorded 2,868 cases of dengue infection this year, more than twice over the same period in 2006. To date in 2007, dengue has already claimed two lives.

77 dengue clusters have been identified in the country. The local National Environment Agency (NEA) has taken to conducting house-to-house inspections in these cluster zones. Between January and May, 2014 homes were discovered to be breeding mosquitoes; this is almost double the number for the same period last year. The main method adopted by the NEA of controlling the epidemic is through eliminating breeding grounds of the Aedes aegypti mosquito, the carriers of the dengue virus.

Besides the erratic weather, the spike in dengue cases in the country has been partly a result of the lack of immunity of the population to a different dengue virus. This year, Den-2 virus is dominant instead of the Den-1 virus prevalent in the last decade. Everyone except those hit by Den-2 virus a decade ago is vulnerable to this type of dengue. Furthermore, in the 15 years up to 1990, the very low number of dengue cases then meant many Singaporeans who grew up during that period were not exposed to the virus, and thus do not have immunity to it.

To boost efforts in understanding the dengue virus and facilitate the development of prevention, treatment and eradication strategies, eleven key scientific bodies came together to form the Singapore Dengue Consortium on June 21. It is made up of both public and private health organizations, education providers, and scientific research institutes. Currently, there are no vaccines or drug therapies for dengue, and dengue prevention relies solely on mosquito control.

Indonesia

According to Indonesian Health Ministry data, the country has recorded 68 636 cases and 748 deaths by May 2007. The surge in dengue cases was partly due to the massive floods in Jakarta this February. The numbers of dengue cases have however waned in recent months towards the end of the rainy season.

Thailand

Thailand has recorded 11 000 cases of dengue fever and 14 deaths by mid 2007, an increase of 18 percent from the same period in 2006. In May 2007, a record 3649 people were diagnosed with dengue.

Sources

Dengue surge 'due to erratic weather', *The Straits Times*, 15 June 2007

Dengue cases hit epidemic levels, *The Straits Times*, 19 June 2007

New consortium formed to fight dengue in Singapore*, The Straits Times*, 21 June 2007

South East Asia battles dengue surge, *Reuters*, 14 June 2007

A buzz that could spoil your holiday, *Asia Views*, 21 June 2007

NEA says halting Aedes breeding the way to go, *The Straits Times*, 14 June 2007

Dengue: Why it's different this time around, *The Straits Times*, 21 June 2007