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The ONE HEALTH PLATFORM Communicator

it's all connected

Expert warns of disaster if lessons are not learned from Ebola outbreak

The Ebola outbreak that has swept across West Africa is the biggest ever reported, with more than 25,000 cases and more than 10,000 deaths in Liberia, Sierra Leone and Guinea. Failure to learn the lessons of this outbreak will have unthinkable consequences when the next global health emergency erupts, the director of the Center for Infection Medicine and Zoonoses Research in Hannover warns.

"7 or 8 years ago, we could have done the extensive clinical trials that are necessary to develop a preventive medicine or a treatment for Ebola. But we didn't. Because the threat was thought to be of minor importance", says Ab Osterhaus, who heads the Center for Infection Medicine and Zoonoses Research in Hannover, Germany. This statement holds an important message for public health professionals: the preparation for a public health threat must start well in advance, in "times of peace".

PROF. AB OSTERHAUS:
"WE NEED TO INVEST IN VACCINE DEVELOPMENT IN PEACE TIME."

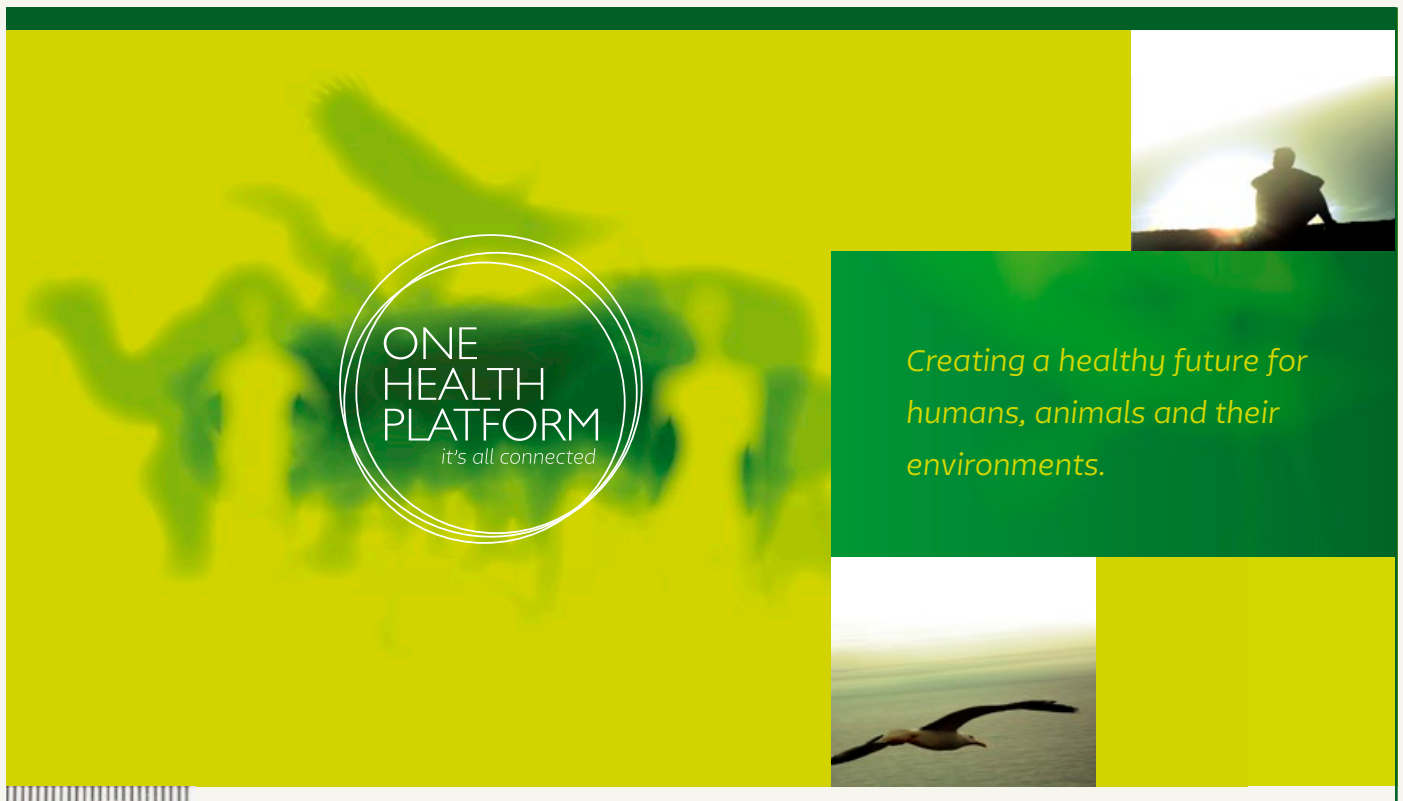
"By now, thousands of people have died from Ebola infection. The social and economic costs already amount to several billion Euros. If we had spent not more than €20 million some seven years ago, we'd have had a vaccine available at the start of the Ebola virus outbreak, which would have saved so many lives and expenses. However, we were not prepared. And are we prepared for the next virus outbreak? There is Rift Valley Fever, MERS CoV... The biggest surprise about pandemics is in fact that we are still surprised they happen. We really should invest in candidate vaccines and therapies. We need to convince the donors that this is money very well spent, that it is cost-effective in the end. We've had Ebola and we should not make the same mistake twice." ■

> " THE BIGGEST SURPRISE ABOUT PANDEMICS IS IN FACT THAT WE ARE STILL SURPRISED THEY HAPPEN."

SARS CHANGED INTERNATIONAL COOPERATION AS WE KNEW IT

BLAME THE SOOTEY MANGABEY

More stories inside



Creating a healthy future for humans, animals and their environments.

MESSAGE FROM THE EDITOR

Dear Reader,

Welcome to the first edition of The One Health Platform Communicator, a brand new periodical issued by the One Health Platform Foundation.

The foundation builds on the belief that governments, health science professionals, key opinion leaders and public health officials need to work together to attain optimal health for people, domestic animals, wildlife, and our environment. After all, the emergence of MERS CoV, the continuous outbreaks of avian influenza strains like H5NI and H7N9, the re-emergence of Ebola in West Africa and the antimicrobial resistance of an ever-increasing range of infections, have demonstrated that the health risks of our interconnected and fast-paced world continue to grow, especially in developing countries. The One Health Platform therefore creates a multidisciplinary network of leading experts, offering a framework for information-sharing, cooperation and awareness raising activities between the many parties involved in One Health.

The One Health Platform was officially inaugurated during the 3rd International One Health Congress, held in Amsterdam in March 2015. At that event, the Platform brought together public health professionals, policy makers and academics in a parallel I-day Science Policy Interface (SPI) programme. This track was specifically designed to bridge the gap between science and health policy. In a series of eleven lectures, the world's leading experts evaluated recent health crises like the outbreaks of Ebola, Q-Fever, BSE, pandemic swine flu and SARS. They also covered the most imminent public health challenges, unmasking potential killers like avian influenza, the henipavirus and Rift Valley Fever. Special attention was given to the antimicrobial resistance and the question how to avoid a post-antibiotic era, in which common infections and minor injuries can once again kill.

The Science Policy Interface has proven a successful concept to integrate science and health policy. It is a unique format for public health professionals to exchange information and ideas with their colleagues, academics and other members of the One Health Community. This first issue of the One Health Platform Communicator brings you the conference highlights in short lecture reports.

Prof. A.D.M.E. Osterhaus,
Chair of the One Health Platform

ABOUT ONE HEALTH

One Health recognizes that the health of humans, animals and ecosystems are interconnected. About 75% of new emerging human infections have their origin in zoonotic agents, meaning that they are naturally transmitted from animals to humans. Other infectious agents rely upon vectors, such as mosquitoes, ticks or sandflies to transmit from one host to the other. In addition, environmental and ecosystem health negatively influence human and animal health through issues like contamination, pollution and poor conditions that may lead to new infectious agents.

ONE HEALTH PLATFORM

An independent network organization that promotes an integrated approach to combat (re-) emerging neglected viruses, antiviral and antibiotic resistance, and bacterial and parasitic infections.

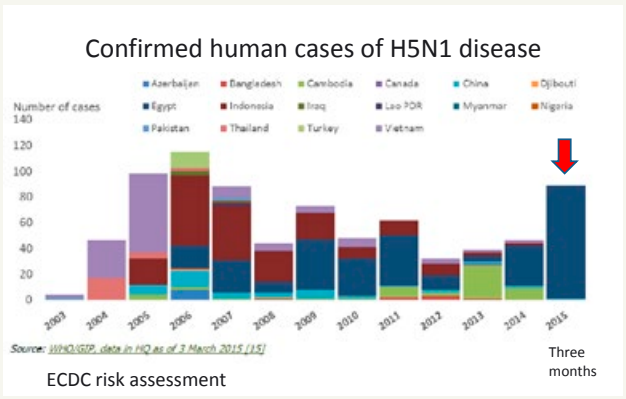
↘ **www.onehealthplatform.com**

Current One Health Coalition partners

ZOONOSES

LOOMING RESPIRATORY INFECTIONS THREAT

From influenza to MERS



▲ *2015: already large numbers of human H5NI cases in Egypt, although no change on molecular level*

H5NI AVIAN INFLUENZA

H5N6 viruses have infected humans in China, while H5N8 viruses have the potential to get established in poultry and thus also to infect humans. Research and experiments in ferret systems have demonstrated the pandemic capacity of H5 viruses. Close monitoring and surveillance is hence key.

H7N9 AVIAN INFLUENZA

A virus of even greater concern than H5NIis the H7N9 bird flu virus, which was first recognized in China in 2013. The concern relates to two basic parameters for risk assessment:

I. probability of virus becoming pandemic (Is it easily transmissible or not?)
2. impact/severity

H7N9 is of concern, because it combines high probability and high impact, as opposed to H5NI.

TRANSMISSIBILITY VS SEVERITY

Transmissibility of influenza viruses is closely related to the position in the human respiratory tract where the viruses bind. Normal seasonal influenza viruses bind in the upper respiratory tract, basically in the throat and nose. This makes it is easy to get the virus out of the body and spread. In comparison, avian influenza viruses predominantly bind in the lower respiratory tract, deep in the lungs and that makes the transmission process difficult.

So for an avian influenza virus to become a pandemic virus, it has to switch its binding position in the human respiratory tract. The binding pattern of H7N9 is hence of concern, since these viruses bind to both the upper and the lower human respiratory tract.

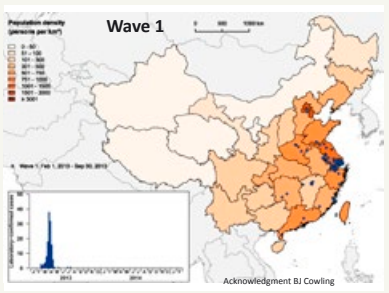
SOURCES OF INFECTION

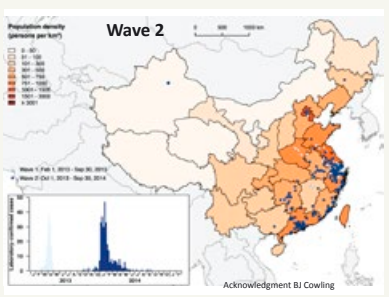
The greatest risk of infection comes from live poultry markets. Restrictions to trade, however, are very difficult to implement since a considerable part of the Chinese population (both in Hong Kong and mainland China) is dedicated to having freshly killed chicken, in spite of all the risks. To contain virus spread, Hong Kong has installed rest days in live poultry markets and a ban on keeping live poultry over night.

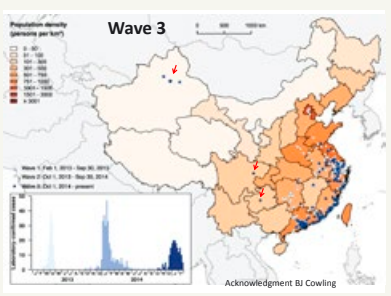
MERS COV

MERS CoV is a new coronavirus that had emerged in Saudi-Arabia in 2012. The number of human infections with MERS coronavirus is increasing still because of on-going transmission of the virus from animals to humans.

The important search for the source of infection is still going on. Camels are indicated as one animal source, but it is not exactly clear how the virus is getting from camels to humans. Or, put differently, the virus is so common in camels, so why aren't more humans getting infected? ■





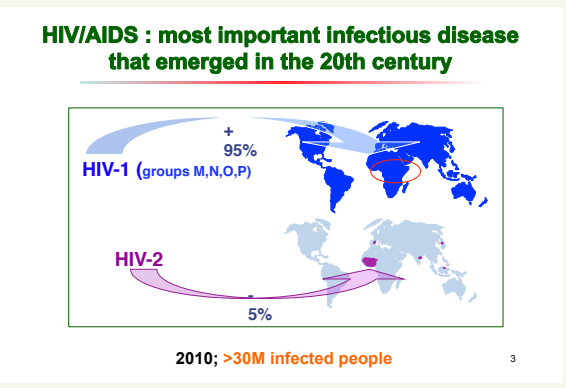


▲ *H7N9 spreading over multiple Chinese provinces in three distinct waves*

HIV: Blame the sooty mangabey

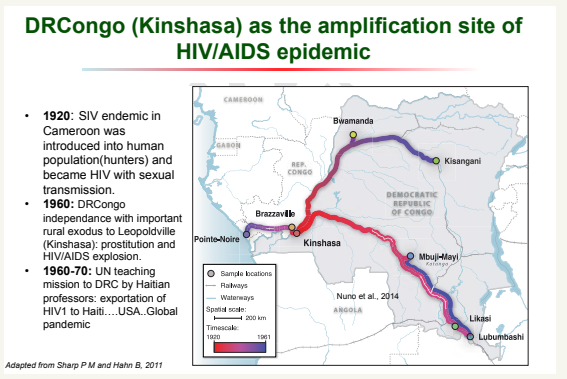
By Prof. Jean-Jacques Muyembe, Kinshasa University in DR Congo

The first research project on HIV/AIDS in Africa was established in the DRC in 1980. The major finding of the study was that HIV/AIDS was an heterosexual epidemic, in contrast to what was seen in the West. The study's main achievements included the prevention of HIV infection in high-risk women, the prevention of transmission of HIV from mother to child as well as the prevention of transmission through blood transfusion. The latter is quite important because blood transfusion is necessary in cases of anaemia caused by malaria. In addition, we were the first to show that prevalence of AIDS is high in tuberculosis patients and vice versa.



▲ *HIV/AIDS is caused by two different virus strains*

HIV is a zoonotic disease from non-human primates, more specifically HIV-2 comes from sooty mangabeys in West Africa, whereas HIV-I originates from chimpanzees and gorillas in Central Africa. Both strains have transmitted to humans due to hunting activities, i.e. hunters butchering primate bush meat. From epidemiological studies, we have derived that HIV/AIDS was introduced in the human population in Cameroon around I920 and subsequently spread via sexual transmission. The spread of HIV accelerated dramatically after the DRC gained independence, sparking an exodus from rural areas to the country's capital, leading to increased spread via sexual contacts. A Haitian professor subsequently exported HIVI from Africa to his homeland, marking the start of the global HIV/AIDS pandemic.



▲ *Spread of HIV/AIDS via railways and waterways*

Simian Foamy Virus

Little is known, however, about HIV diversity and prevalence in African animals. For example, more than 30 species of non-human primates have not been studied yet. We are now trying to monitor the history of HIV/AIDS in chimpanzees and gorillas, using non-invasive methods like stool sampling. This is an extremely important effort in light of the continued risk for transmission from non-human primates to humans. After all, more than 70% of the populations in Central and West Africa rely on bush meat as a source of animal proteins. The risk of transmission therefore continues to exist, not only for HIV/AIDS but also for new viruses, like Simian Foamy Virus. We urgently need international cooperation to provide African countries with well-equipped laboratories and well-trained staff. After all, we are at the frontline.

NEGLECTED INFECTIOUS DISEASES

Learn from HIV/AIDS to stop the **RIFT VALLEY FEVER** threat

Rift Valley Fever Virus outbreaks laid heavy burdens on people and livestock in Africa and the Middle East. What can we learn from our HIV/AIDS outbreak management to minimize the impact of Rift Valley Fever?

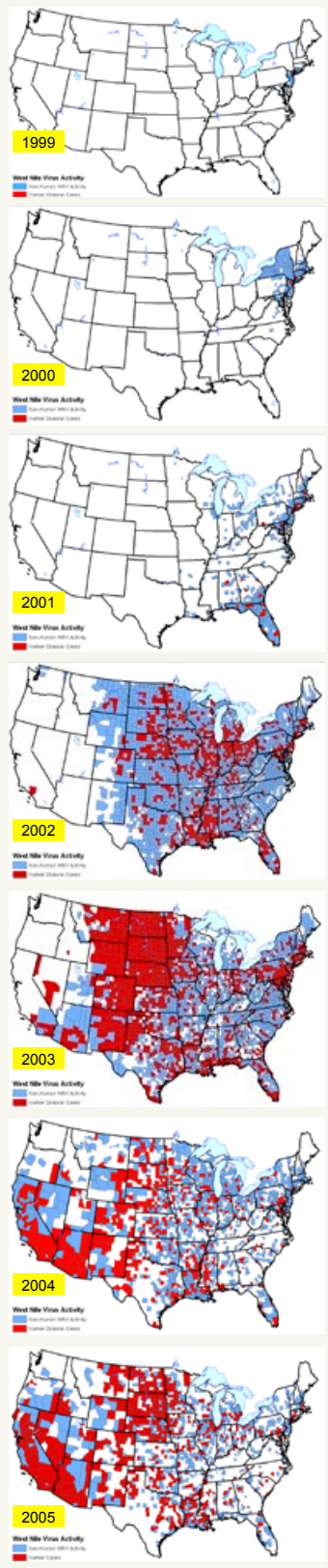
Rift Valley Fever can cause severe disease in domestic animals and humans. In adult animals (such as buffalo, camels, cattle, goats and sheep) disease causes fever, severe illness and abortions. Young lambs and calves develop a fever, become weak and may die. While most human cases are relatively mild, a small percentage of patients develop a much more severe form of the disease.

> " WE URGENTLY NEED INTERNATIONAL COOPERATION TO PROVIDE AFRICAN COUNTRIES WITH WELL-EQUIPPED LABORATORIES AND WELL-TRAINED STAFF."

IMPORTANT OUTBREAKS

- **Senegal**, Africa, 1987
- **Kenya**, 1997-1998
  - Est. 89,000 humans cases
  - 478 deaths
- **Saudi Arabia**, 2000
- First outbreak outside of Africa
- **Egypt**, 2003
  - 45 cases, 17 deaths

RVF outbreaks typically occur when areas that are normally dry experience a period of heavy rainfall and/or flooding. In these warm, moist conditions mosquitoes breed in stagnant water and can then become carriers of the disease.



Disease transmitted by mosquito can spread very fast: West Nile virus as an example

RFV is a mosquito borne disease and such disease can spread very fast as is shown by the example of another well-known mosquito borne infectious agent: West Nile virus.

ONE HEALTH SYMPOSIUM

9 March 2016

Chatham House London, UK

Scientific symposium for decision makers and public health officials

CO-ORGANIZED BY THE ONE HEALTH PLATFORM
AND THE CHATHAM HOUSE CENTRE ON GLOBAL HEALTH SECURITY

Renowned scientific experts will bring a series of tailor-made lectures, translating One Health science to policy practice on four major topics:

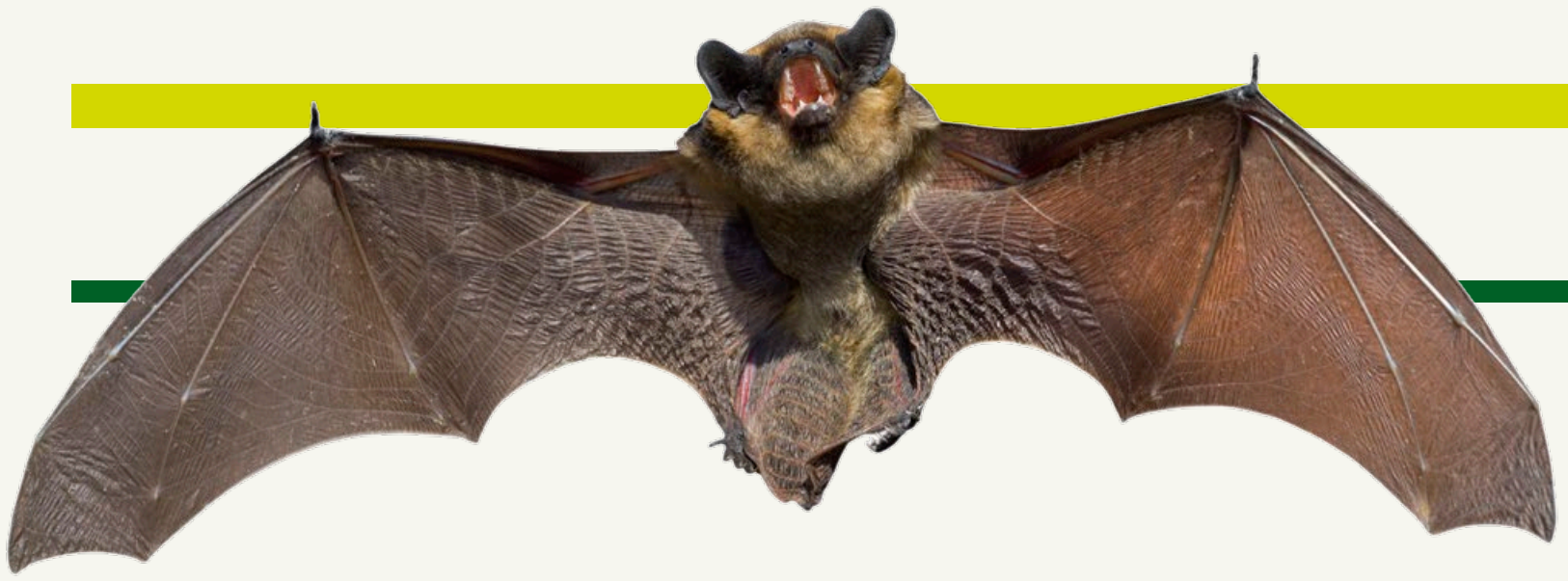
Neglected infectious diseases

(re-)emerging infectious diseases

Antimicrobial resistance

Scientific and societal intervention strategies

More information soon available at www.onehealthplatform.com



Bats may hold henipavirus threat

HENIPAVIRUS

Family: Paramyxoviridae
Genus: Henipavirus
Species:
- Hendra virus (HeV)
- Nipah virus (NiV)
- Cedar virus (CedPV)
- Several other henipa-like viruses

Henipaviruses have been emerging quietly over the past 15 years. And they definitely have the potential to cause more widespread outbreaks. "They deserve our full attention given their broad host range, capacity to repeatedly spill over to the human population, their high mortality rate in people, and their ability to be transmitted from human to human", says Jon Epstein of EcoHealth Alliance.

HENDRA VIRUS

Hendra virus was the first henipavirus to be discovered in Australia in 1994, when it spilled over to a group of race horses and eventually also infected a trainer and a veterinarian. The source of infection was soon traced back to fruit bats. Jon Epstein elaborates: "Since 1994, we have seen seven cases of human henipavirus infection, four of which were fatal, including the horse trainer who was among the first humans to be infected. In horses, we have seen about 50 different outbreaks along the east coast of Australia, with a fairly high mortality rate of 75%."

"Hendra virus does not spread directly from bats to humans or from humans to humans. So all human patients contracted the virus via sick horses. This is crucial knowledge to determine effective management strategies, as we now know it is key to limit virus spread in paddocks and horse farms. The good news is that there is an effective equine vaccine available and hence the main strategy is to vaccinate horses. An additional important measure is to protect horses from grazing under fruit trees and thus to limit exposure to bat excreta."

"THERE HAVE BEEN MORE THAN 20 NIPAH VIRUS OUTBREAKS IN INDIA AND BANGLADESH SINCE 2001."

NIPAH VIRUS

The second member of the Henipavirus group is Nipah virus, which was discovered in Malaysia in 1997 during a large outbreak in a pig farm. Scientists could rely on the knowledge gained from Hendra virus research and soon identified bats as the main source of infection. The virus causes severe respiratory and neurological disease in pigs, but does not have high mortality rates in these animals. Whereas most pigs recover, about half of the farmers who contracted Nipah virus infection from sick pigs have actually died. "In total, we have seen 265 human cases, about 40% of them were fatal due to encephalitis," according to Jon Epstein. "There was no evidence of bat-to-human or human-to-human transmission, so all human cases contracted the infection from pigs. Normally, pigs and bats do not interact, but due to the fact that fruit orchards were grown next to the pig enclosures (fruit production was a supplemental form of income), pigs got exposed to this bat virus."

NIPAH VIRUS CONTROL STRATEGIES IN MALAYSIA

- Depopulate farms during outbreak
- Ban on fruit orchards near pig enclosures in order to adjust the man-made interface between pigs and bats
- Advice not to feed dropped fruit to animals

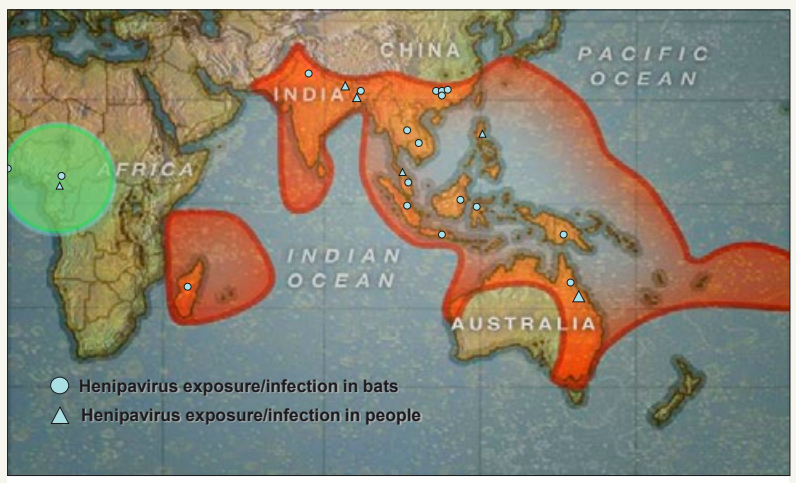
"THE MAIN STRATEGY IS TO VACCINATE HORSES."

"In contrast to the single Nipah virus outbreak in Malaysia, there have been more than 20 outbreaks in India and Bangladesh since 2001. In Bangladesh, these outbreaks mainly occur in the western part of the country, most often between November and April. Case fatality rates have been extremely high, varying from 75 to 100%. And here we do see bat-to-human and human-to-human transmission."

"The most frequent route of transmission from bats to humans appears to be the consumption of raw date palm sap. This sap is harvested by shaving the bark of palm trees allowing the sap to flow along the trunk of the tree into pots. The Indian flying fox (Pteropus giganteus) has learned to exploit this sweet juice as a food resource, contaminating the sap with its saliva, or other excreta, and occasionally Nipah virus while drinking from the sap flow. Another potential pathway is through livestock, like goats, cows and pigs." ■

NIPAH VIRUS SURVEILLANCE AND CONTROL STRATEGIES IN BANGLADESH

- One Health approach: Integration of Human & Animal Surveillance
- Active hospital surveillance (early detection of cases)
- Integrated outbreak response
- Anthropological studies to learn about modes of exposure and incentives to adopt a different behaviour
- Prevent contamination of sap (f.i. bamboo cover of sap flow)
- Public outreach/educatio
- Discussion of experimental vaccine and therapeutics use during outbreaks



▲ *Known henipavirus distribution*

SUMMARY

- Henipaviruses are omnipresent in Southeast Asia and the Pacific. The number of reported human cases is probably a small portion of the actual number of infections. Better surveillance is therefore urgently needed. After all, henipaviruses have pandemic potential and high case fatality rates.
- Human activities drive henipavirus spillover
- Education, public outreach, surveillance and further development of vaccine/therapeutics can mitigate risk

ANTIMICROBIAL RESISTANCE

"We are losing the battle for powerful and effective antibiotics."

by Dik Mevius, Professor in Antimicrobial Resistance at Utrecht University, The Netherlands

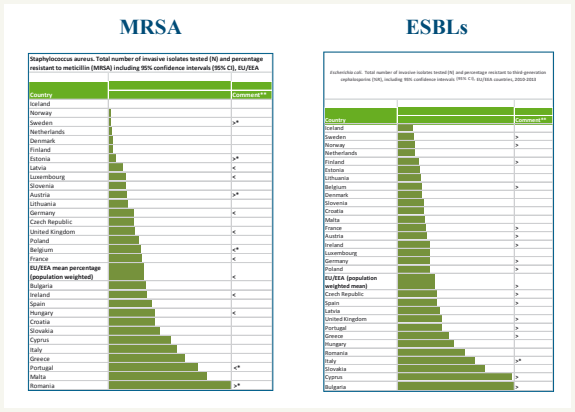
The discovery of penicillin in 1928 initiated a period of antibiotics innovation and use. No less than 14 classes of antibiotics have been introduced for human use between 1935 and 1968. However, since than only five have been introduced, and new antibiotics have selected for resistance quite rapidly. We are losing the battle for powerful and effective antibiotics.

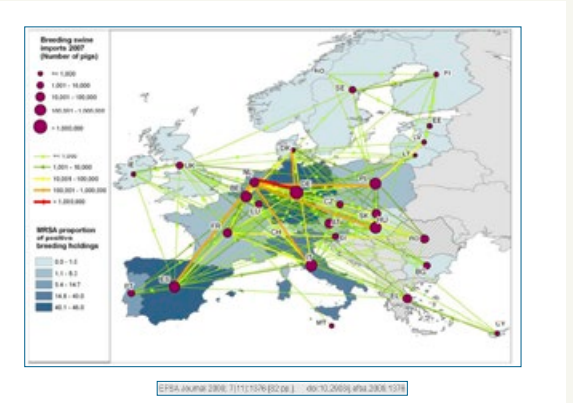
TWO EXAMPLES: MRSA AND ESBL

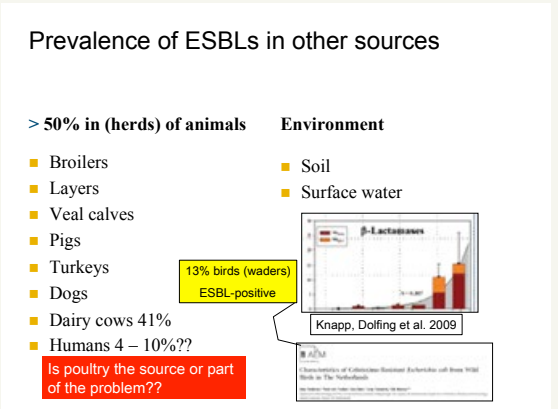
The class of beta-lactams, which includes penicillin, is the most effective and most widely used group of antibiotic in humans and to a lesser extend also in animals. Surveillance and control of organisms that are resistant to this group of antibiotic drugs is therefore of utmost importance. MRSA is an organism that is resistant to methicillin, which first appeared in hospitals and after adaptation was able to spread to the community and to livestock. ESBLs show a similar type of evolution. Initially, they were typically seen in hospitals, and as of 2000, we've seen a pandemic spread in the community, in animals and even in the food chain.

MRSA are well controlled in Northern European countries in hospitals and a decrease in prevalence is seen in most EU countries due to implementation of effective control measures in hospitals. ESBLs emerged at the turn of the century and in all EU countries there is an increase in ESBL producing organisms.
Livestock associated MRSA was first discovered in a pig farm in The Netherlands. It was soon demonstrated that pigs carried a specific MRSA variant, designated ST398, and the prevalence of ST398 could soon be linked with carriership of MRSA in humans with an occupational risk (e.g. farmers). It was also soon demonstrated that livestock MRSA was not a Dutch problem but rather a European and global one. We now know that it also occurs in veal calves, poultry, horses and companion animals. On the positive side, there is no human-to-human spread of this MRSA variant and food products are not considered to be an important source.

"LIVESTOCK MRSA IS NOT A DUTCH PROBLEM BUT RATHER A EUROPEAN AND GLOBAL ONE."







Globalisation of animal trade and the extensive use of antibiotics are risk factors for the emergence and spread of those antimicrobial resistant agents.
ESBLs are enzymes that inactivate the class of beta-lactam antibiotics and the genes involved are transferrable via plasmids, which renders limitless possibilities for transmission. Food and the environment are hence also sources of transmission to humans. This means that, in contrast to MRSA, these ESBLs cause a food safety issue.

"ESBLS ARE A TRUE ONE HEALTH PROBLEM"

Studies have shown that up to 90% of broilers in The Netherlands (and we produce about 450 million broilers per year) were ESBL positive. This is a large reservoir that goes into the food chain and into the environment. Genetic associations have been demonstrated between plasmids and genes in poultry products and human infections, suggestion transmission from poultry to humans.

Challenges

For scientists

- Understand the complex epidemiology of strains, mobile genetic elements, resistance and virulence determinants
- Relation with antibiotic use and change in use practices
- New antimicrobial active agents

For policy makers

- Humans (Bottom-up: professionals conduct policy)
  - Antibiotic prudent use policy and benchmarking of hospitals
  - Infection control measures
  - Identification of persons/populations at risk
- Animals (Top-Down: risk-manager needed to implement policy)
  - Definition of targets
  - Law changes
  - Antibiotic prudent use policy and benchmarking of farms/vets
  - Routes of transmission: food, faeces and transports

Public health challenge:

- Are we prepared to cope with the spread of carbapenemases in animals?

ANTIVIRAL DRUG RESISTANCE: ROOM FOR OPTIMISM

Many viral families exist and they all have different genomes, replication strategies and proteins. Consequently, a wide variety of antiviral drugs is needed. In this article, Prof. Johan Neyts of the REGA Institute at Leuven University sheds light on the challenges and possible solutions to overcome antiviral drug resistance.

HERPESVIRUS

Herpesvirus is a good example to demonstrate the challenges in developing new antiviral strategies. One of the first antiviral compounds that had been discovered and that is still widely used to treat herpesvirus infection is acyclovir, while cidofovir is a second generation drug that can be used to treat infection with acyclovir-resistant strains.

HOW ANTIVIRAL DRUGS WORK

STEP 1
The antiviral compound is taken up and activated by an enzyme (thymidine kinase) in the infected cell.

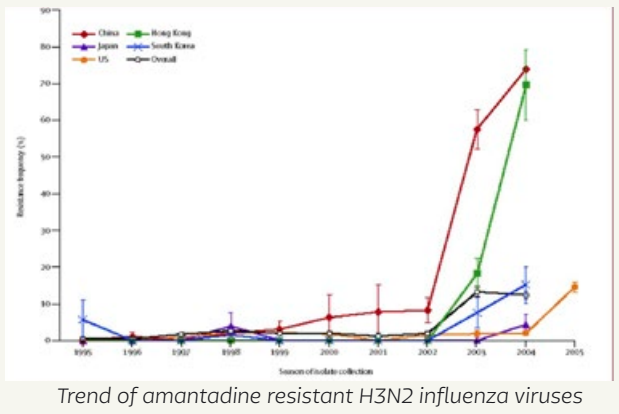
STEP 2
The activated compound starts building up metabolites that actually block the viral DNA polymerase, i.e. the replication machinery of the virus.

Novel compounds, like cidofivir, are designed to bypass the first step and hence do not need kinase activation.

Herpesvirus drug resistance mainly occurs in immunocompromised patients, transplant recipients and HIV patients. It is therefore important to develop new sorts of antiviral medicines that have a different type of action. Pretilivir and letermovir are two examples of such new compounds that use completely different mechanisms to block virus replication. They therefore have non-overlapping resistance profiles and can both be used to treat resistant infections.

INFLUENZA

The first generation of antivirals against flu were amantadine and rimantadine. Both drugs were only active against influenza A, and influenza strains rapidly develop resistance against these channel blockers.



Trend of amantadine resistant H3N2 influenza viruses

The barrier for antiviral resistance is higher in the second generation of flu drugs, the neuraminidase inhibitors. However, resistance still occurs, and in light of influenza viruses' pandemic potential, new antivirals are urgently needed. The third generation, the so-called polymerase inhibitors, are very promising in this respect as their resistance profile does not overlap with the neuraminidase inhibitors and the channel blockers.

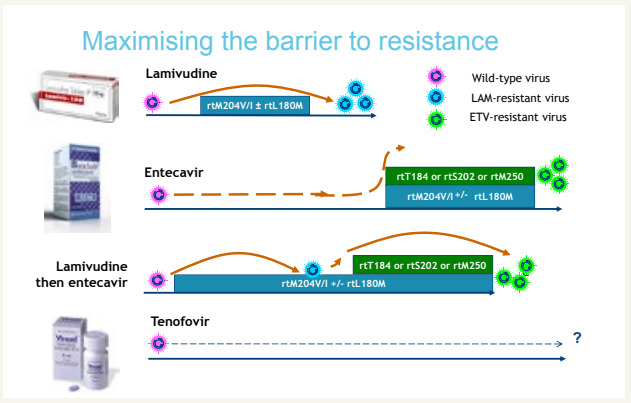
HIV

Today, 25 compounds exist against HIV infection and they are all used in fixed combinations. Whereas some 20 years ago, patients had to take a handful of pills at specific time points each day, the infection and also drug resistance can now be kept under control with just one pill a day. One of the cornerstones of HIV treatment is the compound called tenofovir, a molecule discovered at Leuven University. Studies have shown that tenofovir has a very high barrier to resistance.

"ONE OF THE CORNERSTONES OF HIV TREATMENT IS THE COMPOUND CALLED TENOFOVIR, A MOLECULE WITH A VERY HIGH BARRIER TO RESISTANCE."

HEPATITIS B

Hepatitis B, a virus that can cause cirrhosis and liver cancer, has again another replication mechanism. The first molecule used to treat hepatitis B infection, called lamivudine, had a low barrier to resistance. New generation compounds, like entecavir, are more potent and resistance is very rare. However, viruses that have developed resistance against lamivudine do develop resistance against entecavir rather easily, and the new compound should therefore not be used in patients with lamivudine-resistant virus infection. Fortunately, tenofovir – used, as mentioned, also against HIV infection - can provide a solution here as it acts effectively against hepatitis B virus replication, while resistance is non-existent.



" SOME CHRONIC VIRAL INFECTIONS CAN ALREADY BE KEPT UNDER CONTROL OR EVEN CURED, WHILE AVOIDING THE DEVELOPMENT OF RESISTANCE. THIS SHOULD BE POSSIBLE FOR ALMOST EVERY VIRAL INFECTION."

COMMON COLD

Common colds are unpleasant, but the main problem is that they can cause exacerbations of asthma and COPD. Potent drugs with a high barrier to resistance are therefore needed. The first generation of antivirals, the picornavirus capsid binders, have a low barrier and are hence inappropriate for use against rhino and enterovirus infection. A new, promising class of replication inhibitors with a high resistance barrier, however, is now under development.

DENGUE

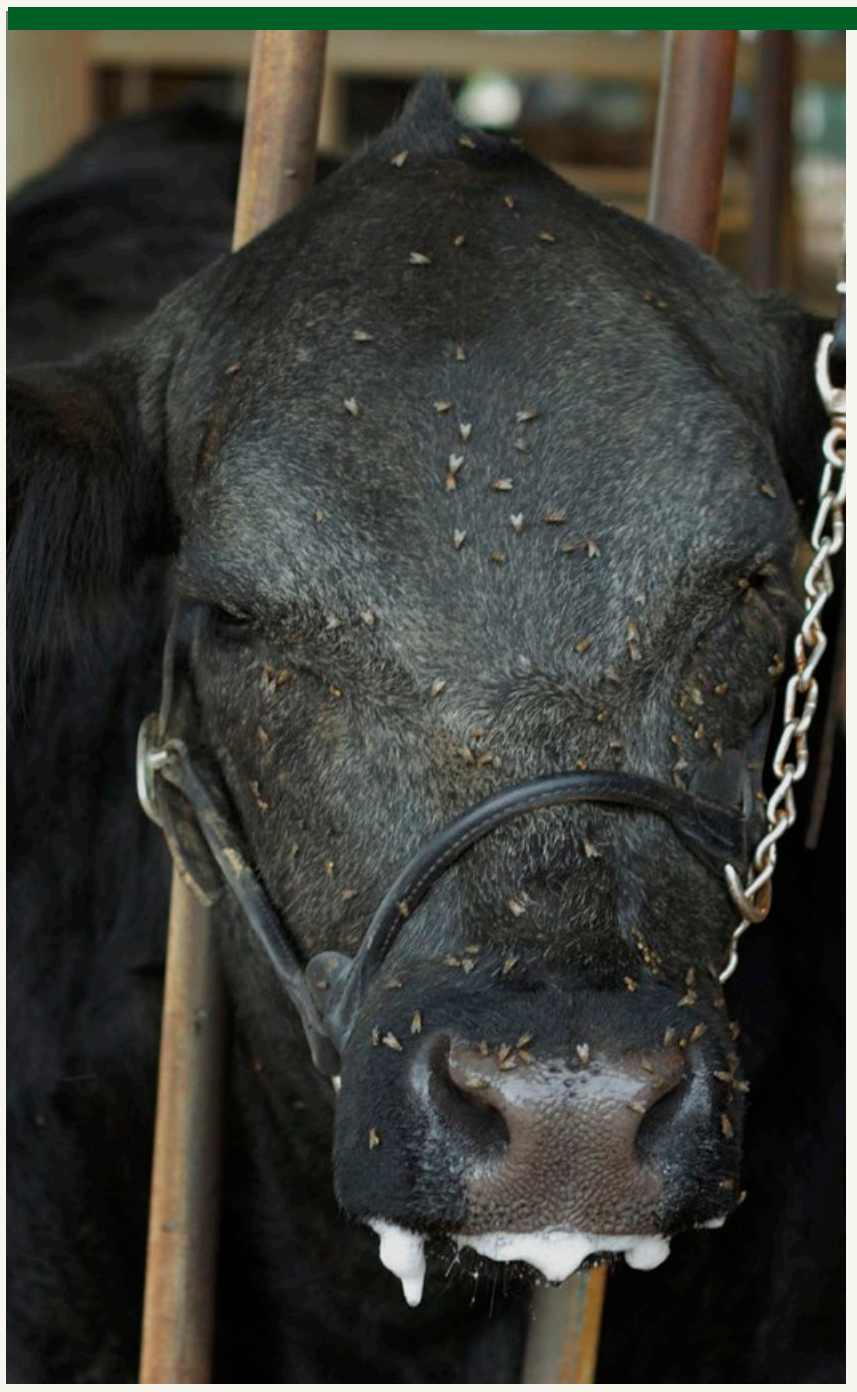
Antiviral drugs have been developed against a wide range of virus families, but definitely not against all of them. Dengue virus is a good example of an infectious agent for which we lack therapeutic drugs. Dengue infects about 100 million people every year and vaccine development has proven to be rather complex, so antivirals are dearly needed. We are therefore currently working on dengue inhibitors in our lab at Leuven University and a promising compound is now under development in cooperation with Johnson&Johnson. Of course, we need to select compounds with a high resistance barrier and an efficient selection procedure is put in place: we incubate infected cells with suboptimal concentrations of the tested compound to monitor the development of resistance. In the case of our new dengue inhibitor, it took almost half a year for the virus to develop resistance. ■

"DENGUE INFECTS ABOUT 100 MILLION PEOPLE EVERY YEAR AND THERAPEUTIC DRUGS ARE DEARLY NEEDED."

IN A NUTSHELL

- Many viral families exist and they all differ in terms of genomes, replication strategies and proteins. A plethora of antiviral drugs is needed.
- It is key to select drugs that have a high barrier to resistance
- For long treatments, we need to use drugs with non-overlapping resistance profiles
- Focus on the rational design of combinations largely reduces or prevents resistance development
- Antiviral agents should not be used to treat infections in animals if the same virus can also infect humans (cfr amantadine resistant influenza viruses emerged due to the use of amantadine in chickens)
- There is room for optimism as some chronic viral infections can already be kept under control or even cured, while avoiding the development of resistance.

HEALTH POLICY



BEYOND THE BEEF WARNING:

THE BSE STORY

PROF. MARTIN GROSCHUP:
"UNTIL 1996, INFECTED ANIMALS WERE STILL PROCESSED IN THE FOOD CHAIN."

by Prof. Martin Groschup, director of the institute for novel and emerging infectious diseases at the Friedrich Loeffler Institute, Germany

When the first cases of Bovine Spongiform Encephalopathy (BSE) occurred in the UK almost 30 years ago, nobody expected this infection to grow into a major epidemic in Europe. And yet, in 20 years time, 190,000 animal cases of BSE and 229 human fatalities have occurred, mainly in Europe. In this sense, BSE is also a zoonotic disease: people contracted the human variant of BSE by consuming contaminated food.

It was only in 1996 that a complete ban of feeding animal proteins to livestock was installed. Until then, infected animals were still processed in the food chain.

This and other important measures were taken as soon as the crisis gained political impetus. For instance, until 2001, the risk assessment and risk management of health crises had not been regarded as separate responsibilities. The BSE outbreak has led to a fundamental change in this area with the establishment of the European Food Safety Agency (EFSA), the Food Standard Agency (FSA) and several national entities. In part, these political actions were an attempt to counter the perception of insecurity that lived with the public at large. After all, the infection had long incubation times (so you could be infected without even knowing it) and infection was always fatal. There was hence a strong urge for public health authorities to show leadership and to manage the crisis decisively.

STRONG MEASURES, STRONG RESULTS

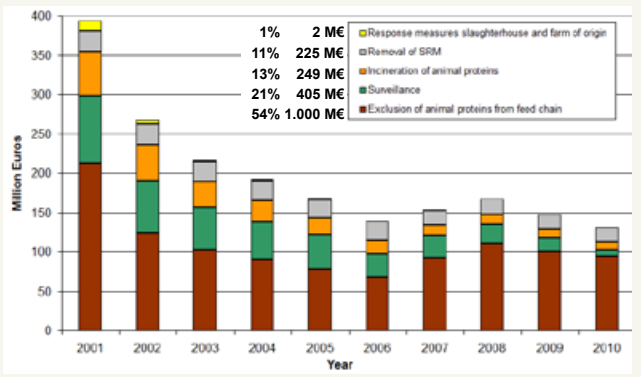
Today, BSE is virtually eradicated in the EU and most parts of the world. To achieve this, several important measures had been taken:

1) BSE RAPID TESTING
The rapid testing of all risk animals and slaughter animals above 13 months of age. Over time this age limit was increased in order to test only those animals that had been exposed to BSE. In total, some 100 million animals have been tested. Today, BSE testing is no longer obligatory in the EU.

2) PROHIBITION OF MEAT AND BONE MEAL FEEDING TO MAMMALS
A very important measure is the ban on the feeding of animal proteins to ruminants and other livestock. As a result of the BSE crisis, the EU countries have installed strict procedures to avoid intra-species recycling. This implies that cattle cannot be fed bovine material ever again.

3) REMOVAL OF SPECIFIED RISK MATERIAL (SRM)
SRM are the organs and sites with assumed or shown BSE prion replication. SRM from all slaughter animals must be burnt or buried to avoid inclusion in the human and animal food/feed chain. This is a rather drastic measure indeed.

"THERE WAS A STRONG URGE FOR PUBLIC HEALTH AUTHORITIES TO SHOW LEADERSHIP AND TO MANAGE THE CRISIS DECISIVELY."



For Germany alone, estimated direct costs amount to 2 billion Euros. This estimation does not include the economic cost of reduced beef consumption.

EXIT STRATEGIES

Effective but costly measures (as taken to counter the BSE crisis) call for exit strategies. To that end, the EU and the World Organization for Animal Health (OIE) jointly developed a BSE risk categorisation of countries, with three levels: negligible, controlled and unknown BSE risk. In negligible risk countries, specified risk material no longer needs to be removed and animal products are more qualified as source material for pharmaceutical products.

SUCCESS FACTORS AND LESSONS LEARNED

- EU-wide and global approach with BSE measures receiving support from all political levels
- Veterinarians and medical doctors cooperated in a true One Health spirit
- Long lasting strategy resulted in disease eradication and safeguarded public health
- BSE rapid testing of risk animals should remain obligatory for a very long time
- Feed bans must be maintained as to avoid, cannibalism'
- SRM definition can be amended according to epidemiological situation and state-of-the-art BSE pathogenesis knowledge

HEALTH POLICY

Balancing public health and economic interests during Q fever outbreak

In 2007, healthcare professionals saw a sudden and unusual rise in adult pneumonia cases in a rural area in the south of The Netherlands. It was soon clear that Q fever infection laid at the basis of this increase. The source of infection was traced back to a relatively new and fast growing type of farming in this part of the country: goat farms. "We had to balance public health and economic interests", said Roel Coutinho, the former Director of the Netherlands Center for Infectious Disease control.

"PATIENT ORGANIZATIONS ARE INSTRUMENTAL TO HIGHLIGHT THE MEDICAL URGENCY OF AN EPIDEMIC."

THE EARLY MONTHS

As a first set of measures, the Dutch Outbreak Management Team recommended an improved hygienic regulation and the voluntary immunisation of goats with a new - as yet non-registered - vaccine. "It soon became clear, however, that this level of intervention was not enough. In 2009 the number of reported Q fever cases rose to nearly 2,500", Prof. Coutinho elaborated. "We then imposed a mandatory vaccination programme and very strict hygienic measures. We also started to monitor bulk milk produce to detect infected farms instead of relying on farmers' reports and at the end of 2009 all pregnant goats at infected farms were culled. As a result of these measures the number of infections declined strongly in 2010 and there have been practically none since 2011."

Q FEVER REMAINS POORLY UNDERSTOOD

"A first important hurdle for a prompt and adequate response to the Q fever outbreak was our limited knowledge of the medical consequences of this bacterial infection. Should we screen pregnant women for Q fever infection, and how could we prevent transmission via blood and blood products? These questions were difficult to answer for us, experts in human medicine. Which brings us to the second challenge: the cooperation with veterinary experts. We had very limited experience in this area and we had to invent and build new cooperation structures. This distinction also translated on the political level: since two ministers were involved in this crisis, the decision-making process was suboptimal."

THE IMPORTANCE OF PATIENT ORGANIZATIONS

"The third barrier was a scientific one. Epidemiological evidence clearly pointed at goats as the source of the Q fever outbreak. People living within a two km range from infected farms had a 30 times higher risk of contracting Q fever than people living more than 5 km away from these farms. And yet, the Ministry of Agriculture was not convinced and demanded biological evidence. Which we could not provide at short notice." The lack of patient organizations played an important role in managing the crisis too. "Patient organizations are instrumental to highlight the medical urgency of an epidemic, as we have seen at the start of the HIV/AIDS outbreak. The same goes for press attention. The Q fever crisis was long considered a local problem in a rural area of the country and hence did not make it into the news headlines."

HUMAN VS ANIMAL VACCINATION

"Finally, and this is a general challenge that goes with any zoonotic outbreak that affects farmers and their livestock, we had to balance public health and economic interests. A crucial issue since this crisis involved intensive farming in one of the most densely populated countries in the world. The latter also explains why we made very little use of the human vaccine, as 100,000 to 150,000 people should have received the shot and the human Q fever vaccine is non-registered in Europe. Animal vaccination was hence the better option." ■

Q FEVER IN A NUTSHELL

- Zoonosis with a wide animal reservoir: wildlife, pets, ticks, cattle, sheep, goats
- Transmission to humans occurs mainly through inhalation of contaminated aerosols (abortions, amnion fluid, placenta, manure)
- Disease is caused by Coxiella burnetti: a very infectious intracellular bacterium that is highly resistant (spore-like structures)
- Clinical course in humans: mostly asymptomatic or flu-like, 20% of infected patients develop pneumonia (or hepatitis), 1-2% becomes chronically ill (pregnant women and persons with valve abnormalities are specifically vulnerable), death may occur in patients with co-morbidity
- Q fever responds well to treatment with doxycycline (2 weeks)
- Clinical course in animals: generally asymptomatic. May lead to abortion and stillbirth in small ruminants (goats/sheep)

IMPACT ON THE MANAGEMENT OF ZOONOTIC CRISES IN THE NETHERLANDS AND LESSONS LEARNED

- The Dutch government has installed monthly meetings of veterinarians and human medical specialists to discuss potential zoonotic disease threats.
- The crisis structure for zoonoses has been adapted. Human medical specialists do now also provide scientific advice to the agricultural authorities.
- Improved collaboration between veterinarians and medical doctors (yet there is still a large gap between both professions).
- Open and transparent communication during crises is essential to gain the public's trust.

HEALTH POLICY

TThe UK government had given high priority to preparedness for a pandemic outbreak of influenza. That explains why the country had a comprehensive plan in place when the 2009/10 HINI pandemic broke out. "But there has also been a backlash against antivirals and pandemic preparedness after the swine flu pandemic," warns Peter Openshaw, professor at Imperial College London and a member of the UK Pandemic Influenza Committee.

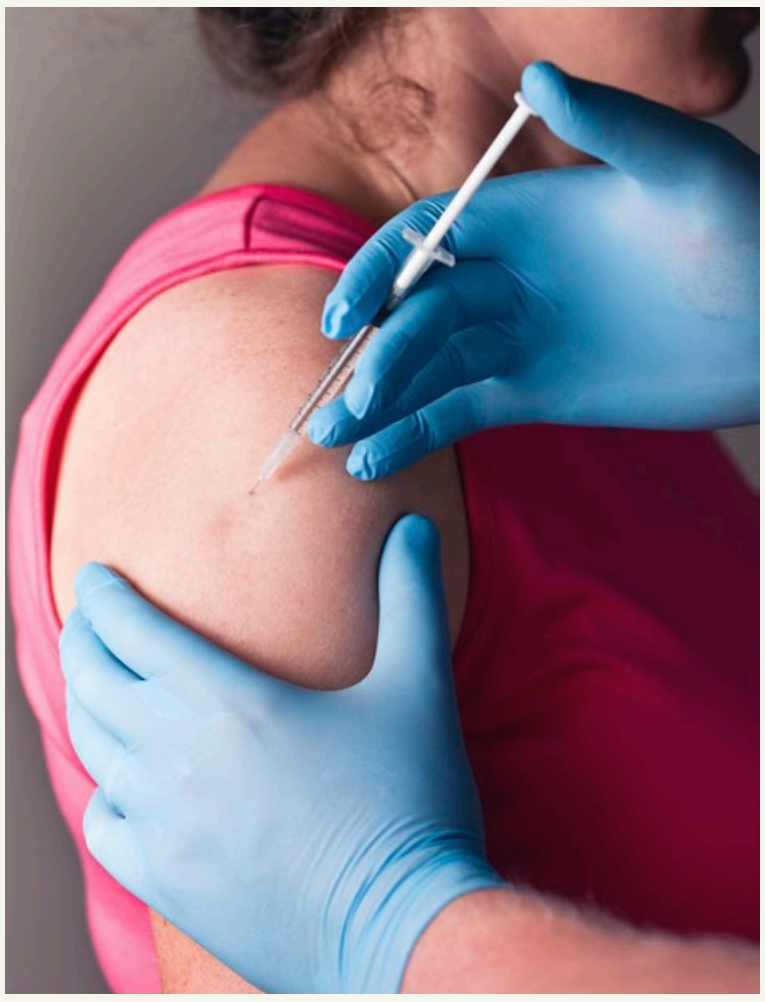
Billions spent on pandemic flu vaccines and antivirals!

Was it worth the while?

The UK applied an exceptional yet successful pandemic strategy. In what way was it different from most European pandemic response plans?

PROF. OPENSHAW: "The UK went for a widespread prophylaxis. We had an extensive stockpile of oseltamivir and some zanamivir. We were giving prophylaxis to household contacts, again in the aim to blunt the peak. To take the strain of the general practitioners, we set up the National Pandemic Flu Service, a novel telephone access system. If you contacted the call centre and gave the right answers, you were given an electronic voucher that entitled you to obtain antivirals directly from pharmacies without a prescription. About a million courses of antivirals were distributed in this way. But the proportion of people who developed flu wasn't very high, probably around 8%."

> " OSELTAMIVIR GIVEN EARLY DURING THE COURSE OF DISEASE CAN BE VERY BENEFICIAL."



Well-coordinated communication is key during a pandemic outbreak of any infectious disease. How did the UK handle this?

PROF. OPENSHAW: "In terms of communication, I think Liam Donaldson, England's chief medical officer, did a marvellous job. He went before the press every week, and he told it as we saw it. He was very sensible and very measured in what he said. And generally, the press was very reasonable in the way they interpreted his statements. With some exceptions though. In February 2010, The Daily Mail wrote: 'Billions of pounds have been wasted on swine flu vaccines that will never be used'. The newspaper said that we'd vaccinated millions of people, spent £13.5 million on the flu phone service and issued approximately 1 million courses of oseltamivir. While 'only' 411 people died. By the time the third (post-pandemic) wave hit the UK in November 2010, we had already moved back to the regular, seasonal guidelines. We had reverted to the policy that antivirals should only be used under very strict conditions. As a result, the use of antivirals in the third wave had dropped dramatically and we saw a high increase in the number of inpatients with confirmed influenza, outnumbering those admitted in the first and second wave put together. As a matter of fact, the number of confirmed deaths in the third wave is thought to be at least 602, probably much more. And then the Daily Mail came swinging back again. It had a front-page feature accusing our health authorities of irresponsibility in not having acted more strongly."

The use of influenza antivirals has long been in the centre of the public health debate. Yet, antivirals are a cornerstone of pandemic response planning.

PROF. OPENSHAW: "My absolute belief is that early administration of antivirals is crucial. Studies show that if you give antivirals at six or twelve hours after onset of symptoms, they are much more effective in terms of reducing the duration of illness than if you give them later. Hence consensus is that antivirals should be given within the first 48 hours of the course of disease. Obviously, problems will arise if everyone is going to their general practitioners and ask them for antivirals. So we need to find a solution that allows early treatment without overwhelming primary care."

"There has also been a backlash against antivirals. Most notably from the Cochrane Collaboration. The authors attack the use of oseltamivir, saying that there is not a very significant shortening of symptoms. They are even suggesting that the drug's mode of action is as a central nervous system depressant, implying that it reduces symptoms because it makes you feel drowsy and lie down. Interestingly, the same data that was assessed by the Cochrane Collaboration was re-analysed by a group of experts under the umbrella of the MUGAS Foundation. They used more sophisticated and more detailed methods and have come up with the conclusion that there is a reduction of about 50% in mortality if oseltamivir is administered within 48 hours and 20% overall. So using the very same data you can come to quite different conclusions."

- **Cochrane report in BMJ:** http://www.bmj.com/content/348/bmj.g2630
- **MUGAS meta-analysis in The Lancet:** http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)62449-1/abstract

THE UK INFLUENZA PANDEMIC PREPAREDNESS PLAN: THREE DISTINCT PHASES

1. Preparation: getting ready by stockpiling antivirals and vaccines, by making advance purchase agreements with pandemic vaccine manufacturers, and by very extensive modelling. The UK government relied on mathematical modelling to try to anticipate what sort of measures would be useful.

2. Containment to slow the speed, blunt the peak and buy time. The idea was to reduce the impact on national service, health service, transport etc. The UK was unusual in investing heavily in contact prophylaxis, self-isolation and school closures.

3. Treatment, based on clinical diagnosis. Intention to treat everyone who developed influenza.

INTERNATIONAL PUBLIC HEALTH COOPERATION

New diseases have been emerging at the unprecedented rate of one a year for the last two decades. The sudden and deadly arrival of SARS early in 2003 was in some ways the most dramatic of all. Its rapid containment is one of the biggest success stories in public health in recent years. But how much of that success was a result of good fortune as well as good science? How narrow was the escape from an international health disaster? "The international response to SARS will shape future strategies against infectious epidemics", David Heymann, the former executive director of communicable diseases at the World Health Organization (WHO), explains.

PREPARING FOR THE NEXT DISEASE OUTBREAK: lessons from SARS

FORTY DAYS OF ISOLATION

"In order to understand SARS, and the changes to international efforts to stop the spread of infectious diseases that occurred afterwards, we need to go back to the Middle Ages in history", says David Heymann. "In those days, a measure to control the international spread of infectious diseases like plague, cholera, yellow fever and smallpox was being used with limited impact: quarantine – an attempt to stop disease at borders."

"This required international agreements on public health measures during the following centuries that carried through, in a series of international treaties and conferences, from the fourteenth century until 1969, when WHO established its International Health Regulations (IHR). These IHR and the accompanying sanitation guidelines for seaports and airports attempted to achieve a balance between ensuring maximum public health security against the international spread of the four infectious diseases with minimum interference in global commerce and trade. Measures in the IHR were aimed at stopping disease at international borders. Countries in which one of the four reportable diseases was occurring, were required to notify WHO, and other countries were then permitted to take specified measures at airports and seaports to attempt to prevent the entry of disease. For instance, during the period between reporting and certifying that the outbreak was contained, countries could require vaccination certificates from passengers arriving from an affected country."

REVISING THE INTERNATIONAL HEALTH REGULATIONS

"The original IHR were revised in 2005 based on the following vision: 1. to be able to detect and collectively respond to international infectious disease threats within 24 hours using the most up-to-date means of global communication and collaboration; 2. to change the international norm for reporting infectious disease outbreaks so that countries were not only expected to report outbreaks, but also respected for doing so. Until then, countries had been hesitant to report the outbreak of infectious disease to WHO as required by the IHR, primarily because of potential damage to national economies. In the early 1990s, for example, the spread of cholera in Peru cost the country more than $770 million in lost trade and tourism. That same decade, India reported a loss of over $1 billion in travel, trade and tourism revenues after plague struck a small area of the country. A few years later, a cholera outbreak in Tanzania came with an estimated loss of $36 million in revenue."

"THE DIRECTOR GENERAL OF WHO, DR. GRO HARLEM BRUNDTLAND, TOOK SOME BOLD YET NECESSARY POLICY DECISIONS."

GRO HARLEM BRUNDTLAND

"Around the turn of the century, the new director general of WHO, Dr. Gro Harlem Brundtland, took some bold yet necessary policy decisions that led to the revision of the IHR. For instance, WHO was now allowed to accept and act on information about disease outbreaks from sources other than countries. This led to the creation of the Global Public Health Information Network (GPHIN), and the Global Outbreak Alert and Response Network (GOARN). GPHIN is an early warning system that searches open sites on the Internet for key words associated with infectious diseases, performs a preliminary analysis of the information collected and provides this information every 24 hours to WHO, where it is verified as rapidly as possible."

"THE SARS OUTBREAK WAS A TURNING POINT IN INTERNATIONAL COLLABORATION ON INFECTIOUS DISEASE CONTROL."

"Early 2003, GPHIN reported cases of an atypical pneumonia with high mortality in China. WHO feared that these cases signaled the beginning of an influenza pandemic because H5N1 was known to be present in that region of the country. WHO hence issued precautionary policy measures and recommendations on patient management and eventually issued travel recommendations in an attempt to counter the international spread of this new virus."

WORLDWIDE COOPERATION TO STOP SARS

"The SARS outbreak was a turning point in international collaboration on infectious disease control. Virus experts from around the world worked together virtually — by phone, videoconference and through the Internet — to share information and report progress. Within weeks, they identified the virus responsible for SARS. Epidemiologists soon confirmed that health workers were at greatest risk and that air travel was spreading the disease. Doctors shared their knowledge about what treatments worked and what did not via standardized patient management forms."

"Most countries cooperated in reporting incidents of SARS. With the exception of China, whose cooperation was key to tracing how the disease emerged. The WHO director general then took another bold decision and she spoke openly about China's reluctance to collaborate. Shortly afterwards, Chinese vice-premier, Madame Wu Yi, arrived in Geneva to meet with the director general, and after a constructive discussion, China began to work with the rest of the world to stop the outbreak."

"The disease spread around the globe over a period of eight months, with the outbreak peaking in April and May. By July 2003, the outbreak had been contained. By then, an estimated 774 people had died of SARS infection."

AFTER THE SARS OUTBREAK, IT WAS CLEARLY UNDERSTOOD THAT INTERNATIONAL BORDERS COULD NOT STOP THE SPREAD OF INFECTIOUS DISEASES, AND THE IHR REVISION IN 2005 INCLUDED A MAJOR REQUIREMENT THAT COUNTRIES DEVELOP 8 CORE CAPACITIES IN PUBLIC HEALTH TO BE BETTER ABLE TO DETECT AND RESPOND TO INFECTIOUS DISEASE OUTBREAKS BEFORE THEY SPREAD NATIONALLY, AND INTERNATIONALLY.

OPINION

by Prof. John MacKenzie,
Curtin University, Australia

ONE HEALTH: *from concept to practice*

In the past decades, we have seen the emergence of many new pathogens and the resurgence of others. But the most important thing is that they may cost the governments of countries huge amounts of money, as we have seen during the outbreaks of SARS and avian influenza. The majority of these pathogens are zoonoses, and an understanding of the interplay of factors at the interface between humans and animals is absolutely crucial for their detection, response and control. And this is exactly what One Health is about: an integrated, holistic approach. Indeed, the role of the wildlife-livestock- human-ecosystem interfaces has been fundamental to the development of the One Health paradigm.

ONE HEALTH DRIVERS

There are many different drivers for the One Health concept. The 2003 SARS outbreak has been a real wake-up call, as it demonstrated that a previously unknown pathogen could emerge from a wildlife source at any time and in any place and, without warning, threaten the health, well-being and economies of all societies. Secondly, the "Manhattan Principles", a series of strategic goals issued by the Wildlife Conservation Society, nicely encapsulate the aims of One Health. And of course, concerns about novel zoonotic diseases were heightened by the spread of H5NI avian influenza and its potential to become the next worldwide pandemic. So, it is fair to say that the SARS and H5NI outbreaks have highlighted the urgent need of effective alert and response systems, data-sharing platforms and global leadership.

Our important principles, taken from The Manhattan Principles on 'One World, One Health' (2004), describe the fundaments of One Health:

- To recognize the link between human, domestic animal, and wildlife health, and the threat disease poses to people, their food supplies and economies, and the biodiversity essential to maintaining the healthy environments and functioning ecosystems we all require
- To recognise that decisions regarding land and water use have real implications for health. Alterations in the resilience of ecosystems and shifts in patterns of disease emergence and spread manifest themselves when we fail to recognize this relationship
- To include wildlife health science as an essential component of global disease prevention, surveillance, monitoring, control, and mitigation.
- To devise adaptive, holistic, and forward-looking approaches to the prevention, surveillance, monitoring, control, and mitigation of emerging and resurging diseases that fully account for the complex interconnections among species

BREAK DOWN THE BARRIERS

To achieve the goals of One Health, we will need to break down the silos between human health and veterinary medicine and to ensure effective stakeholder engagement. In other words, we need to enhance collaboration and cooperation between all parties through the development of an integrated approach to human, animal and ecosystem health. To break down the silos, however, we need One Health training and education. Only by including the concept in academic curricula will we ever achieve integration of human health and veterinary medicine. In the mean time, several studies and cases support the added value of the One Health concept and have demonstrated that an integrated surveillance approach is more effective at predicting outbreaks of diseases that affect both man and animals, and that a One Health approach to control is more sustainable than that with a human-centric approach. But obviously, more studies are needed still, particularly those involving cost-benefit analysis.

Some four years ago, we had great hopes that the WHO-OIE-FAO Tripartite Memorandum would provide the leadership that we needed. But it hasn't, there is still need for global leadership. On the other hand, the World Bank, the European Union, ASEAN, and other multi-national organizations have assisted the successful development of regional One Health networks and national and regional activities. And on a national level, we see an increasing number of excellent One Health activities, notably in South-East Asian countries like Thailand, Laos, Cambodia, Mongolia and Bhutan, as well as in African countries.

ONE HEALTH PLATFORM

In the absence of global leadership it is good to see that new One Health initiatives are still taken, and in this context I'm very proud to present the newly founded One Health Platform. This international Foundation brings together key opinion leaders of the One Health topic and provides them with a framework for information-sharing, cooperation and awareness raising activities.

"THERE IS URGENT NEED FOR GLOBAL ONE HEALTH LEADERSHIP.

For more information, contact
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FORUM

World Veterinary Association joins the International One Health Coalition

The World Veterinary Association (WVA) is a federation of over 80 veterinary medical associations representing over 500,000 veterinarians across the world on six continents. The association works to promote animal health, animal welfare, and public health globally with the understanding that they are intricately interconnected. In alignment with the Zoonosis strategic priority, the WVA now joins the International One Health Coalition as part of the newly established One Health Platform.

The One Health Coalition is a collaborative partnership with existing international governmental and non-governmental organizations and institutions with the aim to reinforce the One Health concept. The main objectives of the One Health Platform include the promotion of a cross-sectoral and collaborative approach to improve the health and well-being of humans, animals and their environments, to advocate a scientific research agenda into zoonoses, neglected emerging infectious diseases and antimicrobial resistance, and to disseminate novel scientific findings to anyone who might benefit from them.