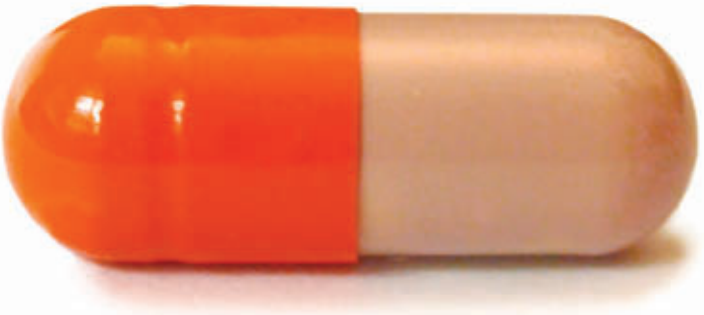
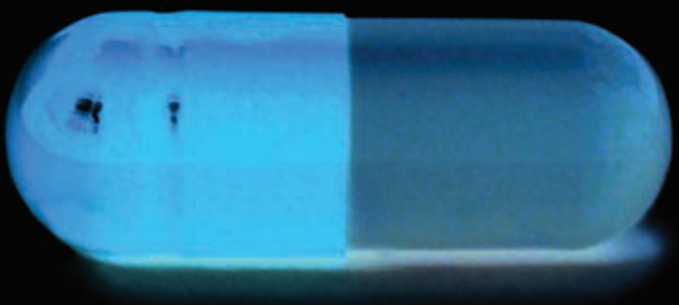
Martin Khor



When Medicines Don't Work Anymore

ANTIMICROBIAL RESISTANCE: The World's Gravest Health Threat



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Antibiotic resistance, now widened to be called antimicrobial resistance, is the world's greatest public health risk and threat. We are now so used to using antibiotics that it is almost unthinkable what would happen to our state of health if there were none available. Or if the antibiotics don't work anymore.

Health leaders are sounding the alarm bell. The Chief Medical Officer of the United Kingdom has warned of a looming "catastrophe"so widespread that we would be back to a pre-antibiotic era when many diseases could not be treated. The World Health Organisation's then Director General has said the world is heading towards a post-antibiotics era in which common infections such as strep throat or a child's scratched knee could once again kill. It may even bring the end of modern medicine. And heads of states and governments in 2016 adopted a landmark Political Declaration recognising that antibiotic resistance is the "greatest and most urgent global risk".

This book is a collection of articles written over two decades, tracing the antimicrobial resistance problem as it evolved through the years into a full blown crisis. It also contains the author's speaking notes at the UN General Assembly summit-level special event on AMR. It provides news and opinions in popular language on various aspects of AMR, as the problem emerged and then developed into the present day public health catastrophe.

MARTIN KHOR is the Executive Director of the South Centre, an inter-governmental research organisation of developing countries based in Geneva. Previously he was the Director of the Consumers' Association of Penang as well as of the Third World Network, two public interest organisations based in Malaysia.

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Contents

Introduction

ANTIBIOTIC resistance, now widened to be called antimicrobial resistance, is today arguably the world's greatest public health risk and threat. We are now so used to using antibiotics that it is almost unthinkable what would happen to our state of health if there were none available. Or if the antibiotics don't work anymore.

Health leaders have sounded the alarm bell for some years now. The Chief Medical Officer of the United Kingdom Dame Sally Davies warned in 2013 of a looming "catastrophe" of antibiotic resistance being so widespread that we would be back to a 19th century medical situation, a pre-antibiotic era when many diseases were difficult or impossible to treat.

The then Director General of the World Health Organisation Dr Margaret Chan told world leaders at the United Nations in 2016 that if current trends continue, the world is heading towards a post-antibiotics era in which common infections such as strep throat or a child's scratched knee could once again kill. Sophisticated interventions like organ transplantation, joint replacements, cancer chemotherapy and care of pre-term infants will be more difficult or too dangerous to undertake. Her grim conclusion: "This may even bring the end of modern medicine as we know it. We need to act now to make sure this does not happen."

And heads of states and governments, meeting in the UN in New York in September 2016 adopted a landmark Political Declaration

on Antimicrobial Resistance (AMR) that recognised that antibiotic resistance is the "greatest and most urgent global risk" and that due to AMR many 20th century achievements are being gravely threatened, particularly the reduction in illness and death from infectious diseases.

The Declaration was adopted by the political leaders in a one-day special high-level event of the UN Summit in 2016. I was invited to speak at a panel discussion during that event, representing the South Centre, of which I am the Executive Director.

The event and the Political Declaration were the culmination of the decades-long efforts of public health organisations, civil society groups and scientific and medical experts to alert the public that the rapid development of antibiotic resistance was about to overwhelm the work done to treat and cure many diseases, with catastrophic health consequences for all.

If climate change is the greatest environmental threat, then antimicrobial resistance is the greatest health threat the world is facing. This has been a message that I have been promoting in recent years. In fact, I have said, only half-jokingly, that if we do not solve the antibiotic resistance crisis, then the climate change crisis will be much reduced. There would be less humans to generate the greenhouse emissions that fuel climate change. But this would be the worst solution ever to the climate crisis.

This book is a collection of some popular articles that I have written through the years on antibiotic resistance.

I first became aware of this problem when I was working in the Consumers' Association of Penang (Malaysia). In the 1980s, CAP's senior researcher Evelyne Hong produced 15 or so studies to expose the unethical marketing practices of drug companies in Malaysia and other developing countries, in which many medicines, including antibiotics, were being promoted to doctors and the public without proper care about side effects or appropriate use. CAP's

studies showed that unethical marketing practices and inappropriate dispensing were significant factors causing irrational drug use. The studies yielded good results as several of the drugs were banned or heavily regulated by the health authorities after CAP sent the reports to the government.

In the 1990s, CAP continued to do regular work on the issue and published a path-breaking book, *Revenge of the Killer Germs*, which in popular language highlighted the problems of antibiotic resistance and what should be done to address this threat.

CAP was "ahead of the curve." It took a long time for the medical establishment and the international organisations to wake up to the problem and to act sufficiently. The situation became much worse as time went by and the bacteria and other microorganisms that cause many ailments and diseases, such as tuberculosis, K. pneumonia, urinary tract infections and gonorrhoea, have become increasingly resistant to antibiotics and other antimicrobials.

A few years ago, as the situation reached crisis proportions, action developed at the global level. The World Health Assembly in May 2015 adopted a Global Plan of Action on AMR, and the UN General Assembly adopted the Political Declaration on AMR in September 2016. Health Ministries, as well as Agriculture Ministries, are now translating the global plan into national action plans, and attempting to implement them. But this is only the start of the actions that are needed. Many obstacles and challenges remain, not only in the health sector, but also in the agriculture and livestock and environment sectors, as these are all major sources of the spread of resistance.

The articles in this book were written mainly for the columns that I have been writing in *The Star* (Malaysia), namely *Earth Trends* and *Global Trends*, as well as for the *Inter Press Service* and the South Bulletin. The first of the articles in this book was published in May 1996, and the last one in December 2017, thus recording my reports on news and opinions on the subject over more than two decades.

However the book begins not with an article but with a paper that I wrote as a background speaking note which I used when speaking at the panel at the UN General Assembly special event on AMR in September 2016. This paper summarised my views at that time of how the crisis is affecting developing countries and what are the special interests and needs of the developing countries in facing up to the crisis.

I hope that this little book will help the public to better understand the antimicrobial resistance problem as it evolved through the years into a full blown crisis now acknowledged by many public health leaders and by the political leaders of the world.

I would like to thank my colleagues and friends in the Consumers' Association of Penang (especially S.M. Mohamed Idris and Lim Jee Yuan), the Third World Network (especially Evelyne Hong, Chee Yoke Ling, Umadevi and Lean Ka-Min), the South Centre (especially Viviana Munoz and Miza Alas), the World Health Organisation, the Fleming Fund and the media, especially *The Star* and the *Inter Press Service*. Another thank you to Jee Yuan for helping to design and put this book together in record time.

Martin Khor,
March 2018,
Penang

I
OVERVIEW

The Global Threat of Antimicrobial Resistance and the Challenges and Needs of Developing Countries*

Speaking notes at high-level event on AMR at the UN General Assembly, New York, 21 Sept 2016

1. Antimicrobial resistance has become a major global health crisis

ANTIMICROBIAL resistance (AMR) is a major and serious problem. It represents possibly the greatest global crisis in public health in the world today, akin to climate change as the top environmental problem.

Antimicrobial resistance is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it. Resistant microorganisms (including bacteria, fungi, viruses and parasites) are able to withstand attack by antimicrobial drugs, such as antibacterial drugs (e.g. antibiotics),

* This is a background paper used as speaking notes by Martin Khor when he participated in a panel discussion during the UN General Assembly high-level event on antimicrobial resistance on 21 September 2016, which was convened at the level of heads of states and governments.

antifungals, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist, increasing the risk of spread to others.[1]

Resistance by bacteria and other microbes to antibiotics and other medicines may be a natural process, as the microbes causing diseases evolve through time in response to the medicines. However, the rate of resistance is accelerated and the scope of resistance is broadened by several factors: the inappropriate use of antibiotics, due to inappropriate marketing methods and lack of awareness by patients; the inappropriate and widespread use of antibiotics in the animal husbandry and agriculture sector, which passes on resistant microbes to humans; and the existence of certain genes that specialize in accelerating and spreading resistance among bacteria, thus greatly increasing the rate and spread of resistance to many species of bacteria that cause diseases.

AMR is now a global crisis, with many pathogens becoming resistant to many antibiotics. As leading public health officials and senior scientists have warned, we are now entering a post-antibiotics world, in which it is increasingly difficult to treat simple ailments and dangerous diseases. The incidence of multi-drug resistance has risen significantly, and for a few diseases there is almost no cure left. In 2012, World Health Organisation Director General Dr Margaret Chan warned that every anitibiotic ever developed was at risk of becoming useless. "A post-antibiotic era means in effect an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill."

According to WHO[2]:

- Antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi.

1 World Health Organisation, 2015. Fact Sheet on Antimicrobial Resistance.
2 WHO 2015, Fact Sheet on Antimicrobial Resistance

- In 2012, WHO reported a gradual increase in resistance to HIV drugs, albeit not reaching critical levels. Since then, further increases in resistance to first-line treatment drugs were reported, which might require using more expensive drugs in the near future.
- In 2013, there were about 480,000 new cases of multidrug-resistant tuberculosis (MDR-TB). Extensively drug-resistant tuberculosis (XDR-TB) has been identified in 100 countries. MDR-TB requires treatment courses that are much longer and less effective than those for non-resistant TB.
- In parts of the Greater Mekong subregion, resistance to the best available treatment for falciparum malaria, artemisinin-based combination therapies (ACTs), has been detected. Spread or emergence of multidrug resistance, including resistance to ACTs, in other regions could jeopardize important recent gains in control of the disease.
- There are high proportions of antibiotic resistance in bacteria that cause common infections (e.g. urinary tract infections, pneumonia, bloodstream infections) in all regions of the world. A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant Gram-negative bacteria.
- Treatment failures due to resistance to treatments of last resort for gonorrhoea (third-generation cephalosporins) have been reported from 10 countries. Gonorrhoea may soon become untreatable as no vaccines or new drugs are in development.
- Patients with infections caused by drug-resistant bacteria are generally at increased risk of worse clinical outcomes and death, and consume more health-care resources than patients infected with the same bacteria that are not resistant.

The World Health Assembly in 2015 adopted the Global Action Plan

on Antimicrobial Resistance. It has five objectives: to use medicines properly in human and animal health; reduce infection by sanitation, hygiene and infection prevention measures; strengthen surveillance and research; educate the public as well as doctors, veterinarians and farmers on proper use of antibiotics; and increase investment in developing new medicines, diagnostic tools and vaccines.

Implementation of this Plan at global and national levels will be a good start in the long battle against AMR. It is important to recognize the conditions and challenges faced by developing countries and assist them to address these challenges, to facilitate their implementation of the Global Action Plan.[3]

2. The global fight against AMR has to involve the developing countries as a top priority

It is to be expected that the developed countries will take the lead in the global fight against AMR. This is due to the greater availability of financial resources, and higher levels of scientific knowledge, research capability and technology as well as institutional and organizational capabilities including in the health care sector. Thus much of the global progress in the fight against AMR, in science, technology, surveillance, regulations, and discovery of new anti-microbials, is expected to take place first in the developed countries.

However, the developing countries will have to play a central role in the global battle against AMR, since it is in the developing countries that the majority of the world population reside, that there is the highest number (and in some cases highest incidence) of people

3 The major development at global level since the adoption of the WHA Global Plan of Action is the adoption by the UN General Assembly of a political high level Declaration on AMR. This Declaration was approved in September 2016 by the heads of states and governments at the high level event on AMR during which the panel discussion (at which the author was a panel speaker) took place. It was subsequently formally adopted by the General Assembly.

suffering from drug-resistant diseases, and that pathogens with the genes specializing in spreading resistance have been mainly found in patients. Moreover, in an increasingly globalised world with a high degree of travel and trade, there can be the easy spread of drug resistant bacteria and diseases.

Therefore, the special needs and interests of the developing countries have to be given the highest priority in the global fight against AMR if we are to make adequate progress.

3. Developing countries are becoming more aware of the AMR crisis

Political leaders and public health officials in developing countries are becoming more aware of the AMR crisis.

At the Summit meeting of the Group of 77 and China held in Santa Cruz (Bolivia) in May 2014, the political leaders of the developing countries adopted a Declaration which included the following paragraph 66:

"We are concerned about the increasing problem of antimicrobial resistance to existing drugs, including those against TB and malaria. As a result, increasing numbers of patients, especially in developing countries, face the prospect of dying from preventable and/or treatable diseases. We urge the international health authorities and organizations, especially WHO, to take urgent action and to work together upon request with developing countries that do not have adequate resources to address this problem."

The Health Ministers of the WHO's SE Asia Region, at a WHO regional workshop in Jaipur (India) in September, 2011 adopted the Jaipur Declaration on AMR, which included the following: "We the Health Ministers of SEAsia Region…recognise it is imperative that national governments accord utmost priority to this neglected problem, to preserve efficacy of anti-microbial agents in our fight against

microbial diseases." It was followed by 18 action points.

In May 2015, the World Health Assembly, of which the majority of members are from developing countries, adopted the Global Action Plan on AMR, with a commitment that national action plans will be drawn up by all countries within two years.

However, in most developing countries, the public is still lacking knowledge and awareness of the threat of AMR, while coordinated and systematic action is also at only a beginning stage. Therefore, much more has to be done, while time is running out.

4. People in developing countries are most affected by AMR

Developing countries will be most affected by the AMR crisis. At present AMR is estimated by the UK-sponsored Review on AMR to globally cause 700,000 deaths annually (and this is a low estimate)[4]. The annual deaths attributable to AMR are projected to rise to 10 million in 2050. Of these deaths, it is projected that 390,000 will be in Europe, 317,000 in North America, 22,000 in Oceania, 4.7 million in Asia, 4.2 million in Africa and 392,000 in Latin America.

For most diseases the majority of people affected by AMR are in developing countries. The Review on Antimicrobial Resistance (2014: p9) concludes that "countries that already have high malaria, HIV or TB rates are likely to particularly suffer as resistance to current treatments increases." Particular countries at risk include India, Nigeria and Indonesia (malaria) and Russia (TB) and Africa will suffer greatly as the HIV and TB co-morbidity is likely to get worse.

The Review also estimates that 300 million people are expected to die prematurely because of drug resistance over the next 35 years and world GDP will be 2 to 3.5% lower than it otherwise would be in 2050. Between now and 2050 the world can expect to lose USD 60 to

4 Review on Antibiotic Resistance (Dec 2014): AMR: Tackling a crisis for the health and wealth of nations, pages 5, 13.

100 trillion of economic output if AMR is not tackled. (World GDP will be 1.4% smaller by 2030 with over 100 million people having died prematurely.) OECD countries are expected to have USD 20-35 trillion in cumulative loss of output by 2050; which means that about two-thirds of the losses will be borne by non-OECD countries.

The case of tuberculosis is most illustrative. Of the 10 million deaths in 2050 attributable to AMR, the Review estimates that a quarter (or 2.5 million) will be due to resistant TB. There is an increasing incidence of multi drug resistant and extensive drug resistant TB and most cases are in developing countries. The Review on Antimicrobial Resistance (2016) found that of "the 10 million deaths that might be associated with drug resistance each year by 2050, around a quarter will come from drug-resistant strains of TB."[5] Most of these anticipated cases and deaths from resistant TB will be from developing countries, although TB is also affecting several developed countries.

There is also increasing resistance to drugs treating malaria and to the first-line treatments for HIV-AIDS and the majority of people affected are from developing countries. Also, pathogens that are increasingly resistant to powerful antibiotics (E coli, K. pneumonia, S. Aureus, salmonella, shigella, gonorrhoea) are prevalent in developing countries.

Therefore developing countries must recognize that the AMR crisis is mainly taking place in their countries and they have to give priority to this. On the other hand, the international community has to pay special attention to the needs of developing countries and to assist them in addressing the AMR crisis.

5. Genes that specialise in accelerating rate of resistance have been found in developing countries

5 Review on Antimicrobial Resistance (2016), Tackling Drug-Resistant Infections Globally: Final Report and Recommendations

In recent years, at least two types of genes have been found that have the characteristic of being able to make bacteria highly resistant to known drugs and to also spread from one species of bacteria to other species through horizontal gene transfer. Bacteria containing these genes were first found in developing countries, and have now been found to have spread to many other countries.

The NDM-1 gene has the ability to alter bacteria and make them highly resistant to known drugs. In 2010, only 2 types of bacteria were found to host the NDM-1 gene (E coli; K.pneumonia). Most of the initial cases were found in South Asian countries. It has since spread to many countries.The gene has been found to jump among various species of bacteria at superfast speed, making more species of bacteria drug resistant. NDM-1 has now been found in over 20 species of bacteria. The gene makes the bacteria highly resistant to all known drugs, except two, including colistin.

In 2015, scientists found a gene, MCR-1, which creates resistance to colistin, a powerful antibiotic used as a last resort to treat infections when other medicines do not work. The gene also has the characteristic of being able to move easily from one strain of bacteria to other species of bacteria. Yi-Yun Liu and colleagues published a paper in the *Lancet Infectious Diseases* journal in November 2015 revealing they found the MCR-1 gene in pigs at slaughter that they tested, chicken and pork being retailed and hospital patients.The study indicates there is a chain in the spread of resistance from the use of colistin in livestock feed, to colistin resistance in slaughtered animals, in food and human beings.

One of the authors, Prof. Jian-Hua Liu from South China Agricultural University, was quoted by *The Guardian* as saying these are extremely worrying results, which reveal the emergence of the first polymyxin resistance gene that is readily passed between common bacteria such as E. coli and K. pneumonia. This suggests that "the progession from extensive drug resistance to pandrug resistance is inevitable", added

Liu. Extensive resistance is when a bacterium is resistant to many drugs while pandrug resistance indicates resistance to all drugs.

Colistin is part of a category of antibiotics known as polymyxins. In the past they had not been widely used in humans as they are known to have toxic effects, but they have recently become a last-resort treatment when other antibiotics don't work because of resistance.

Another of the paper's co-authors, Prof. Timothy Walsh from University of Cardiff, told the BBC News website:"All key players are now in place to make the post-antibiotic world a reality. If MCR-1 becomes global, which is a case of when and not if, and the gene aligns itself with other antibiotic resistance genes, which is inevitable, then we will have very likely reached the start of the post-antibiotic era. At that point, if a patient is seriously ill, say with E. coli, then there is virtually nothing you can do."

A major reason for the emergence and spread of the gene is suspected to be the heavy use of colistin to feed livestock to promote their growth. The *Lancet* journal published a Comment in February that we must take the call to curtail the use of polymyxins (including colistin) in agriculture to the highest levels of government or face more patients for whom we need to say, "Sorry there is nothing I can do to cure your infection." Other antibiotics that are used by human beings should also be prohibited or heavily restricted in the livestock sector, especially if they are used as growth promoters.

The paper mentions that besides China, the MCR-1 gene had also been found in Malaysia and Denmark. After the paper was published, new papers and information have shown that the MCR-1 gene has been found in bacterial samples in many other countries, including Thailand, Laos, Brazil, Egypt, Italy, Spain, England and Wales, the Netherlands, Algeria, Portugal and Canada.

The discoveries of NDM-1 and MCR-1 add urgency to the task of addressing anti-microbial resistance.

6. At the same time, developing countries face many challenges in addressing AMR

Developing countries face many challenges in addressing AMR. There is a lack of awareness, expertise, funds, technical equipment and personnel to take the range of multiple actions required to tackle the AMR problem. Unless these factors are resolved, they will remain obstacles to concrete implementation of AMR action plans.

The developing countries also have other problems that compete with AMR for attention. Although it is a major problem, AMR is more like a ticking time bomb that gradually builds up and is not such an obvious problem as compared to other issues in the health sector (such as malnutrition) as well as outside the health sector (such as violence and terrorism; floods, drought, water scarcity and climate change; unemployment, poverty, migration and refugees).

In the competition for scarce funds and personnel, it is difficult for AMR to obtain the resources and attention it deserves.

7. Actions needed to address AMR comprehensively at national level

Boosting the capacity of developing countries to take required actions is therefore of key importance. The actions that need to be taken at national level include:

- Research in science, analysing bacteria mutation, gene transfer, rates and ways of spread of resistance, and AMR in the food chain
- Vastly improving surveillance and data collection on resistance in various pathogens and drugs, and resistance of bacteria in food-related animals, in food, and in the environment
- Upgrading equipment and technology, including diagnostic tools

- Infection control in hospitals, including hygiene, upgrading of rooms and theatres, equipment, air-flow systems etc.
- Formulating and implementing a national policy for rational and appropriate use of antibiotics and other anti-microbials
- Regulation and enforcement in the sale, prescription and dispensing of antibiotics
- Guidelines or regulations for medical personnel, hospitals and clinics on the appropriate use of antibiotics, and on relations with industry sales representatives
- Regulating drug companies in marketing practice to improve their role in appropriate drug use, and address incentives to sales personnel and to medical and veterinary personnel linked to volume of antibiotic sales.
- Regulation of the agriculture and livestock sector to phase out the non-therapeutic use of antibiotics, as this inappropriate use is a major factor in the AMR crisis. As a first step, antibiotics that are used for treatment of life threatening diseases in humans should be prohibited for use in animals as growth promoters, and the list should be extended.
- Addressing the contamination of the environment by residues of antibiotics.
- Educating the consumer and community on the appropriate use of antibiotics.
- Establishing a national action plan on AMR and the institutional framework for implementation, including coordination within the health sector and with other Ministries including Ministries of Agriculture, Education, Information.
- Boosting the capacity of health related NGOs, the media and educational institutions to take on AMR issues as a priority.

8. Making resources available for developing countries

In order to implement the necessary actions, the developing countries require international cooperation for the following:

- Obtaining adequate financial resources for addressing AMR. The developing countries will have to mobilise some of their own resources to carry out activities to address AMR. However some of these countries, especially the lower income countries, will require international funding to augment the nationally-sourced resources, due to the high cost involved and the competing issues that also require financing. Countries should prepare their comprehensive AMR action plans together with cost estimates and a budget with estimates of the resources that can be mobilized nationally and resources that are sought from international cooperation.
- Obtaining equipment and technology needed to address AMR. This would include equipment for surveillance and for diagnosis whether the patient's infection is due to virus or bacterium, and the presence and nature of resistance.
- Upgrading hospital facilities to improve infection control, surveillance and diagnosis, the ward and surgery environment, aimed at providing an appropriate environment for patients with resistant infections and minimising the spread of AMR within the hospital.
- Obtaining antibiotics and other anti-microbials to treat patients including those with drug-resistant ailments.
- Phasing out the non-therapeutic use of antibiotics in the animal husbandry sector and to deal with the issue of transition costs, if it arises.
- The recruitment and training of adequate numbers of personnel including for management and coordination of the AMR action

plan, surveillance, administration and enforcement of guidelines and regulations.

- Boosting the capacity of communities, civil society organisations, educational institutions and the media to raise awareness and to take actions relating to AMR.

An international fund should be established to boost the capacity of developing countries to implement the above actions to comprehensively address AMR.

Part of the fund should be used for making available technical equipment that may be required for surveillance, diagnosis and treatment.

9. The case of resistant TB shows the importance of adequate funding

Tuberculosis is expected to account for a quarter of AMR related deaths by 2050, according to the Review on AMR. According to the WHO 2014 report on TB, in 2013, there were 480,000 new cases of multi-drug resistant TB and 210,000 deaths from MDR-TB. The report states that health service capacity to treat patients has not kept up with the pace of diagnosis, creating 'waiting lists' for MDR-TB treatment. The report also makes the following points:

- "Without political commitment, financing and action by stakeholders, the MDR-TB crisis cannot be effectively addressed…"
- "The MDR-TB response needs to be fully financed for current interventions and research for new tools."
- "Key challenges in MDR-TB response include ….insufficient funding including for research."
- US$8 bil per year is required to respond to the TB epidemic, of which one fifth ($1.6 bil) is for MDR-TB detection and

> treatment…. There is an annual funding gap of $2 bil, plus another $2 bil is needed for R&D.

Similarly, significant financial resources are also required to take actions to respond to resistance in other diseases.

There are also reports that new treatments for treating resistant TB are too expensive for most patients in low-income countries to purchase and for their governments to supply at free or subsidized rates.

10. Developing countries also need affordable access to existing and new antibiotics and other antimicrobials

Another major issue of concern to developing countries is their need for affordable access to antimicrobials, including existing and future ones. Even when the medicines are not patented and there is competition from generics, many poor patients cannot afford treatment. If the antimicrobials are patented, the prices escalate and pose a big barrier to access. As resistance builds, 2nd and 3rd line drugs are needed to treat existing diseases; these new drugs are likely to be patented and expensive.

Access to the new antibiotics being developed will thus be a major issue. They should be considered international public goods accessible to people especially in developing countries which do not have financial resources to afford them.

Developing countries also need access to vaccines to prevent infections, as well as laboratory and diagnostic equipment capacity that is necessary for detecting pathogens and the existence of resistance, that will help health workers to determine the best course of treatment.

When patents become a barrier to access, countries have the policy option of making use of the flexibilities in the WTO's TRIPS Agreement, such as establishing patent criteria that improve the quality of patents by awarding patents only for genuine inventions; and issuing compulsory licenses or government use orders to increase market

competition by enabling the production and importation of generics. However, countries that exercise their right to make use of these flexibilities often find strong opposition from originator companies and their governments. The legitimate use of flexibilities should not be opposed.

It is important and beneficial if the principle of access is given priority when evaluating and developing the models for research and development of new antimicrobials.

11. The issue of financing and of access was prominent in the discussions at the WHA leading to the Global Action Plan

The issue of affordable access to antimicrobials was taken up in the discussions and negotiations at the WHA leading up to the adoption of the Global Action Plan on AMR. During the WHA session in May 2014 that adopted the resolution on AMR mandating the formulation of the Global Action Plan, several developing countries stressed the need for access to medicines.

For example, India made a statement that included the following points:

- Ways to ensure financial accessibility of people to new antibiotics have to be better addressed in the global action plan. Otherwise prices will be prohibitive for developing countries
- New ways are needed to fund R&D based on delinkage principle.
- There is need to support technology transfer to low income countries for laboratory work, surveillance etc
- There is need to mobilise financial and technical resources to support developing countries

Ghana (speaking for African countries) also stated that there is need for the global plan to consider specific needs of developing countries, as well as access to new antibiotics and diagnostics.

Responding to the statement by India on access and financing, the UK delegation said it recognised the legitimate concerns of developing countries on access to antibiotics and said that technical capacities as well as affordable drugs must be supported.

The Antibiotic Resistance Coalition of NGOs said at the WHA that the Global Plan should give clear leadership role to WHO and member states should provide resources to WHO for this. The Plan must also include delinking the costs of R&D from price of medicines.

At the closing of the session on AMR, which adopted the resolution, the Assistant Director General of WHO, Keiji Fukuda, stated: "To have successful global action plan, the specific needs of developing countries such as capacity building have to be considered."

The issues of financial resources, technology transfer and access were also highlighted by various delegations at the discussions on AMR at the WHA sessions in 2015 and 2016.

12. Also needed is an R&D model consistent with access to new antibiotics

It is imperative to develop new antimicrobial medicines, diagnostic tools, vaccines and other products, as a major part of addressing the AMR crisis. There are deep-rooted problems with R&D in relation to antibiotics. One is that there have been few or no new categories of antibiotics discovered in the past two to three decades, and there are few promising new products in the present pipeline. A reason for this may be that there is less profit to be made from antibiotics compared to drugs for diseases which require long-term treatment.

Second is that the dominant R&D model links medicine prices to the cost of R&D, with patents for the company, which results in high prices for new drugs which are unaffordable to most people in developing countries.There is thus a need for an R&D model that is compatible with access to medicine, one which delinks the cost of innovation from

the price of new medicines as well as from sales volume. This is often referred to as innovation models based on the de-linkage principle.

There are at least two main strands of thinking on what kind of R&D model to encourage. The first is to continue with the dominant model but increase the incentives to companies by providing more R&D grants to them and allowing an extended patent term for new antibiotics in the hope that this will provide more incentives to the major drug companies and result in new products. The downside is that this increases the period of monopoly and high prices, and worsens the problem of access.

The second is to establish public funding by governments and donations by charities, so that the cost of innovation is not borne by the companies. The proprietary rights to the new products would belong to the public fund or charity, which has the option of providing licenses freely to companies or institutions, at least to those from developing countries; or licenses granted to companies would be linked to conditions that favour access. This would delink the cost of innovation from the prices of the new products, which can be set at affordable levels. The WHO has been exploring options for new partnerships for open collaborative models of R&D. It is partnering with the Drugs for Neglected Diseases initiative to set up a non-profit partnership, the Global Antibiotic Research and Development Facility, to develop new affordable antibiotics that will also be subjected to a conservation scheme.[6] Another example of this new approach to R&D is the 3P Project, an initiative of MSF with other organisations involved in TB that aims to conduct collaborative research to develop new treatment regimes for TB by sharing data and intellectual property, and by paying for research using a novel combination of grants and prizes[7].

6 WHO, Global action plan on AMR: Options for establishing a global development and stewardship framework (Doc A69/24 Add.1 13 May 2016).

7 Medicins Sans Frontieres, 2016. (i) Lives on the Edge; (ii) Issue Brief on Time to Align Medical Research with People's Health Needs; and (iii) Press Release on medical research policies (14 Sept 2016).

Another idea, championed by the Review on AMR, is to establish an innovation fund to provide large payments or "market entry rewards" to companies that have succeeded in producing new antibiotics. This would provide incentives by enabling the companies to recover their innovation cost. However it is not clear whether this will result in setting affordable prices by the recipient companies, which may be allowed to obtain patents or even extended terms for patents, or whether they will use their monopoly to set high prices, in which case the objective of access would not be met. For it to be viable socially and not only commercially, the market entry reward scheme should be matched with the access objective.

The establishment of R&D systems combined with meeting the access objective should also be undertaken for diagnostics and vaccines and other products.

The UN Secretary General's High-Level Panel on Access to Medicines states that its report "emphasizes that market-based models of innovation for AMR are unsustainable. Funding for R&D to address AMR and related challenges must be operationalized through delinkage models. Indeed, the challenge of AMR represents an important and incontestable context in which the viability of delinkage innovation models can be fully explored."[8]

13. Summary of the recommendations regarding meeting the needs of developing countries

Future programmes dealing with implementing actions on AMR should include the following points:

- Fully take into account the challenges and needs of developing countries

8 Report of the UN Secretary-General's High-Level Panel on Access to Medicines, p31.

- Strong international cooperation for building capacity of developing countries to address AMR
- Mobilising of financial resources to support capacity building and implementation of AMR action plans in developing countries.
- Establish a fund for capacity building in developing countries on AMR issues, to be based in WHO, and linked to implementing the Global Action Plan on AMR.
- Technology transfer and the provision of technical equipment including diagnostics and knowhow to developing countries on grant or concessional terms.
- Ensuring affordable access to existing and new anti-microbials, especially to people in developing countries; also, affordable access to vaccines and diagnostics.
- Developing and encouraging R&D models which delink the price of anti-microbials and other products from the cost of R&D; including where the innovation costs are financed through public funds and charities, and the license to produce the new products is available cheaply or at low cost, at least to companies and institutions in developing countries.
- Support to developing countries for capacity building and financing of the comprehensive range of activities in addressing AMR at national level, including prevention of infections, appropriate use of antibiotics, new regulations including on marketing, prescription and dispensing of drugs and their enforcement, reform of antibiotic use in agriculture, improvement of practices in hospitals and clinics, educating the public, etc.

II

Dangers of Modern Animal Farm and Antibiotic Resistance

The Star, 12 April 1996

The Mad Cow Disease outbreak has exposed the dangers inherent in the modern intensive livestock system, where animals are kept in cramped and unnatural conditions which are ideal for the generation and spread of many infections.

The proteins and drugs put in animal feed have also led to new diseases like BSE and to new strains of antibiotic-resistant ailments which in turn pose an increasing threat to human health.

THE Mad Cow Disease outbreak has brought to public attention the dangers inherent in the modern intensive system of livestock production.

A review of this system, and a search for better alternatives, including traditional methods, is now urgently needed to prevent the spread of diseases amongst animals as well as people.

The intensive rearing of animals, and the centralised distribution of artificial feed, set the framework within which the Mad Cow Disease or BSE spread from infected sheep to cattle, and then to humans, in which it is known as CJD (Creutzfeldt-Jakob disease).

The intensive livestock system started in the United States early this century but in the United Kingdom it increased dramatically

only during and after the Second World War.

Some developing countries still practise traditional ways of livestock rearing, but in many others (like Malaysia) there has also been a recent shift to the intensive system.

In his 1994 book *Hard to Swallow*, Leeds University microbiologist Professor Richard Lacey decribes intensive rearing as being "concerned with the maximum yield of meat, milk or eggs from the minimum resources."

The main aim is to attain "efficiency", defined by the profit-oriented goals of increasing the amount of meat and other products, and reducing costs and prices.

The animals are kept in crowded and confined conditions such as in sheds, cages and pens. Besides being cruel to the animals, intensive rearing involves dangerous farming practices.

Because of the cramped and unnatural conditions, the animals develop ailments which can spread widely among them.

A new book by the Consumers' Association of Penang, *The Revenge of the Killer Germs* published in 1996, describes how US farm chickens typically suffer from retarded growth, eye damage, blindness, kidney and brain damage, deformed beaks and joints.

"Also the stress, overcrowding, lack of exercise and unnatural conditions lead the animals to go mad with fear and hysteria, with some pecking viciously at each other or in extreme cases to eviscerate and eat each other.

"A US government report found that over 90% of chickens from many flocks have chicken cancer. Living in a relentless state of stress, they are also prone to a whole range of infectious diseases."

A prime example is the infection of chickens and eggs with salmonella, the group of bacteria that can cause severe food poisoning, vomiting and diarrhoea or even typhoid and paratyphoid fever.

Says Lacey: "It has been known for years that modern intensive methods of broiler and egg production are addled with salmonella."

The bacteria develop in a minority of chickens at the farm, and then spread during the slaughtering and preparation stages. At the point of sale in the UK, most chickens will contain salmonella, anything from a thousand to a million bacteria on each chicken.

Salmonella is also spread directly from the chickens' ovaries to the eggs as they are being formed, in a process called "transovarian." Lacey estimates that one in 5,000 eggs in the UK is salmonella-contaminated, whilst a recent study in Devon found a rate of one in 200.

In 1988, the UK Junior Health Minister announced that most of the country's egg production was contaminated with salmonella.

Recent surveys in the United States showed a high extent of salmonella contamination of intensive chicken and egg production.

For example, 60 percent of samples of recycled chicken protein going into animal feed contained salmonella.

European surveys published in 1993 show salmonella present in up to 75 percent of chicken samples.

If the modern farming system produces a high incidence of diseases in the animals, these ailments are passed on to humans through consumption of infected meat and other routes.

There is now a fast-rising incidence of food poisoning and food-related diseases. Lacey estimates that food poisoning cases jumped four-fold in the UK and 2.5 times in the US between 1982 and 1992.

According to *Time* magazine in 1994, at least 500 people in the US die annually from microbes in meat and poultry and an additional 6.5 million fall ill.

Besides ailments caused by conditions of the animal farms, another major way in which diseases originate and spread is through the artificial animal feed.

Added to the cereal base of the feed compounds are vitamins, antibiotics and other drugs, protein supplements and minerals.

Each of the additives could give rise to health problems.

In the case of BSE, the infection route was through brains and organs of infected sheep processed into protein concentrates and fed to cattle.

The use of antibiotics in feed has caused serious problems. These drugs are fed to animals to counter diseases. They are also used to promote animal growth and weight.

In time many new strains of bacteria develop that are resistant to the drugs. The antibiotic-resistant germs can spread to humans through food consumption, touching meat, contact with the animal, by air, dust, flies and other insects.

Another problem is that there are drug residues in meat, which can pass on to humans. For instance, in 1990, the UK government admitted that 5 percent of pork samples tested were tainted with the anitibiotic sulphanamide.

According to *Time* magazine, a 1992 study by the US Congress office found traces of 64 antibiotics in milk at levels that "raise health concerns" as they could produce resistant germs in milk drinkers.

In developing countries, where laws are more lax, the situation may be worse. For Malaysia, CAP's 1996 book gives disturbing evidence of "rampant" use of antibiotics in livestock farms.

More disturbingly, CAP tests on meat samples sold in Malaysian markets found that a majority of bacteria were resistant to two types of antibiotics, thus demonstrating the existence of food-poisoning "supergerms" that could not be treated with some medicines.

Another problem is that in people who unknowingly take in antibiotics through their food, resistance to the drugs can also build up in the bacteria.

These two factors (the spread of drug-resistant bacteria from animals to man, and the buildup of drug-resistant bacteria in humans consuming drugs in their food) have led to an increase in new strains of human infections that cannot be treated by antibiotics.

This is now contributing to the wave of new, resurgent and drug-resistant diseases.

According to the CAP book, US government scientists reported that 90 percent of resistant strains of salmonella found in humans could be traced back to livestock.

For example, in 1985 several hundred people developed diarrhoea due to antibiotic-resistant salmonella newport after eating hamburgers, and two died. Researchers traced the bacteria to a farm where the cattle had been dosed regularly with penicillin and tetracycline drugs.

In 1984, Dr Scott Holmberg and colleagues at the US Centres for Disease Control concluded that "antimicrobial-resistant enteric bacteria frequently arise from food animals and can cause serious infections in humans."

In his book, *Overcoming illusions about biotechnology*, Filipino agricultural scientist Nicanor Perlas reveals additional hazards to human health resulting from intensive animal production systems.

Besides drugs, other hazardous residues in meat include pesticides, environmental contaminants and cancer-causing agents.

Says Perlas: "Many of the substances used in sustaining intensive animal production systems are known to cause or are suspected of causing cancer, birth defects, reduced fertility, reproduction effects, neurotoxicity or other toxic effects."

He points out another problem associated with intensive livestock rearing: the rapid decline in genetic diversity within each animal species.

The intensive systems have led to greater uniformity of breeding stocks for commercial production. For example, over 90 percent of dairy cattle in the US by the early 1980s was accounted for by just the Holstein breed because of economic factors favouring maximum milk output per cow.

"This loss of genetic diversity is a very serious problem," says Perlas. "Genetic uniformity makes animal production systems vulnerable to changing biophysical and social environments."

For example, in November 1983, the US declared a state of "extraordinary emergency" due to an outbreak of avian flu among poultry flocks.

"The genetic, chemical and drug defence system of the poultry industry were breached by the avian flu virus, which spread rapidly because of the relative genetic uniformity of poultry breeds," explains Perlas.

"By the time the disease was controlled, 12 million poultry animals had to be destroyed. In Pennsylvania alone, farmers lost US$51.9 million."

III

Revamp Needed of Livestock System Itself

The Star, 12 April 1996

The Mad Cow Disease outbreak would have served some positive purpose at least if it heightens public awareness of the dangers of modern animal production and spurs policy makers to reform it.

There should be regulations to improve the cramped conditions of the animals and to stop the use of dangerous components in animal feed. More basically, what is needed are a review of the intensive system itself, a revival of traditional livestock rearing methods and less meat consumption.

GIVEN the wide range of problems associated with intensive livestock production, and the threats posed to human health, policy makers everywhere should urgently review the whole system of animal production.

The tragic incident of the Mad Cow Disease (BSE-CJD) outbreak would perhaps have some beneficial effect if it could highlight the ecological and health aspects of modern intensive animal rearing.

At the least, drastic controls should be imposed on the components of animal feed, especially drugs and protein supplements.

The inclusion of animal organs and remains in feed should be banned or severely curtailed, as this can spread infection in disastrous fashion, as evident in the Mad Cow Disease.

The liberal use and misuse of drugs in animal feed should be addressed equally urgently, as this has increased the resistance of many bacteria to many types of antibiotics.

The spread of drug-resistant supergerms due to feeding of drugs to animals (and also to antibiotic over-prescription by doctors) has led to ailments like food poisoning that are less susceptible to medical cure.

There is also the resurgence of diseases such as tuberculosis, cholera and malaria as medicines have less and less effect on many strains of the infections.

One of the reasons antibiotics are fed to animals is to boost their growth and weight. This is purely a profit-making objective, and should be banned (as suggested by Prof. Lacey) for the sake of our health.

There is really no sane reason why this practice, which contributes to the development of resistant strains of serious and potentially life-threatening diseases, should be allowed.

As for the use of antibiotics to prevent or treat illness in the animals, there should surely be much stricter controls. Drugs that can cause harm in humans, and which are importantly used by people, should be banned so as to prevent a higher incidence of drug resistance.

In Australia, the use of antibiotics and hormones in livestock feed was stopped twenty years ago, whilst most developed countries restrict the use of certain drugs. In Malaysia, the laws are much more lax, and thus the use of antibiotics in animal farms is more rampant.

But regulating animal feed alone would be inadequate. There should be a review and revamp of the system of modern intensive livestock rearing itself.

At least a reform is in order. There should be regulations that prevent such excessively cramped conditions that chickens are placed in. The treatment of other animals should also be subject to guidelines.

Examining the horrors of Mad Cow Disease and after detailing the

difficulties in acting on the disease, Lacey in his 1994 book had already advocated that: "Prevention of such a disease is surely preferable, and this is one very good reason to abandon current methods of animal farming and feeding."

Indian scientist and ecologist, Dr Vandana Shiva, contrasts the problem-filled modern intensive system with India's "culturally sophisticated and ecologically sound livestock economy."

According to her, this traditional system is characterised by "diverse disease-resistant animal breeds and the decentralised sustainable and integrated livestock-crop production systems of small farmers."

Unfortunately, says Dr Shiva, the traditional system itself is under severe threat in India from trade-driven policies promoting beef exports, factory farming and giant slaughterhouses.

"Is this globalisation of non-sustainable and hazardous systems of food production not symptomatic of a deeper madness than what the infected cows in UK are suffering from?" she asks.

Scientists like Lacey, Shiva and Perlas advocate a return to (or in the case of some developing countries, the preservation of) more traditional systems of livestock production, with the following features:

- The animals are not kept confined, but allowed to roam quite freely, thus the term "free range."
- Livestock rearing goes together with agriculture in mixed farms, unlike in the modern system. The manure from free-ranging animals is used to maintain soil fertility.
- The animals are given natural food. Part of the agricultural produce, straw and waste is used to feed the animals. Drugs and hormones are not given to promote their growth or weight.
- A wider diversity of each species is reared, and this guards against susceptibility to disease outbreaks.

What if the traditional systems produce less meat and milk, and lead to higher costs and prices?

That, say the advocates, is a small price to pay, or indeed no price at all.

Firstly, the modern intensive system also has high hidden costs, paid for by the health of consumers and their medical bills. That system is also not sustainable as eventually the health of animals and humans is affected, as the BSE outbreak shows.

Secondly, the production of meat products may be a sure case in which "quality is more important than quantity."

Consumers today are more aware of the health drawbacks of over-consumption of meat, such as cholesterol build-up and greater susceptibility to heart ailments and stress.

They may be willing to eat less meat and pay a higher price if they are sure that the meat is safe from bacteria, BSE-carrying prion proteins, drugs and other poisons.

For the better-off consumer who is already taking too much meat, a switch in balance towards more vegetables and fruits would surely be healthy. It was recently reported that as a result of the Mad Cow Disease scare, the number of vegetarians has risen in the UK.

Lacey says: "The realisation that we do not need to eat meat daily, or even weekly, or even at all, still has to come about for most consumers...

"Let us suppose farming methods do improve towards organic, free-range husbandry and the mixed farm, one inevitable consequence is that the price of the product will increase, but perhaps by not too much.

"More expensive meat, and probably fish, does not, however, mean that the total food bill will increase, because the alternative vegetable-based food that we will eat could well be cheaper, even than the cheapest burger."

Consuming less meat would also give a positive boost to the environment. The rearing of animals for food takes up much land and results in deforestation.

For example, it is well known that cattle rearing in Central and South America to provide beef for burgers in the US, is one of the major sources of tropical forest loss.

Moreover, a lot of land and resources are used to produce crops to feed the animals. Much more energy resources are used for livestock rearing than the energy contributed by these animals as food to humans.

Less meat consumption would thus free land and other resources to produce crops that directly feed people, and thus help prevent a looming crisis of food shortages that some scientists predict in the next century.

IV

The Dangers of Antibiotics in Animal Feed

The Star, 12 Aug 1996

When Malaysian Health Minister Datuk Chua Jui Meng revealed that half the chickens sold in the country contained cancer-causing nitrofuran, it reopened a long-standing controversy over the widespread use and dangers of antibiotics in animal feed. Reviewing the debate, Martin Khor explains why the use of such drugs in animal feed should be banned or tightly regulated.

IS it safe to consume chickens that have been fed antibiotics?

This question occupied the attention of Malaysians after revelations in August that half the chickens sold in the local markets may be contaminated with high levels of nitrofuran, an antibiotic known to cause cancer.

Health Minister Datuk Chua Jui Meng revealed that a Ministry survey found 51% of the chicken samples bought from various towns to contain nitrofuran at levels up to 4,000% above the Veterinary Department's guideline level.

Datuk Chua said his Ministry did not permit nitrofuran in chickens, and criticised the chicken industry for double standards in exporting nitrofuran-free chicken whilst selling unsafe meat locally.

The following day saw a response from the Veterinary Department, which oversees the practices of the livestock industry. Its deputy director-general Datuk Dr Anwar Hassan defended the use of

nitrofuran. He claimed its level in chickens would be nil seven days after the feeding as it would be excreted.

The use of alternative antibiotics would raise the chicken price by 50 cents, and if chickens were bred in a microbe-free environment, an egg would cost RM14.50, Dr Anwar added.

The Federation of Livestock Farmers' Association claimed it would take a person 28,500 years eating chicken containing nitrofuran to contract cancer.

Consumer groups, led by the Consumers' Association of Penang (CAP), called for an immediate ban on the use of nitrofuran in animal feed.

The Domestic Trade and Consumers' Affairs Minister Datuk Abu Hassan Omar called for a safe level of nitrofuran to be determined to dispel public fear about eating chicken.

Datuk Chua, meanwhile, stuck to his point. He did not know how many years it would take for someone to get cancer from eating nitrofuran-contaminated chicken, but 'all chickens sold must be nitrofuran-free.'

The Veterinary Department allows the livestock industry to use antibiotics. There is hardly any restriction or control on the sale or use of drugs in animals and animal feed.

On the other hand, the Food Regulations 1985 prohibit the presence of antibiotics in meat, meat products and milk.

This implies that whilst livestock farms are allowed to feed antibiotics to their animals, by the time the meat is sold in the markets it must no longer contain the antibiotics.

In theory, if the antibiotics are no longer fed to the animals several days before they are slaughtered, the medicines would all have been excreted, and the meat would be free from contamination.

In practice, as the Health Ministry test showed, half the chickens sold still had nitrofuran. Obviously the farmers had not followed the

'withdrawal schedule' and the drug had been given up to a few days before the chickens were slaughtered.

Nitrofuran is only one of the drugs used to feed chickens. If the tests had covered other antibiotics as well, the incidence of contamination would have been much higher. Maybe even 100%.

There are good reasons why the law prohibits antibiotic residues in meat.

In the case of nitrofuran, as Datuk Chua noted, there are stringent laws against its use in developed countries, and the Food and Agriculture Organisation does not stipulate any permissible level for it.

When no permissible level is set, the implication is that the substance is 'unsafe at any level'.

In the United States, the Food and Drug Administration ordered the poultry and pork industry to stop treating stock with two nitrofurans (furazolidone and nitrofurazone), citing cancer risks.

As early as 1984, CAP had called for a ban on nitrofuran and several other drugs in animal feed in Malaysia.

The nitrofuran scare is only the tip of a large iceberg. Many different drugs are used in the livestock industry, such as antibiotics (to treat illness and promote growth); hormones (to fatten and promote growth); steroids (to build up bulk and weight); tranquilisers (for anti-stress). Their risks to human health are increasingly being exposed.

The health risk is clear when a cancer-causing drug like nitrofuran is passed on from chicken meat to humans.

Other drugs used in animal feed can also have serious side-effects. For instance, residue of drugs in the penicillin family can cause allergic reactions in some people.

Neomycin, gentamicin and streptomycin can have toxic side-effects, such as deafness and kidney trouble after high doses and prolonged use. Tetracycline can worsen a kidney disease. Trimethoprim is not for the newborn or pregnant or people with impaired kidney function.

All the above drugs are found in animal feed and animal health products manufactured by multinational companies, sold in shops in Malaysia, and used in livestock farms.

Perhaps even more dangerous is that consumption of these antibiotics builds up resistant strains of bacteria in the animals.

These super-germs are resistant to antibiotics. When these resistant bacteria are passed on to people who consume the meat, they are exposed to diseases which would now become difficult or impossible to treat with antibiotics.

The World Health Organisation has recently sounded the alarm bell on the reemergence of deadly diseases caused by antibiotic-resistant bacteria.

Universiti Sains Malaysia's pharmacy professor, Dr Dzulkifli Abdul Razak, warned that nitrofuran in chicken could cause a build-up of antibiotic resistance in humans. 'Once there is a resistance to the drug, it would not be effective in treating an infection.'

According to a recent CAP book, *The Revenge of the Killer Germs*: 'If these mutant, disease-causing germs cannot be killed by standard antibiotics, then a simple illness they cause like food poisoning can become a killer.

'People who are most vulnerable — children, the aged or infirm — may die before doctors can find an antibiotic that works.

'Even if the resistant germs don't cause you to fall sick, they can nonetheless multiply in your body, and transfer their antibiotic-resistant factor to other unrelated bacteria in your body. Should you get an infection by other harmful germs which have acquired drug resistance, then antibiotic treatment may not work.'

CAP surveys through the years have found that there is rampant use of antibiotics in Malaysian farms to treat and to fatten chickens and pigs. They use a wide range of drugs, including standard ones commonly used on patients in clinics and hospitals.

Recent CAP tests also found many types of meat (chicken, beef, mutton and pork) containing super-germs that are resistant to antibiotics:

- 86% of bacteria samples from the meats were resistant to ampicillin, and 28% were completely resistant to it.
- 58% of bacteria samples were resistant to amoxycillin and 3% were completely resistant.

Both ampicillin and amoxycillin belong to the penicillin family of drugs and are widely used for a large range of ailments.

A finding that bacteria are resistant to the drug means that the antibiotic cannot kill the germs. This means the drug will also not work on people who are sick as a result of eating such bacteria-infected meat.

Earlier CAP tests on chicken, pork and mutton also found four strains of disease-causing bacteria resistant to common antibiotics.

- In chicken meat, penicillin failed to kill the E. coli bacteria and the drugs chloramphenicol and neomycin had little effect on E. coli and two other types of bacteria.
- In mutton, three types of bacteria were completely resistant to penicillin, while chloramphenicol and neomycin had little effect.
- In pork, the various kinds of bacteria were all resistant to penicillin; neomycin was almost useless against three bacteria strains; tetracycline and chloramphenicol had very little effect on the E. coli bacteria.

E. coli has been in the news recently as a particular strain of this bacteria (E. coli O-157) has caused Japan's most serious outbreak of food poisoning, in which over 9,000 people have been stricken and seven killed.

Given the growing evidence of the dangers, many countries have banned or severely restricted antibiotics in animal feed.

Australia, France and Switzerland are among countries that have banned the use of any antibiotics in animal feed. Australia and France also disallow the use of hormones.

The US has banned nitrofurans, chloramphenicol and ampicillin in animal feed, whilst Germany forbids penicillin and tetracycline, and the Netherlands has prohibited penicillin and tetracycline.

There is now more than enough evidence that self-regulation for safety in the livestock industry does not work.

The outbreaks of Mad Cow Disease in Europe and the food poisoning epidemic in Japan are warnings that cannot be ignored. Food safety of the public must come before profits of a few.

V

"Super Germs" Causing Global Health Crisis

The Star, 10 February 1997

With more bacteria acquiring resistance to a wide range of antibiotics, many diseases that were once thought defeated have made a dramatic and deadly comeback. The situation has reached such alarming proportions that health epidemics could well displace other issues at the top of the global agenda very soon.

OPEN up a newspaper these days and you will find yet another frightening health report.

"Malaria makes ferocious comeback, deadlier than ever." "Japan reels under e-coli epidemic." "100,000 new CJD cases predicted." "Crisis in infectious diseases."

These articles are now coming in a flood. They comprise an issue that has increasingly grabbed attention: new and re-emerging infectious diseases. The way the crisis is developing, it may soon jump to the very top of the global agenda.

The most frightening aspect is the growing resistance of the disease-causing bacteria and microbes to antibiotics.

Some strains have become immune to a wide range of different antibiotics, a condition called "multiple drug resistance". And a few strains of some microbes are already immune to all drugs, making the diseases untreatable by modern medicine.

The ability of the bacteria to change themselves to survive an attack

of antibiotics has led to the re-emergence of diseases that were once thought to have been largely defeated.

Recently in India, a leading medical social worker told me she had just visited a community where a thousand people had died of malaria. Though the numbers are shocking, this is just the tip of an iceberg, as the reemergence of old infectious diseases has reached epidemic proportions in that country.

Worldwide, malaria strikes up to 500 million people a year, killing at least two million, and the numbers are going up. With this disease, there are two resistance problems at the same time.

The anopheles mosquitoes, which carry the malaria parasite, are getting resistant to insecticides whilst the malaria parasites are getting resistant to anti-malarial drugs.

This drug resistance is most serious in the case of flaciparum malaria, the deadliest form of the disease. Resistance to choroquine is widespread and in South-east Asia resistance to multiple drugs is now common.

Last year, the outbreak of food poisoning epidemics caused by a new deadly strain of the Escherichia coli bacterium hit the headlines. About ten thousand people in Japan were struck down by E. Coli 0157 (with several deaths) and the same ailment killed 16 people and made hundreds ill in Scotland.

This strain was unknown before 1982 but has since spread. According to the London-based *Independent*, there were 792 cases of E. Coli 0157 in 1995 in England and Wales, a 93 per cent increase.

The bacterium spreads in undercooked beef, milk and cheese. It causes bloody diarrhoea, severe cramps and vomiting, and death in the most serious cases.

In January, the World Health Organisation issued a report on another food-borne disease, salmonellosis, which is contracted by eating meat, poultry, eggs and milk.

Antibiotic-resistant strains of salmonella bacteria that are difficult to

control have emerged due to use of antibiotics in animal husbandry.

Compared to 1980 some European countries saw a staggering 20-fold increase in cases of the disease in the last ten to 15 years. The same pattern is seen in Southeast Asia and West Asia.

"The bad news is that since the beginning of the 1990s, strains of salmonella typhimurium which are resistant to a range of antibiotics have emerged and are threatening to become a public health problem," says the WHO.

One strain, salmonella typhimurium 104, has become resistant to seven types of antibiotics. The incidence shot up more than ten times in England and Wales, from 300 to 3500 cases a year between 1990 and 1996. Those infected with this strain are twice as likely to be hospitalized, with ten times higher death rates.

To make things worse, adds the WHO, a particular variant has developed multiple drug resistance as an integral part of the genetic material of the organism. This means it is likely to retain its drug resistance genes even when drugs are no longer used.

The case of salmonella is part of a general trend, concludes the WHO. "The incidence of bacterial resistance has increased at an alarming pace in recent years and is expected to continue rising at a similar or even greater rate in the future as antimicrobial agents or antibiotics lose their effectiveness."

Another WHO report presents many more examples of this serious phenomenon.

Staphylococci, which can cause food poisoning, skin infections and other serious disorders, have developed resistance to all antibiotics except vancomycin.

"If vancomycin-resistant strains were to emerge, some of the most prevalent hospital-acquired infections would become virtually untreatable," the WHO says.

This could be disastrous as infections acquired by patients whilst in hospitals are, ironically, already a leading cause of deaths.

About two million people suffer infectious complications acquired in hospitals every year in the United States alone, including about 70,000 deaths.

The highest frequencies of hospital infections are in the Eastern Mediterranean and South East Asia. In Mexico they are the third leading cause of death.

The problem became serious due to increasing drug resistance of bacteria. Such bacteria caused 60 percent of the hospital-acquired infections in the US.

By the early 1980s, many hospitals detected methicillin-resistant staphylococcus aureus infections, which cause wound infections and pneumonia and can be fatal.

"In many cases they are treatable only with vancomycin, an antibiotic that is increasingly regarded as the last defence," the WHO says.

"But if methicillin-resistant bacteria also become resistant to this drug, many life-threatening infections would be untreatable, and hospital outbreaks involving these strains would be very difficult to contain."

Another type of bacteria, enterococci, which also commonly causes hospital infections, is also multiple-drug resistant and can be treated only with vancomycin.

However, resistance to vancomycin has already developed in recent years. In the US in 1994, 14 percent of enterococci found in patients in intensive care units were resistant to vancomycin.

Other diseases that are getting harder to treat due to drug resistance include:

- TUBERCULOSIS: Strains of the m. tuberculosis bacterium that are resistant to anti-TB drugs are already widespread. The most dangerous form of TB occurs when cases become virtually untreatable.
- TYPHOID: Salmonella typhi, the bacterium that causes typhoid fever, has developed resistance to commonly used drugs.

Resistant strains caused outbreaks in India and Pakistan recently. Without effective treatment, typhoid kills 10 percent of those infected. In Southeast Asia, over half the strains already have multiple drug resistance.

- PNEUMONIA AND INFLUENZA: The pneumococci and haemophilus influenzae bacteria cause acute respiratory infections in children. Both are becoming more and more resistant to drugs. Strains of pneumococci are resistant to penicillin in 18 percent of cases in the US and 40 percent in South Africa.

  The most virulent type of h. influenzae is now frequently resistant to ampicillin and other strains are also resistant to other drugs. "In brief, doctors wordwide are losing some of the most useful and affordable antibiotics against the two bacteria which are the major cause of death in children," says the WHO.
- DYSENTERY: Shigella dysenteriae has caused severe diarrhoea outbreaks in Africa recently, with the epidemic strain acquiring increasing resistance to standard antibiotics. Epidemic dysentery caused by this strain kills up to 15 percent of those infected.
- GONORRHOEA: The bacterium causing this sexually transmitted disease is resistant to penicillin and tetracyclines in most countries. More expensive drugs needed to treat it are often unavailable.

This grim catalogue of events has led the usually cautious WHO to ring alarm bells in crisis-laden terms. "The next few years are certain to be critical for the future of antimicrobial drugs," it concludes.

Drug resistance will increase, and doctors worldwide may resort to methods used before the antibiotic era. For example, in New York, TB patients who refuse to comply with recommended treatment are sometimes isolated on a former prison island, used much as sanatoria were used in the past.

"Disease control strategies will be seriously threatened by mounting

drug resistance levels among bacteria which cause the most important and frequent diseases worldwide.

"Developing countries will be facing the impossible task of controlling diseases with only scarce expensive drugs which will not be affordable for all sick patients."

VI

The Threat of New Diseases

The Star, 17 February 1997

The resurgence of old infectious diseases is now joined by the emergence of new diseases (such as AIDS, Ebola and the human variant of Mad Cow Disease) to threaten human health in the years ahead. Martin Khor examines some of these new diseases and the causes.

WHILST the resurgence of infectious diseases such as malaria, tuberculosis and cholera is sounding warning bells around the world, equally alarming is the emergence of new diseases with high fatality rates.

In the past 20 years, at least 30 new diseases have emerged, threatening the health of hundreds of millions, according to the World Health Organisation.

The situation is grave because the new bacteria or viruses spread rapidly, whilst health policy makers and scientists are still groping to find solutions.

As the WHO's World Health Report 1996 put it: "For many of these diseases there is no treatment, cure or vaccine and the possibility of preventing or controlling them is limited."

The best-known new disease is AIDS, which emerged in the late 1970s. The HIV (human immunodeficiency virus) causing AIDS was unknown until 15 years ago but it has since infected 24 million adults and 4.5 million of them have since developed AIDS.

The number of HIV cases could grow to 40 million by the year 2000.

A new breed of deadly haemorrhagic fevers has also struck in Africa, Asia, the US and Latin America.

The most notorious is Ebola, which appeared in Africa in 1976. In the past two years it has struck in Cote d'Ivoire, Liberia and in Zaire. The well publicised Ebola epidemic in Zaire in mid-1995 affected 316 people, of which 245 died, giving a very high 77 percent fatality rate.

In the US, the hantavirus pulmonary syndrome was first recognised in 1993. It causes respiratory failure and has a fatality rate of 50 percent. Cases were also found in Canada, Argentina, Brazil and Paraguay.

Also newly identified were the guanarito virus in 1991 (causing Venezuelan haemorrhagic fever) and the sabia virus in 1994 (causing Brazilian haemorrhagic fever).

New animal diseases also pose risks to human health through the food chain. These are difficult to evaluate or predict, says the WHO.

The most dramatic example of this is the "mad cow disease" or BSE (bovine spongiform encephalopathy). Fears have grown that the infectious agent may be passed through the food chain to cause a variant of the incurable CJD (Creutzfeldt Jakob disease) in humans.

Other new diseases, reported by the WHO, include the following:

- A completely new strain of cholera, called Vibrio cholerae 1038, appeared in India in 1992 and has since spread to Southeast Asia and Western China.
- Several new hepatitis viruses have recently been identified. Hepatitis B has infected 2 billion people alive today, of whom 350 million are chronically infected and at risk from death from liver disease. Similarly at risk are another 100 million who are chronically and incurably infected by Hepatitis C.
- Epidemics of foodborne and waterborne diseases due to new organisms (such as cryptoporidium) or new strains of bacteria

(such as E. coli) have hit rich and poor countries alike.

- The threat of a new global influenza pandemic is increasing. Major shifts in the make-up of influenza viruses occur every 20 years or so, triggering large epidemics and causing thousands of deaths. The next such shift is expected very soon.

The new and re-emerging diseases are part of the totality of infectious diseases that cause about 17 million deaths a year worldwide. This is a large part of the 52 million deaths from all causes annually.

What causes the rapid spread of infectious diseases? The following have been identified by the WHO:

- The rise in poverty has made more people vulnerable to diseases. A fifth of the world's people suffer extreme poverty, half of the population lack access to essential drugs and a third of children are malnourished.
- Population growth and urbanisation leading to overcrowded and unhygienic conditions (including lack of water and sanitation) provide breeding grounds for infectious diseases;
- Economic and social crises in many countries have led to under-development or even collapse of public health systems. "The immediate result is a resurgence of diseases that were once under control or should be controllable, given adequate resources."
- Rapid increases in air travel, tourism and trade in food have transported disease-producing organisms rapidly across continents;
- The global food trade creates new opportunities for infections to flourish, such as livestock shipment; food production, storage and marketing; and altered eating habits;
- Migration and movement of refugees and displaced people provide breeding grounds for infectious diseases and their spread.
- Environmental change is a major cause. Expanding areas of

human habitation put millions at risk from pathogens previously rare or unknown as causes of human disease. The effects of climate change may also give some diseases the opportunity to spread to new areas.

- Antimicrobial drugs have become less effective. Microbes continue to evolve and adapt to their environment, adding antibiotic resistance to their evolutionary pathways.

Of these factors, it is the growing resistance of disease-causing microbes to antibiotics that has received special attention from the WHO report.

It says the emergence of drug-resistant strains of micro organisms or parasites is promoted by treatments that do not result in cure.

"The increasing use of antimicrobials worldwide, often in subtherapeutic doses and sometimes in counterfeit form, guarantees that this problem will increase," it says.

The WHO adds: "There is strong evidence that a major cause of the current crisis in antimicrobial resistance is the uncontrolled and inappropriate use of antibiotic drugs, in both industrialised and developing countries.

"They are used by too many people to treat the wrong kind of infection, in the wrong dosage and for the wrong period of time."

Expensive drugs designed to treat a range of infections are being overused, especially in rich countries. The problem is compounded in developing countries by ready availability of over-the-counter drugs.

This allows patients to treat themselves with the wrong medicine or in quantities that are too small to be effective. Substandard drugs lacking enough amounts of active ingredients worsen the resistance problem.

The WHO also pinpoints the overuse of antibiotics in animal feed. "More than half the total production of all antimicrobials is used in farm animals, either for disease prevention or for growth promotion.

"Drug resistant bacteria are passed through the food chain to the consumer, where they may cause disease or transfer the resistance to human pathogens."

More and more drugs are now ineffective against many strains of infections. The implications are "awesome", says the WHO. Drugs that cost a lot to produce and take ten years to reach the market have only a limited life span in which they are effective.

"As resistance spreads, that life span shrinks. As fewer new drugs appear, the gulf widens between infection and control. So far, the pattern of excessive or inappropriate use and development of resistance has been repeated after the introduction of each new antimicrobial."

In other words, the bacteria and viruses are winning the race against drugs. They are transforming themselves faster to resist drugs, than the rate of introduction of new effective drugs to overcome the super germs.

Given that a large part of the problem is the overuse and inappropriate use of antibiotics by doctors and in animal husbandry, it is surprising that the WHO is so mild in its action proposals in this regard.

It notes that "more appropriate use of drugs by doctors and patients is essential to slow the emergence of resistance."

The WHO itself has introduced a network to monitor drug resistance, and calls for appropriate regulations concerning drug promotion and accessibility, and says that all doctors should have access to guidelines on rational drug use.

These "soft" proposals are hardly going to make a dent. What are required, at minimum, are effective campaigns to regulate the marketing practices of drug companies; to set up a system whereby doctors are made more accountable for the medicines they prescribe; to curb the wrong and excessive use of drugs in farms that rear animals

for food; and to educate patients to know about the medicines they are given and their side effects.

Moreover, much more research should be done on why and how microorganisms are able to develop resistance to drugs, how this resistance spreads among different bacteria and viruses, and also why new diseases emerge. Factors promoting these should be tackled quickly and strongly, or else the deadly microbes will keep spurting ahead in their race against humans.

VII

Diseases Emerge as Germs Break "Species Barriers"

The Star, 24 February 1997

As medical experts and health authorities puzzle over the rise of new diseases and re-emergence of old diseases, scientists are concerned about the way in which disease-causing microbes have been able to "break species barriers" and cross over from one species to another. This article looks at "horizontal gene trasfers." A subsequent article examines the role of genetic engineering. (See article VIII.)

A major aspect in new and re-emerging diseases is that infection-causing microbes have found ways to cross over from surviving in one species to another.

For example, viruses that used to inhabit animals such as monkeys or cows, could also affect human beings.

This "breaking of species barriers" has emerged as a very significant part of the chain of developments leading to the global crisis in infectious diseases.

In many cases, specific viruses, bacteria and other microbes exist only in specific organisms, be they plants, marine life, insects, animals or humans.

In other words, a particular microbe may be "host-specific", surviving only within one or a narrow range of life-forms, and unable to transfer to or live within other organisms.

Some of the most dramatic of the new diseases emerged when viruses that used to only inhabit animals were able to "cross species barriers" and infect humans.

The origins of the HIV that causes AIDS are still unknown, but the virus is related to viruses that cause AIDS-like illness in monkeys. It is widely believed that the crossing of the virus from monkeys to humans led to AIDS.

In the case of Ebola fever, which first appeared in 1976, the natural carrier of the virus that causes it has not yet been identified. The carrier is presumably an animal, and again the successful crossing of the virus from animal to human is believed to be the source of the Ebola disease's emergence.

The most recently publicised case is the "Mad Cow Disease". The origins of this infection are believed to be in sheep (where the disease is known as scrapie).

It was transferred to cows, in which the disease is known as BSE (bovine spongiform encephalopathy). The infectious agent, known as a prion protein, passed on through beef consumption to humans to cause CJD (Creutzfeldt-Jakob Disease).

The health authorities had for many years maintained that BSE could not be passed on to humans. But last year the breaking of species barriers was officially acknowledged by the British government, which announced that a new variant of CJD had affected young people (CJD normally affects only the elderly), and that this had probably been caused by the victims eating BSE-contaminated beef.

The examples above should serve as a warning that the crossing of species barriers by microbes can be a major health problem and its causes should be much better understood.

Microbes which used to exist in one or a narrow range of host organisms are broadening their host range, and when this includes humans, the result is the emergence of new diseases or new varieties of existing diseases which are harder to treat.

Scientists also describe the phenomenon as "horizontal gene transfer." This is the transfer of genes by infection, between species that do not interbreed and are unrelated.

Formerly this phenomenon was not thought to exist, but horizontal gene transfer has been known to occur among bacteria and viruses for at least 20 years.

"For a long time it was supposed that horizontal gene transfers did not involve higher organisms, and certainly not organisms such as ourselves, because there are genetic barriers between species, and viruses and other genetic parasites are species-specific," says Dr Mae-Wan Ho, a scientist at the Open University in the United Kingdom.

"Within the past two to three years, however, the full scope of horizontal gene transfer has come to light," she added. Dr Ho is the director of the Bioelectrodynamics Laboratory of the University's Biology Department and was for several years a molecular geneticist.

In a computer search on the subject, Dr Ho found over 90 papers published in prestigious journals between 1993 and 1996, all but two giving evidence of horizontal gene transfers.

The evidence shows that transfers occur between very different bacteria, between fungi, between bacteria and protozoa, between bacteria and higher plants and animals, between fungi and plants and between insects.

"There is even a report of a gene that has jumped from fruitflies to humans where it causes a neurological wasting disease," said Dr Ho.

There are three different ways for the genes to be transferred: through conjugation (or the mating process); transduction (transfer with the help of viruses); and transformation (direct uptake of DNA by the bacteria).

Although horizontal gene transfers have occurred in the past, they were relatively rare among multicellular plants and animals.

Some scientists and ecologists are concerned that genetic engineering could greatly accelerate the gene transfers and thus pose a serious health hazard.

A recent paper by Dr Ho and Dr Beatrix Tappeser (from the Institute of Applied Ecology in Germany), on the transgression of species boundaries, explains that genetic engineering technology is designed to enable genes to cross species barriers.

"It recombines genetic material in the laboratory between species that have very little probability of exchanging genes otherwise."

According to the paper, it is not easy to transfer genes naturally between species, as there are cellular mechanisms to excise or inactivate foreign genes.

Genetic engineering is designed to break these natural barriers so that a gene from one species can be transferred into another.

The technology uses artificially constructed parasitic genetic elements (viruses, plasmids or mobile genetic elements) as "vectors" to multiply copies of genes and in many cases to carry and smuggle genes into cells (of the target plant, animal or human being) which normally exclude them.

In this way transgenic organisms are made carrying the desired transgenes.

The vector is used to enable the gene to more easily cross the species barrier successfully.

"Vectors are now increasingly engineered to overcome the cellular defence mechanisms, thus further undermining the ability of the species' system to resist invasion by exotic genes carried on such transgenic vectors," said Drs. Ho and Tappeser.

VIII

Scientists Warn of Genetic Engineering Link to Antibiotic Resistance

The Star, 3 March 1997

Some scientists and ecologists are worried that genetic engineering technology may be contributing to the transfer of genes from one species to another, and to the spread of antibiotic resistance in disease-causing microbes. They are calling for caution in the development of genetically-engineered foods and crops.

AS global concern grows over the spread of new and old infectious diseases alike, and the increasing ineffectiveness of antibiotics, some scientists and ecologists are questioning whether genetic engineering technology could add to the problems.

A recent paper by Dr Mae Wan Ho of the Open University in the United Kingdom and Dr Beatrix Tappeser of the Institute of Applied Ecology in Germany states that a high proportion of gene transfers in genetic engineering is done using vectors which have three undesirable characteristics:

- Many are derived from disease-causing viruses, plasmids and mobile genetic elements that have the ability to invade cells and can cause genetic damage;
- They are designed to break down species barriers so that they can shuttle genes between a wide range of species. Their wide

host range means they can infect many animals and plants, and in the process pick up genes from viruses of all these species to create new pathogens.

- They carry genes for antibiotic resistance that are used by scientists as "markers" to enable them to identify the cells that have been successfully penetrated by the desired gene.

Thus, it is the use of these vectors that poses potential problems and hazards. The following are listed by Dr. Ho and Dr Tappeser.

Firstly, the vectors themselves can cause severe immune reaction. For example, the virus used as vector in attempted gene therapy for Parkinson's disease, Alzheimer's disease and Cystic Fibrosis has been reported to cause direct health hazard.

Secondly, the scope of horizontal gene transfer will increase as the vectors constructed for genetic engineering are "mosaic" recombinations of viruses, plasmids and mobile genetic elements that are designed to transgress species barriers.

They are thus capable of infecting many species. In the process, these vectors will recombine with a wide range of natural pathogens.

Thirdly, the problem of antibiotic resistance could be greatly worsened. Already, horizontal gene transfers include the spread of antibiotic resistance genes, making diseases more difficult to treat.

"The rapid spread of antibiotic resistance is the result of the indiscriminate use of antibiotics which predates genetic engineering," says the paper. "However, using antibiotic resistance markers in transgenic vectors will exacerbate the situation.

"The transgenic tomatoes currently marketed in the UK and US both carry genes for kanamycin resistance. Kanamycin is used to treat tuberculosis, which is making a comeback, and the TB bacteria are already resistant to many antibiotics."

As pathogens become antibiotic-resistant, they also exchange and recombine virulence genes by horizontal gene transfer, thereby

generating new virulent strains of bacteria and mycoplasm, add Drs. Ho and Tappeser.

Quoting references to several papers, they say that this process has been shown for vibrio cholerae (involved in new pandemic cholera outbreak in India); streptococcus (involved in world-wide increase in severe infections including the epidemic in Scotland in 1993) and Mycoplasma-genitalium (implicated in urethritis, pneumonia, arthritis and AIDS progression).

"Many unrelated bacterial pathogens, causing diseases from bubonic plague to tree blight, are now found to share an entire set of genes for invading host cells, which have almost certainly spread by horizontal gene transfer.

"Public health is approaching a major crisis everywhere in developed as well as developing countries as at least 30 new infectious diseases have appeared together with the re-emergence of old ones."

Drs Ho and Tappeser are also concerned that the vectors containing transgenes can spread through the teeming microbial populations in the soil (where transgenic plants are grown) and in aquatic environments (where transgenic fish and shellfish are now being reared).

"Aquatic environments are known to contain some 100 million virus particles per millilitre, all capable of transferring genes, of helping vectors move and recombining with them to generate new viruses.

"Microbial populations in all environments form large reservoirs supporting the multiplication of the vectors, enabling them to spread to all other species.

"There will also be opportunity for the genetic elements to recombine with other viruses and bacteria to generate new genetic elements and pathogenic strains of bacteria and viruses which will, at the same time, be antibiotic resistant."

This possibility cannot be ignored as horizontal transfers of transgenes and marker genes have been experimentally shown in the laboratory: from transgenic potato to a bacterial pathogen; and between

transgenic plants and soil fungi under co-cultivation.

Drs Ho and Tappeser conclude: "There is sufficient evidence that horizontal gene transfer is responsible for the emergence of both old and new pathogens, and for the evolution of mutiple antibiotic resistance.

"We certainly do not need any more releases of transgenic organisms that would provide yet more vehicles for horizontal gene transfer. The transboundary movement of transgene and marker genes by horizontal gene transfer cannot be controlled if current transgenic practices are allowed to continue."

They add that once transgenic organisms are released, by intent or accident, neither they nor the transgenes can be recalled.

"That is why adequate monitoring procedures must be put in place which includes tracking horizontal gene transfers at and around the site of release."

In an interview in London, Dr Ho said that there is no evidence (at least not yet) that genetic engineering has been responsible for the spread of drug resistance in bacteria, or for creating new pathogens.

She stressed, however, that genetic engineering is inherently a technology that increases the likelihood of horizontal gene transfer and thus has the potential of spreading resistance and contributing to new diseases.

Dr Ho warned that transgenic foods could have some potential dangers, such as vector-mediated infection of cells after ingestion of the foods, and vector-mediated spread of antibiotic-resistance to gut bacteria and to pathogens.

She also expressed concern about research being conducted to make "transgenic pigs" with organs suitable for transplanting to humans.

The pigs are genetically engineered so that the pig organs would not be rejected in humans after transplantation.

"This is worrying because there is a possibility that pig viruses may then be able to cross species barriers to affect human beings."

Dr Ho said that a laboratory experiment had shown that if pig viruses were cultured in human cells for only one generation they would already be able to infect human cells.

"The existing already inadequate guidelines for releases of transgenic organisms and for marketing of transgenic foods should not be relaxed," concluded Dr Ho.

"On the contrary a moratorium on environmental releases of transgenic organisms and the marketing of transgenic foods should be imposed until the possibility of horizontal gene transfer and its consequences can be fully assessed."

IX

Irrational Drug Use Causing Rise of Anti-Microbial Resistance

SUNS (South-North Development Monitor), 27 May 2005

THE irrational use of pharmaceutical drugs, contributing to increasing resistance by microbes that cause infectious diseases to anti-microbial medicines, was one of the more interesting issues brought up at the World Health Assembly (WHA), which concluded Wednesday after a nine-day session.

The World Health Organisation says that anti-microbial resistance is one of the world's most serious public health problems. A major cause is the wrong use of medicines.

Though the WHA debated these inter-related issues, measures to control irrational drug use were downplayed because some major developed countries did not want the spotlight to be placed on the marketing tactics of drug companies.

Provisions aimed at controlling the sales of drugs as growth promoters in animals were dropped in a draft resolution at the insistence of these countries.

However, the topic of the irrational use of drugs in general (and not just as a part of the issue of anti-microbial resistance) is expected to be placed as an agenda item of its own at next year's WHA, at the suggestion of some countries.

Worldwide, more than 50% of all medicines are prescribed, dispensed or sold inappropriately, and 50% of patients fail to take them correctly. These startling facts were presented by WHO officials at a briefing for WHA participants on "Irrational use of medicines damages health and wastes resources."

"Only two thirds of the world's population have regular access to medicines, and of the people who do receive medicines, more than half of those people are prescribed medicines incorrectly," said Dr. Kathleen Holloway, Medical Officer at the WHO Department of Medicines Policy and Standards. "And of the people that are prescribed medicines, more than half of those people fail to take them correctly."

Arithmetically, that would mean that less than a quarter of medicines prescribed are used appropriately.

Data on trends in medicines use showed that the average number of drugs used increased from 1990 to 2003 from 2.2 to 2.7 per patient. Only 40-50% of patients were treated in compliance with standard treatment guidelines.

Holloway gave some data on the adverse consequences of irrational drug use:

- 2.3 to 4.7 million new cases of hepatitis B and C and 160,000 new cases of HIV per year, resulting from 15 billion injections per year, half of which are non-sterile.
- 4% to 10% of hospital in-patients suffer an adverse drug reaction in developed countries. This is the fourth to sixth leading cause of death in the US and costs $130 billion in the US and 466 million pounds sterling in the UK yearly.
- There is increasing anti-microbial resistance, with resistance of up to 70-90% to original first-line antibiotics for dysentery (shigella), pneumonia (pneumococcal), gonorrhoea, and hospital infections (staph. Aureus).

According to Dr Hans Hogerzeil, director of the WHO Department of Medicines Policy, although there have been previous WHA resolutions, and a WHO programme on rational drug use, not much has been done in countries, and there is a "big and unnecessary problem."

Holloway said very little is being spent to promote rational use of medicines. The global sales of prescription drugs in 2000 were $282.5

billion and drug promotion costs in the US were $15.7 billion the same year. In 2002-03, global WHO expenditure was $2.3 billion, of which the WHO expenditure on promoting rational drug use was only 0.2%.

The WHO is tackling the issue through advocacy, the essential medicines list, training programmes and a WHO global strategy on anti-microbial resistance.

There was inadequate implementation of rational medicines use in countries, with only 26% of countries having a national strategy and only 50% of countries having public education in the past two years, she said.

Holloway recommended that countries implement national programmes to improve medicines use, scale up successful interventions and implement measures to address community medicines use.

"Irrational drug use is a very serious global public health problem and much more policy implementation is needed at national level," she concluded. "Rational use could be greatly improved if a fraction of the resources spent on medicines were spent on improving use."

Examples of successful national programmes for rational drug use were presented by Dr Surya Suryawati of the Centre for Clinical Pharmacology in Gadjah Mada University, Indonesia, and by Prof. Otto Cars, Director of the Swedish Strategic Programme for Rational Use of Anti-microbial Agents, Sweden.

During question time, a member of an Asian consumer organization remarked that a major cause of irrational medicines use in developing countries was the unethical promotion of drugs by drug companies, which practised double standards in marketing and labelling (in developed and developing countries) and gave incentives to doctors to induce them to use more medicines.

He added that a large portion of antibiotics produced were sold as inputs in animal feed to fatten the animals, and as there was little control of this in developing countries, this had contributed to

resistance in the bacteria and viruses in the animals which were then passed on to resistance in microbes that affect humans.

He expressed concern that part of a draft WHA resolution on anti-microbial resistance that dealt with the need to regulate drugs in animal feed had been removed.

There were other interventions from the floor, stating that sales promotion methods by drug companies were a very important problem, and that ways should be found to lower prices of medicines as they were very expensive, and asking whether the WHO was still having alliances with the drug industry as in the period of the former WHO Director General.

Hogerzeil of the WHO replied that the WHO was working with Consumers International on responsible promotion of drugs. He observed that sales promotion by companies is effective in influencing the decisions of doctors on their use of drugs. On what can be done towards more responsible sales promotion, he said regulation seems to be the measure that works as it was shown to prevent the worst aspects of promotion.

On the use of drugs in animals, Hogerzeil said that the drafting group for the WHA resolution had decided that the resolution should only deal with the medical problem as there are other international agencies that deal with drug use in animals.

He added that the previous Director General had held roundtables with drug companies, generic companies and NGOs. At present, discussions are still going on, but at the technical level, based on technical issues.

In his response, Prof. Otto Cars from Sweden agreed that the ethical standards of drug companies are a very important issue, and that there needs to be regulation on sales promotion. On drugs in animal feedstuff, he agreed it was a major issue, and that the European Union was going to prohibit the use of drugs as growth promoters in animals in 2006. Although this issue had been taken away in the present

resolution, it had been dealt with in a previous resolution, and thus measures can be taken to implement that.

Holloway said that the WHA resolution this year was focused on anti-microbial resistance. However, at the next WHA there would be a special resolution on the rational use of drugs, which could address more issues linked to this topic.

As the discussion at the briefing indicated, there have been serious differences behind the scenes on how the issue of irrational drug use (which the WHO has clearly indicated is a major problem) should be brought up at the WHA.

According to NGOs which have been following the issue, the original agenda item was to have been irrational drug use, but this had been narrowed down to anti-microbial resistance at the insistence of some developed countries. They were apparently concerned that the marketing strategies and tactics of drug companies should not become the focus of attention and proposed measures for action.

As a result, the WHO paper for WHA and the resolution was on containment of anti-microbial resistance, and there was no agenda item or paper on rational drug use.

During the discussions on anti-microbial resistance, an amendment was made to the original draft resolution to include action on the use of antibiotics in animals.

The two amendments on this topic were that the 58th WHA: "urges member states to monitor and control the non human use of antibiotics, specifically the quantity and therapeutic group of those antibiotics used to promote growth in animals intended for human consumption;" and "requests the Director General to promote the appropriate use of antimicrobial agents in spheres other than human, specifically in the practice, considered hazardous since the 1970s, of using antibiotics as growth promotion agents in animals intended for human consumption."

These two paragraphs were struck off at the working group level,

at the insistence of a major developed country, according to sources close to the negotiations.

During the discussion on the agenda item on anti-microbial resistance last week, many countries stressed the link between this issue and the rational use of medicines in general and asked WHO to expand its work on the latter.

The United Kingdom suggested that the general topic of the rational use of medicines be put on the agenda of the next WHA and to work towards a resolution on this. The WHO secretariat responded that it welcomed this proposal.

In a note on its technical briefing on irrational drug use, the WHO had stated that: "Inappropriate use wastes scarce resources and results in poor patient outcome, adverse drug reactions and increased anti-microbial resistance - a major public health threat.

"Evidence presented in 2004 made it clear that misuse of medicines continues to be widespread and has serious health and economic implications. There is an urgent need to move away from small-scale research projects towards implementing programmes that achieve large-scale and sustained improvements within health systems."

The final WHA resolution on improving the containment of anti-microbial resistance, adopted on Wednesday, asked the Director General to strengthen the leadership role of WHO in containing anti-microbial resistance, and to work with others to promote the appropriate use of anti-microbial agents in the context of the rational use of medicines.

The WHO was also asked to provide support for generating up-to-date information on anti-microbial resistance, and evidence on cost-effective interventions to prevent and control anti-microbial resistance.

The resolution also urged Member states to develop a coherent, comprehensive and integrated national approach to implement the strategy for containment of anti-microbial resistance; to enhance the

rational use of anti-microbial agents including through using national standard-practice guidelines for common infections; and to strengthen legislation; and to mobilize resources to minimize the spread of resistance by promoting rational use of medicines by providers and consumers.

An April 2005 WHO policy paper on "Containing anti-microbial resistance" says that anti-microbial resistance is one of the world's most serious public health problems. Many of the microbes that cause infectious disease no longer respond to common anti-microbial drugs such as antibiotics, antiviral and antiprotozoal drugs.

"The problem is so serious that unless concerted action is taken worldwide, we run the risk of returning to the pre-antibiotic era when many more children than now died of infectious diseases and major surgery was impossible due to the risk of infection."

According to the paper, WHO country data for 2002-03 show the following anti-microbial resistance global prevalence rates: malaria (chloroquine resistance in 81 out of 92 countries); tuberculosis (0-17% primary multi-drug resistance); HIV/AIDS (0-25% primary resistance to at least one antiretroviral drug); gonorrhoea (5-98% penicillin resistance); pneumonia and bacterial meningitis (0-70% penicillin resistance in streptococcus pneumonia); diarrhoea: shigellosis (10-90% ampicillin resistance, 5-95% cotrimoxazole resistance); hospital infections (0-70% resistance of staphylococcus aureus to all penicillins and cephalosporins).

Emergence of resistance is a natural phenomenon that follows use of anti-microbials but it is being accelerated by inappropriate anti-microbial use, and higher consumption is associated with higher resistance, says the paper.

Another WHO paper for the WHA says that irrational medicines use includes use of more medicines than are clinically necessary, inappropriate use of anti-microbial agents for non-bacterial infections; inappropriate selection or dosing of antibiotics for bacterial infections;

over-use of injections when oral formulations are more appropriate; failure to prescribe in accordance with clinical guidelines; and inappropriate self-medication often of prescriptions-only medicines.

"The extensive misuse of anti-microbial agents leads to bacterial pathogens becoming resistant, thereby rendering treatment ineffective," says the paper. "The rapid and alarming spread of anti-microbial resistance around the world has not been matched by a concerted and powerful public health response." Despite two previous WHA resolutions and a WHO strategy paper, action has been limited. "Moreover, few new antibiotics are being developed to replace those rendered ineffective through resistance."

Referring to the HIV/AIDS, TB and malaria epidemics, the paper says "concerns are growing about accelerating rates of anti-microbial resistance and rising prices for alternative anti-microbial agents to treat infections due to resistant pathogens."

The WHO paper lists measures that governments can take. One of the interventions suggested relates to drug sales promotion. "Pharmaceutical promotion often has negative effects on prescribing and consumer choice, but regulation of promotional activities has been proven to be one of the few effective interventions," says the paper.

"Countries should therefore consider regulating and monitoring the quality of drug advertising and of the pharmaceutical industry's promotional practices, and enforcing sanctions for violations."

X

World Health Assembly Reviews World's Health Problems

The Star, 30 May 2005

In the past two weeks, the World Health Assembly (the supreme body of the World Health Organisation) debated a wide range of health problems ranging from malaria and bird-flu to how to deal with public health emergencies, and disasters like the tsunami. Decisions were taken on some of these major global health problems.

THE World Health Assembly is an interesting event for those involved in medical and health issues. As the premier meeting of the World Health Organisation, it brings together Health Ministers, senior officials and NGOs to review major health problems.

This year's Assembly on 16-25 May in Geneva was attended by 2200 people. It discussed and took decisions on topics ranging from specific diseases such as malaria and influenza pandemic to how governments should deal with health emergencies, ineffective medicines and health financing.

The highlight was the adoption of the International Health Regulations (2005) which spell out obligations by countries and the WHO secretariat, as well as procedures, on responding nationally and internationally to public health emergencies of international

concern. The IHR will come into force in two years.

The Regulations guide governments on how to decide when a health emergency has occurred, and oblige them to build the capacity to respond to it. They also have to provide information promptly to the WHO, which can issue recommendations on measures that have to be taken, aimed at minimizing the spread of the disease to other countries.

Other important issues discussed were the imminence of an avian influenza pandemic, the threat of resistance to anti-microbial medicines, and the prevention and treatment of malaria, tuberculosis, HIV/AIDS and cancer.

The WHA's most controversial issue was the proposal by a WHO scientific committee to allow new research involving genetic engineering of the remaining stocks of the smallpox virus that the WHA has allowed two laboratories (in the US and Russia) to hold.

Many countries voiced concern over the proposal and asked for a review of the proposed research. However, the WHO secretariat issued a press release that implied that four of the five research activities proposed had been approved by the WHA members, while one activity (transferring genes from the smallpox virus and inserting them into other pox viruses) would be reviewed.

The most politically charged issue was the deteriorating health conditions and humanitarian crises facing the Arab population in the occupied Palestinian territory. A resolution expressing concern on the situation, asking Israel to halt its practices affecting the Palestinians' health, and asking WHO to take several actions, was adopted by majority vote after a heated debate.

The WHO's Director General Lee Jong-wook warned that "avian influenza was the most serious health threat the world is facing today". Other WHO officials at a briefing session warned that an imminent influenza pandemic could make over a billion people sick, hospitalize 28 million and kill up to 7 million.

A WHA resolution called on countries to develop national plans for preparing for pandemic-influenza to limit health impact, and asked the WHO to solve the global shortage of influenza vaccines, and to assess the use of antiviral-medication stockpiles to contain an influenza outbreak.

A related resolution on biosafety noted that the containment of microbiological agents and toxins in laboratories is critical to preventing outbreaks of diseases such as SARS, and urged countries to review safety of the laboratories and promote biosafety laboratory practices.

Another resolution, on health action in crises and disasters (such as the Asian tsunami), urged countries to have disaster preparedness plans and called on WHO to provide early warning of disease outbreaks, and tackle water and sanitation problems.

The WHA recognized the increasing threat posed by antimicrobial resistance, and called for action through the rational use of medicines. Resistance by bacteria and viruses to existing drugs is rising faster than the development of new drugs, and current effective medicines for infections cannot keep pace.

It called on countries to develop an integrated approach to contain resistance, to encourage the appropriate use of antimicrobial agents, and monitor the use of these agents and the level of resistance occurring. It also urged WHO to promote the rational use of medicines.

On malaria, which causes a million preventable deaths annually, the WHO is to work with countries to reach malaria control goals, including through WHO undertaking bulk purchases of insecticide-treated nets and antimalarial medicines.

The WHA discussed the rise of multidrug-resistant tuberculosis, and worsening morbidity and mortality among HIV-positive TB patients. It asked countries to set up collaboration between TB and HIV programmes and to mainstream TB prevention and control in health development plans.

The Assembly also focused on the rise of the cancer epidemic, now the second leading cause of death, with over 20 million living with cancer and 7 million dying annually. The WHO attributes this epidemic to increased exposure to tobacco use, unhealthy diet, physical inactivity, some infections and carcinogens.

A resolution on cancer called for improved cancer prevention measures, better early detection and treatment, and increased palliative care. The WHO will develop a cancer prevention and control strategy to help countries address this growing crisis.

On infant and young child nutrition, the Assembly asked countries to promote exclusive breastfeeding for the first six months of a baby's life as a global public health recommendation. They were also urged to promote best practices for preparation and use of powdered infant formula to minimize health hazards, and to inform the public that powdered infant formula may contain pathogenic microorganisms and must be prepared and used appropriately.

The Assembly reviewed progress made so far in polio eradication and identified what needs to be done to interrupt the final chains of wild-type poliovirus transmission worldwide by the end of this year. The Assembly also noted the progress made in scaling-up treatment for HIV/AIDS.

More than 1000 million people will be over 60 years old by 2025 and this will double by 2050. The WHA reviewed implementation of WHO's policy on ageing and adopted a resolution on promoting active and healthy ageing.

The WHA also called on countries to promote the rights and dignity of people with disabilities; support community-based rehabilitation; and include a disability component in national health policies and programmes, with WHO giving support.

The meeting discussed iodine deficiency disorder (IDD), a leading cause of brain damage in childhood. A lack of iodine intake during pregnancy and early childhood results in impaired cognitive and

motor development in young children. WHO estimates 2 billion people are at risk of becoming iodine deficient. The solution to IDD is simple and cost-effective as iodine can easily be added to table salt.

The WHA discussed alcohol-linked health problems, caused by rising consumption, and excessive drinking among young people. Harmful alcohol use results in 4% of the global burden of disease as a causal factor in more than 60 diseases, including cardiovascular disease, mental disorders, road traffic injuries and death, and high-risk behaviours. WHO will develop policies on this.

A resolution on sustainable health financing and universal coverage and social health insurance urged the WHO to help countries evaluate the impact of changes in health-financing systems on health services as they move towards universal coverage.

At the closing ceremony, WHO Director General Lee Jong-wook again warned that "we have a little time left to prepare for a pandemic" and urged countries to prepare for it, pledging secretariat assistance. He said the Assembly had adopted many resolutions that had profound effects for global health and said the secretariat will work to follow up on them.

XI

Alert on New Untreatable Diseases

The Star, 6 Sep 2010

The recent discovery of a gene carried by bacteria that makes some diseases practically untreatable has raised alarm bells on the growth of antibiotic-resistant bacteria.

THE discovery of a new and dangerous gene that can make bacteria resistant to powerful antibiotics has once again raised alarm about the spread of infections that cannot be treated by medicine.

Last month, the *Lancet* journal reported on the international spread of extensively antibiotic-resistant bacteria called carbapenemase-producing Enterobacteriaceae. The article identified a new gene that enables some types of bacteria to be highly resistant to almost all antibiotics.

The gene has been termed NDM-1 (New Delhi metallo-lactamase). It is found in India, Pakistan and Bangladesh, and has spread to Europe via patients who travelled to South Asia for medical treatment which is popularly termed as health tourism.

NDM-1 is a gene that can live inside different bacteria, and a bacterium that carries it would become resistant to carbapenem

antibiotics. These are powerful antibiotics used for infections that are hard to treat.

So far the gut bacterium e-coli and the klebsiella pneumoniae bacterium that invades the lungs have been found to be hosts to NDM-1. Scientists fear that it can also jump to other bacteria.

This highlights the dangers to humanity from the fact that many bacteria and other disease-causing microbes can no longer be effectively combated by many antibiotics and other antimicrobials.

They have become "resistant" to these medicines because new strains of the bacteria have developed to be "stronger" than the medicines intended to deal with them.

The reason for the build-up of bacterial resistance is that there has been an over-use and wrong use of the antibiotics. This is due to companies over-promoting their medicines, doctors over-prescribing to patients, and patients themselves wrongly using the medicines.

In view of the finding of the new NDM-1 bacteria, the World Health Organisation has issued a statement urging countries to take measures to combat antimicrobial resistance (AMR).

It defines AMR as the ability of micro-organisms to find ways to evade the action of the drugs used to cure the infections they cause. It hampers the control of many infectious diseases. Some bacteria have developed mechanisms which render them resistant to many of the antibiotics normally used for their treatment (multi-drug resistant bacteria).

This is a serious health threat as there may be few or no alternative options for therapy. WHO called on countries to implement hospital infection control measures to limit the spread of multi-drug resistant strains and to reinforce national policy on prudent use of antibiotics, so as to reduce the growth of antibiotic resistant bacteria. WHO said governments should take control and prevention measures which include:

- Surveillance for antimicrobial resistance;

- Rational antibiotic use, including educating health-care workers and the public in the appropriate use of antibiotics;
- Introducing or enforcing legislation related to stopping the selling of antibiotics without prescription; and
- Strict adherence to infection prevention and control measures, including the use of hand-washing measures in hospitals.

New strains of pathogens causing diseases such as TB and malaria are now multi-drug resistant, thus increasing the numbers of deaths.

Many surgical procedures and cancer therapies are not possible without antibiotics to fight infection. Resistance prolongs illnesses and hospital stays can also cause death, and leads to costs of US$4bil (RM12.4bil) to US$5bil (RM15.6bil) per year in the United States and 9bil euro (RM36.16bil) per year in Europe. There is thus an urgent need to tackle antibiotics misuse. Data from WHO show that:

- More than 50% of all medicines are prescribed, dispensed or sold inappropriately, and half of all patients fail to take medicines correctly. The misuse of medicines harm people and waste resources.
- More than 50% of all countries do not implement basic policies to promote rational use of medicines.
- In developing countries, less than 40% of patients in the public sector and 30% in the private sector are treated according to clinical guidelines.

In these countries, less than 60% of children with acute diarrhoea receive necessary oral rehydration therapy yet more than 40% receive unnecessary antibiotics;

- Only 50% of people with malaria receive the recommended first-line antimalarial medicine.
- Only 50% to 70% of people with pneumonia are treated with appropriate antibiotics, yet up to 60% of people with viral upper respiratory tract infection receive antibiotics inappropriately.

According to WHO, a major factor for drug over-use is the

inappropriate unethical promotion of medicines by pharmaceutical companies. Most prescribers get medicine information from the companies rather than independent sources such as clinical guidelines. This can often lead to overuse.

The profit motive in selling medicines is another factor. In many countries, drug retailers prescribe and sell medicines over-the-counter. The more they sell the more income they generate, leading to overuse of medicines.

Third is unrestricted availability of medicines. In many countries, prescription medicines such as antibiotics are freely available over-the-counter.

This leads to overuse, inappropriate self-medication and non-adherence to dosing regimes.

And fourth, there is a lack of coordinated national pharmaceutical policy. Less than half of all countries implement the basic policies recommended by WHO to ensure the appropriate use of medicines.

To improve the rational use of medicines, WHO proposes that countries form a national body to coordinate policies on medicine use and monitor their impact; and set up guidelines for training, supervision and supporting decision-making about medicines.

The Government should introduce regulations to ensure that drug promotional activities meet ethical criteria, and to eliminate financial incentives that lead to improper prescribing.

There should also be a medicines committee in districts and hospitals to improve the use of medicines; and publicly available independent and unbiased information about medicines for health personnel and consumers.

XII

New Super-Bugs a Threat to Human Life

The Star, 6 June 2011

The outbreak of disease caused by a new strain of E-Coli once again shows the increasing vulnerability of human beings to bacteria and viruses that are getting more deadly and more resistant to antibiotics.

THE outbreak of a deadly disease caused by a new strain of the E-Coli bacteria is the latest chapter of the victory of new forms of bacteria and viruses over medicines and thus over human beings.

By last Saturday, 20 people had died and more than 1,800 were affected by a new strain of the already rare 0104 type of E-Coli. There are other common types of E Coli which normally cause only a mild ailment.

The World Health Organization said the variant had "never been seen in an outbreak situation before."

The centre of the outbreak is Hamburg in North Germany and almost all the deaths took place in Germany, and the others affected were either in Germany or people in 20 countries who had visited Germany.

The place of origin of the disease is still a mystery and also through what specific foods it spread. Meanwhile, there are warnings against eating raw cucumber, tomato and lettuce, the stuff of which salads are made.

Although the "normal" E-coli usually produces mild sickness in the stomach, the new strain of E-Coli 0104 causes bloody diarrhea and severe stomach cramps, while in over 500 of the more serious cases so far it also causes haemolytic-uraemic syndrome (HUS), which damages blood cells and the kidneys.

A major problem is that the bacterium is resistant to antibiotics. The treatment recommended under intensive care has been plasma exchange, kidney dialysis and blood transfusions.

Eradication of these kinds of bacteria is impractical partly because they are able to evolve so rapidly, according to Stephen Smith, a lecturer in clinical microbiology at Trinity College in Dublin, as quoted in the *New York Times*.

"These microbes are always exchanging information and there's always new ones appearing," he said. "What we've got now is a fusion of two different types that's taken the worst elements of each." Instead, prevention is probably the best approach.

This view depicts a serious situation. E-coli is only one example. There are several dangerous microbes that are difficult to fight because they continuously evolve or mutate and become resistant to more and more powerful antibiotics.

One way in which they evolve is when separate genes from various strains of the bacteria, or even of different types of bacteria, come together, in a kind of hybrid.

The United Kingdom's Health Protection Agency said the outbreak was due to a new strain of E Coli O104 with possibly a newly acquired ability to infect large numbers of people.

The BBC News quoted Professor Gad Frankel, from Imperial College London, the Sanger Institute and the Medical Research Council, as saying: "This is a new combination and a deadly combination. It has a gene which produces a toxin and another which helps the bacterium colonise the gut more efficiently, which effectively means even more toxin is produced."

Dr Mae Wan Ho, director of the Institute of Science in Society, and an expert on genetics, said this is a case of horizontal gene transfer and recombination.

In this process, she said, new combinations of genetic material are created at unprecedented speed, affecting species the most that reproduce the fastest — bacteria and viruses that cause diseases.

Another related and worrying development is the discovery of a gene, known as NDM-1, that has the ability to alter bacteria and make them highly resistant to all known drugs, including the most potent antibiotics.

Last year there were reports of many cases in India and Pakistan and in European countries, especially among those who had visited the Indian sub-continent. At the time, only two types of bacteria were found to be hosting the NDM-1 gene — E Coli and Klebsiella pneumoniae.

But it was then feared that the gene would transfer to other bacteria as well, since it was found to easily jump from one type of bacteria to another. If this happened, antibiotic resistance would spread rapidly, making it difficult to treat many diseases.

These concerns have been proven to be justified. On 7 May, the *Times of India* published an article based on interviews with British scientists from Cardiff University who had first reported on NDM-1's existence.

The scientists found that the NDM-1 gene has been jumping among various species of bacteria at a "superfast speed" and that it "has a special quality to jump between species without much of a problem".

While the gene was found only in E Coli when it was initially detected in 2006, now the scientists had found NDM-1 in more than 20 different species of bacteria. "We know that NDM1 can move at an unprecedented speed making more and more species of bacteria drug-resistant," said Dr Mark Toleman.

What is also worrying is that there are very few new antibiotics in the pipeline. Thus when the resistance grows among the whole range of bacteria to the existing drugs – and this growth will be assisted by spread of the NDM-1 gene – human beings will be more and more at the mercy of the increasingly deadly bacteria.

The E Coli outbreak demonstrates the large threat this can pose to health. Thus, antibiotic resistance and the emergence of new strains of diseases should be taken up by policy makers and international agencies like the World Health Organisation as a top-priority issue.

XIII

Worrisome Rise of Super Malaria

The Star, 9 April 2012

The danger of drug resistance is coming uncomfortably close to home, as scientists report the rapid spread of super malaria resistant to the best drugs, and warn of the need to contain this resistance.

JUST a fortnight after the World Health Organisation chief warned about the possible end of modern medicine because of the resistance of disease-causing micro-organisms to drugs, there was alarming news last week of the rapid spread of a strain of malaria in Asia that is resistant to the most effective drugs.

A new study published last week found resistance growing in a malaria strain in the Thai-Myanmar border. It had earlier been found in Western Cambodia. The study's authors warn that the deadly form of malaria could spread through Myanmar to other countries, unless swift action is taken.

Malaria is caused by parasites carried by mosquitoes, and killed 655,000 people worldwide in 2010.

It had earlier been treated with quinine then chloroquine. When malaria developed resistance to chloroquine it was no longer effective and the new effective drug ingredient was artemisinin (derived from the sweet wormwood shrub), which is now mainly used in combination with other ingredients.

Resistance to artemisinin-based drugs is now causing alarm bells

to ring, because there are no other effective drugs, and no new anti-malaria drug is expected to be in the market in the next several years.

Malaria that is resistant to artemisinin was first found in 2006 in Cambodia. In Western Cambodia, 42% of malaria cases were found to be resistant in 2007-2010. That's a shockingly high percentage, and if this kind of prevalent resistance spreads to other regions, there will be a malaria emergency.

A team of British and Thai scientists studied 3,202 patients along Thailand's northwestern border with Myanmar from 2001 and 2010 and measured the time it took them to clear malaria infections from their blood after treatment. An article in *The Lancet* journal reported that the number of slow-clearing infections rose from 0.6 per cent of cases treated in 2001 to 20 per cent in 2010, indicating a rapid rise in drug resistance.

In that period, the average time taken to reduce the number of parasites in the blood by half rose from 2.6 hours to 3.7 hours. The proportion of slow-clearing infections rose from six to 200 out of every 1,000 cases, indicating resistance has reached 20% of cases.

According to a report by Sky News, the lead researcher, Professor Francois Nosten, director of the Shoklo Malaria Research Unit in Thailand, warned of a "race against time" to halt the resistance trend.

"If the situation continues to deteriorate then it could mean that the newest drugs that we have to treat malaria now which are the derivatives of artemisinin, will be progressively inefficient, ineffective."

Nosten said the consequences, as seen in the past, would be an increasing number of cases of malaria and more deaths.

He said the reason why the malaria strain has evolved resistance to the new treatments is probably because they have been used a lot over the last 20 years, as they were the only effective treatments.

"We can still treat the patient with these drugs and they get better

and they get cured, it just takes longer for them to clear the disease," he said.

"We have now seen the emergence of malaria resistant to our best drugs, and these resistant parasites are not confined to western Cambodia. This is very worrying indeed and suggests that we are in a race against time to control malaria in these regions before drug resistance worsens and develops and spreads further. The effect of that happening could be devastating.

"Malaria already kills hundreds of thousands of people a year – if our drugs become ineffective, this figure will rise dramatically."

Another of the researchers, Prof. Nicholas White at the Faculty of Tropical Medicine in Mahidol University in Bangkok, urged that support be given to Myanmar to fight the spread of drug-resistant malaria there.

Support is needed to contain the resistance in this region, otherwise it is going to spread to India and Africa, said White.

The spread of resistant malaria is but one more example of a critical situation, one in which Margaret Chan, director general of the World Health Organisation, warned of an emerging era of the end of modern medicine.

There should be a worldwide campaign to identify the sources of this problem and to contain drug resistance, including through the proper prescription and use of drugs.

XIV

Drug Resistance Now a "Catastrophe"

The Star, 18 March 2013

Top health officials in the UK and US warn that resistance of bacteria to medicines is a catastrophe and nightmare, and as serious a threat as terrorism and climate change.

MANY a Malaysian has lost a family member because of an infection contracted during an operation while in a hospital.

Several office colleagues and friends have told me of a close relative (a mother, a husband, a brother) who died after being infected by a superbug like MRSA, that was so toxic that it could not be eliminated by antibiotics.

This in essence is the problem of antibiotic resistance – that a bacterium can evolve and change so that it becomes immune to the medicines given to a sick patient and that are meant to kill it.

When a bacterium becomes resistant to one antibiotic, scientists develop a more powerful antibiotic to kill it. But bacteria can then change to also become immune to the new medicine.

These bacteria have then developed multi-drug resistance. And when the dangerous pathogens out-run the drugs developed to combat them, humanity is at risk of losing the race between life and death.

More and more diseases are becoming very difficult to treat or even

incurable, as some pathogens are becoming immune to all antibiotics, including the most powerful ones.

And equally problematic is that many of these incurable diseases are contracted when patients stay in hospitals, especially during operations.

In the past two weeks, two top health officials – the Chief Medical Officer of the United Kingdom Dame Sally Davies and the director of the United States Centres for Disease Control and Prevention (CDC) Dr. Thomas Frieden – have sounded alarm bells in the most alarming terms.

Davies, the top health official in the U.K., warned of a looming "catastrophe" of antibiotic resistance being so widespread that we would be back to a 19th century medical situation, a pre-antibiotic era when many diseases were difficult or impossible to treat.

And Frieden evoked a "nightmare" scenario, a "very serious" problem caused by the advance of a highly drug-resistant bacteria known as CRE.

A major cause of the acceleration of antibiotic resistance is the inappropriate use of the medicines, and the inadequate action (or even inaction) of health authorities.

Drug companies often over-promote the use and sales of their medicines; some doctors over-prescribe or wrongly prescribe antibiotics (sometimes for the wrong ailment), patients who are not informed enough sometimes pressure their doctors for antibiotics for a quick cure and often do not use the medicines properly by not completing the course of medicines.

And there's not enough action to make the public aware of the proper use of antibiotics, and not enough regulations (or their implementation) to ensure drug companies and medical personnel sell or prescribe the medicines properly.

The alarm raised by the two top health officials was aimed at pushing the regulators and also the patients into action.

Davies, in media interviews, even placed antibiotic resistance on par with terrorism and climate change as critical risks facing the nation.

She said: "Antimicrobial resistance poses a catastrophic threat. If we don't act now, any one of us could go into hospital in 20 years for minor surgery and die because of an ordinary infection that can't be treated by antibiotics. And routine operations like hip replacements or organ transplants could be deadly because of the risk of infection.

"That's why governments and organisations across the world, including the World Health Organisation and G8, need to take this seriously."

Although there has been a great reduction in cases in English hospitals of MRSA (methicillin-resistant Staphylococcus aureus) which is a skin disease, this has been replaced by many times more cases of "gram-negative" bacteria which are found in the gut.

These bacteria include E coli and Klebsiella (which causes pneumonia) which are resistant to many drugs. In the U.K. about 5,000 people die annually from gram negative sepsis, in which the bacteria infects the patients' blood; half the deaths were due to drug resistant organisms.

In Europe as a whole, "25,000 people die each year as a result of hospital infections caused by resistant bacteria, adding €1.5 billion to hospital, treatment and societal costs," according to a 152-page report issued by Davies.

Besides the new drug-resistant pathogens, resistance is also emerging in old pathogens. In particular the report cites tuberculosis, which has re-emerged in Europe in the form of new strains of TB that are resistant to many or even all available drugs. Another classical disease with increasing drug resistance is gonorrhoea.

The report also warned of a "discovery void" with few new antibiotics developed in the past two decades. "While a new infectious disease has been discovered nearly every year over the past

30 years, there have been very few new antibiotics developed leaving our armoury nearly empty as diseases evolve and become resistant to existing drugs," says a press release on the report.

Meanwhile, Dr Frieden of the CDC has warned about the rapid spread of CRE or the carbapenem-resistant variety of Enterobacteriaceae, a group of more than 70 bacteria which dwell in the gut, including Klebsiella, Salmonella, Shigella and E. coli.

Carbapenems are powerful drugs that are used as a last resort when the bacteria have become resistant to other drugs. The occurrence of resistance has risen four-fold in ten years. According to Frieden, CRE was found in 4.6 percent of hospitals and 17.8 percent of long-term care in 2012.

While resistance is building up, there have been few new antibiotics. No new classes of antibiotics have been developed since 1987, and none are in the pipeline across the world, said Davies.

She said: "Antimicrobial resistance is a ticking time-bomb not only for the UK but also for the world. We need to work with everyone to ensure the apocalyptic scenario of widespread antimicrobial resistance does not become a reality. This threat is arguably as important as climate change."

According to a London-based paper, the U.K.'s Chief Pharmaceutical Officer, Keith Ridge, said although the control mechanism for prescribing antibiotics had been strengthened in hospitals, there needs to be tighter and more thoughtful control of antibiotic prescriptions in GPs' surgeries.

The report also contains 17 recommendations, including putting antimicrobial resistance on the national risk register, better surveillance data to monitor the developing situation; and more work carried out between the healthcare and pharmaceutical industries to preserve existing drugs and encourage the development of new antibiotics to fill the "discovery void" of the last 20 years; and champion the responsible use of antibiotics.

XV

When Drugs Don't Work Anymore

Inter Press Service, 10 April 2014

Martin Khor, executive director of the South Centre, warns that humanity is looking at a future in which antibiotics will no longer work, unless an effective global action plan is launched to address the crisis.

THE growing crisis of antibiotic resistance is catching the attention of policy-makers, but not at a fast enough rate to tackle it. More diseases are affected by resistance, meaning the bacteria cannot be killed even if different drugs are used on some patients, who then succumb.

We are staring at a future in which antibiotics don't work, and many of us or our children will not be saved from TB, cholera, deadly forms of dysentery, and germs contracted during surgery.

The World Health Organisation (WHO) will discuss, at its annual assembly of health ministers in May, a resolution on microbial resistance, including a global action plan. There have been such resolutions before but little action.

This year may be different, because powerful countries like the United Kingdom are now convinced that years of inaction have cause the problem to fester, until it has grown to mind-boggling proportions.

The UK-based Chatham House (together with the Geneva Graduate Institute) held two meetings on the issue, in October and last month, both presided over by the Chief Medical Officer for England, Dame Sally Davies.

This remarkable woman has taken on antibiotic resistance as a professional and personal campaign. In a recent book, *The Drugs Don't Work*, she revealed that for her annual health report in 2012, she had decided to focus on infectious diseases.

"I am not easily rattled, but what I learnt scared me, not just as a doctor, but as a mother, a wife and a friend. Our findings were simple: We are losing the battle against infectious diseases. Bacteria are fighting back and are becoming resistant to modern medicine. In short, the drugs don't work."

Davies told the meetings that antibiotics add on average 20 years to our lives and that for over 70 years they have enabled us to survive life-threatening infections and operations.

"The truth is, we have been abusing them as patients, as doctors, as travellers, and in our food," she says in her book.

"No new class of antibacterial has been discovered for 26 years and the bugs are fighting back. In a few decades, we may start dying from the most commonplace of operations and ailments that can today be treated easily."

At the two Chatham House meetings, which I attended, different aspects of the crisis and possible actions were discussed. In one of the sessions, I made a summary of the actions needed, including:

- More scientific research on how resistance is caused and spread, including the emergence of antibiotic-resistance genes as in the NDM-1 enzyme, whose speciality is to accelerate and spread resistance within and among bacteria.
- Surveys in every country to determine the prevalence of resistance to antibiotics in bacteria causing various diseases.

- Health guidelines and regulations in every country to guide doctors on when (and when not) to prescribe antibiotics, and on instructing patients how to properly use them.
- Regulations for drug companies on ethical marketing of their medicines, and on avoiding sales promotion to doctors or the public, that leads to overuse.
- Educating the public on using antibiotics properly, including when they should not be used.
- A ban on the use of antibiotics in animals and animal feed for the purpose of inducing growth of the animals (for commercial profit), and restrictions on the use in animals for the treatment of ailments.
- Promoting the development of new antibiotics and in ways (including financing) that do not make the new drugs the exclusive property of drug companies.
- Ensuring that ordinary and poor people in developing countries also have access to the new medicines, which would otherwise be very expensive, and thus only the very rich can afford to use them.

On the first point, a new and alarming development has been the discovery of a gene, known as NDM-1, that has the ability to alter bacteria and make them highly resistant to all known drugs.

In 2010, only two types of bacteria were found to be hosting the NDM-1 gene – E Coli and Klebsiella pneumoniae.

It was found that the gene can easily jump from one type of bacteria to another. In May 2011, scientists from Cardiff University who had first reported on NDM-1's existence found that the NDM-1 gene has been jumping among various species of bacteria at a "superfast speed" and that it "has a special quality to jump between species without much of a problem".

While the gene was found only in E Coli when it was initially detected in 2006, now the scientists had found NDM-1 in more than

20 different species of bacteria. NDM-1 can move at an unprecedented speed, making more and more species of bacteria drug-resistant.

Also in May 2011, there was an outbreak of a deadly disease caused by a new strain of the E Coli bacteria that killed more than 20 people and affected another 2,000 in Germany.

Although the "normal" E Coli usually produces mild sickness in the stomach, the new strain of E Coli 0104 causes bloody diarrhoea and severe stomach cramps, and in more serious cases damages blood cells and the kidneys. A major problem is that the bacterium is resistant to antibiotics.

Tuberculosis is a disease making a comeback. In 2011, the WHO found there were half a million new cases of TB in the world that were multi-drug resistant (known as MDR-TB), meaning that they could not be treated using most medicines.

And about nine percent of multi-drug resistant TB cases also have resistance to two other classes of drugs and are known as extensively drug-resistant TB (XDR-TB). Patients having XDR-TB cannot be treated successfully.

Research has also found that in Southeast Asia, strains of malaria are also becoming resistant to treatment.

In 2012, WHO Director General Margaret Chan warned that every antibiotic ever developed was at risk of becoming useless.

"A post-antibiotic era means in effect an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill."

The World Health Assembly in May is an opportunity not to be missed, to finally launch a global action plan to address this crisis.

XVI

WHO Sounds Alarm Bell on Antibiotic Resistance

The Star, 5 May 2014

Last week the World Health Organisation released the most comprehensive report to date on the alarming worldwide growth of antibiotic resistance, warning that we are already entering a world without antibiotics.

THE World Health Organisation (WHO) has sounded a loud alarm bell that many types of disease-causing bacteria can no longer be treated with the usual antibiotics and the benefits of modern medicine are increasingly being eroded.

The WHO last week released a comprehensive 232-page report on antimicrobial resistance with data from 114 countries showing how this threat is happening now in every region of the world and can affect anyone in any country.

Antibiotic resistance – when bacteria evolve so that antibiotics no longer work to treat infections – is described by the WHO report as "a problem so serious that it threatens the achievements of modern medicine."

"A post-antibiotic era, in which common infections and minor injuries can kill, far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century," said Dr Keiji Fukuda, WHO assistant director-general who coordinates its work on antimicrobial resistance.

"Without urgent, coordinated action, the world is headed for a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades can once again kill.

"Effective antibiotics have been one of the pillars allowing us to live longer, live healthier, and benefit from modern medicine. Unless we take significant actions to improve efforts to prevent infections and also change how we produce, prescribe and use antibiotics, the world will lose more and more of these global public health goods and the implications will be devastating."

The report, "Antimicrobial resistance: global report on surveillance", shows resistance is occurring in many bacteria causing different infections.

The report focuses on antibiotic resistance in seven bacteria responsible for common, serious diseases such as bloodstream infections (sepsis), diarrhoea, pneumonia, urinary tract infections and gonorrhoea.

What is especially alarming is that the bacteria's resistance has also breached "last resort" antibiotics, which are the most powerful medicines that doctors resort to when the usual ones do not work.

When patients do not respond to the usual medicines (known as first-line or first-generation medicines), doctors prescribe newer (second line) medicines which usually also cost more.

When these also don't work, newer and often more powerful (but sometimes with also more side effects) antibiotics are used, and they are even more expensive.

If these third-line or "last resort" medicines are not available or too costly for the patient, or if they don't work on a patient because of antibiotic resistance, the patient remains ill or dies if the infection is a serious one.

New antibiotics have been discovered in the past to treat infections when the old ones became useless due to resistance. But these

discoveries dried up in the past 25 years. The last completely new classes of anti-bacterial drugs were discovered in the 1980s.

Pathogens that are becoming increasingly resistant including to the more powerful antibiotics include E. coli, K. pneumoniae, S. aureus, S. pneumonia, salmonella, shigella and n. gonorrhoeae.

Key findings from the report include:

- Resistance to the treatment of last resort for life-threatening infections caused by a common intestinal bacteria, K. pneumoniae – carbapenem antibiotics – has spread worldwide. K. pneumoniae is a major cause of hospital-acquired infections such as pneumonia, bloodstream infections, infections in newborns and intensive-care unit patients. In some countries, because of resistance, carbapenem antibiotics would not work in more than half of people treated for K. pneumoniae infections.
- Resistance to one of the most widely used antibacterial medicines for the treatment of urinary tract infections caused by E. coli – fluoroquinolones – is very widespread. In the 1980s, when these drugs were first introduced, resistance was virtually zero. In many countries today, this treatment is ineffective in more than half of patients.
- The sexually transmitted disease, gonorrhoea may soon be untreatable unless there are new drugs. Treatment failure to the last resort of treatment for gonorrhoea – third generation cephalosporins – has been confirmed in several countries. In 2008, there were 106 million new cases of gonorrhoea.
- Antibiotic resistance causes people to be sick for longer and increases the risk of death. For example, people with MRSA (methicillin-resistant Staphylococcus aureus) are estimated to be 64% more likely to die than people with a non-resistant form of the infection. There are many cases of patients being infected by MRSA in hospitals.

The report also gives useful information on the worrisome building

up of resistance in four serious diseases – tuberculosis, malaria, HIV and influenza.

The re-emergence of tuberculosis (TB) is especially of great concern. Increasing cases of TB cannot be treated by most known antibiotics. In 2012, 8.7 million people developed TB and 1.3 million died; 3.6% of new cases and 20% of previously treated cases had multidrug-resistant TB.

The malaria-causing bacteria have become increasingly resistant firstly to chloroquine and pyrimethamine and now resistance to artemisinin has been identified in some cases in Cambodia, Myanmar, Thailand and Vietnam. In 2010, 219 million cases of malaria occurred worldwide and 660,000 died from the disease.

A major factor accelerating resistance is in the animal husbandry sector, where there is a liberal use of antibiotics mainly to promote the growth of the animals used for food, for commercial purposes.

This builds up resistance in the bacteria present in the animals. These resistant germs are passed on to humans who consume the meat.

The WHO report has a small section on the animal-food chain, which has been identified as a major problem. The European Union has banned the use of antibiotics as growth promoters in animals, but it is still allowed in other countries.

The WHO report mainly provides information on the prevalence and problems of microbial resistance, rather than what to do about the emerging crisis.

However, a WHO press release on the report calls for some actions. These include:

- Setting up basic systems in countries to track and monitor the problem;
- Preventing infections from happening in the first place to reduce the need for antibiotics.
- Only prescribing and dispensing antibiotics when they are truly

needed; and prescribing and dispensing the right antibiotic(s) to treat the illness.

- Regulating and promoting appropriate use of medicines.
- Patients using antibiotics only when prescribed by a doctor and completing the full prescription, even if they feel better, and never using leftover prescriptions.
- Developing new diagnostics, antibiotics and other tools to stay ahead of emerging resistance.

XVII

State of the World's Health

The Star, 2 June 2014

The pulse of the state of health in the world was taken at the recent World Health Assembly which promoted universal health coverage and pledged to act on antibiotic resistance and on several diseases.

THE premier international conference on public health policy is the World Health Assembly (WHA), organised by the World Health Organisation (WHO), which attracts Ministers of Health and other top health officials as well as NGOs to Geneva every year.

This is where the latest trends in public health problems are presented and debated on, and action plans for solutions are adopted.

This year's Assembly, which closed on 24 May, had 3,500 participants and saw a record number of issues debated and resolutions adopted.

One of the key buzz words during the Assembly was "universal health coverage" (UHC). This is being promoted by the WHO and several governments to be one of the goals for the United Nations' post-2015 Development Agenda.

There is no precise definition for the term, but it is widely taken to mean that everyone, including the poor, should have access to medical treatment and other health services.

Inability to pay should not prevent someone from being "covered"

by the health system, and people should not become financially burdened by having to pay, or to pay so much, to get treatment.

The UHC concept is a great one, similar to the "health for all by the year 2000" slogan that the WHO adopted in the 1980s as its umbrella goal. It resonates with or is even rooted in the "right to health", which is one of the human rights recognised by the UN.

UHC was the centre of discussion at the panel session on the post-2015 Development Agenda half way through the WHA. WHO Director General Margaret Chan stated that there are various ways to finance and achieve UHC and it is for each country to choose its own model.

If UHC is adopted, it will be a big step forward towards equity (another term much used at the Assembly) in the health system. How to make it happen, especially the method to finance it, will be a key question.

In a resolution on health in the post-2015 development agenda, the Assembly proposed priority for the health of the new-born, non-communicable diseases, mental health, neglected tropical diseases and completion of existing health Millennium Development Goals.

It also stressed the importance of universal health coverage and the need to strengthen health systems.

The Assembly also adopted a resolution on antibiotic resistance after many delegates expressed their concerns that the bacteria's growing resistance to medicines was making it difficult to treat many diseases.

The WHO had recently issued a report showing increasing prevalence of resistance in many diseases including TB, pneumonia, diarrhoea, malaria, skin diseases, and gonorrhoea. It warned of a post-antibiotic era, where drugs will no longer be able to cure infectious diseases.

The resolution urges governments to strengthen the proper use and management of drugs, support research to extend the lifespan

of existing drugs, and to develop new antibiotics and diagnostic technologies.

The WHO was asked to develop a draft global action plan within a year to combat antimicrobial resistance, that includes rational drug use, better surveillance, access to medicines and discovery of new drugs.

The Assembly adopted the first-ever global plan to end preventable deaths of newly born babies and stillbirths by 2035, and called for all countries to aim for fewer than 10 newborn deaths per 1000 live births and less than 10 stillbirths per 1000 total births by 2035.

Every year almost 3 million babies die in the first month of life and 2.6 million babies are stillborn (they die in the last 3 months of pregnancy or during childbirth). Most of these deaths could be prevented.

The Plan's goals will require every country to invest in high-quality care before, during and after childbirth for every pregnant woman and newborn.

The Assembly also approved the WHO's strategy to help countries improve access to essential medicines. Key principles include selecting a limited range of medicines using best evidence, efficient procurement, affordable prices, effective distribution systems, and rational use.

Another new global strategy was adopted for TB, aimed at ending the global TB epidemic, with targets to reduce TB deaths by 95% and to cut new cases by 90% by 2035.

TB remains a deadly disease. In 2012, 8.6 million people fell ill with TB, 1.3 million died from it and 450 000 people developed multidrug-resistant TB.

Non-communicable diseases, including those caused by diet, were also discussed. At her opening speech, Dr Chan highlighted the increase in childhood obesity, especially in developing countries and announced a Commission on Ending Childhood Obesity.

The health plight of the poor in middle-income countries was also a theme at the Assembly.

Dr Chan highlighted that 70% of the world's poor live in middle-income countries and asked if there will be polices to ensure benefits are fairly shared, or else the world will see "a growing number of rich countries full of poor people."

But it is not only domestic policy that affects the poor. A side-event by health NGOs focused on how the middle income countries were being left out of schemes such as supply of free medicines or the relaxation of patent rules to help the poor, as these are often reserved for low-income countries.

However most of the poor people in the world live in middle-income countries, some of which have large populations.

Some developing countries voiced frustration on how they are being picked upon by the United States for having patent laws that prioritise making medicines affordable to the public.

Dr Chan in another speech also criticised free trade agreements that enable tobacco companies to challenge measures taken by governments to curb cigarette sales.

Other issues the WHA discussed include autism, psoriasis, an action plan for disabilities, palliative care, financing for research and development for diseases that affect developing countries, strengthening of medicines regulations, and assessment of health technologies.

XVIII

Action to Use Medicines Wisely?

The Star, 16 June 2014

A resolution by Health Ministers to formulate a global plan to deal with antibiotics resistance and a new coalition of NGOs to campaign on this issue gives hope that action may finally be coming.

MOMENTUM is building to get doctors to prescribe and patients to use medicines properly in order to slow down the increasing ineffectiveness of antibiotics to treat dangerous infections.

The World Health Organisation (WHO) was recently given the go-ahead to draw up a global plan of action to combat antibiotic resistance, which experts and health leaders have warned will cause "the end of modern medicine" if nothing is done.

Health Ministers asked the WHO to present them with the plan within a year, with a draft to be ready by January 2015.

In a resolution adopted at the World Health Assembly (WHA) in May, they also agreed to accelerate their own efforts to use antibiotics responsibly and develop national plans to contain the resistance of bacteria to antibiotics and other antimicrobials.

Resistance is making many antibiotics ineffective for increasing numbers of patients around the world who suffer from stomach, skin and respiratory infections and from serious diseases including TB, malaria, pneumonia and gonorrhoea.

Patients in hospitals are also commonly infected with dangerous

"superbugs" like MRSA which are difficult to treat, including when they undergo surgical operations.

Although this problem has been known for decades, little action has been taken at global level or in most countries to prevent the over-use and wrong use of antibiotics, and the build up of resistance in the bacteria has now reached crisis proportions.

Health leaders such as WHO director-general Margaret Chan and the United Kingdom's Chief Medical Officer Dame Sally Davies have sounded the alarm bells about the crisis leading to a pre-antibiotic age where millions will die from presently treatable diseases or from non-dangerous operations because of the resistant bacteria.

At the WHA session, Malaysia was one of the countries speaking in favour of the resolution.

The Malaysian health delegate said there is need for awareness and action at the highest level, and need for concrete action including sanitation and hygiene, use of vaccines when possible, innovation in service delivery as well as health promotion and communication programmes to change the present culture on anti-microbials use.

India and Ghana, representing Africa, voiced a common concern of developing countries. The action plan must take account of the special needs of developing countries, including supporting the measures they have to take, and making sure they have access to the new antibiotics at affordable prices.

This touches on one of the crucial issues in the resistance discussion. The situation is very worrying because no new class of antibiotics has been discovered since the mid-1980s.

There is no guarantee that new ones will be found. Since the existing antibiotics may become ineffective in some years due to resistance, people worldwide will be defenceless against the superbugs.

Even if new antibiotics are discovered and sold, they will likely be under patent protection. The prices could be so high that most people, especially in developing countries, can't use them.

The developing countries were asking the WHO to make sure its action plan deals with these issues. The United Kingdom, a champion of the resistance issue, assured India and Africa that their concerns would be addressed.

According to the WHA resolution, the action plan should contain proposals on establishing a national plan to fight resistance, as well as to strengthen surveillance and laboratory capacity, ensure access to medicines, enhance infection prevention and foster research to discover new antibiotics.

Importantly, the plan will also propose how to "regulate and promote rational use of medicines, including for animal husbandry, and ensure proper patient care."

Just before the WHA, 50 health groups from Asian countries (including Malaysia), Africa, the US, Europe and Latin America met at the South Centre in Geneva and formed a new alliance, the Antibiotic Resistance Coalition, to campaign for actions to be taken to curb the resistance trend.

The actions they call for include:

- End the use of antibiotics given to livestock to promote their growth. Much of the antibiotics that are sold are used for fattening animals, and resistance in bacteria in the livestock is transferred to humans through the food chain.
- Promotion of antibiotics including incentivising medical personnel to overuse or inappropriately prescribe antibiotics is harmful and should be prohibited.
- Guidelines should be given to hospitals and private doctors on the proper use of antibiotics in treating patients.
- Introduce comprehensive monitoring of the medical and farm use of antibiotics and the trends of the state of resistance in various pathogens.
- Support innovation towards new antibiotics, and in ways that

delink the costs of R&D from the price of medicines so that they can be affordable.

Although the moves in the WHA towards a global plan were widely supported, there is also a danger that after its adoption it will remain only on paper, like many similar previous plans, and not implemented.

Thus the start of a campaign by civil society to highlight the dangers of resistance and the need for many types of urgent action is just as significant.

With an official global plan and concerted NGO action, there is finally some hope that antibiotics resistance will be tackled more seriously in future.

XIX

Antibiotic Resistance: A Global Plan At Last

The Star, 25 May 2015

This week the World Health Assembly will adopt a global plan to address antibiotic resistance and other forms of antimicrobial resistance, which poses a threat to human health and survival. But will the plan be implemented?

ACTION may be coming at last to deal with one of the most important threats facing humanity – the fast-increasing resistance of bacteria to antibiotics and other medicines.

For years and decades this problem has been growing, without serious efforts being taken across the world to stop it in its tracks.

Patients are the ones that suffer the most. Old medicines no longer work against many diseases and newer and more potent medicines (often with stronger side effects) are also getting useless.

Pathogens are getting increasingly resistant to drugs, affecting treatment for tuberculosis, malaria, influenza, HIV-AIDS, gonorrhoea, and common infections such as pneumonia and urinary tract infections.

Patients going to hospitals are now increasingly acquiring infections unrelated to their original ailment, caused by highly resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA), which have caused thousands of deaths.

Despite the publicity about resistance, there has been little action in

most countries, until the problem has blown up to crisis proportions at national and global level. The World Health Organisation director-general Margaret Chan has called ours a post-antibiotic era – meaning that we are now living in a world where antibiotics may not work anymore.

The consequences are horrifying to contemplate. In Thailand, antimicrobial resistance was found to kill 30,000 people a year and its economic impact amounted to 0.6% of the country's GNP, according to the Thai Minister of Public Health, speaking at a panel discussion at the World Health Assembly last week.

A similar study should be done in Malaysia. I wonder what it will reveal.

There is no time to lose for comprehensive action to be taken before the resistance crisis worsens.

Fortunately, a global action plan on antimicrobial resistance (AMR) will be adopted this week by Health Ministers gathered at the World Health Assembly in Geneva.

The plan has five objectives – to use medicines properly in human and animal health; reduce infection by sanitation, hygiene and infection prevention measures; strengthen surveillance and research; educate the public as well as doctors, veterinarians and farmers on proper use of antibiotics; and increase investment in developing new medicines, diagnostic tools and vaccines.

The plan calls for actions by governments, the WHO Secretariat, international organisations, civil society groups and professional bodies.

Most importantly, all governments are expected to have in place a national action plan on antimicrobial resistance within two years.

These national plans are to be aligned with the global action plan and with international agencies' standards and guidelines.

The national actions should include:

- Developing a national surveillance system for antimicrobial

resistance to collect data on resistance by bacteria to various medicines, as well as surveillance in the animal health and agriculture sectors.

- Effective regulation and governance for the licensing, distribution, prescription, dispensing and use of medicines in human and animal health.
- Improve laboratory capacity to identify pathogens and their antimicrobial susceptibility in order to guide optimal use by doctors of antibiotics.
- Elimination of economic incentives in all sectors that encourage inappropriate use of antibiotics and introduction of incentives to optimise use.
- Introduce policies for proper use of antibiotics in animals, fishery and agriculture sectors, including phasing out the use of antibiotics for animal growth promotion.
- Actions to reduce infection through sanitation, hygiene and infection prevention measures.
- Increase national awareness of antimicrobial resistance through public education programmes, medical and school curricula, and establish coalitions including of civil society groups, scientific and industry bodies.
- Participate in research for developing new medicines, diagnostic tools and vaccines.

At the World Health Assembly session discussing the global plan, some developing countries' health officials highlighted the special needs of developing countries in implementing the global and national action plans.

These include obtaining the necessary funding and technical equipment to implement a national action plan, as well as assurance that people in their countries will have access to the new medicines, vaccines and diagnostic tools that will be developed in future, and at affordable prices.

It would be terrible if the present antibiotics don't work anymore and when new ones are developed, the patients in developing countries cannot have access to these, because they are patented and thus have high prices.

The global plan also calls on WHO to support countries to develop and implement their national plans, and to lead and coordinate support to countries to implement their investment needs and to publish progress reports.

The adoption of the global action plan will be a landmark and gives hope that international and national actions will now take off in a serious way to tackle antimicrobial resistance.

Now that the plans are drawn up and approved, the difficult part has to be done: implementation. Our lives depend on it.

To remind us of the seriousness of the problem, the WHO issued a Fact Sheet on antimicrobial resistance. Its key points include:

- Antimicrobial resistance is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it.
- Resistant microorganisms (including bacteria, fungi, viruses and parasites) are able to withstand attack by antimicrobial drugs, such as antibacterial drugs (e.g. antibiotics), antifungals, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist, increasing the risk of spread to others.
- Antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi.
- In 2012, WHO reported a gradual increase in resistance to HIV drugs, albeit not reaching critical levels. Since then, further increases in resistance to first-line treatment drugs were reported, which might require using more expensive drugs in the near future.

- In 2013, there were about 480 000 new cases of multidrug-resistant tuberculosis (MDR-TB). Extensively drug-resistant tuberculosis (XDR-TB) has been identified in 100 countries. MDR-TB requires treatment courses that are much longer and less effective than those for non-resistant TB.
- In parts of the Greater Mekong subregion, resistance to the best available treatment for falciparum malaria, artemisinin-based combination therapies (ACTs), has been detected.
- Spread or emergence of multidrug resistance, including resistance to ACTs, in other regions could jeopardize important recent gains in control of the disease.
- There are high proportions of antibiotic resistance in bacteria that cause common infections (e.g. urinary tract infections, pneumonia, bloodstream infections) in all regions of the world. A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as MRSA or multidrug-resistant Gram-negative bacteria.
- Treatment failures due to resistance to treatments of last resort for gonorrhoea (third-generation cephalosporins) have been reported from 10 countries. Gonorrhoea may soon become untreatable as no vaccines or new drugs are in development.
- Patients with infections caused by drug-resistant bacteria are generally at increased risk of worse clinical outcomes and death, and consume more health-care resources than patients infected with the same bacteria that are not resistant.

XX

Super Drug-Resistant Gene Raises New Health Alarm

The Star, 9 May 2016

A recently discovered gene that is resistant to an antibiotic used as a last resort and which can spread easily among bacteria has raised fresh concerns about the coming end of the use of antibiotics – if action is not taken immediately.

ANTIBIOTIC resistance – a process by which antibiotics no longer work because bacteria have become resistant to them – has climbed up the global agenda because of growing awareness of the immense threat this poses to human health and survival.

However, there is still not enough action to tackle this crisis. Health Ministers meeting at the World Health Assembly in Geneva later this month have an opportunity to review the extent to which a Global Action Plan adopted last year has been implemented.

In the background is the recent disturbing news of the discovery by scientists of a gene, MCR-1, which creates resistance to colistin, a powerful antibiotic used as a last resort to treat infections when other medicines do not work.

Even more worrying is that the gene has the characteristic of being able to move easily from one strain of bacteria to other species of bacteria. This raises the spectre of many infections eventually

becoming untreatable, bringing us closer to the nightmare of a post-antibiotics era.

Malaysia is one of the first countries in which scientists found the MCR-1 gene. Thus there is an even more serious need for our policy makers to deal with this issue, including to consider banning the use of colistin in animal feed.

The gene was discovered during a study undertaken in China. Last November, Yi-Yun Liu and colleagues published a paper in the *Lancet Infectious Diseases* journal revealing they found the MCR-1 gene in 166 out of 804 pigs at slaughter that they tested, 78 of 523 samples of chicken and pork being retailed and in 16 of 1,322 hospital patients.

The study indicates there is a chain in the spread of resistance from the use of colistin in livestock feed, to colistin resistance in slaughtered animals, in food and human beings.

One of the authors, Prof. Jian-Hua Liu from South China Agricultural University, was quoted by the *Guardian* as saying these are extremely worrying results, which reveal the emergence of the first polymyxin resistance gene that is readily passed between common bacteria such as E. coli and K. pneumoniae.

This suggests that "the progession from extensive drug resistance to pandrug resistance is inevitable", added Liu. Extensive resistance is when a bacterium is resistant to many drugs while pandrug resistance indicates resistance to all drugs.

Colistin is part of a category of antibiotics known as polymyxins. In the past they had not been widely used as they are known to have toxic effects, but they have been recently more used as a last resort when other antibiotics don't work because of resistance.

"All key players are now in place to make the post-antibiotic world a reality," another of the paper's co-authors, Prof. Timothy Walsh from University of Cardiff, told the BBC News website.

"If MCR-1 becomes global, which is a case of when and not if, and

the gene aligns itself with other antibiotic resistance genes, which is inevitable, then we will have very likely reached the start of the post-antibiotic era. At that point, if a patient is seriously ill, say with E. coli, then there is virtually nothing you can do."

A major reason for the emergence and spread of the gene is suspected to be the heavy use of colistin to feed livestock to promote their growth. Much of the worldwide annual use of 12,000 tonnes of colistin in animal feed takes place in China, according to the paper by Liu and colleagues.

The paper mentions that besides China, the MCR-1 gene has also been found in Malaysia and Denmark. It revealed that Malaysian scientists had found bacterial DNA sequences in December 2014 with genes that look like MCR-1. The possibility that E.coli with the MCR-1 gene had spread into other South-east Asian countries is "deeply concerning", said the authors.

After the paper was published, new papers and information have shown that the MCR-1 gene has been found in bacterial samples in many other countries, including Thailand, Laos, Brazil, Egypt, Italy, Spain, England and Wales, the Netherlands, Algeria, Portugal and Canada.

The most frightening thing about MCR-1 is the ease with which it can spread resistance to other species of bacteria through a process known as horizontal gene transfer.

A few years ago, there was a similar scare about NDM-1, a gene with the ability to jump from one bacteria to other species, making them highly resistant to all known drugs, except two, including colistin.

If the colistin-resistant MCR-1 were to combine with NDM-1, then the bacteria having the combined gene would be resistant to virtually all drugs.

In 2010, only two types of bacteria were found to be hosting the NDM-1 gene – E Coli and Klebsiella pneumoniae. Within a few

years, NDM-1 had been found in more than 20 different species of bacteria.

The discoveries of NDM-1 and now of MCR-1 add urgency to the task of addressing anti-microbial resistance.

In 2012, World Health Organisation Director General Dr Margaret Chan warned that every anitibiotic ever developed was at risk of becoming useless. "A post-antibiotic era means in effect an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill."

The World Health Assembly is an opportunity to take stock of the Global Action Plan on antimicrobial resistance.

An immediate action needed is to ban the use of colistin in livestock production. The well-respected *Lancet* journal published a Comment in February that we must take the call to curtail the use of polymyxins (including colistin) in agriculture to the highest levels of government or face more patients for whom we need to say, "Sorry there is nothing I can do to cure your infection."

Other antibiotics that are used by human beings should also be prohibited or heavily restricted in the livestock sector, especially if they are used as growth promoters.The Global Action Plan has five objectives: to use medicines properly in human and animal health; reduce infection by sanitation, hygiene and infection prevention measures; strengthen surveillance and research; educate the public as well as doctors, veterinarians and farmers on proper use of antibiotics; and increase investment in developing new medicines, diagnostic tools and vaccines.

XXI

World Leaders Pledge Action to Control Superbugs

The Star, 27 September 2016

World leaders at the Summit of the UN General Assembly last week spoke on the need to save millions of lives by controlling the crisis of antibiotic resistance and adopted a landmark political declaration calling for global action.

AT the opening of the summit of the United Nations General Assembly on 20 September, it sounded much like the swansong of two of the regular stalwarts of this annual affair.

It is the last General Assembly to be attended by UN Secretary General Ban Ki Moon and the United States President Barack Obama.

Both made interesting speeches. Ban listed all the woes afflicting the world, especially terrorism, while praising the Paris agreement and the sustainable development goals as big achievements of his eight years as the UN leader.

Obama, sounding like a professor, gave a lengthy analysis of the state of the world and the role of the US, earning a laugh when he said it sometimes seemed the US was being blamed for all the ills of the world and at the same time it was being asked to solve all its problems.

At the lunch for heads of states and organisations, Ban and

Obama praised each other for their leadership in the past eight years. Someone at my table wondered aloud what would happen to next year's lunch if Donald Trump, who is known to dislike and distrust the UN, won the US election. Perhaps as leader of the host country, he would have the traditional lunch cancelled.

This year's UN summit will be remembered most for its high-level event on anti-microbial resistance (AMR), held on 22 September, with many heads of governments and Ministers speaking on the need to fight this crisis.

The leaders adopted a landmark Political Declaration on AMR that recognized that antibiotic resistance is the "greatest and most urgent global risk" and that "due to AMR many 20th century achievements are being gravely challenged, particularly the reduction in illness and death from infectious diseases…"

This is the first ever statement by the heads of all the countries that recognize the AMR crisis and in which they pledge to take action.

Ban Ki-Moon said that AMR has become one of the biggest threats to global health. "All around the world, many common infections are becoming resistant to the antimicrobial medicines used to treat them, resulting in longer illnesses and more deaths. At the same time, not enough new antimicrobial drugs, especially antibiotics, are being developed to replace older and increasingly ineffective one."

World Health Organisation Director General Margaret Chan warned that "AMR poses a fundamental threat to human health, development, and security. Common and life-threatening infections like pneumonia, gonorrhoea, and post-operative infections, as well as HIV, tuberculosis and malaria are increasingly becoming untreatable because of AMR."

Referring to the Declaration, she said "the commitments made today must now be translated into swift, effective actions…We are running out of time."

I was invited to be part of a panel discussion during the AMR event.

Others in the panel were the Russian and Kenyan health ministers, the chairman of Doctors Without Borders, the European Commissioner for Health and the CEO of drug company GSK.

I made the point that AMR was as serious a threat to human life as climate change. The crisis is caused by the overuse of antibiotics in people, and its use in feeding livestock to fatten them, passing on resistant bacteria to humans through the food chain.

The problem is made much worse by certain genes that accelerate resistance and that move from one type of bacteria to others, thereby spreading resistance to many diseases.

People in developing countries are the most affected. It is estimated that the number of AMR-related deaths will rise from the present 700,000 a year to 10 million in 2050 and of this more than 9 million will be in developing countries.

The adoption of the Declaration is a big step forward, but more important is the implementation of the actions agreed to. To help make that happen, developing countries should be supported with funds, technical equipment and access to existing and new antibiotics, vaccines and diagnostic tools at low prices.

Among the actions needed are regulation of the sale, prescription and use of antibiotics, the phasing out of antibiotics used as growth promoters in livestock, the prevention of infections, the control of AMR in hospitals, better surveillance and data collection, provision of equipment such as microscopes and diagnostic tools.

There must also be the discovery of new antibiotics to replace those that no longer work because of resistance.

However the dominant system of research and development has a lot of weaknesses. Although governments provide R&D subsidies, the companies that produce the new medicines are granted private patents and are able to charge high prices, beyond the reach of most patients.

There is need for another system in which adequate public funding

of R&D leads to discoveries of new medicines, and licenses are easily and cheaply provided to manufacturers to make them available at affordable prices.

Such a model is implicitly recognised in the political declaration, which acknowledges the importance of delinking the cost of investment in R&D from the price and volume of sales so as to facilitate equitable and affordable access to new medicines, diagnostic tools and vaccines.

The declaration also stressed that "affordability and access to existing and new antimicrobial medicines, vaccines and diagnostics should be a global priority,"

The declaration established a task force of agencies (co-chaired by the WHO and Secretary General's office) which would provide guidance for global action on AMR and requested the Secretary General to report on progress of implementation of the Declaration and to make further recommendations.

The elevation of the AMR issue to the highest political level at the UN General Assembly is a landmark event in the battle against AMR, a crisis that has been neglected too long and which is now recognised.

The next steps are important, for the world cannot wait longer for implementation of the action plans, if the lives of millions or billions are to be saved.

XXII

Action Needed to Avoid the End of Modern Medicine

Inter Press Service, 5 December 2017

Antibiotic resistance is rising to dangerously high levels in all parts of the world, threatening our ability to treat common infectious diseases. Without urgent action, we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill.

THE next time you have a bad cold and reach for the antibiotics left over from your last visit to the doctor, think again.

Firstly, the antibiotics won't work as they only act against bacteria while the cold is caused by a virus.

Secondly, you will be contributing to arguably the world's gravest health threat – antibiotic resistance.

The wrong use and over-use of antibiotics is one of the main causes why they are becoming increasingly ineffective against many diseases, including pneumonia, tuberculosis, blood disorders, gonorrhoea and foodborne diseases.

While an effective antibiotic kills most of the targeted germs, a few may survive and develop resistance which can spread to other bacteria that cause the same infection or different infections. The rate of resistance and its spread can increase if antibiotics are wrongly

or over used, and they then become increasingly ineffective to treat bacterial infections.

Global health leaders are now ringing the alarm bell. "Antimicrobial resistance is a global health emergency," warned the World Health Organisation's Director-General Tedros Adhanom Ghebreyesus. "The world is facing an antibiotic apocalypse," said the United Kingdom's Chief Medical Officer Dame Sally Davies. "It may spell the end of modern medicine."

Warns the WHO: "Antibiotic resistance is rising to dangerously high levels in all parts of the world. New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases…Without urgent action, we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill." (WHO Fact Sheet on antibiotic resistance, Nov. 2017).

These warnings were highlighted on World Antibiotics Awareness Week on 13-19 November when activities were held in many countries.

Antibiotic resistance is part of the wider phenomenon of anti-microbial resistance (AMR), which includes resistance of bacteria, fungi, viruses and parasites to medicines.

About 700,000 people die annually due to antimicrobial resistant infections, and this is estimated to rise to 10 million deaths a year by 2050 if action is not taken, with a cumulative economic cost of US $100 trillion, according to a 2016 review on AMR sponsored by the UK government.

A key tipping point was reached recently when it was found that some bacteria had evolved to be resistant to colistin, the antibiotic of last resort which is used on a patient when all other antibiotics are found ineffective.

In 2016, researchers in China found colistin-resistant E. coli bacteria in 20 per cent of animals, 15 per cent of raw meat and 1 per cent of

hospital patients that were sampled. The colistin resitance gene (mcr-1) could easily be transferred among different bacteria.

Malaysia was also one of the first countries where scientists found colistin-resistant bacteria. "Since the publication of our findings, mcr-1 gene has been found in many other countries," said Associate Professor Dr Chan Kok Gan of University Malaya. "This is a frightening scenario and the whole world should sit up and take action to prevent further abuse of antibiotics."

If this resistance continues to spread, colistin will become less and less effective and we will eventually lose the "antibiotic of last resort."

The colistin story also carries another lesson. It is widely thought that resistance is due to over-use of antibiotics by consumers or the spread of infections caused by resistant bacteria to patients in hospitals.

However resistance is also spread through the agriculture sector and the food chain, as shown in the study on colistin in China.

In many countries, much of the antibiotics used (80 per cent in the case of the United States) are fed in farms to animals as growth promoters, to make them grow fatter and faster, as well as to prevent or treat diseases.

Resistant bacteria build up in the animals and are present in raw meat. Some of these bacteria are passed on to humans when they eat the meat.

In Malaysia, the Department of Veterinary Services in 2012 found that half of the domestic chickens tested had bacteria that were resistant to three types of antibiotics (ampicillin, sulphonamide, tetracycline), as cited in a memorandum by the Consumers' Association of Penang.

The environment is another source of the spread of resistance. Residues and wastes containing resistant bacteria flow from farms and hospitals and contaminate soils, drainage systems, rivers and seas. Some of these bacteria find their way to humans.

The European Union banned the use of antibiotics as growth

promoters in animal feed in January 2006 while the US started action to phase them out in December 2013.

In most developing countries, little action has so far been taken. Hopefully that will start to change. In November 2017, the World Health Organisation issued its first ever guidelines on the use of antibiotics in food-producing animals.

"Scientific evidence demonstrates that overuse of antibiotics in animals can contribute to the emergence of antibiotic resistance," said WHO's Food Safety Director, Dr Kazuaki Miyagishima.

A WHO-sponsored study published in *The Lancet Planetary Health* in November 2017 found that interventions that restrict antibiotic use in food-producing animals reduced antibiotic-resistant bacteria in these animals by up to 39%, according to a WHO press release.

The research paper (authored by William Ghali and 10 other scientists) reviewed thousands of studies, and selected 179 relevant ones, to find if there is an association between interventions that restrict antibiotic use and reduction in the prevalence of antibiotic-resistant bacteria in animals and in humans.

The key findings are that:

- "Overall, reducing antibiotic use decreased prevalence of antibiotic-resistant bacteria in animals by about 15% and multidrug-resistant bacteria by 24-32%."
- The evidence of effect on human beings was more limited but showed similar results, "with a 24% absolute reduction in the prevalence of antibiotic-resistant bacteria in humans with interventions that reduce antibiotic use in animals."

This study influenced the development of the WHO's new guidelines, which are aimed at influencing policy makers in the agriculture and health sectors. According to a WHO press release, the guidelines include:

- An overall reduction in the use of all classes of medically important antibiotics in food-producing animals.

- Complete restriction of these antibiotics for growth promotion and for disease prevention without diagnosis.
- Healthy animals should only receive antibiotics to prevent disease if it has been diagnosed in other animals in the same flock or herd or fish population.
- Antibiotics used in animals should be from the WHO list as "least important" to human health and not from "highest priority critically important."

In 2015, Health Ministers attending the World Health Assembly adopted a Global Plan of Action on anti-microbial resistance, and they agreed that each country should prepare national action plans by 2017.

Since there are many sources of antibiotic resistance, the national effort must include not only the health authorities but also those responsible for agriculture and the environment.

The health authorities should take action to control the spread of infections (including in hospitals), carry out surveillance of antibiotic resistance, introduce and implement regulations and guidelines on proper prescriptions, ethical marketing of drugs and rational drug use.

The agriculture authorities should phase out inappropriate use of antibiotics for animals, especially for growth promotion, while the environment authorities should prevent resistant bacteria and genes from contaminating soils, drainage systems, rivers and seas.

There should be campaigns to make the public aware of the dangers of wrongly using antibiotics and that they should not demand that doctors give them antibiotics unnecessarily.

The medical profession should adhere to guidelines on the proper use of antibiotics, while drug companies should not push for maximum sales but instead advocate prudent use of their antibiotics in both the health and animal sectors.

These are the more obvious actions that need to be taken and

urgently if we are to succeed in slowing down the alarming rate of antibiotic resistance. If we fail, it may well be "the end of modern medicine", as the health leaders and the scientists have warned us.

XXIII

Superbugs are Super Dangerous

The Star, 26 Mar 2018

THERE is a threat to the future of humanity so silent that few people notice it, so pervasive that many families have suffered from it and so dangerous that it may soon be the leading cause of premature deaths worldwide.

If climate change has now become more obvious and visible as the No.1 risk to our civilisation, antibiotic resistance will soon rival it as the gravest threat to human life and health.

Many friends have told me of how their relatives have contracted infections while staying in hospitals and could not be cured with a normal dose of antibiotics. Some of them have died.

For example, the mother of a close friend of mine died from MRSA (methicillin-resistant Staphylococcus aureus) after a visit to the hospital for an unrelated minor ailment.

MRSA is an antibiotic-resistant pathogen that causes a variety of serious infections. It is well known for being spread in hospitals, but it is also a problem elsewhere in the community.

Resistance of bacteria to many antibiotics is growing. The genes of some bacteria that survive an antibiotic attack change and adapt

to better defend themselves, and tougher new generations of these bacteria have become increasingly immune to the same or other antibiotics that are stronger.

Unfortunately, in the never-ending race between stronger bacteria and stronger medicines, the bacteria are winning.

The war zone is our bodies. The bacteria that survive, widely called "superbugs", are growing and becoming more immune to antibiotics treating the same disease.

Their resistance genes can also spread to bacteria that cause other diseases, thus jumping species barriers and resulting in that resistance moving quickly to threaten our ability to treat many diseases.

In fact, there are specific genes that specialise in resisting antibiotics and jumping species barriers to enter other pathogens. These "jumping genes" are accelerating the problem.

In 2013, there were about 480,000 new cases of multidrug-resistant tuberculosis. There are high proportions of antibiotic resistance in bacteria that cause common infections like urinary tract infections, pneumonia and bloodstream infections in all regions of the world. Gonorrhoea is now almost untreatable in many countries.

The problem is not confined to antibiotics and resistant bacteria. Besides bacteria, there are other pathogens such as viruses that cause AIDS and hepatitis, and parasites which cause malaria that are treated by other anti-microbials.

These other microbes are also becoming resistant to medicines. For example, malaria is becoming more resistant to artemisinin-based therapy in some South-East Asian countries, and AIDS patients are increasingly not responding to first-line anti-AIDS medicines.

So, the problem of antibiotic resistance has now broadened to anti-microbial resistance (AMR) and the crisis now covers more people and more diseases.

At present, an estimated 700,000 people worldwide die annually from anti-microbial resistance. This number is projected to swell to

10 million deaths a year by 2050, according to a 2015 review on AMR commisioned by the British government.

The report also estimates that 300 million people will die prematurely because of drug resistance in the 35 years from 2016 to 2050 and that between now and 2050, the world could lose US$60 trillion to US$100 trillion (RM234 trillion to RM391 trillion) of economic output if AMR is not tackled. Most of the deaths and economic losses will be in developing countries.

Health leaders are finally sounding the alarm bell. Britain's chief medical officer Dame Sally Davies has warned of a "catastrophe".

Before her term as head of the World Health Organisation ended last year, Dr Margaret Chan spoke of the end of modern medicine in a post-antibiotics era, in which common infections such as strep throat or a child's scratched knee could once again kill.

These warnings have come very late, but it is better late than never. In the 1980s, the Consumers' Association of Penang (CAP), where I used to work, published studies on unethical marketing by drug companies of almost 20 medicines, which led to their inappropriate use and contributed to resistance. The health authorities took action by banning or restricting the sales of most of those medicines.

CAP also published a book in the mid-1990s titled *Revenge of the Killer Germs*, warning of the looming AMR crisis and calling for urgent action.

CAP was ahead of the curve and its warnings have been vindicated.

A recent international action is the 2015 Global Action Plan on AMR adopted by the World Health Assembly, which has spurred most countries to formulate their own national plans. Malaysia launched its AMR plan earlier this month.

Another action is the United Nations summit-level event on AMR in 2016, where heads of governments pledged to take action to address the crisis. This led to an inter-agency coordinating group that

will come up with recommended actions in 2019.

At the national level, a lot more can be done, including surveillance and data collection, infection control, better diagnosis aided by diagnostic tools, introduction of many new regulations and guidelines on drug marketing, proper prescription and dispensing, and a policy ensuring that new antibiotics are freely or cheaply available to the public.

The recognition of AMR as a crisis is only at the beginning stage. Much needs to be done. Every day of delay will allow the bugs to become super-bugs and super-superbugs with dire consequences for all of us.