



INTERACADEMY MEDICAL PANEL

Combating the threat of new emerging infections

IAMP Working Group
10-12 June 2007, Shanghai, China

Under the auspices of the
Chinese Academy of Engineering

Co-chairmen: Professor Wen Yu-Mei and Professor Sir Peter Lachmann

REPORT

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I Introduction

The IAMP Project on Emerging and Re-emerging Infectious Disease was approved at the IAMP Global Meeting in Beijing in 2006 and this workshop was its first event. The intention was to provide an overview of the field from the perspective of various Academies with a special emphasis on the problems affecting the developing world.

It was inevitable that this approach would lead more to the identification of problems than their solution. Nevertheless a number of conclusions emerged from our discussions which we believe deserve to be pursued further. These fell into two major categories: matters of health policy which require further consideration and action by policy makers; and suggestions directed at scientists for research to be taken up.

We hope that the member Academies will promote the first category with their national authorities. We would encourage interested scientists to pursue the second category.

II The need to implement new technologies for the diagnosis and surveillance novel infections

Zoonotic spread of micro-organisms from wild animal populations to domestic or food animals and directly or indirectly to man is a major factor in new emerging infections. Special importance is attached to novel contacts between such populations being brought about as a result of habitat destruction, global warming or other environmental changes.

The Nipah virus outbreak in Malaysia (which continues in Bangladesh now) was attributed to changed environmental conditions probably brought about by a powerful El Niño effect and by extensive forest fires. This had caused fruit bats to come into contact with pigs whose food had been contaminated with the Nipah virus from bat droppings. This caused infection of pigs which then spread within the pig population and from pigs to humans. It took some time and some excellent classical virology to discover that this was a novel virus which passed directly from pig to man and was not an insect born infection such as Japanese encephalitis (for which the preventative measures are, of course, quite different).

We suggest that policy makers consider:

- **that a risk assessment for creating novel contacts between different animal populations should be included as a part of all environmental assessments.** (The prediction of Rift Valley Fever in East Africa on the base of satellite information about flooding is an example where such techniques are already employed);
- **that there should be much closer and more formal association between veterinary practitioners and medical practitioners dealing with the diagnosis and control of infectious disease;**
- **that greater attention be paid to the improvement of veterinary 'public health' - especially clean food and water for domestic and farm animals.**

III Vaccination

Although great advances in vaccinology in the last half century are recognized and have had immense effects on human morbidity and mortality, it was nevertheless recognized that there are still major unmet needs and that these apply not only to human vaccination, but also to the vaccination of animals, both domestic and food animals, and even of animals in the wild.

In some cases the development of vaccines had turned out to be scientifically extremely difficult and the likelihood of producing an effective prophylactic vaccine in the immediate future is not high. This is the case for HIV where in spite of very substantial scientific efforts there is no immediate prospect of a prophylactic, sterilizing vaccine, although some success has been achieved in vaccines to stimulate T-cell responses and reduce viral load.

Progress has been made on vaccines against malaria but there is also not yet a vaccine available that is likely to have a major impact on the incidence of holoendemic malaria, particularly in sub-Saharan Africa, where this disease has its largest impact. For this reason it was pointed out that other attempts to control such diseases should not be neglected. Impregnated bed nets have proved to be a very successful and relatively inexpensive, control measure with recent evidence from Kenya showing beyond doubt of the value of this approach.

Transmission-blocking vaccination is immunologically attractive since plasmodial antigens which are expressed only in the mosquito have not been subject to the pressure giving rise to antigenic variation. However, a transmission-blocking vaccination will be successful only where a very high proportion of the population is immunized and the political will to undertake such vaccination programs has not been forthcoming, so that the development of transmission-blocking vaccines has not advanced as rapidly as their scientific promise might justify.

We suggest that appropriate funding bodies are encouraged to further support the development of vaccines against HIV and malaria. In the latter case, we recommend that research on transmission blocking vaccines should be included. However, we recognise that effective vaccines may not be available for some time and emphasise that other methods for preventing and treating these diseases should be strongly supported, bearing in mind that effective treatment of an individual also can have dramatic impact on the continued community transmission of malaria and HIV and other infectious diseases such as TB and Typhoid.

In other diseases, immunopathology may be found after second or subsequent infections and there is a danger that this may occur when infection occurs after vaccination. A major example here is Dengue where subsequent infections may be more severe than initial ones but the situation is more complicated than had previously been realized and there are possibilities of making vaccines that reduce both the incidence and severity of the disease. However there is a theoretical risk that vaccine-induced immune pressure will lead to viral evolutionary pressures that create escape mutants. This is a concern particularly for RNA viruses.

A further cause for unmet vaccination needs is that for a number of diseases the market is not considered large enough to attempt manufacturers to develop vaccines. The development of a vaccine for prophylactic use in children, in particular, is extremely expensive because of the very high safety requirements that are rightly required.

There is also an urgent need for vaccines that are active against certain bacteria. There are no satisfactory vaccines against staphylococci and a vaccine active against MRSA would be of immense value – medically and financially - throughout the world. Here the basic understanding of what it needs to make a good vaccine is still lacking. It is clear that deficiencies in the humoral immune system do increase pyococcal infections but for those with a normal humoral immune response, there seems to be no great advantage to be gained either from prior infections or from such vaccines as have been used. This is the sort of area where advanced microbiological techniques based on gene expression patterns in vivo as

compared to in vitro identifying novel targets seems to be the only way to go. Although these approaches have been pursued for some time they are not easy and no really successful vaccines have yet been derived from them.

Vaccines against *Clostridium difficile* are also needed as well as better vaccines against a number of other enteric organisms - *Salmonellae*, *Vibrios* and *Shigella*. Another major unmet need is improved vaccine against *Mycobacterium tuberculosis*. The coexistence of HIV and tuberculosis has proved particularly dangerous and not only to those who are affected. The dissemination of multi-antibiotic resistant mycobacteria from HIV/TB patients may prove to be a major public health problem for the whole world. The value of BCG vaccination against tuberculosis should not be underestimated – it does largely prevent tuberculous meningitis and miliary tuberculosis wherever it is used. Its value in preventing pulmonary tuberculosis is however limited in the tropics, possibly because of interference by other prevalent mycobacterial infections. A better vaccine would again be of huge benefit to world public health.

We suggest to appropriate funding agencies and to research workers in the area that the neglected field of vaccines against pyogenic bacteria be given greater support and that the development of antibacterial vaccines in general be given more attention

For some new emerging infections, for example Hanta virus and the SARS coronavirus, vaccines are potentially available but it is currently unclear how they should best be used. While the diseases are as uncommon as they are at present, mass vaccination may be unjustified and how vaccines should be deployed should further epidemics occur requires further study. The same is certainly true for vaccination against H5N1 influenza, which will be discussed below.

“First aid” vaccines - aimed at stimulating the innate immune response to raise an initial response to a novel or unidentified infection – were suggested as a novel concept. This was agreed to be an attractive proposition which required proof of concept experimentation.

We suggest that the concept of “first aid vaccines” be evaluated in a number of experimental infections.

Scientific and immunological considerations apart, it was felt that inducements should be offered to industry to develop new vaccines through the taxation system (and potentially by agreements to prolong patents in the West on “blockbuster” drugs developed by major pharma in exchange for the development of vaccines and drugs targeted at the developing world) and it was also agreed that the current regulatory practice whereby any significant modification to an existing vaccine required complete re-licensing at enormous cost was in fact inimical to public health and potentially unethical. Improvements to living polio vaccine as well as improvements to vaccines against hepatitis B have never been introduced because of the great cost that would be involved. The regulators should be persuaded to look at this again.

We suggest that policy makers explore the possibility of offering to companies to undertake the development of new vaccines to meet the large unmet needs in this area

In parts of the world, immunization coverage remains sub-optimal and the vaccine preventable diseases continue to be prevalent. This is particularly troubling for those diseases (for example polio and measles) that vaccination can eradicate from the population. The eradication effort has, however, to be world-wide if any country is to remain confidently free of these infections. It also would clearly be beneficial to have vaccines that are easier to use and to administer. The increasing use of multiple vaccines which reduce the number of injections has been helpful. The introduction of “needle-less” administration techniques would also help. Accessibility of vaccines is a problem in the developing world and the use of vaccines that do not require a cold chain (such as plasmid vaccines), would have considerable advantages (once their immunogenicity has been improved sufficiently).

In the past the developing world, it has often been found that killed vaccines against viruses (e.g. polio) are more effective than living vaccines because of the problem of interference from other virus infections.

We believe that research into formulating vaccines for easier storage and administration be given adequate priority.

Finally, there was discussion of the difficulties of achieving a high level of vaccine acceptance and the problem of vaccine scares. This is a topic that has been extensively discussed and is included in a project that the Federation of European Academies of Medicine is submitting to the European Commission on the public health aspects of vaccination. It is, however, substantially a matter for social psychologists since it concerns behavioural modification and is indeed just one example of the rejection of science and of the values of the enlightenment which has been so damaging in recent years.

IV H5N1 Influenza

The threat of a human pandemic of flu by changes occurring in the H5N1 flu virus is regarded as one of the major public health threats facing the world at the present time. There has not been a pandemic caused by an entirely avian flu virus since 1918 and this epidemic showed how lethal such infections can be. Where H5N1 has infected humans it has also shown the same tendency to spread from the lungs to other parts of the body and to have a very high mortality. Vaccines to H5N1 have been made by a number of companies and these are being stockpiled in a number of countries. It is not clear that stockpiling a vaccine would help in a rapidly developing pandemic. If experimental use shows the vaccines to be safe, it may be wiser to use anticipatory vaccination in selected populations. The H5N1 virus has been found to undergo progressive mutational change and this emphasizes the desirability of producing non-clade specific vaccines. The incidence of H5N1 infection in the Far East has suggested that infection is seen less on large poultry farms where workers are often exposed to avian flu viruses, than it is in smaller enterprises where such exposure is less. This does suggest that some background immunity may occur even from antibodies or cellular immunity to viruses which are not identical to the current strain and which may not be neutralizing.

We encourage investigators to conduct experiments to establish whether background immunity with non-neutralising antibodies does reduce disease severity even if it does not prevent infection. If this proves to be the case, there would be a strong case for vaccinating even with non-clade-specific vaccines.

There is also a case for stockpiling antibody to H5N1 either or both, from immunized volunteers or from human monoclonal antibodies. A limited amount of monoclonal antibody has been made from the B-cells of patients who have recovered from H5N1 and a single monoclonal antibody has been shown to be highly effective in protecting mice or even treating them up to 72 hours after infection (longer time frames have yet to be tested).¹ This approach will be tried in humans in due course.

We suggest that volunteers be immunized with the current experimental vaccines to produce high titres of neutralizing antibody and that immunoglobulin from these be stockpiled. We suggest further that monoclonal antibody production is set in train to produce multiple monoclonal antibodies from convalescent patients. It is recognized that scaling up the production of these antibodies is likely to be a technical problem for which advance preparation is required.

Recently, an interferon and a single chain Fv have been produced in chicken egg white by genetic manipulation and these transgenes were found to be stable on breeding.⁽²⁾ This may provide a promising

1 Cameron P. Simmons, Nadia L. Bernasconi, Kimberly Mills, Amorsolo L. Suguitan, Jr, Jerrold M. Ward, Nguyen Van Vinh Chau, Tran Tinh Hien, Federica Sallusto, Do Quang Ha, Jeremy Farrar, Menno De Jong, Antonio Lanzavecchia, Kanta Subbarao Prophylactic and therapeutic efficacy of human monoclonal antibodies against H5N1 influenza PLoS Medicine 2007 May;4(5):e178

2 S. G. Lillico, A. Sherman, M. J. McGrew, C. D. Robertson, J. Smith, C. Haslam, P. Barnard, P. A. Radcliffe, K. A. Mitrophanous, E. A. Elliot, and H. M. Sang (2007) "Oviduct-specific expression of two therapeutic proteins in transgenic hens" PNAS 104 1771-1776

approach to protecting the chicken population from H5N1 if either single chain Fv or even larger antibody insert could be put into the ovalbumin of chickens. How well such antibody is taken up into the circulation of the developing chick and how long it would last requires study. Since broiler chickens have an average lifespan of only 6 weeks, very long persistence would not be needed for this population.

We suggest that the technique of introducing antibodies into egg white be explored to obtain proof of concept evidence that this is a feasible method of protecting chickens from avian flu.

This technology could also be extended to introducing antibodies against enteric organisms, for example *E. coli Vero toxin* or *rotavirus* which would enable passive protection to be available to children in the developing World from food rather than from pharmaceuticals. Clearly eggs containing such antibodies could not be boiled and the egg white could be need incorporated into some locally acceptable food which could be bacterially sterilized by ultrafiltration, irradiation or gentle Pasteurisation. The possibility of using genetically modified bananas for the same purpose was also discussed.

We suggest that the use of passive antibodies made in eggs should be explored as what is sometimes called a “neutraceutical” for prevention of enteric infections in the developing world.

V Antibiotic and Antiviral Resistance

The meeting endorsed the recommendations of the EASAC report on this topic ⁽³⁾. The group recognized that resistance to antimicrobial drugs was already a major problem and was likely to become worse. It is highly likely that anti-microbial drug resistance may be considerably more dangerous to mankind than epidemics of emerging diseases and urgent action is required to try to prevent the development of further resistance.

We recommend:

that regulations are put in place at a global level to ensure that antimicrobial drugs are only for infections of proven susceptibility;
that they be provided only on prescription;
that, wherever possible, combination therapy of antimicrobials are used rather than a single agent;
that the highest permissible doses are given, preferably for shorter periods than is often the case, and that the current highest permissible levels should be reinvestigated as the recommendations were often developed years before resistance became an issue.

We recommend further:

that the mechanisms be put in place to ensure adherence with treatment and the prevention of the passage of drugs to other people.
Finally, we are aware that there is a serious problem with counterfeit drugs which may either be completely inactive or may contain only smaller amounts of the drug than the label would suggest. This also gives rise to problems of resistance.

These recommendations are equally applicable to antibiotics and to antiviral drugs, of which there is still a great shortage. Thus there are only two potential antiviral drugs available for treating flu – one is the neuraminidase inhibitor Oseltamivir (Tamiflu) which is currently available only as an oral formulation which it is difficult to administer to seriously sick patients. (Administering this drug by suppository might overcome this problem) The other is Zanamivir (Relenza) which is mainly available for inhalation, although systemic preparations are being developed and a new injectable NAI Peramivir is currently undergoing Phase III trials. However both Oseltamivir and Peramivir are susceptible to the same single point mutation which confers absolute drug resistance.

³ Tackling antibacterial resistance in Europe. EASAC policy report 07, June 2007

There are serious problems impacting the development of new antimicrobial drugs. In part these scientific as the traditional method of antibiotic discovery - based on organisms competing with each other in soil - has probably yielded most of the compounds that are readily obtained by this method, and the development of new antimicrobials requires new technologies, usually based on the identification of targets from studies of microbial genome expression in different situations. These are expensive and have been rather slow to deliver new drugs. It is also recognized as a problem the current regulations for approval of new drugs are too slow, too demanding and too risk-averse, and greatly increase the cost. Both the regulatory environment and the risk policies of big pharmaceutical companies appear to be dominated by fears of litigation rather than by genuine risk/benefit calculations. Solving these problems will require a cultural shift and a change in litigation practice that go beyond our immediate remit but which are essential for further drug development.

VI Summary and Conclusions

The discussions which are reported above centred on the problems associated with emerging infectious diseases, concentrating particularly on developing countries although it is clear that the dangers that this class of disease poses is global. Microbes do not respect national borders! Nevertheless remedial action is needed for the “Three Neglected” – neglected diseases, neglected technologies and neglected populations. The first was given considerable attention in the discussions. Neglected technologies were not discussed in detail but there is a great need for simple diagnostic techniques for infections that can be used near the bedside without elaborate instrumentation. The seminal contributions of Professor Helen Lee and her colleagues in developing dipstick techniques for this purpose are an important advance in this field⁽⁴⁾. The problem of ensuring access to vaccines, diagnostics and therapeutics to neglected populations lies beyond the remit of the present project but is also essential for the global control of emerging infectious disease.

Our recommendations as given above are all addressed to the member academies of IAMP but require action to a varying extent by policy makers and public health authorities; and by scientists in the biomedical area (as well as by funding bodies and by industry).

⁴ Magda Anastassova Dineva, Daniel Candotti, Fiona Fletcher-Brown, Jean-Pierre Allain, and Helen Lee (2005) “ Simultaneous Visual Detection of Multiple Viral Amplicons by Dipstick Assay” JOURNAL OF CLINICAL MICROBIOLOGY, Vol. 43, 4015–4021;

Claude-Edouard C Michel, Anthony W Solomon, Jose P V Magbanua, Patrick A Massae, Ling Huang, Jonaice Mosha, Sheila K West, Elpidio C B Nadala, Robin Bailey, Craig Wisniewski, David C W Mabey, Helen H Lee (2006) “Field evaluation of a rapid point-of-care assay for targeting antibiotic treatment for trachoma control: a comparative Study” Lancet 367: 1585–90

(Appendix 1)

Participants

新发、再发传染病防控对策国际研讨会

Workshop on Emerging Infectious Diseases

代表通讯录

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(Appendix 2)

Programme

Monday 11th June

9-9.30 am **Opening Ceremony**

Chair: Wen Yumei

Speeches:

1. Wen Yumei, Member of CAE
2. Peter Lachmann
3. Shi Qianghua, administrative Vice-Director of CAE-Shanghai Center
4. Hou Yunde, Member of CAE

9.30-12.15

Session 1:

Introduction of experiences of combating emerging and re-emerging diseases

Chair: Peter Lachmann

1. *Lai Meng Looi (Malaysia)*, **Lessons from the Nipah virus outbreak in Malaysia**
2. *Volker Ter Meulen (Germany)*, **EASAC Recommendations on infectious diseases - importance of coordinated activity in Europe**
3. *Jeremy Farrar (UK-Vietnam)*, **Globalization and emerging infectious diseases. A threat and an opportunity for collaborative clinical science.**
4. *De-Xing Li (China)* **Emerging and re-emerging viral diseases in China**
5. *Viktorija Calovska-Ivanova (Macedonia)*, **Hepatitis B and hepatitis C in the Republic of Macedonia - current status and future perspectives**
6. *Guoping Zhae (China)*, **SARS molecular epidemiology and SARS-CoV evolution**

14-16.45

Session 2:

New ideas or new approaches for prevention and control of emerging and re-emerging diseases

Chair: Wen Yumei

1. *Peter Lachmann (UK)*, **The role of passive immunisation in combating infection**
2. *Victor Maleev (Russia)*, **Perspectives of IAMP involvement into emerging diseases problem**
3. *Yu-mei Wen (China)*, **Vaccines for stimulating innate immune responses: possible “first aid vaccines” to combat new emerging infectious diseases**
4. *Abiodun Adesiyun (Trinidad and Tobago)*, **Public health: provision of clean water, effective sewage disposal, sexual hygiene - the Caribbean experience**
5. *Prema Ramachandram (India)*, **Immunisation programme in India - challenges and opportunities**

Tuesday 12th June

9-12 **Discussion and draft summaries and suggestions**