



Advisory Group of Independent Experts to review the smallpox research programme (AGIES)

Report to the World Health Organization

Geneva, Switzerland

November 2013

PANDEMIC AND
EPIDEMIC DISEASES



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Acronyms and abbreviations

ACVVR	WHO Advisory Committee on Variola Virus Research
AGIES	Advisory Group of Independent Experts to review the smallpox research programme
CDC	Centers for Disease Control and Prevention, United States of America
DNA	Deoxyribonucleic acid
HIV	Human immunodeficiency virus
PCR	Polymerase chain reaction
SAGE	Strategic Advisory Group of Experts on Immunization
SRC VB VECTOR	The Russian Federation State Research Centre of virology and Biotechnology
USFDA	United States Food and Drug Administration
USA	United States of America
WHO	World Health Organization

Introduction

Background

In May 2007, the World Health Assembly in resolution WHA60.1 requested the Director-General of the World Health Organization (WHO) to undertake a major review, in 2010, of the state of the smallpox research and additional related research needed for global public health purposes. This review was undertaken to enable the Sixty-fourth World Health Assembly, in 2011, to reach consensus on the timing of the destruction of existing variola virus stocks.

In May 2011, the World Health Assembly in resolution WHA64.1 decided, however, to defer discussion of the destruction of the existing stocks of variola virus until the Sixty-seventh World Health Assembly in 2014.

Since 2011, the WHO smallpox secretariat has continued its work supported by the Advisory Committee on Variola Virus Research (ACVVR), which oversees all essential work with live variola virus for public health benefit (resolution WHA52.10). ACVVR held its 15th meeting in September 2013 in preparation for the discussions at the Sixty-seventh World Health Assembly. On 19 and 20 September 2013, an expert consultation was convened to review the evidence on smallpox vaccines and propose recommendations for the size and composition of the WHO smallpox vaccine stockpile to the Strategic Advisory Group of Experts (SAGE) on Immunization. The recommendations from the expert consultation will be considered during the SAGE meeting (Geneva, 5-7 November 2013). Other major activities have included the biennial inspections of the two repositories of variola virus (the Centers for Disease Control and Prevention in Atlanta, Georgia, USA, and the Russian Federation State Research Centre of Virology and Biotechnology (SRC VB VECTOR), Koltsovo, Novosibirsk Region, Russian Federation). The reports of the latest inspections, in 2012, are being posted on the WHO website.

The Advisory Group of Independent Experts to review the smallpox research programme (AGIES) was established by the Director-General of WHO in order to provide advice on matters of strategy and evaluation of the smallpox research programme, and to assess whether additional research with live variola virus is necessary from the public health perspective. Both the approach and the process of the AGIES have been welcomed by Member States, and would thus appear to be well suited for preparation for a historic discussion at the World Health Assembly. The recommendations made by AGIES would represent the Groups' scientific judgement.

Both the report of ACVVR's 15th meeting and the present report of AGIES, together with a report from the WHO Secretariat, will be submitted to the Executive Board of WHO for consideration at its 134th session in January 2014 and then to the Sixty-seventh World Health Assembly in May 2014.

Method of work of AGIES

The WHO Secretariat prepared a series of documents and scientific papers (see below for more details) that were made available to members of AGIES prior to its meeting, which was held on 5 and 6 November 2013 at WHO Headquarters in Geneva.

AGIES' members were asked to read, review and assess these documents and other publications found through searches of the scientific literature.

All members of AGIES discussed and reviewed the smallpox research programme at a meeting organized at WHO Headquarters on 5 and 6 November 2013. Discussions were held under five subheadings: diagnostics, genetics, vaccines, antiviral drugs and other therapeutics.

The members of AGIES prepared and reviewed the current report; it summarizes discussions on the value of smallpox research achievements to date and whether additional research work with live variola virus would be needed to ensure a sufficiently high standard of global public health security from a potential re-emergence of smallpox.

Documents reviewed by AGIES

The following documents were reviewed by members of AGIES:

- WHO Advisory Committee on Variola Virus Research, report of the twelfth meeting, 2010, Geneva, WHO.
- WHO Advisory Committee on Variola Virus Research, report of the thirteenth meeting, 2011, Geneva, WHO.
- WHO Advisory Committee on Variola Virus Research, report of the fourteenth meeting, 2012, Geneva, WHO.
- WHO Advisory Committee on Variola Virus Research, report of the fifteenth meeting, 2013, Geneva, WHO.
- Scientific Review of Variola Virus Research 1999-2010, December 2010, Geneva, WHO.
- Advisory Group of Independent Experts to review the smallpox research programme (AGIES), comments on the Scientific Review of Variola Virus Research 1999-2010, December 2010, Geneva, WHO.
- Selected scientific papers on smallpox (the list of these papers is available on request)
- Five documents prepared by the WHO Collaborating Centre for Smallpox and other Poxviruses at the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America. These reports described the research conducted on five of the current variola virus research protocols for the past three years (2011-2013), as well as a report on the use of the repository materials.
- One document prepared by the WHO Collaborating Centre repository the Russian Federation State Research Centre of Virology and Biotechnology (SRC VB VECTOR), Koltsovo, Novosibirsk Region, Russian Federation. The report described the research conducted as part of WHO-approved research proposals during 2011-2013, as well as variola virus strains maintained in the repository at SRC VB VECTOR.

Terms of Reference and Membership of the Advisory Group of Independent Experts to review the smallpox research programme (AGIES)

Terms of Reference

The Advisory Group of Independent Experts to review the smallpox research programme (AGIES) has been formed to advise WHO on matters of strategy and evaluation of smallpox research and more specifically:

1. To provide, from a global public health perspective, an assessment on whether additional research using live variola virus is necessary or desirable based on their assessment of the results of smallpox research already undertaken and the plans and requirements for further research essential for global public health purposes.
2. To deliver, within one week of the conclusion of their meeting, a report to WHO summarizing their discussion on the value of smallpox research achievements to date and whether or where additional research work using live variola virus would be needed to ensure sufficient public health security from a potential re-emergence of smallpox.

Membership of AGIES

Members of the AGIES were selected and appointed by the Director-General of WHO to serve in their personal capacities, and represent the broad range of disciplines relevant to the review of the smallpox research programme as well as diversification and balance of personal experience, professional background, gender, and geographical origin.

A full list of these members and their short biographies is available as an appendix of the AGIES report.

WHO Secretariat

The Secretariat provided all necessary logistical support for AGIES to meet its terms of reference, including a series of documents related to smallpox research during the period 1999 to 2013.

Declaration of Interests

In line with WHO policy all members of AGIES have completed and signed a Declaration of Interests. No relevant conflict of interest in the subject matter of the meeting has been declared by any expert.

Review of documentation on smallpox research 2010-2013

Members of AGIES discussed the issues related to smallpox under five subheadings, including laboratory diagnostics, variola genomics, animal models and pathogenesis, smallpox vaccines, and antiviral agents and smallpox treatment.

1. Laboratory diagnostics

The AGIES 2010 report

AGIES members were of the view that live variola virus is not required either for the further development of diagnostic tests or for technical assay validation.

Discussion

Despite the eradication of smallpox, laboratory methods to diagnose variola virus infection are needed because of potential bio-warfare or bio-terrorism threats, for confirmation of diagnosis of smallpox in the event of an outbreak, and lack of experience of most clinical personnel with this disease.

Diagnostic tests for smallpox fall into four categories - detection of: whole virus; viral genetic material (nucleic acid); viral protein component(s); and antibodies against antigens of the variola virus (serological assays).

A literature search of work on variola virus diagnostics since 2010 identified publications on new PCR (nucleic acid)-based methods for detection of poxviruses and an improved antigen-capture assay. These developments represent only minor modifications or improvements on the assays already available, without a paradigm shift.

Of note, a PCR-based variola/orthopoxvirus assay was licensed in the Russian Federation in 2011. In addition, two variola-specific real-time PCR assays have undergone regulatory review. Members of AGIES agreed with the ACVVR's statement in its 15th meeting report that a specific PCR-based test for variola virus is desirable but not essential, as follow-up of a positive PCR result with genomic sequencing to identify variola virus would definitively be done as a matter of routine. In addition, on the basis of experience with other infectious agents, protein-based tests are highly likely to remain less sensitive and specific than PCR tests.

Members of AGIES agreed that appropriate nucleic acid-based diagnostic tests are available and have been adequately validated. Although it was debated whether protein-based tests would have a place as screening tests for smallpox, it was noted that, in the event of suspected variola virus infection, a negative protein-based test would not obviate the need for PCR- and sequencing-based testing. Thus it was agreed that further development of such protein/antigen or antibody-based tests was not important from public health point of view.

Conclusion

Members of AGIES concluded that there is no need to retain live variola virus stocks for the development of further diagnostics for smallpox.

2. Variola virus genomics

The AGIES 2010 report

AGIES' members concluded that there was no public health need to sequence the genomes of additional variola virus isolates. This conclusion was based on the fact that near-complete genomic sequences are available for some 50 isolates of variola virus, analysis of which indicates that the variola virus genome shows very limited genomic diversity.

Discussion

ACVVR's previous reports (from the twelfth in 2010 to the present) concluded that there is no need to sequence additional variola virus isolates. At its 15th meeting, ACVVR observed that CDC's "use to completion" of 70 of its 420 variola virus stocks in the process of approved research potentially set a precedent for the progressive reduction of all live virus material being held in the two repositories.

Conclusion

Consistent with the conclusion they reached in 2010, members of AGIES reiterated that there is no public health need to sequence the genomes of additional variola virus isolates.

3. Animal models and pathogenesis

The AGIES report 2010

AGIES members noted that there was no animal model with variola virus (including non-human primates) that replicated human disease. On the other hand, there are surrogate models using poxvirus infection of animal (including natural hosts), such as ectromelia virus, cowpox virus, rabbitpox virus, monkeypox and vaccinia virus. Given that human smallpox cannot be reproduced in animal models, members of AGIES concluded that research should be focussed on improving surrogate animal models using other poxviruses and on determining acceptable criteria for regulatory approval of drugs and vaccines using these models.

Discussion

In recent reports in the literature, monkeypoxvirus infection in prairie dogs was proposed as a suitable model for evaluating smallpox vaccine candidates, and vaccinia virus (WR) infection of immunodeficient mice was investigated as an alternative animal model to evaluate the immune correlates of protection. With regard to mouse models, as summarized in the report of the 15th ACVVR meeting, preliminary data were presented on infection of CAST/EiJ mice with live variola virus. Mice inoculated with different virus doses showed clinical signs of disease, the severity of which increased with an increased dose of virus and younger age of the mice. The report stated that further experiments using younger mice are planned. AGIES questioned the relevance of this mouse model, which still does not reproduce human smallpox, and reiterated its previous conclusion that there is no animal model of variola infection that does so.

Conclusion

Members of AGIES considered that, despite extensive efforts by several research groups, there has been very limited progress in developing an animal model using variola virus. Members of AGIES therefore reiterated their previous conclusions, namely that:

- research be focused on improving surrogate animal models and determination of acceptable criteria for approval of drugs and vaccines
- the “Animal Rule” for regulatory approval of smallpox vaccines and antiviral agents be reconsidered.

Furthermore, members of AGIES concluded that there is no public health reason to retain live variola virus for use in animal models.

4. Smallpox vaccines

The AGIES 2010 report

AGIES concluded that live variola virus was not needed for the development of safer vaccines assuming that regulatory issues around vaccines were resolved.

Discussion

Members of AGIES agreed that from a public health perspective, smallpox vaccines with good safety, efficacy and immunological profiles are needed for prevention and containment of smallpox in the event of an outbreak. First-generation vaccines have proven to be effective in human smallpox but cause significant side effects (reactogenicity). A second-generation vaccine (ACAM2000) has been licensed in the USA in 2007 for use in healthy individuals. Members of AGIES noted that neither the first- nor second-generation vaccines are safe to use in immunosuppressed individuals (e.g. those with HIV infection) because of the risk of disseminated infection with the strains of vaccinia virus contained in these vaccines.

The LC16m8 vaccine, one of the third-generation vaccines that have been developed, was the subject of most of the recent papers in the scientific literature. There was considerable discussion on the type of neutralizing antibody response elicited by this vaccine and whether as a result the vaccine would be as effective in protecting individuals against smallpox as the earlier generation vaccines.

Overall, it was concluded that the third-generation vaccines are likely to be efficacious and safer (that is, free from serious adverse side effects) than the first- or second-generation vaccines. However, as they have not been used to protect against human variola virus infection, it is not possible to determine how effective they would be in an outbreak.

They will be valuable, however, in protecting individuals against disease caused by other orthopoxviruses and, in the event of a smallpox outbreak or a bioterrorism event, would be required for individuals who cannot be vaccinated with first- or second-generation vaccines (for example, people infected with HIV and other immunocompromised people).

The members of AGIES noted that the ACVVR at its 15th meeting was of the opinion that live virus was not needed for the development of safer smallpox vaccines beyond those studies already approved.

Conclusion

Members of AGIES concluded there is no need to retain live variola virus for the further development of smallpox vaccines.

5. Antiviral agents and smallpox treatment

The AGIES 2010 report

AGIES members concluded that retention of live variola virus was needed for *in vitro* (cell culture) studies of new antiviral compounds but not for use in animal models.

Discussion

From a public health point of view, the members of AGIES noted the need for antiviral agents and therapeutics that are safe and effective in the treatment of clinical smallpox or in treating rare cases of poxvirus infection arising from immunisation with live virus.

ACVVR at its 15th meeting was informed that the two lead compounds, tecovirimat (ST-246) and brincidofovir (CMX001), were in advanced stages of development. For tecovirimat there seems to be an overwhelming set of data to support its licensure for use as a therapeutic against smallpox. In the USA tecovirimat has been given status of an Investigational New Drug (IND) and two million doses have been ordered for the National Strategic Stockpile. The pathway for regulatory approval is well defined. FDA requires additional data from the intradermal rabbitpox animal model but no further data with live variola virus. Brincidofovir also has IND status and is being tested in more than 200 patients (mostly with cytomegalovirus infections) in open-label study. Discussions with USFDA suggest that regulatory approval will follow the “Animal Rule” with data derived from the rabbitpox model and the ectromelia virus mousepox model but no further studies with live variola virus.

ACVVR also received data on research using live variola virus, including the *in vitro* testing of new synthetic compounds, the use of tecovirimat and, in particular, brincidofovir in animal models. New candidate drugs being investigated include proteasome inhibitors, an extract of the plant *Sarracenia purpurea*, kinase inhibitors and pyridopyrimidinones, which act at different stages of the orthopoxvirus life cycle.

Tecovirimat has been studied for prophylactic, post-exposure and therapeutic activity against monkeypoxvirus infection in prairie dogs, with confirmed efficacy against lethal challenges. Only a small number of wild-bred dogs were studied but emergence of drug-resistant viruses was not seen. Other recent research suggests the possibility of targeting poxvirus immune evasion proteins for therapeutic purposes, a novel and elegant approach with a highly suitable surrogate model (mousepox). Targeting viral inhibition of NFκB signalling might be an additional therapeutic approach. Further, an alternative drug candidate to the DNA-synthesis inhibitor brincidofovir showed broad antiviral activity against orthopoxviruses.

ACVVR at its 15th meeting discussed the need to retain live variola virus for drug development. Proponents of retention argued the uncertainty of regulatory approval of the two lead compounds and the possible need for additional antiviral agents to be developed, which would require thorough testing (including the use of live variola virus). Some participants maintained that the development of an animal model of smallpox was highly desirable. Opponents of retention argued that regulatory approval of tecovirimat and brincidofovir was highly unlikely to fail and, if needed, suitable surrogate orthopoxvirus infection models could be used for drug testing and development.

Members of AGIES considered these opinions and other points of view. The view that additional research on new drug targets with live variola virus might reveal important insights into the pathogenesis of human smallpox was challenged by the fact that no animal model for smallpox is available to allow such research. With regard to the potential need to develop additional drug candidates, it was suggested that live variola virus could be rescued from viral DNA (stored in repositories) if urgently needed. The need to retain live virus for reasons of regulatory uncertainties was discussed. The AGIES members supported the great likelihood that the two lead compounds in late stages of development would be approved. Nevertheless some members felt uncomfortable about the uncertainty of regulatory decision-making and it was argued that the technical and logistical feasibility of swift resurrection of live variola virus from DNA should be verified.

Conclusion

The majority view of members of AGIES was that there is no need to retain live variola virus for the further development of antiviral agents against smallpox.

Summary and concluding remarks

Following review of the ACVVR reports (from 2010 to 2013), other reports and recent publications, the members of AGIES commended the quality of the smallpox research undertaken and of the material made available for review.

In line with the terms of reference of AGIES, namely to provide, from a global public health perspective, an assessment of whether additional research using live variola virus is necessary or desirable based on their assessment of the results of smallpox research already undertaken, and the plans and requirements for further research essential for global public health purposes and after detailed debate and discussion, the members of AGIES agreed on the following:

1. Members of AGIES conclude that there is no need to retain live variola virus for the further development of diagnostics. This confirms the previous conclusions reached by AGIES in 2010.
2. Members of AGIES conclude that there is no indication for additional sequencing of the variola virus genome and hence no need to retain live variola virus for this purpose. This confirms the previous conclusions reached by AGIES in 2010.
3. Members of AGIES conclude that there is no reason to retain live variola virus for use in animal models.
4. Members of AGIES conclude that there is no need to retain live variola virus for the further development of smallpox vaccines.
5. The majority of the members of AGIES concludes that there is no need to retain live variola virus for the further development of antiviral agents against smallpox.

AGIES notes that recommendations 1, 2 and 4, but not 3 and 5 are in line with the conclusions of ACVVR at its 15th meeting.

Appendix 1. Profiles of members of AGIES

Dr Ximena Aguilera, Santiago, Chile

Dr Aguilera is a MD Specialist in Public Health, Residence in International Health at PAHO. She is Director of the Centre of Epidemiology and Public Health Policies at the Faculty of Medicine Clínica Alemana - Universidad del Desarrollo in Chile.

She was Senior Advisor in Communicable Diseases at the WHO Regional Office for the Americas (2008-2010) where among other duties she coordinated the technical response to the influenza A(H1N1) pandemic. Previously she was the Chief of Health Planning Division at the Ministry of Health in Chile (2005-2008) and Head of the Department of Epidemiology at the same institution (1999-2005). She was the Chilean representative during the negotiations on the revision of the International Health Regulations, and official delegate for Asia-Pacific Economic Forum Health Working Group, and for MERCOSUR sub-working group on health. In addition she was primarily responsible for pandemic preparedness and for the implementation of the International Health Regulations (2005) at the Ministry of Health of Chile. She has worked as consultant for the WHO Regional Office for the Americas, the United Nations Development Fund, the Inter-American Development Bank and the World Bank in several countries in Latin America and participated in the WHO mission in response to the SARS outbreak in China (2003). She has been a member of the Advisory Committee of the Global Outbreak Alert and Response Network of WHO.

Professor Rakesh Aggarwal, Lucknow, India

Professor Aggarwal obtained his MD at the All India Institute of Medical Sciences, New Delhi in 1986. He trained as a gastroenterologist-hepatologist, and also holds a postgraduate degree in epidemiology from the London School of Hygiene and Tropical Medicine, United Kingdom. He is working as a Professor of Gastroenterology at the Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Professor Aggarwal has conducted extensive research on various aspects of hepatitis viruses, in particular hepatitis E virus, including studies on epidemiological, clinical, laboratory and immunological aspects of this infection. He has also undertaken health economic analyses on the impact of hepatitis B vaccination.

His current duties and responsibilities include caring of inpatients and outpatients with liver disease, teaching and supervision of gastroenterology-hepatology fellows, and running an active hepatitis research laboratory. He is Principal Investigator of several clinical and laboratory studies, primarily in the field of viral hepatitis and other liver diseases.

Dr Suleiman Al-Busaidy, Muscat, Oman

Dr Al-Busaidy graduated in 1977 with a BVM&S degree, followed by a Diploma in Tropical Veterinary Medicine, at the University of Edinburgh. He went on to acquire an MSc degree

in veterinary microbiology and a PhD in arboviruses at the University of Surrey, United Kingdom.

Currently he is Director of the Central Public Health Laboratory in the Ministry of Health, Muscat, Oman. His responsibilities include the provision of scientific and managerial leadership in developing, promoting and integrating public health laboratory services into practice, towards surveillance, prevention and control of diseases.

Dr Al-Busaidy developed the Virology Laboratory within the Central Public Health Laboratory into a Centre of Excellence within the WHO Eastern Mediterranean Region where the Central Public Health Laboratory has now attained WHO recognition as a Regional Reference Laboratory for Polio, Measles/Rubella, Influenza and Tuberculosis, as well as being the provider for the Eastern Mediterranean External Quality Assurance Scheme in Microbiology.

Dr Luciana Barros de Arruda, Rio de Janeiro, Brazil

Dr Barros de Arruda has a Bachelor's degree in microbiology and immunology from the Federal University of Rio de Janeiro (1997), an MSc degree in biological sciences (biophysics) from the Federal University of Rio de Janeiro (1999), and a PhD in life sciences (biophysics) from the Federal University of Rio de Janeiro (2003). She is an associate professor at the Department of Virology, Institute of Microbiology, at the Federal University of Rio de Janeiro. She gained her MSc degree there, in the Department of Immunology, where she studied the modulation of B lymphocyte responses to the parasite *Trypanosoma cruzi*. Her PhD was performed at the same institution and Johns Hopkins University (Baltimore, Maryland, USA), where she started to work on the development of DNA vaccine against HIV.

Currently, she coordinates the Laboratory of Genetic and Immunology of Viral Infections at the Department of Virology, Federal University of Rio de Janeiro. Her research group focuses on the immune response to arboviruses (dengue and Sindbis viruses) and HIV, including the study of virus sensing by innate receptors, humoral and cellular immune response in human and animal experimental models, and the development of antiviral vaccines.

Associate Professor Suok-Kai Chew, Singapore, Republic of Singapore

Dr Chew received his MBBS degree in 1978 and the MSc degree (public health) in 1990 from the National University of Singapore. He received his Master in Science (epidemiology) and Diploma in Epidemiology in 1997 from the London School of Hygiene and Tropical Medicine, University of London, United Kingdom. He was a Fogarty Fellow at the Department of Epidemiology, School of Public Health, University of California Los Angeles, USA, in 1993.

He has held a wide range of positions in the field of medicine and public health. He was the Director of Epidemiology and Disease Control at the Singapore Ministry of Health from 1997 to 2003. Since 2003, he has been the Deputy Director of Medical Services with national level

responsibilities for public health, health services and health regulation. He is an adjunct associate professor at the Saw Swee Hock School of Public Health, National University of Singapore, and has published extensively in the field of infectious diseases and non-communicable diseases.

Professor Zhihong Hu, Wuhan, People's Republic of China

Professor Zhihong Hu received her BSc degree (Virology and Molecular Biology) in 1986 from Wuhan University, China, and her MSc degree (Virology) in 1989 from Wuhan Institute of Virology, Chinese Academy of Sciences (CAS), afterwards becoming a staff member of the institute. She obtained her PhD degree (Virology) from Wageningen Agricultural University in 1998.

Since 1997, she has been Professor at Wuhan Institute of Virology (CAS), and was the Director General of the Institute from 2000 to 2008. Professor Zhihong Hu's research interest focuses on virology, especially on molecular biology and application of baculovirus. Since 2003, her research has extended to emerging infectious viral diseases, such as Severe Acute Respiratory Syndrome (SARS) and Crimean-Congo haemorrhagic fever (CCHF).

Professor Siripen Kalayanaroj, Bangkok, Thailand

Professor Siripen Kalayanaroj has a Bachelor's degree in the field of Medical Science from Mahidol University, Bangkok (1975) and a Medical Doctorate with honours (1977), Certificate of Proficiency Board in Pediatrics (1981) and Sub-Board in Pediatric Infectious Diseases (1983) from the University of California Los Angeles, USA.

Since 1997, she has been the Director of the WHO Collaborating Centre for Case Management of Dengue, Dengue Haemorrhagic Fever and Dengue Shock Syndrome at the Queen Sirikit National Institute of Child Health - previously known as the Children's Hospital - in Bangkok, where she is now Consultant of Infectious Diseases Unit. The Queen Sirikit National Institute of Child Health is a tertiary care/referral hospital under the Department of Medical Services at the Thai Ministry of Public Health, and is affiliated with the Faculty of Medicine of Rangsit University.

Her duties and responsibilities are the following:

- policy advocacy: acting as the national team leader in Thailand, responsible for the clinical management of dengue, DHF and DSS, in order to minimize the dengue case fatality rate;
- teaching: supervising paediatric fellows in infectious diseases, residents and medical students in general paediatrics and paediatric infectious diseases; giving lectures, providing consultations, and organizing the workshops for all physicians and paramedical personnel for national and international participants concerning dengue, DHF and DSS;
- research: acting as the Principal Investigator of the collaborative studies to conduct clinical and biomedical research on dengue.

Professor Michael C Kew, Cape Town, South Africa

Professor Kew was Professor of Medicine at the University of the Witwatersrand in Johannesburg from 1978 to 2007, and Director of the South African Medical Research Council Molecular Hepatology Research Unit. His early research interests were in heat illnesses, but his career-long interest was in diseases of the liver, in particular hepatocellular carcinoma, which occurs with very high frequency throughout the population of sub-Saharan Africa. He researched the causes, presentation, prognosis and treatment of the cancer. Much of the work, however, centred around hepatitis B and C viruses as causes of the tumour. He took part in one of the first hepatitis B vaccine trials and was partly instrumental in the introduction of universal immunization of all new-borns against hepatitis B in South Africa.

He is the author of more than 450 articles in peer-reviewed journals, 71 chapters in books, and one book, entitled *Hepatocellular Carcinoma in Sub-Saharan Africa*. He has served on numerous medical advisory committees in South Africa.

He is currently an Honorary Professor in the Department of Medicine at the University of Cape Town and Emeritus Professor of Medicine and Honorary Research Professor at the University of the Witwatersrand.

Professor Mohammad Hossein Nicknam, Tehran, Islamic Republic of Iran

Professor Nicknam, an MD graduate of the Medical School of Tehran University of Medical Sciences in 1985, pursued his post-graduate education in immunology, leading to a PhD degree from the same university in 1998. He completed a post-doctoral fellowship at the University of Pittsburg in Pennsylvania, USA, in the year 2000. Professor Nicknam became a full professor of Tehran University of Medical Sciences.

He is Director of Immunology Department of the Medical Faculty of Tehran University of Medical Sciences and Director of the Molecular Immunology Research Center in that institution as well. He is Associate Editor of the Iranian Journal of Allergy, Asthma and Immunology and member of Editorial Board of Iranian Journal of Immunology. He is also a permanent member of the Academy of Medical Sciences of the Islamic Republic of Iran.

Professor Nicknam has contributed to many medical and public health publications (in English and Farsi). Parallel to his scientific achievements, he has held high-level executive posts such as Acting Minister of Health and Medical Education in International Relations. He currently is the Senior Adviser to the Minister of International Affairs.

He was Chairman of Committee B of the Sixty-fifth World Health Assembly in May 2012. He is a member of Technical Advisory Committee to the Regional Director of the WHO Eastern Mediterranean Region and a member and one of the vice-chairs of the Executive Board of WHO.

Professor Rosemary Sang, Nairobi, Kenya

Professor Sang is the Head of the Arbovirology and Hemorrhagic Fevers unit of the Centre for Virus Research at the Kenya Medical Research Institute, a state corporation under the Ministry of Health established as the national body responsible for carrying out health research in Kenya. She is an expert in arbovirology with interests in arboviral epidemiology, surveillance, outbreak response and pathogen discovery and has conducted research in the field for more than 15 years. She trained in the fields of medical entomology to PhD level at the University of Nairobi (1996) and in medical virology to MSc level at the Liverpool John Moores University (2008).

Professor Sang also serves as honorary lecturer in virology at the Institute of Tropical Medicine and Infectious Diseases, Jomo Kenyatta University of Agriculture and Technology, Kenya, teaching and supervising Masters and PhD students. She also works in collaboration with other partners including the Walter Reed Project, implementing arbovirus and viral haemorrhagic fever surveillance programmes under the Global Emerging Infection Surveillance and Response System of the United States and also with the International Centre for Insect Physiology and Ecology implementing projects on Rift Valley fever in the new Martin Luischer Emerging Infectious Diseases laboratory. She is also a member of the IHR Roster of Experts for Rift Valley fever, 2012 to 2017. Professor Sang has published widely on arbovirus surveillance and response, pathogen discovery, epidemiology and ecology.

Professor Tania Sorrell, Sydney, Australia

Professor Sorrell is the Director of the Marie Bashir Institute for Infectious Diseases and Biosecurity, Director of the Centre for Infectious Diseases and Microbiology and Professor of Clinical Infectious Diseases at the University of Sydney, and a Senior Physician (previously Department Director) in Infectious Diseases at Westmead Hospital, Sydney, Australia.

She has long-standing interests in prevention, diagnosis and treatment of infectious diseases, especially in immunocompromised hosts, and in the emergence of resistant micro-organisms. Recently she has developed interests in the concept and practice of “One health” (environmental, animal and human health). Her research into cryptococcosis has provided new insights into host-microbial interactions and new drug development. She has developed new diagnostics for fungal diseases and sits on international committees developing guidelines for antifungal therapy. She has authored more than 200 publications in refereed journals, 20 invited reviews and 30 book chapters, and is on the Editorial Board of *Clinical Infectious Diseases*.

Professor Sorrell established clinical infectious diseases as a specialty within internal medicine in Australia, training or fostering the careers of many of the current national leaders in clinical infectious diseases and translational research in infectious diseases and microbiology.

She has served or is serving on many bodies, including state and national advisory committees in infectious diseases, pandemic planning for influenza, approval of therapeutic agents. In addition she has served on the Research and Human Ethics Committees of the National Health and Medical Research Council of Australia. She is a past president of the Australasian Society for Infectious Diseases.

Professor Gerd Sutter, Munich, Germany

Professor Sutter is Full Professor and Chair for Virology and Director of the Department of Veterinary Sciences at the Ludwig-Maximilians-Universität München. From 2003 to 2009, he headed the Division of Virology of the Paul-Ehrlich-Institut, an institution of the Federal Republic of Germany reporting to the Federal Ministry of Health, with duties concerning German and European medicinal product legislation, such as the approval of clinical trials and the marketing authorization of biological medicinal products including human and animal vaccines. From 1994 to 2003, he served as Research Group Leader at the National Research Centre in the Helmholtz Zentrum München. From 1990 to 1993, he was a post-doctoral fellow at the Laboratory of Viral Diseases, National Institutes of Health, Bethesda, Maryland, USA.

He is an awardee of the Bundesministerium für Bildung und Forschung on Infectious Disease Research (1990–1996). He has served as an expert to various international institutions, such as the National Institute of Allergy and Infectious Diseases (USA), and WHO advisory committees, such as the WHO Initiative for Vaccine Research's Informal Consultation on Characteristics and Quality Aspects of Vaccines.

Professor Sutter's research interests include vaccine development, with emphasis on the use of poxvirus vaccines and vectors and the prevention of zoonotic and emerging virus infections, and the study of (pox)viral modulation of the host immune system, including evasion of innate and adaptive responses to infection.

Dr Stefan Wagener, Winnipeg, Canada

Dr Wagener is the Scientific Director, Biorisk Management at the National Microbiology Laboratory (Public Health Agency of Canada), in Winnipeg. He is an advisor to national and international entities and programmes on laboratory biosafety, biosecurity and bioethics.

After obtaining his MSc degree and PhD in Germany, he joined Michigan State University in the USA, working as a research scientist, before switching to the field of Occupational Health and Safety. At Michigan State University, he served as a biological hazard specialist to local and state emergency agencies for bioterrorism, and as a specialist in containment-facility and biological safety. From 2001 to 2006, he managed all operational and safety aspects of Canada's Biosafety Level 4 facility in the Canadian Science Centre for Human and Animal Health in Winnipeg, Manitoba, as the Chief Administrative Officer for the Canadian Food Inspection Agency and Health Canada.

Currently, he manages a comprehensive scientific programme involving biological risk management, training and research, as well as developing new and advanced tools for biosafety, biosecurity and bioethics. He is a Past-President of the American Biological Safety Association and was the Chair of the 2007 European Committee for Standardization workshop which developed the first international laboratory biorisk management standard, CWA 15793:2008, and was the chair of the European Committee for Standardization's workshop 55, developing the CWA 16393:2012.