



Report of the exploratory meeting of Emerging Diseases Clinical Assessment and Response Network (EDCARN) Venice, 3-4 December 2015

EXECUTIVE SUMMARY

WHAT IS EDCARN

EDCARN has evolved from a virtual WHO clinical network since SARS. It is a network of: clinicians directly involved in the clinical management of Emerging Infectious Diseases (EIDs) identified through the International Health Regulations (IHR) mechanism, subject experts from governmental and non-governmental organizations, academia, WHO, and other stakeholders. It aims to share information and experience to enhance clinical care and scientific understanding of EIDs. The network strengthens the essential link between front-line health workers and global EID clinical experts and researchers to provide technical expertise at the clinical interface of EIDs, contributing to the capacity of clinicians worldwide to detect and safely and effectively treat diseases such as Ebola virus disease, MERS and SARS coronaviruses, and epidemic and pandemic influenza.

EDCARN serves as a pool of expert clinicians to be deployed during outbreaks for technical support, training and mentoring of the local, national and international health workforce.

THE PURPOSE OF THE MEETING

This exploratory meeting was designed to strengthen the network by assembling stakeholders engaged in clinical care and research on EIDs, especially during epidemics. At the meeting, front-line health workers, scientists, epidemiologists and public health regulatory bodies shared their expertise and experience in order to support EDCARN in advancing optimal evidence based detection strategies and clinical management for EIDs.

THE MAIN OUTCOMES

- A meeting report to be made available on the WHO website
- A draft guideline document for EDCARN including its overall structure, membership criteria and governance arrangements
- Topic working groups to develop a draft working plan, with key priorities and indicators, for the next five years, including knowledge gaps and clinical research needs

NEXT MEETING: Robert Koch Institute, Berlin 4-6 April 2016



Thursday 3rd December, 2015 – Morning Session

The first half of the morning was used to introduce members of the network to each other, to introduce the event and to provide an outline of the purpose of EDCARN and its proposed way of working. There was also a presentation on the training programme to support the response to the Ebola virus disease (EVD) outbreak.

INTRODUCTION TO THE EVENT

The two day event was introduced by Nikki Shindo (WHO), Rossella Miccio (EMERGENCY) and Giuseppe Ippolito (INMI Spallanzani). This is the third clinical meeting, following events in Geneva and Rome. EDCARN is a WHO network created to support WHO's voice as a powerful force for improvement in managing emerging infectious diseases both during and between outbreaks. EMERGENCY is very happy to host the event, having been present in Sierra Leone since 2001, and is looking for practical proposals and decisions. INMI Spallanzani views this as a new adventure that will enable us to be really prepared and to share information.

Daniel Bausch (WHO) outlined how the two days were planned to work in addressing the explicit objectives for the event: (i) to develop the network through an increased understanding of its role and ways of working; (ii) set the broad context for EDCARN as part of the wider system; (iii) share information and experiences from across the world from recent outbreaks; and (iv) start to agree on key priorities and indicators for the identified work areas.

INTRODUCTION AND HISTORICAL CONTEXT OF EDCARN, Nikki Shindo (WHO)

This EDCARN meeting is taking place at a time of major changes at WHO involving the organizational arrangements for the management of outbreaks of infectious diseases. These include the recent decision to merge the Health Security Cluster with the Emergency Cluster to form the Outbreaks and Health Emergency Cluster. This 'super' cluster is being led at Deputy Director General level. The opportunity and ambition for EDCARN is to place patients at the centre of outbreak response, creating a focus on care and treatment and change the dynamic of outbreak response for the 21st century.

Implementing optimal care requires great support from laboratories, regulatory agencies, research institutions, and clinical trialists. Key contributions from WHO include, through the support of the network: (i) the identification, training and support of key individuals so that we are much better prepared to respond to outbreaks; (ii) setting the norms and standards for treatment and care worldwide; (iii) the ability to increase our knowledge through accelerated learning throughout an outbreak; and (iv) identifying and detecting outbreaks by 'tightening the net' across regional and country officers and frontline clinicians. WHO has a unique role through rigorous processes for the production of authoritative international guidelines.

EDCARN has a critical role to play in the treatment and care of patients during an infectious disease outbreak by:

- deploying expert personnel
- developing WHO guidance
- supporting clinical trials

To do this effectively, EDCARN requires support from laboratory, epidemiological, and other areas, with the goal of placing patient treatment and care at the centre of effective outbreak response. EDCARN is part of a system of international response, coordinated by the newly established WHO Outbreaks and Health Emergency Cluster. That cluster is itself part of the wider UN and international disaster relief system.

Between outbreaks, EDCARN has a clear role and remit to support improved outbreak preparedness in the following areas:

- Identification, training and development of key personnel for deployment
- Training staff in resource limited countries in preparation for outbreaks
- Supporting the implementation of the WHO Research & Development Blueprint
- Advancing the standardization and sharing of data, especially related to data sharing during outbreaks
- Collecting evidence and developing guidelines for infection prevention and control (IPC) (including the use of personal protective equipment (PPE)) in the care and treatment of patients
- Working with other networks to improve working relations

- Building close ties and working relations with civil society organizations in advance of likely deployment during an outbreak

EDCARN recognizes that excellent working relations built on shared goals and values with its many stakeholders are critical to improve outbreak response in the future.

WHO CLINICAL DEPLOYMENT AND TRAINING IMPACT ASSESSMENT, Elizabeth Mathai (WHO)

The EVD outbreak required an unprecedented training response in terms of scale and speed. This was an essential part of the emergency response. Regardless of prior experience, all deployed personnel required training. After mobilization and deployment the clinical management training was operationalized through: (i) developing the content; (ii) training the trainers; (iii) local logistics; (iv) coordination of the process especially deployment of lead trainers; and (v) quality assurance. These processes involved WHO HQ, Country Offices, Ministries, experts and networks, and partnership with other agencies. An evaluation is underway using a review of existing documents, an online questionnaire and structured interviews. Pending the outcome of the evaluation, Elizabeth shared some key lessons learned. We need to move from a reactive to a planned programme and from international to national health worker capacity development with a focus on outcomes and impact. Improving the quality of the training as we learn more and collating and standardizing training tools are big benefits.

What helped the training were: timely availability of WHO-led guidelines, a network for experts rapidly deployed, the focus on treatment to save lives while ensuring health worker safety, the engagement of expert patients and mentoring in the treatment area at individual locations.

The perception from the survey and interviews is that better clinical management of patients did increase survivor rates and was a factor in regaining the trust of communities.

WHO NETWORKS, COLLABORATING CENTRES AND EDCARN PARTNER NETWORKS

The second half of the first morning comprised nine presentations of partners and networks within which EDCARN operates.

WHO Global Outbreak Alert and Response Network (GOARN), Billy Fisher (University of North Carolina, presenting on behalf of WHO)

Billy briefly introduced GOARN which, since being established in 2000 and hosted by WHO, has grown to a network of over 200 partners and institutions with access to a further 500 members. The network pools human and technical resources for rapid identification, confirmation and response to outbreaks of international importance.

WHO Emerging and Dangerous Pathogens Laboratory Network (EDPLN), Eric Bertherat (WHO)

EDPLN has 23 members globally providing laboratory support to outbreak response through high security animal and human diagnostic labs designated BSL3 and selected BSL4.

EDPLN's goals are to (i) reduce spread of emerging diseases; (ii) improve long term preparedness; and (iii) encourage sharing of information.

Global/European Networks, Giuseppe Ippolito (INMI Spallanzani)

Giuseppe described a journey in Europe from consensus to application. Consensus is achieved through the development of the European Network of Infectious Diseases (EUNID), and application through the European Network of Highly Infectious Diseases (EuroNHID) project funded by the EU. The project aims to develop evidence-based checklists to assess hospital capabilities on infection control and health workers' safety in a network of centres involved in the management of patients affected by highly infectious diseases.

International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), Ken Baillie (ISARIC)

ISARIC aims to be inclusive, collaborating and enabling as it looks forward to what the next outbreak is going to look like and how to undertake research effectively. As a minimum we must collect data even if we cannot undertake trials. ISARIC challenges the current approach to global collaborative patient oriented research during epidemics to generate new knowledge, maximize the availability of data and save lives. Fundamental to this is to accelerate the clinical research response so that it begins earlier during an outbreak, in parallel with, not after the public health response. To do this we need to be ready with standard research protocols adopting an 'open source' approach to data collection and sharing. Ideally this would entail collecting the same data/samples in the same way with common core reports and data definition whilst maintaining respect for sovereignty and primacy of local investigators.

SPRINT-SARI (Short PeRIod IncideNce sTudy of Severe Acute Respiratory Infection), Ken Baillie

This is an international, multi-centre, prospective, short period incidence observational study of patients in participating hospitals and intensive care units (ICUs) with SARI. The primary aim of this study is to establish a research response capability for a future epidemic / pandemic through a global SARI observational study. The secondary aim is to investigate the descriptive epidemiology and microbiology profiles of patients with SARI. The tertiary aim is to assess the Ethics, Administrative, Regulatory and Logistic (EARL) barriers to conducting pandemic research on a global level.

***Epidemic and Biological Risk Clinical Coordination (EBRC) in France,
Catherine Leport (U. Paris Diderot/INSERM)***

Starting from the field, we build expertise linked to health using a generic approach to addressing the individual and collective (social) consequences of epidemic and biological risk. The end of the journey is the operational coordination of responses to epidemic and biological risk with a coherent and reliable expertise available for the care of the first patient. In linking individual with collective measures we aim to: (i) detect; (ii) protect; (iii) care; (iv) alert; and (v) orientate. This is through the generic standard operating procedure for the care of patients by infectious disease departments and infectious disease regulations linked with health authorities at a Département level.

***The Alliance for International Medical Action – ALIMA, Alie Ouattara
(ALIMA)***

Created in 2009 and based in France, ALIMA focuses on partnership, emergency response, innovation and research operating in eight countries in western and central Africa. Through **partnership** ALIMA provides a network of six NGOs in five countries: Burkina Faso, Niger, Chad, Mali and Senegal. ALIMA's **emergency response** is to outbreaks, conflict, nutritional crises and natural disasters including work in Haiti. By putting mothers at the centre, ALIMA uses **innovation** for a high impact package of pediatric care to scale up access to treatment. In **research** ALIMA aims to improve levels of care by overcoming operational obstacles and change humanitarian medical practice.

EMERGENCY, Rossella Miccio (EMERGENCY)

EMERGENCY offers free of charge and high quality health care to war and poverty victims. It has treated 6.5 million patients worldwide. Its key principles for human rights medicine are Equality, Quality and Social Responsibility. All its projects are designed to: (i) achieve top clinical results; (ii) have transparent and effective managements; (iii) provide qualified training; and (iv) contribute to build a health system.



Thursday 3rd December, 2015 – Afternoon Session

The afternoon session commenced with context presentations on WHO supporting mechanisms – guideline development, Collaborating Centres and the research and development blueprint. It concluded with a Network discussion on the scope and governance of EDCARN.

WHO GUIDELINES DEVELOPMENT PROCESS, COTA VALLENAS (WHO)

WHO Guidelines constitute any document containing recommendations for clinical practice or public health policy. They are initiated whenever WHO, an expert or other stakeholder asks for guidance on a clinical or public health problem or policy. WHO provides normative, science and evidence-based guidelines to fulfill its technical leadership role in health. Guidelines are based on principles of the ‘right to health’ and transparency produced in a manner that is multidisciplinary, balanced and inclusive, with minimized bias.

There are four types of guidance: (i) Standard Guidelines; (ii) Consolidated Guidelines; (iii) Guidelines in response to an emergency or urgent need; and (iv) Interim Guidelines. Type (iii) guidelines are produced very rapidly, sometimes within days. Type (iv) guidelines are produced typically in a three to six month timeframe.

WHO COLLABORATING CENTRES, COTA VALLENAS (WHO)

These are WHO Director General designated institutions forming part of an international collaboration network. They are time limited (four years, renewable for maximum further four years). The formal agreement always includes the specific and concrete deliverable developed with or for WHO.

WHO RESEARCH AND DEVELOPMENT (R&D) BLUEPRINT, PIERRE-STEPHANE GSELL (WHO)

The purpose of the R&D Blueprint is to assure better preparedness for diseases that might lead to epidemics through: (i) identification of the five to ten priority diseases; (ii) their better understanding; (iii) mapping of pipelines for relevant priority technologies; (iv) Target Product Profiles for medical technologies; (v) diagnostic tools to identify emerging outbreaks; (vi) innovative approaches to leverage industry expertise; (vii) improvements to global R&D preparedness; and (viii) a portfolio of promising experimental medical technologies. Being better prepared, the blueprint then proposes better readiness promptly to conduct R&D during an emergency. Fundamental to the blueprint are: (i) it is possible to accelerate R&D; and (ii) it is safe to implement trials in an affected country. At its Executive Board

meeting in January 2015, WHO mandated the capacity to coordinate and encourage such a strategy. At a subsequent consultation event in September, 2015, it was unequivocally agreed that, 'prepublication disclosure must not and will not prejudice journal publication and should become the global norm in the context of public health emergencies.' We must not leave the clinician empty handed.

EDCARN DISCUSSION, DANIEL BAUSCH (WHO)

A draft overview of EDCARN had been circulated previously and the purpose of the session was to allow discussion of that proposal with regard to the objectives and scope, overall structure, membership criteria, governance, legal status and performance evaluation strategies of EDCARN.

The underpinning principle of EDCARN is to change the paradigm of outbreak response from solely a public health intervention to putting quality patient care and treatment at the centre. Fundamental to this is to challenge the continuing acceptability of having two systems of health care – one for people with resources and another one for those without. If you start with the premise that there are two levels of care, then that is what you end up with. If you start with the premise that the same level and system of care should be available everywhere, then that is what you aim for and work to implement. The case fatality ratio (CFR) is a telling statistic. For those with EVD treated in Europe and North America the CFR is <20% while in Africa it is 40-60%.

There was a discussion of how EDCARN is differentiated from and might learn from other networks. First, EDCARN is focused specifically in supporting quality patient care and treatment supported by developing WHO guidelines and training to support their implementation. Alongside this is the need for accelerated R&D during and between outbreaks. This depends on, but is additional to, the work of laboratories and epidemiologists. EDCARN will need to draw on a pool of experts for outbreak response with defined capabilities and experience in clinical medicine, scientific research, and languages. EDCARN also has a very real role between outbreaks to focus on preparedness.

There was a general level of content with the main thrust of the paper and confidence that Nikki and Dan could develop this appropriately. The discussion points were more reflections on how EDCARN could develop and some of the issues and obstacles it would need to address. The ensuing discussion covered the following points:

- EDCARN was compared with the Global Influenza Surveillance Response System (GISRS). Unlike GISRS, which deals with a known entity (influenza), EDCARN needs to be more open since it deals specifically with emerging diseases.
- By their nature, emergencies require specific expertise in dealing with the unknown and can draw on expertise in other sectors, such as disaster relief and aviation security.

- Whilst training and mentoring is a vital contribution, it should not impede innovation using operational research methodologies during an outbreak.
- From a lab perspective, we need to ensure that old-fashioned virus detection methods are maintained and that EDCARN actively promotes the need for this resource.
- Logistics during an outbreak are very challenging and are an area where NGOs bring specific skills and expertise.
- What are the hooks and incentives for institutions to join EDCARN and release their people and resources? Perhaps being a WHO Collaborative Centre is one lever.
- It is no good just sending any doctor. It needs to be the right doctor with the right skills and support. EDCARN is about organizing and coordinating the right skill sets and expertise to make sure that the best care is delivered.

In summary, EDCARN needs to retain its focus on care and treatment, training, and R&D backed by the importance of preparedness. This will be reflected in two converging processes: (i) building expertise between outbreaks and (ii) assembling a network of expertise – individually and institutionally – for immediate deployment on detection of a potential outbreak.

Friday 4th December, 2015

The majority of the second day was dedicated to a series of case study presentations. These notes provide a brief overview for each case study. Slide sets from each presentation are available and email addresses of each presenter are included on the list of meeting participants. Please follow up with network members if you would like more detailed information.

CASE STUDY AREA 1: INFECTION PREVENTION AND CONTROL AT THE PATIENT INTERFACE

Ebola Virus Disease, Frederique Jacquieroz (IMAI-IMCI Alliance)

Presentation of impact on health workers (HWs), not just healthcare workers, so including laboratorians, ambulance drivers, etc., with CFR of 58% in this group, concentrated in first part of outbreak with last cases in May, July and August 2015 depending on country. Rate of infection is 21-32 times higher in HWs compared to the general population, with highest rates in nurses, followed by doctors and lab workers. Potential sources of infection:

- Care of/working alongside infected colleague
- Care of patients with unrecognized infection – especially non-Ebola treatment unit
- Working in triage area
- Lack of appropriate PPE (especially in first six months)
- Inside the Ebola treatment unit from lack of IPC measures

Preventative measures focus on training backed by interim guidance on PPE and IPC plus improving the layout of the triage and Ebola treatment units. Other measures outside the immediate clinical area include: daily temperature screening, salary and other benefits for HWs, discouraging providing medical care in the community (e.g. at home and in private clinics), no sharing policy, implementing triage and contact precautions in non-Ebola healthcare facilities.

SARS Coronavirus, Neill Adhikari, University of Toronto

Patients congregate in ICU with 75% requiring mechanical ventilation, which led to recognition of aerosol generation in the ICU setting. Neill highlighted, using video, the impact of high flow oxygen on aerosol production and dissemination – about a metre. There was big need for quarantine ICU capacity in Toronto during outbreak, taking up 41% of total ICU capacity in the city. There were 164 HWs quarantined during the outbreak, of whom 10% were infected. Main risk factors: (i) tremendous aerosol during interrupted

ventilation; (ii) high importance of aerosol generating procedure as mechanism for transmission; (iii) need for PPE during intubation.

Emerging Viral Outbreaks in SE Asia, Yee Sin Leo, Tan Tock Seng Hospital, Singapore

Multiple outbreaks between 1999 and 2014. Nipah virus outbreak initiated lessons learned for IPC after being found to be ill prepared for an outbreak. Significant measures now in place, including triage and one stop screening, much improved PPE, re-engineering of infrastructure support, thermal screening and temperature monitoring and rigorous health screening for HWs, (e.g. no private medical certificates). New major isolation facilities under development.

MERS-Coronavirus, Gayeon Kim, National Medical Centre, Republic of Korea

Case study of recent MERS-CoV outbreak. High nosocomial transmission with no evidence of sustained transmission in the community. Outbreak followed previously known patterns but more extensive. Three super spreaders with similar characteristics to other MERS patients, e.g. admission to ICU. 182 infected, of whom 178 were HWs, 3 ambulance workers and 1 household member. Emphasizes high importance of IPC in hospital, e.g. standard protocols, contact precautions, airborne precautions. For example, to enter MERS patient's room, required to wear N95 mask. For patient undergoing mechanical ventilation or intubation/bronchoscopy, require PAPR equipment.

Avian Influenza, Bin Cao, Department of Respiratory and Critical Care Medicine, China-Japan Friendship Hospital, Department of Respiratory Medicine, Capital Medical University

Bin Cao presented on the 2013 H7N9 outbreak in China. Three waves were reported to WHO in 2013/14, distributed in as many as 84 cities. 568 cases were identified in China, with 212 deaths. Majority of patients with H7N9 infection suffered from severe pneumonia with a mortality ratio of 30%, largely in the elderly population with comorbidities (n=111). A small (n=5) cohort suffered mild-to-moderate pneumonia. The broad similarity of viral pneumonia caused by A(H7N9), A(H5N1), and pH1N1viruses suggest that therapeutic recommendations for other viruses are also appropriate for A(H7N9). But, high level evidence of clinical management is still lacking. Study on pneumonia is the right way to investigate human infections with avian influenza and severe influenza.

Summary of Key Concepts, Cota Vallenias (WHO)

- Amplification in health care settings
- Culture of self-protection is absent
- Inconsistent IPC measures
- Isolated measures are inefficient

Once an outbreak is declared it is too late to establish an IPC programme and now may be an opportunity to place it higher on the public health agenda.

To address this we require: (i) research; (ii) development – behavior change interventions to target HWs; (iii) implementation.

Stress the importance of clinicians' role outside direct clinical settings.

CASE STUDY AREA 2: CLINICAL TRAINING FOR EMERGING INFECTION DETECTION AND RESPONSE

Clinical Training for Emerging and Infectious Diseases, Sandy Gove, IMAI-IMCI Alliance

Four stage process: (i) Simplified guidelines; (ii) Training; (iii) Mentoring; (iv) Quality Improvement. The focus was on operationalization, assuming limited resource settings (i.e. no ICU/mechanical ventilation). Limited fully qualified doctors, so targeted at clinical officers, medical assistants and senior nurses. Not intended for pediatricians, intensivists, etc. In addition to pocket guide, produced wall charts, hard copies of material, ebooks and smart phone agile App. 60% of targeted HWs had a smart phone in a limited resource setting.

SARI Critical Care Training Project, Janet Diaz, WHO

Call to action for WHO providing standardized guidelines for clinicians working with SARS, Avian Flu, and MERS-CoV. Aim to enable participants to perform critical care for patients with SARS. Based on systematic evidence-based practice with a learning approach characterized by problem solving, interaction, knowledge sharing and working peer to peer. 700 clinicians trained across several countries in central Asia, Europe and SE Asia, targeting limited-resource settings. Evaluation shows 20% improvement and that the training is received very positively. Next steps: scale up and adapt to specific settings (e.g. translations) and establish a clinical network for frontline clinicians. For course content and outline, contact Janet.

Emerging Infectious Diseases Training Programme for Health Care Personnel, Piyarat Suntarattiwong, Queen Sirikit National Institute of Child Health, Thailand

Ministry of Public Health policy for EIDs:

- Surveillance and Control – animal and human
- Provide Support
- Prepare Health Centres
- Provide Knowledge
- Integrate

Package includes:

- Clinical management
- Medical Care

- Screening Guidance
- Infection Control – isolation, PPE, hand washing

Very positive evaluation and Ministry continues to support the programme. The next priority is capacity building for laboratory diagnosis and networking.

Emerging Infectious Disease Outbreak Response, Gino Strada, EMERGENCY

Contrasted intensity of treatment compared with their availability with an approach which assumed availability of treatment is only inhibited by the time it takes to establish them in situ – for EMERGENCY this was between September and December 2014. The right question is not whether resources are available, but how long will it take to provide the resources. For example, 24 hour medical care: It is possible to provide 24 hour medical care in a purpose brick built facility with air conditioning. If you wish to speak about clinical treatment, then you require standard clinical monitoring and standard laboratory monitoring. Although we cannot conclusively demonstrate that this has been effective, we are sure that it is crucial to have a severity score that itself depends on standard clinical and laboratory monitoring.

CASE STUDY 3: DATA COLLECTION AND MANAGEMENT FOR RESPONSE AND CLINICAL RESEARCH OF EIDs, Laura Merson, Oxford University

Laura introduced an interactive session asking network members to identify key obstacles and propose solutions for how these can be overcome. Key points during the discussion included:

- There is a problem with the ability and time to store clinical data during an outbreak.
- Government sovereignty can sometimes impede data sharing.
- Example of sharing HIV cohort data in France.
- Example of Pandemic Influenza Preparedness (PIP) framework, with mandatory requirement to share data within a network.
- Difficulty of different groups collecting data during an outbreak in very different ways.
- Resistance to sharing data from PIs, academic institutions and publishers.
- Could WHO play a role in consolidating data from different sources?
- Example of informal data sharing through teleconferences on patient care during outbreak.

The main proposals focused on the need to standardize definitions and data collections in advance of an outbreak; the need to find a network solution – with the involvement/leadership of WHO – to the lack of sharing; and the need for this to happen quickly from the outset of an outbreak, so once again an emphasis on preparedness. Laura concluded by reminding the Network of ‘the ethics of inaction’.

CASE STUDY AREA 4: PRIORITIZING INTERVENTIONS WITH EXPERIMENTAL THERAPEUTICS – LEARNING FROM EXPERIENCE

Christopher Davis, Biomedical Advanced Research and Development Authority (BARDA), Office Of the Assistant Secretary for Preparedness and Response, US Department of Health and Human Services

The global biomedical community needs to move on from describing what happened during the Ebola outbreak in West Africa and how ideas for candidate therapeutics were gathered, considered, tested and selected for entry into the clinic to agreeing how we can do things better and faster in the future. Whilst a great deal of professional effort worldwide was put into 'qualifying' candidate drugs for use in treating EVD in West Africa and around 10 WHO 'approved' and non-approved drugs were actually used, at the conclusion of the outbreak not one drug emerged having publicly available evidence of efficacy. In November 2014 WHO and its partners agreed upon four essential criteria for a potential therapy to be considered for use as a treatment for EBOV. After scrutiny at an October 2015 WHO meeting called to review the pre-clinical screening process and standardize procedures and processes these criteria were still found to hold good. The formal report from that meeting is still pending. Broadly speaking, to make the process faster and more productive the community needs leadership, organization and a recognized structure in which to coordinate work across the globe with adequate funding.

Denis Malvy, Bordeaux University

Evaluation of favipiravir trial. Further analysis is underway, with further findings by end of 2015. Still awaiting final results. JIKI-ZMapp trial for efficacy of ZMapp started early July 2015 and is still ongoing. Key message is that emergency trials are possible in outbreak conditions.

CASE STUDY 5: FEASIBILITY OF CLINICAL TRIALS DURING EPIDEMICS

Why Do Clinical Research when Epidemics are about People, Peter Horby, Oxford University

Good clinical observational studies provide critical data to inform both disease control and patient care. A great deal of the knowledge base for public health interventions relies on clinical data that is required over and above therapeutic care. Challenges to collecting these data include very limited resources, often extremely rare diseases as defined in Europe and the USA in terms of population impact, very short epidemic timeframe (EVD being the exception to this, although still very short) and very short course of illness. Nonetheless, the public health value argument remains for much greater preparedness for conducting clinical research during epidemics.

CASE STUDY 6: POST EXPOSURE PROPHYLAXIS

Mike Jacobs, Royal Free Hospital, UK

Managing repatriated HWs who have had a high exposure to EVD provides re-assurance that there would be an intervention for an exposure. This should be available to all HWs, not just foreign HWs. We have a window of opportunity for post-exposure prophylaxis. This is not a mutually exclusive approach to immunization. There will always be situations where people are exposed to pathogens. The very challenging part is to assess risk of an exposure since there are numerous possibilities for exposure for HWs. This is less of a problem for household exposure. However, it remains extremely difficult to define who is at risk and who would benefit. The risk/benefit equation is difficult to balance in any case, and this is much more so with rare diseases. A final thought, which might sound like a heresy, but we are much less likely to move forward through clinical trials than through observational studies, which, in turn will depend on pooling standardized data.

CASE STUDY AREA 7: SEQUELAE AND VIRUS PERSISTENCE

US EVD Survivor Survey, Tim Uyeki, US CDC

11 EVD patients of whom two have died. Eight were included in the survey and as of 15th March 2015 one patient remained hospitalized. The study is a cross-sectional survey with seven telephone and one face-to-face interview. Patients treated at five different facilities. Only one survivor reported complete resolution of symptoms. Survivors may benefit from psychological and sub-specialty assessment. Frequency of ocular symptoms suggests that ophthalmologic evaluation is important. No assessment of whether reported symptoms were related to EVD. Evidence of EVD persistence in semen.

MERS-CoV Outbreak, Oh Myoung-don, Seoul National University Hospital

Featured the speed of transmission of the disease; after 58 hours in Emergency Department, secondary cases developed in two to seven days. Four large clusters of hospital outbreaks accounted for 80% of total cases - patients (44%), visitors (35%), HWs (21%). One patient with severe immunodeficiency experienced a prolonged MERS-CoV RT-PCR positive, and this posed challenges to the healthcare facility.

CASE STUDY 8: ADVANCED MEDICAL COUNTER MEASURES/CARING FOR CRITICALLY ILL PATIENTS DURING OUTBREAKS

Preparedness for Severe Acute Respiratory Failure Outbreaks - Role of ICU Networks, Antonio Pesenti, University of Milan

Reviewed use of ECMO and acute respiratory failure prior to setting up Italian ECMO Network, the aims of which are:

- Early referral of all potentially severely acute patients to tertiary hospitals able to provide advanced treatment options, including ECMO
- Assured safe transportation, even on ECMO if needed
- Institution of a stable network for possible future respiratory and circulatory diseases

Initially five sites in Italy, later expanded to 14, with regional and national transportation capability. Coordinating call centre for hospitals and ICUs for support/counseling or referral to functioning ECMO centre.

Treated 49 patients during the 2009/10 H1N1 outbreak and 65 in 2010/14.

Conclusions:

- Network is an effective strategy
- ECMO is viable therapy
- ECMO allows safe transportation
- Earlier intervention improves effectiveness

Andre Kalil, University of Nebraska Medical Centre

Historical control or no control trials are significantly ineffective compared with randomized controlled trials (RCTs). Wishful thinking, anecdotes and historically controlled trials are no substitute for well done RCTs. An adaptive trial is a very efficient way to run an RCT to study treatment. Proposal is that we should: (i) use RCT from outset of outbreak; (ii) cannot manage without that; (iii) platform trial design; (iv) multiple therapies should be evaluated; (v) once proved effective should be extended to all sites.

A strict selection process should be adopted for the selection of drugs to be tested. To achieve this, a universal research protocol for medical counter measures should be adopted. Clinical research should not add to HW workload, but be supported by dedicated resource. A research training core curriculum with metrics should be available to develop local Institutional Review Boards, Principal Investigators and nurse coordinators always ready to institute research protocols.

Mike Jacobs addressed some of Andre's points which he considered controversial with the following rebuttal:

- Many compassionate intellectuals disagree that RCTs are the only acceptable method.
- Medicine is the only industry that uses only RCTs. All other walks of life use alternative improvement methodologies.
- It is not correct to conflate compassion with favoring a type of trial design.

The case study part of the Network meeting concluded at this point. The meeting then broke into small groups to consider the following areas:

1. IPC/Preventing HW Infections
2. Clinical Training and Performance Indicators
3. Data Collection and Management
4. Experimental Therapeutics and Vaccines
5. Post Exposure Prophylaxis
6. Sequelae, Virus Persistence and Survivor Care
7. Point of Care Diagnostics

Each group was charged to develop a draft working plan, with key priorities and indicators, for the next five years, including knowledge gaps and clinical research needs.

The reports from these working groups will be issued subsequent to the distribution of these notes.