

Proceedings of the 3rd Seminar Emerging Infectious Diseases

Current trends and proposals

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Proceedings of the 3rd Seminar Emerging Infectious Diseases

1. Introduction

This third annual seminar on Emerging Infectious Diseases (EIDs) held at Val-de-Grâce Hospital brought together roughly 160 participants: researchers, clinicians, decision-makers, administrators, and continuity managers from the business sector. Following on the July 2011 High Council of Public Health (Haut Conseil de la santé publique - HCSP), recommendations and on the two preceding annual seminars (December 9, 2011 and December 7, 2012), this most recent gathering helps ensure the permanence of expertise and prospective activity concerning EIDs. The seminar is held under the auspices of the High Council of Public Health, the French Military Health Services Division of the Val-de-Grâce School (Services de Santé des Armées - SSA), the School for Advanced Public Health Studies (École des Hautes Études en Santé Publique - EHESP), University of Paris - Diderot, the Sorbonne Paris-Cité, the Institute for Research in Developing Countries (Institut de Recherche pour le Développement - IRD), the Institute for Public Health Surveillance (Institut National de Veille Sanitaire - InVS), the French Infectious Diseases Society (Société de Pathologie Infectieuse de Langue Française - SPILF), the National Institute for Health and Medical Research (Institut National de la Santé et de la Recherche Médicale - INSERM), the Health Studies Chair at Science Po, and the Pasteur Institute of Paris.

Opened by Professor Stephen Morse and closed by Professor Françoise Barré-Sinoussi, this seminar reemphasized the importance of preparation, which takes into account economic constraints and incorporates international mobilization around EIDs. After treating the subject of synthetic biology in 2012, this year's afternoon special session focused on the relationship between biodiversity and EIDs.

2. Current trends: presentations and debates

2.1 Keynote presentation by Pr. Stephen Morse: “Anticipating and Preventing Future Pandemics”

Moderator: Patrick Zylberman (EHESP)

On November 9, 2009, the vaccination campaign against the H1N1 influenza virus was in full swing. (USAID), the United States development agency, decided to create a new program called PREDICT, whose function would be to detect and prevent microbial threats at a worldwide level. Influenza pandemic, avian influenza, SARS (severe acute respiratory syndrome) or Ebola virus (currently ravaging Guinea-Conakry, Liberia and Sierra Leone) were some of the pathologies that were aimed at by the program. Professor of Epidemiology at the Mailman School of Public Health at Columbia University in New York, Stephen S. Morse has co-directed this brand-new early warning organisation for the past five years.

"We are all engineers of microbial circulation". S. Morse reminded his listeners that an EID is defined by three characteristics: its incidence and/or geographic reach rapidly increasing and expanding; it is often “new”; some of its causes are anthropogenic. Of animal origin in over half the cases, EIDs benefit from the globalisation of exchanges, travel and migrations as well as from relatively recent ecological shifts at the global level: climate change, agriculture, food, deforestation, changes in aquatic and land-based ecosystems etc. EIDs' emergence, often of undetermined origin, and EIDs' evolution remain difficult to predict. For the last twenty years experts have called for a

worldwide surveillance system in order to rapidly identify the first cases (MERS in 2012) and to improve response based upon past experience (SARS in 2003).

It must be emphasized that progress has been made in the setting up of a network for better cooperation and surveillance: since 1994 the Pro-MED program (www.promedmail.org) has provided an up-to-date, open-access source of information. The WHO reinforced international regulation of these surveillance systems in 2005 via the revision of the International Health Regulations (IHR). IHR has had a motivating influence on member states and it helps to reinforce health safety at regional, national and international levels. Research projects have been financed by various programs in the United States (such as PREDICT) and in Europe (such as the EDEN program). New tools such as Next-Generation Sequencing (NGS) can finally be put to work in detecting new microorganisms.

Better knowledge of the interactions between human activity and conditions presenting a high risk of exposure and transmission of a new infectious disease agent, in particular contact with wildlife, makes it possible to fight infection emergence at its source. Understanding is not enough; it is also necessary to protect, explain, and at times to intervene under uncertainty of information and knowledge. In conclusion, Morse calls for the development of research to boost predictive capability and political reaction/policymaking.

2.2 The role of the private sector

Moderator: François Bricaire (Pierre and Marie Curie University)

Presenters: Olivier Lafond and Hervé Arki (Business Continuity Club – Club de continuité d'activité – CCA)

The CCA, a non-profit organization created in 2007, is a forum for sharing experiences and practices among businesses (around a hundred), the objective of which is to define measures for each to ensure the continuity of business operations. The development and assessment of continuity plans currently concerns, primarily, major corporations. The organisation of work committees has generated the production of practical guidelines for events such as "major risks" and "crisis management", intended for use by the crisis management committee of companies. Directed by a continuity manager, each committee sets up a "toolbox" from within which different items (Intranet communication, health directive signage, barriers, cloth handwipes, soap dispensers, masks for travellers, etc.) are taken for use in the event of a crisis. The presenters emphasize the crucial need for valid information which is both clear and adequately transmitted; they also point up at the frequent lack of institutional recognition by the State of these crisis committees, whose existence depends upon human and financial resources and on the interest taken in them by the company directorship.

The final assessment of the management of the H1N1 flu crisis of 2009 is thus mitigated. It revealed the need for dialogue among public crisis managers. It seems necessary to improve feedback and in particular to take advantage of referential structures, following the example of previous collaborations with the DILGA (Interministerial Delegation for the fight against avian flu). While they recognize the existence of a well-organized health surveillance system, the presenters nevertheless decry the "cacophony" which reigns in terms of crisis management information on the part of governmental bodies. They are particularly critical of the lack of a clear response to their concrete questions on several topics (right to employee work stoppage, telecommuting, requisition, personal safety gear, vaccination, etc.). One criticism concerns the lack of data which, particularly at the early stage of the alert, overburdened the decision-making capacity of leaders; another concerns an unfortunate lack of dialogue.

2.3 Emerging infectious phenomena: how to prepare within economic constraints

2.3.1 Round table discussion: Modelisation and cost-effectiveness approach to the H1N1 flu applied to emerging multi-resistant bacterial infections

Moderators: Bruno Coignard (InVs), Benoit Dervaux (Lille University)

Presenters: Yazdan Yazdanpanah (Bichat-Claude Bernard Teaching Hospital, Paris), Sylvain Godreuil (Arnaud de Villeneuve Teaching Hospital, Montpellier), Isabelle Durand-Zaleski (Henri Mondor Teaching Hospital, Créteil)

Economic analyses referred to as "cost-effective" are one response to increased healthcare costs under financial constraints. Their goal is to identify the most economically efficient way to reach a predefined goal, in this case to optimize medical intervention and the distribution of resources. During the H1N1 flu pandemic, these analyses showed that treating all patients stricken with the flu syndrome was relatively cost-effective, compared to targeted treatment of at-risk or hospitalized patients. More recently they have been used to compare several strategies for fighting the transmission of resistant enterobacteria (producers of wide-spectrum beta-lactamase). They show that handwashing remains the most highly cost-effective strategy compared to 'cohorting' and restricting use of antibiotics.

This study points up the importance of handwashing and raises the question of curtailment of these practices. Systematizing this gesture is nonetheless far from simple, as it involves changing human behaviour, which can prove highly expensive: it in fact requires reorganizing the hospital system, training personnel, restructuring the space, educating general practitioners and patients and, finally, taking into account individual blocks to adopting preventive measures. Studies on financial incentives for hospitals, be they negative (non-reimbursement of "preventable" nosocomial infections [NIs]) or positive, to combat NIs are hardly conclusive. Furthermore, the 'added value' of prevention is difficult to objectify and to convince policymakers of; it is difficult to quantify the "profit" factor of a prevented 'crisis', as the gains do not necessarily translate into revenue for the hospital - particularly difficult over time; hence the interest of modelisation and simulations of crises scenarios. The European study MOZAR assessed training costs at hundreds of hours, with highly variable results. Social science research, with social psychologists and cognitive science specialists to study the factors which determine risk perception and behaviour, would be worthwhile to muster around these issues.

The interest of a cost-effectiveness approach in the early detection of multiresistant bacteria was also pointed out, with its influence on morbidity and mortality as well as on the reduction of antibiotic consumption.

2.3.2 International collaboration

Moderator: Antoine Flahault (Paris-Decartes and Geneva Universities)

Presenters: Sylvie Briand (WHO), Bernadette Murgue (IMMI/AVIESAN)

In existence since the WHO's founding, the IHR last revised in 2005 (applied in 2007) is the legal framework for international exchanges on EIDs. It was ratified by 194 Member States of the WHO. Its goal is to manage any "events which may constitute a public health emergency of international concern" be it epidemic, nuclear or chemical in nature, while attempting to limit impact on tourism, travel and international commerce. In the wake of the avian flu, certain developing countries (for example Indonesia) raised the question of fair sharing of information and of the benefits of the characterization of new infectious strains for scientific publications, such as the development of diagnostic tools, treatments and vaccines. First discussed in 2007 these negotiations were finally concluded in 2011, with the signature by 110 countries of the *Pandemic Influenza Preparedness Framework* (PIP). This legally binding document stipulates that pathogenic viruses shall be supplied free of charge to vaccine manufacturers, whose responsibility shall be to 1) provide each year the

stock of vaccine required for global preparedness, and 2) in case of pandemic, to supply, or contribute to the transfer of, technology required for developing countries to have access to vaccines. Indispensable for global health safety, these exchanges can nevertheless be disrupted by the many factors at stake: economic, political, scientific or intellectual property (patent filing, addressed in other international protocols, including the Nagoya protocol on access to genetic resources and fair and equitable sharing of benefits generated by their use). It remains that these practices reflect a radical change in the ways nations cooperate around EIDs.

In France, researchers are in the process of organizing research so that financial support of projects does not arrive at the end of the epidemic. To complement existing structures, a multidisciplinary research network called "REACTING" ("Research and action targeting EIDs") was set up in 2013. More flexible and reactive, it seeks to reinforce collaboration between laboratories and Southern Hemisphere countries (creating AVIESAN-South), preparing research tools (modélisation, protocol 'prototypes'), encouraging links between clinical and fundamental research, identifying research priorities, and rapidly drawing out funding sources. The AVIESAN (Alliance for life and health – Alliance pour la vie et la santé) Alliance was mandated by the research and health ministries to coordinate this effort. It should be part of the current European and international efforts on the same theme.

2.4 Pandemic 13 Exercise

Moderator: Patrick Zylberman (EHESP)

Presenters: Jean -Marc Philippe (DUS - French Ministry of Health, Department of Health Emergencies), Nicolas Favro (SGDSN, the French General Secretariat for Defense and National Security), Fanny Brouant (SGDSN), Claude Wachtel (SGDSN)

The goal of this presentation is to describe the learnings gleaned from the "Pandemic 13" exercise, at the Health Ministry level on the one hand, and at the cabinet crisis management level on the other hand. This drill, conducted in November 2013 by the French General Secretariat for Defence and National Security (SGDSN), tested the national prevention and protection plan against "Flu Pandemic" (tools and policy) which had been revised in 2011. This plan sets forth four stages of implementation: impede the introduction of the virus; slow its geographic propagation; dampen the effects of the epidemic wave; and, finally, restore the situation to its pre-pandemic state.

Two days of information sharing were organized among the various ranks of crisis coordination and management: the Prime Minister (politico-strategic level: broad axes of action), the cabinet crisis committee, the Operation Center in the Home Office, the prefect at the level of the defence zone, and the prefect at the level of the département.

The first day, which focused on the ability of the actors to adapt public health strategy to the evolving pandemic and the resulting uncertainties, inspired intense involvement and great interest on the part of the participants. Other points are noteworthy for policy-makers: differences of opinion among experts (particularly on antivirals, antibiotics and immunization strategy); clarity of medical strategies; difficulty for both the public and for health professionals in gaining access to information; finally, the need to take into account the priorities of the population.

The second day, which focused on the cabinet level, addressed the capacity to anticipate disruptions in services; this also concerned testing governmental communication. The measures adopted appear strikingly timid (perhaps a backlash from the controversy surrounding the flu pandemic of 2009); these also seem to ignore the teachings of the 2009 experience (little feedback developed, teams having changed since etc.). Much too much unilateral, communication during the exercise, failed to justify decisions and did not take into account sufficiently concerns of professionals. And yet, given the lack of public trust in the authorities, the role of these frontline professionals seems a key factor.

2.5 Biodiversity and infectious diseases

Moderators: Jean-François Guégan (IRD) and Philippe Sansonetti (Pasteur Institute Paris, member of The French Institute)

Presenters: Gilles Bœuf (Collège de France, chair "Sustainable Development, Energy, Environment and Societies"), Philippe Sansonetti (Pasteur Institute), Benjamin Roche (IRD), Christian Lannou (INRA, the National Institute for Agriculture and Agronomy), Michel Gauthier-Clerc (Scientific Director, Nyon Zoo, Switzerland)

This session dealt with the significant links between biodiversity, defined as "the living fraction of Nature" and EIDs. The study of biodiversity at different levels of life organization (from that of an organ such as the human intestine which hosts a vast number of microorganisms, to that of a natural ecosystem and its vegetal and animal communities, and including agricultural systems) has revealed its major role in the organization, stability and dynamics of biological systems in general. One of the many services rendered by biodiversity is its regulatory role in the transmission of numerous EIDs.

Current biodiversity is founded upon what is currently called 'geodiversity', which is 4.6 billion years old. Molecular biology studies have shown that microorganisms, bacteria, viruses, parasites, microalgae, represent life forms which preceded, and will undoubtedly succeed, the human species on our planet. We have a very fragmentary knowledge of the different microorganisms currently living on Earth: 5,000 to 6,000 species per square meter coexist in the coral reefs, for example. The vast majority of these microorganisms are neutral or beneficial to humans; but some - in fact, a minor proportion - can have harmful effects. These can harbor intrinsic pathogenic factors or become pathogens by chance, exposure or due to ecosystem imbalance. Recent transformations in human lifestyle have resulted in a loss of biological diversity, on various organizational levels, which can encourage the appearance of EIDs, but also can contribute to the development of new chronic diseases (auto-immune diseases, asthma, atopy, chronic intestinal inflammatory diseases, obesity, diabetes ...).

There is much research which underlines the importance of working on the points of interface between humans (which can also be considered true of animal and plant life) and the microbial world. The human body itself, made up of several microbiota, can act as a 'barrier' to invasion by external pathogenic microorganisms, as well as acting to stimulate the immune system, the legacy of their co-evolution. Mutualist, symbiotic and pathobiotic microbial agents live, generally speaking, in balance with their hosts. It is of their imbalance, the source of a loss of diversity, that are born certain diseases, the incidence of which is currently on the rise in the population. The decrease in intestinal microbiome diversity may be linked to environmental factors, to new eating habits, to hygiene, to antibiotics, to perinatal medicine, etc. Some of these effects appear early on in life: among newborns exposed to antibiotics during the first six months of life, 22% are at risk of becoming obese as adults. New medical practices which seek to increase biological diversity (fecal implants, for example) are producing interesting positive effects.

Current research is also addressing the complex connections between biological diversity in the animal kingdom and transmission of infectious agents, and their consequences for public health. Such research invites a rethinking, in the most integrative and systemic manner, of means of transmission of infectious pathogens of animal origin affecting humans (60 to 70% of infections). Far from limiting their considerations to interactions among a primary vector species, a reservoir host species and the human population, researchers are looking into the transmission of pathogens between different host species and non-hosts through an ecological approach. American studies on Lyme disease and on West Nile fever have revealed what is known as "dilution effect": a broad local diversity of animal species, particularly because it groups together individuals of the species barely able or incapable of transmitting an infection, tends to slow the overall circulation of the pathogen and consequently decrease the risk of infecting humans. The decline in biodiversity we are currently witnessing could thus lead to an increased circulation of pathogens and favor the appearance of

EIDs. The dilution effect raises opportunities in terms of public health (in unfragmented forests, we observe a lower transmission rate of Lyme disease) and of zoonophylaxis (adding an animal species to detour insect bites and thus generate a dilution effect, although the risk of introducing a new pathogenic agent with the introduction of a species must also be assessed cautiously).

The same dilution effect on the general circulation of pathogens can be found on the scale of farms. Historically the evolution of the agricultural system was accompanied by a decrease in genetic diversity, be it in plants or animals. The presence of a single genotype of grass, for example, on farmed acreage encouraged the spread of pathogens and, in return, the massive use of pesticides. Mixing varieties, called polyvarietal planting, particularly of wheat, creates a dilution effect by exposing plant varieties which are resistant or less permissive, thus making it possible to reduce dependency on pesticides. On the scale of the landscape, better organizing of agricultural fields of different varieties of plant species, by reintroducing natural barriers such as embankments and fallow fields, makes possible the sustainable management of the genetic resource represented by species of agricultural interest while reducing the infectious risk as well as the use of pesticides.

Finally the preservation of animal species - and the same can be said for vegetal species - is essential, particularly because some can serve as pathogen "traps". In the same vein, predatory and scavenging species play an important role in ecosystems in eliminating prey which often carry infectious diseases, or cadavers which also carry pathogens. The massive destruction of farm-raised animals (ducks, chicken, pigs ...) as well as wild ones (such as the open billed stork in Thailand) during recent public health crises (BSE, avian flu), the homogenization of livestock raising practices and of "natural" habitats continues to pose both an ethical and functional problem. The existence of beneficial microorganisms, inherent to all human life but to animal and plant life as well, since most are originally commensal or symbiotic with their hosts, requires that we now change our view from that of "fighting against" to that of "living with" - more laudable, but also closer to natural reality.

2.6 Keynote presentation by Pr. Françoise Barré-Sinoussi, Nobel Laureat in Medicine, 2008, Pasteur Institute : What are the lessons learned in 30 years of action against HIV/AIDS for the fight against (re)emerging infectious diseases?

Moderator: France Mentré (Paris Diderot University)

At nearly 25 million fatalities, HIV-AIDS is considered the most devastating infectious disease of the 20th Century. The virus was discovered in 1983 thanks to the observation of patients presenting the same unknown clinical syndrome. The Pasteur Institute team therefore studied the role of a possible retrovirus. That step sets in motion the pursuit of a long collaboration between patient advocacy groups (Aides, Act Up, etc.), the hospital, research and private sectors and a vast international mobilization for the fight against HIV.

The development of translational research, with the creation of research networks and programs, as well as collaboration with industry, made possible as of 1985 the release on the market of serological tests (Sanofi-Pasteur), followed by the development of antiretroviral drugs. The first antiretroviral, zidovudine in 1986, decreased the risk of materno-fetal transmission; however, its effects were quickly limited by the appearance of treatment failure linked to viral resistance. The advent of HIV multitherapies in 1995 finally marked the end of HIV replication, the restoring of immunity, AIDS prevention, and 85% reduction in mortality, with a life expectancy near to that of the general population. Elsewhere the fight against the HIV pandemic has had other positive 'collateral benefits': decrease in STIs, infections in drug-addicted patients; the liberation of women; reduction in infant mortality; respect of human rights.

Militant activists played a decisive role in encouraging the production of generic, lower-cost drugs. Even so, only 13 of the 28 million people infected with HIV worldwide have access to antiretrovirals,

and very unequally according to country: local advocacy is often still necessary to convince policy-makers. As the UN and the WHO have reminded us, access to treatment for all therefore remains a priority. Prevention is also indispensable. In order to be effective, the means of prevention proposed must be diverse (pills, gels, vaginal films and rings, injection, etc.) and take into account the needs of the population. It has been shown in 2011 that treating partners also reduces the risk of transmission by 96%. Following a strategy of early screening and treatment, screening coverage must be improved, as 30 to 50% of persons infected by HIV are unaware of their infected status.

Today there exist several prevention tools in the fight against AIDS which can be combined and should be put at the disposal of affected populations according to their needs (condoms, risk reduction, treatment, microbicides etc.).

Many challenges - social, cultural, behavioral and biomedical - lie along the path to a world without AIDS. Political will, and the fight against discrimination of all types, are still among the top priorities. It is also necessary to pursue research efforts, particularly regarding vaccines, but also to develop new therapeutic strategies which make possible permanent infection monitoring after termination of treatment (remission) and/or reducing/monitoring chronic inflammation under treatment due to long-term co-morbidities.

The battle against AIDS is at the origin of the concept of world health, and has elicited an international response to health-related matters on an unprecedented scale, notably with the creation of massive global solidarity initiatives such as the World Fund, PEPFAR or UNITAID. This is a striking example of what the response should be to an emerging pathology : global, integrated, coordinated.

This example can and should serve in the fight against new EIDs to which we are witness today, particularly Ebola. It should also serve to help build bridges in researching other chronic pathologies such as cancers, cardiovascular illnesses or those linked to aging which, like HIV, all involve altered immunity and inflammatory processes.

The battle against AIDS could be effective because it was waged in a spirit of solidarity; it is this same spirit which should prevail in the fight against all emerging infectious diseases.

3. Summary and proposals

This third symposium of the Séminaire du Val-de-Grâce is the expression of a renewed interest in understanding, predicting and managing EIDs. At the national level, administrations, research units, non-profit associations and companies devote resources (human, technological, economic, etc.) to better understanding, knowing about, monitoring and reacting to EIDs. It is now a question of supporting and intensifying an international movement begun some twenty years five ago by a group of experts.

The seminar elucidated the extent of what is at stake with EIDs, from the corporate level to that of diplomatic relations between nations, in particular concerning their ties to partner countries in the South. Following on previous meetings, researchers and institutional representatives underscore the limits to both knowledge and competencies relative to emergence situations. Tools and recommendations must be sufficiently flexible to adapt to evolutions in EIDs.

3.1 Crisis management preparedness

The contribution of private company representatives and the feedback from the Pandemic 13 exercise may support the following recommendations.

One priority would be to establish permanent concertation around issues that arise from EIDs. All players in crisis management (whether from companies or, healthcare structures) lament the lack of designated spokespersons within the central administration. It appears necessary to create among

the French cabinet a special council for the fight against EIDs (Délégation inter-ministérielle pour la lutte contre les maladies infectieuses émergentes) along the lines of the former cabinet delegation for the fight against avian flu (DILGA) created by General Director of Health, Professor Didier Houssin, in 2006 and disbanded in 2010. Personnel from the ministries concerned (Health, Home Office, etc.) would sit together on a standing committee.

Regarding governmental management and communication tools, two recommendations are in order: 1) to encourage the participation of all those involved in crisis management monitoring, and 2) to develop sufficiently flexible tools to keep pace with EIDs' evolution. Concerning the former, presenters underlined the fact that crisis management policies failed to take into account the needs and expectations of professionals in the field and of targeted populations. These groups should therefore be involved in the work of defining and putting these tools in place, in order to better adapt those tools to the reality in the field. Establishing deliberative bodies, particularly 'open participative' forums for citizens or community representatives, would help further involve them in public policy decisions. Concerning the latter recommendation, experts and institutional representatives encourage organizations to keep in place sufficiently flexible crisis management measures. Given the uncertainties around EIDs, "toolbox" style instruments make it possible to more closely follow EID evolution. Finally, current decision-making on EIDs has difficulty building on past experiences (H1N1, avian flu, etc.) Debriefing and feedback should thus be formalized and systematized. These recommendations therefore imply educating and training a division of crisis managers who share an integrational and comparative view of their mission.

3.2 Research development

EIDs are the subject of a multidisciplinary research, from entomology to clinical, epidemiological and biological research to social sciences. This new framework, theoretically as well as in practice, should be reinforced in order to favor a better understanding and managing of EIDs.

The AVIESAN Alliance was mandated by the French Research and Health ministries to organize research on emerging infectious diseases through the REACTING network. This network uses resources provided by national multi-organizational research units and by platforms existing in both the Northern and Southern hemispheres whose focus is directed toward emerging pathogens sites.

The session devoted to "cost-effectiveness" research showed that simple acts (such as hand washing) can represent an effective preventive measure against infectious disease transmission. Public policy response, however, remains far from being self-evident. Encouraging what is considered as simple practice is not solely a matter of "educating" patients and physicians, but also requires reflection on organizational, political and economic factors which encourage or on the contrary hinder adopting these practices. Cognitive as well as human and social science (political science, sociology, economics etc.) research should be promoted; remembering that these can also be applied to other domains such as the struggle against vector-borne disease.

Finally, understanding local realities and patients' expectations is crucial to battling infectious pandemics. The case of HIV, and more recently of Lyme disease, are exemplary in this area. Field research must also play an important role in research programs. For this to be possible, it is vital to finance both in-depth, fundamental, research (such as the ANR-MIE type) but also *ad hoc* research projects in emerging situations.

As EIDs are global phenomena, the organization of research should also be global and establish collaboration between networks and teams in Europe and worldwide. Partnerships and mergers with institutions currently active in the South (AVIESAN-South) must be supported. Worldwide collaborative networks for research and surveillance, the indispensable precondition for effective responding, are being set up under the auspices of the World Health Organisation (WHO). The fortunate establishment of the PIP (Pandemic Influenza Preparedness Framework) in 2011 has

shown that it is possible to encourage sharing scientific information on a global scale. This system should be expanded in order to include all infectious diseases. It would however be better if a framework for the discussion upon the economic, political and intellectual property (patent) stakes, the managing of which currently tend to exacerbate the inequality between North and South could be created on a comprehensible scale.

The session on biodiversity revealed significant progress over the last several years, in both research subjects and in collaboration. Questions around means of transmission of pathogens between host and non-host species open up major topics of research, on the condition that one takes a more systemic view of these issues. Recent developments in molecular biology have helped advance the identification of new microbial forms, some of which may prove to be pathogenic in the next future. The research nonetheless requires better integration of knowledge: microorganisms must be considered in their entirety (microbiome/microbiote). Located in French Guiana, the laboratory of Excellence CEBA (Center for the study of biodiversity in Amazonia) brings together a network of French research teams specialized in the study of Amazonian biodiversity who are working on several programs whose goal is to better understand the circulation of pathogens within the present systems. These examples among others illustrate the importance of adopting an ecological and integrative approach to infectious systems. The complexity of biological systems, ranked according to organizational level, from the gene to global ecosystem, requires us now to integrate different disciplines (molecular biology, immunology, cellular biology, physiology, pathology, transmission dynamics, complexity biology, etc.) in order to understand the emergence process which, by definition, occurs on different spatial and temporal scales.

It also appears essential to support conservation biology, not only to explore biological diversity and to find therein new molecules or active principles, but also to understand situations of ecological imbalance which foster emergence, and thus anticipate or imagine new states of equilibrium. Finally, the creation of observatories (long-term ecological surveys) follows the monitoring of the spatial and temporal dynamics of ecosystems (including human) to develop in view of predicting and preventing infectious disease risk.

Priority proposals

The Séminaire du Val-de-Grâce would suggest to:

1. Reinforce the links between the state and the private sector in the area of crisis management: appoint a spokesperson within the Health Ministry mandated to dialogue and act with "crisis management" representatives from organizations involved
2. Educate and train a crisis management personnel section
3. Formalize and systematize debriefing and feedback procedures which should be periodically enhanced and supported
4. Given the uncertainties around EIDs, maintain flexible crisis management kits - a sort of "toolbox" - in organizations
5. Involve all actors (public authorities, private sector, healthcare professionals, field workers) in defining and setting up tools for crisis management and communication.
6. Develop approaches allowing a deeper understanding into the complexity of living organisms in their hierarchical systems, from the gene to the global ecosystem
7. Be more attentive to the relationships between biodiversity and infectious diseases, at various organizational levels, particularly in their functional and service delivery aspects
8. Support conservation biology, which seems equally necessary in order to explore further biological diversity (researching and developing new molecules such as antibiotics, peptides, repellants ...)
9. Create observatories enabling to follow the evolution of systems, their dynamics and any potential imbalances that may occur, of which emerging viruses are but one expression
10. Set up long-term financing for research preparation as well as means for *ad hoc* subsidies in the case of emergence
11. Encourage research in social sciences and in health systems management, applied research (acceptability of public health measures) and fundamental research (history and sociology of international institutions, geopolitics, economics, anthropology of health crises etc.) as well.
12. Encourage information sharing at the global level, especially with partners/collaborators in the Southern hemisphere where EID epidemics most often originate.

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Speakers

Hervé Arki – (Business Continuity Club)
Françoise Barré-Sinoussi – (Institut Pasteur of Paris)
Henri Bergeron – (Sciences Po Health Chair)
Gilles Bœuf – (National Museum of Natural History)
Sylvie Briand – (World Health Organization)
Fanny Brouand – (French Secretariat for Defense and National Security)
Bruno Coignard – (Institute for Public Health Surveillance)
Xavier Deparis – (French Military Health Services Division)
Benoît Dervaux – (Lille University)
Isabelle Durand-Zaleski – (Henri Mondor Hospital)
Nicolas Favro – (French Secretariat for Defense and National Security)
Antoine Flahaut – (School for Advanced Public Health Studies)
Michel Gauthier-Clerc – (Nyon Zoo)
Sylvain Godreuil / Arnaud de Villeneuve (Montpellier Teaching Hospital)

Olivier Lafond – (Business Continuity Club)
Christian Lannou – (National Institute Agriculture and Agronomy)
Jean-Claude Manuguerra – (Institut Pasteur of Paris)
France Mentré – (Paris Diderot University)
Stephen Morse – (Columbia University)
Bernadette Murgue – (IMMI/AVIESAN)
Jean-Marc Philippe – (French Ministerial Department for Health Emergencies)
François Pons – (Val de Grâce School)
Benjamin Roche – (French Institute for Research in Developing countries)
Philippe Sansonetti – (Institut Pasteur of Paris)
Claude Wachtel – (French Secretariat for Defense and National Security)
Yazdan Yazdanpanah (Bichat – Claude Bernard Teaching Hospital)

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EHESP—French School of Public Health (Ecole des hautes études de santé publique)
Paris Diderot University
French Institute for Research in Developing countries (Institut de Recherche pour le Développement - IRD)
Infectious Diseases Society (member of the French Federation of Infectiology – Société de Pathologie Infectieuse de Langue Française - SPILF)
Institute for Public Health Surveillance (Institut de Veille Sanitaire – InVS)
Institute of Public Health (Institut de Santé Publique – ISP) - National Institute for Health and Medical Research (Institut National pour la Santé et la Recherche Médicale – Inserm)
Pasteur Institute (Institut Pasteur)
Sciences-Po Health Chair

Steering Committee : *Henri Bergeron (Sciences Po Paris), François Bricaire (SPILF), Didier Che (Institut de Veille Sanitaire), Geneviève Chêne (ISP), Jean-François Delfraissy (IMMI), Jean-François Guegan (IRD), Catherine Leport (Université Paris Diderot), Jean-Claude Manuguerra (Institut Pasteur), Jean-Baptiste Meynard (SSA – EVDG), Patrick Zylberman (EHESP)*

Contacts : catherine.leport@univ-paris-diderot.fr
jean-francois.guegan@ird.fr
patrick.zylberman@ehesp.fr

Please see website : <http://www.malinfemerg.org/>