Emerging Infectious Diseases Roundtable 2

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Background
The Emerging Infectious Diseases (EID) Round Table was initiated because of the general understanding that a harmonized global approach is needed to react timely and efficiently to new emerging pathogens. The EID Round Table concept provides a platform where regulators, patients and industry establish a meaningful dialogue and work closely together. At the first EID Round Table in March 2004 consensus was reached that a framework is needed to address EID policy making. The facilitation of communication and coordination among patients, regulators and industry was viewed as the highest priority. Effective and timely communication is an important first step to focus available resources in a coordinated approach to develop "best practices" for addressing EID threats.

Introduction to 2nd EID
Based on the outcomes of the first EID Round Table the proposed meeting objective was the development of a plan that will allow real-time communications, using current information technology as a venue for generating notices of EID threats, asking questions of participants, and sharing information. Lessons learned from the past should be used to optimize and streamline the communication. Early, effective communication will ensure that available resources are focused on:

- Surveillance and epidemiology
- Research
- Risk assessment and risk communication
- Mitigation (process change and/or regulatory intervention)

The coordination of activities will support a harmonized approach to addressing risk and the communication of risk while eliminating gaps and avoiding unnecessary redundancies. The aim of an ongoing EID Round Table initiative would be predictable decision-making in the face of an emerging pathogen.

Participants (listed in appendix) agreed that an effective communication tool is key in responding to the continuous threat of new emerging pathogens allowing decision making in the face of uncertainty as informed as possible. The EID should be an ongoing learning process to apply general rules by going through examples of past experience. Particular attention needs to be paid to vigilance ideally including blood, plasma and tissue (biovigilance) on a global scale. Vigilance should be part of the policy making process to avoid that in the absence of all available information the

precautionary principle is applied. Available information should be channeled through a decision tree framework, which needs to take into account the different aspects of both blood and plasma which might lead to different outcomes.

Regulatory agencies would welcome the provision of information through the EID framework, which will help to preserve the global perspective in the agencies' own decision making processes.

Patients have expressed their desire to be part of the communication process from the beginning, because experience has shown that in the global market communications are often inconsistent and regional decisions often incomprehensive because of the lack of information about the decision making processes. There is a need to rationalize decision-making processes.

The discussion resulted in an agreement on the need of the following elements:

- There is a need to share information
- Plasma, blood and tissues should be included
- Patient advocacy stakeholders should be part of 1st line of communication
- A communication strategy needs to be institutionalized by providing a venue or platform where involved parties can meet
- A communication strategy should be two tiered: internal and external communication
- The audiences for communication need to be defined
- Policy making should not default to regulators
- Appropriate information can lead to decision tree

However, it cannot be ignored that regulators have a responsibility for decision making in collaboration with other national bodies as well as politicians. Thus the EID communication strategy would only be a supportive tool to obtain all available information for policy making processes, which occur regionally and on different levels. Consequently, EID should focus on timely communication.

Two case studies that represent different perspectives on EIDs were each presented by a regulator and industry participant. The first case study focuses on true emergence of a pathogen in humans; the second, on technological advances and their implications in the continuing concerns around transmissible spongiform encephalopathies.

Case Study 1: Emergence of "new" Parvoviruses in humans

The Parvovirus case study provided an example of long-term experience with a virus, where the awareness of its association with clinically significant diseases (hepatitis, myocarditis, arthritis) developed over time. Parvovirus reduction during the manufacture of plasma protein therapies is demonstrated with a number of model viruses. Model viruses resemble the virus which could be a contaminant and represent a wide range of physicochemical properties. This may provide reassurance versus a specific target, and potentially also versus newly emerging viruses. It is important to

keep in mind that all viruses propagated under laboratory conditions and used in validation studies are considered model viruses (CPMP/BWP/268/95).

Elimination of Parvovirus B19 from plasma protein therapies is following a two-tiered approach.

First, the introduction of a cut-off limit of Parvovirus B19 of 10^5 IU/ml in the manufacturing pools resulted in an average reduction of the viral load in the order of > 5 $\log_{10}$.

Secondly, in the manufacturing process validated inactivation methods for Parvovirus B19 have been implemented. However, the inactivation capacity of a given method has to be evaluated for each step, because factors like the presence of stabilizers have to be taken into account. Also, variations in the capsid proteins, like for Type I (classical B19V) and type II (A6-like) variants, might influence the stability of the capsids towards high temperatures or low pH. Available data show that both variants behave similarly when pasteurized or treated with low pH, but this might be different for other variants of human parvoviruses.

In humans, a number of new parvoviruses have recently been identified, for example PARV4, which has been isolated from patients with Acute Viral Infection Syndrome, or bocavirus, which has been isolated by molecular screening of respiratory tract samples. The pathogenicity and clinical relevance of these two variants is still unclear, but it as likely to assume that there will be no reduction by testing, because it is not effective for these viruses.

To study inactivation of Parvovirus B19 model, viruses are appropriate however caution is advised when partitioning of virus particles is considered. In this case different behavior has been observed. These differences are not well understood and are under investigation.

Parvovirus Types I and II can be crossneutralised in serum of convalescent patients infected with genotype 1, albeit to slightly lower extent for Type 2. The epidemiology of different parvovirus genotypes in Europe has been described. Genotypes II and III can be found in Europe, with the latter being prevalent in West Africa. Genotype II DNA has also been detected in clotting factor products.

Animal parvoviruses share the critical characteristics of human viruses in that they cause high viremia in the hosts and are highly resistant to inactivation methods. Whether canine parvoviruses are relevant for humans is questionable, however some concerns exist for simian parvoviruses, which can be replicated in human and simian bone marrow cells although so far no evidence for a potential pathogenicity in humans exists.

In conclusion, although Parvovirus B19 is recognized as being clinically more relevant than initially assumed, current measures, i.e. Parvovirus B19 NAT, result in a significant

average reduction of plasma pool loads. In addition, inactivation data provide increasing reassurance and prove the validity of the model virus concept.

The significance of emerging parvoviruses is unclear because of unsubstantiated clinical significance. Since current testing is probably not effective, continuous assessment of new developments is prudent.

Instead of considering any new and/or emerging pathogen individually it would be better to define the ranges of pathogens and the knowledge available as well as focusing on the increasing robustness of processes.

Discussion

In addition to scanning of published literature surveillance is important but needs to take into account the ongoing research activities. Usually, contacts among researchers are good and well established; however, the exchange of material for research is sometimes cumbersome. Efficiency of the exchange process would probably be enhanced if a defined process was established rather than to rely on informal expert knowledge and personal contacts.

Surveillance is an important tool to gather timely information about the prevalence of a pathogen within a population. Repositories of samples are currently only available on a national/regional basis, but an effective surveillance on a global basis would need to enhance the capacity of the repositories significantly. Industry and regulators should cooperatively enhance the capacity to collect and analyze samples for epidemiological surveillance.

Particularly when communicating with patients the aim should be to establish a level of trust. The community thinking should be shifted from a given virus of concern to the robustness of decision-making processes. Early communication should contain information about emerging pathogens, the unanswered scientific questions, potential gaps and steps taken by manufacturers and regulators. West Nile Virus was a good example where patients trusted the model virus concept and the robustness of the process.

The availability of a decision tree with a series of questions with yes/no responses or actions would allow to frame the debate on decision making processes, however prevalence in a given population might need a more refined process rather than purely based on the yes/no principle.

Case Study 2: Prion removal filters and test kits/implication to plasma therapies industry

The traditional paradigm of measures to decrease blood safety risks - Donor selection, elimination and removal – has been superseded by the emerging more complex paradigm which also takes into account optimal use and alternatives, blood management, haemovigilance and bloodless medicine. The new paradigm is based on the increasing knowledge that has accumulated as well as on more refined policy

making by regulators, which is reflected in available regulatory guidance documents and statements.

vCJD has imposed one of the biggest challenges on blood and plasma derivatives and in view of the available data, existing uncertainties and gaps do not allow definitive decision making processes.

Implemented donor selection/donor exclusion policies have led to the loss of donors to different degrees depending on the travel history of certain regions to the regions in question. Australia already had established a database on travel history of donors. On the basis of this data it could be predicted that the new procedures instituted in the US would lead to a loss of 6% of donors overall. The repeat donor population would be even more affected, with a resultant 26% loss to the blood supply. In view of these consequences the Australian authorities had to weigh the implications of "doing everything" versus having no donors and no blood.

The CHMP position statement on Creutzfeldt Jakob Disease and plasma-derived and urine-derived medicinal products (EMEA/CPMP/BWP/2879/02/rev1, 23June04) presented a pragmatic approach to donor exclusion to ensure safety and availability. Also FDA has been very proactive in terms of carving out an exception from the pan-European ban for Source Plasma to avoid shortages.

Particularly, the lack of a donor screening test prohibits investigating the prevalence of the disease and the course of infection. Therefore, the safety of blood and plasma is dependent on donor screening and partitioning measures implemented into the manufacturing processes. Until suitable donor screening tests are available the US FDA is recommending interim preventive measures that they deemed to be prudent based on the available scientific data and the evolving state of knowledge regarding these diseases.

There are currently no screening tests available, but assays based on different technologies are under development. But even if a test would be available, leading scientist are doubtful that this situation will be manageable. The need for a confirmatory test, technical issues and most importantly the expected false positive results and the necessary donor counseling impose issues that are difficult to resolve.

The impact of a donor screening test for the safety margin of a product can be illustrated with a theoretical example. Under the assumption that blood contains 10 ID_{50}/ml in the preclinical phase and this donation would enter a 10.000 l plasma pool from which 1 vial of final products would be manufactured per 10 L the interdiction of this donation would result in an increase of the safety margin of approximately 1 $\log_{10}$.

The CPMP position statement states that the prion reduction capacity of manufacturing processes, that in cases where the reduction capacity is limited (based on comparison of own processes with published data or own product-specific investigational studies) manufacturers should consider the addition of steps that may increase the removal

capacity where this is feasible without compromising the safety, quality and availability of the existing products.

Prion reduction by manufacturing processes needs to be carefully considered based on investigational studies employing animal brain-derived spiking material and methods for prion quantification in spiked intermediates and fractions. With methods to inactivate prions affecting the desired therapeutic protein and adsorption and precipitation steps designed to purify the therapeutic protein, any process changes may have considerable impact on the overall product capacity. Nanofiltration is a method to remove undesired material (especially pathogens) by filtration based primarily on size exclusion. This has been demonstrated for removal of viruses as well as for removal of prion spike material. However, for the latter, the potential impact of previous treatment of the material, for example with solvent detergent has to be taken into account. Documented prion reduction by nanofiltration is in the order of 4.4 to 3.1 $\log_{10}$ depending on the filter used. These data demonstrate that nanofiltration as a dedicated prion removal step enhances the safety margin significantly. Nanofiltration is usually performed down-stream in the manufacturing process, where the therapeutic protein is already of high purity ensuring an effective filtration process.

Introduction of an additional step, such as nanofiltration in the manufacturing process, requires assurance that protein integrity is preserved. If clinical trials are required to assess efficacy one has to keep in mind that for plasma protein therapies the number of eligible patients is small, which is one of the biggest hurdles. The limited number of patients has to be carefully used for important clinical trials. But is the physicochemical characterization physiologically relevant? A number of different methodologies are available today, enabling a manufacturer to utilize a range of different tests to relate more closely to the in vivo behavior of the protein. Regulators in Australia and Germany have acknowledged the difficulties and delays with conducting clinical trials. Thus the manufacturers were asked to submit a physicochemical package with no or limited supporting clinical trials but monitoring after introduction.

Discussion

On the basis of the case studies some general conclusions can be drawn. If a test for vCJD would be available, it is not clear who would lead the decision making processes to implement the test. As outlined in the case study, implications of testing donors for vCJD are significant and probably more subject to political decision making with support from regulatory authorities. In the UK implementation of a test if available would be unavoidable, but other countries with different epidemiologies of BSE and vCJD might take different views which could result in a disharmonised approach, which would significantly impact the availability of plasma as seen in the past with different donor exclusion criteria. For the sake of a sustained plasma supply it is important to educate patients and politicians about differences in risk between transfusible components and fractionated products.

Patients are very influential when politicians make decisions and it is important to provide them with accurate information. However, experience has shown that policy making is not always based on scientific data alone.

Donor questioning about travel, particularly when associated with prion risks, is complicated. In order to establish a database on travel history on a global scale, harmonization of the approaches on donor questioning is needed.

Build a communication strategy and a communication platform
There are examples for interactive communications via the Internet, for example the web site of the California Association of Blood Banks. Other organizations sponsor forums under different disciplines with alert systems for participants in place. The US government conducts quarterly discussions on EIDs, but the group would not be open to the public.

A communication strategy would be structured around defined elements:

- Person(s) to control communication processes: procedure, messages audiences
- Platform for communication
- Decision making process and rules
- 1st level – internal communication
- 2nd level – external communication

The installation of such a strategy and group requires the following decision making process:

1. What are the goals and objectives?
2. How would the group operate?
3. Who would participate?
4. Would the group meet routinely?
5. Would an alert system to take actions be necessary?
6. Who would be responsible for maintenance?
7. Who would fund the initiative?
8. Would there be an existing structure/organization to host the initiative?

A small task force (Holmberg, Kreil, Skinner, Ruiz, Waxman, PPTA secretariat Gustafson, von Hoegen) will prepare a proposal on the basis of the discussions to be presented to the entire group for discussion and endorsement.

In conclusion, it was agreed that the expectations were met and progress on this project was made. It was highly recommended that both the WHO and US CDC be part of the initiative.

Appendix

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