REPORT: WHO MEETING ON MONOCLONAL ANTIBODIES AGAINST RABIES AND EVALUATION OF MECHANISMS TO IMPROVE ACCESS TO OTHER BLOOD-DERIVED IMMUNOGLOBULINS

Silver Spring, MD, USA, 18 July 2017
WHO meeting on monoclonal antibodies against rabies and evaluation of mechanisms to improve access to other blood-derived Immunoglobulins

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# List of Abbreviations

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<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DAT</td>
<td>Diphtheria anti-toxin</td>
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<td>EU</td>
<td>European Union</td>
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<td>EUAL</td>
<td>Emergency Use and Assessment listing</td>
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<td>F(ab’)_2</td>
<td>Fragment Affinity-Purified Secondary Antibodies</td>
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<td>GAVI</td>
<td>Global Alliance for Vaccines, Initiative</td>
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<td>GMP</td>
<td>Good Manufacturing Practices</td>
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<td>mAb</td>
<td>Monoclonal antibody</td>
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<td>MSF</td>
<td>Médecins Sans Frontiers</td>
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<tr>
<td>Ni</td>
<td>Non-inferiority</td>
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<tr>
<td>NRA</td>
<td>National Regulatory Authority</td>
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<td>PAHO</td>
<td>Pan American Health Organization</td>
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<td>PEP</td>
<td>Post-exposure prophylaxis</td>
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<td>RCT</td>
<td>Randomized controlled trials</td>
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<td>RIG</td>
<td>Rabies immunoglobulin</td>
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<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization</td>
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<td>SII</td>
<td>Serum institute of India</td>
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<tr>
<td>TAT</td>
<td>Tetanus anti-toxin</td>
</tr>
<tr>
<td>tDAP</td>
<td>Tetanus, Diphtheria, Pertussis Vaccine for Adults</td>
</tr>
<tr>
<td>TIG</td>
<td>Tetanus immunoglobulin</td>
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<tr>
<td>US FDA</td>
<td>US Food and Drug Administration</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Executive summary

Among other indications, blood-derived immunoglobulins are used to provide early preventative passive immunity to individuals who have been exposed to, and are at risk for, developing Rabies, Diphtheria, Tetanus, and snake envenoming. As such they are included in the WHO essential medicines list. These human- or equine-derived life-saving products are provided to patients with a high disease transmission risk related to severity of exposure and absence of previous vaccination status. In low-income countries Rabies Immunoglobulin (RIG) is estimated to be available for less than 1% of category III exposed patients due to lack of availability and high-costs,[1] while lack of demand for Diphtheria anti-toxin (DAT) and Tetanus immunoglobulin (TIG) due to comprehensive vaccination programmes in most countries has led to product shortages as companies cease production. Administration of human blood-derived products is preferred due to the decreased risk for adverse events, but unavailability and the higher cost has countries and NGOs, such as Médicins Sans Frontiers still using equine immunoglobulins. The inability of countries and organizations to forecast their needs exacerbates the situation and has led to difficulties of the PAHO revolving fund to ensure continuous supply.

For rabies, monoclonal antibodies (mAbs) might provide cost-effective and safe alternatives with more reliable and scalable production methods. One Rabies mAb product has now received licensure for the Indian market and other candidates are being evaluated in various stages of development. Group discussions by meeting participants identified that clear criteria need to be developed by regulatory authorities for acceptable pre-clinical data and clinical trial endpoints. Regulatory authorities should facilitate the approval of rabies mAbs to improve access when products are shown to be safe and effective, and efforts need to be made to ensure cost-to-consumer pricing is at a level where high-risk individuals can afford treatment. Blood derived polyclonal immunoglobulins, for the time being, are likely to remain the mainstay for preventative passive immunization for Tetanus and Diphtheria as mAbs are currently in the investigational stage, and the global market is expected to remain small. The situation for snake anti-venoms is even more complicated by the need for regional specific products due to a high degree of antigen diversity, lack of standardization and product quality control. For these products, strengthening of current producers of blood derived products is needed and processes for recognition and identification of manufacturers with high quality products are needed. Consultations with regional and national regulatory authorities will facilitate this process and the evaluation of how WHO could facilitate the process should be evaluated.

Introduction and scope of meeting

Immunoglobulins, when administered early post infection, can in some circumstances help to prevent infectious disease development. Most products available in the market are human or equine derived polyclonal antibody preparations isolated after immunization of horses or humans with antigens of interest. Yet, for Diphtheria and Tetanus the global need for immunoglobulins has decreased as most individuals, and populations, are protected through preventative vaccination. This is not the case for Rabies and snake envenomings where the need for immunoglobulins remains high but issues with ensuring supply of affordable products in health facilities leads to decreased utilization of these life-saving treatments.

Anti-rabies immunoglobulin (RIG), Diphtheria anti-toxin (DAT) and anti-tetanus immunoglobulin (TIG) are included on the WHO’s list of essential medicines and current recommendations for treatment still include these immunoglobulins for patients with high disease transmission risk and/or those who are under vaccinated. Additionally, polyclonal equine-derived immunoglobulins are the only treatment option against snake envenomings around the world. As global vaccination coverage increases and disease incidence rates decrease, many producers of equine or human immunoglobulins for Diphtheria and Tetanus have ceased production of these life-saving interventions due to lack of demand, limited return on investment, and high regulatory requirements linked with their production.

The limited global supply of DAT and TIG, as well as snake anti-venoms and RIG, coupled with the continued reporting of disease cases has led to discussions on how to strengthen current producers and investigate their replacement with monoclonal antibodies (mAbs) produced through recombinant DNA technologies. Specific potential advantages of mAbs over polyclonal immunoglobulins are: 1) possibility for standardized production practices and increasing production capacity; 2) improved safety; 3) possibility of highly purified and...
concentrated products. Additionally, the possibility to produce these antibodies through cell culture in a GMP environment will improve scalability and may decrease costs, thus improving access and supply. Currently, out of the above described diseases, one company has successfully developed a mAb for rabies post exposure prophylaxis (PEP) that has been approved by local regulatory authorities in India, while several others are in the pipeline. Diphtheria and Tetanus mAb development remains in the experimental, pre-clinical phase.

On 17 July 2017 the US Food and Drug Administration hosted a public workshop “Developing Rabies Monoclonal Antibody Products as a Component of Rabies Post-Exposure Prophylaxis” for stakeholders to discuss data, issues, and opinions related to laboratory assays, animal models and clinical trials that might be involved in the development of rabies mAbs [2]. WHO, through funding provided by the European Union, convened a side meeting to continue discussions on rabies mAbs and to further expand discussions into improving access to diphtheria, tetanus and snake-bite immunoglobulins. This report summarizes selected statements and opinions expressed by individual attendees at the WHO meeting and is not a statement of policy of any regulatory entity.

An overview of Rabies Immunoglobulins

Background

Rabies is a viral disease, transmitted to humans primarily through bites of infected animals. They are lyssaviruses that are RNA viruses that replicate within muscle and nerve cells. Upon infection, the virus migrates from the peripheral nervous system to the brain where uncontrolled inflammation and brain damage occurs. Once clinical symptoms are evident death is almost always inevitable and post-exposure prophylaxis with vaccines and Rabies immunoglobulins are no longer effective.[3]

Ninety nine percent of Rabies cases are transmitted through dog bites but in areas that have good dog vaccination coverage disease may still be transmitted through the wild-type reservoir animals (such as bats, and mongoose). Many countries have controlled rabies, and as a result most cases occur in Asia and Africa with tens of thousands of deaths per year. Rural communities who often have limited access to healthcare are particularly affected.[3]

Rabies is a vaccine preventable disease and timely administration of post exposure prophylaxis (PEP) is life-saving with more than 15 million people worldwide receiving rabies PEP per year. PEP includes extensive wound washing, rabies vaccination and the administration of rabies immunoglobulins. RIG is currently recommended in severe category III bite cases where there are extensive wounds near the head and neck areas and hands, contact with bats or contamination of mucous membranes with saliva from licks.[3] However, less than 1% of these rabies exposures in developing countries receive RIG due to high relative costs and lack of availability[1].

Currently, the rabies immunoglobulin market is composed of blood derived equine and human RIG. However, several mAb-based products are in development and one has recently received regulatory approval from the Indian authorities. This product, manufactured by the Serum Institute of India Pvt. Ltd (SIIL), is derived from a single cell line and recognizes a single conserved epitope of the rabies virus. Considering both the scientific and the practical issues involved in approaches to evaluating safety and efficacy of new products in this area, the FDA meeting and the WHO side meeting aimed to address how regulatory authorities can facilitate better understanding of available information and approaches to regulatory approval for these products for international use and to improving availability of safe and effective products to those in need.

Facilitating approval and uptake of rabies monoclonal antibodies

Highlights from the U.S FDA workshop on rabies mAbs

Erin Sparrow, WHO technical officer within the Department of Essential Medicines and Health Products, summarized the key points that were raised at the FDA workshop on rabies mAbs for Post-exposure prophylaxis. The presentations and subsequent discussions addressed issues related to passive immunization with rabies immunoglobulins as an important component of rabies PEP and uncertainties regarding its supply. RIG is recommended by WHO for category III exposed individuals to provide passive immunization while patients’ immune system mounts a protective host-derived antibody response following vaccination. US CDC
has similar recommendations for including RIG in postexposure prophylaxis after suspected rabies exposures in previously unvaccinated persons.

Several advantages that mAbs, secreted and purified from immortalized cell lines, might have over polyclonal RIG of equine or human origin are minimal batch-to-batch variability, scalable technology, and that they are able to be produced in a more refined and concentrated format. Some participants suggested that cost of goods estimates are favourable for rabies mAbs being competitively priced as compared to RIG, since a relatively small amount of mAb is needed. New technologies for mAb production could further lead to lowering the cost.

Workshop participants discussed topics such as preclinical studies using serological/neutralization assays, coupled with the hamster challenge models for preclinical studies to evaluate specificity and potency; and suggested a broad range of rabies isolates and laboratory strains should be included to ensure broad spectrum protection against a sufficiently broad range of rabies isolates. Although the genetic diversity of existing rabies strains was acknowledged to be an issue when considering substitution of a monoclonal product or cocktail for previously used polyclonal products, the impact of escape mutants was dismissed by some participants, especially since there is no human to human transmission of rabies. For clinical trials of rabies mAbs, numerous participants suggested that safety profiles need to be confirmed and dose ranges established ensuring that immune responses to rabies vaccines given concomitantly during PEP are not impaired. For phase III clinical trials, optimum trial design was discussed. There was general acknowledgment that control arms receiving only placebo would not be ethical when the trial population consisted of rabies-exposed patients who would otherwise be considered to need RIG. There was debate regarding topics such as the potential ethics, feasibility, and interpretability issues raised by a variety of trial designs including add-on and noninferiority designs, populations including healthy volunteers and various subsets of suspected rabies exposures, endpoints including mortality and biomarkers (including issues related to timing), and logistics involved in both pre-market and post-marketing data collection.

**Group discussion on how to facilitate rabies mAbs product approval and use**

Participants were separated into groups for discussion to identify the main challenges, considerations and possible solutions. Many points raised were related to preclinical data and clinical trial endpoints needed for regulatory authorities to approve rabies mAbs; how to facilitate rabies mAb regulatory approval in countries; and how to assure that mAbs are competitively priced and made available to disease endemic countries. To overcome many of these challenges there is a clear need for strong leadership from WHO consultations with both endemic countries and regional regulatory networks to elucidate regulatory approval processes required and address the points of consideration listed in Table 1.

**Table 1: Challenges, solutions and points for consideration needed to facilitate approval of rabies mAbs**

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Points for consideration (examples raised as individual opinions for further discussion)</th>
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<tr>
<td>1. Preclinical studies for mAb(s) development</td>
<td>A broad range of rabies isolates should be tested through serological/neutralization assays. Good surveillance needs to be implemented to assess strain diversity and ensure ongoing coverage of mAbs.</td>
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<tr>
<td>2. Clinical trial design&lt;br&gt;Acceptable trial endpoints</td>
<td>Serological antibody responses may be an acceptable surrogate endpoint instead of survival. Assessment of mortality endpoints may be difficult but could be performed during post-market surveillance. The presence of appropriate infrastructure and healthcare personnel needs to be considered when selecting study sites. Urban areas provide adequate infrastructure for centralization of efforts. Clinical scoring for rabies exposures and laboratory diagnosis of biting animal, where possible should be evaluated in clinical trial design, however it was acknowledged that diagnosis of biting animal may be difficult to implement and costly.</td>
</tr>
<tr>
<td>3. mAb(s) or RIG need to be available for all “at risk” populations</td>
<td>More accurate cost-to-consumer pricing is needed for Rabies mAbs to evaluate their potential. Anticipation of market needs and potential market failure needs to include assessing access strategies and mechanisms with countries,</td>
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</table>
Regional networks and development partners.
Regional regulatory networks should be engaged to discuss rabies mAbs regulatory approval strategies.
Strong leadership from WHO is essential (Prequalification/Assessment, Strategic Advisory Group of Experts on Immunization-SAGE).
Strengthening of current RIG producers is needed to improve access in “at risk” populations.

4. Approval process for Rabies mAbs

Given that the SII rabies mAb has been approved by the Indian regulatory authorities, strategies need to be evaluated to make the product available to other countries.
Regulatory authorities could provide accelerated approval using serological endpoints with provision of post-market surveillance to assess efficacy in the long term.
Development of a WHO prequalification or joint-assessment process could be used to assess Rabies mAbs coming to market.

Procurement mechanisms for Immunoglobulins, potentially mAbs

PAHO revolving fund perspective
Oscar Vargas, Procurement Specialist, Revolving Fund, PAHO-WHO, Washington DC, USA, presented the PAHO revolving fund, a regional and financially self-sustaining mechanism that provides countries in Latin America and the Caribbean access to WHO pre-qualified or reference NRA approved vaccines, biologicals, medicines and ancillary products for purchase by country’s public health services. Challenges in procurement of sufficient immunoglobulins to ensure continuous supply within the region are linked with discrepancies between forecast needs by country and actual demands made from the fund, lack of specific demand for selected products of public health importance (Diphtheria anti-toxin) and instability of immunoglobulin production by manufacturers. Currently anti-venoms are procured through a separate mechanism and, specifically for anti-venoms, there are a limited number of animal species targeted and anti-venom purchase is often in emergency situations which is not conducive to maintaining manufacturing lines. To improve the situation improved biological forecast planning is required.

The GAVI Perspective
Deepali Patel, Senior Programme Officer at GAVI, presented GAVI’s Vaccine Investment Strategy for prioritization of future vaccine investments through an evidence-based, decision-making process. GAVI is investigating the possible expansion of its portfolio into passive immunization products, including RIG. In 2013, GAVI highlighted three main benefits for investing in Rabies vaccines as: positive mortality impact, potential catalytic effect within rabies elimination programmes, good value for money and the equity provided by improved access in marginalized populations. However, they also highlighted that there were limitations in surveillance data, challenges of implementing a programme that incorporates RIG, and the possibility that there would need to be significant changes in GAVI policies and investment in health systems to ensure implementation. Consequently, GAVI invested in a feasibility assessment to evaluate what the GAVI support could look like and what implementation challenges could be overcome. GAVI will re-evaluate Rabies vaccines and RIG in 2018 taking into consideration the data collected from the research investments. The main considerations that GAVI will take into account: 1) can mAbs replace RIG as a more cost-effective option? 2) does the absence of a prequalification procedure exclude GAVI from providing RIG? 3) How to ensure RIG availability without predictable demand forecasting from countries and the role of stockpiles.

MSF Access to Medicines perspective
Julien Potet, Médicins Sans Frontiers (MSF) provided insight into immunoglobulin usage within MSF programmes. He noted that despite MSF guidelines and recommendations to exclusively use human immunoglobulin products, unavailability of human TIG may lead to a revision of these guidelines to allow for the re-inclusion of equine TIG into MSF programmes. Administration of RIG for potential rabies exposures is
more dependent on product availability over clinical case evaluation. To improve its response to potential Diphtheria outbreak situations, MSF is currently evaluating the creation of a small stockpile for DAT. For snake anti-venoms, they have noted a surge in demand for treatment but the high cost is a problem. Switching from equine anti-sera to mAbs would need to have support for manufacturers and suppliers to ensure seamless integration. Market shaping mechanisms such as stockpiles with quality products, demand consolidation, subsidizing treatments and long-term agreements with manufacturers could strengthen key suppliers and new manufacturers.

WHO Prequalification and Assessment Possibilities
Emer Cooke, Head of Regulation of Medicines and other Health Technologies of the Essential Medicines department at WHO presented existing WHO approval processes for medicines, vaccines, interventions and other products. Multiple assessment possibilities exist within WHO such as prequalification, Emergency uses and assessment listing (EUAL), snake anti-venom assessment and listing process, the Expert review panel, smallpox vaccines stockpile risk assessment, and facilitating regional joint assessments. Currently, no pre-qualification process exists for blood derived immunoglobulins. Snake anti-venoms for sub-Saharan Africa are evaluated by WHO using a time limited special procedure for special public health circumstances to support regulatory authorities within countries. The manufacturing and quality data and the preclinical and clinical results of selected polyclonal equine anti-venoms products are evaluated using the “Guidelines for the production, control and regulation of snake anti-venom immunoglobulins” reviewed alongside with a provision for post-market analysis.

Developing mAbs and blood-derived immunoglobulin assessments within WHO would need to take into account the evidence, the context of use (routine administration, use only in emergency situations or use to address shortages within countries), and if a Scientific Regulatory Affairs assessment is available. One possibility would be for WHO to facilitate a joint assessment with regulatory agencies of recently licenced rabies mAbs in combination with risk management plans that include data collection protocols, however resources would need to be found to support this activity.

An overview of Diphtheria antitoxins

Background
Diphtheria is caused by infection with exotoxin producing Corynebacterium diptheriae that is transmitted via contaminated sputum released from coughs or sneezes. The disease progresses with formation of a respiratory tract pseudomembrane along with clinical symptoms of lymphadenitis, neuropathy, and cardiomyopathy and death is due to heart failure or suffocation[4]. Much of the distal pathogenicity of disease may be linked to toxin induced cardiac and nerve damage. Current treatment of Diphtheria requires hospitalization, the administration of Diphtheria anti-toxin (DAT) polyclonal equine immunoglobulin and antibiotics. Passive immunization through the administration of DAT is life-saving, and prevents irreversible toxin related damage[5].

Prior to the broad availability of the vaccine in the 1920’s and the launch of the Expanded Programme on Immunization (EPI), Diphtheria was a leading cause of childhood death with 32 deaths per 100,000 and a death rate of almost 50% of cases [6]. Global incidence rates have decreased to around 5000 cases per year, since 2006, when vaccination coverage of DTP3 stabilized at 97% coverage[7], see figure 1.[8] Although, most countries report rare sporadic disease cases, over 50 cases have been reported in 8 countries, another 17 have reported over 5 cases since 2011(GHO data).[8] Yet, these figures underestimate the real situation due to a lack of case reporting in many countries.[7] Historical evidence from the Former Soviet Union in the 1990s, where 157,000 cases and 5000 Diphtheria deaths occurred, show that a diminished vaccination coverage or
incomplete vaccination as well as decline in socioeconomic conditions in countries can lead to disease recurrence and outbreaks[6]. The reasons to assure the continued availability of DAT for the treatment of Diphtheria are the following: 1) Diphtheria cases are still reported; 2) Compliance to vaccine administration regimens are not universally high; and 3) Immunosenscence in aging populations could increase risk.[9]

Supply issues with equine DAT and mAb development
Heidi Smith of MassBiologics of the University of Massachusetts Medical schools presented the supply challenges of DAT, and elaborated upon mAbs in development. Equine DAT is included in the WHO essential medicines list. Yet the availability of the product is limited with many producers having ceased production due to lack of demand, limited return on investment for continuing production and the high regulatory requirements required to assure safety of blood-derived products[9]. Most countries do not have DAT stockpiles and rely on donations from the small number available in stockpiles. A manufacturers’ survey undertaken by UNICEF, following an increase in DAT requests in 2016, demonstrated the supply issues with only 3 manufacturers confirming product availability for UNICEF, none of which were prequalified[10]. In 2016, WHO SAGE recognized that the DAT supply issues were concerning and recommended WHO resolve global shortages through 1) Establishing global procurement mechanisms and DAT stockpiles; 2) Developing regulatory pathways for rapid DAT deployment; 3) Support the development of mAb replacements[10]. Although human polyclonal serum derived immunoglobulins is technologically possible the anti-toxin titre levels are relatively low and would require affinity purification[11]. All research and development of mAbs against Diphtheria toxins are in the pre-clinical investigation stage, with 5 published reports and development of a DAT replacement mAb by MassBiologics ongoing[9]. Several issues surrounding mAb development and regulatory approval still remain to be resolved including 1) the lack of an animal model for the respiratory phase of disease precludes consideration for FDA approval under the Animal Rule, 2) Clinical trial designs are difficult as efficacy trials are not feasible in many settings due to low incidence, 3) lack of serological correlates for protection, 4) financial incentives need to be put into place. MassBiologics expressed interest in FDA’s Expanded Access to Investigational Drugs for Treatment Use in the US, but it is still unclear how this would be applicable in a global setting.

An overview of Tetanus Immunoglobulins

Background

Tetanus is caused by infection with spore producing Clostridium tetani. It is transmitted to humans through open wounds contaminated with bacteria infected objects, soil or saliva. The bacteria replicate within the host and secrete tetanus toxins of tetanospasmin and tetanolysin that block the release of inhibitory neurotransmitters (glycine and GABA) and impact regulation of the body’s nervous impulses. Clinical presentations of disease involve muscle rigidity, painful contractions, seizure-like spasms, and an eventual inability for the patient’s body to regulate heart rate, blood pressure or temperature.[12] If left untreated, the death rate is almost 100%. There is no naturally-acquired immunity to tetanus and prevention of disease requires active immunization with tetanus toxoid vaccines. Tetanus prophylaxis in wound management requires immunization with vaccines and administration of tetanus immune globulin for wounds not assessed as clear minor wounds. Cases and fatalities still exist around the world where 10,337 cases were reported to WHO in 2015, see figure 2, and it is endemic in over 50 countries worldwide.[8] In most cases, post-exposure prophylaxis includes extensive wound washing and vaccine administration, however, passive immunization through the administration of human Tetanus immunoglobulin (TIG) is currently recommended for patients with contaminated wounds who have not been completely vaccinated or whose vaccination status is uncertain present.[12] TIG is included on the WHO essential medicines list.
Supply issues of TIG and mAb development

Deborah Molrine, from Mass Biologics of the University of Massachusetts presented the current landscape of anti-tetanus immune globulins where the market currently includes private manufacturers and state funded research institutions with at least 16 producers situated around the globe known to produce either TIG or TAT/ATS. Most of the world’s TIG usage, in 2014, was in Asia and Pacific in countries without widespread vaccination coverage.

Global shortages in TIG are linked with growing country demands and difficulties in reliably forecasting patient needs coupled with changing market dynamics, product recalls, plasma availability, and production lead times. TIG production lead time can be markedly shortened if producers keep a supply of frozen hyperimmune plasma to be released when needed and lot release can be as short as six weeks in this case.

From safety, efficacy and quality perspectives, development of a human mAb to tetanus toxin would be beneficial. All tetanus mAbs are still in the preclinical investigation stage but several promising cell lines producing tetanus toxoid neutralizing antibodies that confer protection in mice have been developed. However, questions relating to the actual need to improve supply of TIG, the unmet medical needs that are not fulfilled by TIG treatment and what business models for commercial development of new technologies that will address the current supply needs still need to be elucidated.

An overview of Snakebite and access to anti-venoms

Background

Global burden of snake bites and envenoming is estimated at up to 5.4 million bites with up to 2.7 million envenomings causing up to 138,000 deaths and three times as many amputations and other permanent disabilities per year.[13] Figures underestimate the global burden of disease due to under-reporting. Venomous snakes are classified within the families of Viperidae, Elapidae, Colubridae and Atractaspididae and their venoms induce cytotoxic, hemotoxic, myotoxic and neurotoxic effects that commonly result in death, if left untreated. Over 600 species of venomous snake exist[14], in most areas of the world there are more than one species of venomous snake and species identification is only rarely feasible. Recently, snakebite has been included by the WHO as a neglected disease of poverty. Current anti-venoms are polyclonal, polyspecific immunoglobulins derived from the purification of sera from the hyperimmunization of horses with snake venom.

Snakebites and access to anti-venoms

David J. Williams of the Australian Venom research unit at the University of Melbourne, Australia and of Charles Campbell Toxinology Centre at the University of Papua New Guinea presented the current reasons behind the global supply issues for snake anti-venoms and described the key challenges for improving the situation. Lack of investment and knowledge by countries into improving access of “at-risk” populations to anti-venoms leads to countless deaths around the world. To improve the situation there needs to be improved governance, better surveillance data, product innovation, clear regulatory approval procedures and guidelines, and implementation of funding mechanisms. Financial support to procure anti-venoms will expand the market by creating demand that would incentivize manufacturers to produce high quality products, which would in turn increase supply, expand the number of players on the market and improve affordability and access in the long term. Initiatives, such as that of WHO sub-Saharan anti-venom assessment have led to a list of WHO recommended products and a support programme to assist with improving production or quality.

The global anti-venom market is largely un-regulated, with regions including Asia and South America producing their own anti-toxins relevant for the local context. Yet little standardization or application of manufacturing best practices is performed. Current issues with manufacturing of snake anti-venoms include 1) lack of reference venoms for batch standardization and product development, 2) poor quality control practices of manufacturers in the production of equine hyperimmune plasma, purification procedures and pathogen testing, 3) No standardization of activity units per vial or dose, means that often a substantial number of vials are needed to treat a single patient, which significantly increases treatment costs, 4) poorly designed clinical trials. Establishing preclinical and clinical trial best practices and defining regulatory pathways that facilitate anti-venom approval would facilitate innovation in the field. Scientific advances in proteomic and genomics
could lead to more defined antigens that target conserved immunogenic sequences to broaden the target species specificity or the used of novel adjuvants could be explored. Monoclonal antibodies for snake antivenoms are unlikely to replace equine polyclonal immunoglobulins in the near future but improvements in current technologies have been promising and include: F(ab')2 products, validation of manufacturing processes, increased purification and validated potency and safety testing.

**Industry Perspective: Anti-venoms, present and future strategies**

Juan Silanes, of Inosan Biopharma, presented their company and perspective in how manufacturers could improve the global situation for snake bites. Current anti-venoms produced by Inosan Biopharma are pyrogen free, purified F(ab')2 fragments that are region specific with broad polyvalent species coverage and have a decreased risk for adverse events. Products are stable and lyophilized, produced under GMP conditions with validated shipping to assure quality on arrival. Since its first commercially available product in 2012 the company produces anti-venoms for sub-saharan Africa as well as scorpion sting. Their products are registered in 12 countries, available in a further 15 countries, they currently have a clinical trial underway in the US and process has commenced for EMA registration. From an industry perspective, prequalification and promotion of GMP compliant manufacturers, financing made available to countries, improvement of distributions infrastructures, and investment in R&D are needed to improve the situation.

Dr Alejandro Alagon, National Autonomous University of Mexico, Mexico, stated that although the company is developing mAbs against scorpion sting three mains considerations make development of mAbs as anti-venoms difficult including: 1) Venom complexity between species, developmental stage and geographic location; 2) the high amount of anti-venom needed for neutralization; 3) Antibody formats for production. In agreement with David Williams, they stated that equine polyclonals are likely to remain the dominant immunoglobulin for the treatment of snakebite for the future.

**Key outcomes of the meeting and next steps**

The replacement of polyclonal anti-sera with mAbs is an area of active interest and has the potential, in the long term to be a safe and cost-effective alternative to blood-derived immunoglobulins. Rabies mAbs are expected to be available for purchase in India shortly and other mAb cocktails are undergoing various stages of evaluation, post-market surveillance will be essential for continued evaluation for the efficacy of these products should products be approved based upon serological endpoints. Clear criteria and mechanisms need to be established for regulatory approval, including clinical trial design and acceptable end-points. Access issues for “at risk” populations still remain to be addressed and consumer purchase price of Rabies mAbs will be an important consideration for countries.

For Diphtheria, Tetanus and snake anti-venoms polyclonal immunoglobulins of human or equine origin are unlikely to be replaced by mAbs in the near future given the current market demand and the challenges associated with development. Strengthening of polyclonal immunoglobulin producers needs to be assured as well as reliable demand forecasting to support manufacturers. Recognition should be provided to manufacturers who produce quality products. Engagement of regional and national regulatory agencies and evaluation of how WHO could facilitate the approval processes should be conducted.

**References**

Annex I: Meeting Agenda

WHO side meeting on monoclonal antibodies against rabies &
evaluation of mechanisms to improve access to other blood-derived Immunoglobulins

Hilton Double Tree Hotel, Meeting Room: Inspiration Ballroom
Silver Spring, MD, USA, 18 July 2017

Agenda:

08:00-08:30  Registration

08:30-08:45:  Meeting open and introductions

08:45-09:05:  Highlights from FDA workshop on rabies mAbs (Erin Sparrow)

09:05-09:40:  Group Discussion on rabies mAbs: Following on from the discussions at the FDA workshop, how can we facilitate product approval and use?

09:40-10:15:  Procurement mechanisms for Immunoglobulins and potentially mAbs
•  PAHO revolving fund perspective (Oscar Vargas)
•  GAVI perspective (via WebEx, Deepali Patel)
•  MSF Access to Medicines perspective (Julien Potet)

10:15-10:30:  WHO prequalification and Assessment Possibilities (Emer Cooke)

10:30-11:00:  Coffee break

11:00-11:20:  Diphtheria antitoxin: BoD, supply issues, mAb development, SAGE recommendation (Heidi Smith)

11:20-11:40:  Anti-tetanus immunoglobulin: BoD, supply issues, mAb development (Deborah Molrine)

11:40-12:00:  Presentation on snakebite and access to antivenoms (David Williams)

12:00-12:15:  Industry Perspective: Antivenoms, present and future strategies (Juan Silanes & Alejandro Alagon)

12:15-13:00:  Group Discussion: how can we improve supply of DAT, TIG and antivenoms
•  Strengthening of current producers (equine, human) – what is needed?
•  Replacement with mAbs – what is needed?

13:00  End of meeting

13:00-14:00  Lunch (optional)
Annex II: List of participants

Dr Alejandro Alagon, National Autonomous University of Mexico, Mexico

Dr Ilona Bebenek, toxicologist, US FDA, Silver Spring, USA

Dr Tanvir Bell, Center for Drug Evaluation and Research, FDA, Silver Spring, USA

Dr Leslie Boyer, the VIPER Institute, College of Medicine, University of Arizona, Tucson, Arizona, USA

Dr Catherine Brown, Deputy State Epidemiologist and State Public Health Veterinarian, Massachusetts Department of Public Health, State Laboratory Institute, MA, USA

Dr Sarah Connelly, Medical Officer, Center for Drug Evaluation and Research, FDA, Silver Spring, USA

Dr Ed Cox, Director Office of Antimicrobial Products, Center for Drug Evaluation and Research, FDA, Silver Spring, USA

Dr Damon Deming, Microbiologist, Center for Drug Evaluation and Research, Office of Antimicrobial Products, FDA, Silver Spring, USA

Mr Samir Desai, Zydus Cadila Healthcare, Ahmedabad, India

Dr Christine Fehlner-Gardiner, Research Scientist and Leader, Centre of Expertise for Rabies, Science Branch, Canadian Food Inspection Agency, Canada

Dr Zhen Fu, College of Veterinary Medicine, The University of Georgia, Athens, USA

Dr Bhagwat Gunale, Senior Manager - Clinical Research, Clinical Research and Pharmacovigilance, Serum Institute of India, Pune, India

Prof José María Gutiérrez, Instituto Clodomiro Picado, Universidad de Costa Rica San Jose, Costa Rica

Prof Amine Kamen, Department of Bioengineering, McGill University, Montreal, Canada

Dr Michael Kennedy, Plasma Derivatives Branch, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA, Silver Spring, USA

Dr Robin Levis, Center for Drug Evaluation and Research, FDA, Silver Spring, USA

Dr Jenny Mellquist, BioBasics Consulting, Erie, Pennsylvannia, USA

Dr Deborah Molrine, Deputy Director, Clinical Affairs, Professor of Pediatrics, MassBiologics, Boston, MA, USA

Dr Susan Moore, Clinical Assistant Professor; Director, KSVDL Rabies Laboratory, Kansas State University, USA

Dr Robert Nelson, Deputy Director and Senior Pediatric Ethicist, Office of Pediatric Therapeutics (OPT), Office of the Commissioner (OC), US FDA, Silver Spring, MD, USA

Ms Deepali Patel, Senior Programme Officer, Policy, GAVI, Geneva, Switzerland (via WebEX)

Mr Julien Potet, Policy Advisor Neglected Tropical Diseases, Vaccines, Médecins Sans Frontières - Access Campaign, Paris, France

Report of WHO meeting on monoclonal antibodies against rabies and evaluation of mechanisms to improve access to other blood-derived Immunoglobulins, Silver Spring, MD, USA, 18 July 2017
Dr Beatriz P. Quiambao, Chief, Clinical Research Division, Research Institute for Tropical Medicine, Alabang, Muntinlupa city, Philippines

Dr Trina Racine, Centre Hospitalier de l'Université Laval (CHUL), Quebec, Canada

Dr Sergio Recuenco-Cabrera, Professor, Universidad Nacional Mayor de San Marcos, Faculty of Medicine, Lima, Peru

Dr Dorothy Scott, Chief, Plasma Derivatives Branch, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA, Silver Spring, USA

Dr Juan Silanes Jr. Inosan Biopharma, Alcobendas (Madrid), Spain

Dr Juan Silanes Sr. Inosan Biopharma, Alcobendas (Madrid), Spain

Dr Olga Simakova, Center for Biologics Evaluation and Research, FDA, Silver Spring, USA

Dr Sally Slavinski, New York City Department of Health and Mental Hygiene, Assistant Director Zoonotic, Influenza and Vector-borne Disease Unit, Bureau of Communicable Disease, New York, USA

Dr Heidi Smith, Director, Clinical Affairs, MassBiologics, Boston, MA, USA

Dr Geetha B. Srinivas, Head of Virology, APHIS/VS/CVB, US Department of Agriculture, Ames, IA, USA

Dr Barbara Styr, Medical Officer, Office of Antimicrobial Products, Center for Drug Evaluation and Research, FDA, Silver Spring, USA

Dr Louise Taylor, Scientific Director, Global Alliance for Rabies Control, Manhattan, Kansas, USA

Dr Yang Wang, Associate Deputy Director, Discovery Research, MassBiologics, Boston, MA, USA

Dr Fan Hui Wen, Núcleo Estratégico De Venenos e Antivenenos, Instituto Butantan, Sao Paulo, Brazil

Dr Henry Wilde, Division of Infectious Diseases, Chulalongkorn University Hospital, Bangkok, Thailand.

Dr David Williams, Head, Australian Venom Research Unit, Department of Pharmacology and Therapeutics, University of Melbourne, Australia and Head, Charles Campbell Toxinology Centre, School of Medicine & Health Sciences, University of Papua New Guinea

World Health Organization secretariat:
Ms Emer Cooke, Head Regulation of Medicines and other Health Technologies, WHO, Geneva, Switzerland

Dr Adriana Oxman, Revolving Fund, PAHO-WHO, Washington DC, USA

Ms Erin Sparrow, Technical Officer, Health Systems and Innovation, WHO, Geneva, Switzerland

Mr Oscar Vargas, Procurement Specialist, Revolving Fund, PAHO-WHO, Washington DC, USA

Dr Marco Antonio Natal Vigilato, Adviser, Veterinary Public Health (Zoonosis and Food Safety), Communicable Diseases and Health Analysis Department, PAHO-WHO, Peru

Meeting Rapporteur:

Dr Annette Ives, Consultant, Neglected Zoonotic Diseases, WHO, Geneva, Switzerland