Animal antisera production
Quality, safety and efficacy problems

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Animal therapeutic antisera

- A pharmaceutical preparation of either whole antibodies (IgG) or antibody fragments \([F(ab')_2]\) against an antigen of clinical relevance.
- Rabies virus
- Scorpion venoms
- Snake venoms
- Spider venoms
- Tetanus toxin
- Diphteria toxin
- Botulinic toxin
Why are antisera essential?

- No alternative successful therapy
- High degree of mortality and morbidity in the absence of treatment
- The diseases in which they are used represent a heavy toll of human suffering
- Largely affects children and farmers in rural communities

Snake bite victim in Ecuador
Photo: D.A. Warrell
The ‘universe’ of antisera producers
A heterogeneous *collage* of many actors, all of whom should contribute

- Different technological platforms
- Different national/regional scenarios
- Different volume of production
- Different needs to fulfill their roles
How are antisera manufactured?

Selection and collection of venom → Immunization of horses (or sheep) → Bleeding and separation of plasma/serum → Fractionation and purification of IgG or fragments → Final quality control

Final product
Strengths and opportunities

• The technology is in the public domain
• Possibilities for transfer of technology
• Information available on the immunologic characteristics of venoms
• There is knowledge generated in the field of human-derived blood products that can be transferred to animal antisera production
But there are problems

- Poor efficacy
- Adverse Reactions
- Low volume of production
Poor efficacy of some antivenoms

- Low potency (quality control and regulatory issues).
- The design of immunizing mixtures of venoms is not well founded in some cases.
- There is little work on preclinical and clinical assessment of antivenoms (a good experience in Latin America but not in Africa and Asia).
The problem of poor efficacy

- The distribution and commercialization of antivenoms to regions and countries where they are not effective against some medically-relevant venoms.
- The issue of regulatory policies at national and regional levels (authorization for the introduction and use of an antivenom in a country).
The problem of poor efficacy to prevent local tissue damage

- Snake venom-induced local tissue damage develops very rapidly and induces, in many cases, permanent tissue loss and disability.
- The problem of antivenom distribution to health facilities in rural communities and of the delay in the transportation of the patient.
Problems of safety: adverse reactions

- Urticaria, itching, fever, vomiting, headache, colics, bronchospasm, hypotension, angioedema.

- A high incidence of early adverse reactions (anaphylactic and anaphylactoid) occur when administering some antivenoms, whereas others induce a relatively low incidence of these reactions.
The issue of viral safety of antisera

- Viral inactivation/removal steps need to be introduced in antisera preparation, following international guidelines.
- The validation of viral inactivating effect of some fractionation steps already in use is required.
- Acid pH, pepsin digestion, caprylic acid, pasteurization have viral-inactivating effect.
Early adverse reactions: poor physicochemical characteristics of antisera

- Protein aggregates
- Residual non-IgG proteins and fragments
- Poor stability of proteins
- Presence of bacterial products (LPS)
- Inadequate lyophilization
- High protein load
Poor investment in technologies, infrastructure and quality assurance

• Since rabies and envenomations are of low priority for many governments and agencies, there is little investment.
• Decisions of when and where to locate investments are sometimes made with an inadequate technical basis.
• Poor national and international technical advice.
Poor implementation of GMPs

- Handling and care of animals used for immunization
- Plasma fractionation
- Ultrafiltration
- Aseptic filling
- Lyophilization
- Production of water
- Cleaning and sanitization of equipments and clean rooms
- Design of systems and equipments
Little technological innovation

• The active search for better immunizing mixtures, i.e. the design of novel antivenoms, is deficient.

• Activities related to innovation (seminars, discussions, following up of scientific literature) are scarce.

• Activities related with transfer of technology are not systematic.
How should these problems be confronted?
A global, integrated strategy, best coordinated by WHO, should be structured
Final remarks

• A multicomponent scenario is required, involving producers and regulatory authorities at national, regional and global levels, with an appropriate coordination by WHO and with financial support of the international community.

• We need *competence, collaboration and coordination* more than competition.