

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
- Diphtheria toxin
- Botulinic toxin

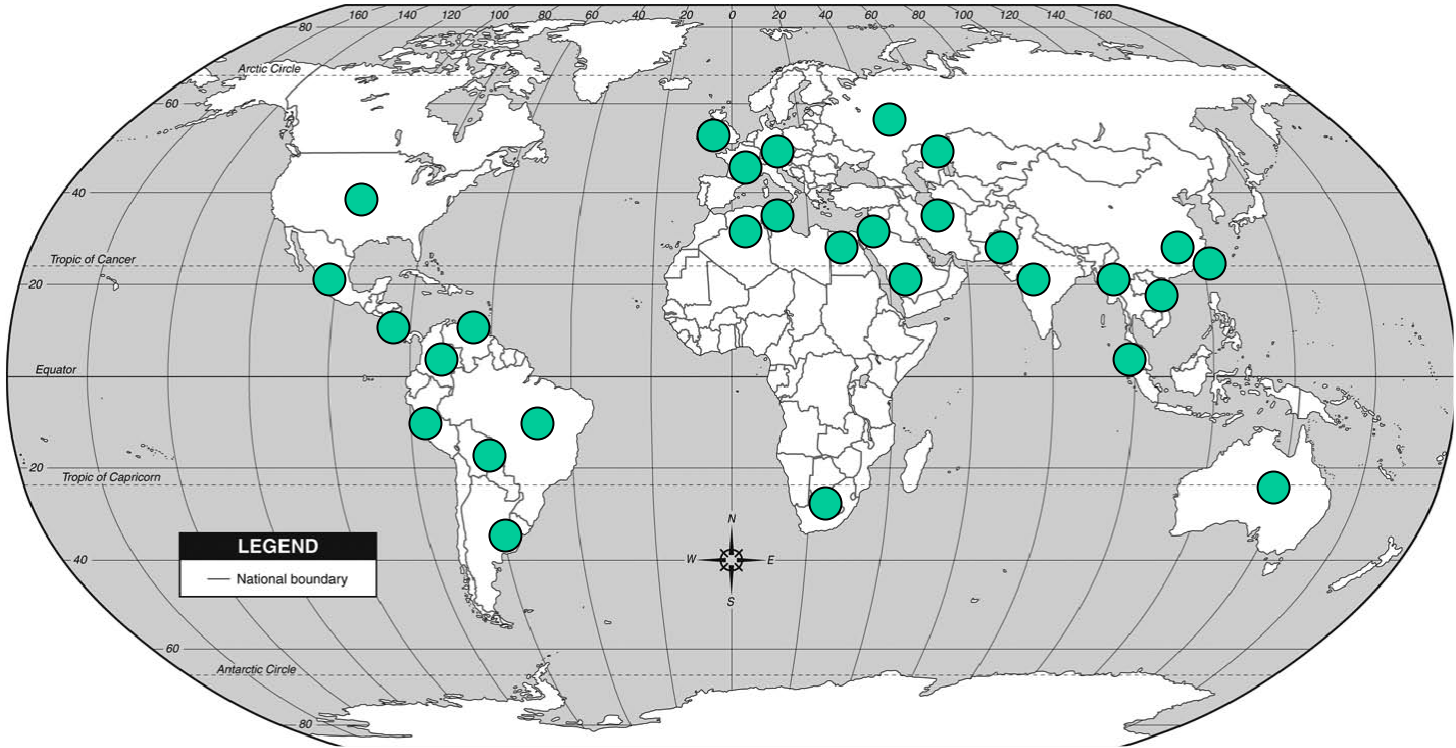
Why are antisera essential?

- 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

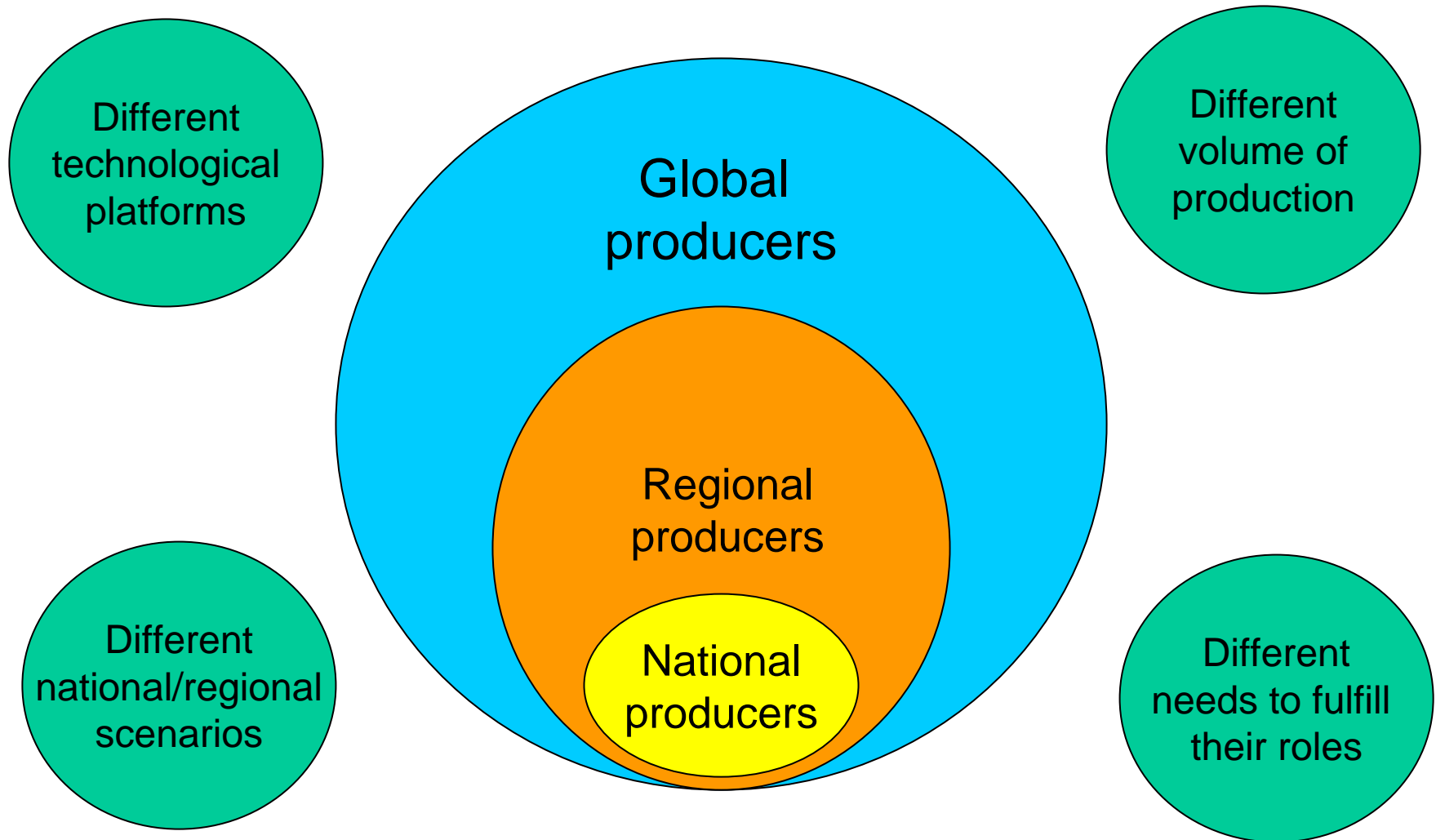


Snake bite victim in Ecuador
Photo: D.A. Warrell

The 'universe' of antisera producers



A heterogeneous *collage* of many actors, all of whom should contribute



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 product

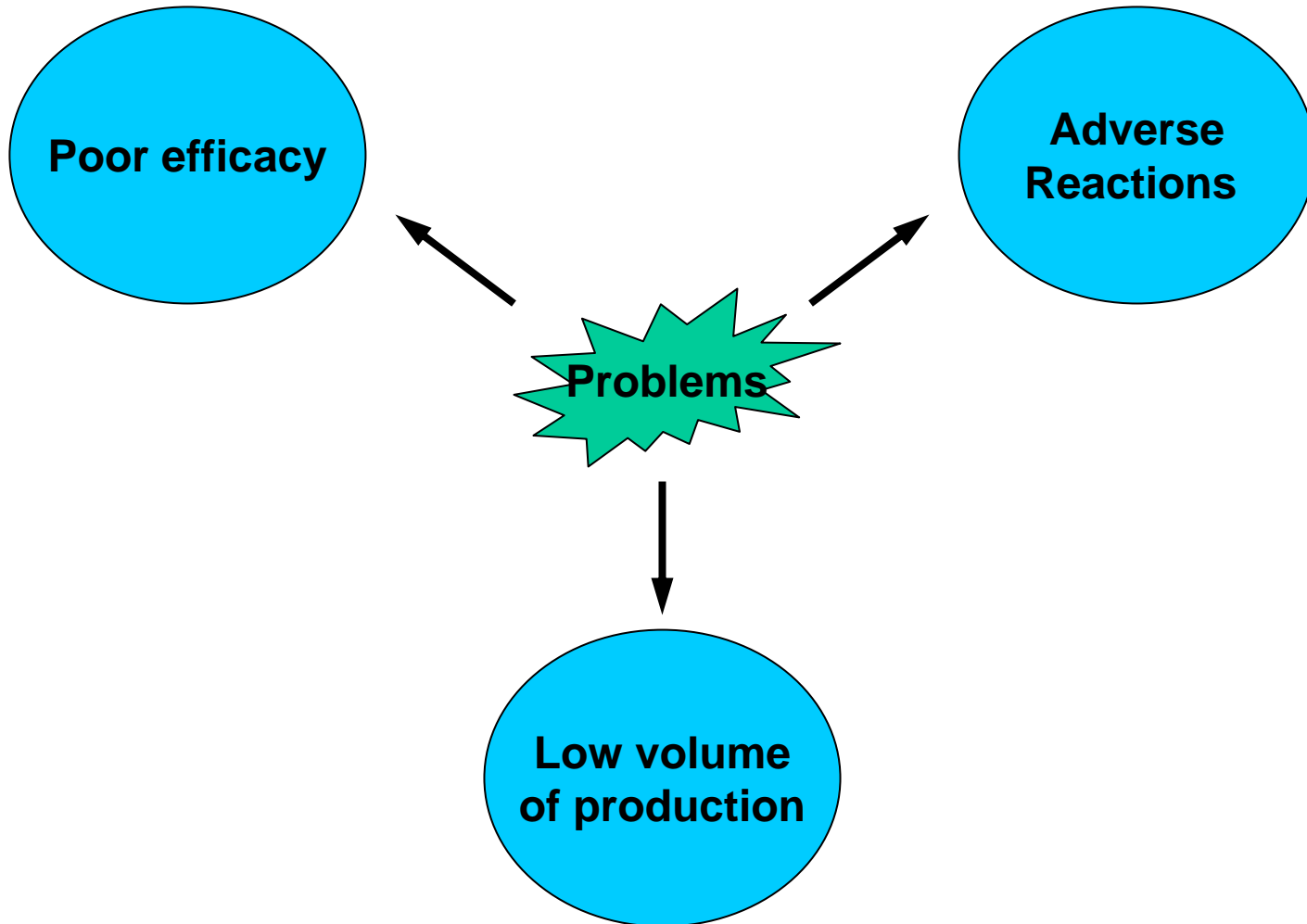


Final quality control

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 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.



Snake bite victims in Ecuador
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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.



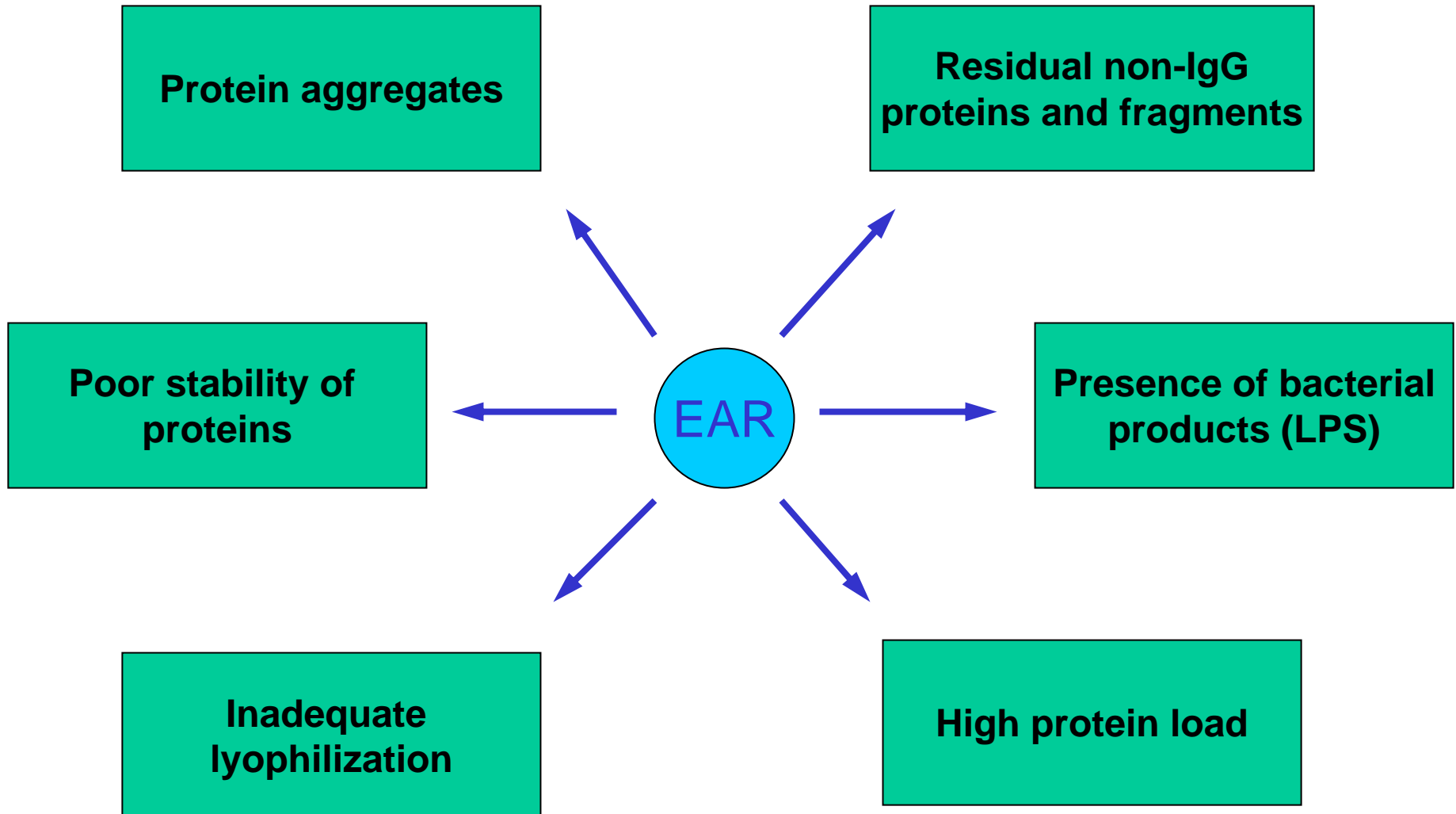
Cutaneous reaction

Photo: Instituto Butantan

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



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.