Rabies post-exposure prophylaxis

David A. Warrell
Scene setting:
Epidemiological and geographical distribution of rabies and envenomings, and the need for more good quality animal derived sera

All images copyright D. A. Warrell
Rabies, snake bite and scorpion sting: what do they have in common?

Essential treatment involves the use of *serum* produced in animals immunised with rabies vaccine or venom.

*hyperimmune serum, antiserum, antivenom, antitoxin*
Clinical applications of animal-derived hyperimmune sera

- **Infections**: rabies, tetanus, diphtheria, botulism, gas gangrene
- **Poisonings**: drugs (digoxin), colchicine, plants
- **Envenomings**: snakes, lizards, scorpions, spiders, bees, caterpillars, fish, jellyfish, ticks
- **Emerging pathogens**: avian influenza, new haemorrhagic fever viruses
- **Bio-terrorism agents**: diagnosis and antidote
- **Immuno-diagnosis**: of all the above
Animal-derived hyperimmune sera

- Raised in horse or sheep
- Refined immunoglobulin
- Liquid preparation or freeze-dried to prolong shelf life in tropical climates

All images copyright D. A. Warrell
Global distribution of **classic rabies** and European and Australian bat lyssaviruses
Human rabies in India in 2005

- 16 million bites
- 18,500-19,700 deaths
- 4 million post-exposure prophylaxis courses

Knobel DL et al. Bull WHO 2005;83:360-8
Human rabies in China in 2006

- 2,600 deaths (30% more than 2005)
- ~8 million post-exposure prophylaxis courses
Annual deaths from human rabies

Global annual total rabies deaths ~56,000

All images copyright D. A. Warrell
Rabies
100% untreatable
100% preventable
with modern post-
exposure prophylaxis

URGENT!

• Wound cleaning
• Passive immunisation
  (rabies immune
globulin - RIG)
• Active Immunisation with
  rabies vaccine

Image copyright D.A.Warrell
Rabies immunoglobulin (RIG): efficacy

- Proved effective in study of 29 Iranian villagers attacked by rabid wolf in 1954
- Neutralises virus inoculated into wound immediately: before it invades nervous system before antibody response to vaccination
- Recommended by all national/international authorities (WHO, CDC, HPA etc) for all category 3 exposures* (~ 65% of all post-exposure courses)

*transdermal bite(s)/scratch(es) or contamination of mucosae with saliva

- Unaffordable and unavailable in most developing countries
Current use of rabies immune globulin (% of post-exposure courses)

- Africa: 1%
- Asia: 6% (Philippines 8%)
- Americas: ?

- **Overall in developing countries:** <1%
Annual Global need for rabies immune globulin (RIG) (post-exposure treatments) if international guidelines were to be fully implemented

- Africa: 600,000
- Americas: 350,000
- Eastern Mediterranean: 200,000
- West Pacific (including China): 9 millions
- SE Asia (including India): 3.2 millions

Total 13.35 millions

**Annual global requirement:**

16 million vials*

* Assuming that 60% of PET courses require RIG, average dose 2 vials/patient
The horror of snake bite!

Spitting cobra bite Nigeria

All images copyright D. A. Warrell
Long term complications of snake bite

All images copyright D. A. Warrell
Snake bite: the global burden of human suffering

- How many bites?
- How many fatalities?
- How many permanent sequelae?
Snake bite: annual global mortality

Swaroop & Grabb 1954
(Bull World Health Organ 1954;10:35–76)
• 500,000 bites
• 30,000-40,000 deaths

Chippaux 1998
(Bull World Health Organ. 1998;76(5):515-24)
• 5 million bites
• 125,000 deaths
• 100,000 severe sequelae
### Estimated annual burden of snake bite envenomings and deaths

<table>
<thead>
<tr>
<th>Region</th>
<th>Bites</th>
<th>Envenomings</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Americas</td>
<td>500,000</td>
<td>200,000 (40%)</td>
<td>4,000 (2%)</td>
</tr>
<tr>
<td>Africa</td>
<td>1 million</td>
<td>400,000 (40%)</td>
<td>20,000 (5%)</td>
</tr>
<tr>
<td>Asia</td>
<td>3 millions</td>
<td>1.2 millions (40%)</td>
<td>60,000 (5%) (India 50,000)</td>
</tr>
<tr>
<td>Oceania</td>
<td>5,000</td>
<td>2,500 (50%)</td>
<td>250 (10%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>&gt;4.5 millions</strong></td>
<td><strong>&gt;1.8 millions</strong></td>
<td><strong>&gt;80,000</strong></td>
</tr>
</tbody>
</table>
Scorpion stings: annual incidence

- México: formerly 300,000 stings, 2,000 deaths/year; now 250,000 stings, <50 deaths/year
- Iran Khuzestan province: 25,000 stings treated/yr fourth major cause of death
- Tunisia: ~ 40,000 stings, ~1,000 hospital admissions, 100 deaths/yr
Scorpion sting in Latin America (*Tityus serrulatus*)

All images copyright D. A. Warrell
Antivenoms for snake bites and scorpion stings

- Antivenom is the only specific antidote
- Effective in saving lives and preventing persistent complications
- Crisis in supply for Africa
Early anaphylactoid reaction to antivenom

- Urticaria, angioedema, bronchospasm, hypotension, shock, vomiting, diarrhoea
- Incidence: 3-84% (pyrogenic 0-100%)
- Rx immediate im epinephrine/adrenaline

Images copyright D.A. Warrell
1.8 million snake bite envenomings/year: therapeutic implications

• Assume each case needs a treatment course of 1-20 (average 5) vials of antivenom
• **Annual global requirement = 9 million vials**
• + guidelines and training for appropriate use
Scorpion stings: therapeutic implications

- Mexico alone records ~250,000 stings and produces 500,000 vials of scorpion antivenom/year
- Globally perhaps >1 million cases needing antivenom treatment/year
- **Annual global requirement for scorpion antivenom, assuming average dose of 1 vial/patient = 1 million vials**
- + guidelines and training for appropriate use
Global requirements for animal derived antisera: summary

• Rabies:
  annual global requirement: **16 million vials of RIG**

• Snake bite and scorpion stings
  annual global requirement: **10 million vials of antivenom**
Rabies, snake bites and scorpion stings kill >200,000 people each year

- Less than one tenth of the deaths attributed to each of the “multi-million killers” TB, HIV, malaria, ARI
- But the the total burden of human suffering attributable to rabies, snake bites and scorpion stings is not adequately reflected merely by the number of fatalities
Contributing to the total burden of human suffering

- Rabid mammal (dog) bites, snake bites and scorpion stings are terrifying and painful
- In the case of suspected rabies exposure, the victim is condemned to a protracted period of anxiety (“Will I develop rabies?”)
- In the case of a snake bite, the victim may be permanently maimed
Conclusions

• Hyperimmune sera are essential drugs for prevention of rabies and treatment of venomous bites and stings (and some other conditions)

• Quantity and quality of global production can be improved by a new WHO initiative