Re-evaluating the burden of rabies in Africa and Asia

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of post-exposure treatments (PETs) for rabies was compared with no PET. Approximately one third of all human rabies PETs are carried out using crude nerve-tissue vaccines. Nerve-tissue vaccines are classified into two groups based on differing incidence rates and clinicopathological signs of adverse reactions. One group was the Semple type (made from phenol-treated sheep-brain or goat-brain tissue), while the other comprised vaccines derived from suckling-mouse brain.

Type of intervention
Primary prevention and treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The target population was the human population at risk from canine rabies. This was taken to be the number of people living in areas affected by canine rabies where the density of the dog population exceeds the threshold density at which canine rabies is capable of being maintained endemically.

Setting
The setting was the community. The economic evaluation was carried out for 48 African countries and 20 Asian countries in four basic scenarios (Africa and Asia, both rural and urban) and two additional scenarios for India and China depending on the data series. The authors reported the full list of the 68 countries in an appendix.

Dates to which data relate
The studies providing effectiveness evidence and utilisation and cost data dated from 1954 to 2003. The price year was 2003.

Source of effectiveness data
The evidence was derived from a review or synthesis of published sources, augmented by expert opinion and authors’ assumptions.

Modelling
Data from African and Asian countries were applied to a series of linked epidemiological and economic models. The human population at risk from endemic canine rabies was predicted using data on dog density. Human rabies deaths were estimated using a series of probability steps to determine the likelihood of clinical rabies developing in a person after being bitten by a dog suspected of having rabies. Full details of the methods used in the dog-bite probability model have been published elsewhere (Cleaveland et al. 2002, see Other Publications of Related Interest- below for
Dog-population densities were inferred from human densities, with adjustments made to account for population growth.

**Outcomes assessed in the review**
The parameters used in the model with their most likely values were:

- the annual incidence of suspect bites from rabid dogs per 100,000 humans;
- the probability of an individual bitten by a dog suspected to be rabid receiving successful PET;
- the probabilities of a bite to the head or neck, an upper extremity (arm or hand), the trunk of the body, and a lower extremity (leg or foot); and
- the probabilities of developing rabies following a bite by a rabid dog to the head, an upper extremity, the trunk, and a lower extremity.

Base-case values and data sources were reported for all parameters, as well as their confidence intervals (CIs) and probability distribution when appropriate.

**Study designs and other criteria for inclusion in the review**
No inclusion criteria were reported. The authors appear to have used several sources and a variety of study designs.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Parameter estimates and confidence distributions were fixed using a three-stage consensus approach within the WHO Burden of Rabies Working Group. First, a workshop was held during which parameter estimates were presented and discussed, and preliminary predictions were made using the model. Second, a comprehensive analysis using agreed upon estimates was conducted, and the model was validated against known data. Third, each participant was sent the results of this analysis, along with the data and assumptions. These were reviewed and adjusted, as appropriate, before final agreement was reached. The final model parameter estimates and distributions were reported as an appendix.

**Number of primary studies included**
The authors reported that approximately 37 primary studies provided effectiveness evidence.

**Methods of combining primary studies**
A consensus approach was adopted to combine the studies, although it was unclear how the synthesis was achieved, if and when such a synthesis took place.

**Investigation of differences between primary studies**
Not reported.
Results of the review
For the base-case, the input parameters of the model were as follows.

The annual incidence of suspect bites from rabid dogs per 100,000 humans was 100 for Africa urban (AfU), 100 for Africa rural (AfR), 120 for Asia urban (AsU) and 100 for Asia rural (AsR).

The probability of an individual bitten by a dog suspected to be rabid receiving successful PET was 0.85 for AfU, 0.60 for AfR, 0.097 for AsU and 0.75 for AsR.

The probability of a suspected rabid dog being confirmed rabid on laboratory diagnosis was 0.64 for African countries, 0.50 for India and 0.38 for other Asian countries.

The point probability of a bite was 0.07 for a bite to the head or neck, 0.38 for one to an upper extremity (arm or hand), 0.06 for one to the trunk of the body, and 0.49 for one to a lower extremity (leg or foot).

The most likely probability of developing rabies following a bite by a rabid dog was 0.45 for a bite to the head, 0.28 for one to an upper extremity, 0.05 for one to the trunk, and 0.05 for one to a lower extremity.

Methods used to derive estimates of effectiveness
The study was based on published data, expert opinion and authors’ assumptions. For the expert opinion inputs, see the consensus methodology reported in the 'Methods Used To Judge Relevance Data' section above.

Estimates of effectiveness and key assumptions
Implicit in the study was the assumption that all human urban populations were at risk in rabies-affected areas.

The total numbers of vaccine doses (i.e. injections) administered and visits made to rabies-treatment centres were derived from national estimates of the proportion of patients receiving treatment who were vaccinated with each schedule, after adjustment to account for patient drop-out during the course of treatment. Few published accounts dealing with treatment-seeking behaviour and compliance could be found, so conservative estimates were made.

Due to the erratic frequency of reporting, national numbers of patients receiving PET annually were averaged over 5 years (1996 to 2000). Countries for which no reports could be found for this period were considered not to have treated any patients. Also because the data suggested that PET for rabies was more accessible and used more frequently in China than in the rest of Asia, the probability of a person being bitten by a suspected rabid dog and receiving PET was assumed to be equally high in both urban and rural settings in China.

Other assumptions about dog vaccination and livestock losses were reported.

Measure of benefits used in the economic analysis
The measure of benefit used was the disability-adjusted life-years (DALYs). To calculate a DALY score for rabies, a direct DALY score (derived from mortality due to the disease) and an indirect DALY score (which accounted for morbidity and mortality following side-effects of nerve-tissue vaccines) were considered. The DALYs were discounted at an annual rate of 3%. Full details were provided in the paper.

Direct costs
For this analysis, the direct medical costs included the costs of biologicals (rabies vaccines and immunoglobulin) and their administration, including materials and staff salaries. The costs associated with the treatment of dog bites and the administration of antibiotics and tetanus immunisations were not included. Discounting was not carried out. The quantities and the costs were analysed separately and were reported in detail. The quantities and the costs were estimated on the basis of actual data and were derived using modelling. The price year was 2003.
Statistical analysis of costs
The costs were treated stochastically. Triangular probability distribution functions were used as an attempt to model the uncertainty surrounding parameter estimates, with range values set as +/- 10% of each parameter's value.

Indirect Costs
The indirect costs included out-of-pocket expenses for patients, such as transport costs to and from treatment centres for rabies, and loss of income while receiving treatment. In addition, the costs to control rabies among dogs, livestock losses, and surveillance costs were included. Discounting was not carried out. The quantities and the costs were analysed separately and were reported in detail. The quantities and the costs were estimated on the basis of actual data and were derived using modelling. The price year was 2003.

Currency
US dollars ($).

Sensitivity analysis
Confidence distributions were assigned to input parameters in order to analyse uncertainty in parameter estimates and inherent parameter variability due to between-country differences. A Monte Carlo simulation procedure was used for parameter distributions sampled iteratively until convergence at <1.5%. A full account of the technical details of the model was reported in an appendix.

Estimated benefits used in the economic analysis
The estimated DALY score per component was 1,787,886 (90% CI: 799,615 to 2,984,109) for total rabies deaths, including nerve-tissue vaccine reactions, for both regions. This corresponded to a total score of 747,918 (90% CI: 217,954 to 1,449,014) for Africa and of 1,039,119 (90% CI: 302,324 to 1,983,646) for Asia. The total number assuming no PET was 9,504,237 (90% CI: 4,848,684 to 15,264,050). Deaths due to rabies were responsible for 1.74 million DALYs lost each year (90% CI: 0.75 to 2.93). An additional 0.04 million DALYs were lost through morbidity and mortality following side-effects of nerve-tissue vaccines.

In terms of human mortality, there were 31,539 deaths (90% CI: 8,149 to 61,425) in Asian countries and 23,705 deaths (90% CI: 6,903 to 45,932) in African countries. There were 55,270 deaths (90% CI: 23,910 to 93,057) in total and an overall number of 1.38 deaths/100,000 people (90% CI: 0.60 to 2.33). The number of predicted deaths in the absence of any PET was 327,160 (90% CI: 166,904 to 525,427).

Cost results
The total estimated annual expenditure for PET costs (in $ millions) due to rabies was $485.0 (90% CI: 443.4 to 530.1), corresponding to $9.1 (90% CI: 8.2 to 10.0) in Africa and $475.9 (90% CI: 435.0 to 520.5) in Asia.

The total estimated annual expenditure for dog rabies control costs (in $ millions) was $86.7 (90% CI: 80.7 to 92.8), corresponding to $9.7 (90% CI: 8.8 to 10.6) in Africa and $77.0 (90% CI: 71.5 to 82.3) in Asia.

Therefore, the total estimated annual expenditure due to rabies (in $ million) was $583.5 (90% CI: 540.1 to 626.3), corresponding to $20.5 (90% CI: 19.3 to 21.8) in Africa and $563.0 (90% CI: 520.0 to 605.8) in Asia.

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors' conclusions
Despite the existence of proven cost-effective control measures, rabies continues to impact upon human health.
Vaccinating domestic dogs against rabies results in a significant reduction in the incidence of bites among the human population from dogs suspected to be rabid, and this control strategy has been shown to be the most cost-effective in the medium-to-long term; the costs are typically recouped within 5 to 10 years, mainly through decreased expenditure on human post-exposure treatment (PET).

CRD COMMENTARY - Selection of comparators
The authors justified their choice of the comparators. You should judge whether these interventions are relevant in your own setting, or whether other comparators from other commonly used control measures and treatments could also be relevant.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. Although this is a common practice with models, it does not always ensure that the best data available are used in the model. The authors used data from the available studies selectively, but included publications from peer-reviewed journals and grey literature sources. One cannot be sure that all relevant literature was identified, although it is positive that the authors made few assumptions. The estimates of effectiveness were derived credibly from the studies identified and the consensus methodology. The authors used data from published sources, expert opinions and their own assumptions. They justified their assumptions with reference to the medical and veterinary literature. The estimates were investigated in sensitivity analyses using ranges from the literature, and the authors justified the ranges selected and reported. The use of probabilistic distributions will help to capture the uncertainty in the parameter estimates, and this should enhance the robustness of the results presented.

Validity of estimate of measure of benefit
The authors used DALYs as the measure of benefits, and these were derived through modelling. The literature source used to derive the disability weights was reported. For the purpose of the analysis of the indirect DALYs for side-effect estimation, years of life lived with a disability were taken as those reported for similar conditions in the medical literature. Sensitivity analyses over adjusted DALYs were conducted and the ranges were reported.

Validity of estimate of costs
The authors reported that the costs were estimated from a societal perspective, thus the indirect costs were appropriately included. Although some costs could have been omitted from the analysis, it is unlikely that these would have affected the authors’ conclusions. To estimate the total direct costs, the authors considered the medical costs and the drug acquisition cost. While these were taken from published sources, the variation among the different countries in the use of resources might have affected the authors’ conclusions, especially since some of the costs and resource use were considered globally. In other cases, countries for which no reports could be found for the period analysed were considered not to have treated any patients; this also might have affected the authors’ conclusions. However, sensitivity analyses of the costs were conducted and reported. Discounting was not carried out, which was appropriate as the long-term costs were not considered.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. The results of the modelling were consistent with those of other studies that had estimated the true incidence of rabies at a national level. The authors’ conclusions reflected the scope of the analysis. The issue of generalisability was addressed by the population and countries selected.

The authors highlighted several limitations of the model. First, the final result was likely to be an underestimate of total mortality and morbidity caused by rabies in these regions, despite an attempt to incorporate the entire range of parameter variability. Second, only deaths due to canine rabies were assessed; the fraction of human cases resulting from exposure to rabid wild animals was omitted. Finally, in determining the number of humans at risk, only populations in areas where canine rabies was endemic were included. This ignored the possibility of sporadic outbreaks
in areas of low dog density or the introduction of the virus into a previously rabies-free population, as has happened in some other cases reported.

**Implications of the study**
The burden of rabies is not evenly distributed across all sectors of society but is influenced by age-related and socioeconomic factors. Even if medical costs are fully subsidised by the government, out-of-pocket patient expenses are still high. Often government subsidies extend only to the provision of cheaper nerve-tissue vaccines, with tissue-culture vaccines being provided only to those patients able to pay for them. There is therefore an income-related risk factor in exposure to the side-effects of nerve-tissue vaccines. This is compounded by occupational and socioeconomic risk factors in the initial exposure to infection, further skewing the burden of rabies towards those sectors of society least able to bear it.

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