Abstracts of the Coral Snake Antivenom Conference, January 28, 2009

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BACKGROUND TO THE CORAL SNAKE ANTIVENOM CONFERENCE, JANUARY 2009.

In March 2007, the American Academy of Clinical Toxicology sent a letter drafted by its Envenomation Special Interest Group to the US Food and Drug Administration (FDA) noting that coral snake antivenom was no longer being manufactured in the United States and would soon be unavailable. The letter summarized the clinical aspects of coral snake envenomation, which made antivenom an integral part of its management. Short- and long-term consequences were explored, leading to the conclusions that: 1) in the near future, coral snake–envenomated patients would either receive antivenom in an untimely manner, receive expired antivenom, receive foreign antivenoms not approved for use in the United States, or not receive antivenom at all; and 2) that there was an uncertain future regarding the development or FDA approval of a new antivenom. Because of the estimated 10% mortality rate prior to the introduction of antivenom in 1967, the near absence of deaths in the 40 years since, and the potential need for long-term intubation and ventilator support in the absence of antivenom, a significant increase in morbidity and mortality rates could be anticipated. Additional discussions with the FDA ultimately led to the convening of this conference, sponsored by the National Institutes of Health Office of Rare Diseases and coordinated through the FDA's Center for Biologics and Research, at which clinicians, basic scientists, venom researchers, antivenom developers, and representatives of regulatory agencies could explore ways to continue to provide US practitioners with coral snake antivenom.

CORAL SNAKEBITE DEMOGRAPHICS, CLINICAL EFFECTS, AND TREATMENT IN THE US, 2001–2005

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Background: Although there have been a few case series and many case reports, there has never been a systematic study of coral snake envenomation in the United States.

Methods: The database of the American Association of Poison Control Centers (AAPCC) was analyzed for the period 2001–2005. Demographics, clinical effects, and treatment of snakebites were compared among the major snake groups of coral snakes, rattlesnakes, copperheads, and cottonmouths. Outcome severity was compared between Florida, Texas, and Arizona.

Results: Over the 5-year period, there were 80 coral snakebites per year reported to US poison centers. Florida had the largest number of human exposures, as well as having the highest number of bites per population. Some coral snakebites occurred far outside of the known geographic range of the snake in the wild. Demographics were similar to other venomous snakebites, including a male preponderance (82%) and a significant portion of bites occurring in children (28%). More than half of coral snakebite victims (51%) were admitted to a healthcare facility, with 42% admitted to an ICU. Although 61% of cases resulted in no or only minor effects, 25% resulted in moderate or greater effects. During this period, in which antivenom was generally available at hospitals in endemic areas, antivenom was used in almost half (46%) of cases. 2% were coded as developing motor weakness and 1% required intubation and ventilation. There were no deaths. Clinical effects resolved quickly, usually within 24 hours, and in less than 3 days

in the vast majority of patients. Outcome codes, as well as intubation rates, were similar between Florida and Texas. Coral snakebites in Outcome codes in Arizona, which has a smaller snake of a different genus, were of minor effects or less.

Discussion & Conclusions: Coral snakebites result in significant morbidity, which has been mitigated by the availability of antivenom. Some envenomations occur far outside of the normal geographic range, posing logistical problems in obtaining antivenom. Rapid availability of antivenom is required over a large geographic area.

CLINICAL AND DEMOGRAPHIC ASPECTS OF CORAL SNAKE ENVENOMATIONS IN FLORIDA

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Coral snakes are elapids and produce predominantly neurotoxicity, manifested by muscle weakness and paralysis, which can progress to respiratory arrest. Antivenom treatment stops progression of paralysis but does not readily reverse it. They have a distinctive coloration pattern, but there are variations and they can be confused with nonvenomous snakes. There is no good biologic marker for envenomations and local tissue effects are present in only about 30% of cases. An illustrative case involved a 39-year-old female who received delayed treatment with antivenom, resulting in respiratory paralysis, intubation, and a prolonged requirement for ventilatory support. Because of the potential for respiratory arrest, and the inability of antivenom to readily reverse venom toxicity, patients have traditionally been treated early in the course following a coral snake envenomation, often in advance of any clinical signs. Using a pharmaco-economic model, the costs of a prolonged ICU stay resulting from delayed treatment outweigh the costs of treating some patients who are not envenomed. According to the database of the American Association of Poison Control Centers, between 2004 and 2009, 234 coral snakebites were reported to the three Florida poison centers. In this time, few hospitals received more than one patient per year, indicating the need for distributed supplies of antivenom and elucidating the difficulty in setting up controlled trials. With the impending loss of coral snake antivenom, ongoing distribution of antivenom to Florida hospitals is problematic. Currently, the Miami-Dade fire department maintains a sufficient supply of coral snake antivenom to treat envenomations within the state.

CLINICAL AND DEMOGRAPHIC ASPECTS OF CORAL SNAKE ENVENOMATIONS IN TEXAS

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Texas coral snakebites account for approximately 35% of the nearly 100 coral snakebites reported to US poison centers each year. It is likely that coral snakebites are undercounted, given that reports to poison centers are voluntary and practitioners in endemic areas who are familiar with treating them may not contact poison centers for assistance. Comparative studies in recent years suggest significant differences in venom LD50 and clinical envenomation signs and symptoms between the Texas coral snake (*Micrurus tener tener)* and the larger Eastern coral snake (*M fulvius fulvius*). Although venoms from both species contain alpha-neurotoxin and phospholipase A2, *M t tener* envenomation reportedly tended to produce more local effects, while ptosis and bulbar signs were the most common neurotoxic effects reported in *M f fulvius* envenomations. Progression to respiratory compromise requiring ventilator support has been reported only in *M f fulvius* envenomations. In one rat study, *M f* fulvius–specific North American coral snake antivenom was effective in neutralizing *M f fulvius* venom, but not *M t tener* venom, while a (Fab)2 antivenom specific against *Micrurus nigrocinctus nigrocinctus* (black-banded coral snake) was effective against both. The optimal strategy for evaluation and management of potential *M t tener* envenomations has not been definitively established.

CURRENT AND POTENTIAL FUTURE CORAL SNAKE ANTIVENOM PRODUCTS: CHALLENGES TO STUDY AND LICENSURE

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Background: As Coral Snake Antivenom, Wyeth™ (CSAW) supply dwindles, toxicologists seek safe, effective alternatives. Challenges include: vast geography, low incidence, species differences, costly studies and commercialization.

Geographic Region Affected: Coral snake bites involve the Southeast and Southern United States, *Micrurus fulvius fulvius* inhabiting Florida, the Carolinas, Georgia, Mississippi, and eastern Louisiana, while *Micrurus tener tener* is found in western Louisiana and Texas. The bites involve hundreds of hospitals, making stocking of antivenoms problematic. Bites often occur in rural areas and treatment is often sought too late.

Incidence: Bites are rare. In Texas, from 1998 to 2007, 210 coral snake bites were recorded, about 21/year. The National Poisoning Data System (NPDS) reported 58 to 90 coral snake bites/year from 2005 to 2007, with few major outcomes and no deaths.

Antivenom: A "hub-and-spoke" arrangement could alleviate geographic challenges. Poison centers could serve as "hubs" for the study, helicopters serving as the "spokes" to reach out to peripheral hospitals, treating in place or transporting to the hub. This might eliminate some Institutional Review Board reviews and myriad investigators. Sanchez et al. have demonstrated a potency ratio of 2.8:1 in favor of *M fulvius fulvius* over *M tener tener,* with the consequence that any clinical efficacy trial would have to account for the species involved and its particular toxicity.

Efficacy Studies: NPDS data suggest serious outcomes are on the order of 4%. One would need thousands of patients to detect improvements in outcomes with a new antivenom. In short, it appears next to impossible to demonstrate efficacy of coral snake antivenoms in humans. Proving efficacy under the "animal rule" (21 CFR 601 Subpart H) is viewed by FDA as a last resort. Equivalence must be shown between animal and human pharmacokinetics and "pivotal" studies must be done under Good Laboratory Practices (GLP), greatly increasing costs. Approving a new antivenom will cost several million dollars. With less than a hundred bites per year, a financially viable product is doubtful.

Conclusions: CSAW will be exhausted as early as 2010. The economic and research challenges ahead are manifold. Solution will require beneficence of the manufacturer, hard work by researchers, flexibility by the FDA, and undoubtedly, money.

ANTIVENINS WITH ANTI-CORAL SNAKE VENOM ACTIVITY: EFFICACY AGAINST *MICRURUS FULVIUS* VENOM IN ANIMAL MODELS

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Principal toxic components of *M fulvius* venom are α-neurotoxins. Limited amounts of neurotoxic and myotoxic phospholipases A2 are also present. The intraspecial variability of the venom should always be considered in antivenin production as well as in testing of antivenin efficacy. Two antivenins, Coralmyn from Inst. Bioclon (Mexico) and Anticoral from Inst. Clodomiro Picado (Costa Rica), were shown highly effective to neutralize lethal effects of *M fulvius* venom in mice (Arce V et al., 2003; de Roodt AR et al., 2004; Wisniewski MS et al., 2003; Sanchez EE et al., 2008). The Anticoral was also shown to neutralize myotoxic activity of *M fulvius* venom in mice (Arce V et al., 2003); no results on Coralmyn are available in this respect. Although both antivenins, Coralmyn and Anticoral, are produced using *M nigrocinctus* venom as an immunogen, it was demonstrated that *M nigrocinctus* and *M. fulvius* venoms are antigenically similar (Bolanos R et al., 1978; Alape-Giron A et al., 1994; de Roodt A et al., 2004). In addition, the Australian Tiger Snake Antivenom *(Notechis scutatus)* from CSL (Australia) was also effective in preventing death from *M fulvius* venom in mice (Wisniewski MS et al., 2003). Due to a highly conserved structure of α-neurotoxins in *Elapidae,* it is likely that some other anti-elapid antivenins will also be effective to neutralize lethal effects of *M fulvius* venom, and possibly its myotoxic activities.

All presented studies were done only in mice. Neutralization of lethal and myotoxic effects of *M fulvius* venom was tested by preincubation of the venom with antivenin prior to administration. Thus, data from these experiments have limited value for predicting clinical efficacy. Further preclinical testing, including a post-exposure treatment animal model, may be useful.

Disclaimer: The findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

LESSONS AND CHALLENGES: CONDUCTING SNAKE ENVENOMATION CLINICAL TRIALS

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Background: Although antivenom is currently approved and actively produced in the United States for the most common envenomations for which antivenom treatment is indicated. (see table) However, scorpion antivenom is currently available only as an investigational drug, antivenom for coral snake envenomation is no longer produced, and no antivenom is FDA-approved to treat envenomation by non-native snakes.

Table 1

Envenomation Type	Patients Seen in HCF per Year	Antivenom Status
Crotalid snake	3,500	Available*
Black widow spider	2,500	Available*
Scorpion	1,500	Phase 3 trial
Coral snake	100	No longer manufactured
Exotic snake	50	None approved

** Approved AV available, and new Fab2 in phase 3 trials*

Antivenom Development: Studies of low-incidence envenomation face unique challenges. Patients cannot be recruited in advance. Even tertiary referral centers rarely see more than 10–20 patients per year, many of whom may have received antivenom prior to transfer. Anxiety, intoxication, language barriers, and physician factors pose a barrier to informed consent. Referral of patients for possible study enrollment requires "partial exemption" to HIPAA confidentiality requirements be obtained from each referring institution. Transfer of patients for research purposes prior to informed consent is ethically difficult, and the costs of such transfers are significant. Follow-up for safety and long-term outcome is difficult in a setting where there is no ongoing physician-patient relationship and costs of travel and time off work are burdensome to patients. Multicenter research involves severe logistical hurdles involving multiple IRBs, institutional concerns, mandatory site visits, protocol deviations, data quality, and coordination of adverse event reporting. Given these realities, it is difficult to conceive a prospective human clinical trial of coral snake antivenom that could be completed with adequate power before the current supply of Wyeth coral snake antivenom is exhausted.

Potential Solutions: Potential solutions might involve approval of antivenom via the Animal Rule, and/or a structured compassionate use program that incorporates active safety surveillance. Any rules developed to address this problem should take into consideration the effect these rules would have on access to non-native snake antivenoms.

SCORPION ANTIVENOM TRIALS IN ARIZONA: LOGISTICS AND LESSONS

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Background: Management of the recent scorpion antivenom shortage in Arizona provides a model of public health response, in circumstances analogous to the current coral snake antivenom shortage. Like coral snake venom, scorpion venom causes neurotoxicity in fewer than 300 US residents annually, and without specific treatment in these cases intensive supportive care is necessary. The goals in Arizona included both product licensure and patient care. Critically ill patients at geographically isolated primary care hospitals required rapid treatment, while the small number of cases presenting to tertiary care sites were eligible for enrollment in a controlled clinical trial.

Scorpion Antivenom Project: Careful endpoint selection enabled study design for a very small "n." Multiple protocols were established allowing for prospectively controlled studies at tertiary sites, historically controlled studies at selected secondary sites, and a simple treatment protocol at sites with compelling patient care needs. A university-based clinical team worked closely with the INDA sponsor, state government, and the FDA to complete this set of studies in a coordinated fashion. Distribution of the investigational antivenom was accomplished through collaboration among the central team, the INDA sponsor, and a contract distributor. Regulatory support, IRB oversight, data management, analysis, and reporting required for compliance with Biological License Application (BLA) standards proved to be costly and complicated; but cost savings from reduced need for helicopter transport and intensive care more than offset the cost to citizens of Arizona.

Results: Over the course of 6 years, over 600 patients were enrolled in the studies, a large enough population for safety analysis in addition to the smaller subset that provided critical efficacy data. From conception to BLA submission, the scorpion antivenom project has taken 10 years. Funding for the study network came from federal and state grants, state legislative appropriations and private contracts.

Conclusions: Overall, the Arizona scorpion antivenom experience demonstrates that it is possible to conduct methodologically defensible, geographically diffuse clinical trials of antivenom. Accomplishing similar goals for coral snake antivenom is likely to be

more difficult, because fewer patients present across a wider geographic range. In particular, study endpoint selection, IRB considerations, funding, and distribution logistics will be more challenging for coral snake studies.

ANTIVENOM LICENSURES, HISTORICAL AND ONGOING

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Background: Historically, antisera and antivenoms in North America have included named-donor blood transfusions, whole serum infusions, whole immunoglobulin preparations, and Fab and F(ab')2 fragments, from a variety of vertebrate biological sources. Before 1960, whole-IgG preparations from horse, rabbit, and cat serum were marketed or distributed by Merck, Wyeth, Arizona State College, various serpentaria, MYN, Zapata, and the Mexican Instituto de Higiene, with sales across the US-Mexico border known to occur but not formally tracked. During the years 1960–1990, sales across the border slowed essentially to a halt as manufacturers on both sides merged and modernized processes in response to changing regulations and manufacturing standards. By the end of this period, the United States had three licensed antivenoms: Merck's black widow product, Wyeth polyvalent anticrotalidae, and Wyeth anticoral, all equine IgG antivenoms. In Mexico, MYN and Zapata had merged to form Pharma, and the Institute of Hygiene had transitioned to become Birmex, also producing a variety of whole-immunoglobulin antivenoms. Beginning in the 1990s, there has been only one antivenom approved in the United States: CroFab, an ovine Fab for treatment of Crotaline viper envenomation. In Mexico, Bioclon (which subsumed Pharma) and Birmex have converted operations toward exclusive manufacture of F(ab')2 or mixed Fab/F(ab')2 preparations, including antivenoms against scorpion, spider, pit viper, and coral snake envenomations.

Ongoing: Today, CroFab is the only licensed product in widespread US distribution, with both Wyeth-Ayerst products out of manufacture and the Merck Latrodectus in short supply. Clinical trials are underway for scorpion, black widow, and pit viper antivenoms manufactured by Bioclon; but no other company has active studies listed under Clinicaltrials.gov. No antivenom for coral snake bite is currently under study, and economic and design considerations make it unlikely that any manufacturer will find it cost effective to sponsor a formal INDA under current laws and regulations. Some combination of animal model, surrogate endpoint monitoring, and expedited approval with Phase 4 monitoring may be necessary if the United States is to attract a manufacturer to fill this rare, but critical, need.

CLINICAL TRIALS FOR CORAL SNAKE ANTIVENOM: TREATMENT OUTCOME MEASURES AND SURROGATE ENDPOINTS (LABORATORY OR CLINICAL)

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Envenomation by coral snakes has the following characteristics: (1) In the United States, fewer than 100 cases are reported per year and most patients present for care within a few hours of snakebite. (2) Not all bites by positively identified coral snakes result in venom injection (scratches or dry bites). (3) Not all "slender and colorful snakes" are actual coral snakes (false coral snakes), therefore no neurotoxicity is expected even if they bite. (4) The mean time to the onset of neurotoxicity is thought to be around 3 hours (range 30 minutes to 12 hours). (5) Neurotoxicity, once established, is considered to be refractory (to an unknown extent) to treatment by antivenom. (6) Before the introduction by Wyeth of North American Coral Snake Antivenin, mortality was 10% (less by some authors), whereas after no deaths have been recorded. Therefore, how do we determine if treatment by antivenom is of therapeutic value? Points 2 and 3 require that we identify those patients at risk of developing a significant envenomation. At the same time, we must evaluate the potential for prevention of neurotoxicity, since points 4 and 5 necessarily imply that there is a variable amount of time for onset of symptoms and that rescue may not be an indicator of antivenom effectiveness, respectively.

Plasma venom levels have not been used routinely as endpoints in human studies of envenomation. However, several studies suggest that venom levels may be valuable for monitoring the suppression of venom antigenemia and for developing correlations with ongoing venom toxicity. In addition, the presence of detectable venom at baseline (albeit retrospectively) serves as a confirmation of the validity of clinical diagnosis of the envenomation syndrome, and its disappearance following antivenom treatment supports the expectation that antivenom works by binding venom and removing it from availability. We propose, as pointed out by Dr. David Theakston more than a decade ago (*Ann Trop Med Parasitol*. 1997, 91:857–865), that the disappearance of venom antigenemia following antivenom administration is a surrogate endpoint to measure accurately the efficacy of antivenom.

SUPPORT AND INCENTIVES FOR DEVELOPMENT OF CORAL SNAKE ANTIVENOM

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A number of challenges face a sponsor hoping to develop a coral snake antivenom, including the expense of developing the new drug for an uncommon condition. Because rare diseases and conditions such as coral snake envenomations affect a small number of people, drug companies may initially demonstrate limited interest in performing research or development of new products to treat such uncommon conditions. The Orphan Drug Act offers a drug developer financial benefits and incentives in exchange for performing research and development and fulfilling requirements to get a drug approved for a rare disease or condition. The benefits help manufacturers recover the costs of developing a drug for a small number of people. These financial benefits and incentives associated with that under the Orphan Drug Act include:

- Grant funding to defray the cost of clinical testing
- Tax credits for the costs of clinical research
- 7-year period of exclusive marketing after an orphan drug is approved
- Waiver of Prescription Drug User Fee Act (PDUFA) filing fees (over $1,000,000 per application for FY 2009)

A developer of a new coral snake antivenom would be urged to take advantage of the benefits from the Orphan Drug Act and apply for an Orphan Drug Grant and Orphan Drug Designation. Orphan grant proposals to support human clinical trials are accepted once per year, generally in February, and are announced in a Federal Register Notice which can be found at www.fda.gov/orphan. The grant awards can be for up to $200,000/year for up to 3 years for a Phase 1 study or up to $400,000/year for up to 4 years for a Phase 2 or 3 study.

Orphan Drug Designation can be applied for once a rationale is determined for the use of the drug for the proposed indication/disease and a justification that the prevalence is below 200,000 in the United States. Having a designation permits the use of tax credits for clinical research in obtaining safety and efficacy data to support marketing as well as receipt of the waiver of PDUFA Users Fees and 7-year marketing exclusivity once approved. These incentives have proven highly successful for developing products for rare conditions such as a new antivenom product.

POTENTIAL REGULATORY PATHWAYS FOR CORAL SNAKE ANTIVENOM LICENSURE

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FDA regulations define licensure pathways for products, and all licensures require a demonstration of clinical efficacy and safety. Orphan products have been licensed under these requirements, but it is challenging to identify a specific strategy that optimizes the time to licensure and economic feasibility. The four frameworks under which products can be licensed are:

Table 2

Conventional licensure[1]	Safety and efficacy demonstrated in clinical trials
Conventional licensure with surrogate endpoint[2]	Efficacy demonstrated in humans by effect on an endpoint validated shown shown to be a marker predictive of clinical benefit (e.g., cholesterol levels as a surrogate for coronary artery disease/angina/myocardial infarction); safety studies in humans
Accelerated approval[3]	Licensure based on an endpoint that is "reasonably likely" to be a surrogate marker of clinical benefit, safety studies in humans. Postmarketing study required.
Animal efficacy[4]	Licensure based on efficacy in an animal model, and safety studies in humans; *only* in cases where human studies are "not ethical or feasible," and cannot be used if any other licensure mechanism could be used. Postmarketing study required.

1. *Code of Federal Regulations: 21 CFR Part 314, Subpart D (21 CFR 314.126)*
2. *Discussed in the Federal Register, volume 57, No. 239, December 11, 1992: 58942–58945*
3. *Code of Federal Regulations: 21 CFR Part 601, Subpart E*
4. *Code of Federal Regulations: 21 CFR Part 601, Subpart H*

Challenges to Coral Snake Antivenom clinical studies to support licensure include a very low incidence of envenomations, unpredictable location of patients, need for urgent treatment to prevent neurological progression, validation of surrogate markers for efficacy, and lack of systematically acquired historical control data in treated or untreated patients. Proposed surrogate markers for efficacy have included 1) effect on venom levels in patients, as correlated with lack of onset/progression of neurological symptoms, and 2) pharmacokinetics (PK) in humans related to PK and efficacy in animal models. In either case or for yet-to-be-proposed surrogates, FDA may consider seeking advisory opinions. To assure availability in the absence of any licensed product, use of an investigational antivenin under IND can be achieved through treatment use programs.[1] Licensure may be facilitated by use of the fast track process and priority review timelines.[2]

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References:

1. Code of Federal Regulations: 21 CFR Part 312, Subpart B, (21 CFR 312.34–35)
2. At www.fda.gov/oashi/fast.html (accessed February 11, 2009)