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CONCEPTS

The "Worldwide Shortage" of Antisnake Venom: Is the Only Right Answer "Produce More" Or Is It Also "Use It Smarter?"

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A frequent tenet of snakebite literature is what has been described as the ''worldwide shortage of antisnake venom'' (ASV) and the demand for greater production. Antisnake venom is the mainstay of snakebite management, and thus this principle of ''shortage'' can impact the view of policy makers when it comes to framing solutions to the problem. This paper presents a model to enable policy makers to assess the amount and utilization of ASV in their areas. The model assesses ASV usage according to 2 criteria: risk and wastage. The actual usage of ASV is segmented in the model into the following main areas: (1) victims who receive too little ASV (high risk/low wastage); (2) victims who receive ASV either unnecessarily or in too great a quantity (low risk/high wastage); (3) victims who receive ASV that is not effective (high risk/high wastage); (4) victims who receive ASV according to effective local protocols (low risk/low wastage). The current proposition about the ''shortage'' of ASV and the proposal to simply produce more addresses only a small part of the high-risk/low-wastage group and does not address the 2 high-wastage groups. Until the high-wastage groups are recognized and resolved with training and local protocols and moved into the low-risk/low-wastage group, the true requirement for ASV worldwide cannot be assessed.

Key words: snakebite, snake envenomation, antivenom, policy maker, model, developing world

Introduction

One of the frequent tenets of snakebite publications is that there is a worldwide shortage of anti snake venom (ASV).[1–3] Papers have been published and consultative meetings have been held to determine how this perceived problem can be overcome. Not unsurprisingly, increasing production and quality of ASV is the key recommendation, accompanied by a brief reference to increasing training in the management of snakebites.[4] A recent World Health Organization (WHO) meeting in Geneva, including a significant number of ASV manufacturers, again unsurprisingly, echoed this view.[5]

According to WHO published statistics, the 2 countries with the largest annual snakebite mortality in the world are India, with 50 000,[5] and Pakistan, with 20 000.[6] Together, these 2 countries constitute approximately 55% to 85% of overall world snakebite mortality, depending on the overall mortality figure used.[5,7] An extensive review of the situation regarding supply and usage in these 2 countries has led to the development of a model that can be used by policy makers and health officials to determine the actual supply/demand position in their areas. It can also assist those interested in snakebite research or treatment to assess current practice relating to ASV utilization. The purpose of this article is to present an ASV utilization effectiveness model.

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The ASV utilization assessment model

The current argument for increasing the supply side of the ASV usage equation focuses almost entirely on pro-

viding more and better quality ASV.[8] However, there is evidence that there is overuse of currently available ASV on the demand side that could fulfill some of the perceived shortfalls, but this is not being considered as part of the debate.[6] To assess the adequacy of the current ASV supply, it is useful to reconsider the relationship between supply and demand. The appropriateness of supply is only achieved if it matches or slightly exceeds demand. This is the optimal position in terms of volume of supply, cost of supply, and risk. In cases where supply is less than demand, risk clearly ensues in terms of patient care.

The balance between supply and demand can therefore be viewed as one between risk and wastage. The ideal state is one that minimizes both risk and wastage. Patient care is maximized in an environment of minimal wastage of resources that could otherwise be deployed elsewhere in the medical system. The ASV usage model is thus based on determining the current uses of ASV and plotting them against the axes of risk and wastage to identify areas where risk is minimized and wastage reduced such that the supply and demand for ASV can be optimized. The model is shown in the Figure and contains 4 quadrants based on the correlation between risk and wastage. Both risk and wastage are categorized as high or low.

Risk

High risk is defined as ASV under-usage that increases the probability of a poor patient outcome. In any use of ASV in treating snakebites, there is an underlying risk in that the initial dose may not be effective in neutralizing the venom injected at the time of the bite. The variability of venom injected results in a level of uncertainty that is normal during snakebite treatment, and the use of rational initial and repeat doses solves this problem. The correct initial or repeat dose is defined as that based on a level intended to neutralize the amount of circulating venom present at the time of ASV administration. In the case of the initial dose, it represents the average amount of venom injected by the species. High risk is thus defined as an ASV dosage or repeat dosage strategy that is below the correct level either due to unavailability of ASV or for some other cause. Low risk is defined as a quantity that is in line with the optimal profile of ASV usage.

Wastage

High wastage is defined as an ASV dosage or repeat dosage that is above the correct or optimum level as defined above. This may be the result of ASV being administered to a patient who has no need or by using an amount of ASV in excess of the required level.

Quadrants of the model

The actual usage of ASV is segmented in the model into the following quadrants:

1. Victims who receive too little ASV (high risk/low wastage);
2. Victims who receive ASV either unnecessarily or in too great a quantity (low risk/high wastage);
3. Victims who receive ASV that is not effective (high risk/high wastage); and
4. Victims who receive ASV according to effective local protocols (low risk/low wastage, ie, the optimal condition).

The model examines the impact on ASV usage methodology, diagnostics, timing, and supply within each quadrant and outlines the current situation.

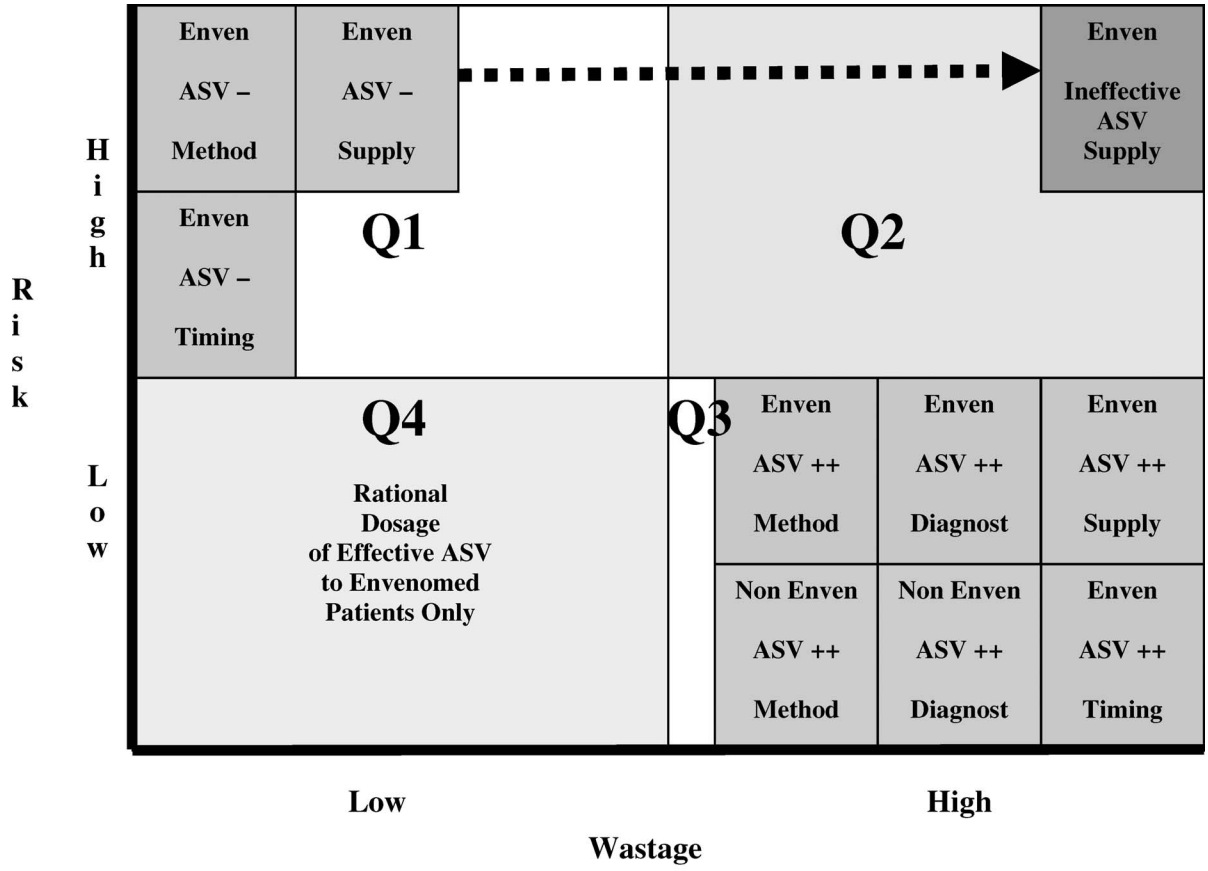
Quadrant 1: High-risk/low wastage group

The premise of the high-risk/low-wastage group is that ASV is either not available when required for a definitive envenomation or that it is available but used in insufficient quantities to neutralize the circulating venom load for a variety of reasons. It is useful to further segment this category into a number of causes.

METHODOLOGICAL CAUSES

The methodology adopted by the physician in treating snakebites will determine each activity performed during treatment. This methodology or protocol will be the result of medical training and training gained as a result of working with seniors and colleagues. Medical education in both India and Pakistan is heavily dependent on textbooks produced in the Western developed world.[9–11] These general textbooks, some with recommendations specifically intended for use only in the United States, are supplemented by local textbooks that, in the case of India and Pakistan, are written by authors with forensic medicine or community medicine training.[12,13] Forensic medicine specialists have virtually no experience in treating patients resulting from an envenomation and thus their work tends to repeat ''accepted'' methods that they themselves were taught by forensic medicine tutors.

A further source of guidance is the product guideline (package insert), included by the manufacturer, with each vial of ASV. Indeed, some authors have recommended using these guidelines to determine ASV dos-



Key

Enven.	**Patient is Envenomed**
Non Enven.	**Patient is Not Envenomed**
ASV ++	**Patient has received ASV above the correct or optimal level**
ASV –	**Patient has received ASV below the correct or optimal level**
Method	**Methodological/ Protocol Driven Causal**
Diagnost	**Incorrect Use of Diagnostic Tools Causal**
Timing	**Timing of Initial and Repeat Doses Causal**
Supply	**Supply/ Availability Causal**

Figure. ASV utilization assessment model of risk and waste. Enven indicates patient is envenomed; Nonenven, patient is not envenomed; ASV++, patient has received ASV above the correct or optimal level; ASV−, patient has received ASV below the correct or optimal level; Method, methodological/protocol drive causal; Diagnost, incorrect use of diagnostic tools causal; Timing, timing of initial and repeat doses causal; Supply, supply/availability causal.

age.[10] The poor quality of these guidelines has been highlighted previously.[14]

The use of inappropriate western textbooks, textbooks written indigenously by nonsnakebite specialists, and/or product guidelines directly affects the methodology approach to ASV dosing strategies in snakebite management. For example, the most widely used western textbook recommends a starting dose, in cases of mild envenomation of 0 to 5 vials of ASV,[10] and ASV package inserts recommend a starting dose of 2 vials.[14] In both India and Pakistan, current optimal initial doses of ASV are 8 to 10 vials.[9,15] Victims given ASV in the 0 to 5 vial range as the result of either western or product manufacturer recommendations will have lower levels of circulating venom neutralized, with the result that more venom is available to bind to target tissues.[13,16–20] This U.S. dosing strategy is also used in other countries in addition to Pakistan and India, and often the U.S. source is cited.[18,21–26] Risk is thus increased.

TIMING CAUSES

In the case of timing of ASV administration, clearly the ideal situation is that ASV should be administered to an envenomed patient early enough to enable it to neutralize the entire amount of circulating venom. If ASV administration is delayed to an envenomed patient, greater quantities of venom will be circulating unopposed. In both India and Pakistan, ASV administration is frequently carried out on a daily basis. Each day, typically first thing in the morning, coagulation tests are carried out, and the results determine whether ASV is administered. No further tests are done until the next day. The result is that any remaining, unbound, unneutralized venom will be unopposed until the next coagulation test the following day. During that period it is highly likely that the venom will bind to target tissues and thus be unavailable for neutralization with ASV. In this case, the risk of unattached venom causing major damage, particularly hemorrhagic damage, is greatly increased.

SUPPLY CAUSES

There are undoubtedly cases where ASV is unavailable due to no supply or cost levels that are unsustainable for the government, hospital, or victim in cases where ASV is not funded by government hospitals. There are empirical findings of this in the published literature.[27] The difficulty with these findings is determining whether the shortage is localized to that particular study area (ie, a specific shortage in that hospital or district) and what the usage profile is in other hospitals in that area. If ASV is available elsewhere but being used in inappropriate ways, then the shortage must be assessed in light of this.

Quadrant 2: High-risk/high-wastage group

The high-risk/high-wastage group is extremely significant, and the twin consequences of high risk and high wastage determine that it is a key focus for policy makers in solving snakebite management issues. This quadrant is often triggered in direct response to the high risk/low wastage quadrant in so far that where shortages of ASV are perceived, it is tempting for policy makers to decide to import ASV from other countries to use locally without any appreciation of the possible consequences.

Indian ASV is used in many of the neighboring countries that either have no production facilities or produce less ASV than is currently demanded. It is also used in Africa,[15,28] which does not have any of the species used in production of the ASV.

For example, in the Tharparker District of Pakistan, province funds were allocated directly to the district to purchase medical supplies. Due to the perception that the indigenous producer, the National Institutes of Health in Islamabad, could not meet demand, 14 000 vials of Indian ASV were purchased by the purchasing authorities. However, doctors in Tharparker regard the Indian ASV as having greatly reduced effectiveness against Pakistani snakes and simply use double or much higher doses. ASV had previously been imported from Saudi Arabia and Korea!

There is little doubt that locally produced ASV, manufactured using snakes from the local area, is the most effective strategy and emphasis should be placed on this option where available.

The problem of ineffective ASVs is exacerbated by the presence of fake or counterfeit ASVs, produced by unscrupulous manufacturers in response to the supply shortage and perception of ready revenue.[29] The net result in areas that import ineffective ASVs is that there is no strategic shortage of ASV—there is plenty available. Rather, there is a tactical shortage of effective ASV. ''Shortage'' is a term that is frequently used and yet the issue is rather more complex than simply the number of available vials of ASV.

Quadrant 3: Low-risk/high-wastage group

The low-risk/high-wastage group, as its name suggests, mainly concerns those victims who receive ASV when it is not required at all (eg, a nonenvenomation or bite by a nonvenomous snake) or who receive ASV in dosage levels that are excessive. In both cases, resultant risk is low given that poor patient outcome is very unlikely.

It is the prime responsibility of policy makers to ensure that appropriate quantities of ASV of proven effectiveness against local species is readily available to treat envenomed victims. The role of the ASV utilization effectiveness model is to assist policy makers in arriving at the appropriate level, balancing risk and wastage. Again, there are a number of practices that account for such excessive or unnecessary administration.

METHODOLOGICAL CAUSES: NONENVENOMED PATIENTS

Methodological weaknesses not only contribute to inadequate use of ASV, they also contribute to ASV being used unnecessarily. The most frequent case of methodological issues causing patients to receive unnecessary ASV is when they are nonenvenomed. A prime cause of this is the use of protocols based on western textbooks.[10] These textbooks advocate the administration of ASV based on western snakes or protocols that emphasize local swelling as a criterion for administering ASV. In the developing world, purely local swelling is not grounds for administering ASV, as many nonvenomous species, scorpions, centipedes, wasps, and thorns are capable of causing swelling.[18,20,25,30] The potential negative consequences of misusing U.S. criteria in determining envenoming have been additionally noted in China.[31]

Further evidence of overuse of ASV can be found in published articles where large percentages of patients admitted to hospital with snakebites are given ASV.[19] With nearly 80% of snakebite victims in India being from nonvenomous species or dry bites from venomous species, high percentages of patients receiving ASV is a good indication that it is potentially being overused.[9]

Methodological problems also arise with reference to specific types of envenomation. For example, neurotoxic victims are often given ASV purely on the history of the bite. If the snake is a confirmed to be a cobra, krait, or mamba, some authors have recommended starting ASV in the absence of any other symptoms.[10,32,33] Fear of rapid action of the neurotoxic venom and life-threatening respiratory failure results in patients being given ASV when there is no evidence that they have been envenomed. However, the likelihood of a patient not being envenomated is still very high. Exposing the victim to the risk of anaphylactic reactions without evidence of envenomation is not justified. ASV should only be administered when definitive evidence of envenomation such as ptosis or neurologic impairment is present.

METHODOLOGICAL CAUSES: AMBIGUOUS CRITERIA

The inclusion of criteria such as acute renal failure, elevated serum creatinine, or oliguria as grounds for administering ASV cause confusion.[6,15] For example, doctors in West Bengal, India, have used renal failure as a criterion for administering ASV, despite the fact that the victim was bitten several days earlier, had arrived late at the hospital with coagulable blood, but had raised serum creatinine levels. Renal failure is not necessarily a sign of current, unbound venom in circulation. Rather, it is a sign of previously unbound venom that has already caused damage that is not reversible by ASV. Guidelines such as these are ambiguous and cause unnecessary administration of ASV.

Further confusion is evident concerning recommendations for giving ASV following bites by species capable of causing necrosis. Authors recommend conflicting guidelines. In one report, ASV is recommended for species that cause necrosis when the bite is on the finger or thumb. In another report, ASV is recommend for any bite on the digits.[6,34] Both of these recommendations in the Indian subcontinent would result in virtually all victims with digit bites receiving ASV, as all venomous species, with the exception of the kraits, are capable of causing necrosis. Clearly this is irrational and leads to major wastage of ASV.

METHODOLOGICAL CAUSES: REPEAT DOSAGE STRATEGIES

A further methodological cause of overuse of ASV is the guidelines concerning repeat ASV doses. A repeat dose of ASV can only be justified if there is unbound, unneutralized venom currently circulating at the time of the repeat dose. Methodological guidelines result in much confusion in this area, often caused by ambiguous descriptions of symptoms. For example, Modi recommends giving ASV until ''the complete disappearance of the symptoms.''[12] Dutta recommends giving ASV ''till signs of envenomation, both clinical and laboratory, disappear completely.''[21] Other authors advise that ''continued signs of envenomation indicate the need for continued antivenin administration, especially in viperine bites,''[33] and ''additional doses of antivenom should be given if neurotoxicity or shock persists.''[35]

The issue here is the lack of definitions as to what constitutes ''signs,'' ''symptoms,'' and ''neurotoxicity.'' For example, respiratory failure is a ''sign'' of neurotoxicity and yet there is no benefit to administering further ASV to a victim who is undergoing respiratory support on a ventilator days after the bite when a neutralizing dose of ASV has already been given. Such common practice arises from a fundamental misunderstanding as to the action of ASV, arising from ambiguous guidelines. Swelling is a frequent sign of both viperine and neuro-

toxic envenoming. Should ASV be administered to a patient until the swelling has disappeared?

Each of these examples are not useful as clinical endpoints for antivenom administration, as none are signs in themselves that venom is still circulating and requires neutralization by an additional dose or doses of ASV. Some texts argue that there is no known endpoint to ASV administration.[36] The use of such guidelines leads to very large and unnecessary doses of ASV being administered to victims.[18,37–39]

METHODOLOGICAL CAUSES: RECURRENT ENVENOMATION

Methodological guidelines from the United States[40] recommend methods for dealing with recurrent signs and symptoms of envenomation. In the U.S. literature, ''recurrence'' is a key topic that requires significant attention. The most likely cause of this phenomenon is the short serum half-life of the U.S. Fab fragment ASV.[6] However, the use of western textbooks has led to recurrence becoming a major theme in the Indian subcontinent, with some authors recommending the use of additional prophylactic ASV to prevent recurrence, even after normal coagulation has been restored.[24,41] There is very little evidence of recurrent envenomation being a feature of snakebite in India or Pakistan, certainly not to the extent of using prophylactic ASV to prevent it. This is a further example of noncontextual subjects influencing mainstream treatment and ASV usage.

DIAGNOSTIC CAUSES: NONENVENOMED PATIENTS

The most significant effect of viperine snake venoms is procoagulation causing clotting, which following the action of the fibrinolytic system, leads to consumption coagulopathy with the elimination of one or more clotting factors. Clotting time measurements (eg, the 20-minute whole blood clotting test [20WBCT]) are the cornerstones of detecting consumption coagulopathy in the developing world. In India and Pakistan, most viperine bites are managed using clotting time. However, little guidance has been provided by the key textbooks as to how this test should be carried out.[10–13,24,42] Consequently, bedside clotting tests are carried out using old drug ampoules, washed bottles, and plastic syringes. All of these methods are highly unreliable as these containers may not activate the contact clotting mechanism, despite the presence of normal coagulation factor levels.[43] The proper container for the 20WBCT is a clean, new, dry glass test tube. Readings of incoagulable blood resulting from use of an improper container triggers the use of ASV by the treating physician, even when the patient has not been envenomed. This situation has also been noted in Africa.[44]

TIMING CAUSES

A further cause of excessive administration of ASV relates to the timing of repeat doses in viperine envenomations. Once the initial dose of ASV has been administered to the patient, as an alternative to daily checking of coagulation function, many physicians in both India and Pakistan opt to recheck the 20WBCT after only 1 to 4 hours.[18] If this test indicates incoagulable blood, additional doses of ASV are given. Guidelines in key textbooks are either not clear or recommend repeat administration of ASV conforming to time periods that do not allow the liver the 6 hours necessary to restore clotting factors to adequate levels.[9] Repeat blood tests after 1 hour will simply reconfirm the original clotting test abnormality and again cause ASV to be administered unnecessarily. The correct pattern is to reassess coagulation on a 6 hourly basis.

EXCESSIVE SUPPLY CAUSES

Although a much less significant cause of excess doses of ASV being administered, organizations, such as the armed forces, frequently adopt dosage levels that are very high due to the luxury of a guaranteed high supply and rapid logistic support. The rationale is to restore the soldier to active duty as soon as possible.

Quadrant 4: Low-risk/low-wastage group

This quadrant represents the optimum usage of ASV levels with minimal risk to patient outcomes. This quadrant is the desired endpoint of usage strategies for ASV in snakebite management. Risk and wastage are both minimized and ASV usage is at its most effective level.

Discussion

The ASV utilization assessment model outlines the potential ways that ASV can be used. The high-risk quadrants identify areas where patient risk is uppermost. The model makes it clear that there may be many causes for apparent shortage in ASV other than a simple shortage of supply. Methodological and timing issues in themselves can result in the underuse of ASV and directly increase patient risk. Supplying more ASV to these scenarios will not result in increased usage or decreased patient risk, because there is often adequate ASV available. The issue is whether the doctor has the right train-

ing and protocol to use the ASV effectively. On the other hand, in the high-wastage quadrant, there are a great many instances where ASV is used unnecessarily.

These are all practical issues that are certainly very common in the 2 countries with the highest snakebite mortality. These issues are not restricted to India and Pakistan, however, as the dosage pattern of ASV utilized in the United States is recognizable in other countries as well.[22,23]

The ASV utilization assessment model is a useful tool that can be employed by a number of key groups.

Strategic health organizations

Organizations with strategic health responsibility, such as WHO, frequently respond to health issues based on advice from external experts. The advice should be based on the widest understanding of the problem and not colored by vested interests, such as those of ASV manufacturers. The ASV utilization assessment model enables strategic organizations to commission studies in a structured way to determine the actual situation before committing to increasing resource supply. This recommendation assumes particular importance in terms of proposals to increase production capacity. Certainly, private sector enterprises will base any increase in capacity on projected demand and therefore revenue for each product. If reports of great shortage encourage increased capacity building by ASV manufacturers, they will anticipate a level of demand for their new ASV, which may not materialize once the model has ''right sized'' actual ASV usage. The history of the provision of ASV is colored by suppliers entering and then leaving the market due to poor returns.[1,45] Where a real ASV shortage exists, we will not improve the situation by subjecting providers to overestimates of actual demand. Before scarce health funds are utilized, it would be prudent to establish the complete picture of demand.

A further area where strategic organizations can assist is by developing protocols by local experts which, in addition to guiding locally specific aspects of snakebite management, should address key areas of common treatment across regions such as methods to deal with anaphylactic reactions. These protocols can then be disseminated to hospitals at the forefront of snakebite management. It is essential that these are developed by specialists knowledgeable in local treatment and infrastructural conditions. A key failing of previous attempts has been minimal local involvement with consequent lack of key information, such as dosages of ASV, recommendations to use drugs that are not generally available, and inadequate knowledge dissemination.[6]

A key deliverable would be developing a worldwide protocol with sections of common treatment alongside specialized information for specific countries. These protocols can be disseminated in workshops presented locally and via local medical associations, such as the Pakistan Medical Association. The lack of consistency of basic treatment, such as the use of adrenaline as the first-line drug in cases of anaphylactoid reactions, must be addressed if patient outcomes are to be improved.

Tactical health organizations

The model should also be used as a key tool of policy makers who are responsible for snakebite management, including training of providers and provision of ASV within their geographic area. National, provincial or state health departments should provide both training support to ensure their doctors are familiar with the latest techniques of treatment and support in terms of ASV provision. A key use of the model is to assess whether methodological, diagnostic, and timing approaches are sound and based on local species and circumstances. If medical training for snakebites is dependent on textbooks or protocols that are not locally developed, these should be carefully assessed for relevance. Local snakebite experts should be tasked with developing locally applicable protocols and these should be disseminated. Local protocols have proven their effectiveness in developing world settings. In the West Midnapore District of West Bengal, the introduction of an effective local protocol resulted in ASV usage being reduced by 50% (unpublished data). Similarly, in Africa, there was a 50% increase in snakebite admissions and a reduction in mortality.[44] In some countries, for example Venezuela and Sri Lanka, ASV is readily available, but the validity of use has been questioned.[46,47]

The forecasting and provision of ASV should be based on credible definitions of envenomation. Snakebite statistics should be gathered and segmented into snakebites and envenomations, as these are very different numbers. The use of applicable protocols, with local criteria for what constitutes an envenomation, will greatly benefit this exercise. ASV is required for an envenomation, not for a nonvenomous snakebite or a nonenvenomation by a venomous snake.

ASV should be assessed to ensure that it is effective against local species. Often ASV is sourced from other countries, based solely on the manufacturer's assurances that it has the same effectiveness against local species that it has in the country of origin. These assertions must be carefully validated and include clinical expertise to verify efficacy in a clinical setting. While the importation of quantities of ineffective ASV may appear to reduce the strategic shortage of ASV, it does nothing to

reduce the tactical shortage of effective ASV and may, in fact, increase overall medical costs as doctors respond by increasing dosage.

Conclusion

If an accurate assessment of ASV shortage, in the sense of legitimate demand not being met by effectively used current supply, is to be identified and addressed, it is vital that the actual shortage level be identified. This involves improvements in supply only after improvements in demand usage. Simply increasing the supply side will potentially waste resources, providing capacity that may well not be needed. In addition, it is fundamentally linked to supplier forecasting and thus economics of ASV provision. We do not improve the situation by offering suppliers a ''poison chalice'' that contains poor forecasting of actual demand. The net result will be unsound business economics and suppliers leaving the market due to unreachable expectations of revenue, precipitated by reduced demand. The history of ASV provision is littered with the problem of the economics of ASV supply, with many suppliers entering and subsequently leaving the market.

The recommendation is that the ASV utilization assessment model be used to establish the current usage profile to ensure rational and effective use of ASV. Once the nonsupply issues of quadrants 1, 2, and 3 have been addressed we will be in a far better informed position to handle increasing quantity. Only when all usage strategies can be placed in Quadrant 4 can we truly quantify the relative levels of ASV supply and demand.

More attention needs to be given by strategic and tactical organizations, as well as researchers, to providing both the training and protocols necessary to better use the ASV we already have.

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