Vector-borne disease management on the Colorado Plateau: research and challenges for public health management in Arizona

Marisa Donnelly, PhD candidate in Epidemiology
March 7th, 2018

Abstract:

The management of vector-borne diseases can be challenging for public health agencies as vector-borne diseases often have complex ecologies, and can be subject to change with fluctuations in climate, host and vector population dynamics, and human behavior. As humans continue to expand their range into new and previously uninhabited territories, contact with new vectors and pathogens and vector-borne disease transmission may continue to increase. In Arizona, several vector-borne disease outbreaks have occured in recent decades. Human cases of tick-borne relapsing fever, plague, and Rocky Mountain spotted fever have been identified (the last two caused several deaths) in Arizona. Health systems in Arizona, including the Arizona Department of Health Services, the National Park System, and Indian Health Services, develop unique vector-borne disease management strategies and face unique challenges characteristic to their respective regions. This paper synthesizes research on the three most burdensome vector-borne diseases in Arizona, tick-borne relapsing fever, plague, and Rocky Mountain spotted fever, and suggests an integrated vector management strategy to improve surveillance and minimize transmission of these pathogens.

Introduction:

With increases in globalization and human expansion into new ecologies and biomes, vector-borne disease transmission poses challenges for public health agencies in the United States. Vectors are defined as living organisms that can transmit infectious diseases between humans, or from animals to humans. Often, vectors are bloodsucking insects which digest disease-producing microorganisms during a bloodmeal. In order for a human to become infected with a vector-borne disease, one must come into contact with an infective vector within a climate and environment that allow for both the vector and the pathogen to survive. Outbreaks of vector-borne diseases are likely to occur when there is high vector and pathogen host density, susceptible humans, high human-vector contact and a suitable climate for both the vectors and the pathogen to survive in.

Arizona has a favorable climate for several different vectors, and tick, flea, and mosquito-borne disease transmission is something Arizona health departments must work hard at to manage. What makes Arizona a unique region for vector-borne disease management is that there are several public health organizations working independently within their own unique jurisdictions, all within the same state. These public health agencies include the Arizona Department of Health Services (ADHS), the National Park System (NPS) working in Grand Canyon National Park (GCNP), and Indian Health Services (IHS), which works in several of the 21 American Indian reservations within the state. Each of these public health agencies has their own funding, unique logistical challenges, and differences in prevalences of specific vector-borne diseases. The ADHS aids each of the 15 counties in Arizona with funding and logistical support, however each county runs their own public health department and designs their own vector-borne disease management protocol. County public health departments have to manage local transmission of plague, hantavirus, West Nile virus, St. Louis encephalitis virus, and Rocky Mountain spotted fever. The NPS in GCNP receives federal funds from the Centers for Disease Control to manage health issues for the 5.5 million annual park visitors. Vector-borne disease transmission that has occured within the park includes plague, tick-borne relapsing fever and hantavirus. IHS is federally funded from the US Department of Health and Human Services and is the principal health care provider for American Indian people. Each tribe has a unique relationship with IHS; some tribes use IHS to design and run their public health programs while other tribes only use funding from IHS and manage their own public health programs. On tribal territories in Arizona, vector-borne diseases of concern include Rocky Mountain spotted fever, plague, hantavirus, and West Nile.

Each vector-borne disease present in Arizona has its own unique ecology, and requires an individually designed management approach. Additionally, each of the public health systems previously described faces unique operational challenges, and must function with limited resources. In the following paragraphs, I will describe the three most burdensome vector-borne diseases in Arizona, tick-borne relapsing fever, plague, and Rocky Mountain spotted fever, and propose an integrated vector management approach to minimize their transmission.

Tick-borne Relapsing Fever

Epidemiology: Tick-borne relapsing fever (TBRF) is a disease caused by bacteria *Borrelia hermsii* and transmitted by ticks in the genus *Ornithodoros.* It is endemic in forested mountainous areas of western North America [1]. TBRF infection in humans is typically characterized by recurring episodes of fever (2-6 episodes), with general symptoms including headache, myalgia, nausea, arthralgia, and vomiting. Cases and outbreaks of TBRF are usually associated with overnight stays in rustic cabins in which rodents infested with *Ornithodoros* ticks have nested [2]. While *B. hermsii* can infect several small rodents, allowing for the pathogen to occupy a large geographic range, most human cases of TBRF cluster in a small and focal number of locations [3]. Areas endemic for TBRF and with repeated outbreaks include popular tourist destinations including the North Rim of Grand Canyon National Park, Estes Park (CO), and Lake Tahoe (CA) [4]. This focal clustering of human cases suggests that factors outside the presence or absence of suitable rodent hosts for the tick vector are constraining outbreaks of TBRF. In GCNP, there have been two outbreaks of TBRF and one individual case identified. The first outbreak occurred in 1973, when 62 confirmed cases of TBRF were identified. In 1990, a second outbreak occurred, and 17 cases of TBRF were confirmed. In 2015, one visitor to the North Rim of GCNP was treated for TBRF, and no other cases were identified.

Recent research: Research on TBRF has focused on understanding the risk factors associated with infections and outbreaks, and modelling the distribution of *Ornithodoros* ticks as well as *B. hermsii* pathogen. In the 1973 outbreak in GCNP, a risk factor analysis was conducted to identify risk factors associated with infection of TBRF. After surveying 7,525 guests and employees retrospectively, illness was found to be significantly associated with persons sleeping in rustic log cabins, and bites of “unknown” insects [5]. Researchers removed and examined rodent nesting material found in the walls and attics of the cabins where cases had occurred, and recovered several infective *Ornithodoros hermsi* ticks. It appeared that increased frequency of tick bites on humans resulted from a decreased population of the ticks' usual rodent hosts [5]. This identification of rodent infestation in rustic cabins as a risk factor for TBRF led NPS to establish a formal "rodent-proofing" protocol that is still in practice [6]. After the second outbreak of TBRF occurred at the North Rim of GCNP, another epidemiological study was conducted to determine risk factors. After surveying over 10,000 people, the strongest risk factor was having stayed in a group of cabins that had not been rodent proofed after the 1973 TBRF outbreak; all but one of the 17 cases had spent the night in a cabin in the park [7].

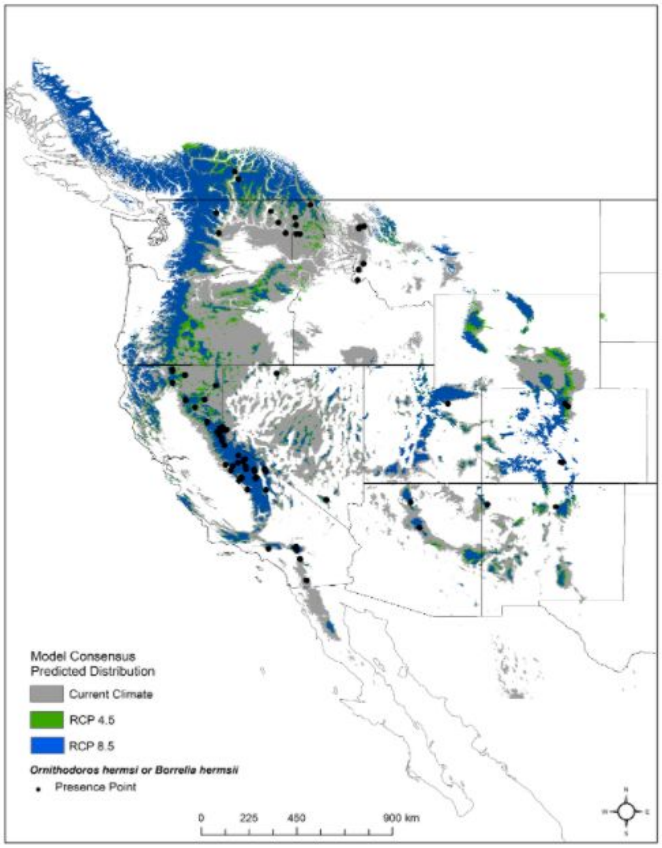


Figure 1. Current versus future distribution of *Ornithodoros hermsi* and *Borrelia hermsii* predicted by Maxent (Sage et al. 2017).

Structural flaws and rodent nests were common in the implicated cabins, and rare in the unaffected cabins. This study indicated that using the NPS rodent proofing protocol in regions where TBRF is endemic prevents reinfestation of cabins by infected rodents, and therefore prevents the spread of TBRF [7]. Sage et al. (2017) used Maximum Entropy Species Distribution Modeling (Maxent) to model the current and future species distribution of both *B. hermsii* and *O. hermsi* in the US, based on current climatic trends and future projected climate changes. They found that their projected current distributions of both the tick and the pathogen align with known endemic regions of the disease, and that global climate models predict a shift in the distribution of suitable habitat for the tick vector to higher elevations [3] (figure 1). While risk factors for TBRF have been identified in epidemiological studies, there is no ongoing surveillance to detect TBRF. All measures to reduce transmission are reactionary to the identification of human cases. Increasing surveillance between outbreaks in pair with understanding the risk factors for human infection and the ecological range of both the tick and the pathogen will allow public health and vector control agencies to target surveillance efforts to areas of high risk in North America.

Plague

Epidemiology: Plague is a flea-borne zoonotic disease caused by the bacterium *Yersinia pestis* Yersin. Plague was thought to have been introduced to the United States in 1900, brought to San Francisco by infected rats and fleas from ships arriving from plague endemic regions of Asia [8]. Despite control efforts, plague is now widespread across the western United States, and most human cases occur in the four-corners region, which includes Arizona, Colorado, New Mexico, and Utah. Plague is rare in the US; on average, 1-17 plague cases are reported each year, however, mortality rates for plague are high [9]. For untreated plague infections, the mortality rate is 50-60% for bubonic plague to nearly 100% for pneumonic or septicemic plague [10]. When treated with antibiotics, however, the outcome of infection is greatly improved. Plague has been detected in GCNP, and alarmingly, in 2007 a wildlife biologist employed by GCNP died of pneumonic plague after conducting a necropsy on an infected mountain lion without wearing personal protective equipment [11]. Currently, no ongoing surveillance for plague exists in the GCNP, nor elsewhere in Arizona. Although only five cases of plague have been reported in Arizona since 2000 [12], the high mortality rates of the different forms of plague make understanding plague transmission risk a priority for public health departments in the south western US.

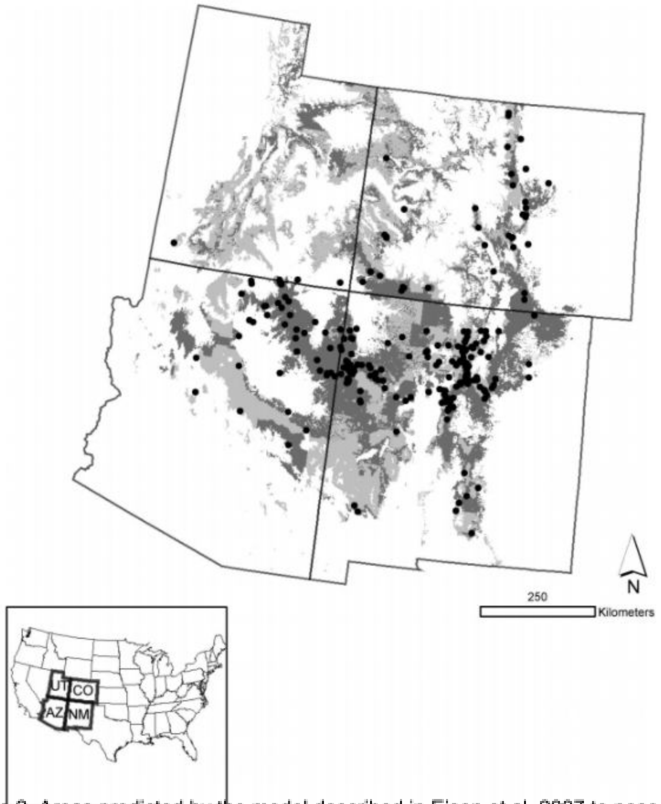


Figure 2. Areas predicted by the model described in Eisen et al. 2007 to pose high risk to humans throughout the four-corners region (AR, CO, NM, UT) are depicted in light gray. Those high-risk areas on privately owned or tribally owned land are shown in dark gray. Black circles represent locations of acquired human plague cases from 1957 to 2004 (Eisen et al. 2007).

Recent research: While plague is a rare disease, there has been significant research conducted to understand the disease ecology of the pathogen and climatic and environmental risk factors associated with infections. The majority of human plague cases are thought to occur during susceptible host (squirrels, prairie dogs, or chipmunks) die-offs, and infected fleas are forced to feed upon hosts that they would not ordinarily feed on, like humans [10]. Certain climatological factors have also been associated with increases in plague activity; in the southwestern US, epizootics intensity increases during El Nino years and when cool summer temperatures follow wet winters, and black tailed prairie dogs increase in population size [13,14]. The risk of human exposure to plague has also been found to increase as elevation increases up to approximately 2,000 ft (at which point risk begins to decrease as you increase elevation) and as distance to key rodent habitat decreases [8]. These key habitats include southern Rocky Mountain piñion juniper, CO plateau piñion-juniper woodland, Rocky Mountain Ponderosa pine, and southern Rocky mountain juniper woodland and savanna. Eisen et al. (2007) used these risk models to map the geographic distribution of risk of plague transmission in the four corners region (figure 2). The ecology of plague transmission is well understood relative to TBRF and RMSF, however, surveillance for plague transmission is lacking. In Arizona, surveillance only occurs in response to a human case, or a prairie dog-die off [12]. Given the conclusions from these climate models, it is possible that encouraging surveillance during climatically suitable time periods and in ecologically suitable regions may increase plague transmission detection and reduce human infections in Arizona.

Rocky Mountain Spotted Fever

Epidemiology: Rocky Mountain spotted fever (RMSF) is a tick-borne rickettsial disease caused by the bacterium *Rickettsia rickettsii.* RMSF is thought to have been endemic for at least a century in many parts of the US, however it was first identified on tribal lands in Arizona in 2003 [15]. RMSF can cause acute febrile illness that can result in severe sequelae or death. Symptoms include fever, headache, abdominal pain, and rash. When antibiotic treatment is delayed past 5 days of initial symptoms, severe sequelae, such as neurological deficits or damage to internal organs, may occur [16]. Because RMSF has the potential to result in severe outcomes, it is considered a notifiable condition in the US, although surveillance for the pathogen is passive. In the US, the case fatality rate for RMSP is <1%, however in Arizona the case fatality is 7% [12,17]. Additionally, American Indians experience significantly higher incidence than any other group, and four times the disease burden of white populations [17]. During 2003-2012, more than 250 RMSF cases and 19 deaths were documented among Arizona's American Indian population. RMSF has emerged as a significant health risk to American Indian reservations in Arizona; understanding the risk factors associated with high incidence of infection and the effectiveness of different control measures are vital to minimizing the burden of this disease.

Recent research: While RMSF has been endemic in parts of the US for over a century, recent outbreaks on American Indian reservations necesitate a better understanding of the disease ecology and risk factors. Research on RMSF has been focused on developing appropriate control efforts for infected communities, and assessing the economic burden of this disease. Until 2005, the principal disease vectors for RMSF were considered to be *Dermacentor variabilis* (the American dog tick) and *D. andersoni* (the Rocky Mountain wood tick) [15]. Both of these ticks feed on small mammals, which are capable of harboring *R. rickettsii,* and neither of these species are found in Arizona. And epidemiological study conducted from 2002 to 2004 identified risk factors for RMSF infections during the first Arizona outbreak, which identified 16 confirmed cases of the disease [15]. All cases had contact with tick-infested dogs, and all ticks collected from the patient's domestic dogs and free-roaming dogs in the community were *Rhipicephalus sanguineus* (the brown down tick). *R. rickettsii* was identified in multiple ticks collected from dogs in the community. This study was the first to identify the brown dog tick as a vector of RMSF, and indicates that dogs serve as important transport hosts by carrying infected ticks close to their owners. This study also indicates that the personal protective measures traditionally used to avoid RMSF, including using DEET in wooded areas and staying to the inside of trails, will not be applicable to avoiding contact with the brown dog tick, which is primarily in domestic and peridomestic settings. To determine if brown dog tick control could be attained in a heavily infested community, Drexler et al. (2014) designed and evaluated an integrated tick prevention campaign aimed at killing ticks on dogs in peridomestic environments in Arizona. This study found that after 1 year of placing long-acting tick collars on all dogs in the community, applying environmental acaricides to yards monthly, and encouraging animal care practices such as spay and neuter and proper tethering procedures, <1% of dogs in the intervention community had visible tick infestations, compared to the 64% with infestations in the non-intervention community [18]. At the end the second year of the intervention, which only included using long-acting collars on dogs, <3% of dogs in the intervention community had visible tick infestations. This study demonstrated the an integrated tick prevention program can successfully reduce tick burdens in infested communities.

A study conducted in 2015 estimated the cost associated with medical care, loss of productivity, and death among cases of RMSF on two American Indian reservations between 2002 and 2011 [19]. They found that acute medical care costs due to RMSF totaled more than $1.3 million, acute productivity loss due to illness totaled $181,000, and lifetime productivity lost from premature death totaled $11.6 million [19] (table 1). The aggregated costs of RMSF cases in these two communities in Arizona totaled $13.2 million. The high cost of this epidemic highlights the severity of this disease and encourages strengthening control efforts. While surveillance for RMSF has been conducted on tribal lands in northeastern Arizona since 2003, other parts of Arizona do not participate in ongoing surveillance of the pathogen. Given the high burden of the disease, and that recent studies have shown that the brown dog tick is an efficient vector, other regions in Arizona, and especially those with larger populations of roaming dogs, may be able to prevent outbreaks of this disease by enacting surveillance programs before human cases are detected.

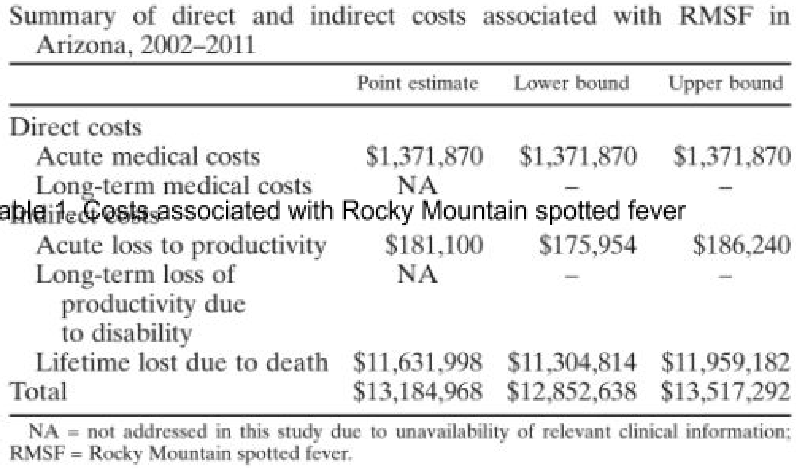


Table 1. Costs associated with Rocky Mountain spotted fever

Summary of direct and indirect costs associated with RMSF in Arizona, 2002–2011

	Point estimate	Lower bound	Upper bound
Direct costs			
Acute medical costs	$1,371,870	$1,371,870	$1,371,870
Long-term medical costs	NA	–	–
Indirect costs			
Acute loss to productivity	$181,100	$175,954	$186,240
Long-term loss of productivity due to disability	NA	–	–
Lifetime lost due to death	$11,631,998	$11,304,814	$11,959,182
Total	$13,184,968	$12,852,638	$13,517,292

NA = not addressed in this study due to unavailability of relevant clinical information; RMSF = Rocky Mountain spotted fever.

Suggested policy strategies and research:

The challenges facing public health management of vector-borne diseases in Arizona are complex, and likely difficult to resolve. Multiple vector-borne diseases requires that Arizona public health agencies prioritize control efforts, however, it is difficult to prioritize public health needs when the disease burden for each of these pathogens is unknown. Therefore, to effectively strengthen vector-borne disease management and reduce disease transmission in Arizona, I propose that priorities for vector-borne disease management are defined by calculating the disease burden for each of the previously described pathogen, and that public health agencies in Arizona develop an integrated vector management (IVM) protocol.

Defining disease burden: The burden of disease is used to describe death and loss of health due to diseases, injuries and risk factors. The burden for a particular disease is estimated by adding together the number of years of life a person loses as a consequence of dying early because of the disease Years of Life Lost or YLL, and the number of years of life a person lives with disability caused by the disease called Years of Life Lived with Disability or YLD.

$$\text{YLL} = \text{Number of deaths}*\text{Standard life expectancy}$$

$$\text{YLD} = \text{Number of incident cases}*\text{Disability weight (0=perfect health, 1=dead)}*\text{Mean duration of disability}$$

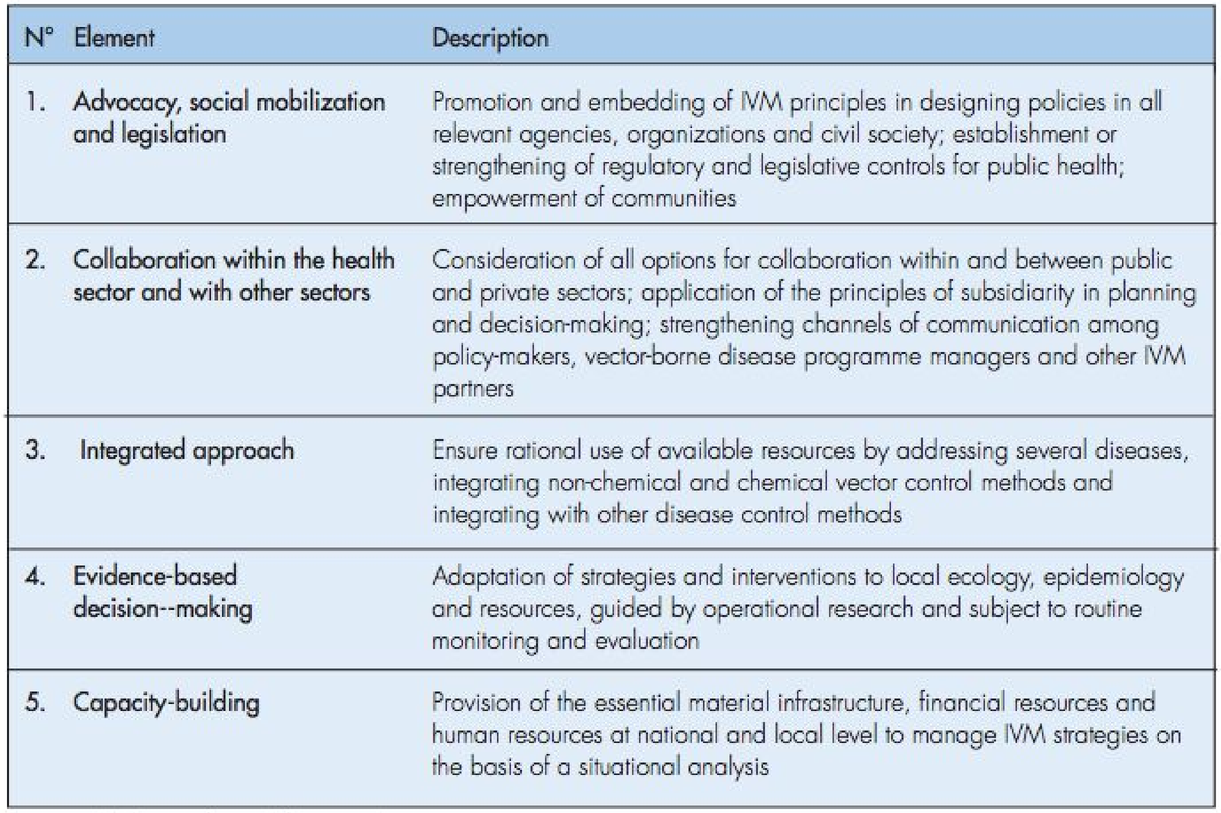
Adding together YLL and YLD gives a single-figure estimate of disease burden, called the Disability Adjusted Life Year (or DALY) [20]. One DALY represents the loss of one year of live lived in full health. Estimating the burden of disease allows health systems to overcome issues with fragmented and partially available data, overestimations of mortality often due to coexisting morbidities, traditional statistics that are non-comparable in determining cost-effectiveness of different health treatments. In short, estimating disease burden allows for a standardized method to compare the severity and strain different diseases place on a community, allowing public health agencies to prioritize and make evidence-based disease management decisions.

Thus far, out of the previously described diseases, the only economic analysis conducted pertained to RMSF in two American Indian reservations. While this study found that the average lifetime productivity lost per fatal case of RMSF was $775,467 and that this was higher than that of West Nile virus ($293,960), there was no other comparison to other vector-borne diseases in Arizona, like plague or TBRF. Global comparisons have been done comparing disease burdens, including calculating DALYs, for several vector-borne diseases, and it is surprising that this has not been done regionally in Arizona [21]. Future analyses should either employ the same methods carried out by Drexler et al. (2015) and calculate lifetime productivity losses for plague and TBRF., or calculate DALYs for all three diseases to compare relative disease burdens. Accomplishing either of these would allow public health agencies to target their efforts and funding towards the most burdensome diseases and reduce disease transmission.

Integrated vector management:

With human cases of TBRF, plague, and RMSF and deaths due to plague and RMSF in Arizona, it is alarming that no widespread ongoing surveillance occurs for any of these pathogens. Surveillance for these pathogens is reactionary, with surveillance for RMSF in northeastern Arizona being the exception. The disease ecology of each of these pathogens is complex and varies regionally, however, improved of surveillance is possible. For both flea and tick vectors, integrated vector management (IVM) has been shown to be effective in controlling vector populations and reducing disease transmission [22–24]. IVM is a rational decision-making process to optimize the use of resources for vector control and aims to make vector control more efficient, cost effective, ecologically sound, and sustainable. Classic IVM involves the selection, integration, and implementation of several vector control actions based on predicted ecological, economic, and sociological consequences. IVM incorporates all components of disease control, including vector control, prevention, treatment, and human vulnerability. The key elements of IVM, as defined by the World Health Organization, are in table 1, and include collaboration amongst all relevant agencies, strong communication, rational use of available resources and vector control methods, and routine monitoring and surveillance to make evidence-based decisions. If ADHS, NPS, and IHS can develop a management agreement that includes defined collaboration, the pooling of resources and control methods, consolidation of epidemiologic data, and support and collaboration in a disease burden analysis of the three major vector borne diseases in Arizona, pathogen transmission and disease burden of these vector-borne diseases can surely be reduced.

Table 2. Instruments that governments and public health agencies could use to implement public policy, listed according to the basic concepts of integrated vector management (IVM) as defined by the World Health Organization.



N°	Element	Description
1.	Advocacy, social mobilization and legislation	Promotion and embedding of IVM principles in designing policies in all relevant agencies, organizations and civil society; establishment or strengthening of regulatory and legislative controls for public health; empowerment of communities
2.	Collaboration within the health sector and with other sectors	Consideration of all options for collaboration within and between public and private sectors; application of the principles of subsidiarity in planning and decision-making; strengthening channels of communication among policy-makers, vector-borne disease programme managers and other IVM partners
3.	Integrated approach	Ensure rational use of available resources by addressing several diseases, integrating non-chemical and chemical vector control methods and integrating with other disease control methods
4.	Evidence-based decision--making	Adaptation of strategies and interventions to local ecology, epidemiology and resources, guided by operational research and subject to routine monitoring and evaluation
5.	Capacity-building	Provision of the essential material infrastructure, financial resources and human resources at national and local level to manage IVM strategies on the basis of a situational analysis

References

1. Southern, P. M. & Sanford, J. P. RELAPSING FEVER: A Clinical and Microbiological Review. *Medicine* **48,** 129 (1969).

2. Dworkin, M. S. *et al.* Tick-borne relapsing fever in the northwestern United States and southwestern Canada. *Clin. Infect. Dis.* **26,** 122–131 (1998).
3. Sage, K. M., Johnson, T. L., Teglas, M. B., Nieto, N. C. & Schwan, T. G. Ecological niche modeling and distribution of Ornithodoros hermsi associated with tick-borne relapsing fever in western North America. *PLoS Negl. Trop. Dis.* **11,** e0006047 (2017).
4. Dworkin, M. S., Schwan, T. G., Anderson, D. E., Jr & Borchardt, S. M. Tick-borne relapsing fever. *Infect. Dis. Clin. North Am.* **22,** 449–68, viii (2008).
5. Boyer, K. M. *et al.* Tick-borne relapsing fever: an interstate outbreak originating at Grand Canyon National Park. *Am. J. Epidemiol.* **105,** 469–479 (1977).
6. NPS Rodent Exclusion Manual --- Mechanical Rodent Proofing Techniques.pdf.
7. Paul, W. S., Maupin, G., Scott-Wright, A. O., Craven, R. B. & Dennis, D. T. Outbreak of tick-borne relapsing fever at the north rim of the Grand Canyon: evidence for effectiveness of preventive measures. *Am. J. Trop. Med. Hyg.* **66,** 71–75 (2002).
8. Eisen, R. J. *et al.* Human Plague in the Southwestern United States, 1957–2004: Spatial Models of Elevated Risk of Human Exposure to Yersinia pestis. *J. Med. Entomol.* **44,** 530–537 (2007).
9. Maps and Statistics | Plague | CDC. (2018). Available at: https://www.cdc.gov/plague/maps/index.html. (Accessed: 2nd March 2018)
10. Levy, C. E. & Gage, K. L. Plague in the United States, 1995-1997. *Infect. Med.* **16,** 54–64 (1999).
11. Wong, D. *et al.* Primary pneumonic plague contracted from a mountain lion carcass. *Clin. Infect. Dis.* **49,** e33–8 (2009).
12. Arizona Department of Health Services. Available at: http://azdhs.gov/index.php. (Accessed: 2nd March 2018)
13. Parmenter, R. R., Yadav, E. P., Parmenter, C. A., Ettestad, P. & Gage, K. L. Incidence of plague associated with increased winter-spring precipitation in New Mexico. *Am. J. Trop. Med. Hyg.* **61,** 814–821 (1999).
14. Stapp, P., Antolin, M. F. & Ball, M. Patterns of Extinction in Prairie Dog Metapopulations: Plague Outbreaks Follow El Niño Events. *Front. Ecol. Environ.* **2,** 235–240 (2004).
15. Demma, L. J. *et al.* Rocky Mountain spotted fever from an unexpected tick vector in Arizona. *N. Engl. J. Med.* **353,** 587–594 (2005).
16. Regan, J. J. *et al.* Risk factors for fatal outcome from rocky mountain spotted Fever in a highly endemic area-Arizona, 2002-2011. *Clin. Infect. Dis.* **60,** 1659–1666 (2015).
17. Openshaw, J. J. *et al.* Rocky mountain spotted fever in the United States, 2000-2007: interpreting contemporary increases in incidence. *Am. J. Trop. Med. Hyg.* **83,** 174–182 (2010).
18. Drexler, N. *et al.* Community-based control of the brown dog tick in a region with high rates of Rocky Mountain spotted fever, 2012-2013. *PLoS One* **9,** e112368 (2014).
19. Drexler, N. A. *et al.* Medical and Indirect Costs Associated with a Rocky Mountain Spotted Fever Epidemic in Arizona, 2002-2011. *Am. J. Trop. Med. Hyg.* **93,** 549–551 (2015).
20. World Health Organization. Burden of disease: what is it and why is it important for safer food? *Burden of Disease Studies* Available at: http://www.who.int/foodsafety/foodborne_disease/Q&A.pdf. (Accessed: 2nd March

2018)

21. World Health Organization. Global burden of major vector-borne diseases, as of March 2017. *World Health Organization* (2017). Available at: http://www.who.int/vector-control/burden_vector-borne_diseases.pdf. (Accessed: 3rd March 2018)
22. Nature & Science » Biology Resources » Integrated Pest Management Manual. Available at: https://www.nature.nps.gov/biology/ipm/manual/fleas.cfm. (Accessed: 7th March 2018)
23. Handbook for Integrated Vector Management. *World Health Organization* Available at: http://apps.who.int/iris/bitstream/10665/44768/1/9789241502801_eng.pdf. (Accessed: 3rd March 2018)
24. Stafford, K. C., Williams, S. C. & Molaei, G. Integrated Pest Management in Controlling Ticks and Tick-Associated Diseases. *J Integr Pest Manag* **8,** (2017).