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Consideration of Vector-Borne and Zoonotic Diseases during Differential Diagnosis

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Objective: Recognition and reporting of vector-borne and zoonotic disease (VBZD) cases is largely dependent upon the consideration of such diseases by healthcare practitioners during the initial diagnosis and ordering of specific confirmative diagnostic tests. This study was conducted to assess the general knowledge and understanding of VBZD transmission and clinical presentation.

Methods: Healthcare practitioners were surveyed to determine the extent of training and educational experiences they received relative to VBZDs, and their likelihood to consider such diseases during differential diagnoses. In addition, an assessment of their knowledge of arthropod species that may transmit VBZD pathogens was conducted.

Results: Having postprofessional school training relevant to VBZDs significantly influenced diagnostic accuracy for such disease cases based on the presented clinical signs and symptoms.

Conclusions: The prevalence of VBZDs in the United States likely is significantly underestimated. The authors suggest the enhancement of VBZD-focused education as an important initiative that would significantly improve timely diagnosis, treatment, and, ultimately, prevention of these diseases.

Key Words: initial differential diagnosis, medical education, vector-borne disease, zoonotic disease

The Centers for Disease Control and Prevention reported in 2018 that the incidence rate of vector-borne and zoonotic diseases (VBZDs) more than tripled during the past 15 years in the United States, with nine new arthropod-vectored pathogens identified or introduced during that time period.[1] The World Health Organization estimates that half of the world's population is at risk of contracting a vector-borne disease.[2] Of the >1400 identified infectious pathogens known to cause disease in humans, >300 are of clinical importance, and at least 88 are known to be vector borne.[3,4] Vector-borne diseases are spreading in their geographic ranges at an alarming rate, and this rapid spread significantly increases the threat to global public health.[2,5]

Recognition, diagnosis, and reporting of VBZD cases is largely dependent upon a healthcare practitioner's willingness to consider such diseases during initial patient assessment and the ordering of specific confirmatory diagnostic tests. We suggest that a healthcare practitioner's consideration of a VBZD is largely dependent on the scope of VBZD-specific education received during professional training. Lack of knowledge and understanding of the evolving epidemiology of VBZDs and respective potential vectors likely contributes to the underreporting of these diseases in the United States.[6] To gain a better understanding of causes of this knowledge gap, an assessment of the extent of training and education healthcare practitioners received specific to the biology, distribution, and transmission dynamics of VBZDs is critical. It also is important to determine the likelihood of healthcare practitioners to consider VBZDs based on the specific clinical signs and symptoms presented by a patient during his or her initial assessment.

To explore this perceived knowledge gap relative to recognition and clinical diagnosis of VBZDs, we surveyed local healthcare practitioners from Lubbock, Texas to determine their training and experience relative to such diseases and their likelihood to consider

Key Points

- The incidence rate of emerging and resurgent vector-borne and zoonotic diseases has more than tripled during the past 15 years in the United States.
- Vector-borne and zoonotic diseases are often misdiagnosed by healthcare practitioners, which may in turn lead to the underreporting of such diseases.
- The lack of knowledge and understanding of the epidemiology of vector-borne and zoonotic diseases, and their respective potential vectors, likely contributes to the underreporting of these diseases in the United States.
- Our findings suggest a need, and most important, a desire for improved and increased education and training focused on vector-borne and zoonotic diseases for healthcare practitioners.

them during initial differential diagnoses of patients. We also assessed healthcare practitioner knowledge of arthropods that are potential vectors of VBZD pathogens, and their recognition that patient exposure (ie, fed upon) to specific vectors may enhance their diagnostic accuracy. The survey focused on the healthcare practitioners most likely to initially assess and diagnose symptomatic patients, including doctors of medicine (MDs), doctors of osteopathic medicine, physician assistants (PAs), and nurse practitioners (NPs), as well as specialties including Emergency Medicine, Family Practice, Pediatrics, and Urgent Care.

Methods

Survey participation invitations were distributed to 681 healthcare practitioners, regardless of their area of specialty, in Lubbock, Texas, using e-mail that was linked to an online survey platform (Qualtrics, Provo, UT). To encourage participation, upon completion of the survey, participants were offered the opportunity to be included in a drawing for one of 50 $10 gift cards. The survey consisted of 30 questions and was estimated to require 5 to 8 minutes to complete. Four reminder e-mails were sent to potential participants during a 2-month period to encourage survey completion.

Survey participants were provided a series of questions listing clinical signs and symptoms presented by fictitious patients and were asked to identify their most likely and second most likely diagnoses. Questions included typical signs and symptoms for the following VBZDs found in the United States, including Chagas disease, chikungunya, dengue fever, West Nile fever (WNF), West Nile neuroinvasive disease, and Zika fever.[7] Symptoms presented for these specific VBZDs are provided in Table 1. Participants also were asked whether they had ever diagnosed a patient with any VBZD listed above, as well as Heartland virus disease, Lyme disease, lymphocytic choriomeningitis, Rocky Mountain spotted fever, and tularemia.

Table 1. Clinical signs and symptoms of vector-bone and zoonotic diseases presented to healthcare practitioners for consideration for initial differential diagnoses

Disease	Signs and symptoms presented
Chagas disease	Headache, fever, vomiting, nausea, diarrhea, rash, fatigue, unilateral eyelid swelling resulting from an apparent insect bite, and swollen lymph nodes
Chikungunya disease	Prolonged arthralgia (focused in wrist, knees, and ankles), rash focused on the trunk and limbs, severe congenital infection, fever, and headache
Dengue fever	Fever, myalgia, headache, bone pain, arthralgia, rash, retroorbital pain, vomiting, and bleeding gums
West Nile fever	Headache, slight fever, myalgia, arthralgia, vomiting, diarrhea, and a maculopapular rash
West Nile neuroinvasive disease	High fever, stiff neck, tremors, muscle weakness, encephalopathy, and vision loss
Zika fever	Fever, rash, headache, myalgia, conjunctivitis, and arthralgia

Symptoms derived from APHA 2014.[7] APHA, American Public Health Association.

Survey participants also were asked to identify what arthropods were potential vectors of the following pathogens: *Borrelia burgdorferi* (Lyme disease), chikungunya virus, dengue virus, Heartland virus, *Rickettsia rickettsii* (Rocky Mountain spotted fever), *Francisella tularensis* (tularemia), *Trypanosoma cruzi* (Chagas disease), *Rickettsia prowazekii* or *R typhi* (epidemic or murine typhus), West Nile virus (WNV), *Yersinia pestis* (bubonic plague), and Zika virus. The arthropod vector species options listed as choices included cockroach, flea, fly, kissing bug, louse, mosquito, and tick.

Finally, survey participants were asked about their educational and professional training, specifically relative to VBZDs (ie, the number of required or elective classes completed during professional school, or any postprofessional school VBZD-specific training). Data, including years in practice and hours per day spent in direct patient care, were collected. Participants were provided an opportunity for additional comments or opinions regarding the topics addressed in the survey.

Data analyses included compiling descriptive statistics of survey responses, and analyses of variance were calculated to determine whether area of specialty, degree type, hours per day spent in direct patient care, years in practice, prior diagnosis by participant of a VBZD, elective or required classes attended during their professional school education, and whether any postprofessional school training relative to VBZDs had any influence on the accuracy in their differential diagnoses of diseases during this survey. Diagnostic accuracy was calculated by the cumulative accurate VBZD diagnoses within the first (ie, most likely disease) or second (ie, second most likely disease) diagnostic attempt for all scenarios. This study was reviewed and approved by the Texas Tech University institutional review board.

Results

The overall survey response rate was 7.6% (52/681) of invitees. An additional 12.2% (83/681) started the survey but did not complete and submit their answers and were thus excluded. Of the 52 respondents, 71.2% (37/52) were MDs, 13.5% (7/52) were NPs, 9.6% (5/52) were PAs, and 5.8% (3/52) identified themselves as a doctor of nursing practice. The number of years that participants had worked as direct healthcare practitioners ranged from <5 years to >30 years, with an overall average range of 11 to 15 years. Relative to the amount of time each workday that respondents spent providing direct patient care, participants reported an overall average of 7.6 hours/day (±3.1 hours, coefficient of variation 0.408). The reported average time each workday spent providing direct patient care by MDs was 7.3 hours, NPs spent 9.0 hours, PAs spent 7.8 hours, and doctors of nursing practice spent 7.7 hours.

Participant survey completion time ranged from 4 minutes 27 seconds to >32 days. The survey design allowed participants to start and stop the survey as desired, and thus likely led to the high variation of time required for completion. To determine a more realistic average time to complete the survey, we eliminated the surveys requiring >40 minutes to complete, leaving

Table 2. Participant responses of the most likely and second most likely initial diagnoses of diseases based on patient presentation of signs and symptoms listed in the survey

Survey participant responses (%)	Diseases corresponding to signs and symptoms presented to survey participants[a]											
	Chagas		Chikungunya		Dengue		WNF		WNND		Zika	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
	(n = 39)	(n = 25)	(n = 33)	(n = 19)	(n = 39)	(n = 25)	(n = 48)	(n = 34)	(n = 45)	(n = 21)	(n = 41)	(n = 28)
Correct diagnosis	10.3	4.0	6.1	0	51.3	8.0	0	0	13.3	0	2.4	10.7
Other VBZDs	48.7	44.0	15.2	10.5	2.6	36.0	16.7	8.8	4.4	4.8	2.4	10.7
Influenza	0	0	0	0	0	0	12.5	5.9	0	0	12.2	7.1
Other/nonspecific viral	20.5	24.0	30.3	36.8	12.8	16.0	50.0	47.1	6.7	42.9	63.4	17.9
Bacterial	5.1	20.0	12.1	10.5	0	4.0	6.3	8.8	11.1	4.8	2.4	21.4
Meningitis/encephalitis	0	0	9.1	10.5	5.1	4.0	6.3	11.8	62.2	33.3	2.4	3.6
Other	17.9	8.0	27.3	31.6	28.2	32.0	2.1	17.6	2.2	9.5	14.6	28.6
Uncertain	28.2	–	54.5	–	30.8	–	10.4	–	17.8	–	31.7	–

VBZD, vector-borne and zoonotic disease; WNF, West Nile fever; WNND, West Nile neuroinvasive disease. [a] 1st, the most likely disease selected by survey participants; 2nd, the second most likely disease selected by survey participants.

44 surveys to be averaged. This resulted in an average time to complete the survey of 12 minutes 40 seconds.

Signs and Symptoms Presentation

The signs and symptoms presentation section of the survey evaluated the healthcare practitioner's likelihood to consider VBZDs based on their initial assessment of patient signs and symptoms presented. Participants were asked to provide their most likely and second most likely diagnoses for the following diseases based on a list of clinical signs and symptoms (Table 2).

Chagas Disease

Respondents correctly selected Chagas disease (10.3%, 4/39) as their most likely diagnosis and (4.0%, 1/25) as their second most likely diagnosis. Most frequently selected diagnoses (48.7%, 19/39) were various VBZDs other than Chagas disease, and 28.2% (11/39) of respondents indicated that they were uncertain of a diagnosis.

Chikungunya Disease

Only 6.1% (2/33) of participants correctly selected chikungunya as their most likely diagnosis, while 54.5% (18/33) were unsure of the correct diagnosis. Ten of the 33 respondents (30.3%) selected "other/nonspecific viral" as their most likely diagnosis. None of the respondents selected chikungunya as their second most likely diagnosis.

Dengue Fever

Dengue was correctly selected as the most likely diagnosis by 51.3% (20/39) of respondents and by 8.0% (2/25) as their second most likely diagnosis; however, 30.8% (12/39) of respondents indicated that they were uncertain of a diagnosis. Thirty-six percent (9/25) of respondents selected "other vector-borne disease" as their second most likely diagnosis.

WNF

None of the 48 respondents correctly diagnosed WNF as their most likely choice; however, 47.1% (16/34) considered it as their second most likely diagnosis. Despite no participants selecting the correct answer as their top choice, 50.0% (24/48) selected "other/non-specific viral" disease as their most likely diagnosis.

West Nile Neuroinvasive Disease

West Nile neuroinvasive disease was correctly selected as the most likely diagnosis by 13.3% (6/45) of respondents, but none of the respondents selected it as their second most likely diagnosis. The most frequent selection by respondents, 62.2% (28/45), was "meningitis/encephalitis" as their most likely diagnosis, and 33.3% (7/21) selected it as their second most likely diagnosis.

Zika Fever

"Other/non-specific viral" illness was the most common response by 63.4% (26/41) of participants as their most likely diagnosis. Zika was correctly selected as the most likely diagnosis by 2.4% (1/41), and as the second most likely diagnosis by 10.7% (3/28) of respondents. Respondents were unsure of a diagnosis 31.7% (13/41) of the time.

Previous Diagnoses and Vector Identification

Twenty-seven of 52 (51.9%) healthcare practitioners reported having diagnosed at least one patient in their career with either Chagas disease, chikungunya disease, dengue fever, Lyme disease, lymphocytic choriomeningitis, Rocky Mountain spotted fever, tularemia, West Nile fever/neuroinvasive disease, or Zika fever (Table 3).

Ticks were correctly identified as the arthropod vector of *B burgdorferi* (Lyme disease), Heartland virus, *R rickettsii* (Rocky Mountain spotted fever), and *F tularensis* (tularemia) by 98.1% (51/52), 10.2% (5/49), 72.9% (35/48), and 33.3% (16/48) of respondents, respectively. Mosquitoes were correctly identified

Table 3. Participants indicating they previously diagnosed a patient with the diseases outlined

Disease	Previously diagnosed disease, %
Chagas disease	13.5 (7/52)
Chikungunya disease	9.6 (5/52)
Dengue fever	17.6 (9/51)
Heartland disease	0 (0/51)
Lyme disease	36.5 (19/52)
Lymphocytic choriomeningitis	3.9 (2/51)
Rocky Mountain spotted fever	19.6 (10/51)
Tularemia	9.8 (5/51)
West Nile fever/neuroinvasive disease	28.9 (15/52)
Zika fever	2.0 (1/50)

as the arthropod vector of chikungunya virus, dengue virus, WNV, and Zika virus by 73.5% (36/49), 81.3% (39/48), 100% (50/50), and 100% (48/48) of respondents, respectively. The kissing bug was correctly identified by 44.7% (21/47) of respondents as the arthropod vector of *T cruzi* (Chagas disease). Lice and fleas were correctly identified as potential vectors of *R prowazeki* (epidemic typhus) or *R typhi* (murine typhus) by 31.9% (15/47) and 29.8% (14/47) of respondents, respectively. Fleas also were correctly identified as a vector for *Y pestis* (bubonic plague) by 65.3% (32/49) of respondents. All of the responses are provided in Table 4.

Education and Training Background

When asked how many classes that focused on or discussed VBZDs they were required to take during their professional training, 46.2% (24/52) of respondents did not recall. Sixty-four percent (32/50) of those responding indicated that they did not

remember how many elective classes they attended that focused on or discussed VBZDs. Twenty-three percent (12/52) of respondents indicated that they had completed postprofessional school training that focused on to some extent or discussed VBZDs.

Diagnostic Accuracy

Participant area of specialty, degree type, hours per day spent in direct patient care, years in practice, whether they had ever diagnosed a VBZD, and if they had taken elective or required classes during their professional school education had no statistically significant influence on their diagnostic accuracy within this survey ($F_{14,36} = 1.10$, $P = 0.39$; $F_{3,47} = 1.48$, $P = 0.23$; $F_{10,40} = 1.04$, $P = 0.43$; $F_{6,44} = 0.69$, $P = 0.66$; $F_{7,43} = 1.32$, $P = 0.26$; $F_{1,49} = 0.02$, $P = 0.90$; and $F_{1,49} = 0.71$, $P = 0.41$, respectively). There was, however, a statistically significant difference in the accuracy of diagnoses by respondents with postprofessional school training that focused on or discussed VBZDs ($F_{1,49} = 15.80$, $P \le 0.001$).

Free Response

Participants were asked to share comments regarding individual experiences with VBZDs during their professional education or since beginning their professional practice. The following are several selected quotes that were submitted by participants: "Need more!!" "Could use more education"; "I learned more in college and the Army than in medical school"; "Hard to keep up"; "They seem to be multiplying"; "Seems to be more common and should be included (during medical school)"; "Education on this topic is underrepresented and needs to be better emphasized. It is underemphasized in training"; "Very little experience treating vector-borne illnesses and very little formal education on such topics. I would love to have more information/education regard [ing] all infectious disease topics"; "I would like more education on these (topics)"; and "Clinically these viral syndromes don't

Table 4. Percentage of respondents matching arthropod vectors to the various listed pathogens

Pathogen (total respondents)	Arthropod vectors, %							
	Flea	Fly	Kissing bug	Louse	Mosquito	Cockroach	Tick	Uncertain
Borrelia burgdorferi (52)	—	1.9	—	—	—	—	**98.1**	—
Chikungunya virus (49)	—	—	2.0	2.0	**73.5**	—	—	22.5
Dengue virus (48)	4.2	12.5	—	—	**81.3**	—	—	8.3
Heartland virus (49)	2.0	6.1	—	—	10.2	—	**22.4**	67.3
Rickettsia rickettsii (48)	10.4	—	—	14.6	8.3	—	**72.9**	8.3
Francisella tularensis (48)	25.0	20.8	—	6.3	4.2	—	**33.3**	22.9
Trypanosoma cruzi (47)	—	12.8	**44.7**	2.1	4.3	—	12.7	27.7
Typhus fevers (47)	**29.8**	4.3	—	**31.9**	8.5	—	17.0	23.4
West Nile virus (50)	—	—	—	—	**100**	—	2.0	—
Yersinia pestis (49)	**65.3**	6.1	—	14.3	2.0	2.0	—	12.2
Zika virus (48)	—	—	—	—	**100**	—	—	—

Bold text indicates the correct vector (respondents were allowed to select more than one arthropod per pathogen).

matter ... they are all treated the same in the case of the viruses. Symptomatic and supportive care."

Discussion

Our findings suggest both an interest in and need for more robust emphasis on VBZDs during and after the professional training of healthcare practitioners. Because healthcare practitioners are the first line of recognition and treatment for cases of VBZDs, it is critical they are trained to recognize the signs and symptoms of such diseases. This knowledge would likely influence health practitioners in considering such diseases during differential diagnosis, especially for patients who present with unexplained summertime fevers and other nonspecific febrile or undifferentiated viral illnesses.[8]

As demonstrated by this study, VBZDs are often misdiagnosed by healthcare practitioners, which may in turn lead to the underreporting of such diseases. As an example of this real-world misdiagnosis/underreporting, Lyme disease is the most common VBZD in the United States, but it is known to be vastly underreported to the Centers for Disease Control and Prevention by healthcare practitioners.[9–11] Underreporting of Lyme disease minimizes the true economic and public health resource burdens (eg, healthcare costs, lost working hours) on communities, and this same principle can be applied to most other VBZDs.[10,11] The difficulty in accurately diagnosing VBZDs may be partially attributable to the fact that clinical signs and symptoms of many of these diseases are similar to other common diseases, such as the common cold or seasonal influenza.[1,11–14]

Increased educational emphasis on arthropod species that likely vector-specific pathogens within geographic regions may significantly benefit the accuracy of VBZD diagnoses. Although our study findings suggest a partial understanding by survey participants, the number of "uncertain" or incorrect responses is alarming (Table 3). Collectively, healthcare practitioner awareness and initiative to query patients about recent arthropod bites, such as those of mosquitoes or ticks, and the practitioner's understanding of geographic distribution and seasonality of arthropod activity, may significantly improve the accuracy of differential diagnoses.

Although there was no statistical association between remembering a VBZD focus during professional training and diagnostic accuracy, it is clear from the qualitative findings that healthcare practitioners would welcome more robust emphasis on this topic during education and training. Furthermore, our findings suggest that accurate diagnoses of VBZDs may improve as a result of VBZD-focused postprofessional training. The authors suggest that the advancement of VBZD education may provide significant improvement in the timely and accurate diagnosis and treatment of these diseases.

One comment submitted by a survey participant highlights the failure to recognize the public health ramifications of VBZDs by suggesting that determining the specific identity of viral infections is not relevant since "they are all treated the same [with] symptomatic and supportive care." On the contrary,

accurate and timely diagnosis is essential, not just for the individual patient but also for the health of the entire community. Accurate and timely disease diagnosis and reporting allows public health agencies to execute more effective and targeted vector control, thus decreasing the vector population and risks for disease transmission. The delay or lack of effective vector control may result in substantial increase in human illness.[15] Epidemiological data provided to public health agencies also trigger responses such as making diagnostic tests available, providing diagnosis and treatment guidelines, and providing local community education to prevent further spread of the disease. Community education focused on behavioral changes (eg, vaccination, using insect repellent, draining breeding sites, adding window screens) can significantly reduce disease transmission. Once a patient has been diagnosed as having a vector-borne disease, it is paramount that the local public health and vector control authorities be notified and take appropriate actions to stop the potential spread of the disease.

Considering WNV as an example, vector control authorities often monitor local mosquito populations for WNV infection. Ideally, upon the detection of WNV-infected mosquitoes in their jurisdiction, vector control authorities will notify public healthcare entities, such as hospitals and clinics, to ensure that healthcare practitioners are aware. Conversely, if healthcare practitioners can identify a case of WNF before a vector control authority is able to isolate the virus from mosquito populations, then the practitioner will notify the public health and vector control authorities to initiate mosquito control operations. The communication among healthcare practitioners, vector control, and public health entities is critical because the presence of human disease and infected arthropod vectors amplifies the incidence of VBZDs in a community. Even though the medical management of many VBZDs is similar to other common viral illnesses, it is critical to properly identify such diseases in a timely and accurate manner.

As a cost-saving measure and a strategy to prevent insecticide resistance from developing within vector populations from overuse of insecticides, some vector control authorities delay the treatment of potential vector populations until after the first human case of a VBZD is reported during a season. In such instances, the rapid and accurate diagnosis of human cases is even more critical for a community. Delayed diagnosis of human cases may delay targeted vector control efforts, resulting in control efforts being largely ineffective in preventing the spread of human disease and the potential for large-scale outbreaks requiring costly emergency response.[16]

Recognizing that there were limitations to this survey (eg, small sample size, narrow geographical representation of healthcare practitioners), we believe that the findings suggest a need, and most important, a desire for improved education and training regarding VBZDs among healthcare practitioners. Continued research on this subject is needed to further emphasize the need for more education and training, and how best to accomplish it. Such efforts on the state and national scales may be

beneficial for identifying and addressing additional knowledge gaps related to VBZDs within the public health and healthcare practitioner communities.

Acknowledgments

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