TOWARD AN INDIVIDUALIZED APPROACH TO DEFINE FEVER AMONG TRAVELERS FROM EBOLA-AFFECTED COUNTRIES OR PERSONS WITH EXPOSURE TO AN EBOLA PATIENT

OVERVIEW

Early detection of Ebola virus disease (EVD) is critical to preventing its spread. With the occurrence of EVD cases outside of West Africa, the US screened and monitored travelers from affected countries. Because fever is a key indicator of possible EVD among monitored travelers, high sensitivity in defining fever is critical.

We evaluated two novel methods that defined fever as a temperature increase of $\geq$1°C (1.8°F) over baseline using data from 45 travelers monitored by the Los Angeles County Department of Public Health (LAC DPH) between October 20 and December 30, 2014. Individual baselines were defined as either the cumulative moving average of all temperatures before the peak measurement or the mean of the first six measurements.

Temperatures measured by travelers ranged from 33.2°C (91.8°F) to 37.3°C (99.1°F). Individuals' mean temperatures ranged from 35.3°C (95.6°F) to 36.9°C (98.4°F). Applying our proposed definitions, each individual's fever threshold would be less than the Center for Disease Control and Prevention's (CDC) reference level of 38.0°C (100.4°F), and for 62% would be less than that of the Dallas nurse who traveled with a temperature of 37.5°C (99.5°F) and later was diagnosed with EVD. While no traveler to Los Angeles County (LAC) developed EVD and sensitivity could not be calculated; nonetheless, a better method for determining a threshold for travelers would be helpful. One monitored traveler who was not diagnosed with EVD had a peak temperature 1.3°C (2.3°F) higher than the mean; thus, the specificity of our fever definition was 97.8%.

A limitation of this analysis is the relatively small number of persons monitored in California and for whom data are available. Analysis of data from other health departments would help refine the specificity estimate. This strategy may be useful not only for EVD but also other infectious conditions where temperature monitoring is done.

Early detection of persons with EVD is critical to preventing the spread of infection. As EVD cases have occurred outside of West Africa, screening and monitoring of travelers from affected countries have been implemented in several countries. In October 2014, US health officials began airport screening of travelers from affected countries. Initial screening includes identifying exposures and defining risk-level, measuring temperature and assessing other symptoms that may be compatible with EVD. Subsequent monitoring by the health department at the traveler's final destination includes twice daily temperature measurements and assessment of other symptoms for a 21-day period during which EVD becomes manifest among the large majority of infected people [1,2].

Fever is a key indicator in the detection of EVD as an early and common symptom among ill persons. Among 1,152 EVD patients in the West Africa outbreak, 87.1% had a measured temperature of >38°C (100.4°F) or a history of fever [2]. Among 103 persons in an earlier Democratic Republic of Congo outbreak, 93% were febrile [3]. The threshold for defining fever among travelers arriving from affected countries and for contacts of EVD patients in the US initially was defined as 38.6°C (101.5°F) but subsequently was lowered to 38.0°C (100.4°F) to increase sensitivity.

The suitability of this definition was questioned, however, when a nurse who cared for a US EVD patient traveled by airplane with a temperature of 37.5°C (99.5°F) and was later diagnosed with EVD [4]. For the CDC and state and local health departments monitoring travelers, fever detection is an important component of monitoring to protect public health and to maintain public confidence.

The widely used definition of 37.0°C (98.6°F) as normal body temperature and 38.0°C (100.4°F) as fever is based on an 1868 study by Wunderlich and Seguin [5]. More recent studies have challenged this definition, finding variation between individuals and systematic differences based on age, gender, time of day, and method of measurement [6-8]. For example, among 148 healthy Baltimore adults ages 18 through 40 years, 700 temperature measurements showed a mean temperature of 36.8°C (98.2°F) and a range from 35.6°C (96.1°F) to 38.2°C (100.8°F); women's temperature was significantly higher than that of men and temperatures in the morning were significantly lower than in the evening [6].

High sensitivity in defining fever is critical for early detection of EVD. An unrecognized case ("false negative" from monitoring) may transmit infection, expose additional persons posing a greater burden for public health agencies, and increase fear of EVD in the community. High specificity also is important given the resources required for diagnosis and the potential disruption of the healthcare system in evaluating a suspected case. Following a report showing low sensitivity of temperature cutoffs of 38.6°C (101.5°F) and 38.0°C (100.4°F) for Ebola among five patients who had serial temperature measurements, we re-evaluated our approach to defining fever among monitored travelers in LAC [9]. Another example that prompted our re-evaluation is the experience from Spain where an infected nurse assistant had "low-grade fever" <38.0°C (100.4°F) for several days before Ebola diagnosis [10].

Whereas using a single fever threshold is necessary when a person is evaluated for infection *de novo*, in a setting where serial measurements are obtained before illness occurs (e.g. where a person is being monitored), healthcare providers have the ability to refine the definition of fever as a difference from the individual's own baseline. In this report, we analyze data from travelers monitored by LAC DPH and the California Department of Public Health (CDPH) to evaluate two potential definitions of fever that may increase the sensitivity of EVD detection while remaining highly specific.

METHODS

During the EVD West Africa outbreak, the CDC informed CDPH of all people from an Ebola-affected countries traveling to the state. CDPH then forwarded traveler contact information to the local health department where the traveler would reside, and that health department monitored the traveler for fever and other Ebola-associated symptoms for 21 days following their last possible exposure, generally their departure from West Africa [11]. Travelers were given a digital oral thermometer on their entry to the US and asked to take their temperature twice daily, in the morning and evening, although specific times were not defined. Measured temperatures and other symptoms were recorded on a diary card and reported in a daily telephone call with the local health department. As a public health surveillance and emergency response activity, informed consent was not required to collect these data from persons being monitored. This study used anonymized data that was maintained in encrypted form and was approved as exempt research by the LAC DPH Institutional Review Board.

At the onset of monitoring for persons in LAC, public health nurses provided education to all adult travelers about how to take oral temperatures. At an initial home visit, travelers were asked to demonstrate taking their temperatures orally. Two children, ages 2 and 3 years, had axillary temperatures measured. Because temperatures from these children were low (with some measurements <34.0^{o}C [93.2°F]) and variable, suggesting difficulty with accurate measurement using this method, they are excluded from the analysis.

Between October 20 and December 31, 2014, 47 travelers were monitored by the LAC DPH (n=38) and by other counties reporting to CDPH (n=9). Data from travelers with at least six temperature measurements are included in this report. For each traveler, we determined the overall mean temperature, the mean temperatures in the morning and evening, and the maximum temperature. We established an individual's baseline temperature in two ways: 1) as the mean of all temperatures before the person's maximum temperature (cumulative moving average, CMA), with a minimum of at least 6 measurements, and 2) as the mean of the first six temperatures recorded (first-6 mean). We calculated the specificity of definitions of fever as 1.0^{o}C (1.8°F) higher than a person's CMA or first-6 mean temperatures. While sensitivity could not be assessed as none of the travelers were diagnosed with EVD, we determined individual and overall mean differences between our definitions of fever and that of the CDC (38.0^{o}C [100.4°F]).

Data were entered into a Microsoft Excel 2010 file and analyzed using Excel and SAS software, version 9.3. Associations of temperature with time of day, age group, gender, and gender-specific age groups were assessed using a student t-test.

RESULTS

Data from 45 travelers who had six or more oral temperature measurements were analyzed. Overall, 1,335 measurements were recorded (mean 29.7 per person). No travelers were identified as having EVD. Ages ranged from 4 to 67 years, and 44 (97.8%) were age 20 years or greater; 66.7% were male. Compliance with measuring temperature was 98.7% (18 of 1,335 potential observations missing).

The temperatures measured and reported by travelers ranged from 33.2°C (91.8°F) to 37.3°C (99.1°F). Individuals' mean temperatures ranged from 35.3°C (95.6°F) to 36.9°C (98.4°F) (Figure 1). The mean and median of the individual mean temperatures were 36.3°C (97.3°F) and 36.4°C (97.5°F), respectively. The morning mean and the evening mean were not different (both 36.3°C [97.3°F]) (Figure 2). Women's mean temperature was higher than that among men (36.5°C [97.7°F] and 36.2°C [97.2°F], respectively, $p=0.07$). Among adults age 20 to 59 years, women had a significantly higher mean temperature than men ($p<0.01$). Individuals' maximum temperatures were on average 0.59°C (1.06°F) greater than their mean temperatures. The mean differences between mean and maximum temperatures for women and men were 0.61°C (1.10°F) and 0.51°C (0.92°F), respectively.

Applying a proposed definition of fever as at least 1.0°C (1.8°F) greater than an individual's mean temperature, using the CMA of all temperature measurements before the maximum value, the temperature cutoff for fever would be from 36.7°C (98.1°F) to 37.9°C (100.2°F). Thus, for all travelers, this threshold would be lower than CDC's 38.0°C (100.4°F) reference level. In addition, for 28 (62%) of 45 travelers, the threshold would be lower than the temperature at the time of travel (37.5°C [99.5°F]) of the Dallas nurse who later developed EVD. For one traveler, the maximum temperature was 1.3°C higher than the mean; thus, the specificity of our fever definition was 97.8%. This 52-year old male's reported temperatures ranged from 33.2°C (91.8°F) to 36.8°C (98.2°F) and eight of his 24 measurements were lower than 35.0°C (95.0°F). His mean temperature of 35.3°C (95.6°F) was lower than that of any other traveler.

Using the first six temperature measurements to define a person's baseline temperature yielded very similar results to defining a baseline as the mean of all measurements before their maximum temperature. Of 45 travelers with more than six measurements, for 23 (51%) the means using the two methods were the same, for 18 (40%) were within 0.1°C (0.2°F), for 3 (7%) were within 0.2°C (0.4°F), and for 1 (2%) was within 0.3°C (0.5°F). Where results differed, for 12 persons the first-6 mean was higher, and for 10 it was lower than the CMA. For two travelers, maximum temperatures exceeded the first-6 mean temperature by >1.0°C (1.8°F): one was the same traveler who exceeded the CMA threshold described above, and the other was a traveler whose maximum temperature was 1.0°C (1.8°F) over the first-6 mean baseline and 0.9°C (1.6°F) higher than the CMA baseline.

DISCUSSION

Early identification of EVD among travelers and case-contacts is a public health priority. Given the significance of fever as an early sign of illness and recognizing that people's baseline temperatures may substantially vary; it may be beneficial to explore fever definitions other than the classical single threshold identified almost 150 years ago. Based on the range of mean temperatures we observed, the increase among persons monitored in California required to exceed the CDC 38.0°C (100.4°F) threshold, ranged between 1.1°C (2.0°F) and 2.7°C (4.9°F). Where this increment is smaller, the specificity of this definition may be lower whereas where the difference is greater, the sensitivity would be lower. Fever due to infection occurs with the release of cytokines which act at the hypothalamic thermoregulatory center to elevate the temperature set point [12]. Thus, it is plausible that the temperature of people early in their Ebola illness varies with their baseline temperature and the elevation of their own temperature set point.

The temperature increase with infection has been shown to be less among the elderly [13] making a more sensitive fever threshold particularly important in this group.

To our knowledge, there are limited data on serial temperature measurements in persons early in the course of EVD. A description of the first case acquired in Europe associated with the West Africa epidemic noted “low-grade fever” (temperature <38°C [100.4°F]), which continued for three days, but the specific temperatures were not published [10]. A note about five EVD patients who had serial temperature measurements suggested sensitivities of 79% and 53% for cutoffs of 38.0°C (100.4°F) and 38.6°C (101.5°F), respectively [9]. However, this analysis assessed all temperatures measured during the course of their illness rather than focusing on temperatures at the time of presentation. Reviewing data from the five patients cited shows one of five with temperatures less than 38.0°C (100.4°F) during the first two days of their illness [14-16]. Data from the current EVD outbreak in West Africa may be available to better define the sensitivity of different fever thresholds at the onset of illness.

The performance of our two proposed definitions of fever was similar. For one false positive identified by both methods, the variability in temperature measurements and the frequency of temperatures less than 35.0°C (95.0°F) suggests measurement error. Intervention by a public health nurse reinforcing the proper way to take an oral temperature and elimination of very low measurements from calculating the baseline may increase accuracy. Applying the first-6 mean method would be easier for nursing staff since this value could be calculated after the first three days of monitoring and daily temperatures compared with this value. Because the CMA method requires recalculating the mean after each measurement, the monitoring process would be more complex. With either method, during the first three days before a baseline is established, using a single threshold for all persons monitored would be necessary. Based on our data and experiences from EVD among nurses from Dallas and Spain, an initial 37.5°C (99.5°F) threshold may be reasonable. Importantly, identifying a temperature that exceeds the threshold or identifying other EVD-compatible symptoms only signals the need for more evaluation including a thorough clinical and epidemiological assessment; thus, a “false positive” result for fever would lead to additional evaluation and potentially laboratory testing for Ebola.

A limitation of this analysis is the relatively small number of persons who have been monitored in California and for whom data are available. Further data from travelers we monitor and from those who are monitored by health departments elsewhere can be analyzed to refine the estimate of specificity. Because none of the travelers monitored developed EVD, we cannot quantify the increment in sensitivity of our fever definitions. Necessarily, sensitivity would be similar to or greater than the CDC reference level because each individual’s cutoff would be equal to or below 38.0°C (100.4°F). Because we did not observe temperatures being measured and cannot ensure the correct placement of the thermometer, some temperatures may be falsely low, and the mean and range from our population may not be directly comparable with the data from Wunderlich [5] or Mackowiak [6] where temperatures were measured by healthcare personnel. We also did not collect data on the use of antipyretics or assess other factors that may have influenced temperature measurements. Finally, we emphasize that decisions about evaluating a traveler for EVD should be based on a complete assessment including their exposure history, symptoms, and contextual factors such as ill contacts.

While the focus of this analysis is to develop and test hypotheses that may lead to improved early detection of EVD among travelers from outbreak-affected countries, this approach also may be relevant to other public health settings. It could be used for other emerging infections such as Severe Acute Respiratory Syndrome (SARS) or Middle East Respiratory Syndrome (MERS), for which travelers from specific countries or those who have had defined exposures may be monitored. For hospitalized patients where vital signs are regularly measured, graphing the temperature and identifying increases, which do not exceed an arbitrary cutoff, may trigger further investigation and diagnostic testing, increasing detection of nosocomial infection [17]. Finally, as the current EVD outbreak is likely to continue well into 2015, monitoring and early detection of this illness remain important.

REFERENCES

1. CDC. Ebola virus disease: algorithm for evaluation of the returned traveler. http://www.cdc.gov/vhf/ebola/pdf/ebola-algorithm.pdf. (Accessed January 12, 2015)
2. WHO Ebola Response Team. Ebola virus disease in West Africa – the first 9 months of the epidemic and forward projections. *N Engl J Med* 2014;371:1481-95.
3. Bwaka MA, Bonnet M-J, Calain P, et al. Ebola hemorrhagic fever in Kikwit, Democratic Republic of Congo: clinical observations in 103 patients. *J Infect Dis* 1999;179(suppl 1):S1–7.
4. Levs J, Yan H. CDC: US health worker with Ebola should not have flown on commercial jet. Cable News Network http://www.cnn.com/2014/10/15/health/texas-ebola-outbreak/. (Accessed January 12, 2015)
5. Wunderlich CA, Seguin E. *Medical Thermometry and Human Temperature*. New York, NY: William Wood & Co, 1871.
6. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6^{o}F, the upper limit of normal body temperature, and other legacies of Carl Reinhold August Wunderlich. *JAMA* 1992;268:1578-80.
7. Adhi M, Hasan R, Norman F, Mahmood SF, Naqvi A, Rizvi A-U-H. Range for normal body temperature in the general population of Pakistan. *J Pak Med Assoc* 2008;58:580-84.
8. Lu S-H, Leasure A-R, Dai T-Y. A systematic review of body temperature variations in older people. *J Clin Nursing* 2009;19:4-16.
9. Dananche C, Benet T, Vanherns P. Ebola: fever definitions might delay detection in non-epidemic areas. *Lancet* 2014;284:1743.
10. Parra JM, Salmeron OJ, Velasco M. The first case of Ebola virus disease acquired outside Africa. N Engl J Med. 2014;371:2439-40.
11. CDC. Interim US guidance for monitoring and movement of persons with potential Ebola virus exposure. www.cdc.gov/vhf/ebola/exposure/monitoring-and-movement-of-persons-with-exposure.html (Accessed 5/12/15)
12. Dinarello CA. Cytokines as endogenous pyrogens. *J Infect Dis* 1999;179(suppl 2):S294-304, JID 1999.

13. Kelly G. Body temperature variability (Part 1): a review of the history of body temperature and its variability due to site selection, biological rhythms, fitness and aging. *Altern Med Rev* 2006;11:278-93.
14. Emond RTD, Evans B, Bowen ETW, Lloyd G. A case of Ebola virus infection. *BMJ* 1977;2:541-44.
15. Formenty P, Hatz C, Le Guenno B, et al. Human infection due to Ebola virus, subtype Cote d'Ivoire: clinical and biologic presentation. *J Infect Dis* 1999;179(suppl 1):S48-53.
16. Isaacson M, Sureau P, Courteille G, Pattyn SR. Clinical aspects of Ebola virus disease at the Ngaliema Hospital, Kinshasa, Zaire, 1976. In Pattyn SR, ed.: *Ebola Virus Hemorrhagic Fever*. Amsterdam: Elsiever, 1976;22-26.
17. Wlodaver CG, Fever notions of the misinformed: a quality improvement project. J Oklahoma State Med Assn 2014;107:21-22.

Acknowledgements: The authors gratefully acknowledge the Public Health Nurses, Area Medical Directors and Area Health Officers, Division of Community Health Services, Los Angeles County Department of Public Health, for their work communicating daily with travelers to monitor temperatures. We also acknowledge Liora Schwartz whose insistence that she had a fever with a temperature < 37.5°C (97.5°F) because it was higher than her baseline provided the idea for this analysis.

Figure 1. Distribution of mean temperatures among 45 travelers from EVD affected countries being monitored by the LAC and CDPH

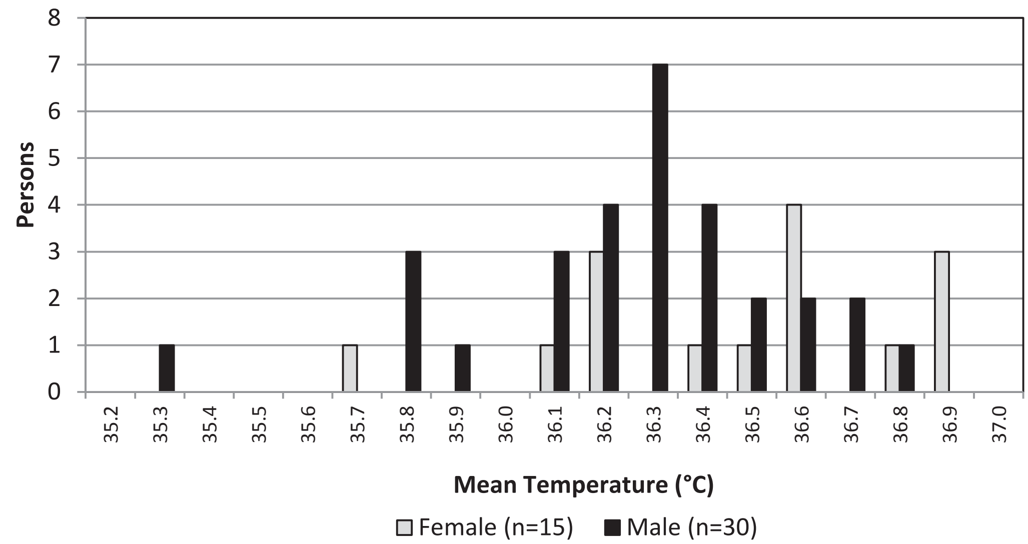
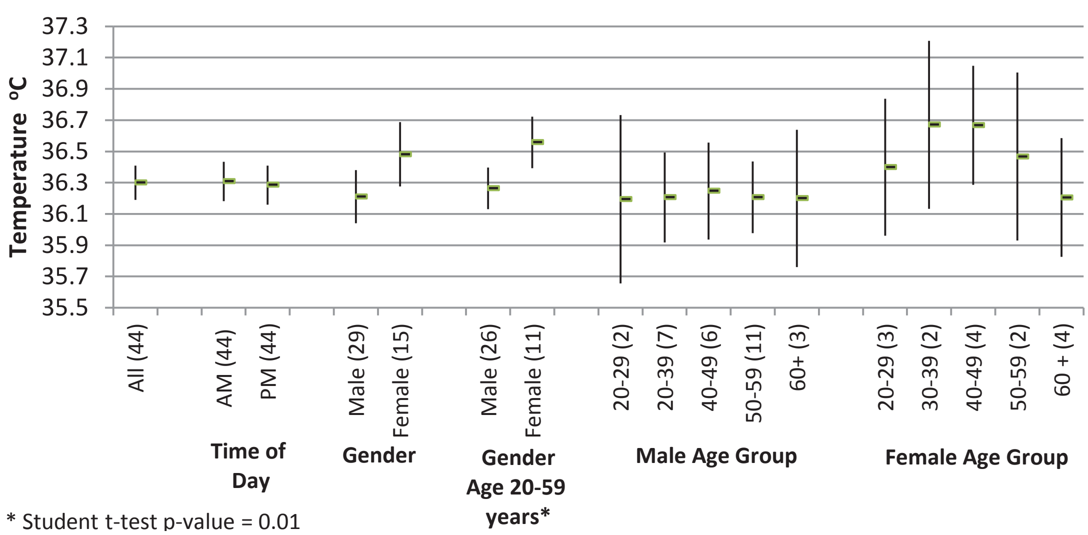


Figure 2. Mean oral temperatures and 95% confidence interval (vertical bars) for 44 travelers (adults >20 years old) monitored by the LAC and CDPH



* Student t-test p-value = 0.01