A Systematic Review of Risk Analysis Tools for Differentiating Unnatural From Natural Epidemics

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ABSTRACT   Introduction: In the era of genetic engineering of pathogens, distinguishing unnatural epidemics from natural ones is a challenge. Successful identification of unnatural infectious disease events can assist in rapid response, which relies on a sensitive risk assessment tool used for the early detection of deliberate attacks (i.e., bioterrorism). Methods: A systematic review was conducted according to the outline of Preferred Reporting Items for Systematic Reviews. Published papers related to the detection of unnatural diseases were searched in MEDLINE (January 1927–April 2016), EMBASE (January 1937–March 2016), and Web of Science (January 1978–March 2016). Full texts were reviewed for the selection of studies on scoring systems specially designed to discern between unnatural and natural outbreaks. Results: A total of 1,753 papers were reviewed, of which we identified the following five scoring systems specifically designed for detecting unnatural outbreaks: (1) the Grunow–Finke epidemiological assessment tool, (2) potential epidemiological clues to a deliberate epidemic, (3) bioterrorism risk assessment scoring, (4) and (5) two modified scoring systems based on (3). Various criteria ranging from the information on perpetrators, type of agents, spatial distribution, and intelligence of deliberate release were involved. Of these systems, the Grunow–Finke assessment tool remains the most widely used, but has low sensitivity for correctly identifying unnatural epidemics when tested against actual historical outbreaks. Others were applied into a few scenarios but provided different perspectives for bioterrorism detection and bio-preparedness. Conclusion: There are few risk assessment tools for differentiating unnatural from natural epidemics. These tools are increasingly necessary and valuable, but improved scoring systems with higher sensitivity, specificity, timeliness, and wider application to biological attacks must be developed.

INTRODUCTION

Infectious diseases are a constant threat as new pathogens are emerging and re-emerging from various parts of the world. Infectious disease agents that originate from one region may spread to other regions through people travelling, as well as trade, and tourism, which happened during the recent outbreaks of Ebola Virus disease[1] and Middle East respiratory syndrome coronavirus.[2] With quantum advances in science such as gene-editing with clustered, regularly interspaced short palindromic repeats associated protein 9,[3] it is easier than ever for infectious agents to be engineered in a laboratory and released deliberately.[4–7] The risk of unnatural outbreaks (e.g., bioterrorism) has increased in recent decades due, not only to the development of advanced scientific technology, but also to the relatively easy accessibility to scientific methods, open access availability of these methods, geopolitical instability, and global conflict.[8,9]

Unnatural epidemic events have continued to occur throughout history, illustrating a close link with war zones, which can be traced back to the first recorded event in 600 BC when the Helleborus roots were deliberately used by the Athenian dictator Solon to contaminate water supplies during the siege of Kirrha.[10–13] During World War I, anthrax and glanders were used as biological warfare agents by Germany to infect horses being shipped to the Allies.[14] During World War II, a plague epidemic broke out among Chinese military and civilian populations, which was the result of Japanese planes dropping plague-infected fleas over China.[10,15] In September 2001, an anthrax attack via the U.S. Postal Service occurred in the United States leading to 22 cases of anthrax infection.[16,17] Since then, there has been an increased public awareness of biosecurity.[4,18,19] However, many biological attacks and deliberate contaminations have not been recognized at the time, or were not documented.[20] In 1984, a Salmonella epidemic occurred in the U.S. state of Oregon and was assumed to be a natural food-borne outbreak by health authorities during their initial investigations. It was not confirmed as a bioterrorism event perpetrated by the cult of Bhagwan Shree Rajneesh until 1 year later when Rajneesh himself confessed.[21–23] In the absence of the confession, this attack would never have been recognized as bioterrorism.[21]

Early detection of infectious disease outbreaks, whether natural or unnatural, directly impacts disease prevention and control. Most microorganisms occur naturally in nature, so when an epidemic is detected, some form of risk analysis should be conducted to differentiate natural and unnatural events, and assess the likelihood of a deliberate attack. Scoring systems are useful to assess the likelihood of an unnatural epidemic when conclusive proof is not available.[22] The aim of this paper is to examine currently available scoring systems and criteria used to differentiate unnatural disease outbreaks from natural outbreaks.

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METHODS

The authors conducted a systematic review which followed the methods outlined in the Preferred Reporting Items for Systematic Reviews.[24] We sought to identify published papers of scoring systems designed for risk assessment of unnatural outbreaks including biological attacks, bioterrorism-related diseases, or potentially unnatural diseases. We searched for relevant articles from MEDLINE (January 1927–April 2016), EMBASE (January 1937–March 2016), and Web of Science (January 1978–March 2016). The following keywords were included: "bioterrorism," "biological warfare," "biological attacks," "bio defense," "bio strategy," "infectious agent," "unnatural outbreaks," "natural outbreaks," "infectious diseases," "communicable diseases," "disease outbreaks," "algorithms," "new virus," "identification," "unusual outbreaks," "epidemiology," "score system," "scoring system," "risk assessment," "deliberate outbreak," "artificial outbreak". Studies published in the English language were included. The initial search was made by one author (X.C.), and titles and abstracts were reviewed to select full papers. Full papers were independently reviewed by two reviewers (X.C. and A.A.C.).

In case of any discrepancies, a senior reviewer (C.R.M) was consulted for the final determination on selection of papers which have scoring systems specially designed to discern between unnatural and natural outbreaks.

RESULTS

We reviewed 1,753 papers to identify potentially relevant articles, of which 67 papers on risk analysis/assessment for infectious diseases outbreaks investigation were included for full-text review (Fig. 1). Of these, we identified five scoring systems designed specifically for detecting unnatural infectious disease outbreaks. The numbers of criteria used within each scoring system vary and range from 10 to 33 among the different scoring systems. Generally, the most common criteria in these various scoring systems are focused on information about perpetrators (e.g., motivation, number, and distribution), type of agents (e.g., category A, B, and C bioterrorism agents), spatial distribution, and intelligence on deliberate release (e.g., direct evidence, uncommon disease, and unusually high mortality). Qualitative and quantitative parameters involved in each scoring system are listed in Table I.
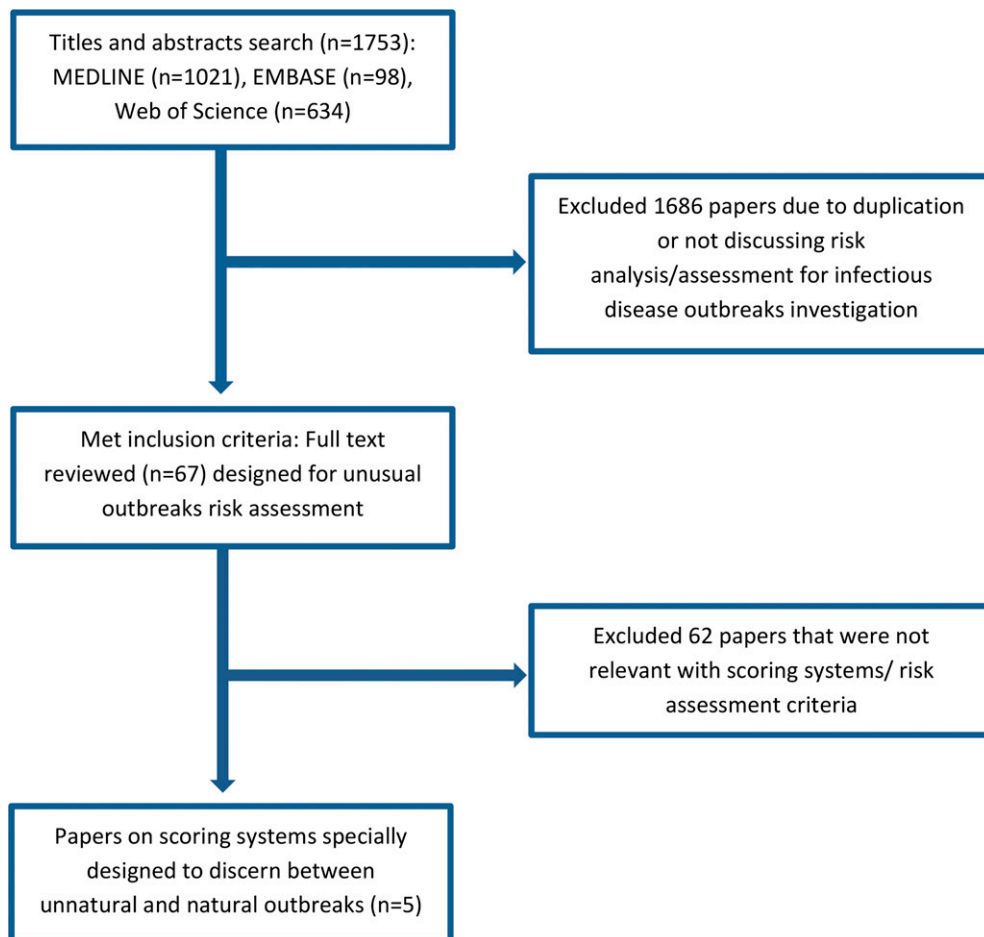

FIGURE 1. Search strategy and selection of papers.

TABLE I. The Peer-Reviewed Papers Associated with Scoring Systems of Bioterrorism-Related Outbreak Detection

Reference of Study	Name of Scoring System	Number of Criteria	Listed Criteria	Maximum Score (Cutoffs)	Used for Agents or Previous Outbreaks	Correct Identification[7]	Applicable to Other Diseases	Real Time Use	Objective	Strengths/Limitations
Grunow et al. 2002[25]	Grunow-Finke epidemiological assessment tool[22]	13	1. Bio-risk 2. Bio-threat 3. Peculiarities of the intensity and dynamics of the epidemic 4. Peculiarities of the transmission mode of the biological agent 5. Peculiarities of the time of the epidemic 6. Unusually rapid spread of the epidemic 7. Limitation of the epidemic to a specific population 8. Peculiarities of the clinical manifestation 9. Special aspects of the biological agent 10. Peculiarities of the geographic distribution of the biological agent 11. High concentration of the biological agent in the environment 12. Identification of the agent as a biological warfare agent 13. Proof of the release of the agent by a biological weapon	54 (0-17: Unlikely; 18-35: Doubtful; 36-50: Likely; 51-54: Highly Likely)	1. 1915, Anthrax, USA 2. 1971, Smallpox, Aralsk 3. 1979, Anthrax, Sverdlovsk 4. 1984, Salmonella, Oregon 5. 1995, Anthrax, Tokyo; 6. 1996, Shigella, Texas 7. 1999, WNV, NYC; 8. 1999, Tularaemia Kosovo 9. 2000, Tularemia, USA 10. 2001, Anthrax, USA 11. 2011, Haemolytic-uremic syndrome, Germany[42] 12. 2003, Ricin, USA 13. 2013, Rabies, Taiwan, China[32]	8 of 13 (62%)	Yes	Yes	Differentiating between natural and unnatural outbreaks	Most widely used; Quantitative measurements for criteria; *Subjective scoring; Time-consuming; Lowest correct identification rate in comparison with other scoring systems.*
Dembek et al. 2007[29]	Potential epidemiological clues to a deliberate epidemic	11	1. A highly unusual event with large numbers of casualties 2. Higher morbidity or mortality than is expected 3. Uncommon disease 4. Point-source outbreak 5. Multiple epidemics 6. Lower attack rates in protected Individuals 7. Dead animals 8. Reverse spread 9. Unusual disease manifestation 10. Downwind plume pattern 11. Direct evidence	NA	1. 1984, Salmonella, Oregon; 2. 1996, Shigella, Texas; 3. 2001, Anthrax, USA; 4. 1979, Anthrax, Sverdlovsk; 5. 1999, WNV, NYC; 6. 2000, Tularemia, Kosovo	4 of 6 (67%)	Yes	Yes	Evidence-based clues of deliberate epidemic	Widely used; Zoonotic diseases included; *Lack of algorithm for differentiation between natural and unnatural outbreaks.*

(continued)

TABLE I. Continued

Reference of Study	Name of Scoring System	Number of Criteria	Listed Criteria	Maximum Score (Cutoffs)	Used for Agents or Previous Outbreaks	Correct Identification[7]	Applicable to Other Diseases	Real Time Use	Objective	Strengths/Limitations
Radosavljevic et al. 2009[28]	Bioterrorism risk assessment (BTRA) scoring	23	1. Type of perpetrator (government institutions/organizations, terrorist groups, individuals) 2. Sophistication, motivation, ability, capacity 3. Intelligence/secrecy (global and local) 4. Number of perpetrators 5. Distribution of perpetrators (accessibility to sources of agent and accessibility to the target) 6. Type of agent 7. Accessibility to terrorists 8. Amounts of the available agent 9. Air 10. Food 11. Water 12. Fomites 13. Munitions 14. Delivery systems 15. Dispersion systems 16. Intelligence/secrecy (global and local) 17. Personal/individual control 18. Control of media (air, food, and water) 19. Control of fomites (office equipment, postal letters, etc.) 20. Parameters of protection (physical, chemical, immunological) 21. Number of people in the target 22. Distribution of people in the target 23. Location of the target	23 (NA)	2001, Anthrax, USA	1 of 1 (100%)	Yes	Not yet	The likelihood of a bioterrorism risk	Subtle and detailed criteria; *Lack of the application into other outbreak scenarios; Lack of algorithm for differentiation between natural and unnatural outbreaks.*
Radosavljevic et al. 2012[26]	NA	14	1. Unusual/atypical disease/manifestation (symptoms/signs) or unexpected fulminant course of disease in humans and/or animals 2. Failure of patient to respond to usual therapy or illness in a population (human, animal) despite immunizations 3. Several unusual/unexplained syndromes co-existing in the same case without any other explanation 4. Sudden unexplainable increase in the number of cases or deaths in human and/or animal populations	14 (1-4: Natural epidemic; 5-9: Probable deliberate or accidental outbreak; 10-14: Highly probable deliberate or accidental outbreak)	1. 2009, Swine flu, Mexico and North America; 2. 2000, Tularemia, Kosovo; 3. 1979, Anthrax, Sverdlovsk;	2 of 3 (67%)	Yes	Not yet	Early detection and quick orientation of UEEs	Refined criteria; *Lack of quantitative measurements for criteria.*

TABLE I. Continued

Reference of Study	Name of Scoring System	Number of Criteria	Listed Criteria	Maximum Score (Cutoffs)	Used for Agents or Previous Outbreaks	Correct Identification[7]	Applicable to Other Diseases	Real Time Use	Objective	Strengths/*Limitations*
			5. Morbidity and/or mortality higher than expected 6. Clustering of patients with fever and/or fever and respiratory symptoms and/or lymphadenopathy 7. Disease identified in the region for the first time ever or again after a long period of time 8. Disease with an unusual/atypical seasonal distribution 9. Simultaneous occurrence of epidemics and/or epizootics 10. Explosive epidemics and/or epizootics with indicators on a point-source origin 11. Disease with an unusual geographic distribution 12. Occurrence of a non-endemic (imported) or previously eradicated disease 13. Epidemiological data suggesting a common exposure 14. Simultaneous epidemics and/or epizootics occur at different locations							
Radosavljević et al. 2016[27]	NA	33	Perpetrator/source of infection/reservoir of pathogen 1. Sophistication 2. Motivation 3. Intention 4. Intelligence 5. Secrecy 6. Number of perpetrators 7. Number of sources of infection/reservoirs 8. Accessibility to sources of agent/pathogen 9. Accessibility to targets/population at risk Biological agent/pathogen 10. A category 11. B category	33 (0-8: Lowly probable type of outbreak (TO); 9-16: possible type of TO; 17-24: Highly probable TO; 25-33: Certain TO)	2011, Haemolytic-uremic syndrome, Germany	1 of 1 (100%)	Yes	Yes	Differentiating scoring for a natural outbreak of an endemic disease, a natural outbreak of a new/re-emerging disease, an accidental release and a deliberate outbreak	Most refined criteria; *Lack of the application into other outbreak scenarios; Lack of quantitative measurements for criteria.*

(continued)

TABLE I. Continued

Reference of Study	Name of Scoring System	Number of Criteria	Listed Criteria	Maximum Score (Cutoffs)	Used for Agents or Previous Outbreaks	Correct Identification[7]	Applicable to Other Diseases	Real Time Use	Objective	Strengths/*Limitations*
			12. C category 13. Emerging pathogen 14. Amount of the available agent/pathogen Means/media of delivery/factors of transmission 15. Air 16. Food 17. Water 18. Fomites 19. Vectors 20. Biological ammunition 21. Delivery systems 22. Dispersion systems/mechanism of release Target/susceptible population at risk 23. Intelligence 24. Secrecy 25. Personal control 26. Control of means/media of delivery/factors of transmission 27. Physical protection 28. Protection by chemoprophylaxis 29. Protection by immuno-prophylaxis 30. Importance of target/population at risk 31. Location of target/population at risk 32. Number of people in a target/population at risk 33. Distribution of people in a target/population at risk							

NA, not applicable.

The earliest scoring model is the Grunow–Finke epidemiological assessment tool[25] published in 2002, which is initially applied to bioterrorism-associated outbreak assessment by analyzing a tularemia outbreak in Kosovo that occurred from 1999 through 2000. It contains the following 11 nonconclusive criteria: *biorisk*, *biothreat*, *special aspects*, *geographic distribution*, *environmental concentration*, *epidemic intensity*, *transmission mode*, *time*, *unusually rapid spread*, *population limitation*, and *clinical*, and two conclusive criteria: *identification of the agent as a biological warfare agent* and *proof of the release of the agent as a biological weapon*. Each criterion is given an assessment point ranging from 0 to 3 based on the data and findings collected in the outbreak investigation, multiplied by a weighted factor (a value of 1, 2, or 3). The sum of the nonconclusive criteria were then ranked into four levels of the likelihood that this was an actual event of biological warfare. Based on Grunow–Finke epidemiological assessment tool, the tularemia outbreak in Kosovo was judged as a naturally occurring event. The nonconclusive criteria were widely used in many retrospective case studies to evaluate the potential possibility of bioterrorism, including the anthrax outbreak in the Eastern United States in 1915, the smallpox outbreak in Aralsk in 1971, and the Salmonella outbreak in Oregon in 1984.

Of the five scoring systems used for detection, three were developed by Radosavljevic V and other authors[26–28] from 2009 to 2016. In their first paper published in 2009,[28] 23 criteria are classified into the following four components in their bioterrorism risk assessment scoring system: perpetrator, agent, delivery, and target. Each component contains more detailed parameters than those used in the Grunow–Finke epidemiological assessment tool. For example, in the component of perpetrator, there are three qualitative criteria: *type of perpetrator (government institutions/organizations, terrorist groups, and individuals)*, *sophistication/motivation/ability/capacity*, *intelligence/secrecy (global and local)*, and two quantitative ones: *number of perpetrators* and their *distribution*. Each criterion is scored with a value of 0 (low probability) or 1 (high probability). However, in their evaluation, only the total score of perpetrator was calculated for the U.S. anthrax attack in 2001 without any other evaluation.

The second scoring system of Radosavljevic V and Belojevic G[26] published in 2012 has three variables: *cases*, *time*, and *spatial distribution*, with a total of 14 criteria. This scoring system correctly scored three unusual disease outbreaks, including the swine flu outbreak in Mexico and North America in 2009, the Kosovo tularemia outbreak in 1999–2000, and the Sverdlovsk anthrax outbreak in 1979. These criteria were mainly based on the 11 potential epidemiological clues to a deliberate epidemic by Dembek Z, Kortepeter M, and Pavlin J.[29] However, they provide more detailed quantitative and qualitative parameters, with a score of 0 or 1 (low or high probability of a deliberate or accidental outbreak) given to each parameter, and cutoff scores indicating the likelihood of unusual epidemic events.

Both scoring systems were further clarified and modified in their latest study,[27] in which differentiated scoring was developed for four types of outbreak: natural outbreak of an endemic disease, natural outbreak of a new or re-emerging disease, outbreak by accidental release of a pathogen, and deliberate outbreak. This scoring system was applied to analyze the German Escherichia Coli O104:H4 outbreak which occurred in 2011.[27] There were 33 criteria in four components: *perpetrator/source of infection/reservoir of pathogen*, *biological agent/pathogen*, *means/media of delivery/factors of transmission*, and *target/susceptible population at risk*. Compared to their first scoring system, in this new method, old criteria were regrouped, and new criteria were added. Each criterion was scored with a score of 0, 1, or not applicable, indicating low probability, high probability, or no data of certain type of outbreak. The total score was compared with four cutoff scores ranging from low probability, possible, high probability, and certain type of outbreak.

DISCUSSION

We identified five scoring systems for differentiating bioterrorism from naturally occurring outbreaks. These studies evaluate scoring systems for their intended purposes; some also apply them to other outbreak scenarios such as anthrax[29] and tularemia[26] outbreaks to show the usefulness for bioterrorism response, yet of which few have correctly differentiated between unnatural outbreaks and natural ones.[8,30,31] Only the Grunow–Finke criteria were applied to an ongoing outbreak,[32] thus it was difficult to evaluate the various systems in the field for early detection. Although some excellent work has been performed in developing scoring systems to detect unusual epidemic events, there is a need to evaluate these in a field environment and to build on this work to develop new, highly sensitive tools.

Successful unnatural epidemic detection requires a scoring system that is highly sensitive, highly specific, timely, and applicable to other threats.[8,33,34] So far, the Grunow–Finke epidemiological assessment tool has been applied to 13 scenarios,[29,32] and is more widely used than other scoring models. Although it is subjectively scored by the user,[22,35] the Grunow–Finke epidemiological assessment tool has correctly identified natural outbreaks, such as the U.S. West Nile outbreak in 1999, the Kosovo tularemia outbreak in 1999, and the U.S. tularemia outbreak in 2000.[8,29] However, of the eight actual bioterrorism attacks, only three incidents were correctly classified,[8] indicating its high specificity but low sensitivity for unnatural events. The 11 epidemiological clues to a deliberate epidemic, including the criterion of *dead animals*, would be sensitive for zoonotic disease detection, but zoonosis-related criteria are absent in other assessment tools, thus the animal data are assumed to be a good parameter to increase sensitivity.[36] In terms of correctly classifying natural epidemics, this is not of practical use because public health authorities tend to assume all

outbreaks are natural as a default position.[8,21] The far greater need is to correctly and with a higher degree of sensitivity, identify unnatural epidemics. For other scoring models, neither sensitivity nor specificity could be accurately assessed from the very limited number of scenarios. However, these models could be tested against historical outbreaks and refined to increase the sensitivity of unnatural epidemic identification.

The application of these scoring models in real time is different from retrospective application, given the timely accessibility of infectious disease intelligence for epidemic response. The Grunow–Finke assessment tool is considered to be time consuming for implementation in attacks where mass casualties are involved. The methods developed by Radosavljevic V, Belojevic G,[26,28] and Finke EJ,[27] which cover similar epidemiological parameters of deliberate epidemics but weighs criteria with better measurability, perhaps can provide a quicker detection of an unnatural outbreak. During a suspected, unnatural outbreak, the rapid identification of a bioterrorism event usually depends on the early diagnosis of the disease agent,[37,38] but it is always difficult, particularly for the new emerging infectious pathogens and genetically modified bioterrorism agents.

Though bioterrorism agents are categorized into three types,[39,40] different agents are scored with the same points in each system mentioned above. To some extent, this means that the likelihood of a bioterrorism event is unrelated to the category (A, B, or C) of the agent. However, an agent with a high score may suggest the high risk of a deliberate attack and priority of bio-preparedness. In terms of prioritization of bioterrorism agents for preparedness, MacIntyre CR, Seccull A, Lane JM, and Plant A,[41] developed a scoring method that prioritizes the risk levels of category A agents using 10 disease impact criteria: *infectivity of the agent*, *case fatality rate*, *stability in the environment and difficulty of decontamination*, *incidence of disease in worst-case scenario of release*, *reports of genetic modification to increase virulence*, *global availability and ease of procurement of the agent*, *ease of weaponization*, *historical examples of use or attempted use of this agent*, *lack of preventability*, and *lack of treatability of the disease*. Each criterion is scored with a score of 0 (no risk), 1 (some/low risk), or 2 (yes/high risk), and the total score is used to rank priority. It shows that anthrax has the highest risk-priority score for preparedness, followed by smallpox, viral hemorrhagic fevers, botulinum toxin, plague, and tularemia.[41] These perspectives would be helpful for developing an improved risk-assessment tool in the future. The limitation of our literature review is that we searched the available information from published papers. We may therefore have neglected to include potentially relevant scoring systems that are not yet published or publicly available yet. This is probably the case for systems developed by the military or intelligence communities whose objective is to collect, analyze, and explore information in support of national security, law enforcement, and policymaking.

CONCLUSION

Globally, there has been comparatively little effort to develop scoring systems to identify unnatural epidemics, yet there exists a growing need for such tools given the escalating potential for such events occurring. Only five risk assessment tools for discerning between unnatural and natural outbreaks of diseases were identified, of which the Grunow–Finke assessment tool remains the most widely used. However, the Grunow–Finke tool has low sensitivity for correctly identifying unnatural epidemics when tested against actual, historical outbreaks. We summarize the existing scoring systems and criteria used for the detection of unnatural disease outbreaks, their strengths, and limitations. The existing tools are valuable, but more work should be performed to improve sensitivity, specificity, timeliness, and the application to biological attacks. There is a critical need for such tools to facilitate the understanding of complex outbreaks, rapid epidemic response, and decision-making in public health.

ACKNOWLEDGMENTS

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