Early Detection of Public Health Emergencies of International Concern through Undiagnosed Disease Reports in ProMED-Mail

Camille Rolland, Clément Lazarus, Coralie Giese, Bastien Monate, Anne-Sophie Travert, Jérôme Salomon

We conducted a retrospective analysis of all reports in ProMED-mail that were initially classified as undiagnosed diseases during 2007–2018. We identified 371 cases reported in ProMED-mail; 34% were later diagnosed. ProMED-mail could be used to supplement other undiagnosed disease surveillance systems worldwide.

To preserve human health security, a global surveillance system able to rapidly detect, verify, and assess burgeoning outbreaks is key. The World Health Organization (WHO) International Health Regulations (2005) (1) provides an international and legally binding framework for the early detection of, reporting of, and response to any public health threat (e.g., infectious disease outbreaks) that might be of international concern using an all-hazards approach (2).

Event-based surveillance through informal sources now represents a critical source for epidemic intelligence (3). Almost all major outbreaks during 1994–2017 investigated by the WHO were early reported and identified through informal sources (4–7). One of the most valued, internationally acknowledged sources for epidemic intelligence activities that is also available as an open source is ProMED-mail (4,8). By relying on local media, professional networks, and on-the-ground experts, ProMED-mail staff produce reports on occurrences of emerging infectious diseases and outbreaks in near real-time. Specialist moderators curate these reports and provide subject matter expert commentaries.

ProMED-mail captures many reports of undiagnosed diseases (i.e., reports of public health events for which the diagnosis has not yet been found or reported by field professionals and cannot be classified). Events in these reports take place all around the world, and reports are provided without enough information to formulate a comprehensive risk assessment.

Even though an undiagnosed disease report in ProMED-mail might be an early signal of a major future event (e.g., outbreak), such reports have not been described in the literature. In this study, we aimed to provide a descriptive analysis of reports of undiagnosed disease events related to human health published on ProMED-mail since 2007 to determine whether these reports should be considered in further risk assessments.

The Study

We conducted a retrospective analysis of all reports of undiagnosed diseases in the ProMED-mail registry that were published during January 1, 2007–June 14, 2018 (Figure 1). ProMED-mail staff provided all the archives for undiagnosed diseases and unknown diseases relative to humans, animals, and plants. We also collected data directly from Disease Outbreak News on the WHO website (https://www.who.int/csr/don/archive/country) for the period of the study; these data are also open access and disseminated as specified by Article 11 of the International Health Regulations (2005). From ProMED-mail reports, we collected data on case location (WHO zone), source of information, date of publication, number of cases, geographic distribution (i.e., regional, national, or international) of cases, affected population, and final diagnosis. We searched the WHO website for the existence of a related Disease Outbreak News report. We sought information on the confirmation (i.e., biologic confirmation) of the final diagnosis both in subsequent ProMED-mail reports and in Disease Outbreak News reports.
Detection of Health Emergencies through ProMED

News reports. When several notifications were linked to 1 undiagnosed disease event, we made the link between notifications using the date of occurrence and location data. We described quantitative variables using median and range and qualitative variables using percentages.

During January 1, 2007–June 14, 2018, a total of 775 ProMED-mail reports accounted for 371 individual undiagnosed disease events in humans (Figure 1). The median number of undiagnosed disease events per year was 34 (range 15–45) (Figure 2). The sources of these reports were mainly the national press (67%, 250/371); 25% (93/371) were from international media, and 8% (28/371) were from experts.

The countries most affected by undiagnosed diseases were India (68/371), Sudan (20/371), Bangladesh (16/371), Nepal (15/371), China (14/371), the Democratic Republic of the Congo (13/371), Uganda (13/371), the United States (13/371), Vietnam (11/371), and Nigeria (9/371) (Appendix Figure, https://wwwnc.cdc.gov/EID/article/26/2/19-1043-App1.pdf). Overall, 44% of undiagnosed disease events were in rural areas and 56% were in urban areas; 8% (31/371) took place within a capital city. For 54% (200/371) of undiagnosed disease events, no specific population (e.g., children <18 years of age, persons >65 years of age, health professionals) was identified. For 2.4% (9/371) of undiagnosed disease events, healthcare professionals were affected.

We found a Disease Outbreak News report for 6.5% (24/371) of the undiagnosed disease events described in ProMED-mail. The median delay between the first ProMED-mail notification and the Disease Outbreak News publication was 18.5 (range –1 to 254) days (Table).
A final diagnosis was found for 34% (127/371) of undiagnosed disease events (Appendix Table). Among the 127 events for which a final diagnosis could be determined, the most frequent diseases were chikungunya (6/127), leptospirosis (6/127), Nipah virus infection (6/127), Ebola (5/127), meningitis (5/127), yellow fever (5/127), anthrax (4/127), Crimean-Congo hemorrhagic fever (4/127), and nodding disease (4/127).

undiagnosed diseases might be reported in various medical situations. They often occur in cases of delayed diagnosis of common diseases when access to appropriate medical care or services (e.g., epidemiologic investigations, laboratory testing) is limited. As such, most undiagnosed disease events occurred within low-resource countries. Undiagnosed disease reports less frequently account for unusual or unexpected diseases, such as imported or emerging diseases.

Reporting of undiagnosed diseases through ProMED-mail can be limited by climatic or geopolitical events in the region, which was probably reflected by the yearly and geographic variation in the reporting of undiagnosed disease events we observed. Although informal sources of public health information are valuable, the editorial content of the news sources the reports are based on can strongly limit their usefulness. Hence, our data analysis was limited by missing data.

Conclusions
The impact of ProMED-mail on the public health emergency preparedness response is reflected by the percentage of undiagnosed disease events published through this informal reporting system (6.5%) that were also shared internationally through WHO’s Disease Outbreak News website. Regions and countries could benefit from complementing their undiagnosed disease surveillance systems with ProMED-mail (9). Using this approach would help further establish undiagnosed disease event-based monitoring as an invaluable public health tool. ProMED-mail provides critical content and an alternative to standard indicator-based outbreak reporting for undiagnosed diseases (4).

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About the Author
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References

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Appendix

**Appendix Table.** Undiagnosed disease events in which diagnoses were later determined and list of diagnoses, by location (WHO zone), 2007–2018*

<table>
<thead>
<tr>
<th>Category</th>
<th>AFRO</th>
<th>PAHO</th>
<th>EMRO</th>
<th>EURO</th>
<th>SEARO</th>
<th>WPRO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undiagnosed disease events, n = 371, no. (%)</td>
<td>99 (27)</td>
<td>39 (11)</td>
<td>50 (13)</td>
<td>17 (5)</td>
<td>118 (32)</td>
<td>50 (13)</td>
</tr>
<tr>
<td>Disease events diagnosed, no./total no. (%)</td>
<td>40/99 (40)</td>
<td>12/39 (31)</td>
<td>15/50 (30)</td>
<td>2/17 (12)</td>
<td>32/118 (27)</td>
<td>26/50 (52)</td>
</tr>
<tr>
<td>Main diagnoses</td>
<td>Ebola (n = 5), meningitis (n = 4), yellow fever (n = 4), nodding disease (n = 4)</td>
<td>Leptospirosis (n = 2), Zika virus infection (n = 2)</td>
<td>Cholera (n = 2), dengue fever (n = 2), food poisoning (n = 2), Rift Valley fever (n = 2)</td>
<td>Hantavirus (n = 1), meningitis (n = 1)</td>
<td>Nipah virus infection (n = 6), chikungunya virus infection (n = 3), Crimean Congo hemorrhagic fever (n = 3)</td>
<td>Aflatoxin poisoning (n = 3), hand, foot and mouth disease (n = 3); leptospirosis (n = 3); methanol poisoning (n = 3)</td>
</tr>
</tbody>
</table>

*AFRO, African Regional Office; EMRO, Eastern Mediterranean Regional Office; EURO, Europe Regional Office; PAHO, Pan American Health Organization; SEARO, South-East Asia Regional Office; WHO, World Health Organization; WPRO, Western Pacific Regional Office.

†Two undiagnosed disease events were found in >1 WHO zone.
**Appendix Figure.** Geographic distribution of undiagnosed disease events posted in ProMED-mail from the 1 January 2007 to 14 June 2018 over the world.