Using network theory to identify disease outbreaks of unknown etiology

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Abstract

The identification of undiagnosed disease outbreaks is critical for mobilizing efforts to prevent widespread transmission of novel virulent pathogens. Recent developments in online surveillance systems allow for the rapid communication of the earliest reports of emerging infectious diseases and tracking of their spread. The efficacy of these programs, however, is inhibited by the anecdotal nature of informal reporting and uncertainty of pathogen identity in the early stages of emergence. We developed theory to connect disease outbreaks of known etiology in a network using an array of properties including symptoms, seasonality and case-fatality ratio. We tested the method with 125 reports of outbreaks of ten known infectious diseases causing encephalitis in South Asia, and showed that different diseases frequently form distinct clusters within the networks and the approach can correctly identify unknown disease outbreaks with an average sensitivity of 76% and specificity of 88%. Outbreaks of some diseases, such as Nipah virus encephalitis, were well identified (sensitivity = 100%, PPV = 80%), whereas others (e.g., Chandipura encephalitis) were more difficult to distinguish. These results suggest that unknown outbreaks in resource-poor settings could be evaluated in real-time, potentially leading to more rapid responses and reducing the risk of an outbreak becoming a pandemic.

Keywords: emerging infectious disease, encephalitis, complex networks, South Asia, Nipah virus encephalitis, cluster analysis, early warning system

Introduction

Despite the enormous social, demographic, and economic impact of emerging infectious diseases, and billions of dollars spent to control them, there has been limited progress in the development of tools for early intervention that could prevent the emergence and spread of pathogens in the initial stages of an epidemic (1-5). This is an acute problem in resource-poor nations that have limited surveillance capacity and often lack laboratory facilities to diagnose unusual outbreaks.

To address this issue, online databases and surveillance reporting networks have been developed to identify and monitor the emergence and spread of infectious agents. These include tools to aid in the clinical diagnosis of single cases of infectious diseases (6-12), tools that process unverified epidemic

intelligence using specific keywords, e.g. HealthMap.org (13, 14) and Google Flu Trends (15), those that compile verified outbreak data, e.g. GLEWS (16), GAINS (17), and GIDEON (6), and those that disseminate expert-moderated outbreak reports and anecdotal information, e.g. ProMED-mail (18). To the best of our knowledge, no decision support tool exists for the rapid and inexpensive assessment of outbreaks, particularly in the face of minimal information and limited resources to make the clinical assessments necessary to parameterize one of the existing diagnostic models.

We developed a method based on network theory to evaluate potential causes of outbreaks of disease. While many statistical approaches exist for assigning multivariate data records into categories, e.g. Bayesian network analysis or Discriminant Functions Analysis (19), the method we present here has the advantage of allowing for multiple equitable solutions for symptom assignment. Our method employs an ensemble of adequate solutions and this ensemble allows one to assess certainty of outbreak diagnosis assignment.

Network theory is the study of relationships between entities ('nodes') and connections between these entities ('edges') (20). Network theory has previously been used effectively to describe social and biological datasets (21, 22), and it has been shown to be a useful tool for cluster analysis (23). Here, we consider outbreaks as nodes, and create an edge between any two outbreaks if they share symptoms, or have similar properties such as case fatality ratio or seasonality (Fig. 1). We give an edge greater weight if the two outbreaks at either end are more similar in that sense (see supplementary methods for details). Groups of outbreaks that are more strongly connected to each other than to other outbreaks in the network can be said to form a 'cluster' or, more commonly in network theory, a 'community'. If outbreaks of different diseases were perfectly distinguishable on the basis of the properties we consider, each disease would form a single and distinct cluster of outbreaks of that disease. In that case we could use this to link unidentified outbreaks to those of known etiological agents with similar properties (e.g. seasonality, case fatality ratio, symptoms) by adding them to the network and testing which cluster they are most similar to (in the sense that they are strongly connected to outbreaks within that cluster). We applied this method to 125 outbreak reports of ten different diseases causing encephalitis in South Asia. Furthermore, we analyzed 97 outbreaks of encephalitis in South Asia reported on ProMED-mail that were reported without a definitive diagnosis. We associated each of them with one of the ten diseases based on which cluster in the network they are most strongly linked to. As such, our approach uses a novel interpretation of an abstract network to link (unidentified) outbreaks to those of known etiological agents with similar properties (e.g. seasonality, case fatality ratio, symptoms). We chose South Asia as it has been identified as an emerging infectious disease 'hotspot' (24), and has a history of recent pathogen emergence, including those causing encephalitis, e.g. Nipah virus encephalitis, Japanese encephalitis, and cerebral malaria (25). Further, investigations into encephalitis outbreaks in South Asia have been limited and diagnoses are sometimes controversial (26).

Methods

Differential Diagnosis of Diseases in South Asia

Our aim was to develop a method that could be used to identify the pathogens causing undiagnosed outbreaks of encephalitis in South Asia. We first built a library of potential pathogens, and then developed a model to quantify associations between the symptoms, seasonality, and case fatality ratio (CFR) caused by infection with these pathogens

We used the Global Infectious Disease and Epidemiology Network (GIDEON) online database to create a library of potential diseases and pathogens and to establish a differential diagnosis for diseases in South Asia with encephalitis as a potential symptom. The GIDEON database contains a diagnostic module that utilizes information on symptoms, country, incubation period, and laboratory tests to construct a ranked differential diagnosis (27). Using common characteristics of outbreaks reported in ProMED-mail, we queried GIDEON for the most likely diagnoses for such diseases in each of the eight nations comprising the South

Asian Association for Regional Cooperation (SAARC): Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka. Search criteria included "outbreak or case cluster", "severe/fatal", "fever", "neurological/headache", and "neurological/encephalitis". For each nation, we recorded all potential diagnoses with >1% probability of occurrence. Potential diagnoses with <1% probability of occurrence and "first case scenario" diagnoses were excluded. The ten diseases identified and their diagnoses were compiled into an inclusive list of differential diagnoses for the SAARC region. Two diseases, influenza and rabies, appeared in the region-wide differential diagnosis but were excluded from the analysis because symptoms associated with their outbreaks are distinct and relatively easily distinguished from encephalitides (e.g. for rabies, due to rapid fatality, lack of human-to-human transmission and distinct symptoms). Two other diseases, Chandipura encephalitis and chikungunya fever, were added to the differential diagnosis based on their increasing incidence within the region.

We then conducted a literature search to compile a dataset of the clinical and epidemiological features of known outbreaks of each of the ten diseases (Supplementary Appendix, Table S1): Chandipura encephalitis, chikungunya fever, dengue fever, Japanese encephalitis, malaria, measles, aseptic meningitis, bacterial meningitis, Nipah virus encephalitis (NiV), and typhoid/enteric fever. We searched the literature for the clinical and epidemiological features of each disease, and we restricted the results to the SAARC nations in order to capture the seasonality and disease etiology in this region. For each published report, we recorded the location of the outbreak or study, the month and year of recorded cases, CFR, and the prevalence of symptoms among cases (recorded as % of patients). Results for malaria include only complicated and cerebral malaria, and results for "dengue" include dengue fever, dengue hemorrhagic fever, and dengue shock syndrome.

Network Analysis

We developed a network model to determine how outbreaks of the same disease cluster together and how distinct they are compared to outbreaks of other diseases, with respect to seasonality, CFR, and symptoms. Our method is based on the assumption that in outbreaks of the same disease patients will show similar symptoms, occur in similar times of the years, and/or have similar CFRs. If this assumption is correct, outbreaks will be linked by similar traits and would be clustered into groups of the same disease (Fig 1) (28). We constructed a network from the set of 125 diagnosed outbreak reports from the literature of the ten diseases selected, with each node representing a single outbreak report. A connection (edge) is created between two outbreaks (nodes) if they share a symptom or property, with the weight of the edge given by a weighted sum of all symptoms/properties shared. We used a previously developed algorithm to detect densely connected clusters of outbreaks in networks (29). As some symptoms may be more important than others in distinguishing one disease from another, we allowed for unequal weights to each of the symptoms in the model. We determine appropriate symptom weights using a method that yields maximal within-cluster similarity and between-cluster dissimilarity (called network modularity, see Supplemental Appendix Methods and Table S2). Because multiple sets of symptom weights could result in similar maximal network modularity, we created an ensemble of sample networks, each with its own set of symptom/property weights, and averaged over all of them in evaluating the outbreak reports to increase the reliability of our analysis.

Model Testing

We tested the reliability of our method by removing each of the reference reports from the network, running the model with the removed reference report as an 'undiagnosed' report, and checking if the model-predicted diagnosis matched the actual diagnosis. This allowed us to determine the sensitivity (proportion of true positives correctly identified as such) and specificity (proportion of true negatives correctly identified as such) of the model for each disease. We calculated positive predictive values (PPV) and negative predictive values (NPV) for each of the ten diseases. PPV

is the proportion of positive results that are true positives (e.g. the proportion of outbreaks identified by the model as dengue that were laboratory confirmed as dengue cases), whereas NPV is the proportion of negative results that are true negatives (e.g. the proportion of outbreaks identified by the model as not dengue and were confirmed as something else). We assumed that each of the ten diseases considered was equally likely to be the correct diagnosis for any given 'mystery case' presented, and that all of our reports could be diagnosed as one of the ten diseases considered.

Undiagnosed Outbreaks

We reviewed ProMED-mail for reports of undiagnosed encephalitis between 1994 and 2008. Search terms included "encephalitis", "fever", "mystery", "undiagnosed", and "unknown origin". Search results were again restricted to the SAARC nations. For each ProMED-mail report, the geographic location, month and year of the first recognized case, number of people affected, number of deaths and clinical symptoms were recorded. We calculated the CFR as the number of deaths per total number of cases reported for each outbreak. For outbreaks with multiple associated incident reports over time, we recorded the total number of reports and final diagnosis, if provided.

For the period under study (1994-2008), a sample of 99 outbreaks of undiagnosed encephalitis was selected from ProMED-mail (Supplementary Appendix Table S3). We removed two outbreak reports that had incomplete information (lacking symptoms, CFR, or seasonality), reducing the dataset to 97 outbreaks. We added the undiagnosed outbreaks to each of the sample networks, using the weights as determined before. For each undiagnosed outbreak added, we determined the cluster the outbreak associated best with (see supplementary material), and recorded each disease present in that cluster. We used a bootstrap method across the sample networks to identify the disease associated most frequently with a given undiagnosed outbreak, and we consider this its primary diagnosis. We calculated the number of times a disease was associated with a given outbreak out of the total number of networks tested to determine an association score and a corresponding 95% confidence interval around this association. When multiple diseases had overlapping percent association confidence intervals, they were all considered to be plausible diagnoses (Supplementary Appendix Table S4), thus increasing sensitivity but reducing specificity of our method.

Results

Seven communities or clusters of outbreaks based on symptoms, seasonality and CFR were identified from associations of the original set of 125 outbreak reports from the literature of the ten diseases tested (Fig. 2, outer ring). Ideally, each cluster of outbreaks would consist of reports of a single disease. However, given overlapping sets of symptoms, CFR, or seasonality, most clusters included outbreaks of more than one disease. Of the ten diseases included in this study, NiV infection was identified most reliably (100% sensitivity, Table 1 and 80% PPV, Table 2), and forms a distinct cluster (Fig. 2). It was unique in our analysis in having a high CFR (~70%), a distinct seasonality (spring), and symptoms of respiratory difficulty, seizure, unconsciousness, vomiting and weakness. Other diseases with relatively high PPV were chikungunya fever (75% PPV) on the basis of low CFR and symptoms of nausea, joint pain, rash, and myalgia, and typhoid fever (58% PPV) based on the symptom of pneumonia and low CFR (a few percent). Diseases that were moderately difficult to identify were malaria (47% PPV) on the basis of CFR (~30%) and the symptoms of unconsciousness, jaundice, acute renal failure, seizure, respiratory difficulty and neck rigidity; and bacterial meningitis (PPV 42%) on the basis of CFR (~15%) and neck rigidity. The diseases most difficult to identify were dengue fever (31% PPV), Chandipura encephalitis (27% PPV), Japanese encephalitis (25% PPV) and measles (21% PPV), all of which had properties that made them similar to other diseases. As the reference dataset contained only three entries of aseptic meningitis the PPV of 49% is tentative.

Of the 97 unidentified outbreaks from ProMED that we analyzed, our model evaluated

27 as uniquely associated with a single disease (Fig. 2, white circles of the inner network; Supplementary Appendix Table S4). A further 38 diseases were associated with two diseases and 16 were associated with three of the ten diseases. Of these 54 that yielded multiple diagnoses, six were associated with NiV. Sixteen outbreaks were marked as inconclusive because they either did not contain enough information or associated with more than three diseases.

Since NiV was the best-predicted disease in our dataset (PPV 80%) and is relatively new and therefore easily misidentified on the ground, we investigated further the possible outbreaks of NiV (Fig. 3). Of the six associated with NiV in our model, two were clinically confirmed as NiV in follow-up studies. For the other four, two were never identified, one was diagnosed as dengue (but moderators speculated that it may have been NiV), and one was diagnosed as avian influenza, which was not represented in our reference dataset.

Attempts to identify two unknown outbreaks highlight the importance of accurate data in the initial reports. Our model associated two other outbreaks that were later reported in the literature to have been diagnosed as NiV with malaria, bacterial meningitis, Japanese encephalitis or typhoid fever (30, 31). This misidentification resulted from the fact that in the initial ProMED-mail reports for these two outbreaks, the CFR was significantly lower than in the post-outbreak data in the literature (30, 31). The CFR may have been understated in ProMED-mail reports due to incomplete recording or right-censoring of the CFR when estimated during an ongoing outbreak (32). When the later estimates for CFR from the literature were used for these two outbreaks, our method correctly identified them as NiV.

Discussion

We have developed a novel method to identify disease outbreaks based on their similarity in properties and symptoms reported. Our method yielded high PPV, sensitivity and specificity for an important virulent disease, NiV, and relatively high values for several other causes of encephalitis in South Asia. We then used this method on unidentified reports of encephalitis outbreaks in South Asia, and identified several outbreaks as likely being caused by NiV, which was new to the region at the time when the outbreaks occurred. Retrospective studies of several of the NiV outbreaks identified the causative agent, and our method provided the correct identification in all cases, but with a key caveat: when the original outbreak contained inaccurate information on one or more outbreak traits (in this case, the CFR), the method incorrectly classified the outbreaks. This highlights the strength of the method when the original outbreak has accurate information, as well as the importance of the quality of information in the reporting system. Unfortunately, inaccurate initial estimates of the CFR are not infrequent (and difficult to correct if they result from right-censoring) and can lead to allocations of public health resources that might retrospectively be considered less than ideal, e.g. the 2009 H1N1 pandemic (33-35).

There are limitations to our approach, and this study provides a proof-of-principle for a potentially powerful method. As just noted, the accuracy of our method relies critically on the accuracy of the data reported and the completeness of the reports. Furthermore, it is possible that some outbreaks continued beyond the last posting of details on ProMED-mail, and CFRs estimated during an outbreak are known to be biased (32). Some of these problems could be mitigated by including data taken at different stages of outbreaks or by comparing the unidentified outbreak reports with identified outbreaks reported via the same source (ProMED-mail). In addition, even with accurate information, our method can only provide probabilities for association with each of the diseases based on the assumption that it is one of the diseases. However, while our method is currently limited by the list of reference diseases provided, it can also be used to flag reports which do not seem to fit any of these well. If, for example, several outbreak reports for a region were highly clustered with each other but not with any known disease in the model, then this would be evidence for a potentially new disease, or new disease to the region, and could be prioritized for further investigation. Similarly, this approach may have value in determining

whether exotic pathogens have been introduced to a region either inadvertently or deliberately. The ensuing outbreaks may have characteristics that cause them to cluster with diseases outside those normally encountered in a region, and an expanded network analysis may be able to identify their etiology more rapidly than sample collection would allow.

Further, this method can be applied more broadly to extend the range of diseases as well as hosts under consideration (e.g. zoonotic disease in wildlife reservoir hosts). Disease communities with distinct symptoms will be the best candidates for use with this method. Encephalitis was an ideal candidate symptom as it was less common than a symptom such as fever, but common enough to be shared by a set of diseases within a single region. Diseases with respiratory illness, on the other hand, would be significantly more difficult to differentiate because of the ubiquitous nature of this symptom across many possible diseases. Further research is required to determine the full potential of this approach and the applicability of this method to other diseases.

A major strength of our approach is that it does not require expert judgment or laboratory analysis, and provides a way to quickly and inexpensively assess outbreaks. A key direction for future research would be to compare the approach we have proposed here to expert opinion. Comparisons of our method to other clustering techniques would also be of substantial interest, but we note that an important challenge is that many other methods have substantial difficulty with incomplete data and unequal weighting of traits, whereas our method is able to overcome both of these obstacles. Given the opportunistic nature of outbreak reports, this is an important strength.

Our method has the potential to greatly increase the value of surveillance systems like ProMED-mail, and online surveillance systems in general, which rapidly disseminate information on outbreaks prior to the results of laboratory diagnostics. Although our initial analysis was restricted to ProMED-mail it is likely that this method would also be effective using data that has been collected by filtered searches such as those used by HealthMap (14). More generally, the recent increase in the number of online surveillance tools, and their speed and efficiency at reporting novel outbreaks, combined with our analysis approach, could become a significant rapid identification tool for diagnosis.

With increasing availability and capacity of Internet surveillance systems, our application of network theory to outbreak assessment demonstrates the inherent, and underestimated value in collecting key data on novel outbreaks, and disseminating it early and openly. There is immense potential in using methods for automatic text recognition combined with improvements to our method and integration with alternative methods for cluster analysis, to extract as much information as possible from these reports. Many new infections such as NiV first emerge in resource-poor regions, making an intensive and/or active surveillance system difficult. With relatively little additional development, the method presented here could provide a low-cost tool that allows for the rapid, objective assessment of outbreaks of diseases at the onset of their emergence.

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Table 1: The sensitivity and specificity for every disease pair using the outbreak assessment model. The values on the diagonal (shaded cells) give the sensitivity, that is, the proportion of actual positive diagnoses that are correctly identified as such. The off-diagonal values (non-shaded cells) give the specificity for each disease pair, that is, the proportion of actual negatives that are correctly identified as such.

	Aseptic Meningitis	Bacterial Meningitis	Chandipura encephalitis	Chikungunya fever	Dengue	Japanese Encephalitis	Malaria	Measles	Nipah virus encephalitis	Typhoid Fever
Aseptic Meningitis	0·33	1	0·75	1	0.98	0·92	1	1	1	1
Bacterial Meningitis	1	0·53	1	1	1	0·77	0·67	0·91	1	0·91
Chandipura encephalitis	1	0·94	0·25	1	1	0·92	1	1	0·55	0·91
Chikungunya fever	1	1	1	0·86	0·8	1	1	0·91	1	1
Dengue	0·67	0·88	1	0·14	0·95	0·77	0·94	0·55	1	0·91
Japanese Encephalitis	0·67	0·47	0·75	0·86	1	0·62	0·61	0·91	1	0·91
Malaria	1	0·59	1	0·86	1	0·85	0·72	0·91	1	1
Measles	0·33	0·71	0·75	0·71	0·8	0·77	1	0·55	1	0·82
Nipah virus encephalitis	1	1	0·75	1	1	1	1	1	1	1
Typhoid Fever	1	0·82	1	1	0·95	1	1	0·64	1	0·82

Table 2: Positive and negative predictive values for every disease pair using the outbreak assessment model. Positive predictive values (PPV) on the diagonal (shaded) give the proportion of actual model predicted positive diagnoses that are true positives. Negative predictive values (NPV) on the off-diagonals (non-shaded) give the proportion of negative model predictions that are true negative diagnoses.

	Aseptic Meningitis	Bacterial Meningitis	Chandipura encephalitis	Chikungunya fever	Dengue	Japanese Encephalitis	Malaria	Measles	Nipah virus encephalitis	Typhoid Fever
Aseptic Meningitis	0·49	1	0·63	1	0.96	0·89	1	1	1	1
Bacterial Meningitis	1	0·42	1	1	1	0·82	0·74	0·93	1	0·93
Chandipura encephalitis	1	0·94	0·27	1	1	0·92	1	1	0·51	0·90
Chikungunya fever	1	1	1	0·75	0·83	1	1	0·92	1	1
Dengue	0·89	0·96	1	0·72	0·31	0·93	0·98	0·85	1	0·97
Japanese Encephalitis	0·86	0·78	0·90	0·94	1	0·25	0·84	0·96	1	0·96
Malaria	1	0·73	1	0·91	1	0·90	0·47	0·94	1	1
Measles	0·75	0·89	0·91	0·89	0·93	0·91	1	0·21	1	0·93
Nipah virus encephalitis	1	1	0·8	1	1	1	1	1	0·8	1
Typhoid Fever	1	0·87	1	1	0·97	1	1	0·74	1	0·58

Figure 1: The method to cluster disease reports of similar properties, here demonstrated using a network consisting of six outbreak reports of bacterial meningitis and six of Nipah virus encephalitis: (A) Each outbreak report is associated with a single network node (circle). (B) Edges (lines) between nodes are created if the two reports represented share a symptom or other property. Edges are thicker if more symptoms are shared, and the size of a node represents the total number of symptoms/properties shared with other nodes. Edge length, however, is not significant. (C) Each symptom and outbreak property is then given a weight, and the edge thickness (or edge weight) is now representative of the sum over all the weights of symptoms/properties shared between the two disease reports at the end of the edge. The symptom weights are optimized for greatest clustering of reports. The size of a node now represents the sum over the weights of all edges connected to it, which can be interpreted as the amount of information contained in the report that is relevant for the clustering of reports. (D) An algorithm for community detection finds two clusters: edges that connect two nodes within the same cluster are black, and ones that connect two nodes in two different clusters grey. Here, the algorithm was successful at distinguishing between bacterial meningitis (red) and Nipah virus encephalitis (cyan). Note that in all figures, lengths of edges and positions of nodes have no meaning as such, and have been chosen based on an algorithm for optimal visualization (36).

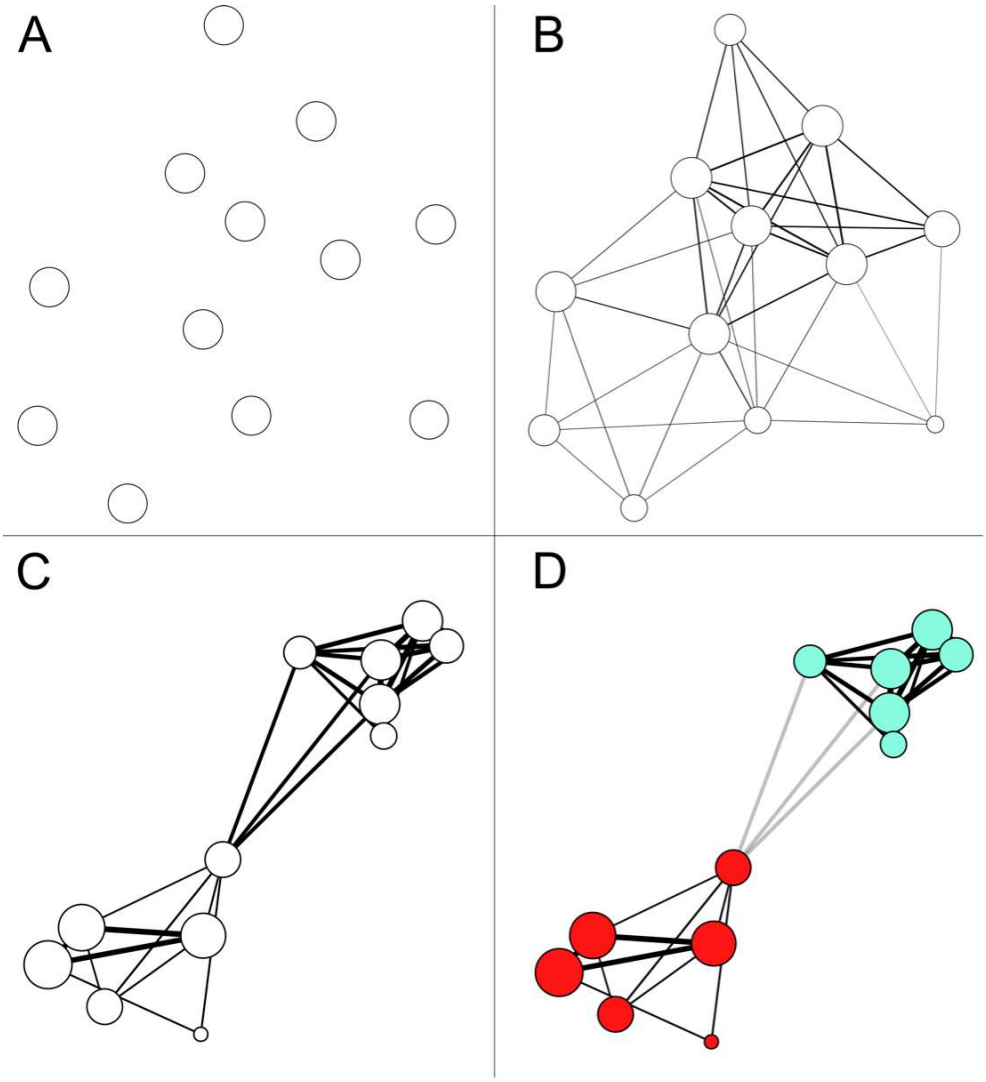


Figure 2: Visualization of the network of diagnosed outbreaks of diseases with the potential to cause encephalitis (colored) and outbreaks of undiagnosed encephalitis (white). The inner network describes the strength and relationship of individual outbreaks to each other, while the outer ring gives the composition of the seven communities of disease that are found by the community detection algorithm. Outbreaks of the same disease (color) tend to cluster together. The network model acts to minimize the number of edges between outbreaks in different communities of disease and maximize the number of edges between outbreaks within a single community of disease. Each circle, called a 'node', represents a single outbreak report. Lines connecting two nodes indicate shared traits between two outbreak reports, in symptoms reported, the case fatality ratio or seasonality. Lines connecting two outbreaks within a single community are black, and lines between two outbreaks in different communities are in grey. Thicker lines represent a greater number of shared traits and thinner lines indicate fewer shared traits. Where nodes overlap, they are strongly connected. The size of a node (circle) representing an outbreak is proportional to the sum over the thicknesses of all edges connected to it, which can be interpreted as the amount of information contained in the outbreak report. Note that in all figures, lengths of edges and positions of nodes have no meaning as such, and have been chosen based on an algorithm for optimal visualization (36).

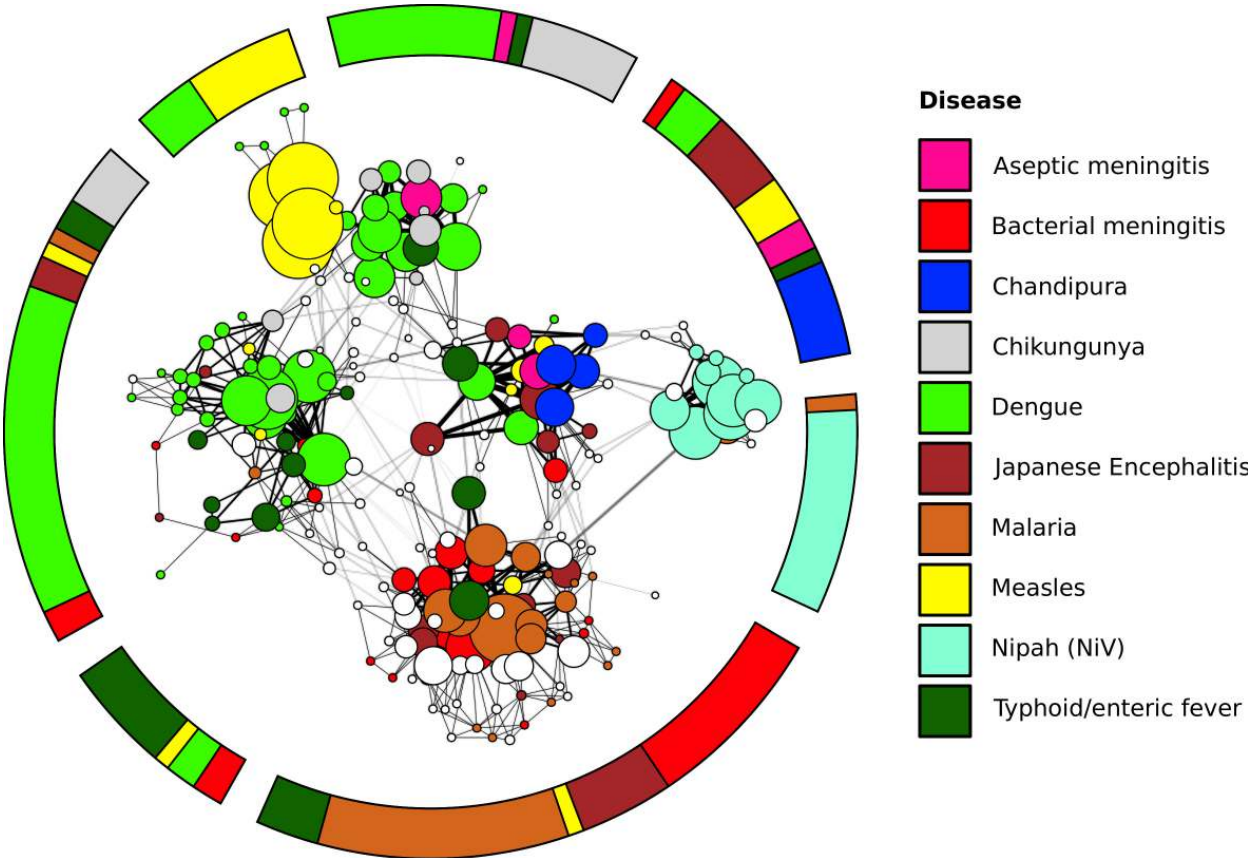
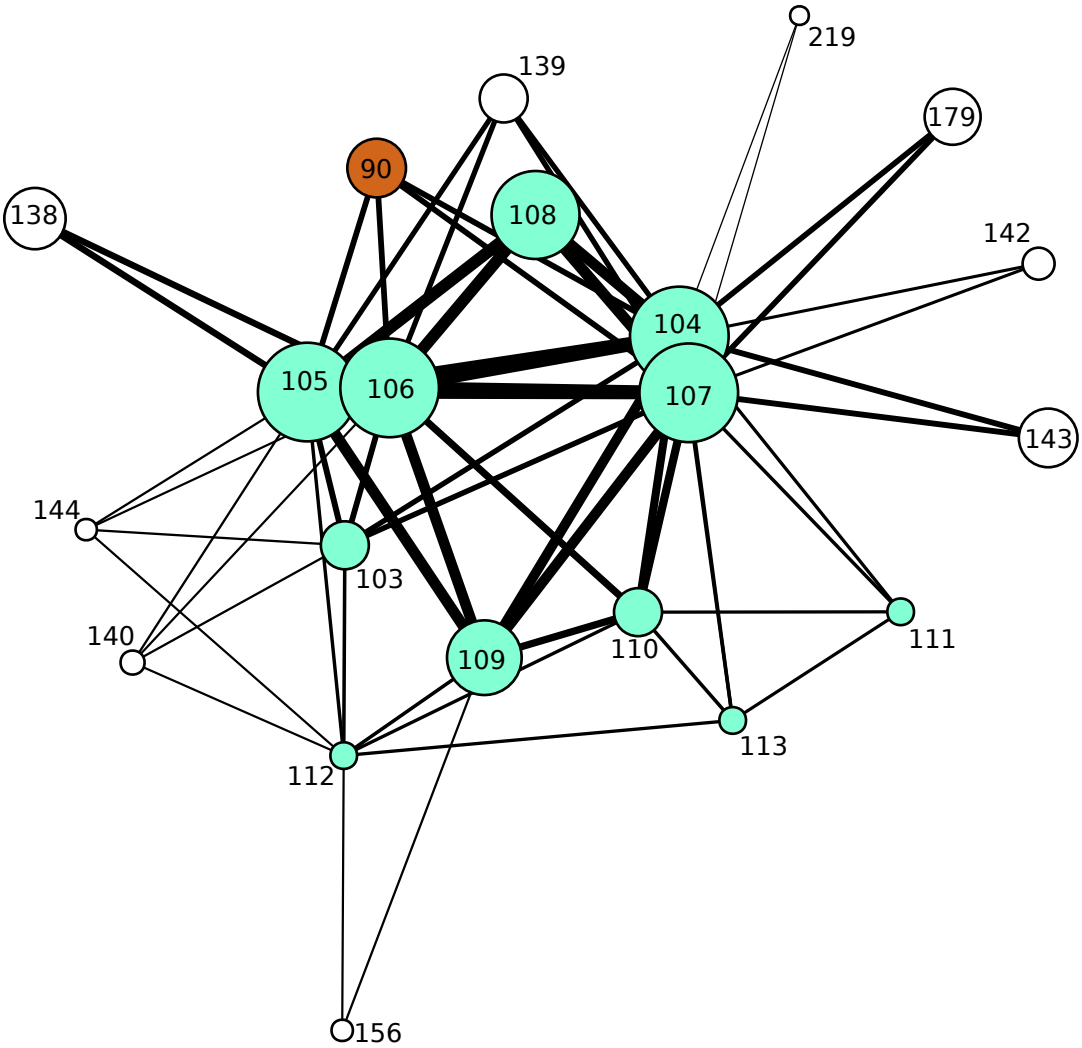


Figure 3: Zoomed in visualization of diagnosed (colored circles) and undiagnosed outbreaks (white circles) in the Nipah cluster (Fig. 2). Outbreaks are given by ID number (Supplemental Tables S1 and S3), with outbreaks of Nipah virus encephalitis in cyan and malaria in brown, with undiagnosed outbreaks in white, as in Fig. 2.



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