

How to do it

Investigating outbreaks: Practical guidance in the Indian scenario

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ABSTRACT

The new International Health Regulations, 2005, which came into force in 2007, establish a national focal point in each country to manage public health emergencies of international concern, including outbreaks. Investigating outbreaks is a challenging task. Often, pressure from decision-makers to hasten investigation may preclude proper evidence-based conclusions. Furthermore, the task of outbreak investigation is given to senior staff, who have limited time for field activities.

The classical 10-step approach includes 4 main stages of (i) confirmation of the presence of the outbreak and of diagnosis using laboratory tests, (ii) generation of hypotheses regarding causation using descriptive epidemiology findings, (iii) hypothesis-testing using analytical epidemiology techniques, and (iv) institution of prevention measures. Peer-review at all stages of the investigation and reporting is the keystone of the quality assurance process.

It is important to build capacity for outbreak investigation. Two Field Epidemiology Training Programmes in India are trying to do this. In these programmes, epidemiologists-in-training take a lead in investigating outbreaks, while learning the ropes, with full technical support from the faculty. This training should spawn a culture of generating and using evidence for decision-making in the context of public health, and help strengthen health systems even beyond the domain of outbreaks.

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INTRODUCTION

Outbreaks affect vulnerable populations and are a challenge for public health officers, policy-makers and community leaders. The worldwide trend towards urban migration and globalization means that outbreaks can spread more rapidly and more easily through national and regional boundaries. The SARS outbreak, which

began in China in November 2002, spread to 27 countries within the first few weeks of 2003.¹ The 2009 influenza pandemic, which started in Mexico and USA in March 2009, spread to almost every country in the world within a few months.

In the context of the new International Health Regulations, 2005 (IHR), which came into force in 2007,² each country has a national focal point (in India, the National Institute for Communicable Diseases [NICD], New Delhi which became the National Centre for Disease Control [NCDC] in 2009) to manage public health emergencies of international concern (PHEIC). Those must be assessed within 48 hours and reported within further 24 hours to the WHO. However, everywhere in the world, outbreaks are often initially identified by astute clinicians, laboratory scientists or surveillance officers in the course of their normal duties. Effective communication and cooperation between those who first suspect a problem and those who investigate it to implement interventions are essential. As a public health system improves, it is expected to detect and respond to more, not fewer, outbreaks and detect these at an earlier stage.

The objectives of this paper are to review (i) why outbreaks should be investigated, (ii) the recent evolution of the guiding principles used to investigate outbreaks, (iii) the methods that should be used to investigate outbreaks, (iv) the strategy used to build capacity to investigate outbreaks in India, and (v) the reasons why capacity developed for outbreak investigations can strengthen critical public health capacity to address non-outbreak health challenges.

WHY SHOULD OUTBREAKS BE INVESTIGATED?

Events happen for a reason. Thus, disease outbreaks have causative factors, whether these are discovered or not. Finding a reason allows institution of steps to terminate the ongoing outbreak and prevent future recurrences. For any disease, occurrence of an outbreak reflects a change in the usual relationship between (i) the host (e.g. individuals' immune function, lifestyle, nutrition, exposures, etc.), (ii) the agent (e.g. a microorganism, toxin or physical force) and (iii) the environment (e.g. climate, crowding, poverty, social conditions, etc.). Thus, to implement appropriate control measures for an outbreak, each of these 3 factors, and their interaction, must be investigated and understood. If this is not done, then the control measures are not based on the best scientific evidence.

Outbreaks constitute unique experiments of nature from which much can be learnt about the natural history and spectrum of a particular disease, the underlying risk factors, and the impact of existing public health programmes on its epidemiology.³ Therefore, investigating outbreaks is also valuable for research and training.

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EVOLVING CONCEPTS IN THE AREA OF OUTBREAK INVESTIGATIONS

In India, as in many other countries, there has been a shift in the way acute outbreaks are responded to. We have gone from the traditional approach, in which the cause of outbreak was assumed to be whatever had been thought likely for similar outbreaks in the past (e.g. contaminated water system explains acute diarrhoeal disease outbreaks) to systematic, evidence-based field epidemiological methods.

Traditional approach

Traditionally, disease-specific experts investigated outbreaks by counting cases, analysing laboratory specimens and conducting other environmental studies as needed. Such investigations required subject expertise in the pathogen or toxin that caused the outbreak. They led to generic prevention measures based on the case diagnosis or the mode of transmission identified (Table I). A typical scenario, for example, would be a disease prevention specialist who would conduct a cholera outbreak investigation. The steps would include counting the cases, taking water specimens from sources of water, examining the water supply and recommending chlorination of the sources of water in the absence of specific evidence that the water source had caused the outbreak. In this approach, no defined, sequential steps or precise methodology were followed.

Systematic, field epidemiology methods

Current field epidemiological methods make use of quantitative data, generated from a study of relationship between the host, agent and environment, and compare exposures in the outbreak cases to appropriate comparison groups to come to evidence-based conclusions (Table I). The latter are based primarily on epidemiological methods but usually call for collaboration with other disciplines (e.g. statisticians, laboratory experts, environmental specialists, clinicians, entomologists, to name a few). These methods use a systematic, step-by-step approach that includes (i) confirmation of the presence of an outbreak and of the diagnosis, (ii) generation of hypotheses on the basis of descriptive epidemiology and other elements, (iii) testing of these hypotheses using analytical epidemiology methods, and (iv) proposing evidence-based control measures. Use of these methods requires, besides subject expertise, skills in applied epidemiology and an open-mind, which can develop only from field experience.

This approach to outbreak investigation leads to recommendations that are adapted for the actual field situation and based on the results of a specific investigation. These methods can be

applied to any kind of outbreak, regardless of the cause (infectious or non-infectious), source or mode of transmission. In western Uttar Pradesh, a team led by local paediatricians recently proposed an explanation to recurrent clusters of encephalopathy using field epidemiology methods.⁴⁻⁶ A typical scenario is of an epidemiologist who investigates a cholera outbreak, confirms the diagnosis with rectal swabs, counts the cases, studies the cases to look for clues, and then test these clues by comparing the ill and the well to find risk factors for disease. For instance, the infection may be food-borne rather than water-borne, and thus controlled by measures aimed at improving food hygiene rather than chlorination of water supply. A recent cholera investigation in India illustrated that the disease can be either water-borne or food-borne, and that only a systematic, step-by-step, field epidemiological approach could differentiate between the two.⁷

HOW SHOULD OUTBREAKS BE INVESTIGATED?

Various textbooks have proposed slightly different sequential steps for investigating an outbreak. However, all of these follow a logic that includes hypothesis generating through descriptive epidemiology and hypothesis testing through analytical epidemiology. One of these lists has 10 steps, which makes it easy to remember.³ For each of the 10 steps, common pitfalls should be avoided (Table II).

1. *Determine the existence of the outbreak.* Before a full investigation is initiated, the team must determine the existence of an outbreak to eliminate the possibility of a pseudo-outbreak. This process can be referred to as transformation of a 'signal' (e.g. a report of a cluster of jaundice cases in a village) into a proper 'alert'. To determine the existence of an outbreak, the team needs to (i) characterize the cluster of cases, (ii) compare the current incidence with the background rates, and (iii) exclude any artifact caused by a change of numerator (e.g. change in the case definition or surveillance system) or of the denominator (e.g. change in the population size because of migration). In 2005, an apparent cluster of leishmaniasis cases in West Bengal turned out to be a pseudo-outbreak, which was noticed because of sudden reporting of chronic cases detected within the preceding few months following intensified case search.^{8,9} In contrast, in December 2004, following the South Asian tsunami, post-emergency surveillance allowed the rapid detection of a number of cases of measles in excess of the baseline that led to the identification of a real outbreak.¹⁰
2. *Confirm the diagnosis.* The next step of outbreak investigation is confirmation of the diagnosis. This takes place in two

TABLE I. Traditional versus field epidemiology methods for outbreak investigation

Item	Traditional methods	Systematic, field epidemiology methods
Approach	<ul style="list-style-type: none"> • Subject-matter centred • Disease-specific 	<ul style="list-style-type: none"> • Epidemiology centred • Multi-disciplinary
Investigation methods	<ul style="list-style-type: none"> • Case count • Laboratory studies • Additional studies (e.g. entomology, parasitology, environmental assessment) 	<ul style="list-style-type: none"> • Confirming the outbreak and the diagnosis • Generating hypotheses using descriptive epidemiology • Testing hypotheses using analytical epidemiology • Additional investigations (e.g. vectors, environment) • Formulating recommendations
Competencies needed	<ul style="list-style-type: none"> • Facts +++, skills ++, attitude + 	<ul style="list-style-type: none"> • Facts +, skills ++, attitude +++++
Field of application	<ul style="list-style-type: none"> • Known infectious diseases 	<ul style="list-style-type: none"> • All outbreaks (known infectious diseases, emerging infectious diseases, injuries, toxic agents)
Control measures	<ul style="list-style-type: none"> • Generic, according to the agent identified and the mode of transmission 	<ul style="list-style-type: none"> • Specific, based upon the conclusions of the investigation

TABLE II. Outbreak investigation checklist: Recommended steps and common pitfalls

Steps	Specific recommendations	Pitfalls to avoid
Determine the existence of an outbreak	<ul style="list-style-type: none"> ✓ Determine whether there is a clustering of cases. ✓ Review past incidence in the area. ✓ Check recent changes in surveillance practices. ✓ Check recent changes in population size. 	<ul style="list-style-type: none"> ✗ <i>Taking all reported clusters at face value</i> Reported clusters may be pseudo-outbreaks (e.g. batch reporting of old cases of chronic diseases).
Confirm the diagnosis	<ul style="list-style-type: none"> ✓ Describe signs and symptoms to shortlist diagnoses. ✓ Confirm the diagnosis with laboratory tests. 	<ul style="list-style-type: none"> ✗ <i>Failing to obtain a laboratory diagnosis</i> Every effort must be made to obtain an early diagnosis.
Define a case	<ul style="list-style-type: none"> ✓ Formulate a time, place and person case definition, using template(s) if applicable. 	<ul style="list-style-type: none"> ✗ <i>Poor case definition:</i> This can undermine the ability to detect mode of transmission of the outbreak
Search for cases	<ul style="list-style-type: none"> ✓ Search for cases within the limits of the case definition. ✓ Compile and update a line-listing of cases with date of onset, age, sex, residence and outcome. 	<ul style="list-style-type: none"> ✗ <i>Conducting a door-to-door case search or a survey upfront:</i> Often, at least for the initial descriptive component, it may be enough to search for cases through surveillance and obtain a denominator separately.
Generate hypotheses using descriptive findings	<ul style="list-style-type: none"> ✓ Draw an epidemic curve (TIME). ✓ Draw a map (PLACE). ✓ Calculate population-based incidence by age and sex groups and conduct hypothesis-generating interviews with case-patients (PERSON). 	<ul style="list-style-type: none"> ✗ <i>Merging the hypothesis-generating and the hypothesis-testing stages</i> Surveys conducted in the absence of a clearly defined hypothesis on the basis of descriptive epidemiology blur the distinction between the two stages of the investigation and may impair the capacity to formulate a conclusion.
Test hypotheses with analytical study	<ul style="list-style-type: none"> ✓ Write a mini-protocol to spell out the hypotheses to test and the design to use. ✓ Conduct an analytical study (case-control or cohort). 	<ul style="list-style-type: none"> ✗ <i>Believing that a questionnaire constitutes a study protocol</i> The analytical epidemiological study requires a design and an analytical plan. A case-control study is not always the answer (e.g. high attack rates in a small community or defined group such as wedding attendees calls for a cohort study).
Draw conclusions	<ul style="list-style-type: none"> ✓ Analyse the analytical epidemiological study. ✓ Formulate conclusions that explain the facts observed on the basis of the analytical study, causality criteria and proportion of cases exposed. 	<ul style="list-style-type: none"> ✗ <i>Having excessive confidence in the conclusions:</i> Merely a p value of <0.05 does not lead to a firm conclusion. Double check to see whether the hypothesis considered explains all the initial descriptive findings.
Conduct additional investigations	<ul style="list-style-type: none"> ✓ Conduct an environmental assessment guided by the results of the analytical study. ✓ Review the literature. 	<ul style="list-style-type: none"> ✗ <i>Rushing to conduct an environmental assessment</i> The environmental assessment is guided and focused by the analytical epidemiology findings to confirm a hypothesis. Avoid collecting all kinds of specimens in the absence of any hypothesis at the early stages of the investigation.
Communicate findings	<ul style="list-style-type: none"> ✓ Write immediately a short report to leave in the field. ✓ Communicate findings with supervisors, the laboratory and local public health authorities. 	<ul style="list-style-type: none"> ✗ <i>Failing to communicate the results to decision-makers</i> An investigation is not complete until the results have been communicated to those who need the information to act.
Enforce prevention measures	<ul style="list-style-type: none"> ✓ Formulate evidence-based, clear, specific and feasible recommendations on the basis of findings (Who? What? When? How?). ✓ Ensure implementation of the recommendations. ✓ Evaluate the effectiveness of the recommendations. 	<ul style="list-style-type: none"> ✗ <i>Formulating general recommendations that are not based upon findings</i> Do not re-formulate all the recommendations of hygiene but focus on the specific ones that are the key issues during the outbreak.

steps. The first is description of the clinical picture (i.e. frequency of signs and symptoms among cases) to shortlist a number of possible diagnoses. During this step, close collaboration with clinicians is critical to ensure that the right diagnosis is included in this shortlist. The second step is confirmation of the diagnosis through laboratory investigations. This requires knowledge of diagnostic strategies, collection of appropriate specimens on the right media, safe and effective transport, and good rapport with a laboratory that can deliver quality results. In India, strengthened surveillance and investigations have led to a larger number of laboratory-confirmed outbreaks of measles.¹¹

3. *Define a case.* Once a diagnosis has been established, a case definition must be formulated to ensure uniform application of the criteria used to count cases.¹² Typically, a case definition includes specific criteria of who, where (i.e. residence) and

when (i.e. date of onset) to define which instances of disease will be included in the official count. In terms of epidemiology, this is referred to as the triad of 'person', 'place' and 'time'. One example of a case definition would be the occurrence of fever and joint pain in a resident of village 'X' between January and March 2006.¹³ Epidemiologists must explain to clinicians that case definitions are not diagnostic criteria for therapeutic decisions, but instead provide a set of defined criteria that triggers reporting so that reports are standardized and comparable. Template case definitions for various syndromes or diseases are available from various international and national organizations including WHO and the USA Centers for Disease Control (CDC), and from the Indian Integrated Disease Surveillance Project (IDSP).^{14,15} Several levels of a case definition may be used to differentiate, with an increasing level of specificity and a decreasing level of

sensitivity, possible cases (e.g. fever with rash) from probable cases (e.g. cases meeting the WHO clinical measles case definition of presence of fever and maculopapular rash and cough, coryza or conjunctivitis)¹⁵ and confirmed cases (e.g. cases confirmed through laboratory investigations).

4. *Search for cases.* Once a case definition has been formulated, it may be used to search for cases. This search needs to be performed consistently and uniformly in the area of the outbreak to generate an accurate assessment. Depending on the outbreak and the goals of the investigation, the search for cases does not necessarily involve a systematic, labour-intensive, door-to-door survey. In a hepatitis E outbreak in Baripada, Orissa, door-to-door case search mobilized 44 team members for 7 days.¹⁶ Often, the use of passive, stimulated, or active surveillance data are possible, as long as the surveillance intensity has not changed over the period of study and rates are calculated using population denominators. In Hyderabad, Andhra Pradesh, passive surveillance with limited resources provided a good description of a similar urban hepatitis E outbreak.¹⁷ Irrespective of the method used for case-search, it results in a 'line-listing' of all the cases (i.e. a paper or computer list that contains essential data of individual cases, including time, place and person characteristics).
5. *Generate hypotheses using descriptive findings.* During this stage of investigation, the team orients the data by time (i.e. an epidemic curve showing the distribution of cases by dates of disease onset), place (i.e. map showing the distribution of cases by geographical area) and person (e.g. incidence by age and sex) and studies it for clues. During a hepatitis E outbreak in Nainital, Uttarakhand, the time, place and person distribution was highly suggestive of contamination of a single source of water.¹⁸ In some outbreaks, cases that do not fit the typical patterns, called 'outliers', can provide valuable clues from which to generate hypotheses about causes. An early case may represent a background (unrelated) case, a source of the epidemic, or a person who was exposed earlier than most of the people affected (e.g. the cook who tasted her dish hours before it was served). Similarly, late cases may have especially long incubation periods, may indicate later exposure than most of the people affected, or may be secondary cases. In addition, open, hypothesis-generating interviews (using a 'trawling' questionnaire) are conducted with case-patients, family members (e.g. mothers of affected children) and community leaders to identify what is common to most cases and to receive suggestions as to what may be happening (e.g. What did you do last week? Did you travel? Where do you take lunch? Where do you obtain your drinking water from? Did you attend a wedding?). The combination of clues from the 'time, place and person' descriptive epidemiology, from outliers and the hypothesis-generating interviews usually leads to some good hypotheses regarding the source(s) of infection. In addition, review of the disease from the subject expertise point of view ('round up the usual suspects': If it is an outbreak of gastroenteritis, check the water and food) and field visits to examine the environment (e.g. leaking pipes, uncovered wells) also help raise hypotheses. Having a good hypothesis is a critical step in finding the cause and controlling an outbreak.
6. *Test hypotheses with an analytical study.* In the next stage, the hypotheses are tested using analytical epidemiological methods. This involves quantitative comparisons to determine whether a particular exposure or risk factor is associated with the occurrence of disease. This may consist of a case-control study, where a subset of cases is compared with a select group of non-cases or 'controls' to determine how these differ in various exposures. Case-control studies are usually used for rare diseases with lower attack rates (<5%).¹⁹ Alternatively, a cohort study may be done, where those exposed to a particular risk factor of interest are compared with an unexposed group, to see how these differ in their rates of illness. This type of study is often used with rare exposures and in situations where the illness occurs with a high attack rate (>5%), such as after a wedding dinner.²⁰ The academic consonance of the terms 'case-control' or 'cohort' should not deter public health officials as these field studies represent useful tools and can be completed rapidly in the field, sometimes in a matter of few hours.
7. *Draw conclusions.* Once the data have been analysed, the team reviews the findings and proposes a conclusion in the light of the (i) strength of the association between the possible causes and the disease of interest, (ii) statistical significance of this association, (iii) proportion of cases that would be adequately explained by this association (the 'attributable fraction'), (iv) temporal relationship of exposures with outcomes, (v) biological plausibility of the conclusion, and (vi) its consistency with other studies.²¹ Additional evidence may come from a relationship of dose of exposure with frequency of outcome. At this step, experience and judgement are especially important, and may lead to a decision by the investigators to do further studies.
8. *Conducting additional investigations.* These are done to gather evidence to support the hypothesis under investigation. These may include an entomological investigation to identify a vector, a microbiological investigation to test the quality of the water of an incriminated source or an environmental investigation to understand how the preparation of a food item led to a food-borne outbreak. Additional studies may contradict early conclusions, sending the investigators back in search of a new hypothesis or may strengthen their conclusions. The results and conclusions then need to be articulated clearly and disseminated widely.
9. *Communicate findings.* Communication of the finding of the results of an investigation typically occurs in two stages. First, a report in writing is left in the field (e.g. slide presentation, one-page briefing) so that local stakeholders (e.g. public health officials and clinicians) have something to act on. This report may come with disclaimers (e.g. mention that it is based upon a preliminary analysis). Second, a final report is sent after completion of the final analyses. In addition, other relevant target groups may need to be considered for communication of the findings including the press, healthcare workers or other stakeholders (e.g. poultry workers for an avian influenza outbreak).
10. *Execute prevention measures.* An outbreak investigation serves no purpose if it is not followed by useful recommendations and interventions. The recommendations and proposed interventions need to be evidence-based, specific, feasible, cost-effective, acceptable and ethical.²² Prevention measures include measures for case management (e.g. rehydration of cholera cases) and prevention of secondary spread (e.g. patient isolation) that may be initiated before the results of the investigation are known. Again at this stage, a good collaboration with clinicians is important. Some interventions may be justified even before a final conclusion or diagnosis

is made. However, other specific prevention measures need to be guided by results of the investigation and thus need to wait for completion of data analysis. Follow up work will also be important to evaluate these recommendations so that only effective interventions are perpetuated.

STRENGTHENING CAPACITY TO INVESTIGATE OUTBREAKS IN INDIA

Training a workforce competent to investigate outbreaks, though important, is not easy. Decision-makers may pressure the investigators to quickly reach conclusions and execute prevention measures, and may not always allow adequate time to conduct a thorough investigation of the outbreak. As a result, decisions may not be based on specific evidence.

To address these problems, and build a cadre of professionals capable of using field epidemiology to investigate outbreaks, many countries are using Field Epidemiology Training Programmes (FETPs),²³ an international version of the Epidemic Intelligence Service (EIS) of the United States Centers for Disease Control and Prevention (CDC). FETPs are working to overcome the traditional approach to outbreak investigations. Two 2-year FETPs have been established in India, including a Master of Applied Epidemiology (MAE) at the National Institute of Epidemiology (NIE) in Chennai, Tamil Nadu and a Master of Public Health, Field Epidemiology (MPH-FE) at the NICD, New Delhi. In these programmes, epidemiologists-in-training take the lead in outbreak investigations, with full technical support from the faculty, as per the 'learning through service' idea. According to this concept, the mandate comes from the public health system rather than from an academic supervisor. The 'fellow', 'scholar' or 'officer' (rather than a 'student') takes the lead in the investigation under a close, iterative supervision (mentoring) from senior epidemiologists. S/he communicates the results of the investigation to the health system. S/he graduates from the training programme with documented field experience and competence.

HOW TO BUILD CAPACITY BEYOND OUTBREAK INVESTIGATIONS?

A culture of systematic outbreak investigation and a workforce trained in field epidemiology will strengthen the public health system in many other ways. Outbreak investigations incorporate the key principles of the use of evidence for decision-making.²⁴ Learning to investigate outbreaks teaches broader public health skills such as designing and improving surveillance systems; conducting observational public health research to answer key policy questions; learning scientific communication skills and collaborating with multi-disciplinary teams to design, implement and evaluate prevention programmes.

CONCLUSION

Investigating disease outbreaks often helps in understanding the change in the usual relationship between the host, agent and environment. This process guides control measures and prevents additional cases. This systematic approach is now becoming the international standard in the context of the revised IHR. EIS officers and graduates with training based on outbreak investigation approaches have constituted the backbone of the United States public health service since 1951.²⁵ Other countries, including India, are now developing a similar culture through FETPs. With

commitment to training, excellence in field epidemiology, and in time, the FETPs can transform the practice of public health in India.

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