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Outbreak science: recent progress in the detection and response to outbreaks of infectious diseases

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ABSTRACT

The frequency of reported outbreaks of infectious diseases has increased over the past 3 decades, with predictions that this rise will continue. Outbreak response continues to follow nine basic principles: establish the presence of an outbreak, verify the diagnosis, make a case definition, find cases and contacts, conduct basic epidemiology, test hypotheses, institute control measures, communicate the situation and establish ongoing surveillance. Within each of these areas, significant advances have been made over the past 5 years using progress in digital, laboratory, epidemiology and anthropological equipment or techniques. Irrespective of these, future outbreaks of high-consequence are inevitable, and vigilance and preparation must continue in order to prevent significant mortality, morbidity and socio-economic crisis.

Background

Large recent outbreaks of highly pathogenic or highly transmissible infectious diseases include plague (Madagascar), diphtheria (Bangladesh), Ebola (West Africa (WA) and Democratic Republic of Congo (DRC)), monkeypox (Nigeria), Zika (South and Central America), middle east respiratory syndrome coronavirus (MERS-CoV; Saudi Arabia and Korea) and Lassa fever (LF; Nigeria). Outbreaks of more familiar diseases such as chikungunya, cholera, polio, measles and seasonal influenza have also occurred. The number of reported outbreaks has increased over the past 3 decades. This trend is expected to continue with further zoonotic spill-over events occurring due to population expansion and movement into previously uninhabited regions and the influence of climate change on vector distribution.

Outbreak response continues to follow nine established epidemiological principles. We summarise progress made in these steps using examples of recent outbreaks and future possibilities in Fig 1.

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Establishing the presence of an outbreak (and surveillance systems)

An outbreak is defined as more cases of a disease than expected in a specific location over a specific time period. Suspicion often arises when health care workers report an unusual cluster or a single, unexpected presentation. This passive surveillance leads to a delay in the detection of an outbreak. Various efforts have been made to improve this; monitoring social media and internet searches of symptoms have been used detect and report influenza epidemics.[1] Online platforms have been used to rapidly share or access information about potential outbreaks for 2 decades (ProMED-mail and Global Public Health Intelligence Network), and newer tools have emerged, for example HealthMap, an app which aggregates formal notifications, online news and eyewitness reports.[2] The World Health Organization's (WHO's) Early Warning and Response System (EWARS) provides a box of electronic equipment, allowing a surveillance system to be deployed rapidly during a humanitarian crisis or outbreak. In rural parts of sub-Saharan Africa, a portable device is used by minimally-trained

Key points

The frequency of outbreaks of highly contagious or highly pathogenic diseases is increasing

Surveillance methods now include both digital media and animal surveillance, and electronic tools are increasingly used on the ground to report and monitor outbreaks

Mathematical modelling of outbreaks and molecular sequencing of pathogens have become key components of outbreak response

An ethical framework now exists for the testing of unproven therapies during outbreaks

Anthropologists, social scientists and communication experts are now considered essential members of an outbreak response team

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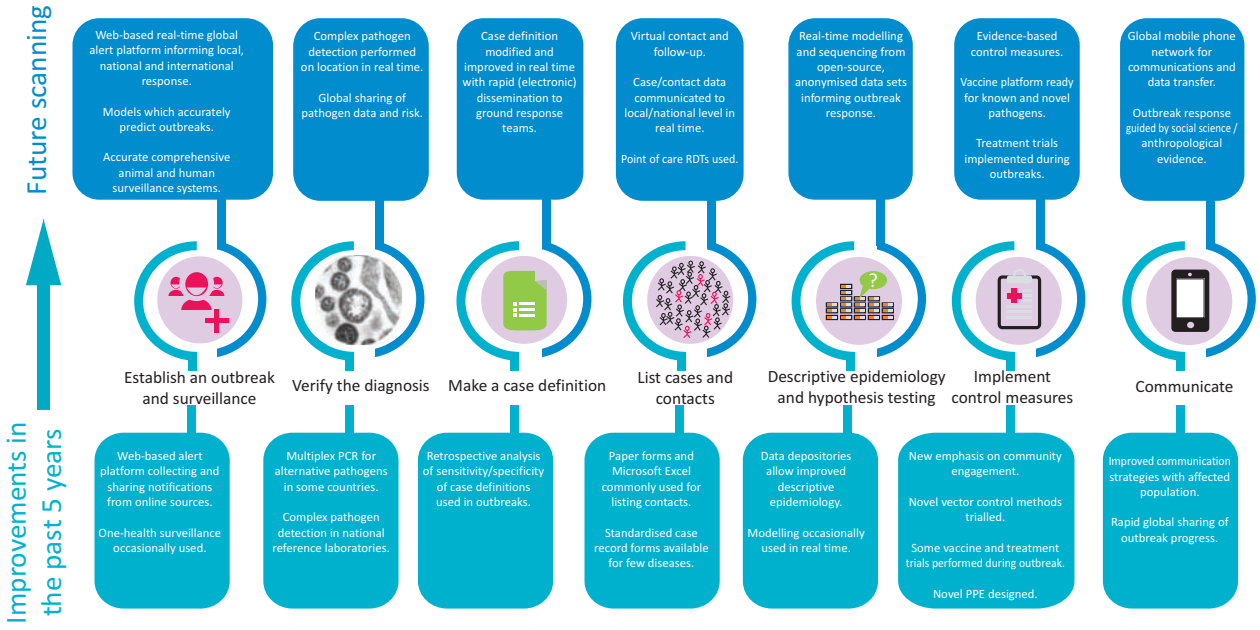

Fig 1. Condensed summary of the epidemiology principles for outbreak response summarising scientific progress made in the recent past (below in teal) and future possibilities (above in blue). PCR = polymerase chain reaction; PPE = personal protective equipment; RDT = rapid diagnostic test (should be sensitive, specific, heat-stable, cheap, simple to use, electricity-free and disposable). Note: the nine outbreak steps have been condensed to seven for space.

surveillance officers to send encrypted images of patients with suspected acute flaccid paralysis, aiding the identification of polio cases.[3] Importantly, surveillance now includes animals, an approach consistent with 'One Health',[4] for example, surveillance by Public Health England allowed the detection in the Thames estuary of *Culex modestus*, a mosquito capable of transmitting the West Nile virus.

Verify the diagnosis

Pathogen identification commonly relies on the transport of samples to reference laboratories with a typical reporting delay of 2–3 days. Suspicion must be maintained that an outbreak may be due to non-infectious causes such as poisoning or nutritional deficiencies. Metagenomic techniques, involving amplifying and sequencing all ribonucleic acid and deoxyribonucleic acid in a sample, is increasingly used to identify new pathogens when standard diagnostic tests are unforthcoming. Metagenomics led to the identification of previously unknown viruses causing haemorrhagic fever including Bas Congo and Lujo.[5,6]

Make a case definition

Defining cases is notoriously challenging during outbreaks when symptoms are non-specific and mimic other diseases. Broad case definitions are used to ensure cases are not missed, but as the 2017 plague epidemic in Madagascar demonstrated, the sheer number of suspect cases can overwhelm control efforts. Progress has been made through real-time analysis of case definitions. In WA in 2015, the sensitivity of the case definition for Ebola was increased from 69% to over 90%.[7]

Finding cases

Currently, most national and international outbreak response groups use paper forms for reporting. During recent outbreaks, the use of mobile technology has facilitated the listing, location (using Global Positioning System) and subsequent follow up of cases and contacts using intuitive electronic data-entry platforms. These allow information to be collected in areas without mobile reception, and automatic upload when back online. This mobile technology has assisted in recent outbreaks in the rapid isolation of symptomatic contacts, potentially reducing onward transmission, and allowing improved real-time resource planning.[8–11]

The International Severe Acute Respiratory and Emerging Infection Consortium has generated an open-access portfolio of case record forms for several outbreak diseases and syndromes (https://isaric.tghn.org/protocols) with the aim of standardising clinical and epidemiological information collected during outbreaks.

Rapid diagnostic tests

The size of an outbreak can be substantially reduced by quick identification of cases using rapid diagnostic tests (RDTs). Three RDTs were validated during the WA Ebola outbreak; some do not require electricity or a high degree of training.[12–14] GeneXpert, although requiring a power supply, has >95% sensitivity and specificity, and is currently used in the DRC for diagnosis and patient discharge.[12] On the other hand, during the 2017 plague outbreak in Madagascar, an antigen-based RDT had limited specificity and its utility in the response has been questioned.[15]

Health systems

Weak health systems and widespread poverty are key risk factors for outbreaks. Therefore, provision of adequate resources (human, laboratory, logistics and materials) are critical components of every response. Recently, WHO has created a minimum set of standards for accreditation of foreign medical teams, allowing WHO to coordinate complementary groups to respond, as evidenced in the Bangladesh diphtheria outbreak. Countries such as Sierra Leone have capitalised on international assistance to strengthen their health system after an epidemic, improving primary health care provision, laboratory systems, and specialist diagnostics and treatment.[16]

Descriptive epidemiology and hypothesis testing

Over the past decade, there has been a movement towards rapid sharing of anonymised outbreak data to strengthen the power of findings from small cohort studies, test hypotheses, develop standards for clinical trials and direct research priorities. This is now a common requirement of journals and funders.

During the WA Ebola outbreak, mathematical modelling was used to predict the rate of increase of the epidemic, and the resources required for an adequate response.[17] The contribution of risk factors was modelled, allowing targeted interventions like safe burial to gain more focus than, for example, border restrictions.[18] During the Zika outbreak in Brazil, modelling aided understanding the effect of rising herd immunity on the epidemic's trajectory.[19] However, accuracy of the models depends on high-quality epidemiological data, which are often lacking.

Hypothesis testing during outbreaks has evolved from attempting to confirm the origin of an outbreak by adding data points to a map of cases (a procedure pioneered by John Snow during the 1854 London cholera outbreak; Fig 2a), to bioinformatic interrogation of the pathogen's genomic data over time and space (Fig 2c). Technology for sequencing of viral and bacterial genomes has advanced significantly; sequencing can now be performed and reported in the field.[20] During the WA Ebola outbreak, whole genome sequencing identified the origin and spread of the virus with reasonable certainty (Fig 2b). It also identified episodes of sexual transmission, effective control measures and provided

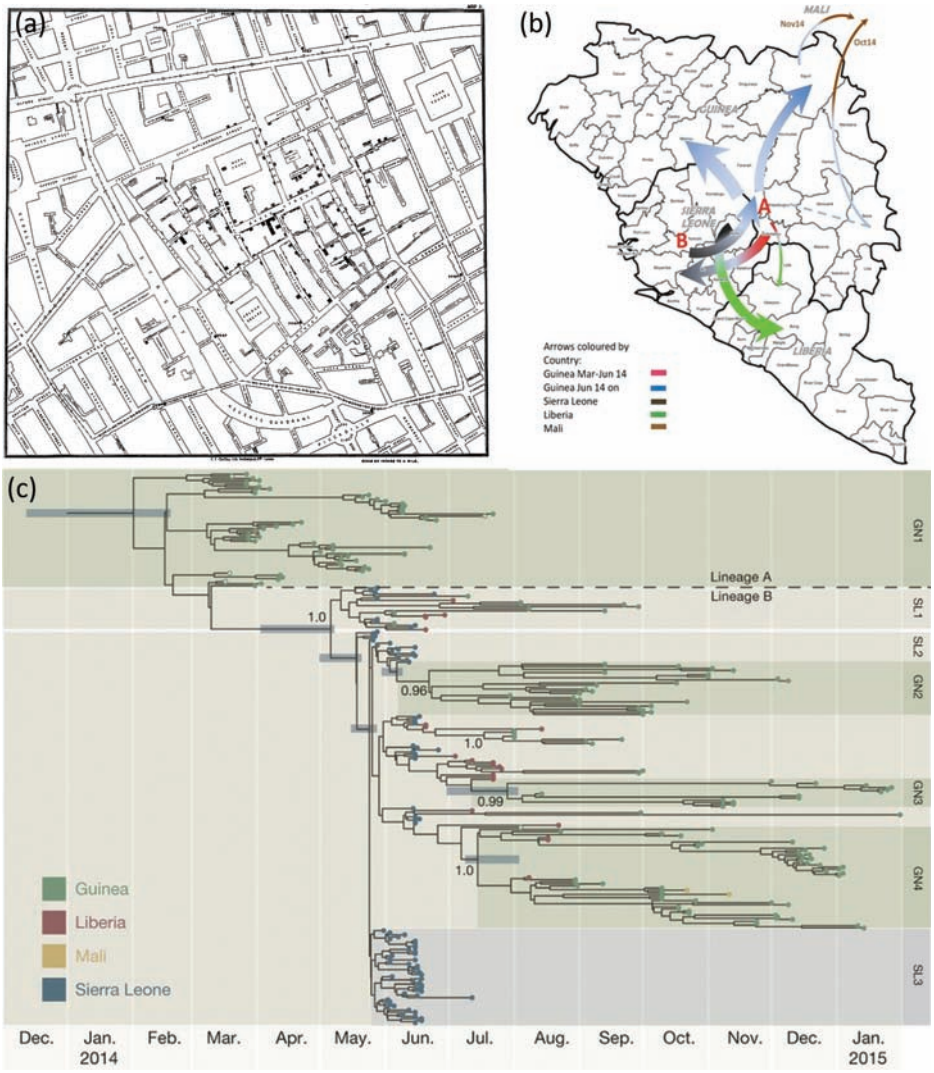

Fig 2. (a) Map of cholera cases in Soho district of London in 1854 illustrating clustering of cases around the Broad Street pump. (b) Spread of Ebola through west Africa over time in 2014–15 based on phylogenetic tree (in Fig 2c). Lineage A is the initial focus of the outbreak from 2014. Lineage B emerged from A in 2014–15 and spread into Sierra Leone, Liberia and further into Guinea. EBOV entered Mali from two separate routes. (c) Phylogenetic probability tree illustrating EBOV lineages A and B as they emerge over time and geographical location in west Africa. Reproduced with permission from www.nature.com/articles/nature14594

important details for vaccine and therapeutic design. 'Live' maps which document outbreak movement are now available for multiple outbreaks, created using openly available pathogen sequences (www.youtube.com/watch?v=j4Ut4krp8GQ). During the Zika outbreak in Brazil, sequencing was performed using the Oxford-Nanopore MinION, a credit card sized device powered through a laptop USB connection.[20] Remaining challenges include the sequence accuracy from portable devices, cost and data-sharing agreements.

Control measures and communication

Community engagement is increasingly recognised as a key component of outbreak response, allowing responders to engage the affected population and alter behaviours which may propagate an outbreak. In the Brazil Zika epidemic, messages targeting vector breeding sites were relatively simple. In the WA Ebola outbreak, changing traditional burial practices and isolating sick individuals from family members was more challenging. Anthropologists, communication experts and social scientists are now routinely included in outbreak response teams.

Innovative control measures for arboviruses have been developed. Zika, yellow fever and dengue are transmitted by day-biting mosquitos, meaning that malaria control strategies such as bed nets are less effective. The release of mosquitos infected with the Gram-negative bacteria *Wolbachia* has significantly reduced vector population size and transmission in experimental settings.[21]

Outbreaks of vaccine-preventable diseases still occur due to a lack of coverage of common childhood vaccines. For most outbreaks (LF, plague, Zika, MERS-CoV, monkeypox, Rift Valley fever) vaccines for human use are only available in trials. Ebola vaccination broke the mould: a novel trial design involving ring vaccination with recombinant vesicular stomatitis virus vaccine given to contacts of cases demonstrated high efficacy in Guinea,[22] allowing this vaccine to be deployed in DRC in 2018. The need for rapid vaccine development led to the formation of the Coalition for Epidemic Preparedness Innovations, a public–private partnership which is funding the development of vaccines for MERS-CoV, LF and Nipah viruses.

The trial of novel therapeutics is now being considered during outbreaks where no effective treatment exists. WHO has developed an ethical framework 'Monitored Emergency Use of Unregistered Interventions' and currently two antivirals and three monoclonal-antibody cocktails are approved for use in Ebola in DRC. Trial designs during emergency response have been carefully critiqued and novel randomisation strategies developed.[23] Excellent basic clinical care is challenging to deliver in viral haemorrhagic fever outbreaks but remains essential for reducing mortality. Well-designed isolation centres, near-patient monitoring devices and portable, rapid biochemistry analysers have revolutionised this.

Innovation in personal protective equipment (PPE) proliferated during the WA Ebola outbreak. Rapid removal PPE suits (www.youtube.com/watch?time_continue=7&v=kRab2bGahCE), improved fabrics and simulation mannequins have been created, enhancing our ability to safely deliver care.

Conclusion

Outbreak response has made significant and impressive progress involving a wider range of disciplines, embracing modern technology, and recognising the importance of research during and between outbreaks. More progress is needed and requires that funders and governments recognise the inevitability of the next outbreak of a disease of high consequence and our global vulnerability to it. ■

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