Rev. Sci. Tech. Off. Int. Epiz., 2019, **40** (1), ... - ...

Emerging and endemic zoonotic diseases: surveillance and diagnostics

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Summary

In this paper, the authors list the methods used to diagnose zoonotic diseases in humans and animals; identify the differences in diagnostic approaches among species, providing commentary on the benefits that might arise from simultaneous interpretation of data from human and animal health surveillance systems; and reiterate the importance of using species-specific, validated diagnostic tests for surveillance and disease outbreak investigations.

Emerging and endemic zoonotic diseases are likely to provide a continued threat to global health in the short- to medium-term future. A good deal of knowledge has been developed about the drivers of infectious disease emergence, based on numerous examples from the recent past. Sharing diagnostic resources across human and animal health sectors, pooling human and animal health surveillance data, developing skills in the interpretation of those data and being aware of the issues related to the validation and interpretation of diagnostic test data are necessary prerequisites for an effective endemic disease surveillance system. A good understanding of the epidemiological patterns of endemic disease will allow human and animal health professionals to detect the presence of emerging disease threats more quickly and more effectively.

Keywords

Diagnostic tests – Emerging infectious disease – One Health – Surveillance – Zoonoses.

Introduction

A zoonosis is defined as a disease, infection or infestation transmitted under natural conditions from vertebrate animals to humans (1). In a 2008 review, Jones *et al.* found that over half of all emerging infectious diseases detected internationally since 1940 were zoonotic, and since 1960 the relative frequency of new zoonotic disease detections has increased (2). Examples of globally important, zoonotic diseases identified since 1990 include Nipah virus (3); severe acute respiratory syndrome (SARS) (4); Ebola virus (5); and Middle East respiratory syndrome coronavirus (MERS-CoV) (6). The global impact of the COVID-19 pandemic, and the fact that the causative agent of COVID-19, SARS-coronavirus-2 (SARS-CoV-2), is more than likely zoonotic (7), fully supports the statement that the emergence of novel zoonotic pathogens is one of the greatest challenges to global health security (8). In the context of this paper, the authors use the term 'emerging infectious diseases' to refer to diseases that are either newly recognised, newly introduced or newly evolved, or have recently and rapidly changed in incidence or expansion in their geographical, host or vector range (9).

While increasingly sophisticated diagnostic tools have improved the ability to detect the presence of emerging infectious diseases in susceptible host populations, this ability comprises only a relatively small component of the suite of tools required to detect and then successfully manage emerging health threats. Other necessary components for disease detection within a health system include the presence of both:

a) sufficient numbers of appropriately skilled professionals with the experience to identify disease events unusual for their jurisdiction, who are then able to collect and submit appropriate samples for further investigation

b) diagnostic laboratories with appropriate facilities to allow non-routine test procedures to be carried out and sufficient resources to allow staff to spend time and laboratory resources on what might (often) be investigations with no clear aetiological diagnosis.

The last requirement is perhaps the most important. Funding agencies (typically governments) spend considerable amounts of money developing laboratory capacity, and a common means of offsetting this expense is to put business systems in place to ensure that facilities are run on a full cost-recovery basis. Emerging infectious diseases are less likely to be detected when these constraints are rigorously adhered to. Sufficient resources need to be available to allow laboratory staff to carry out non-routine diagnostic procedures on suspected emerging infectious disease samples if and when the need arises.

The scenarios by which infectious diseases emerge are extremely varied, which represents a major challenge when educating health professionals on early detection and the design of fit-for-purpose surveillance systems to detect their presence (10). Situations of disease emergence range from the appearance of diseases that have never been described before, such as pandemic influenza H1N1 2009 (11), MERS-CoV (12) and COVID-19 (7), to the movement of known diseases into new geographical locations, such as the incursion and subsequent spread of West Nile virus in the United States of America in 1999 (13). Other scenarios include known pathogens infecting new host species, as in the case of highly pathogenic avian influenza H5N1 causing disease in humans (14) and Nipah virus spilling over from bats to pigs and then from pigs to humans (15).

Other factors responsible for disease emergence include ecosystem change. In south-west Russia and Turkey in the early 2000s, the reversion of farmland to dense undergrowth, as people migrated from rural areas to cities when rural economies collapsed (16), provided habitat for wildlife that hosted tick vectors, leading to a marked increase in the incidence of Crimean−Congo haemorrhagic fever. Other examples include new strains of *Leptospira* that have been detected in Australia and New Zealand (17, 18). Changes in animal feed processing and the way in which animal feed ingredients are used is yet another mechanism by which diseases may emerge. The most striking example of this was the replacement of solvent extraction in combination with high-temperature treatment of meat and bonemeal with high-temperature treatment alone that allowed the emergence of bovine spongiform encephalopathy (BSE) in cattle in the United Kingdom in the late 1980s (19), and new-variant Creutzfeldt-Jakob disease in humans in the mid-1990s (20, 21).

As can be appreciated from the examples above, a broad range of factors contribute to infectious disease emergence. Adding to this complexity are factors related to human behaviour. Increases in population size and the presence of a reliable source of relatively cheap labour have promoted the development of large, secondary industry sectors in middle-income countries (22). Foreign income earned from the export of manufactured goods has increased gross domestic product in these countries and given rise to middle classes with greater discretionary spending power. Increases in population density, enhanced mobility and changes in lifestyle and food choices (including the ability to spend money on ‘delicacy’ items, such as wild animal meat products) all contribute to conditions that facilitate disease emergence, some of which have been listed above (23, 24, 25, 26).

When new diseases emerge and become established in a population, social media allow individuals to exchange ideas and opinions quickly and easily with those sharing their same

world view. Social media groups with a distrust in biomedical science, particularly in relation to control measures (such as mass vaccination campaigns), have an unprecedented ability to influence the opinion and healthcare-seeking behaviour of others (27). This phenomenon, which is often more prevalent in higher-income countries, together with poor vaccination rates in countries in which there is political unrest (28), has the potential to markedly reduce the effectiveness of control measures (29) and provide ideal conditions for disease re-emergence (30).

In most jurisdictions, the activities of government human and animal health services charged with emerging disease detection and management have not, for the most part, kept pace with the changes outlined above. While dealing with emerging infectious disease outbreaks is, to a large extent, a reactive process, much work needs to be done to develop an internationally consistent approach for identifying locations and time frames that are at risk of disease emergence, and then setting up appropriate surveillance systems to facilitate the early detection of emergent pathogens, if and when they occur. If such systems worked without error (with the key word in this sentence being 'if'), the emergence of SARS-CoV-2 in late 2019 might have been detected some weeks earlier and, if subsequent management had been appropriate, the pandemic of COVID-19 that followed (7) might have been averted.

With this background, the objectives of this paper are to:

a) list methods used to diagnose zoonotic diseases in humans and animals

b) identify differences in diagnostic approaches among species, and provide commentary on the benefits that might arise from simultaneous interpretation of data from human and animal health surveillance systems

c) reiterate the importance of using species-specific, validated diagnostic tests for surveillance and disease outbreak investigations.

Emerging and endemic zoonotic diseases are likely to provide a continued threat to global health in the short- to medium-term future. The development of surveillance systems to simultaneously monitor the health of human and animal populations for endemic disease, as well as experience and expertise in the interpretation of the data generated by such systems, will be essential in developing the institutional knowledge needed for the timely detection of changes in disease patterns, where interventions are necessary.

Diagnostic methodologies for zoonotic diseases in humans and animals

Table I lists known zoonotic diseases, grouped by pathogen type. Table II provides details of diagnostic methods for agent identification and the detection of immune response for a selection of the conditions listed in Table I, for both humans and animals. In both humans and animals, polymerase chain reaction (PCR) and culture are the predominant diagnostic methods for agent identification (for further details, see Michel *et al*., this issue [31]).

Between-species differences in diagnostic approaches

Consideration of the reservoir-host status of the species affected by zoonotic diseases provides a useful framework for diagnostic test selection in both humans and animals. A reservoir is defined as any person, animal, arthropod, plant, soil, or substance, or combination of these, in which an infectious agent normally lives and multiplies, on which it depends primarily for survival, and where it reproduces itself in such a manner that it can be transmitted to a susceptible host (1). Disease may, or may not, occur in a reservoir. Replication and shedding of a pathogen from a reservoir often occur in response to environmental or physiological stimuli.

This pattern is different from that which takes place in non-reservoir host species, where the presence of infection (usually) results in the activation of an immune response with one or more of the following outcomes: elimination of infection altogether (with or without disease), the establishment of persistent or latent infection, the establishment of a carrier state, or death.

Procedures used to detect the presence of zoonotic diseases in either humans or animals should consider the reservoir-host status of the individuals subject to examination. A 'rule of thumb' is that diagnostic tests to detect an immune response are generally more useful in reservoir species, whereas diagnostic tests to detect the presence of an infectious agent are more useful in actively infected, non-reservoir species. The date on which a test is carried out in relation to the date of infection or date of onset of clinical signs or symptoms (if known) needs careful consideration, since it is possible for testing to be carried out before the host has mounted an immune response, which means that diagnostic tests designed to detect an immune response in the host will return a negative result. Similarly, the presence of antigen may take time to develop after the date of infection and again, if testing is carried out before this time, a negative result will be returned, even though the individual is disease positive. Line plots showing (a) the relative quantities of infectious agent present in a host as a function of the number of days since infection, and (b) immune response as a function of the number of days since infection (see, for example, Fig. 1) (32) are useful because they provide a means to guide decision-making around appropriate

diagnostic test selection, depending on the time at which a patient is examined relative to the estimated date of infection (C. Wilks, personal communication, 2015). This information helps to ensure that appropriate specimens are collected to provide the best chance of identifying a suspected causative agent.

In an emerging disease outbreak response, where this information is not known, it is important that key details for each case are recorded, including (in particular) the date of likely exposure to the causative agent, the date of onset of clinical signs or symptoms, and the date of testing. In this way, plots showing, for example, PCR cycle threshold values and the magnitude of serological response can be plotted as a function of the number of days since exposure. Of the three date variables listed above, investigators are most likely to have difficulties estimating the date of pathogen exposure. Standard operating procedures for outbreak response should provide detailed instructions on how to solicit an estimated date of exposure in confirmed cases. Recording an approximate date of exposure (with a note to flag the uncertainty of the estimate, if any) is much more desirable than no data at all.

Some comments are now provided on how the One Health model (33) might be applied in terms of surveillance and diagnostics for emerging and endemic zoonotic diseases. First, sharing laboratory facilities to diagnose diseases in both humans and animals provides several benefits, including sharing expertise in the conduct of complex diagnostic test methodologies and the development and validation of diagnostic tests (34). The animal health sector, led by the World Organisation for Animal Health (OIE), is in a strong position in this regard, largely driven by a long history of the need for validated diagnostic tests to support the international trade of animals and animal products. In 2019, the World Health Organization (WHO), OIE and Food and Agriculture Organization of the United Nations (FAO) jointly published a guide providing details of a multisectoral approach to zoonotic disease control (35). While this document clearly defines high-level aims and objectives, details of the exact form of collaborative linkages – particularly in terms of diagnostic test development and validation – need to be more clearly defined. The COVID-19 pandemic has essentially forced better collaboration, with veterinary diagnostic laboratory facilities recruited to assist with testing large numbers of COVID-19 samples (36).

Second, information on the incidence of zoonotic diseases across the human and animal health sectors should be shared: if there has been an increase in the frequency of a given zoonotic disease of humans in a given area, has there been the same increase in disease frequency in animals – and if not, why not? The epidemiology of specific disease conditions needs to be

considered carefully here because, in many situations, an increase in the incidence in one species may not result in a simultaneous increase in the incidence in another. In the epidemic of Q fever that began in the Netherlands in 2007, an increase in the frequency of abortions in dairy goats (presumed to be Q fever-related) preceded the Q fever outbreak in humans by at least two years (37). Parallels between the frequency of disease in humans and animals need to be considered on an individual, pathogen-by-pathogen basis. The success of this approach relies on a detailed understanding of the epidemiology of individual disease conditions and recognition that, in many situations, data need to be collected over several years before sufficient information is available to allow appropriate inferences to be made. This is particularly important because the intensity of surveillance for human diseases tends to be greater than that for animal diseases, which means that, in some situations, identifying zoonotic disease in humans provides an indication of the presence of undiagnosed and unreported disease in animals (see, for example, Minh *et al.*) (38). In other situations, the reverse situation can occur, as with the epidemic of Q fever that took place in the Netherlands in 2007.

Given differences in the intensity of surveillance, sampling and testing for diseases in human populations, as compared to animal populations, the benefit of combined human-animal surveillance is likely to arise from detections of epidemiologically important changes to a previously stable disease profile, as opposed to changes in absolute measures of disease frequency (39). To be able to detect these changes with confidence, human and animal health authorities need to develop experience in interpreting surveillance data, since disease frequency patterns in human and animal sectors vary over time (usually associated with season) and by factors such as affluence (in the case of human diseases), industry sector, and region (in the case of animal diseases).

For example, animal health surveillance allocates major resources to the detection of transmissible spongiform encephalopathies, substantially less to Shiga-toxin-producing *Escherichia coli* O157 or campylobacteriosis, and none to leptospirosis, theileriosis or malaria, whereas the inverse holds for human surveillance, all of them being of zoonotic origin. Development of this skill set is extremely important because a thorough understanding of the epidemiological patterns of endemic diseases will allow human and animal health professionals to detect changes in disease patterns which may, in some situations, be due to the presence of an emerging disease.

Species-specific, validated diagnostic tests

The OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* chapter on the principles and methods of validation of diagnostic assays for infectious diseases provides

recommendations on the design of studies to validate diagnostic test procedures. The key requirement is that all diagnostic assays should be validated for the species in which they will be used (40). For zoonotic diseases, there are three relatively common situations where this condition may not be adhered to. The first is where a diagnostic test has been developed for a primary host species and, on infrequent occasions, spillover occurs to a secondary host species for which a validated diagnostic test does not exist. For example, WHO has established testing protocols for the detection of SARS-CoV-2 in samples from human patients. Animal health laboratories have used these tests to screen for SARS-CoV-2 in a range of animal species, particularly farmed mink (41). For indirect serological diagnosis, a multi-species enzyme-linked immunosorbent assay to detect antibodies against SARS-CoV-2 is available, with a reported diagnostic sensitivity and specificity of 1.00 and 0.98, respectively (42). Because mink can be infected with other coronaviruses (e.g. transmissible gastroenteritis virus and porcine epidemic diarrhoea virus) (43), cross-reactivity is likely to lead to a decrease in diagnostic test specificity, causing false-positive test results, particularly when large numbers of animals are sampled.

The second situation typically arises when wildlife is studied to determine either the prevalence of disease or the prevalence of pathogen exposure. Here, it is common for samples to be assayed using a diagnostic test validated and approved for use in another, usually domestic animal, species. Results are reported as apparent prevalence estimates and inferences made accordingly (see Banazis *et al.* and Cooper *et al.* for examples) (44, 45).

The third situation arises where there are differences in the purpose of testing. Animals are tested to rule in or rule out the presence of specific infectious agents (to make a diagnosis of disease) and to determine if an individual has been exposed to an infectious agent, which might then mean that they are a carrier of infection. In contrast, diagnostic tests in humans are most often used to rule in or rule out the presence of a specific infectious agent in an individual. An example is leptospirosis where, in animals, evidence of exposure is based on either a microscopic agglutination test (MAT), using a relatively low threshold titration (e.g. 1: 50), or by detection of DNA traces in the urine using quantitative PCR (46). Humans with symptoms consistent with leptospirosis would be subject to a MAT using a much higher titration threshold, e.g. eight-fold higher (1: 400) or by repeated testing to establish a two-step, increasing MAT titre (47).

The authors argue that the use of unvalidated diagnostic tests to estimate the prevalence of endemic diseases at the population level is inappropriate and will return biased results, with the direction and magnitude of that bias difficult to predict. For example, if 50 animals are sampled and 25 return a positive result, using a test with a diagnostic sensitivity of 0.85 and a diagnostic specificity of 0.99, the estimated true prevalence will be 0.58 (95% confidence interval [CI], 0.42

to 0.74), based on the Rogan-Gladen estimator (48). If the diagnostic sensitivity of the test was only 0.75 (a 0.10-unit change, which would be typical of the difference in diagnostic sensitivity of tests used across different species), the estimate of true prevalence is 0.66 (95% CI, 0.48 to 0.84) – a substantial difference and a difference likely to, in many situations (but depending on the specific situation), change clinical decision-making. In the emerging infectious disease situation, unvalidated diagnostic tests must, by necessity, be used, particularly in the early stages of an outbreak. Over time, it is essential, however, for validation studies to be carried out since this will provide clarity around, for example, the likely number of false- positive test results that will occur if the test is used for screening, and/or the confidence that a population is free of disease if all of those tested return a negative test result.

Conclusions

Emerging and endemic zoonotic diseases are likely to provide a continued threat to global health in the short- to medium-term future. In light of the evidence and commentary provided in this paper, the authors provide the following recommendations:

1. Diagnostic laboratories need sufficient resources for staff to carry out non-routine diagnostic procedures on suspected emerging infectious disease samples, if and when the need arises.

2. Instruction on emerging infectious disease epidemiology needs to be included in postgraduate degree programmes in population health. A good knowledge of factors that contributed to recent emerging infectious disease events will provide health professionals with greater awareness of the different mechanisms and circumstances of disease emergence.

3. Sharing information on the incidence of zoonotic diseases across the human health and animal health sectors holds some promise as a means for improving how quickly emerging infectious diseases might be detected. For this approach to work, human and animal health authorities must also develop experience in interpreting surveillance data since surveillance intensity will vary markedly by sector. Both the WHO and OIE could play a key role in this, by first identifying specific zoonotic diseases to be used as initial case studies (e.g. rabies), and then showcasing particular countries and time frames where shared surveillance data have resulted in better human and animal health decision-making.

Maladies zoonotiques émergentes et endémiques : surveillance et diagnostic

Résumé

Après avoir répertorié les méthodes utilisées pour diagnostiquer les maladies zoonotiques chez l'homme comme chez les animaux, les auteurs définissent les différentes approches diagnostiques suivant les espèces considérées et commentent les avantages qui pourraient découler d'une interprétation simultanée des données par les systèmes de surveillance en santé animale et en santé publique ; il réitèrent ensuite l'importance de recourir à des tests diagnostiques validés et spécifiques de l'espèce considérée dans le cadre de la surveillance et des enquêtes suite à l'apparition d'un foyer.

Les maladies zoonotiques émergentes et endémiques représentent potentiellement une menace continue pour la santé mondiale à court et à moyen terme. Les facteurs favorisant l'émergence des maladies infectieuses sont désormais beaucoup mieux connus grâce aux enseignements tirés de nombreux exemples récents. Le partage des ressources diagnostiques entre les secteurs de la santé humaine et animale, les échanges des données de la surveillance sanitaire réunies par les deux secteurs, le renforcement des compétences en matière d'interprétation des données et la sensibilisation aux problématiques de la validation et de l'interprétation des données générées par les tests de diagnostic sont des conditions préalables à la mise en place d'un système efficace de surveillance des maladies endémiques. Une bonne compréhension des profils épidémiologiques des maladies endémiques permettra aux professionnels de la santé humaine et animale de détecter plus rapidement la présence de menaces émergentes.

Mots-clés

Maladie infectieuse émergente – Surveillance – Tests diagnostiques – Une seule santé – Zoonoses.

Vigilancia y diagnóstico de enfermedades zoonóticas emergentes o endémicas

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Resumen

Los autores proceden aquí a: a) relacionar los métodos empleados para diagnosticar enfermedades zoonóticas en personas y animales; b) señalar las diferencias que existen entre los distintos planteamientos de diagnóstico según la especie de que se trate, comentando asimismo las ventajas que podrían derivarse de la interpretación simultánea de los datos de los sistemas de

vigilancia sanitaria y de los de vigilancia zoosanitaria; y c) reiterar la importancia que reviste el uso de pruebas de diagnóstico no solo validadas, sino también adaptadas específicamente a cada especie, para las labores de vigilancia y estudio de brotes.

Lo más probable es que a corto y medio plazo las enfermedades zoonóticas, ya sean emergentes o endémicas, sigan constituyendo una amenaza para la salud mundial. Gracias a numerosos ejemplos del pasado reciente se ha ido constituyendo un buen conocimiento de los factores que propician la aparición de enfermedades infecciosas. Para disponer de un eficaz sistema de vigilancia de enfermedades endémicas hay una serie de requisitos previos indispensables: utilización compartida de los recursos de diagnóstico entre los sectores de la salud humana y la sanidad animal; intercambio de los datos de vigilancia sanitaria y de vigilancia zoosanitaria; adquisición de competencias para interpretar esos datos; y buen conocimiento de las cuestiones ligadas a la validación de pruebas de diagnóstico y a la interpretación de los datos que arrojan. Si los profesionales de la salud humana y la sanidad animal conocen debidamente los patrones epidemiológicos de las enfermedades endémicas, estarán en condiciones de detectar con más celeridad la presencia de enfermedades emergentes que constituyan una amenaza.

Palabras clave

Enfermedad infecciosa emergente – Pruebas de diagnóstico – Una sola salud – Vigilancia – Zoonosis.

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Table I

Examples of zoonotic disease, by pathogen type

Pathogen type	Diseases
Bacterial	Anthrax, bovine tuberculosis, brucellosis (multiple species), campylobacterios malaria, plague (*Yersinia pestis*), psittacosis, Q fever, salmonellosis, Lyme di fever, Shiga-toxin-producing *Escherichia coli*, tularemia
Fungal	Blastomycosis, coccidioidomycosis, histoplasmosis
Viral	Ebola haemorrhagic fever, Eastern equine encephalomyelitis, hantavirus pul encephalitis, highly pathogenic avian influenza, Nipah virus infection, Hendra caused by influenza A viruses, Marburg virus disease, rabies, Venezuelan ec Nile virus infection, Western equine encephalomyelitis, Crimean−Congo hae monkeypox, Rift Valley fever, St Louis encephalitis, Middle East respiratory s respiratory syndrome
Parasitic	Cryptococcosis, ehrlichiosis, leishmaniosis, trichinellosis, taeniosis, echinoco
Prion	Bovine spongiform encephalopathy (including variant Creutzfeldt-Jacob disea

Table II

Examples of agent identification and immune response detection methods for a selection of zoonotic diseases in humans and animals

Condition	Humans		Animals	
	Agent identification	Detection of immune re	Agent identification	Detection of immune
Anthrax	Swabs from skin lesior (gastrointestinal anthra Blood culture. PCR on in case of a non-interp	Electrophoretic immunotra blot	Light microscopy examinat or fresh tissue; PCR on wh available for field use	ELISA
Bovine tuberculos	Culture of sputum Cult Culture followed by mc MALDI−TOF−MS		Tuberculin skin test PCR and culture of affecte	Gamma interferon relea mediated immune resp *Mycobacterium bovis*
Brucellosis	Blood culture PCR on whole blood. M culture required for ant	Serum IgM often present nature of infection. ELISA	Staining, culture, PCR	STAT, SPAT, BPAT, R competitive ELISA
Echinococcosis	Aspirated fluid from su for acid-fast protoscole cannot rule out presen	Indirect haemagglutinatio	Identification of adult worm Identification of proglottids	IgM murine MAb
Leishmaniosis	Cytology on skin scrap Amastigotes observed	Gel diffusion, CFT, indirec indirect immunofluoresce immunoelectrophoresis E	PCR on affected tissue or	Indirect immunofluores agglutination assays

Rabies	Live patient: direct fluo nuchal skin with hair fo saliva, cerebrospinal fl Deceased patient: imm smear; PCR and IHC c thalamus, cerebellum c	Direct fluorescent antibod	Immunofluorescence test c brainstem, hippocampus, t oblongata	Direct fluorescent antib
Taenia solium, Ta	Microscopic detection cysts in muscle or cere Detection of *T. solium*- and muscle or cerebra Nested PCR, multiplex PCR for simultaneous *solium* and *T. saginata*	Detection of *T. solium*-spe cerebrospinal fluid	Post mortem inspection of	ELISA
Q fever	PCR on whole blood ir A single, high-phase 2 with a compatible clinic infection	Phase 1 IgA by IFA. In un fever serology at six mont progression to chronic dis high phase 1 IgG and IgA not fall over time, and ma treatment has begun, afte fall slowly over many mor serological pattern that cc fatigue syndrome	PCR whole blood or vagina	Phase 1 and phase 2 Ig serology and titres, pre

BPAT: buffered antigen plate agglutination test

CFT: complement fixation test

dFA: direct fluorescent antibody test

EITB: electrophoretic immunotransblots

ELISA: enzyme-linked immunosorbent assay

ICT: immunochromatographic test

IFA: immunofluorescence assay

IgA: immunoglobulin A

IgG: immunoglobulin G

IgM: immunoglobulin M

IHC: immunohistochemistry

MAb: monoclonal antibody

MALDI−TOF−MS: mass spectrometry, matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry

PCR: polymerase chain reaction

RBPT: Rose Bengal plate test

SPAT: serum plate agglutination test

STAT: short turnaround testing

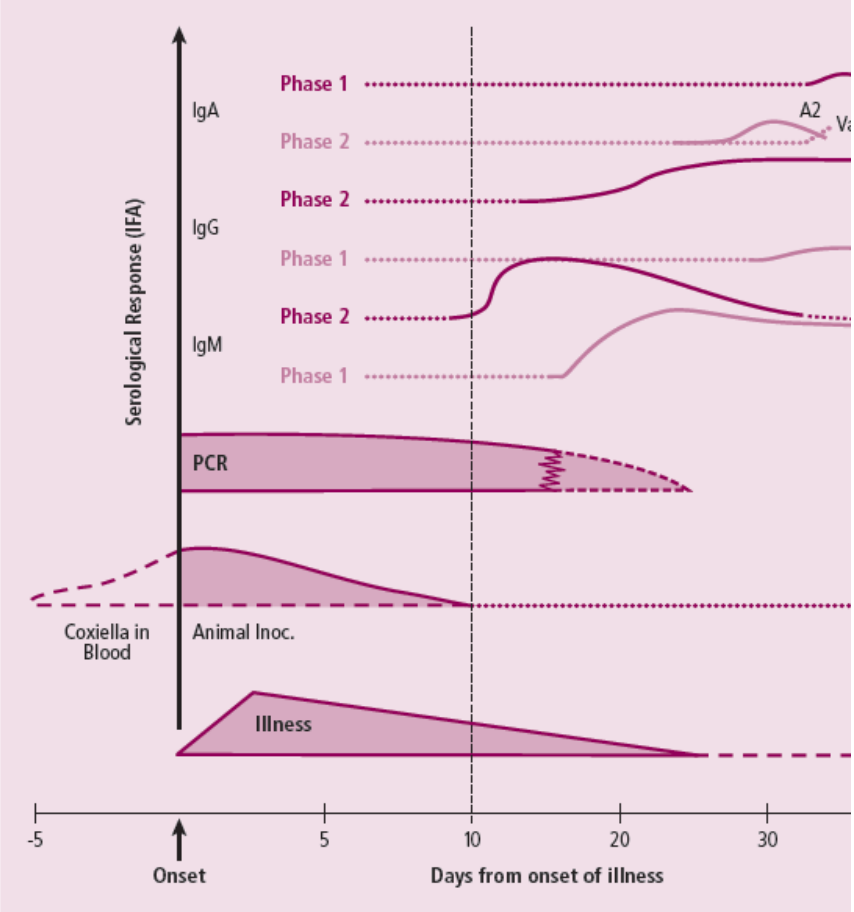

Fig. 1

Line plot showing relative change in quantitative polymerase cha serological (immunoglobulins A, G, and M) response to *Coxiella b* the number of days since the onset of illness

Values shown on the vertical axis are qualitative, relative estimates. Ada

IFA: immunofluorescence assay

Inoc.: inoculation

PCR: polymerase chain reaction