Current and Developing Technologies for Monitoring Agents of Bioterrorism and Biowarfare.  Daniel V. Lim, Joyce M. Simpson, Elizabeth A. Kearns, and Marianne F. Kramer.  583–607

Summary: Recent events have made public health officials acutely aware of the importance of rapidly and accurately detecting acts of bioterrorism. Because bioterrorism is difficult to predict or prevent, reliable platforms to rapidly detect and identify biothreat agents are important to minimize the spread of these agents and to protect the public health. These platforms must not only be sensitive and specific, but must also be able to accurately detect a variety of pathogens, including modified or previously uncharacterized agents, directly from complex sample matrices. Various commercial tests utilizing biochemical, immunological, nucleic acid, and bioluminescence procedures are currently available to identify biological threat agents. Newer tests have also been developed to identify such agents using aptamers, biochips, evanescent wave biosensors, cantilevers, living cells, and other innovative technologies. This review describes these current and developing technologies and considers challenges to rapid, accurate detection of biothreat agents. Although there is no ideal platform, many of these technologies have proved invaluable for the detection and identification of biothreat agents.


Summary: Among animal viruses, arboviruses are unique in that they depend on arthropod vectors for transmission. Field research and laboratory investigations related to the three components of this unique mode of transmission, virus, vector, and vertebrate host, have produced an enormous amount of valuable information that may be found in numerous publications. However, despite many reviews on specific viruses, diseases, or interests, a systematic approach to organizing the available information on all facets of biological transmission and then to interpret it in the context of the evolutionary process has not been attempted before. Such an attempt in this review clearly demonstrates tremendous progress made worldwide to characterize the viruses, to comprehend disease transmission and pathogenesis, and to understand the biology of vectors and their role in transmission. The rapid progress in molecular biologic techniques also helped resolve many virologic puzzles and yielded highly valuable data.
hitherto unavailable, such as characterization of virus receptors, the genetic basis of vertebrate resistance to viral infection, and phylogenetic evidence of the history of host range shifts in arboviruses. However, glaring gaps in knowledge of many critical subjects, such as the mechanism of viral persistence and the existence of vertebrate reservoirs, are still evident. Furthermore, with the accumulated data, new questions were raised, such as evolutionary directions of virus virulence and of host range. Although many fundamental questions on the evolution of this unique mode of transmission remained unresolved in the absence of a fossil record, available observations for arboviruses and the information derived from studies in other fields of the biological sciences suggested convergent evolution as a plausible process. Overall, discussion of the diverse range of theories proposed and observations made by many investigators was found to be highly valuable for sorting out the possible mechanism(s) of the emergence of arboviral diseases.

**Antimicrobial Stewardship Programs in Health Care Systems.**

Conan MacDougall and Ron E. Polk

Summary: Antimicrobial stewardship programs in hospitals seek to optimize antimicrobial prescribing in order to improve individual patient care as well as reduce hospital costs and slow the spread of antimicrobial resistance. With antimicrobial resistance on the rise worldwide and few new agents in development, antimicrobial stewardship programs are more important than ever in ensuring the continued efficacy of available antimicrobials. The design of antimicrobial management programs should be based on the best current understanding of the relationship between antimicrobial use and resistance. Such programs should be administered by multidisciplinary teams composed of infectious diseases physicians, clinical pharmacists, clinical microbiologists, and infection control practitioners and should be actively supported by hospital administrators. Strategies for changing antimicrobial prescribing behavior include education of prescribers regarding proper antimicrobial usage, creation of an antimicrobial formulary with restricted prescribing of targeted agents, and review of antimicrobial prescribing with feedback to prescribers. Clinical computer systems can aid in the implementation of each of these strategies, especially as expert systems able to provide patient-specific data and suggestions at the point of care. Antibiotic rotation strategies control the prescribing process by scheduled changes of antimicrobial classes used for empirical therapy. When instituting an antimicrobial stewardship program, a hospital should tailor its choice of strategies to its needs and available resources.

**Extended-Spectrum β-Lactamases: a Clinical Update.**

David L. Paterson and Robert A. Bonomo

Summary: Extended-spectrum β-lactamases (ESBLs) are a rapidly evolving group of β-lactamases which share the ability to hydrolyze third-generation cephalosporins and aztreonam yet are inhibited by clavulanic acid. Typically, they derive from genes for TEM-1, TEM-2, or SHV-1 by mutations that alter the amino acid configuration around the active site of these β-lactamases. This extends the spectrum of β-lactam antibiotics susceptible to hydrolysis by these enzymes. An increasing number of ESBLs not of TEM or SHV lineage have recently been described. The presence of ESBLs carries tremendous clinical significance. The ESBLs are frequently plasmid encoded. Plasmids responsible for ESBL production frequently carry genes encoding resistance to other drug classes (for example, aminoglycosides). Therefore, antibiotic options in the treatment of ESBL-producing organisms are extremely limited. Carbapenems are the treatment of choice for serious infections due to ESBL-producing organisms, yet carbapenem-resistant isolates have recently been reported. ESBL-producing organisms may appear susceptible to some extended-spectrum cephalosporins. However, treatment with such antibiotics has been associated with high failure rates. There is substantial debate as to the optimal method to prevent this occurrence. It has been proposed that cephalosporin breakpoints for the Enterobacteriaceae should be altered so that the need for ESBL detection would be obviated. At present, however, organizations such as the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards) provide guidelines for the detection of ESBLs in Klebsiella and Escherichia coli. In common to all ESBL detection methods is the general principle that the activity of extended-spectrum cephalosporins against ESBL-producing organisms will be enhanced by the presence of clavulanic acid. ESBLs

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represent an impressive example of the ability of gram-negative bacteria to develop new antibiotic resistance mechanisms in the face of the introduction of new antimicrobial agents.

Vaccines for Tuberculosis: Novel Concepts and Recent Progress.  
T. Mark Doherty and Peter Andersen ......................... 687–702

Summary: Three-quarters of a century after the introduction of Mycobacterium bovis BCG, the first tuberculosis vaccine, new vaccines for tuberculosis are finally entering clinical trials. This breakthrough is based not only on advances in proteomics and genomics which have made the construction of new vaccines possible, but also on a greatly expanded knowledge of the immunology of tuberculosis. Here we review our current understanding of how Mycobacterium tuberculosis subverts or survives the host’s immune response to cause disease and why the current vaccination strategy, which relies on BCG, is only partially successful in countering the pathogen. This provides a background for describing the new generation of vaccines designed to supplement or replace the current vaccine and the different approaches they take to stimulate immunity against M. tuberculosis.

Baylisascariasis.  
Patrick J. Gavin, Kevin R. Kazacos, and Stanford T. Shulman................................................. 703–718

Summary: The raccoon roundworm, Baylisascaris procyonis, is the most common and widespread cause of clinical larva migrans in animals. In addition, it is increasingly recognized as a cause of devastating or fatal neural larva migrans in infants and young children and ocular larva migrans in adults. Humans become infected by accidentally ingesting infective B. procyonis eggs from raccoon latrines or articles contaminated with their feces. Two features distinguish B. procyonis from other helminthes that cause larva migrans: (i) its aggressive somatic migration and invasion of the central nervous system and (ii) the continued growth of larvae to a large size within the central nervous system. Typically, B. procyonis neural larva migrans presents as acute fulminant eosinophilic meningoencephalitis. Once invasion of the central nervous system has occurred, the prognosis is grave with or without treatment. To date, despite anthelmintic treatment of cases of B. procyonis neural larva migrans, there are no documented neurologically intact survivors. Epidemiologic study of human cases of neural larva migrans demonstrate that contact with raccoon feces or an environment contaminated by infective eggs and geophagia or pica are the most important risk factors for infection. In many regions of the United States, increasingly large populations of raccoons, with high rates of B. procyonis infection, live in close proximity to humans. Although documented cases of human baylisascariasis remain relatively uncommon, widespread contamination of the domestic environment by infected raccoons suggests that the risk of exposure and human infection is probably substantial. In the absence of early diagnosis or effective treatment, prevention of infection is the most important public health measure.

Philippe Parola, Christopher D. Paddock, and Didier Raoult ................................. 719–756

Summary: During most of the 20th century, the epidemiology of tick-borne rickettsioses could be summarized as the occurrence of a single pathogenic rickettsia on each continent. An element of this paradigm suggested that the many other characterized and noncharacterized rickettsiae isolated from ticks were not pathogenic to humans. In this context, it was considered that relatively few tick-borne rickettsiae caused human disease. This concept was modified extensively from 1984 through 2005 by the identification of at least 11 additional rickettsial species or subspecies that cause tick-borne rickettsioses around the world. Of these agents, seven were initially isolated from ticks, often years or decades before a definitive association with human disease was established. We present here the tick-borne rickettsioses described through 2005 and focus on the epidemiological circumstances that have played a role in the emergence of the newly recognized diseases.

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Summary: The genital mycoplasmas represent a complex and unique group of microorganisms that have been associated with a wide array of infectious diseases in adults and infants. The lack of conclusive knowledge regarding the pathogenic potential of Mycoplasma and Ureaplasma spp. in many conditions is due to a general unfamiliarity of physicians and microbiology laboratories with their fastidious growth requirements, leading to difficulty in their detection; their high prevalence in healthy persons; the poor design of research studies attempting to base association with disease on the mere presence of the organisms in the lower urogenital tract; the failure to consider multifactorial aspects of diseases; and considering these genital mycoplasmas only as a last resort. The situation is now changing because of a greater appreciation of the genital mycoplasmas as perinatal pathogens and improvements in laboratory detection, particularly with regard to the development of powerful molecular nucleic acid amplification tests. This review summarizes the epidemiology of genital mycoplasmas as causes of neonatal infections and premature birth; evidence linking ureaplasmas with bronchopulmonary dysplasia; recent changes in the taxonomy of the genus Ureaplasma; the neonatal host response to mycoplasma and ureaplasma infections; advances in laboratory detection, including molecular methods; and therapeutic considerations for treatment of systemic diseases.