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Editorial introductions

Current Opinion in Infectious Diseases was launched in 1988. It is part of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of infectious diseases is divided into 12 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editors for this issue.

Section Editors

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Paul Heath a is Senior Lecturer and Honorary Consultant in Paediatric Infectious Diseases at St George's Hospital and St George's Vaccine Institute, University of London. He trained in paediatrics and infectious diseases at the Royal Children's Hospital, Melbourne, the John Radcliffe Hospital, Oxford and St George's Hospital, London. Dr Heath's particular research interests are in the epidemiology of vaccine-preventable diseases, clinical vaccine trials – particularly in at-risk groups – and perinatal infections.

He has coordinated national surveillance studies on *Haemophilus influenzae* and Group B streptococcal infections in British children. He sits on national committees concerned with meningitis, Group B streptococcus prevention, Pneumococcal and Hib infections, hospital-acquired infections, and on vaccination of the immunocompromised host.

Dennis L. Stevens

Dr Stevens received his PhD in Microbiology from Montana State University and his MD from the University of Utah College of Medicine. Following a residency in internal medicine at the University of

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Dr Stevens has published over 150 original research papers, 60 book chapters, 110 abstracts and two books, *Streptococcal Infections: Clinical Aspects, Microbiology and Molecular Pathogenesis* (co-authored with Dr Edward Kaplan) and *An Atlas of Infectious Diseases: Skin and Soft Tissue, Bone and Joint Infections*.

Dr Stevens is a member of the American Society of Microbiology, a Fellow in the American College of Physicians, a Fellow in the Infectious Disease Society of America and a member of the Association of American Physicians. In 2000, Dr Stevens received the Infectious Disease Society of America's Society Citation Award, and The William Altemier Award from the Surgical Infectious Disease Society in 2001. He has served as a consultant for the CDC Working Group on Invasive Group A streptococcal infections, and for the WHO and NIH on similar matters. Dr Stevens is currently Chairman of the Infectious Disease Society of America's Guidelines Committee on Skin and Soft Tissue Infections.

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Adverse events following immunization: perception and evidence

Jan Bonhoeffer and Ulrich Heininger

Purpose of review
The aim of this article is to highlight the evidence on new and ongoing vaccine safety concerns in the light of several vaccines recently licensed and others made available and recommended more widely.

Recent findings
There is increasingly convincing epidemiologic and laboratory evidence against a causal relation of several alleged adverse events following immunization. The scientific framework to detect and investigate adverse events following immunization is increasingly robust.

Summary
Currently available vaccines are safe in immunocompetent individuals and there is no evidence to deviate from current immunization schedules.

Keywords
adverse events, immunization, safety

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Abbreviations

AEFI	adverse event following immunization
DTP	diphtheria, tetanus, pertussis
GBS	Guillain-Barré syndrome
ITP	idiopathic thrombocytopenia
MCV4	tetravalent conjugated meningococcal vaccine
MMR	measles, mumps and rubella
MS	multiple sclerosis
ORS	oculo-respiratory syndrome
SIDS	sudden infant death syndrome
SMR	standard mortality rate

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Introduction

Immunization safety is a real concern because all vaccines may cause side effects. Both healthcare workers and patients need reminding that immunization is an induced, controlled stimulus to the immune system, so some adverse reactions can be expected. Most reactions, however, are transient and mild. Immunization safety concerns have existed since the day of the first available vaccine. Since the introduction of Jenner's cowpox vaccine, however, the benefits of saving children from tragic outcomes of common diseases outweighed the risks of perceived adverse events following immunization (AEFIs).

Immunization safety concerns are different from concerns about other medical interventions, because they are administered to generally healthy individuals and the tolerance of AEFIs is substantially lower compared to adverse events following medication for an existing illness. As successful vaccination programs span several generations over time, no doctor, nurse or parent may have ever seen the prevented diseases. It will be an increasing challenge to communicate the benefits of immunization in the apparent absence of disease and the presence of AEFIs, even if mild.

Also, safety concerns are increasing as the success of immunization systems increases. With a decreasing incidence of disease, public attention shifts towards AEFIs. It is then only a matter of time until a concern will be raised and publicized, public confidence might be lost, immunization rates will then decrease and a resurgence of disease is likely to follow. Therefore, maintaining the success of immunization programs critically relies on public confidence, which is based on public perception. Public perception depends on the quality of information provided. Information about the safety of immunizations needs to be placed on the most rigorous scientific basis possible, because concerns may lead to withdrawal of the product from the market, modification of the pertinent recommendations, or loss of public confidence.

Immunization safety concerns often follow a recognizable pattern: the alleged AEFI is a prevalent medical entity of increasing prevalence or unknown cause; the AEFI is suggested to be caused by immunization by some investigators; the methodology of the 'index study' (and subsequent studies by the same study group) is inadequate (typically poorly or not controlled case series); public communication is made prematurely, resonating with

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individuals suffering from the medical entity, but underestimating the potential of harming those who could be protected by the vaccine; the results of the 'index study' are not reproducible by other study groups; regaining public confidence is a slow process over several years.

The aim of this article is to highlight recent evidence on immunization safety concerns related to currently licensed vaccines.

Definition of term and concept

The lack of a common language and clear understanding of what AEFIs are is at the heart of generating and spreading myth. AEFIs are potentially harmful and unintended medical incidents taking place after immunization. Hence, they are temporally associated with, but not necessarily the result of, administration of a vaccine. Although a temporal association is a necessary condition, it is insufficient to establish a causal relation. Even a biologically plausible temporal association is not sufficient to assume a causal relation. In fact, assumed biological plausibility has often been misleading and thus provided a more sophisticated variant of the post *hoc ergo propter hoc* fallacy. The term 'adverse reaction' or 'side effect' should only be used if a causal relation between an AEFI and immunization has been established based on the appropriate Hill's criteria (e.g. consistency, strength of association, specificity, temporality, biological plausibility) [1,2].

Table 1 Adverse events following immunization for which current scientific evidence does not support the hypothesis of a causal relation with immunization

AEFI	Alleged vaccine
Atopic disease	Several
Autism	Measles–mumps–rubella
Crohn's disease	Measles–mumps–rubella
Chronic arthritis	Rubella
Insulin-dependent diabetes mellitus	*Haemophilus influenzae* b, hepatitis B
Intussusception	Rotavirus (current products)
Encephalopathy	Pertussis, measles
Ethyl mercury toxicity	Several
Guillain–Barré syndrome	Influenza (current), meningococcal
Macrophagic myofasciitis	Aluminum adjuvant
Multiple sclerosis	Hepatitis B
Squalene toxicity	Influenza, Anthrax
Sudden infant death syndrome	Several

AEFI, adverse events following immunization.

Adverse events following immunization

Table 1 outlines typical AEFIs for which current scientific evidence does not support the hypothesis of a causal relation. Table 2 outlines typical AEFIs for which there is limited scientific evidence indicating a causal relation with immunization. Allocation to either group has not changed for any of the AEFIs during the last few years.

Atopic disease

Based on the 'hygiene hypothesis' some infectious diseases are claimed to protect from atopic disease, because microbial pressure leads to a reduction in Th2 responses in favor of Th1 responses [3•,4•]. The claim is that vaccines reduce microbial pressure and thus have contributed to the increasing incidence of atopic disease. This is probably not the case, however, because the driving force of microbial pressure in early life is colonization of the gastrointestinal tract, which is unchanged by immunization; in infancy and childhood, microbial pressure is driven by common organisms which are not (yet) widely prevented by vaccines (e.g., rotaviruses, influenza, rhinoviruses, adenoviruses, and enteroviruses); changes in the prevalence of atopic disease were not associated with changes in immunization schedules; potential IgE synthesis is vaccine-specific and does not expand to environmental antigens associated with atopic disease [5,6]. A recent study on more than half a million children challenged the hygiene hypothesis and concluded that atopic constitution is associated with increased susceptibility to acute infections and protection by immunization might be particularly warranted [7••].

Recent data from an observational cohort study with secondary record linkage including 8443 Australian children underlines this evidence. This study has shown positive associations between diphtheria immunization and asthma [odds ratio (OR) 1.3, 95% confidence interval (CI) 1.1–1.7] and between diphtheria, tetanus, pertussis (DTP) and polio immunization and excema and food allergies with OR between 1.4 and 1.5 and 95% CI

Table 2 Adverse events following immunization for which there is some scientific evidence in support of the hypothesis of a causal relation with immunization

AEFI	Vaccine	Pathogenesis
Anaphylaxis	Measles–mumps–rubella (gelatine)	Coombs type 1
Extensive limb swelling	Diphtheria–tetanus–acellular pertussis (booster doses)	Unknown (sensitization of Langerhans cells?)
Intussusception	Rotavirus (recombinant Rhesus)	Unknown
Meningitis	Mumps (Urabe, Leningrad–Zagreb)	Unknown (insufficient attenuation of live virus?)
Oculo-respiratory syndrome	Influenza	Unknown (virion aggregates?)
Paralysis	Oral polio vaccine	Reversion of live attenuated virus to pathogenicity
Thrombocytopenia	Measles–mumps–rubella	Unknown (cross-reacting antibodies?)

AEFI, adverse events following immunization.

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between 0.99 and 2.1 at 7 years of age [8•]. Associations were age dependent, however, with a considerable interval to immunizations, included selected antigens and isolated symptoms of the atopic spectrum, and were weak considering the methodological limitations of the study. Therefore, this study does not suggest that atopic disease is causally related to DTP or polio immunization.

A recent Dutch study on 1875 children investigated the relative risk of atopic disorders at 8–12 years of age following DTP, DTP-polio (inactivated, IPV) and *Haemophilus influenzae* type b immunization and lacked evidence for a causal relation (OR 1.00; CI 95% 0.80–1.24) [9•,10•].

An increased risk of asthma or reactive airway disease following live attenuated influenza vaccine (LAIV) was suggested for children aged 18–35 months, leading to the restricted licensure of the vaccine to children above 5 years [11]. Another recent large study, however, including 11 000 children (aged 18 months to 18 years) receiving almost 20 000 doses of vaccine during four seasons suggested the absence of an association comparing the pre-vaccination and post-vaccination periods [12]. Passive surveillance data on the first two seasons after licensure comprising administration of 2.5 million doses confirm the excellent safety profile of LAIV [13].

Autism

An association between measles, mumps and rubella (MMR) immunization and inflammatory bowel disease and autism was claimed in the late 1990s [14,15]. These studies were not scientifically stringent and had serious methodological limitations.

A recent Canadian study [16••] added to the evidence against an association between pervasive developmental disorder (including autism) and the exposure to MMR. The same study failed to show an association between ethyl-mercury (thiomersal), a preservative in some vaccines, and neurobehavioural disorders. For three birth cohorts included in the study, autism was increasing with decreasing thiomersal exposure. The highest rates of pervasive developmental disorder were observed in children with no vaccine-related thiomersal exposure. This is in line with previous studies demonstrating that diagnosis of autism spectrum disease continued to increase while MMR uptake was decreased or discontinued [17–20].

Two independent studies in Canada and the United Kingdom involving a total of 69 children with autism spectrum disorder did not detect a single copy of the measles genome in peripheral blood leukocytes of cases and controls by highly sensitive PCR [21••,22••]. These studies also elegantly highlighted technical and methodological errors and flaws of previous studies and thus refuted the hypothesis that persistence of measles nucleic acid is associated with an increased risk of developing autism [23–25].

Encephalopathy

Encephalopathy was an alleged AEFI, most prominently following whole cell pertussis and measles vaccine. A recent case–control study, however, including 452 cases (57 immunized) added to the evidence against a causal association. Odds ratios for any time window following immunization were smaller than 1.2 with wide confidence intervals spanning 1 and P values over 0.05 [26•]. The background to another recent study is the increasing recognition of severe myoclonic epilepsy as an epileptic syndrome in infancy. It appears to be associated with mutations in the *SCN1A* gene, coding for a neuronal sodium channel subunit. This study has shown *SCN1A* mutations in 11 of 14 patients with encephalopathy following immunization, suggesting a genetically determined epileptic encephalopathy presenting coincidentally or triggered rather than caused by immunization [27••].

Multiple sclerosis

A causal association between multiple sclerosis (MS) and hepatitis B vaccine was suggested by several case reports during the French immunization campaign [28]. Increased reporting to the national surveillance system following publication of the first concern augmented public misconception. Many subsequent epidemiological studies showed no association. In 2004, a case–control study in the UK claimed evidence in support of an association [29]. This study, however, suffered from a number of methodological problems, undermining the validity of the conclusions. The attempt to reproduce these results failed in a larger study using a large linked database in the US [30–32]. In 2006, Hernan and Jick [33] concurred that there is no conclusive evidence for a causal relation to date.

Piaggio *et al.* [34] investigated T-cell responses to hepatitis B surface antigen among subjects vaccinated with hepatitis B virus and did not detect a difference between responses in healthy subjects and those with MS. Ozakbas *et al.* [35•] could not demonstrate differences in human leukocyte antigen haplotypes between immunized and nonimmunized MS patients. The sample size of this study was small ($n = 11$ immunized, 71 nonimmunized MS patients, 20 healthy volunteers) and the method of selection and allocation was not fully transparent. The general approach, however, aiming to achieve immunological insight into the pathophysiology of MS and its relation to infection (e.g. cross reactive antibodies with neuronal tissues) might be worth pursuing.

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Guillain-Barré syndrome

Thirty years ago, an increased frequency of Guillain-Barré syndrome (GBS) was observed following a swine influenza vaccine [36]. Different influenza vaccines have been used ever since, and no increased risk of GBS could be associated with any of them. One study during the 1992–94 seasons, however, demonstrated a relative risk of 1.7 (CI 1.0–2.8; $P = 0.04$) within 6 weeks following immunization and a peak at 2 weeks, suggesting a potentially increased risks of less than one additional case of GBS per 1 million persons vaccinated [37]. Ever since then the reporting rate of GBS had remained stable while the number of doses administered has increased disproportionately, rendering a causal relation in a defined subpopulation unlikely.

During introduction of the tetravalent conjugated meningococcal vaccine (MCV4) in the US, several cases of GBS were identified to be temporally associated with immunization by the national passive surveillance system. Fifteen cases of GBS within 6 weeks of immunization related to a reporting rate of 0.2 per 100 000 person–months. The corresponding background rate of GBS derived from two large linked healthcare databases was 0.1 per 100 000. The reporting rate ratio for GBS following MCV4 was 1.77 (95% CI 0.96–3.07). Hence there appears to be no significant increased risk of GBS following MCV4 [38•].

A recent study in the United Kingdom involving 228 cases of GBS of which seven cases (3%) presented within 42 days following immunization could not demonstrate an increased risk of GBS following any immunization with a relative risk of 1.03 (95% CI 0.48–2.18) [39•].

Macrophagic myofasciitis

During a hepatitis B vaccine campaign in France the presence of aluminum deposits after vaccination was noted in patients biopsied at the site of injection for suspected systemic inflammatory muscular disease [40]. The entity was termed macrophagic myofasciitis and a causal relation with the vaccine was hypothesized. While this study described a focal histological phenomenon, there is no evidence for macrophagic myofasciitis to be a specific systemic disease [41]. It remains to be elucidated why aluminum salts persists in a small number of vacinees and whether there is an association between the focal microscopic finding and otherwise unspecific generalized weakness. Now that infant immunization schedules increasingly include hepatitis B vaccine immunization, reports in this population increase [42]. Case reports, however, are not helpful to go beyond the stage of speculation. Hence, there remains a lack of evidence for an inappropriate immune reaction and for a causal relation to immunization.

Extensive limb swelling

Swelling at the injection site extending to the adjacent joints was observed following acellular pertussis vaccine, particularly after the fourth and fifth doses. A dose dependency could be shown in a large trial including 20 000 subjects aged 15–27 months receiving nine different formulations [43•].

Sensitization by Langerhans cells and subcutaneous injection was also hypothesized. A reduction of local reactions by using a longer (25 mm) needle was observed in a recent study of 696 children receiving diphtheria–tetanus–whole cell pertussis, *Haemophilus influenzae* type b and a serogroup C meningococcal conjugate vaccine [44••]. It would be interesting to determine whether a correlation with needle size can be observed for extensive limb swelling, as the main site of the reaction appears to be the subcutaneous tissue [45•,46•].

Anaphylaxis

Anaphylaxis is a rare but well recognized AEFI with allergic sensitization occurring to a given vaccine's immunogens or excipients (e.g., preservatives, antibiotics and adjuvants). The incidence of anaphylaxis following any vaccine is estimated to be less than one case per 1 million doses [47–49].

There is no evidence that egg allergy and MMR vaccine are associated. Viruses are not cultivated on eggs but chick embryo cell cultures. Hence, egg allergy does not prevent or warrant delayed immunization. Because anaphylaxis is exquisitely rare in children with known allergic predisposition, more often occurs in children not allergic to eggs, there is no reliable predictor of anaphylaxis as an AEFI, community-based MMR immunization has repeatedly been shown to be safe, and every physician should be able to respond to allergic reactions to any administered substances including vaccines, community based immunization of children with egg allergy is widely recommended and increasingly encouraged [50,51]. It is hypothesized, however, that allergic predispositions to any of the excipients including gelatin or neomycin may be involved in the development of anaphylaxis as an AEFI [48,52•].

Oculo-respiratory syndrome

Oculo-respiratory syndrome (ORS) was first reported in Canada in 2000 and is a clinical entity consisting of various combinations of red eyes, facial swelling, respiratory symptoms and fever [53]. The initial reporting rate was about 10 per 100 000 doses of influenza vaccine. Particularly affected was the age group 40–60 years, females, first time recipients, and those with an allergic predisposition [54]. Recurrence of ORS following revaccination was observed. Symptoms were generally milder, however, despite their increased number [55–58].

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ORS was primarily associated with a single manufacturer's inactivated trivalent split-virus influenza vaccine. Electron microscopy found a disproportionate number of virion aggregates in the Canadian vaccine used during the 2000–2001 season [59]. A change in the manufacturing process resulted in a reduced number of large virion aggregates. A reduction of reports to one per 100 000 doses was observed [53]. Incidence rates were then similar to other inactivated influenza vaccines [54,56]. In a prospective study including 690 immunized infants and toddlers and their household contacts, no difference between immunized and nonimmunized household members was observed regarding symptoms of ORS [60•].

In retrospect, it appears that ORS might not be a new AEFI specific to a single vaccine, but was detected as a passive surveillance signal during the 2000/2001 season, subsequently augmented by increased reporting [61].

With the aim to differentiate rather mild and unspecific symptoms, occurring frequently in exposed and unexposed individuals during the winter season, from those rare cases requiring medical attention to the degree that influenza might elicit, a more stringent case definition might be useful to guide further investigations at this stage.

Bell's palsy

An increased risk of Bell's palsy was observed following a novel nasal influenza vaccine during the 2003/2004 season in Switzerland with an OR of 84.0 (95% CI 20–352), a relative risk almost 20 times that of controls and 13 excess cases per 10 000 vaccinees [62]. It was hypothesized that the adjuvant, a heat-labile enterotoxin of *Escherichia coli*, could have been the causal agent. As a consequence the vaccine was withdrawn. Concern about an increased risk of Bell's palsy following different influenza vaccines was then raised by passive reporting data from the United States and the United Kingdom [63•,64]. A recent self-controlled case-series using a large linked database in the United Kingdom, however, rejected the hypothesis for both parenteral influenza and pneumococcal vaccines with a relative incidence estimate of 0.92 (95% CI 0.78–1.08) [63•].

Immune overload

The notion that immunization poses a burden to the immune system in early life is still a widespread belief [65•,66•,67,68]. The most prevalent aspects of this variably interpreted term are discussed here.

First, the capacity to respond to simultaneous stimuli depends on the general 'fitness' of the immune system. The immune system of a healthy vaccinee has the estimated capacity to react to over 10^9 antigens simultaneously [69]. The number of antigens presented to an individual in the frame of immunization is 6–8 logs less. Infants are estimated to be able to cope with 10 000 theoretical vaccines of 100 antigens with 10 epitopes each [68]. Children with febrile illness at the time of immunization have been shown to mount immune responses similar to healthy individuals, indicating that reaction to administered antigens does not limit the immune systems reactions. Data on the reactogenicity of immunizations in patients with acquired immune deficiency, however, are limited. In view of the globally increasing burden of HIV, optimal prelicensure and enhanced postlicensure surveillance are necessary.

Second, there is insufficient evidence supporting the concern that vaccines would weaken or otherwise harm the immune system. Immunogenicity of combination vaccines generally is not inferior to separate administration [70,71•,72•,73,74•]. Some studies even observed a cross-protective effect against infectious diseases not targeted by a given vaccine and hypothesized that the simultaneous presentation of multiple antigens might unspecifically stimulate the immune system resulting in increased 'immunological fitness' rather than compromising it [75]. There is a need for optimized communication of these findings by healthcare providers [65•,66•].

Intussusception

The first oral rotavirus vaccine, previously licensed in the US (Rotashield; Wyeth, Marietta, Pennsylvania, USA), was a tetravalent rhesus-human reassortant rotavirus vaccine, highly effective in preventing severe rotavirus gastroenteritis. Nine months after licensure, however, the vaccine was withdrawn due to concerns about an increased risk of intussusception [76,77•]. In subsequent clinical trials, it was estimated to be between one in 10 000 and one in 30 000 vaccine recipients in industrialized countries. The withdrawal of Rotashield in the USA had a global effect and remains an issue of controversy in view of the global burden of rotavirus disease: since the date of withdrawal several million children's lives could have been saved, if the vaccine was still available, particularly in developing countries where mortality is high. The Rotashield incident has emphasized the value for postlicensure surveillance of the highest standards available and highlighted the challenges of weighing risks and benefits of a vaccine for a given population with a global perspective in mind.

Two novel rotavirus vaccines were recently developed. A pentavalent human–bovine reassortant vaccine (WC3 strain) and a monovalent human rotavirus vaccine (HRV). Both were shown to be safe in prelicensure studies specifically designed for optimized safety monitoring and including a unprecedented sample size of over 60 000 infants [78•,79•]. The relative risk of intussusception was 1.6 (95%CI 0.4–6.4) for WC3 and 0.85 (95%CI 0.3–2.4) for HRV. Both vaccines have been tested in

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the target age groups and in healthy individuals. Intussusception, however, may occur later in life and safety in immunocompromized patients has not been shown yet. Thus, in countries introducing these vaccines, enhanced postlicensure surveillance is being implemented to optimize detection of potential rare AEFI including intussusception as well as the effects of vaccine virus shedding. A globally coordinated safety assessment with standardized methodology (including a uniform case definition for intusssusception [80]) will be key for successful monitoring. Safety and efficacy studies of oral rotavirus vaccines in HIV positive infants are underway.

Sudden unexpected death

An association of sudden infant death syndrome (SIDS) has been alleged and rejected following several vaccines. On the contrary, a decreased risk was shown and hypothesized to be due to the protection from infectious diseases in early life [81–86].

Five reports of SIDS accumulated after licensure of hexavalent vaccines by the European Medicines Agency (EMEA). This led to analysis of immunization as a risk factor in an ongoing case-controlled study of SIDS in Germany [87••]. In this study, 129 SIDS victims were included during the first 2 years after licensure of two hexavalent vaccines. Twenty cases and 100 controls received hexavalent vaccines. Mulivariate analysis resulted in an OR of 0.77 (95%CI 0.26–2.24). Two infants (five infants if adjusted for underreporting) died within 2 days after immunization. The expected number of deaths (i.e., number of SIDS expected within 2 days of any day of the year), however, was two resulting in a standard mortality rate (SMR) of 2.38 (95% CI 0.77–5.55). Thus, the number of deaths was within the 95% CI.

Passive surveillance data 3 years following introduction of the vaccine in Germany, also showed that SMRs did not exceed expected rates in the first year of life. The SMR for sudden unexpected death (SUD) within 1 day and 2 days following one vaccine administered in the second year of life were 31.3 (95% CI 3.8–113.1; two cases observed; 0.06 cases expected) and 23.5 (95% CI 4.8–68.6; three cases observed; 0.13 cases expected). This was considered a true signal and intensified surveillance for SUD was recommended [88]. Further scientific discussions related to the methodological challenges of case ascertainment and study design reflect the complexity of monitoring and evaluating associations between ill defined syndromes of unknown cause and pathophysiology and immunization.

Thrombocytopenia

Thrombocytopenia (platelet count below 150×10^9/l) is observed following several wild-type virus infections and some immunizations. The pathophysiology, however, remains to be elucidated. In an early elegant trial with live measles vaccine, an asymptomatic decrease of the platelet counts of more than 25×10^9/l was observed in 86% of vaccinees. The decrease was observed after several reexposures, indicating a causal relation. Clinical manifestation of thrombocytopenia after immunization, however, is rare. It appears to be most frequent following MMR vaccine with an estimated hospitalization rate of three per 100 000 immunized children [89,90•]. Clinical presentation resembles acute idiopathic thrombocytopenia (ITP) of childhood, which in itself is an ill-defined condition [91•]. The use of the term ITP appears to be a misnomer in the context of AEFI assessment. The observed event is thrombocytopenia, with or without clinical manifestation. The cause of an idiopathic event is unknown. Hence, exploring ITP as an AEFI invokes *petitio principii:* a logical fallacy in which the proposition to be proven is assumed implicitly or explicitly in one of the premises.

Squalene

Squalene is an oil produced by plants, animals and in the human skin. For over 10 years, it has also been licensed as part of an adjuvant (MF59) in commercially available influenza vaccines and various vaccines in development, including prepandemic influenza vaccines. Millions of doses have been administered and there was no signal in any surveillance system. Yet, health problems of Gulf War veterans have been claimed to be related to antisqualene antibodies as a consequence of exposure to immunization against anthrax [92]. The initial allegations were refuted, however, based on methodological deficiencies of the study, the presence of such antibodies independently of immunization status, and the absence of squalene administration to veterans [93]. More recently a controlled study on subunit influenza vaccine demonstrated that antibody responses against squalene were neither induced nor boosted by vaccination [94•].

Immunization safety organizations

Vaccine safety concerns generally follow a pattern of sudden onset, rapid progression and prolonged recovery. The beginning is often a case series (i.e. a number of exposed subjects with a common outcome), which is followed by broadcasting of the finding through multiple channels. It is then the task of scientific investigations to gradually increase the evidence base to confirm or reject the hypothesis. Generating high quality information at times where opinions are prevailing can be challenging. Recommended resources aiming to provide information based on the highest scientific standards are listed in Table 3.

The Brighton Collaboration (website: www.brightoncolloaboration.org) is establishing globally standardized case

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Table 3 Vaccine safety organizations providing information based on highest scientific standards

Organization	Website
WHO	www.who.int/immunization_safety
Institute for Vaccine Safety: Johns Hopkins	www.vaccinesafety.edu
Health Protection Agency: UK	www.hpa.org.uk
Center of Disease Control and Prevention: USA	www.cdc.gov
The Brighton Collaboration	www.brightoncollaboration.org
Immunization Action Coalition	www.immunize.org

definitions for AEFIs and guidelines for collection, analysis and presentation of vaccine safety data. This will advance immunization safety by facilitating comparison of adverse events across trials and surveillance systems. An up-to-date list of available case definitions and guidelines is posted on the collaboration's website as they become available. The use of Brighton Collaboration definitions is also increasingly recommended by national and international organizations including the WHO, Food and Drug Administration (FDA), European Medicines Agency (EMEA), Council for International Organizations of Medical Sciences (CIOMS), and the American Academy of Paediatrics (AAP).

Conclusion

Several new vaccines have recently been licensed and introduced in national immunization programs (e.g., rotavirus, influenza, human papilloma virus, pneumococcal, meningococcal, and hexavalent vaccines). While high quality epidemiological data are suggestive for or against safety concerns, discussions around the methodological quality of such data are needed to weigh statistical significance. Strategies to promote the preferential implementation of laboratory studies including immunological and genetic testing to explore potential pathophysiological mechanisms as early as possible in the course of investigating a safety signal would be useful to develop. Such studies would also allow sub-analyses of affected patients aiming to identify confounders in epidemiological studies. While it is comforting to know that most children will not experience adverse events following immunizations, some do and we might learn from analyzing such cases more closely rather then disregarding them entirely as part of statistical background noise. It is the study of these subgroups that will provide further insight into specific and nonspecific reactions to immunological stimuli in terms of safety and immunogenicity. Safety data of recently licensed and more widely recommended vaccines indicate that the observed AEFI are mild and transient and do not outweigh their protective benefits.

The association of Bell's palsy and ORS with influenza vaccines have raised concern about the challenging regulatory control of vaccines. This is particularly so for vaccines, which are evaluated annually for modification and potentially redesigned to optimize protection for the expected circulating strains. Optimizing prelicensure safety assessment and enhancing postlicensure surveillance of influenza vaccines will be paramount for continued public confidence, particularly in view of outbreak control of endemic or pandemic strains.

The scientific framework to detect and investigate vaccine safety concerns, however, is increasingly robust and the risk–benefit ratio for the individual and the community is much in favor of widespread use of currently licensed vaccines.

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Managing congenital syphilis again? The more things change . . .

Rana Chakraborty[a,b] and Suzanne Luck[a,b]

Purpose of review
Untreated syphilis may have profound adverse effects on pregnancy outcome, resulting in spontaneous abortion, stillbirth, premature delivery or perinatal death, or can result in significant morbidity during infancy, childhood or adolescence. In this article, we review current strategies for the management of maternal and congenital syphilis nationally and in resource-poor settings.

Recent findings
Since 1998, a dramatic increase in syphilis diagnoses has been documented among women of child-bearing age in the UK and elsewhere. The low prevalence of congenital syphilis in many developed countries may have led to complacency, hindering modern-day management of this historically important condition. Follow-up studies indicate that present antenotal and postnatal interventions could be improved. This conclusion extends to resource-poor settings endemic for syphilis in which rapid diagnostic techniques are currently being validated.

Summary
A stringent follow-up of pregnant women with syphilis before delivery and a proactive approach to identifying and treating exposed neonates born to such patients are needed.

Keywords
congenital, diagnosis, syphilis, treatment

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Abbreviations

EIA enzyme immunoassays
VDRL Venereal Disease Research Laboratory

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Introduction

To prevent cases of congenital syphilis, detection and treatment of infectious syphilis antenatally are essential through effective screening programmes. Associated with this is the necessity to address the healthcare inequalities in populations at increased risk of syphilis, in both the developed and developing worlds. Recent outbreaks in developed countries indicate that a heightened awareness of this condition remains essential.

Historical background

The first well documented outbreak of syphilis occurred in Naples in 1494 and rapidly swept throughout Europe, and spread to India and China occurred thereafter [1,2]. In 1905, the association of *Treponema pallidum* with syphilis was described by Schaudinn and Hoffman [3], who demonstrated spirochetes in Giemsa-stained smears of fluid from secondary syphilitic lesions. In 1943, Mahoney and co-workers [4] treated the first cases of syphilis with penicillin. This drug has remained the mainstay of treatment.

The perinatal transmission of syphilis

The majority of infants with congenital syphilis are infected *in utero*, but the newborn can also be infected by contact with an active genital lesion at the time of delivery. The primary mode of horizontal transmission is by sexual contact, although anecdotal studies [5] cite kissing, contact with infected secretions and blood transfusion as potential sources of acquisition and transmission.

Kassowitz's law states that the risk of vertical transmission of syphilis from an infected, untreated mother decreases as maternal disease progresses. Thus, transmission ranges from 70 to 100% in primary syphilis, 40% for early latent syphilis to 10% for late latent disease [6]. Although unusual, transmission to newborns from mothers with tertiary syphilis has also been reported [7].

Global and national epidemiology

In 2001, the World Health Organization (WHO) estimated that there were approximately 12 million new cases of syphilis in adults globally, with increased prevalence noted in South and Southeast Asia, and sub-Saharan Africa [8]. Such data may have been skewed by high numbers of false-positive assays, however, reflecting the low specificity of nontreponemal tests.

In the UK, data on sexually transmitted infections is notified to the Health Protection Agency (HPA) by

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KC60 statutory notification. Since 1998, a dramatic increase in syphilis diagnoses has been documented among heterosexual populations and men who have sex with men (MSM) [9,10]. Among women, syphilis primarily affects those who are most likely to conceive, mandating screening for syphilis antenatally. Localized outbreaks have been associated with commercial sex workers and cocaine usage [9,11,12], with an over-representation of pregnant women from ethnic minorities born outside the UK [13]. Recent studies [13,14,15•] have raised concerns that current antenatal strategies may be inadequate in the identification and treatment of women at risk. These concerns are reinforced by data from the HPA, which identified 36 cases of congenital syphilis in the UK in 2005 – the highest number in 10 years.

The clinical manifestations of congenital syphilis

Globally, the WHO estimates that one million pregnancies are affected by syphilis. Of these, 460 000 will result in abortion or perinatal death, 270 000 infants will be born prematurely or with low birth weight, and 270 000 will be born with stigmata of congenital syphilis [16]. At least two-thirds of all fetuses of mothers with infectious syphilis are affected [17]. Most affected infants are asymptomatic at birth, with two-thirds developing symptoms by 3–8 weeks. Almost all exhibit symptoms by 3 months of age [18].

The syndromes of congenital syphilis can be classified as either early or late.

Early manifestations

Early features are similar to the manifestations of secondary syphilis in adults. Persistent rhinitis (snuffles) is often the earliest presenting symptom (occurring in 4–22% of newborns with congenital syphilis) [19]. Nonspecific symptoms of congenital syphilis include hepatosplenomegaly and nontender generalized lymphadenopathy (Table 1) [20–22]. The rash in early syphilis is classically a vesiculobullous or maculopapular rash occurring on the palms and soles and may be associated with desquamation. Associated erythema multiforme has been documented [22,23]. Asymptomatic cerebrospinal fluid changes [elevated protein, positive Venereal Disease Research Laboratory (VDRL) test] may be found in 80% of infants [24] but acute syphilitic meningitis occurs rarely [25]. Glomerulonephritis resulting in nephrotic syndrome may also occur. Necrotizing funisitis – a deep-seated infection of the umbilical cord – occurs in premature neonates with congenital syphilis and is associated with a high incidence of intrauterine or perinatal death [26].

Table 1 Incidence of symptoms in early and late congenital syphilis

	Percentage of cases
Early	
Abnormal bone radiograph	33–95
Hepatomegaly	51–56
Splenomegaly	49
Petechiae	41
Skin lesions	35–44
Anaemia	34
Lymphadenopathy	32
Jaundice	30
Pseudoparalysis	28
Snuffles	23
CSF abnormalities	25
Late	
Frontal bossing	30–87
Palatal deformation	76
Dental dystrophies	55
Interstitial keratitis	20–50
Abnormal bone radiograph	30–46
Nasal deformity	10–30
Eighth nerve deafness	3–4
Neurosyphilis	1–5
Joint disorder	1–3

Data taken from references [20–22].

Radiographic abnormalities may be noted in 20% of infants with asymptomatic infection. Bony lesions present within the first 8 months of life and commonly affect the tibia, the tubular bones of the hands and feet and, more rarely, the skull and clavicles. Osteochondritis, or Parrot's pseudo-paralysis, is the most common and earliest lesion, characterized by an asymmetric, painful, flaccid paralysis of the upper limbs and knees [27]. Diaphyseal periostitis is asymptomatic and radiographic changes are often not seen until after 3 months of age.

The late manifestations of congenital syphilis

Late onset is defined as symptoms developing in children older than 2 years of age and is characterized by chronic granulomatous inflammation. Late congenital syphilis most often presents in puberty [17] and can affect many organ systems, although the sites most often involved include bones, teeth and the nervous system. A poor response to intensive treatment is often noted [28].

Symptomatic neurosyphilis, tabes dorsalis and cerebrovascular lesions develop rarely, with juvenile paresis occurring in 1–5% of children/adolescents. Once over 2 years of age, 25–33% of infants with untreated congenital syphilis have asymptomatic neurosyphilis [27]. When symptomatic, neurosyphilis can result in eighth nerve deafness. The onset of deafness is sudden, usually at 8–10 years of age, and, when associated with notched incisors and interstitial keratitis, it forms part of Hutchinson's Triad. Other ocular lesions include iridocyclitis and chorioretinitis.

Radiological changes (Wimberger's lines) reflect metaphyseal destruction secondary to focal erosion of the inner

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aspect of the proximal tibia [21,29]. Early bony changes can be reversed with timely treatment. Pathological fractures may result from untreated congenital syphilis along with the other permanent deformities associated with congenital syphilis, such as saddle nose, palatal erosions and sabre tibia. Clutton's joints (hydrarthrosis) involving the knees or elbows may develop between 8 and 15 years of age. Other characteristic signs of late congenital syphilis include mulberry molars and fissuring around the mouth (rhagades), and localized rashes primarily consisting of nodules and gummata.

Diagnosis

Definitive diagnosis of congenital syphilis is by identification of spirochetes using darkfield microscopic examination or direct fluorescent antibody tests of lesion exudate or tissue including placenta or umbilical cord. Such specimens are highly infectious, however, and false-negative microscopic results are common, making serologic testing necessary.

Antenatal testing

Effective antenatal screening programmes are the cornerstone of effective diagnosis and prevention of congenital syphilis. Screening has been reported [30•] to be cost-effective in populations with syphilis prevalence as low as 5/100 000. In a recent survey [31] of sub-Saharan African countries, 17 out of 22 reported that antenatal screening was a national policy. Of 19.9 million pregnant women in these countries, however, only 5.7 million had access to syphilis screening. Effective prevention of congenital syphilis depends on the identification of active infection in pregnant women by routine serologic screening with a quantitative nontreponemal test [VDRL or rapid plasma reagin (RPR)]. Generally, these tests are carried out antenatally at 11–20 weeks' gestation, although, in populations with a high underlying prevalence of syphilis, there is evidence to support repeated screening in the third trimester to exclude acquisition in late pregnancy [32]. These nontreponemal tests correlate with disease activity and response to therapy in women with positive serology at initial screening [33].

Nontreponemal tests performed on serum samples containing high concentrations of antibody against *T. pallidum*, however, can be falsely negative; this reaction is termed the 'prozone phenomenon'. The sensitivity of nontreponemal tests can therefore be compromised during early primary syphilis; false negatives can also occur with latent acquired syphilis of long duration, and late congenital syphilis. False-positive reactions can occur secondary to viral infections (infectious mononucleosis, hepatitis, varicella, measles), lymphoma, tuberculosis, malaria, endocarditis, connective tissue disease, pregnancy, laboratory error or Wharton jelly contamination when cord blood specimens are used [33,34]. To exclude a false-positive nontreponemal test, serology should be sent for confirmatory treponemal antibody detection by fluorescent treponemal antibody absorption (FTA-ABS) or *T. pallidum* particle agglutination (TPPA). Treatment should not be delayed while awaiting the results of the treponemal test. Treponemal test antibody titres remain reactive for life, even after successful therapy, and correlate poorly with disease activity, and should therefore not be used to assess response to therapy. Treponemal tests may not be specific for syphilis, as positive reactions variably occur in patients with other spirochetal infections, including yaws, pinta, leptospirosis, relapsing fever and Lyme disease.

In women treated during pregnancy, follow-up nontreponemal testing is important to assess the efficacy of therapy, as demonstrated by a fourfold decrease in titre. These usually become nonreactive 1 year after prompt treatment of primary or secondary infection if the initial titre is low ($<1:8$) and within 2 years with congenital infection or if the initial titre is high. Differentiating treated syphilis from active (re)infection may be difficult in the absence of increasing titres. The combination of nontreponemal and treponemal tests provides sensitive and specific screening for all stages of syphilis but requires subjective interpretation and cannot readily be automated [35].

The nontreponemal and treponemal serologic combination is being replaced in many UK diagnostic microbiology laboratories by enzyme immunoassays (EIAs) that detect treponemal IgG or IgG and IgM. Advantages include the production of objective results, the ability to link EIA plate readers directly to laboratory computer systems, and the facility for automation [36]. A quantitative nontreponemal test and serology for specific antitreponemal IgM provides a baseline for monitoring the effect of therapy. IgM becomes undetectable within 3–9 months after adequate treatment of early syphilis but may persist up to 18 months after treatment of late disease [37]. The treponemal IgG EIA is still regarded as investigational in the USA [33]; there are published data, however, showing that screening with recombinant antigen-based treponemal IgG and IgM has comparable sensitivity and specificity compared to the nontreponemal and treponemal serologic combination [38–40], and may be useful for detecting treponemal antibody in HIV-infected patients [41].

One of the challenges to implementing effective screening programmes in developing countries is the lack of facilities (electrical generators, refrigeration) to be able to carry out such screening tests locally. If global targets relating to decreasing rate of under-five mortality and maternal health are to be met, then it has been acknowledged that new solutions need to be found in such

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settings. This has led to the search for Affordable, Sensitive, Specific, User-friendly, Robust and Rapid, Equipment-free, Deliverable (ASSURED) rapid diagnostic methods [30•] (www.who.int/std_diagnostics/). Most of these methods are based on antisyphilis antibody in a sample binding specifically to antigen immobilized on a nitrocellulose membrane while the sample is being transported by capillary flow over the membrane. The reaction is then revealed by dye bound to an antiimmunoglobulin. Preliminary results of pilot studies [42••] evaluating the sensitivity and specificity of a number of such tests have recently been published and show high sensitivity (84.5–97.7%) and specificity (84.5–98%) with low inter-reader variability. The use of such tests offers hope that antenatal testing and treatment can be offered at one appointment, of special importance when women might travel miles to attend such clinics during early pregnancy.

Evaluation of newborns with perinatal exposure to syphilis

An exposed infant should be evaluated for active syphilis if:

(1) Symptomatic.
(2) Maternal titre has increased fourfold.
(3) Infant titre is fourfold greater than maternal titre.
(4) Maternal syphilis was untreated or inadequately treated during pregnancy, with insufficient serologic follow-up.
(5) Maternal syphilis was treated with a nonpenicillin regimen.
(6) After treatment of maternal syphilis (with an appropriate penicillin regimen), the expected decrease in nontreponemal antibody titre after therapy did not occur.
(7) Treatment for maternal syphilis was commenced less than 1 month before delivery.

Detection of specific antitreponemal IgM may be useful in the diagnosis of congenital infection but a negative result around the time of delivery does not exclude this diagnosis. Serological follow-up is indicated and should include repeat IgM testing, and quantitative nontreponemal and treponemal serology to demonstrate loss of passive maternal antibody.

In addition to blood for treponemal and nontreponemal testing, the evaluation should also include a CSF VDRL test and analysis for the detection of white cells and elevated protein, and long-bone radiography. A negative VDRL on CSF does not exclude congenital neurosyphilis. Pathologic examination of the placenta or umbilical cord (if available) is also indicated.

Treatment

Various treatment regimes exist and European guidelines have recently been reviewed [43•] (Table 2). Treatment recommendations are based on chronologic, not gestational, age.

Parenteral penicillin G is the only documented effective therapy for patients who have neurosyphilis, congenital syphilis or syphilis during pregnancy. Aqueous crystalline penicillin G is preferred over procaine penicillin G because adequate CSF concentrations may not be achieved with the latter. If more than 1 day of therapy is missed, the entire course should be restarted.

Newborn infants

In newborn infants, the dosage for aqueous crystalline penicillin G is 100 000–150 000 U/kg per day, administered as 50 000 U/kg per dose, intravenously, every 12 h during the first 7 days of life and every 8 h thereafter for a total of 10 days. Procaine penicillin G is administered in a daily single dose of 50 000 U/kg per day, intramuscularly, for 10 days.

Follow-up

Treated infants should be followed-up at 3, 6 and 12 months of age, until serologic nontreponemal tests become nonreactive or the titre has decreased fourfold. With adequate treatment or in cases in which antibody is transplacentally acquired in the absence of congenital infection, nontreponemal antibody titres should decrease by 3 months of age and be nonreactive by 6 months of age. Previously treated infants at 6–12 months of age with increasing or persistent titres should be re-evaluated, including CSF examination, and treated with a further 10-day course of parenteral penicillin G.

Treated infants with congenital neurosyphilis should undergo repeated clinical evaluation and CSF examination at 6-month intervals until their CSF examination is normal. A persistently reactive VDRL test of CSF is an indication for re-treatment [44].

Older infants and children

Infants of more than 4 weeks of age who possibly have congenital syphilis or who have neurologic involvement should be treated with aqueous crystalline penicillin, 200 000–300 000 U/kg per day, intravenously (administered every 6 h), for 10 days. This regimen also should be used to treat children over 1 year of age who have late and previously untreated congenital syphilis [44], although a poor response to intensive treatment is often noted in this group [28].

During pregnancy

Patients should be treated with penicillin according to the dosage schedules appropriate for the stage of syphilis as recommended for nonpregnant patients. Penicillin-allergic pregnant women should be treated with penicillin after desensitization [43•,45].

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Table 2 Treatment of congenital infection

Country	Alternatives				Penicillin allergy
Europe					
Treatment	Benzyl penicillin	PBP	BBP if cerebrospinal fluid normal		No guidelines
Dose	150 000 units/kg	50 000 units/kg	50 000 units/kg		
Regimen	Over six doses/day	q.i.d.	q.i.d.		
Route	i.v.	i.m.	i.m.		
Duration	10–14 days	10–14 days	1 day		
UK					
Treatment	Benzyl penicillin		PBP		No guidelines
Dose	50 000 units/kg		50 000 units/kg		
Regimen	b.i.d.	Then t.i.d.	q.i.d.		
Route	i.v.	i.v.	i.m.		
Duration	7 days	3 days	10 days		
USA					
Treatment	Benzyl penicillin		PBP	BBP*	Penicillin
Dose	50 000 units/kg		50 000 units/kg	50 000 units/kg	
Regimen	b.i.d.	Then t.i.d.	q.i.d.	o.w.	
Route	i.v.	i.v.	i.m.	i.m.	
Duration	7 days	3 days	10 days	1 day	
Russian					
Early congenital syphilis					
Treatment	Benzyl penicillin	NBP	PBP	BBP	Ceftriaxone or oxacillin or ampicillin
Dose	100 000 u/kg	50 000 u/kg	50 000 u/kg	50 000 u/kg	100 000 u/kg
Regimen	Over six doses/day	Over two doses/day	q.i.d.	o.w.	Over four doses/day
Route	i.v.	i.m.	i.m.	i.m.	i.m.
Duration	14 days	14 days	14 days	3 weeks Only if cerebrospinal fluid normal and not >2 kg	14 days
Late congenital syphilis					
Treatment	Benzyl penicillin	NBP	PBP		No guidelines
Dose	50 000 u/kg	50 000 u/kg	50 000 u/kg		
Regimen	Over six doses/day	Over two doses/day	q.i.d.		
Route	i.v.	i.m.	i.m.		
Duration	28 days, 14 days off, 14 days	28 days, 14 days off, 14 days	28 days, 14 days off, 14 days		

* Normal examination + titres, mother untreated; nonpenicillin regimen – see text of guidelines [43•] for more details. BBP, benzathine benzyl penicillin; NBP, novocaine benzyl penicillin; PBP, procaine benzyl penicillin; b.i.d., twice daily; i.m., intramuscularly; i.v., intravenously; o.w., once per week; q.i.d., four times daily; t.i.d., three times daily. Previously published in [43•].

Conclusion

Despite the introduction of effective treatment and the availability of diagnostic testing in the mid-twentieth century, syphilis still remains a national health issue. In this article, we have reviewed the management of congenital syphilis. At a time at which syphilis has re-emerged in the UK as a major public health problem, we hope that this review will assist clinicians in familiarizing themselves again with the subtleties of one aspect of this age-old affliction. To re-phrase Osler, (s)he who knows syphilis knows the more things change, the more they stay the same!

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 318).

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Rotavirus vaccines in developed countries

Jim P. Buttery[a,b] and Carl Kirkwood[b]

Purpose of review

Rotavirus is the most common cause of diarrhoea and dehydration in early childhood. The recent licensure in many nations of vaccines against rotavirus offers promise to significantly reduce this toll. The present review describes recent developments regarding rotavirus vaccines and the challenges they face.

Recent findings

Rotavirus causes significant morbidity and impact upon healthcare systems, at both inpatient and outpatient levels. An earlier rotavirus vaccine, since withdrawn, was temporally associated with intussusception causing small bowel obstruction, especially in infants receiving their first dose at an older age. Large-scale safety and efficacy studies of two new live, oral, attenuated vaccines have shown excellent efficacy against severe rotavirus gastroenteritis. Importantly, both studies detected no association with intussusception with these new vaccines when administered at the scheduled ages. Developed using different rotavirus vaccinology philosophies, questions remain regarding their coverage against new rotavirus serotypes. Ongoing intussusception surveillance following introduction should answer whether they may be safely administered beyond scheduled ages.

Summary

Safe, efficacious rotavirus vaccines are available in many developed countries, offering significant promise to reduce the burden of gastroenteritis and dehydration. The impact of these vaccines upon not only morbidity, but also circulating rotavirus serotypes, will be monitored with interest.

Keywords

gastroenteritis, intussusception, rotavirus, vaccines

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Introduction

Acute gastroenteritis is a major cause of death and morbidity in early childhood, accounting for more than 2.5 million estimated deaths under the age of 5 each year [1••]. While the death toll is overwhelmingly born by developing nations, acute gastroenteritis accounts for a large number of primary care consultations and hospital admissions in all countries.

Rotavirus is the most common cause of dehydration, hospitalization and death due to acute gastroenteritis in early childhood [1••]. A ubiquitous and democratic virus predominantly affecting healthy children, rotaviral disease is most common and severe between 6 and 24 months of age. In developed countries, children at particular risk of developing rotavirus disease are those attending facilities where young children are grouped, including out-of-home child daycare and hospitals [2,3]. The ascertainment of moderate and severe rotavirus infections reaching hospital services has traditionally been measured, allowing estimates of severe disease burden and some direct impacts upon health systems [4•]. Annually, rotavirus is estimated to cause 58 000–70 000 admissions to hospital with acute gastroenteritis in the USA, more than 87 000 in Europe and 10 000 in Australia [4•,5,6]. Rotaviral disease presentations to primary care and their impact upon these services have been described less frequently. The true incidence of rotavirus infection is unclear in many settings, however, as many infections are presumed to be asymptomatic or very mild, not requiring presentation to healthcare facilities. Most studies addressing diarrhoeal aetiology across different healthcare settings have found rotavirus is more commonly identified with increasing severity of gastroenteritis presentation [7].

Rotavirus virology

Rotavirus, a member of the family *Reoviridae*, is a double-stranded RNA virus with 11 gene segments coding for six structural and six nonstructural proteins. The genome length is approximately 18 000 base pairs. A triple-capsid virus that infects many species, rotavirus serogroups are determined by the inner capsid layer protein VP6 (termed Groups A–E). Almost all symptomatic human disease is caused by Group A rotavirus, with Group B described causing occasional outbreaks in China and Bangladesh, and Group C rotavirus thought to cause predominantly asymptomatic infection.

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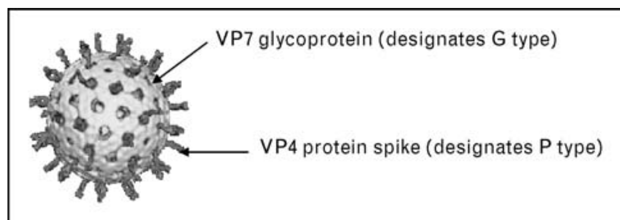
Figure 1 The external structure of rotavirus



Courtesy of Dr B.V.V. Prasad, Baylor College of Medicine, Houston, Texas, USA.

A dual-typing classification system exists for rotavirus based on the two outer capsid proteins, the glycoprotein VP7 (G types) and the protease-sensitive protein VP4 (P types, Fig. 1). Both proteins contain antigenic regions that induce serotype-specific and serotype cross-reactive antibody responses which neutralize the virus. A complete concordance of serotypes and genotypes occurs for G types while for P types this is not the case. For example, the most common serotype G1P1A[8] is described as G type 1, and P serotype 1A, genotype 8. At least 15 G types and 23 P types have been documented [8].

Although 10 G types and 11 P types have been isolated from humans, four serotypes (G1P[8], G2P[4], G3P[8], G4P[8]) have typically comprised 90–95% of samples identified, with serotype G1P1A[8] comprising 60–80% of circulating strains each year [8]. A fifth common G type, G9 in association with P[8], has emerged since the mid-1990s as a significant cause of diarrhoea in many countries, including the USA, the UK, Australia, India, France, Belgium, Hungary, Bangladesh, Thailand and Japan [8,9]. In some instances, G9 was identified as the dominant strain causing disease during the winter epidemics, and it has been associated in a Latin American setting with more severe disease than other prevalent serotypes [10].

Several recent epidemiological surveys have identified the presence of rare G types such as G5, G6 G8 and G10 causing disease in children. While not globally common, these rare G types are often important types in specific locations, which include the identification of G5P[8] in Brazil, G8P[8] and G8P[4] in Malawi and G6P[8] in Hungary [8,9]. More recently, genotype G12 strains have emerged as a cause of disease in humans. G12 strains were initially identified in the Philippines in 1987–1988, but G12 strains have been reported in several locations around the world since 2000. Reports from Belgium, the USA, the UK, Japan and Korea highlight the spread of this emerging type [11]. Whether it continues to emerge and becomes a globally important strain will require continued comprehensive epidemiological studies.

Rotavirus disease and protection

Following severe rotavirus diarrhoea and some asymptomatic infections, antirotavirus-specific antibodies (IgG, IgA, and neutralizing antibodies) are detectable in serum and intestinal secretions, including specific antibodies to antigenic epitopes present on viral structural and nonstructural proteins, such as the VP7 and VP4 proteins. These antibodies neutralize virus in cell culture and have been associated with a degree of protection against the same (homotypic protection) and different serotypes (heterotypic) [12••]. First infections generally produce homotypic responses, and subsequent infections, even if with the same serotype, produce heterotypic responses [13]. IgA levels correlate with intestinal IgA production, which commences within 10 days of first infection, with the intestinal mucosal gut-associated lymphoid tissue potentially the major source of IgA found in the serum. IgA has been detected in faeces within 14 days of initial infection [12••]. In animal models, passively transferred IgG has been shown to inhibit not only viral shedding in challenged naive animals, but also antibody and B-cell memory immune responses to rotavirus [14,15].

Challenge studies using virulent human rotavirus in adults have helped explore protective measures of immunity. Neutralizing serum antibodies against specific VP7 and VP4 antigenic types were shown to protect against illness and shedding following virus challenge. These same initial studies, however, did not demonstrate a protective role for intestinal neutralizing antibody. Subsequent adult volunteer studies investigated the role of neutralizing antibodies in serum and jejunal fluid, IgA in serum, jejunal fluid and stool, and IgG in serum. Only serum IgG protected from infection, and jejunal neutralizing antibodies from disease. Examination of serum IgG and IgA in children has found conflicting results, with the relative importance of each in protecting from disease varying between studies, as well as the protective threshold level of each. Cellular immunity is thought, at least in animal models, to limit duration of excretion of rotavirus [16].

The lack of clearly defined immune correlates of protection was underlined by the phase II studies of the two recently licensed rotavirus vaccines [17,18]. The developers used markedly different definitions for seroconversion, or 'vaccine take' for infants receiving the GSK RIX4414 or Merck pentavalent WC3-human bovine reassortant vaccine. Both developers have suggested these definitions were subsequently validated by the published phase III efficacy; however, these validation studies are yet to be made available [19••,20••].

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Rotavirus vaccines

The first licensed rotavirus vaccine, the live attenuated rhesus reassortant tetravalent vaccine (RRV-TV) (Rotashield; Wyeth Vaccines, Radnor, Pennsylvania, USA), was withdrawn from sale in the USA in August 1999 following reports of intussusception following vaccination [21••]. Intussusception occurs when a section of bowel invaginates adjacent proximal bowel like a telescope, typically at the ileocolic junction. Typically manifesting as episodes of pain, pallor and vomiting in infants, disruption to intestinal blood supply can result in gangrene and perforation [22•]. Fortunately, development of other rotavirus vaccines progressed after the US Food and Drug Administration agreed guidelines for the approval of clinical trials large enough to detect similar associations with intussusception. Two commercial candidate vaccines, Rotarix (GSK Vaccines, Rixensart, Belgium) and RotaTeq (Merck Research Laboratories, Philadelphia, Pennsylvania, USA), have completed phase III large-scale safety and efficacy trials each involving at least 60 000 children, and are now licensed in many countries [19••,20••]. Both being expensive, the task of making rotavirus vaccines affordable for developing nations where the toll of rotaviral acute gastroenteritis is greatest is a pressing priority for both the Global Alliance for Vaccines and Immunisation and the WHO.

Rhesus reassortant tetravalent vaccine and intussusception

Since the initial reports of an association between intussusception and RRV-TV, numerous studies in different North American populations confirmed a strong temporal association, particularly from day 3 to day 7 following the first dose of vaccine [21••]. Recent reanalysis of Center for Disease Control case–control data suggested increased age at first dose (≥90 days) as a risk factor for RRV-TV-associated intussusception. Over 80% of intussusception cases occurred in this older group that comprised only 38% of vaccine recipients [23].

Interestingly, ecologic studies involving populations where RRV-TV was introduced widely failed to detect any increase in overall rates of intussusception [24]. This has led to suggestions that while RRV-TV triggered intussusception in susceptible hosts, RRV-TV may have been protective against intussusception in others. Pathologic studies were conducted on tissue collected from eight children who underwent surgical resection of their intussusception within 2 weeks of receipt of RRV-TV. Histological examination was able to detect vaccine-specific RNA in the tissue from six children, but no pathogenic mechanisms were identified, including no hyperplasia of Peyer's patches, which have been hypothesized to act as potential lead points [22•].

The temporal association of RRV-TV administration with subsequent intussusception has been particularly perplexing, as numerous investigations have failed to demonstrate an association between wild-type rotavirus infection and intussusception. These have included case–control studies where only one of three studies found an association, and several epidemiological studies from numerous countries demonstrating no increase in intussusception during the rotavirus diarrhoea season [21••]. The organism most consistently associated with intussusception has been adenovirus, found in up to 40% of intussusception cases, significantly more commonly than in matched community controls [25••]. These adenoviruses appear similar to circulating adenoviruses, predominantly respiratory rather than enteric adenoviruses [26]. The pathogenesis of intussusception remains poorly understood [22•].

Licensed rotavirus vaccines

During 2006, large-scale clinical safety and efficacy trials were reported for the vaccines developed by GSK Vaccines (Rotarix) and Merck Research Laboratories (RotaTeq). Developed using distinctly different principles of rotavirus vaccinology, both vaccines have been demonstrated to be safe, immunogenic and highly efficacious against severe rotavirus acute gastroenteritis, with no association with intussusception detected when administered at the recommended ages as used in the phase III trials [19••,20••]. Importantly for comparison, different definitions were used by the two major vaccine developers for the clinical endpoints of severe rotavirus gastroenteritis, as well as sample size calculations for the detection of intussusception, making direct comparison between the two vaccines difficult. Additionally, they were trialled in relatively different settings, with the majority of RotaTeq trials occurring in developed nations, while the Rotarix programme included more developing nations. Rotarix (RIX4414) has been licensed in many European and Latin American countries as well as some in Asia and Australia. RotaTeq has been licensed in the USA, several European nations and Australia.

RIX4414, a monovalent human attenuated rotavirus vaccine

Rotarix is derived from the G1P1A[8] monovalent human strain 89–12, isolated from a child and initially developed in Cincinnati, Ohio. Attenuated by serial tissue cell-culture passage, the isolate was cloned and further passaged in approved Vero cells by GlaxoSmithKline and designated RIX4414 [27]. It relies upon induction of heterotypic immunity by multiple doses as has been described for natural rotavirus infections, with the immunodominant VP4 protein eliciting most neutralizing antibody [28]. Although the VP7 protein G type is shared by only one of the four main circulating G types (five including serotype G9), the VP4 P type is shared by all

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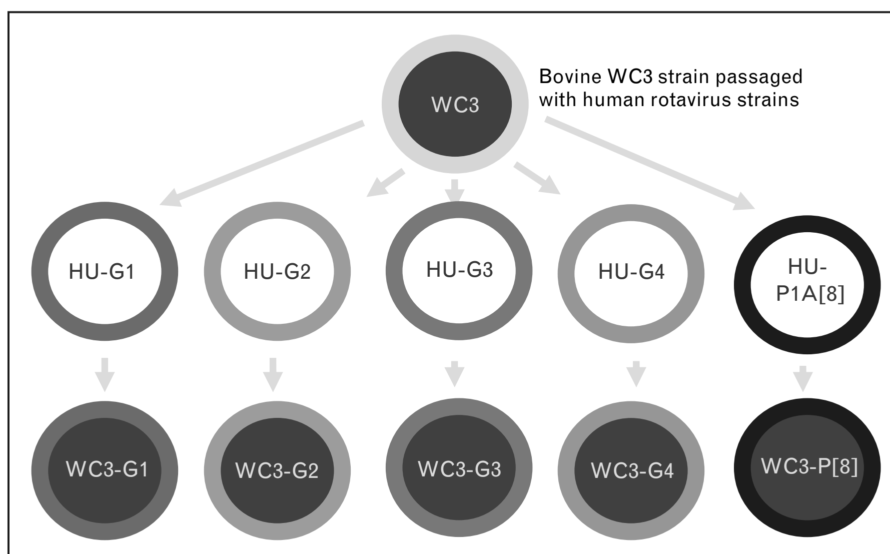
Figure 2 WC3 bovine–human reassortant vaccine development

HU, human rotavirus strain.



except the G2P[4] strain. Each dose contains $10^{6.5}$ median cell-culture infective doses of the vaccine strain and is administered with a calcium carbonate buffer [20••]. Administered orally at 2 and 4 months of age, the vaccine has been trialled in 63 225 Latin American, European and South-East Asian infants, with ongoing African studies yet to be reported [20••,29•]. Extremely well tolerated, the overall efficacy against severe rotavirus gastroenteritis was 84.7% [95% confidence interval (CI), 71.7–92.4]. Efficacy against rotavirus-associated hospitalization rate was 85.0% (95% CI, 69.6–93.5) [20••]. When restricted by rotavirus serotype to those that shared only a P type, efficacy appeared similar at 87.3% (95% CI, 64.1–96.7). When only G2P[4] episodes were examined, however, the possibility of lower efficacy remained unresolved due to low numbers of episodes overall (14 episodes in total, 45.4% efficacy; 95% CI, −81.5–85.6) [20••]. As with all published rotavirus vaccine trials, the efficacy calculation improved with increased severity of clinical rotaviral illness measured.

WC3 bovine-human reassortant vaccine

The Merck vaccine RotaTeq was developed using reassortment between human and bovine rotavirus strains. The original 'backbone' strain was derived from the WC3 bovine strain developed in Philadelphia [27]. Reassortant strains, obtained by coculturing WC3 with human rotavirus strains, were then able to express human VP7 antigens. When development was assumed by Merck, a pentavalent vaccine was developed, containing five human–bovine reassortant strains expressing the four common human VP7 serotypes and the most common human VP4 type, G-types 1–4, and P-type 1A[8] (Fig. 2). Administered as part of a three-dose oral schedule at 2, 4 and 6 months, each dose contains 6.7×10^7–12.4×10^7 infectious units. To achieve protection, RotaTeq relies predominantly on eliciting serotype specific responses. In phase III trials of 70 300 infants conducted in Europe, North America and Latin America, the efficacy subset was restricted to Finland and the USA [19••]; 68 038 infants received at least one dose of vaccine. Efficacy against the predefined outcome of severe rotavirus gastroenteritis due to serotypes G1–G4 was 98% (95% CI, 88.3–100), and against any gastroenteritis due to G1–G4 was 74% (95% CI, 66.8–79.9) [19••].

Analysis of efficacy against specific serotypes was limited by relatively small numbers of episodes of non-G1 serotypes; however, clear efficacy against serotype G9 (sharing the P type with the vaccine) was demonstrated [19••].

Other rotavirus vaccine candidates

There are a variety of alternate candidate vaccines to the existing licensed vaccines. The original RRV-TV vaccine remains licensed. Re-evaluation of the dose timing, suggesting a much lower attributable risk of intussusception if neonatal dosing is utilized [23]. Another tetravalent bovine–human reassortant vaccine developed by scientists at the US National Institutes of Health has been shown to be immunogenic and efficacious in phase II trials in Finland [30]. This candidate is currently being licensed to several vaccine manufacturing companies in India and China. An Indian attenuated human neonatal strain II6E (G9P[11]) has shown encouraging tolerability and immunogenicity in a single-dose, phase I trial in infants [31]. Phase II trials in Australia of another attenuated human neonatal strain, RV3, a human G3P[6] strain, demonstrated low reactogenicity, but

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further development of this vaccine is underway to improve immunogenicity [1••]. The Lanzhou Lamb Rotavirus vaccine, an attenuated a G10P[12] vaccine, is licensed and marketed in China; however, no safety or efficacy data have been published [32].

Challenges facing rotavirus vaccines

Despite the largest clinical trial programmes since polio vaccine, important questions remain for rotavirus vaccines. These include the vaccines efficacy, funding and implementation in developing settings; their ability to prevent disease due to existing and emergent rotaviral serotypes; and their safety outside the recommended age of administration.

Developing nations

Rotavirus vaccines will be expensive, at least in the short term. Innovative national initiatives, such as the agreement reached between GSK Vaccines and the Brazilian Government, offer promise as a way of reducing costs to make these life-saving vaccines available where the burden of mortality is greatest. Similarly, support by the GAVI Alliance (formerly Global Alliance for Vaccines and Immunisation) and the WHO for newer candidates and tiered pricing of licensed vaccines remains critical. Efficacy trials in developing settings are also critical, as generally rotavirus vaccine efficacy against disease has been lower than that shown in developed nations.

Heterotypic immunity and emerging serotypes

The efficacy shown by both RotaTeq and Rotarix was against serotypes prevalent during the trials, predominantly serotype G1P[8]. Containing the four most common G types (G1–G4) and the P type (P[8]), RotaTeq shares the P type with most G9 strains, as does Rotarix, which relies upon shared P type for non-G1 strains for much of its protective immunity. Rotateq efficacy against severe disease due to G9 serotypes, sharing only a VP4 protein, was high at 100% (95% CI, 67.4–100), although limited by low numbers of cases [19••]. Rotarix efficacy against G2P[4] offers the opportunity to estimate protective benefit of the human non-VP4/7 rotaviral proteins. This was calculated as 45% (95% CI, −81.5 to 85.6) against severe disease for the initial report, but subsequent presentations using accumulated data have quoted improved efficacy of 75% [20••,33]. These results are encouraging for potential efficacy against emergent serotypes that may not share VP4/7 serotypes. The protective role of immunity to other proteins has been encouraging, at least in animal models, with roles for VP6, VP8 and VP2 suggested in challenge models [15,34,35].

Intussusception

Both successful phase III safety and efficacy trials for RotaTeq and Rotarix were designed to detect whether an association with intussusception similar to that seen with RRV-TV existed. Administered within monitored study conditions at the recommended times (2 and 4 months for Rotarix, and 2, 4 and 6 months for RotaTeq), no increase in intussusception cases were seen in vaccine recipients. Persisting concerns regarding the potential influence of age at first vaccine dose, however, caused both manufacturers to recommend against children receiving these vaccines outside the ages studied. Only careful postlicensure surveillance ascertaining intussusception cases as well as clinical information including vaccine dosing details appears likely to provide information to fully reassure manufacturers and authorities whether older children may safely receive rotavirus vaccines [21••]. Similarly, as newer rotavirus vaccine candidates near phase III clinical trials, it remains uncertain whether they will be required by regulatory authorities to recruit sufficient children to similarly detect a similar association with intussusception as seen with RRV-TV. Such a requirement will have major feasibility and cost implications on clinical development programmes.

Conclusion

The recently licensed oral, live attenuated rotavirus vaccines offer promise to reduce the toll of rotavirus gastroenteritis upon young children and healthcare systems in the developed nations able to afford them. When administered at scheduled times, large-scale trials showed no association with intussusception, with ongoing surveillance following introduction important to answer whether older children may also safely receive vaccine. Ongoing collaborative efforts are crucial to make rotavirus vaccines available in developing nations as soon as possible, where they offer the greatest potential impact upon morbidity and mortality.

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The burden of influenza in children

Mary Iskander[a], Robert Booy[a] and Stephen Lambert[b]

Purpose of review
This review summarizes recent studies that better address the burden of influenza from the medical and socioeconomic perspectives. The issue of influenza in children is one that has implications for future universal vaccination policies.

Recent findings
In the past, the burden of influenza in children was largely defined by hospital-based studies that quantify the incidence of influenza hospitalization and, consequently, the benefit of prevention in young children. The medical and the socioeconomic impact have been better appreciated recently with population-based studies because the great majority of children are managed as outpatients. Children with influenza may not have direct contact with medical services but still generate substantial costs in carer illness or work-day loss. Furthermore, the specificity offered by laboratory confirmation of influenza has enabled influenza to be separated from other respiratory viruses that may have confounded previous studies looking at the medical and economic costs of illness.

Summary
Better understanding of the burden of influenza in healthy children regarding hospitalization rates, outpatient medical visits, community-managed illness and socioeconomic impact on families and society exists; this has potential implications for universal vaccination policies under consideration.

Keywords
burden, children, hospitalization, influenza, socioeconomic impact

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Abbreviations

ACIP American Advisory Committee on Immunization Practices
AOM acute otitis media
CI confidence interval
RSV respiratory syncytial virus

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Introduction

Influenza has long been considered as a disease of elderly people because of the high incidence, hospitalization and mortality rates in those of over 60 years of age. The generally good prognosis of influenza in healthy children further added to that misconception. Among children, influenza has been considered serious only in those with chronic medical conditions at higher risk of developing complications. In healthy children, the burden of influenza has increasingly become apparent, with new studies examining the medical and, more recently, the socioeconomic impacts. Many studies have used nonspecific outcomes such as respiratory illness without laboratory testing, or relied on International Classification of Disease (ICD) codes that are not specific for influenza; this will have affected evaluation of the true burden of influenza in children and, consequently, the cost-effectiveness of universal influenza immunization in children.

Despite debate regarding the economic benefit of influenza vaccination in children, in 2004, the American Advisory Committee on Immunization Practices (ACIP) recommended routine influenza vaccination in children of 6–23 months old. This decision was largely based on the medical burden of influenza.

In 2006, the ACIP extended its recommendations to include all children up to the age of 5 years. The cost-effectiveness of such a programme requires an accurate evaluation of the burden of influenza disease in the inpatient as well as the outpatient and community settings.

Recent studies have attempted to examine both the direct and indirect burden of influenza and to distinguish this from other respiratory viruses, such as respiratory syncytial virus (RSV), which co-circulates in the same age group. In this review, we will examine recent studies that address the epidemiological and clinical characteristics of influenza infection in children, as well as the socioeconomic impact of this infection for children and their families.

Epidemiological characteristics

The morbidity of influenza in children is clearly demonstrated by hospitalization data that show hospitalization rates in young children aged under 5 years to be equivalent to those in people aged over 65 years [1]. Australian data reveal that children aged under 5 years have

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hospitalization rates second only to those aged over 85 years [2]. Moreover, these rates are inversely related to the age of the child, with children younger than 6 months at maximum risk [1–4]. Clinicians have tended to underestimate influenza-related hospitalizations in children [5,6••] and, despite this, Australian hospitalization data still show a rate approximately twice that in those over 60 years old [2].

A more precise estimate of hospitalization in children has been provided by prospective surveillance studies of laboratory-confirmed influenza. With such an approach, over 4 years, a multicentre study by Poeling *et al.* [6••] has shown that an average of 0.9 per 1000 children of 0–59 months of age were hospitalized with laboratory-confirmed influenza [95% confidence interval (CI) 0.8–1.1 per 1000]. The average annual rate was highest in children aged 0–5 months (4.5 per 1000 children) and decreased with older age groups. A similar age distribution was demonstrated by Moore and colleagues [7••] where nearly 50% of children admitted to hospital with laboratory-confirmed influenza were younger than 6 months of age, and 80% were less than 2 years old.

In contrast to elderly people, the mortality rate related to influenza in children is approximately one-tenth that of those aged over 60 years (0.1 compared with 1.1 per 100 000) [2].

Nevertheless, in the 2003–2004 influenza season, a national survey [5] of influenza-associated deaths in the United States showed that the laboratory-confirmed mortality rate in children younger than 6 months was much higher, at 0.88 per 100 000.

Apart from the extremes of age, there are certain other groups at higher risk of hospitalization and related complications, including death, due to influenza. The ACIP-designated high-risk conditions for which annual influenza vaccination is recommended are asthma, chronic pulmonary disease, immunosuppression, hemoglobinopathies, chronic renal dysfunction, metabolic and endocrine conditions, long-term salicylate therapy and pregnancy [8].

More recently, neurological and neuromuscular disease was found to be a risk factor for respiratory failure and other influenza-related complications. This was demonstrated for the winter of 2003–2004 by Keren *et al.* [9] in a retrospective cohort study in which the likelihood for a child with a neurological or neuromuscular disease to develop respiratory failure was six times that of a previously healthy child (OR 6.0; 95% CI 2.7–13.5). Furthermore, in the same year, a national US survey by Bhat *et al.* [5] of influenza-associated deaths demonstrated that chronic neurologic conditions, including developmental delay, seizure disorder and cerebral palsy, made up one-third of the influenza-associated deaths in children aged under 18 years. As a result of these findings, the ACIP, in 2004, recommended annual influenza vaccination to include all persons with conditions that compromise handling of respiratory secretions [5].

Even though hospitalization data are impressive, only about 5% of children presenting to medical attention with influenza are hospitalized [10••], making the burden of outpatient childhood influenza more substantial. It should be recognized that hospitalization studies will underestimate the burden of disease, as many children are not hospitalized until several days after symptoms have appeared, when viral titres are lower and the chance of isolating the virus using culture from secretions is reduced.

Regarding the outpatient burden of disease, the propensity of influenza viruses to periodic but haphazard antigenic drift causes appreciable variation in attack rates from one year to another; typically, it ranges from 20 to 30% of children each year, with rates of up to 50% in children attending day-care [3,11].

A prospective cohort study by Poeling *et al.* [6••] addressed the issue of case ascertainment as well as timeliness of obtaining the samples from children attending emergency departments over two influenza seasons. The outpatient visits to clinics and emergency departments attributable to influenza were approximately 10, 100 and 250 times as high as hospitalization rates for children aged 0–5, 6–23 and 24–59 months, respectively.

Apart from the fact that the outpatient burden of influenza far exceeds that of the inpatient population, these data also reflect the reality that older children (older than 2 years) tend to be managed as outpatients and thus play a major role in transmitting infection to contacts at home, school and childcare. Furthermore, influenza infection is more likely to occur where children mix, such as in day-care centres or schools – a fact that lends itself to the argument that influenza vaccination in children may have considerable impact on the reduction of influenza-associated morbidity [10••].

Clinical characteristics

Influenza typically manifests as an upper respiratory tract infection, and the clinical characteristics are difficult to distinguish from other respiratory pathogens [12]. It also causes a spectrum of other respiratory illnesses, including croup [7••,10••], acute otitis media, bronchiolitis, asthma exacerbation [7••,10••,13] and pneumonia [14•], depending on an interplay between host susceptibility and viral virulence.

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Prospective hospital-based studies [7••] as well as outpatient population-based studies [6••] have shown fever, cough and rhinorrhoea to be the most frequent symptoms. Children younger than 6 months of age are more likely to present with rhinorrhoea compared with older children, whereas those between 6 and 24 months are more likely to be hospitalized with wheezing and otitis media (OR 2.03 and 3.47, respectively). Children older than 5 years were more likely to suffer pharyngitis compared with younger age groups [7••].

One of the most frequently reported influenza complications managed in the outpatient setting is acute otitis media (AOM). Two prospective outpatient studies by Tsolia *et al.* [10••] and Heikkinnen *et al.* [15] have shown otitis media to be the most common influenza complication, as it was diagnosed in 18.5 [10••] and 39.7% [15], respectively, of children presenting with influenza. Analysis of the results by age revealed that AOM was diagnosed more commonly in children aged less than 2 years (27%) and in those aged between 2 and 5 years (23%) compared with those aged between 5 and 14 years (10.3%) ($P = 0.001$) [10••]. The contribution of influenza to AOM was further demonstrated by a prospective single blinded intervention study [16•] that showed a significant difference between the incidence of AOM in vaccinated children compared with unvaccinated children (2.3 compared with 5.2%; $P < 0.01$) and, earlier on, by Belshe *et al.* [17], in an interventional study demonstrating the efficacy of live attenuated cold-adapted trivalent influenza vaccine. The study illustrated a 30% reduction in the incidence of febrile otitis media in vaccinated children (95% CI 18–45%; $P < 0.001$).

Despite the fact that asthma is the most prevalent high-risk condition for which influenza vaccination is recommended and influenza-induced asthma is responsible for excess cardiopulmonary disease, outpatient presentations and antibiotic prescriptions in children with asthma [13], the rate of influenza vaccination in children with asthma remains suboptimal, probably due to lack of physician recommendation or parental perception that their child does not have increased susceptibility to influenza [18]. Lack of physician recommendation might be partially due to uncertainty about the degree of protection that vaccination affords against asthma exacerbation. A recent systematic review [19] did not support a major benefit from vaccination, and a recent randomized double-blinded study [20] in children with asthma did not show a significant reduction in asthma exacerbations in influenza-positive children. Nevertheless, further research is needed in this area before a change of policy is considered.

The rate of influenza-related pneumonia was estimated as 14% in a retrospective survey [14•] of both outpatient and hospitalized children with influenza. Although the contribution of influenza to the overall burden of childhood pneumonia may be slight, influenza pneumonia may be underestimated, as the illness is difficult to differentiate from uncomplicated influenza as well as other respiratory infections on the basis of clinical picture [14•].

Nonrespiratory complications of influenza include febrile convulsions [10••,21•,22•], especially in children with a family history or a past history of febrile seizures (OR 7.58; 95%CI 1.48–38.84; $P = 0.015$) [21•].

Other serious complications of influenza include encephalopathy, meningitis, myocarditis and secondary bacterial infection such as those caused by *Staphylococcus aureus* [23,24], while pneumococcal and meningococcal infections are well recognized complications [25,26].

Socioeconomic burden

Like the medical burden, the socioeconomic burden of influenza tends to fluctuate with severity of the season but, in general, influenza is associated with substantial socioeconomic consequences on families, healthcare services and society [27,28]. Socioeconomic impact includes physician visits, medications, school absence, missed work days, either due to secondary illness in a carer or to care for a sick child, and hospitalization. In the past, studies [29] demonstrated economic benefit of universal influenza vaccination in children only when indirect effectiveness was considered.

Recent studies [30–32] have found the direct medical costs related to hospitalization as well as outpatient influenza in children to be higher than initially calculated. This may be due to the fact that previous studies did not separate influenza from other respiratory pathogens, depending mainly on ICD codes that are not completely specific to influenza. A recent hospitalization study by Keren *et al.* [33••] demonstrated that the cost of influenza-related hospitalization in children may be up to three times higher than previously estimated. This retrospective cohort study, spanning 4 years, determined the cost of influenza-related hospitalization in children with laboratory-confirmed influenza. The mean hospitalization cost of true influenza in children involved greater resource utilization than the cost of hospitalizations for noninfluenza-related pneumonia and bronchitis – a fact not considered in previous studies that failed to differentiate influenza from other respiratory illnesses.

Children at high risk of complications of influenza had higher mean total costs compared with those at low risk (\$15 269 compared with \$9107; $P < 0.001$), probably due to longer hospital stay, as room charges and hospital

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supplies accounted for the majority of hospitalization costs [33••].

In addition, children over 2 years of age were found to suffer higher complication rates compared with those of less than 6 months of age. A retrospective study over three influenza seasons showed that children aged over 2 years had an increased rate of pneumonia, intensive care stay and mechanical ventilation, and accounted for 55% of total hospital costs and longer hospital stay compared with younger children. Forty per cent of these children did not have high-risk conditions [34•].

The higher direct cost of influenza also extends to children managed in the community. A population-based prospective cohort study [35] in 234 Australian children of under 5 years of age showed that outpatient laboratory-confirmed influenza incurred two to three times the cost of other respiratory viruses. This suggests that annual influenza vaccinations for healthy children may be more cost-effective than previously thought.

The indirect economic burden, including secondary infection of household contacts of sick children, leading to parental illness, missed work days and transmission of influenza to the workplace, overshadows the direct costs of paediatric influenza and has not been adequately assessed in the past.

Recently, a study [10••] using virological confirmation separated the effects of influenza infection from other respiratory viruses. The study found that for each child with influenza, a mean of 1.34 work days were lost by the parents to care for the sick child and a further 0.36 days for their own illness. The secondary infection rate for influenza, however, was significantly higher than that for other respiratory viruses (17 compared with 11%; $P < 0.0001$), suggesting a higher rate of intrafamilial spread compared with other infections.

The indirect burden was further illustrated in a prospective study by Esposito *et al.* [36] that compared influenza with RSV infection in children aged 15 years or younger presenting to the emergency department for acute conditions. The study demonstrated that previously healthy children with influenza were more likely to use antipyretics compared with those with RSV (82.5 compared with 50.0%; $P < 0.0001$), and missed more school days than RSV-positive children (12 compared with 5 days; $P = 0.003$). Household contacts of influenza-positive children had significantly higher incidence of similar disease, antipyretic use, work and school day loss than those of RSV-positive children [8,36].

The role of children in influenza transmission to their elderly contacts was demonstrated by Ghendon *et al.* [37••] when the rate of influenza-like illness was 3.4 times lower in the elderly contacts of immunized children than in contacts of the control group (0.07 compared with 0.24%; $P < 0.01$.

Conclusion

The burden of influenza is becoming better appreciated as recent studies have considered both the medical and the socioeconomic burden in inpatient and outpatient populations. In addition, most recent studies have distinguished influenza from other respiratory viruses when considering socioeconomic impact, giving more specificity and certainty to the question of economic burden. The issue of burden remains a central factor in determining the cost-effectiveness of influenza vaccination in children and recent data appear to support the opinion that with a greater burden than previously recognized, the economic benefit of universal influenza vaccination is more than originally anticipated.

References and recommended reading

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T cell-based diagnosis of childhood tuberculosis infection

Ajit Lalvani and Kerry A. Millington

Purpose of review

T-cell interferon-gamma release assays (TIGRAs), available as enzyme-linked immunospot (ELISpot) and enzyme-linked immunoassay (ELISA), potentially significantly advance on the tuberculin skin test (TST) for diagnosis of tuberculosis infection. We review all publications using TIGRAs in children to appraise paediatricians of the advantages and limitations of these new blood tests.

Recent findings

Unlike TST, both tests are independent of Bacille Calmette-Guérin vaccination status, providing higher diagnostic specificity. In children with active tuberculosis ELISpot is more sensitive than TST and is unaffected by HIV infection, age under 3 years or malnutrition; ELISA data are currently limited. In the absence of a gold-standard test for latent tuberculosis infection, tuberculosis exposure was used as a surrogate marker; ELISpot generally correlates better with tuberculosis exposure than TST, while ELISA correlates broadly similarly. Indeterminate test results in young children are rare with ELISpot and are more common with ELISA.

Summary

Although longitudinal studies quantifying risk of progression to tuberculosis in tuberculosis-exposed children with positive TIGRA results are required urgently, the small but rapidly expanding evidence-base since the first application of TIGRAs to childhood tuberculosis in 2003 combined with recent national guidelines makes a strong case for judicious use of TIGRAs in clinical management of paediatric tuberculosis.

Keywords

children, *mycobacterium tuberculosis*, T-cell interferon-gamma release assays, tuberculin skin test

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Abbreviations

BCG	bacille Calmette-Guérin
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
LTBI	latent tuberculosis infection
TIGRA	T-cell interferon gamma release assay
TST	tuberculin skin test

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Introduction

The burden of childhood tuberculosis is difficult to delineate, in part because of the inherent difficulties in accurately diagnosing tuberculosis in children. Estimates indicate, however, that in 2004 childhood tuberculosis accounted for 10% of all new cases in Africa and 2% in the established market economies [1]. Clear estimates of HIV-related tuberculosis in children are lacking because of insufficient and conflicting data [2]. Several studies in countries with high HIV infection rates, however, have shown an increasing proportion of children with tuberculosis who are infected with HIV, and higher mortality rates in these patients [3,4].

Active tuberculosis

Childhood tuberculosis is commonly extrapulmonary, disseminated and severe, especially in children under 3 years of age, and is associated with high morbidity and mortality [5•]. The gold standard for the diagnosis of active tuberculosis is a positive *Mycobacterium tuberculosis* culture from a clinical specimen. Suitable specimens from children are difficult to obtain, however, since a high proportion of childhood tuberculosis is extrapulmonary, requiring invasive procedures, and children younger than 5 years old with pulmonary tuberculosis rarely expectorate sputum. Even when specimens are obtained from children, fewer than 20% are smear-positive for acid-fast bacilli [6] and culture results are frequently negative and usually too late to affect initial management. In the absence of accurate diagnostic tools for tuberculosis in children, both underdiagnosis and overdiagnosis are common [2]; the latter is exacerbated in areas with a high prevalence of HIV and tuberculosis because both share many clinical features and it is often impossible to exclude tuberculosis in HIV-infected children. Moreover, untreated tuberculosis in HIV-infected children is rapidly fatal. The tuberculin skin test (TST) is widely used to support clinical and radiological findings in the evaluation of children with suspected tuberculosis. A positive TST result can help in

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the decision to start treatment while bacteriological confirmation is awaited or when it is lacking. The clinical utility of a rapid test of infection lies in its potential to rule out a diagnosis of tuberculosis when other tests are negative, but the poor sensitivity of TST in children precludes reliable exclusion of tuberculosis.

Latent tuberculosis infection

Children who develop active tuberculosis often do so within several months after initial infection and, since infection in children is usually recent, prompt diagnosis and treatment of asymptomatic infection are essential. The risk of progression to active tuberculosis is highest in children younger than 3 years old and approaches 40% in infants, with a second peak occurring in late adolescence [5•,7,8]. Many adults who develop infectious reactivation tuberculosis acquired the infection during childhood. Given the effectiveness of isoniazid preventive therapy in preventing progression to active tuberculosis [9], therefore, accurate diagnosis and treatment of *M. tuberculosis* infection in children would prevent many cases of contagious adult tuberculosis in the future. Finally, diagnosis of latent tuberculosis infection (LTBI) and active tuberculosis in children is important epidemiologically as it signals recent transmission of *M. tuberculosis* in the community.

TST was until recently the only method of detecting *M. tuberculosis* infection. The TST is based on the detection of a cutaneous delayed-type hypersensitivity response to purified protein derivative, a poorly defined mixture of antigens present in *M. tuberculosis*, *Mycobacterium bovis* Bacille Calmette-Guérin (BCG) and several nontuberculous mycobacteria. Whilst this assay is relatively cheap and does not require a laboratory, there are numerous limitations. The antigenic cross-reactivity of purified protein derivative compromises specificity in BCG-vaccinated persons and in people previously exposed to nontuberculosis mycobacteria, resulting in false-positive results [10]. In contrast, HIV infection, disseminated tuberculosis or malnutrition commonly result in false-negative results and cutaneous anergy. Sensitivity of TST in young children is unknown, and because of this uncertainty, along with the confounding effect of BCG in vaccinated children, guidelines for the interpretation of TST results in child tuberculosis contacts vary widely. Operational constraints include operator errors, variability in placement and reading of the test, and the need for a return visit that leads to poor compliance.

T-cell interferon-gamma release assays

T-cell interferon-gamma release assays (TIGRAs) have been developed as an alternative immunodiagnostic approach to the TST for detecting *M. tuberculosis* infection [11–14] (Table 1 [15–21,22••,23•,24••,25,26,27•,28]). TIGRAs are based on the ex-vivo detection of interferon-gamma (IFN-γ) released from presensitized *M. tuberculosis*-specific T cells in response to two immunodominant secreted proteins: early secretory antigen target-6 (ESAT-6) and culture filtrate protein 10 (CFP-10). T-cell responses to these antigens that are absent from BCG [29] and most environmental mycobacteria [30] are not confounded by prior BCG vaccination and potentially represent a more specific immune marker of *M. tuberculosis* infection than the TST. Three commercially available TIGRAs for diagnosing *M. tuberculosis* infection have been developed: T-SPOT.*TB* test (Oxford Immunotec Ltd, Abingdon, UK), based on the ex-vivo 16–20 h enzyme-linked immunospot (ELISpot) assay developed by Lalvani; and QuantiFERON-TB Gold (Cellestis, Carnegie, Australia) and QuantiFERON-TB Gold in-tube (Cellestis), which are both based on the 16–24 h whole blood enzyme-linked immunosorbent assay (ELISA) (see Fig. 1). The ELISpot evidence-base in childhood tuberculosis is comprised predominantly of studies using the Lalvani ELISpot test (Table 1), which has since been developed into T-SPOT.*TB* (Oxford Immunotec Ltd).

Table 1 Published studies on sensitivity and specificity of T-cell interferon-gamma release assays in children with latent tuberculosis infection and active tuberculosis

		ELISpot and T-SPOT.*TB* study design	*n*	ELISA and QuantiFERON-TB Gold study design	*n*	QuantiFERON-TB Gold in-tube study design	*n*
Latent tuberculosis infection	Sensitivity	Cross-sectional screening [15]	718	Prospective [16]	101	Convenience sample [17]	184
		Contact tracing [18]	41	Cross-sectional screening [19]	75		
		Contact tracing [20]	535	Contact tracing [21]	125		
		Prospective community-based [22••]	979				
	Specificity	Contact tracing [20]	535			Case–control [23•]	207
Active tuberculosis	Sensitivity	Case report [24••]	1	Prospective [16]	101	Prospective [25]	105
		Prospective [26]	70	Case report [27•]	2		
		Prospective cohort [28]	293				
	Specificity						

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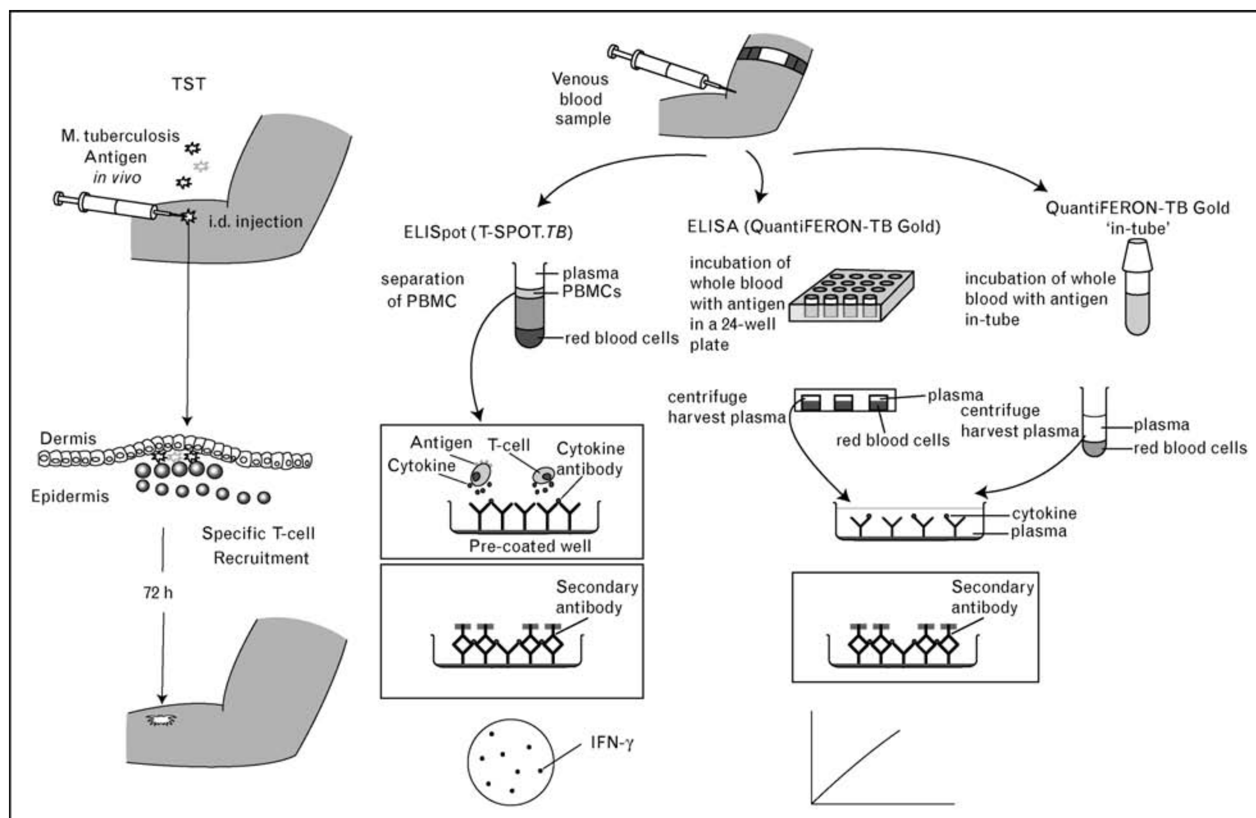
Figure 1 Schematic of the four immune-based methods for diagnosis of *M. tuberculosis* infection



Schematic of the tuberculin skin test (TST) and the different T-cell interferon-gamma release assays (TIGRAs): the enzyme-linked immunospot (ELISpot) T-SPOT.*TB*, the enzyme-linked immunosorbent assay (ELISA) QuantiFERON-TB Gold, and the in-tube ELISA QuantiFERON-TB Gold in-tube. TST: purified protein derivative is intradermally injected into the volar surface of the forearm and induration of any delayed-type hypersensitivity response is measured 72 h later. ELISpot: peripheral blood mononuclear cells (PBMC), which include T cells, are separated from the blood sample by density centrifugation, and are washed, counted and then incubated with ESAT-6 and CFP-10 in a standard 96-well microtitre plate for 16–20 h. If the patient is infected with *Mycobacterium tuberculosis*, T cells will recognize the antigens and secrete IFN-γ. This cytokine is captured in the immediate vicinity of the cytokine-secreting T cell by antibodies specific for IFN-γ coated on the bottom of each well. The cytokine-bound antibodies are subsequently detected with another antibody conjugated to an enzyme that catalyses a colorimetric reaction resulting in visible spots, where each spot represents the footprint of one T cell that responded to the antigens. These spots are counted and the frequency of *M. tuberculosis*-specific T cells quantified. ELISA: whole blood from the patient is incubated with either ESAT-6 and CFP-10 in a 24-well plate or with ESAT-6, CFP-10 and TB7.7 (p4) in the blood collection tube for 16–24 h. If the patient is infected with *M. tuberculosis*, T cells will recognize the antigens and secrete IFN-γ. Either the plate or tube is centrifuged and the plasma transferred to a 96-well microtitre plate. IFN-γ in the plasma is captured by antibodies specific for IFN-γ coated on the bottom of each well. The cytokine-bound antibodies are subsequently detected with another antibody conjugated to an enzyme that catalyses a colorimetric reaction. The optical density of each well is measured and the concentration of IFN-γ determined using a standard curve. Although a laboratory is needed to process the blood samples from patients, which optimally need to be processed within 8–16 h (within 8 h for ELISpot, within 12 h for QuantiFERON-TB Gold and within 16 h for QuantiFERON-TB Gold in-tube), multiple patient samples can be analysed at the same time, interpretation of the tests is standardized and the internal positive control allows assessment of the performance of each assay.

Maturation of neonatal cell-mediated immunity

The especially high risk of progression to active tuberculosis in infants suggests that protective T-cell-mediated immune responses are less effective in early life. Maternal lymphocytes normally do not cross the placental barrier, and are present at relatively low concentrations in breast milk [31]. Infants are therefore dependent on their own cell-mediated immune response to resist or contain infections caused by intracellular pathogens such as *M. tuberculosis*. Interestingly, neonates develop adult-like T-helper 1 responses when vaccinated with BCG [32–35], but cellular immune responses to infections with several intracellular pathogens including cytomegalovirus and HIV are reduced or delayed in infants compared with those in adults [31]. There were no published data on cellular immune responses to *M. tuberculosis* infection in infants and young children until the recent application of TIGRAs [16,18,24••,27•,36•,37]. These studies have provided information on mitogen-induced lymphocyte responses as well as *M. tuberculosis* antigen-specific responses; the former are discussed in the next paragraph while the latter are reviewed in the sections on performance of TIGRAs in children with active tuberculosis and LTBI.

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Does young age affect IFN-γ production or reliability of TIGRAs?

Given that cell-mediated immunity matures during infancy and early childhood, it is important to determine whether IFN-γ production as measured by TIGRAs is age-dependent. Significantly lower production of IFN-γ in response to the positive control mitogen phytohaemagglutinin was observed in children younger than 4 years old compared with children 4–15 years old ($P < 0.0001$) using an in-house ELISA [37], and Connell and coworkers [16] reported a significant positive correlation of the IFN-γ phytohaemagglutinin response with increasing age up to 17 years using the commercial ELISA (Spearman's coefficient 0.53, $P < 0.001$). Using ELISpot, in contrast, no age-dependent production of IFN-γ in response to phytohaemagglutinin was observed in 125 children younger than 2 years old compared with 825 children 2–16 years old ($P = 0.52$; Lalvani and Millington, unpublished observations). Although a significantly smaller IFN-γ response to phytohaemagglutinin when measured with ELISpot was observed in 11-week-old babies ($n = 41$) compared with adults ($n = 51$), all results were determinate with no instances of a failed positive control phytohaemagglutinin response [18]. IFN-γ production detected by ELISpot, except in the first weeks of life, is therefore not age-dependent probably because of ELISpot's high analytical sensitivity, which enables it to detect even low numbers of IFN-γ-secreting T cells.

The difference in age-dependence of IFN-γ detection between ELISA and ELISpot probably accounts for the markedly different rates of indeterminate results generated by the two assays in young children. In a prospective study in Italy [36•] in which the performance of the commercially available ELISA and ELISpot were compared in routine clinical practice in the same 25 children younger than age 5 years, the number of indeterminate results with ELISA was significantly higher than with ELISpot (32% versus 0%, $P = 0.02$). Additionally, there was a significantly higher proportion of indeterminate ELISA results in children aged 5 years and younger than in individuals aged older than 5 years (32% versus 10%, $P = 0.003$). Moreover, in a study of 101 children in Australia, 17% of ELISA tests were indeterminate [16]. In contrast, in a study in India [25], none of the 105 children tested with the in-tube ELISA were indeterminate. In general, therefore, indeterminate results are very rare with ELISpot and are more common with ELISA.

Clinical performance of TIGRAs in children with active tuberculosis

Although TIGRAs cannot distinguish between active tuberculosis and LTBI, *M. tuberculosis* infection is a prerequisite for active tuberculosis. TIGRAs may therefore provide useful information in children being evaluated for suspected tuberculosis. In a prospective cohort study of 293 South African children with a high prevalence of HIV coinfection and malnutrition, in whom accurate diagnosis of tuberculosis is commonly extremely difficult, the sensitivity of ELISpot was significantly higher than the TST in children with tuberculosis (83% versus 63%, $P < 0.001$) [28]. Moreover, while the sensitivity of TST was substantially reduced in children younger than 3 years old, in children coinfected with HIV and in malnourished children, the diagnostic sensitivity of ELISpot was not significantly affected by these factors. Used together with TST, ELISpot provided a diagnostic sensitivity of 91% in this challenging population. As this study was carried out in routine clinical practice in rural and urban kwaZulu Natal, its results are likely to be generalizable to other areas with a high prevalence of tuberculosis and HIV infection. A smaller South African study [26] using a different format to the Lalvani ELISpot (i.e. recombinant antigens instead of peptides) reported positive ELISpot responses to ESAT-6 or CFP-10 in 10 (83%) of 12 children with culture-confirmed tuberculosis.

In a recent study of ELISA in routine practice [16], all nine children diagnosed with active tuberculosis by a combination of clinical symptoms, radiographic abnormalities and response to antituberculosis therapy were ELISA-positive. Of the six children tested with the TST, all were TST-positive. In eight children with active tuberculosis in India [25], of whom five had microbiological confirmation, five were in-tube ELISA-positive and the same five children were TST-positive. Although the cumulative number of children with active tuberculosis tested by ELISA is too small to estimate sensitivity, both ELISA and in-tube ELISA results appear comparable with the TST.

Two case reports describe the use of TIGRAs in three infants. One infant with intense perinatal multidrug-resistant tuberculosis exposure tested positive with ELISpot when he presented with active pulmonary tuberculosis [24••], and two infants with perinatal tuberculosis tested positive by ELISA in the context of negative TST results [27•]. Together with the study by Liebeschuetz and co-workers using ELISpot [28], these data suggest a useful role for TIGRAs in evaluation of infants and young children with suspected tuberculosis.

Reliable estimates of the specificity of TIGRAs or TST in routine clinical practice necessitate definitive exclusion of tuberculosis in large numbers of children with initially suspected tuberculosis. The absence of a positive *M. tuberculosis* culture cannot reliably exclude tuberculosis, however, because of its poor sensitivity. A better criterion is the continued absence of clinical tuberculosis at 6 months follow-up. The only study to attempt this was limited by the logistical difficulties of achieving 6 months

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follow-up in rural kwaZulu-Natal and therefore yielded only a few children in whom tuberculosis was definitively excluded. As those authors pointed out [28], accurate estimates of the specificity of TIGRAs when used to evaluate children with suspected active tuberculosis are a research priority.

Clinical performance of TIGRAs in children with latent tuberculosis infection

Determining whether a new test for diagnosing LTBI is better than the TST is difficult because there is no gold standard test for LTBI. Airborne transmission of *M. tuberculosis*, however, is promoted by infectivity of the index case and by increasing duration and proximity of contact [38–40]; thus a key determinant of infection is the amount of time spent sharing room air with the source case [41]. If a new test is more accurate than the TST, it should therefore correlate more closely with the degree of exposure to *M. tuberculosis* than the TST, but should be independent of the BCG vaccination status [42]. In a large UK school outbreak with 69 secondary cases of tuberculosis and 254 cases of LTBI, the investigators [20] accurately quantified tuberculosis exposure in 535 students based on the number of classes shared with the single highly infectious source case. Although there was high agreement between ELISpot and TST results ($\kappa = 0.72$), ELISpot correlated significantly more closely with *M. tuberculosis* exposure than did TST on the basis of measures of proximity ($P = 0.03$) and duration ($P = 0.007$) of exposure to the index case. In another point-source institutional outbreak [18], where contacts, including 41 neonates, had less exposure to the source case and the *M. tuberculosis* strain was multidrug-resistant, ELISpot results correlated significantly with three of four predefined measures of tuberculosis exposure, while the TST results did not correlate with any measures of exposure. In a community-based study of 979 child household contacts with a median age of 7 years (interquartile range 3–11) in Istanbul [22••], positive ELISpot and TST results were significantly associated with two predefined measures of exposure to *M. tuberculosis*; the index patient being a parent rather than another household member, and the number of cases of sputum smear-positive pulmonary tuberculosis per household. In a study of child contacts of sputum smear-positive adult tuberculosis in The Gambia [15], concordance between TST and ELISpot results was 83% ($\kappa = 0.62$) and both tests were significantly more likely to be positive with increasing exposure to the index case. In contrast to all the above studies, the proportion of TST-positive ELISpot-negative children increased with more exposure while the proportion of TST-negative ELISpot-positive children decreased; however, measures of exposure in high-prevalence countries with high background levels of *M. tuberculosis* transmission in the community may be unreliable.

In a small school tuberculosis outbreak in a predominantly non-BCG-vaccinated population, there was high agreement between ELISA and TST results ($\kappa = 0.87$). There were more ELISA-positive contacts in the high-exposure group compared with the low-exposure group [21]. In contrast, in an Australian study [16] of children referred for suspected LTBI there was poor agreement between TST and ELISA results ($\kappa = 0.30$); and of the 21 unvaccinated TST-positive children with a very high likelihood of LTBI, 16 had determinate results – of whom only four were ELISA-positive. There were no instances of a negative TST and positive ELISA result. These data suggest ELISA may have lower sensitivity than the TST in diagnosing LTBI in children. In a community-based case–control study in Nigeria [23•], the proportion of children with positive in-tube ELISA and positive TST results was higher in contacts exposed to smear-positive tuberculosis than in contacts exposed to smear-negative tuberculosis or controls. The agreement of TST and in-tube ELISA results was 74% ($\kappa = 0.50$) in contacts exposed to smear-positive source cases and 74% ($\kappa = 0.25$) in contacts exposed to smear-negative source cases or in controls. Most in-tube ELISA-positive TST-negative discordant results were in contacts exposed to smear-positive source cases, whereas most in-tube ELISA-negative TST-positive discordant results were in contacts exposed to smear-negative source cases or in controls. In a South African study of children at high risk of LTBI, 43.5% of children had a TST result of at least 10 mm and 33.2% had a positive in-tube ELISA result. Agreement between the TST and in-tube ELISA results increased as the cut-off point of a positive TST result was raised from at least 5 mm to at least 10 mm to at least 15 mm induration [17].

The high specificity of TIGRAs has been amply demonstrated in adults and confirmed in children. The high specificity of ELISpot was confirmed in a large contact-tracing study of 535 school children (87% BCG-vaccinated), which showed that ELISpot results were independent of BCG vaccination whereas TST was significantly more likely to be positive in BCG-vaccinated than in nonvaccinated students [20]. The ELISA was shown to be independent of BCG vaccination in a Danish school tuberculosis outbreak [21] where the proportions of students with positive results were similar between BCG-vaccinated and unvaccinated contacts. Additionally, in-tube ELISA results were not associated with BCG vaccination in 105 children with suspected tuberculosis [25].

Conclusion

In children with active tuberculosis, ELISpot is more sensitive than the TST. The sensitivity of the ELISA has not hitherto been systematically compared with the TST since only 19 children with tuberculosis have been tested

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(11 with ELISA and 8 with in-tube ELISA). The higher sensitivity of ELISpot compared with the TST will improve diagnostic evaluation of children with suspected tuberculosis, and a small further increase in the sensitivity of TIGRAs (e.g. by incorporation of novel *M. tuberculosis*-specific antigens [43]) could enable reliable and rapid exclusion of tuberculosis in children. Specificity of TIGRAs in evaluation of children with suspected active tuberculosis has not yet been demonstrated in routine clinical practice and remains a research priority.

For LTBI, the ELISpot, ELISA and in-tube ELISA assays have higher specificity than the TST because they are unaffected by BCG vaccination. Higher specificity will reduce or eliminate false-positive test results in BCG-vaccinated children and in children exposed to nontuberculous mycobacteria, thereby reducing unnecessary chemoprophylaxis and its associated toxicity. Diagnostic sensitivity of TIGRAs for LTBI is difficult to quantify because of the lack of a gold standard. The fact that ELISpot results correlate better with tuberculosis exposure than TST suggests improved sensitivity, but longitudinal studies of child cohorts are needed to confirm the true sensitivity of TIGRAs. Such studies would quantify the risk of progression in tuberculosis-exposed individuals with positive TIGRA results; this would determine whether a positive TIGRA result reflects infection with viable bacilli and whether this predicts subsequent development of active tuberculosis rather than merely reflecting past exposure and immune memory. Moreover, if a positive TIGRA result reflects infection with viable bacilli, IFN-γ responses should decline with bacterial killing during treatment – this was recently observed for ELISpot in a cohort of 38 tuberculosis-exposed school children undergoing chemoprophylaxis [44•].

The first example of a TIGRA-positive tuberculosis-exposed individual progressing to active tuberculosis was recently reported. An asymptomatic infant born to a mother with multidrug-resistant tuberculosis was persistently ELISpot-positive but TST-negative, and developed active tuberculosis aged 2 years [24••]. If the proof-of-principle provided by this sentinel case is confirmed in large-scale studies of the predictive value of positive TIGRA results, TIGRAs will enable more accurate targeting of chemoprophylaxis to children with LTBI at risk of progression to tuberculosis. While positive ELISpot results have been observed to turn negative in TST-negative child contacts in the absence of therapy, suggesting *M. tuberculosis* infection may have been spontaneously cleared in a minority of contacts [44•,45], the key determinant of net treatment benefit will be the overall population risk of progression to active tuberculosis in ELISpot-positive contacts, just as with TST [46,47]. Other key research priorities to better define the role of TIGRAs in clinical paediatric practice are presented in Table 2.

Table 2 Research priorities to better define the role of T-cell interferon-gamma release assays (TIGRAs) in clinical paediatric practice

Number	Research need
1	Further reporting of the performance of TIGRAs in routine clinical practice
2	Assessment of the predictive value of TIGRAs for subsequent development of active tuberculosis in children, especially in young children.
3	Evaluation of whether dynamic changes in the magnitude of the ELISpot response can serve as an early marker of progression to incipient active disease before the onset of symptoms.
4	Evaluation of TIGRAs for site of disease testing, especially in childhood tuberculosis meningitis
5	Assessment of the risk of progression to active tuberculosis in TST-negative TIGRA-positive child contacts

TIGRAs cost more than TST and transfer the workload from the clinic to the laboratory. Economic analyses, however, show that TIGRAs are cost-effective [48••,49,50], and the National Institute of Health and Clinical Excellence recently proposed a two-stage strategy (i.e. TST followed by confirmatory TIGRA in those who test TST-positive) as the most cost-effective in contact tracing [51]. The same guidelines (and the Centers for Disease Control and Prevention guidelines [52]) recommend use of TIGRAs instead of the TST for diagnosis of LTBI in people prone to false-negative TST results, which includes young children and people with suppressed cellular immunity due to HIV infection, concomitant illness or iatrogenic immunosuppression. On the basis of guidelines and a rapidly expanding published evidence-base, therefore, TIGRAs and, in particular, ELISpot are set to revolutionize management of paediatric tuberculosis infection in the next few years.

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Aseptic meningitis

Bonita E. Lee[a] and H. Dele Davies[b]

Purpose of review
To highlight some of the recent key epidemiologic and clinical diagnostic dilemmas of aseptic meningitis and to evaluate some tests that may help distinguish aseptic compared with bacterial meningitis.

Recent findings
Enteroviruses remain the most common cause of aseptic meningitis. Certain enteroviruses (e.g. coxsackie B5, echovirus 6, 9 and 30) are more likely to cause meningitis outbreaks, while others (coxsackie A9, B3 and B4) are mostly endemic. Nucleic acid tests are more sensitive than cultures in diagnosing enteroviral infections. In centers where the turnaround time for these tests is less than 24 h, there can be substantial cost savings and avoidance of unnecessary treatment of aseptic meningitis with antibiotics. Serum and stool specimens are important adjunct samples for diagnosing enteroviral infections in children. Cerebrospinal fluid protein (≥0.5 g/l) and serum procalcitonin (≥0.5 ng/ml) appear to be useful laboratory markers for distinguishing between bacterial and aseptic meningitis in children aged 28 days to 16 years, but they have relatively low sensitivity and specificity.

Summary
Enteroviruses are the major causes of aseptic meningitis. The major focus of diagnosis remains ruling out bacterial infection or confirming enteroviral etiology of infection. Properly implemented nucleic acid tests have the potential to reduce cost and unnecessary treatment.

Keywords
aseptic meningitis, enterovirus, nucleic acid tests

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Abbreviations

CSF cerebrospinal fluid
NAT nucleic acid amplification tests
PCR polymerase chain reaction
RNA ribonucleic acid
TAT turnaround-time

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Introduction

In this review, we will focus on some of the challenging aspects of diagnosing and managing aseptic meningitis. Specifically, we will examine the recent epidemiology of enteroviral infections, the recent evidence for the role of polymorphonuclear pleocytosis in early compared with late aseptic meningitis, the roles of surrogate laboratory tests including procalcitonin and protein levels in distinguishing bacterial compared with aseptic meningitis and the potential impact of nucleic acid tests on the outcomes of aseptic meningitis.

Etiology of aseptic meningitis

The term 'aseptic meningitis' can be used broadly to include all types of meningitis with negative bacterial cultures from cerebrospinal fluid (CSF). The etiologic agents have been nicely summarized in a recent review article by Kumar [1] (Table 1). While viral meningitis constitutes the most common cause of aseptic meningitis, from a clinical management point of view, the most pressing issue is ensuring that a treatable bacterial infection is not missed and that culture-negative bacterial meningitis is not due to the common diagnostic dilemma of partial treatment by antibiotics. Different approaches have been taken to try to rule out partially treated bacterial meningitis. A 10-year retrospective study [2] in Boston found that latex agglutination test for bacterial antigen in CSF was not helpful in this type of clinical situation. Recently, there have been more published studies [3–6] on the use of advanced molecular diagnostic techniques, such as 16S rRNA PCR with direct DNA sequencing, as a more sensitive diagnostic approach for bacterial detection in CSF and blood samples. These methodologies are not yet widely available, however, and false-positive tests due to contamination have been reported. Other types of bacterial infections such as tuberculosis, mycoplasma, leptospira and Lyme disease can also present as aseptic meningitis. For clinicians seeing children from Lyme-endemic regions, longer duration of headache, presence of cranial neuritis and predominance of CSF mononuclear cells were found to be more common in Lyme meningitis than other types of aseptic meningitis [7••]. Interestingly, CSF pleocytosis and aseptic meningitis have been identified in 11.9% of young infants who had lumbar puncture as part of septic work-up during urinary tract infection [8]. In terms of noninfectious aseptic meningitis, drug-related aseptic meningitis is more frequently reported in adults than in children. It is useful to be aware of this potential complication in medications commonly used in children,

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Table 1 Etiology of aseptic meningitis

I Infectious causes	II Noninfectious causes
1. Viruses:	1. Postinfectious/postvaccinial
Enteroviruses – polio, coxsackie, ECHO virus	Rubella
Herpes group of viruses	Rubella
Herpes simplex virus types 1 and *2*	Varicella
Varicella zoster virus	Variola
Cytomegalovirus	Rabies vaccine
Epstein–Barr virus	Pertussis vaccine
Human herpes virus 6 (HHV-6)	Influenza vaccine
Respiratory viruses	Vaccinia
Adenovirus	Yellow fever vaccine
Rhino virus	2. Drugs
Influenza virus types A and B	Nonsteroidal anti-inflammatory drugs (NSAIDs)
Arboviruses	Trimethoprim–sulfamethoxazole, amoxicillin
Mumps virus	Muromonab CD3 (OKT3)
Lymphocytic choreomeningitis	Azathioprine
HIV	Intravenous immunoglobulin
2. Bacteria:	Isoniazid
Partially treated meningitis	Intrathecal methotrexate
Parameningeal infection	Intrathecal cytosine arabinoside
Endocarditis	Allopurinol
Mycoplasma pneumoniae	Carbamazepine
M. tuberculosis	Sulfasalazine
Ehrlichiosis	3. Systemic disease
Borrelia burgdorferi	Collagen vascular disorders
Treponema pallidum	Systemic lupus erythematosus
Brucella	Wegener granulomatosis
Leptospirosis	Central nervous system vasculitis
3. Fungi	Rheumatoid arthritis
Cryptococcus neoformans	Kawasaki's disease
Histoplasma capsulatum	Sarcoidosis
Coccidiodes immitis	Leptomeningeal cancer
Blastomyces dermatitides	Posttransplantation lymphoproliferative disorder
Candida	Behcet disease
4. Parasites	Vogt–Koyanagj syndrome
Toxoplasma gondii	4. Neoplastic disorders
Neurocysticercosis	Leukemia
Trichinosis	Carcinomatous meningitis secondary to primary or secondary tumours of the brain
Naeglaria	5. Inflammation of neighbouring structures
Hartmannella	Brain abscess
Bartonella henselae	Epidural abscess
5. Rickettsiae	6. Miscellaneous
Rocky Mountain spotted fever	Arachnoiditis
Typhus	Migraine
	Urinary tract infection

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such as amoxil, trimethoprim–sulfamethoxazole (TMX) and ibuprofen, however, especially highlighted by a recent report [9,10,11••] of neurological symptoms due to TMX intake in an adolescent. Overall, viral infection is the most common form of aseptic meningitis and enteroviruses are the most common causes of viral aseptic meningitis. For this reason, enteroviral aseptic meningitis will be the major focus of this review.

Epidemiology of enteroviruses

Enteroviruses belong to the family of *Picornaviridae* and are small, nonenveloped, single-stranded RNA viruses that have been classified into 68 serotypes in the International Committee on Taxonomy of Viruses classification [12]. New enteroviruses are being described based on molecular characterization and updates on enterovirus classification can be found at the website of the International Committee on Taxonomy of Viruses Picornavirus Study Group (www.picornastudygroup.com/). The USA has recently published serotype data collected on over 50 000 cases of enterovirus infections from 1970 to 2005 reported to the National Enterovirus Surveillance System – a voluntary, passive laboratory-based surveillance program [13••]. Some serotypes were epidemic and associated with outbreaks, such as high rate of coxsackievirus B5 and echovirus 6, 9 and 30 in various years from 2003–2005, and some serotypes were endemic throughout the period, such as coxsackievirus A9, B3 and B4, and enterovirus 71. While enterovirus 71 had an endemic pattern in the USA, the serotype was associated with severe outbreaks in Taiwan with hand, foot and mouth disease and severe brainstem encephalitis from 1998 to 2001 [14,15]. During the outbreaks in Taiwan, some patients had mild illness while others developed severe neurological

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syndrome and died. A recent publication [16•] found that, in comparison with enterovirus 71 strain isolated from patients with herpangina, the strain isolated from patients with encephalitis was more temperature-resistant at 40°C, had more efficient replication in an astrocytoma cell line and had better tropism for peripheral blood monocytes. All those findings are likely related to viral pathogenesis. Worldwide, predominant strains of enterovirus change over time, with a summer–fall seasonality of the infections [17,18•–20•]. On the other hand, a persistence of enteroviral aseptic meningitis cases in the winter of 1999 was reported in France, which preceded a large outbreak in the spring and summer of the following year [21]. A few studies reported a male predominance in enterovirus infection that was also identified in the USA for cases under 20 years old. In a very interesting study [22••] on intrafamilial transmission of enterovirus in 29 households in Mongolia, there was a tendency towards higher detection rate of enterovirus in males than females in the younger age groups and a reverse pattern in the older age group. Young siblings were the main source of enterovirus and hand washing after defecation protected against infection. These observations confirm the faecal–oral and person-to-person transmission of enterovirus. In the outbreak setting, recreational water such as in swimming pools has been suggested as a potential source for enterovirus in several investigations [23,24,25•].

CSF findings in aseptic meningitis

Earlier studies suggested that more than 50% of CSF samples in aseptic meningitis cases could have neutrophil predominance (>50% of differential count) early in the illness [26]. In a recent small cross-sectional study [27,28•], however, there was no significant correlation between the percentage of mononuclear cells in the CSF and the duration of symptoms – a finding that contradicted the previous observations that the percentage of neutrophils in the CSF from patients with aseptic meningitis decreased over time. Nucleic acid amplification tests (NAT) are more sensitive than traditional viral culture in the detection of enterovirus. A cross-sectional study and a study of 34 adults with diagnosed enteroviral meningitis or encephalitis [29,30] suggested that the recovery of virus from CSF by NAT in patients was highest within the first 2 days of symptoms and decreased dramatically after 5 days of illness. Another study [31] that did not distinguish enterovirus from other viruses identified in CSF suggested that the recovery of virus was highest on day 3 of illness onset. The difference in findings among studies might be related to the variation of the sensitivity and specificity of the various in-house NAT assays. Cost-saving measures can be implemented at diagnostic laboratories if CSF parameters can be established to limit unnecessary NAT for enterovirus. Studies [32,33] reviewing CSF parameters in enteroviral positive samples, however, have reported high rates of normal protein (44%) and leukocytes (9–15%). Normal CSF cell count was more commonly observed in young infants who would be more likely to have a lumbar puncture in their septic work-up [20•].

Bacterial compared with viral aseptic meningitis

Strong clinical interest in having a laboratory test that can distinguish between bacterial and viral meningitis exists. A study [34••] that reviewed CSF parameters from 9111 neonates of at least 34 weeks' gestation with CSF culture showed that 10% of neonates with bacterial meningitis had up to 3 CSF WBC/ml, suggesting that CSF cell count is not a reliable tool to distinguish between bacterial and viral infection in this age group. Dubos *et al.* [35••], in a retrospective cohort study of 167 patients with suspected meningitis, identified CSF protein ($\geq$0.5 g/l) and serum procalcitonin ($\geq$0.5 ng/ml) as the most useful laboratory markers identifying bacterial compared with aseptic meningitis in children aged 28 days to 16 years, with a sensitivity and specificity for the CSF protein of 89 and 78%, respectively, and for serum procalcitonin of 89 and 89%, respectively. A few cases of bacterial meningitis would still have been missed using these criteria, however, and serum procalcitonin is not readily available at most centers.

Several clinical decision rules to differentiate between bacterial and septic meningitis have been published in the past. One of the major issues with clinical decision rules is that the rules that were validated in one center might not be applicable for another center [36]. In one study [37••], five clinical decision rules were evaluated using data from a retrospective cohort of 167 children. The authors identified the best clinical rule as the one described by Nigrovic *et al.* [2] (seizure, blood neutrophil count, CSF Gram stain, protein and neutrophil count), which had a sensitivity of 100% and specificity of 66%. A major disadvantage of published clinical rules or laboratory assays is that they were set up to ensure that no bacterial meningitis cases will be excluded, which necessitates admission and treatment of a large proportion of patients with aseptic meningitis with empirical antibiotics.

Another important clinical discussion concerning diagnosis of bacterial compared with enteroviral meningitis is the utility and impact on patient care of enteroviral NATs for rapid diagnosis as compared with traditional viral cultures that could take up to 10 days. A review [38] of resource implications for enterovirus meningitis identified cost of hospitalization as the highest cost driver in the overall management of cases. A modeling study [39] assuming high sensitivity and turnaround time (TAT) for enteroviral NAT concluded that there would be potential cost savings with early discharge of patients with positive NAT tests. In a retrospective study in which positive

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enteroviral NAT results were available within 48 h, there was significant reduction in the length of stay (~30 h), number of ancillary tests, antibiotics used (1.5-day reduction) and re-hospitalization in enterovirus-positive compared with enterovirus-negative patients. Patients who tested positive for enterovirus were discharged faster than patients with negative NAT after the NAT result was reported (5 compared with 27 h). Of note, during the height of the enteroviral season, there was a subgroup of patients with long TAT of the NAT who were discharged before the availability of the NAT results, emphasizing the importance of having rapid TAT of results in order to impact patient care. Another study [40] has shown a direct correlation between the length of hospitalization and TAT for NAT results. From a practical point of view, a TAT of up to 24 h for NAT was required to have significant impact on early patient discharge compared with hospitalization [41]. Since 2003, there have been no studies that have evaluated the cost-effectiveness of using NAT for the diagnosis of enteroviral aseptic meningitis. It is important to review this issue, as recent advancements in molecular assays from conventional NAT assay to real-time NAT that have higher sensitivity, specificity, through-put and faster TAT offer more opportunity to impact patient care [42,43,44,45•].

Alternate specimen types in the diagnosis of enteroviral aseptic meningitis

Lumbar puncture is an invasive procedure and some studies have explored the recovery of enterovirus in other specimen types, such as upper respiratory swabs, stool and blood samples, using NAT as a more sensitive diagnostic tool. While CSF samples were more likely than serum samples to be tested positive for enterovirus in a large-scale study [46] of 1061 infants younger than 90 days who had septic work-up in the emergency department, serum and CSF were equally likely to be the only specimen type testing positive by NAT, suggesting that both specimen types should be collected in the investigation of systemic enterovirus infection. A high degree of discordance in serum and CSF results (40%) was observed, but the interpretation of these results is difficult in the context of aseptic meningitis, as there was no clinical ascertainment of the diagnosis of meningitis in cases that tested positive in blood samples only. Using advanced NAT, higher enterovirus viral load was found in stool samples as compared with serum samples in a group of 19 neonates with symptoms of sepsis and stool samples were also found to be a good specimen type for NAT in adults with enteroviral meningitis [30,47]. Interestingly, all the serum samples in the adult study tested negative for enterovirus by NAT, suggesting there was a higher rate of viremia in paediatric patients as compared with adults. Overall, there is an advantage to submitting stool samples (and blood samples if NAT is available at the local site) besides CSF in the diagnosis of enteroviral meningitis. It is important to keep in mind that the detection of enterovirus in stool samples in the absence of blood or CSF might represent carriage and ongoing excretion of the virus and the final diagnosis needs to be made in the appropriate clinical context.

Management of enteroviral aseptic meningitis

The mainstay of management remains supportive treatment, with no licensed drugs that are efficacious against enteroviruses. Pleconaril is a drug that showed promise, as it inhibits the uncoating of viral RNA and production of progeny virions during enterovirus replication and has good oral bioavailability [48]. A double-blind placebo-controlled trial [49] of pleconaril in infants up to 12 months of age with suspected enterovirus meningitis had a low rate of enrolment and confirmed the generally short and benign course of the infection, however, and there was a lack of demonstrable efficacy of the treatment. A recently published study [50••] analysing previous clinical trials data in patients older than 14 years with enteroviral meningitis only showed significant benefit in terms of shorter duration of headache (7 compared with 9.5 days).

Conclusion

Numerous causes of aseptic meningitis exist. The focus of diagnosis of aseptic meningitis in most clinical settings, however, remains ruling out bacterial meningitis or positively diagnosing enteroviral meningitis through the use of culture or NATs. NATs performed with a rapid TAT offer the advantage of early positive diagnosis, leading to cost savings through earlier hospital discharges and unnecessary ancillary therapies. Further research is needed on specific CSF parameters that may help to rule our bacterial meningitis with high (>90%) certainty, as well as reliable, easy-to-perform and inexpensive NAT kits that can aid early diagnosis.

References and recommended reading

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Herpesviral–bacterial synergy in the pathogenesis of human periodontitis

Jørgen Slots

Purpose of review

Periodontitis is an infectious disease, but the specific mechanisms by which tooth-supportive tissues are lost remain obscure. This article proposes an infectious disease model for periodontitis in which herpesviral–bacterial interactions assume a major etiopathogenic role.

Recent findings

Epstein–Barr virus type 1, cytomegalovirus and other herpesviruses occur at a high frequency in aggressive periodontitis lesions. Also, herpesvirus-infected periodontitis lesions tend to harbor elevated levels of classic periodontopathic bacteria, including *Porphyromonas gingivalis*, *Dialister pneumosintes*, *Prevotella intermedia*, *Prevotella nigrescens*, *Campylobacter rectus*, *Treponema denticola* and *Actinobacillus* (*Aggregatibacter*) *actinomycetemcomitans*.

Summary

Conceivably, a herpesvirus active infection in the periodontium impairs local defenses, thereby permitting overgrowth and increased aggressiveness of periodontopathic bacteria. In turn, periodontal pathogenic bacteria may augment the virulence of periodontal herpesviruses. It is suggested that interactions among herpesviruses and specific bacterial species constitute an important pathogenetic feature of periodontitis and maybe also of various non-oral infections.

Keywords

cytomegalovirus, Epstein–Barr virus type 1, herpesviral–bacterial interaction, periodontopathic bacteria

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Abbreviations

ANUG acute necrotizing ulcerative gingivitis
EBV Epstein–Barr virus
HCMV human cytomegalovirus
MCMV murine cytomegalovirus

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Introduction

Periodontal disease represents a variety of clinical manifestations of infectious disorders affecting the tooth-supporting tissues. Traditionally, periodontal disease is divided into gingivitis and periodontitis. Gingivitis refers to an inflammatory disease that is limited to the gingiva with no clinical evidence of the loss of periodontal ligament fibers or alveolar bone, and with periodontal pocket depths typically ranging from 2 to 4 mm. Periodontitis denotes an inflammatory destruction of the periodontal ligament and supporting bone, and the disease affects approximately 30% of US adult individuals. Periodontitis patients often have a history of sporadic advancing disease interspersed with periods of disease stability that may last for several years. The burst-like progression of periodontitis reflects the opposing actions of aggressive infectious agents and protective host immune responses. Some periodontitis patients experience almost continuously advancing disease that eventually leads to tooth mobility and possibly tooth loss.

The significance of bacteria in the development of virtually all types of periodontal disease is indisputable. Culture and culture-independent molecular studies have identified at least 700 bacterial species in the human oral cavity and over 400 bacterial species in the periodontal pocket, and any particular individual may harbor approximately 100–200 oral bacterial species [1]. It is also clear that relatively few bacterial species are legitimate pathogens of periodontitis. Important periodontopathic bacteria include Gram-negative anaerobic rods (*Porphyromonas gingivalis*, *Tannerella forsythia*, *Dialister pneumosintes*) and facultative rods [*Actinobacillus* (*Aggregatibacter*) *actinomycetemcomitans*] [2,3]. Organisms of probable periodontopathic significance are *Prevotella intermedia*, *Prevotella nigrescens*, *Campylobacter rectus*, *Micromonas micros*, *Fusobacterium* species, *Eubacterium* species, β-hemolytic streptococci, *Treponema* species, and perhaps *Candida*, staphylococci, enterococci, pseudomonas, and various enteric rods [4]. During the past decade, herpesviruses have emerged as putative periodontal pathogens [5]. Of the eight known human herpesvirus species, Epstein–Barr virus (EBV) and type 1 human cytomegalovirus (HCMV) seem to play a major pathogenic role in aggressive periodontitis.

As herpesviruses and anaerobic bacteria are both closely associated with periodontitis, it may be that these two types of infectious agents act cooperatively in the

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breakdown of periodontal tissues. This article proposes a model for aggressive periodontitis that is based on a combined herpesviral–bacterial causation of the disease. Emphasis is placed on the possible role of EBV and HCMV in the development of human periodontitis.

Herpesviruses

Herpesviruses are composed of a double-stranded DNA genome and a host-derived envelope, and can occur in a latent and an active stage. EBV infects mainly B-lymphocytes, in which it establishes latency [6•]. HCMV infects several cell types and establishes latency in macrophage-granulocyte progenitor cells and in peripheral blood mononuclear cells [5]. Reactivation of herpesviruses may occur spontaneously or as a result of concurrent infection, fever, drugs, tissue trauma, emotional stress, exposure to ultraviolet light, or other factors impairing the host immune defense. Herpesvirus reactivation causes further immunosuppression. Herpesvirus infections show a distinct tendency to cellular and tissue tropism.

Most individuals become infected with herpesviruses early in life, and between 60 and 100% of adults are carriers of EBV and HCMV [5]. The clinical outcome of herpesvirus infections ranges from subclinical or mild disease to encephalitis, pneumonia and other potentially lethal infections, and even to cancer, including lymphoma, sarcoma and carcinoma [5]. EBV is the causative agent of infectious mononucleosis and oral hairy leukoplakia, and is implicated in the etiology of nasopharyngeal carcinoma and various lymphomas [6•]. HCMV is of major clinical significance in pregnant women, newborn infants with congenital infection, immunosuppressed transplant patients, and HIV-infected individuals [5].

Herpesvirus infections induce strong antiviral innate and adaptive immune responses, which, although incapable of eradicating the infection, are generally effective in controlling viral replication and preventing clinical disease [5]. The cellular immune response plays a key role in controlling herpesviral infections by means of major histocompatibility complex class I-restricted cytotoxic CD8 T lymphocytes that recognize viral peptides on the surface of infected cells. Infants and children infected with EBV–HCMV dual infection may experience markedly stronger T-lymphocyte responses and more severe disease than children mono-infected with either of the viruses [7]. In order to evade antiviral immune responses, herpesviruses encode genes that interfere with the activation of major histocompatibility complex class I and class II-restricted T lymphocytes and natural killer cells, modify the function of cytokines and their receptors, interact with complement factors, and modulate signal transduction and transcription factor activity and other cellular functions [8].

Herpesviruses in periodontal disease

The occurrence of herpesviruses and selected periodontopathic bacteria in various types of periodontal disease has been studied by means of qualitative and quantitative polymerase chain reaction identification techniques [5]. Table 1 shows the distribution of various herpesviruses in periodontitis lesions [9].

Localized juvenile (aggressive) periodontitis debuts at puberty, is confined to permanent incisors and first molars, affects mainly black individuals, and has a familial predisposition. In Afro-Caribbean individuals living in Jamaica, the presence of EBV, HCMV and *P. gingivalis* was determined in subgingival plaque from 15 adolescents with localized juvenile periodontitis, 20 adolescents with incidental periodontal attachment loss, and 65 randomly selected healthy adolescents [10]. The most parsimonious multivariate model for localized juvenile periodontitis included HCMV [odds ratio (OR) 6.6] and *P. gingivalis* (OR 8.7). The odds of having localized juvenile periodontitis increased multiplicatively in individuals with HCMV–*P. gingivalis* combined occurrence (OR 51.4), compared with the odds associated with harboring neither of the two infectious agents [10]. HCMV and *P. gingivalis* were thus independently and strongly associated with localized juvenile periodontitis in Jamaican adolescents, and HCMV and *P. gingivalis* seemed to act synergistically to influence the risk of both the occurrence and the extent of disease.

The relationship between HCMV activation and disease-active versus disease-stable periodontitis sites was studied in 11 localized juvenile periodontitis patients aged 10–23 years living in Los Angeles [11]. HCMV transcript of the major capsid protein, a feature consistent with viral activation, was detected in the deep periodontal pockets of all five HCMV-positive patients with early periodontitis (aged 10–14 years), but in only one of three HCMV-positive patients older than 14 years, and not in any shallow pocket tested. In addition,

Table 1 Herpesviruses in gingival biopsies from periodontitis and clinically healthy sites[a]

Herpesviruses	Periodontitis (14 subjects)	Healthy periodontium (11 subjects)	*P* (χ^2 test)
Herpes simplex virus type 1	8 (57)[b]	1 (9)	0.04
Epstein–Barr virus type 1	11 (79)	3 (27)	0.03
Human cytomegalovirus	12 (86)	2 (18)	0.003
Human herpes virus 6	3 (21)	0 (0)	0.31
Human herpes virus 7	6 (43)	0 (0)	0.04
Human herpes virus 8	4 (29)[c]	0 (0)	0.17

[a] Adapted from Contreras *et al.* [9].
[b] No. (%) of virus-positive samples.
[c] Three patients were confirmed HIV-positive.

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HCMV activation was found exclusively in periodontal sites with radiographic evidence of ongoing periodontal bone breakdown. Furthermore, juvenile periodontitis sites revealing HCMV transcript were more heavily infected with *A. actinomycetemcomitans*, a major pathogen of the disease [12,13], than sites showing a latent HCMV infection. Herpesvirus-like virions have also been identified electron-microscopically in localized juvenile periodontitis lesions [14]. Ting *et al.* [11] hypothesized that during the root formation of permanent incisors and first molars at 3–5 years of age, an HCMV active infection in tissue surrounding the tooth germ might have altered the root surface structure, thereby increasing the susceptibility to future periodontal breakdown. HCMV infections in infants are able to cause changes in tooth morphology [15], and teeth affected by localized juvenile periodontitis frequently show cemental hypoplasia [16]. At the debut of puberty, hormonal changes may then cause a reactivation of periodontal HCMV or other herpesviruses, the effect of which may be an overgrowth of periodontopathic bacteria and a subsequent breakdown of tissue around teeth with a previously damaged periodontium.

Herpesviruses have been associated with rare types of aggressive periodontitis in young individuals [5]. In a Hopi Indian population, a single adolescent presented generalized juvenile periodontitis and was the only study subject demonstrating a periodontal EBV-1–HCMV dual infection. One patient with Papillon–Lefèvre syndrome periodontitis also presented periodontal EBV-1–HCMV dual infection. One patient with Fanconi's anemia presented herpes simplex virus–HCMV dual infection in advanced periodontitis lesions.

Acute necrotizing ulcerative gingivitis (ANUG) affects immunocompromised, malnourished and psychosocially stressed young individuals, and may occasionally spread considerably beyond the periodontium and give rise to a life-threatening infection termed 'noma/cancrum oris'. In Nigerian children 3–14 years of age, a significantly higher prevalence of herpesviruses was detected in ANUG lesions of malnourished children than in periodontal sites of malnourished but periodontally normal children (Table 2) [17]. In Europe and the United States, ANUG affects mainly adolescents, young adults and HIV-infected individuals, and almost never young children. The earlier occurrence of ANUG in Africa may be the result of an acquisition of herpesviruses in early childhood [18], impaired immune defenses caused by malnutrition [19], and a periodontal presence of highly virulent bacteria [20].

Periodontitis in HIV-infected patients may resemble that of periodontitis of non-HIV-infected individuals, or be associated with profusely gingival bleeding or necrotic gingival tissue. HIV-induced immunosuppression facilitates herpesvirus reactivation. EBV type 2 occurs with high frequency in HIV-infected individuals [21], and was detected in 57% of biopsies from HIV periodontitis lesions, but was absent in non-HIV periodontitis biopsies [22]. HCMV DNA was identified in 81% of HIV-associated periodontitis lesions and in 50% of the non-HIV periodontitis lesions, and was the most common herpesvirus identified [22]. In HIV-infected individuals, HCMV has also been implicated in acute periodontitis [23], periodontal abscess formation and osteomyelitis [24], and refractory chronic sinusitis [25]. Human herpes virus 8 was detected in periodontitis lesions of 24% of HIV-infected individuals with no clinical signs of Kaposi's sarcoma, but was not identified in any periodontitis site of non-HIV-infected individuals [26]. In HIV-infected individuals, herpes simplex virus, EBV, HCMV and human herpes virus 8 genomes are frequently present in the saliva [27,28], and have been related to ulcerative oral lesions [29–32] and widespread gingival and mucosal inflammation [30]. The clinical characteristics of HIV-associated periodontal pathoses and the high rate of oral herpesviruses in HIV patients are consistent with the involvement of herpesvirus active infections in these diseases.

Table 2 Epstein–Barr virus type 1 and human cytomegalovirus in acute necrotizing ulcerative gingivitis and normal periodontal sites of Nigerian children suffering from malnutrition[a]

Herpesviruses	ANUG + malnutrition (22 subjects)	Normal periodontium + malnutrition (20 subjects)	P (χ^2 test)
EBV-1	6 (27.3)[b]	1 (5.0)	0.13
HCMV	13 (59.0)	0 (0)	<0.001
EBV-1/HCMV co-infection	8 (36.4)	0 (0)	0.009

ANUG, acute necrotizing ulcerative gingivitis; EBV-1, Epstein–Barr virus type 1; HCMV, human cytomegalovirus.
[a] Adapted from Contreras *et al.* [17].
[b] No. (%) of virus-positive samples.

Herpesvirus–bacterium–host response interactions in periodontitis

A herpesvirus periodontal infection has the potential to increase the level and the pathogenicity of specific periodontopathic bacteria. In a study of 140 adults with gingivitis or periodontitis [33], periodontal EBV-1 and HCMV were related to the elevated occurrence of the pathogens *P. gingivalis*, *P. forsythia*, *P. intermedia*, *P. nigrescens* and *Treponema denticola* (Table 3). In 16 adult patients, who each contributed specimens from two disease-active and two disease-stable periodontitis sites of similar pocket depth, EBV, HCMV and EBV–HCMV co-infection were significantly associated with disease-active periodontitis [34]. Significant associations were also found between *D. pneumosintes*, *P. gingivalis* and *D. pneumosintes–P. gingivalis* co-infection and the presence

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Table 3 Associations between Epstein–Barr virus type 1, human cytomegalovirus and periodontopathic bacteria[a]

Herpesviruses	Bacteria or disease	Odds ratio	*P* values
EBV-1	Severe periodontitis	5.1	0.05
	P. gingivalis	3.4	0.01
	P. gingivalis + *P. intermedia*	4.4	0.005
	P. gingivalis + *T. denticola*	4.2	0.004
	P. gingivalis + *T. forsythia*	3.8	0.006
	P. gingivalis + *P. nigrescens*	2.7	0.05
	P. gingivalis + *T. forsythia* + *T. denticola*	4.1	0.005
	P. gingivalis + *P. nigrescens* + *T. denticola*	3.3	0.03
HCMV	Severe periodontitis	4.7	0.03
	P. gingivalis + *P. nigrescens*	3.2	0.01
	P. gingivalis + *P. nigrescens* + *T. denticola*	2.6	0.05
	P. gingivalis + *T. forsythia* + *P. nigrescens*	3.2	0.01

EBV-1, Epstein–Barr virus type 1; HCMV, human cytomegalovirus.
[a] Adapted from Contreras *et al.* [33].

of disease-active periodontitis [34]. Each periodontitis site that demonstrated EBV-1/HCMV co-infection and all but one site showing *D. pneumosintes–P. gingivalis* co-infection revealed bleeding upon probing, a clinical sign of the increased risk of progressive disease. Periodontal HCMV showed a particularly close association with the occurrence of *D. pneumosintes* [35] and *P. gingivalis* [36], as well as with progressive periodontitis. As discussed above, HCMV-associated localized juvenile periodontitis lesions also exhibit elevated levels of *P. gingivalis* [10] and *A. actinomycetemcomitans* [11].

The close relationship between periodontal herpesviruses and periodontopathic bacteria lends credence to the notion that both types of infectious agents are involved in the development of periodontitis. In the same way, evidence is accumulating that otitis media [37], respiratory tract infections [38], and other non-oral infections [39,40], which were previously thought to be solely of bacterial origin, may be caused by viral–bacterial combined infections.

Pathogenic mechanisms of herpesviruses in periodontal disease

Herpesviruses may cause periodontal pathosis as a direct result of the virus infection and replication, or as a result of a virally induced impairment of the host defense. Herpesvirus-mediated periodontopathogenicity may take place through at least five mechanisms, operating alone or in combination.

First, herpesviruses may cause a direct cytopathic effect on fibroblasts, keratinocytes, endothelial cells, inflammatory cells such as polymorphonuclear leukocytes, lymphocytes, macrophages, and possibly bone cells. These cells are key constituents of inflamed periodontal tissue. Herpesvirus-induced cytopathic effects may also hamper tissue turnover and repair. It is likely that the early stages of periodontitis in immunologically naive hosts mainly comprise cytopathogenic events, whereas most clinical manifestations in immunocompetent individuals are secondary to cellular or humoral immune responses.

Second, herpesvirus active infection may significantly impair cells involved in the periodontal defense, thereby triggering an overgrowth of periodontal pathogenic bacteria [5]. Herpesvirus active infection may predispose to secondary infections by generating antineutrophilic antibodies and neutropenia, and by inducing abnormalities in adherence, chemotaxis, phagocytic, oxidative, secretory, and bactericidal activities of polymorphonuclear leukocytes [41]. Polymorphonuclear leukocytes are of major importance in controlling periodontal infections. EBV and HCMV can also infect and alter functions of monocytes, macrophages and lymphocytes in periodontitis lesions. EBV may act as a potent polyclonal activator of B lymphocytes, capable of inducing the proliferation and differentiation of immunoglobulin-secreting cells, features that can be observed in progressive periodontitis.

The interaction between herpesviruses and bacteria may be bidirectional, however, with bacterial enzymes or other inflammation-inducing products having the potential to activate periodontal herpesviruses (the vicious circle concept). As an example, mice infected with murine cytomegalovirus (MCMV)–*P. gingivalis* exhibit significantly higher mortality rates than mice infected with MCMV, *P. gingivalis* or MCMV–*Escherichia coli* [42]. The increase in cytomegalovirus pathogenicity may result from an ability of *P. gingivalis* to suppress interferon-γ antiviral host responses [42].

Third, HCMV can infect and multiply in cultured human gingival tissue [43], and may thereby enhance the attachment and colonization of pathogenic bacteria. Viral proteins expressed on eukaryotic cell membranes may act as bacterial receptors and generate new bacterial binding sites. Also, the loss of virus-damaged epithelial cells may expose the basement membrane and the surface of regenerating cells, providing new sites for bacterial binding.

Fourth, herpesvirus infections induce an expression of proinflammatory cytokines and chemokines [44]. EBV and HCMV infection can upregulate interleukin-1β and tumor necrosis factor-α gene expression of monocytes and macrophages [44]. In turn, interleukin-1β and tumor necrosis factor-α may upregulate matrix metalloproteinase, downregulate tissue inhibitors of metalloproteinase, and mediate periodontal bone destruction. High levels of proinflammatory cytokines in periodontal sites have been associated with an enhanced risk of periodontal tissue destruction [45].

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Fifth, herpesviruses may produce tissue injury as a result of immunopathological responses [5]. EBV infection induces the proliferation of cytotoxic T lymphocytes, whose major purpose is to recognize and destroy virally infected cells, but which may secondarily hamper aspects of the periodontal immune response. EBV-infected B lymphocytes may shed viral structural antigens that result in the production of blocking antibodies, immune complex formation, and T-suppressor cell activation. HCMV can induce cell-mediated immunosuppression by downregulating the cell surface expression of major histocompatibility complex class I molecules, thereby interfering with the cytotoxic T lymphocyte recognition of virus-infected cells. In addition, HCMV can cause decreases in circulating CD4 cells and increases in CD8 suppressor cells. Maybe as the result of a herpesvirus periodontal infection, aggressive periodontitis lesions contain fewer overall viable cells, more T-suppressor lymphocytes, and more B lymphocytes (EBV effect) than chronic periodontitis lesions or healthy periodontal sites [46].

Conclusion

Several lines of evidence implicate herpesvirus species in the etiology or pathogenesis of human periodontal disease. These include the following: (1) the presence of nucleic acid sequences of EBV-1, HCMV and other herpesviruses in aggressive periodontitis lesions of children, adolescents, and adults; (2) an association between periodontal HCMV-active infection and disease-active periodontitis; (3) an association between herpesviruses and ANUG in malnourished African children; (4) the increased frequency of periodontopathic bacteria in herpesvirus-positive periodontitis lesions; (5) the detection of nucleic acid sequences of herpesviruses in inflammatory periodontal cells; (6) the probable profound effect of herpesviral infection on periodontal defense cells; and (7) the potential of herpesviruses to augment the expression of tissue-damaging cytokines and chemokines in periodontal cells.

Herpesviruses have been suggested to play a major role as activators of the periodontal disease process. The notion of herpesviral–bacterial interactions in the etiopathogenesis of periodontitis may elucidate some of the clinical characteristics of the disease. An alteration between prolonged periods of latency interrupted by periods of activation of herpesvirus infections may be partly responsible for the burst-like episodes of periodontitis disease progression. Tissue tropism of herpesvirus infections may help explain the localized pattern of tissue destruction in periodontitis. Frequent reactivation of periodontal herpesviruses may account for the rapid periodontal breakdown in some patients even in the presence of relatively little dental biofilm. The absence of herpesvirus infection or viral reactivation may occur in individuals who harbor periodontopathic bacteria while still maintaining periodontal health or minimal disease.

Periodontitis is a multifactorial disease that probably is contingent upon the simultaneous occurrence of several infectious disease events, including: (1) adequate herpesvirus load (gingivitis level) in periodontal sites; (2) the activation of herpesviruses in the periodontium; (3) an inadequate protective antiviral cytotoxic T-lymphocyte response; (4) the presence of specific periodontal pathogenic bacteria; and (5) an inadequate protective antibacterial antibody response. In most individuals, these five suggested pathogenic determinants of periodontitis may collaborate in detrimental constellations relatively infrequently and mainly during periods of suppressed immune response.

Basic research on herpesvirus infections may benefit from the finding of herpesviruses in periodontal disease. One difficulty in herpesvirus research is the unavailability of readily accessible study material, especially in systemically healthy individuals with latent herpesviral infections. As viral samples can be collected in a non-invasive manner from the periodontium, herpesvirus-infected periodontal sites may constitute a valuable research model for studying the pathophysiology of herpesvirus latency and reactivation, as well as herpesvirus interactions with bacterial pathogens.

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Leptospirosis: pathogenesis, immunity, and diagnosis

Raghavan U.M. Palaniappan, Subbupoongothai Ramanujam and Yung-Fu Chang

Purpose of review

Leptospirosis is among the most important zoonotic diseases worldwide. Completion of the genomic sequences of leptospires has facilitated advances in diagnosis and prevention of the disease, and yielded insight into its pathogenesis. This article reviews this research, emphasizing recent progress.

Recent findings

Leptospirosis is caused by a group of highly invasive spiral bacteria (spirochetes) that can infect both people and animals. Spirochetes can survive in the environment and host, and therefore outer membrane and secretory proteins that interact with the host are of considerable interest in leptospire research. The genetic approach to studying pathogenesis is hindered by fastidious growth of pathogenic leptospires. Integrated genomic and proteomic approaches, however, have yielded enhanced understanding of the pathogenesis of leptospirosis. Furthermore, studies of innate immune response to the organism have enhanced our understanding of host susceptibility and resistance to infection. In-silico analysis and high-throughput cloning and expression have had major impacts on efforts to develop vaccine candidates and diagnostic reagents.

Summary

In the future, we must effectively utilize the wealth of genetic information to combat the disease. More studies into genetics, immune mechanisms that may be exploited to prevent leptospirosis, and pathogenesis of the disease are necessary.

Keywords

diagnosis, immunity, leptospirosis, pathogenesis

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Abbreviations

MAT microscopic agglutination test
TLR Toll-like receptor

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Introduction

Leptospirosis is a serious worldwide zoonotic disease that is caused by infection with *Leptospira* spp. Leptospires are Gram-negative spirochetes that comprise 24 serogroups and 250 serovars [1]. Infection of animals and humans leads to a variety of adverse effects, including chronic interstitial nephritis, mastitis, myocarditis, and hemolytic crisis, resulting in multiorgan failure [2]. Infection can also be asymptomatic, with the only sign being bacteriuria [2]. *Leptospira*-associated uveitis is relatively common in horses and humans [3–5], and a case report of *Leptospira*-induced meningitis was recently published [6]. Leptospirosis has been identified as a re-emerging infectious disease, particularly in Nicaragua, Brazil, India and Malaysia, and in other tropical and subtropical regions [7].

In contrast to the study of many bacterial pathogens, use of genetic and molecular biologic approaches in pathogenic *Leptospira* is difficult. Fortunately, completion of the genomic sequence of leptospires has revealed a number of interesting features [8–10]. This information, however, is not sufficient to determine the role played by a gene product during the various phases of the pathogenic cycle.

Pathogenicity of leptospires

The molecular mechanisms underlying the pathogenicity of *Leptospira* spp. are not well understood; however, several virulence determinants such as surface proteins, lipopolysaccharide, motility and chemotaxis, and secretory proteins have been characterized. This enables pathogenic spirochetes to penetrate host tissue barriers during infection [11] and to establish successful niches in the tissue. Interestingly, there is a genomic island in the genome of pathogenic strain Lai but not in serovar Copenhagani [12].

Immunogens and surface proteins of leptospires

Study of outer membrane proteins is essential because leptospires utilize membrane proteins extensively during infection. The extraction of leptospiral membrane proteins using Triton X-114 revealed the presence of various lipoproteins [13]. A number of outer membrane proteins/lipoproteins including OmpL1, LipL32, LipL36, LipL41, LipL45, LipL48, and LigA have been cloned and characterized [14–26]. Leptospires can survive outside as well as inside the host, and some of the outer membrane proteins have been found to be differentially regulated between in-vivo and in-vitro conditions. For example, lipoprotein LipL36 is present in in-vitro cultures but it

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is downregulated *in vivo* [27]; also, LigA, Qlp42, LipL32, and Loa22 have been found to be upregulated during infection [19,24,28,29••]. LipL32 triggers an inflammatory response in renal proximal tubule cells of mouse through a mechanism involving nuclear factor-κB and Toll-like receptor (TLR)2 [30,31,32•]. Novel immunogenic proteins such as LfHA, LruA, and LruB have been identified and characterized [33,34••]. A fibronectin-binding protein produced only by virulent strains has been reported to play an important role in adhesion [35].

Motility and chemotaxis

The *L. interrogans* genomes of both serovars Copenhageni and Icterohaemorrhagiae contain at least 79 motility-associated genes, including orthologs for gliding motility [36]. Similar to other spirochetes, *L. interrogans* uses FlaA sheath protein and FlaB core protein as essential components of its endoflagellar filament [36]. Motility and chemotaxis encoding genes of *L. interrogans*, *Treponema pallidum* and *Borrelia burgdorferi* are well conserved among 42 genes. Genomic analysis indicated that the chemotaxis system of *L. interrogans* is more complex than that of either *T. pallidum* or *B. burgdorferi*. The reason for the greater number of motility-associated genes in *L. interrogans* than in other spirochetes is not clear.

Lipopolysaccharide

Leptospiral lipopolysaccharide has a composition similar to the lipopolysaccharide of other Gram-negative bacteria [37], but it has lower endotoxic activity [38,39]. Changes in lipopolysaccharide of pathogenic leptospires has been reported to affect the lethality of infection [40]. The genetic basis for serologic differences among serovars of *Leptospira* is attributed in part to the effect of leptospiral lipopolysaccharide. The lipopolysaccharide of *L. interrogans* is a structurally unique molecule of relatively low toxicity [41] that activates macrophages in a distinct manner [42]. The O-antigen component of *Leptospira* lipopolysaccharide mainly contains rhamnose biosynthetic cluster (*rfb* locus), and it is well characterized in six serovars of *Leptospira* [10,36,41]. The 3′ end of *rfb* locus is highly conserved, whereas the 5′ end exhibits clear genetic differences between serovars [43–46]. Although lipopolysaccharide elicits the production of agglutinating opsonin and protective antibodies in animals, these do not confer effective cross-protection against the various serovars [45,46].

The uniqueness of leptospiral lipopolysaccharide in comparison with Gram-negative bacteria is that it triggers the innate system through TLR2 [42]. Recently, the resistance of mice to *Leptospira* infection was found to be due to efficient recognition of murine cells through TLR2 and TLR4, which eventually provide an effective innate immune response to this pathogen [42]. In contrast, the lack of efficient recognition of leptospiral lipopolysaccharide by human TLR4 may lead to susceptibility to *Leptospira* infection in humans [47]. The role played by TLR4 in determining the clinical outcome of infection has been established *in vivo* using a murine model [48]. The TLR4-dependent pathway of the innate immune response therefore plays a vital role in protection against death in severe murine leptospirosis, and in controlling leptospiral proliferation during chronic infection.

Secretory proteins

The production of toxins by pathogenic leptospires was primarily identified by Arean *et al.* [49]. Hemolysin from serovar Lai has been reported to play an important role in pore formation, and the gene that encodes this hemolysin is located upstream of the gene encoding sphingomyelin, which is another secretory protein that influences hemolytic activity [50,51]. It has also been reported that the hemolytic activities of hemolysin and sphingomyelin are additive [50,51]. Their interactions with host cells are unclear, however. Genomic sequences also suggest the leptospires may express numerous novel secretory proteins, such as protease and collagenase, among others, but the unique functions of these proteins in pathogenesis remain to be determined.

Adhesion and invasion

Attachment of bacteria to host cells is the first step in the establishment of infection [52,53]. The ability of *L. interrogans* to cause disease is both complex and multifactorial [54–56]. Barocchi *et al.* [57] reported that rapid translocation of leptospires across tissues might be due to virulence factors, which distinguished pathogens from nonpathogens. Studies have shown that leptospires enter both phagocytic as well as nonphagocytic cells [58–60]. The interaction of leptospires with cultured fibroblasts, and microglial, endothelial and epithelial cells indicates that surface molecules of leptospires play an important role in attachment and invasion [61–63]. A 36 kDa fibronectin-binding protein is an important adhesion protein that is responsible for virulence in leptospires [35]. A 24 kDa lipoprotein was recently reported to bind laminin [64•]. Expression of Lig proteins upon infection and their homology with cell binding proteins such as intimin from *Escherichia coli* and invasin from *Yersinia* spp. [65–67] suggest that Lig proteins are also among the adhesion molecules present on the surface of leptospires [21,23,24]. Genomic sequencing revealed that *L. interrogans* possesses several genes that are related to attachment to and invasion of eukaryotic cells (*mce*, *invA*, *atsE*, and *mviN*) [10]. The functions of these leptospiral proteins require elucidation, however.

Well known pathogens, including *Salmonella* spp., *Yersinia* spp., *E. coli*, and *Shigella* spp., enter mammalian cells by

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various mechanisms [68–75]. Spirochetes such as *B. burgdorferi* and *T. pallidum* disseminate through interjunctional spaces [76,77] or through the cell membrane, but studies of leptospires have yielded disparate findings with respect to cellular localization [54,58,59,78–80]. Spirochetes have been considered to be more evolved than other bacteria because of their ability to change their physical/chemical properties [81]. An understanding of the mechanism by which *L. interrogans* attaches and invades mammalian cells would be a great step forward in our knowledge of leptospirosis.

Genetic studies of *Leptospira* spp.

Genetic manipulation of pathogenic *Leptospira* is difficult because of the restriction–modification system in *Leptospira* spp. [82]. The replication of LE1 bacteriophage, however, as a plasmid in nonpathogenic *L. biflexa* led to the construction of an *L. biflexa–E. coli* shuttle vector using the *ori* site from the bacteriophage [83,84]. The insertional inactivation of the genes encoding flagellin and *recA* using the shuttle vector provided the first mutant of nonpathogenic *L. biflexa* [85]. Although this shuttle vector was successfully used to delete the genes encoding flagellin and recA flagellin in a nonpathogenic *Leptospira* spp., further study is urgently needed to establish allelic exchange techniques in pathogenic *Leptospira* spp. It was recently shown that a kanamycin resistance cassette interrupted the tryptophan biosynthetic gene *trpE* of the spirochaete *L. meyeri* by homologous recombination [86].

Importance of host-induced genes

Infection processes have been determined to be coordinately regulated or stimulated by host factors encountered *in vivo*, and these were found to be mulitifactorial and dynamic [87]. Consequently, a gene that appears important in in-vitro studies may not be important *in vivo*, and genes that appear unimportant in an in-vitro assay may play a vital role in infection [88]. The spirochetal proteins are differentially expressed, presumably for the purposes of adapting to different environmental conditions [28,89,90]. Genes expressed *in vivo* are most likely to encode virulence-associated factors or products essential for survival within host cells [91,92]. It has been confirmed that culture of pathogenic leptospires in medium that does not mimic in-vivo conditions leads to loss of virulence [93], but inoculation of these leptospires into susceptible animals restored virulence. For example, LigA was primarily identified by immunoscreening a genomic library of the *L. interrogans* serovar Pomona strain kenniwicki, using naturally infected equine serum samples [24]. These Lig proteins have not been identified in animals infected with killed leptospiral proteins, however [21]. Recently, sphingomyelinase-like protein was also been found to be expressed *in vivo* only [94]. The molecular pathogenesis, environmental signals encountered, and genes specifically induced within the host are yet to be unraveled.

A variety of in-vitro systems have been developed to mimic certain aspects of infectious processes for the purposes of virulence gene expression [95]. Recently, new technologies such as in-vivo selection technology [96], signature tagged mutagenesis [97], differentiation fluorescence induction [98,99], and subtractive hybridization were developed to study gene regulation and function in micro-organisms *in situ*. Unfortunately, these in-vivo technologies require modification before they may be applied to the study of pathogenic *Leptospira* spp.

Genomic and proteomic approaches: appropriate tools to study *Leptospira* pathogenicity

The genomic sequences of *L. interrogans* serovar Icterohaemorrhagiae (Lai strain) and *L. interrogans* serovar Copenhageni strain Fiocruz L1–130 indicate that there is no plasmid in *Leptospira* spp. [10,36]. The recently released genomic sequence of *L. borgpetersenii* has a lower coding density than that of *L. interrogans*, indicating genomic reduction in *L. borgpetersenii* [8].

There are many gaps in our knowledge of leptospiral pathogenicity, and genetic and molecular approaches to identifying environmentally regulated or in-vivo expressed/induced genes are necessary in this spirochete [89]. The new field of integrated genomics and proteomics, however, may help us to elucidate leptospiral pathogenicity at the genome level. In recent years numerous reports have been published on the use of transcriptomics to conduct genome-wide screening of extracellular pathogens such as *Helicobacter pylori* [100,101], *Yersinia entercolitica* [102], *B. burgdorferi* [103–105] and other intracellular pathogens [106–109]. Only few studies on leptospires have been reported, however. Bioinformatic and transcriptomic studies in pathogenic leptospires have predicted that there are 226 genes that could be exploited in candidate vaccines [110]. Global approaches using proteomic studies have also led to the identification of novel genes that are involved in host–bacterium interaction [14,29••,40], but novel secretory proteins of pathogenic leptospires have not yet been globally characterized. Analyzing culture supernatants of *Pseudomonas aeroginosa*, *Staphylococcus aureus*, and *H. pylori* using proteomics led to the identification of numerous novel secretory proteins [111–113]. Further studies into functional aspects by applying both proteomic and transcriptomic tools to leptospires grown at different temperatures [114], in media containing iron [115•], or to in-vivo cultivated leptospires will enhance our knowledge on the pathogenicity of *Leptospira* spp. and will

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provide us with clues that may lead to novel vaccine candidates.

Comparative genomics is a powerful approach to elucidating changes in genetic constitution that occur in a given phenotype, including strain differences in virulence modes and/or antibiotic resistance. For example, comparison of different strains of *Mycobacterium bovis* bacille Calmette-Guérin indicated genetic diversity that probably accounted for variability in findings of trials of vaccines against tuberculosis [116,117]. Comparison of genomic sequences of pathogens revealed remarkable details on host restriction [118]. The genomic sequences of *L. interrogans* serovar Icterohaemorrhagiae strain Lai, *L. interrogans* serovar Copenhageni, and *L. borgpeterseni* serovar Hardjo have been completed [8,10,36]. The basis for the phenotypic differences between and within the species and serovars has not been adequately addressed in leptospires. Therefore, comparative genomics will provide us with knowledge about speciation, host restriction, and differences in genotype, which in turn will help us to establish a strategy to control this important zoonotic disease.

Diagnosis

A prerequisite for the control of infectious diseases is the availability of suitable (i.e. reliable, sensitive, and inexpensive) diagnostic tests. The currently available microscopic agglutination test (MAT) is considered the 'gold standard' test, but it does not permit early diagnosis because it relies on detection of antibodies to leptospiral antigens and cannot detect infection until 5–7 days after exposure. The reported sensitivity and specificity of MAT are high, at 92% and 95%, respectively, in detecting human leptospirosis [119]. Animal leptospirosis is influenced by vaccine-induced antibodies, however, and MAT has a tendency to react to vaccine-induced antibodies and so yield false-positive results. Some of the commercially available vaccine can raise the MAT titer into the 3200–12 800 range [120,121], which makes it difficult to identify true infection. Although a MAT titer in excess of 1 : 1600 (800 in some laboratories) is considered positive for leptospirosis. Most veterinarians use information as clinical symptoms, a four-fold rise in MAT titers within a 2–3-week interval and also other assays such as PCR, culture, and immunofluorescent for the diagnosis.

The drawbacks of MAT in the diagnosis of leptospirosis have prompted development of several other diagnostic methods, including serologic testing by immunofluorescence, enzyme-linked immunosorbent assay, and Western blot analysis. A commercially available whole cell antigen based enzyme-linked immunosorbent assay had low sensitivity [122]. Screening for immunoglobulin M antibodies was recently evaluated for its ability to detect human leptospirosis, but these tests exhibited less sensitivity compared with *Leptospira* MAT [123]. Several recombinant antigens of leptospires have also been screened for their potential in the diagnosis of *Leptospira* infection [124–130]. Only a few papers have attempted to differentiate vaccination from infection titers, however [23]. As far as animal leptospirosis is concerned, addressing the influence of vaccination titer on the diagnostic assay is necessary if an effective diagnostic tool is to be developed. Human leptospirosis is not influenced by vaccination titer, and so the antigens that are conserved among the serovars of *Leptospira* could serve in an effective diagnostic tool.

Isolation of the organism from urine or tissues of animals is the most reliable method to confirm leptospiral infection. Culture is labor intensive, however, and days or weeks are required for growth; furthermore, it can be rather insensitive in detecting leptospires. Nucleic acid amplification (PCR)-based techniques have therefore been developed to diagnose leptospirosis [131–133]. PCR assays targeting 16S rRNA gene sequences [134] are considered powerful methods, but the 16S rRNA gene sequence is not sufficiently polymorphic, and a complete 1500 base pair sequence is necessary for accurate identification at the serovar level. Several assays targeting genes such as those encoding OmpL1, DNA gyrase, RpoB, Lig, LipL32/Hap1, putative transcriptional regulator, and repetitive DNA elements have therefore been developed [135–142]. A new multiplex PCR assay to differentiate pathogenic and saprophytic leptospira has also been developed [143]. Real-time, quantitative TaqMan PCR or with molecular beacons has also been reported to detect leptospires [139]. PCR-based diagnosis of leptospirosis cannot identify the infecting serovar, which reduces its value in terms of epidemiologic research and public health. Therefore, several assays have been developed to overcome the typing of *Leptospira* spp., such as single-strand conformation analysis, restriction enzyme analysis of PCR products, direct sequencing of amplicons, low-stringency single specific PCR, and multilocus variable number tandem-repeat analysis [144].

Vaccine

Currently, there is no human vaccine against leptospirosis. Most veterinarians use commercially available heat-killed or formalin-killed leptospires, which may produce incomplete, short-term immunity. The role of T-helper-1 immune response in immunoprotection is evident from recent studies [145,146,147••]. The increasing number of serovars, however, provides us with a challenge to develop, a vaccine that could confer complete cross-protection against the pathogenic leptospires.

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Hamsters, guinea pigs, dog, mice, and cattle have been used to study leptospiral pathogenesis and to test vaccine efficacy [146,148–155]. Hamsters and guinea pigs are the most common models and are recommended by both the WHO and the European Pharmacopeia [156–158].

Studies of isolated outer membrane have retained most, if not all, of the protective antigens found in whole-cell vaccines [20,159,160••]. Interestingly, lipopolysaccharide fractions confer protective immunity against homologous but not heterologous challenges, whereas protein extract induced significant protection against both types of challenge [161]. Thus, cross-protection within *L. interrogans* was related to the protein extract. Several outer membrane proteins/lipoproteins have been identified [14–20,25,26]. However, the development of recombinant vaccine has been demonstrated only with certain outer membrane proteins such as LipL32, OmpL1, LipL41, and Lig proteins. OmpL1 and LipL41 provide only partial immunoprotection in a hamster model [20], whereas hemolysin-associated protein 1 (Hap-1 or LipL32) can induce a cross-protective immunity by DNA vaccine and adenovirus-mediated vaccination but not with recombinant protein [159]. Lig proteins provide protection against leptospirosis in mice and hamster models, and appear to be the most promising vaccine candidates [160••,162]. Its protective mechanism and protection against heterologous challenge need to be determined, however.

The role of cell-mediated immunity in host defense against *Leptospira* spp. remains poorly understood in both animal models and human disease. A recent study, however, has shown that cattle immunized with killed *Leptospira* vaccine have $CD4^+$ T cells and γ/δT cells that give in-vitro proliferative responses and produce interferon-γ following stimulation with a *Leptospira* antigen preparation [145]. Nevertheless, both animal models and human clinical studies have provided indirect evidence that T-cell receptor γ/δ^+ T cells may play an important role in host defense against bacterial, viral, and parasitic infections [163–171]. The identification of adjuvants and immunomodulators that can promote selective induction of these distinct populations of T cells will provide effective vaccines against leptospirosis.

Whole-genome sequencing of bacteria and advances in bioinformatics has revolutionized the vaccinology field, leading to the identification of potential vaccine candidates [172]. In-silico and microarray-based genomic approaches identified 226 open reading frames as potential vaccine candidates [110]. A combination of conserved protective antigens may also serve as an ideal candidate for vaccine development. In the past, DNA vaccines encoding viral [173–175], parasitic [176], and tumor proteins were studied in animal models. DNA vaccines can also be used to conduct rapid screens for protective antigens in leptospires.

Conclusion

The available genome sequences of *Leptospira* spp. reveal several interesting features of gene structure and function. Given the importance of the disease and lack of sufficient genetic and molecular tools, integrated genomics and proteomics approaches will enhance our knowledge of the pathogenicity of leptospires, and will provide the basis for development of novel and efficient therapeutic strategies to control this disease.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 330).

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Experimental infections with West Nile virus

Richard A. Bowen[a] and Nicole M. Nemeth[b]

Purpose of review

West Nile virus emerged recently in North America as a serious human and animal pathogen. This review summarizes the use of experimental infections with West Nile virus in diverse vertebrate species that have been used to answer fundamental questions about the host response, pathogenesis of West Nile virus infection and virus evolution.

Recent findings

West Nile virus has an extremely broad vertebrate host range. Infection of common species of birds has defined those with high vs. low potential to serve as amplifying hosts for the virus. In general, mammals (primates, horses, companion animals) are dead-end hosts for West Nile virus, although some circumstances (i.e. immunosuppression) may allow individuals to become capable of transmitting the virus to mosquitoes. Some mammals (rodents, rabbits, squirrels) and reptiles (alligators) have been found to develop a viremia of sufficient magnitude to predict at least low competence for infecting feeding mosquitoes. Finally, experimental infection of rodents, horses and primates with West Nile virus has been integral to developing and evaluating the efficacy of West Nile virus vaccines.

Summary

Experimental infection with West Nile virus has assisted in delineating those hosts important and not important to the transmission cycle, in understanding how the virus induces disease in susceptible hosts, and in validating the efficacy of vaccines used for control of disease.

Keywords

flavivirus, mosquito-borne, viremia, West Nile virus

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Abbreviation

WNV West Nile virus

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Introduction

West Nile virus (WNV) is a mosquito-transmitted pathogen that has been recognized since the 1930s in large regions of the Old World, but which received little attention as a public health or veterinary threat until its incursion into North America in 1999 [1,2]. Since then, this agent has spread throughout much of North, Central and South America, causing widespread morbidity and mortality in humans, horses and a broad range of birds. Experimental infections with WNV have been used to assess the potential of different species to serve as amplifying hosts for the virus, to characterize the pathogenesis of infection with different strains of virus, and to evaluate the efficacy of vaccines and therapeutic agents.

Routes of transmission

The major route of transmission of WNV in nature is through the bite of infected mosquitoes that have become infected by ingesting a blood meal from an infected bird [3]. Several species of *Culex* mosquitoes are considered the principle and most efficient vectors of WNV throughout the world, although other species (i.e. *Aedes albopictus*) have also been shown to be highly competent for virus transmission [4–6]. Mosquitoes used for experimental transmission of WNV to vertebrates can be infected by allowing them to feed on an infectious blood meal (either spiked or from a viremic host), or more simply by intrathoracic inoculation of virus. As has been pointed out by several virologists, mosquitoes are not simply little flying syringes, but purveyors of a host of pharmacologically active substances delivered in saliva along with virus that could potentially contribute to pathogenesis of infection. Although it is not a universal finding with arboviruses, there are several examples in the literature where the dynamics of infection were different when virus was inoculated into animals by needle vs. mosquito bite [7,8]. A disadvantage of using infected mosquitoes to transmit virus in experimental settings is that one is never certain of the dose delivered [9]. Numerous experimental infections with WNV have utilized mosquito-borne transmission, but rarely in direct comparison to direct inoculation of virus [10–13]. A recent study [14•] evaluated the course of infection in chickens inoculated by needle and syringe compared to delivery by *Cx pipiens* or *Cx tarsalis* mosquitoes. Infection by mosquito bite resulted in more rapid development of viremia, but ultimately a similar course of infection, and the enhancement in early infection were largely attributed to virus dose. Nonviremic transmission of WNV between cofeeding mosquitoes was also demonstrated in laboratory

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experiments, with naïve ('recipient') mosquitoes becoming infected after feeding on naïve mice simultaneously with infected ('donor') mosquitoes [15]. Finally, inoculation of mice with WNV by needle into a site where uninfected mosquitoes had recently fed resulted in higher mortality, enhanced viremia and accelerated neuroinvasion relative to inoculation of the same dose of WNV into mice that had not received mosquito bites [16].

Direct contact and oral transmission are two other routes that have been investigated for transmission of WNV. Birds that develop high-titer WNV viremia also excrete large quantities of virus in oral and cloacal secretions [11,17], which has been exploited as a readily sampled source of virus for diagnosis of infection [18–20]. Housing inoculated and noninoculated birds together in the same cage frequently results in transmission to the latter [11,21]. The relevance of this experimental finding to what occurs in nature is unknown, but it is possible that some such virus transmission may occur where birds congregate [22]. Another potential means of WNV transmission is through consumption of infected prey. This has been demonstrated experimentally in cats [12], raptors [11,17,23] and alligators [54].

Pathogenesis of West Nile virus infection: amplifying vs. dead-end hosts

Birds are widely recognized as the most important amplifying hosts for WNV [1] and laboratory infections have delineated which species are likely of greatest importance to virus transmission in nature. The importance of a particular species in the WNV transmission cycle depends upon several factors, including magnitude and duration of viremia, and species abundance. Magnitude of viremia is particularly important because there is a threshold titer of virus in blood necessary for efficient infection of feeding mosquitoes; this threshold is not abrupt and varies with mosquito species, but is probably in the range of 10^4–10^5 plaque-forming units/ml of blood [24]. Experimental infections have revealed a continuum in magnitude of viremia among avian species, which allows a rough classification into those that develop low-, moderate- and high-titer viremia (Table 1) [5,11,17,23,25–33]. Birds such as the American crow (*Corvus brachyrhynchos*), blue jay (*Cyanocitta cristata*) and house sparrow (*Passer domesticus*) that routinely develop high-titer viremia are considered the most important reservoir hosts [11,25–27]. Some experimental infection studies of birds specifically examined the effects of WNV in selected species, demonstrating that additional species also experience relatively high viremia levels, including various raptor species [17,23], greater sage grouse (*Centrocercus urophasianus*) [34], Western scrub jays (*Aphelocoma coerulescens*) [5] and house finches (*Carpodacus mexicanus*) [5]. Greater sage grouse (a threatened species), were discovered to be a noncorvid species with particularly high morbidity and mortality rates resulting from experimental WNV infection. Also, there are circumstances where birds normally thought of as incompetent hosts develop viremia sufficient to be classified as amplifying hosts. For example, adult domestic chickens and turkeys infected with WNV develop a low-titer viremia that is unlikely to allow transmission to feeding mosquitoes [30–32], but the viremia experienced by infected chicks can be significantly higher than adults and are clearly sufficient to infect mosquitoes [33,35,36]. These higher viremia levels are also associated with increased rates of morbidity and mortality.

Among mammals, horses are the most severely affected by natural WNV infection. Initial experimental studies with the North American (New York 99) strain of WNV indicated that horses develop low-titer viremia that is frequently only intermittently detectable and that feeding mosquitoes on such animals failed to result in transmission [10]. The apparent incompetence of horses as amplifying hosts for WNV has subsequently been demonstrated in several vaccine efficacy trials [37–40]. Experimental infections of horses with WNV by subcutaneous inoculation or mosquito feeding has only rarely resulted in overt clinical disease [10,37–39].

Companion animals are another group for which great public concern was evident after WNV emerged in North America. Experimental infection by infected mosquito feeding indicated that both dogs and cats were readily infected with WNV, but that neither developed significant clinical disease or a level of viremia above 10^4 plaque-forming units/ml serum, suggesting that they are unlikely to serve as amplifying hosts [12]. Subsequent vaccine efficacy trials in dogs and cats reinforced this conclusion [41]. Although species such as dogs are now

Table 1 Avian competence as amplifying hosts for West Nile virus as determined by viremia levels from experimental infections

Competence level	Typical peak viremia in healthy adult birds ($\log_{10}$ plaque-forming units/ml serum)	Examples	References
High	9–12+	American crows, blue jays, house sparrows, common grackle	[11,25–28]
Moderate	5–8	Fish crows, European starlings, American robin, house finch, kestrels, hawks, owls	[5,11,17,23,29]
Low or absent	2–5	Doves, pigeons, quail, chickens, pheasants, turkeys, budgerigars	[11,30–33]

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considered incompetent as amplifying hosts, individual differences may alter this general conclusion. For example, dogs treated with glucocorticoids developed a level of WNV viremia much higher than control dogs [42]. Similarly, chemical immunosuppression of hamsters also resulted in elevated viremia and high mortality [43•], and viremia was elevated in genetically immunodeficient mice [44].

Numerous other free-ranging and domestic mammals have been evaluated for clinical and pathologic responses to WNV infection with variable results. Laboratory mice (*Mus musculus*) and golden hamsters (*Mesocricetus auratus*) developed moderate viremia levels (mean peak viremia levels between 10^4 and 10^6 plaque-forming units/ml serum on 2–3 days postinfection), and experienced encephalitic symptoms and death [44,45]. The hamster model of WNV infection has proven to be particularly interesting because some animals develop a persistent renal infection and excrete an avirulent WNV in urine for prolonged periods of time [46,47]. Others have demonstrated that mosquitoes were either infected or potentially infected by feeding on viremic cottontail rabbits (*Sylvilagus floridanus*) and fox squirrels (*Sciurus niger*) [48,49], although viremia levels in these animals did not approach levels those of highly competent bird species previously mentioned. Experimentally infected big brown (*Eptesicus fuscus*) and Mexican free-tailed bats (*Tadarida brasiliensis*) [50] and pigs [13] experienced absent or low titer viremia following mosquito-mediated WNV infection, again with no evidence of clinical disease.

The response of primates to WNV infection is clearly of interest because of their close relationship to humans. Rhesus macaques [51,52] and baboons [53] infected with the North American strain of WNV developed low-level viremia without clinical disease.

Reptiles and amphibians have been shown to support replication of a number of arboviruses and were of interest as hosts for WNV [54]. In a survey experiment, green iguanas (*Iguana iguana*), red-ear sliders (*Trachymes scripta elegans*), garter snakes (*Thamnophis sirtalis sirtalis*) and bull frogs (*Rana catesbeiana*) were inoculated with WNV by needle or via infected mosquito bite, and, except for turtles, low levels of virus were detected in blood and secretions from some of each of the other species [55]. In contrast to these species, American alligators (*Alligator mississippiensis*) have been shown to develop relatively high-titer viremia (peak viremia levels were approximately 10^5–10^6 plaque-forming units/ml serum) following experimental infection by needle inoculation, consumption of infected mice or contact with other infected alligators [56]. Viremia in alligators was prolonged (lasting up to 14 consecutive days of detectable viremia) in comparison to that observed in infected mammals and birds.

Vaccine efficacy trials

Horses have been the most prominent target for WNV vaccine development, and experimental infection of horses has been an indispensable tool in evaluating efficacy and promoting licensing of such vaccines [37–40]. In addition, most of the equine vaccines were initially tested for their ability to protect mice from WNV challenge [37,39]. As a prelude to human clinical trials, a yellow fever–WNV chimeric vaccine virus was tested for safety and efficacy against WNV challenge in Rhesus macaques [52]. Efficacy of these vaccines was demonstrated following either mosquito-mediated, subcutaneous or intrathecal/intracranial inoculation of WNV. A canarypox-vectored WNV vaccine has also been evaluated, and proven efficacious for protecting dogs and cats against a mosquito-mediated WNV challenge [41].

Given the high mortality of some bird species following WNV infection, the need to vaccinate birds for WNV has arisen for both valuable zoo collections, free-ranging endangered species and, in some instances, farmed birds. Commercial equine WNV vaccines have been widely used in zoological collections, but little information is available regarding protective efficacy. A DNA vaccine previously developed for use in horses [37] was evaluated in fish crows and American crows, and found moderately efficacious against experimental WNV challenge [28,29]. That vaccine was then utilized in wild populations of California condors and, although not tested in the laboratory, field observations support the utility of this vaccine in protecting this endangered species [57]. On the domestic bird front, there has been some demand for WNV vaccines to protect young geese, particularly in Israel, and an inactivated WNV vaccine was confirmed by challenge to be efficacious in geese [58].

Determinants of virulence

A prominent feature of the North American strain of WNV is its high virulence for many species of birds – a characteristic that, with few exceptions, had not been noted during outbreaks of infection in other parts of the world. The obvious question was whether high avian virulence reflected characteristics of the New York 99 strain of virus or, conversely, infection of a population of birds that had not coevolved with this pathogen. Although differences in avian host genetics have not been ruled it, it is clear that the WNV that emerged in North America is more virulent than prototype viruses from other areas of the world. In a direct comparison, American crows inoculated with the New York 99 strain of WNV developed high-titer viremia associated with universal mortality, whereas crows inoculated with

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Kenyan or Australian isolates of WNV showed significantly lower viremia and low mortality [26]. A similar experiment [27] conducted with house sparrows differed in that the New York 99 and Kenyan strains of WNV behaved similarly, while the Australian isolate was relatively avirulent. The genetic determinants of avian virulence for the North American strain of WNV are not yet completely mapped, but in comparison to the Kenyan strain, have been shown to replicate significantly better at elevated temperatures, such as occur during fever of infected crows [59].

Strains of WNV from around the world also differ significantly in virulence for mice and the response of mice to experimental infection has been studied as a surrogate for virulence in humans. The North American strain of WNV, along with closely related viruses from the Old World, showed a high degree of neuroinvasiveness in mice when compared to other WNV genotypes [60]. Genetic analyses and inoculation of mice with viruses generated through site-specific mutagenesis revealed that differential glycosylation of the envelope protein was, at least in part, responsible for differences in neuroinvasiveness [61]. Additional potential determinants of virulence have been identified in naturally occurring isolates of WNV from Texas that show an attenuated phenotype in mice [62].

Conclusion

WNV has had profound effects on human and animal health since its emergence in North America. A multitude of vertebrate species have been evaluated by experimental infection with WNV in order to identify those important to virus transmission and to characterize host response to infection. A number of bird species suspected of being important amplifying hosts based on field observation have been confirmed as such through experimental infection. Certain nonavian species may play an occasional role in WNV transmission and maintenance, but none is recognized as epidemiologically important for the transmission cycle. WNV has become endemic throughout much of the New World and will continue to pose a challenge to both humans and animals.

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The role of superantigens of group A *Streptococcus* and *Staphylococcus aureus* in Kawasaki disease

Kousaku Matsubara and Takashi Fukaya

Purpose of review
Since the first suggestion of a superantigen hypothesis for Kawasaki disease over a decade ago, debate on the aetiology remains inconclusive. This article reviews recent publications that address the role of superantigens of group A *Streptococcus* and *Staphylococcus aureus* in the pathogenesis of Kawasaki disease.

Recent findings
Over the past few years, new superantigens produced by group A *Streptococcus* and *S. aureus* have been increasingly identified, bringing the total known number to more than 30. Several studies on T-cell Vβ repertoires and seroloepidemiology have demonstrated evidence for the involvement of single or multiple superantigens produced by the two pathogens. The associated superantigens differed in those studies, including streptococcal pyrogenic toxins A and C, staphylococcal enterotoxins A–C, and toxic shock syndrome toxin 1. These disparate findings suggest that the inflammation of Kawasaki disease does not result from a single agent but rather a final common inflammatory pathway in genetically susceptible individuals after numerous infectious agents.

Summary
Certain staphylococcal and streptococcal superantigens are suggested to be responsible for the development of Kawasaki disease. A better understanding of the precise role of the causative agents will lead to accurate diagnosis, more targeted therapy and an improvement of coronary outcomes.

Keywords
group A *Streptococcus*, Kawasaki disease, pathogenesis, *Staphylococcus aureus*, superantigen

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Abbreviations

GAS	group A *Streptococcus*
IVIG	intravenous immunoglobulin
KD	Kawasaki disease
MHC	major histocompatibility complex
SPE	streptococcal pyrogenic exotoxin
STSS	streptococcal toxic shock syndrome
TNF-α	tumour necrosis factor alpha
TSS	toxic shock syndrome
TSST-1	toxic shock syndrome toxin 1

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Introduction

Kawasaki disease (KD) was first described by Tomisaku Kawasaki as an acute febrile mucocutaneous lymph node syndrome in the Japanese literature in 1967 [1]. With the subsequent English language report published in 1974 [2], this condition has been recognized worldwide. The most serious complications of KD are coronary aneurysms that affect 20–25% of untreated patients and may lead to myocardial infarction and sudden death. Although intravenous immunoglobulin (IVIG) therapy has significantly reduced the prevalence of coronary artery abnormalities, KD is the leading cause of acquired heart disease in children [3,4••,5••]. The incidence of KD has been steadily increasing in Japan since 1987 [6], and this trend has also been similarly observed in the United States [7], the United Kingdom [8], and China [4••,9]. An understanding of the aetiology and pathogenesis of KD is thus an important and worthwhile public health concern.

Despite comprehensive attempts to delineate the causative agents over four decades, the aetiology remains to be identified. There are currently no specific diagnostic tests for KD, and therefore, the diagnosis is still based on clinical features [10•]. Several lines of epidemiological evidence suggest that the aetiology is an infectious agent: the acute onset of a self-limited illness, increased susceptibility in toddler age groups with only rare cases under 6 months of age and virtual absence in adulthood, and geographical and temporal clustering with seasonal predominance [3,4••,5••,11••]. Furthermore, the similarities in clinical features and immunological reactions between KD, toxic shock syndrome (TSS), and streptococcal toxic shock syndrome (STSS) have led to the speculation that the three diseases share a superantigen-mediated aetiology. The current review focuses on

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recent insights into the role of superantigens, especially those produced by group A *Streptococcus* (GAS) and *Staphylococcus aureus*, on the development and pathogenesis of KD.

Microbial superantigens and immunological responses

Microbial superantigens are a family of proteins with particular structural and sequence features that result in the shared ability to bypass the mechanisms of conventional major histocompatibility complex (MHC)-restricted antigen processing [12]. Superantigens bind, as intact proteins, directly to the MHC class II molecule and to the T-cell receptor, extracellularly, at sites away from conventional peptide binding sites. On the T-cell receptor, binding is to the variable region of the β chain (the Vβ region) [12]. In contrast to a conventional antigen that usually stimulates only one in 10^5–10^6 naive T cells, a superantigen is able to induce global changes in the lymphocyte composition by stimulating up to 25% of the naive lymphocyte pool, resulting in the massive systemic release of cytokines [12]. The excessive uncoordinated release of proinflammatory cytokines is thought to be responsible for many of the clinical and immunological features of TSS, STSS and KD [12–14,15••]. Other actions of superantigens include the activation of natural killer cells, polyclonal B-cell activation, enhancement of endotoxin activity, and a toxic effect on the endothelium [12,14,15••]. Concentrations less than 0.1 pg/ml of a bacterial superantigen are sufficient to induce TSS [12,16]. To date, the bacteria that have been conclusively shown to produce superantigens are certain strains of *S. aureus*, GAS, groups C and G *Streptococcus*, and Gram-negative bacteria *Yersinia pseudotuberculosis* and *Mycoplasma arthritidis* [16].

The prototype superantigens from *S. aureus* and group A *Streptococcus*

Staphylococcal superantigens are composed of a large family of: (i) staphylococcal enterotoxins; (ii) toxic shock syndrome toxin 1 (TSST-1); and (iii) exfoliatins A and B [13,16,17•]. Five major staphylococcal enterotoxins, A–E, have been characterized on the basis of their antigenicity. These classical staphylococcal enterotoxins are emetic toxins and causative agents in staphylococcal food poisoning. In recent years, however, many new types of staphylococcal enterotoxin or staphylococcal enterotoxin-like putative toxins have been identified by their sequence similarity to classic staphylococcal enterotoxins [16]. To date, 19 different staphylococcal enterotoxins have been described in the literature and all are potent T-cell mitogens; staphylococcal enterotoxins A–E, G–R, U, and V [13,16,17•,18,19]. With the sudden explosion of novel superantigen sequences, a confusion of nomenclature has occurred. The International Nomenclature Committee for Staphylococcal Superantigens has recommended that only staphylococcal superantigens that induce emesis after oral administration in a monkey model should be designated as a staphylococcal enterotoxin, whereas other related toxins that either lack emetic properties in this model or have not been tested should be designated as staphylococcal enterotoxin-like superantigens [20]. On the basis of this recommendation, the toxins staphylococcal enterotoxins J–Q, U, and V should be renamed staphylococcal enterotoxin-like J–Q, U, and V, respectively [18–20].

As for GAS, 12 superantigens have been identified, predominantly but not exclusively produced by *Streptococcus pyogenes*. These include the streptococcal pyrogenic exotoxins (SPEs) A, C, G–M, the streptococcal superantigen, and the streptococcal mitogenic exotoxins 1 and 2 [13,15••].

Similarities of clinical features between Kawasaki disease and superantigen-mediated diseases

KD, TSS, and STSS share clinical features, characterized by fever, desquamation rash and mucous membrane erythema. In contrast, a major complication of KD is coronary involvement, whereas hypotension is a central symptom of TSS and STSS. A case report was published describing an adolescent male who fulfilled the criteria for both KD and TSS [21]. Additional intriguing evidence came from Anderson *et al.* [22], who described four members of a family with an illness that had clinical and laboratory findings of KD and GAS infection. All four demonstrated a good clinical course after antibiotic and IVIG therapy, but the youngest developed a coronary aneurysm [22]. Furthermore, the superantigen theory may be supported by anecdotal reports of patients showing a combination of guttate psoriasis and KD [23], as guttate psoriasis has been suggested to result from toxin-mediated T-cell activation. In addition, two KD cases immediately after scald injuries were documented, and could be explained by the entry of infectious agents or superantigenic toxins through the compromised skin barrier, leading to the development of KD [24]. Collectively, these overlapping and concurrent cases suggest that superantigens produced by *S. aureus* and *S. pyogenes* may be involved in the pathogenesis of KD.

Evidence that superantigens are involved in the pathogenesis of Kawasaki disease

Several lines of evidence support the involvement of superantigens in the pathogenesis of KS: the skewed distribution of the Vβ repertoire; superantigen-producing bacteria has been isolated from KD patients; the serological responses to superantigens produced by *S. aureus* and GAS from case–control studies; and animal models have demonstrated all the hallmarks of a superantigen-mediated response.

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Skewed distribution of Vβ repertoire

The strongest evidence of a superantigen-mediated disease is the demonstration of a disproportionate number of T cells expressing T-cell receptor Vβ families that have been stimulated by the superantigen; a 'skewed' T-cell receptor repertoire [12]. Abe *et al.* [25] first shed new light on this perspective in 1992. They found that Vβ2^{+} and Vβ8.1^{+} T cells were significantly elevated compared with healthy controls and febrile controls in the acute phase of KD, and that such changes resolved during the convalescent phase [25]. Subsequently, there have been numerous studies that support the superantigen theory, showing a skewed T-cell repertoire in KD patients [26–32]. The expanded T-cell Vβ subfamilies may differ among these studies, partly because of methodological differences (polymerase chain reaction or monoclonal antibody assay) and partly because of differences in the Vβ families examined [25–32]. On the basis of in-vitro and in-vivo studies, Yoshioka and colleagues [29,32] suggested the contribution of SPEC in the pathogenesis of KD; this was the only study demonstrating a specific superantigen involvement by T-cell repertoire analysis. Reichardt and colleagues [30] also showed that expansion of the Vβ2^{+} T cell is a useful diagnostic marker for KD, and they emphasized the significance of collecting appropriate age-matched controls because of the age-related dynamic changes in the T-cell subpopulation.

In contrast, some studies were not capable of detecting Vβ skewing in KD patients [33–35]. Several explanations have been proposed for these inconsistencies. Curtis *et al.* [27] showed that a selective increase of Vβ2^{+} T cells was detected during the second week of illness and that the distributions of these cells can normalize rapidly. Yamashiro and colleagues [36] used an immunohistochemical technique to demonstrate that Vβ2^{+} T cells were selectively increased in the small intestinal mucosa of patients in the acute phase of KD. T-cell Vβ skewing has also been found in affected myocardium and the coronary artery, with extensive junctional region diversity within T-cell populations [37]. Brogan *et al.* [38] have reported that class II MHC peptide endothelial cells operate as competent superantigen-presenting cells for CD4 and CD8 lymphocytes, suggesting that activated T cells may immigrate from the peripheral circulation through endothelial cells during acute KD. Taken together, changes induced by superantigens in the percentages of specific families of T cells are dynamic processes, migrating to the inflamed tissues through endothelial cells, and thereby T-cell repertoire changes could be detected in peripheral blood during a short period.

Isolation of superantigen-producing *S. aureus* and group A *Streptococcus*

The second line of evidence supporting superantigen theory was derived from the isolation of superantigen-producing bacteria from KD patients. In an initial study, superantigen-producing bacteria were isolated from 13 out of 16 consecutive KD patients and only one of 15 febrile controls [39]. Eleven of the 13 superantigen-positive cultures from KD patients demonstrated TSST-1-secreting *S. aureus* and the remaining two demonstrated SPEB and SPEC-producing GAS [39]. A subsequent study also found superantigen-secreting *S. aureus* in patients complicated by coronary artery disease [40]. Controversy about such findings [39,40] from a single centre has, however, prompted a prospective multicentre study in the United States [41]. In that study, cultures were obtained from the pharynx, rectum, and groin of 45 patients with KD and from 37 control subjects in six large centres, and there were no significant differences between KD patients and controls with regard to overall isolation rates of superantigen (TSST-1, SPEB, SPEC, staphylococcal enterotoxins B and C) producing bacteria [41]. Similar observations were obtained from two independent studies in Japan [42,43]. The absence of significant differences in the isolation of superantigen-producing *S. aureus* and GAS from KD patients may not, however, directly indicate their negative contribution, because a very low dose of superantigen may potentially induce KD, as in TSS [12,16], particularly in susceptible hosts.

Serological responses to superantigens produced by *S. aureus* and group A *Streptococcus*

The third line of evidence supporting the role of superantigens in the pathogenesis of KD is the serological evidence from case–control studies. Early serological studies did not show any evidence of staphylococcal or streptococcal toxin involvement [44,45]. In a study by Yoshioka and colleagues [32], it was demonstrated that serum levels of anti-SPEC IgG antibodies were higher in patients with acute KD than in age-matched controls [29]. Nomura *et al.* [46] proposed that KD in very young infants (< 6 months of age) might be related to a lack of passive placental transfer of anti-TSST-1 antibodies, because the mean anti-TSST-1 IgG titre in the mothers of KD infants was shown to be significantly lower than that in controls. They also subsequently showed that KD patients older than 6 months had a significantly elevated mean anti-SPEA-IgG antibody titre compared with controls, suggesting that SPEA may be involved in KD patients older than 6 months [47].

In the studies using IgG titres, however, it is particularly difficult to interpret the seroconversion rate and accurately determine temporal changes in antibodies during the early convalescent phase, because immunoglobulin products contain substantial amounts of antisuperantigen IgG antibodies [48]. To overcome such limitations, we recently investigated the kinetics of IgM antibodies against superantigens. We analysed antitoxin IgM antibodies

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during clinical weeks 1–4 without any reflection by IVIG treatment [49••]. Serum IgG and IgM antibodies against four staphylococcal (A, B, C, and TSST-1) and one streptococcal (SPEA) superantigens were measured using an enzyme-linked immunosorbent assay in 293 serum samples from 65 KD patients and 120 controls. There was a significant elevation of IgM antibodies against staphylococcal enterotoxin A in KD patients from the first to the fourth weeks, compared with the controls [49••]. Significant differences in IgM antibodies were also true for staphylococcal enterotoxin B, TSST-1, and SPEA throughout the first to fourth weeks, and for staphylococcal enterotoxin C throughout the second to fourth weeks [49••]. The prevalence of KD patients having high IgM titres (> mean + 2 SD of the control values) to the five superantigens was increased with the clinical weeks, and reached 29–43% of KD patients at the fourth week [49••]. In addition, in the analysis of pretreatment samples we also found that the median levels of IgG antibodies against staphylococcal enterotoxins A, B, C, and SPEA, but not against TSST-1, were significantly elevated [49••]. Collectively, we showed the first strong evidence that multiple superantigens are involved in the pathogenesis of KD.

The inconsistent results regarding the kind and number of superantigens involved shown among the studies cited above [29,32,46,47,49••] may be a result of the following differences: sources of control subjects; immunological classes in analyses; enzyme-linked immunosorbent assay methods; and the timing of blood collection. More plausibly, any of several different superantigens may be involved in the pathogenesis of this disease [4••,5••,14], and these superantigens may differ according to the isolates [50•] and their geographical locations throughout the world. The clinical phenotype may reflect a stereotyped response in a genetically susceptible host to one of a variety of infectious agents. If this is the case, this illness seems not to be a disease triggered by a single agent or toxin, but a syndrome caused by several microbial toxins.

Animal model of Kawasaki disease

An animal model of coronary arteritis was developed by the intraperitoneal injection of *Lactobacillus casei* cell wall product, and the resultant vasculitis mimics KD, demonstrating similar histological changes, time course to coronary involvement and response to IVIG treatment. Duong and colleagues [51] demonstrated, in a mouse model, marked proliferation of naive T cells, non-classic MHC restriction, a requirement for antigen presentation, but not processing, and the stimulation of T cells in a non-clonal, T-cell receptor Vβ chain-dependent fashion: all the hallmarks of a superantigen-mediated response. Of note are the recent findings that the production of tumour necrosis factor alpha (TNF-α) in the heart is coincident with the presence of inflammatory infiltrate in the coronary arteries [52••]. Mice treated with the TNF-α-blocking agent etanercept are resistant to the development of both coronary arteritis and coronary aneurysm formation [52••], suggesting a critical role for TNF-α in superantigen-induced vasculitis in KD. This mechanism is reminiscent of a new promising therapy using infliximab, a blocking antibody against TNF-α, in refractory KD [53•].

Evidence for an aetiology other than superantigen

It is also very important to emphasize that the superantigen theory is not universally accepted by all investigators in this field. Some researchers have shown refuting evidence for superantigen involvement by the absence of T-cell Vβ skewing [33–35] or serological responses [44,45,54]. Moreover, Rowley and colleagues [55] used synthetic antibody to demonstrate an antigen in the bronchial epithelium and macrophages, and cytoplasmic inclusion bodies in ciliated bronchial epithelium [56•], suggesting the involvement of as yet unidentified conventional antigens. In a retrospective analysis of respiratory secretions, significantly more children with KD were found to have a novel human coronavirus, New Haven coronavirus [57•]. Subsequent studies [58,59], however, did not duplicate these results.

Conclusion

Although no single unifying superantigen has been implicated, and there is still considerable debate about the precise aetiology, accumulating evidence suggests that KD is a response to one or many of a variety of superantigens in genetically susceptible individuals. Furthermore, over the past few years numerous new superantigens have been described, bringing the total number of known staphylococcal superantigens to over 20 and streptococcal superantigens to 12 [16,17•,18]. Therefore, it is possible that there are still other candidates involved in the pathogenesis of KD among superantigens that have not yet been investigated. Finally, irrespective of aetiology, the identification of the precise role of causative agents will ultimately result in the development of novel strategies for disrupting or preventing the development of KD. Such measures will hopefully reduce the morbidity and mortality caused by KD.

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Distinction between bacterial and viral infections

Jari Nuutila and Esa-Matti Lilius

Purpose of review
To commence proper treatment as rapidly as possible and to reduce unnecessary antibiotic treatments, timely knowledge of whether the infection is bacterial or viral in origin would be beneficial for the clinician. As a reliable prediction of the causative agent of bacterial infection is not possible based on clinical features, there is an ongoing need for sensitive and specific markers of bacterial infection.

Recent findings
The most common differential diagnosis methods are reviewed here. It is also demonstrated that the measurement of the expression of complement receptors, particularly CR1 (CD35), on neutrophils can be a useful preliminary test to differentiate between bacterial and viral infections. In addition, a novel marker of local and systemic bacterial infections designated 'clinical infection score (CIS) point', which incorporates quantitative analysis of complement receptors on neutrophils and standard clinical laboratory data and displays 98% sensitivity and 97% specificity in distinguishing between bacterial and viral infections, is presented.

Summary
We conclude that the diagnostic yield of measured individual variables in distinguishing between bacterial and viral infections increases upon combination.

Keywords
bacterial infection, CR1/CD35, differential diagnosis, neutrophil, viral infection

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Abbreviations

CAP	community-acquired pneumonia
CIS	clinical infection score
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
MFI	mean fluorescence intensity
PCT	procalcitonin
ROC	receiver operating characteristic
TREM-1	triggering receptor expressed on myeloid cells

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Introduction

Doctors depend on antibiotics to treat illnesses caused by bacteria. If there is any doubt whether the infection is bacterial or viral in origin, clinicians may be tempted to prescribe antibiotics just to be on the safe side, to eliminate the risk of a life-threatening bacterial infection. Treating viral illnesses or noninfective causes of inflammation with antibiotics is ineffective, however, and contributes to the development of antibiotic resistance, toxicity and allergic reactions, leading to increasing medical costs [1,2]. A major factor behind unnecessary use of antibiotics is, of course, incorrect diagnosis. For this reason, timely and accurate information on whether the infection is bacterial in origin would be highly beneficial in the fight against antibiotic resistance.

Methods for distinguishing between bacterial and viral infections

Several methods have been developed which help the clinician to decide whether the infection is bacterial or viral in origin. The most precise way to diagnose bacterial infections is by culturing them. Tests to confirm viral infections include determination of antibody titres and tests for viral antigens. Microbiological cultures are time-consuming, however, and are often negative in patients who are receiving antibiotics [3•,4]. The standard laboratory evaluation parameters of bacterial infection, such as leukocyte and neutrophil counts, serum C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR), have relatively poor sensitivity and specificity [5].

Procalcitonin

On the basis of meta-analysis, the diagnostic accuracy of procalcitonin (PCT) seems to be higher than that of CRP among patients hospitalized for suspected bacterial infections [6]. The serum level of PCT is a potential marker of bacterial infection in critically ill patients [7•], but this analyte appears to be correlated more to the severity of

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the infection [8], particularly sepsis [9], rather than being an unequivocal marker of bacterial infection.

Inflammatory mediators

Although studies have reported the use of inflammatory mediators, such as G-CSF, TNF-α, IL-1b, IL-6 and IL-8, to detect infection and identify bacteraemia [10–12,13•, 14•,15], a common problem with the use of such mediators is that they are nonspecific to bacterial infection.

TREM-1 and soluble TREM-1

The triggering receptor expressed on myeloid cells (TREM-1) – a new promising marker of bacterial infection – has been reported to be upregulated on peritoneal neutrophils of patients with microbial sepsis [16]. In addition, soluble TREM-1 (sTREM-1) may be useful in establishing or excluding the diagnosis of pneumonia [17]. Recent study [18•] evidences, however, that exposure of human neutrophils to filoviruses can activate TREM-1, resulting in TREM-1 shedding. Thus, it is controversial whether TREM-1 or sTREM-1 alone is applicable for reliable differentiation between bacterial and viral infections.

Neutrophil FcγRI (CD64)

The expression of FcγRI (CD64) on human neutrophils has been proposed as an improved diagnostic test for the evaluation of infection and sepsis [19•]. As the expression of FcγRI on neutrophils is increased in both bacterial and viral infections [20,21,22••], however, it appears to be a useful infection marker but cannot be used effectively for differential diagnosis.

Clearly, there is an urgent need for new sensitive and specific markers of bacterial infection. One candidate is the determination of phagocyte complement receptors.

Phagocyte complement receptors

Phagocytes include monocytes, which circulate in the blood, and macrophages, which are found in tissues throughout the body, as well as neutrophils, which are cells that circulate in the blood but can move into tissues wherever they are needed. Neutrophils are not only phagocytes but also granulocytes, meaning that they contain granules filled with potent bactericidal chemicals. Neutrophils are voraciously phagocytic to such an extent that they, along with the macrophages, have been termed 'professional' phagocytes, thereby distinguishing these cell types from other granulocytes, eosinophils and basophils.

The importance of complement receptors in infection

Activation of the complement system and the involvement of peripheral blood phagocytes, mainly neutrophils, are the major effector pathways in bacterial infection. The receptors for the complement molecules CR1 and CR3 are only weakly expressed on the surface of resting neutrophils, being mostly stored intracellularly in specific granules, in gelatinase granules and in secretory vesicles [23]. In infection, exposure to pro-inflammatory cytokines and chemoattractants primes neutrophils for rapid degranulation of intracellular granules. The fusion of vesicles and granules with the plasma membrane leads to an upregulation of CR1 and CR3 to the cell surface. The complement molecules C3b, C4b and C1q are ligands for CR1 on the pathogen surface [24,25], while C3bi specifically binds CR3 [26]. Both complement receptor types, together with Fc-receptors, provide an essential link between the humoral and cellular immune systems by functioning as key molecules for phagocytosis, for the clearance of immune complexes and for triggering the release of inflammatory mediators [27–29]. Data support the idea that the stable adhesion of complement-opsonized particles to cells expressing CR1 and CR3 is actually a dynamic molecular process in which an important function of leukocyte CR1 is to generate the ligands for CR3 [30] and that both CR1 and CR3 can initiate transmembrane signalling in human neutrophils and, in particular, activation of phospholipase D [31].

Complement receptors also have functions that are unrelated to the phagocytosis of complement-opsonized pathogens by phagocytes. For example, CR3 plays a crucial role in the migration of neutrophils from the bloodstream into the site of inflammation [32,33] and human erythrocyte CR1 serves as the main system for the processing and clearance of complement opsonized immune complexes [34]. Immune complexes bound to the erythrocyte CR1 are cleared from the circulation and localized to phagocytic cells in the liver and spleen without erythrocyte destruction. In addition, CR1 can operate as a membrane-bound or soluble complement regulator, inhibiting the classical and alternative complement pathways, and thus protecting host cells against autologous complement lysis [35••,36].

Expression of neutrophil complement receptors in bacterial and viral infections

Flow cytometry is the most widely used method for quantifying receptor expression on cell surfaces. It is well documented [10,37–39] that the expression of CR3 on neutrophils is increased in infections, but, until recently, there were few data regarding expression of neutrophil CR1 during infections. This has been rectified by our previous prospective study [40••] in which quantitative flow cytometric analysis of neutrophil CR1 and CR3 were obtained from 135 febrile patients having either bacterial ($n = 89$) or viral ($n = 46$) infection and from 60 healthy controls. In that particular study, the average expression levels of CR1 and CR3 on neutrophils in bacterial infections were over three-fold and two-fold

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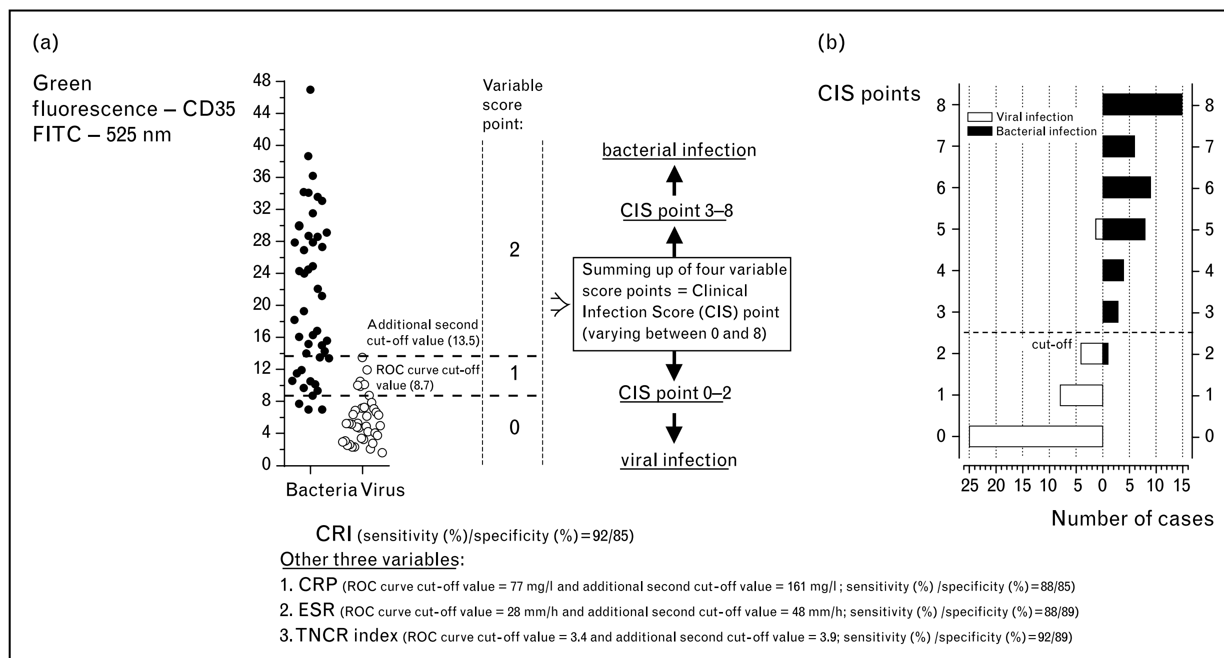
Figure 1 Formation and use of clinical infection score (CIS) points



(a) Formation of clinical infection score (CIS) points. CR1 data used as an example on how ROC curves and additional second cut-off values are settled and on how variable score points are obtained by means of them. (b) CIS point-based differentiation between microbiologically confirmed bacterial ($n = 46$) and viral ($n = 38$) infections.

higher, respectively, compared with viral infections and controls. According to receiver operating characteristic (ROC) curve analysis, neutrophil CR1 displayed 92% sensitivity and 85% specificity in distinguishing between bacterial and viral infections (Fig. 1a). Compared with other measured variables, such as neutrophil CR3, neutrophil count, CRP and ESR, neutrophil CR1 had the most effective differential capacity. The lower diagnostic accuracy of CR3 compared with CR1 may be explained by the phenomenon that CR3 is expressed not only from rapidly releasing secretory vesicles like CR1, but also from specific and gelatinase granules [23]. The behaviour of CRP and ESR was similar to the expression of neutrophil CR1 in that they were significantly higher in bacterial than in viral infections. An advantage of flow cytometric receptor analysis compared with CRP and ESR methods is rapidity, however. Notably, the time window from procuring the blood sample to data handling is less than 1 h.

Clinical infection score point: a novel marker of bacterial infection

As noticed, the expression of neutrophil CR1 is higher in classical bacterial than in viral infection. Therefore, it can be proposed that determination of the expression of CR1 on neutrophils could be of value as an additional rapid tool in the aetiological diagnosis of bacterial infection. Although a high expression of neutrophil CR1 correlates with the likelihood of bacterial infection, however, it would be surprising that any single parameter of inflammation alone could reliably differentiate between bacterial and viral infection. In fact, it is more probable that diagnostic accuracy could be improved by the combination of several analytes, namely CRP, ESR and cell receptors like CR1. This idea that the diagnostic yield of measured individual variables increases upon combination is supported by previous studies in which the clinical pulmonary infection score (CPIS) point, consisting of six clinical and laboratory variables (fever, leukocytosis, tracheal aspirates, oxygenation, radiographic infiltrates and semi-quantitative cultures of tracheal aspirates with Gram stain), displayed a sensitivity of 93% and specificity of 96% for diagnosing ventilator-associated pneumonia [41].

Accordingly, neutrophil CR1-based differentiation between bacterial and viral infections can be improved by generating the clinical infection score (CIS) point, consisting of four variables, including CRP, ESR, amount of CR1 on neutrophil and total neutrophil complement receptor (TNCR) index [40••]. The latter can be obtained by multiplying neutrophil count, relative number of CR1 on neutrophils and relative number of CR3 on neutrophils and by taking the base-10 logarithm of this factorial thereafter. For every variable in the CIS point method, a result less than the ROC curve cut-off point

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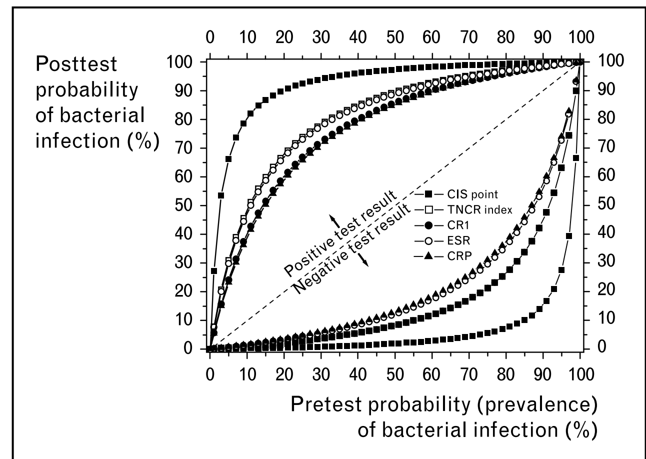
value is converted to a variable score point of 0, that between the cut-off point value and an additional second cut-off value, is converted to a variable score point of 1, and that greater than the additional second cut-off point value is converted to a variable score point of 2 (Fig. 1a). An additional second cut-off value of a variable is the maximum value detected in patients with viral infection. CIS points that vary between 0 and 8 can be obtained by combining variable scores. At a cut-off point of over 2, the CIS points differentiated between microbiologically confirmed bacterial infection ($n=46$) and viral infection ($n=38$) with 98% sensitivity and 97% specificity (Fig. 1b). Addition of neutrophil count – the fifth variable that differentiated between bacterial and viral infections with 81% sensitivity and 83% specificity – to the CIS point calculations (CIS points varied between 0 and 10, cut-off >3) did not improve differentiation between microbiologically confirmed bacterial and viral infections.

In our test material, there was one neutropenic patient (*Campylobacter jejuni* enteritis; neutrophil count $<1.5 \times 10^6$/ml) having a CIS point of 4, suggesting that neutropenia does not result in false-negative diagnosis. On the other hand, one (microbiologically confirmed *Escherichia coli* sepsis) of the 27 sepsis patients was false-negative (CIS point of only 2) (Fig. 1b). This seemed to be due to exceptionally low CRP and ESR values, however, as the CR1 value was clearly above the ROC curve cut-off value of bacterial infection.

The median CIS point value did not differ significantly between microbiologically confirmed ($n=46$) and clinically diagnosed ($n=43$) bacterial infections or between microbiologically confirmed systemic ($n=27$) and local ($n=19$) bacterial infections. In addition, CIS point-based differentiation between bacterial and viral infections was not interfered with by antibacterial treatment or underlying diseases.

Figure 2 Posttest probability of bacterial infection presented as a function of prevalence of bacterial infection



Positive likelihood ratios of 37.2, 8.48, 6.05, 8.09 and 5.75 and negative likelihood ratios of 0.02, 0.09, 0.09, 0.14 and 0.15 for CIS point, TNCR index, neutrophil CR1, ESR and CRP, respectively, were used to calculate posttest probabilities for positive or negative test results, as described in the text.

Diagnostic value of CIS point

Statistics from the ROC curve analysis, like sensitivity and specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (PLR or NLR), can be used for assessing the performance of a diagnostic test [42,43]. At the level of population, the posttest probability of disease, given a positive or negative test result, varies from pretest probability (prevalence) of disease, while test-specific sensitivity and specificity stay constant. Therefore, even relatively high sensitivity and specificity, as such, provide only a rough estimation of the test's diagnostic value, especially when the disease is rare. On the contrary, as likelihood ratios are useful across an array of disease frequencies, they are more useful in interpretation of clinical findings and laboratory tests than traditional indices of test validity. Even so, likelihood ratios are still relatively little used among clinicians.

If sensitivity and specificity of the test have already been determined, then PLR and NLR are sensitivity/(1 – specificity) and (1 – sensitivity)/specificity, respectively. The likelihood ratio has an interesting property: posttest odds = pretest odds [prevalence/(1 – prevalence)] × likelihood ratio of the test. In consequence, when prevalence of disease among patients can be estimated and likelihood ratios of the test are known, then the posttest probability of diseases, given a positive or negative test result, can be calculated [posttest probability = posttest odds/(posttest odds + 1)]. In comparison with the individual variables, the reliability of CIS point in distinguishing between bacterial and viral infections is superior over a wide range of prevalence of bacterial infection (Fig. 2). Thus, when the prevalence of bacterial infection is 20–100%, a CIS point of higher than 2 is highly suggestive of bacterial infection. Correspondingly, at a prevalence of 0–85%, a CIS point of less than or equal to 2 practically rules out bacterial infection.

Cause of community-acquired pneumonia

Community-acquired pneumonia (CAP) – one of the most common infectious diseases addressed by clinicians – can be caused by a range of agents, which can sometimes be identified from the medical history of the patient and direct clinical observations [3•]. In most cases, however, it is not possible to reliably identify the causative agent of CAP on the basis of clinical features alone. Likewise, radiographs of the chest are not specific

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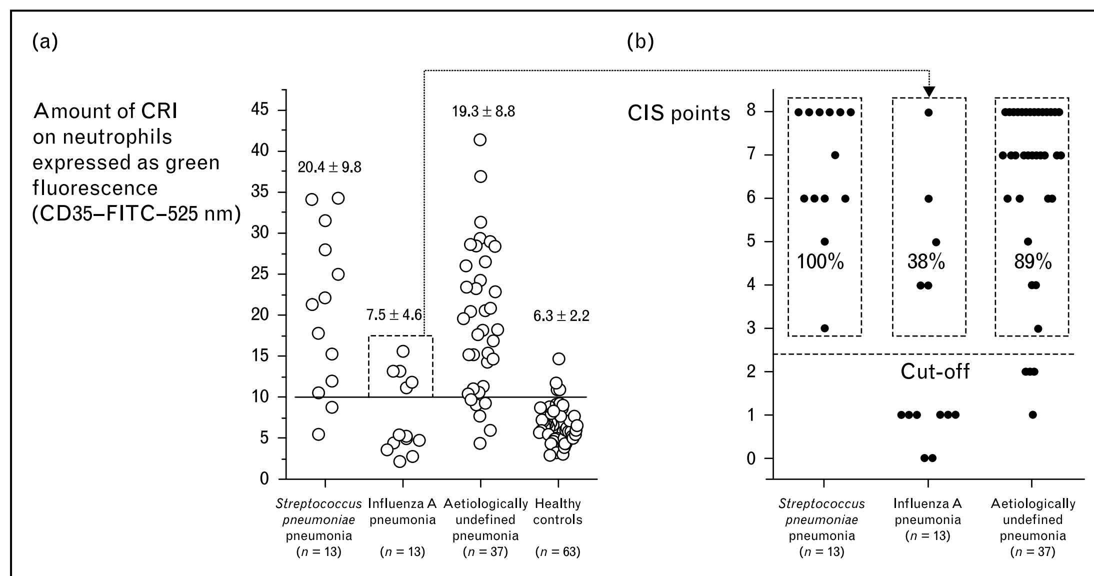
Figure 3 Neutrophil CR1 and CIS points in CAP patients



(a) The amount of CR1 on neutrophils in pneumococcal pneumonia ($n=13$), influenza A pneumonia ($n=13$), aetiologically undefined pneumonia ($n=37$) and healthy controls ($n=63$) expressed as mean fluorescence intensity (MFI) of FITC-conjugated CR1-specific monoclonal CD35-antibodies on neutrophils. Mean values ± SD of groups are also presented. The horizontal line represents MFI value of 10. (b) CIS points in pneumococcal pneumonia, influenza A pneumonia and aetiologically undefined pneumonia.

enough to enable aetiological diagnosis of CAP [44•]. Besides being often negative in the early stage of pneumonia, the blood culture is too slow for rapid differentiation between bacterial and viral infections. Although there is some evidence [45,46] suggesting that the serum concentration of CRP is higher in pneumonias caused by *Streptococcus pneumoniae* or *Legionella pneumophila* than in those caused by other agents, the precise relation of CRP to the cause of pneumonia is still controversial. While PCT is a potential marker of bacterial infection in critically ill patients, its sensitivity in differentiating between bacterial and viral pneumonia is relatively low [9].

The expression of neutrophil CR1 in CAP patients

In another previous study, we measured the expression of neutrophil CR1 in 63 CAP patients and 63 healthy controls in order to see whether it could be used to differentiate between bacterial and viral pneumonia [22••]. It was found that the average expression of CR1 on neutrophils was significantly higher in pneumococcal pneumonia than in influenza A pneumonia and in healthy controls (Fig. 3a). The expression of CR1 was also significantly higher in aetiologically undefined pneumonia than in influenza A pneumonia, but there was no difference between pneumococcal and undefined pneumonia. Patients with influenza A could be divided in two subgroups on the basis of the expression of CR1 on neutrophils: eight patients with low CR1 level [mean fluorescence intensity (MFI) < 10] and five patients with high CR1 level (MFI > 10). The subgroup of influenza A patients with high CR1 levels is interesting; this could be explained by concomitant bacterial pneumonia. Of healthy controls, 6% had high CR1 level (defined as MFI > 10) while 85% of patients with pneumococcal pneumonia and 84% patients with undefined pneumonia had high MFIs.

Aetiological diagnosis of CAP by CIS point

Afterwards, when the CIS point method was used for the diagnosis of 63 CAP patients, it was found that 100% of patients with pneumococcal pneumonia and 89% of patients with undefined pneumonia had CIS points of 3–8 (Fig. 3b). In the five patients with influenza A pneumonia who had a high level of CR1, the CIS points varied between 4 and 8, indicating that they most probably had concomitant bacterial pneumonia. Thus, compared with blood culture, the CIS point method is a much more powerful and faster tool for differentiation between bacterial and viral pneumonia.

Conclusion

A novel marker of local and systemic bacterial infections, designated CIS point, which incorporates quantitative analysis of complement receptors CR1 and CR3 on neutrophils and standard clinical laboratory data, CRP and ESR, could potentially assist physicians in deciding whether antibiotic treatment is necessary. The reduction

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of unnecessary antibiotic treatments is cost-effective and prevents development of antibiotic resistance.

The cornerstones of the CIS point method are:

(1) The quantitative analysis of CR1 and CR3 on neutrophils.
(2) The use of two cut-off values in determining variable score points.
(3) Diagnostic yield of measured individual variables increases upon combination.

We speculate that the CIS point method is not a closed system, and can be supplemented with other variable(s), provided that they display higher than 80% sensitivity and specificity for distinguishing between bacterial and viral infections. Also, it is possible to substitute some new variable(s) for present variable(s). Potential candidates for supplementary or substitutive variables could be, for example, PCT and soluble CR1.

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New concepts in vaccine development in malaria

Bernard N. Kanoi and Thomas G. Egwang

Purpose of review
To focus on recent novel concepts in the development of malaria vaccines.

Recent findings
There is a renewed interest in whole attenuated sporozoite vaccines, either as irradiated or genetically modified sporozoites, because they consistently elicit solid protection against challenge infections. Enthusiasm about these vaccines is, however, tempered by technical, logistical, safety and even cultural hurdles that might need to be surmounted. Less than a score of *Plasmodium falciparum* proteins are currently in the development pipeline as malaria vaccines. There is an urgent need to ratchet up the process of candidate vaccine discovery, and reverse vaccinology and genome-wide surveys remain promising strategies. The development of malaria vaccines for placental malaria is an active area and chondroitin sulfate A-binding epitopes of the variant PfEMP1 have been identified. Live bacteria and viral vectors hold special promise for vaccine delivery.

Summary
Attenuated sporozoite vaccines have made a resurgence to center stage in malaria vaccine development. There is an urgent need to identify more subunit vaccine candidates that can enter into the development pipeline, identify surrogate markers of immunity and design vaccines which induce long-lasting immunity.

Keywords
attenuated sporozoite, malaria, subunit vaccines

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Abbreviations

CSA chondroitin sulfate A
GAS genetically attenuated sporozoites
RAS radiation-attenuated sporozoites

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Introduction

Falciparum malaria, a mosquito-borne disease caused by the protozoan parasite *Plasmodium falciparum*, is one of the world's biggest scourges [1]. Severe and complicated malaria kills more than 2 million people annually in sub-Saharan Africa [2]; children under 5 years old, pregnant women and people living with HIV/AIDS bear the brunt of the morbidity and mortality. Over a dozen reviews on malaria vaccines appeared during the past year [3–7]. Here, we will focus on novel concepts in malaria vaccine development, highlighting recent advances on live attenuated sporozoite vaccines, the discovery of new vaccine candidates, novel adjuvants and delivery systems.

Attenuated sporozoite vaccines

Immunization experiments with irradiated sporozoites have consistently provided solid and sterile immunity in experimental animals [8] and human volunteers [9]. Whole sporozoite vaccines were, however, relegated to the back burner because advances in recombinant DNA technology led to a quest for protective recombinant subunit vaccines. Two decades later and with less than 20 *P. falciparum* proteins in the vaccine development pipeline and no viable malaria vaccines yet in clinical practice, attenuated sporozoites are receiving renewed attention [9]. Technological advances in culturing *P. falciparum in vitro* and in transfection have made it possible to produce irradiated or transgenic sporozoites [10,11•].

Radiation-attenuated sporozoites

Sporozoites are irradiated when infected mosquitoes are subjected to radiation. Like normal sporozoites, upon inoculation into a susceptible host, the irradiated sporozoites penetrate the hepatocytes and begin intracellular development. Unlike their normal counterparts, however, irradiated sporozoites are not capable of nuclear division and do not develop further, but persist for several weeks or months [9]. It is probably the prolonged sojourn in the liver and the state of the sporozoites that somehow results in the stimulation of protective immune responses mediated by cytotoxic CD8 T lymphocytes and antibodies, which target infected hepatocytes and sporozoite surface proteins, respectively. Whereas the overall balance of evidence suggests that whole organism sporozoite vaccines are superior, there are technical and safety concerns that need to be addressed including mass production of sterile parasites, proper storage by cryopreservation to maintain low infectivity and high immunogenicity, the correct

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irradiation dosage, and the safety of a mosquito-derived vaccine with the risk of coadministration of unknown pathogens. Given the coendemicity of malaria and HIV in many endemic countries, the safety of radiation-attenuated sporozoites (RAS) in the general population especially in people living with HIV/AIDS remains an overriding concern. Finally, the duration of protection provided by RAS is under 1 year [9]. This suggests that, in addition to boosting by natural infections, booster doses of RAS vaccines might have to be administered annually. This might not be practical and sustainable in resource-limited endemic countries.

Sanaria, Inc., a US-based privately held company in Rockville (Maryland), has made the development of a RAS vaccine its major portfolio and is poised to address some of the issues raised above [9,12]. In order to maintain a constant supply of a RAS vaccine to meet the high demand in endemic countries, however, assuming that all safety, technical and logistic hurdles are met, it will be vital to have several vaccine production centers in operation, since it would be inherently risky to rely on vaccines from a single supplier.

Genetically attenuated sporozoites

Genetically attenuated sporozoites (GAS) are sporozoites that, like RAS, have low infectivity, undergo arrested development in the liver and stimulate potent protection against challenge infections in murine models of malaria [13]. GAS differ from RAS in that the sporozoite attenuation is not due to irradiation, but the deletion of specific genes such as *UIS3*, *UISE4* and *P36p* which are essential for the preerythrocytic stage of malaria parasites [13–15]. Sporozoites in which these genes have been deleted have an arrested sporozoite development in the liver, cannot mature into the blood stages and are able to induce complete protection against challenge infections in a *P. berghei*/mouse model [14]. The complete protection provided by GAS constituted the proof-of-concept that genetically modified whole sporozoite vaccines might, like RAS, be useful malaria control tools. Furthermore, GAS produced by double-crossover recombination might not pose the safety concerns associated with RAS because the risk of breakthrough infections due to genetic reversion is considerably lower [14,15]. The sustainable production of GAS will, however, be constrained by the same technical and logistic problems listed above for RAS. So far *P. falciparum* GAS have yet to be generated. With the availability of malaria genomes and the advances in *P. falciparum* transfection technology, it is possible that prototype GAS vaccines for *P. falciparum* malaria might be just round the corner. This optimism must, however, be tempered by the caveat that there is widespread distrust in developing countries of genetically modified products.

Subunit recombinant vaccines

The most important impact that advances in recombinant DNA technology made on parasitology in the early 1980s was the watershed cloning in 1983, for the first time, of a malaria candidate vaccine – the circumsporozoite protein of *P. falciparum* [16]. This gave rise in subsequent years to a flood of reports of cloned and expressed recombinant parasite proteins, and the elusive hope that the control of malaria by recombinant subunit vaccines was just a matter of years away. That hope has not materialized. Over 20 years later, despite considerable efforts and resources, less than 20 *P. falciparum* antigens are under research and development for malaria vaccines. Current research and development efforts are focused on only four preparasitic stage antigens (CSP-1, LSA-1, LSA-3, and TRAP), 13 blood stage antigens (AMA-1, MSP-1, MSP-3, MSP-4, GLURP-1, RESA, SERA5, EBA-175, EBP-2, MAEBL, RAP-2, EMP-1 and DBL-α) and sexual stage antigen (Pf25) of *P. falciparum* [3]. The *P. falciparum* genome encodes about 5300 proteins [17]. There is an urgent need to accelerate the pace of discovery of new malaria vaccine candidates using innovative screening approaches. Reverse vaccinology and high-throughput genome-based screens are two interrelated techniques that hold much promise in this regard.

Reverse vaccinology and genome-wide surveys

The reverse vaccinology approach uses the genomic information (genomics, proteomics and transcriptomics) on pathogens to systematically screen their components for protective efficacy. It is uniquely suited for organisms that are not easy to culture, and has yielded promising results for chlamydial infections and bacterial diseases. Phase I trials with a meningococcus B vaccine derived from reverse vaccinology have been done [18]. Such approaches began in earnest several years ago when the first extensive microarray and proteomics studies of *P. falciparum* were reported [19,20]. Recently, Mu *et al.* [21••] carried out a genome-wide survey for polymorphisms and signatures of selections which led to the identification of potential vaccine targets. A comprehensive proteome analysis of ookinetes allowed a systematic assessment of predicted ookinete surface proteins [22]. The discovery of the vital *P. berghei* preerythrocytic stage-specific gene *UIS3*, the genetic target for a novel GAS vaccine, was made using gene-profiling studies [13]. The hopes engendered by these novel concepts and approaches are tempered by two major bottlenecks, i.e. the lack of an in-vitro surrogate marker for predicting malaria vaccine efficacy and the very ephemeral nature of immunity induced by recombinant malaria subunit vaccines.

In-vitro surrogate markers of vaccine efficacy

The ideal approach would be to develop an assay for a marker of functional immunity in individuals with immunity conferred by natural infections or vaccination. This

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issue was addressed in a recent MSP3 clinical trial in which specific antibody levels correlated with antibody-dependent cellular inhibition activity [23]. Antibody-dependent cellular inhibition is an in-vitro functional assay in which serum antibodies are incubated with parasites in the presence of monocytes. Different antigens have been shown to induce antibodies with different effector functions; the same antigen produced from different strains may yield antibodies of differing functions [24•]. Thus, it would be desirable to have a robust functional assay that predicts the immunity elicited by all antigens.

Immunity and memory in malaria

In malaria natural immunity is slow to develop and is not complete even after years of endemic parasite exposure. Adults living in a malaria-endemic country quickly become infected following radical cure of malaria, indicating a lack of complete immunity [25]. There is also evidence that memory and protective immunity is short-lived, and that it is lost when an individual is not continually exposed to the parasite [26,27]. Novel concepts in malaria vaccine development must include intervention strategies that include as a major goal, in addition to vaccine antigen presentation, the generation and maintenance of specific memory T cells. Recently, alternating immunizations with recombinant attenuated fowlpox 9 virus or modified vaccinia virus Ankara encoding preerythrocytic malaria antigens was reported to enhance memory responses [28•]. Dendritic cells, antigen-specific T helper 1 cells and memory T lymphocytes are crucial for the development of immunity in malaria [29–34]. C-C chemokines such as RANTES, which enhance T helper 1 responses, and CCL20, which recruit and activate dendritic cells and memory T lymphocytes [35], have been incorporated into vaccine constructs [36,37]. New malaria vaccine constructs could incorporate RANTES and CCL20 in order to boost T helper 1 immunity and sustain immunological memory. The design of such vaccines must be based on a solid understanding of the molecular and cellular components of immunity and memory in *P. falciparum* malaria. The role of RANTES in clinical immunity has emerged over the past 2 years [38,39•,40•], but that of CCL20 is virtually unknown. Our unpublished studies have shown that serum CCL20 levels are not only increased in severe malaria, but are correlated with serum levels of IgG antibodies against a recombinant construct of *P. falciparum* SERA5; serum titers of these antibodies are associated with protection against severe malaria in Ugandan children [41].

Malaria vaccines for pregnant women

Placental malaria is due to chondroitin sulfate A (CSA)-binding parasites which sequester in the placenta resulting in adverse pregnancy outcomes [42]. The highly polymorphic protein PfEMP1 is the major ligand for CSA-binding and is the target for current efforts to develop a pregnancy-specific malaria vaccine. Recent studies in a primate model confirmed the usefulness of the PfEMP1 DBL1α domain for the development of a vaccine for severe malaria [43•]. Immunization with the PfEMP1 DBL1α domain abolished sequestration and substantially inhibited parasite adhesion in immunized rats and monkeys, respectively [26]. Moreover, mouse monoclonal antibodies raised against *P. falciparum* variant surface proteins expressed by CSA-binding parasites were found to be protective [44•]. Two var2CSA domains expressed on the surface of CHO cells were identified as the targets of three of four antibodies inhibiting CSA-binding; two of these antibodies recognized either DBL2x or DBL3x, suggesting that some epitopes may be common to many var2CSA domains [44•]. A combination of in-silico tools including peptide arrays and structural modeling was used to define protective epitopes and sequence motifs that were specific for primigravid and multigravid women, respectively [45••].

Novel adjuvants

Alum, traditionally employed as an adjuvant in human vaccines, is a suboptimal adjuvant for subunit recombinant vaccines and synthetic peptides. There is therefore a need for novel and alternative adjuvants. Immunization studies in mice using a recombinant liver stage antigen 1 with two different adjuvants showed variability in immune responses. Higher antibody titers were induced by ASO2A, while higher numbers of interferon-γ-producing cells were induced by ASO2B in an antigen-specific way [46]. A formulation of the preerythrocytic stage malaria vaccine candidate RTS,S/ASO2A, which incorporates the adjuvant ASO2A has been reported [47•]. NF-κB-inducing kinase has been employed to enhance immunogenicity by activation of NF-κB [48•]. NF-κB-inducing kinase increases dendritic cell antigen presentation in allogeneic and antigen-specific T cell proliferation assays *in vitro*. NF-κB-inducing kinase also augments immune responses to a vector-encoded antigen, and shifts them toward a T helper 1 response with increased IgG2a levels, T cell proliferation, interferon-γ production and cytotoxic T lymphocyte responses *in vivo* [48•]. Toll receptors are also useful as adjuvants [49]. Importantly, to facilitate adjuvant selection, potency assays for adjuvants should be quintessential components of malaria vaccine development [50].

Novel vaccine delivery systems

Subunit recombinant vaccines are administered through several delivery systems including needle-free injection, viral vectors, edible vaccines and bacteria. Some of these systems have not yet been employed for malaria vaccines.

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Needle-free injection

Needle-free vaccine delivery systems have been developed for efficient delivery of particulate vaccines into the epidermal tissue [51]. Particle-mediated epidermal delivery of DNA vaccines is based on the delivery of DNA-coated gold particles directly into the cytoplasm and nuclei of living cells of the epidermis, facilitating DNA delivery and gene expression [51]. Alternatively, protein vaccines are formulated into a dense powder which can be propelled into the epidermis using similar delivery devices and principles [52].

Viral vectors

Classic viral vectors like poxvirus, adenovirus and alphavirus vectors have successfully delivered malaria antigens [53•]. Novel viral vectors like measles virus, vesicular stomatitis virus and yellow fever virus hold promise as delivery vehicles for future vaccines. Animal model studies suggest that each viral vector has a unique ability to induce humoral and/or cellular immune responses [53•]. An attenuated yellow fever vaccine containing a circumsporozoite protein T cell epitope was highly immunogenic and safe [54]. There is a need for suitable carrier and adjuvant systems that enhance protective immune responses by delivering protein and peptide antigens in appropriate conformations [53•]. New approaches currently being explored involve combining peptide-based malaria vaccine candidate antigens with immune stimulatory carrier-systems based on influenza virosomes [55,56].

Edible vaccines

Oral delivery is associated with simple administration, improved safety and can induce mucosal immune responses. It has been hypothesized that edible antimalaria vaccines in transgenic tomatoes might be a possible solution to the logistical problems of distribution, stability and costs [57•]. The immunogenicty of such vaccines has been demonstrated in a mouse model [58]; however, there remain significant technical hurdles to be overcome regarding vital issues such as yield, purity and dosage. The effect of proteolytic digestion by gastrointestinal enzymes on the immunogenicity of edible vaccines also remains unknown. The usefulness of edible vaccines in human *P. falciparum* malaria will therefore remain an unproven concept for some time.

Live bacteria

The use of live bacteria to induce an immune response to a vaccine cargo component is an attractive vaccine strategy [59]. Advantages of live bacterial vaccines include their mimicry of a natural infection, intrinsic adjuvant properties and the possibility of oral administration [60]. High-titer antibody responses to recombinant Pfs25H, a transmission-blocking vaccine candidate, were induced after chemical conjugation to the outer-membrane protein complex of *Neisseria meningitidis* serogroup B and adsorption to aluminum hydroxyphosphate [61••]. Pathogenic bacteria must, however, be attenuated in order to eliminate their virulence since they might pose some risks. The acceptability of genetically modified bacteria carrying malaria vaccines might, like GAS, also be compromised by distrust by the target populations.

Conclusion

There is a renewed interest in whole attenuated sporozoite vaccines, but technical, logistical and safety hurdles still remain. At present, less than a score of *P. falciparum* proteins are under development as subunit vaccines. Reverse vaccinology and genome-wide surveys promise to increase the number of subunit vaccine candidates. Additional obstacles to be overcome include the lack of validated surrogate markers of immunity and the short duration of protection induced by subunit vaccines. Vaccine constructs which incorporate RANTES and CCL20 and other biological adjuvants hold promise, and should be urgently investigated and tested in malaria clinical trials in endemic countries.

Acknowledgement

We acknowledge Dr Brenda Okech for constructive suggestions and critical editing of earlier drafts.

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This bibliography is compiled by clinicians from the journals listed at the end of this publication. It is based on literature entered into our database between 1 February 2006 and 31 January 2007 (articles are generally added to the database about two and a half months after publication). In addition, the bibliography contains every paper annotated by reviewers; these references were obtained from a variety of bibliographic databases and published between the beginning of the review period and the time of going to press. The bibliography has been grouped into topics that relate to the reviews in this issue.

• Papers considered by the reviewers to be of special interest
•• Papers considered by the reviewers to be of outstanding interest

The number in square brackets following a selected paper, e.g. [**7**], refers to its number in the annotated references of the corresponding review.

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Paediatric and neonatal infections

Adverse events following immunisation: real and perceived

Related review: Adverse events following immunization: perception and evidence (pp. 237–246)

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