



The chronic health effects of exposure to biological agents

A systematic literature review

Prepared by the
Public Health Laboratory Service in Wales
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The aim of this report was to review and critically evaluate the scientific evidence for chronic health effects associated with infection by biological agents of occupational relevance and to highlight any knowledge gaps. Two systematic literature reviews were conducted. The first searched for documented evidence of occupational transmission for each of the listed agents. The second searched for evidence of chronic health effects in those agents with a documented occupational relevance.

Databases were chosen for their relevance to the subject being reviewed and interrogated using a defined search strategy. All papers published in English between 1970 and the present day were included. The reference details and abstracts (where available) of relevant papers identified were stored on a Reference Manager database.

A summary of the published evidence for each postulated health effect was produced in the form of a table with an accompanying bibliography. A maximum of 10-15 papers relating to each postulated health effect was critically reviewed. Papers at the highest level of evidence were reviewed first (ie reviews and prospective studies) followed by papers in lower categories. Papers were reviewed using a data extraction sheet according to standard criteria. The conclusions of each paper were accepted or rejected. Accepted papers were allocated to a level of evidence for causation.

The occupational transmission search identified 4124 references, the chronic health effects search, more than 2000. Comparatively little convincing evidence exists. Many studies have concentrated on particular age and sex groups. There have been no prospective studies commencing in childhood. We recommend that the feasibility of conducting a large prospective cohort study examining the chronic health effects of several biological agents should be investigated. The reference database produced here should be updated annually to ensure it remains accurate and relevant to current working practices

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EXECUTIVE SUMMARY

Two systematic literature reviews were conducted of the evidence for chronic health effects associated with infection by biological agents that can be acquired occupationally. The first searched for documented evidence of occupational transmission (OCCUPATIONAL SEARCH) for each of the listed agents. The second searched for evidence of chronic health effects in those agents with a documented occupational relevance (CHRONIC HEALTH EFFECTS SEARCH).

Databases (Medline, Embase, ISI- Science Citation Index, Cochrane Collaboration, Indexed Conference Papers and WHO International Agency for Research on Cancer Monographs) All papers published in English between 1970 and the present day were included. The reference details and abstracts (where available) of the relevant papers identified in all the databases were stored on a Reference Manager (Version 9) database (OCCUPATIONAL DATABASE). This database is available on CD-ROM as part of this report.

A summary of the published evidence for each postulated health effect was produced in the form of a table with an accompanying bibliography. A maximum of 10-15 papers relating to each postulated health effect could be critically reviewed. Papers at the highest level of evidence were reviewed first (i.e. reviews and prospective studies) followed by papers in the lower categories. Comprehensive (but not necessarily systematic) reviews were selected in preference to case series and retrospective studies. Papers were reviewed using a data extraction sheet (Appendix 2) according to standard criteria. The conclusions of the paper were either accepted or rejected. Accepted papers were allocated to a level of evidence for causation set out in the introduction. A total of 4,124 references were identified on the occupational transmission of biological agents search and more than 2,000 papers were identified in the chronic health effects search. Each organism /disease section concludes with the critical appraisal and a discussion of the available evidence. Overall, comparatively little convincing evidence exists. Many studies are small and have concentrated on particular age and sex groups (e.g. Middle aged men in heart disease). There have been no prospective studies commencing in childhood. There is some evidence that all of the biological agents included in this report can be acquired in certain occupational settings. We recommend that the feasibility of conducting a large prospective cohort study which would simultaneously examine the chronic health effects of several biological agents should be assessed. In addition, the reference database produced here should be updated, ideally annually, to ensure that it remains accurate and relevant resource for current working practices.

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1 INTRODUCTION AND EXPLANATION OF TERMS

1.1 GENERAL INTRODUCTION

Chronic infectious diseases are as old as mankind. Polio is depicted in Egyptian tomb decorations. Leprosy has been well known since at least biblical times and early mediaeval graveyards occasionally reveal the involucrum and sequestrum of chronic osteomyelitis. These are just a few examples. However the proliferation of molecular techniques for the detection of very low numbers of organisms, particularly, has enabled, in recent years a re-examination of the whole field. This has resulted in infectious aetiologies coming under consideration for a number of diseases whose aetiology previously might have been ascribed to degeneration, auto-immunity or diet. The combination of this with the continual change in work and social patterns over time prompted the Health and Safety Executive (HSE) to fund the Public Health Laboratory Service (PHLS) in Wales, via its Communicable Disease Surveillance Centre (CDSC Wales), to perform a systematic review of existing literature on chronic ill health due to biological agents.

Over the century and a half, or so, that the germ theory of disease causation has been appreciated, numerous biological agents have been linked with numerous diseases. In many instances the aetiological mechanisms has been unraveled and documented. Notwithstanding these advances, there is still much to learn about the interaction between biological agents and humans. Each decade new microbes are discovered or re-classified and well-known organisms emerge as human pathogens. At the same time, our understanding of those pathogenic processes becomes more sophisticated. Whilst the aetiology of many chronic diseases remains unexplained, it is, therefore, logical to consider to what extent biological agents might be involved in the aetiology of chronic disease. Particularly with some common illnesses such as coronary heart disease and Alzheimer's disease, the possibility that they are caused by infectious agents could have major implications for successful prevention and treatment. Might, for example, they be preventable by vaccination? Many infections are treatable in a relatively straightforward way with antimicrobials. Are there similar therapeutic opportunities in some of the diseases currently considered chronic.

There are also wider public health issues around prevention that may arise from this. Occupationally acquired diseases account for over 1,000 reported cases of infectious disease annually (Ross et al.) and the true incidence is likely to be much higher. Employers have a legal responsibility to protect their employees from hazards (including biological agents) in the working environment (Health and Safety at Work Act 1974). Chronic health conditions arising as a result of exposure, at work, to biological agents present a further hazard from which employees need to be protected. In the wider environment they may constitute further reasons, if such were necessary, for clean water, safe food, clean air and the avoidance of overcrowding and squalor.

Presented here is a systematic literature review of evidence linking chronic health conditions with exposure to biological agents with critical appraisal of selected studies. This is supplemented by a further systematic search of the literature for evidence of occupational transmission of the agent.

United States Centers for Disease Control and Prevention (CDC) strategy for preventing emerging infectious diseases highlights their intention to conduct research in this area.(1). One of us (RLS) visited the US to meet with CDC staff in Atlanta and to learn more about initiatives in North America more generally. A report of this visit accompanies this report.

1.2 EXPLANATION OF TERMS

1.2.1 Chronic health effects

The spectrum of health effects attributable to biological agents range from acute to chronic illness. In acute illness, the organism (or its products) enter the host (possibly multiply to sufficient numbers to cause disease), cause local or disseminated tissue damage and is either overcome by the host's defences (recovery) or overcomes the host (death). Even acute disease may have chronic health implications in the form of complications or permanent disablement. In chronic disease, a slowly progressive, persistent clinical picture emerges where the initial (primary) infection may even go unnoticed by the host. However, chronic health effects are difficult to define and the term covers several major categories of chronicity. Table 1 below summarises a review of currently identified infectious diseases (listed in Chin, 1999) where a chronic health effect is acknowledged. From this review, five categories of chronic health effect could be established (Figure 1).

Table 1 Diseases with chronic health effects (adapted from Chin, 1999)

<i>Infectious agent</i> *	<i>Disease</i>	<i>Occurrence</i>	<i>Chronicity</i>	<i>Notes on potential occupational transmission</i>
HIV-1 HIV-2	AIDS	Global	Incubation period can be 15 years or longer	Employees exposed to blood and blood products
<i>Actinomyces israelii</i>	Actinomycosis	Global	Chronic bacterial disease	Humans are reservoir, commensal in plaque/tonsillar crypts. Cause disease after penetration of tissues during trauma
<i>Entamoeba histolytica</i>	Amoebiasis	Global	Intermittent dysentery/colitis of long duration. Incubation period can be years	
Tick-borne virus (flavivirus)	Viral encephalitis (Louping Ill)	Russia, Europe, Scandinavia, UK	? Huntington's chorea	Ticks around sheep so potentially transmitted to animal handlers etc.
<i>Aspergillus fumigatus/flavus</i>	Aspergillosis	Global	Susceptible individuals (i.e. allergy plus chronic lung disease) can develop intermittent bronchial plugging – allergic bronchopulmonary aspergillosis	Decaying vegetation * growing on certain foods produce aflatoxins which are carcinogenic (oil press workers/dockers)
<i>Babesia divergens</i>	Babesiosis	Global – in scattered locations	Recrudescence of symptoms after prolonged asymptomatic parasitemia may occur more than a year after initial exposure	Tick borne? animal handlers
<i>Bartonella bacilliformis</i>	Bartonellosis (Verruga peruana)	Peru, Ecuador, Columbia	Prolonged course Incubation period up to ¾ months	Transmitted from human to human via bite of sand flies
<i>Bartonella henselae</i>	Cat scratch disease	Global	Complications – prolonged high fever, osteolytic lesions, hepatic/splenic granulomata.	Employees handling cats
Blastomycosis	Blastomyces dermatitidis	USA, Canada, Africa, India, Israel, Saudi Arabia	Chronic pulmonary blastomycosis	Undisturbed soil – possibly agricultural and other outdoor workers
Brucellosis	Brucella abortis / melitensis Suis	Global	Chronic localised infections can occur as can osteoarticular complications and relapses	Farm workers, vets, abattoir workers
Campylobacter enteritis	<i>Campylobacter jejuni/coli</i>	Global	Reactive arthritis Guillain-Barre syndrome	Animal handlers

Candidiasis	<i>Candida albicans</i> and others	Global	Repeated clinical skin eruptions	
Chlamydial genital Infection	<i>Chlamydia trachomatis</i>	Global	Asymptomatic chronic infections of endometrium and fallopian tubes may lead to infertility, ectopic pregnancy or chronic pelvic pain	Transmitted through sexual intercourse
<i>Chlamydia trachomatis</i>	Chlamydial conjunctivitis	Global	Chronic phase with scant discharge persisting for over a year	Transmission of genital secretions to the eye in sexually active adults
<i>Chlamydia trachomatis</i> Serovars A, B, Ba and C	Trachoma	Global	Eye-lid deformities, corneal scarring, blindness	Infectious discharges – possibly healthcare workers
Chromomycosis	Several including <i>Phialophora verrucosa</i>	Global but mainly warmer countries	Chronic spreading mycosis of skin and subcutaneous tissue	Primarily a disease of rural, barefooted agricultural workers in tropical regions
Clonorchiasis	<i>Clonorchis sinensis</i>	China and some other far eastern countries	Chronic trematode disease of bile ducts	Life cycle completed via snail and fish. Ingested in raw/undercooked fish
Coccidioidomycosis	<i>Coccidioides immitis</i>	Arid areas of Western Hemisphere	Dissemination results in lung lesions and abscesses throughout the body and may occur years after the primary infection	Inhalation from soil, laboratory accidents, dusty fomites from endemic areas (archaeologists)
Adenovirus/ Picornavirus	Enteroviral acute hemorrhagic conjunctivitis	Tropical countries and some parts of Europe	Neurological complications starting a month after the conjunctivitis and leaving some residual weakness	Via discharge from infected eyes and in swimming pools
Coxsackievirus	Pharyngitis, hand foot and mouth disease	Global	Juvenile onset insulin dependent diabetes	Frequently occurs in outbreaks among children in day care centres. ? child carers
<i>Cryptococcus neoformans</i>	Pulmonary disease and Meningitis	Global	Pulmonary disease may precede brain infection by months/years	Saprophytic growth on old pigeon nests/droppings and soil. ? pet shop employees etc
<i>Corynebacterium diphtheriae</i>	Diphtheria	Temperate zones	Chronic nasal diphtheria	Contact with patients ? healthcare workers
<i>Echinococcus granulosus</i>	Hydatid disease	Global	Infections pass unnoticed until cyst reaches noticeable mass	Contact with infected dogs (near grazing pasture)
Prion	Creutzfeldt-Jakob disease	Global	Incubation period may be over 30 years	Hypothesised risk of acquiring from animals

Human parvovirus B19	Erythema infectiosum	Global	In adults may cause arthritis lasting years. ? rheumatoid arthritis/systemic vasculitis/fulminant hepatitis/myocarditis	Person to person via infected respiratory secretions. Epidemics among children? child carers
<i>Helicobacter pylori</i>	Chronic gastritis Duodenal ulcer Gastric adenocarcinoma	Global	Chronic gastritis Duodenal ulcer Gastric adenocarcinoma	Ingesting organisms
<i>Giardia lamblia</i>	Giardiasis	Global	Chronic diarrhoea, reactive arthritis	Faecal-oral
<i>Neisseria gonorrhoea</i>	Gonorrhoea	Global	Arthritis and permanent joint damage	Sexually transmitted
<i>Calymmatobacterium granulomatis</i>	Granuloma inguinale	Tropical and sub-tropical areas	Chronic skin disease	Contact with infected skin and sexually
Hepatitis B virus	Hepatitis	Global	Chronic hepatitis – cirrhosis and hepatocellular carcinoma	Employees in contact with blood and blood products
Hepatitis C virus	Hepatitis	Global	Chronic hepatitis – cirrhosis and hepatocellular carcinoma	Mainly parenterally transmitted – employees exposed to blood and blood products
Herpes simplex virus	Genital infection and cold sores	Global	Latent infection and recrudescence	Herpetic whitlow in dentists
<i>Histoplasma capsulatum</i>	Fungal respiratory disease	Rare in Europe	Chronic pulmonary disease	? Reservoir is undisturbed bird/bat droppings
<i>Leishmania tropica</i>	Leishmaniasis	Not reported in Europe	Chronic skin lesions	Zoonotic via sand flies. Occupational groups working in forested areas
<i>Leishmania donovani</i>	Visceral leishmaniasis	Tropical and sub-tropical areas	Chronic systemic disease	Human-human and dog-human via sand flies
<i>Mycobacterium leprae</i>	Leprosy	Tropical and sub-tropical areas	Chronic bacterial skin disease with incubation period up to 20 years	Via nasal discharges and ulcers? healthcare personnel
Loa loa (nematode)	Loiasis	Africa	Chronic filarial disease	Via deer fly
Borrelia	Lyme disease	USA, Europe, USSR, China, Japan	Joint pain can recur for several years, neurologic abnormalities may become chronic	Tick-borne
Pasteurellosis	Pasteurella multocida		Chronic respiratory tract disease in elderly patients with underlying disease	Cat or dog bites – animal handlers
<i>Pseudomonas pseudomallei</i>	Melioidosis (Glanders)	Asia	Chronic abscesses. Incubation period can be years	Via soil and water (Glanders in occupations involving animal contact)
(Poxviridae family) Molluscipoxvirus	Molluscum contagiosum	Global	Skin lesions can persist for 2 years	Human-human direct contact

Paramyxovirus	Mumps	Global	Sensorineural hearing loss, permanent sequelae such as paralysis, seizures and hydrocephalus	Airborne transmission
<i>Acanthamoeba polyphaga</i>	Acanthamebiasis	Global	Chronic granulomatous skin lesions Eye infections have resulted in blindness	Aquatic and soil habitats – spas, hot-tubs, contact lens wearers
<i>Nocardia asteroides</i>	Nocardiosis	Global	Chronic bacterial disease – abscesses of brain and other organs	Inhalation or inoculation with contaminated dust/soil
<i>Onchocerca volvulus</i>	Onchocerciasis	South America Africa	Chronic filarial disease	Human-human via fly bites
<i>Paracoccidioides brasiliensis</i>	Paracoccidio- mycosis	Tropical and sub- tropical regions	Chronic mycosis with incubation period up to many years	Soil reservoir – workers in contact with soil (farmers/builders) most at risk
<i>Treponema carateum</i> (spirochete)	Pinta	American tropics	Chronic nonvenereal treponemal skin infection	Direct contact with skin lesions
<i>Mycoplasma pneumoniae</i>	Pneumonia	Global	Stevens-Johnson syndrome?	Droplet inhalation? healthcare
<i>Chlamydia pneumoniae</i>	Pneumonia	Global	Chronic bronchitis and sinusitis in older adults	? contact with secretions/fomites
<i>Coxiella burnetti</i>	Q fever	Global	Chronic Q fever manifests as endocarditis	Airborne in dust from animals (sheep, cattle, goats, cats,dogs)
Schistosoma	Schistosomiasis	Africa, South America, Eastern countries	Bladder cancer	Penetration of skin of persons working in water
<i>Streptococcus pyogenes</i> group A	Sore throat, skin infection, scarlet fever, erysipelas, toxic shock Syndrome	Temperate zones	Rheumatic heart disease	Respiratory droplets
<i>Treponema pallidum</i>	Syphilis	Global	Long periods of latency	Sexual contact. Primary lesions on hands of health professionals
<i>Toxocara canis and cati</i>	Toxocarisis	Global	Chronic infection, blindness	Infected cats and dogs – mainly occurs in children
<i>Toxoplasma gondii</i>	Toxoplasmosis	Global	Dormant organisms (following asymptomatic primary infection) from latent infection can reactivate and cause cerebral toxoplasmosis	Via cat faeces
<i>Bartonella quintana</i>	Trench fever	Wherever human louse exists	Symptoms may continue to recur many months after primary infection	Human-human via lice
<i>Trypanosoma brucei Gambiense</i>	African Trypanosomiasis	Africa	Incubation period can be years	Human-human via tsetse fly bite

<i>Trypanosoma cruzi</i>	American Trypanosomiasis	Central and South America	Chronic irreversible sequelae involving heart and colon	Infected blood sucking insects, accidental laboratory infection
<i>Mycobacterium tuberculosis</i>	Tuberculosis	Global	Latent phase with life-long risk of reactivation	Airborne droplets – healthcare workers
<i>Mycobacterium paratuberculosis</i>	Mycobacteriosis		Crohn's disease suggested	
<i>Rickettsia prowazekii</i>	Typhus fever	Mexico, Central and South America	Recrudescence years after primary attack	Human-human via body louse
Human papilloma virus	Warts	Global	Can become malignant	Type 7 is associated with warts in meat handlers and veterinarians
<i>Treponema pallidum</i> (spirochete)	Yaws	Tropical areas	Chronic relapsing treponematosi s (destructive lesions of skin and bone)	Direct contact with exudates

Infectious agent = an organism (virus, rickettsia, bacteria, fungus, protozoan or helminth) that is capable of producing infection or infectious disease.

The infectious agent of spongiform encephalopathies (“prions”) are not considered further. Their relationship to chronic neurological disease is well established. Occupational risk has been postulated but never unequivocally shown and is a considerable subject in its own right.

Categories of chronic health effects include:

1. Complications or sequelae occurring as part of or shortly after the primary infection (e.g. reactive arthritis in salmonella infection and haemolytic uraemic syndrome (HUS) in VT+*E.coli* O157(VTEC) infection)
2. Chronic diseases - diseases with a prolonged course (e.g. many skin conditions including leprosy)
3. Diseases where symptoms recrudescence following the primary illness (e.g. Q fever)
4. Infestations (lice) and helminthic (worms) infections of lungs and intestines
5. Chronic or latent infections inducing a response in the host (Hepatitis C causing hepatocellular carcinoma)

To this can be added

6. Autoimmune diseases where the autoimmune activity persists after eradication of the trigger pathogen. In this case the role of a biological agent has to be inferred from evidence of an immune responses. (e.g. rheumatic fever and Lancefield Group A streptococcal pharyngitis). Alternatively, the microbe may continue to replicate at very low levels in the host providing antigenic stimulation for an on-going autoimmune injury. This will respond to antimicrobials.
7. Unsuspected host-pathogen relationships may exist which cannot be categorised as either parasitism nor commensalism. Some viral genes are incorporated into the human genome and may be expressed during local inflammation.
8. Pathogens which may be difficult to detect or identify, even with sequence-based methods. Also, non-pathogens that acquire virulence-associated genes and micro-organisms without universal sequences.

1.2.2 Persistent, chronic and latent infections

A pathogen that kills its host cannot, as a rule, itself survive. For a pathogen to establish a persistent infection it must have some mechanism to evade the host immune system and replicate over a long period. The clinical course of chronic infections varies markedly and the variation is determined by factors relating to the pathogen or the host. Host factors include strain variation, numbers of infecting organism and site of entry into the host. The effectiveness of the hosts defence mechanism is influenced by genetic and environmental factors.

In most chronic bacterial infections the pathogen survives intracellularly. In chronic viral infections the virus is shed over long periods and often can be cultured and identified. The virus is held in check and tissue damage may even be repaired (with some notable exceptions such as CNS).

In latent infections the virus is sequestered from the host immune system within host cells and cannot be detected by conventional methods such as culture and electron microscopy (e.g. herpes virus and retrovirus infections). Only when they are reactivated do they make detectable infectious virus particles.

Among viruses well known as producing persistent infections in human are: rubella, measles, retroviruses (HTLV-I, HTLV-II, HIV-I and HIV-II), herpesviruses (cytomegalovirus, Epstein-Barr virus, herpes simplex 1 and 2, herpes zoster), papovaviruses (Polyomavirus, papillomaviruses), adenoviruses and hepatitis B. In persistent viral infections a high serum level of antibody to the virus is likely but not invariable.

1.2.3 Causation

Key to the acceptance of an infectious aetiology for any given disease are the criteria used to establish causation. Epidemiological features such as clusters in space and/or time may suggest an infection especially if combined with clinical features such as high fever and a raised white blood cell count. Pathological characteristics may also suggest a specific pathogen. For example, granuloma formation suggests mycobacterium or a fungus. (F&R, 1996, CMR). However, proving a causal relationship between an organism and a disease is problematic and has vexed scientists for more than a century. The first problem is trying to find a microorganism. The responsible organism may not be identified for any number of reasons (see below). Any organism that is found may indeed be the “true” pathogen but it may be a transient or permanent commensal or an opportunist, taking advantage of the pre-existing pathology of the chronic disease.

Koch's postulates, originally proposed in 1890, are among the first and certainly the most well known criteria for linking an organism with a disease. Koch proposed that if the following three conditions are met then the organism can be considered to cause the disease in question:

- 1 The parasite occurs in every case of the disease in question and under circumstances which can account for the pathological changes and clinical course of the disease.
- 2 The parasite occurs in no other disease as a fortuitous and non-pathogenic parasite
- 3 After being fully isolated from the body and repeatedly grown in pure culture, the parasite can induce the disease anew.

The limitations of this approach were acknowledged at the outset. Particularly as diagnostic methods, not requiring pure culture have been developed, Koch's postulates have been increasingly viewed as offering guidance. Nevertheless, they set a standard for the scientific rigour and evidence necessary in judging a pathogen to be the cause of a disease.

Frequently today, evidence is provided by advanced microbiological techniques that do not grow the organism in pure culture taken together with epidemiology and serology. Criteria for causal associations in virology (Rivers, Heubner, Johnson and Gibbs), epidemiology (Hill) and immunology (Evans) have all been, from time to time proposed.

In particular, traditional microbiology has been supplemented by nucleic acid sequence-amplification technology and in situ oligonucleotide hybridisation with the growing reliance on genotypic methods for microbial identification. Using these techniques, viral and bacterial gene sequences have been identified in some lesions of chronic disease (e.g. *Chlamydia pneumoniae* in atherosclerotic plaques) generating new hypotheses on the aetiology of such diseases. The disadvantages of these methods for ascribing causation may be summarised.

- 1 Only amplified sequences of nucleic acid are obtained. Therefore, the biological role and even the very existence of the viable living organism remain uncertain. Furthermore, as it is unlikely that the sequence that has been propagated will encode virulence factors sufficient for producing disease in a new host. Thus experimental reproduction of the disease is ruled out. However, the sequence may contain phylogenetic information which provides a clue to the type of laboratory conditions which will allow cultivation.

- 2 As the methods are very sensitive, “contaminants” may be detected from laboratory reagents or anatomical sites. Hence, multiple reagent-only controls and clinical control samples analysed in parallel with the disease-associated samples are essential.
- 3 When a sequence is amplified from a digested biological sample in a tube its relevance to the disease process is more difficult to ascertain. It is no longer possible to tell which part of the infected cell was involved. *In situ* nucleic acid techniques overcome this as they facilitate subcellular localisation of the nucleic acid.
- 4 Sequences in some microbial agents exhibit great variation (microheterogeneity), for example HIV. This may be due to *Taq* polymerase incorporation errors, variation among different gene copies from the same organism and the presence of multiple strains of the same species within the clinical sample. Databases of gene sequences for all microorganisms are currently too limited reliably to define species.
- 5 Further difficulties include, heterogeneity of sample, wide variation in the numbers of microbial targets in any given sample, resistance of some micro-organisms to digestion and subsequent release of nucleic acid, the presence of PCR inhibitors in varying amounts and types and contamination. (Relman, EID, 1998, 4,3)

However sequence-based methods do, equally, have advantages:

- 1 They do not require viable and intact micro-organisms and therefore can detect latent/dormant organisms such as those involved in chronic Lyme arthritis and some cancers.
- 2 They can provide evidence of an infectious involvement in diseases which are due to inflammatory processes caused or perpetuated by microbial components (cell wall, membrane-bound DNA) of organisms which are long dead.

Finally it should be noted that, the failure to find microbial nucleic acid in diseased tissue does not rule out an infectious aetiology as the organism may be residing at a remote site and attacking the tissue via circulating toxins (e.g. tetanus).

Fredricks and Relman proposed guidelines for establishing causation using sequence based technology that should provide strong evidence of a clinically important host-parasite relationship. They are:

- 1 A nucleic acid sequence belonging to a putative pathogen should be present in most cases of an infectious disease. Microbial nucleic acids should be found preferentially in those organs or gross anatomic sites known to be diseased (i.e. with anatomic, histologic, chemical or clinical evidence of pathology) and not in those organs that lack pathology.
- 2 Fewer, or no, copy numbers of pathogen-associated nucleic acid sequences should occur in hosts or tissues without disease.
- 3 With resolution of disease (for example, with clinically effective treatment) the copy number of pathogen-associated nucleic acid sequences should decrease or become undetectable. With clinical relapse, the opposite should occur.
- 4 When sequence detection predates disease, or sequence copy number correlates with severity of disease or pathology, the sequence – disease association is more likely to be a causal relationship.

- 5 The nature of the microorganism inferred from the available sequence should be consistent with the known biological characteristics of that group of organisms. When phenotypes (e.g. pathology, microbial morphology, and clinical features) are predicted by sequence-based phylogenetic relationships, the meaningfulness of the sequence is enhanced.
- 6 Tissue-sequence correlates should be sought at the cellular level: efforts should be made to demonstrate specific in situ hybridisation of microbial sequence to areas of tissue pathology and to visible microorganisms or to areas where microorganisms are presumed to be located
- 7 These sequence-based forms of evidence for microbial causation should be reproducible.

(Fredricks and Relman, 1996)

Definition of causation (Elwood, 1988), a factor is the cause of an event if its operation increases the frequency of the event. Necessary and sufficient causation are merely extremes within this definition.

Using the above definitions, data extraction sheets were constructed to review evidence on causality.

- 1 Centers for Disease Control and Prevention. Preventing Emerging Infectious Diseases: A Strategy for the 21st Century. Atlanta, Georgia: U.S. Department of Health and Human Services, 1998.
- 2 Fredricks DN, Relman DA. Sequence-based identification of microbial pathogens: a reconsideration of Koch's postulates. Clin Microbiol Rev 1996;9:18-33

2 AIM AND OBJECTIVES

2.1 AIM

To conduct a systematic literature review of the evidence for chronic health effects associated with infection by biological agents that can be acquired occupationally.

2.2 OBJECTIVES

1. A search strategy will be implemented to systematically review the literature on chronic health effects of exposure to occupationally relevant biological agents.
2. The breadth of data available will be critically evaluated and the strength of associations identified by investigating the published statistical analysis, taking in to account the validity of the studies
3. Gaps in the knowledge will be identified from the review and areas HSE may wish to pursue will be highlighted.

3 METHODS

An initial trawling literature search was conducted to compile a list of biological agents with postulated chronic health effects. This was discussed with the study commissioners and a list of potential biological agents formulated. Two systematic literature reviews were conducted.

The first searched for documented evidence of occupational transmission (OCCUPATIONAL SEARCH) for each of the listed agents.

The second searched for evidence of chronic health effects in those agents with a documented occupational relevance (CHRONIC HEALTH EFFECTS SEARCH).

3.1 GENERAL EXCLUSIONS

1. Infestations such as lice, scabies excluded
2. Intestinal and lung worms
3. Complications occurring as part of or leading on from the initial disease e.g. arthritis which can complicate many infections

3.2 OCCUPATIONAL SEARCH

Databases were chosen with regard to their relevance to the subject being reviewed. They are as follows:

- ◆ Medline – One of the “major sources for biomedical literature”. Incorporates Index Medicus,
- ◆ Index to Dental Literature & International Nursing Index
- ◆ Embase – “A comprehensive index of world literature on human medicine & related disciplines”
- ◆ ISI- Science Citation Index – a “bibliographic database provided by the Institute for Scientific Information, covering scientific & technical information”
- ◆ Cochrane Collaboration – A database of Systematic Reviews, protocols of reviews in progress and research papers about the effects of healthcare interventions
- ◆ Indexed Conference Papers – A series of catalogues listing discussion topics for conferences given annually around the world (hand search)
- ◆ WHO International Agency for Research on Cancer Monographs (hand search)

(Quotes in “ “ taken from the DialogWeb Blue Papers, Cochrane information from the Cochrane website)

3.2.1 Search development for Medline and Embase

An initial review of ten recent papers reporting studies of occupational transmission of biological agents was carried out to obtain a list of potentially useful terms to include in the search. Also, general recent reviews of each of the listed agents were obtained to identify terms associated with each of the organisms.

The search terms were mapped onto the Medline database and the MeSH (Medical Subject Headings) terms, together with text words, were used to set up the strategy (see Appendix 1). Filters to identify meta-analyses, systematic reviews, randomised controlled trials, (all from Evidence Based Informatics Project, McMaster University, Hamilton, Ontario) prospective and retrospective studies (all from Weightman, A.L., Barker, J., Lancaster, J. Health Evidence Bulletin Wales Project Methodology 3, Cardiff. UWCM 2000 and adapted for this project) were included. Once the strategy showed success in the form of a high hit rate on the

Medline database it was transferred to the Embase database & the search continued. Because the two databases run through the same gateway (Ovid), and are similar in nature, the strategy needed no change or adaptation, and had a similarly high success rate in Embase.

The “NOT” search term was used extensively when combining search groups, eliminating duplicate searches and reducing the number of hits.

All saved entries were combined and imported onto a Reference Manager database.

3.2.2 Search development for science-citation index & Cochrane Collaboration

Because of the different nature of these databases – long strings of search terms cannot be entered as they can on the other databases – a method was devised whereby shorter groups of search terms were entered into the database search mechanism then combined with each other. The following terms were used:

- ◆ Occupational hazard
- ◆ Occupational diseases
- ◆ Name of pathogen

Other search terms used in this way included variations of “healthcare”, agricultural terms, occupational terms and variations on slaughterhouse and abattoir as mentioned in the original strategy. The search results were checked for duplications with the Medline and Embase searches and imported into the Reference Manager database.

3.2.3 Search development for indexed conference papers

A hand-search was undertaken of the printed catalogues of the Indexed Conference Proceedings that are published monthly. Search terms used included:

- ◆ Occupational diseases
- ◆ Biological agents
- ◆ Healthcare
- ◆ Bacteria
- ◆ Virus
- ◆ Parasite
- ◆ Hazard/hazardous

And other closely related terms as they appeared in the search. Any entries found were photocopied and collated for retrieval if necessary.

3.2.4 Exclusion criteria

It was decided to exclude papers that discussed the following:

- ◆ Vaccinations
- ◆ Workers being used as subjects for a study, i.e. military recruits
- ◆ Antibiotic resistance
- ◆ MRSA
- ◆ Sex workers and sexually transmitted diseases
- ◆ Guidance or studies on infection control methods or attitudes
- ◆ Patient to patient transmission or outbreaks of infection in healthcare
- ◆ Treatment studies

- ◆ Non-biological agents
- ◆ Gulf War Syndrome
- ◆ Papers discussing needlestick injuries. This is a well-documented area so review papers and papers discussing new developments only were selected.
- ◆ Language: only papers in English were retained.
- ◆ The USA and UK and other developed countries were given priority over developing or under-developed countries but these were also considered and did figure highly in specific areas of the search.

3.2.5 Inclusion criteria

All other papers published between 1970 to the present day were included. In case of uncertainty throughout the searching process, a paper was always selected for inclusion, to be excluded later, if necessary.

The reference details and abstracts (where available) of the relevant papers identified in all the databases were stored on a Reference Manager (Version 9) database (OCCUPATIONAL DATABASE). This database is available on CD-ROM as part of this report.

The occupational database was searched for papers relating to the specific biological agents listed in table X by entering the agents' name as a text word. Also, general terms (virus, bacteria, protozoan, and fungi) were used.

3.3 CHRONIC HEALTH EFFECTS SEARCH

3.3.1 Search development for Medline

There was insufficient time to apply this search in the Embase database.

An initial review of two or three review papers on each of the biological agents were selected to obtain a list of potentially useful terms to include in the search.

The search terms were mapped onto the Medline database and the MeSH (Medical Subject Headings) terms, together with text words, were used to set up the strategy (see Appendix 1).

The "NOT" search term was used extensively when combining search groups, eliminating duplicate searches and reducing the number of hits.

Filters to identify meta-analyses, systematic reviews, randomised controlled trails, (all from Evidence Based Informatics Project, McMaster University, Hamilton, Ontario) prospective and retrospective studies (all from Weightman, A.L., Barker, J., Lancaster, J. Health Evidence Bulletin Wales Project Methodology 3, Cardiff. UWCM 2000 and adapted for this project) were included.

Some postulated chronic health effects were common to all or several of the herpes virus family i.e. human herpes virus (all types including cytomegalovirus (type 5) and Epstein-Barr virus (type 4)), herpes simplex virus and varicella-zoster virus) and many papers examined an association with all of these in one study. Therefore, a combined search term, namely "herpes" was combined with all of the postulated health effects and the papers later assigned to the relevant herpes viruses.

All saved entries were combined and imported on to a Reference Manager database.

3.3.2 Science-Citation Index and Cochrane Collaboration

The following terms were used:

- ◆ Chronic effects
- ◆ Parasite
- ◆ Bacteria
- ◆ Virus

The search results were checked for duplications with the Medline and Embase searches and imported into the Reference Manager database.

3.3.3 Search development for indexed conference papers

A hand-search was undertaken of the printed catalogues of the Indexed Conference Proceedings that are published monthly. Search terms used included:

- ◆ Chronic effects
- ◆ Biological agents
- ◆ Bacteria
- ◆ Virus
- ◆ Parasite

And other closely related terms as they appeared in the search. Any entries found were photocopied and collated for retrieval if necessary.

3.3.4 Exclusion criteria

- ◆ Papers on treatment
- ◆ Papers on new laboratory techniques
- ◆ Studies on patients with HIV only
- ◆ Studies on transplant patients only

3.3.5 Inclusion criteria

All other papers published between 1970 to the present day were included. In case of uncertainty throughout the searching process, a paper was always selected for inclusion, to be excluded later if necessary.

The reference details and abstracts (where available) of the relevant papers identified in all the databases were stored on a Reference Manager (Version 9) database (OCCUPATIONAL DATABASE). This database is available on CD-ROM as part of this report.

3.4 COLLATION OF EVIDENCE

The final databases were checked for duplicates and the overlap between papers identified by the different sources recorded.

A summary of the evidence found for each postulated health effect (hierarchy of evidence) was compiled. Levels of evidence are given below.

- | | |
|---------|--|
| Level 1 | Decision by an expert panel/committee |
| Level 2 | Systematic literature review (with/without meta-analysis) including randomised controlled trials and prospective studies |

Level 2a	Randomised controlled trials
Level 2b	Prospective studies (cohort and follow-up studies)
Level 3	Retrospective studies (case control sequence based and seroprevalence studies)
Level 4	Descriptive epidemiological studies
Level 5	Mechanistic laboratory-based and animal studies
Level 6	Opinion articles with extensive (but not systematic) literature reviews
Level 7	Descriptions of case series
Level 8	Case reports and letters
Excluded	Paper not relevant to the association under investigation.

Papers were allocated to a particular level of evidence by one of two approaches.

Approach 1

Where the search identified less than 500 papers, the title and abstract (where available) of every paper was read the paper was allocated to one of the evidence categories listed above. For some of the older papers, no abstract was available and it was not possible to ascertain the level of evidence from the title alone. These papers were excluded. This approach was used for the following postulated health effects:

- ◆ Adenovirus and chronic pulmonary disease
- ◆ Adenovirus and obesity
- ◆ Adenovirus and myocarditis
- ◆ Adenovirus and celiac disease
- ◆ Adenovirus and cancer

Cytomegalovirus (Human herpes virus type 5) and coronary heart disease (atherosclerosis)
Cytomegalovirus and Guillain-Barre Syndrome.

- ◆ Epstein-Barr virus and coronary heart disease
- ◆ Epstein-Barr virus and chronic fatigue syndrome
- ◆ Epstein-Barr virus and Alzheimer's disease
- ◆ Epstein-Barr virus and multiple sclerosis

- ◆ Herpes simplex virus and coronary heart disease
- ◆ Herpes simplex virus and Alzheimer's disease
- ◆ Herpes simplex virus and Multiple sclerosis

- ◆ Human herpes virus types 4, 5 and 6 and multiple sclerosis
- ◆ Human herpes virus types 4, 5 and 6 and chronic fatigue syndrome
- ◆ Human herpes virus types 4, 5,6 and 8 and coronary heart disease

- ◆ Varicella zoster virus and multiple sclerosis

- ◆ Measles virus and Crohn's disease
- ◆ Measles virus and chronic anaemia

- ◆ Parvovirus and chronic anaemia

- ◆ Bartonella and endocarditis
- ◆ Bartonella and vasoproliferative disorders

- ◆ Coxiella and endocarditis
- ◆ Coxiella and neuropsychiatric disorders

- ◆ *Helicobacter pylori* and Crohn's disease
- ◆ *Helicobacter pylori* and coronary heart disease

- ◆ *Salmonella typhi* and biliary tree (gall bladder) cancer

Approach 2

Where the search identified more than 400 papers, search filters were applied to the search strategy to identify those papers reporting the highest levels of evidence, i.e. meta-analyses, randomised controlled trials (all from Evidence Based Informatics Project, McMaster University, Hamilton, Ontario) prospective and retrospective studies (all from Weightman, A.L., Barker, J., Lancaster, J. Health Evidence Bulletin Wales Project Methodology 3, Cardiff. UWCM 2000 and adapted for this project) (Appendix 1). This approach was used for the following postulated health effects:

- ◆ *Chlamydia pneumoniae/psittaci* and coronary heart disease
- ◆ *Chlamydia pneumoniae/psittaci* and asthma
- ◆ *Chlamydia pneumoniae/psittaci* and cerebral ataxia
- ◆ *Chlamydia pneumoniae/psittaci* and Guillain-Barre Syndrome

Where this approach failed to identify suitable references, the medline review filter was used. This approach was used for the following postulated health effects:

- ◆ Measles virus and MS (** used medline reviews*)

- ◆ Borrelia and chronic Lyme disease (several clinical presentations) (** used medline reviews*)

- ◆ Campylobacter and Guillain-Barre Syndrome (*used medline reviews, RCT filter etc*)

A summary of the published evidence for each postulated health effect was produced in the form of a table with an accompanying bibliography.

An association was judged to be established only where a level of evidence 1-2b was identified and appraised. A causal association has been established by an International Agency on Research into Cancer Monograph for the following (Level 1 evidence):

- ◆ *Epstein-Barr virus and lymphoma*
- ◆ *Hepatitis B and hepatocarcinoma*
- ◆ *Hepatitis C and hepatocarcinoma*
- ◆ *Hepatitis D and hepatocarcinoma*
- ◆ *Helicobacter pylori and gastric cancer*
- ◆ *Shistosoma haematobium and urinary bladder cancer*
- ◆ *Shistosoma mansoni and liver and colorectal cancer, giant follicular lymphoma*
- ◆ *Shistosoma japonicum and liver, colorectal and gastric cancer*

No further searches were conducted for these associations.

3.5 CRITICAL APPRAISAL OF PAPERS

3.5.1 Selection of papers for critical review

A maximum of 10-15 papers relating to each postulated health effect could be critically reviewed in the timescale. Papers at the highest level of evidence were reviewed first (i.e. reviews and prospective studies) followed by papers in the lower categories. Comprehensive (but not necessarily systematic) reviews were selected in preference to case series and retrospective studies. Reviews were considered to be systematic where the methods clearly reported which electronic databases had been included as well as the details of the search terms adopted.

In nearly all cases it was only possible to appraise a small proportion of the total literature available.

3.5.2 Document retrieval

Once selected, the full text articles for the chosen entries were obtained from a variety of sources:

- ◆ The British Library Document Supply Centre, at a cost of £3.80 per article
- ◆ The PHLs Library
- ◆ The Duthie Library (University of Wales College of Medicine) journals' collection

Copyright forms were signed and the papers, once received, were passed on (to Sharon Parry) for the appraisal stage.

3.5.3 Critical appraisal

Papers were reviewed using a data extraction sheet (Appendix 2) according to standard criteria. The conclusions of the paper were either accepted or rejected. Accepted papers were allocated to a level of evidence. Each section is concluded with the results of the critical appraisal together with a discussion of the available evidence in terms of the criteria for causation set out in the introduction.

3.5.4 References consulted for methodology and design of data extraction sheet and hierarchy of evidence

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Riegelman R K and Hirsch R P (1989) *Studying a study and testing a test. How to read the health science literature.* Little, Brown and Co. Boston

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The University of York. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness.*

Warren, K S (1981) *Coping with the biomedical literature.* Praeger, New York

4 GENERAL RESULTS

4.1 OCCUPATIONAL SEARCH

A total of 4124 references were identified on the occupational transmission of biological agents. The references are stored in a Reference Manager database which is available as part of this report as a CD ROM. The occupational transmission papers relevant to each biological agent are listed in the following chapters.

4.2 CHRONIC HEALTH EFFECTS SEARCH

In excess of 2000 papers were identified. The detailed search strategy and results for each chronic health effects search are in Appendix 1. A summary of the search results for each organism are presented in the following chapters.

No papers were identified for the following associations:

Leptospira and psychiatric disorders

5. ADENOVIRUS

5.1 DESCRIPTION

Adenovirus, particularly types 4, 7 and 21 are associated with acute respiratory disease. Respiratory adenoviral infection occurs worldwide, seasonally in temperate zones with greatest incidence in autumn and winter. The reservoir of infection is human and viruses are transmitted by oral contact or droplet spread or indirectly via fomites infected by respiratory discharges of infected individuals. Latent adenoid and tonsil infection can occur.

Adenovirus types 3, 4 and 7 are common causes of pharyngoconjunctival fever (PCF).

Viruses in faeces are transmitted via the faecal-oral route

5.2 OCCUPATIONAL RELEVANCE

There are published accounts of transmission of adenovirus in the occupational setting. Healthcare workers are considered to be at most risk. In particular, carers working with chronic care psychiatric patients (where there may be both crowding and poor hygienic behaviours), neonatal intensive care nurseries and anaesthetists performing emergency tracheal intubation are mentioned. Employees have been infected by individual patients and during hospital outbreaks.

5.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

- ◆ Coeliac disease
- ◆ Obesity
- ◆ Myocardial disease
- ◆ Carcinoma
- ◆ Lung disease
- ◆ Asthma

5.4 ADENOVIRUS AND COELIAC DISEASE

Table 2 Adenovirus and coeliac disease – medline search results summary

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	3	1 – 3
Randomised controlled trial ?		
Prospective studies		
Mechanism	6	4 – 9
Retrospective – case control – seroprevalence	6	10 – 15
Retrospective – case control – sequence	5	16 – 20
Case series		
Cross-sectional		
Case reports, letters, opinion		
Excluded (language, treatment, prognosis, transplant, HIV)		

5.4.1 Adenovirus and Coeliac Disease – science citation index search

No additional papers were found

5.4.2 Adenovirus and Coeliac Disease - summary of critical appraisal

The literature search identified a total of 20 papers examining the association between adenovirus and coeliac disease. The majority of the papers were mechanistic, animal studies or retrospective studies. The three reviews identified were critically appraised and are highlighted above.

The overall conclusion was that adenovirus may play a role in the pathogenesis of coeliac disease. However, there was insufficient evidence to be confident about the association.

None of the reviews were systematic in their approach. The evidence that they summarised was of limited quality. Although the studies were in agreement with each other and some studies did reach statistical significance, their sample sizes were small (only two subjects in one study). There was no information on whether possible confounders were taken into account.

One of the main issues was the lack of information on temporality which is needed to evaluate causation. The studies undertaken examined patients who already had coeliac disease and could therefore not distinguish whether the adenovirus infection preceded the coeliac disease or if patients were more prone to infection because they already had the illness.

To conclude the evidence linking adenovirus with Coeliac Disease is currently insufficient. There is a need for large prospective studies to be undertaken.

5.5 ADENOVIRUS AND OBESITY

Table 3 Adenovirus and obesity - medline search results summary

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews		
Randomised controlled trial		
Prospective studies		
Mechanism		
Retrospective – case control – seroprevalence		
Retrospective – case control – sequence		
Case series	1	1
Cross-sectional		
Case reports, letters, opinion		
Excluded (language, treatment, prognosis, transplant, HIV)		

5.5.1 Adenovirus and obesity – science citation index search

One additional paper was identified.

5.5.2 Adenovirus and obesity – summary of critical appraisal

The literature search identified only one paper examining the association between adenovirus and obesity. This study was a case series of 52 subjects attending an outpatient obesity program in India. The study found that ten subjects had antibodies to adenovirus and these had greater bodyweights than the other participants.

It is likely that the population attending the clinic will be severely obese and therefore unrepresentative of the general population. Although the results reached statistical significance the sample size was small. There was no control group in the study. No conclusions can be made about the association between adenovirus and obesity from this one study.

There is a need for more research on this topic before any conclusions can be made about the relationship between adenovirus and obesity.

5.6 ADENOVIRUS AND MYOCARDIAL DISEASE

Table 4 Adenovirus and Myocardial disease - medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	2	1 - 2
Randomised controlled trial		
Prospective studies		
Mechanism	2	3 - 4
Retrospective – case control – seroprevalence		
Retrospective – case control – sequence	5	5 - 9
Case series		
Cross-sectional		
Case reports, letters, opinion	2	10 – 11
Excluded (language, treatment, prognosis, transplant, HIV)		

5.6.1 Adenovirus and Myocardial Disease – science citation index search

Two additional papers identified.

5.6.2 Adenovirus and Myocardial Disease - summary of critical appraisal

Papers reviewed 1,2

The literature search identified a total of 11 papers examining the association between adenovirus and myocarditis. The majority of the papers were mechanistic, retrospective or cases reports and letters. The two reviews identified were critically appraised and are highlighted above.

Neither of the reviews were systematic in approach and one of them only reviewed studies published in 1997. The reviews did not provide much details on the studies that they discussed so evaluation of the studies was difficult.

Their overall conclusion was that adenoviruses may be etiological agents of myocarditis. Supporting this theory was the fact that an adenovirus receptor was discovered in the myocardium and there was a relationship between infection of the myocardium by adenovirus and the onset of apoptosis.

The studies reviewed were mechanistic/ animal studies which had small sample sizes. There were no confounders taken into account. One of the reviews discussed that it was possible that the apoptosis seen with adenovirus infection could be a natural defence mechanism of the host against the virus and not be related to myocarditis.

To conclude the evidence linking adenovirus with myocarditis is currently insufficient. There is a need for large prospective, clinically relevant studies to be undertaken which can explore the association postulated by the mechanistic studies.

5.7 ADENOVIRUS AND CARCINOMA

Table 5 Adenovirus and Carcinoma - medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	12	1 - 12
Randomised controlled trial ?		
Prospective studies		
Mechanism	18	13 - 30
Retrospective – case control – seroprevalence	1	31
Retrospective – case control – sequence	3	32 – 34
Case series	1	35
Cross-sectional		
Case reports, letters, opinion	4	36 - 39
Excluded (language, treatment, prognosis, transplant, HIV)		

5.7.1 Adenovirus and Carcinoma – science citation index search

One additional paper was identified.

5.7.2 Adenovirus and Carcinoma – summary of critical appraisal

Papers reviewed 1-12

The literature search identified a total of 39 papers examining the association between adenovirus and carcinoma. The majority of the papers were mechanistic studies. The twelve reviews identified were critically appraised and are highlighted above.

None of the reviews were systematic in approach and mostly reviewed mechanistic/animal studies. The overall conclusion was that although some adenoviruses have shown potential for malignancy in animal experiments there is no reliable data to show that they participate in human cancers.

The reviews reported limited information on the studies that they discussed and therefore it was difficult to evaluate them. Possible confounders were not taken into account and there was limited information on numbers in the studies and any statistical analysis undertaken. In the one review that discussed human studies there was no information on how the cases were selected and there was no control group studied.

In conclusion the evidence available to date exploring the association of adenovirus and carcinogenesis is limited to mechanistic studies which although outline hypotheses, do not provide convincing evidence. For more conclusive information of the causal role of adenoviruses in humans, large prospective studies are required.

5.8 Adenovirus and lung disease

Table 6 Adenovirus and Lung Disease - medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	4	1 – 4
Randomised controlled trial ?		
Prospective studies	1	5
Mechanism	2	6 - 7
Retrospective – case control – seroprevalence	2	8 – 9
Retrospective – case control – sequence	1	10
Case series		
Prevalence	1	11
Case reports, letters, opinion	2	12-13
Excluded (language, treatment, Prognosis, transplant, HIV)		

5.8.1 Adenovirus and Lung disease – science citation index results

No additional papers were identified

5.8.2 Adenovirus and Lung disease – summary of critical appraisal

Papers reviewed 1,3,4

The literature search identified a total of 13 papers examining the association between adenovirus and lung disease. The three reviews that were identified were critically appraised and highlighted above.

None of the reviews were systematic in their approach and each considered a very specific aspect of the association. The studies discussed ranged from animal mechanistic experiments to clinical scenarios but there was limited information available on the details of the studies. One of the studies discussed how animal experimentally induced bronchiolitis in newborn animals stimulated emphysema in the mature animals and that follow-up studies of patients with bronchiolitis, during infancy, reveal persistence of both structural and functional abnormalities in later life. However one of the other reviews found a high rate of isolation of adenovirus from normal control children. The third review postulated that latent adenoviral infection resulted in amplification of cigarette smoke-induced lung inflammation.

In conclusion there is not enough evidence available with which to be confident of the relationship between adenovirus infection and lung disease. More research in this area is required.

5.9 ADENOVIRUS AND ASTHMA

Table 7 Adenovirus and Asthma - medline search results summary

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	2	1 – 2
Randomised controlled trial ?		
Prospective studies	1	3
Mechanism		
Retrospective – case control – seroprevalence	2	4,5
Retrospective – case control – sequence	2	6,7
Case series		
Cross-sectional		
Case reports, letters, opinion	2	8, 9
Excluded (language, treatment, prognosis, transplant, HIV)		

5.9.1 Adenovirus and asthma – science citation index search

Four additional papers identified.

5.9.2 Adenovirus and asthma – summary of critical appraisal

Papers reviewed 1,2

The literature search identified a total of nine papers examining the association between adenovirus and asthma. The two reviews identified were critically appraised and are highlighted above. There was a lot of overlap with asthma and chronic obstructive pulmonary disease (COPD) and one of the reviews discussed both diseases.

The overall conclusion was that adenoviruses persist as latent infection in the airways of patients with COPD and they are capable of amplifying host genes involved with lung inflammation. The other review discussed how adenovirus could prompt anaphylactic shock in preconditioned mice.

Both of these reviews report preliminary studies and neither are convincing. There was little information provided on the studies in terms of selection, confounders, sample size and statistical analysis. There is also a question about temporal association. Does adenovirus cause asthma or are people with asthma more likely to have adenovirus infections?

In conclusion the evidence to data linking adenovirus and asthma is sparse and more high quality studies need to be undertaken before any conclusions can be drawn.

Other postulated health effects identified in papers found in search combining chronic disease and adenovirus:

Sinusitis

Chronic human adenovirus pneumonia

Chronic fatigue syndrome

Dermatitis herpetiformis

6 CYTOMEGALOVIRUS

6.1 DESCRIPTION

Human (beta) herpesvirus 5, commonly referred to as human cytomegalovirus, is a member of the subfamily Betaherpesvirus of the family Herpesviridae. Severe generalised infection can occur *in utero* but when the virus is acquired later in life it can present as a mononucleosis or as a subclinical infection. It occurs worldwide. The reservoir of infection is humans and the virus is transmitted by contact with infectious tissues. Large numbers of children in day-care centres excrete the virus.

6.2 OCCUPATIONAL RELEVANCE

There are published accounts of transmission of cytomegalovirus in the occupational setting. Healthcare workers and child care workers are mentioned in particular. Follow-up studies in child care centres have been conducted to estimate seroconversion rates among staff. Rates are believed to range between 0 – 22% by 12 months. Seroconversion among staff tends to parallel rates of cytomegalovirus excretion in the children. There is some evidence that fomites contaminated with infected urine or saliva play a role in transmission. Healthcare workers in paediatric departments appear to be more at risk than other healthcare workers.

6.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Guillain-Barre syndrome
Coronary heart disease
Chronic fatigue syndrome
General chronic disease

6.4 CYTOMEGALOVIRUS AND GUILLEIN-BARRE SYNDROME

Table 8 Cytomegalovirus and Guillain-Barre Syndrome - medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	5	(1) – (5)
Prospective studies	1	(6)
Surveillance	1	(7)
Retrospective	9	(8-16)
Mechanism	9	(17 – 25)
Case series	6	(26 – 31)
Case reports, letters, opinion	23	(32 – 54)
Excluded (language, treatment, prognosis, transplant, HIV)	40	

* Papers in bold were critically appraised

6.4.1 Cytomegalovirus and Guillain-Barre Syndrome – science citation index search

Four additional papers identified.

6.4.2 Cytomegalovirus and Guillain-Barre Syndrome – summary of critical appraisal

References reviewed: 1,2,4,6,7,8,9,10,17,18,22,23,24,25,26,29

The literature search identified a total of 54 papers examining the association between Cytomegalovirus and Guillain-Barre Syndrome. There was a full complement of types of papers on the topic. The highlighted papers above were critically appraised

None of the three review papers were systematic in their approach. Overall the opinion was that cytomegalovirus may be associated with Guillain-Barre Syndrome as it occurred as an antecedent events in 5-15% of patients. However, the studies this conclusion was based on were mostly case series and no control group was present. Therefore we do not know the prevalence of cytomegalovirus in the community of people without Guillain-Barre Syndrome. In addition the studies reported had small sample sizes, there was no information on statistical analysis and no confounders were taken into account. Another problem was that there was no information on how the cases were selected and the criteria for inclusion as a case.

Of the seven retrospective case control studies reviewed three found that previous cytomegalovirus occurred more frequently in cases compared to controls. There was also the suggestion that previous cytomegalovirus infection was associated with more severe cases of Guillain-Barre. Two of the studies had a control group matched for age and sex while the others provided little information on demographics of the control group. Some confounders were taken into account. Overall the numbers of cytomegalovirus were very small. For example, only four cases and controls in one study. However, statistical significance was reached in another study. Two of the studies did not find an increased rate of cytomegalovirus infection in cases with Guillain-Barre Syndrome. In general there was little information on how cases and controls were selected and the criteria on which they were included. One of the studies identified did not discuss cytomegalovirus infection but instead considered IgA-cardiolipin antibodies.

Two case series were reviewed in detail. One study found serologic evidence for cytomegalovirus infection more frequently in severely affected patients with Guillain-Barre Syndrome, compared to mildly affected patients. However the results did not reach statistical significance. The other case series determined that patients with cytomegalovirus-associated Guillain-Barre syndrome had a different clinical pattern compared to *Campylobacter jejuni* infection-related Guillain-Barre Syndrome and that of Guillain-Barre syndrome patients without previous infection. The cytomegalovirus group initially had more severe symptoms with respiratory insufficiency and often developed cranial nerve involvement and severe sensory loss. The study had a small sample size and no confounders were taken into account.

Three mechanistic studies were reviewed. One of the studies suggested that antiganglioside antibodies can be induced through molecular mimicry in cytomegalovirus infected Guillain-Barre patients. Another of the studies found that they could not elicit a response with sequence homologies involved with cytomegalovirus. The third study's findings were not accepted as the technique used was poor.

In summary, there is some suggestion that cytomegalovirus may be associated with Guillain-Barre Syndrome, or predispose to a more severe form of the disease. However, no causal link or temporal association has been established and the studies to date have had small sample

sizes and have not adjusted for possible confounders. There is a need for large prospective studies to provide further unequivocal evidence.

6.5 CYTOMEGALOVIRUS AND CORONARY HEART DISEASE

Table 9 Cytomegalovirus and Coronary Heart Disease - medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	25	1 – 29
Randomised controlled trial ?	1	30
Prospective studies	5	31 – 38
Mechanism	13	39 – 53
Retrospective – case control – seroprevalence	5	54 – 60
Retrospective – case control – sequence	7	61 - 67
Case series	4	68 - 71
Cross-sectional	2	72-74
Case reports, letters, opinion	22	75 - 96
Excluded (language, treatment, Prognosis, transplant, HIV)	42	

Table 10 Cytomegalovirus and Coronary Heart Disease - additional papers from herpes medline search

Medline search results summary

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	8	1 - 8
Randomised controlled trial ?	0	
Prospective studies	3	9 – 11
Mechanism	4	12 -15
Retrospective – case control – seroprevalence	4	16 – 19
Retrospective – case control – sequence	0	
Case series	0	
Cross-sectional	0	
Case reports, letters, opinion	6	20 – 25
Excluded (language, treatment, Prognosis, transplant, HIV)		

6.5.1 Cytomegalovirus and Coronary Heart Disease – science citation index search

Twenty nine additional papers identified.

6.5.2 Cytomegalovirus and Coronary Heart Disease – summary of critical appraisal

References reviewed: 2,3,5,6,30,31,32,33,35,40,55,56,57,63,65,69,72,73,

The literature search identified a total of 96 papers examining the association between Cytomegalovirus and Coronary Heart Disease (CHD). There was a full complement of types of papers on the topic. The highlighted papers above were critically appraised.

None of the five review papers evaluated were systematic in their approach. In summary there is a biological plausibility for the association as a similar herpesvirus to CMV (Marek's disease virus) has been shown to cause atherosclerotic lesions in chickens. Additional biological evidence comes from the fact that cytomegalovirus persists lifelong in the body and can be reactivated from a latent state. However, the epidemiological evidence is not strong. The reviews discussed studies which were of limited power and in general did not control for possible confounders. Also the populations studied mostly comprised those patient who already had CHD or heart disease, secondary to other pathologies. As there is a large prevalence of cytomegalovirus seroconversion in the community (approx 70%), the studies required to discuss this issue need to be large and this was not the case. In addition there was a lot of *post hoc* analysis reported with the conclusions drawn from populations not initially selected to investigate the issue.

Four prospective studies were reviewed in detail. Two of the studies found evidence of the association between CHD and cytomegalovirus and the other two disagreed with this conclusion. One of the studies concluded that high levels of cytomegalovirus virus were associated with incident CHD. However this was a *post hoc* analysis and the relative risk was small and did not reach statistical significance, although there was a dose response. The authors did take some confounders into account. However, some important potential confounders such as medication and family history of CHD were not adjusted for. In the other study there was a question concerning the representativeness of the participants who were selected because, although the starting population was large, the paper only described 150 cases and controls. The other two prospective studies did not support the hypothesis and found the distribution of antibodies to cytomegalovirus similar in both cases and controls. One of the studies only included men and the other study found a very high prevalence of cytomegalovirus seroconversion of 85% which would have limited the power of the study.

The one mechanistic study reviewed postulated that cytomegalovirus may act synergistically with *Chlamydia pneumoniae* to cause atherosclerosis. However, how applicable this is clinically is not known.

Of the four retrospective studies reviewed two supported the hypothesis and two did not. The two case series reviewed did not support the hypothesis. Of the two cross sectional studies reported, one supported the hypothesis and one did not. These studies were subject to similar shortfalls to those discussed above, being limited in power and based on post-hoc analysis.

In conclusion, there is a suggestion that there is a hypothetical link between CMV and CHD. However, no causal link has been established and more high quality prospective studies are required.

6.6 CYTOMEGALOVIRUS AND CHRONIC FATIGUE SYNDROME

Table 11 Cytomegalovirus and Chronic Fatigue Syndrome – medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	0	
Randomised controlled trial	1	1
Prospective studies	0	
Mechanism	0	
Retrospective – case control – seroprevalence	2	2 – 3
Retrospective – case control – PCR	2	4 – 5
Case series		
Cross-sectional		
Case reports, letters, opinion	5	6 – 10
Excluded (language, treatment, prognosis, transplant, HIV)		

6.6.1 Cytomegalovirus and Chronic Fatigue Syndrome – science citation index search

No additional papers found.

6.6.2 Cytomegalovirus and Chronic Fatigue Syndrome – summary of critical appraisal

See review for Human herpes virus and chronic fatigue syndrome.

6.7 CYTOMEGALOVIRUS AND GENERAL CHRONIC DISEASE

Table 12 Cytomegalovirus and General Chronic Disease – medline search

Medline search results summary

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	15	1 – 15
Randomised controlled trial	0	
Prospective studies	0	
Mechanism	36	16 – 51
Retrospective – case control – seroprevalence	1	52
Prevalence	1	53
Case series	0	
Cross-sectional	1	
Case reports, letters, opinion	13	54-66
Excluded (language, treatment, Prognosis, transplant, HIV)		

Other postulated health effects investigated in cytomegalovirus papers:

<i>Health effect</i>	<i>Reference number</i>
Kaposi sarcoma	89
Hemimegalencephaly	68
Chronic meningoencephalitis	67
Chronic encephalitis	69
Polymyalgia rheumatica	68
Chronic fatigue syndrome	70, 63
Rasmussens encephalitis	71, 79
Oral mucosal ulcers	72
Schizophrenia	73
Ulcerative colitis	74
Sjogrens syndrome	85
Paletine tonsil carcinoma	80
Placental chronic villitis	75
Chronic mononucleosis	76
Childhood epilepsy	77
Testicular cancer	78
Prostate cancer	88
Chronic erosive gastritis	86
Chronic inflammatory demyelinating Polyradiculoneuropathy	81
Type 1 diabetes	82
Cold urticaria	83
Chronic hematospermia	84
Chronic liver disease	90
Chronic gastrointestinal dysmotility	87

7 HUMAN HERPES VIRUS

7.1 DESCRIPTION

Human herpesvirus 6 and 7 belong to the subfamily betaherpesvirus. HHV 6 causes exanthema subitum (an acute febrile rash illness) in children as well as subclinical and latent infection. It occurs worldwide, in the UK 65-100% seroprevalence is attained by age 2 years. The reservoir of infection is humans and it is transmitted via salivary contact.

7.2 OCCUPATIONAL RELEVANCE

There is very limited published information on transmission of human herpes virus in the occupational setting. One seroprevalence study failed demonstrate an occupational risk of infection in dentists.

7.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Chronic fatigue syndrome
Coronary heart disease
Multiple sclerosis
Kaposi's Sarcoma

7.4 HUMAN HERPES VIRUS AND CHRONIC FATIGUE SYNDROME

Table 13 Human Herpes Virus (6,7,8) and Chronic Fatigue Syndrome
– medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	18	1 – 18
Randomised controlled trial	1	19
Prospective studies	0	
Mechanism	2	20 - 21
Retrospective – case control – seroprevalence	14	22 – 35
Retrospective PCR	1	36
Case series	1	37
Cross-sectional	0	
Case reports, letters, opinion	20	38 – 57
Excluded (language, treatment, Prognosis, transplant, HIV)		
Other biological agents identified in this serach with studies in CFS are:		
Herpes simplex virus (58 and 59)		
HTLV (60)		
Enteroviruses (59 and 61)		

7.4.1 Human Herpes Virus (6,7,8) and Chronic Fatigue Syndrome – science citation index search

Seven additional papers identified.

7.4.2 Human Herpes Virus (6,7,8) and Chronic Fatigue Syndrome – summary of critical appraisal

61 relevant papers were identified and four reviews were critically appraised. Braun et al (1997) (3) present a comprehensive and critical general review of Human herpes virus 6. A section on the association with chronic fatigue syndrome is included. Several important points are made. First, chronic fatigue syndrome comprises a number of different symptoms and some researchers believe that it is a group of heterogeneous disorders rather than a single disease. Secondly, although several seroprevalence studies have been reported, they have conflicting results. PCR tests on peripheral blood mononuclear cells (PBMC) suggest that CFS patients have atypical responses to HHV 6 infection which are consistent with reactivation of latent infection due to immune dysregulation. However, this certainly does not prove causation.

A second review of the general evidence for an infectious etiology for CFS (9) considers epidemiological and immunological evidence and again concludes that a causal relationship is far from proved. The review calls for well-designed studies with clear case definitions and appropriate control groups. Longitudinal studies of well-defined patients are also needed to determine whether immune abnormalities are due to exacerbation of the disease.

Two further reviews, (11) (24) , also conclude that a causal relationship has not been demonstrated.

To conclude, establishing a causal relationship between HHV 6 and CFS is hindered by (a) the heterogeneity of the disease (b) the almost universal exposure of the population to this virus and (c) the lack of a clear pathogenic mechanism for the disease. Research in this area is still in its infancy and future research will need to concentrate on clearly defined cases of the disease.

7.5 HUMAN HERPES VIRUS TYPE 8 AND CORONARY HEART DISEASE

See Cytomegalovirus and coronary heart disease

7.6 HUMAN HERPES VIRUS AND MULTIPLE SCLEROSIS

Table 14 Human Herpes Virus and Multiple Sclerosis – medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	23	1 – 23
Randomised controlled trial	2	24,25
Prospective studies		
Mechanism	24	25 – 48
Retrospective seroprevalence	13	49 – 61
PCR	16	62- 77
Case series		
Cross-sectional		
Case reports, letters, opinion		
Excluded (language, treatment, Prognosis, transplant, HIV)		

7.6.1 Human Herpes Virus and Multiple Sclerosis – science citation index search

6 additional papers identified

7.6.2 Human Herpes Virus and Multiple Sclerosis – summary of critical appraisal

Circumstantial evidence suggests a role for human herpes virus in MS. These include the life-long latency and reactivation of the virus, CNS complications of the acute disease. However, a recent comprehensive review concluded that the association of HHV-6 with MS remains controversial and that a more extensive understanding of the HHV-6 neurotropism is required.(1). Similar conclusions were drawn by four further reviews (2,5,8,11).

7.7 HUMAN HERPES VIRUS 8 AND KAPOSI'S SARCOMA

7.7.1 Human Herpes Virus 8 and Kaposi's Sarcoma – IARC search

- 1 WHO International Agency for Research on Cancer. (1997) IARC Monographs on the evaluation of carcinogenic risks to humans. Epstein-Barr Virus and Kaposi's Sarcoma Herpesvirus/Human Herpesvirus 8. Vol 70 (last updated 14/04/99)

7.7.2 Human Herpes Virus 8 and Kaposi's Sarcoma – summary of critical appraisal

IARC summary of data reported and evaluation concluded that there is compelling but as yet limited evidence for a role of HHV8 in the causation of Kaposi's sarcoma. The overall evaluation is that HHV8 is probably carcinogenic to humans (1).

Human herpes and coronary heart disease

2 papers identified

8 EPSTEIN BARR VIRUS

8.1 DESCRIPTION

Human (gamma) herpesvirus 4, commonly referred to as Epstein Barr virus, causes an acute viral syndrome called infectious mononucleosis as well as giving rise, on occasions to an asymptomatic infection. It occurs worldwide but in developed countries infectious mononucleosis is most common in older children and young adults. The reservoir of infection is humans and it is transmitted by the oropharyngeal route via saliva.

8.2 OCCUPATIONAL RELEVANCE

There is limited published information on transmission of Epstein Barr Virus in the occupational setting. There is some evidence of occupational risk for dentists. Further research has suggested that population groups exposed to some chemical pollutants (xenobiotics) have exacerbation of latent Epstein Barr Virus infection.

8.3 POSTULATED HEALTH EFFECTS EXAMINED

Coronary heart disease
Chronic fatigue syndrome
Multiple sclerosis
Burkitt's lymphoma
Non-hodgkins lymphomas
Nasopharyngeal carcinoma and other tumours

8.4 EPSTEIN BARR VIRUS AND CORONARY HEART DISEASE

See Cytomegalovirus and coronary heart disease

8.5 EPSTEIN BARR VIRUS AND CHRONIC FATIGUE SYNDROME

Table 15 Epstein Barr Virus and Chronic Fatigue Syndrome – medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	10	1 – 10
Randomised controlled trial	1	11
Prospective studies	1	12
Mechanism	1	13
Retrospective – case control – seroprevalence	15	14 – 28
Retrospective – case control – PCR	2	31 – 32
Follow up	4	30, 33 – 35
Case series	1	36
Case reports, letters, opinion	4	37 - 40
Excluded (language, treatment, prognosis, transplant, HIV)		

8.5.1 Epstein Barr Virus and Chronic Fatigue Syndrome – science citation index search

No additional papers found.

8.5.2 Epstein Barr Virus and Chronic Fatigue Syndrome – summary of critical appraisal

38 relevant papers were identified and four reviews were critically appraised. The first review of the general evidence for an infectious aetiology for CFS (8) considers epidemiological and immunological evidence and again concludes that a causal relationship is far from proved. The review calls for well-designed studies with clear case definitions and appropriate control groups. Longitudinal studies of well-defined patients are also needed to determine whether immune abnormalities are due to exacerbation of the disease.

Two further reviews, (9) (10) , conclude that a causal relationship has not been demonstrated.

To conclude, establishing a causal relationship between EBV and CFS is hindered by (a) the heterogeneity of the disease (b) the almost universal exposure of the population to this virus and (c) the lack of a clear pathogenic mechanism for the disease. Research in this area is still in its infancy and future research will need to concentrate on clearly defined cases of the disease.

8.6 EPSTEIN BARR VIRUS AND MULTIPLE SCLEROSIS

Table 16 Epstein Barr Virus and Multiple Sclerosis - medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	7	1 – 7
Randomised controlled trial		
Prospective studies	2	8,9
Mechanism	4	10 – 13
Retrospective seroprevalence	17	14 – 30
PCR	10	31 - 40
Case control	1	41
PCR		
Cross-sectional		
Case reports, letters, opinion	5	42 - 46
Excluded (language, treatment, prognosis, transplant, HIV)		

8.6.1 Epstein Barr Virus and Multiple Sclerosis – science citation index summary

No additional papers found

8.6.2 Epstein Barr Virus and Multiple Sclerosis – summary of critical appraisal

Two reviews were critically appraised (1,2). Neither were systematic nor based on reported literature search strategies but were comprehensive and critical. Similar arguments are presented in both. EBV persists in a latent form in peripheral B-cells as episomes. EBV can be reactivated when the host's defences are impaired and the latency/reactivation pattern of disease mimics multiple sclerosis. Seroprevalence studies are appraised in the reviews which come to the conclusion that all MS patients are seropositive for EBV compared to around 85% of controls. Also, in prospective studies, subjects who developed late EBV infection (post puberty) were significantly more likely to develop MS. Epidemiological studies of migration to and from areas of high MS prevalence further support a role for an infectious aetiology. However, there is, as yet, no definitive evidence of a causal role for EBV alone or in combination with other infectious agents e.g. rotavirus. Ferrante et al (35) found EBV in peripheral blood mononuclear cells in 6/14 MS patients on the first day of the acute attack. This was the most frequently detected viral DNA indicating that EBV may be involved in the induction of relapses (35). (34) Whereas, a study published in the same year (1997) did not detect EBV DNA in cerebrospinal fluid (CSF) and serum samples from 26 MS patients using

a sensitive nested PCR on patients at varying stages of disease. The authors stress that this does not, however, rule out a lesion-associated low grade herpesvirus infection.

8.7 EPSTEIN BARR VIRUS AND BURKITT'S LYMPHOMA, NON-HODGKINS LYMPHOMAS, NASOPHARYNGEAL CARCINOMA AND OTHER TUMOURS

8.7.1 Epstein Barr Virus and Tumours - IARC search

- 1 WHO International Agency for Research on Cancer. (1997) IARC Monographs on the Evaluation of Carcinogenic risks to humans. Epstein-Barr Virus and Kaposi's sarcoma Herpesvirus/Herpesvirus 8. Vol 70 (last updated 14/04/99)

8.7.2 Epstein Barr Virus and Tumours – summary of critical appraisal

IARC summary of data reported and evaluation concluded that there is sufficient evidence for carcinogenicity of EBV in the causation of Burkitt's lymphoma, sinonasal angiocentric T-cell lymphoma, immunosuppression-related lymphoma, Hodgkin's disease and nasopharyngeal carcinoma. The overall evaluation is that chronic infection with EBV is carcinogenic to humans.(1)

9 HERPES SIMPLEX VIRUS

9.1 DESCRIPTION

Herpes simplex virus types 1 and 2 are members of the virus family Herpesviridae, subfamily alphaherpesviridae. They cause local primary lesions and tend to persist as latent infections which can recur. HSV 1, typically, causes cold sores (and herpetic whitlow on the hands of healthcare workers) whilst HSV 2, typically, causes genital herpes. They both occur worldwide. A seroprevalence for HSV 1 of up to 90% in adults is recorded whilst HSV 2 infection occurs with sexual activity and therefore appears later in life. The reservoir of infection is humans. HSV 1 is predominantly spread via saliva, HSV 2 predominantly via sexual contact.

9.2 OCCUPATIONAL RELEVANCE

There are published accounts of transmission of herpes simplex virus in the occupational setting. Herpetic whitlow is a well-documented occupational hazard of medical personnel. Cases of primary herpetic gingivostomatitis (presenting as sore throat and fever) have also been reported in paediatric healthcare workers.

9.3 POSTULATED HEALTH EFFECTS EXAMINED

Alzheimer's disease
Coronary heart disease
Multiple sclerosis

9.4 HERPES SIMPLEX VIRUS AND ALZHEIMER'S DISEASE

Table 17 Herpes Simplex Virus and Alzheimer's Disease – medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	9	1 – 9
Randomised controlled trial		
Prospective studies		
Mechanism	9	10 – 18
Retrospective seroprevalence	2	19 - 20
PCR	11	21 - 31
Case series		
Case reports, letters, opinion	21	32 - 52
Excluded (language, treatment, prognosis, transplant, HIV)		
Parkinsonis (53)		

9.4.1 Herpes Simplex Virus and Alzheimer's Disease – science citation index search

Two additional papers identified.

9.4.2 Herpes Simplex Virus and Alzheimer's Disease – summary of critical appraisal

Dobson and Itzhaki (1999) (2) present a comprehensive and critical review of the current evidence linking Herpes simplex virus type 1 and Alzheimer's disease. Case-control and mechanistic studies are included although the review is not systematic nor based on a reported literature search strategy. It has been established that there is a genetically-based susceptibility for late-onset cases of Alzheimer's disease. However, there is still a convincing argument for environmental factors e.g. Herpes simplex virus influencing the timing of, or the rate of development of, the disease. Several areas of research are presented to support this argument.

Firstly, the association is biologically plausible. The majority of the adult population harbour the virus in a latent state in the peripheral nervous system. It can re-activate in the form of cold sores. Also, viruses are known to cause neurological diseases.

Secondly, carefully controlled sequence-based studies (PCR) (with measures to prevent cross-contamination) have detected viral DNA in brains of cases and controls. The failure of other studies to detect viral DNA is explained by limitations of sensitivity of the methods used. This establishes that HSV is present in a latent form in both elderly cases of AD and elderly controls. Furthermore, viral DNA is most often located in those regions of the brain most affected by AD, i.e. the temporal and frontal cortices.

Thirdly, the difference between cases and controls only emerges when the genotype of the host is taken into account. Neither HSV nor the implicated gene alone were a risk factor for AD but together, they are associated with a twelvefold increase in risk of developing the disease. This association is also found by studies of this genotype, HSV and cold sore development.

Temporality of the association is also explained. Firstly, infection with the virus certainly occurs prior to AD as the majority of the population are infected by the time they reach adulthood but AD develops mainly in the elderly. Also, AD patients cannot be more susceptible to HSV infection of the brain because viral DNA is also found in so many controls. Finally, it is unlikely that the susceptible genotype are more likely to harbour HSV because 90% of adults carry the virus whereas only 25-30% of the general population carry the susceptibility gene.

Two final areas of study are considered. The exact mechanism through which the two risk factors cause AD has not yet been discovered. Furthermore, clinical trials of antiviral therapy have not been carried out.

Despite these omissions, the authors conclude that HSV 1 is a strong risk factor for AD in genetically susceptible individuals. In their opinion, this association has now been "quietly accepted" by the scientific community.

9.5 HERPES SIMPLEX VIRUS AND CORONARY HEART DISEASE

Table 18 Herpes Simplex Virus and Coronary Heart Disease – medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	8	1 – 8
Randomised controlled trial	0	
Prospective studies	4	9 – 12
Mechanism	1	13
Retrospective – case control – seroprevalence	0	
Prevalence	0	
Case series	1	14
Cross-sectional	0	
Case reports, letters, opinion	1	15
Excluded (language, treatment, Prognosis, transplant, HIV)		

9.5.1 Herpes Simplex Virus and Coronary Heart Disease - science citation index search

Five additional papers found

9.5.2 Herpes Simplex Virus and Coronary Heart Disease – summary of critical appraisal

Leinonen and Saikku (2) present a review critically appraising the evidence linking Herpes simplex virus (and other infections) and coronary heart disease although very few studies relating to HSV are cited. The review states that there is limited serological evidence of HSV in human coronary heart disease. Furthermore, HSV have been found in atherosclerotic lesions (plaques). However, it is well known that herpes viruses can be found in healthy tissue and that the viral genome frequently integrates into human cells. The relevance of its presence in atherosclerotic lesions is therefore questionable.

A second review (1) cites three studies (two prospective and one retrospective) which have failed to show an association between HSV seropositivity and coronary heart disease and overall presents an unconvincing picture of a causal association. An association is, however, biological plausible as HSV-1 can infect human endothelial cells, enhance thrombosis and platelet binding and cause generation and release of tissue factors.

One prospective (nested cohort) (9) study of subjects 45-64 years was reviewed. Whilst most major confounders were controlled for some, e.g. family history of heart disease, were not. No association with HSV seroconversion was found on five-year follow-up.

Current evidence does not suggest a link between HSV and coronary heart disease.

9.6 HERPES SIMPLEX VIRUS AND MULTIPLE SCLEROSIS

Table 19 Herpes Simplex Virus and Multiple Sclerosis – medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	1	1
Randomised controlled trial		
Prospective studies		
Mechanism	15	2 – 16
Retrospective seroprevalence	19	17 – 35
PCR	11	36 – 46
Immuno-histo	3	47 – 49
PCR		
Cross-sectional		
Case reports, letters, opinion		
Excluded (language, treatment, Prognosis, transplant, HIV)		

MS and retrovirus = 50 - 58

MS and HTLV 59 – 60

MS and Canine distemper virus: 61 – 62

MS and Newcastle disease virus 62 - 64

9.6.1 Herpes Simplex Virus and Multiple Sclerosis – science citation index search

No additional papers found

9.6.2 Herpes Simplex Virus and Multiple Sclerosis – summary of critical appraisal

The hypothesis that MS is caused by HSV 2 in persons lacking HSV-1 immunity was proposed in 1981. This was based on information relating to the age of onset, geographic distribution, migration patterns and socio-economic characteristics of patients (1). (Myhr et al (1998) (17) report a retrospective seroprevalence study where cases of MS had a similar prevalence of antibodies to herpes simplex virus to age and sex matched controls. Ferrante et al (41) found HSV-1 and HSV-2 DNA in peripheral blood mononuclear cells in 4/14 MS patients on the first day of the acute attack although they were not detected as often as EBV. (39) However, a study published in 1997) did not detect HSV1 nor HSV-2 DNA in cerebrospinal fluid (CSF) and serum samples from 26 MS patients using a sensitive nested PCR on patients at varying stages of disease. The authors stress that this does not, however, rule out a lesion-associated low grade herpesvirus infection. Ultimately this question will only be resolved by prospective studies.

10 VARICELLA ZOSTER VIRUS

10.1 DESCRIPTION

The human (alpha) herpesvirus 3, commonly referred to as varicella zoster or herpes zoster virus is a member of the herpesvirus group. It causes an acute disease (chickenpox), remains latent in the dorsal root ganglia and can reactivate as herpes zoster (shingles) later in life. It occurs worldwide. In temperate zones, at least 90% of the population has suffered chickenpox by age 15 years. The reservoir of infection is humans and it is transmitted via droplet or airborne spread of vesicle fluid or by respiratory secretions.

10.2 OCCUPATIONAL RELEVANCE

Varicella zoster is primarily a disease of childhood and most adults will have seroconverted before they become employees. However, for individuals who are not immune (including workers from countries where Varicella Zoster virus is not endemic) working in healthcare or child care exposes them to increased risk. Many studies on the immune status of healthcare and child care personnel have been reported.

10.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Alzheimer's disease
Multiple sclerosis

10.4 VARICELLA ZOSTER VIRUS AND ALZHEIMER'S DISEASE

See Herpes simplex virus and Alzheimer's Disease.

10.5 VARICELLA ZOSTER AND MULTIPLE SCLEROSIS

Table 20 Varicella zoster and Multiple Sclerosis – medline search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	2	1 - 2
Randomised controlled trial	1	3
Prospective studies	0	
Mechanism	1	4
Retrospective seroprevalence	11	5 - 15
PCR	3	16 - 18
CSF Elisa	3	19 - 21
Outbreaks	3	22 - 24
Epidemiology	5	25 - 29
Case control studies	3	30 - 32
Case reports, letters, opinion	6	33 - 38

10.5.1 Varicella zoster and Multiple Sclerosis– science citation index search

Three additional papers identified.

10.5.2 Varicella zoster and Multiple Sclerosis – Summary of Critical Appraisal

The literature searches identified a total of 38 papers examining the association between Varicella zoster virus and multiple sclerosis. One review was critically appraised (1).

The literature search was not systematic and search strategies were not reported. However, the paper is comprehensive and discusses epidemiological, particularly migration studies. One seroprevalence study failed to demonstrate that MS patients were more likely to be seropositive for VZ than controls. However, a study published in 1997) did not detect Varicella zoster in cerebrospinal fluid (CSF) and serum samples from 26 MS patients using a sensitive nested PCR on patients at varying stages of disease. The authors stress that this does not, however, rule out a lesion-associated low grade herpesvirus infection.(16).

However, with seroconversion rates of nearly 98% in controls, a huge study would be needed to demonstrate a significant difference (6). Currently, the evidence linking varicella zoster and MS is merely circumstantial and at the hypothesis generation stage.

11. PARVOVIRUS

11.1 DESCRIPTION

Human parvovirus B19 is a DNA virus belonging to the family Parvoviridae. It produces a mild disease (erythema infectiosum or Fifth Disease) or can be asymptomatic. It occurs worldwide and in the USA up to 80% of adults have seroconverted. The reservoir of infection is humans and the mode of infection is most likely via respiratory secretions although spread via blood is also likely.

11.2 OCCUPATIONAL RELEVANCE

There are published accounts of transmission of parvovirus in the occupational setting. Healthcare and child care personnel are exposed particularly during outbreaks erythema infectiosum in day care centres or in clinical settings. Rates of transmission to staff during outbreaks are very variable.

11.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Anaemia

11.4 PARVOVIRUS AND ANAEMIA

Table 21 Parvovirus and Anaemia – Medline Search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	34	1 – 34
Randomised controlled trial	0	
Prospective studies	1	35
Mechanism	3	36 – 38
Retrospective seroprevalence	1	39
Prevalence	0	0
Case series	1	40
PCR	2	41 – 42
Cross-sectional		
Case reports, letters, opinion	17	43 – 59
Excluded (language, treatment, prognosis, transplant, HIV)		

Other postulated health effects investigated in parvovirus papers:

Arthropathy (60 – 66)

Neutropenia (67 – 68)

Thrombocytopaenic purpura (69 –71)

Dermatitis (72)
Hepatitis (73)
Necrotising vasculitis (74)
Occupational and *hydrops foetalis* (75 and 76)

11.4.1 Parvovirus and Anaemia – science citation index search

Five additional papers identified.

11.4.2 Parvovirus and Anaemia – Summary of Critical Appraisal

The literature search identified a total of 59 papers. Thirty three reviews were identified but, from the information presented in ths abstracts, only three of these focussed on persistent infection and chronic anaemia.

The first review (10), published in 1995, describes the biological, epidemiological and pathogenic features of persistent parvovirus infection. It is based on 40 references. The review reports an association between persistent parvovirus infection and chronic anaemia (pure red cell aplasia) but only case reports are described. Chronic anaemia was reported only in immunodeficient patients. Similarly, a more comprehensive (187 references) but general review documents case reports of chronic anaemia in immunodeficient patients infected with parvovirus.(11). A third review, published in 1989, of persistent infection (20) reports similar findings. None of the above reviews are systematic or based on reported literature searches.

In one small follow-up study (35), one patient out of 53 was suffering from chronic haemolytic anaemia, approximately 57 months after an initial presentation with acute disease but the report does not mention whether the patient had an underlying immunosuppressive condition.

Heegard et al. (1997), (41) describe a retrospective study of patients with chronic anaemia. Whilst evidence of parvovirus B19 infection (viral DNA/specific IgM antibodies) was demonstrated in 13/43 (30%) of patients, they were all eventually found to have an underlying condition and the parvovirus infection was interpreted as a coincidental complication. Some case reports (51,54) suggest that chronic anaemia can also occur in immunologically competent patients. However, subtle and unrecognised immunodeficiencies cannot be ruled out.

To conclude, there is insufficient evidence to demonstrate an association between parvovirus B19 infection in humans and chronic anaemia.

12. MEASLES VIRUS

12.1 DESCRIPTION

Measles virus is a member of the genus Morbillivirus of the family Paramyxoviridae. It causes an acute disease characterised by cough, fever and a characteristic spreading red blotchy rash. It occurs worldwide but childhood immunisation programmes are reducing the incidence. The reservoir of infection is humans and the virus is transmitted by droplet spread and direct contact with nasal and throat secretions including soiled articles.

12.2 OCCUPATIONAL RELEVANCE

There are published accounts of transmission of measles virus in the occupational setting. Healthcare workers and childrens day care workers are mentioned in particular. Seroprevalence studies show that a small (< 10%) but significant proportion of healthcare workers and child day care workers are susceptible. Case control studies indicate that healthcare workers are at increased risk of contracting measles during community outbreaks compared to other adults in the population.

12.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Crohn's disease
Multiple sclerosis

12.4 MEASLES AND CROHN'S DISEASE

Table 22 Measles and Crohn's Disease – Medline Search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	10	1 - 10
Prospective studies	5	11 - 15
Surveillance	0	0
Retrospective sero-prevalence	3	16 - 18
Mechanism	2	19 - 20
Epidemiology	1	21
Case reports, letters, opinion	16	22 - 37
Excluded (language, treatment, prognosis, transplant, HIV)		

12.4.1 Measles and Crohn's Disease – science citation index search

Six additional papers identified.

12.4.2 Measles and Crohn's Disease – Summary of Critical Appraisal

37 papers examining the hypothesised association between measles and Crohn's disease were identified in literature searches. 10 papers investigating the pathogenesis of inflammatory bowel disease (IBD) and the postulated causal relationship between early measles virus exposure and the subsequent development of IBD were critically appraised. These consisted of 4 historical cohort studies, 1 nested case control study, 4 reviews and a summary opinion from WHO.

The Inflammatory bowel research group in collaboration with other research groups forwarded a hypothesis explaining the potential biologic role measles virus may play in the development of IBD. Despite its plausibility, the work is controversial; techniques used to identify the presence of measles virus in gastrointestinal tissue have been criticised and other infectious agents have since been proposed as causal factors in IBD.

Results from the historical cohort studies are not consistent. The initial study conducted in Sweden generated considerable interest, suggesting a high risk of Crohn's disease in individuals exposed to measles in-utero. Causality was assessed; although the correct temporal relationship exists and the link biologically plausible, other criteria for causality were not fulfilled, and the study has significant methodological problems. The results have not been repeatedly observed in different periods, places and populations and two of the other studies reviewed clearly refuted the relationship.

The nested case-control study used national birth cohorts to identify risk factors for IBD. The number of cases identified was small, and no significant association was found between the development of IBD in the cases and any of the factors studied. All of the study designs have evidence of either significant bias or confounding as a result of failing to adequately consider factors such as genetic predisposition and other environmental or infectious agents.

The reviews clearly outline the inconclusive nature of the evidence of this association and the weakness in both the scientific and epidemiological investigation. The future development of an antiviral agent against measles virus may eventually provide a means definitively to prove or refute the purported causality.

To date, the aetiology and natural history of inflammatory bowel disease remains little understood, but a multi-factoral causality is increasingly suggested. Further scientific and well-designed prospective epidemiological studies are needed to understand the pathogenesis and aetiology of this chronic debilitating illness.

12.5 MEASLES AND MULTIPLE SCLEROSIS

Table 23 Measles and Multiple Sclerosis – Medline Search (using filters)

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Systematic reviews	0	
Randomised controlled trials	2	1 - 2
Prospective /cohort / nested / filter	6	3 - 8
Follow up studies	3	9 - 11
Retrospective filter	21	12 - 22
Medline reviews	39	23 - 61

12.5.1 Measles and Multiple Sclerosis – Science Citation Index Search

No additional papers found

12.5.2 Measles and Multiple Sclerosis – Summary of Critical Appraisal

The literature search identified a total of ? papers examining the association between measles virus and multiple sclerosis.

Five review papers were evaluated. None of these reviews were systematic in their approach. The biological plausibility behind the relationship between measles virus and multiple sclerosis stems from the similarity between brain lesions seen in multiple sclerosis and those observed with encephalitis caused by measles. Also serological studies have found an increase in antibody titres in multiple sclerosis cases. However no causal relationship has been established.

The review articles did not provide much information on the studies on which they were based and seemed subjective in their tone. There was little information on the population studied, control groups, sample sizes, power and statistical results. The studies reported were mostly animal, mechanistic studies and there was little information available from a clinical point of view. The review which was of best quality provided information on numbers in the studies and attempted a meta-analysis and concluded that the frequency of measles was not significantly different between cases and controls. However, there was a suggestion that the cases reported a later age of infection than controls.

In the only mechanistic study evaluated in detail the authors looked for viruses present in post-mortem multiple sclerosis patients but concluded that the techniques used were not sufficiently good to draw any valid conclusions.

In summary an association between measles vaccine has been postulated but the evidence to date is circumstantial and based on a possible biological mechanism and a higher prevalence of antibody titres in cases in some studies. However, no temporal association has been established and no causality. There is a need for large prospective studies to be undertaken to provide more understanding on this subject.

13 HEPATITIS B AND D

13.1 DESCRIPTION

Hepatitis B is a small DNA virus. Infection occurs worldwide and is transmitted from person to person via blood and blood products or via sexual contact. Perinatal transmission is also common in some Asian countries. The course of the disease depends on the age, gender and immune competence of the host. The prevalence of chronic infection varies with the highest rates recorded in China and South East Asia and lower rates recorded in Europe and America. Hepatitis D viral genome is a circular RNA molecule. HBV infection is a prerequisite for formation of Hepatitis D particles. HDV is transmitted with HBV person-to-person parenterally or through sexual contact.

13.2 OCCUPATIONAL RELEVANCE

The transmission of Hepatitis B to workers exposed to blood and blood products is well documented. Occupational groups mentioned in particular include healthcare workers, childrens day care workers, workers in other institutional care settings (homes for the mentally handicapped) laboratory staff, sewage workers, police and customs personnel, refuse workers, barbers and firemen. There are also some reports of an increased risk of Hepatitis B infection in butchers sharing knives.

13.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Hepatocellular cancer

13.4 HEPATITIS B AND HEPATOCELLULAR CANCER

13.4.1 Hepatitis B and Hepatocellular cancer – IARC search

- 1 WHO International Agency for Research on Cancer. (1994) IARC Monographs on the Evaluation of Carcinogenic risks to humans. Hepatitis Viruses. Vol 55 (last updated 26/08/97)

13.4.2 Hepatitis B and Hepatocellular cancer – Summary of Critical Appraisal

IARC summary of data reported and evaluation concluded that there is sufficient evidence in humans for the carcinogenicity of chronic infection with hepatitis B virus. There is inadequate evidence in experimental animals for the carcinogenicity of hepatitis virus. Some other hepadnaviruses closely related to hepatitis B produce hepatocellular carcinoma in susceptible species. The overall evaluation is that chronic infection with hepatitis B virus is carcinogenic to humans.(1)

13.5 HEPATITIS D AND HEPATOCELLULAR CANCER

13.5.1 Hepatitis D and hepatocellular cancer – IARC search

- 1 WHO International Agency for Research on Cancer. (1994) IARC Monographs on the Evaluation of Carcinogenic risks to humans. Hepatitis Viruses. Vol 55 (last updated 26/08/97)

13.5.2 Hepatitis D and Hepatocellular Cancer – Summary of Critical Appraisal

IARC summary of data reported and evaluation concluded that there is inadequate evidence in humans for the carcinogenicity of infection with hepatitis D virus. There is inadequate evidence in experimental animals for the carcinogenicity of infection with hepatitis D virus. The overall evaluation is that hepatitis D virus is not classifiable as to its carcinogenicity to humans. (1)

14. HEPATITIS C

14.1 DESCRIPTION

Hepatitis C is an RNA virus distantly related to flaviviruses and pestiviruses which causes hepatitis in humans. Acute HCV infection is largely asymptomatic and chronic infection commonly develops leading to cirrhosis and advanced liver disease. Transmission is parenteral, sexual, although efficiency by this route is limited and perinatal.

14.2 OCCUPATIONAL RELEVANCE

14.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Hepatocellular cancer

The majority of published evidence regarding the occupational transmission of Hepatitis C refers to workers in healthcare settings exposed to blood and blood products. There is some evidence of increased risk in dentists.

14.4 HEPATITIS C AND HEPATOCELLULAR CANCER

14.4.1 Hepatitis C and Hepatocellular cancer – IARC search

- 1 WHO International Agency for Research on Cancer. (1994 IARC Monographs on the Evaluation of Carcinogenic risks to humans. Hepatitis Viruses. Vol 55 (last updated 26/08/97)

14.4.2 Hepatitis C and Hepatocellular cancer - Summary of Critical Appraisal

IARC summary of data reported and evaluation concluded that there is sufficient evidence in humans for the carcinogenicity of chronic infection with hepatitis C virus. There is inadequate evidence in experimental animals for the carcinogenicity of hepatitis virus. The overall evaluation is that chronic infection with hepatitis C virus is carcinogenic to humans.(1)

15. HUMAN T-CELL LYMPHOTROPIC VIRUS

15.1 DESCRIPTION

HTLV-I and HTLV-II are complex retroviruses (oncovirinae). Prevalence varies worldwide with particular clusters in parts of Japan, South America and Africa. Transmission is person-to-person via breast feeding, sexual intercourse and transfusion of cellular blood products.

15.2 OCCUPATIONAL RELEVANCE

The majority of published evidence regarding the occupation transmission of HTLV refers to workers in healthcare settings exposed to blood and blood products together with skin puncture wounds.

15.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Cancer

15.4 HTLV AND CANCER

15.4.1 HTLV and Cancer – IARC Search

- 1 WHO International Agency for Research on Cancer. (1996) IARC Monographs on the Evaluation of Carcinogenic risks to humans. Human Immunodeficiency Viruses and Human T-cell Lymphotropic Viruses. Vol 67 (last updated 23/05/97)

15.4.2 HTLV and Cancer – Summary of Critical Appraisal

IARC summary of data reported and evaluation concluded that there is sufficient evidence in humans for the carcinogenicity of HTLV-I. There is inadequate evidence in humans for the carcinogenicity HTLV-II. The overall evaluation is that HTLV-I is carcinogenic to humans. HTLV-II is not classifiable as to its carcinogenicity to humans. (1)

16. HUMAN IMMUNODEFICIENCY VIRUSES

16.1 DESCRIPTION

HIV-1 and HIV-2 belong to the lentivirus subfamily of the Retroviridae family and cause acquired immune deficiency syndrome. Occurrence is worldwide. The main routes of transmission are sexual intercourse, blood-blood contact and breast feeding.

16.2 OCCUPATIONAL RELEVANCE

There is considerable published evidence of risks to workers exposed to blood and blood products.

16.3 POSTULATED CHRONIC HEALTH EFFECTS

Cancer

16.4 HIV AND CANCER

16.4.1 HIV and Cancer – IARC Search

- 1 WHO International Agency for Research on Cancer. (1996) IARC Monographs on the Evaluation of Carcinogenic risks to humans. Human Immunodeficiency Viruses and Human T-cell Lymphotropic Viruses. Vol 67 (last updated 23/05/97)

16.4.2 HIV and Cancer – Summary of Critical Appraisal

IARC summary of data reported and evaluation concluded that there is sufficient evidence in humans for the carcinogenicity of HIV-1. There is inadequate evidence in humans for the carcinogenicity HIV -2. The overall evaluation is that HIV-1 is carcinogenic to humans. HIV-2 is possibly carcinogenic to humans. (1)

17. HUMAN PAPILOMAVIRUSES

17.1 DESCRIPTION

Papillomaviruses are small DNA viruses. There are more than 70 human strains. Transmission is via sexual contact with infected cervical, vaginal, vulvar, penile or anal epithelium. Perinatal transmission, digital and oral transfer have also been reported.

17.2 OCCUPATIONAL RELEVANCE

There is some evidence of risk to healthcare workers conducting laser or carbon dioxide treatment of papillomas (laryngeal or genital). Studies suggest that viral DNA is released into the atmospheres during such procedures but the actual risk to personnel in the vicinity is not established. Some seroprevalence studies found no evidence of an increased risk for dentists. There are some reports of a high prevalence of human papillomavirus in butchers and slaughterhouse workers. Postulated transmission routes are shared protective equipment and gloves.

17.3 POSTULATED CHRONIC HEALTH EXAMINED

Cancer

17.4 HUMAN PAPILOMAVIRUS AND CANCER

17.4.1 Human Papillomavirus and Cancer – IARC Search

- 1 WHO International Agency for Research on Cancer. (1995) IARC Monographs on the Evaluation of Carcinogenic risks to humans. Human Papillomaviruses. Vol 64 (last updated 13/08/97)

17.4.2 Human Papillomavirus and Cancer – Summary of Critical Appraisal

IARC summary of data reported and evaluation concluded that there is sufficient evidence in humans for the carcinogenicity of HPV types 16 and 18. There is evidence suggesting lack of carcinogenicity to the cervix in humans of HPV types 6 and 11. There is limited evidence in humans for the carcinogenicity of some other HPV types. The overall evaluation is that HPV types 16 and 18 are carcinogenic to humans. HPV types 31 and 33 are probably carcinogenic to humans. Some other types of HPV are possibly carcinogenic to humans

18. COXIELLA BURNETII (Q FEVER)

18.1 DESCRIPTION

Coxiella burnetii is a rickettsia which causes an acute febrile disease and pneumonia termed Q fever. It occurs worldwide. The reservoirs of infection are sheep, cattle, goats, cats, dogs and some wild animals. The organism is transmitted via dust contaminated with placental tissues, birth fluids and faeces of infected animals or by direct contact with contaminated articles such as straw.

18.2 OCCUPATIONAL RELEVANCE

Employees in closest contact with the animal reservoirs are at most risk, particularly cattle and livestock handlers and slaughterhouse workers. Also, research staff working with goats and sheep in research have been infected directly and indirectly via contaminated fetal lamb tissue.

18.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Neuropsychiatric disorders
Endocarditis

18.4 COXIELLA AND NEUROPSYCHIATRIC DISORDERS

Table 24 Coxiella and Neuropsychiatric Disorders and Endocarditis
– Medline Search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	10	1 - 10
Follow up	3	11 - 13
Mechanism	16	14 - 29
Retrospective sero-prevalence	9	30 - 38
PCR	1	39
Immunohisto	3	40 - 42
Case series	60	43 - 102
Case reports, letters, opinion		
Excluded (language, treatment, prognosis, transplant, HIV)		

18.4.1 Coxiella and Neuropsychiatric Disorders and Endocarditis – science citation index search

Five additional papers identified.

18.4.2 *Coxiella* and Neuropsychiatric Disorders and Endocarditis – Summary of Critical Appraisal

Raoult et al (2000) (12) describe the largest series of *Coxiella burnetii* infections to date (1,383 between 1985 and 1998). 313 cases of chronic Q fever were identified. The most common presentations in chronic Q fever were endocarditis, vascular infection, complications of pregnancy, chronic hepatitis, osteoarticular infection and chronic pericarditis. Neurological involvement is described as an acute rather than chronic syndrome.

In 19 patients, there was an evolution from acute to chronic infection but all had predisposing host factors (e.g. vascular or valvular lesions). Some, but not all, of the remaining patients reported a febrile syndrome within a year preceding onset of symptoms. The majority of patients who developed chronic disease had predisposing risk factors. For example, nearly 90% of the endocarditis patients had valvular disease. Whilst the case series does not have a control group, it is a large comprehensive study by a major reference laboratory.

One review (5) focusses on Q fever endocarditis. It is based on 58 references and pools data from many descriptions of case series but is neither systematic nor based on a reported literature search strategy. The authors estimate that endocarditis occurs in 1-11% of infections with *Coxiella burnetii*. The review identifies both underlying heart disease and immunodeficiency as predisposing factors and argue that these play a more important role in the development, or otherwise, of chronic disease than genetic variation in the infecting strains.

A second review (2) describes Q fever in general and includes endocarditis as a chronic manifestation of the disease.

A cohort study was conducting using subjects investigated as part of a large Q fever outbreak in Switzerland in 1983 (11). Follow-up of subjects 12 years later examined an association between seropositivity in 1983 and presence of endocarditis and other vascular complications. Surprisingly, those subjects acutely infected in 1983 (n=411) or previously infected (n=386) were not more likely to have endocarditis up to 12 years later. However, about 1% of those infected had developed endocarditis, which is consistent with 1-11% quoted in the above review. Also, this study did not separately measure the development of endocarditis in patients with existing valvular disease, where the rate of development may well have been higher. Nevertheless, this study does demonstrate an association with a higher risk of cerebrovascular accident and cardiac ischaemia. However, other risk factors for cardiac disease were not taken into account. The authors argue that they were unlikely to be associated with risk factors for infection with *Coxiella burnetii* (consumption of contaminated milk/meat and contact with infected blood). However, occupational and lifestyle factors could be associated with both the exposure and outcome in this study and are therefore potential confounders which have not been controlled for.

Ayres et al (1998) (13) investigated post-infection fatigue syndrome following Q fever via a case control study. Significantly more cases than controls reported symptoms of chronic fatigue syndrome five years after infection.

There is convincing evidence of a chronic element to Q fever. There is also strong evidence that, at least in the case of endocarditis, the likelihood of developing the disease is dependent on the presence of predisposing host factors such as valvular disease. Neurological symptoms, however, are generally regarded as part of the acute form of the disease.

19. CHLAMYDIA PNEUMONIAE

19.1 DESCRIPTION

Chlamydia pneumoniae causes an acute respiratory disease. It occurs worldwide, seroprevalence reaches about 50% by 20-30 years of age. The reservoir of infection is human and it is probably spread via airborne and direct contact with excretions.

19.2 OCCUPATIONAL RELEVANCE

None

19.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Asthma
Heart disease

19.4 CHLAMYDIA AND ASTHMA (USING FILTERS)

Exposure to birds is a known risk factor for *C.psittaci*. A high seroprevalence to *C.pneumoniae* has also been noted in these groups suggesting that complex interactions may occur in a population exposed to two chlamydial organisms. *C.pneumoniae* is commonly found in young children attending day care and a proportion of staff (around 20%) in these settings are also seropositive.

Table 25 Chlamydia and Asthma – Medline Search (using filters)

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Systematic reviews	2	1- 2
Randomised controlled trials	3	4 - 6
Prospective /cohort / nested /	10	3, 7 – 15
Follow up studies	1	16
Retrospective filter	8	17 - 24
Medline reviews –	12	25 - 36

19.4.1 Chlamydia and Asthma – Science Citation Index Search

No additional papers found

19.4.2 Chlamydia and Asthma - Summary of Critical Appraisal

One review was critically appraised. Studies were located using a systematic literature search between asthma and Chlamydia through a variety of markers of infection. The three studies which did not find an association could be criticised on the grounds of inadequate diagnostic tests and inappropriate control groups. However, the review does not discuss the possibility of publication bias. Case reports, case series and case control studies are reviewed. The nine case reports and fourteen uncontrolled case series suggest a role for Chlamydia in acute wheezing, exacerbation, initiation and promotion of asthma in children and adults. Of the

eighteen case-control studies from 8 countries, 15 demonstrated an association but important confounding factors such as smoking and occupational status were not adequately controlled for in many of the studies claiming to have demonstrated a positive association. Large prospective population-based epidemiological studies are needed to investigate this further.

19.5 CHLAMYDIA PNEUMONIAE AND HEART DISEASE

Table 26 Chlamydia and Heart Disease – Medline Search (using filters)

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Systematic reviews	5	1 - 5
Randomised controlled trials	38	6 - 43
Prospective /cohort / nested / filter	66	44 – 109
Follow up studies	11	110 - 120
Retrospective filter	31	121 - 151
Medline reviews	102	152 - 253

19.5.1 *Chlamydia Pneumoniae* and Heart Disease – science citation index search

Twenty four additional papers identified.

19.5.2 *Chlamydia Pneumoniae* and Heart Disease – Summary of Critical Appraisal

Danesh et al reviewed the evidence for an association between Chlamydia and heart disease in 1997. 18 retrospective studies were identified by a systematic review. Most found a twofold or larger odds ratio. However, several studies did not adequately control for confounders. Others used micrimmunofluorescence to detect antibodies measured by microscopists who were not blind to the status of samples. Cross-reactions giving rise to false positives were also possible in some studies. Furthermore, many studies applied a post-hoc approach to the analysis of antibody titres, deciding on cut-off points after an examination of the data. The conclusion is that evidence is insufficient and that temporal sequence of infection is uncertain. Nevertheless, a role of Chlamydia in coronary heart disease remains biologically plausible as the organism has been found in arterial tissue and found more frequently in atheromatous lesions than in control samples of arterial tissue. It may illicit an autoimmune inflammatory response or alternatively may be an innocent bystander.

A more recent meta-analysis of prospective studies (generally less prone to publication bias) has found that there is no association between Chlamydia and coronary heart disease. A large prospective study published with the meta-analysis and a further prospective study () reached the same conclusions.

The question of an association at younger ages remains unanswered.

20. BORRELIA

20.1 DESCRIPTION

The spirochete *Borrelia burgdorferi* causes a tickborne disease characterised by distinctive skin, neurological, rheumatic and cardiac symptoms termed Lyme disease. It occurs widely in the USA and Europe. Ixodid ticks are the reservoir and vector of infection which is transmitted by the tick bite.

20.2 OCCUPATIONAL RELEVANCE

Workers most exposed to tick bites (i.e. outdoor workers) are most at risk. Reports of infection or increased seroprevalence in forestry workers, hunters and agricultural workers are common. Also, urban park workers in the UK have been found to be at increased risk, implying that visitors to these areas may also be exposed.

20.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

General chronic disease

20.4 BORRELIA AND CHRONIC DISEASE

Table 27 Borrelia and Chronic Health Effects – Medline Search (using filters)

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Systematic reviews		
Randomised controlled trials	5	1 - 5
Prospective /cohort / nested / filter	22	6 - 27
Follow up studies	5	28 - 32
Retrospective filter	7	33 - 39
Medline reviews – musculo-skeletal effects	3	40 - 52
Medline reviews – neurological effects	11	53-63
Medline reviews – cutaneous	6	64-69
Medline reviews – cardio-vascular	3	70-72
Medline reviews – mechanism	6	73 - 78
Medline reviews – general	17	79 - 95

20.4.1 Borrelia and Chronic Health Effects – science citation index search

Sixty four additional papers identified.

20.4.2 Borrelia and Chronic Health Effects – Summary of Critical Appraisal

Evans, 1999 (80) reviews Lyme disease including the epidemiological and clinical aspects of the disease. The review is not systematic nor based on a reported literature search strategy. It reports that Lyme Disease is frequently divided into early and late stages of the disease. The late stages include cardiac involvement (in 8% of cases). However, evidence of chronic cardiomyopathy associated with Lyme Disease is conflicting. Neurologic symptoms occurring in the late stages of Lyme Disease are well recognised and termed neuroborreliosis. Similarly, it is widely accepted that arthritis is a dominant feature of late Lyme Disease, however, it is unclear whether this is due to persistence of the infecting organism or results from a host immunologic response.

A descriptive study of 27 patients with chronic Lyme Disease (15) describes several clinical manifestations including chronic encephalopathy, polyneuropathy and leukoencephalitis. Some patients still had symptoms up to 14 years after the initial infection. This does not provide information on the rate of development of these chronic effects.

A recent large study compared patients who had suffered Lyme Disease (40) with age-matched controls and found no difference in the prevalence of muscle, joint and neurological symptoms between the two groups. Whilst the authors were unable to recruit a substantial number of eligible cases, this was due to inadequate contact information and unlikely to introduce systematic bias. It is also likely that patients with chronic disease would be more willing to take part in the study than well people. Hence, the bias would influence the results towards a positive association whereas no positive associations were found.

Whilst it is generally accepted that chronic manifestations of Lyme Disease exist, the likelihood of these developing and the mechanism which causes them to occur in some patients but not in others is far from clear.

21 BARTONELLA

21.1 DESCRIPTION

The bacteria *Bartonella henselae* causes cat scratch disease, a subacute disease characterised by granulomatous lymphadenitis. Infections are reported worldwide but are uncommon. Domestic cats are the reservoir and most patients are infected by a scratch, bite or lick from a cat.

Bartonella quintana causes Trench fever, a febrile disease characterised by headache and pain and tenderness, especially on the shins. Infection can be subclinical and can recur. In developed countries it is most likely to be diagnosed in homeless persons. Humans are the reservoir of infection. The intermediate host and vector is *Pediculus humanus corporis*, the human body louse, and infection occurs via inoculation of the organism in louse faeces or through broken skin.

21.2 OCCUPATIONAL RELEVANCE

Workers in contact with cats (including veterinarians) are reported at increased risk.

21.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

General chronic disease

21.4 BARTONELLA AND SEVERAL CHRONIC EFFECTS

Table 28 Bartonella and Chronic Disease – Medline Search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	10	1 - 10
Randomised controlled trial	0	0
Prospective studies	0	0
Mechanism	12	11 - 22
Retrospective seroprevalence	3	23 - 25
Prevalence	0	0
Case series	1	26
PCR	0	0
Cross-sectional	0	0
Case reports, letters, opinion	19	27 - 45
Excluded (language, treatment, prognosis, transplant, HIV)	40	

Other chronic health effects i.e. neuroretinitis are in references 46 - 69

21.4.1 Bartonella and Chronic Disease – science citation index search

Five additional papers identified.

21.4.2 Bartonella and Chronic Disease – summary of critical appraisal

Four reviews were critically appraised. None of the reviews were systematic nor based on a reported literature search strategy. The most recent review (1) describes several clinical manifestations of bartonellosis including Oraya fever, Peruvian Warts, Trench Fever and Cat Scratch Disease. Chronic diseases are also described, predominantly in patients also infected with Human Immunodeficiency Virus (HIV), notably endocarditis and bacillary angiomatosis. Two further reviews (4,6) also describe bacillary angiomatosis (presenting mainly as skin lesions but also found in other organs), bacillary peliosis and splenitis, bacteremia and endocarditis in immunocompromised hosts. Nevertheless, case reports of bacillary angiomatosis and endocarditis in immunocompetent hosts are also cited. A further review (5) also lists the above but adds that an acute form of Trench Fever has been described. Finally, Marra (1995) (8) reviews neurologic complications (including irritability and anxiety) of both acute (Cat Scratch Disease) and chronic (bacillary angiomatosis) forms of the disease although the information is based on case reports

Finally, two papers examine the mechanism by which Bartonella induces a vasoproliferative response in endothelial tissue (2,15).

In conclusion, chronic manifestations of Bartonella infection are reported mainly in immunosuppressed individuals, particularly those infected with HIV. Current evidence on chronic conditions in immunocompetent patients is limited to case reports and is therefore insufficient to prove causality although work is underway to demonstrate the mechanisms by which it occurs.

22 HELICOBACTER PYLORI

22.1 DESCRIPTION

Helicobacter are spiral, flagellated, gram-negative bacteria. Their reservoir is the gastrointestinal tract of humans and animals. *H pylori* occurs worldwide and is most prevalent in developing countries and lower socio-economic groups. Most of the population are infected by adulthood. The infection, gastritis, is chronic but usually asymptomatic. Transmission is via oral-oral or faecal-oral routes.

22.2 OCCUPATIONAL RELEVANCE

Some studies report an increased risk of infection in physicians performing UGI endoscopy and in other healthcare workers and dentists because of exposure to potentially infectious gastric secretions although evidence is conflicting. Other occupational groups investigated include sewage workers, submarine crews, child care workers and slaughterhouse workers. Laboratory acquired infections have been reported.

22.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Coronary heart disease

Crohn's disease

Gastric cancer

22.4 HELICOBACTER PYLORI AND CORONARY HEART DISEASE

Table 29 *Helicobacter pylori* and Coronary Heart Disease – Medline Search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	19	1- 19
Prospective studies	5	20 - 24
Retrospective sero-prevalence	14	25 - 38
Case control (isolation/breath antibody)	3	39 - 41
Mechanism	10	42 -51
Cross-sectional	3	52 - 54
Epidemiology (of carriage)	1	55
Case report / letter	8	56 -63
Excluded (language, treatment, prognosis, transplant, HIV)		

22.4.1 *Helicobacter pylori* and Coronary Heart Disease – science citation index search

One additional paper was identified.

22.4.2 *Helicobacter pylori* and Coronary Heart Disease – summary of critical appraisal

Danesh et al present (18) a systematic literature review with critical appraisal of the evidence linking *H.pylori* (and other infections) with coronary heart disease. Reports in any language were sought by a combination of Medline electronic searches and hand searching. The review is very comprehensive and considers epidemiological and pathological published evidence. The authors identify two areas of concern in epidemiological studies claiming an association between *H.pylori* and coronary heart disease. Firstly, it appears that both the disease and the organism are strongly related to socio-economic status yet many, particularly retrospective studies, do not adequately control for this confounder. Furthermore, the selection of controls in many retrospective studies is opportunistic (e.g. hospital controls) rather than controls drawn from the same population as the cases (population controls). In the few studies where these issues are addressed (nested case control analysis in large prospective studies) the association between *H.pylori* and coronary heart disease is very slight (e.g. odds ratios of about 1.5). Furthermore, pathological studies have found only very limited evidence of a link between *H.pylori* and vascular risk factors.

A further comprehensive (but not systematic) review (6) examines in more detail the biological plausibility of a role for *H.pylori* in coronary heart disease. Whilst a variety of mechanisms including direct injury of the endothelial cells and chronic inflammation or cross-reactive antibodies are possible, there has been no convincing evidence to date of one of them. *H.pylori* has not been found in atherosclerotic plaques. This review also concludes that the evidence of a causal association is unconvincing at present.

Finally, a meta-analysis of five prospective (8) studies identified through a systematic literature review has been carried out. It is argued that large prospective studies should be less prone to publication bias than smaller retrospective studies. There was no significant heterogeneity among the studies and the overall analysis yielded a combined odds ratio of 1.13 (95%CI = 0.93 - 1.38). The studies were confined to cases in their late middle age.

To conclude, further large prospective studies are needed to examine the association of *H.pylori* and coronary heart disease. The quality of current evidence is compromised by the fact that both *H.pylori* and coronary heart disease are common in the general population and that both are related to socio-economic status. Furthermore, most of the current evidence is based on studies of middle-aged men and clearly cannot be extrapolated to the rest of the population.

22.5 *HELICOBACTER PYLORI* AND CROHN'S DISEASE

Table 30 Helicobacter and Crohn's Disease – Medline Search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	5	1 - 5
Prospective studies		
Retrospective sero-prevalence	5	6 - 10
Mechanism	4	11 - 14
Case control (Isolation)	5	15 - 19
Case series	3	20 - 22
Epidemiology		
Case reports, letters, opinion		
Excluded (language, treatment, prognosis, transplant, HIV)		

22.5.1 *Helicobacter pylori* and Crohn's Disease – science citation index search

No additional papers found

22.5.2 *Helicobacter pylori* and Crohn's Disease – summary of critical appraisal

Pearce *et al.* (2000) (6) report a limited case-control study comparing seropositivity for *H.pylori* in cases of Crohn's Disease with controls who were patients with irritable bowel syndrome as the working diagnosis. The choice of an opportunistic control group (i.e. other patients) may have resulted in bias as they were not necessarily drawn from the same population as the cases. Furthermore, some of the controls may have had undiagnosed organic disease. Fewer cases than controls were seropositive for *H.pylori* although no statistical comparison is reported. Potential confounding variables such as age, sex and socio-economic status were not taken into account. Unsurprisingly, Crohn's patients treated with antimicrobials were less likely to have current infection with *H.pylori* (diagnosed by urea breath test) than those treated with other drugs. However, there was no attempt to remove these patients from the analysis. Furthermore, the authors concede that the power of the study (42 cases vs 40 controls) was limited. Previous studies cited in this paper also demonstrated an inverse relationship between *H.pylori* infection and Crohn's disease. Duggan *et al* (1998) (7) report a larger case control study comparing 87 patients with Crohn's disease with 174 age and sex matched controls having elective surgery at the same hospital. The principal aim of the study was to examine the relationship between appendicectomy, childhood domestic hygiene and inflammatory bowel disease. *H.pylori* (seropositivity) status was recorded as an additional measure of childhood conditions. There was no significant difference in the rate of seroconversion of cases as compared to controls.

To conclude, some retrospective studies have indicated that cases of Crohn's disease are less likely to have been infected with *H.pylori* than patients without this condition but to date the evidence is unconvincing. A large case-control study recording both current *H.pylori* status

and previous infection (seropositivity) in confirmed cases and controls representative of the population from which the cases were drawn is needed. Major confounding risk factors including age, sex, childhood hygiene, socioeconomic group and antimicrobial useage need to be taken into account in the study design and analysis.

22.6 *HELICOBACTER PYLORI* AND GASTRIC CANCER

22.6.1 *Helicobacter pylori* and Gastric Cancer – IARC Search

- 1 WHO International Agency for Research on Cancer. (1994) IARC Monographs on the Evaluation of Carcinogenic risks to humans. Schistosomes, Liver Flukes and *Helicobacter pylori*. Vol 61 (last updated 26/08/97)

22.6.2 *Helicobacter pylori* and Gastric Cancer – Summary of Critical Appraisal

IARC summary of data reported and evaluation concluded that there is sufficient evidence in humans for the carcinogenicity of infection with *Helicobacter pylori*. There is inadequate evidence in experimental animals for the carcinogenicity of *Helicobacter pylori*.. The overall evaluation is that infection with *Helicobacter pylori* is carcinogenic to humans.(1)

23 SALMONELLA TYPHI

23.1 DESCRIPTION

Salmonella typhi, the typhoid bacillus, causes an acute systemic bacterial disease. It occurs worldwide but is endemic in areas where sanitation is poor. The reservoir of infection is humans and it is transmitted via food/water contaminated by the faeces or urine of carriers. Following the initial illness approximately 2-5% of patients will become permanent carriers.

23.2 OCCUPATIONAL RELEVANCE

Documented occupational transmission involves laboratory acquired infection or exposure to human faeces.

23.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Bile tract neoplasm

23.4 SALMONELLA TYPHI AND BILE TRACT NEOPLASM

Table 31 *Salmonella typhi* and bile tract neoplasm – Medline Search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	0	
Prospective studies	1	1
Case series	3	2 – 4
Retrospective sero-prevalence	3	5 - 7
Mechanism	4	8 – 11
Cross-sectional	0	
Case reports, letters, opinion	13	12 - 24
Excluded (language, treatment, prognosis, transplant, HIV)		

23.4.1 *Salmonella typhi* and Bile Tract Neoplasm – science citation index search

Three additional papers identified.

23.4.2 *Salmonella typhi* and Bile Tract Neoplasm – summary of critical appraisal

The literature searches identified a total of 24 papers examining the association between *S.typhi* and carcinoma of the gall bladder. This is considerably less than for many of the other associations and may reflect the low incidence of this disease in developed countries. The majority of papers were case reports and letters. Five papers were critically appraised and are highlighted above.

The first study, a case series (2), describes abnormal gallbladder sonograph findings in *S.typhi* cases. Whilst this indicates that the gallbladder is frequently (60%) affected in *S.typhi* cases it clearly does not prove an association with gallbladder carcinoma.

Three retrospective studies report an association. Seroprevalence or rates of positive stool cultures in cases of cancer are compared to controls. Two studies do not adequately control for important potential confounders i.e. age, sex, treatment regimes, presence of other predisposing conditions and pathogens and area of residence (5, 7). One study includes an extensive multivariate analysis but it is limited to cases and controls with gallbladder stones making it difficult to extrapolate the results to the general population (6).

Finally, one prospective study (1) compares causes of death (ascertained from death certificates) in registered typhoid carriers to that of controls. Typhoid carriers were six times more likely to die from hepatobiliary cancer. The study includes a large number of subjects and controls for potential confounders.

To conclude, the quantity and quality of evidence linking *S.typhi* with hepatobiliary cancer is convincing. A small number of good studies have been reported but further well designed prospective studies would be useful. Typhoid carriage is relatively easy to diagnose and in many countries carriers are registered. This provides an ideal resource to prospectively study whether carriers are more likely to develop hepatobiliary cancer whilst controlling, in particular, for treatment regimes.

24 CAMPYLOBACTER

24.1 DESCRIPTION

The bacteria Campylobacter causes an acute enteric disease. It occurs worldwide. The reservoir of infection is animals particularly poultry and cattle. It is transmitted by ingesting organisms in contaminated food or by direct contact with infected animals.

24.2 OCCUPATIONAL RELEVANCE

Documented occupational transmission involves laboratory acquired infection or exposure to animals in slaughterhouses.

24.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Reactive arthritis and Reiter's disease

Guillain-Barre syndrome

24.4 CAMPYLOBACTER AND REACTIVE ARTHRITIS AND REITER'S DISEASE

Table 32 Campylobacter and Reactive Arthritis and Reiter's Disease
– Medline Search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	14	1 – 14
Randomised controlled trials	1	15
Seroprevalence	6	16 – 21
Follow up studies	5	22 – 26
Mechanism	9	27 – 35
Case control – isolation	1	36
Cases only – sequence	2	37 – 38
Case series	6	39 – 44
Letters etc	23	45 – 67

24.4.1 Campylobacter and Reactive Arthritis and Reiter's Disease – science citation index search

Three additional papers identified.

24.4.2 Campylobacter and Reactive Arthritis and Reiter's Disease – summary of critical appraisal

Peterson (1994) (9) present a specific review examining the rheumatic manifestations of *Campylobacter jejuni* and *C.fetus*. A medline search identified the characteristics of 29 patients with reactive arthritis or Reiter's syndrome following culture proven *Campylobacter jejuni* infection. The majority of cases involved the knee joint in patients with underlying illnesses such as diabetes, cancer or hypoammaglobulinaemia or an already diseased joint. The pathogenesis of reactive arthritis and reiter's syndrome is not completely understood. This complication occurs in approximately 2-3% of patients with *Campylobacter jejuni* enteritis (11, 22, 24, 42). Arthritic complications of Campylobacter are thus well established but the range of symptoms and true incidence are not known.

24.5 CAMPYLOBACTER AND GUILLAIN-BARRE SYNDROME

Table 33 Campylobacter and Guillain-Barre Syndrome – Medline Search

<i>Type of evidence</i>	<i>Number of papers identified</i>	<i>Reference numbers</i>
Reviews	28	1 – 28
Randomised controlled trials		
Seroprevalence	15	29 – 43
PCR	1	44
Follow up studies	1	45
Outbreak follow-up	2	46 – 47
Mechanism	90	48 –137
Case control – isolation/diarhoea	4	138 - 141
Cases series (CSF antibodies/serotypes)	8	142 - 149
Letters etc	37	150 -186
Supplement	2	187 - 188

24.5.1 Campylobacter and Guillain-Barre Syndrome - science citation index search

Twenty one additional papers identified.

24.5.2 Campylobacter and Guillain-Barre Syndrome – summary of critical appraisal

Nachamkin (9) present a recent, critical and very comprehensive review of the current evidence linking Campylobacter and GBS. They describe GBS as an auto-immune disorder of the peripheral nervous system characterised by weakness, usually symmetrical, evolving over a period of several days or more. It can develop 1-3 weeks after Campylobacter infection and whilst the majority of patients recover, 15 to 20% are left with severe neurologic

deficits. The authors conclude that serologic and culture evidence appears to have firmly established that GBS is associated with *Campylobacter*. However, the mechanism by which it causes the disease, the presence or otherwise of host factors and the involvement of different strains in GBS have not been fully evaluated. The National Institutes of Health in the USA have outlined several areas for future research. These include studies on the epidemiology of *Campylobacter*-induced GBS, studies on host susceptibility, standardised and improved typing systems and serologic assays.

25 SCHISTOSOMES

25.1 DESCRIPTION

Schistosomes are trematode worms which live in the human bloodstream. Infection is caused by exposure to infective larvae in water. The lifecycle is completed in freshwater snails.

25.2 OCCUPATIONAL RELEVANCE

Workers in closest contact with the reservoir (worms living in water) are at most risk. Fishermen, farmers and canal cleaners are mentioned in the literature although this is a tropical disease and not an issue in the UK. Laboratory acquired infection has been reported.

25.3 POSTULATED CHRONIC HEALTH EFFECTS EXAMINED

Urinary bladder cancer

25.4 SCHISTOSOMES AND URINARY BLADDER CANCER

25.4.1 Schistosomes and Urinary Bladder Cancer – IARC Search

- 1 WHO International Agency for Research on Cancer. (1994) IARC Monographs on the Evaluation of Carcinogenic risks to humans. Schistosomes, Liver Flukes and *Helicobacter pylori*. Vol 61 (last updated 26/08/97)

25.4.2 Schistosomes and Urinary Bladder Cancer – summary of critical appraisal

IARC summary of data reported and evaluation concluded that there is sufficient evidence in humans for the carcinogenicity of infection with *Schistosoma haematobium*. There is inadequate evidence in humans for the carcinogenicity of infection with *Schistosoma mansoni*. There is limited evidence in humans for the carcinogenicity of infection with *Schistosoma japonicum*. There is limited evidence in experimental animals for the carcinogenicity of infection with *Schistosoma haematobium*. There is limited evidence in experimental animals for the carcinogenicity of infection with *Schistosoma mansoni*. There is limited evidence in experimental animals for the carcinogenicity of infection with *Schistosoma japonicum*. The overall evaluation is that *Schistosoma haematobium* is carcinogenic to humans. Infection with *Schistosoma mansoni* not classifiable as to its carcinogenicity in humans. *Schistosoma japonicum* is possibly carcinogenic to humans. (1)

26 DISCUSSION

Occupational transmission of infectious diseases and the association of chronic health effects with biological agents has given rise to a large and varied scientific literature.

We accessed this via three electronic databases of published literature, namely, Medline, Embase and ISI. Medline is widely recognised as the premier source of biomedical literature. It holds 9.5 million records from 3,900 journals. 67% have abstracts. Embase covers all aspects of human medicine and related biomedical research. 3,500 journals from 110 countries are included and one third have abstracts. The databases were chosen to provide maximum coverage of this subject area. Papers in English, French or German were included where the abstract was written in English. Whilst some papers in other languages will have been missed, the majority of research was published in English language peer-reviewed journals.

Publication bias may have reduced the inclusion of studies failing to demonstrate association in this review. Nevertheless prospective studies, which are the highest level of evidence, are generally regarded as less prone to this phenomenon and large prospective studies, in particular, are likely to be published irrespective of their conclusions. In this controversial area, where very few associations have been proved, evidence for and against associations were frequently encountered.

The unanticipated volume of literature meant that there was insufficient time to critically appraise all of the published evidence. Therefore, papers were categorised according to their abstracts. Where papers were later selected for critical appraisal, the abstracts were found to be an accurate indicator of the level of evidence provided by the study although not of the quality of the data. In each category a small selection of papers representing the highest levels of evidence were selected for appraisal.

Levels of evidence ranged from systematic reviews and meta-analyses of prospective studies to case reports. Many of the methodological problems and limitations were common to a large number of papers reviewed and are discussed below.

Evidence of occupational transmission was reported as outbreaks, case control studies, seroprevalence studies, case series and case reports. Workers employed in healthcare, child care and in occupations with animal contact were most often affected.

The majority of evidence regarding chronic health effects is currently retrospective. A variety of methods are used to detect the organism under investigation in cases and controls. Seroprevalence studies are particularly numerous but frequently include very low numbers of subjects. However, high rates of seroconversion are recorded in the general population for many of the implicated infections e.g. CMV, HHV and HSV. The power of such studies to detect a significant difference between cases and controls is therefore limited. Cross-reactions can also occur. A further common criticism of these studies is potential bias introduced by the selection of cases and controls. Frequently, no details at all are provided on the source of cases or controls and it is impossible to judge whether they are representative of the diseased or well populations. Where details are given, cases are frequently recruited at tertiary care centres and thus, studies, may be biased towards the more serious manifestations of the disease. Controls are frequently recruited opportunistically from other patient groups and not drawn from the general population.

Sequence-based studies use sensitive methods such as PCR to detect gene-sequences in tissue from cases and controls. Conflicting results between studies can often be attributed to differences in sensitivities of the methods used. A particular problem occurs in viruses in a

latent state are particularly difficult to detect. There is a need for standardisation of these methods so that results can be compared properly.

At best, retrospective studies can indicate an association between the organism and the disease but cannot demonstrate causality. The temporal sequence of events requires prospective investigation.

Some large prospective studies have been reported. Studies of heart disease and several biological agents e.g. Chlamydia, CMV and *H.pylori* have been reported. Baseline antibody levels of a cohort are measured and subjects are followed up later to assess development of disease. Some studies analyse results *post-hoc*, deciding on cut-off levels for titres after the data has been examined. Commonly, the study population was not recruited with the study hypothesis in mind. Several major confounders have to be taken into account when examining these associations. However, some confounders e.g. socio-economic group are difficult to assess accurately and the relationship between the confounder and the biological agent are not always completely understood. Nevertheless, well-conducted large prospective studies are the best way of demonstrating an association although they frequently rely on evidence from one section of the community e.g. middle-aged men and the findings are not necessarily relevant to other population sub-groups.

Mechanistic studies and animal studies provide further evidence of the biological plausibility of an association. Suitable animal models have not been found for many diseases. Furthermore, finding evidence of the agent in lesions associated with the disease does not prove causality as it could be an innocent bystander, a role suggested for example, for *Chlamydia pneumoniae*. Conversely, failing to find it does not rule out autoimmune mechanisms and action from a remote site.

The majority of reviews identified in this report were not systematic and therefore can only be accepted as expert opinion. Some, however, were based on reported research strategies and critically appraised the evidence in detail.

Large, well-designed prospective studies are still needed to address all of the associations examined in this report. The heterogeneity of many of the diseases will also have to be considered and studies focussed on well-defined presentations of the disease. Alzheimer's disease and Guillain-Barre Syndrome, for example, may contain within the broad rubric distinct clinical patterns that may have different aetiologies.

Host factors also need to be examined. The genotype of the host is likely to play a major role in some associations (e.g. HSV and Alzheimer's). Also, several chronic health effects are only apparent in hosts with underlying disease (e.g. vascular disease) or whom are immunosuppressed.

Finally, the timing of the initial infection may be a critical factor in the development of a chronic health effect. For example, late onset EBV infection may be associated with MS. Study designs should include a measurement of these factors.

27 CONCLUSIONS AND RECOMMENDATIONS

- 1 Despite the huge quantity of published literature and considerable effort that has been directed at this area of research, comparatively little convincing evidence has been generated.
- 2 Many studies have concentrated on particular age and sex groups (e.g. middle aged men in heart disease). There have been no prospective studies commencing in childhood.
- 3 There have been several studies examining the role of more than one biological agent in chronic disease including potential interactions between agents.
- 4 There is some evidence that all of the biological agents included in this report can be acquired occupationally.

We recommend the following:

- 1 Chronic health effects of several biological agents should be investigated. A cohort study commencing in childhood would be most suitable as this would allow childhood socio-economic factors to be recorded most accurately. Furthermore, the age of onset (or seroconversion) could be included. Saliva antibody testing should be investigated as a non-invasive measurement of seropositivity. A collaborative study with another European or USA centre should also be investigated.
- 2 The research strategy detailed in this report provides a valuable resource of both occupational and chronic disease published research which will be of use to occupational health practitioners and employees. The search should be updated annually to ensure that it remains accurate and relevant to current working practices. New areas of interest could be added to the search as necessary.