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The Impact of Infectious Disease on Chronic Disease: A Review of Contemporary Findings

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Infectious diseases are among the top causes of death in adults and children. Chronic diseases such as cardiovascular disease and cancer are among the top causes of death in adults. Associations between bacterial and viral infectious agents and subsequent development of chronic disease have been made in the past but are currently being re-examined with more rigor and specificity. This review examines infectious disease agent causes and associations with cancer, cardiovascular disease, metabolic disease, and neurodegenerative disease. These associations will impact future research, surveillance, treatment, and prevention of both infectious and chronic diseases.

Keywords: *chronic disease, epidemiology, infectious disease, interactions, review*

Introduction

Infectious diseases represent the second-top cause of death worldwide and are among the top causes of death in children under age 5 (Institute of Medicine, 2004; Kochanek, Xu, Murphy, Minino, & Kung, 2011). The Institute of Medicine's report on emerging infections in the United States pointed to complacency regarding infectious disease, particularly, emerging infectious diseases and re-emerging infectious diseases. The report also called for examination of established as well as potential relationships between infectious diseases and chronic diseases (Institute of Medicine, 2004). The Institute of Medicine also argues that a communication gap exists between research, public health, and allied health care providers that require further examination.

Though there have been observed associations between chronic disease and infectious disease since the beginning of epidemiological research, increased emphasis on this relationship began in the late 1970s when new associations between specific infectious and chronic diseases were observed. At that time, the assumed cause of peptic ulcers was environmental variables such as chronic stress but was alternatively determined to be *Helicobacter pylori*, an infectious bacterial agent. It is argued that this discovery shifted the paradigm relative to causative factors that contribute to chronic health conditions and stimulated subsequent research linking infectious and chronic diseases (SoRelle, 1998).

Critical also to the consideration of infectious causes of chronic diseases was the advent of genetic characterization of organisms using molecular methods in vitro to identify a causal relationship (Nelson & Williams, 2007, pg. 482). During this period, epidemiological studies have linked infectious agents to cardiovascular disease, cancer, rheumatoid inflammatory disease, and cognitive diseases such as dementia and Alzheimer's disease (Itzhaki, Wozniak, Appelt, & Balin, 2004). Considering that the field of epidemiology examines the determinants and distribution of disease in communities as well as the application of this data to disease control measures (Aschengrau &

Seage, 2008, pg. 6), the objectives of this review include the provision of a brief history of specific infectious chronic disease relationships followed by discussion of how these associations have impacted or may impact the etiology of the infectious disease. The proposed causative agents; clinical aspects of the disease including research findings, associated epidemiology, and prevention; and control methods are also outlined for possible infectious causes of cancer, obesity, cardiovascular disease, and neurodegenerative diseases.

Cancer

The predominant theory in cancer pathophysiology for the past 50 years has argued that most cancers are caused by mutations that dysregulate cellular proliferation in tissues (Ewald, 2009). Recently, it has been recognized that infectious agents may be significant initiators of the mutations and the dysregulated cellular proliferation that follows (Ewald, 2009), though associations were observed as early as 1908 (Calkins) linking an infectious agent not only to cancer but also to the growth and proliferation of cancer cells in mice. Ellerman and Bang (1908) also pursued an infectious cause for avian leukemia via experimental transfer of the disease between chickens. Ochsner (1921) pointed to a de-emphasis among members of the medical profession of the relationship between infectious agents and cancer within the context of the public's perception that an association did exist. Mollari and Chinn (1949) pointed to specific etiological relationships between viruses and cancer while Epstein (1987) acknowledged 80 years of animal-species-associated links and argued for emphasis on human infectious agents in their role in subsequent development of cancers given that up to 25% of all cancers have a causal or associative viral variable.

Associations between infectious agents and cancer of the gastrointestinal tract, breast, lung, cervix, prostate, and skin support theories that the initial cause of most cancers may be of an infectious disease origin (Ewald, 2009). For example, *H. pylori* was associated with gastric cancer and lymphoid tissue lymphoma as early as the 1970s with studies linking *Schistosoma haematobium* with bladder cancer and hepatitis B and C with liver cancer. Human papillomavirus (HPV) is highly associated with cervical cancer, and herpes and Kaposi's sarcoma have also been linked with specific cancer types (SoRelle, 1998).

Hepatitis, initially detected in the 1600s, is a viral infection characterized by inflammation of the liver and associated jaundice and gastrointestinal symptoms. In addition to evidence pointing to hepatitis as a possible direct cause of inflammation and cellular proliferation in cancer, epidemiological evidence finds that populations with high prevalence rates of hepatitis also demonstrate high prevalence rates of liver cancer. Further support argues that the United States has seen drops in liver cancer since the advent of increased good hygiene habits after the early 1900s, while developing nations continue to see liver cancer rates unchanged (Hendrickx et al., 2007).

Hepatitis B, C, and D are typically transmitted sexually or via exposure to blood. Secondary presentation of hepatitis can also occur subsequently to exposure to other viruses such as Ebola. Hepatitis is most prevalent in healthcare settings or environments lacking in sanitation and among increased-risk groups such as Native Americans and Hispanics, as well as in regions of the world such as Africa, Asia, Central and South America, and the Middle East. In addition, individuals with frequent and variable sexual partners and intravenous drug users represent an increased risk group. Additionally, low socioeconomic status among other variables has been associated with an increased prevalence of hepatitis (Nelson & Williams, 2007, pp. 895–939).

Regarding worldwide prevalence of hepatitis relative to the United States, though regions previously noted (Africa, Asia, Central and South American, Middle East) have higher rates of all forms of hepatitis compared with the United States, great variability exists in states and regions in which increased-risk residents—such as Native Americans and Hispanics—reside and communities characterized by low socioeconomic status. Specifically in the United States, Native Americans are three times more likely to be diagnosed with hepatitis, and Hispanics are two times more likely to contract the disease compared with Caucasian individuals. In countries outside of the United States with highest prevalence rates, up to 80% of children and 90% of adults have been diagnosed with hepatitis (Nelson & Williams, 2007, pp. 895–939).

Hepatitis B is transmitted via blood, and though most infected individuals do not develop chronic liver disease, 25% of infants and children who are infected later develop liver cancer. In fact, the link of hepatitis B to future development of cancer has driven research and prevention strategies such as administration of immunoglobulin and vaccine distribution. Specific increased-risk situations have also directed specific prevention strategies such as the prevention of cases contracted during childbirth. As a result, the World Health Organization has added the hepatitis B vaccine to children's scheduled vaccinations (Nelson & Williams, 2007, pp. 895–939).

It is relevant to note that the association between hepatitis B and C and liver cancer was among the first identified associations between infectious disease agents and chronic disease (Choo et al., 1989). Subsequent studies revealed that chronic inflammation in the liver produced by hepatitis B and C infection caused tissue fibrosis and proliferation of cells. In addition, it has been observed that the hepatitis virus also modulates pathways that promote malignancies in liver tissue (Levrero, 2006).

Hepatitis C infection in the majority of cases does not present acute symptoms; however, when symptoms present themselves, they are difficult to distinguish from those associated with other hepatitis viruses. Similar to hepatitis B, hepatitis C is transmitted via blood, and as a result, individuals with frequent sex partners and intravenous drug users are at increased risk. It is estimated that over 170 million individuals are infected with hepatitis C worldwide. Similarly, hepatitis C has also been linked to liver cancer (Nelson & Williams, 2007, pp. 895–939). Hepatitis B and C infection relative to their relationship to cancer potentiates different courses for prevention. Early diagnosis and treatment is argued to be important pursuant to reducing hepatitis-associated liver cancer as well as the identification of other risk factors. For example, in individuals who have hepatitis B or C, smoking presents an additional risk in the future development of cancer. Alcohol consumption is also associated with increased risk of cancer diagnosis post hepatitis infection (Hassan et al., 2008). The World Health Organization argues that global surveillance strategies (Hendrickx et al., 2007) are likely needed to aid in combating an infectious disease whose forms in aggregate affect hundreds of millions of individuals with acute and chronic health implications.

The epidemiology of hepatitis B and C will be impacted by their association with liver cancer in the following ways: Individuals with a history of hepatitis B infection are 60 times more likely to develop liver cancer—a more compelling association than established between smoking and lung cancer in which smokers are 20–25 times more likely than nonsmokers to develop cancer (Beasley, Lin, Hwang, & Chein, 1981). Healthcare and public-health-associated costs for treatment and prevention of cancer have doubled in the past 20 years, and cancer diagnoses account for a significant proportion of total public health resources (American Cancer Society, 2010). An association or link between hepatitis and cancer can impact the epidemiology of hepatitis through collaborated surveillance, treatment, and prevention programs in addition to the potential for pooled resources specific to funding and research that may result from an established link. Public health and allied health professionals are more apt to more aggressively detect and treat hepatitis infection due to a

secondary and significant risk of chronic disease. Longitudinal surveillance data in the coming years will support or refute a decrease in incidence and prevalence due in part to increased awareness of the impact that hepatitis infection has on chronic disease morbidity and mortality.

Prostate cancer epidemiology is distinguished by several unique factors relative to the proposed role of infectious agents in the development of disease. Specifically, prostate cancer incidence rates vary widely within the context of location and race with up to a 90-fold difference between African Americans living in the United States and males living in Asian countries (Strickler & Goedert, 2001). Further support for examination into these contrasts is revealed by data that indicates that immigration from a low-incidence region to a high-incidence region increases the risk of developing prostate cancer fourfold (Strickler & Goedert, 2001). Data finds that differences in sexual behavior in African American and Asian males supports an infectious agent association with the development of prostate cancer, as males with more sexual partners and a diagnosis of one or more sexually transmitted disease are at increased risk of developing cancer (Strickler & Goedert, 2001). Specifically, an examination of 250 cases and over 400 controls found that a history of sexually transmitted disease was positively associated with prostate cancer (Mandel & Schuman, 1987). Similar studies led to examinations of the possibility of an infectious agent's association with the disease.

Among the first viruses examined in association with prostate cancer were herpes viruses, the Epstein-Barr virus, and the Kaposi's sarcoma virus, which have all been previously associated with cancer (Strickler & Goedert, 2001). Subsequent to a failure to find associations with other cancer viruses, HPV was examined due to its association with cervical cancer in women with inconclusive results (Strickler & Goedert, 2001). More recent studies have associated HPV with 70% of anal cancers and precancerous lesions of the penis in men. Cancers of the anus and penis are previously rare cancers whose rates have doubled in the past 30 years (Geipert, 2005).

HPV has been associated with cancer of the cervix in women and is also associated with cancers of the head, neck, oral region, and lungs (Spano, Marcelin, & Carcelin, 2005). The prevalence of HPV is 23% overall in men and women, 35% in 14–19-year-olds, 29% in 20–29-year-olds, 13% in 30–39-year-olds, and 11% and 6% in men and women 40–49 years of age and over 50 years old, respectively). HPV is a sexually transmitted disease with human carriers, wherein the mucosal membrane is the site of infection (CDC, 2010b). HPV is also distinguished by an inability to be cultured in vitro, which challenges accurate diagnosis. Also confounding accurate diagnosis is the fact that HPV is asymptomatic with a varied incubation period between 3 weeks and 8 months. Incidence rates are estimated to be as high as 90% in some populations such as young adults. Specific to the etiological link to cancer, HPV has been found to cause several changes linked to malignancy and dysregulation of tissues of the cervix and other organs. Koilocytosis, a hypertrophy of cervical epithelial cells, is accompanied by inflammation and dysplasia. The link of HPV to cancer is also dependent upon persistent HPV infection, but within that context, the risk of cervical cancer is over 40 times greater compared with uninfected women (Nelson & Williams, 2007, pg. 989).

H. pylori infection rates worldwide are estimated at 50% of the population with humans representing the primary reservoir; however, rates vary greatly according to geographical area, race, socioeconomic status, and age. Transmission of *H. pylori* is through oral-oral or fecal-oral routes via contaminated water or soil sources and then transmitted from person to person (Brown, 2000). *H. pylori* is associated with chronic gastritis and gastrointestinal disease in hundreds of epidemiological studies, including self-induced case studies involving the researchers infecting themselves to demonstrate a causal link to chronic disease. In one case, antibiotics failed to rid the researcher of *H. pylori*, leading to chronic gastric symptoms and complications (Nelson & Williams, 2007, pg. 483).

In 1990, it was estimated that 10% of all cancers may have an infectious cause or contributor. For example, *H. pylori* is estimated to be responsible for 5% of all stomach cancers, HPV is estimated to be responsible for 5% of cancers of the cervix and vulva, 4% of liver cancers are argued to be attributed to Hepatitis, and .5 to 1% of Kaposi's sarcoma, bladder cancer, leukemia, and cholangiocarcinoma are caused by an infectious agent (Nelson & Williams, 2007, pg. 44). More recently, HPV was associated with up to 70% of cervical cancer diagnoses (Geipert, 2005).

An intriguing example of how infectious/chronic diseases associations can affect public health and subsequent epidemiology is the direction of clinical trials examining treatments and prevention for infectious diseases linked to chronic conditions. For example, HVP infection is associated with cervical and vulvar cancer (among others) and women most commonly contract HPV through sexual contact with infected male partners. As a result, several clinical trials are examining the effect of HPV vaccinations for men and the potential impact on cervical cancer incidence in women (Geipert, 2005). Recently, a 4-year study has examined the HPV vaccine in men focusing on Latin and South American countries where cervical cancer rates are two to three times higher than in the United States.. This study divides heterosexual and homosexual men into groups who will be vaccinated and compared with matched control subjects. Subsequent tracking of cancer in their partners may lead to data pointing to the impact of providing HPV vaccinations to partners for the prevention of HPV and cancer (Geipert, 2005). In fact, a recent mathematical population model has estimated the direct and indirect public health impact of vaccinating boys and men for HPV. Compared with vaccinating females only, the additional decrease in cervical-cancer-associated cases as well as deaths are predicted to be over 800,000 within a 100-year period (Elbasha & Dasbach, 2010).

One caveat produced by epidemiological data is that there is a dramatically different incidence rate in the infectious agents with a proposed link to cancer and the cancers themselves. Specifically, the rates of all cancers are lower than the rates of the infectious diseases (Morris, Eddleston, & Crook, 1999). This logically points to likelihood that the infectious causal agent must be combined with other variables to initiate cellular proliferation dysfunction (Morris, Eddleston, & Crook, 1999). Other challenges relative to surveillance and epidemiology are the varied etiology that is associated with each of these interactions as in the relationship between HPV and later development in cancer. For example, HPV infection can take between 1 and 10 years to initiate precancerous lesions (Moscicki, Schiffman, Kjaer, & Villa, 2006).

Obesity and Metabolic Disease

Adenovirus 36 (AD-36) is a moderately sized virus composed of a double-stranded linear DNA genome and has been associated with obesity in animal and human case studies and epidemiological studies. Adenoviruses in aggregate account for up to 10% of upper respiratory infections in children and adults and are spread through droplet or fecal routes. Specific prevention strategies include optimal hygiene and sanitation practices and behaviors (Pasarica & Dhurandhar, 2007). AD-36 was first associated with obesity in an examination of chickens (Dhurandhar et al., 2000). Subsequent associations between AD-36 and obesity were observed in monkeys, mice, and rats with up to 100% of infected animals developing obesity relative to uninfected animals (Salehian et al., 2010). Human studies have observed correlations between AD-36 and increased adiposity, including a study that found triple the likelihood of obesity in individuals who presented with AD-36 antibodies including a mean difference in weight of 25 kg in infected individuals. Twin sibling studies also support an association between AD-36 and obesity with infected twins presenting with obesity more frequently compared with their uninfected siblings. Human studies have also documented a paradoxical decrease in lipid profiles—specifically, observations of lower total cholesterol and low-density lipoprotein in AD-36-infected individuals compared with those uninfected (Salehian et al., 2010).

The physiological mechanism or causal link between AD-36 and adiposity is the result of gene expression changes subsequent to AD-36 infection. Specifically, AD-36 modifies enzymes and transcription factors in adipocytes, increasing the binding potential of protein with fatty acid synthase. As a result, an increase in transport of lipids into cells is augmented by an increase in fatty acid synthesis. The net presentation of inducing enzymes that transport fat and increasing adipose tissue is accumulation of excess visceral and subcutaneous fat (Salehian et al., 2010).

The emergence of AD-36 and its possible association with obesity could significantly impact the epidemiology of obesity as we continue to observe increased proportions of obesity in all age groups in the United States (Flegal, Carroll, Ogden, & Curtin, 2010). The potential impact on the epidemiology of adenoviruses and obesity will alter surveillance, treatment, and prevention strategies associated with adenovirus infection and obesity (Whigham, Israel, & Atkinson, 2005). Currently, adenoviruses are not routinely tracked, as they typically present with mild or no symptoms; however, incident rates of adenovirus among children from 1976 to 2001 indicated seasonal patterns and increased infections between January and April and low infection rates during the summer months (Nelson & Williams, 2007, pg. 709). It was also found that most individuals infected with one type of adenovirus are infected with others, and additionally, it is speculated that serotypes other than AD-36 will be associated with obesity (Whigham, Israel, & Atkinson, 2005).

Relevant to surveillance is the potential need for the identification of increased risk populations for AD-36 infection such as individuals living in developing countries, urban environments, and schools and health care settings that all present opportunities for droplet transmission illnesses to optimally spread. In addition, there will be a potential shift away from the paradigm of associating obesity with a chronic disease largely caused by lifestyle factors toward considerations that obesity might be the result of viral infection (Greenway, 2006). Greenway (2006) argues further that a significant proportion of obesity may have a viral cause and supports his argument with the discovery of AD-36 and the onset of the increase in obesity, both taking place simultaneously. Greenway (2006) also argues that additional adenoviruses may contribute to obesity, including AD-37 and AD-5, which are being examined in animal studies with similar outcomes to preliminary AD-36 studies using animal subjects. Finally, given a potential shift in epidemiology associated with obesity and adenoviruses, it is argued that prevention and treatment should consist of screening individuals for AD-36 and the redevelopment of a vaccine (Greenway, 2006) that was previously developed for service men and women during World War II.

Metabolic syndrome is characterized by specific limits exceeded for weight, blood glucose, blood pressure, and lipid profiles and has been associated with prior infection with *Chlamydia pneumoniae* (CP), *H. pylori*, cytomegalovirus, and herpes simplex type 1 (HSV 1). Specific odds ratios for the development of metabolic syndrome for each are 1.81 for CP, 1.5 for *H. pylori*, 1.69 for cytomegalovirus, and 1.95 for herpes for men and women. Though the causative process for these relationships have not been established, it is likely that the observed endothelial dysfunction, elevated C-reactive protein levels, and chronic subclinical inflammation are contributing to the criteria for metabolic disease including hypertension, dyslipidemia, glucose intolerance, and obesity (Nabipour, Jafari, Pazoki, & Sanjdideh, 2006).

Cardiovascular Disease

Cardiovascular disease (CVD)-related deaths account for the highest proportion of total deaths in the United States (CDC, 2011b). Though top risk factors for CVD are largely of a behavioral origin, a number of infectious agents have also been associated with increased risk of CVD, including *H. pylori*, cytomegalovirus, periodontal bacteria, and CP. In addition to associations with

arthrosclerosis, associations with stroke and peripheral vascular disease have also been explored (Larsen, Moern, Fuller, Andersen, & Ostergaard, 2002). CP has also been associated with acute myocardial infarction, but these relationships are confounded by CP's status as an independent risk factor for other known and top correlates with CVD, such as smoking and high cholesterol. Additional support for a relationship stems from histological studies showing modified lipid metabolism following viral infection (Fabricant, 1986) and from associations between viral infections and cardiomyopathy, pericardiopathy, and myocarditis (Kawana, 1985).

Estimated incidence of CP includes 2.5 million cases per year and 500,000 associated hospitalizations. Approximately 50% of adults have been infected by age 20 with reinfection likely throughout their lifetime). CP is transmitted via droplet respiratory secretions and has been associated with asthma, arthritis, and Alzheimer's disease in addition to CVD (CDC, 2010a).

The role of CP in CVD is associated with the discovery that individuals who tested positive for the immunoglobulin G antibody were at increased risk of later developing a myocardial infarction in addition to aggregate evidence from retrospective, prospective, and cross-sectional studies. Supporting pathophysiology includes the ability of CP to directly infect cells that constitute atheromas, such as coronary artery endothelial cells, macrophages, and aortic smooth muscle cells, in addition to promoting intimal lining inflammation and damage (Contini et al., 2009). Studies have found double the rate of CP antibody presence in individuals with CVD diagnosis compared with individuals with no current CVD. In addition, CP antibodies are essentially absent in cells of arterial walls of individuals without CVD (Nelson & Williams, 2007, pg. 486). Dissimilar to several other infectious and chronic disease relationships, treatment with antibiotics has not provided attenuation of CP infection. Evidence refutes the effectiveness of antibiotic therapy in its prevention of subsequent heart attacks (Cercek et al., 2003) in several randomized controlled trials over the short and long term (Nelson & Williams, 2007, pg 486).

Ironically, the association between infectious agents and heart attacks was first proposed in the late 1800s and persisted through the early 1900s but was replaced by the paradigm and associated research linking CVD primarily to behavioral and genetic risk factors (Nelson & Williams, 2007, pg. 484). The impact of the association between infectious agents and CVD include modifications to treatment and prevention programs that acknowledge this relationship and consider infection a viable risk factor for a heart attack. For example, over 5% of physicians in the United States recommend including antibiotic treatment for the diagnosis of CVD (Larsen et al., 2002). A study of over 200 individuals treated with antibiotics for the prevention of cardiovascular events demonstrated a fourfold increase in adverse events in the placebo group, and up to 10 longitudinal controlled studies of over 20,000 subjects are currently examining the possible protection provided by antibiotics for cardiovascular disease (Larsen et al., 2002).

Neurodegenerative Disease

Approximately 5 million Americans have Alzheimer's disease, with about 5% of men and women over 65 and 50% of men and women over 85 estimated as having the disease (CDC, 2011a). Behavioral risk factors such as high blood pressure, diabetes, high cholesterol, and a sedentary lifestyle are now examined within the context of infectious disease agents including CP and HSV 1 infection (Itzhaki et al., 2004). CP epidemiology is discussed previously; however in addition to its relatively high prevalence in the community, the incubation period associated with CP is longer (several weeks) as compared with most other respiratory pathogens, increasing the spread and transmission of the disease relative to other respiratory illnesses (Contini et al., 2009). The association between CP and neurodegenerative disorders including Alzheimer's, multiple sclerosis (MS), and neurobehavioral

disorders was established via statistical analysis and empirical associations and also due to the ability of CP to live and persist in tissues for a long period of time and circumvent the blood-brain barrier. CP also activates endothelial cells and causes inflammation, deterioration, and progression of the pathophysiology associated with neurodegenerative disease (Itzhaki et al., 2004). For example, 90% of postmortem brain samples of late onset Alzheimer's disease victims tested positive for CP bacterium (Balin et al., 1998).

MS is diagnosed in 1–2 individuals per 1000 and is associated with 3000 deaths each year. Epidemiological studies suggest that MS is caused by a combination of an infectious agent and genetic predisposition. The proposed link between CP and MS is based on the observation that modulation of immune activity and “pathogen-associated molecular patterns” is varied depending on past CP infection; more compelling, the response is greatest among individuals with multiple past CP infections (Itzhaki et al., 2004). Further support associating CP with neurodegenerative disorders is the effectiveness of antibiotic treatment in the cases of neurological behavioral disorders, encephalitis, Guillan-Barre syndrome, paralysis, aphasia, and neurological sleep disorders (Itzhaki et al., 2004).

HSV 1 virus is not typically transmitted through sexual contact but, alternatively, contracted during childhood and presents symptoms including facial lesions. HSV 1 has also been associated with genital herpes for specific populations, including residents of developing countries and college students in the United States. Overall prevalence of HSV 1 in the United States was 62% between the years 1999 and 2004 (Xu, Sternberg, Kottiri, McQuillan, & Lee, 2006). With over 70% of the population infected by age 50 and lifelong presence of herpes infection, numerous associations and causal links with chronic health conditions are probable (Letenneur et al., 2008).

HSV 1 has been found to be highly correlated with Alzheimer's diagnosis. Specifically, a cohort study examining over 500 elderly individuals with no diagnosis of Alzheimer's for 14 years found hazard ratios of 2.55 in subjects with previous HSV infection compared with controls (Letenneur et al., 2008). Unlike CP testing and screening, individuals with HSV 1 infection are more easily and accurately detected and, as a result, primary and secondary prevention strategies might be more specifically applied.

Discussion and Conclusion

Public desire to identify a singular cause or “magic bullet” pursuant to chronic diseases can potentially hinder the exploration of infectious and chronic causal relationships in several ways. For example, the influence of the infectious agent will, in many cases, present similar to other risk factors for chronic disease or may play a role as an accelerant to environmental or behavioral risk factors. SoRelle (1998) argues that a preemptive conclusion relative to the impact of infectious agents may slow epidemiological studies and undermine already established findings. Costs associated with researching these associations will be significant as most associations are recently discovered and will require long-term controlled studies. For example, a longitudinal study similar to the Framingham Study—which has examined CVD epidemiology among three generations of individuals since 1948 (National Heart, Lung and Blood Institute and Boston University, 2011)—is proposed to analyze the role of infectious agents on chronic diseases (SoRelle, 1998). Data linking infectious agents to chronic disease is compelling enough to merit long-term epidemiological studies to determine their impact and direct treatment and prevention programs.

The CDC has responded to emergent infections, re-emergent infections, and potential associations between infectious agents and chronic disease with four specific objectives:

1. Increasing the rigor associated with surveillance and reporting so that early detection of trends or new infections and relationships can be assured
2. Identifying and supporting applied research activities, including longitudinal studies, development of diagnostic tests, and exploring contemporary research areas such as genetics and the associations between infectious agents and chronic disease
3. Strengthening training within the public health system to provide experts in the fields of surveillance, program implementation, and assurance roles
4. Implementing effective treatment and prevention programs that should be directed by and be the outcome of the preceding objectives (Hughes, 2001). Known trends in infectious disease epidemiology support a need for vigilance in place of complacency due to the tendency of microbes to evolve and modify to human demographic and behavior patterns (Hughes, 2001).

Furthermore, the G8 (or Group of Eight industrialized nations) has identified infectious disease as a global and national threat to national security with associated goals for reducing HIV infection, tuberculosis, and malaria, among other infectious diseases (Hughes, 2001). Recent complacency as identified by the Institute of Medicine (2004) and specific gaps in knowledge—as well as communication gaps between researchers, public health, and allied health in the United States—are critical weaknesses in the area of surveillance, prevention, and control efforts. Increased involvement from groups such as the G8 in coordinating these efforts along side the CDC and World Health Organization may direct and inform “best practices” associated with surveillance, research, and treatment using antibiotics and antiviral medications.

As previously discussed, the field of epidemiology examines disease distribution and determiners to reduce morbidity and mortality (Aschengrau & Seage, 2008, pg. 6). Though there are complexities associated with linking viral and bacterial agents to cancer, CVD, cognitive disease, and others, it is speculated that the aggregate impact of this emerging topic in infectious disease epidemiology will have at least two specific impacts on the epidemiology of infectious disease. Expressly, identification of infectious causes of prevalent chronic diseases will likely require research followed by associated education, resources, and treatment and prevention programs. Secondly, research examining the epidemiology of infectious diseases will increasingly include the possible impact infectious agents may have on chronic disease. This will impact the study design of infectious disease research. For example, a call for “the Framingham Study of infectious disease” was made in reference to a shift in the paradigms associated with infectious and chronic disease epidemiology (SoRelle, 1998). Specific to surveillance, it is logical to assume that screening for the infectious agents identified as causes will be increased, including screening and testing for currently (and formerly less frequently) tracked infectious diseases of a more benign nature and increased screening among suspected cases. For example, CP testing may be indicated in the absence of any symptoms, while currently testing for CP is not recommended or subject to state or national surveillance or mandatory reporting procedures (CDC, 2010a). We may also see resources directed toward screening and detection services. With regards to treatment, thousands of subjects are engaged in infectious-agent-correlative chronic disease longitudinal studies at the present time, and many are being managed or treated with antibiotics. As a result, subsequent studies are required to determine the effectiveness and prudence of antibiotic use for the treatment of chronic diseases given the context of increasing resistance of organisms to antibiotics. Caution should be taken when considering increased use of antibiotics for the treatment of chronic disease (SoRelle, 1998), and alternate treatment courses may need to be determined, such as prevention of infection in place of widespread antibiotic use. For example, present and emerging health threats associated with influenza and other infectious diseases with

equal or surpassing morbidity and mortality rates compared with chronic diseases may have a higher priority relative to antibiotic research and associated treatment.

Antibiotic use and effectiveness must also be considered within a context of identifying infectious disease agents as causes of chronic diseases. Antibiotic treatments for infectious diseases typically last weeks in duration, while treatment courses for chronic control of infectious agents can last months or years. The impact on microbial resistance is likely to be increased according to current studies that monitor antibiotic use and resistance. Specifically, a cross-European study compared “high” (32 daily doses per 1000 residents) countries to “low” (10 daily doses per 1000 residents) countries and found significantly increased rates of antibiotic resistance in the countries administering and consuming the most antibiotics (Goossens, Ferech, Stichele, & Elseviers, 2005). If more individuals are prescribed antibiotics for longer treatment courses, it is speculated that the aggregate effect on resistance would be increased. In addition, a long-term prevention strategy proposed for decreasing microbe resistance has been a reduction in overall antibiotic use, which contradicts the proposed increase in prescription and treatments for chronic-disease-associated treatment courses of infectious agents.

An argument for consideration of infectious disease prevalence in healthcare settings may also be impacted by aggregate and specific data that points to infectious causes of chronic disease. For example, a study linking CP with Alzheimer’s disease found a higher association in skilled nursing facilities compared with subjects who lived at home (Contini et al., 2009). Infectious causes of chronic illnesses in traditional nosocomial environments may bring more attention to the issue of nosocomial infections, which currently account for 2.5 million illnesses and 250,000 associated deaths (Nelson & Williams, 2007, pg. 505).

The Institute of Medicine (2004) characterizes the future of infectious- and chronic-disease-related research as facing both challenges and opportunities. Among the challenges are the myriad of ways infections interact with other chronic disease variables in acute and chronic manners. High degrees of variability are present relative to a viral or bacterial agent’s resistance in the body, degree and type of symptoms, and future impact on chronic disease development or acceleration. An inability to physically detect or identify the viral or bacterial organism within diseased tissue also presents challenges when arguing temporal or associative relationships. Additionally, the mere presence of the associative infectious agent will not adequately identify existing or future disease, as other behavioral or environmental factors may also need to be present in order for chronic disease to be initiated or perpetuated.

A final consideration permits a discussion of association relative to causation. In several of these infectious and chronic causal links, a specific and plausible etiology is proposed or has been discovered, such as in the argument for CP and neurodegenerative disease (Itzhaki, 2004). Specific to future links that may be proposed, given the prevalence of several of these infectious agents approaching or exceeding the majority of the population, it is likely that most individuals will have been previously infected by a highly prevalent infectious disease and will later develop a highly prevalent chronic disease. In other words, this issue may impact the majority of the population. As a result, consideration of the association in isolation is not adequate and must be supported by evidence to suggest plausibility and probability that the link is causal in nature, in addition to thorough assessment of the costs relative to the health benefits associated with prevention, screening, and treatment.

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