There has been a traditional view that divided epidemiology into infectious and chronic diseases. Since we now know that at least 15% of cancers worldwide are caused by infections,\(^1\) that infections frequently have a natural history lasting decades and that the same epidemiological methods can be applied to both infectious and non-infectious diseases, this view can be considered purely historical. However, the nature of infectious diseases has implications for the application of epidemiological approaches including the specific example of life course epidemiology. Whilst the definition of this is still debated, it clearly refers to the way in which influences at different stages of life affect and modify risks of disease. Life course epidemiology particularly focuses on disease in adult life and so that is what we discuss here. We are not going to consider childhood or adolescent diseases. In addition it recognizes two types of influence on risk: (1) a simple accumulation of risks and (2) ‘programming’.\(^2\) The latter is the way in which an influence modifies a biological system so that it responds differently to subsequent exposures. The epidemiological paradigm for this has been David Barker’s hypothesis that intra-uterine nutrition determines physiological responses in the cardiovascular system.\(^3\)

When we come to talk about infections we have to deal with a few semantics. Susceptibility means that the subject is vulnerable to infection if they are exposed. Infants may not be susceptible because of transferred immunity from their mother. Many, but not all, infections result in a loss of susceptibility due to immune memory. Exposure is traditionally used to define exposure to the infectious agent. We will use it in that context here and use the term ‘influence’ for non-agent exposures. There is a critical difference between infection and disease. The proportion of individuals infected who develop disease varies from 0% (as with infection with the hepatitis G virus) to virtually 100% (with measles and the human immunodeficiency virus [HIV]) depending on the infection. However, for many infections the relationship is strongly dependent on the age at which infection occurs—an obvious entrée for life course epidemiology. Thus Epstein-Barr virus infection in childhood hardly causes any symptoms whereas in adolescence it results in glandular fever. Severity and rate of disease progression are also influenced by age at infection. Hepatitis A becomes an increasingly severe disease the older the subject. We return to this point below. Finally, we use the term ‘reactivation’ for persistent infections that produce disease after a prolonged period of latency following a first disease episode. Varicella zoster virus remains latent for years following chickenpox until around a fifth of infected people develop shingles. The simple model in Figure 1 shows how influences may affect various stages of the process. This emphasizes proximate biological factors. Clearly there are more distal factors that may be more easily measured. For example, exposure to the infectious agent is highly dependent on behaviour—mixing patterns with other young children may determine exposure to childhood infections and sexual activity modulates risk of sexually transmitted infections.

The timing from susceptibility to disability, death or recovery is incredibly variable. With many infections that do not persist, symptoms of disease occur, if they are going to, within days—at most months—after initial infection. Agents, such as hepatitis B and C viruses, that persist and replicate within the body may not lead to disease (in this case primary liver cancer) until 50 years after infection. Once infectious disease is recognized the natural history is as variable as that of non-communicable diseases. The reasons for all this variation are the influences at each stage.

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**Figure 1** Simplified model of influences that may affect infectious disease

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These influences reduce down to characteristics of the exposure to the agent (route, dose, genetics of the agent), the role of other infections in modifying immune response (prior exposure, co-infection), immune functional status and a miscellany of more minor influences such as anatomical factors and physical trauma (where mucosal barriers are more easily breached by organisms). Human genetics is likely to have its major role when considering infections. Thus much of the interest in infectious disease lifecourse epidemiology will revolve around influences on the integrity and functionality of immunity. The natural history of immune responses is still relatively little understood. We know that the immune system has to be specially modified in utero in order to be able to recognize what is self and what is foreign. Then within minutes of birth the system faces a world full of hostile agents that must be rejected and controlled, but which may at times bear a striking resemblance to self. Not surprisingly it is not fully up and running at that instant. Thus for example, key responses to encapsulated bacteria, such as the *Pneumococcus*, occur primarily through a specific type of antibody that is not fully developed until after 2 years of age. Some would even consider that the immune system is not fully developed until adolescence. It then functions at an optimal level—although perturbed by events such as pregnancy—until around the age of 40 years when it begins to decline. This is the canvas that we can now colour with life influences. What factors moderate neonatal immune development, the adolescent peak and its height, the timing of commencement of decay and its rate? There are interesting analogies to bone density—that also develops through childhood, may be programmed in early life, peaks in adolescence or early adult life and declines from middle age onwards.

Nutritional status is very important to current immune competence. Its role at different ages in determining the lifetime pattern of immune competence is much less clear. Infections are also known to be critical to current immune responsiveness—HIV is an obvious example, but measles, Epstein-Barr virus and many others are known to modify the immune response both in the short term and over longer periods. Infections also appear to influence the immune system qualitatively—the strong epidemiological evidence for a shift in T_h1/T_h2 balance related to early life infection is now receiving direct biological support from the measurement of cytokines.4

So how does this all relate to life course epidemiology? Let us consider first a cumulative risk model. A child has poor lung development *in utero* and ends up with smaller airways than the norm. Since she is firstborn in the family and does not attend day care she is relatively protected from infections until she goes to school. This shifts her immune system towards an atopic state. In adolescence she lives in a polluted urban environment and develops asthma. At the age of 35 she begins drinking heavily and her immune system is impaired as a result. Her youngest child brings home a virulent serotype 1 pneumococcus from the school environment—she gets pneumonia. This puts her at a marked increased risk of a subsequent pneumonia in the next 12 months.

Although we have separate conceptual models of cumulative risk and programming, these may occur in the same individual as in the example above. In the immune system it is particularly programming that has received little attention. One intra-uterine example is lymphatic filariasis. Children born to mothers infected with this worm tolerate postnatal infection with the same worm. In contrast, children born to uninfected mothers are at high risk of developing acute lymphangitis when they are infected.5

Another interesting area with regard to immune programming is that of the role of diet. This arose from the observation that the risk of adult mortality—particularly from infectious disease—in a village in tropical West Africa was related to season of birth with the implication that this was due to early life nutrition.6 Other influences on early life immunity need careful attention. Infections may exert effects on cells other than T helper lymphocytes. We know that ultraviolet radiation has important systemic effects on current immunity and could play a role during childhood on immune programming. Psychological and physical stress both have important measurable effects on immune competence. Again they may play a role in programming. Programming may be particularly important for diseases resulting from reactivation of latent infections. It would be particularly apparent in younger cases since in those older than 40 years age related immune decay will potentially disguise the effects of programming.

Thus the exact mechanisms and influences that programme the immune system need to be clarified, as do relationships between programming and cumulative risks. So there is an important place for life course epidemiology in the study of infectious diseases and an important role for the consideration of infections in the life course study of diseases of unknown aetiology.

References