Mims' Pathogenesis of Infectious Disease

Sixth Edition

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Preface

It has been 12 years since the fifth edition of this book was published. In that time, we have witnessed a revolution in the technologies underpinning studies of the pathogenesis of infectious disease. In the fifth edition, 30 bacterial genomes had been completed. We now have access to thousands of completed pathogen genomes and those of many mammalian, avian and piscine 'host' species. This has led to new ways of exploring how pathogen and host interact, and how they evolve. In turn the new insights gained into pathogenesis are leading to improvements in diagnostics, vaccines and therapeutics.

The sixth edition maintains the standards and unique style of earlier editions despite the absence of Professor Mims whose vision was paramount in bringing pathogenesis to a wider audience. In particular, we have endeavoured to use accessible language and simple but colourful diagrams to convey the mechanisms of pathogenesis to students of infectious disease.

Tony Nash
Bob Dalziel
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CHAPTER

1

General Principles

When writing a book about infectious diseases, it is important to define exactly what we mean in using the term in order to provide a context for the information to come. In general biological terms, the relationship between two distinct but associated organisms can be classified as parasitic, where one benefits at the expense of the other, or symbiotic (mutualistic), where both benefit. There is another commonly used category called commensalism, whereby the organisms co-exist without damage to either organism. It is often difficult to use this category with confidence, because an apparently commensal association often proves on closer examination to be really parasitic or symbiotic.

The classification system can be applied to the association between microorganisms and vertebrates. Generalised infections such as measles, tuberculosis or typhoid are clearly examples of parasitism. On the other hand, the microbiota inhabiting the rumen of cows or the caecum of rabbits, enjoying food and shelter and at the same time supplying the host with food derived from the utilisation of cellulose, are clearly symbiotic. In addition, recent and on-going research is revealing the great variety of ways by which resident bacteria are contributing to the normal function of their host species. For example, the bacteria that live on human skin may at first be considered as commensals. They enjoy shelter and food (sebum, sweat, etc.) but are normally harmless. If the skin surface is examined by the scanning electron microscope, the bacteria, such as *Staphylococcus epidermidis* and *Proprionibacterium acnes*, are seen in small colonies scattered over a moon-like landscape. The colonies contain several hundred individuals[1] and the bacteria adhere to the epithelial squames that form the cornified skin surface, and extend between the squames and down the mouths of the hair follicles and glands onto the skin surface. They can be reduced in numbers, but never eliminated, by scrubbing and washing, and are most numerous in more moist regions such as the armpit, groyne and perineum. The dryness of the stratum corneum makes the skin an unsuitable environment for most bacteria, and merely occluding and thus hydrating an area with polythene sheeting leads to a large increase in the number of bacteria. The secretions of apocrine sweat glands are metabolised by skin bacteria, and odoriferous amines and other substances such as 16-androstene steroids are

[1]The average size of these colonies is determined by counting the total number of bacteria recovered by scrubbing and comparing this with the number of foci of bacterial growth obtained from velvet pad replicas. The sterile pad is applied firmly to the skin, then removed and applied to the bacterial growth plate.

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produced, giving the body a characteristic smell that modern man, at least, finds unpleasant.[2] Deodorants, containing aluminium salts to inhibit sweating, and often antiseptics to inhibit bacterial growth, are therefore often applied to the apocrine gland areas in the axillae. However, body smells have been of great significance in the social and sexual life of humans and mammals in general. Not all body smells are produced by bacteria, and skin glands may secrete substances known as pheromones that are themselves odoriferous but some skin bacteria do contribute to body smells and could for this reason be classified as symbiotic rather than parasitic. There is also evidence that harmless skin bacteria inhibit the colonisation and growth of more pathogenic bacteria, again indicating benefit to the host and a symbiotic classification for these bacteria.

A microbe's ability to multiply is obviously of paramount importance; indeed, we call a microbe dead or nonviable if it cannot replicate.[3] The ability to spread from host to host is of equal importance. Spread can be horizontal in a species, whereby one individual infects another by contact, or via insect vectors (Figure 1.1). Alternatively, spread can be 'vertical' in a species, with parents infecting offspring via sperm, ovum, the placenta, the milk, or by contact. Clearly if a microbe does not spread from one individual to another it will die with the individual and cannot persist in nature. The crucial significance of the ability of a

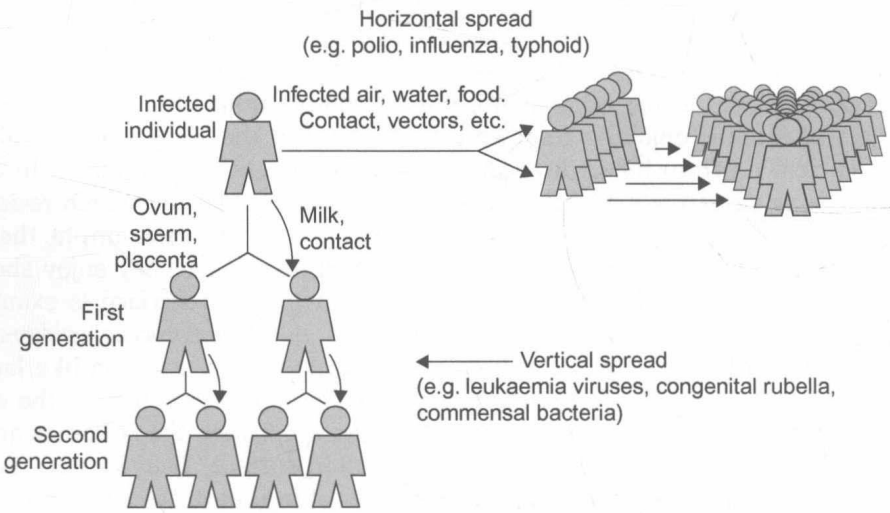

FIGURE 1.1 Vertical and horizontal transmission of infection.

[2]The smell of feet encased in shoes and socks is characteristic, and in many European languages it is referred to as cheese-like. Between the toes lives *Brevibacterium epidermidis*, which converts L-methionine to methane thiol, a gas that contributes to the smell. A very similar bacterium is added to cheeses such as Brie to enhance odour and flavour.

[3]Sterilisation is the killing of all forms of microbial life, and appropriately the word means making barren, or devoid of offspring.

microbe to spread can be illustrated by comparing the horizontal spread of respiratory and sexually transmitted infections (STIs). An infected individual can transmit influenza or the common cold to a score of others in the course of an innocent hour in a crowded room. An STI also must spread progressively from person to person if it is to maintain itself in nature, but even the most energetic lover could not transmit a venereal infection on such a scale. A chain of horizontal infection in this case, however, requires a chain of sexual contact between individuals. If those infected at a given time never had sexual contact with more than one member of the opposite sex, the total incidence could double in a lifetime, and when the infected people died the causative microbe would be eliminated. In other words, STIs must be transmitted to more than one member of the opposite sex if they are to persist and flourish. The greater the degree of sexual promiscuity, the greater the number of sex partners, the more successful such infections can be. Further discussion of STIs are included in the next chapter.

Only a tiny proportion of the microorganisms associated with humans have the potential to give rise to pathological changes or cause disease. Vast numbers of bacteria live harmlessly in the mouth and intestines, on the teeth and skin, and most of the 150 or so viruses that infect humans cause no detectable illness in most infected individuals, in spite of cell and tissue invasion. This is to be expected because, from an evolutionary point of view, successful microbes must survive, multiply, and leave viable descendants. A successful parasitic microbe lives on or in the individual host, multiplies, spreads to fresh individuals, and thus maintains itself in nature (Table 1.1).

A successful parasitic microbe, like all successful parasites, will obtain what it requires for proliferation from the infected host without causing much damage. If an infection is debilitating or even lethal, there will be a reduction in numbers of the host species and thus in the numbers of the microorganism. Thus, although a small number of microbial pathogens cause disease in a majority of those infected (so-called true pathogens), most are comparatively

TABLE 1.1 Obligatory Steps for Infectious Microorganisms

Step	Phenomenon	Requirement	Chapter
1. Attachment ± entry into body	Infection (entry)	Evade host's natural protective and cleansing mechanisms	2
2. Local or general spread in the body	Local events, spread	Evade immediate local defences and the natural barriers to spread	3, 5
3. Multiplication	Multiplication	Multiply; many offspring will die in host or *en route* to fresh host	
4. Evasion of host defences	Microbial answer to host defences	Evade phagocytic and immune defences long enough for full cycle in host to be completed	4, 6, 7
5. Shedding (exit) from body	Transmission	Leave body at site and on a scale that ensures spread to fresh host	2
6. Cause damage in host	Pathology, disease	Not strictly necessary but often occurs[a]	8

[a]Some damage may be inevitable if efficient shedding is to occur (e.g. common cold, diarrhoea, skin vesicles).

harmless, causing either no disease, or disease in only a small proportion of those infected. Polioviruses, for instance, are transmitted by the faecal–oral route and cause a subclinical intestinal infection under normal circumstances. But in an occasional host the virus invades the central nervous system and causes meningitis, sometimes paralysis, and very occasionally death. This particular site of multiplication is irrelevant from the virus point of view, because growth in the central nervous system is quite unnecessary for transmission to the next host. Well-established infectious agents have therefore generally reached a state of balanced pathogenicity in the host and cause the smallest amount of damage compatible with the need to enter, multiply, and be discharged from the body.

The importance of balanced pathogenicity is strikingly illustrated in the case of the natural evolution of myxomatosis in the Australian rabbit. After the first successful introduction of the virus in 1950 more than 99% of infected rabbits died, but subsequently new strains of virus appeared that were less lethal. The less lethal strains of virus were therefore selected during the evolution of the virus in the rabbit population, because they persisted longer and were therefore more successful parasites. The genetics of the rabbit population also changed, because those that were genetically more susceptible to the infection were eliminated. Rabies, a virus infection of the central nervous system, seems to contradict, but in fact exemplifies, this principle. Infection is classically acquired from the bite of a rabid animal and the disease in man is almost always fatal, but the virus has shown no signs of becoming less virulent. Man, however, is an unnatural host for rabies virus, and it is maintained in a less pathogenic fashion in animals such as vampire bats and skunks. In these animals, there is a relatively harmless infection and the virus is shed for long periods in the saliva, which is the vehicle of transmission from individual to individual. Rabies is thus maintained in the natural host species without serious consequences. But bites can infect the individuals of other species, 'accidentally' from the virus point of view, and the infection is a serious and lethal one in these unnatural hosts.

Although successful parasites cannot afford to become too pathogenic, some degree of tissue damage may be necessary for the effective shedding of microorganisms to the exterior, as for instance in the flow of infected fluids from the nose in the common cold or from the alimentary canal in infectious diarrhoea. Otherwise there is ideally very little tissue damage, a minimal inflammatory or immune response, and a few microbial parasites achieve the supreme success of causing zero damage and failing to be recognised as parasites by the host. Different microbes show varying degrees of attainment of this ideal state of parasitism.

The concept of balanced pathogenicity is helpful in understanding infectious diseases, but many infections have not yet had time to reach this ideal state. In the first place, as each microorganism evolves, occasional virulent variants emerge and cause extensive disease and death before disappearing after all susceptible individuals have been infected, or before settling down to a more balanced pathogenicity. Secondly, a microbe recently introduced into a host (e.g. human immunodeficiency virus (HIV) in humans) may not have had time to settle down into this ideal state. Thirdly, some of the microbes responsible for serious human diseases had appeared originally in one part of the world, where there had been a weeding out of genetically susceptible individuals and a move in the direction of a more balanced pathogenicity. Subsequent spread of the microorganism to a new continent has resulted in the infection of a different human population in whom the disease is much

more severe because of greater genetic susceptibility. Examples include tuberculosis spreading from resistant Europeans to susceptible Africans or North American Indians, and yellow fever spreading from Africans to Europeans. Finally, there are a number of microorganisms that have not evolved towards a less pathogenic form in man because the human host is clearly irrelevant for the survival of the microorganism. Microorganisms of this sort, such as those causing rabies (see above), scrub typhus, plague, leptospirosis and psittacosis, have some other regular host species which is responsible, often together with an arthropod vector, for their maintenance in nature.[4] The pathogenicity for man is of no consequence to the microorganism. Several human infections that are spillovers from animals domesticated by man also come into this category, including brucellosis, Q fever, anthrax, and livestock-associated meticillin-resistant *Staphylococcus aureus* (MRSA) infections. As humans colonise every corner of the earth, they encounter an occasional microbe from an exotic animal that causes, quite 'accidentally' from the point of view of the microorganisms, a serious or lethal human disease. Examples include Lassa fever and Marburg disease from African rodents and monkeys, respectively.[5]

On the other hand, a microorganism from one animal can adapt to a new species. Advances in DNA sequencing and phylogenetic analyses are revealing much about the evolutionary history of pathogens. Measles, which could not have existed and maintained itself in humans in the Palaeolithic era, probably arose at a later stage from the closely related rinderpest virus that infects cattle. New human influenza viruses continue to arise from birds, and the virus of the acquired immunodeficiency syndrome (AIDS), the modern pestilence, seems to have arisen from a very similar virus infecting monkeys and chimpanzees in Africa. In addition, livestock strains of *S. aureus* most likely originated in humans but jumped into animal hosts since domestication occurred several thousand years ago.

Microorganisms multiply exceedingly rapidly in comparison to their vertebrate hosts. The generation time of an average bacterium is an hour or less, as compared with about 20 years for the human host. Consequently, microorganisms evolve with extraordinary speed in comparison with their vertebrate hosts. Vertebrates, throughout their hundreds of millions of years of evolution, have been continuously exposed to microbial infections. They have developed highly efficient recognition (early warning) systems for foreign invaders, and effective inflammatory and immune responses to restrain their growth and spread, and to eliminate them from the body. If these responses were completely effective, microbial infections would be few in number and all would be terminated rapidly;

[4]These infections are called *zoonoses*.

[5]Lassa fever is a sometimes lethal infection of man caused by an arenavirus. The virus is maintained in certain rodents in West Africa as a harmless persistent infection, and man is only occasionally infected. Another serious infectious disease occurred in 1967 in a small number of laboratory workers in Marburg, Germany, who had handled tissues from vervet monkeys recently imported from Africa. The Marburg agent is a virus and has since reappeared to cause fatal infections in Zaire and the Sudan, but nothing is known of its natural history. Monkeys are not natural hosts and are probably accidentally infected, like man. Since 1976, Ebola virus, related to Marburg, has caused dramatic local outbreaks in Zaire and Sudan. In 2014 a major outbreak of Ebola resulted in the deaths of thousands of people in West Africa. Like Lassa fever, it can spread from person to person via infected blood, but its natural host is unknown. However, bats are a likely reservoir.

microorganisms would not be allowed to persist in the body for long periods. But microorganisms, faced with the antimicrobial defences of the host species, have evolved and developed a variety of characteristics that enable them to by-pass or overcome these defences. In any case, the normal commensal microbiota is tolerated because it performs critical functions required for the general health and well-being of the host. The defences are not infallible, and the rapid rate of evolution of microorganisms ensures that they are always many steps ahead. If there are possible ways round the established defences, microorganisms are likely to have discovered and taken advantage of them. Successful microorganisms, indeed, owe their success to this ability to adapt and evolve, exploiting weak points in the host defences. The ways in which the phagocytic and immune defences are overcome are described in Chapters 4 and 7.

It is the virulence and pathogenicity of microorganisms, their ability to kill and damage the host, that makes them important to the physician or veterinarian. If none of the microorganisms associated with man did any damage, and none was notably beneficial, they would be interesting but relatively unimportant objects. In fact, they have been responsible for the great pestilences of history, have at times determined the course of history, and continue today, in spite of vaccines and antibiotics, as major causes of disease (see Table A.1). Also, because of their rapid rate of evolution and the constantly changing circumstances of human life, they continue to present threats of future pestilences. Importantly, pathogens constantly 're-invent' themselves through evolution in order to counteract human efforts at control such as antibiotic treatment. In fact the emergence of bacterial resistance to virtually all classes of antibiotics is one of the greatest current threats to man's capacity to treat infectious diseases. Overall, it is the purpose of this book to describe and discuss the mechanisms of infection and the characteristics that make microorganisms pathogenic. In addition to understanding the role of commensal microbiota in the health host, this is the central significant core of microbiology as applied to medicine.

In the last 12 years since the previous edition of this book, dramatic advances in molecular biological techniques have been made resulting in broad new insights into our understanding of the biology of microbes and how they impact on our lives. We now have a vastly more detailed understanding of host pathogen interactions at the cellular, genetic and biochemical levels based on our ability to manipulate microbial and host genetics in order to understand the critical interactions and responses involved. By such means a great deal of biochemical information can be obtained about the microbial determinants involved in mediating different aspects of the complex infection process.

But the most dramatic developments in recent years have come in DNA sequencing technologies. New and emerging methods can produce vast amounts of sequence information rapidly and relatively inexpensively. This has resulted in many thousands of whole genome sequences for bacterial and parasite pathogens and several hundred higher order organisms (vertebrates and invertebrates) becoming available in the public DNA sequence databases. In addition, metagenomic studies which qualitatively and quantitatively examine the microbial content within biological samples are informing our understanding of microbial diversity in different ecological niches. In the current 'post-genomic' era as it has come to be known, generating sequence information is relatively facile. It is the mining of the data and the assignment of functional relevance which is the bottle-neck in terms of biological understanding. New sequencing

technologies also allow examination of genome-wide gene expression, building on previous transcriptomic approaches, such as microarrays.

The recent advances made in DNA sequencing technology have resulted in large complex genomes such as the human genome requiring only a matter of days to complete. Now that all the genomes of the major domestic livestock species have been completed, the opportunity exists to study the genome-wide interactions between pathogen and host genomes.

By extracting mRNAs from bacteria grown in culture and from the same organism from an infection site (or grown in conditions which mimic infection conditions), it is possible to identify which gene(s) are expressed or repressed in the two situations. This may point to factors which are essential for survival during infection and which thus may represent novel therapeutic targets. Similar studies can also be carried out in cells infected by viruses, allowing the host cell response to these pathogens to be dissected. In addition to sequencing technologies, major advancements in microscopy and imaging, particularly for *in vivo* analysis, are resulting in very enhanced views of the way by which microbes cause disease. Overall, we are in a very exciting time with tremendous potential for understanding the biology of infectious diseases. Considering that we are also in an age when the options for treating bacterial infections are fast reducing due to the increase in antibiotic resistance, and that the threat of emerging viral pathogens is very apparent, we must utilise our improved understanding of infectious disease to design rational ways for their control.

In order to facilitate an understanding of infectious disease it is possible to distinguish different phases of the 'pathogenic cycle', including an appreciation for the bacterial, host and environmental factors which contribute to infectious disease and the outcome of infection. In addition to the bacterial virulence determinants involved, an understanding of the host's phagocytic and immune defences is important, and these are briefly set out in Chapters 4, 6 and 9. There are additional chapters on resistance and recovery from infection, persistent infection, and the prevention of infection by vaccines.

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CHAPTER

2

Attachment to and Entry of Microorganisms into the Body

OUTLINE

INTRODUCTION

Figure 2.1 shows a simplified diagram of the mammalian host. In essence, the body is traversed by a tube, the alimentary canal, with the respiratory and urinogenital tracts as blind pouches from the alimentary canal or from the region near the anus. The body surface is covered by skin, with a relatively impermeable dry outer layer, and usually fur. This gives a degree of insulation, and the structure of skin illustrates the compromise between the need to protect the body, yet at the same time maintain sensory communication with the outside world, give mechanical mobility, and, especially in man, act as an important thermoregulatory organ. It is the largest 'organ' in the body, with a weight of 5 kg in humans.

The dry, protective skin cannot cover all body surfaces. At the site of the eye it must be replaced by a transparent layer of living cells, the conjunctiva. Food must be digested and

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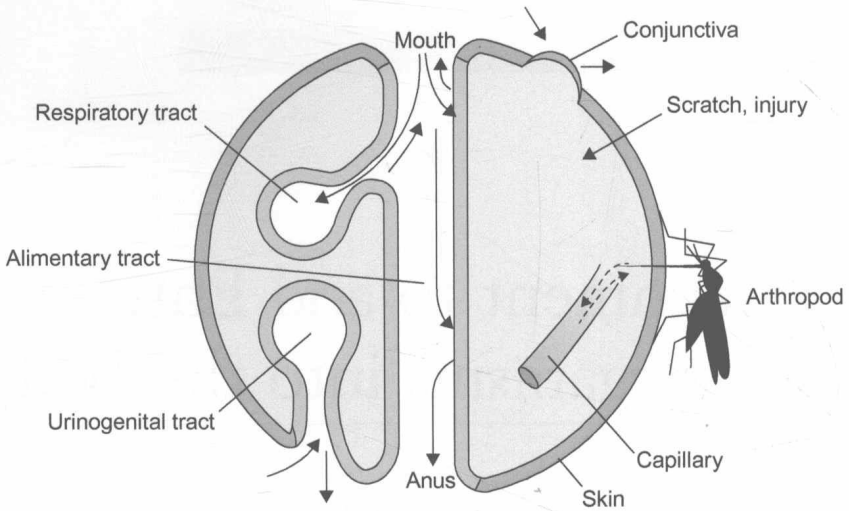

FIGURE 2.1 Body surfaces as sites of microbial infection and shedding.

the products of digestion absorbed, and in the alimentary canal therefore, where contact with the outside world must be facilitated, the lining consists of one or more layers of living cells. Also in the lungs the gaseous exchanges that take place require contact with the outside world across a layer of living cells. There must be yet another discontinuity in the insulating outer layer of skin in the urinogenital tract, where urine and sexual products are secreted and released to the exterior. The cells on all these surfaces are covered by a fluid film containing mucin, a complex hydrated gel that waterproofs and lubricates. In the alimentary canal, the lining cells are inevitably exposed to mechanical damage by food and they are continuously shed and replaced. Shedding and replacement is less pronounced in respiratory and urinogenital tracts, but it is an important phenomenon in the skin, the average person shedding about 5×10^8 skin squames per day.

The conjunctiva and the alimentary, respiratory and urinogenital tracts offer pathways for infection by microorganisms and the penetration of these surfaces is more easily accomplished than for intact outer skin. A number of antimicrobial systems have been developed in evolution to deal with this danger, and also special cleansing systems to keep the conjunctiva and respiratory tract clean enough to carry out their particular function. In order to colonise or penetrate these body surfaces, microorganisms must first become attached, and there are many examples of specific attachments that will be referred to (see Table 2.1 where they are listed in some detail). One striking feature of acute infectious illnesses all over the world is that most of them are either respiratory or diarrhoea-like in nature. They are not necessarily severe infections, but they are the most abundant. In other words, infectious agents are for much of the time restricted to the respiratory and intestinal tracts.

It is possible to divide all infections into three groups (Figure 2.2). First, those in which the microorganisms have specific mechanisms for attaching to and sometimes penetrating the body surfaces of the normal, healthy host. This includes the infections listed in Figure 2.3. In the second group, the microorganism is introduced into the body of the

TABLE 2.1 Examples of Attachments of Microorganisms to Host Cell/Body Surface With Information on Ligand Receptor System Derived from *in vitro* Studies on Cultured Cells

Microorganism/Disease	Target Site or Cell	Microbial Ligand(s)	Receptor
VIRUSES			
Influenza virus/flu	Respiratory epithelium	Viral haemagglutinin	Neuraminic acid
Rhinovirus/common cold	Respiratory epithelium	Viral capsid protein	Intercellular adhesion molecules (ICAM-1)
HIV-1/AIDS	$CD4^+$ T cell	Viral envelope gpl20 proteins	CD4 proteins
Epstein–Barr virus/ glandular fever	B cell	Viral envelope protein	CD21
Herpes simplex virus/ cold sore/genital herpes	Most cells	Glycoprotein	Heparan sulphate
Measles virus/measles	Most primate cells	Viral haemagglutinin	CD46 (membrane cofactor protein)
Foot and mouth disease	Tissue culture cell	VP1	Vitronectin integrin
Virus			Receptor
Coxsackie virus A9	Tissue culture cell	VP1	Integrins
BACTERIA			
Chlamydia/conjunctivitis/ Urethritis	Conjunctivial/urethral epithelia	GAG; MOMP (major outer membrane protein; nonspecific, and specific attachment)	GAG receptors
Mycoplasma pneumoniae/ atypical pneumonia	Respiratory epithelium	'Foot' on *Mycoplasma* surface	Neuraminic acid
Neisseria meningitides/ carrier state	Nasopharyngeal epithelium	Type IV Pili; Opa (opacity associated) proteins	Heparin sulphate proteoglycan. Opa proteins also bind to vitronectin/integrins in HeLa and Hep-2 cells, and CD66 in neutrophils
Vibrio cholerae/cholera	Intestinal epithelium	Tcp (demonstrably important in humans); others	
Escherichia coli			
ETEC/diarrhoea	Intestinal epithelium	K88 (pigs); K99 (calves, lambs); Colonisation factors (humans)	Neu5Glc(α2–3) Gal(β1–4) Glc(β1–1) ceramide
EPEC/diarrhoea	Intestinal epithelium	Bfp, Intimin (an OMP)	Tir (a bacterial protein; translocated intimin receptor), host cell co-factor

(*Continued*)