Mechanisms:

Innate immunity and animal pathogens

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MECHANISMS

INNATE IMMUNITY AND ANIMAL PATHOGENS

Microorganisms and pathogens in animals

What is a pathogen?
The microorganisms that share our environment include bacteria, mycoplasma, viruses, fungi, protozoa and helminths (Figure 1). The animal body provides a favorable habitat for many microorganisms as it is warm and constitutes a ready supply of nutrients and water. Live animals can resist colonization by many microorganisms; with others, a symbiotic relationship develops between the animal and microorganism and the two live together without harming each other. Areas that are highly colonized include the skin, respiratory and gastrointestinal tracts. Microorganisms that live innocuously on the animal are called commensals.¹

A pathogen has traditionally been thought of as a microorganism that causes or can cause damage to the host resulting in disease. Throughout this website, the term pathogen will be used according to this definition. However, more recently, the community has questioned the use of the term ‘pathogen’. The properties of a microorganism that allow it to grow and survive in a host, known as virulence factors, may not always be present on a particular pathogen, meaning it can exist in a pathogenic or non-pathogenic state. In addition, microorganisms may cause disease in some individuals but not others, indicating that differences in the way the host immune system reacts to the microorganism may also contribute to whether it has pathogenic consequences.¹⁻⁴ Disease thus occurs only when the balance between host immunity and microorganism virulence is disturbed.¹ The presentation of a disease caused by a particular pathogen is determined by the type of pathogen and the ways in which they cause damage to the tissues.⁴

Figure 1. Types of pathogen that can cause disease in animals⁵

Bacterium  Virus  Protozoan
Mycoplasma  Fungus  Helminth
Key bacterial pathogens in cattle include:6,7

- *Mannheimia haemolytica*
- *Histophilus somni*
- *Pasteurella multocida*
- *Salmonella* spp.
- *Escherichia coli*
- *Staphylococcus aureus*
- *Streptococcus agalactiae*
- *Corynebacterium bovis*

Key viral pathogens in cattle include:6–9

- Bovine herpesvirus-1 (BHV-1; infectious bovine rhinotracheitis)
- Parainfluenza virus-3 (PI3V)
- Bovine coronavirus (BoCV)
- Bovine respiratory syncytial virus (BRSV)
- Bovine viral diarrhea virus (BVDV)

Key bacterial pathogens in poultry include:10

- *Escherichia coli*
- *Salmonella* spp.
- *Staphylococcus* spp.
- *Ornithobacterium rhinotracheal*
- *Clostridium perfringens*

Key viral pathogens in poultry include:7,11

- Avian influenza viruses
- Newcastle disease virus (NDV), synonymous with avian paramyxovirus serotype 1 (PMV-1)
- Herpes viruses, including Marek’s disease virus (MDV)
- Coronaviruses, including infectious bronchitis virus (IBV)

The immune response to pathogens in animals

Innate immunity protects against pathogens during the early stages of infection

Physical barriers represent the first line of defense against pathogens and once these have been breached, the cells and molecules that comprise the immune system mount a coordinated response to destroy and remove the invading pathogen.12

Different pathogens have different lifecycles, and this means that the immune response must be tailored to a particular pathogen. Most pathogens go through a stage where they reside outside the cells of their host, within the tissues or on the epithelial surfaces that line body cavities. Some pathogens, including the majority of bacteria, only ever inhabit this compartment, while other
pathogens enter the animal’s cells. In order to replicate, all viruses and some types of bacteria, such as Salmonella, need to move inside their host’s cells. While pathogens are outside the cells they are susceptible to removal by a type of cell known as a phagocyte, which surrounds and engulfs the pathogen, then destroys it with toxic products. The phagocyte also becomes activated and can signal to other immune cells (Figure 2). However, some bacteria are surrounded by a mucus-like layer called a capsule that protects them from phagocytic engulfment. The complement system is a group of proteins that can help by binding to invading microorganisms to make them easier for phagocytes to recognize and remove. If a pathogen is not detected and removed by phagocytosis before it enters a host cell, a type of immune cell called a natural killer (NK) cell is able to recognize signals given out by host cells that are infected with pathogens and subsequently destroy the infected host cell as a means of limiting pathogen spread.¹²

Figure 2. Phagocytosis is a receptor-regulated process and can trigger production of inflammatory mediators¹³

Immune evasion
Many pathogenic microorganisms can overcome innate immune defenses, such as those mentioned in the paragraph above, and can replicate and grow within the host body.

Table 1 gives examples of mechanisms through which pathogens may evade the immune system.¹⁴
Table 1.

<table>
<thead>
<tr>
<th>Mechanism of immune evasion$^{14,15}$</th>
<th>Example of pathogens using this mechanism</th>
</tr>
</thead>
</table>
| Interfere with TLR signaling          | *Pseudomonas aeruginosa* secretes a molecule that impairs regulation of immunological gene expression  

*Shigella* species, *Yersinia* species and anthrax can eliminate or modify enzymes involved in signaling |
| Resist antibacterial proteins         | Salmonella species, *Klebsiella pneumoniae* and *Staphylococcus aureus* can secrete enzymes that block expression or binding of defensins or neutralize them |
| Block phagocytosis                    | *Staphylococcus aureus* produces protein A which allows it to evade detection by phagocytes |
| Kill immune cells                     | *Mannheimia haemolytica* and *Fusobacterium necrophorum* secrete leukotoxins that destroy T and B cells |
| Negative cytokine regulation          | Marek’s disease virus produces cytokine-like molecules to modify the immune response |
| Block antigen presentation            | Influenza virus blocks macrophage differentiation and bovine herpesvirus inhibits the expression of molecules that allow antigen presentation |

Adaptive immunity provides a targeted and more robust response to pathogens that are not eliminated by the innate immune system

If the innate immune system fails to eliminate a pathogen and infection becomes established, cells of the adaptive immune system mount an attack targeted specifically at the infecting pathogen. There are two arms of the adaptive immune response: cell-mediated immunity and humoral immunity.

**T cells** and **B cells** are lymphocytes of the adaptive immune system that express receptors that can detect many different patterns. When a type of innate immune cell called a **dendritic cell** detects a pathogen, it alerts and activates the specific B and T cells that express receptors that can bind to that
particular pathogen. These cells proliferate to produce many copies of these targeted lymphocytes. Cell-mediated immunity is one arm of the adaptive immune response. It acts via cytotoxic T cells and phagocytes and predominantly protects against pathogens that reside inside host cells. Humoral immunity, the other arm of the adaptive immune response in which B cells produce antibodies against pathogens, largely protects against pathogens found outside of these cells. Activation of adaptive immunity relies on the recognition of pathogens by innate immune cells, which subsequently alert adaptive immune cells to the presence of the invading microorganism. An immunocompromised animal may not mount an innate or adaptive immune response that is sufficient to completely remove the infecting pathogen.

The role of *Mannheimia haemolytica* in bovine respiratory disease (BRD)

**Bovine respiratory disease (BRD)**

BRD is associated with substantial economic losses, resulting from both the direct effects of disease on animals, and indirect effects associated with treating and/or preventing its spread. BRD describes a multifactorial condition that can be caused by a variety of bacterial and/or viral pathogens. *Mannheimia haemolytica* is a bacterium that is commonly isolated from cattle with BRD. It is also found in the respiratory tract of some healthy cattle as a commensal species.

**Signs of Bovine Respiratory disease**

Clinical signs of BRD include depression, anorexia, nasal discharge and coughing. The presence of lung lesions is also indicative of BRD, even in animals that do not display symptoms. Despite the usage of vaccines and antibiotics, BRD continues to remain a challenge especially in feedlot cattle.

Environmental stressors are thought to contribute to BRD susceptibility, as it is most commonly seen in young cattle within the first 2 months of arrival at the feedlot. Transportation and co-mingling of cattle from multiple sources may increase both pathogen exposure and the animal’s stress level, while procedures such as weaning, dehorning or castration, may also represent stressful events. Stress can lead to increased secretion of stress hormones, which can bind to receptors and lead to secretion of cytokines, the signaling molecules of the immune system, which can alter the way in which the immune system responds.

Cattle displaying symptoms of BRD are often infected with other pathogens in addition to *M. haemolytica*. These may include other bacteria, commonly *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis*, or viruses, including bovine viral diarrheal virus (BVDV), bovine respiratory syncytial virus (BSRV) and parainfluenza 3 virus (PI3V) (figure 3). Many cattle are persistently infected with BVDV. The significance of this is that viral infection can modify the immune system’s capacity to respond to bacterial infection, leaving the animal susceptible to infection and unable to control or clear it.
Pathogenesis of bovine respiratory disease

Within a bacterial or viral species, there may be subgroups known as serotypes, characterized by slight variations in structure or features. *M. haemolytica* serotypes S2 and S4 are found in the nasopharynx of healthy cattle, and generally do not cause disease. Pathogenicity results from an opportunistic infection, usually by serotype S1. Stress or viral infection may modify the microenvironment, allowing serotype S1 to colonize the nasal mucosa; subsequent inhalation enables the bacteria to reach the lungs.23

A number of virulence factors allow *M. haemolytica* to infect the lung and contribute to the lung pathology associated with BRD.23,31

Leukotoxin is a toxin secreted by *M. haemolytica* that targets the immune cells of ruminant species. At low concentrations it can activate macrophages and neutrophils, promoting inflammation. At higher concentrations, it creates pores in immune cell membranes, killing the cell and allowing them to release the toxic products they use to destroy bacteria, which damages the surrounding lung tissue.23,31

Lipopolysaccharide (LPS) is a part of the bacterial cell wall that can bind to receptors on immune cells, such as macrophages and neutrophils. At low concentrations it inhibits phagocytosis, while at high concentrations the cells are stimulated, contributing to inflammation. Inflammatory mediators cause damage to the lung. LPS also binds, and is directly toxic to, the pulmonary endothelium. It binds to epithelial cells causing blood vessel dilation, permitting immune cells and fluid to leave the blood vessels, which can lead to a life-threatening fall in blood pressure.23
**Escherichia coli** infection in poultry and other species

Pathogenic infections can manifest in many forms
The bacterium *Escherichia coli* is a commensal microorganism in healthy poultry. However, certain strains, known as avian pathogenic *E. coli* (APEC), can move from the intestinal lining to invade various internal organs. Antibiotic resistance is common among APEC and resistance traits are often carried on DNA molecules that are separate from the main genome and can be easily transferred between bacteria. This makes APEC difficult to treat. Acute colibacillosis due to *E. coli* causes septicemia and death, while in its subacute form, infected birds may exhibit a whole host of diseases and conditions including, but not limited to (figure 4):32,33

**E. coli infections in poultry**
- Septicemia: may be associated with pericarditis, peritonitis and bile-staining and necrotic foci in the liver33
- Salpingitis: infection of the oviduct may occur via the left abdominal airsac causing salpingitis, which compromises a bird’s egg-laying capacity33
- Swollen head syndrome: causes edema of the cranial and periorbital skin but has a low mortality rate and minimal effect on egg production. It is thought to occur as an opportunistic infection following a viral infection32,33
- Respiratory tract infection: primary site of infection, occurs through inhalation of fecal-contaminated dust. Bacteria may reach the blood, causing stunted growth or death32,33
- Yolk sac infection: often associated with fecal contamination of the egg surface and can lead to embryonic mortality or death during the first few weeks of life33
- Cellulitis: chronic inflammation of the tissue of the abdomen and thighs32
- Coligranuloma: leads to development of granulomas in liver, caeca, duodenum and mesenterium and is associated with a high mortality rate32

Pathogenesis of avian colibacillosis
- The mechanism by which APEC causes infection is not well understood, however a number of risk factors and pathogen virulence factors have been identified32,33

**E. coli risk factors**32
- Housing: poor housing hygiene, e.g. excess ammonia or dust, overcrowding, temperature
- Pathogen: virulence of the strain, duration of pathogen exposure
- Immune status of the bird: infection with other pathogens, such as Newcastle disease virus, infectious bronchitis virus and *Mycoplasma gallisepticum* may increase the risk of colibacillosis, and damage to the respiratory system may also increase susceptibility

**Virulence factors**33
- Outer membrane proteins and/or capsules: help resist bactericidal effects of complement
- Cytotoxins: have been identified in some strains of APEC, although this is not widespread
- Mechanisms to acquire iron: as iron availability is restricted in the animal’s bodily fluids, some bacteria have developed systems to compete with their hosts for iron
- Fimbriae: help improve bacterial attachment to epithelial cells
**E. coli** can infect a variety of livestock species

As in cattle, stress or viral infection can lead to immunosuppression in poultry. In addition to causing disease in young chicks, infectious bursal disease virus (IBDV) also damages immune tissues such as the bursa of Fabricus, reducing the bird’s ability to fight infection by other pathogens.\(^{35}\)

Furthermore, pathogens such as *E. coli* can infect multiple species. Colibacillosis is an animal disease caused by *E. coli* that can affect mammals (including cattle, sheep and pigs), as well as avian species. The avian form is typically a localized or systemic disease, occurring secondarily when host defenses have been impaired or overwhelmed by virulent *E. coli* strains. Conversely, the mammalian form is most often a primary enteric or urinary tract disease.\(^{34}\)

**Other types of pathogens that cause disease in livestock**

**Respiratory infections in poultry**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Avian influenza (AI)</strong></td>
<td>Viruses are typically of low pathogenicity, causing subclinical infections, respiratory disease, or drops in egg production.(^7) However, a highly pathogenic form of the disease ('fowl plague') can cause severe systemic infections with high mortality.(^7)</td>
</tr>
<tr>
<td><strong>Newcastle disease virus (NDV)</strong></td>
<td>NDV is synonymous with avian paramyxovirus serotype 1 (PMV-1).(^7) NDV causes an acute respiratory disease (although depression, nervous manifestations, or diarrhea may be the predominant clinical form).(^7)</td>
</tr>
<tr>
<td><strong>Chronic respiratory disease ('air sac disease')</strong></td>
<td>APEC and mycoplasma coinfection results in a condition known as complicated chronic respiratory disease (CCRD).(^{38})</td>
</tr>
</tbody>
</table>

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\(^{34}\) See figure 4. Disease caused by infection with APEC in poultry.
Gastrointestinal and urogenital infections in livestock

Gastroenteritis can result from infection with various bacteria, e.g. *E. coli* or *Campylobacter* spp. Salmonellosis typically presents as enteritis (systemic septicemia – or typhoid – is the other major form). The serotypes of *Salmonella* typically have a narrow range of host species (‘serovar-host specificity’)?

- Common pathogens causing gastrointestinal (GI) infections include: *Salmonella typhimurium*, *S. dublin*, *S. Newport* (cattle); *S. typhimurium*, *S. choleraesuis* (pigs); *S. typhimurium*, *S. dublin*, *S. abortusovis*, *S. anatum*, *S. Montevideo* (sheep); *S. enteritidis*, *S. typhimurium*, *S. gallinarum*, *S. pullorum* (poultry)

Cattle, sheep and pigs are susceptible to cystitis (inflammation of the urinary bladder) and pyelonephritis (infection of the kidneys)?

- Bacteria that cause these infections include: *Corynebacterium renale* (*C. renale*, *C. cystitidis*, and *C. pilosum*), *E. coli*, *Trueperella pyogenes*, *Streptococcus* spp., and *Staphylococcus* spp.

**Mastitis and metritis in cows**

Mastitis (inflammation of the mammary gland) occurs in almost all domestic mammals, but is of greatest frequency and economic importance in dairy cattle?

- Many microorganisms can opportunistically invade tissue and cause mastitis. Most infections are caused by species of streptococci, staphylococci, and Gram-negative rod bacteria?

Metritis (inflammation of the uterus) occurs in cattle, typically after calving?

- Bacteria that cause these infections include: *Arcanobacterium pyogenes*, *Fusobacterium necrophorum*, *E. coli*, *Streptococcus* spp., *Staphylococcus* spp., and *Pseudomonas* spp.

**Summary**

**Summary of mechanisms in innate immunity and animal pathogens**

- Animals and microorganisms have evolved to live together over a long time, and in many cases microorganisms can inhabit the animal body without causing disease?
- The term pathogen is used to describe a microorganism that causes or can cause damage to the host resulting in disease?
- Infection by a pathogen may occur if a microorganism possesses features that enhance its ability to live in the tissues or cells of an animal, known as virulence factors, or if the immune response mounted by the animal is insufficiently strong to remove the invading pathogen?
- When immunity is suppressed, for example by stress or viral infection, animals may be more susceptible to diseases such as BRD or colibacillosis?
- Once physical barriers protecting the animal are breached (e.g. skin), the innate immune system tries to fight the pathogen, predominantly through phagocytosis?
- Infection may manifest in many ways and depends on the type of pathogen and the location of the infection?
Some microorganisms have evolved mechanisms that allow them to evade the innate immune system, such as interfering with cellular signaling\textsuperscript{39,40}

Adaptive immunity is alerted to the presence of an infection by innate immune cells and offers a more targeted response to pathogens\textsuperscript{39,40}

References
1. Tizard IR. Veterinary Immunology, 9th edn, 2013:3,4.
15. Tizard IR. Veterinary Immunology, 9th edn, 2013:288–90,302–5.