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Influenza in High-Risk Hosts—Lessons Learned from Animal Models

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Factoring significantly into the global burden of influenza disease are high-risk populations that suffer the bulk of infections. Classically, the very young, very old, and pregnant women have been identified as high-risk populations; however, recent research has uncovered several other conditions that contribute to severe infection. By using varied animal models, researchers have identified molecular mechanisms underpinning the increased likelihood for infection due to obesity and malnourishment, as well as insight into the role sex hormones play in antiviral immunity in males, in females, and across the life span. Additionally, novel comorbidity models have helped elucidate the role of chronic infectious and genetic diseases in influenza virus pathogenesis. Animal models play a vital role in understanding the contribution of host factors to influenza severity and immunity. An in-depth understanding of these host factors represents an important step in reducing the burden of influenza among the growing number of people living with one or more chronic medical conditions.

Influenza represents a significant burden for global public health. Worldwide, millions of cases of influenza are recorded per year, resulting in estimates of up to 600,000 deaths (Thompson et al. 2009; Nair et al. 2011; Lee et al. 2018). Most cases are represented by individuals with one or more underlying host susceptibility factors. Comorbidities, sex, and age not only impact the host but can also impact the virus itself, as they were found to be associated with increase in single-nucleotide polymor-

phisms (SNPs) in the influenza genome (Fig. 1) (Nelson et al. 2001; Engels et al. 2017; Zhang et al. 2017). To understand increased pathogenesis in high-risk populations, it is necessary to develop accurate animal models to investigate viral pathogenesis and immunity.

OBESITY

Obese individuals are at high risk for severe influenza infection and account for most influ-

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R. Honce et al.

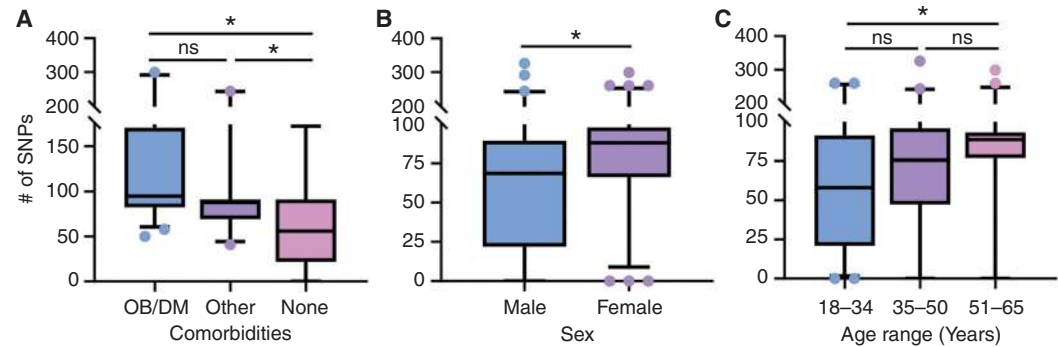


Figure 1. Increased diversity in viruses derived from high-risk hosts. Using the influenza research database, human surveillance influenza A viral samples with clinical metadata were pooled to look at single-nucleotide polymorphisms (SNPs) in various high-risk groups. The same data set was stratified based on (A) comorbid state of obesity or diabetes mellitus, other comorbidity, or healthy adult with no listed comorbidities, (B) sex, and (C) age range on presentation of symptoms of 18–34, 35–50, or 51–65. Number of SNPs for each gene segment was summed and plotted using box-and-whisker plots ranging from the 5th to 95th percentile with data outside the range represented by data points. Data were analyzed first for normality using the Kolmogorov–Smirnov test, and then for differences in SNPs using a Kruskal–Wallis test (A,C) to compare more than two groups and a Mann–Whitney test (B) to compare two groups. (*) $P < 0.05$. Database accessed on 30-July-2019.

enza-related hospitalizations (Milner and Beck 2012). To better understand this increased pathogenesis, most influenza obesity studies to date have been performed in mouse models—specifically, genetically obese mouse strains such as ob/ob (OB) and db/db, achieved by knocking out the leptin gene or the leptin receptor, respectively (Lutz and Woods 2012), and diet-induced obese (DIO) mice, which are thought to better mimic obesity in the human population. DIO mice are fed diets consisting of high-fat (ranging from 40% to 60% calories from fat) or a so-called Western diet with variable composition (Table 1) (Lutz and Woods 2012; Zeeni et al. 2015). These high-fat, calorically dense diets result in weight gain, glucose intolerance, and reduced sensitivity to leptin and insulin (Campfield et al. 1995).

Most murine studies show that obesity increases morbidity and mortality during influenza infection, consistent with clinical observations (Milner and Beck 2012). On infection with influenza virus, both OB and DIO mice develop severe pathology, increased viral spread, decreased pulmonary function, and impaired viral clearance (Kim et al. 2012b; Zhang et al. 2013; Radigan et al. 2014; Moorthy et al. 2016; Karlsson et al. 2017a). A major complication of

influenza infection, especially in obese populations, is the development of secondary bacterial infections (Diavatopoulos et al. 2010). Obese mice are at greater risk of acquiring secondary infections post-influenza challenge (Karlsson et al. 2017a). Conversely, other studies reported no differences in pathology between lean and obese, although they did report mice fed high-fat diets (HFDs) have increased oxidative stress and generation of neutrophil extracellular traps, both of which result in damage to the surrounding tissue (Moorthy et al. 2016).

Besides increased pathology, obese mice mount a poor innate immune response to infection (for review, see Honce and Schultz-Cherry 2019). The baseline obesogenic lung consists of increased expression of proinflammatory cytokines and chemokines (Kim et al. 2012b) resulting in an increased influx of inflammatory cells after infection (Namkoong et al. 2019). Despite the increased inflammation, obese mice have increased expression of suppressors of cytokine signaling (SOCS1 and SOCS3) mRNA in the lung leading to decreased type I interferon (IFN) (Radigan et al. 2014). On infection, IFN- α and IFN- β responses are delayed, along with IL-6 and tumor necrosis factor (TNF)- α production (Smith et al. 2007; Karlsson et al.

Table 1. Animal models of obesity and outcome of experimental influenza virus infection

Model	Genetics	Weight	Diet	Outcome of infection	References
Genetic leptin knockout (ob/ob)	Spontaneous recessive, homozygous <i>Lep^{ob}</i> nonsense mutation	45 g	Normal chow; hyperphagic due to loss of appetite control and satiety	Impaired viral clearance, increased risk of secondary infections, poor wound repair, and diminished memory responses	Campfield et al. 1995; Lutz and Woods 2012; Karlsson et al. 2017a; Meliopoulos et al. 2019
Genetic leptin receptor knockout (db/db)	Spontaneous mutant in <i>Lep^{db}</i> allele causing abnormal splicing	40 g	Normal chow; hyperphagic due to loss of leptin receptor signal transduction	Reduced viral clearance, impaired adaptive immunity, and increased lung pathology	Lutz and Woods 2012; Radigan et al. 2014
Diet-induced obesity (DIO)	Some strains more susceptible than others	35 g	High-fat, Western, or “cafeteria” diet	Mirrors genetically obese models, but generally moderate phenotypes between genetically obese and control models	Campfield et al. 1995; Smith et al. 2007; Lutz and Woods 2012; O’Brien et al. 2012; Zeeni et al. 2015
Control	Any matched genetic background	25 g	Either low-fat diet or regular chow; diet choice may alter results	Controlled viral spread and replication, reduced lung pathology, improved wound repair, and robust antigenic memory	Lutz and Woods 2012; Zeeni et al. 2015

Adapted from data in Honce and Schultz-Cherry (2019).

2010; Lutz and Woods 2012). However, later in infection, DIO mice have increased IL-6 levels versus lean mice (Namkoong et al. 2019). Macrophages, one of the first innate immune cells to sense infection and initiate a response, are functionally impaired in obese hosts. Alveolar macrophages taken from DIO mice and infected *ex vivo* have suppressed IFN- α , IFN- β , and other cytokines compared with lean controls, suggesting dampened macrophage function in DIO mice contributes to poor outcomes (Cho et al. 2016; Namkoong et al. 2019).

The adaptive immune system is also affected by obesity. Pulmonary CD4⁺ T cell numbers are reduced in DIO and OB mice (Milner et al. 2015). Regulatory T cells are reduced in DIO

and OB mice and are 40% less suppressive than those of lean mice (Milner et al. 2013, 2015). Weight loss does not improve memory T-cell function in DIO mice (Rebeles et al. 2019), implying that obesity might continue to have an impact even after an individual loses weight. Humoral responses are also altered. DIO mice have higher B-cell IgM and IgG in unstimulated B cells, but decreased expression of cytokines and early commitment markers such as IL-7, IL-7RA, and STAT5 (Kosaraju et al. 2017). Not only are B-cell frequencies lowered, but DIO mice have diminished antibody titers attributed to reduced plasma levels of docosahexaenoic acid (DHA) (Kosaraju et al. 2017). Many studies have shown differ-

R. Honce et al.

ences in inflammation and immune cell populations—both innate and adaptive—are more pronounced in the genetically obese models compared with DIO mice, drastically affecting the immune response to influenza (O'Brien et al. 2012).

An altered pulmonary microenvironment also contributes to increased pathogenesis and impaired immune response. Prostaglandin E₂, a lipid immune mediator, is higher in DIO mice and mediates decreased expression of IFN- α , IFN- β , and certain cytokines (Zhang et al. 2019b). In addition, during infection, lipid metabolism in DIO mice is up-regulated, including fatty acids and phospholipids (Milner et al. 2015). Although the exact impact of increased lipid metabolism on pathogenesis is unknown, it is speculated that the altered cellular metabolism of obese mice inhibits efficient lung repair after infection (O'Brien et al. 2012; Milner et al. 2015). Mechanisms of pulmonary homeostasis are also altered by the obesogenic state. Recent studies show that the β 6 integrin contributes to increased pathology during influenza infection in mice by suppressing type I IFNs (Meliopoulos et al. 2016), and that β 6 integrin is expressed at much higher levels in genetically obese mice (Meliopoulos et al. 2019). Knocking out β 6 integrin increases type I IFN signaling and improves macrophage functionality, resulting in controlled viral spread and protection from severe influenza infection (Meliopoulos et al. 2016, 2019). Obese mice have increased expression of platelet-activating factor receptor (PAFR) in the lung, which is associated with increased severity of secondary bacterial infection (Ghoneim et al. 2013; Metzger and Sun 2013; Karlsson et al. 2016).

Although the mouse model provides valuable information regarding the influence of obesity during influenza infection, ferrets remain the gold-standard model for human influenza infection. Unlike mice, ferrets are susceptible to human influenza viruses without the need for prior adaptation and have a distribution of sialic acid residues within the respiratory tract that mirrors that of humans (Robinson et al. 1986; Johnson-Delaney and Orosz 2011). Ferret studies are limited by the lack of available ferret

reagents and currently focus on viral pathogenesis and viral transmission. To address this, the National Institute of Allergy and Infectious Diseases (NIAID)-funded Centers for Excellence in Influenza Research and Surveillance has undertaken an initiative to develop ferret immune reagents and antibodies (Albrecht et al. 2018). An obese ferret model is thus currently under development and has the potential to answer many questions about obesity and influenza.

Overwhelmingly, data generated from studies using DIO and genetically obese mouse models suggests increased immunopathology, decreased or delayed immune response, and altered pulmonary microenvironment all contribute to the increased morbidity and mortality seen in obese individuals. Although differences between studies have been noted, this is most likely attributed to differences between obesity models and diets. Even diets of similar composition can be obtained from different vendors with major or minor differences between formulations. Therefore, caution must be taken when extrapolating murine results to studies of human obesity and influenza.

MALNOURISHMENT

Malnourishment is also a risk factor for increased influenza susceptibility and morbidity. Several studies have found that vitamin A and D deficiencies affect the immune response to influenza virus (Stephensen et al. 1993; Surman et al. 2016; Penkert et al. 2017). Mice deficient in vitamin A, vitamin D, or both have decreased mucosal antibody response in the nasal-associated lymphoid tissue and lung; supplementation with vitamin A and/or D was sufficient to restore the antibody response (Surman et al. 2017). Vitamin A- and vitamin D-deficient mice, in addition to decreased overall numbers of CD8⁺ T cells, have decreased virus-specific CD103^{hi} T cells, thought to inhibit recruitment of virus-specific T cells to the airway (Surman et al. 2017). Low vitamin C levels also contribute to poor infection outcome, as Gulo^{-/-} mice, which are unable to survive without vitamin C supplementation, show increased lung pathology and decreased MCP-1, RANTES, and IL-12



during influenza infection (Li et al. 2006). Selenium deficiency increases influenza-associated lung lesions, as well as promotes higher mutation rates in the M1 protein (Beck 2001; Beck et al. 2001; Nelson et al. 2001).

Protein deprivation also increases severity of disease. Mice fed inadequate amounts of protein show increased viremia and delayed viral clearance compared to controls (Pollett et al. 1979; Taylor et al. 2013). This may reflect the altered immune response of these mice, as protein-deprived mice have fewer natural killer (NK) cells, leading to decreased levels of IFN- γ as well as reductions in B cells, T cells, and total numbers of leukocytes during influenza infection (Ritz et al. 2008; Taylor et al. 2013). In addition, protein deprivation results in increased levels of lung neutrophils associated with immunopathology and lower serum hemagglutination inhibition titers (Taylor et al. 2013), suggesting reduced protein intake compromises both the innate and adaptive responses.

SEX DIFFERENCES

Hormonal variations between sexes have a marked impact on antiviral responses (Klein et al. 2010; Vom Steeg and Klein 2019). Although influenza titers are largely similar between sexes, experimental influenza infection of male and female mice reveals a greater induction of proinflammatory cytokines and increased morbidity in female mice, whereas males show less production of humoral immune responses (Lorenzo et al. 2011; Robinson et al. 2011; Klein et al. 2012; Vom Steeg and Klein 2017). This differential response to influenza infection is mitigated after gonadectomy, suggesting a role for sex hormones in the pathogenesis of influenza (Robinson et al. 2011).

17 β -estradiol (E2) alleviates pulmonary inflammatory responses and promotes an antiviral state by recruiting neutrophils and influenza-specific CD8⁺ T cells to the lungs; however, in females, low levels of E2 promote inflammation and immunopathology (Robinson et al. 2011, 2014; Klein et al. 2012; Davis et al. 2017). Exogenous application of E2 protects females from severe influenza by increasing pulmonary mi-

gration of neutrophils and enhancing CD8⁺ T-cell responses (Robinson et al. 2014). Conversely, during pregnancy, high levels of E2 may attenuate the antiviral response, leading to increased morbidity after influenza virus infection (Pazos et al. 2012). Estriol (E3), another endogenous estrogen, protects against pulmonary inflammation but does not reduce lung viral titers (Vermillion et al. 2018b). These findings were confirmed in vitro: Treatment of female-derived, but not male-derived, human nasal epithelial cell cultures with estrogenic compounds improved cellular response to infection (Peretz et al. 2016).

Progesterone (P4) has both detrimental and beneficial roles for the host during infection. P4 treatment of female mice promotes pulmonary up-regulation of amphiregulin, fast-tracking lung repair and recovery (Hall et al. 2016). In contrast, ovariectomized female mice exogenously treated with P4 have increased morbidity following influenza virus infection, which is also noted in pregnant mice during peak P4 levels (Davis et al. 2017). Hormonal contraceptives containing P4 reduce memory responses to heterotypic influenza challenges through decreasing the activity of memory CD8⁺ T cells (Hall et al. 2017).

Testosterone levels can also impact the response to influenza infection, and testosterone decline over the life span contributes to increased severity in the elderly (Vom Steeg et al. 2016; Vom Steeg and Klein 2019). As is seen with estrogens and progesterone, testosterone levels do not alter viral load but rather impact immune responses (Vom Steeg et al. 2016). Castrated young and intact aged male mice suffer increased pulmonary pathology and edema upon infection because of low testosterone levels (Vom Steeg et al. 2016). Testosterone also plays a role in the recovery and remodeling stage of infection. Male mice show greater production of amphiregulin than female mice with responses sensitive to exogenous testosterone treatment (Vermillion et al. 2018c).

Hormonal fluctuations across the life span impact susceptibility to influenza differently in males and females; these differences are highlighted during aging and pregnancy. Prepuber-

R. Honce et al.

tal and elderly males have a higher likelihood of severe influenza infection compared with higher susceptibility in females of reproductive age as discussed further below (Jensen-Fangel et al. 2004; Vom Steeg and Klein 2019). Further, puberty onset may increase disease severity in males and females, as increased production of estrogens exacerbate mortality on infection. Low estrogen levels in prepubertal children—especially females—are protective against severe influenza infection (Suber and Kobzik 2017). Testosterone decline over the life span increases susceptibility to influenza in aging males, and the dynamic interaction between aging and sex hormones impacts influenza pathogenesis as well as host responses to infection and vaccination, as discussed below (Vom Steeg et al. 2016; Potluri et al. 2019).

PREGNANCY

Following the 1918 and 2009 H1N1 pandemics, studies found pregnant hosts had a greater likelihood of hospitalization after influenza infection versus nonpregnant women (Woolston and Conley 1918; Titus and Jamison 1919; Siston et al. 2010). Strikingly, pregnant women account for only 1% of the general population, yet experience an excessive rate of mortality of 5% on influenza virus infection (Centers for Disease Control and Prevention 2010). Interactions between hormones and immune mediators in systemic circulation and at the mother–fetal interface alter influenza pathogenesis in the pregnant host, as well as contribute to sex-based differences in the response to infection (Irving et al. 2000; Raj et al. 2014; van Riel et al. 2016; Littauer and Skountzou 2018). Other comorbidities, including stress, depression, body mass index, aging, puberty, and exercise state, contribute to poor infection responses and can compound morbidity in pregnant hosts (Christian et al. 2010; Avit-sur et al. 2011; Soydinc et al. 2012; Christian 2014; Ingersoll 2017; Vom Steeg and Klein 2017).

Pregnant mouse models, including syngenic mating between like strains of mice and allogenic mating between different strains of mice, yield insights into the altered influenza pathogenesis in pregnant hosts. Reduced viral clearance and

eightfold higher viral titers characterize the lungs of syngenic and allogenic pregnant mice infected during mid-gestation, with allogenic-mated mice showing more severe disease caused by fetal tolerance (van Riel et al. 2016; Engels et al. 2017; Littauer et al. 2017). Increased disease severity is not strain-specific; increased viral loads are observed with influenza B–infected pregnant mice as well (Kim et al. 2014). Higher viral loads in pregnant mice contribute to increased lung pathology, severe pneumonitis, lung edema, cytokine storm, and reduced epithelial regeneration post-acute lung injury (Chan et al. 2010; Gu et al. 2011; Marcelin et al. 2011; Engels et al. 2017; Vermillion et al. 2018a). The trend of increasing maternal mortality as pregnancy advances has been recapitulated in murine models with infection during the third gestational week inducing three times the mortality versus infection in the first gestational week (Williams and Mackenzie 1977; Siston et al. 2010).

Reduced antiviral responses upon influenza virus infection may promote immune tolerance to the fetus; however, this can lead to a detrimental outcome for maternal and fetal health. Reduced type I and III IFN responses are seen in pregnant female-derived human peripheral blood mononuclear cells (PBMCs) and in allogenic and syngenic mated pregnant mice (Forbes et al. 2012; Engels et al. 2017; Littauer et al. 2017). The predominate source of type I IFNs following infection are circulating plasmacytoid dendritic cells (pDCs), a cell type that shows reduction in numbers but heightened Toll-like receptor (TLR) expression during pregnancy (Cordeau et al. 2012; Vanders et al. 2013; Koga et al. 2014; Le Gars et al. 2016). Upon infection, infiltrating pDCs in the maternal decidua—which itself expresses several TLRs—during pregnancy may contribute to preterm labor, preeclampsia, and increased maternal morbidity detected in rat and mouse pregnancy models (Bejar et al. 2006; Ilievski et al. 2007; Koga et al. 2014).

Increased expression of pro-inflammatory cytokines IL-1 α , IL-6, IL-12, TNF- α , G-CSF, RANTES, and MCP-1, increased immunosuppressive cytokines IL-10 and IFN- γ , and type I and III IFNs reduction together alter the cellular

microenvironment of the maternal lung and promote severe immunopathology—alterations that are compounded as pregnancy advances (Gonzalez et al. 2009; Chan et al. 2010; Kraus et al. 2010; Marcelin et al. 2011; Forbes et al. 2012; Kim et al. 2012a; Zheng et al. 2012; Vanders et al. 2013). Pregnancy in the ferret model supports these findings, as increased inflammatory cytokines in the lungs lead to cytokine imbalance and elevated viral replication compared with nonpregnant, influenza virus–infected controls (Yoon et al. 2018).

Some reports suggest no differences or even improvements in antibody levels or T-cell numbers and function in influenza virus infected pregnant animal models (Norton et al. 2010; Marcelin et al. 2011; Kay et al. 2014); however, the majority note impairments in adaptive effector function and memory due to the pregnant state. There is a dearth of knowledge on alterations to antibody-mediated immunity and B cells in influenza infection during pregnancy in animal models and human cohorts. Influenza infection in the pregnant ferret model does show reduced IgG-specific B-cell responses after experimental infection, although it remains to be determined if this occurs during natural infection in humans (Yoon et al. 2018). Interestingly, the complement pathway components C3, C3a, and C4 show diminished antibody-dependent neutralization of influenza in pregnant African green monkeys (Mayer and Parks 2014).

CD8⁺ and CD4⁺ T cells are reduced in numbers and have heightened exhaustion in pregnant women infected with H1N1 (Vanders et al. 2013). In mice, increased programmed cell death (PD)-1 expression on paternal antigen-specific T cells promote fetal tolerance through apoptosis of potentially cytotoxic, fetal-targeted cells. Conversely, up-regulation of PD-1 during pregnancy is mirrored during influenza infection, and blocking the PD-1 ligand improves maternal immunity (Taglauer et al. 2009; Vanders et al. 2015). There is also evidence that pregnancy biases toward a Th2-dominated immunity and results in the reduction of CD8⁺ T cells on influenza infection in mouse, rat, and ferret models (Gu et al. 2011; Vanders et al. 2015; Yoon et al. 2018).

The fetus can experience adverse outcomes on influenza infection of the mother. Severe infections are associated with preterm delivery, increased rates of stillbirth, and low birth weight (Kim et al. 2014; Härtel et al. 2016; Oboho et al. 2016; Fell et al. 2017; Littauer et al. 2017). Influenza can infect fetal-related tissues, with infections of the maternal decidua of the greatest likelihood to support active viral replication (Takeyama 1966; Rosztoczy et al. 1975; McGregor et al. 1984; Uchide et al. 2006). Infection of the fetoplacental tissues induces placental inflammation may precede influenza-induced abortion, as has been shown in human and simian tissues and in murine models (Uchide et al. 2002; Christiaens et al. 2008; Xu et al. 2011; Kim et al. 2012a). Transmittance of influenza infection to the fetus may be a maternal survival strategy, as vertical transmission of highly pathogenic avian influenza H5N1 to the fetus induced preterm delivery or abortion but partly evacuated the virus from the pregnant dam (Xu et al. 2011).

Fewer studies have used the ferret model. An investigation into influenza virus dynamics in the mother–infant dyad using influenza-infected neonatal ferrets found influenza transmission to maternal lung and mammary gland tissue results in cessation of milk production and maternal mortality (Paquette et al. 2015). The converse condition of maternal infection via mammary gland inoculation resulted in infant infection and mortality via breastfeeding, findings that were recapitulated in replication competent primary human breast cells (Paquette et al. 2015).

AGING

Classically, the age groups at highest risk for severe influenza disease are the young and the elderly (Kondrich and Rosenthal 2017; Talbot 2017). This leads to a “U-shaped” age-specific mortality curve with high mortality in young and old with young adults and middle-aged individuals having relatively low mortality (Fig. 2) (Dauer and Serfling 1961; Glezen 1996). Prepubescent children, especially children with comorbidities or children <2 yr of age, are at an

R. Honce et al.

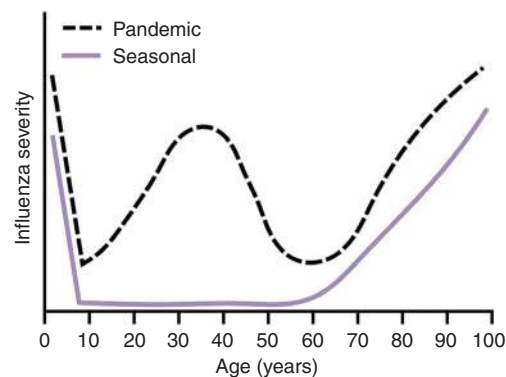


Figure 2. Differential severity of pandemic and seasonal influenza viruses by age. Seasonal influenza viruses cause a “U-shaped” age-specific mortality curve with the young and old susceptible to severe influenza virus disease. Pandemic influenza viruses instead cause a “W-shaped” age-specific mortality curve with the young, old, and middle-aged having peaks in influenza virus disease severity.

increased risk for severe complications following influenza virus infection (Nair et al. 2011; Lafond et al. 2016; Guo et al. 2018). In part, the high risk of severe disease in children is thought to be caused by a lack of enough preexisting immunity, resulting in high infection rates (Ruf and Knuf 2014). The relative lack of sex hormones in prepubescent individuals also makes them more susceptible to severe influenza disease, as discussed above (Vom Steeg and Klein 2019). Work in animals has shown that prepubescent mice are similarly susceptible to severe disease following influenza virus infection (Yasui et al. 2004; Sun et al. 2011). However, young ferrets have decreased fever and weight loss following influenza virus infection (Huang et al. 2012), perhaps because of the differences between the animal models (Thangavel and Bouvier 2014).

At the other end of the “U-shaped” age-specific mortality curve, older individuals (>65 yr of age) also have a higher risk of severe influenza virus disease (Fig. 2). In otherwise healthy, elderly adults, 67% percent of influenza virus-infected individuals become housebound and 25% become bedbound (Falsey et al. 2005). Despite numerous exposures to influenza virus via infection and vaccination, morbidity and mortality

increase with age in the elderly, likely because of immunosenescence and increasing incidence of comorbidities (Talbot 2017). Older mice infected with influenza virus have increased morbidity and mortality associated with increased virus replication, decreased naive T-cell receptor repertoire, and delayed resolution of inflammation (Yager et al. 2008; Gil et al. 2015; Vom Steeg et al. 2016; Nikolich-Zugich 2018; Vom Steeg and Klein 2019). Furthermore, immunosenescence during influenza virus infection is associated with lung macrophage alterations, resulting in decreased phagocytosis and increased pulmonary fibrosis (Samy and Lim 2015; Wong et al. 2017). Immunosenescence is thought to be related to reproductive senescence. Sex hormones decrease with age in older individuals, and, as described above, are important mediators of protection against influenza virus (Robinson et al. 2011, 2014; Hall et al. 2016; Peretz et al. 2016; Vom Steeg et al. 2016; Guo et al. 2018).

In contrast to what is seen during seasonal influenza virus epidemics, there can be an increase in influenza disease severity among young adults and middle-aged individuals during influenza virus pandemics, resulting in a “W-shaped” age-specific mortality curve (Fig. 2). The 1918 pandemic induced high morbidity among all ages, but young adults had a disproportionately higher rate of mortality (Morens et al. 2008; Walters et al. 2016; Taubenberger et al. 2019) potentially attributed to the virus’s ability to induce a dysregulated pro-inflammatory immune response, as shown in mice, ferrets, and cynomolgus macaques (Kobasa et al. 2004, 2007; Kash et al. 2006; Memoli et al. 2009; de Wit et al. 2018; Short et al. 2018). During the influenza virus seasons immediately after pandemics, there tends to be a flattening of the young adult hump in the age-specific mortality curve back into the “U-shape” (Fig. 2; Simonsen et al. 1998; Taubenberger et al. 2019). This likely indicates the selective acquisition of protective immunity among this age group (Simonsen et al. 1998). Older adults, especially those aged 30–60, fared better than expected during such an intense pandemic, likely owing to previous exposure to H1- and N1-containing viruses that were circulating in the 19th century (Luk et al.



2001; Viboud et al. 2013; Short et al. 2018; Taubenberger et al. 2019).

Another possible reason for increased susceptibility to influenza virus infection during middle and old age is original antigenic sin (OAS), also known as immune imprinting. First observed in the 1960s, OAS describes the process by which the first antigenic variant of influenza virus that an individual is exposed to can shape subsequent humoral responses to influenza virus infection or vaccination (Francis 1960; Zhang et al. 2019a). Subsequent exposures to novel strains boost cross-reactive antibodies, resulting in strong humoral immunity to only a few antigens of the original strain, regardless of their effectiveness at neutralizing currently circulating strains. Therefore, after years of influenza virus evolution, novel drift variants can emerge and escape the highly specific humoral responses that have been selected, resulting in adults potentially becoming more susceptible to seasonal influenza viruses. However, it should be noted that in some individuals, OAS can lead to the boosting of antibodies that target conserved, broadly neutralizing epitopes like those in the HA stalk protein. Although it is likely impossible to model the complex influenza immune history of an adult, mice and ferret models have shown that sequential immunization can concentrate HA stalk antibodies (Krammer et al. 2013, 2014; Margine et al. 2013; Nachbaur et al. 2016).

OTHER HIGH-RISK STATES

Allergic Airway and Asthma

Clinical observations have shown that asthmatics and allergy sufferers have increased morbidity on influenza infection. Murine models of allergic asthma differ in the allergen trigger—including ovalbumin, house dust mite, and fungal allergens—and severity of resulting allergic disease (Nials and Uddin 2008; Gold et al. 2015; Debeuf et al. 2016). Allergic mice show prior airway inflammation increases resistance to subsequent influenza infection—a phenomenon opposite of what is seen in epidemiological studies of human asthmatics (Ishikawa et al. 2012;

Samarasinghe et al. 2014; Furuya et al. 2015; Kawaguchi et al. 2017). This protection is conferred to secondary bacterial coinfections caused by heightened TGF- β expression in asthmatic mice suppressing IFN- γ and promoting induction of robust antibacterial responses (Roberts et al. 2019). The protective effects of the allergic airway ameliorate damage to the epithelial surface, increase mucus production, and reduce weight loss on influenza infection during the peak allergic response and heightens eosinophilic responses capable of viral clearance (Samarasinghe et al. 2014, 2017). Alternatively, others have suggested enhanced levels of insulin-like growth factor-1 or NK cell activity in asthmatic mice may mediate protection from influenza (Ishikawa et al. 2012; Samarasinghe et al. 2014).

Asthma-induced protection is largely temporal. Influenza infection during remodeling after an allergic attack is detrimental; increased IFN levels result in immunopathology (Samarasinghe et al. 2014). These time-dependent associations of exacerbated severity are also observed in a model in which allergy induction occurred after influenza infection (Kawaguchi et al. 2017). These models showed a reduction in the numbers of eosinophils migrating to the lung, deteriorated lung function, and increased allergic inflammation (Ravanetti et al. 2017). The bronchoalveolar lavage fluid from infected mice with allergic asthma had significantly higher IL-6, IL-10, TNF- α , IL-5, IFN- α , IFN- β , and IFN- λ levels than those from infected, non-asthmatic mice (Hasegawa et al. 2014).

Although these studies provide a mechanistic explanation for the observation that asthmatics, once hospitalized for influenza, are less likely to die than other patient groups (Van Kerkhove et al. 2011), it also remains possible that different subtypes of asthma display differing degrees of synergism with influenza virus. Approximately 40% of adults suffer from allergic “eosinophilic asthma” modeled in mice by the different allergen triggers mentioned above; a large percentage of asthma patients suffer from nonallergic asthma (asthma is observed in the absence of allergen-specific IgE), neutrophilic asthma (eosinophilia cannot be detected), and

R. Honce et al.

paucigranulocytic asthma (defined by absence of an inflammatory cell infiltrate in sputum) (Simpson et al. 2006). Developing suitable animal models for varying phenotypes will help determine if asthma subsets display a different relationship with influenza virus.

Smoking, Chronic Obstructive Pulmonary Disease, and Emphysema

Active and ex-smokers have increased susceptibility to severe disease upon infection (Kark et al. 1982; Godoy et al. 2018). In mouse models, chronic cigarette smoke exposure (CSE) leads to increased lung inflammation and viral titers on infection compared with mice exposed to only fresh air (Gualano et al. 2008; Wang et al. 2015; Hong et al. 2018). Earlier CSE heightens migration of macrophages and neutrophils to the lungs and blunts the IFN, humoral, and $\gamma\delta$ T-cell responses in infected mice (Gualano et al. 2008; Wang et al. 2015; Hong et al. 2018). Mitigating the CSE-induced proinflammatory state via neutralizing antibodies against IL-1 α and IL-1 β improves infection outcomes (Bucher et al. 2017). Conversely, Han et al. (2014) contend the immunosuppressive effect of nicotine reduces inflammatory cell migration to the lung, thereby reducing immunopathology and promoting survival on influenza infection. These contradictory findings may be due to the duration and intensity of CSE. Work performed with primary respiratory epithelial cells from smokers or nonsmokers suggests a generally immunosuppressive state, as smoking reduced antiviral responses via downregulation of RIG-I- and TLR-3-mediated IFN signaling (Wu et al. 2016).

Smoking exacerbates chronic obstructive pulmonary disease (COPD) and emphysema-like symptoms, and the interactions among these chronic states impact influenza pathogenesis (Leung et al. 2017). CSE has been used to model the development of emphysema and COPD in mice (Bauer et al. 2010; Vijayan 2013; Mebratu et al. 2016). In these mouse models, increased viral titers, pulmonary inflammation, and reduced lung elasticity are reported on influenza infection (Bauer et al. 2010; Hsu et al. 2015). The severe inflammatory response is preceded by di-

minished innate immune responses, including poor mitochondrial antiviral-signaling (MAVS) and phosphoinositide 3-kinase (PI3K) signaling in lung epithelium (Hsu et al. 2015, 2017). CSE-induced COPD mice show NK cell hyperresponsiveness and enhanced neutrophilic responses, which further exacerbate viral-induced inflammation (Wortham et al. 2012; Sichelstiel et al. 2014). Experiments using influenza infection of primary human epithelial cells derived from donors with COPD support these findings, with increased viral entry and replication, impaired IFN responses, and heightened oxidative stress (Hsu et al. 2015; Aizawa et al. 2018).

Therapeutic strategies aimed at reducing lung inflammation are effective in improving antiviral responses in the COPD mouse model. Targeting signaling pathways to induce increased IFN production early in infection, or the application of exogenous IFN, can improve the antiviral response and may improve responses in other high-risk states as well (Hsu et al. 2015, 2017). Further, blocking the cytokine and chemokine signals that heighten NK cell and neutrophilic inflammation constrain aberrant inflammation and preserve lung function (Botelho et al. 2011; Sichelstiel et al. 2014).

Chronic, Genetic, and Infectious Diseases

Although influenza virus infection is typically self-limiting, in those with chronic disease severe sequelae can arise (WHO 2018). Type II diabetes and metabolic syndrome are known risk factors for severe influenza virus disease (Allard et al. 2010) and are prevalent among obese individuals. Type II diabetes results in increased susceptibility to influenza infection as shown by a lower lethal dose-50 and greater morbidity on infection in diabetic mice (Ito et al. 2015). Further, type I diabetics also suffer greater disease, and models of autoimmune diabetes show higher viral titers correlating with blood glucose levels and impaired viral clearance (Huo et al. 2017). (The impact of type I and type II diabetes on influenza severity is further reviewed in Hulme et al. 2017.)

Cystic fibrosis (CF) is one of the most-studied genetic disorders that impacts influenza



pathogenesis, as it increases susceptibility to influenza infection while also increasing CF complications (Conway et al. 1992; Renk et al. 2014). Cell culture models of the CF human respiratory epithelium report reduced antiviral gene induction early on in infection, but heightened inflammatory gene responses late in infection, contributing to the same pathology seen in mouse models (Xu et al. 2006). As influenza infection can result in lung edema and pulmonary fluid imbalance, the CF-related impairments in ion flux and fluid balance are exacerbated (Wolk et al. 2008; Brand et al. 2018). Interestingly, CF transmembrane conductance regulator gene heterozygotic mice have improved outcomes postinfection, including reduced acute lung injury, because of increased TGF- β -induced IL-6 production and stimulation of alveolar macrophages (Aeffner et al. 2013; Woods et al. 2015). Murine models of other genetic diseases, including sickle cell and neurodevelopmental disorders, display increased disease severity and blunted antiviral immunity, thus supporting the higher burdens and increased morbidity reported in clinical and epidemiological studies (Bundy et al. 2010; Strouse et al. 2010; Centers for Disease Control and Prevention 2012; Burton et al. 2014; Cronk et al. 2017; Karlsson et al. 2017b).

Underlying co-infections may also play into poor immune responses during influenza infections (Thompson et al. 2012; Sansonetti et al. 2014). *Mycobacterium tuberculosis* infection is a leading cause of morbidity and mortality worldwide, with increased risks of death in those coinfecting with influenza virus (Walaza et al. 2015). In mouse models, earlier exposure to influenza virus increases mycobacterial growth and decreases survival caused by enhanced antiviral type I IFN signaling that diminishes the IFN- γ signaling crucial for mycobacterial control (Manca et al. 2005; Redford et al. 2014). Concurrent influenza infections are common in those already burdened with mycobacteria and may diminish IFN- γ -dependent CD8⁺ T-cell responses needed to clear the bacterium and increase IL-10 levels (Flórido et al. 2013; Ring et al. 2019). Improved mycobacterial clearance during influenza coinfection is achieved by

blocking IL-10 receptor signaling (Ring et al. 2019). In HIV-infected hosts, other comorbidities drive increased susceptibility to influenza infection (Sheth et al. 2011; González Álvarez et al. 2016). Age, nutritional status, intravenous drug use, and CSE can all impact susceptibility to influenza virus infection and disease severity in the HIV-positive population (Sheth et al. 2011; Short et al. 2018).

PROTECTING HIGH-RISK POPULATIONS

Seasonal vaccination remains the safest and most efficacious way to prevent influenza infection and reduce disease severity, although not all hosts respond adequately to these preventative measures (Kennedy et al. 2012; Green and Beck 2017; Zerbo et al. 2017; Dhakal and Klein 2019). Because of the altered immune system in obese models, it is not surprising that the influenza vaccine is less efficacious in obese individuals (Neidich et al. 2017). Genetically obese mice vaccinated both with and without adjuvant were not protected against homologous viral challenge (Karlsson et al. 2016). Although the addition of adjuvant improves seroconversion in genetically obese animals, the breadth and magnitude of the antibody responses to HA and NA proteins are decreased, with no discernible impact from increasing antigen amount (Karlsson et al. 2016). The antibody response to influenza vaccination also declines faster in DIO mice versus lean controls. By 3 wk postvaccination, antibody titers diminish in obese mice, whereas they continue to increase in lean mice (Cho et al. 2016). Influenza vaccination has no effect on mortality during secondary bacterial infection, although survival could be improved by treating obese mice with β -lactam (Karlsson et al. 2017a). Passive antibody transfer using sera from lean mice also fails to protect obese mice, suggesting the obese host response may be more important than antibody protection (Karlsson et al. 2016). In mice that model type II diabetes, vaccination is shown to be effective (Sheridan et al. 2015), and type I diabetic mice show protection from viral challenge after vaccination with multiple-dose or high-dose vaccines (Zhu et al. 2005; Wu et al. 2010; Kreuzer et al. 2015).

R. Honce et al.

Vaccination is efficacious during pregnancy and can also safely protect the neonate (Beigi et al. 2009; Kennedy et al. 2012). Immunization during later gestational periods shows higher maternal immune activation and transmission to the fetus, but quicker antibody waning in the mother versus vaccination during the first or second trimester (Cunningham et al. 2019). For the fetus and neonate, passive transfer of antibodies via placenta or in breast milk can be protective; however, maternal vaccination during early pregnancy may wane and be ineffective in the neonate (Reuman et al. 1983; Mbawuikie et al. 1990; Honda-Okubo et al. 2014; van der Lubbe et al. 2017; Cunningham et al. 2019). The benefits of maternal vaccination on fetal and neonatal survival is also evident for H5N1 vaccination and challenge in mice, highlighting the benefits of breastfeeding for influenza-infected neonates and the uptake of vaccines in the pregnant cohort (Beigi et al. 2009; Satpathy et al. 2009; Hwang et al. 2010; Steinhoff et al. 2010; Christian et al. 2017). After infection, administration of antivirals can reduce disease severity and limit the duration of infection, with early administration crucial for the pregnant host (Siston et al. 2010; Centers for Disease Control and Prevention 2011). Unlike what was reported in clinical trials, pregnant women may have increased clearance of peramivir (Clay et al. 2011), stressing the need for inclusion of pregnant women in more clinical trials and the use of pregnant animal models to study the pharmacokinetics and efficacy of other antivirals.

Because of the differences in influenza virus immunity and disease severity between age groups, there are age-specific influenza vaccination recommendations worldwide. Because of their short immune history, young children (6 mo to 8 yr of age) in the United States are recommended to receive 1–2 doses of influenza vaccine annually (Neuzil et al. 2006; Campbell and Grohskopf 2018; Dhakal and Klein 2019). In the United States and other select countries, a high-dose influenza vaccine is available for those individuals ≥ 65 yr old. This recommendation is supported by observations that aged mice require higher antigen doses to elicit immune responses comparable to younger mice

because of immunosenescence (Yam et al. 2016). Despite the important role of biological sex on influenza virus immunity and disease described above, sex differences in vaccine efficacy decrease in aged mice (Potluri et al. 2019). Furthermore, the live-attenuated influenza vaccine is not recommended for individuals < 2 -yr-old or > 49 -yr-old because of their higher susceptibility to severe influenza virus disease (Grohskopf et al. 2018). (The role of host factors in influenza virus vaccination efficacy is further reviewed in Dhakal and Klein 2019.)

Vaccination proves effective in mice with allergic airway disease (Jian et al. 2013), but there are limited animal studies defining how other comorbidities impact both vaccination efficacy as well as antiviral efficacy. Further study on vaccination efficacy caused by the underlying coinfections and chronic genetic disorders, as well as understanding the dynamics of all influenza antiviral classes in high-risk hosts, is of exceeding importance; however, appropriate animal models must be developed to answer these targeted questions.

CONCLUDING REMARKS

Differing influenza pathogenesis in comorbid states and across the life span highlights the need for a carefully controlled and appropriately timed immune response to clear the virus and maintain airway integrity. The severity of an influenza virus infection represents a complex interplay between host and viral factors. However, as the number of people living with one or more comorbidity continues to increase, the role of host factors in influenza virus pathogenesis becomes ever more important (Fig. 3). Animal models of disease represent a powerful tool to understand and ultimately prevent severe influenza in vulnerable patient groups. Each animal model has limitations and caveats, but continued investigation into influenza infections in animal models of high-risk hosts represent an important first step toward reducing the burden of influenza in the twenty-first century. With increasing demands for universal influenza vaccines, the availability of such animal models will help ensure that any novel vaccine candidate is

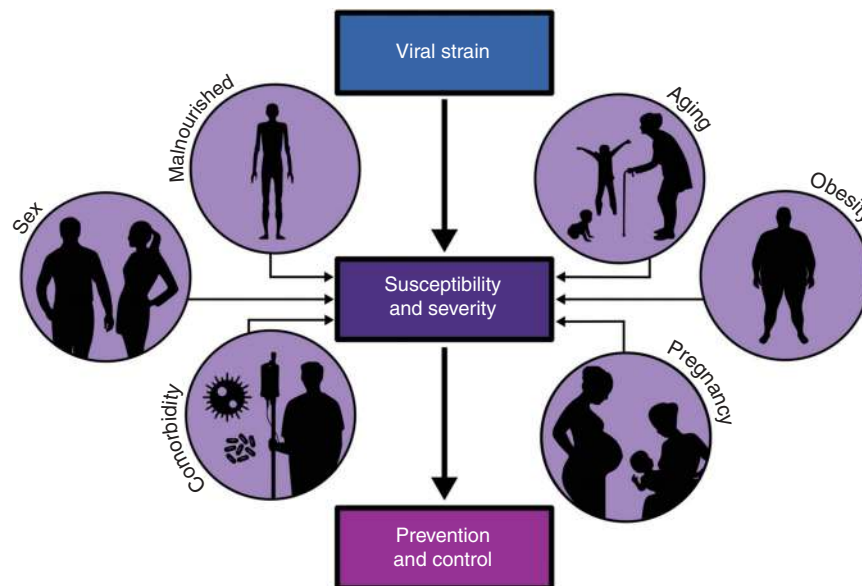


Figure 3. Host characteristics that contribute to influenza virus pathogenesis. High-risk hosts often have aberrant immune responses and baseline characteristics that impact susceptibility to infection with various influenza viral strains, as well as the antiviral response on infection. Studying influenza pathogenesis in the context of these hosts is of paramount importance, as the number of those living with one or more comorbidities continues to increase.

efficacious not only in healthy adults but also in those populations most at risk of severe influenza (Erbelding et al. 2018; Henry et al. 2018).

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R. Honce et al.

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R. Honce et al.

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R. Honce et al.

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