**Antibody**

**IgG, IgM**

[**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903284/**](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903284/)

Log Transformed Data: Median +/I IQR, Mann-Whitney

0 = normal: no tissue affected, 1 = minimal: rare or inconspicuous lesions, 2 = mild: multifocal or small, but prominent lesions, 3 = moderate: multifocal, prominent lesions, 4 = marked: extensive to coalescing lesions or areas of inflammation with some loss of structure, 5 = severe: Extensive or diffuse lesions with effacement of normal structure

Machine learning techniques have been applied to relate respiratory infection severity and hematological data64. Recently, artificial neural networks65 (ANNs) have captured nonlinear influenza dynamics66 to epidemic signals from live internet data67,68.

64. Jhutty, S. S. *et al.* Predicting Influenza A Virus Infection in the Lung from Hematological Data with Machine Learning. *mSystems* **7**, e0045922 (2022).

65. Hopfield, J. J. Artificial Neural Networks. *IEEE Circuits Devices Mag.* **4**, 3–10 (1988).

66. Sabir, Z. *et al.* Artificial neural network scheme to solve the nonlinear influenza disease model. *Biomed. Signal Process. Control* **75**, 103594 (2022).

67. Dong, G. *et al.* Influenza-like symptom recognition using mobile sensing and graph neural networks. in *Proceedings of the Conference on Health, Inference, and Learning* 291–300 (Association for Computing Machinery, 2021). doi:10.1145/3450439.3451880.

68. Aiken, E. L., Nguyen, A. T., Viboud, C. & Santillana, M. Toward the use of neural networks for influenza prediction at multiple spatial resolutions. *Sci. Adv.* **7**, eabb1237 (2021).

**Cytokines and Chemokines**

* **Interferon:**
  + **Type-I:** 
    - **Alpha:** Antiviral, activates immune cells like NK cells and macrophages, enhances antigen presentation.
    - **Beta:** Antiviral, anti-inflammatory, enhances antigen presentation, and augments adaptive immune responses.
  + **Type-II:**
    - **Gamma:** Activates macrophages, antiviral, promotes antigen presentation, and directs cellular immune responses.
  + **Type-III:**
    - **Lambda:** Antiviral, mucosal immunity, less inflammatory compared to Type-I interferons.
* **TNF-alpha:** Promotes inflammation, antiviral, induces fever, and apoptotic cell death.
* **Interleukins:**
  + **IL-1:** Pro-inflammatory, fever induction.
  + **IL-2:** T-cell growth factor.
  + **IL-6:** Pro-inflammatory, fever, and acute-phase response.
  + **IL-8 (CXCL8):** Neutrophil chemoattractant and activator.
  + **IL-10:** Anti-inflammatory, inhibits pro-inflammatory cytokine production.
  + **IL-12:** Induces T cell and NK cell IFN-gamma production, promoting cellular immunity.
* **TGF-beta:** Immunosuppressive, tissue repair, regulatory T cell induction.
* **RANTES (CCL5):** Chemokine, recruits immune cells like T cells, eosinophils, and basophils.
* **MIPs (Macrophage Inflammatory Proteins):** Chemokine, recruits immune cells, mainly macrophages.
* **GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor):** Immune cell growth, differentiation, and survival.
* **CCL2 (MCP-1):** Monocyte chemoattractant

**Cells**

* **Epithelial Cells:** Initial entry point for the influenza virus, crucial for innate immune response, secretion of antiviral factors.
* **Neutrophils:** Early responders to infection, help in phagocytosis of infected cells, release reactive oxygen species.
* **Macrophages:**
  + **Inflammatory Macrophages:** Contribute to immune response, promote inflammation, enhanced microbicidal activity.
  + **Alveolar Macrophages:** Initial defense, phagocytose pathogens, secretion of cytokines, and chemokines.
* **Natural Killer Cells:** Destroy infected cells, early immune response, secretion of IFN-gamma.
* **Dendritic Cells:**
  + **Plasmacytoid Dendritic Cells (PDCs):** Produce interferon, antiviral response, less efficient at antigen presentation.
  + **Conventional/Antigen-presenting Dendritic Cells (cDCs):** Present antigens, bridge innate and adaptive immunity, secretion of cytokines.
* **T Cells:**
  + **CD4 T Cells:** Assist other white blood cells, coordinate immune response, differentiate into various T helper subsets.
  + **CD8 T Cells:** Target and destroy infected cells, secrete antiviral cytokines.
* **B Cells:** Produce antibodies specific to the influenza virus, crucial for adaptive immunity, differentiate into memory and plasma cells.

**Dynamics**

**Days 0-2** (Early Infection):

* **Infection Initiation:** Influenza virus infects respiratory epithelial cells.
* **Interferon-alpha/beta:** Peaked response within the first 1-2 days to inhibit viral replication. <1000 pg/mL.
* **TNF-alpha:** Elevated early to promote inflammation and recruit immune cells. <100 pg/mL.
* **Neutrophils and Alveolar Macrophages:** Respond early to phagocytose infected cells and debris. Neutrophils 10 – 30% of BALF, MA’s 90% (healthy), drops to 60-80% during infection.

**Days 2-5** (Innate to Adaptive Transition):

* **Natural Killer Cells:** Peak activity around day 2-3 to destroy infected cells. <5% BALF.
* **Dendritic Cells:** Migrate to lymph nodes to present antigens, peaking around day 2-4.
* **Interleukin-6 (IL-6):** Elevated to promote T cell responses and B cell differentiation. <500 pg/mL.
* **Interleukin-12 (IL-12):** Promotes Th1 responses, peaks during this transition phase. <50 pg/mL.

**Days 5-10** (Adaptive Response):

* **CD8 T Cells:** Peak around day 5-7, destroying infected cells.
* **CD4 T Cells:** Assist B cells and CD8 T cells, peaking around day 5-7.
* **B Cells:** Antibody production peaks around day 7-10.
* **Interferon-gamma:** Promotes antigen presentation, peaks alongside T cells. <1000 pg/mL.

**Days 10+** (Resolution and Memory):

* **TGF-beta:** Rises to promote resolution of inflammation. <5,000 pg/mL.
* **Memory T and B Cells:** Formation begins for long-term immunity.

Respiratory viruses pose a significant threat to human health, with limited effective interventional strategies. At least 219 virus species1 directly infect humans across 9 major families2. Historic outbreaks of smallpox have caused millions of casualties3. SARS-CoV-2 has viscerally demonstrated the threat of respiratory viral infections, being held responsible for 3 million deaths since 2019, $8-$16 trillion in total economic impact, and pushing up to 500 million people into poverty4. Influenza claims 250 – 500 thousand souls5, with X billion economic impact and 0.Y % - 0.Y % lethality and an estimated (infer) annual cases. SARS-CoV-2’s lethality and cases are more difficult to accurately measure compared to influenza’s steady companionship in human mortality. However, estimates for the current form are 0.Y % - 0.Y % lethality. While there have been XX million estimated cases since 2019, current models predict N annualized cases as COVID-19 shifts from pandemic to endemic.

Despite these clear impacts, and the success of humanity in eradication of smallpox, polio, and rinderpest, limited interventional strategies exist for respiratory viruses. Only four antiviral therapeutics [Rapivab (peramivir6–11), Relenza (zanamivir12–19), Tamiflu (oseltamivir phosphate20–23), and Xofluza (baloxavir marboxil24,24–31)] have been approved for influenza. Antivirals tend to lose effectiveness against over time due selection for treatment-resistant strains32–34, with the CDC currently recommending against amantadine and rimantadine35. Models calibrated to real-world studies of these therapeutics indicate 1-4% relative reduction in overall influenza lethality24. Distinguish between prophylactic (applied before contracting the disease) or therapeutic (treatment applied during course of disease). Prophylactics come with a higher rate of side effects per treated disease instance, since not every person receiving the treatment will contract the disease.

Type-I interferons are a primary component of the innate immune system’s response to influenza24–26.

The lack of universal efficacy of any single approach may be part due to heterogeneity in response due to host genetics5, selection for treatment resistant influenza strains7,8, nutritional deficiencies3,4, socioeconomic status9, population density10 , individual vaccine response11, and the virus’ genetic drift12.

Efficacy of any treatment may be altered in the presence of bacterial or viral coinfections. More recent coinfection papers. Need for coinfection models, recently developed ones. Future direction of coinfection. Co-infection with multiple strains of SARS-CoV-2 have been observed36.

Vaccines must be selected against the most likely dominant strains of any particular virus, are subject to a decline of immunity37 over time, and can have cross-virus interactions. For example, pre-existing influenza immunity decreases lethality in a subsequent coinfection with influenza and SARS-CoV-2, but immunity to SARS-CoV-2 does not confer protection38.

Influenza pandemics are exacerbated in lower socioeconomic status39–41, partially driven by nutritional deficiencies42. Vitamins A and D have been implicated in severity across multiple viral infections and host organisms43,44. As a public health measure, encouraging supplementation is an effective tool to mitigate viral outbreaks and lessen severity for individual patients. Must define which vitamins are both deficient in the patient/population and efficacious in the current disease via mechanistic modeling.

Nonpharmaceutical interventions like border closures and social restrictions are effective at reducing communal infection rates45–47, but are best applied only at the peak of outbreaks (compliance, material limitations). Live modeling of viral outbreaks has been achieved by sourcing data from social media signal analysis48, wastewater monitoring49, wildlife sampling50.

A major hindrance in managing viral disease outbreaks is our incomplete understanding of how the host’s innate and adaptive immune responses limit viral replication (intracellular), spread (within the host), and transmission (between hosts). Recent advances in mathematical modeling of infection dynamics across multiple scales have elucidated interactions between immune responses and their impact on controlling viral outbreaks through these distinct scales.

Summary of IFNs roles, major types, pre- and post- exposure prophylactic treatments (IFN review, other reviews of PEP/PREP studies for flu) show promise but require treatment before symptom onset. Similar drugs (IFNs, others that have also been used as prophylactics) have been used as treatment (ref), with (quantify) success. Relation of blood to lung tissue: more than a correlation.

The dynamics of influenza infection are critical, and any treatment modality must consider the timing of infection and immune response. (timing of drug, timing of coinfection, flu studies). Modeling encompasses many approaches to replicating these real-world events and timing within a mathematical framework. Need for defining data – not just presence of cells, but surface markers, single cell analysis, altered conditions, different time-density sampling (lack of dense time series data during critical phases of infection). While direct monitoring during infection would be ideal (human lung tissue measurements), this type of data borders on impossible to collect. Instead, the application of modeling dynamics can reliably represent the infection. These models go a step further than correlation, building a mechanistic link between cause and effect. This explicit statement of a system allows a robust experimental design to confirm or dispel the hypothesized model.

Models are tied to real world data. Parameter optimization, or model training, is applied to obtain a statistical best-fit of the model’s parameters to the data, resulting in a calibrated model output. Although models are approximations, exhaustive stepwise models are not necessarily better; the increased number of parameters may lead to a statistically indefensible fit (i.e., overfitting), structural and practical identifiability issues, increasing computational cost of parameterization and model evaluation, and loss of general interpretation. Thus, only major rate-defining or data-available system steps are incorporated into models. Further, biology is not mandated to use the simplest mechanism or fewest number of representable parameters.

Refining mathematical descriptions of infection and calibrating this predictions against real world data drives the development of new models. These Calibrated Models have been used to design confirmatory experiments.

Evaluating an ensemble of model structures training against data and selecting the best statistical fit. Model complexity penalization (regularization, information criterion). Validation, testing via second/third or split dataset. Distinction that confirmatory experiment design is to test the model against altered conditions of reality where it did not have constraining information during construction. Rejection of models at the point of follow-up experiments expected and welcome result. Lessons should be taken from newly defined Boundary Conditions.

Since (Year), Standard Viral Dynamics Model (ref). Viruses which result in acute infection (SARS MERV RSV FLU etc models), chronic (HIV AIDS HSV etc models), other (HCV, IAV, West Nile virus, Dengue virus, Adenovirus, yellow fever virus, ZV, BKV, HPV, multi host cycles) have been studied.

Ordinary Differential Equation (ODE) models are a common approach (refs). Several spatiotemporally resolved modeling suites (CC3D, Physicell, and all the rest) exist to extend ODEs, incorporate cell populations (Agents). Diffusion (though rarely advection) of cytokines, travel time of cells. In particular, Physicell has seen a recent 40x speedup via GPU compute as part of OpenACC51.

Recently, Artificial Neural Networks52 (ANNs) have captured nonlinear influenza dynamics53 to epidemic signals from live Internet data54,55. Machine learning techniques have been applied to relate respiratory infection severity and hematological data56, and to differentiate between COVID-19 and inlfuenza57. Such approaches are valuable, built on computationally efficient architecture and leverage GPU parallel scaling.

Classic modeling of cells is that presence:activity. Structure of equations for generic Host, Immune Cell, Cytokine. Implication is that cells with markers are producing, are all producing, are all producing at the same rate, and that the rate does not vary over time separately from their presence. For example, a single CYTOKINE capable (surface marker+) IMMUNE cell is seen to arrive in the lung after X days. Upon entry, the cell is producing CYTOKINE at RATE, and maintains this rate until the cell’s (departure from the compartment, death) X days later. This scenario is unlikely to be the whole truth – surface receptor downregulation is a major driver of type-I IFN production shutdown in CELLS during CASES. Other self-downregulating cytokines produced by immune cells. Further, some cells require interactions with infected tissue (GMCSF and inflammatory macrophages). These factors often justify the use of nonlinear kinetics to produce cytokines from immune cell populations and the regulation of the immune cells themselves.

During sepsis, death of T cell and B cell in lymphoid organs13.

Air liquid interfaces (ALI26 or organoids27) have seen direct applications in respiratory viral infection research28. These engineered experimental systems been developed with mechanical breathing patterns29, multiple influenza strains30, and captured the B- and T- lymphocyte dynamics after influenza vaccination31. Single cells can be selected and infected with a single virion using nanomanipulation32. Organoids with selective immune responses can finally elucidate each source and regulation method.

Known dynamic features of IFNs. Large IFN data sets (human, monkey, mouse).

Scaling of IFNs: TMDD, exogeneous vs endogenous production, route of administration, critical dimensions, scaling laws, host scaling, allometric models, other drug translations, general assumptions for drugs until proven different (pk/pd).

Review of existing IFN models *in insimul.* AIC, AICc, BIC model selection.

Spatial complexity of chasing the most prevalent strains, reservoir sites (immune privilege in the body, different continents in epidemiology).

“For over 20 years, mathematical models have been developed to assess infection kinetics during acute or chronic viral infection to better understand virus replication, elucidate mechanisms of viral persistence and control by host immune responses, disentangle pathogen-pathogen interplay, and evaluate the clinical potential of different antiviral therapies.”

* Founding paper(s) date – current. 25?
* Mathematical models in government decision making, vaccine study, virtual cohort

“These models have been calibrated to data and used to perform in silico experiments and generate novel hypotheses. Moreover, integrated laboratories and improved collaborative efforts have resulted in innovative model-driven experiments being employed and in new biology being defined. These studies, some of which are highlighted here, have advanced the field and opened new research directions.”

* Calibrated -> trained? Least jargon-esque word for tuning, give some expo on this
* Point to predictions made by specific models

What Data can tell us and how it must be interpreted?

* In Vitro
* In Vivo
  + Host differences and scaling rules
* Organoids
* Cytometry
* High Throughput
* Omics/multi-omics
* Single Cell Encapsulation and Treatment

Mathematical models are powerful tools to leverage and incorporate insights from many biological studies at once. Models describing influenza kinetics have yielded invaluable insights into viral production and clearance, cytokine responses, immune cell presence, and pathogen-pathogen interactions. These in silico systems can be rapidly adapted to emerging threats and represent one of the few approaches capable of capturing the highly nonlinear and spatiotemporal dynamics of viral infections, with faster response times than traditional experiments.

Influenza infection models have existed since 197613, with the introduction of compartment-based models of influenza infection. The familiar target-cell limited model emerged in 199614, and has been built upon to add antibodies15,16, strain differences17, link directly to disease pathology 18,19, and immune and cytokine responses16,20–22. Select model structures are viewed in23.

Models calibrated to real-world studies of baloxavir, one of four approved influenza antivirals6, indicated a 1 - 4% relative reduction in overall influenza lethality7.

The lack of universal efficacy of any single approach may be part due to heterogeneity in response due to host genetics5, selection for treatment resistant influenza strains7,8, nutritional deficiencies3,4, socioeconomic status9, population density10 , individual vaccine response11, and the virus’ genetic drift12.

The dynamics of influenza infection are critical, with a sudden onset of symptoms and a rapid viral peak. The first hours to days after initial infection are characterized by the innate immune response, a nonspecific defense system deployed by infected and neighboring host cells. Influenza derived pathogen-associated molecular patterns (PAMPs) are detected by pathogen-recognition receptors (PRRs), including RIG-I14–16 and the Toll-Like receptor family. PRRs are present on resident lung neutrophils17 and epithelial cells18,19. These activated PRRs induce interferons and interferon stimulated genes20,21 (ISGs), which play roles in establishing an antiviral state within cells. Type-I and III22 interferons are detected by both the originating cell (autocrine) and neighbors (paracrine)23,24, activating the JAK/STAT pathway25. The positive feedback of these pathways can lead to an excessively inflammatory state24, called cytokine storm26, primarily characterized by interferon-inducible protein (IP)-10 and interleukins 6, 8, and 1727. Cytokine storm leads to excess programmed cell death (PCD) in airway epithelial cells28 and macrophages29. PCD is accomplished through pyroptosis, necrosis, {other cell death mechanisms} which are mediated by the TNF-A (and?). To control the positive feedback loop of IFN production, the IFNAR receptor is internalized, neutrophils30 and T cells downregulate inflammation at later times.

Role of resident neutrophils (phagocytosis, NETs, other cytokine production). Timing, exhaustion/downregulation. During the same time, {macrophage subtype: alveolar} acting in {roles}. Some cells require interactions with infected tissue (GMCSF and inflammatory macrophages).

Dendritic cells (pDC, antigen DC subtype distinction31). Timing of DCs. Interferons mediate dendritic cells’ activity32, ultimately controlling the bridge between the innate and adaptive immune responses. Antigen presenting DC’s obtain samples of the pathogen on {surface structure}, transit to draining lymph sites, activating T cells33.

The activated CD4+ and CD8+ T cells {traffic, upregulate, multiply}, arriving at the lung from {4 to 7} days after initial infection. T cell activation, antigen specific arrival window, nonlinear (density dependent) clearance of infected tissue. Other cytokines produced by T cells.

These models go a step further than correlation, building a mechanistic link between cause and effect. This explicit mathematical statement of a mechanistic explanation allows a robust experimental design to confirm or dispel the hypothesized model.

Models are tied to real world data through parameter optimization, or model training. Training is applied to obtain a statistical best-fit of the model’s parameters to the data, resulting in a calibrated model output. Although models are approximations, exhaustive stepwise models are not necessarily better; the increased number of parameters may lead to a statistically indefensible fit (i.e., overfitting), structural and practical identifiability issues, increasing computational cost of parameterization and model evaluation, and loss of general interpretation. Thus, only major rate-defining or data-available system steps are incorporated into models. Further, biology is not mandated to use the simplest mechanism or fewest number of representable parameters.

B cells are an integral part of the adaptive immune response to influenza infection. Here's a synthesis of their role based on available scientific literature:

Localization and Migration:

B cells can originate in the bone marrow and mature there. During influenza infection, B-1 cells are activated by innate signals, including type I interferons, and migrate to the draining mediastinal lymph nodes (medLN). Here, they can differentiate into IgM-producing cells. Conventional B cells, upon activation by the influenza antigen, will travel to the T-B border to receive T cell help, leading to their differentiation into either plasmablasts at extrafollicular foci or long-lived plasma and memory B cells in germinal centers.

Cytokine Production:

Upon activation, B cells can produce cytokines such as TNF-α, LT, IL-6, and IL-10. During influenza infection, IL-10 production by B cells has been shown to modulate the inflammatory milieu in the lungs, buffering against the tissue-damaging effects of cytotoxic T cells.

Regulation of Presence and Activity:

The presence and activity of B cells are regulated by several factors including cytokines, the presence of antigen, and interactions with T cells. The B cell response is also influenced by the inflammatory environment within the infected tissues.

Spatial Behavior:

B cells show spatial behaviors such as moving to the spleen and lymph nodes upon activation, and they can also traverse to other tissue compartments if needed. Memory B cells can rapidly migrate to infection sites upon reactivation.

Time Dynamics:

B-1 and extrafollicular responses are quick and can influence viral clearance after a primary challenge. Plasmablasts from extrafollicular foci are thought to live only for about 3–5 days, whereas germinal center responses lead to long-lived plasma cells and memory B cells. The initial B cell response in the local respiratory tract draining lymph node can be induced as early as 48-72 hours after infection, contributing to viral clearance during primary infection​​.

The response and dynamics of B cells during influenza infection involve complex interactions and timing, which are orchestrated to effectively address the viral threat while also avoiding excessive inflammation that could lead to immunopathology.

The internal mechanisms that detect viruses within infected cells primarily involve the innate immune system's pattern recognition receptors (PRRs), which recognize pathogen-associated molecular patterns (PAMPs) that are distinct to pathogens, such as viruses. Here are key PRRs involved in detecting influenza virus within infected cells:

Toll-Like Receptors (TLRs):

TLR3: Recognizes double-stranded RNA (dsRNA), a replication intermediate of many viruses, including influenza.

TLR7/8: Recognizes single-stranded RNA (ssRNA) from viruses like influenza within endosomes.

RIG-I-like Receptors (RLRs):

RIG-I (Retinoic acid-inducible gene I): Binds to RNA with 5' triphosphates and short dsRNA, commonly found in influenza virus replication.

MDA5 (Melanoma Differentiation-Associated protein 5): Recognizes long dsRNA.

NOD-like Receptors (NLRs):

NLRs can sense cellular stress and damage associated with viral infection, although they are more commonly associated with bacterial infections.

Cyclic GMP-AMP Synthase (cGAS):

While cGAS is typically involved in sensing cytosolic DNA, some studies suggest it may also play a role in sensing RNA virus infection through indirect mechanisms.

Parts of the Virus Detected:

For influenza virus, PRRs mainly detect viral RNA. TLR3 detects dsRNA, while TLR7/8 and RIG-I detect ssRNA and dsRNA with 5' triphosphates. The segments of the influenza genome and replication intermediates are the primary PAMPs that are recognized.

Timing of Detection:

The detection of the influenza virus by PRRs occurs rapidly after the virus has entered the cell and begins its replication process. Here is a timeline relative to the virus' entry and eclipse phase:

Virus Entry: The influenza virus enters cells through receptor-mediated endocytosis. Entry is typically marked by the fusion of the viral envelope with the endosomal membrane and release of the viral genome into the cytoplasm.

Eclipse Phase: This is the period when the virus uncoats and begins to replicate but before new infectious virions are produced. During this phase, viral RNA and replication intermediates accumulate in the cytoplasm.

Detection by PRRs: Detection of the viral RNA by PRRs like RIG-I occurs early during the replication cycle, often within hours post-infection. This leads to the activation of signaling pathways that result in the production of type I interferons and other cytokines that inhibit viral replication and spread.

The activation of these PRRs and subsequent signaling cascades are crucial for the initiation of the antiviral response before the virus has the opportunity to spread to new cells. These early detection mechanisms are a vital part of the innate immune response and are essential for controlling the infection and shaping the subsequent adaptive immune response.

# Review of Modeling Within-Host Virus Infection Dynamics

“Numerous mathematical approaches have been employed to evaluate host immune responses, including ordinary differential equation (ODE) models and spatially resolved agent-based models (ABM).”

* PDE, DDE, Boolean, Stochastic
* Crowd data (social media spread study)
* Neural Network (Neural ODEs, adjoint models)
* Compute scaling, predictions

“The most used model is the standard viral dynamics model (Figure 1), which was introduced over 20 years ago (reviewed in [14,15]). The model has since been successfully applied to study a variety of virus infections, including HIV [16], HCV[17], IAV [9], West Nile virus (WNV) [18], Dengue virus (DENV) [19], Adenovirus (ADV) [20], RSV [21], yellow fever virus (YFV) [22], ZV [23], BKV [24,25], and HPV [26,27], among others.”

* More recent viral applications
* Timeline with major points of innovation in Standard Model

“These viruses range from acute to chronic and have varied sites of infection (e.g., lung versus liver) and pathologies (e.g., pneumonia versus cirrhosis). Interestingly, viral kinetics across these systems are relatively similar. That is, virus increases exponentially, reaches a peak, and declines exponentially in a monophasic, biphasic, or triphasic manner until clearance (acute) or until a steady state (chronic) is achieved (Figure 1).”

* Where viruses affect
* Routes of entry
* Host Target Cell similarity, surface markers
* Viral kinetics review
  + Example virus for each decay type
  + Relative concentration by organ type?
  + Define Cyclic, Chronic, Acute, Terminal kinetic profiles
    - Mathematical definitions for each profile
* Growth curve types

## Annotated References

### Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths

<https://doi.org/10.3390/nu12040988>

Grant et al

2020

Argues that supplementation of vitamin D can reduce viral respiratory infection severity.

* The induction of the antimicrobial peptide families, cathelicidins and defensins, lower viral replication rates.
* Vitamin D downregulates the pro-inflammatory cytokines IL-12, IFN-G, IL-6, IL-8, IL-9, and TNF-A
* Upregulating the anti-inflammatory cytokines TGF-B, IL-4, IL-5, and IL-10. Ref
* (Vitamin D immunity review) https://doi.org/10.1177/20503121211014073

**Why**: Peptide incorporation into viral dynamics model. Vitamin regulation of cytokine profiles. Th1, th2 immunity switching.

### Vitamin A corrects tissue deficits in diet-induced obese mice and reduces influenza infection after vaccination and challenge

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7483416/>

Penkert et al

2020

High dose oral vitamin A, followed by influenza vaccination and challenge.

* Tissue level vitamin changes
* Improved antibody response
* Faster viral clearance
* Lower pro-inflammatory cytokines in blood
* Vitamin A Cytokine Regulation paper: https://doi.org/10.1016/j.tiv.2013.03.013

**Why**: Data from vaccinated DIO and Control mice serves as interesting Mild Infection data. Existing models could benefit from antibody modules and consideration of vaccination status. Inter-individual nutrient profiles scales to human implications. Promising, since vitamins are cheap public interventions.

### EZ Clear for simple, rapid, and robust mouse whole organ clearing

<https://doi.org/10.7554/elife.77419>

Hsu et al

2022

Timeline of clear organ development

* Azaripour et al. (2012). Review of iDISCO, BABB, CLARITY tissue clearing techniques. <https://www.sciencedirect.com/science/article/pii/S0079633616300043>
* Scott et al (2014). Whole mouse lungs and human airway. <https://pubmed.ncbi.nlm.nih.gov/24471696/>
* Costantini et al (2019). Review of in-vivo and ex-vivo tissue clearing techniques. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6788593/>
* Zhao et al (2020). Intact whole human organs (SHANEL method, brain and kidney). <https://www.cell.com/cell/pdf/S0092-8674(20)30111-2.pdf>
* Ueda et al (2021). Neuroscience paper, but reviews tissue clearing. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8121164/>
* Hsu et al (2022). EZ Clear for preserved whole-mouse lung processing. <https://pubmed.ncbi.nlm.nih.gov/36218247/>

Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics

<https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30484-9/fulltext>

Petersen et al

2020

Review of international pandemic statistics. SARS-CoV-2 (R0: 2.5) is more transmissible than MERS-CoV (R0: 0.9) and the 2009 influenza pandemic (R0: 1.5). Comparable to SARS-CoV (R0: 2.0-3.0) and the 1918 influenza pandemic. Within-host viral dynamic models can lend mechanistic explanation to epidemiological models. Comparing the field’s three highest impact viruses gives contextual grounding to the review of models.