**Virus-host protein-protein interactions and human disease**

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**Abstract**

Viruses infect their hosts by a series of protein-protein interactions (PPIs), starting with virus binding to surface receptors, and concluding with virus assembly and egress of complete virus particles. We discuss the coverage of human viruses and how well their proteins have been studied for host-virus interactions. Notably, only 4 virus families have accumulated more than 1,000 PPIs when all their PPIs are combined, namely Orthomyxoviruses (5,494), herpesviruses (5,423), papillomaviruses (3,927) and retroviruses (2,285). Thus, some viruses have been extremely well studied, with some viruses, such as HIV, having more than a hundred interactions identified for each of its proteins. While it remains unclear how many of these interactions are physiologically relevant, for many medically important viruses numerous genome sequences are available but relatively few interactions are known (e.g. rhinoviruses). We discuss the conclusions that can be drawn from large- and small-scale PPI studies in human viruses, how they reflect the relevance of important viruses for human health, and finally compare them to some insights gained from phage-bacterial interactions.

**Introduction**

Bacteria and viruses are the most important pathogens on earth. While most bacteria are still easy to treat with antibiotics, viruses are much harder to control therapeutically. That is a direct consequence of being composed of only a few nucleic acids, proteins, sometimes lipids and a few other compounds. Given their simple composition and structure, viruses are completely dependent on their hosts, without a metabolism on their own that can be targeted by drugs, they have to extensively interact with host proteins via protein-protein interactions (PPIs) and other host components. While most bacteria can be directly eliminated using antiobiotics, viruses can only be constrained in their growth and doing so safely for the host remains challenging. Furthermore, viral variation occurs rapidly, often with significant adaptation within each host. Future strategies for development of safe antivirals will likely depend upon precise targeting of virus-host PPIs and a deeper understanding of viral biology.

In this review we provide an overview of virus diversity and how it relates to the diversity of interactions among host and virus proteins. Given the vast body of literature about virus-host interactions, which is nearly impossible to review in a single article, we attempted to provide a bigger picture overview, primarily based on existing databases of virus-host (human) interactions (**Table X**). We surmise that medically important viruses have received more attention and thus more research, hence more interactions should be known and understood. While this is often the case, some highly infectious viruses have received relatively little attention . In fact, being highly pathogenic does not mean a virus is easy to study nor medically important, given there may be a very restricted geographic or host range. For some viruses, such as Zika, the threat is relatively recent so that research has only ramped up during the past few years and while there may be extensive sequence information from next-generation sequencing studies, precise knowledge of virus-host PPIs and thus potential targets for antiviral therapies may be very limited. Note however, that our focus on databases introduces a certain bias to our analysis, caused by the bias which information is submitted to and collected by databases.

**Diversity of human viruses**

Most people are infected by multiple viruses. Wylie et al. detected an average of 5.5 viral genera in each of 102 healthy individuals (1). Given that no more than 5 body habitats were screened (nose, skin, mouth, vagina, and stool) we can safely assume that most people have dozens of different viruses in their body. However, only few lead to clinical symptoms or disease. Conversely, Poon et al. characterized diversity of a single virus, influenza A, in individual human hosts and found numerous variants that changed in abundance over time, suggesting adaptation. Moreover, the types and populations of variants varied widely between individuals. Thus, it appears likely that human viruses rely upon their enormous diversity for survival in most circumstances. We have therefore compiled data on the diversity of human viruses by looking both at sequence diversity (**Table 1**) and epidemiology (**Table 2**).

We also tried to take into account the medical and thus economic importance by summarizing numbers on infected people, sick people (morbidity), and people dying from virus infections (mortality) (**Table 2**). We wondered how much of a disease burden do these viruses put on the human population and whether research has responded accordingly. Not surprisingly, some viruses deserve and have received a lot of attention, such as HIV which has both claimed a large number of victims and an equally large amout of research, including on PPIs. By contrast, other viruses have received rather scant attention with respect to protein-protein interactions, although they do have significant health impact, at least during occasional outbreaks.

**Virus-host interactions in humans**

Our understanding of human-virus PPIs is highly biased towards a few well-studied viruses. For instance, only 2 viruses have more than 1,000 interactions listed in VirusMentha (a major database for virus-host interactions, **Table 3**), namely Epstein-Barr Virus (EBV) with 1,766 and HIV-1 with 1,304 PPIs, respectively (**Table 4**). Only 4 virus families have more than 1,000 PPIs when all their PPIs are combined such as orthomyxoviruses (5,494), herpesviruses (5,423), papillomaviruses (3,927) and retroviruses (2,285), respectively. While these numbers are roughly similar, they represent vastly different genome sizes and virus diversity within families. For instance, HIV encodes only about 10 proteins while it has more than 100 interactions per protein. EBV, by comparison, encodes about 85 proteins leading to “only” 20 interactions per protein on average. Before we can even begin to interpret these interactions, we need to ask if it is biologically meaningful or even possible if a protein has >100 interactions. It is also important to note that the extent of known human-virus PPIs often differs from the extent of known viral sequences. This is particularly true for recent viral outbreaks, such as Zika, and is in large part due to the availability of next-gen sequencing.

**How reliable are published virus-host interactions?**

Only a few studies exist that systematically validated human-virus interactions for their biochemical or even physiological validity.

Among the first attempts to validate human virus-host interactions was our study of KSHV-human interactions (2). We predicted homologous interactions from experimental data *in S. cerevisiae, Caenorhabditis elegans*, and *Drosophila melanogaster* whenever at least one of them had interacting orthologs. Although this is a somewhat far-fetched approach, we predicted 20 interactions between 8 KSHV and 20 human proteins. Nineteen of these 20 virus-host interactions were tested by CoIP and an unexpectedly large percentage (13 out of 19, or 68%) were confirmed.

Zhang et al. found 109 interactions among 33 Vaccinia and ~160 human proteins of which 27 were tested by GST pull-downs (3). 17 of these were confirmed, which translates to a 63% validation rate. While these numbers appear to be rather high, only certain subsets were selected and thus do not necessarily represent an unbiased validation rate of a complete Y2H data set.

While it is possible that many interactions found in high-throughput screens are physiological, this is unlikely. Unfortunately, it is difficult to prove that an interaction has no physiological role, as for viruses even small differences may result in significant survival rates over many generations. In addition, given the high mutation rate of many viruses, small differences may expand to larger ones once more mutations accumulate and add further (small) advantages.

**How many interactions does a virus require?**

The sheer number of host-virus interactions that have been found for many viruses may suggest that we have identified all interactions. Yet, such numbers appear rather large, suggesting that they are likely to contain a large number of false positives. So, the key question is: how many interactions does a virus need or use to infect an organism and how do we identify the physiological interactions among those that have been found overall? While hard to answer, bacteriophages may serve as a model: 50 years of research have identified about 30 host-virus interactions between *E. coli* and phage lambda, which encode ~4,000 and 73 proteins, respectively (4). Assuming that most host-virus interactions in this system have been identified, a large-scale analysis of *E. coli*-lambda interactions revealed 62 interactions in a high-confidence set (among a raw data set of 631 PPIs total) (5). However, of the 62 high-confidence PPIs only two were previously known to be physiological, while the role of the other 60 remains unknown. We surmise that lambda is unusual in the sense that many proteins are processed during maturation and thus interactions are more difficult to detect.

Protein processing seems to be less common among other phage, such as T7, whose 55 proteins are known to be involved in only 15 interactions with its host (4). Both T7 and lambda have about 30-40 interactions among virus proteins, which are easier to detect and possibly more frequent, given the more elaborate virus structure in these tailed phage when compared to the often simple-structured human viruses.

Unfortunately, there seems to be no comprehensive analysis or even a review of published interactions among human and virus proteins that attempted to evaluate these interactions for their plausibility or physiological relevance.

**Databases for human-virus interactions (and related data)**

During the last decade numerous protein interactions between human viruses and their host cells have been more thoroughly investigated. Mostly, such efforts focused on Hepatitis C virus (6-9), Human Immunodeficiency Virus (10, 11), Influenza A virus (12), Herpesviruses (13) and others, including Epstein-Barr (14, 15) and Dengue (16) and numerous other ones (17). As a consequence, many different databases have been designed to capture the abundance of such interactions (**Table 3**). Currently, a number of Web-based resources aim to integrate pathogen–host molecular interactions and related data available in the literature. Some of them specialize on only one specific pathogen species such as HCVpro (18) and HIV-1 Human Interaction Database at NCBI (19). The resources based on a wider range of human specific viruses are VirHostNet (20), VirusMentha (21), PHIDIAS (22), HPIDB (23), and PHISTO (24) that include interactions between human host and different viral and other pathogen proteins.

In particular, HCVPro (HCV interaction database) is dedicated to only HCV, cataloging the characterized protein interactions for intraviral and virus–human systems. Additionally, it includes information on the structure and functions of HCV proteins (18). The HIV-1 Human Protein Interaction Database HIV-1DB at the NCBI includes the interactions between HIV-1 and human proteins (19). Of the over 17,000 HIV-1 – human PPIs reported in HIV-1db as of August, 2017, fewer than 7,000 are direct physical interactions. Many interactions are indirect, e.g. genetic interactions or inferred from mutagenesis experiments. While clear physiological relevance is provided for some PPIs, for others the description is more vague. While NCBI’s HIV-1DB is an invaluable resource for HIV-1 researchers, it can be difficult to “mine” physical PPIs confidently without manual inspection or natural language processing. Therefore, HIV-1DB was omitted from some analyses in this review. In turn, databases were developed specifically for virus host protein interactions such as VirHostNet (20), VirusMentha (21) and HPIDB (23). VirHostNet (Virus–Host Network) is one of the earliest pathogen-host interaction (PHI) resources specialized in the management and analysis of integrated virus–virus, virus–human host, and human host–host protein interaction networks coupled to their functional annotations. The recently developed tool, VirusMentha is another virus-virus and virus–host protein interaction resource and the most comprehensive viral PHI data source without limitation with respect to virus species or host organisms. Apart from viruses, HPIDB (Host–Pathogen Interaction Database) captures protein interaction data between many different pathogens and hosts. Finally, web-based PHI databases comprising all pathogen types with known interactions are PHIDIAS (24) and PHISTO (24). PHIDIAS (Pathogen–Host Interaction Data Integration and Analysis System) stores data on genome sequences, conserved domains, and gene expression data related to PHIs. In addition to data storage, PHIDIAS offers the analysis of these data. PHISTO (Pathogen-Host Interaction Search Tool) is a comprehensive PHI database including data of all pathogenic microorganisms for which experimental protein interactions with human are available. Mostly, human host-virus protein interaction data in the above PHI databases are integrated mainly from other PPI databases using automatic integration tools such as PSICQUIC (25) and by manual literature curation. While the previously mentioned databases focus on host-virus interactions commonly used protein-protein databases collect interactions between human host and virus proteins as well, including databases such as BIND (26), BioGrid (27), DIP (28), HPRD (29), IntAct (30), iRefIndex (31), MINT (31) and Reactome (32).

Given the abundance of human host-viral interactions we collected such information from the databases shown in **Table 3**. Notably, we collected 5,495 interactions with human host proteins involving proteins of orthomyxoviridae. Such a set of interactions is mostly dominated by interactions that occurred between proteins of the human host and the Influenza A virus. Similarly, we found 5,423 interactions of herpesviridae, where most interactions were experimentally determined using the Herpes simplex virus. While our set provided 3,927 interactions of papillomaviridae with most interactions involving the human papilloma virus, 2,285 retroviral interactions were mostly provided by the HIV-1 virus. Pooling interactions of other virus families we obtained 1,193 interactions. In **Fig. 1**, we summarize the sets of human proteins that were targeted by different virus families and their substantial overlap.

Some studies have also focused on “second neighbors” of the viral-host infection network, or partners of viral targets of infection (REFs). As indicated above, VirHostNet was one of the first resources to facilitate such studies. High-quality databases of host-host PPIs are essential, and efforts continue to improve the coverage and quality of such databases. The HINT (High-quality INTeractomes) database is one of the largest and highest-quality database of host-host PPIs (33). In the present review, we assimilate what is known about the topology of human-virus interactions using HINT and Reactome in combination the virus-host PPIs in **Table 3**.

Additional related meta-data for characterizing viral targets include protein function exploration and pathway or signaling analysis (e.g. the Reactome database), as well as conservation (REF), essentiality (e.g. the Database of Essential Genes), disease-network or “diseasome”, and metabolomics analyses (REFs). We review relevant information from such databases in the sections below.

**The topology of human-virus interactions**

The abundance of such virus-host interaction data prompted topological analysis of networks thus obtained. Using a network of more than 50,000 interactions between more than 8,000 human proteins from the HINT database (33), we determined the enrichment of viral targets as a function of their degree. Randomly sampling targets, we found that targets of all families preferably were enriched in increasingly interacting human proteins (**Fig. 2A**). This corroborates previous generally made observations that viral targets are preferably hubs (14, 34-39). As degree is a local measure of centrality, we consider **betweenness centrality** as a more global centrality measure. Betweenness centrality measures how many connection paths go through a particular protein in a network when proteins connected by their shortest path. Even if a protein does not have many connections, it may thus be in a central location of that network. Defining the top 20% of proteins in the human protein interaction network as such bottleneck nodes we determined the number of bottlenecks that were targeted by viruses of different families. Randomly sampling sets of bottleneck proteins, we observed that the expected number of targeted bottlenecks was statistically significant (**Fig. 2B**, P < 10-4) (14, 34-39). As a corollary, we counted the number of times that a protein appears in different pathways of the Reactome database (32) which collects metabolic and signalling pathways in addition to protein-protein interaction networks. Randomly sampling such sets, proteins that occur in many different pathways are preferable targets of any viral family (**Fig. 2C**). Recently, the focus of modern network research has shifted to the determination of nodes that allow the control of a network (40, 41). Notably, such controlling genes were enriched with essential genes, disease genes as well as appeared in regulatory interactions (42, 43). Furthermore, they also played a role as targeted and required genes of viral infections (44). Determining proteins that always appeared in a control configuration (termed *critical nodes*), we observed that targets of different families were enriched in such sets, while we found the opposite when we considered redundant proteins that never appear in such configurations (**Fig. 2D**).

**What are the protein targets of human viruses?**

We expect that different types of viruses will target specific human proteins. In **Fig. 3**, we utilized COGs classes of protein functions (45, 46) to find the common denominators among targets of common human viruses. We determined the frequencies of such classes in sets of targets of different viral families and compared them to a profile of frequencies of functions of all human viral targets. The heatmap in **Fig. 3** suggests that papillomaviridae tend to strongly target various metabolic functions, while retroviridae and orthomyxoviridae show the opposite behavior. In turn, retroviridae mostly intervene in transcriptional functions, cell signaling and cell cycle control. Such differences have already been indicated previously, reminding us that each viral family uses a different strategy to invade a human host cell (47, 48).

Navratil et al. (2011) described a human infectome network (HIN) that linked 416 viral proteins to 1,148 human proteins through 2,099 manually curated virus-host PPIs (49). In fact, 32% of these cellular proteins are targeted by more than one virus protein. A similar fraction, 28% of these cellular targets interact with proteins from more than one virus.

Clearly, virus proteins attack a relatively small number of human proteins that are relevant for their replication. More specifically, these human targets appear to be highly connected: the mean degree of these targets was 38 vs. 10 in non-targeted proteins (49). Even among highly connected proteins (k>5) in the human interactome, the degree of virus targets was twice as large as those of non-targeted proteins. Note that only 50% of all human proteins were known to interact with other proteins in the 2011 human proteome, and 50% of these interacting proteins were interacting with only one other protein.

**How are protein-protein interactions related for viruses with multiple hosts?**

Some viruses are capable of infecting multiple hosts; this includes some viruses of humans. One might expect that such “generalist” viruses enjoy an evolutionary advantage due to their potential to access more hosts. However, in most cases adaptive mutations for one host bring about antagonistic pleiotropy, or a decrease in fitness for replicating within another host, with a possible exception when a host’s population tends to fluctuate widely (Elena et al., 2009). An important distinction between types of multi-host viruses is whether multiple hosts are required as part of the life cycle, or whether the virus often crosses over between different hosts but only requires one host per life cycle. For obligate multi-host viruses, a phenotypic change specific to each host is often developed, which increases the chances of transmission. The hosts themselves are often very different, in terms of pH, temperature, and cell type. Thus, it is likely that PPIs from obligate multi-host viruses vary more than do PPIs from optional multi-host viruses.

Arboviruses (arthropod-borne viruses) are among the most burdensome multi-host viruses for humans; a good example is dengue. The DenvInt database (Dey and Mukhopadhyay, 2017) catalogues PPIs between the 10 dengue proteins, of which 7 are non-structural, and both human and mosquito proteins. The dengue-human network consists of 535 interactions between 10 dengue and 335 human proteins, while the dengue-mosquito network consists of 249 interactions between 10 dengue and 140 mosquito proteins. The dengue-human and dengue-mosquito networks are similar at the higher degrees nodes, with NS5, E and NS3 the most highly-connected dengue proteins. However, the mosquito network is both smaller and more highly-clustered, with the C protein sharing a very similar set of partners with E. No meta-analysis has yet been performed with DenvInt to compared the functions of the human and mosquito targets. However, Mairang et al. (2013) suggested that NS3 and NS5 may be involved in down-regulation of innate host defenses via Toll-like receptor and unfolded protein pathways in both human and mosquito. The importance of host immune suppression may be greater for obligate multi-host viruses, because it is important for the viral titer to become sufficiently high that transmission (often via blood) can be successful (Ebel, 2017).

While not strictly the same virus, different strains of influenza A are well-known to recombine, enabling a “jump” between hosts. This often leads to unusually severe outbreaks [REF]. The host environments don’t vary as widely for viruses like influenza A as for arboviruses, therefore the PPIs are likely to be more similar [REF]. Crossover mutations occur predominantly in hemagglutinin and neuraminidase, which allow for entry and exit, respectively.

**The virus interactome-diseasome connection**

It has been long known that some viruses are involved in diseases not typically associated with infection. For instance, up to 20% of cancers may be caused by viruses such as papilloma or certain herpesviruses (50). Navratil et al used their list of virus targets and compared it to a list of 1,729 human genetic disease-related proteins (derived from OMIM). It turns out that 13% of human virus targets are also associated with at least one human disease (49). That is, a human protein interacting with a virus protein is twice as likely to be involved in a disease than a non-target. Most of the diseases found in this study were related to cancer or neurodegenerative diseases. Surprisingly, type 1 diabetes was also associated with virus infection, as were autoimmune diseases in general. The latter may not be surprising, given that many virus infections elicit a strong immune reaction.

An independent study came to a similar conclusion: Gulbahce et al. analyzed the connection between Epstein-Barr-Virus (EBV), human papilloma virus (HPV) and disease (51). However, these authors not just used PPIs but also metabolic networks and regulatory interactions (**Fig. 4**). Using U.S. Medicare patient medical history data derived from 13 million patients, Gulbahce et al. found that many diseases are often associated with viral infection, including EBV or HPV. For instance, HPV patients have 15.7 and 2.7 times increased chance of developing retina and bladder cancer but also a higher risk of Fanconi anemia (51).

**Virus interactions with the host metabolome**

There is increasing evidence that viruses not just highjack the host replication machinery, but also the host metabolic machinery. For instance, Adenovirus 5 proteins E4ORF1 and E4ORF6 co-immunoprecipitate with MYC in the nucleus, probably by directly interacting with the cancer protein MYC. While MYC has diverse effects on numerous target genes that it regulates, E4ORF1 induces MYC to activate a subset of glycolytic targets (viruses with a deletion of the E4 protein are defective for inducing glycolysis). Thai et al. (52) conclusively demonstrated that adenovirus induced glycolysis generates metabolites for increased nucleotide biosynthesis in infected cells.

It is not surprising that viruses manipulate host metabolism to generate more nucleotides and other compounds that they need for replication (53). However, in most cases it remains unclear whether interactions of virus proteins with host enzymes directly or indirectly reprogram metabolism.

**Conclusions and outlook**

Protein-protein interactions are at the core of any virus infection, hence a detailed understanding of such interactions is critical for understanding viral diseases but also critical for the development of new drugs. For a small group of viruses we have so much interaction data that it has become difficult to evaluate their physiological significance, given that most databases do not provide such a critical assessment. For many viruses only few interactions are known and many more are expected to be detected.

Viruses evolve much quicker than their hosts, especially in RNA viruses, not the least because they can produce numerous (variant) virus particles by the time the host can mount an immune response. Thus viruses can also adapt their host-virus interactions faster than a host population can react by mutating its target proteins, although an individual immune system is usually able to fight off an infection (54).

With a rapidly growing number of human viruses, especially resulting from microbiome studies, we will identify many more viruses in humans. In the course of these studies, we will also find many more commensal viruses which do interact with their human host but may actually be beneficial, and potentially even help us to fight other pathogens and parasites.

**Conflicts of interest**

None.

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**Tables**

**Table 1**. **The 20 best-studied viruses (by number of genomes sequenced)**. Sequence numbers as of July, 2016. Clustered sequenced were clustered at ≥98% sequence identity). U/C = un-/ clustered. Genome data from Genbank.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Type | Family name | Sequences (unclust.) | Disease (examples) | U/C | Total complete genomes | Complete genomes (clustered ) |
| RNA | reoviridae | 65870 | Rare diarrhea | 5.78 | 31945 | 5803 |
| RNA | flaviviridae | 225112 | Zika | 3.20 | 7837 | 2019 |
| DNA | hepadnaviridae\* | 78558 | hepatitis | 8.16 | 7248 | 1946 |
| plant | geminiviridae | 13158 | --- | 3.02 | 6421 | 2316 |
| RNA | picornaviridae | 85636 | Cold etc | 3.60 | 3447 | 1500 |
| RNA | retroviridae | 716088 | AIDS etc | 2.21 | 2890 | 2103 |
| anim | circoviridae | 7838 | --- | 6.92 | 2706 | 542 |
| RNA | phenuiviridae | 4139 | Rift Valley fever | 4.86 | 1678 | 384 |
| RNA | coronaviridae | 19164 | SARS | 5.61 | 1549 | 320 |
| RNA | potyviridae | 16115 |  | 3.63 | 1536 | 843 |
| DNA | papillomaviridae | 17847 | Warts, cancer | 8.14 | 1364 | 359 |
| DNA | polyomaviridae | 8604 | Rare cancers | 10.60 | 1277 | 164 |
| RNA | filoviridae | 2165 | Ebola | 23.53 | 1259 | 37 |
| RNA | togaviridae | 8924 | rubella | 16.25 | 1239 | 137 |
| RNA | pneumoviridae | 22578 | Cold-like | 13.08 | 1231 | 61 |
| plant | nanoviridae | 3110 | --- | 4.92 | 1183 | 282 |
| RNA | caliciviridae | 32405 | gastroenteritis | 5.30 | 1072 | 292 |
| RNA | paramyxoviridae | 29726 | measles | 10.06 | 1008 | 327 |
| RNA | bromoviridae | 4677 | (plants) | 4.08 | 764 | 384 |
| RNA | arenaviridae | 2639 | e.g. Lassa fever | 2.29 | 758 | 469 |

Statistics of viruses known to infect humans, genomes sequenced, genetic diversity?

\* Hepadnaviruses have an RNA intermediate and thus are not strict DNA viruses.

**Table 2**. **Human disease burden by viruses.** Infections include infected number of people while morbidity and mortality include those that get sick or die, respectively. Cost is the economic damage of these viral diseases from hospitalization or lost work time. Unless otherwise indicated, figures are yearly.

Need to add dengue virus, hRSV or rabies virus

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Virus (class)** | **Infections** | **Morbidity** | **Mortality** | **Cost** | **Refs** |
| HSV-1/2 | 3.7 B / ~700M | 3M/yr (US) | low | $540M (US) | (55-59) |
| HIV-1/2 | 36M (world) | 2.1M/yr ww | 25M total1 | $13.7B (US) | (60) |
| Influenza | >30M (US)3 | 100-600K (US)4 | 50M 19182 | $10-90B | (61-63) |
| Measles | >20 M (ww) | 250k ww | 140-500k5 | $3-7B (US) | (64) |
| Hepatitis C | 60-120M (ww) | 4M | 500k ww | $10B 6 | (65, 66) |
| Hepatitis B | 248 M ww/yr, ~2.5 B ww total | 350M ww total | 600k ww | $1B (US) | (67-69) |
| Zika | 740k S Amer | >2,6k 7 | low |  | (70) |
| MERS-CoV | 2067 |  | 720 total | $15-20B | (71) |
| SARS-CoV | 8098 |  | 774 total | $40B ww | (72, 73) |
| Common cold (rhinovirus) | 1B Cold/year (US) | 10-40% of common colds | low | $20B (US) | (74) |
| Norovirus (gastroenteritis) | 19-21M (US); 685M (ww) | 699M ww | 570-800 (US); 200K children ww  219K ww | $4.2B (indirect); $60.3B total ww | (75, 76) |

1 globally, since 1981. 2 Spanish flu of 1918. 3 30 million outpatient visits. 4 100-600 thousand hospitalizations. 5 The death rate is decreasing, from 535,000 deaths in 2000 to 139,300 deaths in 2010. 6 $10·7 billion in direct medical expenditures in the USA for HCV-related disease from 2010 to 2019. 7 cases of microcephaly. K,M,B = thousand, million, billion, WW = worldwide, SA = South America.

**Table 3: Overview of host-pathogen databases that provide human host-virus protein interactions.**

|  |  |  |  |
| --- | --- | --- | --- |
| **database** | **pathogens** | **webpage** | **Ref.** |
| HCVPro | only HCV | http://www.cbrc.kaust.edu.sa/hcvpro/ | (18) |
| HIV-1 @NCBI | only HIV | https://www.ncbi.nlm.nih.gov/genome/viruses/retroviruses/hiv-1/interactions/ | (19) |
| PHIDIAS |  | http://www.phidias.us | (22) |
| PHISTO |  | http://www.phisto.org | (24) |
| HPIDB |  | http://www.agbase.msstate.edu/hpi/main.html | (23) |
| VirHostNet |  | http://virhostnet.prabi.fr | (20) |
| VirusMentha |  | http://virusmentha.uniroma2.it | (21) |
| DenHunt |  | http://proline.biochem.iisc.ernet.in/DenHunt/) |  |
| DenvInt |  | https://denvint.000webhostapp.com |  |

**Table 4: Number of host-virus interactions of major human virus families. HPI = host-pathogen interaction ? Interaction numbers are from XXX**

|  |  |  |
| --- | --- | --- |
| **viral family** | **# HPIs** | **viruses** |
| orthomyxoviridae | 5,495 | influenza A (4,775) |
| herpesviridae | 5,423 | human gammaherpesvirus (2,848); epstein-barr virus (1,766); human alphaherpesvirus (655) |
| papillomaviridae | 3,927 | alphapapillomavirus (2,324); betapapillomavirus (1,132) |
| retroviridae | 2,285 | HIV-1 (1,808); primate t-lymphotropic virus 1 (186) |
| paramyxoviridae | 873 | measles virus strain schwarz (443); henipavirus (184) |
| flaviviridae | 575 | dengue virus (131); hepatitis c virus (127); west nile virus (41); kunjin virus (37) |
| poxviridae | 415 | vaccinia virus (352); vaccinia virus wr (156) |
| polyomaviridae | 322 | macaca mulatta polyomavirus 1 (186) |
| parvoviridae | 292 | adeno-associated dependoparvovirus a (285) |
| adenoviridae | 281 | human adenovirus 5 (201); human mastadenovirus c (172) |
| filoviridae | 172 | ebolavirus (239); marburgvirus (41) |
| bunyaviridae | 159 | california encephalitis orthobunyavirus (84) |
| togaviridae | 126 | sindbis virus (69); rubella virus (57) |
| hepadnaviridae | 99 | hepatitis b virus (90) |
| peribunyaviridae | 85 | california encephalitis orthobunyavirus (84) |
| phenuiviridae | 76 | sandfly fever sicilian virus (50); rift valley fever phlebovirus (26); rift valley fever virus (strain zh-548 m12 (20) |
| arteriviridae | 67 | porcine reproductive and respiratory syndrome virus (16); equine arteritis virus (11) |
| coronaviridae | 66 | sars coronavirus (66) |
| reoviridae | 63 | mammalian orthoreovirus (34); rotavirus c (19); mammalian orthoreovirus 1 lang (16) |
| other | 183 |  |