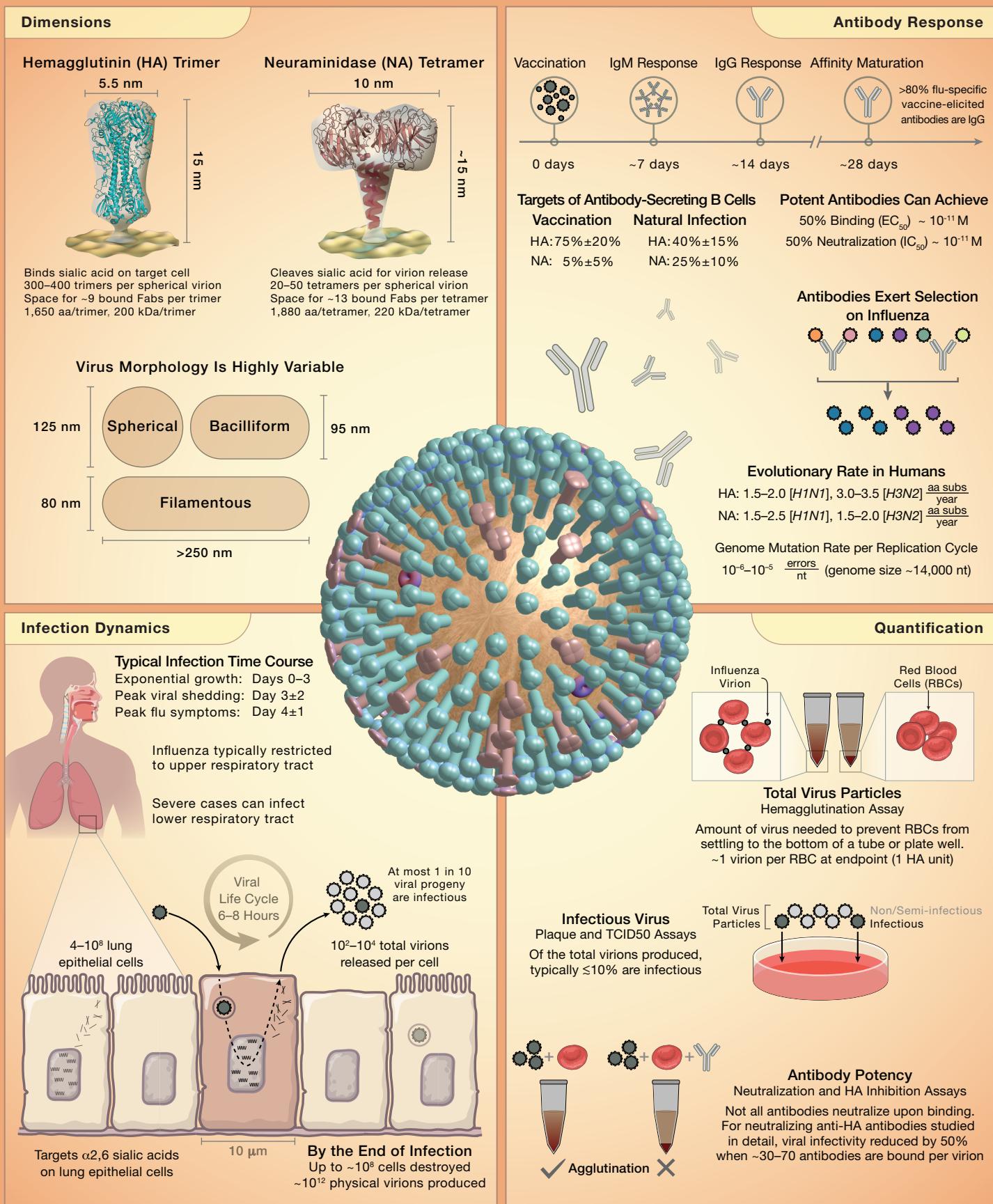


SnapShot: Influenza by the Numbers

Cell

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Cell

Influenza is one of the best-studied viruses of all time, and as such, it serves as a testbed to extend our biological knowledge to the nanoscale. Many of the key processes underlying influenza infection and our antibody response against the virus have been thoroughly investigated. This SnapShot describes these key numbers for prototypical lab-adapted strains of the human influenza A virus.

Because of its rapid mutation rate, multiple strains of influenza circulate around the world, leading to the continual generation of new clades. The following sections highlight some nuances of this viral biology. Detailed information on the scientific basis of these values, together with in-depth discussions of these key processes, is available at <https://github.com/TalEinav/InfluenzaSnapshot.git>.

Dimensions

Each influenza virion is covered in the glycoprotein spike hemagglutinin (HA, teal) that binds to sialic acids on target cells as well as neuraminidase (NA, pink), which cleaves these sialic acids to aid the egress of viral progeny. The diameter of a spherical virion is roughly 10× the length of these spikes, and the size of the cells that influenza infects are 100× larger than a virion.

Spherical versus Filamentous

Although lab-adapted influenza strains are predominantly spherical, in natural infections the virus has a mixture of spherical, bacilliform, and filamentous morphologies. The latter category has a long, cylindrical shape with a diameter of 80 nm (smaller than a spherical virion), whose length can reach many microns. These non-spherical viruses are hypothesized to be more transmissible in humans.

Antibody Response

Antibodies represent an important arm of our immune response against influenza by directly neutralizing the virus or serving as beacons for other molecular defenders. The timeline shown represents the primary immune response elicited by an influenza vaccination. Pentameric IgM antibodies generally bind with low affinity and high avidity, whereas monomeric IgG antibodies can exhibit far stronger binding, especially after affinity maturation. The influenza vaccine gives our bodies the time (~28 days) to elicit these potent antibodies that can help protect against infection later that season.

Perpetual Evolution

Influenza's error-prone RNA polymerase has no proofreading. The virus's high mutation rate helps promote antigenic drift, the accumulation of nucleotide (nt) mutations and amino acid substitutions (aa subs), particularly at sites targeted by antibodies. After several years, our antibody repertoires become less effective against the drifted strains, increasing our susceptibility to infection. Consequently, the components of the influenza vaccine are revised every few years to keep pace with viral evolution. In rarer circumstances, reassortment of gene segments from animal influenza viruses (e.g., from birds or swine) results in a novel strain of virus for which we have little to no prior immunity.

Infection Dynamics

While there is substantial person-to-person variation in the duration and severity of influenza infections, in most cases the virus is cleared within 10 days. Measurements in cell culture have shed light on the virus life cycle, burst size, and mechanisms used to hijack the cellular machinery of the host cell. In order to replicate, influenza enters a cell in an endosome where an acidic environment triggers fusion via HA, allowing the release of viral RNA, which is trafficked to the nucleus. Within the nucleus, the eight influenza gene segments replicate themselves while also creating mRNAs that code for new viral proteins. This virus material assembles into viral progeny that detach from the infected cell using NA.

Not All Virions Are Infectious

Only a small subset (typically 0.1%–10%) of viral progeny are autonomously infectious, while all other virions are referred to as either non-infectious or semi-infectious (e.g., due to large gene deletions or incomplete packaging of gene segments). We denote the combination of all three types as the "total" virions produced by an infected cell. Importantly, multiple semi-infectious virions may successfully co-infect a cell (e.g., if they collectively carry intact copies of the influenza genome), and hence, this silent majority could play a key role during viral infection.

Quantification

A range of experimental assays have been developed to quantify viral growth and antibody activity. While these assays simplify infection to its bare elements and exclude many key processes (e.g., the mucus barrier the virus must penetrate, other immune cells that can target the virus), they have substantially boosted our understanding of the immune response against influenza.

Common Experimental Assays

The hemagglutination (HA) assay measures the amount of virus needed to form a lattice of cells connected to virions, with lower amounts of virus failing to prevent red blood cells from falling to the bottom of a test tube or well plate. The plaque and tissue culture infectious dose (TCID₅₀) assays measure the number of individually infectious virions by either counting patches of dead cells or measuring the amount of virus needed to infect tissue culture cells 50% of the time. The hemagglutination inhibition (HAI) assay measures the smallest amount of (HA head-targeting) antibodies needed to prevent a fixed amount of virus from agglutinating red blood cells. The neutralization assay combines antibody, virus, and tissue culture cells to assess how well antibodies block infection of cells by virus.

Glossary

Half maximal effective/inhibitory concentration (EC_{50}/IC_{50}), the concentration of antibody needed to bind/inhibit-infection of virus by 50% of its maximum value; fragment antigen-binding (Fab), one of binding regions on an antibody; peak titer viral shedding, range of days when virus titer is $\geq 10\%$ of the maximum shedding; peak symptoms, range of days when symptom score is $\geq 90\%$ of the maximum value.

ACKNOWLEDGMENTS

We thank T. Bedford, B. Dadonaite, G. Mahmoudabadi, L. Meyers, L. Moncla, A. Perelson, R. Phillips, S. Sonal, K. Xue, J. Yewdell, and F. Zanini for their help in preparing this SnapShot.

See online version for
legends and references