FEATURE ARTICLE

An Instant Update on Viruses

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Image Source: Johns Hopkins Center for Systems Science and Engineering

Abstract

The current COVID-19 pandemic shows how little many people know about viruses. Yet apart from COVID-19, the world has observed epidemic spread of another SARS virus, of the Ebola virus, and of the Zika virus during the last two decades. The human immunodeficiency virus (HIV) is still one of the most dangerous viruses worldwide. Some types of the human papillomavirus (HPV) are the main cause of cervical cancer. Cases of measles, also caused by a virus, increase in numbers due to lack of access to or refusal of vaccination. Furthermore, there is the widespread belief that viruses are similar to bacteria and may thus be fought off with antibiotics. Yet viruses have no metabolism. Thus, antibiotics cannot work against them, but may instead cause more harm than help, given side effects such as killing beneficial bacteria (e.g., in the intestine). Second, misuse of antibiotics is one key factor in the evolution of antibiotic-resistant bacterial strains – a strong public health issue nowadays. This article informs readers what viruses are, how they are distinct from bacteria, how they may have evolved, and how diseases they cause may be prevented. Additionally, insights from studies concerning students' virus-related knowledge are summarized.

Key Words: *virus; evolution; replication; knowledge; misconceptions; school; antibiotics.*

○ Introduction

Following presidential advice may not always be healthy. Fifteen years ago, an African president claimed that taking a shower after having unprotected sexual intercourse would reduce the risk of contracting HIV (BBC, 2006). This year, several countries' leaders worldwide denied the danger or even existence of the COVID-19 virus (SARS-CoV-2) (e.g., Kramer, 2020; Lotta et al., 2020). From the public health perspective, the criticism they faced was certainly justified. However, could it be that these presidents did not only act the way they did for political reasons, but that they also mirrored misconceptions we encounter in the public to a relatively large degree?

To give an example: in a recent Europe-wide survey, 48% of the 27,474 interviewees believed that antibiotics kill viruses (European Union, 2018). Obviously, a large fraction of the population has severe gaps when it comes to virus-related knowledge. This assumption finds corroboration in a study by Simon et al. (2017) comparing such knowledge between secondary students in grades 7 and 10 and university students in their first year, studying either biology or nonscientific subjects. Biology freshmen displayed the best knowledge in terms of viruses. But even among them a high number of misconceptions were found – for example, several students classified malaria as a viral disease or drew a prokaryotic or eukaryotic cell when asked to draw a virus. Some referred to antibiotics when asked to name ways to prevent infection with a virus. Several named bacterial diseases when asked to list viral diseases. Only a few referred to vaccination as an important means to prevent contraction of certain viral diseases. Perhaps unsurprisingly, >75% of the 646 students participating in this study declared that they would want to know more about viruses, and that they had not gained sufficient virus-related knowledge at school (Simon et al., 2017). Thus, it seems necessary to raise awareness of this topic both in preservice biology teacher education and among biology teachers at school. Based on the knowledge gaps identified in Simon et al. (2017) and on topics explicitly named by several students in this study as of specific interest to them (e.g., "origin and evolution of viruses"), this Instant Update provides a summary of the most important facts related to viruses and offers implications for topics to heed while teaching virology at school.

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The American Biology Teacher, Vol. 83, No. 3, pp. 147–153, ISSN 0002-7685, electronic ISSN 1938-4211. DOI: https://doi.org/10.1525/abt.2021.83.3.147.

○ Differences between Viruses & Bacteria – & Why Antibiotics Do *Not* Work against Viruses

Several features distinguish viruses and bacteria. Yet because both are so tiny that they cannot be seen without microscopic aid, students often have trouble holding them apart. Table 1 provides a list of similarities and differences between viruses and bacteria.

○ The Structure of Viruses & Their Replication inside the Host Cell

Teaching the biological foundations of virology seems even more important, given that some opponents of vaccination claim that some (e.g., measles, SARS-CoV-2) or even all viruses are an invention of the pharmaceutical industry to generate value by selling vaccines. A very prominent case is the German "biologist" Stefan Lanka, who bet 100,000 euros for anyone able to prove the existence of the measles virus (which he declared nonexistent) and first lost a litigation with a German physician proving its existence, but then won due to the terms of the bet. This case received much attention among vaccination critics worldwide – and has also been used for refusal of vaccination against SARS-CoV-2 (e.g., https://www.covid19reader.com/german-court-no-proof-that-measles-virus-exists/).

In this respect, it is worthwhile to realize that many people extract information concerning vaccination from the internet – and apparently often trust in and, in turn, distribute fake (and consequently wrong and dangerous) information. For example, Tseng (2018) found that some of the high school students whom she had confronted with a blogger's text from the internet showed a very simplified understanding of vaccination and made use of incorrect knowledge. Her observations led Tseng to conclude that students must be equipped with profound scientific knowledge to be able to scrutinize (pseudo-)scientific claims and that they need training in scientific reasoning.

To understand what makes viruses unique and why antibiotics do not work against them, one must understand their basic organization and the way they are replicated. In this respect, wording is decisive! Students (and presumably their teachers, too) tend to speak of viruses as "microorganisms" that "reproduce." Although even university textbooks often place viruses under the heading of "microorganisms," this should be avoided by all means. Students need to understand that viruses lack some essential characters of all living organisms (Table 1). For example, viruses are particles, which can be multiplied only by using enzymes, nucleotides, and energy of (mostly) the host cell. Viruses do not possess a metabolism on their own and are not surrounded by a true cell membrane, although some viruses are covered by a membrane of host origin in which viral constituents are integrated (Figure 1). Thus, viruses cannot multiply by themselves (as cells can do). Instead, they are multiplied in the host cell. It is a passive process, not an active one, even though triggered by virus molecules. This needs to be reflected in speech, because it is a strong indication against the view that viruses are living beings.

For replication, all viruses principally undergo the same cycle, as outlined below.

(1) Adsorption

To be replicated, the virus must get into the right host cell. Therefore, it has to bind to a host- and often cell-specific receptor molecule at the outside of the cell membrane. If this molecule is not present or blocked, the virus cannot enter the cell. The receptor may be a protein, carbohydrate, or lipid.

In case of coronaviruses, the virus molecule decisive for binding to the receptor is called "spike." This protein mediates virus entry, influences the range of hosts and tissues to be infected, and is important for causing immune responses (Li, 2016). For SARS-CoV-2, the binding counterpart in the host cell membrane is the angiotensin-converting enzyme 2 (ACE2) (Letko et al., 2020).

(2) Penetration

How a virus delivers its genetic material into the host cell depends on the type of virus. Viruses with an envelope may fuse with the cell membrane (e.g., HIV), emptying the viral content directly into the host cell. Other enveloped viruses are engulfed into endosomes. The endosomes become increasingly acidic, whereby the fusion of the virus envelope and the endosome membrane is stimulated. Only then are the internal components of the virus delivered into the cytoplasm of the host cell. Viruses without an envelope may cross the cell membrane directly or experience endocytosis into an endosome, before crossing or destroying the endosome membrane.

However, these processes are not understood in every detail yet, and they may differ even within a specific group of viruses, as shown for phages: while some phages may inject their genetic material into the host cell due to the pressure present in their capsid, this would not work for others, as theoretical considerations and experiments have shown. Thus, other forces have been discussed that pull single-stranded RNA or DNA of phages into the bacterial host, among them an almost instant binding to the host's DNA-replication machinery, which then continuously pulls the DNA outside the capsid, an active protein-mediated transport across the host membrane, or a hydrodynamic drag due to the high osmotic pressure inside the host cell (Grayson & Molineux, 2007).

For successful entry of SARS-CoV-2 into the host cell, the interplay of the above-mentioned spike protein with a host protease is essential, which cleaves spike (Letko et al., 2020). Thus, at least three molecules (spike, ACE2, protease) decide upon whether or not a SARS-CoV-2 particle gets into a host cell.

(3) Uncoating

In case of the capsid entering the host cell, the DNA or RNA of the virus becomes uncoated by destruction of the capsid. Some viruses possess linear, others circular single- or double-stranded nucleic acid(s), while single-strand RNA- or DNA-viruses may be positive (sense), negative (antisense), or even both (ambisense). In the first case, the nucleotides are ordered in the 5′→3′ direction, in the second in the 3′→5′ direction, while in the third both occur on one strand.

Table 1. Comparison of bacteria and viruses.

Trait(s)	Bacteria	Viruses
Structure	• Prokaryotes • Single-cell organisms lacking a nucleus but with one chromosome with most of the genes needed for survival and reproduction • Many harbor one or several plasmids (ring-like DNA molecules); genes for antibiotic resistance are mostly found on plasmids • Contain ribosomes but no mitochondria, endoplasmatic reticulum, or dictyosomes • Often with a cell wall on top of their membrane, though of different structure than that of plants and fungi • Some additionally coated by a capsule • Many possess one or many flagella for movement • Microorganisms	• No prokaryotes • Consist of a capsid, which is a symmetrical protein shell containing in its inside the viral genome (one or several strands of RNA or DNA) and, depending on the type of virus, other organic molecules such as enzymes or regulating elements; the capsid may be surrounded by another protein layer; in case of RNA viruses, the genome is extremely unstable, which explains the high mutation rate • No organelles, no wall • Some coated by a so-called envelope (a lipid bilayer) of mostly host cell membrane components, but including viral molecules (see Figure 1) • Nonliving particles – thus, not microorganisms
Size	0.3–750 µm	About 20–650 nm
Replication	• Multiply by cell division (mitosis) • May exchange genetic material via fusion of protrusions called sex pili	• Cannot multiply on their own and do not divide; must infect a host cell, whose metabolism is altered to produce many copies of the viral genome and proteins
Metabolism	• Have functioning metabolism and can synthesize new substances (e.g., products used in biotechnology)	• No metabolism
Movement	• Most can actively move (e.g., through flagella)	• Cannot actively move; depend on passive transport for infection (e.g., in aerosols or body fluids)
Treatment	• Many killed by antibiotics and/or their multiplication in the host is prevented by vaccination	• Antibiotics useless, because viruses do not have a metabolism these substances could interfere with • Current therapies (virostatics) interfere with multiplication of some viruses (e.g., by blocking receptor molecules or certain metabolic steps in the host cell); several of the most common viral diseases (e.g., measles, rubella, mumps) are preventable by vaccination
Examples of diseases with their causal agent in parentheses (not listed when virus and disease have the same name)	Lyme disease (*Borrelia* spp.), tetanus (*Clostridium tetani*), plague (*Yersinia pestis*), scarlet fever (mainly *Streptococcus pyogenes*), leprosy (*Mycobacterium leprae*), cholera (*Vibrio cholerae*), syphilis (*Treponema pallidum*), diphtheria (*Corynebacterium diphtheriae*)	AIDS (human immunodeficiency virus, HIV – actual symptoms are brought about by secondary infections with other pathogens due to suppression of the immune system caused by HIV), cervical cancer (human papilloma viruses), measles, rubella, mumps, tick-borne encephalitis, Zika, Ebola, dengue, yellow fever, chicken pox (varicella-zoster virus)

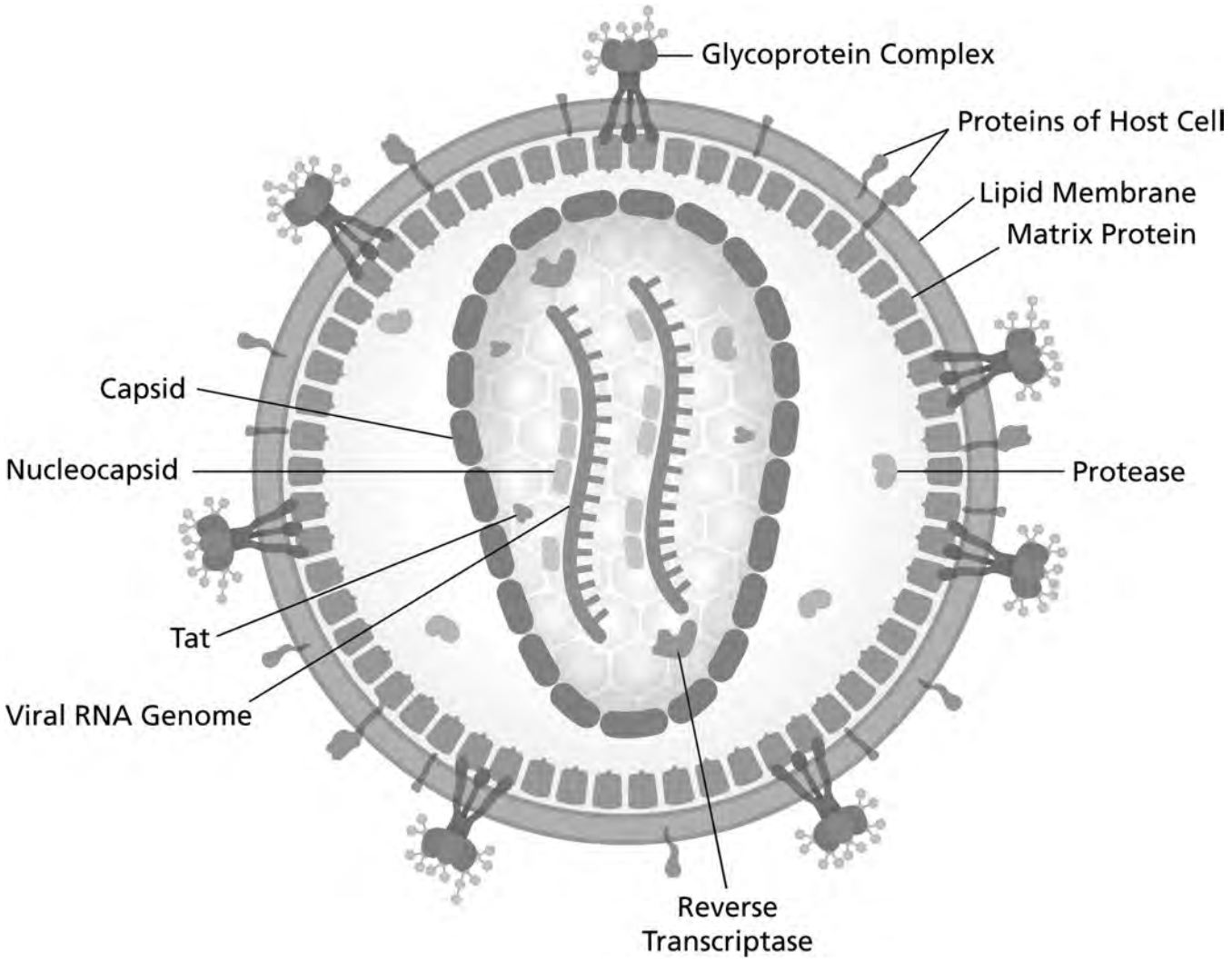

Figure 1. Structure of the human immunodeficiency virus (HIV). The capsid contains two RNA-strands closely associated with nucleocapsid proteins, which protect the viral RNA from degradation in the host cell. Further components are the integrase and the reverse transcriptase (see explanation in text) and Tat. Tat (HIV trans-activator) is a regulating element with key functions in the regulation of the reverse transcription, the synthesis of viral mRNAs, and the release of new virus particles from infected cells. The capsid is surrounded by a lipid membrane of host origin, with viral matrix proteins on the inside and a viral glycoprotein complex decisive for binding to the host cell receptor and co-receptor (see Figure 2). The function of the protease is explained in the main text. (Source: Thomas Splettstoesser/www.scistyle.com)

(4) Synthesis of New Nucleic Acids & Proteins of the Virus

Different types of viruses make use of different replication processes. The genome of DNA-viruses is usually multiplied in their host's nucleus. The genome of RNA-viruses may be replicated in the cytoplasm, in the nucleus, or, in the case of retroviruses, their RNA is first transcribed into DNA by the enzyme reverse transcriptase, before this DNA is then inserted in the host DNA (Figure 2).

Enzymes for virus multiplication are either already present in the host cell nucleus, have to be newly synthesized in the host cell, or come with the virus itself. For example, HIV has three different enzymes (Figure 1), which are delivered into the host cell together with the viral RNA and help to transcribe this RNA into DNA (reverse transcriptase), insert the new DNA into the host genome (integrase), and activate viral protein precursors for the synthesis and maturation of the new virus particles (protease).

(5) Assembly

When all constituents have been synthesized by the host cell (in some cases with the help of viral enzymes), the new particles are assembled.

(6) Release

Again, the way the virus leaves its host cell depends on the type of virus. The virus could be set free after cell lysis (meaning death of the cell), or it may leave via budding (which may or may not kill the cell). In case of influenza, this process is mediated by the viral enzyme neuraminidase (Bassetti et al., 2019).

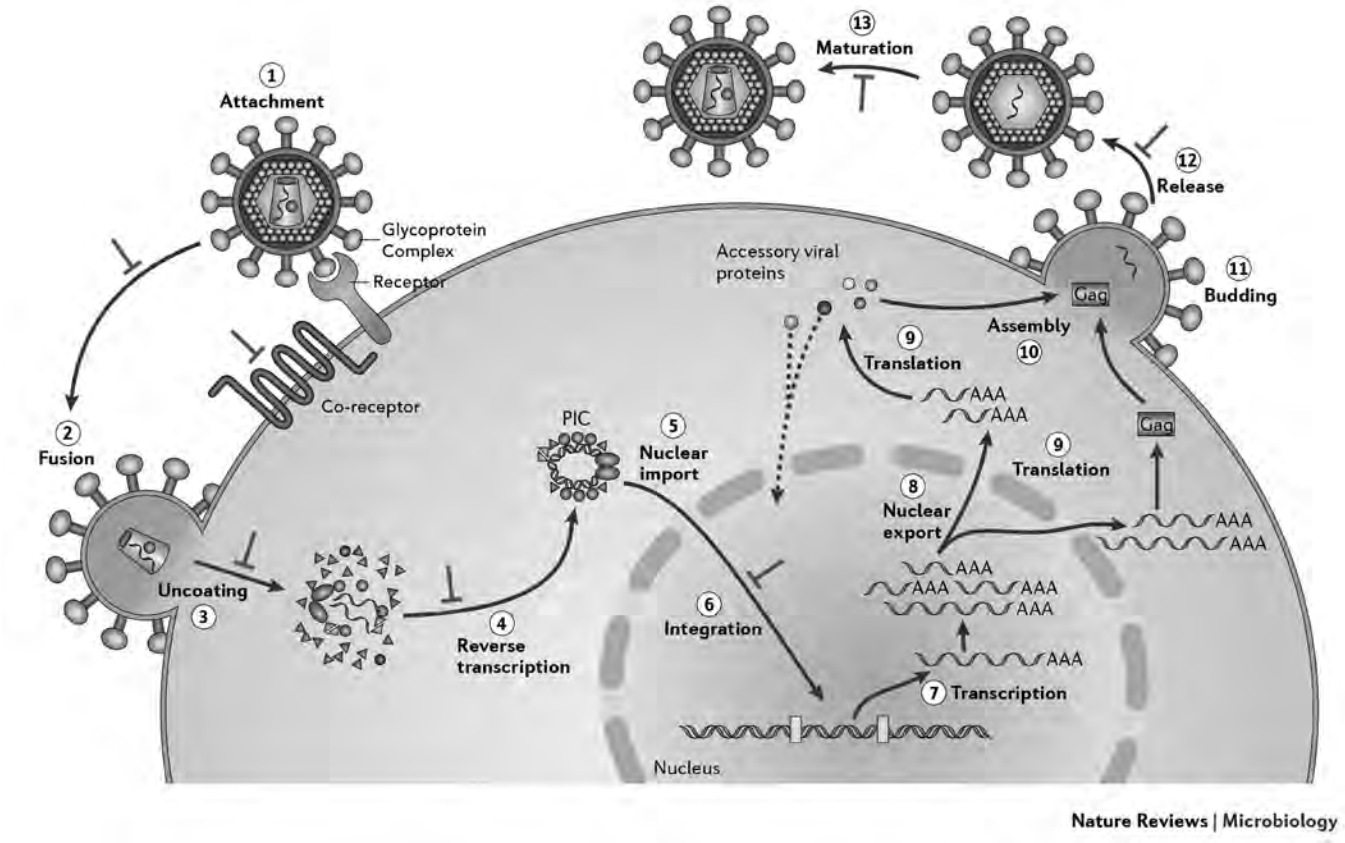

Figure 2. HIV replication cycle, which begins with binding of the virus membrane glycoprotein to the host cell receptor and co-receptor (1) and ends with maturation and release of the new virus particle (12/13). *Notes:* Maturation actually parallels budding, but it has been depicted as outside the host cell for visual reasons. T-shaped lines point to possible mechanisms for disrupting the replication cycle (medicinal targets). Gag is a polyprotein precursor for, among others, the matrix protein and the capsid protein of the virus. PIC is the pre-integration complex, comprising viral proteins, including integrase, host proteins, and the newly produced viral DNA. (Modified from Engelman & Cherepanov, 2012)

○ An Example: HIV Antiretroviral Therapy

Some readers may ask whether it is necessary to teach this complicated process in detail. Yet it is precisely such knowledge that allows the development of therapies (and students' understanding of how such therapies work). For example, in HIV antiretroviral therapy, there are presently four possibilities available:

- *Infection inhibitors* – Such molecules block either a co-receptor on the outside of the host cell membrane or a protein in the virus envelope. Thereby, binding and fusion of virus and host cell membrane are made impossible.
- *Reverse transcription inhibitors* – These are nucleoside and nucleotide analogues, which act as competitive substrate inhibitors for the reverse transcriptase of the virus. Once they are used for DNA-chain elongation in the reverse transcription from viral RNA to DNA, the elongation stops because these artificial molecules lack a 3′ OH group (similar to a process used in sequencing DNA).
- *Integrase inhibitors* – These substances block the enzyme integrase. Consequently, the newly made viral DNA cannot be inserted into the genome of the infected cell.
- *Protease inhibitors* – These inhibitors block the HIV-protease (see above).

Another widely discussed example of antiviral therapy is oseltamivir (Tamiflu), which was stocked for millions of dollars by many governments against influenza. Oseltamivir is a neuroaminidase inhibitor (see above). Yet its effectiveness was doubted strongly in a widely cited Cochrane report (Jefferson et al., 2014), and this led to an intensive discussion between the authors of that report and the World Health Organization (WHO), which can be found at https://www.bmj.com/tamiflu/who.

○ Viruses & Evolution

Some researchers believe that viruses are derived from bits of nucleic acid molecules that "escaped" from the molecule they were part of and "survived" on their own. This idea is grounded in the observation that some viruses possess bits of DNA that are identical to sequences in the hosts they infect. On the other hand, the percentage of such identical nucleotides is rather low. Other scientists think that there were viruses on Earth even before cellular life came into existence, and that it was viruses that left genetic traces in the genomes of the cells they infected once such cells were present. A third group speculates that

the genomes of the first cells were made of RNA, and that the origin of DNA-cells was due to RNA-cells being parasitized by RNA-viruses. In this view, viruses triggered the evolution from RNA- to DNA-cells, because the new DNA-cells could shut out RNA-viruses at first. The question of whether RNA-viruses preceded RNA-cells or vice versa is not answered; however, RNA-viruses would have been around longer on Earth than DNA-cells (Holmes, 2011).

Presently, all this is speculation, and it may well be that the story is different for different viruses. Since modern viruses completely depend on suitable hosts, it is not easy to conceive that viruses were first and the cells they infected came later.

○ Are Viruses All Negative?

In our study, several students asked whether there are actually any "good" viruses. Indeed, while our students usually learn only negative things about viruses at school, it seems justified to supplement their view with recent research throwing a more balanced light on these tiny particles. Viruses, surprisingly, may also have positive effects, in both the short and long terms. One example of each is discussed below.

Bacteriophages

In several biology textbooks for school, phages are used to demonstrate (a) the sometimes strange organization of viruses (bacteriophages may remind us of devices used in space) and (b) the fact that some viruses infect and kill bacteria. Phages undergo two types of cycles: the lysogenic cycle, in which the virus genome is integrated into the DNA of the host cell without many consequences, apart from being delivered to the cell's prodigy during cell division; and the lytic cycle, in which the integrated viral DNA (often stimulated by certain triggers such as specific environmental conditions) is transcribed, which in turn leads to the production of many new viruses and, finally, the host cell's death.

The observation that phages can kill bacteria stimulated research to use them for treating bacterial infections as long as 100 years ago (Abedon et al., 2011). Facing an increasing number of antibiotic-resistant bacterial strains, some researchers believe that phages may be one way to attack such strains, because they can increase in number during treatment, seem to have only little influence on normal bacterial communities in humans, work against antibiotic-sensitive and antibiotic-resistant bacteria, and may even disrupt bacterial biofilms, while the risk of harmful interactions with the host's immune system is apparently low (Loc-Carrillo & Abedon, 2011).

Presently, phage therapy is being tested in clinical trials for its efficiency and safety in treating bacterial infections (e.g., Brüssow, 2017), but additionally there are indications that phages may help the organisms treated indirectly by positively influencing the immune system, for example through anti-inflammatory effects (Górski et al., 2019).

Endogenous Retroviruses (ERVs)

ERVs are sequences that stem from retroviruses that infected mammalian hosts and were then integrated into their genomes ≥100 million years ago (Bannert & Kurth, 2006; Stoye, 2012). Primates display a rather group-specific composition of ERVs in their genome. Furthermore, ERVs contribute about 8% to the human genome – and, apparently, they play important roles as regulatory elements in brain development. Therefore, some authors deem it possible that these viral remnants were involved in the evolution of primates and humans (Brattas et al., 2017). Support for this speculation comes from the observation that different patterns of transcriptional activation of ERVs were noticed in the brains of patients suffering from neurological diseases such as amyotrophic lateral sclerosis, schizophrenia, and bipolar disorders. These diseases may be at least partly due to alterations in the development of the neuronal system (Christensen, 2016). Brattas et al. (2017) thus believe that ERVs are important regulatory elements in brain development in that they control gene networks that become dysregulated in some diseases.

Since only natural viruses are dealt with here, gene therapy will not be discussed in detail. Nevertheless, it should be mentioned that there are several trials and even some therapies already authorized for marketing based on genetically modified viruses, which are used as a carrier to replace genes responsible for severe and mostly deadly illnesses, or by silencing such genes. In the European Union, there are currently six gene-therapy medicinal products with a marketing authorization (European Medicines Agency, 2020, personal communication). Furthermore, in nanoscience therapeutic approaches, there are several attempts to create virus-like particles (VLPs), which are biological structures at nanoscale. They are made of viral proteins and mimic the original virions in appearance, but they do not possess viral genetic material. Instead, drugs could be transported within VLPs to specific target cells (Hill et al., 2018).

○ Viruses & Vaccination: Decrease in Vaccination against Measles as a Threat for the Individual & for Public Health

The attitude toward vaccination becomes an increasingly urgent public health issue. A specific case is measles, about which the media have repeatedly reported in recent years. In several countries, measles experienced a large increase; for example, 151 confirmed cases were reported in Austria for 2019 (WHO, 2020), more than twice as many as for 2018. A similar situation exists in the United States, where the Centers for Disease Control and Prevention (CDC) came up with the following headline on May 30th, 2019: "U.S. measles cases in first five months of 2019 surpass total cases per year for past 25 years" (CDC, 2019). These figures rely on actual reporting. The number of unreported cases may be much higher. Such figures should raise students' (and their parents') awareness that measles is by no means a rare disease. In fact, it is not only widespread, but can also be deadly. According to the WHO (2019):

- "Measles is a highly contagious, serious disease . . . . Before the introduction of measles vaccine in 1963 and widespread vaccination, . . . measles caused an estimated 2.6 million deaths each year."
- "Measles . . . is normally passed through direct contact and through the air. The virus infects the respiratory tract, then spreads throughout the body."
- "During 2000–2017, measles vaccination prevented an estimated 21.1 million deaths. Global measles deaths have decreased by 80% from an estimated 545 000 in 2000 to 110 000 in 2017."

In our study, only two-thirds of university students and less than half of the schoolchildren were able to name viral diseases for which vaccination exists. Furthermore, even among freshman biology

students, only 29% agreed with the statement that vaccination against some viral diseases is possible. This level dropped to 12% for non-biology students. Finally, only 21 participants named measles (Simon et al., 2017). Apparently, the awareness among students that vaccination is essential to decrease the chance of contracting and spreading viral diseases like measles is very low. Clearly, this must be addressed at school much more prominently, which is particularly important for countries without close surveillance of a child's vaccination status. Furthermore, there seems to exist a gap in understanding the role of vaccination on the personal and the societal levels (Rafolt et al., 2019). It will be interesting to see how the current COVID-19 pandemic influences the vaccination debate. In Germany and Austria, there are already people publicly demonstrating against a possibly mandatory COVID-19 vaccination, once this should be available.

Unfortunately, there is no vaccination available yet for many other viral diseases. Thus, it is even more important to discuss and playfully demonstrate at school easy and yet highly effective prevention measures such as sneezing in one's armpit or tissue, hand washing, and social distancing, including mask wearing if required.

○ Conclusion

Virology has many facets, both scientific and public health–related. However, the few studies available concerning knowledge on viruses and the many public debates (often soaked with fake news) demonstrate the need to teach our students a thorough view on viruses, their differences from bacteria, their variety, and means to prevent epidemics. The fact that students are often very interested in both virus biology and related health issues will facilitate teaching – all the more so since the current COVID-19 pandemic has created global publicity for viruses probably not encountered since the outbreak of AIDS in the 1980s. Teachers can make use of a plethora of resources, from WHO/CDC internet pages to YouTube videos (e.g., https://www.youtube.com/watch? v=fgBla7RepXU) to resources on the National Association of Biology Teachers website (nabt.org).

○ Acknowledgments

I would like to express my gratitude to S. Adams, A. Cetin, U. Khom, A. Rico, and E. Rohregger for having read and commented on earlier versions of this article and the reviewers for many helpful suggestions to improve the manuscript. I would also like to thank T. Splettstoesser, A. Engelman, and P. Cherepanov for generous permission to reuse and slightly modify their graphics; and R. Earles from ABT for diligent proofreading; and V. Haff for her wonderful help in dealing with the manuscript.

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