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OSOBINE VIRUSA
BOLEST ZBOG EBOLA VIRUSA (EBOLA HEMORAGIČNA GROZNICA) – JEDNA OD NAJSMRTONOSNIJIH BOLESTI ČOVEČANSTVA

(Opšti pregled)

Vladimir Kanjuh[1], Snežana Kanjuh[1], Marija Zdravković[2], Momir Pušac[3]

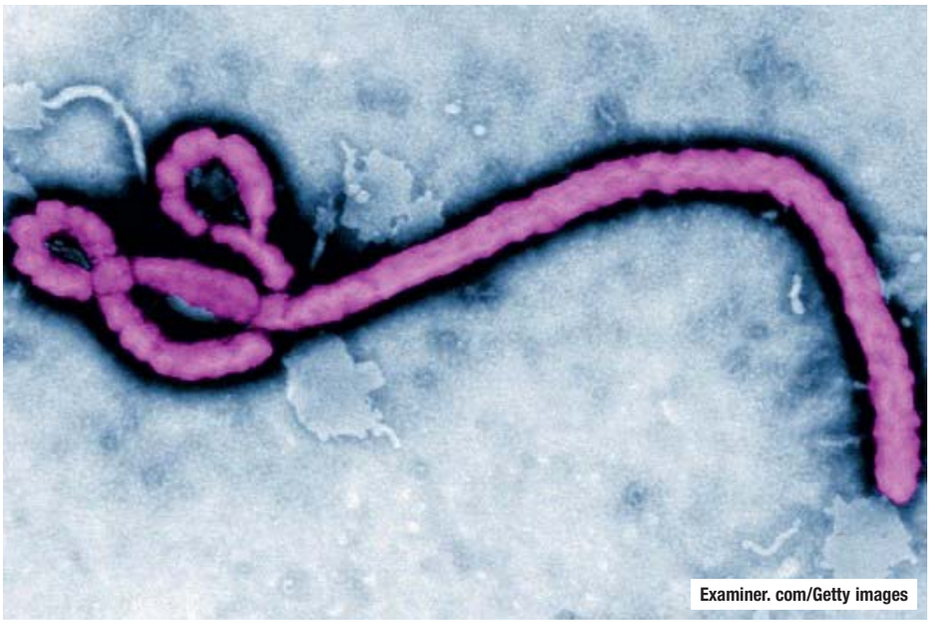
Virusi[1-4] (lat. virus = otrov, ali naziv ne odgovara suštini pojma) su najmanji (20 – 600 nm u prečniku) i najjednostavniji mikroorganizmi. Prolaze kroz bakterijske filtere i mogu se videti tek elektronskim mikroskopom. Sadrže dvostruki lanac DNK ili jedan lanac RNK (nikada oba lanca), koji su okruženi proteinskim ili proteinsko-lipidnim omotačem.

Nemaju enzime i ćelijske organele. Ne mogu da sami stvaraju energiju i sintetišu proteine. Da bi se reprodukovali moraju da uđu u ćeliju i da koriste njenu mašineriju. Njihov genom ima samo informaciju šta treba da se izgradi sredstvima i materijalima ćelije kako bi se stvorile nove virusne čestice. Virusi se, dakle, razmnožavaju od svoje nukleinske kiseline, a ne deobom kao bakterije. Oni su obligatni intracelularni paraziti.

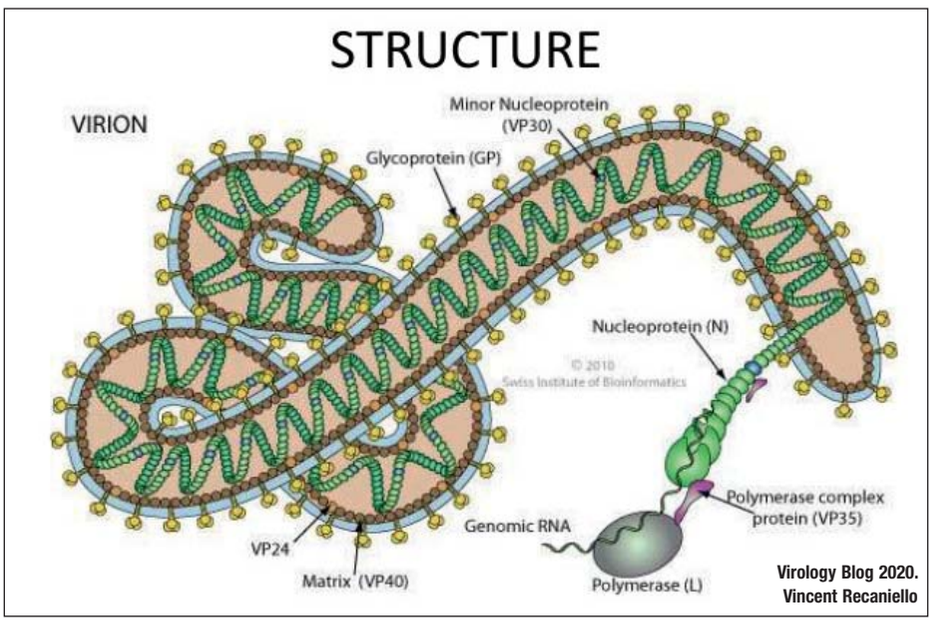
Po svojoj strukturi, virusi se razlikuju od ćelija prokariota i eukariota, tj. ćelija bez ili sa jedrom. Izvan ćelija, virusi su potpuno inertni. Genomi mnogih virusa su pročitani i obznanjeni naučnoj javnosti. Danas se mogu modifikovati genetskim inženjeringom („novi virusi iz laboratorije“) jer je čovek počeo „da se igra Boga“, ubrzava evoluciju virusa, što može biti dobro ali i jako štetno zbog mogućnosti bioterorizma.

Napadaju životinje, ljude, biljke, bakterije (bakteriofagi). Mogu da oštete i ubiju ćeliju (citocidno dejstvo) ili da žive manje - više u koegzistenciji i simbiozi sa ćelijom. Virusi mogu da doprinesu malignoj alteraciji ćelije (Rous-ov sarkom kokoši[5]); da unesu u ćeliju kancerske gene „ukradene“ prilikom ranijeg boravka u nekoj drugoj ćeliji[5]; onkogeni virusi su mnogi DNK i RNK retrovirusi[5,6].

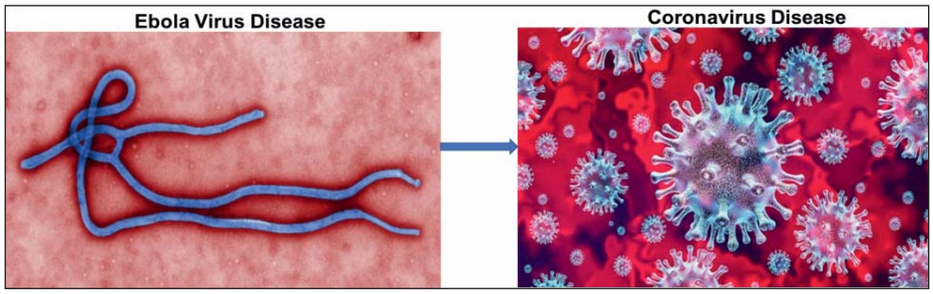
Izazivaju najsmrtonosnija oboljenja (ebola, velike boginje[7], AIDS[8-13], itd.) ili blage bolesti. Nekad postoje samo vironoše. Smrtnost od ebola virusa je bila 25 – 90%. U poslednjoj epidemiji velikih boginja u Jugoslaviji, 1972, zarazilo se 175 ljudi a



Sl./Fig. 1. Ebola virus – kao mikroskopski izvijugani filament.
Ebola virus – like microscopic coiled filament.



Sl./Fig. 2. Detalji strukture i organizacije viriona Ebola virusa (jedan lanac RNK u proteinskom omotaču) i izlaženje RNK genoma iz omotača (i ulazak u ćeliju).
Details of the structure and organization of Ebola virus virion (a single strand of RNA in the protein coat) and the release of the RNA genome from the coat (entering into the cell).



Suliver. Sustainability and Lovelihood Research Organization

Sl./Fig. 3. Poređenje: Levo: Ebola virus kao izuvijani mikroskopski filament sa granama i Desno: Sars-CoV-2 uzročnik COVID-19 kao okrugle loptice sa produžecima na površini - tako da sve liči na krunu.
Comparison: Left: Ebola virus as a twisted microscopic filament with branches and Right: Sars-CoV-2 causative agent of COVID-19 as round balls with extensions on the surface - so that everything looks like a crown.

umrlo 35, ali je 18 miliona Jugoslovena vakcinisano i epidemija je zaustavljena za dva meseca[7].

Zaraznost virusa varira. Najveća je kod morbila, ebole, gripa[14] i sadašnjeg SARS-CoV-2 izazivača COVID-19[15].

Još nisu pronađeni efikasni lekovi protiv virusa. Međutim, postoje vakcine za prevenciju izvesnih virusnih infekcija (koje, nažalost, postaju bezvredne ako se virus dovoljno promeni – mutira).Virusi, manje ili više, često mutiraju (naročito virus gripa), tj. menjaju delove svog genoma. Ova promena je najčešće beznačajna ili nekorisna za virus, ali nekada može da ga ubije ili, suprotno, da mu poveća zaraznost i/ili smrtnost.

* * *

Bolest zbog Ebola virusa (*Ebola virus disease - EVD*) ili **Ebola hemoragična groznica (*Ebola haemorrhagic fever*)**[16-20]

Jedna je od najsmrtonosnijih bolesti čovečanstva (smrtnost se u dosadašnjim epidemijama kretala od 25% do 90%!) i poredi se sa velikim boginjama i antraksom. Zbog povišene temperature i groznice, uz nekontrolisana spoljašnja i unutrašnja krvavljenja, spada u **hemoragične groznice**.

Prema Svetskoj zdravstvenoj organizaciji (SZO = WHO), pored hemoragičnih groznica zbog Ebole i Marburgvirusa (**Filoviridae**), postoje još tri familije virusa (sa oko 30 RNK virusa) koje izazivaju hemoragičnu groznicu. **Arenaviridae**: Lassa fever, Junin, Mechupo; **Bunuaviridae**: Crimean – Congo haemorrhagic fever, Rift valley fever, Haantan haemorrhagic fevers; i **Flaviviridae**: Yellow fever, Dengue, Omsk haemorrhagic fever i Kyasamur forest disease.

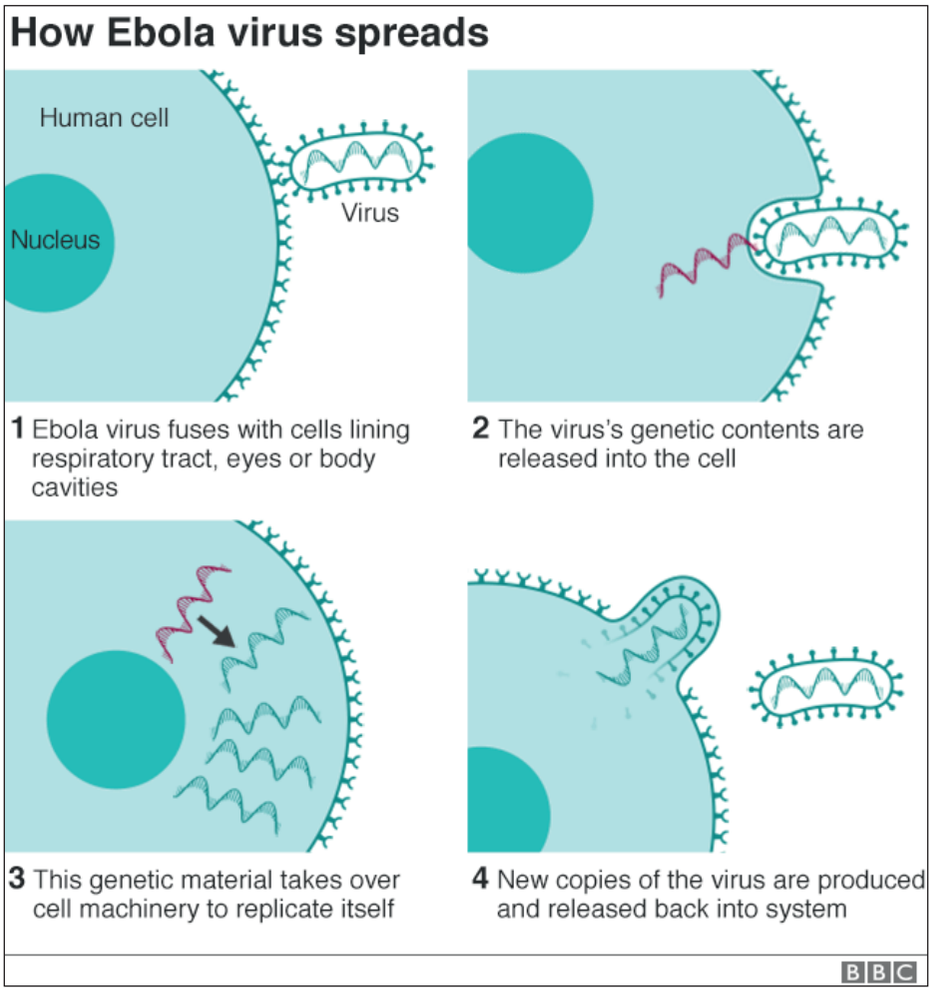
Virus Ebole je probio barijeru vrste i od raznih životinja prešao na čoveka koji je onda zaražavao druge ljude.

Bolest se prvi put pojavila 1976. na dva mesta u Africi: Južni Sudan i Demokratska Republika Kongo u selu Yambuku, uz reku Ebola (otuda ime Ebola), gde je virus prvi put izolovan. Nove epidemije su se pojavile 2014 – 2016. u zapadnoj Africi (Gvineja → Sijera Leone i Liberija) i 2018 – 2019. u istočnom delu Demokratske Republike Kongo. Energičnom i brzom reakcijom SZO sve ove epidemije su lokalizovane i zaustavljene. Pojedinačni slučajevi Ebole importovani i registrovani su i izvan Afrike u Evropi, Americi, Aziji.

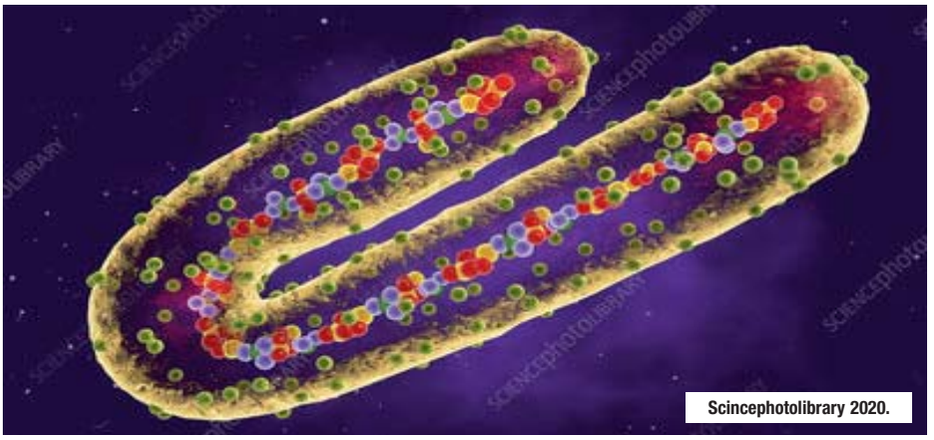
Karakteristike Ebola virusa. Spada u familiju Filoviridae (sa šest vrsta). „Filo" = mikroskopski filament jer tako izgleda (Sl. 1 – 4). Ebola virus je linearan, nesegmentiran, izgleda kao mikroskopska filamentozna partikula, izvijena i sa granama, kao „pastirski štap". Sadrži jedan lanac RNK kao genom u proteinskom omotaču.

Ebola virusu je sličan **Marburgvirus** (Sl. 5) koji je bio zarazio osoblje u nemačkom gradu Marburgu, koje se staralo oko uvezenih (ali zaraženih) majmuna.

Interesantno je da su u našem Institutu za serume i vakcine na Torlaku u Beogradu uvezeni takvi (zaraženi) majmuni, koji su bili potrebni za proizvodnju naše poliovakcine (jer se virusi uspešno odgajaju u kulturi ćelija bubrega majmuna[23]). Veterinar Instituta dr Ž.S. se zarazio Marburgviru-



Sl./Fig. 4. Ulaz i izlaz Ebola virusa iz ćelije: 1 Ljudska ćelija sa jedrom. Ebola virus se dodiruje sa pokrovnim ćelijama respiratornog trakta, očima ili telesnim šupljinama; 2 Virusni genetski sadržaj se oslobađa i ulazi u ćeliju; 3 Genetski materijal preuzima ćelijsku mašineriju da bi se replikovao; 4 Stvorene su nove kopije virusa i vraćene natrag izvan ćelije u sistem.



Sl./Fig. 5. Marburgvirus uzročnik Marburgove hemoragične groznice. Štapići u obliku slova U ili broja 6. Jedan lanac RNK (genom virusa) je u proteinskom omotaču.
Marburgvirus causes Marburg hemorrhagic fever. Sticks in the shape of the letter U or number 6. One strand of RNA (virus genome) is in the protein coat.

som. Bio je hospitalizovan na našoj Infektivnoj klinici u Beogradu i, srećom, ličnim zalaganjem akademika Koste Todorovića, ipak, ostao živ.

Izvor i način zaražavanja virusom Ebole. Prirodni rezervoar Ebola virusa je slepi miš koji se hrani voćem – Fruit-eating Bat (Sl. 6). On zaražava šimpanze, gorile, druge majmune, šumske antilope i bodljikavo prase (Sl. 7). Čovek se zaražava od ovih životinja ili direktno od pomenutog slepog miša kontaktom sa njima (živim ili mrtvim), sa njihovom krvlju, sekretima i telesnim tečnostima i ako jede njihovo sveže meso, odn. nedovoljno kuvano (Sl. 8). Zaraza se sa čoveka na čoveka prenosi direktnim kontaktom preko povređene kože, sluzokoža, krvi ili telesnih tečnosti obolelog, fecesom, povraćenim sadržajem, pljuvačkom, urinom, znojem. Zaraza se prenosi i preko umrlog bolesnika i tokom njegove sahrane ako se leš dodiruje ili kupa. Virus može postojati i u mleku dojilja kao i u spermi, tj. može se dobiti seksualnim odnosom. Mleko i spermu treba testirati. Seksualni odnosi se dozvoljavaju tek posle dva negativna nalaza na virus Ebole. Takođe, zaražavanje je i preko predmeta obolele osobe i kontaminiranog okruženja. Naročito je često kod lečenja bolesnika (zdravstveni radnici) i brige o njemu i oko njegove sahrane u smrtnom slučaju. Dok ima virusa u krvi bolesnik je zarazan. Virus se, dakle, ne nalazi u vodi i vazduhu. Deca i mladi su relativno pošteđeni od Ebole, ali je to možda zbog toga što ređe dolaze u kontakt sa zaraženim materijalom.

Sl./Fig. 6. U ruci istraživača: slepi miš koji se hrani voćem (lubenica) je prirodni rezervoar Ebola virusa.
In the researcher's hand: a fruit-eating bat (watermelon) is a natural reservoir of the Ebola virus.

Inkubacija traje 2 – 21 a najčešće 8 – 10 dana.

Virus Ebole se dokazuje iz oralne tečnosti ili krvi putem nalaza: Odgovarajućih antitela ili antigena, RT–PCR reakcijom (Reverse transcriptase polymerase chain rection), elektronskom mikroskopijom i nalazom virusa u kulturi ćelija.

Etio-patogeneza Ebole. Virus dospeva u ljudski organizam kroz povređenu kožu i sluzokože (oči, nos, usta), preko zaražene hrane, majčinim mlekom, seksualnim odnosom preko sperme. Prodire u krv dovodeći do viremije. **Virus napada: imunski sistem** („imunska paraliza"), tj. makrofage i dendritične ćelije. Zatim, **endotelne ćelije**, **parenhimne ćelije, naročito jetre i bubrega,** dovodeći do likvefakcije ovih organa. Nekad je i **multiorgansko oboljenje sa šokom**. Dolazi do **ekstremnog gubitka tečnosti sa dehidratacijom i sniženjem krvnog pritiska.** Zbog poremećaja u zgrušavanju krvi dolazi do nekontrolisanog **spoljašnjeg i unutrašnjeg krvavljenja**.

Simptomatologija bolesti zbog Ebola virusa je prikazana na Sl. 9-11.

Lečenje. Ne postoji lek protiv Ebola i Marburgvirusa. Primenjuju se eksperimentalni lekovi. Terapija je simptomatska. Najvažnija je hidratacija bolesnika i borba protiv niskog krvnog pritiska i sekundarne infekcije.

Srećom, napravljene su **efikasne vakcine** (ruska i američka) koje su primenjene u Gvineji i Demokratskoj Republici Kongo.

Posledice preležane Ebole. Virus može da perzistira u spermi, tečnostima u vezi sa trudnoćom i drugim telesnim tečnostima, majčinom mleku i u imuno-privilegovanim mestima: testisi, unutrašnjost oka, centralni nervni sistem, placenta, amnionska tečnost i fetus.

Takođe, perzistiraju umor, mišićni bolovi, problemi vida, bol u želucu.

Pitanje obdukcija umrlih od Ebole.[21,22] SZO je zabranila obdukcije kako bi se smanjio stepen zaražavanja!? Isto je to učinila (uslovno, ako ne postoje uslovi za bezbedan rad) i u slučaju SARS-CoV-2 koji izaziva COVID-19. Srećom, u ovom drugom slučaju, nisu je poslušali patolozi Italije, Nemačke, SAD i drugi. Smatramo da je to **nenaučni korak SZO i velika greška** jer se samo obdukcijom uz sledujuću histopatologiju može precizno i najtačnije odrediti osnovno oboljenje („**zbog** ili **sa** COVID-19") kao i suštinske i manje važne morfološke lezije u svim organima, uzrok smrti i direktna dijagnostika virusnih čestica elektronskom mikroskopijom.

Board on Cardiovascular Pathology of Serbian Academy of Sciences and Arts[1]
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THE CHARACTERISTICS OF VIRUSES. DISEASE DUE TO EBOLA VIRUS (EBOLA HEMORRHAGIC FEVER) - ONE OF THE MOST DEADLY DISEASES OF HUMANITY

(General review)

Vladimir Kanjuh[1], Snežana Kanjuh[1], Marija Zdravković[2], Momir Pušac[3]

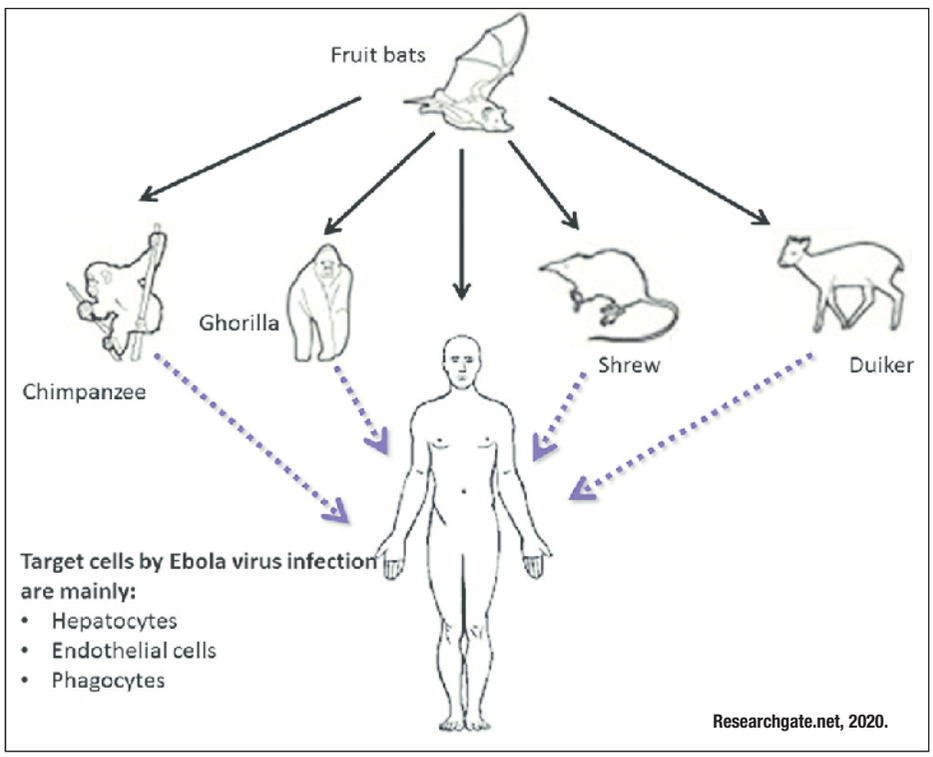
Viruses [1-4] (lat. Virus = poison, but the name does not correspond to the essence of the term) are the smallest (20 - 600 nm in diameter) and the simplest microorganisms. They pass through bacterial filters and can only be seen with an electron microscope. They contain a double strand of DNA or a single strand of RNA (never both strands), which are surrounded by a protein or protein - lipid envelope.

They do not have enzymes and cellular organelles. They cannot create energy and synthesize proteins on their own. In order to reproduce, they must enter the cell and use its machinery. Their genome only has information about what needs to be built with the means and materials of the cell in order to create new viral particles. Viruses, therefore, multiply from their nucleic acid and not by division like bacteria. They are obligate intracellular parasites.

According to their structure, viruses differ from prokaryotic and eukaryotic cells, ie. cell without or with nucleus. Outside the cells, the viruses are completely inert. The genomes of many viruses have been read and disclosed to the scientific public. Today, they can be modified by genetic engineering ("new viruses from the laboratory") because man began to "play as a God", accelerating the evolution of the virus, which can be good but also very harmful due to the possibility of bioterrorism.

They attack animals, humans, plants, bacteria (bacteriophages). They can damage and kill the cell (cytocidal action) or live less - more in coexistence and symbiosis with the cell. Viruses can contribute to malignant cell alteration (Rous's chicken sarcoma[5]); to introduce into the cell the cancer genes "stolen" during an earlier stay in another cell[5]; oncogenic viruses are many DNA and RNA retroviruses.[5,6]

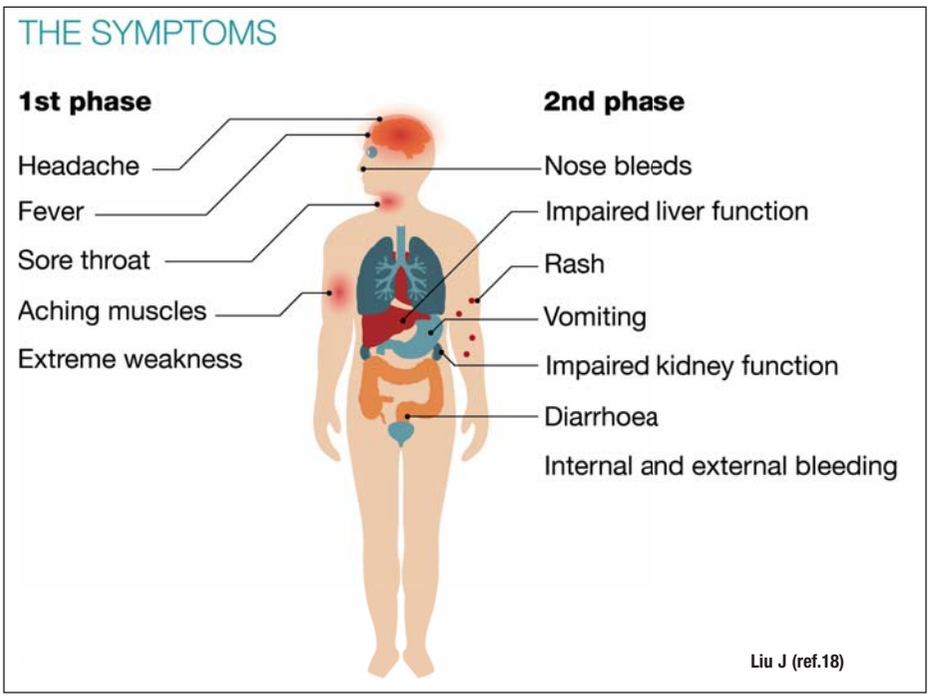
They cause the most deadly diseases (Ebola, smallpox[7], AIDS[8-13], etc.) or mild diseases. Sometimes, people carry the viruses without illness. Ebola virus mortality was 25-90%. In the last smallpox epidemic in Yugoslavia in 1972, 175 people became infected and 35 died, but 18 million Yugoslavs were vaccinated and the epidemic was stopped in two months[7].



Sl./Fig. 7. Prenošenje Ebola virusa od prirodnog rezervoara – slepog miša koji se hrani voćem, preko šimpanza, gorile, rovčice i odrasle duiker antilope (i direktno) na čoveka. Zatim, sa čoveka na druge ljude. Target ćelije kod infekcije Ebola virusom su najviše: hepatociti, endotelne ćelije, fagociti.

Sl./Fig. 8. Upozorenje na francuskom jeziku u bivšim francuskim afričkim kolonijama: Pažnja Ebola. Nikada ne dodirujte i ne manipulišite sa mrtvim životinjama nađenim u šumi.
A warning in French in the former French African colonies: Attention to Ebola. Never touch or manipulate dead animals found in the forest.

The infectivity of the virus varies. It is greatest in measles, Ebola, influenza[14] and the current SARS-CoV-2 cause of COVID-19[15].



Sl./Fig. 9. Simptomi Bolesti zbog Ebola virusa. **Prva faza:** glavobolja, groznica, bolno grlo, bolni mišići, ekstremna slabost. **Druga faza:** krvavljenje iz nosa, oštećena funkcija jetre, ospa, povraćanje, oštećena funkcija bubrega, dijareja, unutrašnje i spoljašnje krvavljenje.

Effective anti-virus drugs have yet to be found. However, there are vaccines for the prevention of certain viral infections (which, unfortunately, become worthless if the virus changes enough - mutate). Viruses less or more often mutate (especially the flu virus), ie. they change parts of their genome. This change is usually insignificant or useless for the virus, but sometimes it can kill it or, conversely, increase its infectivity and / or mortality.

* * *

Ebola virus disease (EVD) or Ebola hemorrhagic fever[16-20]

It is one of the most deadly diseases of mankind (mortality in epidemics so far has ranged from 25% to 90%!). It is compared to smallpox and anthrax. Due to elevated temperature and fever, with uncontrolled external and internal bleeding, it belongs to **hemorrhagic fevers**.

Sl./Fig. 10. U kvadratu: Ebola virus i teritorije Afrike gde se Ebola bolest pojavila (ali je suzbijena). Hemoragična ospa po celom telu (primer ruke).
In the square: Ebola virus and territories of Africa where Ebola disease appeared (but was suppressed). Hemorrhagic rash all over the body (arm example).

According to the World Health Organization (WHO), in addition to hemorrhagic fevers due to Ebola and Marburgvirus (**Filoviridae**), there are three other families of viruses (with about 30 RNA viruses) that cause hemorrhagic fever. **Arenaviridae**: Lassa fever, Junin, Mechupo; **Bunuaviridae**: Crimean - Congo haemorrhagic fever, Rift valley fever, Haantan haemorrhagic fevers; and **Flaviviridae**: Yellow fever, Dengue, Omsk haemorrhagic fever and Kyasamur forest disease.

The Ebola virus broke through the species barrier and passed from various animals to humans, which then infected other people.

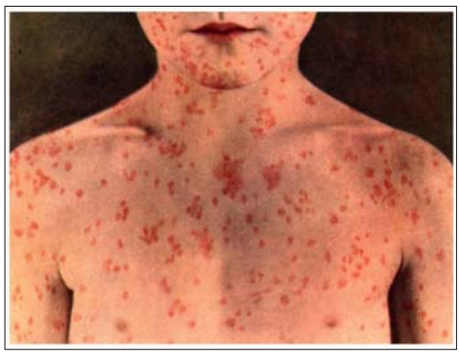
The disease first appeared in 1976 in two places in Africa: South Sudan and Democratic Republic of the Congo in the village Yambuku along the Ebola River (hence the name Ebola) where the virus was first isolated. New epidemics appeared in 2014-2016 in West Africa (Guinea → Sierra Leone and Liberia) and 2018-2019 in the eastern part of the Democratic Republic of Congo. With an energetic and quick reaction of the WHO, all these epidemics were localized and stopped. Individual cases of Ebola virus disease have been imported and registered outside Africa in Europe, America and Asia.

Characteristics of the Ebola virus. It belongs to the family Filoviridae (with 6 species). "Philo" = microscopic filament, because it looks like this (Figs. 1 - 4). The Ebola virus is linear, unsegmented, and looks like a microscopic filamentous particle with curved and branches. It contains a single strand of RNA as a genome in a protein coat.

The Ebola virus is similar to the **Marburgvirus** (Fig. 5), which had infected staff in the German city of Marburg, who cared for imported (but infected) monkeys.

It is interesting that in our Institute for Serums and Vaccines on Torlak in Belgrade, such (infected) monkeys were also imported, which were necessary for the production of our polio vaccine (because viruses are successfully grown in the culture of monkey kidney cells[23]). Veterinarian of the Institute Dr. Ž.S. contracted Marburgvirus. He was hospitalized at our Infectious Diseases Clinic in Belgrade and, fortunately, with the personal efforts of academician Kosta Todorović, he still survived.

Source and method of Ebola infection. The natural reservoir of the Ebola virus is a fruit-eating bat (Fig.6). It infects chimpanzees, gorillas, other monkeys, forest antelopes and prickly pigs (Fig. 7). Man becomes infected from these animals or directly from the mentioned bat by contact with them (living or dead), with their blood, secretions and body fluids, and if he eats their fresh meat, ie. undercooked (Fig.8).



Sl./Fig. 11. Difuzna hemoragična ospa po koži bolesnika obolelog od Ebola virusa.
Diffuse hemorrhagic rash on the skin of a patient with Ebola virus.

The infection is transmitted from person to person by direct contact through injured skin, mucous membranes, blood or body fluids of the patient, feces, vomit, saliva, urine, sweat. Also from the deceased patient and during his burial if the corpse is touched or bathed. The virus can exist in breast milk as well as in semen, ie. it can be obtained through sexual intercourse. Milk and semen should be tested. Sexual intercourse is allowed only after two negative findings of semen on the Ebola virus. Also, the infection is through the objects of the infected person and the contaminated environment. It is especially common during the treatment of the patient by health workers and the care of him by its relatives, and during its funeral in the event of death. While there is a virus in the blood, the patient is contagious. The virus is not found in water or air. Children and young people are relatively spared from Ebola, but this may be because they are less likely to come into contact with infected material.

Incubation lasts 2 - 21 days and usually 8 - 10 days.

The Ebola virus is detected from oral fluid or blood by the findings of: Appropriate antibodies or antigens; RT-PCR (Reverse transcriptase polymerase chain reaction); electron microscopy; and virus detection in cell culture.

Etio-pathogenesis of Ebola. The virus enters the human body through injured skin and mucous membranes (eyes, nose, mouth), through infected food, breast milk, sexual intercourse through sperm. It penetrates the blood leading to viremia. **Virus attack: immune system** ("immune paralysis"), ie. **macrophages** and **dendritic cells**. Then, **endothelial cells**, **parenchymal cells especially of the liver and kidneys**, leading to the liquefaction of these organs. Sometimes it is a **multi-organ disease with shock**. There is **extreme fluid loss with dehydration and lowering of blood pressure**. Uncontrolled external and internal **bleeding** occurs due to blood clotting disorders.

The symptomatology of the Ebola disease is shown in Fig.9-11.

Treatment. There is no drug for Ebola and Marburgvirus. Experimental drugs are used. Therapy is symptomatic. The most important is the hydration of the patient and the fight against low blood pressure and secondary infection.

Fortunately, effective vaccines (Russian and American) have been made and used in Guinea and Democratic Republic of Congo.

Consequences of Ebola. The virus can persist in semen, pregnancy-related fluids and other body fluids, breast milk, and in immune-privileged sites: the testes, the inside of the eye, the central nervous system, the placenta, amniotic fluid, and the fetus.

Also, there is persistent fatigue, muscle aches, vision problems, stomach pain of the patients.

The issue of autopsies of Ebola deaths [21,22]. WHO has banned autopsies in order to reduce the level of infection!? It did the same (conditionally, if there are no conditions for safe work) in the case of SARS-CoV-2 causing COVID-19. Fortunately, in this second case, pathologists from Italy, Germany, USA and others did not listen to her. We believe that this is **an unscientific step of the WHO and a big mistake** because only an autopsy can accurately determine the underlying main disease (''**due to** or **with** COVID-19'') as well as the cause of death and essential and less important morphological lesions in all organs, and direct diagnostics of virus particles by electron microscopy.

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