Global Scientific JOURNALS

GSJ: Volume 9, Issue 11, November 2021, Online: ISSN 2320-9186
www.globalscientificjournal.com

Title: **Three puzzling Questions on COVID-19: are recent vaccines feasible to stop the pandemic; what measures can boost a vaccination; and is corona affects Intimacy?**

Dessalegn Temesgen Leye (PhD)
Addis Ababa Science and Technology University

1. Introduction

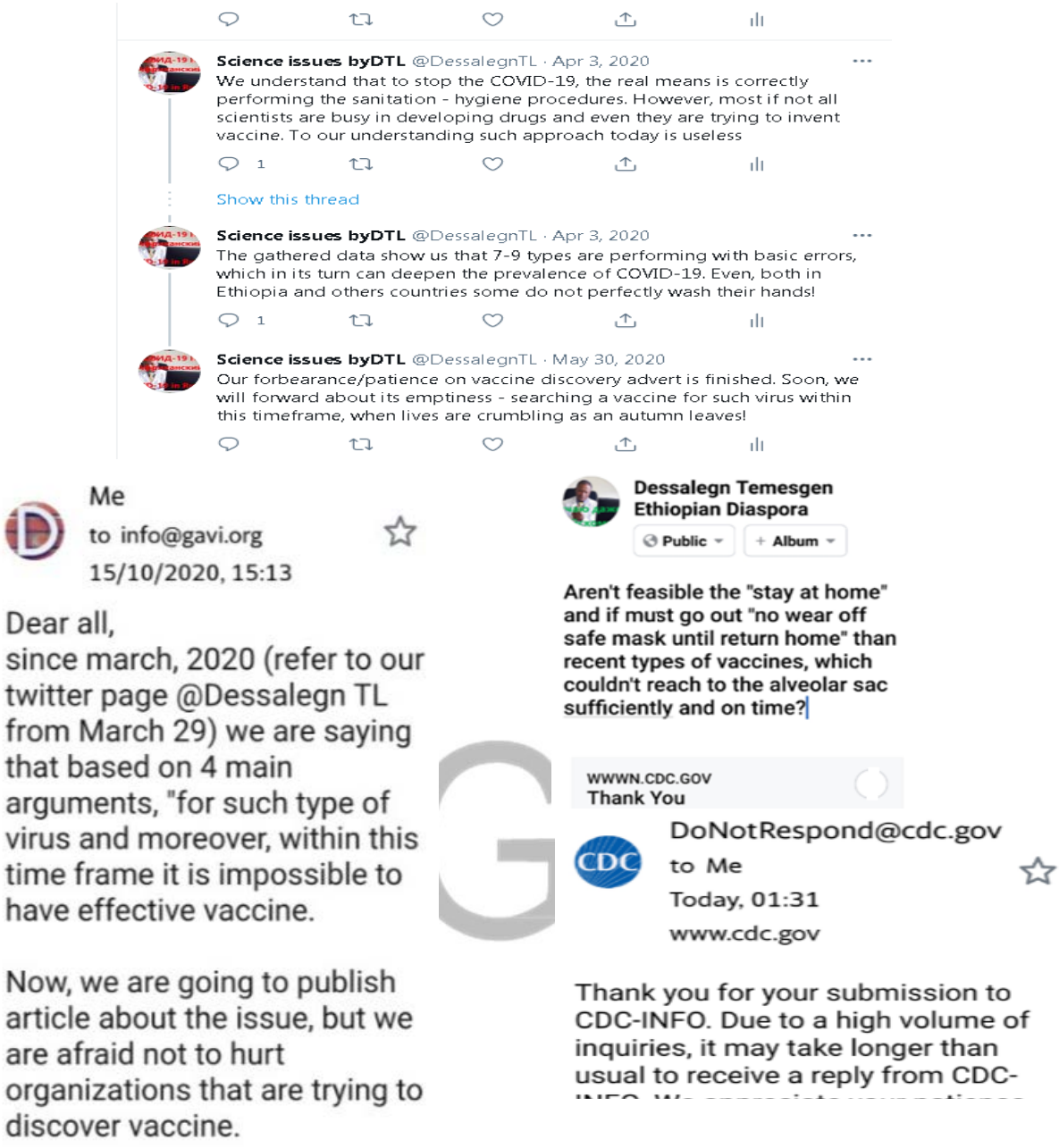
Viruses are the most common biological entities on the Earth [1,2}. Authors of [3} estimate that there are around 10,000,000,000,000,000,000,000,000,000,000 viruses. Some of them that are pathogenic like small pox, HIV, Hepatitis C, Influenza, herpes, etc. habituate in different parts of human body. Mostly, they affect the blood system, peripheral tissues, and human respiratory tracts' tissues (HRTT) [4,5,6,7}. For those that invade the HRTT, comparatively yet no known feasible treatment. In particular, vaccination based prophylactic measures are not fully acknowledged for respiratory based viral infections [8,8a,8b,9,10}. For instance, in this 21st century - world is yet not capable to control such infection.

1.2 statement of the problem:

Sixteen months have passed since the COVID-19 pandemic broke out, caused by a novel coronavirus named SARS-CoV-2 striking the whole globe. The virus with its new emerged variants invade the upper (mainly the nostril-oral cavities up to trachea) and lower (bronchioles and alveolar sacs) parts of the HRTT [11,12,13,14,15}.

To contain the pandemic, world at the beginning raise tablet based medication is trying the control-preventive measures: at the start - through non-proper hygiene-sanitation and recently using experimental vaccine based prophylaxis. Since, March 2020 (refer below in picture 1 our posts in social media and corresponding with CDC) and in our studies [9,16}, we tried to inform that if we are accurate on the usage of the sanitation-hygiene based prophylaxis measures they are more feasible. However, today's prophylaxis measures, not only are less practicable, but also even some people do not properly apply them [9}. Despite such problems, the vaccinating option is at the high pick. In particular, although we tried to suggest others directions of vaccine development [16}, today the Moderna; Astrazeka, Johnson & Johnson, sputnik V, etc that are administering through injection [17,18,19}, become popular and are the only types of vaccinating. We suggest that conclusion. Against such vaccination, together with others issues like analyzing the origin of SARS-CoV-2, in our last (5th) work [9}, we have had forwarded the 5+1 groups of scientific justifications (in question forms). One of them was a questions based hypothesis – whether the recent types of vaccines can be feasible to contain the pandemic? In particular "Is adopted antibody can get in touch with SARS-CoV-2 antigen effectively and on time within the alveolar sac (before the sac being destroyed by the virus)?" However, neither vaccine developers nor any other responsible body replied (refer to scan 1).

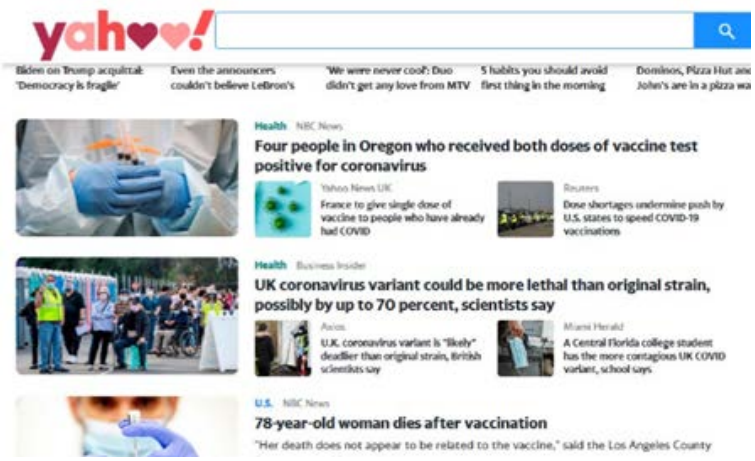
Scan 1: samples from our twitter- facebook pages and of a CDC's replies to our email on 2020




Adopted from our Facebook, twitter and email conversation with responsible stakeholders

This may be, because of the journals' non popularity of the journals in which we are publishing, the business oriented vaccine developers are blocking the articles (may be not for their business achievement, rather as one of developers stated in one of his speech: "Today is a great day for science and humanity. The first set of results from our Phase 3 COVID-19 vaccine trial provides the initial evidence of our vaccine's ability to prevent COVID-19,", they really sure that they developed a feasible vaccine); or ways of our expression for instance language barrier. Recently, within these 4 months of the vaccination's official start, there are several types of reports against it: boom of new mutant-strains (as we predict in the study [16} like, B.1.1.7 (UK), South Africa, and India, etc (of course theoretically it will continue) blood clotting, death, reinfection (vaccinated can be infected and infect others until his antibody (if any at all) able to stop the pathogen, resistances, etc. and although, we are not epidemiologist, the infection's prevalence seems to be rising. In particular, neglecting the social, economical, and political destabilization, lives continue crumpling as an autumn leaf.

Scan 2: news that triggers us to finalize this work (www.yahoo.com on April 14, 2021)




Despite these our pessimism, everyone is intensively adverting vaccination. Ironically, one of the recent vaccines promoters is WHO. However, for mass usage, either their safety or efficacy still could not approve by the relevant organization like FDA, CDC and by the WHO itself too. On the other side, although, we didn't get science based arguments, there are not few anti vaccination suggestions as well as a unscientific "anti vaxxers" social campaign. Even, starting from February 2021 we noticed hitches on vaccinations at all.
refer to the screen shot of yahoo page in scan 2

Hence,

1.3 Hypotheses

Within such conditions, at least for a certain period of time, the feasibility of vaccination to eliminate the pandemic will be vague. Such failures increase, because, vaccine developers are trying to boost the efficacy of vaccines through additional shot. Yet, they do not know or deliberately pretended as if do not understand! - there is nothing supplementary prescribing-adjuventing practices (before, together with or after the vaccine); what amazes us is that world has started relaxing (what we have had warned in our [9,16,20} works) almost a year ago, even trying to lift restrictions: indoor mass entertainments, travel and the "stay at home" options, in short - this vaccination issue is baffling us. Moreover, except for the fever, headache, organ failure, etc., the post infection problems are not rising. For instance, there are no research articles or public-Media opinion-concern about whether the recovered patients encounter sexual based potency problem or not! Therefore,



1.3 Aim of the study: We launched this study to prove our earlier published [9} questions-based hypothesis "Are recent types of vaccines feasible to contain the pandemic?" by launching epidemiology-clinical trial and using the perception of anatomy-physiology-biochemistry, we are going to answer for the above mentioned hypothesis (we have had addressed it to vaccine developers and others relevant bodies) through elaborating it into 3 key points: clinical based experiment on whether vaccinated developed adopted antibody within the mucosal and surfactant surfaces of human respiratory tract tissue (HRTT). Nature of SARS-CoV-2 Vs anatomy-physiology-biochemistry correlation of the HRTT; and literature data on immune of HRTT; and vaccines (if any feasible). Moreover, we included others two extra puzzling questions:- what is effective to boost vaccination? - supplementary diet or extra shot?; moreover, we are going to speculate on the probability of sexual based intimacy problem after recovering from COVID-19.

2. Objectives

2.1 Comparing the antibody count of vaccinated vs. non vaccinated
2.2 Analyzing literature vs anatomy-physiology-biochemistry perception of SARS-CoV-2 nature and its target
2.2.1 Identifying what part of the body and how it is affecting by the SARS-CoV-2
2.2.2 Elaborating the anatomy-physiology exceptionality of HRTT's epithelial cells
2.2.3 Characterizing; the immunity within the HRTT;
2.2.4 Analyzing whether recent vaccines are effective (if any) on HRTT
2.3 Offering measures for boosting the efficacy of a vaccination
2.4 Hypothesizing, whether the COVID-19 infection influences on the sexual potency

3. Methodology

This work is intending to address our concerns on vaccination issue to the vaccine developers and the public.

Therefore, we will show: statistically whether those vaccinated have more antibodies within their HRTT or not and give literature based justification (on SARS-CoV-2 Vs anatomy-physiology of HRTT; our biochemistry based philosophy on adopted antibody; what must be to boost an adopted antibody); and impact of infection on intimacy.

3.1 Design.

3.1.1 Targets: Clinical-epidemiological based experiment: comparing the amount of any type of antibodies in the mucosal (upper HRTT) and if possible the surfactant's surface of the alveolar sac content of control; infected; and vaccinated samples.

Since, this work is set to approve our question based hypothesis that was enclosed in our earlier work [9}, we are going to implement experimental survey and literature review. Therefore, the design named "THREE", is an epidemiology-clinical based survey(antibody count): 3 variables:- control (neither infected nor vaccinated); infected (but not vaccinated) and vaccinated (but not infected). With 3 types of variables by ages: 7-12; 35-40; and 65-70 years. If possible 3 different locations (in cooperation with other countries, three regions: Asia; Africa; and Europe). Samples must be taken (as indicated in [14} at least from nasopharyngeal swap) three times within 7-10 days interval. Each variable must have at least 1000 volunteers (as seen in scan 3, it depends on the institutional budget will man power and for having a large scope to filtrate at the end up to $n \geq 100$), but not less than 100 population size.

Scan 3: application cover letter where proposed for institutional (financial) help and to have a recommendation to health institution

3.1.2 literature review part

The literature review part is relies on gathering data on the SARS-CoV-2 characteristics, anatomy-physiology exceptionality of HRTT [21}; innate and adopted immunity within HRTT; vaccination philosophy – productivity and feasibility of vaccines against HRTT pathogens; results of the recent vaccines that are stated as efficacy against SARS-CoV-2

3.2 materials and procedures

3.2.1 The mucus sample from deep nasal cavities but if from oral, then at the upper part, where less saliva and others chemicals should be collected 3 times with an interval of at least 7 days. And comparing the antibody count of control, infected and vaccinated variables, the 3 ages and the 3 locations (optional, because, possible if we will have co-authors from the location).

3.2.2 Together, with the survey's results, literatures given also will be analyze to justify the survey's result: collecting relevant data from internet and books on the above mentioned materials-questions, and evaluate Vs the control's context of HRTT's anatomy-physiology exceptionalities; conclusion; and discussing (through social media too) for dissemination.

**4. Results:**

Relevant data that are collected from researches (literature given) and books
Since, we differentiate all collected data into variables, we have no right to manipulate (change) neither of the variables' value. Therefore, in this "result" section of the article, almost should have to copy-paste "as it is" (even without rephrasing) the data of the relevant literature.

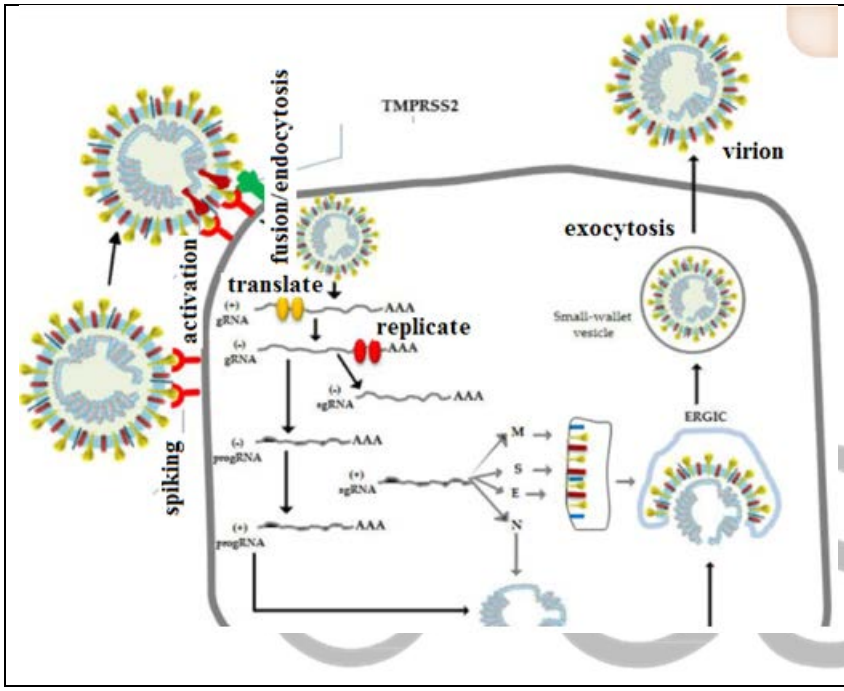
4.1 Relevant data on the nature of: SARS-CoV-2, COVID-19 and the Pandemic as a whole

For today, based on how they are reproducing within a host cell, all viruses can be divided into two groups: RNA and DNA [9a,9b,22}. Among such pathogenic viruses, our target is the RNA based virus called the coronavirus (SARS-

CoV-2) [23,24,25}. It causes the disease COVID-19. Although, relatively it is larger than others viruses 23Kb [22}, 23-36kb/80-120nm [25}, it would take roughly 1,000 coronavirus particles to span the width of a human hair [5} .

The virus can survive out of its host on different surfaces within favorite lower temperature [26,27} and pH. The virus enters to the body through nasal and or oral cavities. Within the HRTT it can only invade the epithelial cells. This is because, on its envelope surface there are glycoproteins [10,25,28}that help to spike with the host's membrane. On the other hand the host epithelial cells in their outer membrane have angiotension-converting enzyme II (ACE2). ACE2 is a facilitator enzyme of fusing the epithelial cell's membrane with the envelop of SARS-CoV-2 [8,29,30,31}. Because of such guarantyfor endocytosis, there is a greater pathogenicity of SARS-CoV-2, After endocytosis into epithelial cell, the virus reproduces itself, but bursting the host cell (figure 1).

Figure 1: illustration on how the virus invades and reproduces itself within epithelial cell of HRTT




As seen in the schematically illustrated figure 1 (to the left, the virus first enters into the host's cytoplasm and it possesses translation; replication; a virion reproduction and exocytose.

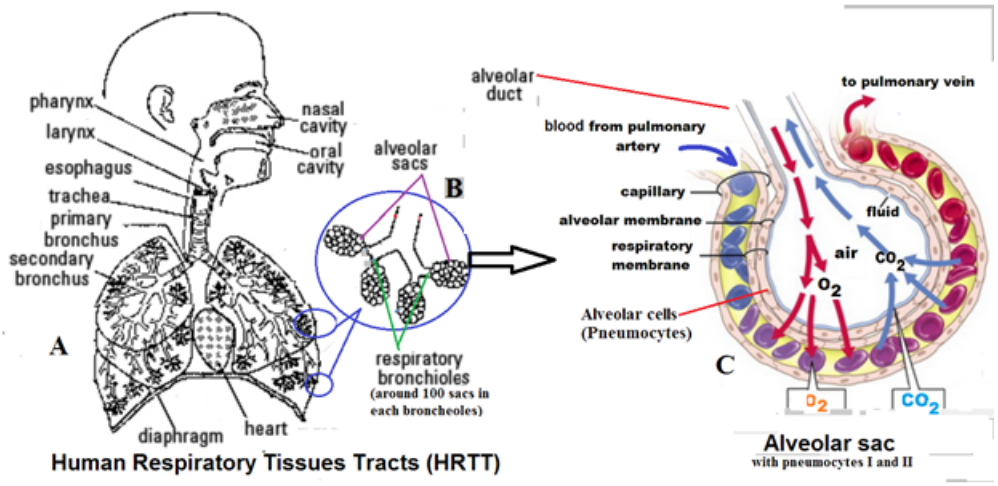
Modified from [10}

Today (within this 16 months), the disease infected 5,236 millions [32].

4.2 Anatomy-physiology of tissues that can be affected by the SARS-CoV-2

Based on our referenced books [33-37}: The anatomy-physiology of respiratory tract, can be divide the HRTT into two: upper HRTT (mouth-nose, pharynx-trachea) and the lower HRTT (the lungs - left and right in figure 2a). Exclusively, the direct target of the virus are the epithelial cells: those lined on the inner surface (lumen) of oral-nostril cavities up to the bronchioles and the two types of alveolus (pneumocytes I and pneumocytes II) that are enclosed within alveolar sac [38-42} (refer to figure 2).

Figure 2: General schematic structure of HRTT (upper - nose-broncheole and lower HRTT - lungs)

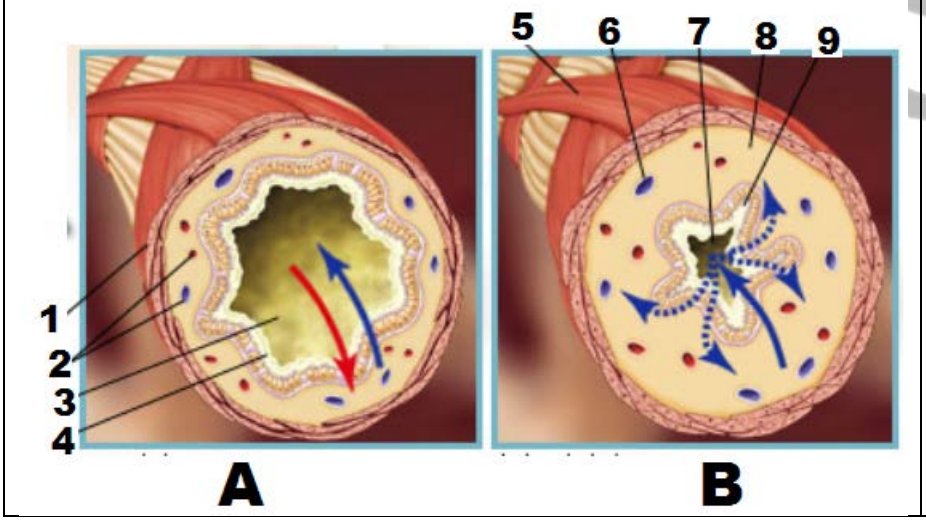



Modified based on [41,45}

4.2.1 Upper HRTT

Following the gates (nasal and or oral cavities), the pharynx-trachea path serves as the passage way for air into (inhale) or exhale [42-44}. The trachea lead the inhaled air into the lung. In the lung (refer to figure 2b,c) the inhaled air spreads through bronchioles to reach to its end destination – the alveolar sac, where external expiration takes place. According to the works [3, 45-47}, epitheliums with their cilia and mucus are lining (blanketing) the inner (lumen) surface of nostrils-oral cavities, pharynx, larynx, trachea; bronchioles (refer to figure 3)

Figure 3: Schematical illustration of innate and infected lumen of the HRTT




Legends for the figure 3:

A is a normal track, B is when inflamation

1. smooth ; 2. blood vesseles; 3.lumen
4.mucus lining: 5. contracted smooth muscle
6. Infiltrated by immune cell blood vessele
7. decreased lumen diametr
8. inflammation and swelling
9. excess mucus

Modified from [43,45}

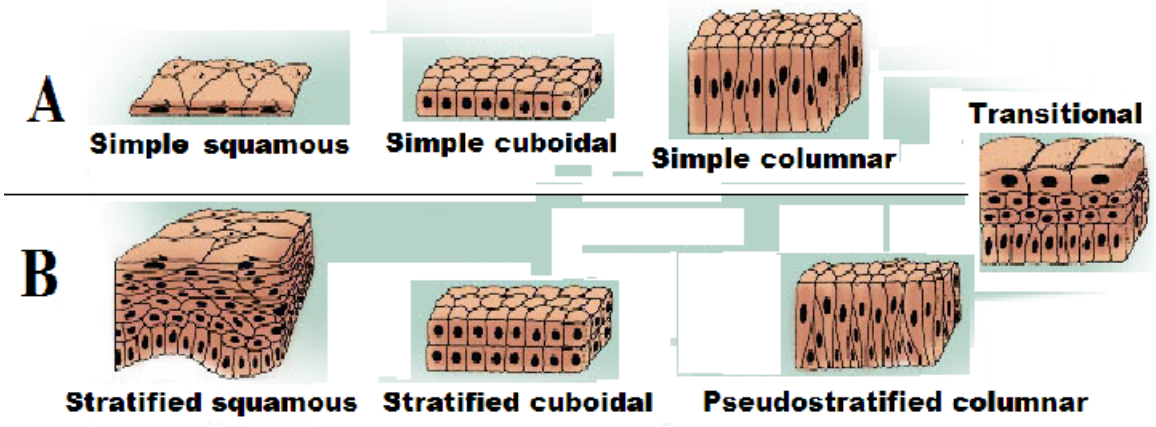
The upper surface (apical) of epithelium is free (exposed to the exterior). The basal surface rests on connective tissue. A thin, extracellular layer called the *basement membrane* (refer to figure 3) forms between the epithelial and connective tissue [45}

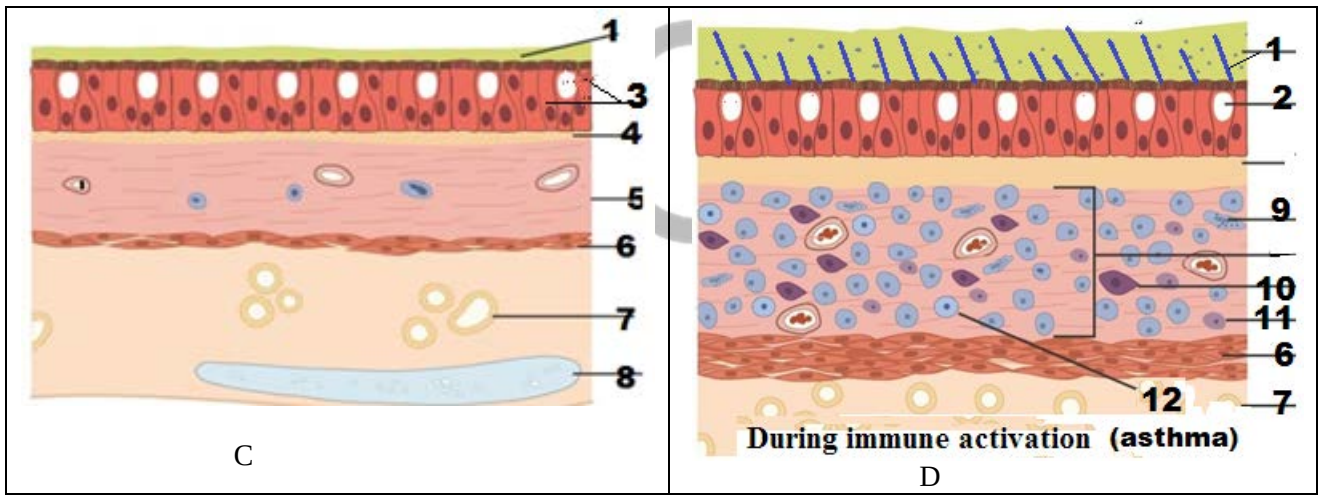
As seen in the figure 4a,b, epithelial tissues of HRTT are classified according to the shape of the cells and number of the cell layers formed. Cell shapes can be squamous (flattened and thin – for instance alveolar cells (the pneumocytes I and pneumocytes II (a simple cuboidal alveolar epithelia), or columnar (rectangular, taller than its width). Pseudostratified single layer of irregularly shaped cells have cilia with association of goblet cells secreting mucus[44,56}. Ciliated

columnar epitheliums are removing particular matters (for instance in bronchi). Pseudocolumnar are in trachea. The epithelium of the upper HRTT is sensitive to irritations and responds either by increasing in thickness while the mucous cells and glands beneath undergo hypertrophy or, with more intense or prolonged irritation, by producing squamous metaphase [48}

The bronchi and bronchioles contain cilia (figure 4d), small hair-like projections that line the walls of the bronchi and bronchioles. These cilia beat in unison and move mucus and particles out of the bronchi and bronchioles back up to the throat where it is swallowed and eliminated via the esophagus [38,49}.

Figure 4: different types of epithelial cells and their surroundings within the HRTT [38,39,45a,48,50}




C D

Adopted from **[45a}**

**Legend for C and D of the above figure 4**

1. Mucus and cilia
2. Goblet cell
3. Epithelium
4. Basement
5. Lamina propria
6. Smooth muscle
7. Gland
8. Cartilage
9. Mast cell } increase during inflammation/infection
10. macrophage
11 Eosinophil
12 Neutrophi

4.2.2 Lower HRTT- alveolar cells' anatomy-physiology

Air enters into the lungs through the two primary (main) bronchi (singular: bronchus). Each bronchus divides into smaller diameter bronchioles as they split and spread through the lung (refer to figure 2a).

Authors of [38) concentrated on different size identification issues: there are around 100 alveolar sacs attached to each bronchiole (figure 2b). In each alveolar sac enclosed 20-30 special epitheli – the alveoli (pneumocytes I and pneumocytes II) and totally around 300 million per lung, necessary a very large surface area that is available for gas exchange. So the surface area of alveoli in the lung is approximately 75$m^2$ [38}. These epithelial cells are alveolar cells, where gas exchange

(external respiration) takes place. As epithelial cells of the upper HRTT covered by mucus and cilia, the alveolar cells (pneumocytes)in their turn are covered by surfactant – composed of mucus like sticky substance made of mucin, a complex glycoprotein, as well as salts and water, with detergent character that traps particulates [53,54}. The alveolar development stage starting from 36 weeks of fetal age and lasts up to two years after birth [48,49}.Type I cell (pneumocytes I) cover 90-95% of the area inside alveolar sac (figure 2c), but the cuboidal type II cells (pneumocytes II) are more in number and from them can be generate the type I cells [55}. In the works [38,48} well expressed about alveoli: Alveoli are made of thin-walled parenchymal cells, typically one-cell thick, that look like tiny bubbles within the sacs. Alveoli are in direct contact with capillaries (one-cell thick) of the circulatory system. Such intimate contact ensures that oxygen will diffuse from alveoli into the blood and the carbon dioxide that was produced by cells as a waste product will diffuse from the blood into alveoli to be exhaled (figure 3). The anatomical arrangement of capillaries and alveoli emphasizes the structural and functional relationship of the respiratory and circulatory systems [33,35}.

Table 1: Expressing alveolus and their surroundings through size related parameters [38,48,49,56,65}

| measures | Alveolar sac | alveoli | capillary | endothelium | Membrane barriers |
|---|---|---|---|---|---|
| Size/thikness | 200-300µm | 0.1 µm | 0.7µm | 0.1µm | <2µm |
| number | 100/duct | 20-30/sac | Each sac | | 4 |
| distance | | | 0.7µm /alveoli | | |
| total | $10^4$ducts | 75$m^2$/lung | | | |

The structural basis for gas exchange is the alveolar wall (sac) [33, 48,49}. On average red blood cell pass away 2-3 alvelus within 0.75s [65}. As seen in table 1 and figure 2 [57} the surface of the red blood cell is only 0.7 µm away from the air in the alveolus. Here, as indicated in table 1, air and blood come into close contact and are separated by an air-blood or tissue barrier as thin as 2 µm [65}.

Nevertheless, this barrier is composed of three layers: the epithelium's basal membrane; sac's membrane barrier, interstitium space, basal membrane of endothelium (their membranes as a whole is called respiration membranes (figure 2c), exposing their thin air-blood barrier to the alveolar air on either side and, thus, accumulating oxygen from alveoli [57a-57c}. Oxygen crosses this thin barrier (diffusionby partial pressure gradient) and reaches the erythrocytes.

Squamous alveoli (pneumocytes I) have small nucleus. Less organelles and if after birth injured, the reformed by mitotic division from type II cells [58-60}. Whereas type II cells have developed nucleus, many mitochondrion, endoplasmatic reticulum, a large Goolge and laminar bodies for producing surfactant [39,46,53,58.61}. Squamous and cuboidal cells type I have microvilli and cytoplasmic lamellar bodies. Works of [58-62} indicate that endothelial and the two types of alveolar cells are working together in the gas exchange processes.

The alveolar cells under intact condition are impermeable for protein [63,64}. However, to the contrary, authors [65}, admitting the impermeability of alveoli for albumin, they wrote that the alveoli are permeable for macrophage!

4.3 Blood, lymph and nerve systems within the HRTT

In general, the circulatory, and nerve systems with HRTT serve as a transport, to smell [33}, speak, and move oxygen into our blood stream and waste out of it. However, in HRTT, they have some restrictions

4.3.1 Vascular Circulatory (blood) system

The circulatory (or cardiovascular) system (refer to figure 5a,b and 6) is a closed network of organs and vessels that moves around the body [66,67}. Within the blood system the capillaries and venules are the end part of the system that are socked (bathes) into the interstitial fluid (refer to picture 5b). The primary purposes of the blood circulatory system through interstitial fluid is delivering nutrients, oxygen, immune cells and antibody into tissues and to carry away their waste products for elimination [The tube like vessels of this system have wall of endothelial cells. These cells are a single celled layer of endothelial cells that are covered by basal lamina. [33,35,67}, they have a capacity of adjusting their number to suit local requirements.

4.3.1.1 Blood system within the upper HRTT

The nasal cavity (refer to figure 6a) receives its arterial supply from the posteriorethmoidal branches of ophthalmic artery [13}. However, as seen in figure 4c,d, the blood vessels are not seen at least around the epithelial cells and in 7c, they are

deep far from the epithelial cells. Because, of which, in addition to educational materials (books) many authors [33,39,45,47,61-61d,68}, stated that epithelial cells are Avascular. Therefore, nutrient and waste exchange occurs through neighboring connective tissues by diffusion through [33}.

4.3.1.2 Blood system within the lower HRTT

As shown in figure 2c, table 1 and [45}, the capillary-venules are firmly attached (space between them 0.2µM) to the alveolar sac –alveolar septa, whereas there where, interstitial fluid is mediating its thickness or distance between the tissues (cells) can be 20µM [70} and [70a-70c}

4.3.2 Lymph system

The lymphatic system is a specialized part of the vascular system that involves in removing interstitial fluid and activate immune functions [70,70a}. Lymph, a lipid and protein-rich fluid containing white cells and derived mostly from local capillary filtration into the interstitial space. Lymphatic vessels recover (drain) fluids that escape into the connective tissue spaces from blood capillaries and venules and return them to the blood.

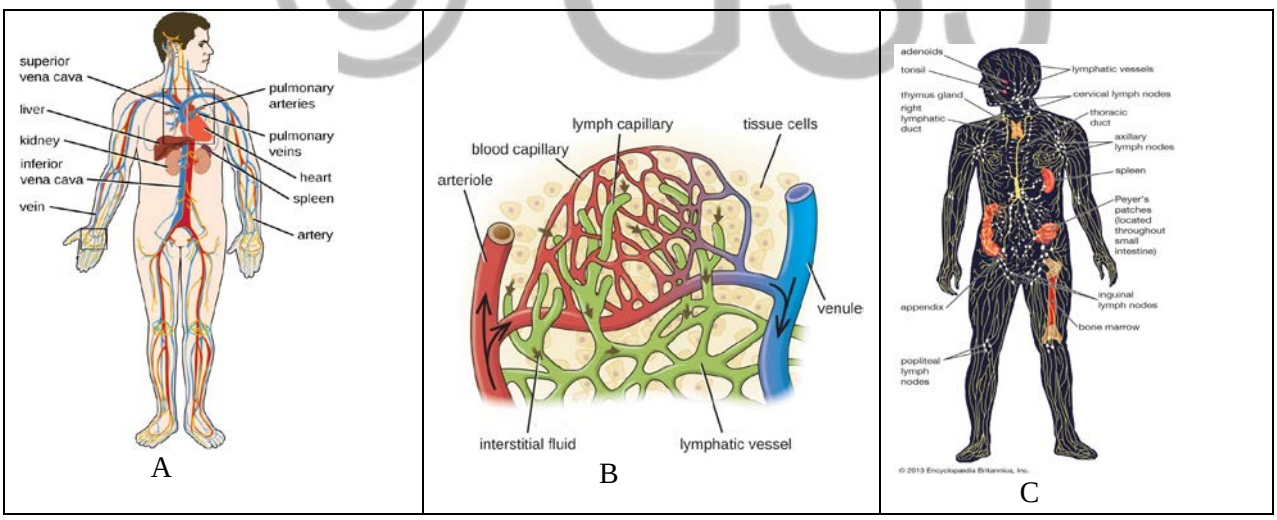
4.3.2.1 The upper HRTT has well expressed lymph system with two nodes

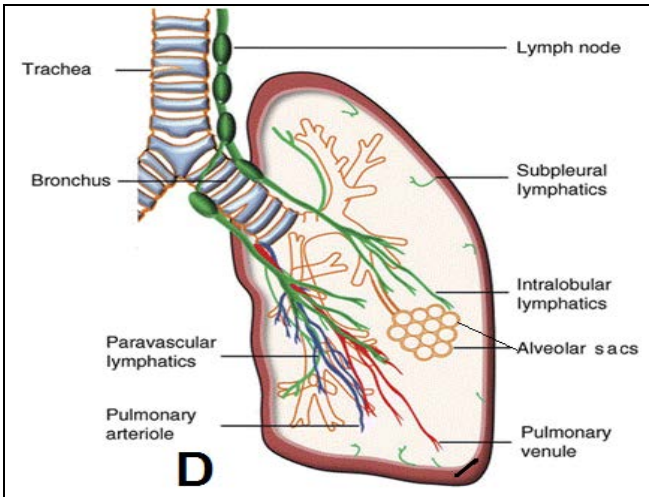
Unlike the blood vessels, lymph do not form a circular system but carry their contents, in only one direction, towards the base of the neck (figure 5c), where two nodes are located. The respiratory tract is, therefore, provided with a unidirectional draining system that clears not only fluid but also free particles and macrophage-containing particles. In the small bronchi there is only a single plexus, which extends as far as the bronchioles but fails to reach the alveoli (figure 5d); and there are no lymphatic vessels beyond the alveolar ducts [48,70}.

4.3.2.2 The lower HRTT has lymph network but do not extended upto the alveolar sac.

Work of [71), which are new results show an important function in the fluid balance of the lung and abdomen. Inflammatory spread may occur from the lung to the periphery by the blood stream and from the abdomen to the lung by lymph flow. In the work **[72}** shows that in a healthy lungs, lymphatic run parallel to the major airways and respiratory bronchioles, and they also exist in close proximity to the intralobular arterioles and small veins.

**Figure 5: Blood and lymph vesseles with the interstetial surface (in the middle)**






Blood as shown in figure 2b,c cover the alveolar sac, where as in this figure 5D indicated the schematic of lymphatic distribution in the healthy human lung. Lymphatic in the lung accompany the major airways and respiratory bronchioles, and they are also present near the interlobular arterioles and small veins. In addition, there is a network of sub pleural lymphatic, which are distributed beneath pulmonary pleura. Under physiological conditions, lymphatic vessels generally do not extend to the distal alveolar spaces [71,71a,71b,72}.
The role of lymph in antibody formation also expressed in the work [69}

Adopted from Encyclopedia Britannica, Inc [66,69,72}

As seen in the figure 5d, the lymph can collect only from bronchioles and above, but not from alveolar sac

4.3.3 The nerve system within the HRTT

The nose inerves by branches of glassopharingial and maxillary nerve [13} and as indicated in figure 6b in receptors in the nose and the paranasal sinuses give rise to afferent fibers that form part of the trigeminal and glossopharyngeal nerves [13,48}. It mainly follows the airway tree but also accompanies the bronchial (nutritive) vessels. Some fibres run superficially in the connective tissue of the adventitia, others more deeply, inside the cartilage.

Bronchi are innervated by nerves of both the parasympathetic and sympathetic nervous systems that control muscle contraction (parasympathetic) or relaxation (sympathetic) in the bronchi and bronchioles, depending on the nervous system's cues. In humans, bronchioles with a diameter smaller than 500µm are the respiratory bronchioles. Dilation and constriction of the airway are achieved through nervous control by the parasympathetic and sympathetic nervous systems.

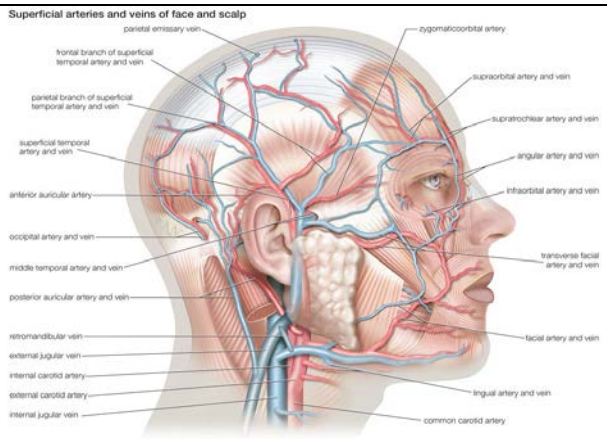
The parasympathetic system causes bronchoconstriction, whereas the sympathetic nervous system stimulates bronchidilation. Stimulation of tracheal irritant receptors causes coughing, bronchoconstriction, and hypertension [73,74}. Central respiratory chemo-sensitivity is caused by direct effects of acid on neurons and indirect effects of $CO_2$ via astrocytes

The automatic respiratory centers in the brainstem respond to inputs from the feedback receptors and adjust neural output to the muscles that control ventilation and upper-airway patency. Neural receptors fall into a number of different classes and are present in the upper airway, respiratory muscles, lungs, and pulmonary vessels [74}.

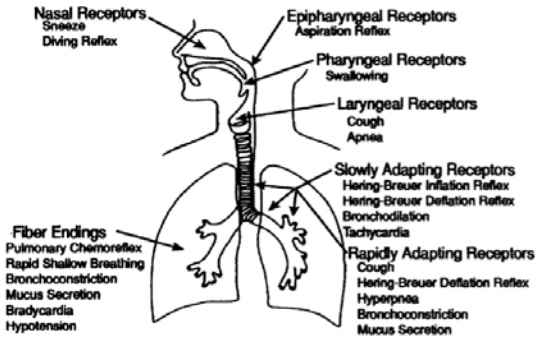
4.4 Immune system with in HRTT

There are, several protective mechanisms to prevent damage or infection. These include the cilia and mucus in the nasal cavity [38,48} that trap dust, dirt, and other particulate matter before they can enter the system [75}. In the airways, mechanical defense appears to predominate and includes the deposition on the nasal and oropharyngeal surfaces and elimination through cough, sneezing, and mucociliary clearance [38,76} or The work [77} inform us that inhaled substances can be isolated by transport up the bronchial mucociliary escalator or by transport through interstitial and lymphatic channels leading to lymph nodes.

Figure 6: Blood circulatory and nerve receptors system within the upper HRTT[74}




A: Blood vessels on the upper HRTT (face)




B: Mechanical receptors involved in respiratory feedback

Adopted from [74,77a}

4.4.1 Epithelium of upper HRTT during inflammation

When, because of exogenesis, objects like atmospheric toxins, dust, microorganisms, their debris, inflammation's results, immune cells and their debris too, etc. enter into the respiratory lumen's surface to cause inflammation that the responses of immune cells and cytokine species. Together with initiating and perpetuate an inflammatory reaction in response to a variety of stimuli, in particular, bronchial epithelial cells produce interleukin (IL)-5 (interfere for eosinophil cells), IL-8 (activate neutrophil), regulated on activation, normal T-cell expressed and secreted, and growth factors such as granulocyte macrophage-colony stimulating factor, all implicated in attraction and/or activation of inflammatory cells. Interestingly, IL-8, the most potent neutrophil chemo-attractant, is released by bronchial epithelial cells in response to bacterial products [75}

4.4.2 Lower HRTT during infection

Although, the article [15} tends to be popular, its authors postulate that substances can be locally detoxified within the lung by interaction with secretory proteins, such as antibodies, or by neutralization and dissolution within phagocytic cells [77}. Humeral and cell-mediated immune responses amplify and direct lung defenses against infection and may also participate in protection against other agents. Immunoglobulin A and G, microbial neutralizing and opsonizing anti-bodies, and macrophage-stimulating T lymphocytes are the major immune-specific forms of lung defense [77}. The respiratory epithelium contribute in the exclusion of microbes and particles. The epithelium also control the inflammatory and immune responses in the airways and in the alveoli [76,77}.

When the alveolar capillary damage remains localized, the edema is over shadowed by the manifestation of infection, as in bacterial or viral pneumonia; when it is diffuse, however, it can produce acute respiratory distress syndrome. The inter alveolar walls are then lined with a thick hyaline membrane. There is also focal collapse of alveoli, as well as patchy interstitial and pulmonary haemorrhage [77}. In prolonged cases, type II epithelial cells may line the alveolar spaces, and intra-alveolar fibrosis may develop [78}.

In the worst-case scenario, the walls of the alveoli begin to break down. Fluid rushes from the blood vessels into the alveoli, filling them up and blocking the exchange of gases. When this happens, we can't excrete enough carbon dioxide, nor absorb enough oxygen [24}. [79} Endothelial apoptosis affect the alveolar-capillary frameworks on the other side the alveolar cells are the cause of damaging the endothelial cells in cause of smoking

4.4.2.1 lymph's direct role in the immunity of lower HRTT

[48} Inhaled particulate matter may enter the interstitial space alone or engulfed by surface macrophages. Free particles may be phagocytised by macrophages and retained permanently, or cleared directly, or ingested by the draining pathway. This material will continue into the tracheobronchial lymph nodes. The respiratory tract lymph, which originates in the interalveolar septa flows through lymphatic vessels in the axial and peripheral connective tissue into the lymph nodes associated with the respiratory tract (figure 5D). These are deep cervical nodes, collecting the lymph of the upper airways and the tracheobronchial nodes, the lower airways, and the lung. The respiratory tract is provided with a unidirectional

draining system that clears not only fluid but also free particles and macrophage-containing particles. Most of these particles will actually be retained in the lymph nodes, which act as filters for the lymph system.

Although lymphocytes are scarce in the normal airway and alveolar lumen, they are detected in the submucosa of the bronchi and when they are abundant, such as in some pathologies, they are sometimes organized in lymphoid tissue called bronchus-associated lymphoid tissue. A part of their role is related to the mucosal humeral immune response and more specifically to the production of immunoglobulin (Ig)-A.To remove particles and micro-organisms reaching the alveolar space the alveolar epithelium lacks mucociliary properties and therefore relies mostly on the alveolar macrophages [76,78}.

4.4.2.2 Immune cells of HRTT: Macrophage, neutrophils, eosinophil, leukocytes, etc.

Macrophages (AM) are types of white blood cells that swallow up and digest germs and dead or dying cells [38,80}. [77} The pulmonary AM is the central figure in the protection of the respiratory membrane, operating in all 3 of the nonspecific modes of defense and augmented by specific immunologic mechanisms as well.The macrophages leave behind part of the invading germs, called “antigens”. These macrophages attack the virus, a battle that the immune system sometimes wins [24,77}. The body identifies antigens as dangerous and stimulates antibodies to attack them [81}.The AM is an important effector of the pulmonary immune response and plays a key role in the pathogenesis of a wide variety of inflammatory, destructive, and fibrotic lung diseases [67}:

Alterations in macrophage function and physiology may be crucial in determining the effectiveness of pulmonary defense. As well as functioning as resident defender of the alveolus [77}. Although, they are the main defense cells, according to [73,74} AM are the most abundant phagocytic cells in the lung, but they present antigen poorly to T cells. They actively tolerize CD4 T cells in an antigen-specific fashion [40}.

Moreover, as [84} stated that AM actively induce T-cell unresponsiveness (functional inactivation) in an antigen-specific manner and reduce the capacity of CD4 protein [33,40}T cells to respond on secondary stimulation [40,76,82}. the authors [40} propose that AMs mediate a form of immune privilege in the lungs that effectively limits immune responses in the pulmonary compartment but has little effect on systemic immunity. In vivo elimination of AM from rats and mice greatly amplifies immune responses to inhaled antigens, in particular T-memory cell-dependent secondary antibody responses [84}.

Anyhow, AMs that have phagocytised particulate matter may enter lymphatic and are then transported into lymph nodes, where they can stay for long periods of time [48}

4.4.2.3 Others immune cells that are participating in antibodies production

[85} cytokines like IL, impaired expression CXCL, C–C chemokine ligand19 (CCL19), and CCL21, which are crucial for the recruitment and placement of lymphocytes and dendritic cells, CCR1, decreases mortality and pro-inflammatory cytokines (TNF, IL-1β, and IL-6) to Serratiamarcescens pneumonia in rats. Though this strategy increases neutrophil numbers, they resolve more rapidly, During RNA virus lung infection IFN-α is produced predominantly by alveolar macrophages (or, to a lesser extent, pDCs) whose depletion impairs viral clearance.192 Dosing with IFN-α and a double-stranded RNA IFN-α inducer, 4 h after SARS coronaviruas infection, reduces lung viral titers. IFN-α, have reduced lung viral titers and inflammatory disease. Neutrophils: playing role in clearance of exogenous pathogen and endogenous cells. The [86} show that macrophages excrete factor that initiate the development of neutrophil in bone morrow.When there is infection they will appear [87,87a} specially in lower HRTT during sever infection. But they may couse inflammation because of their protease [88}. Both Macrophage and neutrophils arephagacytase apoptotic epithelial cells may cause endothelial cell damage to enter into interstitium(refer to figure 7).

Figure 7a: role of B cells in chronic rhinosinusitis: activation of Dendrite cell, Eosinophil , mast, and neutrophil cells degranulation[89}

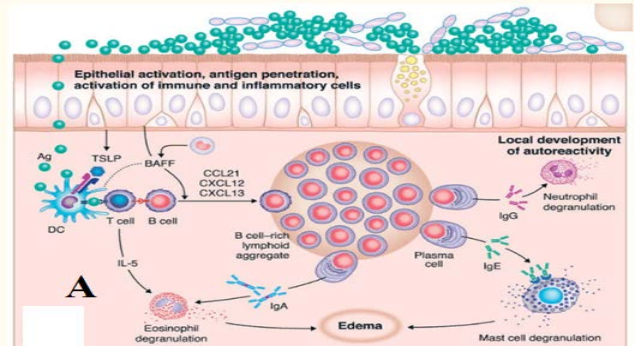
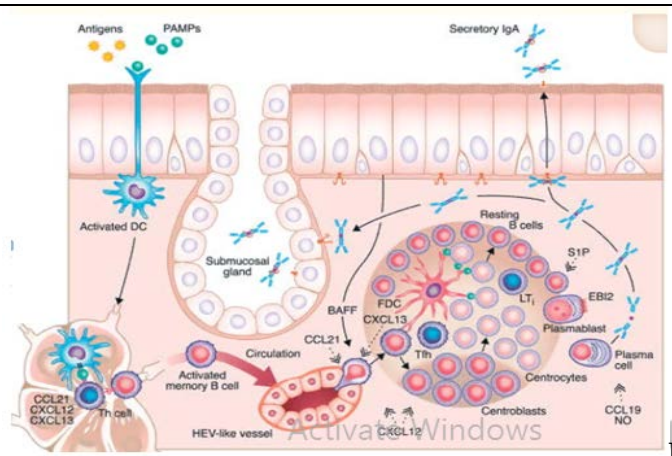
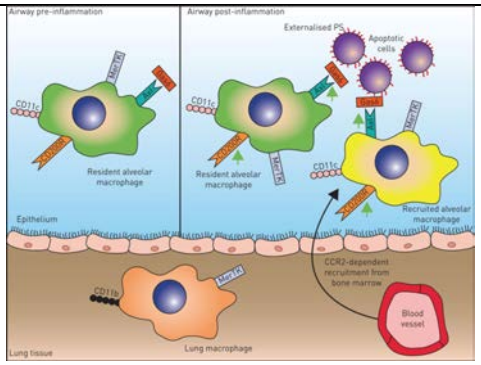



Figure 7b: effector response in the airways




**B**




In the above, although, we are not agree with the AM position, we can see how the blood vessel is far away from the lumen epithelial cells

**C.**

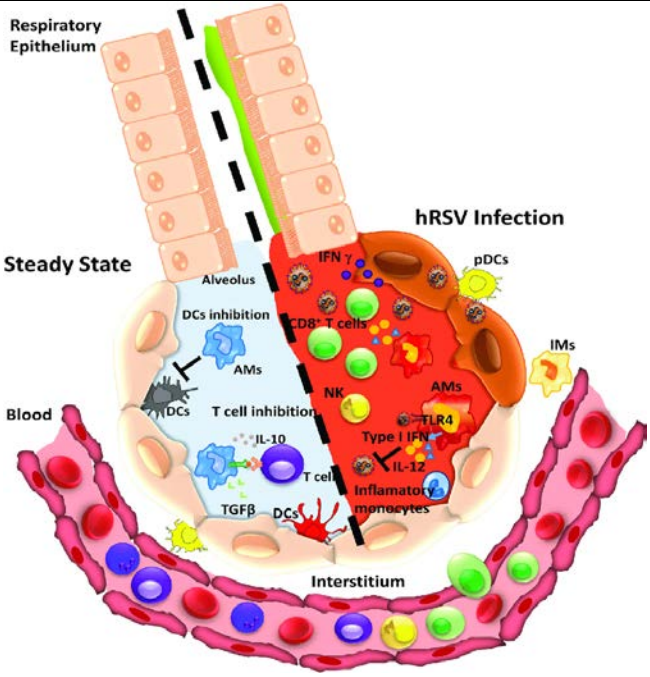
Despite, all these positive roles against pathogens, during inflammation, AMs as shown above tolerate the CD4, disturb T cells, B cell products such as autoantibodies directed against lung cells, components of cells, and extracellular matrix proteins. These autoantibodies may contribute to lung the emphysem inflammation and injury [33-40,91}.

4.5 Role of T and B cells within the HRTT

4.5.1 T-cell

T-lymphocytes (T cells) as macrophages, IL, eosinophil [76,92}, neutrophils [86,87,87a,} and others immune cells are another type of defensive white blood cell. They attack cells in the body that have already been infected: After immunization, dendritic cells (refer to figure 4c,d for their location) take up microbial antigens and traffic to draining lymph nodes where they present processed antigens to naïve T cells. These naïve T cells are stimulated to proliferate and differentiate into effector and memory T cells. Activated, effector and memory T cells provide B cell help in the lymph nodes and traffic to sites of infection where they secrete anti-microbial cytokines and kill infected cells [93}.

Figure 8: comparative conditions between intact and infected alveolar sac (lower HRTT)




AM suppresses the response of T cell in an antigen-dependent manner and secretes cytokines as IL-10 and transforms growth factor β. During infection (The right part of figure 8), AM can recognize the virus and responds by secreting type I IFNs that induce an antiviral state in epithelial cells. Secreting pro-inflammatory cytokines to activate inflammatory monocytes and CD8+ T cells to clear the virus [90}

Adopted from [90}

[94} inform us that infectious agents initiate both innate defence mechanisms and specific T- and B-lymphocyte responses. Cytokine products of activated T-lymphocytes provide crucial macrophage activating signals and drive the development of humoral immunity. Membrane-bound ligands on activated T-lymphocytes provide important lytic signals to infected antigen presenting cells. Antibodies produced by activated B-lymphocytes facilitate clearance of the pathogen through a variety of effector mechanisms, including complement fixation, dependent cellular cytotoxicity, and opsonization. [84} CD4+ T cells: predominantly they are in the peripheral lung wall T cells and their airway counterpart isolated by bronchoalveolar lavage, exhibit markedly reduced capacity to proliferate by comparison to peripheral blood T cells.

4.5.2 B-cell

[95} Antibodies are produced by plasma cells, primarily in the bone marrow, and secreted into the circulation. Circulating antibodies can access a variety of tissues through active or passive transport.

Antibody-secreting cells (mainly the B cells) in respiratory tract tissues provide a first line of defense against invading pathogens. These cells often secrete IgA that is efficiently transcytosed across epithelial barriers into the airway lumen, where pathogens can be blocked at their point of entry. The majority of polymeric IgA (pIgA) and IgM (pIgM) produced at these sites is transported across epithelia into the luminal environment, where secretory Ig is thought to inhibit adherence of noxious micro-organisms and antigens to the epithelium, performing a so-called “immune exclusion”. Virus-specific antibodies were similarly observed in the airways of eosinophil-deficient mice. virus-specificcells were most frequently situated adjacent to epithelial cells rather than eosinophils or neutrophils. Taken together, these data emphasize that rules for cell maintenance are not absolute and that antibody secreting cells can survive in the respiratory tract without eosinophils or neutrophils as their nearest neighbors [92}.

The primary sensitization events that generate B cells responsible for effector responses throughout the airways usually occur in the upper airways, in tonsils and adenoid structures that make up Waldeyer’s Ring [89}. Upon secondary exposure to antigen in the airways, antigen-processing dendritic cells migrate into secondary lymphoid organs such as lymph nodes that drain the upper and lower airways and further B cell expansion takes place at those sites.

[96} B cell production of IL-10 was necessary for macrophage activation and the release of matrix metalloproteinases that have been implicated in air space enlargement. Although many of B cells that are capable to produce adopted antibody die after several days, some survive in the bone marrow for months or years and continue to secrete antibodies [36,75,89,97} into the blood.

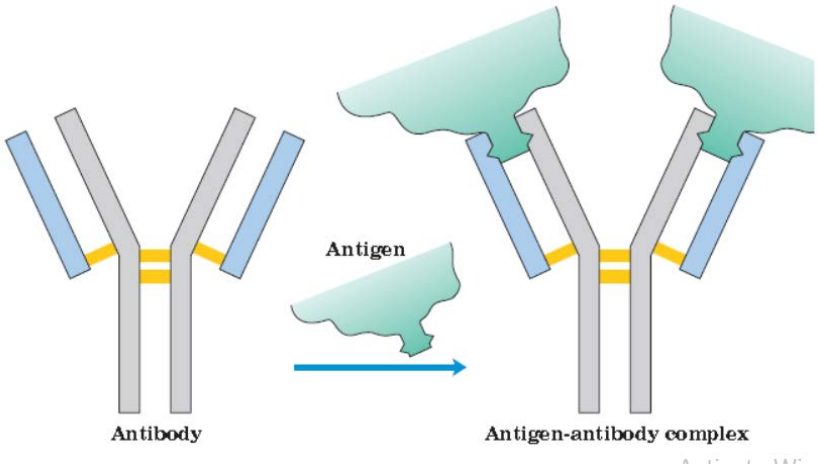
Moreover, the role of T and B cells, AM, cytokines, eosionates, neutrophils, etc. is also well expressed in the work [37,87,98}

4.5.3 Additional: The role of immunoglobulin – protein based antibodies

The recent identification of the immunoglobulin-A leukocyte receptor on phagocytes including alveolar macrophages become interesting today [76,94}

The part of the immune response that can target germs precisely and provide long-term protection is called the adaptive immune response. Two types of white blood cell are important in this: T cells and B cells. B cell receptors lock onto unique structural components of a germ, or an infected cell, directly. T cells, on the other hand, need other immune cells to chew up and present parts of the germ in small fragments, which can then be scrutinised.T cells don't just do one thing. Some – the cytotoxic T cells – attack infected cells directly, while others – the T helper cells – support immune responses by helping B cells produce antibodies.Once T and B cells have been sent to deal with a germ, the immune response subsides and long-lived memory versions of T cells and B cells are retained so that the appropriate response can be mounted much faster if the same germ is encountered again.Understanding the type of immune response that works best against a particular infection is important for vaccine design [99}.

**Figure 9: Immunoglobulin structure for exampleIgG and its binding with antigen (adopted from [97}**




Antibodies provide protection against infectious microorganisms. In addition to providing immunity against pathogens, antibodies mediate clearance of extracellular protein aggregates and cell debris. Different antibody isotypes (IgM, IgG1-IgG4, IgA and IgE) are specialized for different effectors' functions [76a}.

4.5.4 Specific antibodies (immunoglobulin) production within the HRTT

When we come to the HRTT:

[92} Antibody-secreting cells in respiratory tract tissues provide a first line of defense against invading pathogens. These cells often secrete IgA that is efficiently transcytosed across epithelial barriers into the airway lumen where pathogens can be blocked at their point of entry.

according to the study [95}, in some tissues, epithelial cells are equipped with transporters that enable active translocation of certain immunoglobulin isotypes in mice and humans. In the gut mucosa, plasma cells are present in the lamina propria, and epithelial cells express a polymeric Ig receptor (pIgR) that transport dimeric IgA from the basolateral to the luminal side of the gut epithelial cells through transcytosis (refer to figure 1,7). In the gut and other mucosal tissues, epithelial cells express neonatal Fc receptor (FcRn) to transport circulating IgG in both directions [100,101}.

Despite all these, the [40} indicate that there are immunopriviledged sites [102}, include the central and peripheral nervous systems, testes, uterus, fetus, placenta, the retina HRTT [40} Antibody access to these tissues is blocked by the barrier created by microvascular [49} endothelial cells and other supportive cell types

4.5.5 IgA

IgA, the most abundant Ig in the airways, mucosal fluids and nasal surfaces, can also interact with phagocytic cells [89}. IgA is the principal class of antibody in secretions, including saliva, the HRTT, etc. [36}. [103} IgA is much less abundant in serum than IgG, but its catabolism is four-eight-fold faster (considering, respectively, monomeric and polymeric IgA).

Next to IgA the Immunoglobulin G is an important component of the host defense system of the respiratory tract [76a,104}. IgG functions in concert with IgA as part of the local airway host defense against microbial agents, organic antigens, or similar substances that can be aspirated or aerosolized into the airways and must be contained or eliminated.Over the mucosa of the respiratory tract and the alveolar epithelial surface, IgG is also present in the lining fluid and secretions [104}.

4.6 Vaccination, definition, types and functions

4.6.1 What is vaccine in general

Furthermore, the work [99} in short way define the function of vaccine's main roles as follows :The part of the immune response that can target germs precisely and provide long-term protection is called the adaptive immune response. Two types of white blood cell are important in this: T and B cells. B cell receptors lock onto unique structural components of a germ, or an infected cell, directly. T cells, on the other hand, need other immune cells to chew up and present parts of the germ in small fragments, which can then be scrutinized.

Shortly, microbes initiate both innate and especific adaptive immune responses. vaccine also initiate the body to prepare antibody – adopted antibody. Lymphocytes determine the specificity of the immune response and orchestrate effector limbs of the immune response [94}.

4.6.2 Types of vaccines

Vaccines try to mimic the natural immune process by provoking the development of long-lived memory T cells and B cells, without triggering, but may initiate the symptoms of a real infection. It's not the case, though, which each type of vaccine stimulates a similar immune response [99}. There are many types of vaccine and each will trigger a cascade of events that stimulate the immune system in a particular way.

[27} One aspect of vaccinology that is rapidly expanding is the development of so-called T-cell-inducing vaccines; vaccines designed to induce CD4+ and/or CD8+ T cells of sufficient magnitude and necessary phenotype or effector function that directly contribute to pathogen clearance via cell-mediated effector mechanisms, rather than only CD4+ T-cell help for B cells leading to protective antibody responses

4.6.3 Characteristics of vaccines against HRTT based infections

Protection provided by vaccines are short-lived, particularly against pathogens that replicate and cause pathology at their site of entry. In the absence of active immune effector activities, the ability of memory cells to respond quickly enough to control this type of infection is limited [113}. The body keeps a few T-lymphocytes, called "memory cells", that go into action quickly if the body encounters the same virus again. When the familiar antigens are detected, B-lymphocytes produce antibodies to attack them. However, in the work [93} stated that most currently licensed vaccines induce antibody responses capable of mediating long-term protection against lytic viruses such as influenza, malaria, Mycobacterium tuberculosis (TB), human immunodeficiency virus (HIV) and hepatitis C virus (HCV), are currently not available or are ineffective. Understanding the mechanisms by which long-lived cellular immune responses are generated following vaccination should facilitate the development of safe and effective vaccines against these emerging diseases [13-15}. Here, we review the current literature with respect to memory T cells and their implications to vaccine development.

[114} Scientifically, influenza viruses are divided into three types, designated A, B, and C. Types of influenza vaccines include the injection (killed virus), recombinant (made without flu virus), and nasal spray vaccines (containing live virus) and The vaccine is only effective against the strains of the virus that match the vaccine.

Pulmonary tuberculosis (secondary) produces focal Lesions in the parenchyma of the apical region of the lungs [114).

[115} the CDC about effectiveness of vaccine against influenza expressing as follows: Influenza (flu) vaccine effectiveness can vary. The protection provided by a flu vaccine varies from season to season and depends in part on the age and health status of the person getting the vaccine and the similarity or "match" between the viruses in the vaccine and those in circulation. [116} Two types of influenza vaccine are widely available: inactivated influenza vaccines (IIV) and live attenuated influenza vaccines (LAIV). Traditionally, influenza vaccines (both IIV and LAIV) have been produced to protect against 3 different seasonal influenza viruses (also called trivalent vaccines). In most countries this is still the case and the current trivalent vaccines contain influenza A(H3N2), pandemic A(H1N1) and 1 of 2 influenza B lineage viruses. However, recently vaccines which protect against 4 different viruses, including both influenza B lineage viruses (quadrivalent vaccines), have become available in some countries.

[116} Vaccination is one of the most effective and cost-benefit interventions that prevent the mortality and reduce morbidity from infectious pathogens. However, the licensed influenza vaccine induces strain-specific immunity and must be updated annually based on predicted strains that will circulate in the upcoming season. universal vaccines include the matrix 2 protein, the hemagglutinin HA2 stalk domain, and T cell-based multivalent antigens. Authors [94} also tried to define vaccine as:

**[117} Pneumococcal infections are caused by the bacterium Streptococcus pneumoniae and can lead to pneumonia, blood poisoning (sepsis) and meningitis**

The type of pneumococcal vaccine you're given depends on your age and health.

Most vaccines will target B cells and the types of T helper cells that support antibody production. Yet for some infections, the antibody response may not be enough. In such cases, vaccines can also be developed to promote cytotoxic T cell activity, or perhaps a combination of both antibody and cytotoxic T cell immune responses.

The childhood vaccine protects against 13 strains of the pneumococcal bacterium, while the adult vaccine protects against 23 strains. Like most vaccines, the childhood and adult versions of the pneumococcal vaccine can sometimes cause mild side effects.

In some cases, such as autoimmune diseases or inflammatory disease caused by excessive exposure to foreign antigens, these same immune cells (Eosinophil cells [98} A type of white cell that involves in antiparasitic and inflammatory response. Promotion of eosinophil caused by chemokine such as CCL, CCL24, 26. They have granules from which have proteins peroxide etc. for phagocytosis) can cause disease by virtue of overly vigorous responses.

[118} open chromatin profile at effector genes was maintained in memory CD8 T cells isolated even a decade after vaccination, indicating that these cells retain an epigenetic fingerprint of their effector history and remain poised to respond rapidly upon re-exposure to the pathogen.

[69} After infection, lymph fluid flows from peripheral tissues to the draining lymph, carrying along tissue antigens including bacteria and viruses and display them to naïve lymphocytes. Small molecules carried in lymph can enter these channels, called conduits, and are conveyed through the T cell zone to the high endothelial venules that are the sites of lymphocyte entry from the blood. However, this reduction in lymphocyte entry impacted mucosal antibody responses to vaccination.

4.7 Vaccine for SARS-CoV-2

For SARS-CoV-2, there are several offered vaccines that under gone evaluation processes to be declared as efficacy and or already declared efficacy [105-112}! But the other important for this work are focused on the way of using vaccines: There are most vaccines that are administered through injection (into blood stream), under skin, ingestion, oral spray and nasal spray, about which we in our work [16} and [105a} emphasize it. However, today's (recent) vaccines that are accepted for emergency use against SARS-CoV-2 as seen in table 2 are intramuscular injection based vaccines.

4.7.1 How it affects the respiratory tract

The coronavirus first spike (attached) with host membrane [10,25,28,31}, which have ACE2 (enzyme on the host's membrane) facilitate the endocytosis of the SARS-CoV-2 into the host cytoplasm (refer back to figure 1).

The first time if a person is infected with the virus that causes COVID-19, it can take several days or weeks for his body to make and use all the germ-fighting tools needed to get over the infection [106}.

Based on technology of vaccine development, world has developed many vaccines, among which some are already given to the public. For today,there are at least 5 known vaccines against SARS-CoV-2: Novovax, Johnson and Johnson,

Asterzeka, Moderna, Sputnik, etc, (refer to table 2 for more information) with emergency usage permission [19,103,103a,104-107,112}

Table 2: Characteristics of today's vaccines against SARS-CoV-2 [19,105-112}

| № | vaccine | Characteristics | usage | reference |
|---|---|---|---|---|
| 1 | J&J | RNA | a shot intramuscular | [19,112 |
| 1 | Astrezeka | RNA | 2 shots intramuscular | [19,107} |
| 3 | Moderna | RNA | 2 shots intramuscular | [19,,109} |
| 4 | Novovax | | a shot intramuscular | [19,110} |
| 5 | Sputnik V | | A shot intramuscular | [19,111} |

4.7.2 Post vaccination's some drawbacks (Media) here under illustrated as they appeared in the news and social web pages:

[119} A person who was fully vaccinated against the virus that causes COVID-19 died of the disease in Texas, officials announced Friday.

One of the 15 deaths reported in Dallas County was an immunocompromised individual who had received two doses of a COVID-19 vaccine but was a solid organ transplant patient, Judge Clay Jenkins, the top elected official in the county, said in a statement.

[120} A North Carolina Walgreens mistakenly gave some people a saline injection instead of the COVID-19 vaccine.

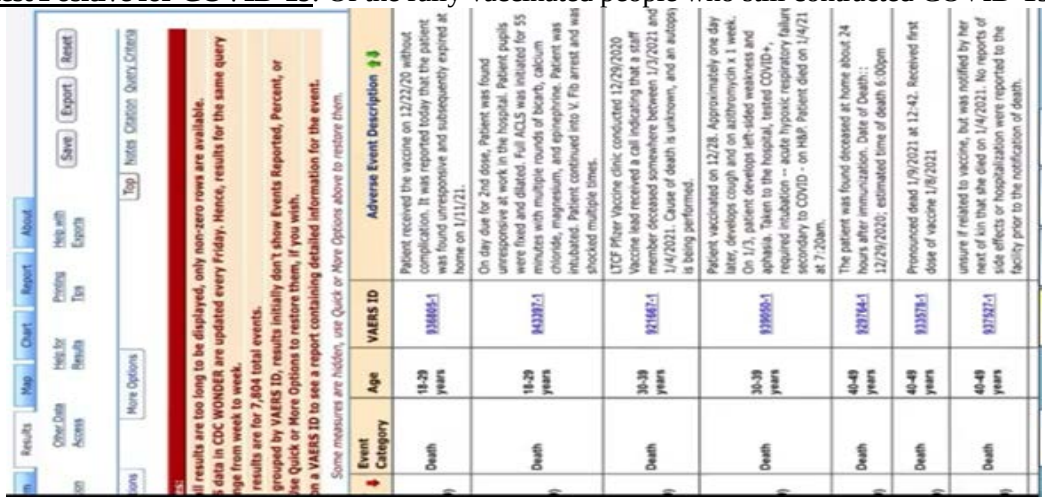
Federal agencies call for pause on Johnson & Johnson COVID vaccine after 1 person dies

[121} Authorities in the United States have recommended a pause in the use of Johnson & Johnson's COVID-19 vaccine "out of an abundance of caution", after six blood-clotting cases were reported in people who received the vaccine. The rare clotting problem is similar to the one linked to the Oxford–AstraZeneca vaccine. In a statement, Johnson & Johnson said it is working closely with medical expert to investigate the issue

[122} The US CDC are ramping up scrutiny of rare cases of COVID-19 in people who have already been fully vaccinated. The precise number of these "breakthrough infections" in the United States is unknown — estimates suggest it is several thousand, a tiny fraction of the 66 million people in the country who have been fully vaccinated. The rarity of these cases reinforces the message from public-health officials that COVID-19 vaccines are safe and effective. wu"There's nothing there yet that's a red flag," said Anthony Fauci, chief medical adviser to President Joe Biden. "We're obviously going to keep an eye on that."

Fully Vaccinated Person Dies of COVID-19 in Texas, Officials Say**April 17, 2021**

*As of April 15, more than 78 million people were fully vaccinated against the virus in the United States.* Roughly 5,800 Americans have contracted COVID-19 despite being fully vaccinated against the virus. **142 Fully Vaccinated People in Houston test Positive for COVID-19**. Of the fully vaccinated people who still contracted COVID-19, 74 died.




4.8. Why such draw backs happening?

This is because:

4.8.1 Although they have been declaredas efficacy, the recent types of vaccines may not effective!
4.8.2 Organism to which was administered the shot is not capable to produce adopted antibody (the required immunoglobulin), because, due to:
Well, if we are planned to answer for the 4.8.1 let at the end of "discussion section", for the second (4.8.2) question should have look for literature given. For this, the question by itself should be fractiond into three: Ability of the organism to produce immune cells that are developing the adopted anti body, age and the material (metabolites) from which the body can construct both adopted antibody producer cells and the raw material from which suchcells are going to prepare the antibody. Well, the ability of the organism to organize the producing processes may depend on the age, immune-compromised and genetic factors. Therefore, since it is obvious, no need to search for a data on this issue. The other thing is – the initial metabolites from which must be build up the antibody developers cell (T and B) and the metabolites from which they should develop the adopted antibody (specific immunoglobulin). Therefore, we were looking for whether there is any research, where raised the necessity of initial metabolites.
Certainly, there are works on vaccine boosters – repeating the same or different contented shot! For instance, a month ago, there appeared an article [105}. However, as a biochemist, this is not satisfied us. Hence, we suggest that the raw materials (initial metabolites for building the adopted antibody builder cells, enzymes and the antibodies themselves) should be administered at least as a supplementary. However, in our data search (looking for a research) on the issue, we couldn't encountered any data about this our third burning question of this work!
4.9 What to prescribe before, during and or after vaccination
Earlier, physicians strongly recommended what to take together with the prescribed drug-treatment. Scientifically, the supplementary to be administered ought to boost the positive side effect of the prescribed drug-treatment. However, today, what we are observing is almost each patient fairly familiar with the prescribed treatment. Pharmacists also do not ask clients why they ask a particular drug, even antibiotics are selling without receipts! A preursor for some adopted microorganisms like bacterial and viral strains! When we come to the vaccination issues, no literature on the recent types of vaccine, in which point out about any prescription to be taken before, with or after vaccination.

[18} discusses the comparative value of the techniques employed in preparing vaccines, and the use of adjuvants in improving the response.

4.9.1 Natural factors that may alter vaccine's activity

depends in part on the age and health status of the person getting the vaccine [97}, for instance, the type of pneumococcal vaccine you're given depends on your age and health [100}

As we have tried to raise on the above points, each B cell produces a single species of antibody, each a unique antigen-binding site. When a naïve or memory B cell is activated by antigen (with the aid of a helper T cell), it proliferates and differentiates into an antibody-secreting effector cell. Such cells make and secrete large amounts of soluble (rather than membrane-bound) antibody (refere to figure 6), which has the same unique antigen-binding site as the cell-surface antibody that served earlier as the antigen receptor [33}. Effector B cells can begin secreting antibody while they are still small lymphocytes, but the end stage of their maturation pathway is a large *plasma cell*, which continuously secretes antibodies at the astonishing rate of about 2000 molecules per second. Plasma cells seem to have committed so much of their protein-synthesizing machinery to making antibody that they are incapable of further growth and division [36}.

[97} B cell produces a single species of antibody, each a unique antigen-binding site. When a naïve or memory B cell is activated by antigen (with the aid of a helper T cell), it proliferates and differentiates into an antibody-secreting effectors cell. Such cells make and secrete large amounts of soluble (rather than membrane-bound) antibody (refer to figure 6), which has the same unique antigen-binding site as the cell-surface antibody that served earlier as the antigen receptor [33}. Effectors B cells can begin secreting antibody while they are still small lymphocytes, but the end stage of their maturation pathway is a large plasma cell, which continuously secretes antibodies at the astonishing rate of about 2000-3000 molecules per second [123}. Plasma cells seem to have committed so much of their protein-synthesizing machinery to making antibody that they are incapable of further growth and division [36}.

Synthesized exclusively by B cells, antibodies are produced in billions of forms, each with a different amino acid sequence and a different antigen-binding site. Collectively called immunoglobulin (abbreviated as Ig), they are among the most abundant protein components in the blood, constituting about 20% of the total protein [97} in plasma by weight. Mammals make five classes of antibodies: IgA, IgG, IgD, etc.[36,76a,100]

4.9.2 Initial metabolites that are necessary for anabolizing immunoglobulin (antibody)

[123} B cell can produce 2000-20000/sec. antibodies (refer to figure 11). Therefore, if one antibody weights X g, then 2000Xg/sXNantibody of body=2000XNg/second of protein or glucoprotein is necessary.

Thus, homeostasis of serum IgA requires a synthesis rate quite similar to that of IgG (21 mg•kg−1•day−1 for IgA versus 30 mg•kg−1•day−1 for IgG) [76a}. By contrast, in the various mucosa and exocrine glands, IgA production is much higher than IgG [75,76a}

4.9.3 calculation of the possible amount of initial aminoacids

Taking into account the mentioned above facts, one can calculate how many initial metabolites need to boost a vaccination. Assume, if 6.022X1023 molecules of IgA weight 380KDa and 6.022X1023IgG molecules weight 150KDa and a cell in general weights 1-12 – 1-11Kg then, neglecting the necessary enzymes and others metabolites, how much protein and carbohydrates needs for the body to produce adopted antibody within a second?

IgA has 6 days life span with 160Kda. More in mucosal sites. But most IgA created in secretary glands, for instance in mucus has 380000g/mol (consists two IgA) and IgG is around 150000g/mol

Insuline5800g/mol

If $6022X10^{20}$ molecules of IgA weights 380000mg. then 1 molecule of IgA weights Xmg:

$380000/6022X10^{20}=38/6022X10^{16}$mg in a second=$0.00631X10^{-16}$mg of IgA. Each second a B cell can produce $3000X0.00631X0.00631X10^{-16}$mg of IgA ($18.93X10^{-16}$mg of IgA). If a B cell life span is around 7 hrs, then it can produce $360X7X18.93X10^{-16} = 0.5X10^{-11}$mg of IgAwithin its life span

Then, let us assume that if there are 1,000,000,000 of B cell in an infected body, then they can produce totally 0.05g IgA throughout their life cycle. These 10billion cells are weighting = $10^{9}X10^{-12}Kg=10^{-3}$= 1g B cell can produce 0.05gimmunoglobulin A each 5-7hrs of life spine [103}.

All these metabolites in particular the amino acids to anabolize immunoglobulin; the enzymes that should facilitate the process and others ingredients are coming from what we eat! Therefore, unless we supply our organism with such raw materials the necessary immunoglobulinabundantly and on time cannot be formulated produced.

4.10 Possible sexual potency problem of COVID-19's patients

4.10.1 Biology of sexual intimacy

Although, no need to show how is important the oder scent of a sexual partner for facilitating mating desire, we can reflect some works that are related to it:

In the work [124},stated the perception of certain body odors may contribute to the concept of sexual pleasure.

[125} steroidal compounds -androstadienone, is present at much higher concentrations in male sweat and can be detected by women

[126} half of people who lose their sense of smell, through infection or injury, report negative impacts on their sexual behaviour

4.10.2 factors that influences on the potency

Certainly, as indicated in [124-1326} together with audio-visual factors, test-smell are one of main players to choose a sexual partner.

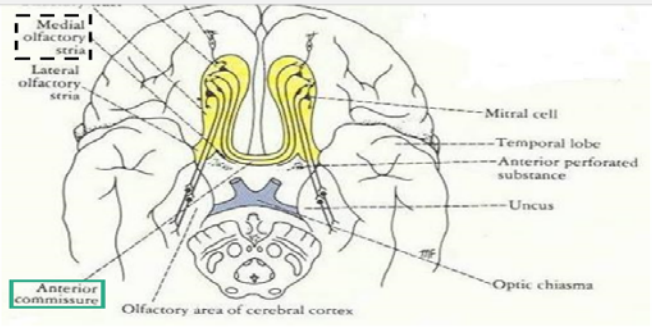
Therefore, let us see how we smell and identify smell scent (odor). It is known that olfactory nerve receptors are responsible for sending messages to brain [49,127,128}

Sensory nerve fibers arise from the valgus nerve, and from the second to fifth thoracic ganglia. The pulmonary plexus is a region on the lung root formed by the entrance of the nerves at the hilum. The nerves then follow the bronchi in the lungs and branch to innervate muscle fibers, glands, and blood vessels [73,74,128}.

The respiratory and nervous systems work together to identify odors in our environment. The cribiform plate of the ethmoid bone support the olfactory bulb and the foramina in the ethmoid give passage to branches of the olfactory nerves [33,128-130}

Figure 11: smelling process within the brain [77a}

2. *Medial root :*
   - crosses midline through anterior commissure and joins the uncrossed lateral root of opposite side.
   - It connects olfactory centers of 2 cerebral hemispheres.
   - So each olfactory centre receives smell sensation from both halves of nasal cavity.
   - **NB. Olfactory pathway is the only sensory pathway which reaches the cerebral cortex without passing through the Thalamus.**




Note: The lateral root goes to the same side while the medial root crosses to the opposite side.



4.10.3 Potency and COVID-19

4.10.3.1 Literature if any on the relation between sexual intimacy and COVID-19

4.10.3.2 Possible impacts of COVID-19 on sexual potency

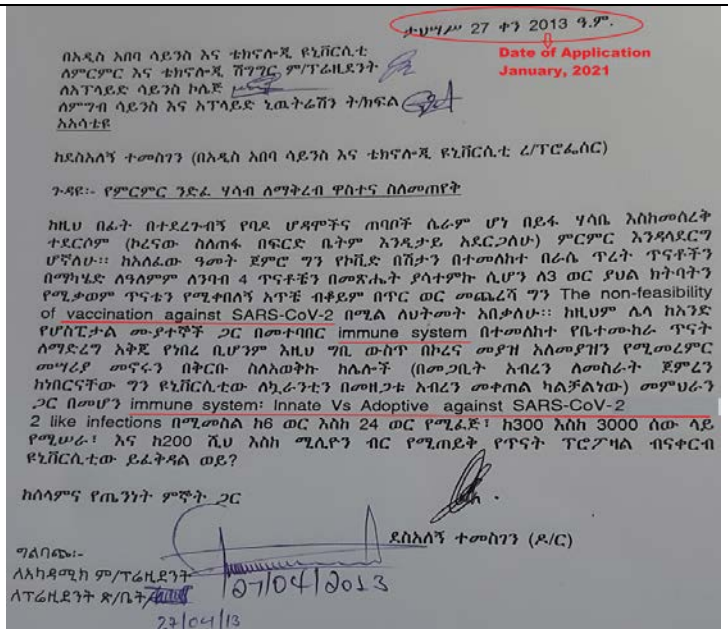
Although, we have had structured this our third puzzling question as mentioned in the above (4.10), since we couldn't found any work about the relation between decreasing sexual intimacy of recovered patients, we left this space (4.10.3) vacuumed.

## 5. Discussion

In this 21st century either there are, who want to spread a disease due to business orientation or as a pedagogic, we are afraid that most if not all scientists that are engaging in vaccine development that have immunology, biotechnology, molecular biology, microbiology, computer science, etc., based back grounds, may not have the concept of anatomy-physiology exceptionalities of the HRTT. Just, they may oriented only how to develop vaccine!

However, although, we have had published [9} a questions based hypothesis to be answered by vaccine developers and responsible international organizations, mainly addressed to WHO, none of them didn't responded. Because of which, we projected this 6th work to self approve. Nonetheless, we couldn't run our designed experiment> An experiment targeted the antibody count of vaccinated vs control and infected but not vaccinated. Again, due to political and or ethnical issues that are pressured on us here in Ethiopia, our application (refer to scanned cover letter) for a permission and assistance to handle the clinical-epidemiology based study didn't get positive support. Therefore, we have forced to perform only the review part, because of which we have this much huge manuscript!

Scan 3: Cover letter of application (support request) to run a research experiment on immune vs adoptive antibody



ታህሣሥ 27 ቀን 2013 ዓ.ም.
Date of Application January, 2021

በአዲስ አበባ ሳይንስ እና ቴክኖሎጂ ዩኒቨርሲቲ
ለምርምር እና ቴክኖሎጂ ሽግግር ም/ፕሬዚደንት
ለአፕላይድ ሳይንስ ኮሌጅ
ለምግብ ሳይንስ እና አፕላይድ ኒዉትሪሽን ትክፍል
አአሳቴዩ

ከደስአለኝ ተመስገን (በአዲስ አበባ ሳይንስ እና ቴክኖሎጂ ዩኒቨርሲቲ ሪ/ፕሮፌሰር)

ጉዳዩ፡- የምርምር ንድፈ ሃሳብ ለማቅረብ ዋስተና ስለመጠየቅ

ከዚህ በፊት በተደረጉብኝ የባዶ ሆዳሞችና ጠባቦች ሴራም ሆነ በይፋ ሃሳቤ አስከመሰረቅ ተደርሶም (ኮረናው ስለጠፋ በፍርድ ቤትም እንዲታይ አደርጋለሁ) ምርምር እንዳላደርግ ሆኖለሁ። ከአለፈው ዓመት ጀምሮ ግን የኮቪድ በሽታን በተመለከተ በራሴ ጥረት ጥናቶችን በማካሄድ ለዓለምም ለንባብ 4 ጥናቶቼን በመጽሔት ያሳተምኩ ሲሆን ለ3 ወር ያህል ክትባትን የሚቃወም ጥናቴን የሚቀበለኝ አጥቼ ብቆይም በጥር ወር መጨረሻ ግን The non-feasibility of vaccination against SARS-CoV-2 በሚል ለህትመት አበቃለሁ። ከዚህም ሴላ ከአንድ የሆስፒታል ሙያተኞች ጋር በመተባበር immune system በተመለከተ የቤተሙከራ ጥናት ለማድረግ አቅጄ የነበረ ቢሆንም አዚህ ግቢ ውስጥ በኮረና መያዝ አለመያዝን የሚመረምር መሣሪያ መኖሩን በቅርቡ ስለአወቅኩ ከሴሎች (በመጋቢት አብረን ለመስራት ጀምረን ከነበርናቸው ግን ዩኒቨርሲቲው ለኢራንቲን በመዘጋቱ አብረን መቀጠል ካልቻልነው) መምህራን ጋር በመሆን immune system: Innate Vs Adoptive against SARS-CoV-2 2 like infections በሚመስል ከ6 ወር አስከ 24 ወር የሚፈጅ፣ ከ300 አስከ 3000 ሰው ላይ የሚሠራ፣ እና ከ200 ሺህ አስከ ሚሊዮን ብር የሚጠይቅ የጥናት ፕሮፖዛል ብናቀርብ ዩኒቨርሲቲው ይፈቅዳል ወይ?

አሰላምና የጤንነት ምኞት ጋር

ደስአለኝ ተመስገን (ዶ/ር)

ግልባጭ፡-
ለአካዳሚክ ም/ፕሬዚደንት
ለፕሬዚደንት ጽ/ቤት

27/04/2013

27/04/13

However, although, we have had published [9} a questions based hypothesis to be answered by vaccine developers and responsible international organizations, mainly addressed to WHO, none of them didn't responded. ***Because of which, we projected this 6th work to self approve. Nonetheless, we couldn't run our designed experiment> An experiment targeted the antibody count of vaccinated vs control and infected but not vaccinated. Again, due to political and or ethnical issues that are pressured on us here in Ethiopia, our application (refer to scanned cover letter) for a permission and assistance to handle the clinical-epidemiology based study didn't get positive support. Therefore, we have forced to perform only the review part, because of which we have this much huge manuscript!***

### 5.1 Nature of SARS-CoV-2 and the COVID-19's pandemic

The gathered data (refer to the result section 4.1), indicates that this β-coronavirus, which took around 5 million lives [32} has exceptional structure: on its envelop there is S protein – glycoprotein [8,25,28-31} that spikes with the epithelial cell's receptor, and its another S2 protein fuses with the epithelial membrane's enzyme (ACE2) to endocytosis (refer to figure 1) into the epithelial host cell for further self-copy (replication). This means that the host cell also should be able to have a receptor-facilitator for these two envelope's twigs [23,24,28,29]. However, the environmental condition (temperature and pH) of epithelial cells in digestive, urinary, etc. tracts (there are different enzymes, immune cells, others organic compounds and high-constant temperature [25-27,117-119}), are not favorite to the virus, because, the envelope's glycoprotein and S2 protein's peptide, hydrogen, sulfide, ionic, etc. bonds, cannot resist a constant high ($37^{o}$) temperature (neglecting the natural defense mechanism – fever, which mostly caused by body's immune response; pH: water's, enzymes' and others chemicals actions to successfully fuse with such epithelial cells. Whereas, the lumen of the HRTT (refer to figure 4 and 10), where, there is moderate ventilation and relatively less: immune cells, organic, and others compounds that able to suppress the invading process (refer to 4.2 and 4.4 of the result part), the pathogen can easily infect HRTT's epithelial cells.

In short, unless the two: host's cells membrane and environmental factors are not soft, the virus cannot invade epithelia. Despite, such facts, some authors inform us as if the virus itself can directly damage nerve system, and even in the work [131,132} postulate that since, RNA's fragment of SARS-CoV-2's was found in the urine and faces of a patient, through facial and urine may transmit the virus!. Certainly, there may be dysentery diarrhea, if the virus may enter into the digestive system, and irritate to some extent. However due to high-constant temperature and others factors like pH and enzymes, etc., the virus cannot survive as a result it will be fragmented and these fragments (debris) may recall diarrhea, and found in the urine (if they are small enough to pass through villi) and facial samples.

### 5.2 Exceptionality of the HRTT's epithelial cells as a host of SARS-CoV-2

Additional to school program (books on anatomy and physiology), in the work [29,31,33,34,39} indicate that epithelial layers contain no blood vessels, so they must receive nourishment via diffusion of substances from the underlying connective tissue, through the basement membrane (refer to figure 3c,d and 10)

Based on our earlier background knowledge of anatomy-physiology of HRTT equally and literature that we retrieved (refer to 4.4 and 4.3) and the mentioned above (5.1) environmental factors, not all epithelial cells of HRTT possess the same characteristics. By their structure, location, and functions the epithelial cells of HRTT can be grouped into two: upper HRTT and lower HRTT epithelial cells.

**5.2.1 Epithelial cells of upper HRTT**

These epithelial cells, in particular those that are lined within the nostrils cavities are easily reachable for the virus, since they are near to the external atmosphere, a location, where the virus can contact with the host without losing time (no to travel long distance) and less (if any at all) barrier to pass through and with minimum chemical and others antivirus' factors (obstructions). Moreover, based on the data enclosed in section 4.2 and as mentioned above in 5.2, epithelial of upper HRTT; are Avascular [39,45-50,56,61}. Which means:-the blood vessels are far deep (figure 3) have less and non-constant temperature (have better ventilation) [25-27,117-119}; no excess enzymes; and others active organic compounds that can able to terminate the SARS-CoV-2's spiking process.

As seen in figures 3, lumen's epithelial cells cover up the lumen surface starting from nostrils up to the bronchiole tracts. With their cilia, in their turn are covered by mucus (figure 4d).

**5.3.1 Lymph**

As indicated in 4.4 and 4.4.2.1, the lymph collect dead cells, debris, antigens, etc. from upper HRTT (up to bronchi) and partially from lower HRTT, into nodes, from where the blood venues carry and transport for further metabolism-utilization. It also plays role in antibody formation [69}. Within the upper HRTT, also the nerve system [73,74} relatively seems to be active (refer to figure 6b). However, both lymph and nerve systems activities in the lower HRTT, particularly around and within the entire part of the alveolar sac (as expressed in 4.3.2 and figure 5D) are said to be minimum (if any at all).

5.3.2 Nerve system

Within the HRTT, its upper part has more nerve receptors, whereas the lower HRTT branched the nerve system up to the bronchiole, where ends only with irritation signal receptors that serve for coughing

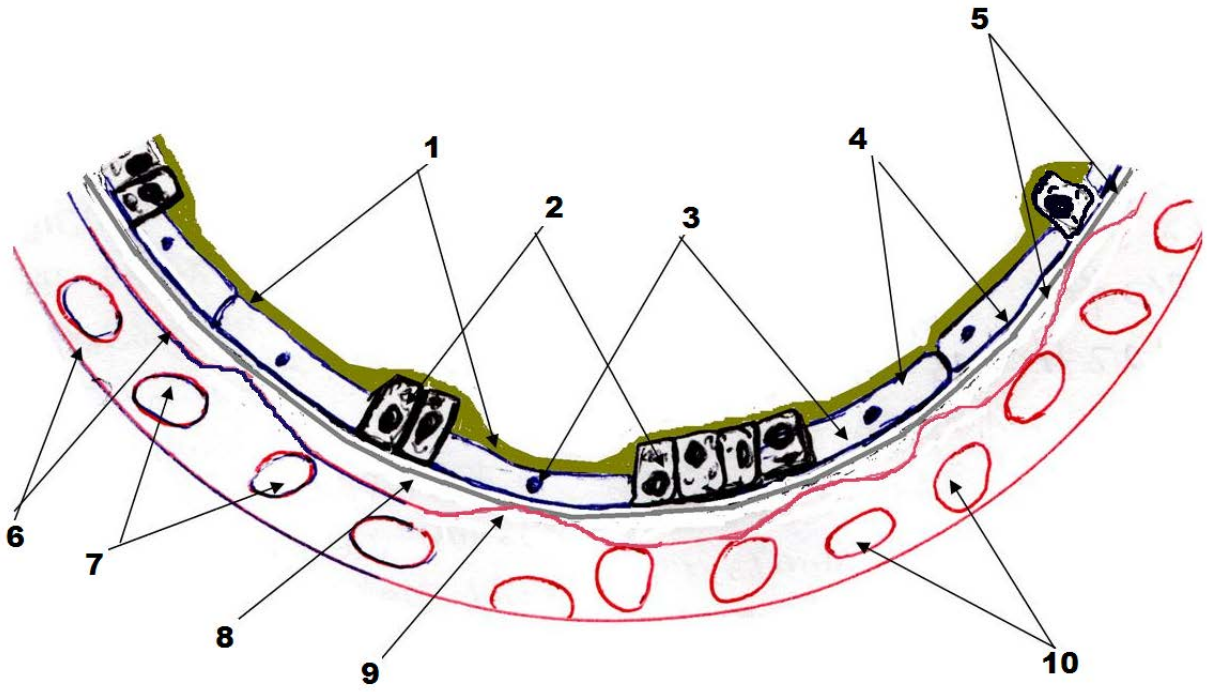
5.3.3 Blood circulatory system

The other issue is – the role of blood system! Certainly, in the upper HRTT's cells, like dendrite and mucus secreting cells more or less can exchange with blood system through interstitial fluids. But, the surface of the tracts' lumen that is covered by the epithelial cells (figure 3 and 7) may not have a direct contact with blood, because of which these epithelial cells are called Avascular [35,39,40,43,44,49,51,54,61-61d,63.68,79,128}. This means that anything couldn't directly exchange through interstitial fluid among the blood system and the epithelial cells. Although, such discontinuity may have advantage (if these epithelial cells were able to have a direct contact with the blood system, all atmospheric content was able to flood the blood or reversely blood contents can be mixed to the external (atmospheric) part – a situation that was able to lead into non closed blood system – a system that probably disappeared through evolution), the epithelial cells may not earn important metabolites from the body!

Such lack of exchange among the cells and blood system (Avascularity) more expressed within the lower HRTT (figures 2c, 8 and 11). All these show us that any metabolite like nutrients, moreover huge antibodies (for instance IgA of 380KDa or IgG with a size of 150KDa [} and refer to figure 9) cannot be conveyed by the blood system into these cells, in particular to the pneumocytes (with less protein, enzyme based membrane) through active or passive diffusion neither from apical nor basal side.

Perhaps, through natural selection (adoption) the distance between the alveolar basement and endothelium of capillary highly decreased. As seen in table 1 the thickness of the whole respiratory membrane can be presented as 0.7-2μM. Which means that the interstitial space lost ability to collect fluids with soluble-insoluble components, whereas around others types of cells the interstitial fluid may be 20μM [70,70a-70c}, a space that can enhance to accumulate fluid with different organic, non-organic metabolites for further diffusion exchange between cell and blood capillaries.

Figure 11: Our perception based n the data of “result” (4) on the pneumocytes and their surroundings




5.4

1. Surfactant
2. pneumocytes II
3. pneumocytes I
4. apical and basal membranes of alveoli
5. hypotheticalsac’s lamina
6. endothelium
7. deoxygenated red blood cells
8. respiratory membranes and interstitium space
9. sights, where periodically spike alveolus and capillary
10. oxygenated red blood cells



immune system during intact and infection-inflammation of HRTT

This section as of 4.3 and 5.3 is the main our research target:

**5.4.1 Immune issues within upper HRTT**

As mentioned above in 5.2 and 5.2.1 these epithelial cells of the upper HRTT have covered by mucus (see figure 3c,d), which traps mainly all sort of harm-unnecessary matters like dust, toxins, bacteria and viruses. Together, the cilia of the epithelia pull back such bodies from passing further into the alveolar sac (may be grouped these two as a mechanical defense system). Additionally, different immune cells also participating in phagocytic processes, killing-changing into debris and engulfing back into the esophagus (4.4,4.5,4.6) to be swallowed (perhaps swallowing may be a more active process for those animals that are not erectus) or addressing all what they captured to the lymph, which collect them in the nodes. The sum of work [77,82-84,89,103,104} inform us about the less functionality of immunoglobulin within the mucosa, since the blood system is relatively far away from the epithelia (refer to figure 3 and 4c,d), antibodies may not appear on the surface of epithelia on time and sufficiently. Authors [89} and the tendency of authors [14,70,76a,77} about the IgA presence on the lumen surface (on mucus) too. However, they contradictorily also inform us – it is not clear whether antibodies appear on the lumen surface of HRTT.

Certainly, if concentration of immune factors like cells and antibodies become high within the blood as in case of sweating through skin’s epidermis, immune cells and antibodies are appearing more during infection-inflammatory condition.

**5.4.2 immune issue within epithelial alveoli (pneumocytes I and pneumocytes II)**

When we come to the immune issue of alveolar epithelium, these cells probably evolutionally have obtained better defense. First of all, they are far away from the atmosphere content, secondly the mechanical and immune defense system of the

upper HRTT do not let foreign matters to reach to these important pneumocytes, and thirdly, their surface as seen in figure 2c and 11 is blanketing by surfactant and of course the AM are guarding them against any foreign bodies, even from T cells [40,84}. To exaggerate, the surfactant and the AM are frontier custodians (4.4.2). However, if inflammation due to infection or caused by atmospheric content (chemicals and microorganisms) and undesirable immune cells activity, these two naturally selected defense mechanisms may not have power. Therefore, if the surfactant destructed, by inflammatory products, dusts, bacteria and more if virus approach them, the alveoli will be damaged (refer to figures 6 and 7 and [9,24,60}). When they become broken continuously, for instance by virus, then loosing ability to be generated (converting Pneumocytes II into pneumocytes I [48,63,65}), they become a passage for any atmospheric content and inflammatory products that enter from the apical direction (from bronchiole and of their own contents). This content further can damage the respiratory membrane (figure 7, 8, and 11) and dissolve endothelial wall of capillary-venules, as a result of which, the entire mentioned above can enter into the blood system for further destruction of vital body's organs [7,33,39,40,78}. On the other side, from achieved data (4.4.2.1 and 4.4.2.2, 4.5) we can extract that at least the neutrophils (richest of protease) that are triggered [86-88} by AMs to be produced within the bone morrow, if they are excess, they can dissolve the endothelial wall of capillary and through the respiratory membrane may approach the basement of the alveoli (although rare, but a situation as ascarid can do with the lung!) to fill the alveolar sac with small molecules like water. On the other side from the alveoli apical side cytokines-interleukins, debris, that result thrombosis, etc of inflammatory based products too [65,71}, can start acting reversely: dissolve the capillary and mix with the blood for further organs' destruction-obstruction through embolism. In such condition the gas exchange process can be highly affected – an example of a situation that results pneumonia. Nonetheless, during our search for data, the [89,113} are against the [96} that questioned about the positive role of B cell within HRTT [69,82,89,92,96,113} more or less emphasis that antibodies are within the alveoli and mucosa of the HRTT. The same positive attitude about the role of neutrophils are raised in several works [20,86-89,87a,}. Anyway, such internal and external factors can start vandalism [89,96,131,132} on vital organs as a result which organs like heart and kidney failure occurs with its lethal results.

**5.5 immune system within HRTT**

As the collected data in 4.4 and 4.5 shows, during intact and inflammation-infection condition, immune system within the HRTT greatly differs from others tissues. This is because of the anatomy-physiology exceptionality of inner-lumen surface of not only HRTT but others tracts like digestive, urinary, breast, etc. However, among these tracts, the HRTT is diverged greatly. Although, we do not encounter literature, in which firmly expressed such remarkable differences, as we tried to mention in 5.2, 5.4, such variation depends up on the evolutional function of HRTT. Furthermore, differences are also significant among the upper HRTT and lower HRTT. It is obvious that as there is an alteration in anatomy, physiology and function – the immune system also differs:

5.5.1 Types of immune system and its activity within the epithelium of HRTT

The literature search reveal (section 4.4) that except mechanical defense, Immune cells like eosinophils, neutrophils, etc and antibodies like, IgA, IgG [71,76a,85,87,91,92,94,96} are said to be those that are identified within the upper HRTT, whereas, the AMs are dominating inside the alveolar sac.

5.5.2 Drawbacks in the immune based defense mechanism

Immune issues within the HRTT are well expressed in figure 6. However, as indicated in 4.4, 4.5, and 5.4 through natural selection – adoption of the environment and own activities have negative impacts.

As we indicated above and tried to visualize by using figures 3b, 7,8, epithelial cells of HRTT faces destructive impact from antigen, debris, dusts, immune cells, etc., in particular probably not well strengthen the epithelium's apical membrane and comparatively with poorly developed (proliferate evolutionally) interstitial fluid around the basement (2c,8 and 11), of the alveolus.

Anyway, as indicated in 4.4.2, if a non-preferable gust enter into the lumen of the tract through the mentioned above (5.2) mechanical barriers and approach the epithelia, then most probably do not have sufficient metabolites from surroundings less interstitial fluid (more than half surface (if any) of the epithelium has no direct contact with the fluid) and may

disappear. Furthermore, we didn't encounter and experimental based research data! Moreover, there is no any logic that functional fluid from the basal side of the alveolar sac, in particular within the respiratory membrane space cannot be antibody's entrance means into the pneumocytes,

5.5.4 the gas exchange sight – alveolar sac with its 20-30 alveoli

Although, due to our profession, earlier we have had encountered with them, we tried to collect any relevant data on the alveoli (respiratory) issues (refer to 4.2.2 and 4.4.2.2,5.2.2). These given show that neither the lymph nor the nerve system has any contact with the alveoli (refer to figure 2c and 11). Yes, this sight is a vital place, where external respiration – gas exchange takes place. Because of this perhaps, evolutionally such excess issues are omitted or were absent at all. More likely, this is why growth of these special epithelial cells – the pneumocytes completed their development until the age of 2-7 [48,49}. Probably, this may be the case that within the alveoli nourishment processes (metabolism) is not significant (if any at all) particularly in case of pneumocytes I, than of epithelium of upper HRTT. The only contact with blood is from their basement membranes (refer figure 2c and 10). Yes, as seen in figure 2c, the capillary firmly has a contact less thickness (refer to table 1) than others interstitial fluid thickness [132}. Moreover, these cells are not floating on the interstitial fluid – a fluid that contains every necessary/unnecessary materials and others cells. Rather, we tried to illustrate here under in figure 11 that alveolar cells are isolated from anything except gases and may be electrolyte and water molecules.

This shows that no possibility to be diffuse fluids into such less thick space with the sac - a contact that only guaranteed effective gas exchange (refer to figure 11).

**5.6 SARS-CoV-2 and adopted antibody within the HRTT**

Within this our 6th research project on COVID-19 issues, first of all answering - which cells are the host cells for SARS-CoV-2 was our one of the priority. Because of which as shown in 4.2.1, 4.4.1 and 5.2.1-5.3 in this section only epithelial cells in particular those that lined on the lumen of HRTT and pneumocytes are the only convenient target's of the pathogen.

5.6.1 the other burning-ablaze and vital issue is that can immune antibody: innate or adopted antibodies stop the virus before it invade the epithelial cells?

Although, all that pointed out in the introduction and result sections, together with the above mentioned in this section indirectly touch this issues, here under is going to be raised more in specified form:

For this, first of all we tried to collect data on those antibodies that are possibly can reach the lumen of HRTT during intact and infect-inflamed conditions: As collected data in 4.4 and 4.5, although the main defense agents for the HRTT are cells like macrophages, eosinophil, protein ILs of cytokines, neutrophils, etc., there we have got data on IgA, IgG, IgM that more or less can be appeared within the HRTT [75}. However, no where we encountered any research with $P \leq 0.05$ that shows a detection of the named antibodies in the lumen of HRTT from COVID-19's patients (because of which we have had launched this research to investigate whether the listed antibodies increase during and after vaccination.

Theoretically, as tried to show in 4.7, it is possible to be produced adopted antibody against SARS-CoV-2- antigen. Yes, although, due to business oriented direction, we do not want fully believe what recent vaccines developers are informing (if any), based on others successful vaccines imaginably, can develop a vaccine that able to recall adopted antibody within the blood stream. However, innate or adopted antibody (refer to 4.7) are transporting mostly (if not at all) within the blood system. Therefore, as discussed above in 5.3, 5.5 and 5.5.1, if we neglect the Avascular principle, may be the epithelia of the upper HRTT can be defend by antibody, before the pathogen spike with the host cell (which is under questions, since the IgA, IgG, etc. need time to pass the barriers (microavascular [49}) and approach the surface (apical part) of the epithelium. Nevertheless, in case of pneumocytes, except the macrophage, no other means of registered defense. In particular, based on the data (4.2.2 and 4.4.2),no possible way of transporting (address) innate or adopted antibody into the alveolar sac, where the pneumocytes are enclosed.

**5.7 Alternative to boost a vaccination**

The other factors for news about drawbacks (non success) of adopted antibody that are listed in 4.7.2 is vital not only for the given virus, but also for others pathogens against which can act adopted antibody principle (of course except the malaria [114}).

5.7.1 How and from what are forming adopted antibodies?

In the work [113}, stated that full protection from disease conferred by vaccination requires the presence of active immune effectors' mechanisms. And authors are questioning the vaccination effectively (feasibility at large)issue. Whereas, the [103} declared that there are antibodies like IgG on the lining epithelial cells. Although, at the end of their work, they forwarded 5 points, which leads to conclusion that no antibody on the epithelial cell surfaces. The authors of [89} are suggesting about the probability of antibody presence within the epithelial host cells.

As we pass through in 4.4 and 4.8 for developing adopted antibodies – the B cells that secrete antibody should be produced abundantly. Together with, there must be also more T cells to trigger B cells production. Since, this work is directing to the public too, among which there are unscientific negative understanding to vaccination's principle (refer to 1.2 of the statement of the problem), let us use simple popular way of showing how immunoglobulin proteins innate/adopted antibodies are forming (anabolism):

5.7.2 Using public based (popular) example

Assume, you are going to buy a cake for your child's birth day ceremony. For this, mostly you go to the bakerhouse and order your favorite cake. However, you should have to pay full or partial price in advance. This is because, it will be a guaranty for the shop that you will collect your order/purchase on time and or there should be expenses to buy some raw materials they should be used to prepare during the cake. So, fully or partially should be compensate the cost in advance. Main purchase must include: flour, sugar, salt, water, electric city, devices etc. and of course the wedge of the bakery himself and his assistances. Imagine, if any of the above is not available sufficiently and on time, you will not get your cake on time and qualitatively-quantitatively.

The same thing applies in cause of vaccination as follows:

Assume, you got a shot, a shot that instruct your body (as you instruct the bakery) producing adopted antibodies from amino acids, monosaccharide, water and others main initial metabolites. Need enzymes too (as electricity necessary for the bakery), different cells in excess amount like T and B cells, etc. (take them as the personnel of the bakerhouse, who are going to involve in cake producing activities). Transporter (lymph and blood system), etc. too are necessary in sufficient amount. Well, all of these components must be in sufficient and within the entire body on time (better before during vaccination, but must be mandatory after vaccination). Hence, the raw materials should be ingested or injected! Unless, we could afford it with such initial metabolites as in case of lack of flour, water, energy etc. of the baking house, our body also couldn't be able to produce the necessary antibody sufficiently and on time. From these comparison (baking a cake and producing antibody), one should synthesize a clue that to construct something need constructing materials. Next, to the raw metabolites, the second group of factor is – the constructer themselves: in case of baking, the bakery's quality and his assistances, in case of vaccination the bodies health like immune-compromised and age issues.

5.7.3 In general all depends up on the metabolism condition. To close this agenda, let us add an European proverb: it is hard to found a black cat in a dark room, in particular if it is not there!

5.7.4 Shot/jab repetition as a means of vaccination boosting

Of course, world practiced and now too practicing a shot options to boost vaccination against SARS-CoV-2. However, to the biochemistry context and human physiology-pathophysiology contexts we are afraid that the phenomena "body adoption" may play negative role. Even, additional to decreasing body (T cells) response to frequent vaccine's injection, the pathogen itself may have a chance to mutate.

**5.8 potency issues after recovering from COVID-19**

Every time when emerges new epidemic-pandemic, there erupts chose: fear of being infected and its existence. For instance, if we remember the AIDS, many still do not believe its existence, others were debating on its origin.

This pandemic is not exceptional, but relatively to HIV that is contaminated only through tight contact (mainly blood), the world reaction in prevention measures are not sufficient for this pandemic – infection that mostly is transmitting through air. In such diseases, what was must to be done is – as we informed almost a year ago [16,20}, organizing relevant bodies to make awareness among the nations and properly handling [option} the control-prevention measures. Instead, everyone is engaged in vaccination and as a football fan – following news on how many infected and how many died, whose vaccine is better, how many is vaccinated – all these are: the century's worst mess of advert not only against science, but also not in favor of human being's social value, which is leading to the life crumbling as an autumn leaves! Although, to study the post infection side effects of COVID-19, yet it is only 16 months, at least we have had to raise some issues. For instance, except its lethal results, the negative impacts that the disease left behind: loose of test; smell; and psychological trauma, after recovery are yet not highlighted.

5.8.2 For instance let us take the last – the smell issue: in the first line it seems simple, since every of us passed through such problem during influenza. However, if we come to the COVID-19 issue, lack of smell may be prolonged for several months. A dangerous situation, what we ourselves experienced 2 decades ago, when we were in danger of explosion from gas linkage in our kitchen! During that time, we were having flu, because of which we temporary lost smelling ability. And we didn't recognize the gas leakage in the kitchen room, until our mate enter and save us. Since then, as a biochemist we are interested about anosmia. Therefore, in this pandemic era, when a recovered patient can experience anosmia for a half of year! We can understand what this does mean to him and his family, in particular to the sexual partner!

5.8.3 What causes loose of smell?

Without any detail – the loose of ability to identify objects through their smell scent (odor) is the dysfunction of olfactory neuron of nasal cavities: Chemicals in a form of vapor enter into the nasal cavity, and irritate the neurons. The irritation-signals send to the brain and brain identified the object that is around us (mainly near the nose) and will take action to continue inhaling or escaping from such source (because of which we today's human species survived from being disappeared: earlier when in a certain location emerges a danger (carnivorousness, catastrophe or infection), our ancestors died massively, but those of them that are irritating by sulfides and ammonia (gases that are decomposed from dead corpuses' proteins) are escaping the dangerous place. We, most of us for whom these gases are not pleasant scent are inherited such sense (odor) from the survived ancestors.

Well, the issue here is not to talk about the gases ammonia and sulfide, rather, a postulation - what is the impact of loosing sexual partner's odor scent for recovered from COVID-19.

5.8.4 Experimental survey on smell (odor) as one of trigger of sexual intimacy

As everyone easily understands, smell is one of the triggers to have a sexual intimacy feeling [128}. Most animals, in particular mammals are using a smell test to choose their sexual partner for mating. To show for those who do not have countryside life, we designed a field survey - picturing animals' sexual coupling procedures. As a sample, we took dogs. After 5 days search and waiting moments, we have shot more or less a successful pictures of initiating sexual intimacy and coupling steps. As seen in the picture 3 below, the gold colored dog first trying to smell the genital part of the black dog. Then, after its brain that gets message from the olfactory neuron produce hormone for sexual intimacy., they are coupling (figure 9b).

Picture 3: Dogs sexual intimacy's main steps

Initiating – smelling (a) Coupling (b)

Certainly, humans too are typically passing through such steps. Because, without deeping into the process: signals from olfactory neuron reached into the olfactory cortex, from which distributes to other parts of the brain like hypothalamus. Additionally sex steroid hormones have receptors in all parts of the brain, which may react on the odor that transmitted by olfactory. If that so, what if, if one lost the ability to smell his sexual partner? In other words, what will happen if olfactory receptors destroyed by the SARS-CoV-2 actions? This question is our third puzzle, that highly concerns us to include within this article.

Nevertheless, as seen in 4.10, we didn't get any literature on the issue, because of which nothing to discuss without comparing secondary literature data.

However, since, this work is hope to be an open access, it is not ethical and moreover, we are not a licensed doctor to write in detail about what to do with such problem. Nevertheless, as a biochemist we can postulate the followings:

5.8.5 smell-odor affects in mate choice, since in most of us [124-126} it trigger brain to process sexual intimacy activities

5.8.6 intensifying or decreasing sex hormones' secretion and blood filling process of genital organs may depends on how often the process is experienced. Therefore,

5.8.7 sexual partners should understand that a sick or recovered from COVID-19, may temporary experiences not only weak physical fitness but also loose smelling, which leads to a temporary limitation in sexual potency – desire to coupling (mate)!

5.8.8 together this, what we shouldn't left is that not only the recovered, but also his/her partner may experience the oder's change of the recovered mate. This is because during infection changes metabolism, as result of which his body order probably can be changed.

5.8.9 at the end of the day, the above suggestions (5.8.5-5.8.7) must not be considered without approval of relevant and licensed specialists!

## 6. Conclusion

Each 3 questions, which are enclosed in a full manuscript (51 pages) of the study under a title: "***Three Puzzling questions on COVID-19: Are Recent Vaccines Feasible to Contain the Pandemic; What Measures can boost a Vaccination; and can SARS-CoV-2 affect Intimacy?,*** are comprised in 6.1; 6.2; & 6.3as follows:

### 6.1. Are recent vaccines that are stated as efficacy feasible to stop the pandemic? THREE groups of answers

6.1.1 Anatomy-physiology-biochemistry facts, based of which since March 2020, we are trying to alert the world

6.1.1.1 Muscular based injected vaccines may trigger immune B cells' production in the bone morrow. In their turn , they are developing adopted antibodies, which will circulate-transport into tissues only via blood stream

6.1.1.2 According to sections 4.3 and 5.3.3, epithelial cells, particularly the alveolus (pneumocytes) are **Avascular.**

6.1.1.3 No interstitial fluid around that can facilitate metabolite exchanges among capillary-venules and alveolus

6.1.1.4 Still now, there is no permanent and feasible vaccine against respiratory based pathogens

6.1.1.5 Organ failure during respiratory infection is due to the entry of mixtures from the alveolar sac

6.1.2 Certainly, human developed feasible vaccines like against polio and smallpox, but in case of those for corona:

6.1.2.1 Vaccinated obviously can be infected and infect others until his antibody stop (if any) the antigen-pathogen

6.1.2.2 Not everyone capable to develop adopted antibody for vaccination's response

6.1.2.3 If inflammation in the upper respiratory tracts is high, then its products can harm the pneumocytes. Thus,

6.1.3 The correlated answer for the question based our earlier hypothesis(are stated as efficacy vaccines feasible…?) are:

6.1.3.1 Corona reproduces itself only within epithelial cells (including the alveolar cells) of respiratory tracts

6.1.3.2 Adopted antibodies that are created (if any) and circulating have no means to reach to the host cells(epithelial cells)on time and sufficiently. In particular, it has no a direct way to contact (interface) with the pneumocytes

6.1.3.3 Although, we couldn't finalize our experimental design that was mentioned in the methodology part (section 3), in case if somebody do not agree with the 6.1.3.2, then should set the experiment (we can verify the design) to show the reverse. Unless, world must stop the vaccination mess. Because, if we neglect the destructions in the social, economic and political world's ties, as we have warned in our first research (June 2020) today's vaccines make us idle-ignorant, as a result which, lives are crumbling as an autumn leaf& SARS-CoV-2 itself is mutating! Therefore,

6.1.3.4 We suggest that if experimental vaccination is preferable, then for respiratory based pathogens may be better to try a local inoculation-spray mode of vaccination. However,

6.1.3.5 As we have tried to enlighten the world since, April 2020, and based on the 7$^{th}$ our study(due to non-acceptance a numerous pages for a single article and aiming to have more attention, we have separated it from this article)through epidemiological survey, for today - a 30 days global campaign: "stay at home, but if forced to go out **NEVER** wear off your face mask until return back" is **the easiest, cheapest and fastest but feasible prophylaxis measure to stop not only this pandemic**, but also helps to minimize (if not eliminating) others respiratory based pathogens!!

### 6.2 What Measures can boost a Vaccination?

6.2.1 Adopted antibodies are more protein and carbohydrate based immunoglobulin molecules. To anabolize them, need extra initial metabolites like amino acids and monosaccharide

6.2.2 For normal anabolize of adopted antibody, the organism must possess active metabolism

6.2.3 Boosting vaccination through repeating shot may cause adoption - dangerous body phenomena!

6.2.4 Instead, need supplementary of initial metabolites if not before, at least together or after the jab. Thus,

6.2.5 Either with the vaccine or separately must be ingested/injected special amino acids, monosaccharide and vitamins

### 6.3 Can COVID-19'saffect Intimacy?

6.3.1 One of the COVID-19 impacts is loose of prolonged smelling ability

6.3.2 Those, that are depending on Oder-scent of their sexual partner may lost intimacy activity if their olfactory receptors are affected by the COVID-19

6.3.3 Such patients and their sexual partners should be consulted by a relevant specialist

6.3.2 Although, it is not ethical and we are not licensed to forward intimacy issue within such openly accessible article, there can be others measures to be taken into account. Thus,

6.3.5 Both or individually, the sexual partners should consult with relevant specialist

**Let this work serves to memorize my sister Mintwab Temesgen and others victims of both COVID-19 and its today's vaccines as well!**

## 7. Bibliography

Here under are literature that consist text books, journal articles and news too. However, due to the issue is new, we have included internet based sources

[1} H Abut, A M Fillet, V Calves /1997/ what is virus/k Rev Part 1997 Mar 15; 47(6):602-7.

[2} AparnaVidyasagar / Live Science Contributor /January 06, 2016/ What are viruses// life Science / https://journals.sagepub.com › doi/pdf/10.1016./0146-6453(94)90039-6

[3} LottiTajouri/ 03.13. 2020/ What is a virus? How do they spread? How do they make us sick?

[4} Adrienne Santos-Longhurstedt. Jill Seladi Schulman / Whatis pathogen? 4 types and how they spread diseaseare pathogens: what you need to know about pathogens and the spread of disease / https://www.healthline.com

[5} Lumen / how pathogens cause disease / microbiology-lumen / https:/courses.lumenlearning.com

[6} SwapnilSubhashBawage, PoojaMunnilaTiwari, ShreekumaPillai, et. al. / Advanced in Virology Recent advances in Diagnosis, Prevention, and Treatmentof Human Respiratory Syncytial Virus / Journal Advances in Virology, Volume 2013 / www.hindawi.com/https://doi.org/10.1155/2013/595768

[7} Shari B. Brosnahan , Annemijn H. Jonkman , Matthias C. Kugler , John S. Munger , David A. Kaufman / COVID-19 and Respiratory System Disorders: Current Knowledge, Future Clinical and Translational Research Questions / https://doi.org/10.1161/ATVBAHA.120.314515 / Arteriosclerosis, Thrombosis, and Vascular Biology. 2020;40:2586–2597

[8} Sitemap / Vaccines that protect against infectious respiratory diseases / J. American Lung Association / https://www.lung.org

[8a}Roujian Lu, Xiang Zhoo, Juan Li, et. Al. /01.29.2020/Genomic Characterization and Epidemology of 2019 Novel Coronavirus: Implication for Virus Origins and Receptor Binding

[8b} Manuel Campos 1 , Dale L Godson /8.8.2020/ The effectiveness and limitations of immune memory: understanding protective immune responses / PMID: 12782062, DOII: 10.1016/s0020-7519(03)00066-3

[8c} Anne M. Davidson, Jan Wysocki, Daniel Batlle 20.09.2020 / Interaction of SARS-CoV-2 and Other Coronavirus With ACE (Angiotensin-Converting Enzyme)-2 as Their Main Receptor/https://www.ahajournals.org / https://doi.org/10.1161/HYPERTENSIONAHA.120.15256 \

[9a} Gelderblom HR. / chapter 14: Structure and Classification of Viruses / Book: Baron S, editor. Medical Microbiology. 4th edition / https://www.ncbi.nlm.nih.gov

[9b} Marc H.V. Regenmortel / Virus classification – an overview – Science direct / https://www.sciencedirect.com

[9} Dessalegn Temesgen Leye / Uncertainties on recent vaccines' feasibility against sars-cov-2; postulating new approaches on drug-vaccine development; and schematizing the possible options for investigating the origin of a pathogen (Interntional Journal of Innovation Scientific Research and Review IJISRR)

[10} IndwianiAstuti and Ysrafil / Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response / doi: 10.1016/j.dsx.2020.04.020 PMCID: PMC7165108 / PMID: 32335367

[11} OSCRice University / 20.12.2020 / The Lungs – Anatomy and Physiology: Respiratory System / https://opentextbc.ca › chapter › the-lungs

[12} Anatomy and Physiology_ The Relationships of the Respiratory System,

[13?} upper respiratory airways-physiopedia / https://www.physio-Pedia.com

[14} Anna Rudin,* Gerdt C. Riise, and Jan Holmgren /20.09.2020 / Antibody Responses in the Lower Respiratory Tract and Male Urogenital Tract in Humans after Nasal and Oral Vaccination with Cholera Toxin B Subunit /Infect Immun. 1999 Jun; 67(6): 2884–2890. /MCID: PMC96596

[15} Jerry R. Balentine, Siamak N. Nabili, and William C. Sheil / upper respiratory infection / https://www.medicinet.com

[16?} Dessalegn Temesgen Leye / Role of the Linkages between Mucus Secreting Intensity and age Differences for Being Infected by SARS-CoV-2 (eScientif volume 3 issue 1)

[17?} Melissa Conrad Stöppler, William C. Shiel Jr./ 26.04.2021/ Flu Vaccine Side Effects, Effectiveness, When to Get It, Ingredients & COVID-19/ MedicineNet / https://www.medicinenet.com › flu_vaccination /Medically Reviewed on 9/16/2020
[18} Thomas Francis, jr / 26.04.2021 / Vaccination against influenza / Bull World Health Organ. 1953; 8(5-6): 725–741 / PMCID: PMC2554195 / PMID: 13094502
[19?} CDC / 09.03.2021 / Understanding How COVID-19 Vaccines Work / https://www.cdc.gov/coronavirus/2019-cov/vaccines/different-vaccines/how-they-work.html
[19} WHO /21.04.21 / Who lists additional COVID-19 vaccine for emergency use and issues interim policy recommendations / https://www.who.int / news
[21} Dessalegn Temesgen Leye / Scientific Writings: Novel Approch in Bibliography-Citation Styles and others Issues to be applied during Publication (Global Scientific Journal GSJ)
[22} Sunit K. Singh ed. /10.11.20 / Viral infection and Global change (book, pp96-201 and 363-366) / John Wiley & sons.Inc /2014 / Ethiopian National Library
[23} Structure, Function, and Evolution of Coronavirus Spike Proteins / Journal List HHS Author PMC5457962 / doi: 10.1146/annurev-virology-110615-042301
[24} Jenny OhLauraKlivans /12.09.2020 / How the Coronavirus Attacks Your Lungs / //www.kqed.org › science › / May 5, 2020
[25} Ali Noman, Mohammed Aqeel, Sameer H. Qari / spike glycoproteibs: their significance for coronaviruses and receptor binding activities for pathogenesis abd viral survival /www.ncbi.nlm.mih.gov / pmc7764473
[26}. RenataTravassos da Rosa Moreira Bastos , Antonio Carlos RosárioVallinoto, and David Normando /16.12.2020 / Effects of temperature and humidity on the spread of COVID-19: A systematic review / Published: September 18, 2020 / https://doi.org/10.1371/journal.pone.0238339
[27} DidacMartí, JuanTorras, OscarBertran, PauTurondCarlosAlemán /16.12.2020 / Temperature effect on the SARS-CoV-2: A molecular dynamics study of the spike homotrimeric glycoprotein / https://doi.org/10.1016/j.csbj.2021.03.037 / Computational and Structural Biotechnology Journal. Volume 19, 2021, Pages 1848-1862
[28} Martina Bianchi, DomenicoBenvenuto, MartaGiovanetti, Silvia Angeletti , et. al. / Sars-CoV-2 Envelope and Membrane Proteins: Structural Differences Linked to Virus Characteristics? / BioMed Research International / 2020 /Article ID 4389089 | 6 pages | https://doi.org/10.1155/2020/4389089
[29} R&D system / ACE-2 is shown to be the entry receptor for SARS-CoV-2_ R&D Systems / https://www.rndsystems.com
[30} Mahmoud Gheblawi, Kaiming Wang, AnissaViveiros, et. al. / 14.09.2020 / Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System / PMCID: PMC7188049 / NIHMSID: NIHMS1583312
[31} Lauren Arcuri / 09.2020 / The Physiology of COVID-19 / The Physiologist Magazine September 2020 issue,
[32] CNN /04.22.2021 / Highest-ever number of new COVID-19 casees reported globally last week, WHO says
[33} Bryan Derrickson / 10.11.2020 / Human Physiology (book pp 298-301 and 625-631) / John wiley& sons. Inc. 2017 / Ethiopian NaionaiLaibrary
[34} LodishBerkMatsudira /Molecular Cell Biology 5th Ed (book) /
[35} Rice University / 149 22.4 GAS EXCHANGE: Chapter 22. The Respiratory System / Anatomy and Physiology
[36} Bruce Alberts, Alexander Johnson, Julian Lewis, et. al. / 16.12.2020/ Molecular Biology of the Cell.4th edition. /Bookshelf ID: NBK26884 / https://www.ncbi.nlm.nih.gov
[37} Lehninger-Principles of Biochemistry 4thEd 2004
[38} Chapter 11: Introduction to the Body's Systems: 11.3 Circulatory and Respiratory Systems / Concepts of biology 1st Canadian Edition /https://opentextbc.ca › biology › chapter
[39} Lumen / Epithelial tissues / Anatomy and Physiology / lumen learning / modules: the structure level of organization / https://corses lumen learning.com

[39a} AliceHuertas, David Montani, Laurent Savale, et. al. /12.08.2020 / Endothelial cells disfunction: a major player in SARS-CoV-2 infection (COVID-19)? / EurRespir J. 2020 Jul; 56(1): 2001634
[40} Robin L. Blumenthal, Dianne E. Campbell, Paul Hwang, et. al. / Human alveolar macrophages induce functional inactivation in antigen-specific CD4 T cells / Mechanisms of Allergy| Volume 107, ISSUE 2, P258-264, February 01, 2001 very important contents
[41} Ernest Z /05.04.2020 / Anatomy & Physiology: what are structure and function of alveoli , 15.06.2016 / https://socratic.org/questions
[42} the-flow-of-air-through-the-respiratory-system / http://blogs.egusd.net/eettalfonso/2012/02/17
[43} Britannica Encyclopedia inc. 2001/ Anatomy of an Asthma attack / 2001 Encyclopedia Inc.
[45} PratikshaPokhrel / Mechanism of respiration in human / microbiologynotes.com
[45a} Lumen / Boundless anatomy and physiology: Epithelial tissue
[46} ME Muse / physiology, Epithelialization-stat pearls NCBI bookshelf / https://www.ncbi.nlm.gov
[47} Soleas J.P. / Engineering Airways Epithelium /https://www.hindawi.com
[48} Gehr P. /10.09.2020 / Annexe A. Anatomy and morphology of the respiratory tract
[49} Peter H. Burri Human respiratory system - Blood vessels, lymphatic vessels, and nerves / https://www.Britannica.com
[50} Lumen / Anatomy and Physiology II /Module 7: The Respiratory System - Organs and Structures of the Respiratory System
[53} Jeffrey A. Whitsett, Susan E. Wert, and Timothy E. Weaver / Alveolar Surfactant Homeostasis and the Pathogenesis of Pulmonary Disease/ Annu Rev Med. 2010; 61: 105–119. / PMCID: PMC4127631 / doi: 10.1146/annurev.med.60.041807.123500
[54} Ursula Mirastschijski1, Rolf Dembinski and Kathrin Maedler / Lung Surfactant for Pulmonary Barrier Restoration in Patients With COVID-19 Pneumonia/ Front. Med., 22 May 2020 | https://doi.org/10.3389/fmed.2020.00254
[56} OpenStaxCollege / 13.01.21 / Epithelial Tissue – Anatomy & Physiology / Epithelial Tissue – Anatomy & Physiology - UH Pressbooks / http://pressbooks-dev.oer.hawali.edu
[57} Keith R. Porter and Mary A. Bonneville, An Introduction to the Fine Structure of Cells and Tissues, 4th. ed., Lea &Febiger, 1973
[58} Joanne L., Wright Andrew, M. Churg / 10.11.2020 / Macro and Micro structure of the Lung / Cliical Respiratory Medicine (4th ed) 2012
[59} Shama Ahmed, Aftab Ahmed /10.11.2020 / Epithelial regulation and Lung stem cells / Lung Epithelial Biology in the pathogenesis of pulmunary diseases / 2017 / https://www.sciencedirect.com
[60} Matheu C Morissette, Julie Parent, and Julie Milot / Alveolar epithelial and endothelial cell apoptosis in emphysemab: What we know and what we need to know / 20.09.2020 / Dove Press / https://www.ncbi.nlm.nih.gov
[61} Quara / what are avascular epithelial tissues? / https://www.quara.com
[61a} Avascular Definition & Meaning – Merriam Webster / Dictionary / www.meriam-webster.com
[61b} Respiratory Epithelium – an overview / sciencedirect /www.sciencedirect.com
[61c} Maina JN / Functional Morphology of the avian respiratory system, the lung-air sac system: efficiency built on complexity/ / https://doi.org/10.2989/OSTRICH.2008.79.21.575 /www.tandfonline.com
[61d} Is epithelial tissue vascular or avascular? / www.Study.com
[62} P. Colombo, G. Colombo, S. Cagnani, et. al. / Comprhensive Medicinal Chemistry II / Volume 5, 2007 / Doi.org/10.1016/BO.08-045044-x/00127-9
[64} YasminBuchackert, Sebastian Rummel, et. al. / megalin mediates transepithelial albumin clearance from the alveolar space of intact rabbit lungs /www.ncbi / the journal of physiology / PMC3497570
[65} MaithriSiriwardena, Eddy Fan /20.09.2020 / Descent into lung and heart failur: Mechanical Circulatory and Respiratory Support , 2018 / https://www.sciencedirect.com
[66} Lumen, Microbiology / Circulatory and Lymphatic System Infections: Anatomy of the Circulatory and Lymphatic Systems / https://courses.lumenlearning.com › anatomy

[67} Alberts B., Johnson A., Lewis J., et. al. /20.12.2020 /Molecular Biology of the cell. 4th edition: Blood vesseles and Endothelial cells /book / garland Science, 2002
[68} CliffsNotes / Anatomy and Physiology – Epithelial Tissue / https://www.cliffsnotes.com › tissues
[69} Heather D. Hickman / 08.08.2020 / Antibodies go with the lymphatic flow / Science Translational Medicine 06 Nov 2019: Vol. 11, Issue 517, eaaz7147 / DOI: 10.1126/scitranslmed.aaz7147
[70} Yao W, Shen Z,, Ding G. / 28.04.2021 / Simulation of interstitial fluid flow in ligaments. Couple / Comparision among Stokes, Brinkman and Darcy Models / Int J. BiolSci 2013; 9(10): 1050-1056 / doi.10.7150 / ijbs 7242 [70} Lymphatic System - an overview | ScienceDirect Topics / https://www.sciencedirect.com › topics
[70a} The interstitium – capillary Fluid Exchange NCBI Bookshelf / https://www.ncbi.nlm.nih.gov NBK53446
[70b}OdiseCenaj, Douglas H. R. Allison, Rami Imam, et. al. / Evidence for continuity of interstitial spaces across tissue and organ boundaries in humans / J. Communications Biology V. 4 art No 436 / www.Nature.com
[7c} Serge E. Parent / Mechanics of Fluid-filled Interstitial Gaps.Modeling Gaps in a compact Tissue /Biophysical Journal V. 113, Issue 4 /https://doi.org/10.1016/j.bpi.2017.06.062
[71??} Benjamin Stump, Benjamin Stump, Ye Cui / 20.12.2020 / Lymphatic Changes in Respiratory Diseases: More than Just Remodeling of the Lung?
[71??} Shan Liao, Pierre-Yves von der Weid / 16.12.2020 / Lymphatic System: An Active Pathway for Immune Protection / doi: 10.1016/j.semcdb.2014.11.012 / https://www.ncbi.nlm.nih.gov
[71?} Heather D. Hickman / 08.08.2020 / Antibodies go with the lymphatic flow / Science Translational Medicine 06 Nov 2019: Vol. 11, Issue 517, eaaz7147 / DOI: 10.1126/scitranslmed.aaz7147
[71} GöranHedenstierna, Marco Lattuada / 20.12.2021 / Lymphatics and lymph in acute lung injury / CurrOpinCrit Care 2008 Feb;14(1):31-6/ PMID: 18195623 DOI: 10.1097/MCC.0b013e3282f2f4b5
[72?} M Riquet, G Hidde\n and B Debesse /20.12.20 / Direct lymphatic drainage of lung segments to the mediastinal nodes. An anatomic study on 260 adults / J. ThoracCardiovascSurg / 1989 Apr;97(4):623-32.
[72} PranavKidambi, PranavKidambi, Anthony M. Lamattina, et. al. /20.12.2021 / Lymphatic Changes in Respiratory Diseases: More than Just Remodeling of the Lung? / American Journal of Respiratory Cell and Molecular Biology / https://doi.org/10.1165/rcmb.2016-0290TR
[73} John G. Widdicombe and Graham M. Sterling /20.12.2020 / The Autonomic Nervous System and Breathing / Arch Intern Med. 1970;126(2):311-329. }
[74} 20.12.2020 / The Neuromuscular Respiratory System: Physiology, Pathophysiology, and a Respiratory Care Approach to Patients / conference proceedings / Respir Care 2006;51(8):829–837
[76a} C. Pilette, Y. Ouadrhiri, V. Godding, J-P.Vaerman, Y. Sibille /20.09.2020 / Lung mucosal immunity: immunoglobulin-A revisited / European Respiratory Journal 2001 18: 571-588
[77} G M Green, G J Jakab, R B Low, G S Davis / 20.09.2020 / Defense mechanisms of the respiratory membrane / Am Rev Respir Dis / . 1977 Mar;115(3):479-514. / PMID: 320925
[77a} NawafAlKhudairy and JawaherAbanumy /Anatomy of the nose and olfactory nerve (lecture materials) /
[78} Kucukcelebi, Plopper, Johansson et. al / Asbestos exposure can lead to pleural plaques (chronic exposure) and asbestos bodies (acute exposure) / The anatomy and morphology of the respiratory tract 1983.
[79} AkitoshiTachihara / 20.09.2020 / Critical roles of capillary endothelial cells for alveolar remodeling and usual interstitial
[80} CDC / 09.03.2021 / Understanding How COVID-19 Vaccines Work / https://www.cdc.gov/coronavirus/2019-cov/vaccines/different-vaccines/how-they-work.html
[81} CDC / 09.03.2021 / Understanding How COVID-19 Vaccines Work / https://www.cdc.gov/coronavirus/2019-cov/vaccines/different-vaccines/how-they-work.html
[84} D H Strickland, T Thepen, U R Kees, G Kraal, and P G Holt /2.9.2020/ Regulation of T-cell function in lung tissue by pulmonary alveolar macrophages / British Society for Immunology / Immunology, 1993 Oct; 80(2): 266–272./ PMCID: PMC1422176 . PMID: 7903277

[85} E L Wissinger, J Saldana, A Didierlaurent& T Hussell / Manipulation of acute inflammatory lung disease / Mucosal Immunology volume 1, pages 265–278 (2008)
[86} Allen B. Cohn and Michael Rossi / 18.04.2021 // Neutrophils in normal lungs / American Review of respiratory Disease Volume 127, iaaue2p2
[87} Jinping Liu, Zhiqiang Pang, Fang Wang, et. al. / Advanced Role of neutrophils in Common RespirationDiseases / J. Immunol Res. 2017; 2017:7610278 / doi: 10.1155/2017/6710278 / PMCID: PMC5447318
[87a} Jeremy V. Camp and Collen B. Jonson / A role for neutrophils in viral Respiratory Disease frontiers / http://www.fronteirsin.org
[88} Liu Zhigiang Pang, Fang Wang et. al. / 18.04.2021 / Advanced role of neutrophils in common /https:://www.ncbi.nlm.nih.gov
[89} Atsushi Kato, Kathryn E. Hulse, Bruce K. Tan, and Robert P. Schleimer, / 04.2013 / B lymphocyte lineage cells and the respiratory system /J Allergy ClinImmunol. 2013 Apr; 131(4): 933–957. doi: 10.1016/j.jaci.2013.02.023 pneumonias /J. Nippon Med. Sch. 08.2006 / https://pumed.ncbi.nlm.nih.gov
[90} Karen Bohmwald, Janyra A. Espioza, Raul A. Pulgar, et. al. / Functional impairment of Mononuclear Phagocyte System by the Human Respiratory Syncytial Virus / https://wwww.frotierssin.org/art Doi.org/10.33389/fimmu.2017.01643
[92} Robert E. Sealy, Sherri L. Surman, Peter Vogel, Julia L. Hurwitz /20.09.2020/ Antibody-secreting cells in respiratory tract tissues in the absence of eosinophils as supportive partners, International Immunology, Volume 28, Issue 11, November 2016, Pages 559–564, https://doi.org/10.1093/intimm/dxw035
[93} Mark T Esser 1, Rocio D Marchese, Lisa S Kierstead, Lynda G Tussey, et. al. / 20.12.2020 / Memory T cells and vaccines / Vaccine 2003 Jan 17;21(5-6):419-30 / PMID: 12531640 / DOI: 10.1016/s0264-410x(02)00407-3
[94} B.B. Moore, T.A. Moore, G.B. Toews /6.8.2020/ Role of T- and B-lymphocytes in pulmonary host defences. /ERS Journals Ltd 2001. / EurRespir J 2001; 18: 846–856
[95} Akiko Iwasaki /12.10.2020 / Immune Regulation of Antibody Access to Neuronal Tissues / Trends Mol Med / 2017 Mar; 23(3): 227–245 / doi: 10.1016/j.molmed.2017.01.004
[96} Leen J. M. Seys, Ken R. Bracke, Caroline A. Owen, and FranceskaPolmeniro/ / B cells in chronic obstructive pulmonary disease: moving to center stage / American Journal of Physiology-Lung Cellular and Molecular Physiology Vol. 311, No. 4
[97} W. H. Freeman / Lehninger Principles of Biochemistry ( book, 2004)
[98} Samuel McKenize, Surat P (ed) / Eosinophil Functions / www.news-medical.net
[99} Daniel M Davis and Sheena Cruickshank / Coronavirus: how T cells are involved and what it might mean for vaccine development / June 11, 2020 / https://theconversation.com
[phys} Buresh R. /10.11.2020 / Essentials of Human Physiology (book, pp509-592)
[sp} Fang Li /28.04.2021 / Structure, and Evolution of Coronavirus Spike Proteins /Annual review of Virology vol. 3:237-261 /doi.org/10.1146/annurevvirology-110615-042301
[112}Johnson&Johnson /latest news invetigational COVID-19 candidate-jnj.com / https://www.jnj.com
[117} NHS / 26.04.2021 / Pneumococcal vaccine overview / https://www.nhs.uk
[100} Dennis J., Dietzen / Principles and Applications of Molecular Diagnostics: Immunoglobulin A – an overview / www.sciencedirect.com
[101} Robert E. Sealy, Sherri L. Surman, Peter Vogel, Jet. Al. / Antibody-secreting cells in respiratory tract tissues in the absence of eosinophils as supportive partners, International Immunology, Volume 28, Issue 11, November 2016, Pages 559–564, https://doi.org/10.1093/intimm/dxw035
[102} Akiko Iwasaki / Immune Regulation of Antibody Access to Neuronal Tissues /Trends Mol Med. 2017 Mar; 23(3): 227–245. / doi: 10.1016/j.molmed.2017.01.004
[104} Reynolds HY and Chrétien J /20.09.2020 /Respiratory tract fluids: analysis of content and contemporary use in understanding lung diseases./ DM. February 1984; 30: 1-103 /PubMed, Google Scholar
[105} optimize prime/boost vaccine strategies [bbost2} from www.frontierison.org

[105a} Dessalegn Temesgen Leye / *Role of the Linkages between Mucus Secreting Intensity and age Differences for Being Infected by SARS-CoV-2 (eScientific volume 3 issue 1)*

[106} CDC / Understanding How COVID-19 Vaccines Work / Mar. 9, 2021
[107} Lindsay R. Baden, Hana M. EI Sahly, Brandon Essink, et. al. / Efficacy and safety of the mRNA-1273-COVID-19-2 vaccine /NEJM
[108} Investigational COVID-19 vaccine candidate Phase 3 Ensable study /https://www.jnj.com/latest news
[109?} Annalisa Merelli /30.04.2021/ The founder of Moderna doesn't think vaccines are all that impressive /quartz/https://qz.com/2001718
[109} Astrezenka / COVID-19 vaccine Astrezeneka – European/ https://www.ema.europa.eu
[110?} novovax} Novovax /20.04.2021 / Novovax COVID-19 vaccine found to be 86% effective against UK variant / https://pmlive.comnovovax
[110} Kelley Lu, Holly Lutmer/ sputnik V Vaccine description / https://www.precisionvaccinations
[111} Dania Nadeem and Carl O'Donnell / 26.04.2021 / Novovax vaccine 96% effective against original coronavirus, 86% vs British variant in UK trial / Yahoo news www.yahoo.com / March 12, 2021, 12:06 AM
[113} Manuel Campos 1 , Dale L Godson /8.8.2020/ The effectiveness and limitations of immune memory: understanding protective immune responses / PMID: 12782062, DOII: 10.1016/s0020-7519(03)00066-3
[114} Dessalegn Temesgen Leye /2018/ Additional (4th) Option for Malaria Elimination Activities / https://www.OMICSonline.org / doi:10.4172/2161-0711-c4-041
[115} CDC / 26.04.2021 / Key Facts About Seasonal Flu Vaccine | CDC / https://www.cdc.gov › flu › prevent › keyfacts
[116} WHO / 26.04.2021 / Types of seasonal influenza vaccine / WHO_Europe _ Types of seasonal influenza vaccine / https://www.euro.who.int › influenza › vaccination
[117a} Young-Tae Lee, Ki-Hye Kim, Eun-JuKo, Yu-Na Lee / 26.04.2021 / New vaccines against influenza virus / ClinExp Vaccine Res. 2014 Jan; 3(1): 12–28 / doi: 10.7774/cevr.2014.3.1.12
[117} spike} Laporte M, Raeymaekers V., Van Berwaer R. et. al / 28.04.2021 / The SARS-CoV-2 and other human coronavirus spike proteins are finetuned towards temperature and proteases of the human airways / pubmed.ncbi.nlm.nih.gov
[118?} Hamada A. Aboubakr, Tamer A. Sharafeldin, and Sagar M. Goyal / Stability of SARS-CoV-2 and other coronaviruses in the environment and on common touch surfaces and the influence of climatic conditions: A review / TransboundEmerg Dis. 2020 Jul 14 : 10.1111/tbed.13707 / doi: 10.1111/tbed.13707 / PMCID: PMC7361302 / PMID: 32603505
[118} Rama S Akondy , Mark Fitch , SrilathaEdupuganti, et. al. / 20.12.2020 / Origin and differentiation of human memory CD8 T cells after vaccination / Nature 2017 Dec 21;552(7685):362-367 / doi: 10.1038/nature24633. Epub 2017 Dec 13.
[119?} OmidMalekahmadi, Akbar Zarei, Mohammad BehzadBotlaniEsfahani, et. al / Thermal and hydrodynamic properties of coronavirus at various temperature and pressure via molecular dynamics approach / Journal of Thermal Analysis and Calorimetry volume 143, pages 2841–2850 (2021)
[119} ZACHARY STIEBER /21.04.2021/ Fully Vaccinated Person Dies of COVID-19 in Texas, Officials Say
[120?} RenataTravassos da Rosa Moreira Bastos , Antonio Carlos RosárioVallinoto, and David Normando /16.12.2020 / Effects of temperature and humidity on the spread of COVID-19: A systematic review / Published: September 18, 2020 / https://doi.org/10.1371/journal.pone.0238339
[120} Bailey Aldridge /20.04.2021/ Some people got saline shots instead of COVID vaccine at a North Carolina Walmarks/ www.yahoo.com / April 18, 2021,
[121} The Washington Post / US advises J&J vaccine pause / https://natureus17.liat-manage.com/track/click?u=2c6057c528fdc6f73fa
[122?} Eurell, Jo Ann C.; et al., eds. / 20.09.20202 / Dellmann's textbook of veterinary histology. Wiley-Blackwell.p. 18.ISBN 978-0-7817-4148-4. / https://en.wikipedia.org

[122} Nature Briefing . email / 12.04.2021 / Investigating post-vaccination infections / https://nature.us17.list-manage.com/track/click?
[123} [M.J. Farabee /24.10.2020/ LYMPHATIC SYSTEM AND IMMUNITY /lymph and immunity.htm / http://www1.biologie.uni-hamburg.de}
[124} Johanna Bendas, Thomas Hummel, IlonaCroy / Olfactory Function Relates to Sexual Experience in Adults / Epub 2018 May 2. / PMID: 29721723 / doi: 10.1007/s10508-018-1203-x.
[125} J. Verhaeghe, R. Gheysen, and P. Enzlin / Pheromones and their effect on women's mood and sexuality/ Facts Views Vis Obgyn. 2013; 5(3): 189–195. PMCID: PMC3987372 / PMID: 24753944
[126} Emma Young / Scientists Study the Effect of Smell on Sexual Arousal /
[127} Victor M. Vulgar / Transcytosis to Cross the Blood Brain Barrier, New Advancements and Challenges / Front.Neurosci., 11 January 2019 | https://doi.org/10.3389/fnins.2018.01019
[128} Blood brain barrier Impermeable barrier that prevents large molecules (antibodies, albumin, and other plasma contents
[129} Jeremy M. Berg, John L. Tymoscko, LubertStryer / Biochemistry 5th ed. / W. H. FREEMAN AND CAMPANY
[131} Dessalegn Temesgen Leye /2018/.Additional (4th) Option for Malaria Elimination Activities.Global Infections Conference, November 12-13, 2018 Melbourne, Australia. https://www. OMICS.org
[132} C. John Sperati / Coronavirus: kidney Damage caused by COVID-19 /www.hopkinesmedicine.org
[133} / COVID-19 (SARS-CoV-2) in urine and semen / www.clinicaltrials.gov / NCT04446169