International Journal of Innovation Scientific Research and Review
Vol. 03, Issue, 02, pp.896-912, February, 2021
Available online at http://www.journalijisr.com

IJISRR

Research Article

ISSN: 2582-6131

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

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Received 10th December 2020; Accepted 20th January 2021; Published online 28th February 2021

ABSTRACT

Infectious diseases are still one of the mass killers. Among them the COVID-19, which caused by a virus SARS-CoV-2 (whose nature is yet not well investigated), is an old-new respiratory infectious disease. This pandemic already took around 1.5 million lives, destructing the socioeconomic structure of the globe. To combat it world is trying the possible-impossible measures. For instance, at the beginning of the pandemic, around hundred research sites were announced about their engagement in drug-vaccine discovery activities. Today, using the Media as a battle of field, developed countries change the vaccine discovery issue into business and political oriented race. Certainly, vaccines, as one of prevention based prophylaxis measures are used earlier too. However, we are afraid that world doesn't distinguish – against which pathogen can achieve feasible vaccine!! Yes, when Media announced as if tomorrow will be developed vaccine to contain COVID-19 pandemic, since March 29, 2020, we are twitting and publishing that for such type of virus and moreover within short of time frame, it is impossible to have practicable vaccine. Rather, we are saying: the cheapest, fastest but effective ways of preventive measures (not to be infected and not to infect others) are: scaling up the public's awareness on the nature of SARS-CoV-2; guiding nations on how to use properly the sanitation-hygiene based prophylaxis measures; seriously take into account the two decisive prevention measures: "stay at home (but not lock down)" and "safe (but not face) masking"; and we tried to caution that a vaccine discovery hope can idle the public and make him negligent for the pandemic. Therefore, after awaiting the results of vaccine discovery duel for 9 months, we decided to publish our biochemistry-physiology-anatomy and literature review based research work to point out our suspicion-doubts on nature and recent vaccines against the pathogen. In this work: in a scheme form, we list more than 13 possible paths on how to identify SARS-CoV-2's and others future pathogens' initial sources; we have elaborate 5+1 groups of scientific justifications, why recent vaccines may not be feasible against corona virus; and as a potential solution, we hypothesized how better to direct the drug-vaccine discovery's activities for such type of pathogens.

Keywords: IL, Cytokines, Blood clotting, Alveolar sac, Heart failure, Macrophages.

INTRODUCTION

Among human progresses in fighting against disease - discovering vaccination is comparatively new approach of healing. Vaccine idea: start dated to 18th century, transferred into using live attenuated vaccines, further grown into using genetic materials as DNA-RNA, and recently, switching into protein combination techniques become a front line [1,2,3,4]. Nonetheless, still there are failures in vaccination development, for instance, vaccination against tuberculosis [5,6] and HRV. Yes, if there is no try and error, no achievement in any field. Medicine too is not an exceptional. Though, we should have proud of vaccine development for instance against smallpox [7] is the pioneer in vaccination's victory. However,

Statement of the problem (study)

- Today, we are afraid that vaccine discovery changes its nature into a net source of business and political achievements [8}. For instance, 3 years ago, we have had encountered about vaccination project as if it is not only possible but also as the main prophylaxis measure against malaria infection! [9].
- The issue is complicating, when business oriented scientists and politicians are feed the media with their biased (if oriented to financial and political benefits) attitude: During the March-April 2020 of such race, there were 115 vaccines projects [10]. At that time, we were anxiety for what is going on the globe. Together such race, there were information as if face masking is not help to protect from being infected. Moreover, Media informed us that WHO itself was opposed face masking for those, who are not health workers and COVID-19's patients. What was aggressively adverting – only hand washing, as if it is the only proper prevention based prophylaxis measures (PPPM). In such battle, the Media become the field of duel: The issue is worsening, when journalists do not want to have scientific reference for what they are talking or writing about. Furthermore, public in such problem (like this pandemic) tends to follow the social media than what science says. Accordingly, we have negative assumption on how the media behaves during this COVID-19's pandemic [11].

Since March 29, 2020, we tried to forward our thoughts (refer to picture 1a-c) that to anatomy-physiology and biochemistry contexts, for antibody (if any at all) the lower human respiratory organs system (HROS) may not give adequate response. Based on this in our earlier two works, we tried to address to the globe through publication [11,12] that "For such type of virus and moreover within this short of time frame, it is impossible to have effective vaccine against SARS-CoV-2".

Picture 1: we wrote to a publisher (29.03.20), and to WHO (27.04.20 WHO), that others PPPM are betters than vaccination

picture 1a: On March 29, 2020 (see the circled in red) we sent email to a publisher. In it, we expressed "vaccines are not the effective solution" (enlarge it to see the underlined in red)
picture 1b: a Letter to WHO on April 27, 2020. In it we claimed that if world want to stop the pandemic, instead of vaccination: "proper public awareness"; "establishing (liberated from governmental-political influence), a task force members which are relevant specialists" that must take a responsibility; and "religious leaders should influence on their believers", etc are the first effective steps

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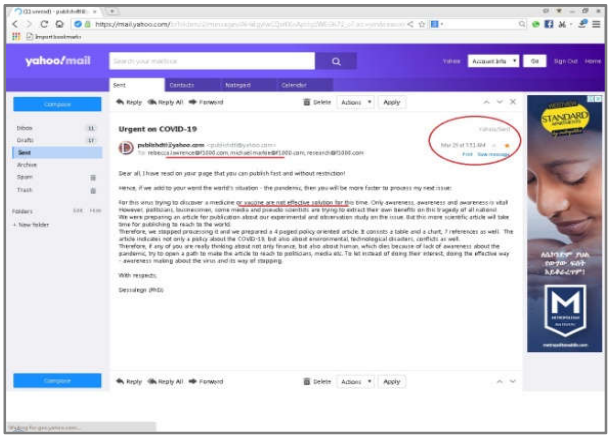
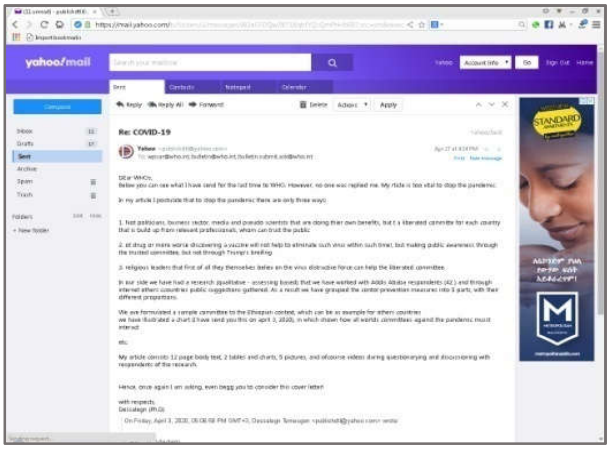
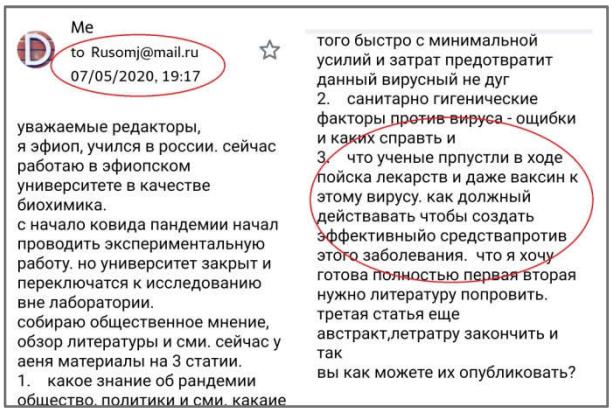


1a



1b

Picture 2: letters to a vaccine developer (May and October 15, 2020), in which we informed that vaccination against SARS-CoV-2 is not feasible

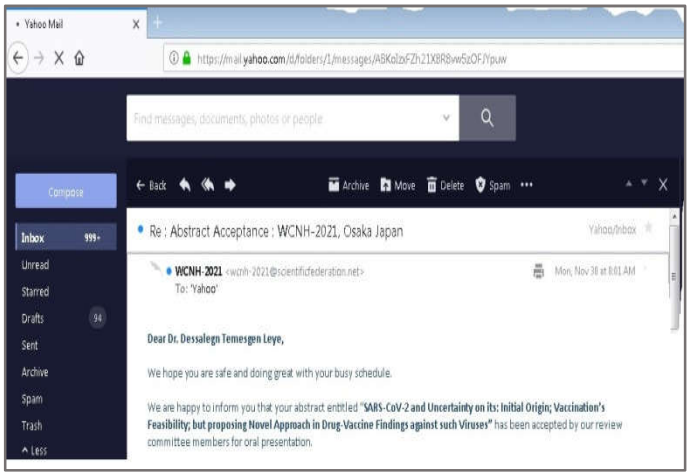


2a

2b

Picture 2a: letter in Russian language, sent on May 7, 2020 (see the circled). In it, we expressed that before starting vaccine development project, there must be issues, which should be solved (enlarge the picture and look into the underlined) Picture 2b: letter to one of vaccine developer. Sent on October 15, 2020. In it we informed that there are at least 4 reasons why it is impossible to have not only a feasible but even hard to achieve effective vaccine against such type of virus. Despite these reasons, two months ago 5 vaccine developers appeared as finalist of the battling with ready products. Well, what make us worry is that they do not want to illustrate what, how they produce and test their product. Certainly, sometimes biopharmaceutical companies and business oriented scientists for us are seemed like a bakery, who do not bother whether there is a good climate to grow the wheat!. Through, not mainly as a biochemist, but since, we are pedagogist, we couldn't neglect all what we think: today's youth do not want to think deeply, just they taking from the internet the same principle for different purposes - during our biochemistry course delivery for different types of students, we gave the same assignments-questions with the following common instructional phrase: "based on your future specialty". However, most of them give similar response: they just copy down similar data from internet. In the same way, we are afraid that developers just only focus on how to develop vaccine through instructions of a text book like in [13,14] or as instruction in the [15,16]. The issue more concern us, when we listen that vaccine developers are going to have special permission (without passing through essential testing procedures) to implement their products - a tendency, which is dangerous not only for this pandemic, but also for the whole scientific principle. Certainly, if vaccination is the only way! let it be. Although, we have had skeptical relation with its effectiveness, not to destruct the vaccine development processes, we decided to wait at least for a while, until there comes vaccination result. Because, as we have cautioned in our earlier work [11,17] that a hope from vaccination will make public ignorant from following the self isolation - following the prevention based proper prophylaxis measures (PPPM), no matter to have one or two shot, if it has no side effect. Therefore, instead of publishing the work, we applied and accepted to present it in a conference (refer below to picture 3b), but tried to contact manufacturers to forward them our thoughts-concerns (refer to picture 2a-b). However there is no response till now. Additionally, we were waiting any transparency as expressed a mRNA design in [18] on how vaccines are acting on the body, in particular how formed antibody (if any at all) can interact with the antigen in the lower respiratory organs' (we were expect information that can convince us). To the contrary, still there are no even full result of testing's phases.

Picture 3: one of the three email about the article's acceptance by conference organizers



Picture 3

at the end of the day, it is sad that in this 21st century, where human is trying to explore the universe, this by implementing the PPPM easily preventable virus, is crumbling million lives as an autumn leaf! Hence,

Aim of this research is to:

- Remind vaccine developers our doubts that vaccination is not feasible than others prevention based proper prophylaxis measures (PPPMs), about we have published [11].
- Broadly elaborate our concerns on vaccination's drawbacks: Yes, we have had prepared this article earlier on May, 2020 (refer to picture 2a). However, although, based on our biochemistry background, we were not agreed on the vaccine development race even among countries, we have hadn't confidence - not to be one of non-logical anti-vaccination (there were anti-vaccination against measles [19] to give this study for publishing. But, today, when many are openly opposing/suspiciously or at minimum skeptically or directly expressing [20,21,22] against vaccination, and even Dr. Fauci, although he is a part of authorities, tries to balance the issue by giving scientific arguments; when known journalists like Mr. Tucker Carlson of Tonight openly show his skeptic about the efficacy of vaccination). Certainly, there were baseless anti-vaccine movements like expressed in [19] during measles epidemic. Anyhow, we decided to publish it, but almost reformed the content, in particular the bibliography part fully changed, since many research articles on the issue are appearing these days.
- Give a clue that this work is advantageous (at least on raised issue in) not only for the current pandemic, but also for the future concerns on disease based disasters [11].

OBJECTIVES

To achieve the above mentioned aims, we constructed the followings 4 objectives (each of them can withstand a criteria of separate article) to the global scientists, not only, due to ethnical pressure on us here in Ethiopia, we ourselves have no possibility to perform experimental proofing our hypothesizes and postulations, but also the urgent pandemic's issues do not give time to publish them separately!

- Analyzing and postulating the possible initial sources/origin of SARS-CoV-2
- Sorting out the international criteria for appraise the effectiveness of vaccines
- Elaborating why it is impossible to have feasible vaccine for SARS-CoV-2
- Suggesting novel approaches in drug-vaccine discovery for: COVID-19 and similar diseases

METHODOLOGIES

As this work is relying more on analyzing with a literature review, to achieve our objectives, we will have:

- structure of the analysis-review design: can be classified into materials, tools and procedures
  - Materials: Gathered literature data, individuals' opinion, and Medias' information. Data collecting policy: Since the pandemic is relatively new, on May, 2020, at the time, when the first variety of this work was ready for publication, there were no enough research works about SARS-CoV-2. Therefore, we were more relied on Media information. However, today, we used at least half of literature from research articles, but most of the data are going to be retrieve from internet sources.
  - Tools: biochemistry concepts and epidemiological principles
  - Instead of comparing literature givens among themselves (Principle of literature review based research works [23,24], this work is a theory-analysis based with constructing several hypothesizes but, due to economical and ethnical pressing in Ethiopia, impossible to handle experiment based research) to be implemented as individual research objects. Hence, the tools are consisting the biochemistry and anatomy-physiology principles.
  - Procedure:
    Analyzing the gathered data (materials) Vs to the biochemistry-anatomy-physiology contexts and epidemiological principles, filtering (leading) them to the reality/facts, and looking for (selecting-sort outing) - what to include in the conclusion-recommendation part of the work.
  - Exceptionality of terminologies to be used within this article Must be list out and mark their meanings, which must serve within the boundary of this work
  - After raw data collection (Result – section 4)
  - Aiming to find solutions for the mentioned problems (refer to the statement of the problem (1.2)) through the objectives (point 2.1-2.4), we should organize the rest 3 sections as follows: the discussion parts are orienting at least on the 4 objectives, whereas, the conclusion and the recommendation parts may be shorten up to three parts (the second and the third objectives may be combined together into a single) or expanded into 5 subsections (points) in each of them.
- Types of data on which this work is going to be focused will be structured as follows: This article will have the followings 5-8 sections: introduction, objective, methodology, results, discussion, conclusion, and bibliography or although for a literature review, it is not advisable, some of them can be paired like introduction-objectives, methodology, result-discussion, conclusion-recommendation, to make the in-text body easily understandable and to make easy to cite any issue within the in-text bodySARS-CoV-2: nature, as a pathogen in particular We will collect data about: the biology (nature) of SARS-CoV-2; its initial source/origin; COVID-19's symptoms; statistical data of infected, cured and death within a year (in table or bar graph form); and SARS-CoV-2 as a pathogen, etc.
  - Measures that are taken and taking against COVID-19 collecting data on how battled and battling against viruses, in particular how are the PPPM for respiratory based infectious virus pathogens: PPPM; treatment; and control measures to combat the COVID-19's pandemic
  - vaccination to combat SARS-CoV-2's pandemic
  - what is vaccine; international criteria to recognize a vaccine as an effective, efficacy and feasible; etc.
  - is vaccination against SARS-CoV-2 feasible for such type of virus what kind vaccines, how they are acting, sites that they should impact on and are these sites easily available for the vaccine's antibody, the exceptionality of the anatomy-physiology of HROS); etc.
  - are there alternative novel approaches to combat COVID-19

RESULTS OF COLLECTED DATA:

Exceptional terms' meanings within this article

Some terms (scientific words), whose definitions must be the same throughout the in text-body at least within this work should be highlighted: This day, if you have a pal Pay card, you can publish any content in a known journal that has Scopus indexation [25] and others. Because, of the "any content" we encounter even at the language-terminology level (no control-peer review on how to use scientific words), as a result, which we even confused on known scientific terminology meanings. Therefore, here under listed some important but with temporary meanings that we are using inside the text-body:

pathogen – microbe (bacteria or virus) that can destruct the normal human metabolism;

antigen–part of pathogen or result of its biochemical reaction's product, which may induce metabolism disorder in the host organism

antibody – protein based specific organic molecules (Ig – immunoglobulin) that are produced by the victim organism (host) to the response of antigen/pathogen's biological actions

alveolar sac is a sac like end (base) part structure of a lung in which the two types of alveolar cells – the pneumocyte I (type I) and pneumocyte II (type II) together with the macrophage cells are included

alveoli/alveolar or alveolus is the specific epithelial cells (pneumocyte I and II) within the alveolar/alveolus sac

effective– a positive desired result at least within in vitro

efficacy– a positive desired result both within vitro and vivo

feasibility – Additional to the efficacy, should contain positive impact on the socio-economy beneficiary

origin – the start place or biological source of a living thing, for instance the initial of a pathogen

picture – an image, which is prepared with a help of camera or scanner

figure – formula or scheme on a paper or screen which is drawn by hand or with a device, for instance mathematical, physical and or chemical, formulas.

chart – a figure like scheme which can be in circle form (pie chart), line (with arrows, others shapes connected each other and lines) or graph form that represent a quantity-quality with a ratio/scale

SARS-CoV-2: nature, as a pathogen in particular

Biology: nature of SARS-CoV-2

Well, although as a contagious study of virus's nature was not enough at the beginning. Recently, there appeared works like [25,26,27], in which one can retrieve more or less some data. **Additionally:** SARS-CoV-2, causing severe disease in about 15% and death in approximately 0.4%, due to diffuse alveolar damage featuring intra-alveolar edema and lymphoplasmacytic infiltrate. SARS-CoV-2 enter into the body through nasal and oral cavity. The virus invade the epithelial cells of HROS. It mostly spikes with epithelial cells through their membrane, in particular spike to angiotensin-converting enzyme 2 (ACE2) [28,29] Then its capsid endocytosis into the cytoplasm of the host cell. There the RNA of the virus will attach to the host cell's ribosome as the mRNA of the host cell doing [29,30] for further processing to produce several virions. After, bursting the host cell (because of the pressure that caused by additional viruses the volume of the host cell increases as a result it bursts (torn apart and the virions released and invading others normal host cells. SARS-CoV-2 is a single-stranded, positive-sense RNA, enveloped, helical virus that synthesizes 4 structural proteins: Its S1 subunit mediates cell entry by binding to ACE after "priming" by transmembrane protease serine S2. Given its size, location, and essential function, spike is predicted to be a key target of antibodies [25,28,29,32, 33]. However, there are information that as if not only the epithelial cells of the HROS, but also mouse models revealed that intranasal administered SARS-CoV enters the brain primarily via the olfactory bulb, followed by rapid transneuronal spread to connected areas, including the thalamus and the brainstem [34] or in [35,36] informed that the virus can invade endothelial cells!

Initial source/origin of SARS-CoV-2

Ways that are applied in identifying the origin of a pathogen, in particular of SARS-CoV-2 deeply understanding the reason from where emerged not only infectious diseases, but also even chronic - is the half way of solving a disease related problem! Yes, not only for infection (communicable) diseases, but even for non-communicable diseases, identifying the source of the pathogen is the third if not half of the way to stop a disease. Therefore, identifying the exact origin of the SARS-CoV-2 is necessary even for the future. Data on the origin of SARS-CoV of 2003 and MERS-CoV serves as a basement to assume about the origin of novo corona virus SARS-CoV-2. However, there are also thoughts as if the SARS-CoV-2 is a result of laboratory manipulation. Certainly, it is not new that many countries are armed with a biological weapon, or when to the sake of science – during experimental study may appeared a pathogen, which because out of control can became pathogenic. On this probability, the USA and China have had a dispute. Except relying on SARS-CoV of 2003 and MERS-CoV of 2012/3, yet no one show the exact origin from where this pathogen appeared. Nevertheless, the research data and Media information on its source are collected: We have assess literature given, where there are information about possible source (from where begin) of the pathogen SARS-CoV-2. The collected literatures lead us to generalize – suggest its source as: bat, pangolin, seafood etc, however most of the researchers' agreement tends to zoonotic character [3,37,38,39,40]. Reversely, there are Media information [41,42,43,44] as if the virus developed within experimental laboratory: issue on which USA president have had disputes with China!

SARS-CoV-2 as a pathogen and the disease COVID-19

SARS-CoV-2, causing severe disease in about 15% and death in approximately 0.4%, due to diffuse alveolar damage featuring intra-alveolar edema and lymphoplasmacytic infiltrate [25,28] Cause: The COVID-19 is causing by a contagious pathogen β-corona virus – sever acute respiratory syndrome β-corona virus 2 (SARS-CoV-2) [25,34,41]

SARS-CoV-2 inflectional symptoms

Under the "symptoms" its definition: asymptomatic, mild, moderate, severe and critical care help full to identify the type of infection and its impact. Therefore, the exact identification of these symptoms is the second decisive factor (after the origin identification task) to combat both communicable or non-communicable diseases. However, regarding to SARS-CoV-2 yet little effort has done to characterize its symptoms and destructive roles, because impossible to have universal symptoms as the: virus has no constant nature; victims are different in age, health, location-environment, and genetic, social interaction-cultural factors, with its hidden (Ebola is better to be discovered since it is visualize), etc. If symptoms were universal for all patients, then its spreading rate was able to be minimized (if not abolished at all). Anyway, Symptoms: sneezing, mucosing, coughing, headache, fever, short breathing, weakness, etc. are indicated in many literatures, among which [25,34,41,42,43] can be taken as

references. If fever; short breathiness; and weakness, then may lead to lethal end [25,44]

Role of proper symptoms' establishment

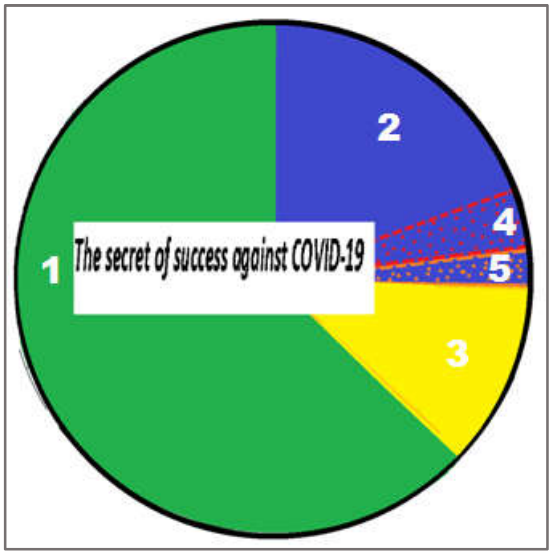
Anyhow, if we properly understand the symptoms, we can take appropriate measures for treatment. For this, it is better to have a medical test, whether there are symptoms or not. Therefore, recently there are two types (swab (PCR test) and blood samples) of technology based detecting [33,49]. However, we again hypothesize that both techniques have drawbacks: during swab sample taking, there may not be found the virus and or its debris on the nasal or oral cavity; we are witnessed when a nurse is taking swab sample from the lower part of oral cavity, where there is enough temperature and enzymes that do not let the virus to reproduce itself (can kill) or terminate its growth [12]; even we have passed through a webpage, in which there is an instruction how and from where to take swab - only from nostrils. The other issue is that, as we have informed in our earlier work [30], mucus may not let the virus to spike with the upper HROS's epithelia on the nasal or throat part may not give the virus a chance to spike with epithelia of upper HROS, but by directing to the alveolus sac it infect the pneumocytes cells [25,47,50,51], a situation that cannot give a chance for swab sampling to reveal the infection.. Just may pass and enter to the alveolus sac for further replication through invading the pneumocytes (the issue that was the main reason why we studied this work). The same faults can be to the blood testing issue, because, not everyone can produce antibody (adopted) against the antigen, as a result, which may achieve false negative result. What next after: Elaborating SARS-CoV-2's biology; investigating its origin; and identifying its main symptoms? We suggested and suggesting since March 29, 2020 (picture 1 and 2) and with published works in [11,12,30] to stop (if not abolish) this pandemic is implementing properly the easiest, fastest, and cheap, but feasible way of stopping this pandemic Scale up the appropriate awareness on how not to be infected, train on the PPPM issues; isolate the infected not to infect others; and of course treat them [11]! Rather, what world now engaging in a fascinated manner is vaccination!, the reason that forced us to prepare this work. Therefore, let us look through the vaccination issue

Role of Vaccination

In our earlier work, we too didn't neglect the vaccination prophylaxis measure, even although it relates to PPPM, we separately indicate it. However, due to the natures of both of the SARS-CoV-2 and its host, as seen in our pie chart (refer below), for vaccination measure we gave it the least portion (5th place) in battling activities):

- Prevention options against a disease depends on its nature, whom and how it infect, etc. However, all measures can be grouped into: PPPM and drug based treatments etc. As we continuously trying to address [disclosing}, for such virus, the easiest, cheapest and with fastest outcome is - the accurate usage of the prevention based prophylaxis measures.
- Proportion (activities load) of measures against the pandemic As we tried to show in the pie chart form, we can group the whole process of combating the pandemic into 5 sections: PPPM, studying the nature of the pathogen, treatment(drug) and vaccine developments. Yes, as seen in the pie chart the vast portion is

Pie chart: proportions of different activities to contain the pandemic



Adopted from [11]

In this pie chart: The PPPMs (№ 1) is the largest portion. This portion is the largest volume of work, which represents the four prophylaxis measures (the "stay at home", "face masking", "distance keeping" and "proper usage of hygiene-sanitation"); № "2" (the blue color) represents "study of the SARS-CoV-2's nature, searching for drug and vaccine development (although vaccine is one of the 5th PPPMs, we included it to the research part; and the yellow; and № "3" is the third volume of the whole against COVID-19 works that goes to treat already infected If we properly take into account the four groups (neglect vaccination) of PPPM: "stay at home"; for those who couldn't stay at home – "safe masking" covering the mouth and the nose (only through which the virus can enter into the body), until we return back to home; the "safe distance" keeping; and "perform proper hygiene-sanitation measures" like hand washing, disinfecting outer garments, including shoes etc. However, world now is engaged in vaccination part of combat's PPPM. Well, yes, one of these PPPM is vaccination, as seen in the pie chart the 5th, we gave it the least portion. However, as 6 months ago, when we were roaring [11] that if we want to cut the COVID-19's prevalence stay at home or face masking should be prioritized, world was focusing on hand washing (although in [35] inform us as if endothelial cells too can be targeted for the SARS-CoV-2; the authors of [34] too propose the nerve cells as a possible victims; and the article [35,52] offer us as if the virus can survive the body's temperature, mechanical and enzymatic (catabolic) digestives to be infectious through faeces!!), if we carry a kilogram SARS-CoV-2 with our hands, it couldn't infect us, unless we transfer even one virus into nasal or oral cavity) and today also world shifted into vaccination style! Thus, is vaccination feasible?

Vaccination and SARS-CoV-2's pandemic

- History and results of vaccine development
  The known start time to a vaccination type of healing dated to the 18th century, since then vaccination grows and till now hundreds tried, but around 20-30 types of vaccine have satisfaction (table 1) [2,10,21,31,35,53,54,55,56,57],
- World's success in vaccine development in table form

Table 1: vaccines' samples, most of which are transmitted through air and direct contact

Disease	Spread through	vaccine
Chickenpox	Air, direct contact	varicella
Diphtheria	Air, direct contact	DTaP
Hib	Air, direct contact	Hib from haemophylus
Hepatitis A	Direct contact, contaminated food or water	HepA
Hepatitis B	Contact with blood or body flood	HepB
Influenza (flu)	Air, direct contact	Flu vaccine
Measles	Air, direct contact	MMR
Mumps	Air, direct contact	MMR
Pertussis	Air, direct contact	DTaP
Polio	Air, direct contact, mouth	IPV
Pneumococcal	Air, direct contact	PCV13
Rotavirus	mouth	RV
Rubella	Air, direct contact	MMR against rubella
Tetanus	Through cuts	DTaP

Adopted from CDC document: Immunization schedules / https://www.cdc.gov/vaccine

Current antiviral vaccine designs can be described as falling into 2 camps: protein based or gene based [25,53,54]. Protein-based vaccines deliver the immune system–stimulating antigen to the body. This category includes whole-inactivated (killed) antigen, as in the polio and flu shots, and subunit vaccines and virus-like particles, like in the hepatitis B and human papillomavirus vaccines (table 2).

Table 2: samples of vaccines list, based on their design technology

Types of vaccines	Name	Types of vaccine	Against which disease
Live, attenuated	Measles, mumps, rubella, varicella, influenza, rotavirus, zoster, yellow fever	Subunit/conjugate	Human papilomovirus, hepatitis B, influenza, type b, pertussis, pneumococcal, meningococcal
Inactivated/killed	Polio, hepatitis A, rabis	Toxoid	Diphtheria, tetanus

Adopted from [54,58,59]

Is vaccination impossible? For some infections, yes!

What a negative attitude of human being is that he do not want to reveal his negative side. Scientists too are not exceptional. Since the history of vaccine implementation, there are numerous failures, but most of them are not registered. Even, within this year according to [} there were 115 design claims. However, we are not sure about their detail processes of design. Anti tuberculoses effective vaccine yet not established, because of many reasons, let us see what some others authors suggest: "…its efficacy is suboptimal [37]"; "…We do not have effective vaccine against tuberculosis [38]"; If we examine the table 3a, the CDC couldn't included any vaccine for this old HROS's disease"; "…less likely have effect vaccine for this the tuberculosis that grows together with human being [39]" have no effective vaccine, because the Mycobacterium tuberculosis has co-evolved with humans for thousands of years; around 15 vaccines on trial, using aerosol vaccination, only one licensed vaccine for today. It more works for infants; moreover, in [40], believes that it is impossible to treat tuberculoses; and in the work [42] too, remind and cautioned us how it is not easy to develop vaccine for strained viruses like influenza. The same researchers' conclusion can be listed out for HRV. Why we do not have still effective vaccine against HRV?
Yes, all these authors yet have no elaborated answer.

How to prove at least vaccine's efficacy

Yes, we tried to get answers, however, because of that in our mind we were searching an answer, which we already want to have (poor pedagogy), although they may satisfy others, but we couldn't trust on them. We need answer in which should raised issues like: is the design fulfill the criteria for vaccination development? Is blind experimenting policies were implemented? Is internal and external evaluators were involved? Is the international relevant organizers are certified it for testing, are all three testing phases' results performed with at least double blind design? And of course, the main our concern as a biochemist is the question - how far the created antibody can reach to its real targets?

Let us start to see the mentioned above each questions independently:

criteria (preconditions) to be recognized as an effective vaccine are:

- According to WHO [WHO/IVB/13.07 / 10.2017 / Vaccination in acute humanitarian Today's vaccination issues to combat COVID-19
- Recently, the only companies that are still on the race are: Pfizer [}, Moderna [}, Novavok [}, Arstemi [}, Sinovacof China, etc. In this month, … however, none of them certified by international organizations like WHO

Table 3: infected and death tolls in each 3 months of 2020 (WHO sources)

March		June		September		December		March 2021
positive	dead	positive	dead	positive	dead	positive	dead	
750890	36405	1002140113	499913	3273000	991224	7923189	1754574	???????

The anatomy-physiology of HROS
are there alternative novel approaches to combat COVID-19

DISCUSSION

Terminology

In research world, using the same language [57} is the decisive factor for a success in having understandings among scientists' society. Therefore, we tried to unified at least within this work some vocabulary for a better understanding.

Nature of SARS-CoV-2

Although understanding of the biology is decisive factor to battle against a pathogen, according our literature given, still there are questions that are not solved. This is an awful practice from those who are call themselves as microbiologist and virologists. This load is their obligation!

Origin of the SARS-CoV-2

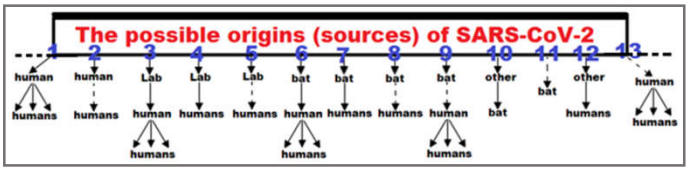
As we tried to remind – for combating whether communicable or non-communicable diseases, investigating its origin together with elaborating its others biological characteristics is at least the third portion of containing it/its destruction role. Therefore, we tried to gather data on the issue:

- 5.2.1.1 Most works that we gather are relying on the SARS-CoV and MERS CoV. Therefore, almost all researchers are accusing the bat, the Wuhan seafood market as it is of animal origin, for instance the pangolin [68,69}, and in general

since it most probably is of zoonotic type. However, there are also information, where directly accusing China: as if it create the SARS-CoV-2 for biological weapon or may be mistakenly emerged out from just a research laboratory during study for the sake of science (certainly we know that many developed countries except missiles and nuclear weapons, they are having chemical and biological weapons), but in the work [70,71] rejected the laboratory version.

- To our part, as a biochemist concern us the animal origin, in particular information like [69]. Because, earlier we tried to think over the probability of HIV, Ebola, Zika's, etc. animal origins. In particular if the animal is from the same origin as ours, then our organism may not reject as foreign organic molecule, for instance if enzyme from such animal ingested and if in cause we do not cook or freeze deeply, then immune system may neglect it, however it may change our metabolism process to anabolize harmful organic compounds or viruses that are originated from such animals will have a chance to enter into our body in active form, unless we cook or freeze the flesh of such relative to us animals! Thus, after 26 years abroad life, when we return to Ethiopia, one of our plan was to teach the public to stop eating flesh. For this reason we tried to study the origin of eating flesh as a culture: when Gragn Mohammed around 1530 invade the Christian/Amhara people, because of smoke they produce during food cooking, partisans in the forest were disclose and attacked by invaders. Therefore, the partisans were stopped using fire to cook fleshes. After the Gragn Mohammed was killed, those who were in the forest return to normal life, but they continue to eat flesh. Since then eating flesh become a culture (refer to picture 5) and a symbol of proudest! Thus, we found out it hard to be against such culture! Picture 5: taken photograph in restaurant, while gusts are 9
- For this virus and for future, we have prepared a scheme sample (refer below), which may lead scientists on – how to investigate origin of a pathogen.

Scheme: formula of searching pathogen's origin: More than 13 hypothetical sources for SARS-CoV-2



In the above scheme shown 13 possible sources (origins) of SARS-CoV-2 and 13 probabilities:

- A human may be the origin of SARS-CoV-2 as expressed in point 5.2.1.2 (above)
- A human may infect other intermediate-vector and in it developed into the SARS-CoV-2
- Accidentally or deliberately the SARS-CoV-2 may developed in a laboratory (refer to 5.1)
- Most of the literatures tends: from bat to yet unknown reservoir then to human
- From bat to unknown then in human become developed into pathogen form
- After developing in several intermediates (unknown), in human developed into pathogen, 14. etc.

What, how, and in what condition the SARS-CoV-2 invading

Almost all works, for example [25, 29,30,54,72,73] are directly or indirectly agree that the virus's gate into the body is our oral and nostrils cavities. Despite these, in a data of [25,35,54] can get information as if endothelial cells too are victims of the virus. Moreover, Why many researchers as all like [54} are thinking that any cell that has ACE2 can endocytosis the SARS-CoV-2? [34,36,74] too are tending into nerve system infection by the SARS-CoV-2. They are thinking that the SARS-CoV-2 can circulate throughout the body in active form. However, they didn't extract active SARS-CoV-2 from deep endothelial cells. They do not take into account the temperature, about which we have had laboratory based experiments [12] and the authors in [52] too showed how differs the virus multiplication under 20 and 40oC, pressure and different enzyme influence on such viruses within the body. Yes, in the work [35,36] also as if there were a clinical report, when a patient was infected through hand's endothelial cell! On the contrary the authors [56] oppose such endothelial version, about which we will continue during the summary part. These contradictions are ignored in the researchers society!, which is erroneous! Instead of hunting business sourced researches like vaccination, it was better experimentally exploring this issue – how the virus enters to the body!

symptom-diagnose issues

Well, identifying the exact symptoms together with identifying the origin of the pathogen is not only for terminating (if not abolishing) infectious but also to stop non infectiousness' diseases. If we add on time procedures, then these three manipulations are vital measures in combating a disease. However, as indicated in researchers are poorly engaged in decisive issues, which were able to lead us to contain the pandemic.

observable signs-symptoms of COVID-19

On time diagnose is vital to contain both infectious and non-infectious diseases. However, when we come to SARS-CoV-2, although, yet it has no different strains that are negatively impact on identifying the symptoms, within this yet a sole type pathogen too, is hard to retrieve common symptoms. In particular many cannot differentiate COVID-19 from flu or symptoms for such disease may depend on: age; immune system condition; habitation-location; seasonal climate; etc. of the patient.

Technology based testing

If it is impossible to prognoses the symptoms easily, then the only possible and effective, practicable way of testing for COVID-19 at this moment is implementing technology: swab and blood samplings. However, these too have their own drawbacks:

- Swab usage
  Even, we were witnessed when a health worker trying to take swab in the oral cavity from the lower part, where there are: constant and high temperature; the saliva; and enzymes, conditions that are not favorable (if do not abolish it) at all for SARS-CoV-2.
- Drawbacks of swab testing options
  We are suggesting that the virus may not have a chance to multiply within the upper part of HROS, because as we have point out in [30}, mucus may not give a chance to obtain contact with the epithelial cells under the mucus. However, if not on time expel out by the cilia, then it may pass directly into the lower HROS, from where it is impossible to swab!
- blood testing
  The doubt that always worry us throughout this year: if the SARS-CoV-2 is directly invade the pneumocytes of the

alveolus sac, may not be impossible to found the antigen-virus on time,

- In some patients the incubation time (to have visual symptoms) may be extended (if any at all). Therefore, may follow, factors of being idle, as a result the infected continue infect others.

Role of vaccination

Obviously, vaccination is a part of PPPMs – it is vital to combat some types of infectious diseases (refer to tables 3). Nonetheless, its vitality and feasibility depends on many factors, some of, which that are concern this work are here under:

Main procedures to launch vaccine development processes:

- Why and how come to make a decision whether vaccination is better than others PPPMs?
- What type of vaccine is favorable (refer to table 3b)?
- Can implement at least a double blind experimental activities during the developing processes?
- Have prepared internal and external evaluators on the development processes?
- Can ensure that the mentioned in subsection 4.4 ought to be applicable ? Etc.

Exceptionality in vaccine developing and vaccination against SARS-CoV-2 Since March 29, 2020 (refer to pictures 1-3 and all three our works [11,12,30}), regarding to COVID-19 issues, what triggered us to say: "for such type of virus and moreover within this short of time frame was the question – "is it possible to have at least effective vaccine against SARS-CoV-2"?

- The contagiousness' nature of SARS-CoV-2: it has a high rate of invading and due to the location in particular alveolus sac, it takes time for body to produce target full antibody (if any)
- The abnormality nature of vaccine discovering races among developers: may lead them to biased-falsification to claim first as if achieved effective or efficacy (of course never feasible! about, which will be in detail in the conclusion's section) vaccine without taking into account all the listed in subsections 4.4 and 5.3 points (question based instructions)
- The duel among developed countries: even politicians may provoke developers to faradism;
- The Media's non ethical role: It serves as a battle of field! Certainly, Media is an engine of improving the quality-quantity of products and or service. However, during a pandemic era, as we have indicated in a chart form in our work [11}, its role should have another status.
- Based on the vaccine development's history against HROS' infectious diseases
- Almost such pathogens, like tuberculosis and HRV (about which we tried to touch in point that attack HROS, in particular if victim is alveolar sac (has no reputable results the site is not easily, sufficiently, and on, about which we are more focusing in this work under subsection "5.5" here under and in the conclusion (6) section.

Is SARS-CoV-2 can be exposed to innate and or to adopted immune system (antibody – immunoglobulin)?

Yes, step by step, i.e. starting from point 5.2, we are narrowing our focusing to alveolar sac. Therefore, to have appropriate answer for this key question, we should have to explore the followings issues:

- as others types of HROS based viruses, it may mutate and have new strains
- If we excluded the probability of deliberately mutating, what is the level of possible self mutation?
- Are all types of population can able to posses innate and or adopted specific Ig (antibody)
- The nature of host cells that are the victim of SARS-CoV-2 and the infection's consequences:
- Well, we hope that the 5.5.1 and 5.5.2 are understandable. If that so, now it is time to elaborate all the relations' issues between the alveolus and antibodies interactions.

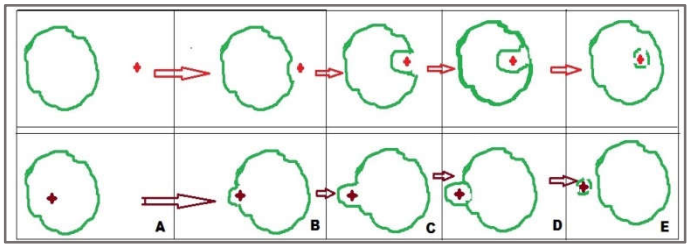
During our biochemistry courses delivery, while we are dealing about secretion and interstitial fluid, we used to highlight the villi of digestive system, the cilia of respiratory organs and alveoli of breast and lungs. Therefore, let us pass through them to have a basement for our conclusion that vaccination is not efficacy for this types of virus:

Anatomy-physiology of HROS After understanding the origin of SARS-CoV-2 and formulating COVID-19's symptoms, next must be designed options to combat SARS-CoV-2: which type of host cell–tissue-organ level SARS-CoV-2 invades and how it affects (outcome). Within this context, at least must be revealed: how the pathogen enters into the body; which organ-tissue and cell level the SARS-CoV-2 can destructed the normal metabolism of the host; and of course how it is multiplying within the host (site).Therefore, each of the above mentioned "how and which" must be answered properly: According to our gathered data result (refer to subsection 4.2.3)

How SARS-CoV-2 enter (contaminate)

Based on our collected data (refer to 4), that there are contradictions about SARS-CoV-2's origin and more worsen – we revealed contradiction about what cell and how it affects (refer to 4.3.2). Therefore, although, yet, we do not well understand its origin and how it affects the initial organism, we understand that the novo corona virus SARS-CoV-2 is a sever acute respiratory syndrome. It enters into HROS through nostrils and mouth. There, most probably it attacks epithelial cells of nostrils and throat of upper HROS (refer to figure 1a), if the mucus and cilia in these tissues are not properly defending the epithelial cells under them. The others types of epithelial cells that most probably victims of the SARS-CoV-2 are pneumocytes of alveolar sac in the lower HROS (figure 1b). For more understanding the damaging process and of evaluating the effectiveness of vaccination and treatments, we here under illustrated the anatomy and physiology of HROS: This means that, although, some authors are trying to tend (refer to section 4) to a conclusion that the SARS-CoV-2's invades others cells: nerve and endothelial cells – they argue that such cells too, have ACE2. However, having ACE2 [54} alone may not be facilitate the virus to endocytosis into cell's cytoplasm (refer to scheme below for understanding endocytosis-exocytosis) (within the same type cells, even there are differences. Furthermore, they didn't show us what happen after spiking: the structure and content of the membrane of these non epithelial cells; what kind enzymes they do have; what content of their cytoplasm; etc. must be elaborated. And at the end of the day – is it impossible to show us at least in vitro that such cells too, can be the target of the virus?!

Scheme: model to illustrate endocytosis and exocytosis phenomena in animal cell



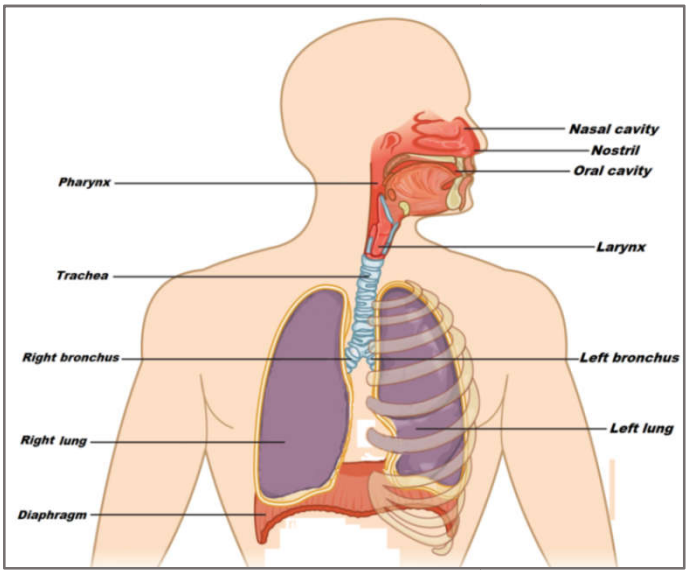
Adopted from our biochemistry course delivery's content

We demonstrate here this scheme of endocytosis and exocytosis processes, because, in most literatures, either due to our poor English do not understand them, or maybe they are not understanding these two phenomena, that these capturing or expelling phenomena cannot be take place within the alveolar sac's cells, since they are firmly attached each other and not on interstitial fluid. In the scheme (above), the upper part is stages of endocytosis (entering foreign matter – mostly large molecules or microorganisms). If it is exocytosis, organic molecules, debris of organelles, etc are releasing from cytoplasm of the cell. The lower scheme shows how organic compounds like anabolic proteins, ferments, organelles' debris, etc. are released from cytoplasm. However, not the virions! Here, we assume that these processes are as any metabolic processes takes place spontaneously!. When a cell is moving in the interstitial fluid, may touch the matter, as a result, its membrane can be deformed by the influence of the compound or microorganism and the process continue. This part is more useful to have treatment and prevention options, which even may serve as the second step to be investigated for having exact and easy options of battling contagious microorganisms. Hence, the SARS-CoV-2 is attacking only the upper and lower HROSs. Yes, to stop such infection this fact has positive and negative issues in our exercises: positive, because to the biology, in particular to the biochemistry context it is the easiest way to defend these organs from being infected. Negative as we have indicated in [11], in: social-culture-economy, and even political factors, are negatively influence to perform simple, fastest but effective of PPPM: avoid contact with the virus or close its gate (mouth and nose). We mean don't expose yourself, there where might be the virus SARS-CoV-2.

Anatomy-physiology of respiratory organs' system in figure and picture form

Our main objective for this work is to ignite a question whether the adopted antibody of vaccination can on time and sufficiently reach or not to the main respiratory gas exchange site – to the alveolar sac, presenting (illustrating) the anatomy-physiology of HROS is the better approach.

Figure 1 HROS in general



In this figure 1a, down up to the trachea we can take it as the upper HROS, whereas, the rest: from trachea down including the distal part can be considered as the lower part of HROS (figure 1b)

Figure 1b HROS in detail with its distal part

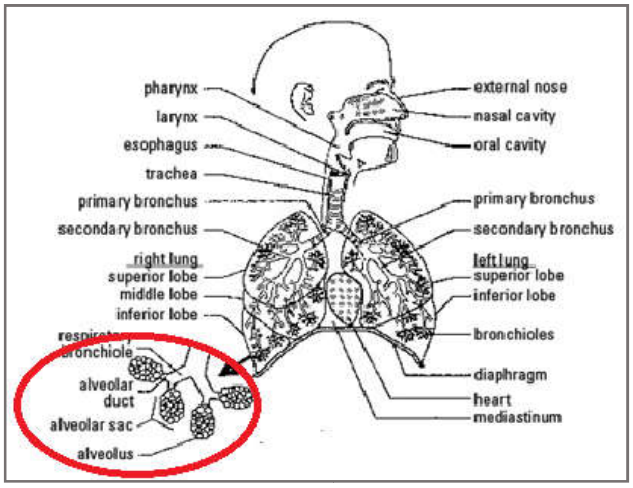
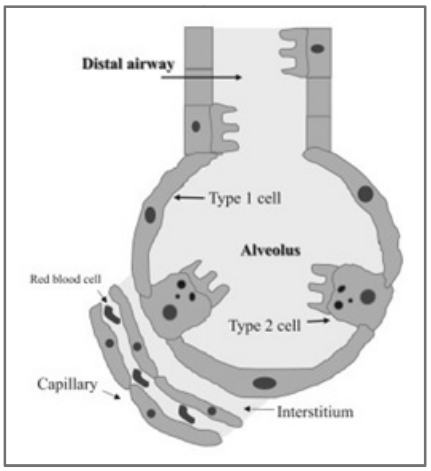


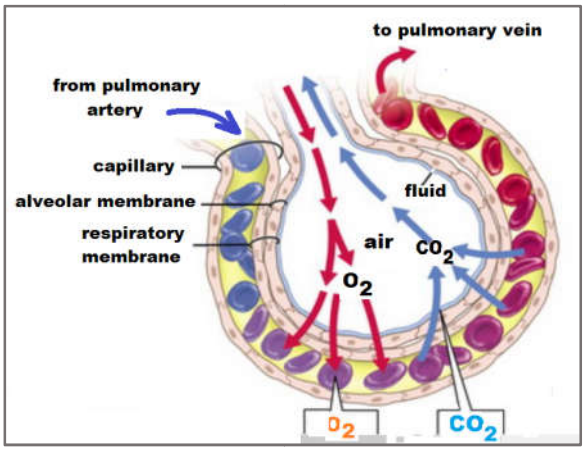
figure 1b adopted from [75]

in this figure 1b, although there are detailed divisions, what more concerns us in it is the circled (lung's distal) part, which contain alveolar sacs. Within each sac there can be three types of cells: pneumocyte I (responsible for gas exchange); and pneumocyte II (responsible for surfactant secretion and repairing or altering into pneumocyte cell I, in case if the last is damaged, dendrite cells and macrophages cells (are responsible for clearance of the alveolar sac from dusts, organic matters and even from pathogens by transporting them into the digestive system for further catabolism (such clearance probably may be more active in others mammals that are walking horizontally! A situation that we are lack, because of evolving into Homo erectus!)

figure 2 alveolar sac by different authors [75,76}



An alveolar sac



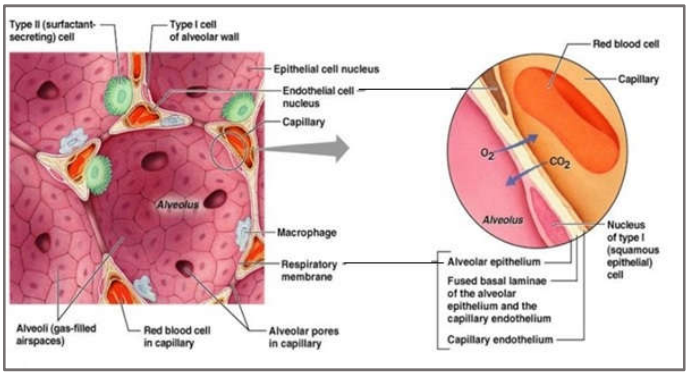
detail of alveolar sac with its surroundings

figure 3 alveolar sac with significant three types of cells: one layer epithelial cells – pneumocytes), macrophage and their proportional size's relation with capillary system

Detail on alveolar sac [76] and blood capillary's relations

Biological important facts on the alveolar sac: Alveolus has 0.2mm. In an alveolus there are two types of pneymocyte cells: type I and II. Type II produce surfactant – it is a lipoprotein with a high phospholipids content which reduces surface tension and the third type cells – macrophages (mobile cells responsible for immune and clearance functions) Within 4 months the alveolus is formed. Within 5 months fetal breathing will start. After 8 months the alveolar sacs formed. And up to 8 years old continue formation. This means that these cells may not be reproducing in further life [25,54] According to almost all literatures [16,17,18,27,29] (except in [28,77] that the virus may transmit into the nerve system "…exactly how SARS-CoV-2 gets to the brain…", and in the work [33] authors suggest that endothelial cells also may be infected by SARS-CoV-2), the upper and lower HROS are the targeted victim of corona virus SARS-CoV-2.

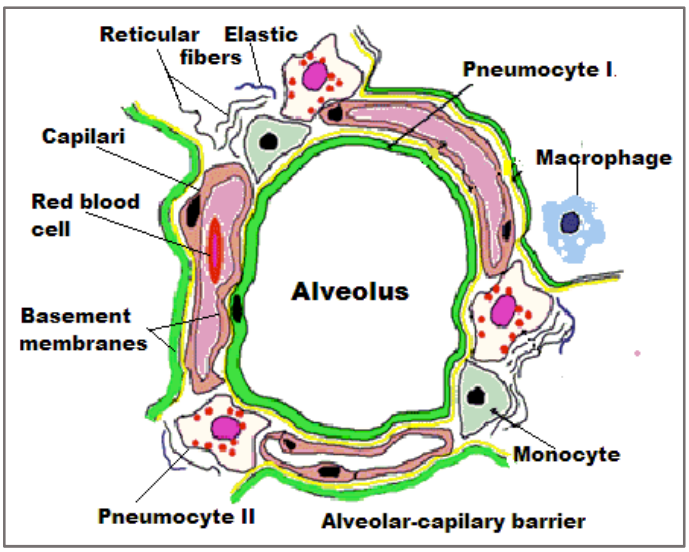
Figure 3a and b: Detail alveolar sac-cap pillar and gas exchange relations



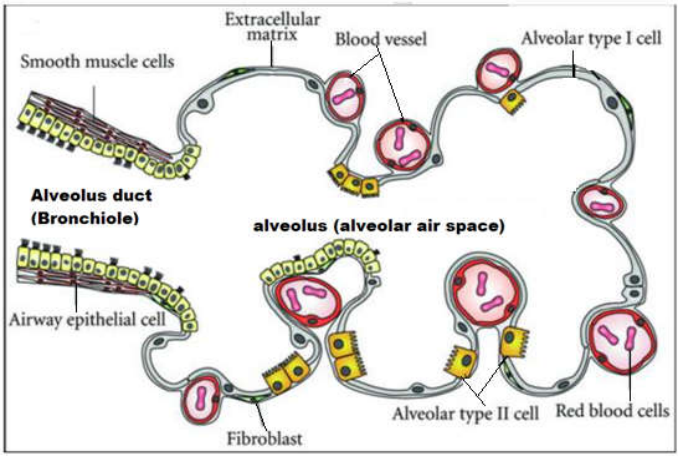
Adopted from [78}

In the figure 3a and b: More or less is a detail illustration that (we have got from internet sources): "a" (general structure and content of an alveolar sac) and "b" (the last site, where CO2 and O2 (refer to the metabolic reactions in respiration process) are exchanging through different concentration gradient principle of diffusion (refer to figure 3 for even more detail expression).

Figure 4 a and b: alveolar sac with cross sectional illustration from the work of [50,79]



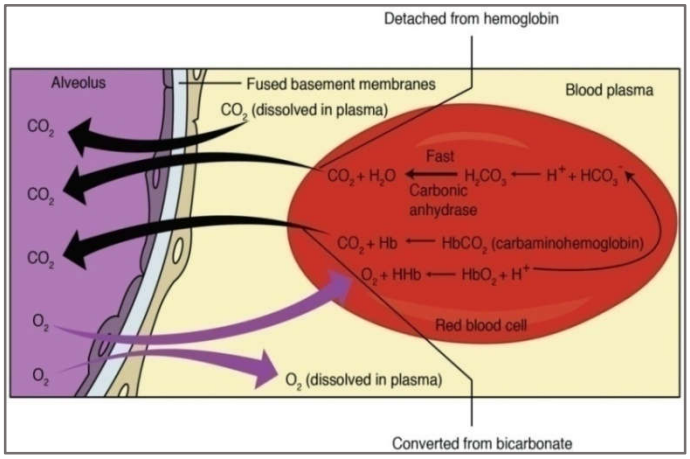
a



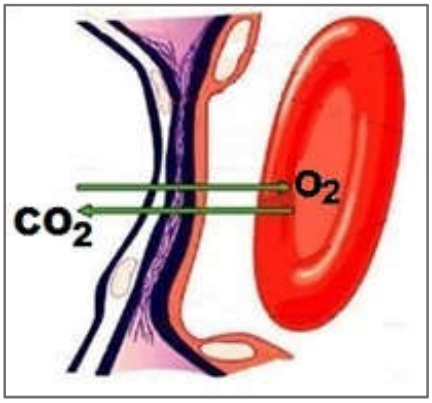
b

Figure 4 shows Detail cross section of the alveolar sac with its content and capilary cells of coronary vesseles (adopted from [78}
Although there is a slight difference between them (a and b) in general show 4 types of cells among which the two pneumocytes and macrophages are more interesting for this work, whereas dendrite cells may be of the upper HROS or at least not included in the alveolar sac if not on its duct.

Figure 5: Illustrate how are interact alveolar sac and blood vessel during gas exchange



a



B

Adopted from [50]

Figure 5 detail gas exchange, types of membranes and types of gases from where they are derived, illustrate proportional structure of membranes (figure 5a), proportional size of capillary red blood cells against alveolar sac (figure 5b)

Physiology and biochemistry of alveolar sac

Physiology of alveolar sac.

Membrane layers: surfactant, the epithelial and its basement; thin space between capillary membrane, capillary membrane and the capillary endothelial membrane figure 4a. The whole thickness of layers together is between 0.2-0.6μm [25,54]. Alveoli type I doesn't replicate! Only the type II alveoli is differentiate into type I cell (if these type I cells by toxic materials damaged). The lungs are frequently involved in infections and injuries. Some infections can destroy vast areas of a lung, rendering it useless. Inflammation from toxic substances, such as tobacco smoke, asbestos, and environmental dusts, can also produce significant damage to the lung. Healed lung tissue becomes a fibrous scar unable to perform respiratory duties. There is no functional evidence that lung tissue, once destroyed, can be regenerated [80]. All these assumptions, if not facts indicate us that the type I cell is not considered as a full optional cell, but there is report that SARS-CoV-2 invade it! Suspicious conclusion! We know that the alveolar epithelial membrane is lipid contented membrane. Therefore, unless there is a new other data, to the biochemistry context, lipid layers with their non-polar tail are not permeable for polar molecules like proteins. Hence, unless from the upper HROS and or apical cells, we are in doubt to believe that from the blood stream the antibody (Ig – immunoglobulin) can enter to the alveolar sac to terminate the destructive action of SARS-CoV-2). For sure, these cells' membrane are adopted for exchange gases, but may also H2O and ions like Na, Cl, K, Ca, etc. However, the pores couldn't permit to pass through some large size molecules like Ig (refer to figure 6), which certainly need energy (active endo-exocytosises as seen on the scheme above) as well as penetrate the cell's membrane barrier! Anyway, if we continue what we started in the figure 1b legend: suggest a question to be raised: in case of respiration, we lost advantages, because of evolution: from horizontal walking (with four feet), we are those who evolved into homo erectus. At least it was be able easy to expel dusts and microorganisms with the help of gravitation (if not negligible!); coughing-sneezing (if we observe how animals are coughing - they direct their head down!) also may be fruitful in those mammals with horizontal position! and for cilia too, which means theoretically the horizontal position is advantageous for at least clearance of alveolar sac. However, is it compensates when we are sleeping? What about the position of the two lungs – is it better to be hang on (vertical, against gravity) or being in horizontal position, etc? issues if it seems fantasy to physiology, to physics context can be considered (we can hypothetically assume that patients are sleeping on their back may load on their lungs, therefore, they can experience pain and coughing. May, help sleeping down on womb, as we have done 10s millions years ago? These hypothesizes need proofs

Biochemistry within the alveolar sac

In intact cell metabolism: included active and passive entrance of monomers of protein, lipid, carbohydrate, nucleic acids, etc. (unless, if the molecule is large enough, either need active transportation or endocytosis process). Such monomers are entering from cell's basin – interstitial fluid (every cell around it has interstitial fluid). In this fluid, the capillaries are socked. Therefore, based on concentration, there will be molecular changes between these tiny blood vessels and the fluid, mostly based on concentration gradient and fluid pressure rule. When we come to the alveolar situation, almost can be said that no fluid (figure 2b-5), furthermore, periodically membranes of capillary and alveolar cell are cuffing (spike) together! Therefore, how Ig enter from capillary? Is a big question: In cause of the SARS-CoV-2, its negative impact can be postulated as follows: ACE2 is highly expressed on the apical side of lung epithelial cells in the alveolar space, and the virus spike and enter to the cell. In the mean time, the dendrite cells (DCs) and macrophages cells serve as innate immune cells to fight against viruses till adaptive immunity is involved. Latter T cell responses are initiated by antigen presentation via DCs and macrophages. How does SARS-CoV-2 enter APCs? DCs and macrophages can phagocytize apoptotic cells infected by virus. For example, virus-infected apoptotic epithelial cells can be phagocytized by DCs and macrophages, which lead to antigen presentation to T cells. Or DCs and macrophages may be infected with virus primarily [25,54}. Another target for SARS-CoV-2, if any, can help the virus to directly infect DCs and alveolar macrophages. These antigen presenting cells move to the draining lymph nodes to present viral antigens to T cells. Particularly CD4+ and CD8+ T cells play a critical role: CD4+ T cells activate B cells to promote the production of virus-specific antibody, while CD8+ T cells can kill viral infected cells. These are what we consider for this time. Virus infected lung epithelial cells produced IL-6 and IL-8. IL-8 attract the neutrophils and T cells. Among innate immune cells, the majority may be neutrophils. Controversially, Neutrophils can induce lung injury. Severe patients also showed pathological cytotoxic T cells derived from CD4+ T cells. These cytotoxic T cells can kill virus but also again contribute to lung injury as do the neutrophils [25,54]. Hence, here, what we want to highlight is that authors are more focusing if not only the upper HROS, at least their suggestions may not include the alveolar sac's cells. These epithelial cells in their membrane have ACE2 that are capable to spike with the glycoprotein of the viruses envelope. Once it spiked, by endocytosis mechanism, or involving host's enzyme, the capsid's content will enter to the host's cytoplasm, and its single strand +RNA, as the mRNA of the host cell do, will attached to the ribosome for further duplication processes into new several virions, etc. By doing so, it terminates the normal metabolism processes of the host cell:- when it multiplies within the host cell, not only metabolites go for building virus, but also the membrane of the host cell couldn't resist such additional foreign mass, as a result it explodes (burst) and destroyed at all. Whereas the viruses become free for further invasion of yet normal host cells. During such burst, the content of the host cell will also can damage its surroundings. When, we are raising the surrounding issue, we can look on how the alveolar epithelial cells are damaged and become the case of severity and lethal outcome through their debris and immune responses: IL, cytokines, trombocyties, etc organic compounds. This is the main reason why the pneumocyte I and pneumocyte II of alveolus sac are disturbed and even destroyed by the SARS-CoV-2. Their reside contain different organic compounds, cells, which can further can affect their surroundings as a result of such chained destruction, there will be damage of blood vessel's membrane, which leads to be disturbed the closed vascular system - imagine what will happen if a water pipe line on a street cracked/broken down and if enter water flood with mud and other dirt to the water system! This can happen if from the damaged alveolar sac then its and atmosphere contents, organic debris, hydrogen peroxide etc., are instead of oxygen enter into blood stream – first of all clotting and fever increase, as a result disturb the function of brain, heart, kidney, etc. Such, negative outcome can result into nerve and myocardial cells' non reversible death or even to lethal at all. However, we suggest that at least the nerve cells and the myocardial cells (with which we were dealing around a quarter century ago in our PhD dissertation [84}) may not regenerated once they are damaged. Because, together with lack of oxygen or high fever induced by cytokines and others and clotting! Certainly, in medical expression: all these are caused by: the destruction of alveolar cells is followed by reduced blood oxygenation, lung fibrosis, edema, impaired regeneration, and ultimately, leads to respiratory failure.

Anyway, let vaccine developers show us that adopted antibody from the blood stream can enter to the alveolar sac efficiently and on time. This is our key question!!

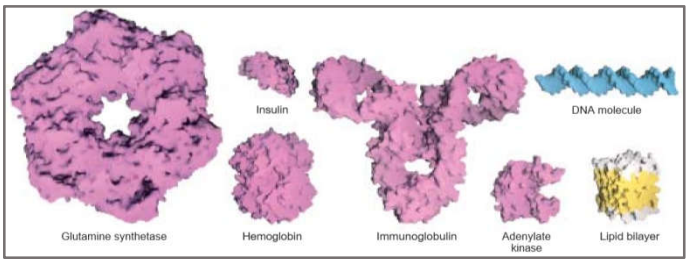
Well, if we agree that half of alveolar sac covered by surfactant and atmosphere gas with carbon dioxide of respiration's product, then where are these cells and bioactive huge molecules (refer to figure 6) within this alveolar sac (figure 3-5)? We indicate (see above) that Alveolar macrophages are mobile cells and serve as gulfers of dust, dead type cells and red blood cells (red blood cells that can be almost at least half in size (refer to figure 3-5) with its at least two cells). Thus, these red blood cells are probably only in the upper HROS or at least not in its distal part – in the alveolar sac or after destructed membranes of both alveolar and capillary, red blood cells can enter into the lung through the sac! Additional to biochemistry of alveolar and capillary-venules interactions processing CO2 and O2 exchanges

What is the main function for alveolar sac?

It is a terminal, where takes place gas exchange (based on partial pressure (Dalton's law) and dissolving rate in the blood (Henry's law)) between the body and atmosphere.

$CO2 + H2O \leftrightarrow H2CO3$ carbonic anhydrase $\rightarrow H+ + HCO3-$

More in the red blood cells with the help of carbonic anhydrase, carbonic acid dissociates into hydrogen ions and bicarbonate ions. Then because of Bohr effect carbon dioxide replace oxygen in the hemoglobin. After changing anti-bicarbonate ion, it will be replaced by Cl ion within red blood cell (figure 4 and 5) to release into the alveolar sac. Figure 6: Comparative illustration between large size organic compounds and Ig with oxygen and carbon dioxide molecules that are passing through membranes' barrier to alveolar sac.



Adopted from [81]

Can alveolar sac exchange others organic compounds with capillaries?

A core question, which may be one of the factors to recognize the effectiveness of vaccine's ingestion-injection against HROS based pathogens. We found no literature except [82,83], where can give hint about the organic molecules' entrance from the capillary into the alveolar sac. Even, we do not agree with such authors because, protein molecules cannot enter into a cell from interstitial fluid in passive way if endocytosis (refer to our scheme on endocytosis principle), then neither the pneumocytes I nor pnemumocytes II membranes may not let to posses such processes. Moreover, as we see in figure 3-5 between membranes no interstitial fluid as of others types of cells, etc. Therefore, this figure (6) will help us to imagine whether the alveolar sac, whose wall is build up from thin (one celled refer to figure 3-5) cells (pneumocytes I and II), only let to pass CO2 and O2 can't capable of letting such huge molecules like immunoglobulin either in passive nor active form of transporting. To the evolution context, the capillaries structure around these alveolar sacs, interstitial sluid like contents and all types of membranes (figure 2b,4) should be transparent for vital molecules CO2 and O2. Hence, there should be any debris, obstacles for these two gas species! Unless there will be respiration problem, about which we will brief here under. These epithelial cells in their membrane have ACE2 that are capable to spike with the glycoprotein of the viruses envelope. Once it spiked, by endocytosis mechanism, or involving host's enzyme, the capsid's content will enter to the host's cytoplasm, and its single strand +RNA, as the mRNA of the host cell do, will attached to the ribosome for further duplication processes into new several virions, etc.

Measures that are taken and taking against the pandemic

In our [11,12] work, we have shown that world is concentrated on treatment than prevention (refer to pie chart), moreover, today continue advertizing for vaccination by naming it "game changer" [85] and now pharmaceutical companies, business oriented scientists, politicians and Media are focusing on vaccination. For instance, when we encountered with "…game changer", we seriously disappointed with the whole world. Is the author [85] really knows that today's vaccination is a game changer?
Well, by illustrating different pictures (1-6) and above red question (refer to 5.5.6.2) aiming to help scientists on the field, we give a clue about the non-availability of alveolar sac for antibodies:

- Is 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)?
- What is the difference whether healthy adult and children are getting vaccine or not?
- Are we sure that elderly; immune suppressed; and infants are able to adopt antibody on time and in sufficient amount at the affected site?
- What relation shows us the difficulty of producing effective vaccine against HRV and TB?
- Is vaccination better (feasible) than others PPPM (refer to the content of our pie chart)?
- Because to our assumption, the anatomy-physiology-biochemistry issues of directly affected organs (by the SARS-CoV-2) are yet not fully explored (widely included)

Others nontraditional way of drug-vaccine discoveries against pathogens

Starting from drinking methanol [12], using anti malaria drug remdesivir, drinking cocktail from, a plant origin, etc. and as indicated in [25] the lopinavir-ritonavir, hydroxychloroquine, and azithromycin also have been tested. Moreover, there were tendencies to use antiviral drugs! Again, we want suggest that not every antiviral can reach to the site, where the SARS-CoV-2 is damaging. However, apart from ventilation, more scientific based drugs are using for treatment like heart, kidney problems, anti blood clotting, etc., but not to impact on the virus. Despite such awful exercises, we have had listen news, in which indicates about a usage of spray to the respiratory organs to terminate the virus's destructive acts. An intention that may really can be "game changer"

Feasible measures to be taken against COVID-19

- Properly identifying the cause and investigating its origin are - the first 3rd portion (if not half) of combating not only infectious, but also non-communicable diseases. Therefore, when we return to COVID-19 issues: identifying means of transmission, revealing its exact symptoms rapidly, and searching feasible means of not to be infected and not to infect others to contain this pandemic are more feasible measures.

- Fast, easy and cheap way of terminating infectious disease like COVID-19 pandemic is PPPM. Nonetheless, today vaccination becomes world engagement.
- For a vaccine to be said at least effective, it should have to pass basic evaluations' procedures
- Capable to answer all our raised issues in question forms in section 4 and 5.6.1-5.6.5
- We need to be convinced by vaccine developers or any other stakeholder that the vaccine's antibody can defend the alveolar sac - the HROS's distal part sufficiently and on time

Conclusion

Understanding the origin of a pathogen is a half way to combat not only an infection, but also the non-communicable diseases. Based on this postulation, a vital question can arise: From where (initial sources) viruses like Ebola, HIV, and even the SARS-CoV-2's are coming from?

6.1 Based on our discussion part 5.2.1, and the scheme 5.2.1.3 we tend to answer – may be flesh-raw diets are the sources. Hence, fleshes should be always deeply freeze and or cook before consuming, but avoid any flesh, animal's genetic structure is similar to ours, can minimize emerging new pathogen

6.2 We constructed a guide scheme (refer to 5.2.1.3) , which helps in investigating pathogen's origin

COVID-19'spandemicsituation

To combat combat the corona virus: From prioritization the 4 our PPPM: "stay at home", but for those who are forced to go out - the "face masking", and "distance keeping" together with the "proper sanitation-hygiene prophylaxis" habit Some authors are thinking that the virus can attack cells that have ACE2. But, we assume that it invades only epithelial cells that are well ventilated. Because, the virus may not resist constant high temperature; enzymes' influence; organic compounds within the interstitial fluid; and such authors probably not take into account that other cells may not possess enzymes on their membrane that help the virus's capsid to endocytosis into cytoplasm. Moreover, yet not researched whether the cytoplasm of other cells suitable or not for the virus to activate its RNA for further multiplication. However, their concerns have grounds that they observe the virus's debris around such cells. Even, one work inform as if the virus identified in digestive system and faeces. Yes, they may found, but these virus's genetic fragments probably come with macrophage (pulmonary macrophages with dusts, microbes and others foreign materials are entering into the digestive system for further catabolism!). Furthermore, such virus's fragments may be found in nerve and myocardial systems, because, when the alveolar sacs are destroyed by the virus, their contents may dissolve the capillaries' endothelial membrane and mixed with the blood, from where can reach to those organs. These virus's and alveolar sacs destruction leads to: embolism, activation of neutrophil, coagulation, fibrinolysis, etc products for further organs' metabolism disturbance and even to death Elaborating why it is impossible to have feasible vaccine for SARS-CoV-2. Some of the steps to be performed before designing vaccine are: thoroughly investigate the nature of the pathogen's origin; its biology (structure, pathogen's characteristics and its possible mutation level, severity, etc.); identifying the possible victim's type by: age, gender, social status, culture, geography, etc.; the differences among today's SARS-CoV-2 with others viruses; targeted host cells' specifications; the being developed vaccine's characteristics (its bio-chemical nature; mode of delivery: injection, ingestion, etc.); how fast antibody creates; what is its destination; and how long antibody production memory lasts; etc.); and whether have followed documents indicated in "4.4 and 5.2". Additionally, here under, we sort out some vital points, which can serve in combating COVID-19. The forwarded since March 29, 2020 (refer to pictures) that vaccination for such type of virus and moreover within this short of time frame, may not be feasible than others means of PPPMs, shall said to be approved.

before starting a vaccine developing project must have positive answers for:

- Is there at least effective vaccine against others HROS based infection disease
- Certainly, we know that there are two dozen efficacy vaccines (refer to table 2). However, it is yet rare to have even effective vaccine against HROS based long aged infectious diseases (for instance the HRV and TB). Since, most respiratory based viruses periodically change (mutate), the organ that they attacking is not easy to be reached by antibodies (through interstitial fluid and permeable membrane as of others types of cells in others tissues) with the targeted host cells (epithelial cells of HROS); and neglecting the mitosis as of others somatic cells, they (in particular the pneumocytes) possesses a slow regeneration processes (if any at all), etc.
- Are we sure that the unusual large size of the corona virus do not negatively influence on the antibodies' (immunoglobulin, in particular to IgA, IgM and more to IgG's species) activities against antigen?
- Within a year, many of those who are exposed to be infected are already infected (around 80 million till today, neglecting those who do not show symptoms but already prepared adopted antibody), what part of a nation and how many of it throughout the globe need the vaccine?
- Is a vaccinated person: can able to produce necessary Ig's types sufficiently and continuously (that can long last) how fast the body develops the particular antibody (Ig - immunoglobulin) against SARS-CoV-2; what is the durability of the antibody production's memory?
- Additional to the mentioned in 4.2 and 5.2, due to the specific nature of affected people (refer to 5.1-5.5 too), necessary to include - can the vaccine force (help) elderly and those with compromised/suppressed immune system, produce the antibody on time and in sufficient amount?

Socio-cultural; political interference; Media; and economy issues

- How the vaccine developed (detailed developing procedures' protocol)? For instance, what and how materials (hard and software) are used?
- unless the reason is the experience's during the SARS-CoV and MERS-CoV, why and how within 2-3 months after the COVID-19 emerged, hundred vaccines' projects announced?

It was looked like advert of business, political ambition, where Media is served and serving as a battle field. All of which are put the efficacy of vaccination questionable Vaccine's nature and characters

- Almost the majority vaccines are biology based products. Hence, comparatively to the chemical; biochemical; and biology based productions vaccines, are more sensitive to the different conditions (temperature, pressure, humidity, durability, etc). Thus, how far it is possible to control such factors during production, delivering, shot (in particular if their needs two shots – will the person appear for the second?), and result assessing processes?
- There were incidents when workers deliberately spoiled the prepared vaccine. Then, can we have a guaranty against awful and snoopy actions from business world, business oriented scientists and politicians on the vaccination safety and efficacy concerns?

Exceptionality of SARS-CoV-2 to the anatomy-physiology and biochemistry concepts In this work we deliberately highlighted on anatomy-physiology and biochemistry related characteristics of alveolar sac, how they are: important in respiratory processes; the most vulnerable for the SARS-CoV-2; their role in severity of the COVID-19 and death toll. Yes, a vaccine may be formulated in the form of organic complex; antigen; fragment of a pathogen for instance Adeno/mRNA type and even attuned pathogen, etc. However, how such big molecules (antibodies – the immunoglobulin), which are created and circulating within the blood stream can sufficiently pass through the barrier of capillary and respiratory-basement membranes (figure 3-5) alveolus sac and reach to the targeted pneumocytes I and II (epithelial cells)? A core question that each vaccine developer must answer to claim that its vaccine is effective (of course alone this is not the fact to be a feasible vaccine!) Suggesting novel approaches in drug-vaccine discovery for COVID-19 and of others similar infections As we have informed 6 months ago, instead of vaccine discovery, first of all, it is more effective to: identify tasks for each stakeholder; scale up public awareness about the nature of the pathogen; avoid direct-indirect contact with such pathogens; scale up immune system through drug-diet supply; and at the end of the day, for stopping not only this pandemic, but also others airborne diseases like HRV and TB the 4 PPPMs: closing the gates (as we do to windows and doors for not to let wind or cold): keep the "stay at home" or if forced to go outside, then never wear off your face mask until you return back home, and use properly the others sanitation-hygiene based prophylaxis measures for a maximum of 30 days.

Despite this feasible option in case if someone is ambitioned in: drug-vaccine discovery, business and political benefits, then:

- May be better to design a vaccine, whose antibody, through lymphatic system, direct ventilating or spray to upper and lower HROS, in particular into the alveolar sac to train macrophages, dendrite cells, others cells and of course if possible the pneumocytes producing defense mechanisms (if any) to act on any of the virus's reproduction stages: spiking; endocytosis; translation; enveloping; etc.
- Is it not better to use others options: balanced diet, a drug based manipulations like spray or powering in a liquid form: antibody, β-viruses (after study the antibody's similarity with SARS-CoV-2) for recalling adopted immune system; selective antiviral chemicals; bio additives for increasing alveolar macrophages, increasing mucus secretion through goblet cells' activation, surfactant producing, etc. but, only for those, who are at risk of being infected?
- Theoretically to have antibody, it may be possible to infect the upper HROS epithelia, but controlling not to spread to the alveolus!

Evaluations of: the safety; effectively; efficacy of vaccine production; vaccination processes and its outcomes (whether it feasible)

- Is the vaccine passed (all necessary phases)?
- Are independent stakeholders evaluate (if impossible to control the vaccine production procedures) and testing phases?
- Are not included: adverting, political battling, competition, etc. in this vaccination race? If yes, couldn't it leads to result falsification?
- If developers able to have a defense for our arguments: 4.4 and 5.2 and 5.3, can they have answers against our biochemistry and anatomy-physiology based doubts?
- Did independent evaluators of internal specialists; others organizations (externals); and specialists from others countries (externals) gave their agreement?;
- Does the developer have protocols of different evaluators (through implementing a double (if not triple) blind tests)?;
- Did the above evaluators are agree on: If for all such tenths questions of point 6.4.1-6.4.5 from the conclusion part have positive answers, then obviously, vaccination may help, but only for COVID-19. However, if we follow the four PPPMs then others respiratory based infectious pathogens can be minimized (if not abolished at all) too.
- Did international responsible organizations like WHO approved-certified the vaccine and vaccination procedures?

Vaccination is one of the fifth PPPMs, therefore, it may be effective or efficacy, but couldn't be feasible, unless developers or any stakeholders are able to give elaborated justifications that a given vaccine is better than others 4 our listed PPPMs!

Recommendation

We are afraid that: biopharmaceutical products' producers; business oriented scientists; politicians and even countries, which are just oriented not for science, may not be satisfied by our: hypothesizes, postulations, and suggestions that are in our discussion part and in particular with the conclusion part. Yes, fearing of this, as we indicated in the introduction part, we tried to contact with the vaccines' developers to offer them our doubts-thoughts that are listed out under 6.4 (5+1 groups of justifications on non-feasibility of vaccination against HROS based viruses like SARS-CoV-2). Therefore, since they didn't respond, we as a pedagogic and biochemist, decided to prepare this article to be considered by molecular biologists, immunologists, virologists, biotechnologists, bio-pharmacologists and of course by responsible authorities; etc. Hence, please

7.1 have a tolerance to read and understand each points of the statement of the problem (introduction section part point 1.1), result, discussion, and conclusion part (mainly the point 6.4, where listed out our "5+1 groups of justifications" - why vaccination against SARS-CoV-2 is not feasible), because at least they may lead you to the inverse during projecting a drug-vaccine development

7.2 Instead of vaccination, for any HROS' infection, better to implement the following steps:

- Thoroughly investigating the origin/s of a pathogen should be the first step to combat any disease, and
- understanding on which host and how influences a given pathogen.

7.3 prevention based prophylaxis measures must be arranged as shown in the pie chart:

implement the mentioned 4 sort of PPPMs

the: pie chart; scheme; and the 5+1 groups of justifications are helpful not only for this pandemic, but also can assist how to identify future pathogens and combat them.

when we come to the COVID-19's pandemic issues, if we really want to eradicate not only this pandemic, but also others aerosol-air droplet based infection diseases like: HRV and TB (about which we have published earlier and may be included in our article of the next month), better firmly perform the "stay at home", but not "lock down" (because, such phrase may recall offensive mind), "safe masking", but not "face masking", and "safe distancing", instead of "distance keeping" must be implemented for a maximum of 30 days throughout the globe,

7.4 Theoretically it is possible to have effective vaccine within experimental level; yes, it is possible to develop a vaccine, which can effectively produce necessary antibody not only in vitro, but also in vivo; of course, we can perform up to the third phase, and earn efficacy result. However, unless developers or others responsible

bodies can justify the necessity of vaccination against such corona virus, mass vaccination campaign must be suspended, because hoping that the vaccination will stop the pandemic, public may become idle and become ignorant for the PPPMs.

7.5 let us stop consuming raw flesh of animals and plant's origin, because, by avoiding flesh raw content from our diet, at least we will minimize the possible digesting process's load, toxicity, and food contamination. However, consuming animals, which are similar to us within genetic level, may be more dangerous even if it is well cooked, unless cooking changes it into the monomer point!

7.6 Neutrally from: business; political ambitions; and battling countries among each other on the vaccination issues:

- Necessary boosting adoptable immune system and must supply metabolites (amino acids' monomers) from which the antibody (immunoglobulin) is anabolized. For this purpose
- Although, we don't hear from any of developers such instructions for those, who are vaccinated, as a biochemist we are sure that should be taken protein contented diet or amino acids' contented medication as extra source and a necessary physical exercise to vaccinated activate metabolism processes.
- Media and all those behind it: please stop spreading scientifically non approved advert contented information. Any your information regarding to COVID-19 (don't relate this with media's freedom limitation!), should have a clear scientific reference: authors, date, title, date of production and source.

7.7 Taking into account the conclusion part (at least the created antibody cannot: easily: sufficiently and on time reach to the alveolus sac); and the above recommendation's points as its summery, we can say that vaccination against SARS-CoV-2 may not be feasible than others PPPMs: "stay at home"; "safe masking"; "safe distancing"; and properly performing "sanitation-hygiene procedures"!

7.8 Media!, please be ethical for not to interfere with health related issues. Leave for authorized relevant specialists any information related to the pandemic

7.9 WHO! Please reevaluate our work [11], which, on April 4, 2020 offered you how to organize pandemic and disaster regulator bodies.

10. This work intends not only to give a clue in battling with this & futures pandemics, but also to be a memorial article for those victims of COVID-19 in this 21st century

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