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# SARS – CoV-2: Reasons of epidemiology of severe ill disease cases and therapeutic approach using trivalent vaccine (tetanus, diphtheria and Bordetella pertussis)

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ABSTRACT

The novel coronavirus Covid-19 follows transmission route and clinical presentation of all community-acquired coronaviruses. Instead, the rate of transmission is significative higher, with a faster spread of the virus responsible of the worldwide outbreak and a significative higher mortality rate due to the development of a severe lung injury. Most noteworthy is the distribution of death rate among age groups. Children and younger people are almost protected from severe clinical presentation.

Possible explanation of this phenomenon could be the ability of past vaccinations (especially tetanic, diphtheria toxoids and inactivated bacteria as pertussis) to stimulate immune system and to generate a scattered immunity against non-self antigens in transit, as coronaviruses and other community-circulating viruses and make immune system readier to develop specific immunity against Covid-19.

The first support to this hypothesis is the distribution of mortality rate during historical pandemics ("Spanish flu" 1918, "Asian flu" 1956 and "the Hong Kong flu" 1968) among age groups before and after the introduction of vaccines.

The immunological support to the hypothesis derives from recent studies about immunotherapy for malignancies, which propose the use of oncolytic vaccines combined with toxoids in order to exploit CD4 + memory T cell recall in supporting the ongoing anti-tumour response.

According to this hypothesis vaccine formulations (tetanus, diphtheria, Bordetella pertussis) could be re-administrate after the first contact with Covid-19, better before the development of respiratory severe illness and of course before full-blown ARDS (Acute Respiratory Distress Syndrome).

The CD4 + memory exploiting could help immune system to recall immunity of already know antigens against coronaviruses, avoiding or limiting "lung crash" until virus specific immunity develops and making it faster and prolonged.

Finally, this administration could be helpful not only in already infected patients, but also before infection. In fact, people could have an immune system more ready when the contact with the Covid-19 will occur.

## Introduction to the hypothesis

Coronaviruses are important human and animal pathogens. During epidemics, they are the cause of up to one-third of community-acquired upper respiratory tract infections in adults and probably play a role in severe respiratory infections in both children and adults. In addition, it is possible that certain coronaviruses cause diarrhoea in infants and children. However, coronaviruses are responsible of only a little amount of diagnosed pneumonia and acute severe ill especially in younger population and very often a coinfection is detected in hospitalized patients. Usually the infection is responsible of mild to moderate symptoms which rapidly spontaneously resolved [1].

Covid-19 belong to beta-coronavirus family and its transmission route and symptoms follows those of all community-acquired coronaviruses. Instead, the rate of transmission is significantly higher with a faster spread of the virus responsible of the worldwide outbreak.

In fact, it is a novel virus which most likely recently passed from bat to human and then almost unknown to human immune system. Besides, as the other coronaviruses, the Covid-19 seems to modify rapidly during spreading, further avoiding immune defences [2].

However, the most clear and troubling difference of the novel coronavirus Covid-19 compared to others alfa and beta coronaviruses is the higher mortality rate, that today reached a value of over 3% [3].

Death rate is over 1% only for patients over 50 years old, whereas until 40 years old is under 0,4%. No fatalities are declared among

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children under 10 years old to date. Death rate is almost double for male rather than female [4].

The explanation of this distribution of mortality rate according to age of infected patients could be only partially ascribed to other co-morbidities in addition to great age.

In fact, patients with no pre-existing conditions have however a case fatality rate of 0,9% [4].

This could be explained by the extraordinary rapid spreading of the virus among population and into the infected patient itself, leading to a very quickly extensive lung injury and following respiratory failure, especially in elderly and comorbid patients.

However, according to this virulence, the almost null rate of severe illness in children and generally in patients younger than 40 years old is quite un-explicable. Among patients of these age groups the virus behaviour is similar to that of seasonal community-acquired coronaviruses which are responsible also of severe but very rarely lethal infections such us pneumonia and bronchiolitis. In fact, even if this virus grows rapidly and continuously change, it is counteracted rapidly and effectively by an efficient immune response that the host has time to implement.

In other words, of course, infant, children and young people could be infected by coronaviruses and by Covid-19 itself. The infection is rapidly self-limited and probably more than we could suspect the infection progresses without symptoms.

The only possible explanation is that the immune system reacts efficiently against the virus.

On the contrary, it would seem to be that older patients undergo severe lung injury as consequence of an immune response that is late in coming, due to the novelty of the virus.

Possible explanation of these phenomena could be something, which assures ability to prompt response to the virus in younger people independently from the novelty of the virus itself. In some words, it would seems to be that younger people are almost already sensitized to the antigens of the virus without a previous contact with that specific serotype of coronavirus. In fact, they become infected and eventually develop a mild to moderate respiratory disease, but the immune system counteracts the virus and limit lung injury that is on its way to restitution ad integrum.

This immunity is not really specific, but “partially specific” for many antigens of the virus, however able to limit the infection in the organism.

Something stimulated the immune system and it scattered immunity against more and more antigens present when the stimulation occurs, as coronavirus antigens, which are always present because the virus is always circulating in the world. Children are the age group mostly exposed to all community-circulating viruses and, among them coronaviruses.

This immunity is not persistent but progressively fades out.

We hypothesize this “partially specific” immunity protects children and young people also against Covid-19. Its drop in elderly could be responsible of more severe acute respiratory illness from coronaviruses in general and of higher mortality from Covid-19, because Covid-19 performs an explosive attack to respiratory system quite similar to that of a major trauma, developing an ARDS (Acute Respiratory Distress Syndrome).

None evident difference could be really find among healthy people among different age groups able to justify the drop in immunity against coronaviruses, except its natural fade-out.

It protects from the age of two, when the hypothetical stimulation occurs, to the fifth decade because of its slow decrease.

Which is the stimulation? The only external stimulation, which healthy people receive are vaccines.

All vaccinations and especially tetanic, diphtheria toxoids and inactivated bacteria as pertussis could stimulate immune system. They develop the specific immunity against tetanus, diphtheria and Bordetella respectively, but generate a sprouting immunity against non-self antigens in transit, as coronaviruses and other community-circulating viruses.

Children receive vaccines during the first year of life. Then they become completely protect against the specific pathogens but also against multiple antigens pathogens in transit. The developed immunity gives some protection against multiple viral infection for years until the natural fade out.

After the fifth decade, that immunity is slower to be recall and reactivated. A viral infection will find immune system almost incompetent and the virus bursts into the body as an unexpected crash.

Among elderly severe pneumonia and ARDS are frequent expressions of coronaviruses, flu, etc.

## Supports to the hypothesis

1) Epidemiological observations

History of pandemic viruses reveals an unexplained phenomenon, which could support the hypothesis.

In fact, “Spanish flu” expressed its higher mortality rate among young people, especially from 20 to 45 years old, only partially explained by conditions of life after the end of the First World War. This epidemiological distribution of mortality rate remains unique and not repeated during the successive pandemics on the 21st century as “Asian flu” 1956, “the Hong Kong flu” 1968 [5].

A possible explanation is the advent of vaccines which use become extensive after the end of 1930s.

The population received vaccines and the pandemics, which developed twenty years later, had their highest mortality rate after the fifth decade of life when the partially specific immunity had faded out.

Based on this hypothesis, which attributes the responsibility of this major stamina of young people to a pre-existing immunity to the community viruses and to Covid-19 itself, a possible approach could be to stimulate again the immune system.

The repetition of non-specific vaccinations after the first contact with Covid-19, better before the development of respiratory severe illness and of course before full-blown ARDS, could help immune system to recall immunity of yet know antigens against coronaviruses. These antibodies could counteract the virus until specific immunity develops avoiding or limiting “lung crash”.

In addition, a more non-specific immunisation against coronaviruses could also be helpful to protect towards reinfections by Covid-19, already described and probably due to tendency to modify of the virus.

2) Immunological observations

The second aspect, which supports this hypothesis, derives by recent studies about immunotherapy for malignancies in vitro and in vivo on glioblastoma patients and it is based on pathophysiology of immune response to virus that is mainly CD8 + T cell-mediated.

In fact, recently, these studies suggest the possibility to limit the growth of malignancies inducing a host immune response CD8 + T cell-mediated against epitope of the tumour [6,7].

The efficacy of cancer immunotherapy relies on the generation of specific anti-tumour CD8 + T cells that recognize peptides presented on the major histocompatibility complex I (MHC-I) [8]. Effective anti-tumour activity requires fast T cell mediated responses, which is highlighted for example by clinical success with the chimeric antigen receptor (CAR) T cells targeting CD19 in B cell malignancies [9]. Importantly, it has been shown that the cooperation of CD4 + and CD8 + T cells is required for efficient anti-tumour immunity to occur [10]. Indeed, CD4 + T cells provide signals that improve the functionality of CD8 + T cells within the tumour microenvironment (TME) [11] and their depletion prior to tumour challenge results in complete loss of tumour rejection in murine tumour models [12].

To develop this immune reaction, antigen presenting cells (APCs) would process the virus and tumour- and pathogen-specific peptides linked to their surface and present the tumour-specific epitopes to CD8 + T cells and the pathogen-specific epitopes to memory CD4 + T cells that would then sustain the CD8 + T cell-mediated immune response as a bystander effect [13].

Actually, this is a technique to vaccinate the host against the antigens of the tumour but, while dendritic cells (DCs) vaccines alone have shown a limited promise in the treatment of patients with advanced cancers, their combination with a potent recall antigen such as tetanus/diphtheria toxoid can significantly improve their efficacy, especially if pre-immunization exist [7].

Basically, to reach an efficient cell-mediated antitumor response is necessary to exploit pre-existing immunity to enhance oncolytic immunotherapy. This highlights the importance of the interplay between the innate and adaptive arm of the immune system as well as the key role of effector memory CD4 + T cells in supporting the ongoing anti-tumour response.

Thus, data suggest that pre-existing CD4 + memory T cell repertoire can be exploited to support the anti-tumour CTL response and some studies demonstrated a slower tumour growth in pre-immunized mice and an improved anti-tumour response in glioblastoma patients. The pathogen-specific pre-existing immunity can enhance the anti-tumour response and the mechanism of action is dependent on the memory T cells.

In conclusion, the tetanus pre-existing immunity improved the overall efficacy of the treatment substantially by modifying the immune environment at the tumour site, especially when the treatment was virus based and contained the tetanus vaccine or the tetanus peptides.

Moreover, this effect is not restricted to tetanus but is adaptable to other pathogens as well and then the principle could be applied to other vaccine formulations. Polioboostrix is a tetravalent vaccine with a high coverage of 85% of infants immunized, making it an attractive study model [14] as suggested by Tahtinen and colleagues [6].

Summarizing:

- vaccine formulations (tetanus, diphtheria, Bordetella pertussis) re-activate CD4 + memory T cell repertoire
- CD4 + T cell exploiting supports DCs migration
- CD4 + T cells potentiate start and activity of CD8 + T cell-mediated immune response.

## Hypothesis of treatment for patient infected by Covid-19

According to this hypothesis vaccine formulations (tetanus, diphtheria, Bordetella pertussis) could be re-administrate to recall CD4 + T memory cell after the first contact with Covid-19, better before the development of respiratory severe illness and of course before full-blown ARDS.

This exploiting of CD4 + T cell could help immune system to recall immunity of already know antigens against coronaviruses. These antibodies could counteract the virus until specific immunity develops avoiding or limiting “lung crash”.

Besides, after vaccine formulations stimulus, specific immune response against novel coronavirus Covid-19 could become faster and prolonged in order to protect from the development of severe lung injury and successive early reinfection.

This result could be obtained also because the immune response will be not direct to only one specific antigen but against more antigens of the virus.

Finally, this administration could be helpful not only in already infected patients, but also before it. In fact, people could have an immune system more ready when the contact with the Covid-19 will occur.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109779.

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