Asian Journal of Immunology

3(2): 16-25, 2020; Article no.AJI.55881

Local Immunity Concept in the Context of the Novel Corona Viral Infection: A Consideration

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

Editor(s):
(1) Darko Nozic, University of Belgrade, Serbia.
Reviewers:
(1) Wuyi Liu, Fuyang Normal University, China.
(2) Vijaya Krishnan, MGM College of Physiotherapy, India.
(3) M. Zamri Saad, Universiti Putra Malaysia, Malaysia.
Complete Peer review History: http://www.sdiarticle4.com/review-history/55881

Opinion Article

Received 20 March 2020
Accepted 30 March 2020
Published 01 April 2020

ABSTRACT

The pandemic of novel corona virus disease (covid 19), is presently sweeping the world over. The causative virus is named, SARS-CoV-2. The rapidity with which the pandemic is advancing is catastrophic. That there is no known treatment for this killer disease is throwing public at large into a state of fear psychosis. The urgent need for preventive vaccine is felt now, more than ever before Though promising research is going on, the goal to achieve a breakthrough vaccine is still a long way to go. Since SARS-CoV-2 is an infection restricted to respiratory system of the affected, vaccines aimed at inducing local (mucosal) immunity may offer better chance of preventing the acquisition and spread of the disease to others, than induction of systemic immunity. With this background theme, this article briefly reviewed the epidemiology, the vaccine trials of the Covid 19 as well as the immune responses to viral infection in general and with a special focus on the concept of Local immunity advanced by Prof Besredka (1924). The historical perspective of the local immunity concept is recapitulated and the diseases, both viral and bacterial, to which vaccines are developed in the past basing on this concept are reviewed. A case is made out for applying this concept for the prevention of covid 19. It is suggested that an approach to boost local immunity, than systemic immunity, might be a better strategy of prevention of covid 19.

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Keywords: Covid 19; local immunity; viral immunity; sars-cov-2(severe acute respiratory syndrome-corona virus 2); mers-cov(middle east respiratory syndrome coronavirus).

1. INTRODUCTION

1.1 Epidemiological Considerations of Covid 19

- The massive awareness programme against the Covid 19 world over, made any introduction to this disease superfluous. Similarly the rapid changes from day to day of statistical data made any cited data meaningless, in no time. Nevertheless, convention demands brief introduction to the disease. A pneumonia of unknown cause detected in Wuhan, China was first reported to the WHO Country Office in China on 31 December 2019.The outbreak was declared a Public Health Emergency of International concern on 30 January 2020. On 11 February 2020, WHO announced a name for the new coronavirus disease. The strain involved is considered novel as it is different from corona virus strains that are known before and hence.
- The name covid 19. SARS-CoV-2 belongs to the Beta coronavirus Genus, which also includes SARS CoV (2003) and MERS CoV (2012). SARS-CoV first emerged in 2002-2003 in Guangdong, China as an unusual pneumonia, that caused life-threatening respiratory failure in certain cases. It quickly became pandemic. MERS-CoV epidemic appeared in Saudi Arabia in 2012, with people experiencing similar symptoms to SARS-CoV but dying at a much higher rate of 34 per cent. Unlike SARS-CoV, which spread quickly and widely, MERS-CoV has been mainly limited to the Middle East. On 11 February, the novel coronavirus that had provisionally been known as 2019-nCoV, was given a new name, SARS-CoV-2. The acronym SARS stands for severe acute respiratory syndrome. Cov2 stands for corona virus 2. The name denotes its close relationship to the SARS virus. According to WHO report as on 18th march 2020, the total globally confirmed cases are 1,90,415 and total confirmed deaths are 7, 800. As on March 23,2020 the total number of cases and total deaths globally are respectively, 292142 and 12784 WHO, data as on 24 march 2020 is total number of cases-372757, deaths 16,231 and countries infected are 195. As on 30 March 2020, 715 660 cases have been reported.
- Including 33 579 deaths. The speed with which the disease is spreading can be inferred from the above figures. The mortality rate is between, 1 t0 3% The economic loss due to covid 19 as estimated in the beginning of march 2020 is about 1 to 3 trillion dollar. Trade and tourism, world over are worst effected. It is considered as a zoonotic infection, reservoirs being the wild bats and certain snakes. The infection starts like flu with cold and dry cough and fever. Soon shortness of breath occurs with developing pneumonia and the patient may require ventilator support. While cold and flu viruses take 2-3 days to develop once you contract the virus, coronavirus symptoms take anywhere from 2-14 days after being exposed to the virus, as per the Centres of Disease Control and Prevention (CDC). According to a study (March 10, 2020). The transmission from man to man is through direct spread by droplet infection and indirectly by coming into contact with objects on which the virus containing infective material is deposited. The survival of the virus outside the human host is variable, depending on the material concerned ranges from 1 to 5 days. The estimated median of IP is 5.1 days. Comorbid conditions in general and respiratory diseases like Asthma/ COPD as well as old age appear to be the risk factors at the individual level. Women and children are mostly spared, but not completely. Presently thereisno specific drug against the virus is available, so, the present emphasis is on prevention of the spread of the infection. Home isolation of the suspected cases, qwarentaining the positive cases, social isolation and self imposed curfew are some of the strategies adopted, which are showing promising results. Some retrovial drugs and Hydroxy chloroquin T-Azithromycine combination are used emparically. There is intense research going on to find a vaccine against the disease.

1.2 Can Covid 19 be Transmitted by Asymptomatic Carriers?

Zhang et al. [1] have reported a familial cluster of COVID-19 indicating virus can be transmitted by asymptomatic carriers. AnBai's study presumed that asymptomatic 2019 nCoV carrier could be a transmitter. [2] A couple with COVID-19 were transmitted infection by their asymptomatic daughter who had travelled from the epidemic center of Wuhan. The sequence suggests that the coronavirus can be transmitted by asymptomatic carriers in their early and middle latent period. Asymptomatic virus carriers should be monitored and isolated as early as possible to facilitate the control of the epidemic. A paper published on NEJM about the first four people in Germany infected with 2019 nCoV found asymptomatic persons can still transmit the virus to others [3] but soon the German government's public health agency announced that the information was wrong. The "asymptomatic" patient actually had some symptoms, it was found later [4].

1.3 Are There Two Strains of the Novel Corona Virus?

At the outset it is made clear that the WHO has not at accepted the 2 strains concept as on now. Since some investigators found two types of mutations in the genome of the Covid virus (see below) and few investigators tried to see difference in virulence patterns of the same virus at different geographical places, (for instance the infection is catastrophic in Italy, but so far appears to be comparatively, mild in India) hazard a guess about the existence of more virulent and less virulent strains of the covid 19 virus. It is probable that the deficiency of timely interventional measures might be the cause, as felt in case of Italy. Xiaolu Tang et al, at Peking University in Beijing and his colleagues studied the viral genome taken from 103 cases. They found common mutations at two locations on the genome. The team identified two types of the virus based on differences in the genome at these two regions. Mutation at region 72 are considered to be the "L-type" and 29 were classed "S-type". S type is believed to be the ancestral strain descended from the animal and s type its human variant that developed later. S is wide spread in distribution Source:(https://www.newscientist.com/article/2236544-coronavirus-are-there-two-strains-and-is-one-more-deadly/#ixzz6HOHp3wF7)

1.4 Recovery of the Novel, Corona Virus from the Feces

Some researchers have reported the recovery of the virus from the feces, but its significance at present is not known. There is no evidence of feco-oral transmission.

1.5 Reinfection

The WHO has not yet confirmed any possibility of reinfection.

1.6 Approaches to Corona Virus Vaccine Production

1.6.1 Structure and antigens of corona virus

The novel Corona virus is an enveloped virus containing a single stranded m RNA and a protein inside and spoke like projections of glycoprotein on the surface. The later earned the virus the name Corona, which means a crown. genome of SARS-CoV-2 (2019-nCoV) encodes the spike protein, the envelope protein, the membrane protein and the nucleocapsid protein. The spike protein (S-protein) mediates receptor binding and membrane fusion. Spike protein contains two subunits, S1 and S2. S1 contains a receptor binding domain (RBD), which is responsible for recognizing and binding with the cell surface receptor. S2 subunit is the "stem" of the structure, which contains other basic elements needed for the membrane fusion. The spike protein is the common target for neutralizing antibodies and vaccines.EuIs been reported that SARS-CoV-2 (2019-nCoV can infect the human respiratory epithelial cells through interaction with the human ACE2 receptor. Indeed, the recombinant Spike protein can bind with recombinant ACE2 protein. It has been reported that SARS-CoV-2 (2019-nCoV) can infect the human respiratory epithelial cells through interaction with the human ACE2 receptor. Indeed, the recombinant Spike protein can bind with recombinant ACE2 protein. The spike protein (s) on the envelope of the virus and m-RNA strand of the virus within the capsid are two novel approached in the vaccine industry (Source: Sino Biological, Inc with headquarters in Beijing, China with branches in the United States and Europe).

1.6.2 The vaccine trials

According to the Kaiser Permanente report "The artificial mRNA produced in the lab, prompts host

cells to build a protein found on the surface of the virus, . A person's immune system would react to this new protein by building up an arsenal of antibodies that target and latch- onto this protein, tagging the virus for elimination. Then, the mRNA should break down and be eliminated by the body, leaving the vaccinated person better prepared to fight off SARS-CoV-2, if they are infected subsequently. A clinical trial is slated on April 2020 to conduct a preliminary human safety clinical trial of this vaccine - a wall street journal reports. In February 2020, Novavax started testing its recombinant nanoparticle vaccine candidate for coronavirus in animal models. The candidates produced antigens derived from the coronavirus spike (S) protein. Novavax is planning to use its Matrix-M adjuvant with its Covid-19 vaccine candidates to boost immune responses. "CureVac has successfully harnessed its biological insights of the life-enabling molecule mRNA to move medicine into the future. Powered by our optimization technology." CureVac AG, a clinical stage biopharmaceutical company is pioneering mRNA-based vaccine against the novel corona virus. Recently The WHO approved hydroxy chloroquine vaccine for prophylaxis against Covid 19. WHO has published a long list of counties working on corona virus vaccine and their different approaches, in this regard. Interested can refer the same as it is out of the scope of this article.

2. DISCUSSION

It is proposed to briefly review the broad principles of immune reaction s to viral infections in general as the specific immune reaction of Corona virus 19 is to early to decipher. However, the intended focus is on the concept of Local immunity and it's possible role in the interventional strategy to contain the disease.

Principles of immune reactions against viral infections in general: There are two types of systemic immunity they are

- Innate immunity
- Adoptive immunity

Innate and adoptive immune mechanisms both operate against the virus or the infected cells of the host.

Cytotoxic cells: NK (Natural killer) and CD8+cells cytotoxic T cell circulate and kills cells that are infected with viruses with toxic mediators. Cytotoxic T cells have specialised proteins on their surface that help them to recognise virally-infected cells. These proteins are called T cell receptors (TCRs). Each cytotoxic T cell has a TCR that can specifically recognise a particular antigenic peptide bound to an MHC 1 molecule. The Virus have TCR receptors which express the viral proteins. The host cells have HLA 1 antigens to which the vral proteins are bound bind.

NK cytotoxic cells are innate defence mechanisms which have fewer than normal MHC 1 receptors on the surface of the cells.

Toxic mediators of T cells: Preformed toxic mediators are stored called granules, in both cytotoxic T cells and NK cells, until contact with an infected cell triggers their release.

One of these mediators is perforin, a protein that can make pores in cell membranes; these pores allow entry of other factors into a target cell to facilitate destruction of the cell.

Enzymes called granzymes are also stored in, and released from, the granules. Granzymes enter target cells through the holes made by perforin.

Once inside the target cell, they initiate a process known as programmed cell death or apoptosis, causing the target cell to die.

Another released cytotoxic factor is granulysin, directly attacks the outer membrane of the

Table 1. Showing the various viral immune mechanisms

Immune mechanisms in viral infections		
	Against the infected cells	**Against the virus**
Innate	NK Cells Alternative compliment pathway	Interferons (a, b and g)
Adaptive	ADCC (Antibody dependant cell mediated cytotoxicity Classical complement pathway Phagocytosis	CD 8 Cytotoxic cells

target cell, destroying it by lysis. Cytotoxic cells synthesise and release, cytokines, after making contact with infected cells. Cytokines include interferon-g and tumour necrosis factor-a.

Interferon: It is one of the most effective innate defence mechanism produced by the infected. Host cell. There are 3 types of interferon, a, b and g the first two are mainly produced by monocytes-macrophages and to a lesser extent by fibroblasts. But interferon-g is produced by CD 4 and CD 8 lymphocytes and NK cells. Mechanisms of Interferon action: "transitory resistance of cells; induction of different molecules with anti-viral activity; activation of genes expressing anti-viral proteins, and increasing the expression of SLA I and SLA II".

Role of Antibodies (Ig G, IgM,):

1. Neutralisation of the virus (both IgG and IgM)
2. Agglutination (IgM)

Effectiveness of Humoral vs Cell mediated immunity (CMI): Some investigators have suggested that serum antibody is responsible for protection in the human, others have observed that influenza infection is not prevented by high levels of serum antibody Still investigators believe that serum antibody correlates with, but does not cause, protection. Cell-mediated immune responses are not only effective during acute phase of viral infection.when infected cells with virus are targeted by the CD 8+ subset of T cell population but also establish long-lived immunological memory by virtue of CD 4 + T cells.. These memory T cells become rapidly activated if they re-encounter virally infected cells and therefore function to protect against secondary exposures to the original viral pathogens. It can be host damaging if hypersensitive reaction develops as a part of immune reaction. It has also been proposed that cell-mediated immunity might be important in protection against viral infections as exemplified by the patients with hypogammaglobulinemia are not prone to more frequent or severe viral infections.

2.1 The Concept of Local Immunity

Historical perspective of the concept of local immunity [5]: Prof Besredka is the founder of this type of immunity. Working in Pasture institute in 1924, he developed his concept and tested on different organisms. He showed that B anthracite inoculated intraperitonially in guinea pig neither produced antibodies in the blood nor protected the animal from subsequent challenge with the live virus. age also proved that the organism when applied to the skin, though it did not also develop any antibodies, protected the animal from subsequent challenge with the microorganism. This study has driven home two truths. One, that immunity against the infection can be achieved even in the absence of raising antibodies against it. Second, vaccinating the site which is the portal of entry of the micro organism conferred immunity, independent of humoral immunity. This type of immunity, he called as "Local immunity".

2.2 Review of Some of the Diseases to Which the Concept of Local Immunity is Applied and Tested

2.2.1 Local immunity in polio virus infection [6]

The Salk polio vaccine, which consists of killed virus administered systemically, elicits serum IgG as the major antibody and induces little or no secretory response. As a result, the immunized individual resists systemic infection, but may become a temporary carrier, with virus persisting at the intestinal portal of entry because of the lack of secretory antibody. The orally administered, live Sabin polio vaccine, on the other hand, induces secretory antibody in the intestine and is effective in preventing replication and subsequent mucosal penetration by the virus. However US stopped OPV in favour of IPV (inactivated polio vaccine) to prevent resurgence of type 2 polio virus.

2.2.2 Local immunity in the influenza virus infection

Influenza infection of the ferret resembles the disease in the human, [7] and has been studied extensively by HENRY BARBER and PARKER A. SMALL, JR, who showed that influenza infection in the ferret is a local phenomenon, whereas recovery from active infection is influenced by systemic immune mechanism" [8]. Several workers [9,10,11] have shown that natural infection with respiratory viruses stimulates the production of immunoglobulin A antibodies in secretions and leads to resistance to reinfection, it has been postulated that a vaccine's ability to stimulate nasal secretary antibody is the deciding factor in protection of humans against influenza infection, and some

field trials of local immunization gave promising results. [12,13,14,15]. On the contrary, trial of local immunization [16] as well as attempts to correlate secretary immunoglobulin A antibody with protection [17] was unsuccessful. The study suggested that srum antibody was irrelevant to prevention of influenza and recovery from influenza in the ferret [18]. Antibodies directed to the 2 major viral surface membrane proteins, hemagglutinin (HA) and neuraminidase (NA), mediate protection against reinfection following natural infection or vaccination. Some investigators have suggested that serum antibody is responsible for protection in the human, [19] others have observed that influenza infection is not prevented by high levels of serum antibody [20]. Several investigators believe that serum antibody correlates with, but does not cause, protection [21]. The lack of virus dissemination is consistent with the inability to detect viremia during influenza infection of ferrets and humans [22].

Mucosal immunity in Shigella et al. [23] explored the mechanisms of protection mediated by Shigella LPS-specific secretory IgA (SIgA), the major mucosal Ab (antibody) induced upon natural infection. They found that anti-Shigella LPS SIgA, mainly via immune exclusion, prevented Shigella-induced inflammation responsible for the destruction of the intestinal barrier. In the form of immune complexes, SIgA guarantees both immune exclusion and neutralization of translocated bacteria, thus preserving the intestinal barrier integrity by preventing bacterial-induced inflammation. These findings add to the multiple facets of the non-inflammatory properties of SIgA.

2.2.3 Mucosal immunity in infection by *V. cholerae* [24]

Bloom PD, et al. reviewing the mucosal immunity against enteric bacterial pathogens states that "*V cholerae*, secretes cholera toxin (CT), a potent enterotoxin that induces a voluminous diarrhea via adenylate cyclase-dependent chloride secretion. Protective immunity is based on secretory (s) immunoglobulin A directed against whole-cell components that prevent attachment to gut epithelial cells and is enhanced by CT, an immunogen with potent adjuvant activity".

Mycoplasma and local immunity: Lisa M. Hodge, Jerry W. Simecka et al. [25] in their study concluded that "local immunity along the respiratory tract plays a major role in resisting and controlling mycoplasma infection and should be considered in vaccine development against mycoplasma respiratory diseases. Generation of immunity in the upper respiratory tract appears to be optimal in preventing the initial mycoplasma infection at this site, but adjuvants (like cholera toxin (CT) enhanced these protective responses. In the lower respiratory tract, pulmonary immune responses seem to be more effective than serum antibody responses and nasal immunization can confer some protection from pulmonary infection".

Role of the secretary IgA in local immunity [26]: Secretory IgA (SIgA) is the principal immunoglobulin (Ig) on mucosal surfaces of humans the respiratory contains equivalent amounts of IgA and IgG in addition to some IgM (Brandtzaeg et al., 1999). The main function of IgA is the neutralization of pathogens and toxins without causing inflammation since it does not activate complement (Cerutti, 2008; Macpherson & Slack, 2007).

The mucosal microbiota, epithelial cells, and the mucosal immune system constitute a stable and interdependent “tripod” that maintains mucosal homeostasis by complex mechanisms (Corthesy, 2007; Hooper, 2004).

1. Bacteria adhere to the surface receptors of the epithelial cells and express the basolateral membrane receptor (polymeric Ig receptor; pIgR) that transports locally produced polymeric (p)IgA into the external secretions (Kaetzel & Mostov, 2005).
2. Endogenous bacterial of the intestinal tract, and the respiratory and genital tracts, are coated in vivo with SIgA (Bos, Cebra, & Kroese, 2000; van der Waaij et al. 2004) that limits their epithelial adherence and penetration, thereby confining them to the mucosal surfaces.

IgA neutralizes inflammatory microbial products inside epithelial cells (Fernandez et al., 2003). Finally, if bacteria trespass the epithelial barrier, IgA transports these bacteria back into the lumen via pIgR or promotes their phagocytosis through Fc (Pasquier et al., 2005; Phalipon Corthésy, 2003).

Killed bacteria seem to be at least 100-fold less effective at inducing IgA responses than live bacteria, presumably due to their inactivity and the digestion of dead bacteria during transit through the stomach and intestine (Hapfelmeier et al. 2010; Macpherson & Uhr, 2004).

2.2.4 Concept on local immunity as applied to in covid 19 immunity

2.2.4.1 Recapitulation of some considerations

1. Belyakov et al. [27] opined that:
   A. "The route of vaccination is important in influencing immune responses at the initial site of pathogen invasion where protection is most effective. Immune responses required for mucosal protection can differ vastly depending on the individual pathogen. For some mucosal pathogens, high-titer neutralizing antibodies (Abs) that enter tissue parenchyma or transude into the mucosal lumen are sufficient for clearing cells, free of the virus."
   B. Induction of the mucosal innate and adaptive immune systems, including CD4+ T helper cells, Th17, high avidity CD8+ CTL and secretory IgA and IgG1 neutralizing Abs, at the site of pathogen entry may be required for effective protection against highly invasive pathogens.
2. The main function of the innate mucosal immune system, to discriminate between dangerous and innocuous organisms, is determined by the recognition of specific pathogen-associated molecular patterns via activation of TLRs, NOD-like receptors, retinoic acid (RA)-inducible gene I-like helicases, and C-type lectins [28].
3. Studies evaluating mucosal infection and immunization in humans and animals have demonstrated the existence of a common mucosal immune system (CMIS) that consists of gastrointestinal, respiratory, and genital mucosa [29].
4. The CMIS implies the ability of Ag-specific lymphocytes to home to mucosal effector sites in addition to the site where initial Ag exposure occurred [30] compartmentalized mucosal immune responses (CMIRs) that consist of innate responses, mucosal Abs (secretory Ig (sIg) A and sIgG) and CD8+ CTLs localized to tissues proximal to the mucosal site of immunization are necessary for protection from mucosal pathogens (Belyakov et al.).
5. Protective immunity against mucosal pathogens will require novel vaccine strategies to induce mucosal immune responses tailored to the anatomic location and the threat of the invading pathogen
6. Protective immunity against mucosal pathogens will require novel vaccine strategies to induce mucosal immune responses tailored to the anatomic location and the threat of the invading pathogen pathogens may require mucosal vaccine strategies that activate multiple arms of the innate and adaptive immune systems [31,32,33,34,35].
7. Optimum mucosal vaccination leading to compartmentalized mucosal immune responses might ensure that the appropriate cells are armed and ready to respond immediately to infection and to confer protection not achieved following natural infection.
8. Protective mucosal immune responses are most effectively induced by mucosal immunization through oral, intranasal (i.n.), intrarectal, or intravaginal routes, and an optimized mucosal vaccination strategy may have a much greater potential for generating local protective mucosal immune responses.
9. Mucosal immunity concept has worked well in case of viral infections like influenza, poliomyelitis and bacterial infections like salmonella and *V. cholerae* and mycoplasma infections, as outlined above.
10. The CDC has not made any comments regarding the relative merits of the inactivated and recombinant vaccine and nasal spray vaccine for influenza.

The proposed hypothesis: Covid 19 is different from other deadly viral infections, say for instance HIV. In the later, the virus is found in all body secretions including semen with variable infectivity of each body fluid. There is no suggestion of any tissue "tropism" in HIV. As against HIV, the corona virus (CoV) enters the body through the nose, multiplies there, and excreted through nasal secretion. In fact, they are limited almost exclusively in the upper respiratory epithelium initially and later if not prevented, spreads locally to lower respiratory epithelium, suggesting some sort of "tissue tropism". Additionally, the novel corona virus is shown not to be disseminated beyond the respiratory tract. The recent reports of involvement of cardiovascular system (myocarditis) and a couple of cases of involvement of the brain, have no proof of direct involvement of the cov, beyond reasonable doubt. It could’ve be due to fallout of the immune reactio mounted against the virus. Consequently

the cause of high mortality associated with Covid 19, is restricted to a deadly type of pneumonia. If the infection could be arrested at portal of entry, i.e. the nasal epithelial level, the disastrous consequences of spread to lower respiratory tract; Ímay be averted. This makes a strong case for creating local immunity at the level of the nasal epithelium itself. Local mucosal infections of the respiratory or gastro-intestinal tract may elicit local cell-mediateld and humoral (IgA) immune responses, but not necessarily systemic immunity. Conversely, systemic immunity does not always lead to local mucosal immunity. localized infections of mucosal surfaces, and the protection derived , does not correlate with the presence of serum antibody, but it does correlate with the presence of local IgA antibody, as has been shown in human studies of viruses restricted to the respiratory tract (e.g., respiratory syncytial virus and influenza virus) or to the gastrointestinal tract (e.g., enteroviruses).

The route of administering the vaccine is the major determinant of the issue immunity. The past experience of intranasal vaccine as is approved for influenza may be taken as an example, in the case of Covid 19. It is also shown that prior systemic vaccination may interfere with the recall memory exercised by the nasal mucosa, should the pathogen cause reinfection the same person. There is no permanent infection-induced immunity conferred by the Covid 19. This factor also supports the suggestion of raising local immunity of nasal epithelium by administering the vaccine intranasally. It is logical that raising local immunity in nasal epithelium may give a multi-pronged protection from the Covid 19. against entry multiplication. As well excretion in nasal sections. The last one is very important from public health point of view , in preventing the spread of the infection to others. Local immunity is found to be effective at least in two diseases. To elaborate this point, the polio virus, whose portal of entry of the infection is the gastro-intestinal tract, oral polio vaccine is the time tested vaccine that conferred immunity to polio virus. It is shown to be effective by raising mucosa immunity both at pharyngeal and intestinal levelled –IPV (inactivated polio vaccine) was less effective than OPV in preventing and limiting intestinal infection, even though it induced higher post vaccination serum antibody levels. While opv (oral polio vaccine) checks the excretion of polio virus through faeces (there by preventing the spread of infection to others, [36] the continued excretion of the polio virus in case of immunisation by the inactivated vaccine administered by parenteral route, poses risk of continued deco-oral transmission, though it offered immunity at the personal level. Secondly, the influenza vaccine administered intranasally as a spray type vaccine has been accepted efficacy-wise by the CDC.

3. CONCLUSION

The COVID 19, as seen from the tropism to airway (nasal) epithelium through which it gains entry, multiplies and even shed in the nasal secretions, indicates that, efforts to raise the local immunity of the respiratory epithelium, especially at the very portal of its entry, may be fruitful in 'nipping the infection in the bud'. Accordingly in the case of Covid 19, vaccine developed might be effective, if administered intranasally, rather than other routes of vaccine administration, it is felt.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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