

An Update on the Place of ART with SARS-CoV-2 around and Influence on Both Reproduction, Transmission Possibilities to, Progeny, Partners and Staff—What is the Answer

Kulvinder Kochar Kaur^{1*}, Gautam Allahbadia², Mandeep Singh³

¹Department of Human Reproduction, Kulvinder Kochar Kaur Centre for Human Reproduction, Punjab, India

²Scientific Director, A Centre for Human Reproduction, Punjab, India

³Department of Neurologist Swami Satyanand Hospital, Punjab, India

*Corresponding author: Kulvinder Kochar Kaur, Department of Human Reproduction, Kulvinder Kaur Centre, India, Tel : 9501358180; E-mail: kulvinder.dr@gmail.com

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Abstract

Since the initiation of COVID 19 infection in Wuhan China, in November 2019 the whole world has been battling with the COVID 19 Disease. We have earlier reviewed COVID 19 with respect to viral structure similarities with other Corona viruses, main clinical features and kept on updating management as and when some insight is gained. We briefly covered the aspect of influence on pregnancy, vertical transmission, lactation safety, along with presence of controversial findings regarding presence of the virus in semen or absence and safety of intercourse with regards to transmission. It had been observed males are more affected by the disease with mortality greater in them both in Chinese studies along with New York statistics probably due to lack of exposure of male antigens getting recognized as self by the immune system. With the spread of COVID 19 to European Countries with so many ICU admissions they faced shortage of OT's, ICU'S and hence all routine procedures were banned in Italy, Spain and then whole world European Society of Human Reproduction and Embryology (ESHRE), American Society of Reproductive Medicine (ASRM) recommendations banned ART worldwide but gradually reintroduction is being considered. Hence it became vital to get an insight into how the virus affects both the male and female reproduction, probability of involving the next generation through embryos and transmission to staff with pandemic not subsiding. Here we tried to update the present day knowledge on the same utilizing a PubMed search engine with the MeSH terminology; SARS-CoV2; male reproduction; female reproduction; gametes; embryos; transmission through placenta till date along with utilizing the WHO worldometer site to update the current disease status in world and the current recommendations for prospective ART introduction back gradually and how to ensure safety of patients, health care personnel dealing with secretions like semen follicular fluid along with safety of embryos and precautions needed in embryology laboratory to be back on the right path as earlier be it with regards to vitrification, medication cycles along with IVF/ICSI Procedures.

Keywords: COVID-19; Male gametes; Female gametes; Endometrium; Vitrification; ART

Introduction

Earlier we have reviewed the pathophysiology of COVID-19 along with possible therapies as and when we are getting updated on this pandemic and have covered step by step presentation, prophylaxis as well as treatment. As of 21st June the global incidence was 8,992,0723 cases with United States of America (USA) accounting for 2.33 million, and then with 1,070,139 cases in Brazil to be followed by Russia with 5,76,952 cases and India was 4th with 411,773 cases (**Table 1**). However today on 7-7-2020 in USA it has escalated to 3,041,950, as well as 1,628,283 in Brazil [1].

To start with India started with social distancing and had slow rise but after the lockdown over rate has been escalating in India as well reaching from 3.44 lakhs on 21st June to 7.23 lakhs on 7-7-2020, 6,94,230 in Russia where US population is 331,034,037 and Indian is 138,019,674, although worldwide escalation keeps continuing with this virus defying all norms, be it temperature, in coolest to hottest countries displaying temperatures of upto 50 degree Celsius in India to cooler USA. On 4th July there was a 50,000 increase in USA in 24 hrs alone. Although there was massive rise in some European countries, initially with lot of mortality like Italy, Spain and UK the process seems to have halted there now with better awareness. Percentage deaths continue to be low in India as compared to America and European countries [2].

Earlier we have tried to update with the controversial reports on male with some studies showing the virus in sperms others contradicting it here we further update on latest work done with reproduction not being given a priority in view of ICU settings of the severe cases and daily new kinds of presentation being unfolded (**Table 1**).

Structure of SARS-CoV along with SARS-CoV-2

Corona viruses represent a family of large enveloped, positive stranded RNA viruses which cause upper respiratory, Gastro Intestinal Tract (GIT), as well as Central Nervous System (CNS) diseases in humans as well as other animals. Human Coronaviruses H CoV-OC43, H CoV-229E, H CoV-NL63 as well as H CoV-HKU1 circulate in humans and cause mild respiratory diseases. But the outbreak of SARS-CoV-2 in 2002 as well as the MERS-CoV in 2012 demonstrated that Corona viruses can cross the species barrier and come out as highly pathogenic viruses. The high mortality rate along with wide spread nature of these new emerging Coronaviruses point that they are a marked threat to global health [3].

The spike glyco protein of the Corona viruses is a class viral fusion protein present on the outer envelope of the virion having a key role [4] in viral infection by recognizing host cell receptors and modulating fusion of the viral as well as cellular membranes. The Coronavirus S glyco protein gets synthesized as a precursor protein amino acids which then gets cleaved into an amino terminal S1 subunit as well as carboxy terminal S2 subunit. S1/S2 heterodimers assemble to develop a trimer spike that protrudes via the envelope. The S1 subunit contains a Receptor Binding Domain (RBD), while the S2 subunit possesses a hydrophobic fusion peptide as well as 2 heptad repeat regions. Triggered by receptor binding, proteolytic processing as well as acidic pH in the cellular compartments, the class 1 viral fusion proteins undergo a transition through a metastable prefusion state to a stable prefusion state at the time of infection.

Country	Total Cases	New Cases	New Deaths	Total Recovered	Active Cases
World	89220723	13518	5258	4743658	3711544
USA	2330578		1373	972941	1235657
Brazil	1070139		621	543186	476895
Russia	576952		542	334592	234358
India	411773	46	4	228307	234358
UK	303110			N/A	N/A
Spain	293018			N/A	N/A
Iran	202584		9507	161384	31693

Table 1: Worldwide epidemiology as on 21/6/2020 at 11:30 pm.

Receptor binding subunit gets cleaved as well as the fusion subunits undergoes large conformational rearrangements for exposure of the hydrophobic fusion peptide, stimulating the development of a 6-helix bundle, and bring the viral along with cellular membranes nearer for fusion. The structure of the SARS-CoV S glyco protein in complex with the host cell receptor ACE2 as shown by cryo-EM [5]. The complicated structure revealed that only one receptor binding domain of the trimeric S glyco protein binds CE2 and takes an protruding up" conformation.

Additionally, they evaluated the structure of the SARS-CoV S glyco protein and its complexes with ACE2 in separate in vitro conditions, that might simulate various conformational states of the S glyco protein at the time of viral entry. Dissociation of the S1- ACE2 complex from certain prefusion spikes was seen and characterized. Further, they characterized the rosette-like structures of the clustered SARS-CoV-2 trimers in the postfusion state seen on electron micrographs. Structural comparisons pointed that the SARS-CoV S glyco protein retains a prefusion architecture following trypsin cleavage into the S1 and S2 subunits along with acidic pH treatment. But binding to the receptor opens up the receptor binding domain of S1, that might aid in the liberation of the S1-ACE2 complex as well as S1 monomers from the prefusion spike and trigger the pre to postfusion conformation transition. The Cryo-EM structure of the 2019-nCoV spike in the pre-fusion conformation is demonstrated [6].

Role in Human Reproduction

Role in male and female gametes

Evaluation into the molecular details of SARS-CoV2 infection have been started at a fast pace, with various crucial truths already found out. The ones we have already highlighted earlier, briefly the viral entry needs the binding of SAR-CoV-2 glycoprotein to the host receptor ACE2. Host proteases like Trans Membrane Serine Protease2 (TMPRSS2) are then required to cleave the viral S protein for stimulating conformational alteration to S that lets the permanent fusing of the viral as well as host cell membranes. The significance of TMPRSS2 has got corroborated as well as is clear in studies projecting that its inhibition blocks the entry of SARS-CoV-2 as well as transmission in targeted lung cells [7].

TMPRSS2 gets more widely expressed within human tissue as compared to ACE2, pointing that ACE2 might be one of the major determinants, regarding a particular cell type can get infected via the virus. Single-cell RNA sequencing in both human as well as nonhuman primates respiratory tissues correlated with COVID-19 [8]. This coexpression has further been proven demonstrated in different tissue kinds like the ileum, heart as well as kidney for which there are proven COVID-19 symptoms. Coexpression of ACE2 as well as TMPRSS2 in pneumocytes within the lungs as well as goblet liberating cells in the nose, pointing that these cell kinds might act as foci for infection as well as potentially reasoning out the range of respiratory symptoms correlated with COVID-19 symptoms. Finding the virus in blood, faeces as well as probably urine points that the influence of SAR-CoV-2 on cardiac, enteric as well as renal function might be secondary to the direct infection of cells in these tissues instead of being following Acute Respiratory Distress Syndrome (ARDS) [9].

With the knowledge that the clinical features of COVID-19 seem to be mainly influenced by the tissue that display coexpression of ACE2 as well as TMPRSS2 in the cells that make them, it can be posited that viral infection might influence the reproductive function. If cells of the male as well female reproductive systems express these genes too. ACE2 as well as

TMPRSS2 expression has been demonstrated in testicular, endometrial, as well as placental cells with different interpretations. Till date the expression of SARS-CoV-2 host entry protein have not been evaluated in human or nonhuman primate ovaries, particularly in the outer ovarian cortex, that are the location sites of germ cells. These reproductive indices are not classically evaluated in Intensive Care Unit (ICU) setting as well as any actions of COVID-19 on fertility might not be easily appreciated till epidemiological results are there. Hence use of publicly data easily accessible the unpublished transcriptomic data, as well publicly available bulk RNA as well as proteomics data, for evaluation of the expression patterns of viral host entry protein in reproductive cells population can be done. Further consideration was given to the expression of the receptor basigin with the minimal data point that it might have the ability to modulate viral host entry, as well as cysteine [10].

With the expression patterns of ACE2 as well as TMPRSS2 in tissue examined upto date are cell type specific, scRNA seq evaluation that shows the coexpression of these genes within individual cells, are anticipated to be especially significant in getting insight in the etiology of the disease. Cell kinds in the reproductive system have different lifespans as well as cells which live for smaller time might not be that harmful for a person's lifetime reproductive potential on infection. Like, somatic spermatogonial cells in the cells are constantly self renewing cells which remain throughout male reproductive life, in contrast to differentiated spermatocytes which are removed from the reproductive system in about 60 days. In the ovary a cohort of approximately. In comparison, the cells of the deciduas differentiating as well as shed in successive menses (usually 21-40 days in case of regular cycles). Cell-kind particular expression pattern of genes which generate viral entry host entry protein, as well as isolation of potential infection loci within the reproductive system, are hence essential to anticipate if SARS-CoV2 will have any influence over fertility. Hence studies carried might anticipate the chances of human embryos getting infected with SARS-CoV-2. During the pandemic, fertility therapies in a lot of countries have been slowed down, cancelled or even banned straight. Knowing the decreased percentage of success with escalating female age, an urgent requirement is to restart these therapies as early as possible once safety is proven. Having insight if SARS-CoV-2 has the ability to infect gametes as well as embryos generated is of vital significance when thinking of risk on naturally as well as Assisted Reproductive Technology (ART) during this COVID-19 pandemic [11].

They utilized the isolation of cell types that coexpress the crucial ACE2 as well as TMPRSS2 genes along with proteins in addition to other candidates that are probably responsible for SARS-CoV2 cell entry. Depending on the single cell RNA-sequencing data this coexpression of ACE2 as well as TMPRSS2 was not found in testicular cells that included sperms. A subpopulation of oocytes in nonhuman primate ovarian tissue was detected to express ACE2 as well as TMPRSS2, but no coexpression was seen in somatic cells. RNA expression of TMPRSS2 in 18 samples of human cumulus cells was demonstrated to be low or absent. A general consensus was found among publicly present bulk RNA as well as protein datasets regarding ACE2 as well as TMPRSS2 expression patterns

in testis, ovary, endometrial along with placental cells. Hence concluding that this examination points that SAR-CoV-2 infection is not likely to exert longtime actions on male as well as female reproductive function. Though one can't assume that these outcomes are definitive, they indicate that certain techniques where oocytes get retrieved as well as fertilized in vitro are correlated with minimal risk of viral transmission from gametes to embryos and might actually have the potential of reducing the exposure of reproductive cell types that are vulnerable to infection in contrast to natural conception.

Role in human Endometrium

TMPRSS2 is essential for the virus to bind ACE2 as well as spread right through the infected host, via cleavage that is essential for the virus to bind ACE2 as well as spread. Other proteases being evaluated having association with SARS-CoV-2 infectivity, in relation to the S protein getting cleaved. FURIN, is another protease that is anticipated to cleave S protein, that is located besides ACE in the epithelial layers of numerous oral mucosal tissues. MX dynamain like-GTPase control neutrophil invading, that promotes infection via protein S modulation through neutrophil elastase [12].

Minimal studies have concentrated on the virus's action on fertility as well as how it influences fertility along with causing injury to reproductive therapies. The endometrium is key for human reproduction as well as embryo getting implanted, although studies had not been done on SARS-CoV-2 infection on menstrual cycle propagation. Finding this has significance for evaluation of the risk of Assisted Reproductive Technology (ART), knowing that a healthy endometrium is required for embryo implantation as well as growth.

This endometrium is a complicated tissue, undergoing a cycle of cell death as well as renewal about each 28days. Various transcriptomic studies have tried to get insight in gene expression alterations right through through menstrual cycle, with maximum data being present in public places like Gene Expression Omnibus (GEO) database. As per the Human Protein Atlas, ACE transcript is low in endometrium as well as not located as a protein. As per the HPA expression amounts, TMPRSS4 as well as FURIN RNA expression is small as well as protein amounts are medium while CTSB, MX1, as well as BSG have medium RNA expression as well as larger amounts of protein expression. Nevertheless, little knowledge regarding how the virus could influence endometrial receptivity as well as embryo implantation has been available. Thus Gene expression data from 5 studies that included 112 women having normal endometrial pathology was utilized to characterize receptor expression throughout the menstrual cycle. Their study population comprised of 29 samples in the proliferative phase, 29 samples in early secretory phase, 43 in the medium secretory phase, and 8 in the late secretory phase. A relative expression value of low, medium, and high expression was established. The thresholds was equivalent to 1%-10%, 11%-50% and 51%-100% categories of gene expression values of the total integrated dataset. Transcriptomic data sets that were present across the various phases of endometrial progression were utilized for assessing the molecularly the risk of transmission of SARS-CoV-2

at the time of this COVID pandemic. In an Infertility research department that was attached with a public, they tried to evaluate gene expression data from five studies in 112 patients with normal endometrium collected throughout the menstrual cycle. Basic idea was to find out the Gene expression and association among viral infectivity genes and age throughout the menstrual cycle. They observed that Gene expression was high for TMPRSS4, CTSL, CTSB, FURIN, MX1, and BSG; medium for TMPRSS2; and low for ACE2. ACE2, TMPRSS4, CTSB, CTSL, and MX1 expression escalated toward the window of implantation. TMPRSS4 expression was positively correlated with ACE2, CTSB, CTSL, MX1, and FURIN during several cycle phases; TMPRSS2 was not statistically significantly altered across the cycle. ACE2, TMPRSS4, CTSB, CTSL, BSG, and MX1 expression increased with age, especially in early phases of the cycle. Thus Concluding that Endometrial tissue is likely safe from SARS-CoV-2 cell entry based on ACE2 and TMPRSS2 expression, but susceptibility increases with age. Further, TMPRSS4, along with BSG-mediated viral entry into cells, could imply a susceptible environment for SARS-CoV-2 entry via different mechanisms. Additional studies are essential to determine the true risk of endometrial infection by SARS-CoV-2 and implications for fertility treatments [13].

General Recommendations

Besides the organizations like the Italian Society, European Society of Human Reproduction and Embryology (ESHRE) gave the scientific recommendations, as far as Assisted Reproductive Technology (ART) was concerned. They have advised to cancel fertility therapies, other than in poor responders, who are allowed to undergo therapy, though this might put more stress for couples who have been very keen to have babies fast. Further suspension of new therapies have been recommended or utilize freeze all protocols in cases where HCG has already been initiated. In patients who need urgent fertility preservation cryopreservation of gametes is advocated. Although the correlation among SARS-CoV-2 as well as pregnancy secondary to ART therapies are not certain as proven by European Society of Human Reproduction and Embryology (ESHRE) along with recommendations from American Society of Reproductive Medicine (ASRM). The influence of virus in the markedly initial stages of embryo formation meaning fertilization to blastocyst as well as from implantation till the 1st trimester is not clear. On the basis of proof as far as pregnancy results that include abortions as well as Live Birth Rates (LBR) is not clear. Knowledge regarding seropositive in women having SARS-CoV-2 would aid although might never be available for ART. Despite the stoppage of all medical techniques associated with infertility therapy did not have any proof behind, the decision has generated a worldwide challenge in health care systems as well as cancellation [14] in fertility therapies will besides ensuring stoppage of transmission of virus, further prevent extra stress added to all these systems. Till now the statements given by ESHRE websites announcements have been made regarding minimal probability of gametes embryos getting contaminated via SARS-CoV-2, since steps involving washing, culture as well as freezing protocols seem to have decreased the probability of potentially spreading the viral load although not totally removed. With the probable lack of SARS-CoV-2 receptors on the

gametes (like spermatozoa as well as oocytes) as well as embryos would corroborate this presumption robustly, whereas the existence of Zona Pellucid (ZP) in the oocytes as well as embryos till the 6th day of formation might not negate our presumption that the virus might have a negative influence of therapies. Usually the health care personnel tend to promote postponement of fertility therapies, if one of the partners is exhibiting symptomatology of or had recent recovering out of any viral infection simulating a flu. The explanation is easy as any viral infection like say Zika virus might result in infertility. The present world experience has exemplified how SARS-CoV-2 results in much more severe illness as compared to any other viral infection like influenza as well as exaggerated morbidity as well as mortality [14]. Considering the cellular level common influenza viruses aid in oxidant-sensitive pathways, resulting in inactivation of the pathogenic modes which the oxidative Stress (OS). Escalated Oxidative Stress (OS) has been pointed to be responsible for male fertility, via a decrease of propagational motility as well as concomitant reduction in motility of spermatozoa as well as enhanced DNA fragmentation. With these results, one can presume that SARS-CoV-2 via getting activated by pathogenic pathways, might escalate DNA fragmentation that might influence the fertilizing capacity. In the same way SARS-CoV-2 might influence the oocytes working via modes which enhance the OS. Actually OS correlates with changes in DNA methylation, whereas in association with procedure it might have a negative influence on the DNA methylation circle, with poor neonatal results. Understanding that SARS-CoV-2, works via the ACE2 receptor, a probable direct action of this particular virus on follicles oocytes as well as spermatozoa can be ruled out. However ACE2 receptors have been demonstrated on human leydig cells that points to a probable direct action of the virus on the male reproductive system. In combination these observations suggest that a direct action of SARS-CoV-2 on as well as spermatozoa, however greater cellular evaluations are required for proof. Regarding probable contamination of the embryology laboratories as well as the embryology staff by SARS-CoV-2 is highly likely, with the usual precautions taken at the time of Oocyte Pick Up (OPU) or gamete/embryo manipulation would get altered during IVF therapy with a virus positive asymptomatic case. Further the spaces that are already getting utilized needs cleaning as well as disinfected with particular products following each case. The whole staff needs to have training with regards to particular protocols to manage those infected via SARS-CoV-2 as well as require to wear particular filtering face masks. While physicians presence is not essential, utilization of telemedicine in case of any fertility queries, that includes embryological outcomes, will aid in reducing the transmission of the virus to the least. The routine workup uniform needs to get replaced by on similar to or identical to the uniform with which they work for SARS-CoV-2 infection, like protective coverall shoes, along with isolation clothes that is combined using a head cover. This aids in forming a physical barrier for avoidance [15] of any probable needs to contamination. Gloves as well as face masks need to be worn all the times on a single utilization basis (meaning besides in SARS-CoV-2 positive asymptomatic cases). These personal protective equipment, that include masks with respirators for health care personnel in fertility clinics is probably needed to be added to

the everyday condition. In case of clinics having lots of stimulation cycles, it would be advisable to limit the numbers of the staff that come in close association with COVID-19 cases. Contamination of the embryology laboratories appears to be a realistic probability, in spite of negative pressure which is present in maximum laboratories. Apparently SARS-CoV-2 appears not to follow the seasonal patterns, as observed in maximum flu outbreaks, and thus the virus might still possess the capacity to contaminate at temperatures over 25°C. Hence it might be of use to reexamine the temperature of laboratories along with pressures, to ensure that the virus is not there in the air or does not get a possibility of survival [16]. Keeping different incubators, for the infected patients with COVID-19 infection might be utilized to prevent any cross contamination potentially as SARS-CoV-2 might still contaminate plastics for about 72 hrs implicating that non embryo toxic dishes might not be free of the virus. In the coming yrs, it might be that quality control of culture dishes with need SARS-CoV-2 free sheets to be sure that exposable dishes as well as all associated equipment are free of the virus. Although this SARS-CoV-2 virus has not been examined for its resistance to cooling rates at the time of vitrification, the resistance of rest of the viruses to cryogenic liquid nitrogen temperatures was documented 2 yrs back reported a couple of years ago. In view of the resemblance to other common viruses it seems it would be safer to utilize different liquid nitrogen cryostorage for SARS-CoV-2 positive women. Further another different tank for storage for COVID-19 positive sperm samples might be a good decision [17]. In the same fashion, all donors will require to show the results of SARS-CoV-2 tests. All liquids need to be examined for the virus, as well as all suppliers need to give a statement regarding the ingredients being free of the virus. In spite of early details with lack of proper scientific proof, one can conclude that this SARS-CoV-2 explosion has presented separate challenges to the world reproductive healthcare community, with probable harmful repercussions for the couples looking for infertility therapy. In the coming few yrs we might witness decreased fertilization, implantation as well as LBR, whereas at the same time innovative challenges will come for embryology laboratories regarding neutralization of any viruses that are present while conducting any delicate procedures [18].

Conclusion

As compared to influenza virus infection, 118 pregnant women in Wuhan, China, presenting with COVID-19 infection did not show any escalated chances with regards to complications or severe disease in contrast to non pregnant women presenting at same age as well as infection. Neonatal throat swabs examination of 8 newborns for SARS-CoV-2, were negative, just like milk samples obtained via 3 patients. In view of the most centres cancelling all ART procedures that included medical therapy in view of uncertainty, considering the reducing success rates in ART/IVF in case, various countries have reintroduced, with a lot more considering starting these therapies once again, to start with in women over 39 yrs and subsequently in younger women as well. Thus it has become essential to have insight if SARS-CoV-2, might infect gamete as well as embryos, understanding the probable effects on natural conception, along with pregnancies secondary to ART/IVF outcome.

More recently in a documentation via Wuhan University hospital from China, neither of the throat swabs of the 6 swabs of newborns of 6 labouring women with corroborated COVID-19 showed SARS-CoV-2 as per reverse-transcription Polymerase Chain Reaction (PCR) examination. However, their neonatal umbilical blood actually showed virus-particular antibodies. Five infants possessed enhanced IgG amounts, while two newborns displayed IgM antibodies. Contrary to IgG, the greater macromolecular IgM, mostly is not anticipated mostly via placenta from maternal compartment to fetus. Another study where mothers presenting with SARS, aberrant weights as well as pathology were seen in the placentas of 2 cases infected with SARS-CoV-2 in the 3rd trimester. It has been posited that the IgM found in the newborns might have evolved secondary to aberrant or injured placentae or, besides the probably might have been formed by the neonates themselves, responding to transplacental viral infection. They observed that BSG had greater broad expression across testicular cell types as compared to ACE2 as well as was coexpressed in CTSL in early as well as late primary spermatocytes. In the same line BSG as well as a CTSL transcripts were found in all of the 18 examined human cumulus cell samples. Yet, none or low expression of TMPRSS2 in the cumulus cell samples was observed.

This is in view of SARS-CoV-2 being observed in urine different liberations like saliva, stool, urine as well as Gastro Intestinal Tract (GIT) secretions. Hence the query if the virus gets transferred in semen needs to be revealed. While the blood testicular barrier is not perfect, SARS-CoV-2 might infect the male reproductive tract, mainly in the existence of inflammation. Till date 27 viruses have been observed in semen correlated with viraemia. It has been posited that the viral existence in semen might be more prevalent than we usually appreciate along with traditional non sexually transmitted viruses might be existing in the genital liberations.

Anticipating that most patients positive for SARS-CoV-2 might refrain from coitus during the acute phase of illness, in view of weakness, erectile problems, fear of transmission of virus to their opposite number, or other reasons this might not hold true for recovering cases. Various other queries need to be immediately answered regarding the general. It was pointed recently that of the monoclonal antibodies that target SARS-CoV-2 protein isolated from memory B cells of a person who got infected via SARS-CoV in 2003, had the ability to neutralize SARS-CoV-2. In the same way about a hundred potential vaccines are getting evaluated, with some of them undergoing human clinical trials for effectiveness as well as safety like cervarex in India, projected for release on August 15. More recently a pharmaceutical laboratory that was located in Massachusetts, has formed a corona viruses vaccine known as mRNA-1273, that has been evaluated in human volunteers and had apparent efficacy. One hopes that these initial reports that seems to give incentive get corroborated and turn out to be reliable.

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