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Some Differences Between RNA-based Vaccines and RNA-viral Infections and Immune Reactivity

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Abstract

Some basic differences between RNA-virus infections and immune reactions elicited after injection of modified biotech-constructed RNA or DNA short viral sequences are briefly presented based on consolidated knowledge on viruses and immunology. Reactivity to manufactured biotech-RNAs are relatively known and controlled within test tubes. As opposed, interactions between inoculated biotech-RNA-DNAs-modified vaccines into the human body and its complex and incompletely known functions are unpredictable. To state the contrary, indicates that present-day technology pretends to know everything on how the human body reacts to the inoculation of these RNA-DNA vaccines, and untenable scientific belief. Unknown pathological reactions might be generated from biotech-RNAs utilized as vaccines, at the cellular and organismal level, as the active spike protein of the SarsCov2 virus has demonstrated, generating many more adverse effects in comparison to previously used vaccines. The present brief paper of general theoretical content, points out some of the main biological differences present between traditional vaccines, based on attenuated viruses or their proteins, and RNA-DNA vaccines, based on randomly delivered short and specific modified RNAs or by virus-carried DNAs. While protein-based vaccines inject inactive proteins with a short turnover for degradation, RNA-DNA-based vaccines give rise to active and pathogenic proteins with unknown certified turnover. Furthermore, biotech-modified nucleotide sequences can penetrate into numerous cell types in different organs, generating spike proteins, autoimmunity, and potential genetic alterations still to be evaluated in future years. The administration of RNA-DNA vaccines appears as an experimental treatment with unknown short-terms and long-term consequences on millions of people, and many years of experimentation are needed before their use might become a common medical practice.

Keywords: RNA-vaccine, viral infection, protein release, monoclonal, polyclonal, immune reaction

1. Introduction to General Viral and Immune Functions

The present paper of general nature is based on basal information on what we presently know about viral infections and immunity, with considerations on modern vaccinations. Viruses are 30-300 nm size biochemical particles containing RNA or DNA, few structural and functional proteins and sometimes lipids, and they behave as *genetic parasites of cells* (Curtis, 1965; Brock and Madigan, 1991). During a viral infection, the viral RNA or DNA enter into cells and replicate giving rise to millions of virus particles ready to infect other cells. This occurs because the viral RNA or DNA contains information (genes) that specifically stop ribosomes of the infected cell to translate their own mRNAs while they mainly or exclusively translate viral RNAs or DNAs. This mechanism allows the high production of viral proteins and of new viral RNAs or DNAs and their virus. The newly generated *viruses are complete*, including the inner and external proteins utilized for binding and penetrate into cells (spikes; see Freire et al., 2015; Krupovic and Koonin, 2017). Most of these proteins *remain attached* to the rest of the virus, in the capsid or in viral core, including the spike, and are not released outside the cells. Releasing viral proteins during the virus cycle instead of complete viruses would distribute spike proteins into body fluids, and potentially limit the infections of other cells from the new viruses since the free spikes might also compete with the complete viruses for the attachment to other cells. In contrast, when only spike proteins are produced in large amount from an RNA-DNA vaccine (Chaudhary et al., 2021; Chavda et al., 2022), these are the only molecules that can exit infected cells. The spike proteins or their fragments are released among cells as *soluble proteins*, and circulate to different regions of the body where they can activate pathological functions, as observed for Covid19 spike (Gambacorti-Passerini and Aroldi, 2022; Acevedo-Whitehouse and Bruno, 2023; Bellavite et al., 2023). As we will see later, the above basic characteristics of an infective viral cycle, the production of complete virus, in addition to others, *are not met* in RNA-based vaccines where the viral cycle is altered (Alibardi, 2023).

The immune system, innate and adaptive, has progressively evolved to preserve the biological self of our multicellular bodies, including *fighting against viral infections* (Danilova, 2006; Sompayrac, 2012; Simon *et al*. 2015). This defense takes place by the production of *numerous varieties of immune cells and antibodies* that neutralize in different ways viruses invading our body. Through a complex mechanism of *gene reshuffling*, our immune system can produce over 500 millions of different antibodies, capable to circulate *inside our body* (IgM, IgG, IgE) and *coat the mucosal surfaces* of nasal, lung, intestine, and genital ducts (IgA). The production of many different types of immune cells and antibodies (*polyclonal immunity*), potentially tagging any type of viral proteins (antigens), determines the success of immunization and has allowed humans *to survive during million years* of biological evolution. For most types of viruses (cold, small pox, chicken pox, yellow fever, measles, influenza, rubella, mumps, SarsCov2 etc.), multiple and specific types of antibodies are produced that are directed to all the varieties of virus proteins penetrated in the body.

The resulting immunization protects us from future infections from the same virus for *various*

years or even permanently. A lasting immunity likely derives from the *successive occasional expositions* of the body to the same viruses during our life, expositions that maintain active our immune system. This is also demonstrated from the presence of developed lymphoid organs such as lymph nodes, spleen and thymus in our body. In fact, in animals kept in sterile environments or in humans born with immunological deficits such agammaglobulinemy or severe immunodeficiency, and kept in sterile environments where no immunity reactivity is elicited, *no or undeveloped lymphoid organs* are present. The presence of these lymphoid organs in our body is therefore a proof of a continuous and variable exposition to microbes, including viruses. Once a person is naturally healed from an infection disease, he/she becomes *permanently immune or however protected for several years* against that disease, and can only be lightly affected from the same viral infection in rare circumstances (immunodepression, other ongoing illnesses, dietary unbalance, lowering immunity during aging etc.).

The process of biological evolution, where any new immunological function was sequentially built, adding new capabilities to previously established immune mechanisms, has been *perfected over millions of years*, giving rise to bodies adapted to efficiently contrast most viruses. A natural immune reaction is not limited to *1-2 viral antigens like modern vaccines*, but instead is potentially directed against *all viral antigens*, providing efficiency and *generating a lasting immune protection* in inner organs and mucosae surfaces. Consequently, *no medical intervention can be more effective than our polyclonal natural immune system*. In fact, while a long biological evolution has proceeded gradually facing multiple stimulations that adapted our bodies to most viruses, immunological medical interventions progresses empirically, according to the level of knowledge acquainted in its short period of history, few centuries (see later).

Only in few but dramatic cases (small pox, rabies, ebola, yellow fever, AIDS etc.), the elaborate adaptive immune system so far evolved *reacts too slowly* to avoid these diseases and, sometimes, even death (Brock and Madigan, 1991). The latter, in particular for airborne viral infections, typical diseases of vertebrates that colonized the land during different Paleozoic Periods, is however generally due to secondary bacterial infections such as pneumonia, not to the virus itself. However, for most viral infections, with a low level of lethality in healthy normal people (chicken pox, rubella, measles, mumps, west Nile disease, adenoma pharyngitis, etc.), the body reacts well with low-mild suffering, and the person *becomes almost permanently immune* or healed from these viral diseases. For other diseases, such as cold and influenza, immunity is not lasting due to the high rate of mutation in particular of the spike/outer external proteins that interact with cell receptors of the host. For influenza viruses this continuous generations of variants derive from combinatory processes among fragmented RNAs of different mutants/variants (Brock and Madigan, 1991). This is the reason why multiple of other influenza antigens (other viral proteins) should be selected to make lasting influenza vaccines. For covid19, insufficient information on a lasting immunity is so far available, although naturally immunized (healed) individuals are better or equally protected with a longer immunity that the vaccinated people with RNA or DNA

vaccines. Because of their polyclonal natural immunization, it is likely that haled people from Covi19 are also more protected from new variants than vaccinated only against the spike protein (monovalent immunization), but contrasting opinions are published and definitive laboratory proofs are inconclusive at the present.

As for other viral infections, also for sarsCov2 virus variants, polyclonal vaccines tagging the other viral proteins aside spike, should be manufactured (Fig. 1).

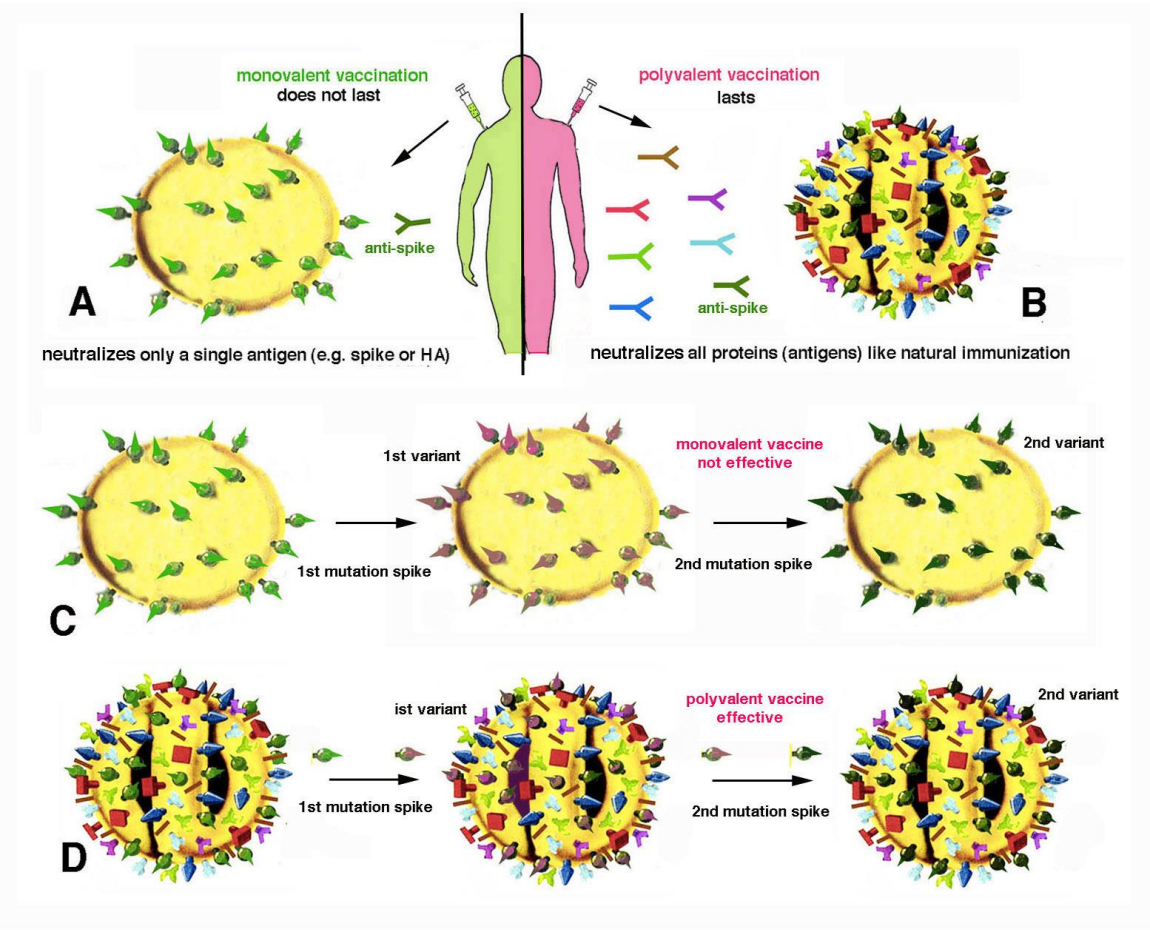

Fig. 1. Comparison between a monovalent and a polyvalent vaccination **A**, only one protein (e.g. spike) is neutralized by anti-spike antibodies. **B**, numerous antibodies (7 here shown, including anti-spike) are produced. **C**, a monovalent vaccination only stimulate production of anti-spike proteins as the virus would be covered only from spike. Mutations of spike would lower or completely abolish any immune protection. **D**, a polyvalent vaccination instead stimulates production of numerous antibodies (polyclonal reaction, only 7 are here shown) that neutralize most or all the antigens (with different shapes and colors) so the protection lasts for the first variant, the second variant and following variants.

In contrast, continuing to manufacture vaccines for influenza or sarCov2, or for other viruses, tagging only the external and most changing (from mutations) viral proteins that are ligands

of cell receptors, appears a poorly driven procedure from a scientific point of view. It is here suggested that the over 100 variants of influenza virus and the 6-8 sarsCov2 variants so far

known, and new ones generated every 6-12 months, might also depend from the selection of variants derived from the use of modern monovalent vaccines. The latter, while contrast the main variant of a certain year, allow the survival and selection of the other variants generated in that specific year that will infect people in the following years (Alibardi, 2023).

In conclusion, since the immune system has evolved polyclonal reactions that continuously save our lives, it is rationale to predict that any *medical procedure meant to permanently immunize* people from potentially dangerous infections should follow the natural rules of the viral cycles (*not liberating functionally active viral proteins*) and those of the activated immune system (*eliciting a polyclonal immunity*; Fig. 1 A, B). Polyclonal or natural immunity hits virus variants because this vaccination tags many changing (from mutations) and non-mutated viral antigens and, although some antigens change from genomic mutations, most of the others remain unchanged, so that polyvalent vaccinations give a lasting protection (Fig. 1 C, D). Unfortunately, from many years these scientific indications are not followed from Pharma industries, that mainly produce and sale continuously new monovalent vaccines.

2. Vaccination and Traditional Vaccines

The intuition, mainly due to Edward Jenner in 1796, that the protection from the lethal or devastating human small-pox disease (40-80% lethality in old ages), by the induction of immunity using a cow small-pox infection, paved the way to vaccination (Curtis, 1965; Aichelburg, 1977). Conferred immunity derived from the *antigenic similarity* of the cow virus to that of the human virus (both pox-viruses) that immunizes and prevents human small-pox. Using this medical procedure, other severe viral diseases such as rabies, yellow fever, blackleg, polio, hepatitis B, ebola etc. have been controlled or even erased in the past. It was learnt that the scarification, injection or oral administration of inactivated viruses, of their proteins or attenuated viruses un-capable to give rise the disease but *preserving the immunogenic capacity*, could avoid the severe infection, providing a lasting immunity. Vaccination was and is an *amazing conquest of medicine* and has saved millions of people, but it is a *voluntary introduction in the body of healthy people* of inactivated viruses or their antigens to prevent the risk of serious infections, not minor affections, and that the benefits should largely overweight the risks of negative effects.

Inactivation of virus proteins eliminates any pathogenic effect but maintains immunogenicity of the injected denatured protein (Fig. 2 A). In contrast, vaccination with RNA or DNA *gives rise to active proteins* which interaction with the body functions *are unknown or even pathogenic* (Wong and Webbing, 2013; Gambacorti-Passerini and Aroldi, 2022; Bellavite et al., 2023; Fig. 2 B).

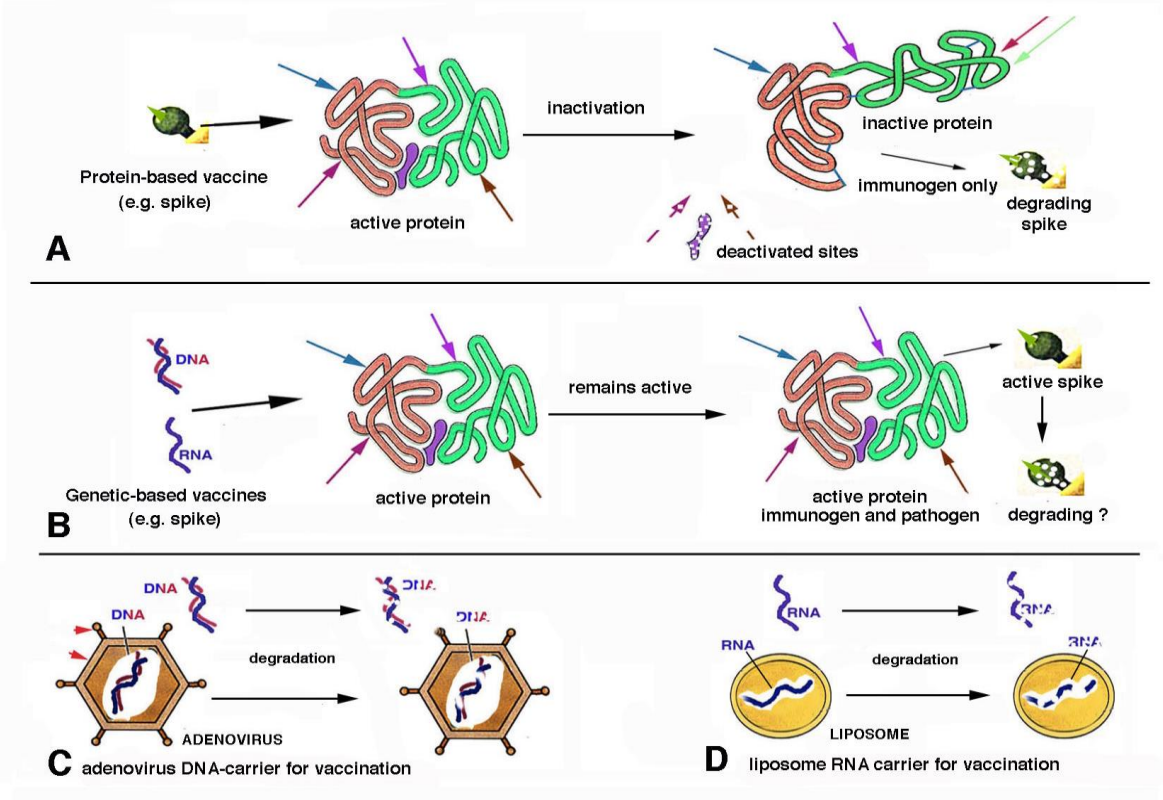

Fig. 2. Differences between a protein-based vaccine (**A**) and a genetic vaccine (**B**), and biotech vectors of RNA or DNA (**C, D**). **A**, the inactivation of the antigenic protein (arrows indicate some tagged epitopes) gives rise to a denatured protein that has lost some epitope sites, formed others epitopes, and changed conformation. The inactive protein however keeps some of the former and new immunogenic epitopes (arrows or the right), and is rapidly degraded. **B**, as opposed, genetic vaccines produce a spike protein that remains active and is released among different tissues or is circulating in the blood, triggering immune-stimulation but also unknown pathological reactions. The time of degradation of the vaccine RNA and its active spike protein is not known (?). **C**, viral carrier of a DNA-vaccine sequence with possible DNA fragmentation and degradation during mass vaccination. Red arrowheads indicate that also the capsid proteins can produce pathogenic effects. **D**, liposome carrier of RNA-vaccine with possible RNA fragmentation and degradation during mass vaccination.

Traditional vaccinations initially mimicked as much as possible the entire immunogenic potential of the viruses, since a polyclonal immune reaction was elicited, like for natural immunity (Curtis, 1965; Aichelburg, 1977; Brock and Madigan, 1991; Wong and Webby, 2013; Fig. 1 B, D). However, a variety of *adverse body reactions* can be activated after vaccination, generally in very few people with severe consequences and, rarely, even death. These adverse reactions depend from the individual health conditions and also from the type of vaccines utilized. Some of the pathological consequences of traditional vaccines derived from *lack of purity of vaccines*, incomplete inactivation of viruses, or to minor pollutions from unwanted substances derived from the processes of viral production. The impurities contained residual cell or organic fragments from the cell culture system where viruses were

produced in high amount, or from the chick eggs utilized for rising a high number of viruses, and later inactivated for vaccination.

To guarantee purity of these traditional vaccines, long and tedious procedures, large infrastructures and costly activities involving numerous dedicated personnel were and are required, a *big investment for any Pharma company* or Public Hygiene Institutions. However, improving the technologies for the safe production of traditional vaccines had to be pursued during the last 40-50 years. This in particular through the *biotechnological production of viral proteins* of known amino acid sequence in high amount and purity, proteins that can be *inactivated and utilized as polyvalent vaccines*. This means that most of the viral proteins can be utilized as antigens so that the numerous antibodies produced following vaccination bind and neutralize all or most of the viral proteins. In case an infection with the same virus or its variants occurs, the immune system elicits a strong reaction that determines a broad protection also against the variants or even a *complete and lasting immunity*, like for natural immunity (Alibardi, 2023). For what is known, inactivated proteins injected as vaccines, *do not replicate, do not penetrate into cells but remain extracellular, do not produce other physiological effects aside immunization*, and they are degraded within 1-3 weeks. During this time, inactivated viral proteins (antigens) are phagocytized from "antigen presenting cells" (APC-cells) distributed in different body organs, and the derived peptides are presented to lymphocytes within lymphoid organs where they stimulate polyclonal immune responses.

Instead to follow this general immunological principle, modern vaccines are manufactured only *against one or few viral proteins or their smaller epitopes that* bind to cell receptors (ACE2 or others), for instance the haemoagglutinin (HA) for influenza viruses or the spike protein for the Sars-cov2 virus (Wong and Webbing, 2013; Chaudhary et al., 2021; Chavda et al., 2022; Bellavite et al., 2023, Fig. 1 A, B). The scope of these monovalent vaccines is to impede the virus attachment to our cell receptors through the HA or the spike protein. Modern vaccines that only neutralize a single viral antigen, e.g. HA of specific influenza viruses or the Spike protein of SarsCov2 variants during a certain Fall-Winter, allow the other variants derived from the frequent mutations for these single proteins, to remain in the environment also in the following Spring-Summer periods. When the seasonal conditions change again from the Summer to Fall in the next year, these new variants, selected by monovalent vaccines, can determine a new contagious. Therefore, epidemics are only limited to that specific year by manufacturing and selling monovalent vaccines, a continuous productive process from Pharma industries. It would be scientifically more correct, and logic, to use polyvalent vaccines instead of monovalent vaccines for obtaining a better and lasting immunization. Therefore, the frequently generated virus variants (mutants) for the HA, the spike or other viral proteins would be completely or partially *neutralized following a polyclonal vaccination*, since also the remaining unchanged antigens are neutralized from the immunity derived from these vaccinations (Fig. 1 C). As opposed, as previously indicated, the monovalent vaccinations that are *routinely utilized today*, likely contribute to the continuous *selection of new virus variants* since these vaccines only hit the variant of a certain month or year, allowing the continuous production and permanence of new variants that will generate the next seasonal epidemics of influenza, covid19 or other viral infections

(Alibardi, 2023, see later). The immunization against one-two proteins *is unnatural and apparently illogical*, also considering that these are the proteins that change more frequently (mutate) in the virus (HA and spike). Therefore, the scientific logic and knowledge would produce vaccines against the least changing viral proteins, not those that more frequently change following genetic mutations. The change of these external viral proteins allows that the mutated viruses (variants) can infect our cells through new binding proteins while the antibodies effective against the initial binding viral proteins result ineffective (Alibardi, 2023). In conclusion, modern monovalent vaccines *do not last* while they are manufactured and sold from Pharma industries at any new epidemic burst.

3. Some Differences Between Viral RNA Infections and Those from RNA-vaccines

The development of molecular manipulation of genes, both RNA and DNA sequences in the last 30-40 years has now become a routine (Brock and Madigan, 1991; Khalil, 2020). Main areas of medical applications are gene therapies, production of transgenic plants and animals, attempts to cure genetic impairments, use of virus for experiments of gene transfections and, recently, also the *manufacturing of vaccines based on viral RNA or DNA* (Pardi et al., 2018; Zhou et al., 2023). The latter technology, indicated as the *future of vaccination*, induces the production of viral antigens in the body, after the injection of parts of the viral RNA or DNA coding for these antigens (Chaudhary et al., 2021; Chavda et al., 2022). The production of the viral antigens (e.g. spike) is completely made by *the patients, the new factories for the production of the viral antigens*, and eliminates the complex and costly production of traditional vaccines made by *Pharma industries* that "only" synthetize RNA or DNA sequences at relatively low cost using the modern biotech platforms.

However, a *number of differences* are present between the natural viral infection and the biotech-RNA or DNA infection induced with this type of vaccination (Gambacorti-Passerini and Aroldi, 2022; Petit and Longo, 2023; Alibardi, 2023). The technical capability of genetic engineer operations in test tubes and laboratory experiments *has been equalized to that of RNA-DNA vaccines*, indicating that there were 20-30 years of experience in using RNA-DNA vaccines. This type of statements is untenable since manipulating RNAs or DNAs for laboratory experiments, agronomical purposes or gene therapy or editing, is not equal to manipulate RNAs or DNAs for vaccination on humans. *Humans are not reacting as test tubes*, but this seems to be neglected from the manufacturers of RNA-DNA vaccines. In the latter case *no experimental testing, evidences and experiences were and are available* for RNA or DNA vaccines before their use for mass vaccination in 2020-2024. A serious scientific evaluation on the risk/benefit ratio and consequences of inoculated genetic material into partially known and complex human bodies has not been done, and these studies are still ongoing (Chaudhary et al., 2021; Chavda et al., 2022; Bellavite et al., 2023). Genetic material such as RNA or DNA is not like any other drug previously utilized, because these molecules determine basal cellular processes and interactions still incompletely known and are mainly academic information, with unknown possible risks in their medical applications and transmissibility to next generations. Consequently, the indiscriminate use of RNA-DNA vaccines appears, also today, a mass experimentation. Also, the administration of biotech-RNAs or DNA inside carrier viruses or liposomes for mass vaccination, outside of

the lab control environment, cannot guarantee that these genetic molecules *remain integral* (Fig. 2 C, D). Fragmented DNAs or RNAs could produce unknown effects on the body, likely pathogenic (Tinari et al., 2021; Zhang et al., 2021; Schoenmaker et al., 2021; Seneff et al., 2022). While the biological evolution of immune mechanisms occurred step by step, any technological novelty based on a partial and empirical knowledge introduces in complex body mechanisms, established from a long evolution, unpredictable interactions that very likely give rise to pathological conditions.

When a virus enters the body and overcomes the multiple physical and chemical barrier, and also innate immune cells (phagocytes such as granulocytes and macrophages), the viral particles penetrate into cells of specific or preferred organs, following their receptors recognition (lungs, liver, nervous system etc.; Fig. 3 A).

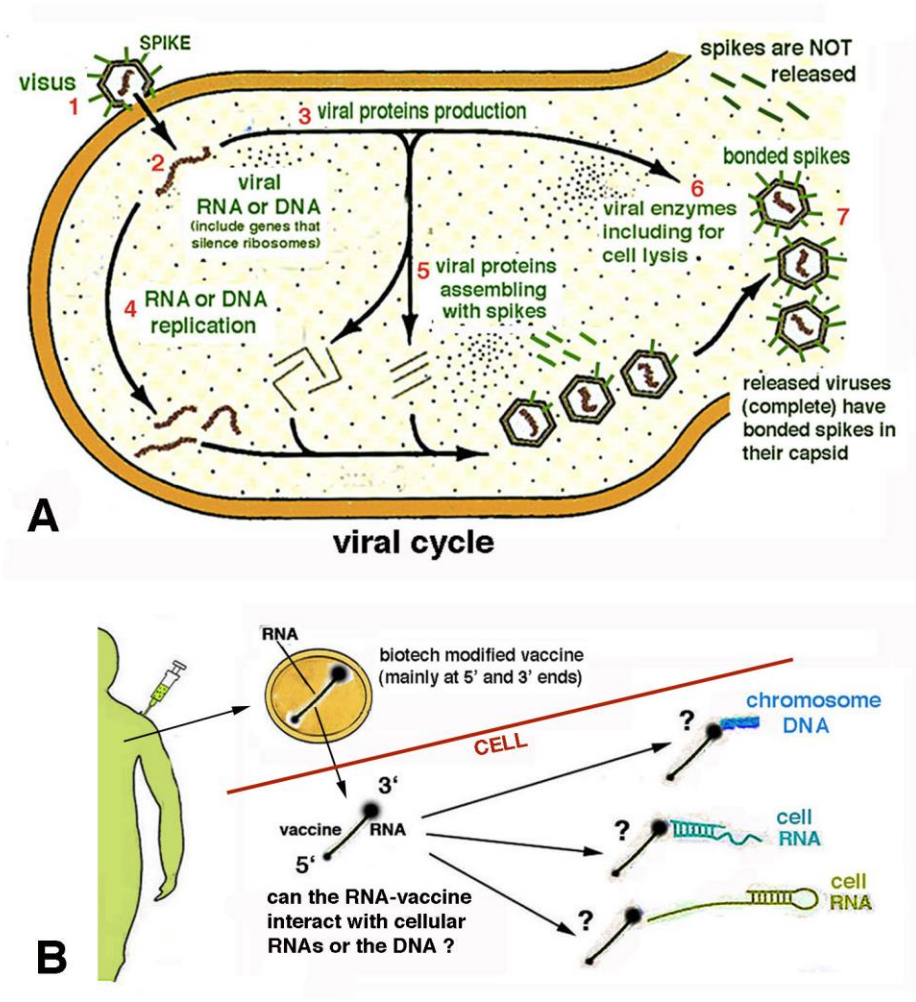

Fig. 3. Classic viral cycle (**A**) and biotech-RNA vaccine potential interactions within cells. **A**, after viral infection, new viral particles are release complete, with spikes attached to the capsid, not released as soluble spike proteins. **B**, after RNA-vaccine (black bar with main modification in the 5' and 3' nucleotide ends of the RNA) injection and penetration into various cells, potential interaction (?) with cellular RNAs or DNA remain unknown because of incomplete knowledge of all cellular functions.

Many different viruses possess specific organ-cell tropisms (skin, intestine, lungs, glands, brain etc.) and *do not infect any cell type* present in the body, limiting the extension of the infection. This does not occurs using vaccines containing RNA for spike that, aside their unknown stability in the blood or intercellular fluids, do not target specific cells but are potentially *incorporated at random into any cells that they encounter* (Schoenmaker et al., 2021; Chaudhary et al., 2021; Chavda et al., 2022; Bellavite et al., 2023). Inside the body, the invading viruses are identified through specific macrophages or dendritic cells (APC, Antigen Presenting Cells) that activate different types of lymphocytes (T helper lymphocytes and B lymphocytes). When viruses penetrate in their target cells, they are detected and later destroyed by specific macrophages and lymphocytes (T-cytotoxic cells) that check the cell surface of these infected cells. Both mechanisms, extracellular (antibody production) and intracellular (viral infection), give rise to broad *polyclonal immune responses and immune memory*, since numerous different clones of lymphocytes are produced and neutralize most or all viral antigens internally and on mucosal surfaces, *not only one or two antigens like modern vaccines* (Sompayrac, 2012; Fig. 1 D).

In contrast, when a simple but alien biotech-RNA-DNA is injected into the body, the *viral cycle is modified since* only the spike proteins or fragments are released inside and outside the cell but not the entire virus (Fig. 3 A-B). The intracellular spike can interact with the DNA of chromosomes during cell division since no nuclear membrane is present for 1-3 hours during this phase (Figs. 3 B, 4 A). The spike proteins are later exposed on the cell membrane associated to MHC I or II or become soluble into biological fluids. Furthermore, such biotech-RNAs have undergone *a number of chemical modifications* to make it more stable and lasting, especially in the 5'- and 3'- nucleotide ends, and even introducing nucleotide base modification (Pardi et al., 2018; Chaudhary et al., 2021; Chavda et al., 2022; Kim et al., 2022; Bellavite et al., 2023; Fig. 3 B). The potential interactions, fate and duration of these biotech-RNAs randomly incorporated in many cells and organs with no specificity, in the complex human body *are unknown*. The human body *cannot be treated as a test tube*, since nobody knows all the functions and interactions of its cells and organs. Nobody can predict or has experimentally tested possible interactions with these RNA-DNA vaccines inside the body (Gambacorti-Passerini and Aroldi, 2022; Alibardi, 2023; Fig. 3 B). The modified biotech-RNAs (or DNAs-carried from viruses) *can penetrate the nucleus* and contact the genomic DNA, especially during the metaphase and anaphase of cell division, when the *nuclear membrane disappears for 1-3 hour* (Fig. 4 A). This potentially dangerous process of penetration and DNA-interaction occurs in particular in bodies where billions of cells are dividing, namely in *embryos, fetuses and children*, aside the stem cells of renewing tissues (skin, intestine, blood marrow etc.) or in the gonads of adults (Alibardi, 2023; Fig. 4 B).

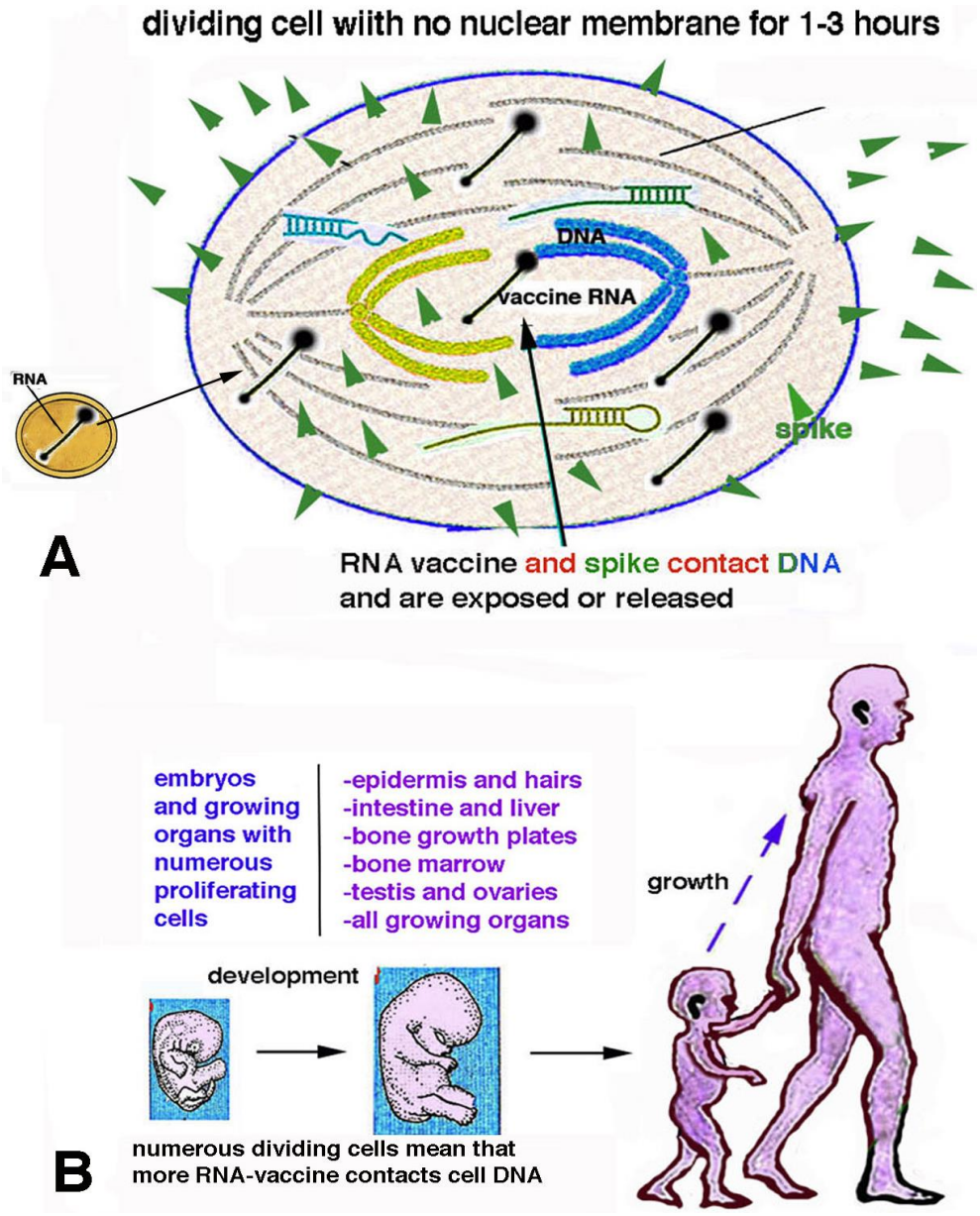

Fig. 4. Contact of vaccine RNA with chromosomes (DNA) during mitosis (**A**), and unknown consequences on bodies containing many dividing cells that can incorporate high amount of biotech-RNA (**B**). **A**, dividing cell containing both biotech-RNAs and their coded spike proteins that are distributed in the cytoplasm and nuclear region contacting the chromosomes (DNA). Spike proteins or their fragments (peptides) are exposed on the cell surface or released extracellularly. **B**, embryos, fetuses, growing children and young individuals contain many dividing cells so that the uptake of biotech-RNA or-DNA is higher than in fully grown-up adult or elderly individuals where a lower number of dividing cells are present. Main affected tissues are physiologically renewal tissues, and some are indicated.

While "*natural cellular mRNAs*" are not interacting with their own DNA, a mechanism that has been likely "perfected" with other cell functions during the 1-2 billion year of evolution of eukaryotic cells, *potential interactions and recombination of biotech-RNAs* with cellular

RNAs, DNA or other molecules *are unknown* (Gambacorti-Passerini and Aroldi, 2022; Bellavite et al., 2023). Again, the human body *cannot be reduced to a test tube* where these interactions and recombination are instead better known, a reductionist approach that could generate adverse or pathological outcomes in numerous people (Petit and Longo, 2023).

Furthermore, without other genes for silencing cell ribosomes as in complete viruses, biotech-RNA sequences only containing the nucleotides for the production of the spike protein or its binding site to cell receptors, likely cannot produce the same high levels of the spike antigen for immunization like the entire RNA of a sarsCov2 virus in a natural infection. Although made more stable through biotech manipulations, the lack of specific ribosome inhibition from biotech-RNAs, may contribute to explain why the spike produced at random in sparse cells of the body cannot induce a strong immune *stimulation that is also limited to few months* (Gambacorti-Passerini and Aroldi, 2022; Bellavite et al., 2023). Even producing relatively high spike concentrations, the duration of the antibodies that are produced remains however limited and does not elicit a lasting protection in comparison to a natural viral infection, as this has become evident after RNA-DNA based vaccinations.

4. Pathological Consequences of RNA-DNA Vaccines

Viral protein antigens in the capsid carry RNA or DNA into specific cells and are captured from APC-dendritic cells that activate the immune response (Sompayrac, 2012). As previously indicated, viral RNAs or DNAs or their generated proteins *do not travel as isolated molecules into the body* since they would be rapidly degraded extracellularly and intracellularly. Potential unknown side effects derived from injecting RNAs through liposomes (Pfizer or Moderna vaccines) or DNA inserted into the carrier capsid of an alien adenovirus (Astrazeneca or Johnson & Johnson), have been reported (Gambacorti-Passerini and Aroldi, 2022; Seneff et al., 2022; Acevedo-Whitehouse and Bruno, 2023; Bellavite et al., 2023; Petit and Longo, 2023; Fig. 2 C, D). The incorporation of a complete or partial viral RNA or DNA produces intracellular spike proteins that *are exposed on the surface of any cell* that received the biotech-RNA or -DNA. The spike-derived antigens, aside penetrating in the nucleus, would also alert the immune sentinels (macrophages and T-helper and/or T-killer lymphocytes) after their surface exposition on various types of cells. In fact, the exposition of spikes on the surface of many different cell types after they have incorporated the RNA-DNA vaccines indicates that these cells are infected and should be destroyed by specific immune cells (e.g., T-cytotoxic lymphocytes). The latter event *determines autoimmunity*, and can hit all organs that contain cells that have randomly adsorbed the RNA- or DNA-vaccines, giving rise to myocarditis, hepatites, nevrites, encephalites etc. (Gambacorti-Passerini and Aroldi, 2022; Acevedo-Whitehouse and Bruno, 2023; Bellavite et al., 2023). Aside the problems indicated above, another complication in the utilization of these vaccines is the production of *active proteins that travel freely* inside the body (Fig. 2 A, B). This information was and is necessary before activating the RNA-DNA vaccination for the Sars-cov2 spike protein, and will be essential for the viral proteins produced in future vaccination programs using RNA-DNA vaccines for most viral infections (Pardi et al., 2018; Chaudhary et al., 2021; Chavda et al., 2022; Kim et al., 2022; Zhou et al., 2023; Fig. 5).

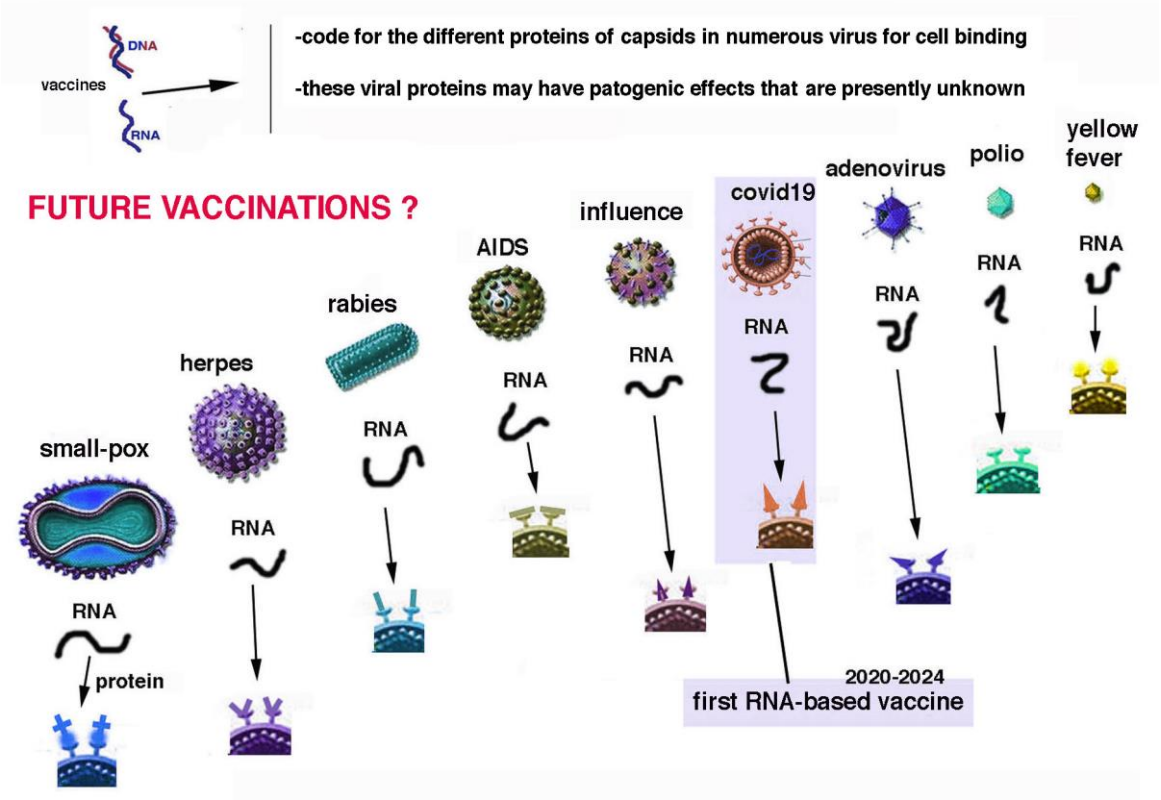

Fig. 5. Future potential RNA-vaccinations against different viruses, planned to replace traditional vaccines. After selecting specific RNAs (or DNAs) coding for the different spikes or external binding proteins to cell receptors that are present in these viruses, these vaccines may be utilized, as the covid19 vaccine, for mass vaccination. Whether these active virus proteins can also determine pathogenic effects, like those of the Sars-cov-2 spike protein, should be evaluated through a long experimentation before inoculating these RNA-based vaccines to people.

Other pathological effects, clearly demonstrated after the RNA or DNA Covid-19 vaccination, are the alterations on *blood pressure (ictus) and increasing blood clotting* with consequent failure of tissues oxygenation and necrosis of affected organs from anoxia, heart, lungs, kidneys etc. (Acevedo-Whitehouse and Bruno, 2023; Bellavite et al., 2023). A more basal alteration of the cellular homeostasis generated from the spike protein, regards the potential alteration of DNA-repair mechanisms, as suggested from a published study (Jang and Mey, 2021). The latter study has been later retracted from the scientific Journal but no follow-up research has been conducted in this direction, for unclear reasons. If confirmed, the alteration of cell genetic mechanisms can be devastating, *increasing tumors, infections and autoimmunity*. In contrast, if not confirmed, the use of RNA-DNA vaccines would have appeared safer, but *unfortunately no further independent research* has been conducted to confirm or deny the initial 2021-study. The uncontrolled distribution of RNAs-DNAs producing "infected cells" for destruction and potential DNA-integrations must be predicted using these types of vaccines based on RNA or DNA (Zhang et al., 2021; Gambacorti-Passerini and Aroldi, 2022; Bellavite et al., 2023). Instead, RNA- and

DNA-based vaccines are reported, neglecting the lack of largely accepted scientific evidence, to be *very successful and even worth of the 2023 Nobel Price* (Chaudhary et al., 2021; Chavda et al., 2022). RNA-DNA vaccines are indicated *to have saved many lives from Covid19*, and these new types of vaccines are planned for mass utilization in the next epidemic outbursts predicted for the coming years (Pardi et al., 2018; Kim et al., 2022; Zhou et al., 2023; Fig. 5).

Unfortunately, little is known on the functionality of isolated viral proteins, especially those binding to our cell receptors on our complex and partially known body functions. The active spike protein has caused many and still poorly known pathological effects on numerous vaccinated people, with light to serious adverse reactions or even *deaths, sensibly higher that using traditional vaccines* (Bellavite et al., 2023; Alibardi, 2023). We do not know the potential damage derived from *other active viral proteins induced by next viral RNA-DNA based vaccines* (Fig. 5). This information requires years of independent, public scientific study and evaluation, not derived from few months or 1 year of research conducted by Pharma industries, organizations that primarily search for profits, their natural goal, before pure knowledge. RNA-DNA vaccines production and mass vaccination should be stopped, and a long experimentation should be done in 10-20 years to come if these vaccines are really indicated as the *future of vaccination*.

5. Conclusions

As indicated above, a scientific-driven and logical approach to make lasting and effective vaccines would be to neutralize first of all the *least changing viral proteins* together those that change frequently such as the HA and spike proteins, and not *only or exclusively* neutralize the more changing proteins. A number of proteins are present inside and on the surface of viruses aside those that binds to cell receptors (Brock and Madigan, 1991; Chaudhary et al., 2021; Chavda et al., 2022; Fig. 1), and they can be tagged by antibodies derived from polyvalent vaccinations. This is how our natural immune system works and *a fair medical system should mimic* what has evolved in nature during million years of evolution. The production of monovalent instead of polyvalent vaccines does not follow a scientific purpose and determines *the continuous selling of new, temporarily working vaccines* offered against new virus variants *every 6-12 months*. These vaccinations provide little help to stop for long periods or permanently viral epidemics. In fact, monovalent vaccines, as typical for flue or covid19 vaccines, do not last that few months since the HA-protein of the influenza virus or the spike protein for Covid19 have changed (following their gene mutation) in the meantime. The new variants are likely also selected from these monovalent vaccines that neutralize only the dominating variant that is present in a certain season, *allowing the survival and therefore the selection of other variants* for future infections, and requiring more new vaccinations. Instead, vaccination like natural immunization should be lasting for the benefit of people. Differences between RNA-viral infections indicated above, and immune reactivity with RNA-biotech vaccines indicate that the latter need many years ahead of scientific-medical research and evaluation.

In conclusion, the numerous researches presently conducted on future vaccines where

sophisticated biotech modifications are experimented should avoid to consider the *human body as a test tube* (Chaudhary et al., 2021; Chavda et al., 2022). The science in these laboratory biotechnological studies is high, but these researchers do not know the body reactions to biotech-RNA-DNA because they *have not generated* the human body and cannot know the entire complexity of its functions. The latter instead derives from million years of progressive, step by step evolution through trials and errors. Some problems with modern vaccines are here summarized: a) RNA-DNA degradation (Fig. 2 C, D) should be eliminated and these vaccines proved safe; b) lasting RNA-DNA vaccines should be made to produce many antigens, not only one protein, the spike or few others; c) RNA-DNA vaccines do not repeat the viral cycle as they release active proteins that can produce pathological effects, and this should be predicted through long studies; d) the random incorporation of RNA-DNA in various cells generate exposed spikes that elicits autoimmunity, and this event should be eliminated, e) the cellular impact on RNA recombination, possible DNA insertions and blocking DNA repair mechanisms within cells must be known before using RNA or DNA vaccines, f) polyvalent vaccines, produced through biotechnological procedures on all or most viral proteins, avoiding using past in-vivo sources (eggs, cell cultures etc.), are probably the best vaccines to use in future after some reasonable period of experimentation. Therefore, the safe utilization of these vaccines requires many years of scientific investigation before they can be commercialized, and some ongoing experimentation is trying to clarify (Chaudhary et al., 2021; Chavda et al., 2022; Kim et al., 2022). The production of lasting vaccines *should be the main goal of Pharma industries*, and the use of protein-based vaccines would really provide lasting benefits on people's health in the present time.

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Authors contributions

Dr. L. Alibardi was responsible for study design and conducting research, data collection, drafting the manuscript and revising it. The author red and approved the final manuscript.

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