Future trend for needle-free vaccine delivery systems

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Outlines

- Problems associated vaccine administration vaccine by injection
- Advantages of dermal and mucosal as alternative route for vaccine delivery
- The possible devices and formulations that can be used for vaccine delivery through skin, respiratory and oral mucosa.

vaccine

“ **a biological preparation that improves immunity to a particular disease**”.

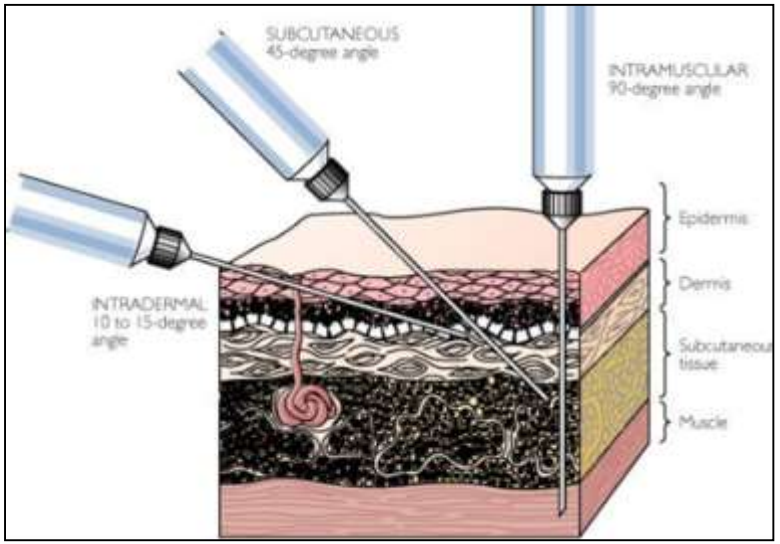
- It is typically made up of attenuated live or killed/inactive forms of the disease-causing microbe, its toxoids or subunit forms of pathogen (proteins, sugar, etc.).

- Vaccines can be **prophylactic** (prevent infectious disease; e.g., tetanus or influenza vaccines) or **therapeutic** (cancer vaccines)

Routes of vaccination

- vaccine delivery: **parenteral by injection** IM, ID or SC

- Most vaccines are formulated, as **liquids** in single- or multi-dose vials or prefilled syringes.



- According to the WHO, about 12 billion injections are delivered worldwide annually of which approximately **600 million** account for vaccinations

Rationale for alternative way of vaccine administration

- Poor compliance (phobia)
- Well trained vaccinators
- Risk of spread infection (e.g needle stick injury)
- Cold chain storage
- Cost and time consume
- Level of immunization

*Sci. Pharm. 2019, 87, 27

Alternative approaches for vaccination

Cutaneous Vaccination

- Topical application on skin for epidermal and dermal delivery

Mucosal vaccination

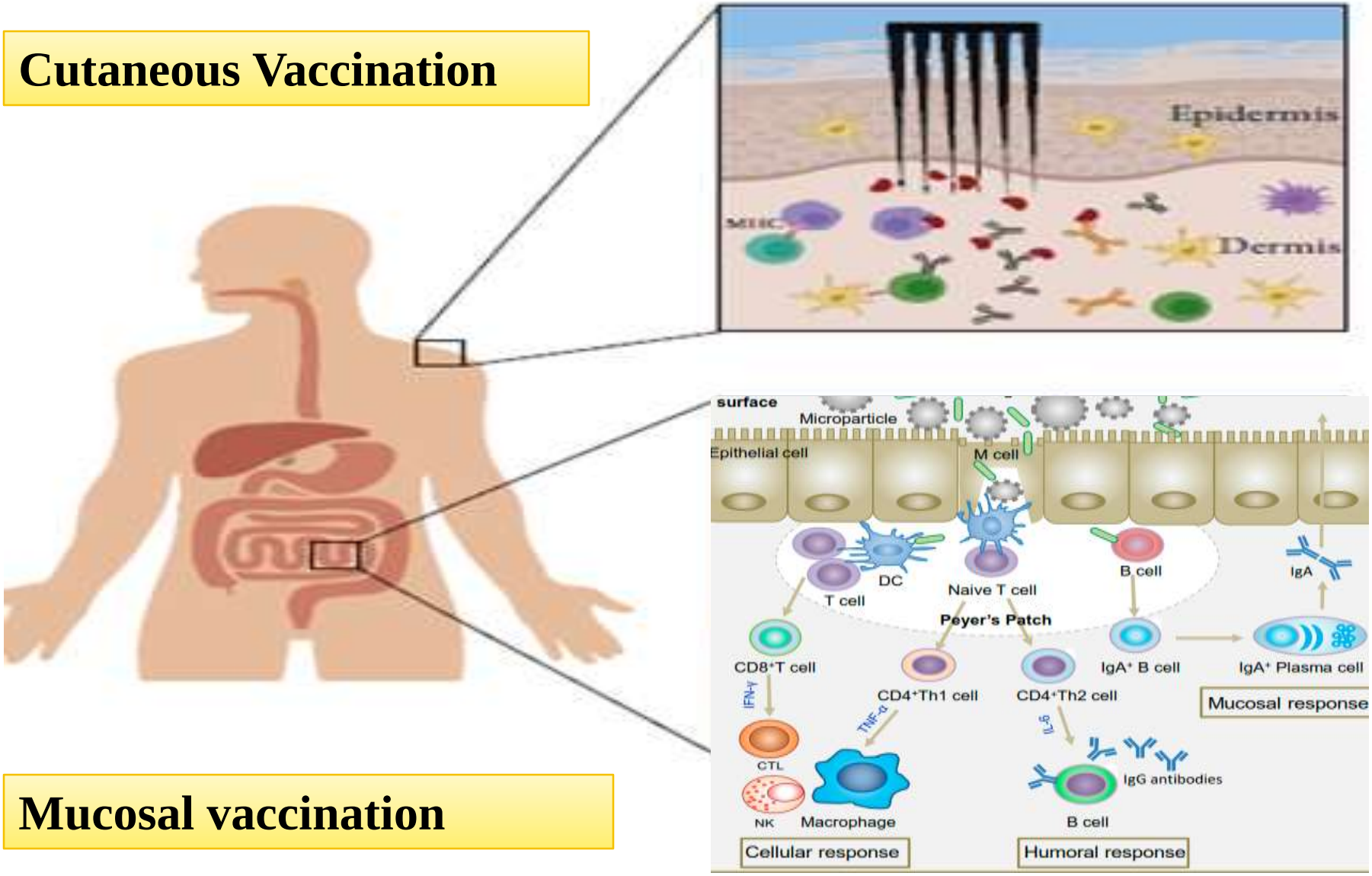
-**Nasal**
-**Pulmonary**
-**Oral**
-Ocular
-Vaginal
-Rectal

- ✓Enhance level of acceptance and safety
- ✓Suitable for mass vaccination
- ✓Capacity to induce both **protective mucosal** (mainly mediated by secretory-IgA [S-IgA]) and **systemic cellular and humoral** responses, (dose-sparing).

Journal of Immunology Research Volume 2019. and Int. J. Mol. Sci. **2018**, 19, 3639

Alternative approaches for vaccination

Cutaneous Vaccination



Mucosal vaccination

Journal of Immunology Research Volume 2019. and Int. J. Mol. Sci. **2018**, 19, 3639

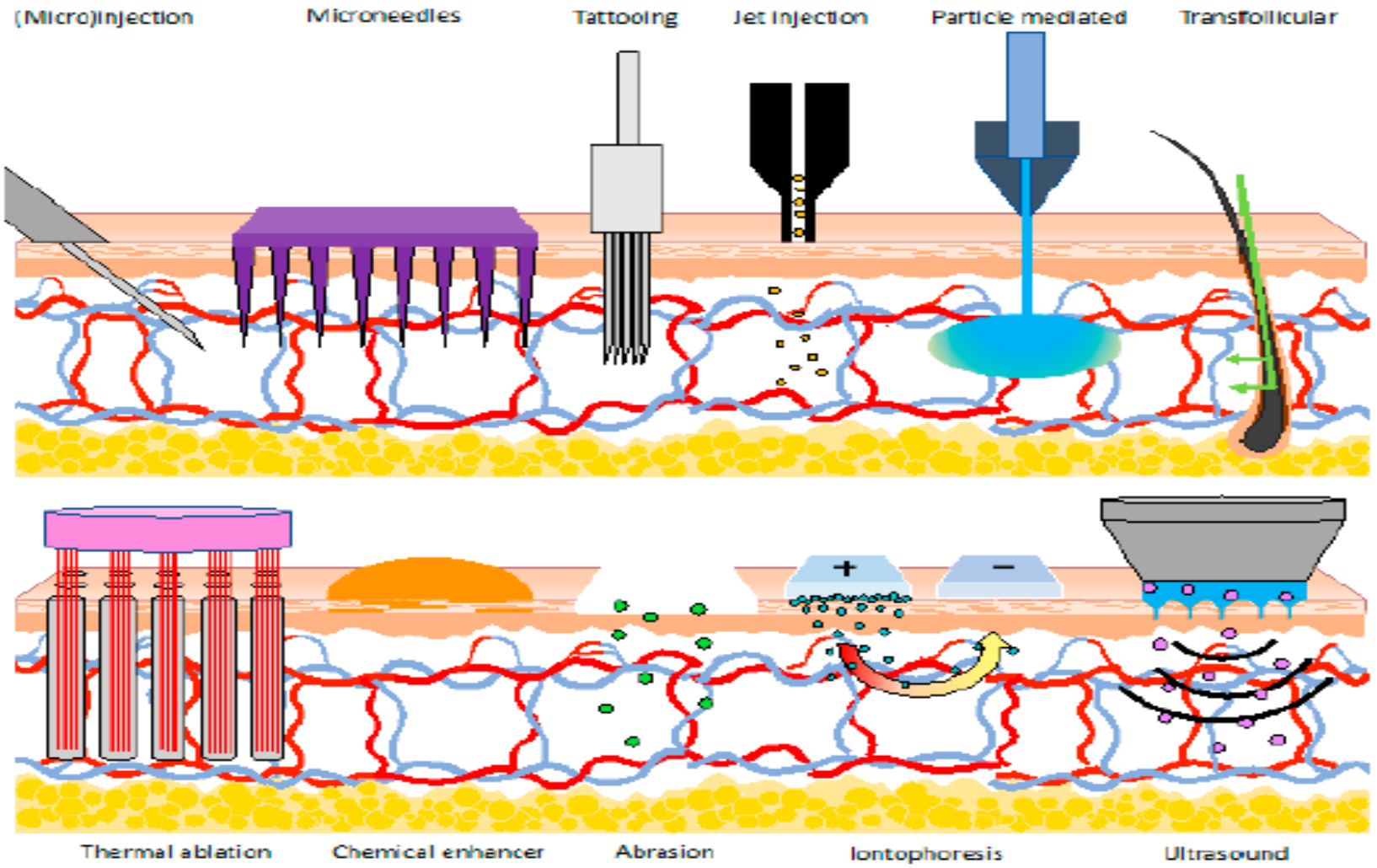
Vaccination through the skin

- The human skin is an obvious site for administration of drugs due to the ease of access, and large surface area.

- The skin (epidermas and dermis) was recognized as a key component of the immune system and not a mere physical barrier.

- The first well-documented practice for increasing immunity against smallpox (variola) virus known as **variolation** is thought to have originated in China and India 2000 years ago and was the foundation of the eradication of the smallpox through **a massive vaccination**.

Vaccination through the skin

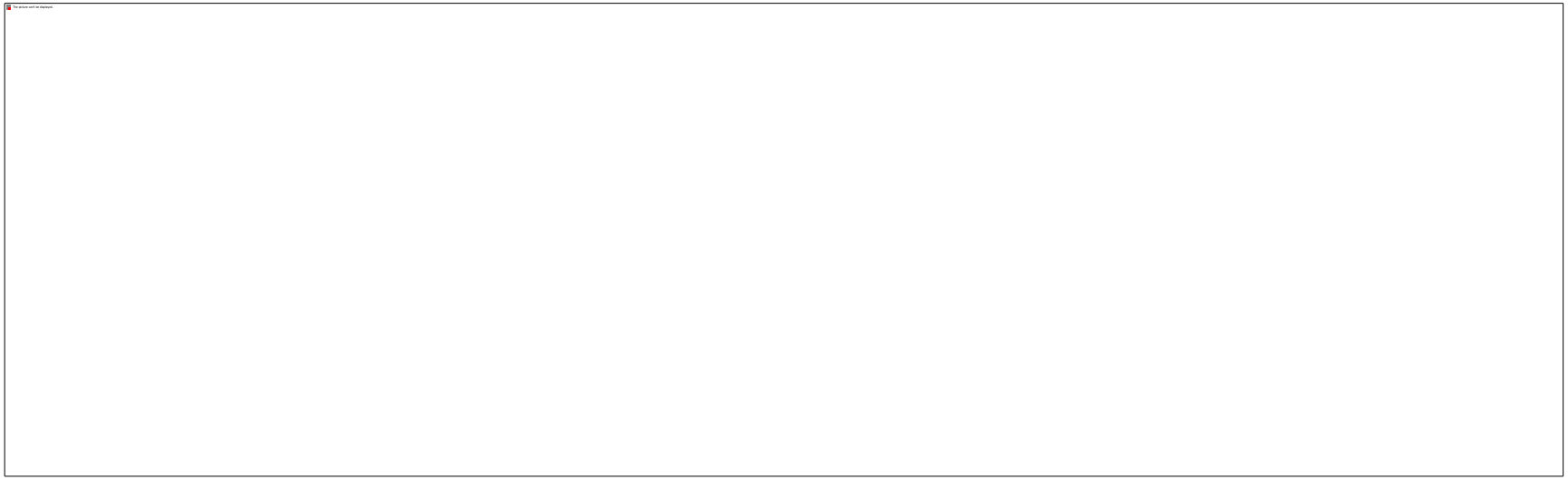


Different techniques can be used for vaccination into the dermal compartment

* Vaccines **2020**, 8, 534

Vaccination through the skin

Skin abrasion by tape-strip or friction simple tool most commonly used method of disrupting the stratum corneum for immunization. **(Skin Preparation System)**

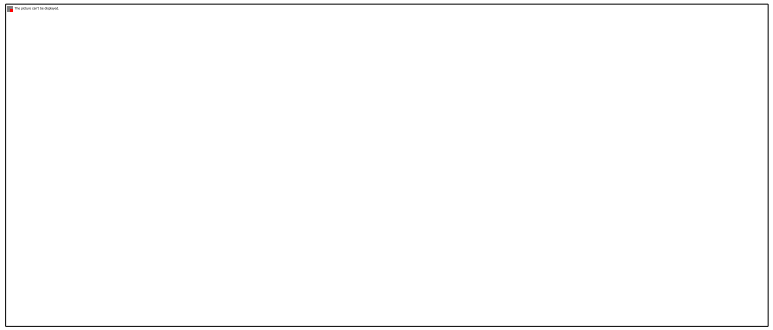


Skin abrasion device, in which a sandpaper device is placed on the skin (1), scraped across the skin in a controlled fashion (2) and then a vaccine patch is applied to the abraded skin

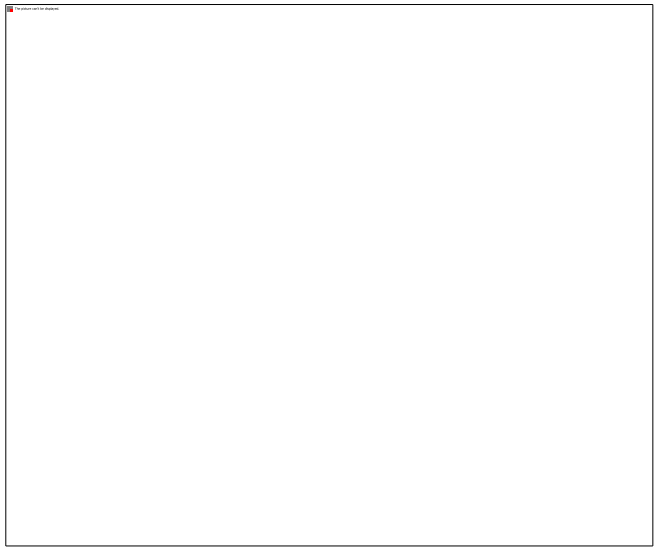
* Intradermal Immunization. 2012; 351: 77–112

Skin vaccination methods : **Jet injection**

Jet injection is portable device forces the drug through skin pores by the help of air pressure, thereby effectively delivering the drug without the help of needle



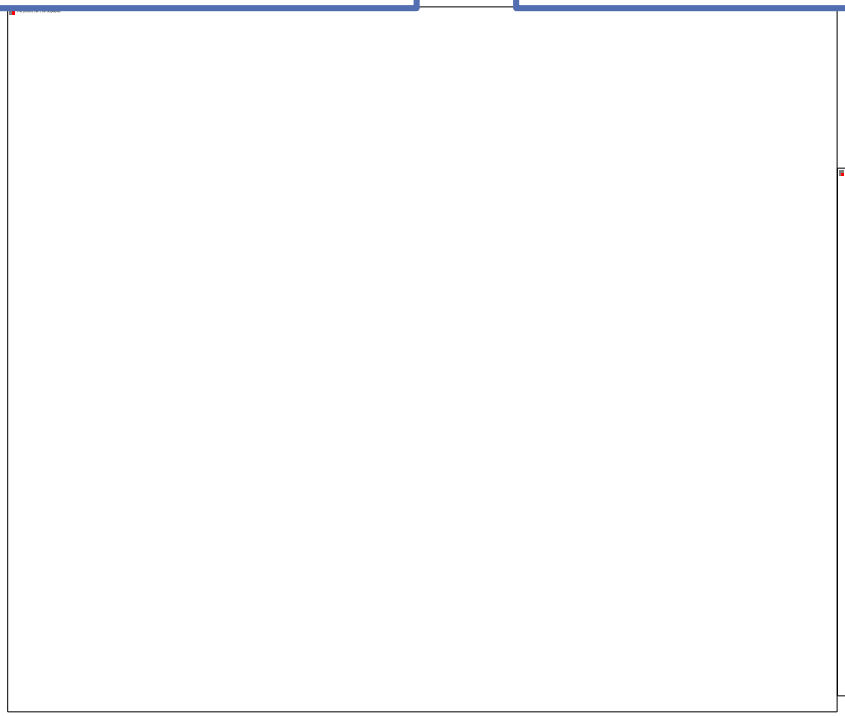
During the **swine influenza** mass campaign of 1976–77 in the US , a substantial proportion of the approximately **43 million doses** administered were by jet injection



Ped-O-Jet (Multiuse nozzle jet injector)

A **spherical bolus** is formed in case of conventional needle system where the **surface area/volume ratio is very less** when compared to needle free injected devices. vaccine is **dispersed** between the cells in case of needle free injected systems

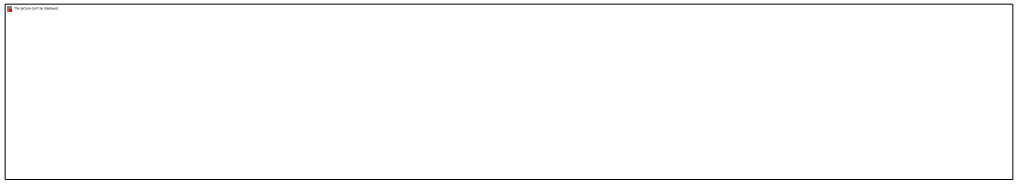
Injection by needle



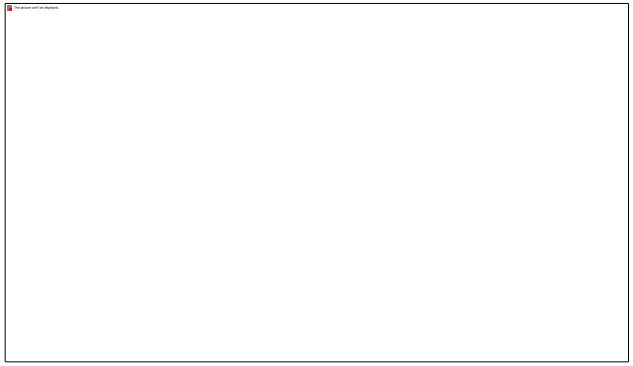
Jet injector

Vaccination through the skin

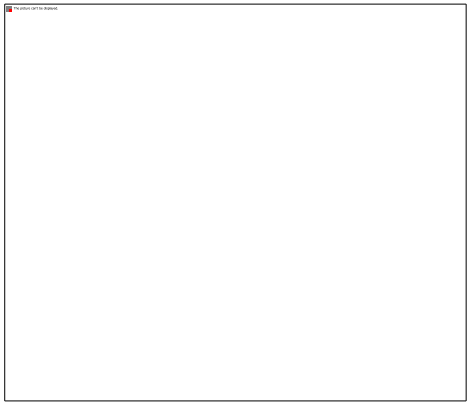
PharmaJet Strait- disposible syringe jet injector DSJI- for delivery of one particular flu vaccine (**AFLURIA®** by bioCSL Inc.)



Biojet ZetaJet – DSJI .



LectraJet HS



Epidermal powder immunization device for ID projectile injection

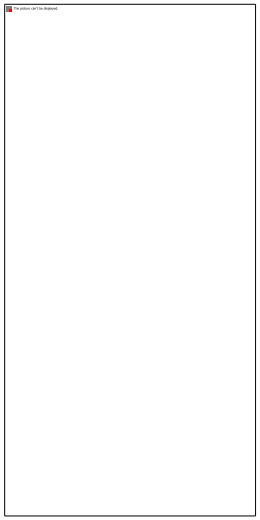
- PowderJect. (PowderJect, Oxford, UK, acquired by Pfizer)----- FDA approved
- Biojector 2000 (Bioject, USA)------- FDA approved
- Bioject ZetaJet (Bioject, USA) ------- FDA approved
- Injex30 (Injex Equidyne, UK) ---------- FDA approved
- PharmaJet Stratis (PharmaJet, USA) -------- FDA and CE approved
- PharmaJet Tropis (PharmaJet, USA) ---------- CE approved
- Trigrid electroporation systems (Ichor medical systems, USA) ---- Clinical trials
- Actranza. (DAICEL Corporation, Japan) ---------- Preclinical

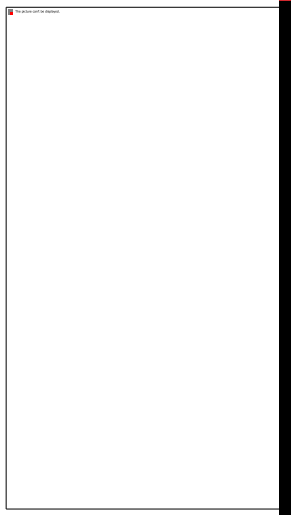
Currently jet injectors used to deliver insulin, recombinant human growth hormone
Occasional pain and bleeding were reported

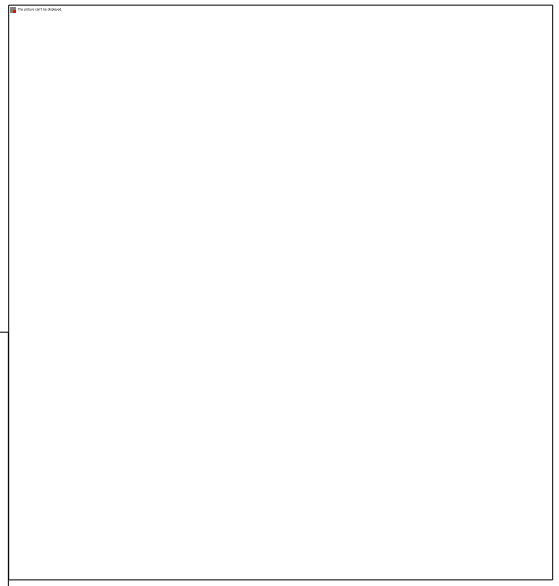
Skin vaccination methods : **Microarray patches or Microneedles patches**

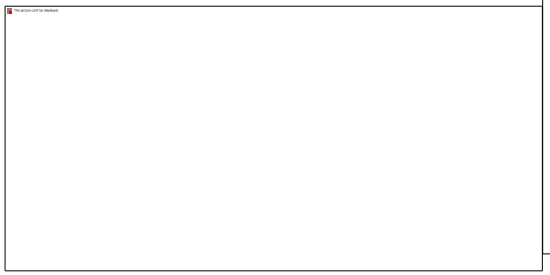
are arrays of micro-projections, typical microneedles vary from **150-1500 µm** in length, 50-250 µm in base width and 1-25 µm in tip diameter

These micro-projections can have a range of geometries and create micropores that can be directly used to transport macromolecules, or microparticles, into the epidermis or the upper dermis

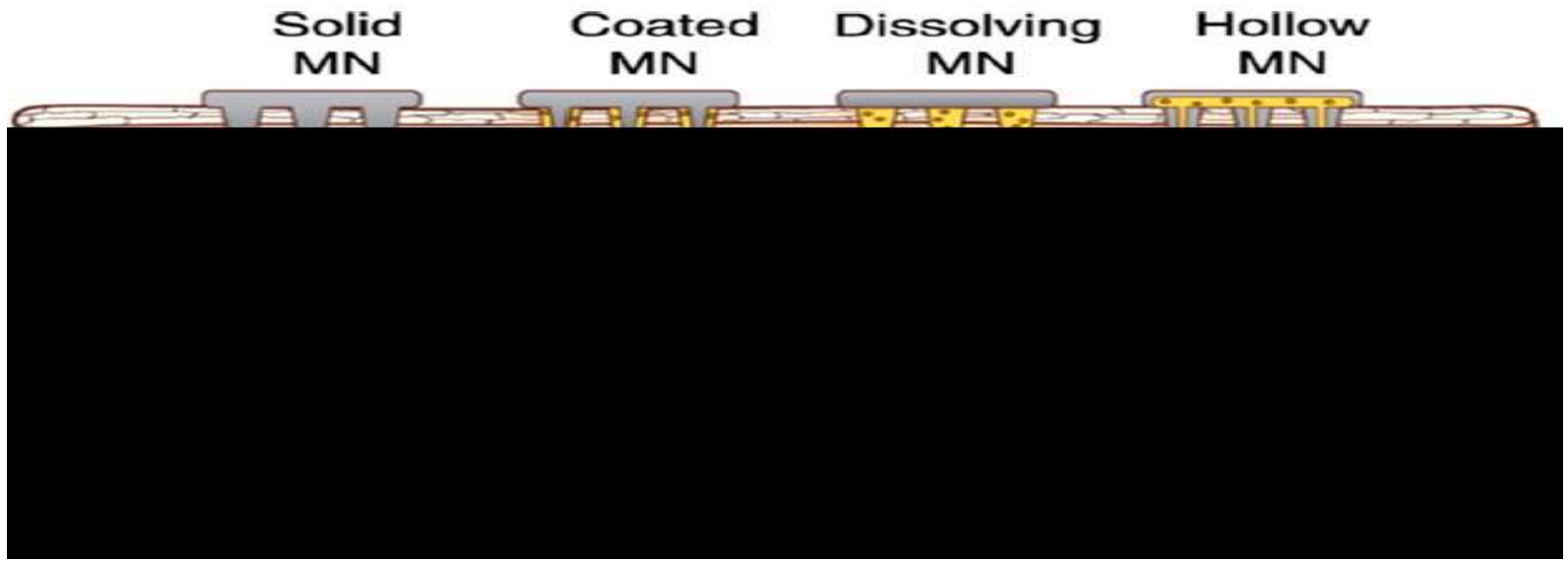








Vaccination through the skin



Vaccine target

Hepatitis B
Hepatitis C
Influenza
Poliovirus
SARS-Cov-2
Shigellosis

Phase 1 clinical trials

Advantages:

- ✓ inexpensive, stable facilitate storage and handle
- ✓ Allows for self-administration

Disadvantages:

Increased pruritus and erythema rates

Vaccine delivery via respiratory tract

- The earliest known route of vaccination was respiratory, by **intranasal insufflation** of powdered scab material containing variola virus from smallpox patients, reportedly practiced in China as early as the 10th century AD

- Respiratory vaccination delivers airborne particles via the **nose** or **mouth** for deposition onto the mucosal surfaces of the **upper** or **lower airways**.

Vaccine delivery via respiratory tract Mucosa

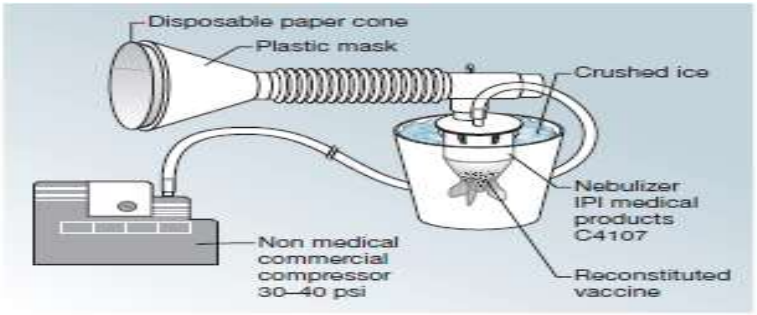
challenges relate to the conventional drugs delivery devices to the respiratory (aerosol, nebulizer, nasal spray)

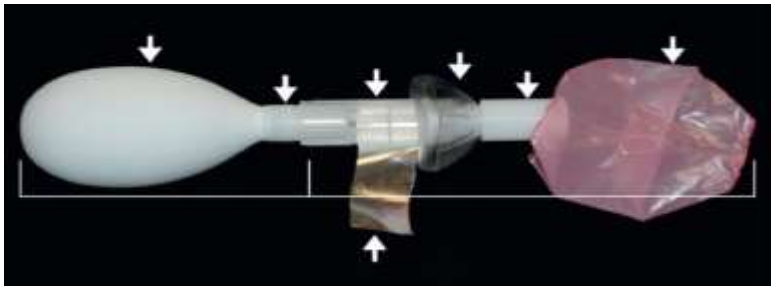
- Most respiratory drug devices deliver **repetitive doses** to a **single** patient.
- Some aerosol-drug delivery devices require **patient education** to obtain the **needed cooperation** for adequate dose delivery.
- The current respiratory drug delivery devices **typically target** the anterior nasal passages or the lower airway, respiratory.

Vaccine delivery via respiratory tract Mucosa

AccuSpray™ nasal sprayer
(FluMist live attenuated influenza)
Is currently licensed

- ✓single-patient-use,
- ✓Its total dose is 0.2 mL
- ✓low cost





Jet nebulizer system (Classic Mexican Device)
Used in multiple clinical trials in Mexico and South Africa, and also to vaccinate over 3 million Mexican children against measles in a mass campaign

Oral mucosal vaccine delivery

The most widely used oral vaccine is Oral **Polio vaccine** (OPV) that developed by Albert Sabin in the 1950s,

Sabin's OPV contributed enormously to the eradication of poliomyelitis worldwide.

During the 2010 Haitian epidemic, oral **cholera vaccination** is a faster way of containing circulating infections and prevention of further outbreak

Several oral vaccines against **rotavirus** and **S. Typhi**, and have been licensed and marketed

Barrier to mucosal vaccine delivery

Oral vaccine delivery

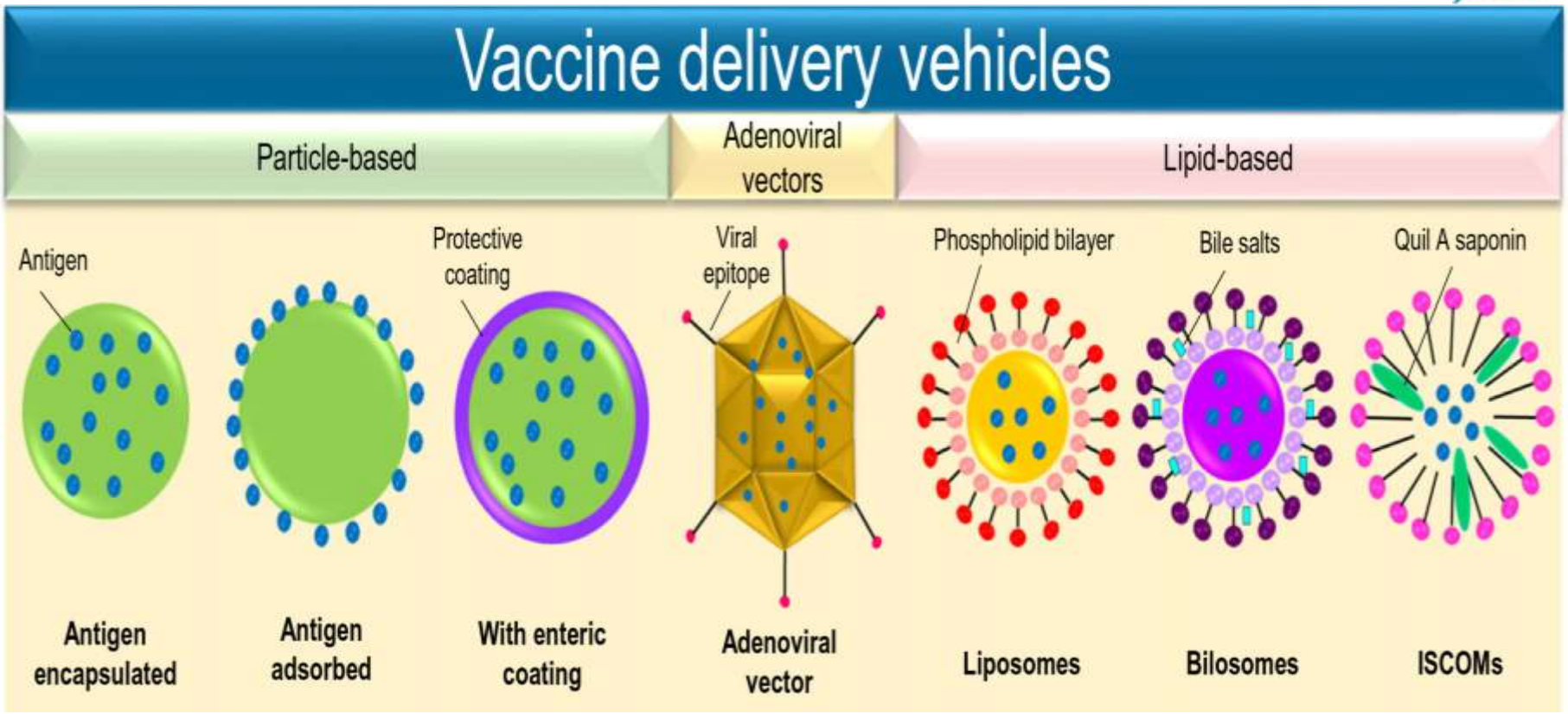
challenge

- pH fluctuation (highly acidic stomach environment), and enzymes-catalyzed hydrolysis
- Poor membrane permeability
- low bioavailability
- High doses of antigen delivered via multiple immunizations are required,

Solutions ????

the need of **novel design** for antigen delivery that can **protect** the cargo, **penetrate** the biological and physicochemical barriers, and possess adjuvant capabilities that can **elicit robust and balanced immune responses**

*Adv Drug Deliv Rev. 2017 May 15

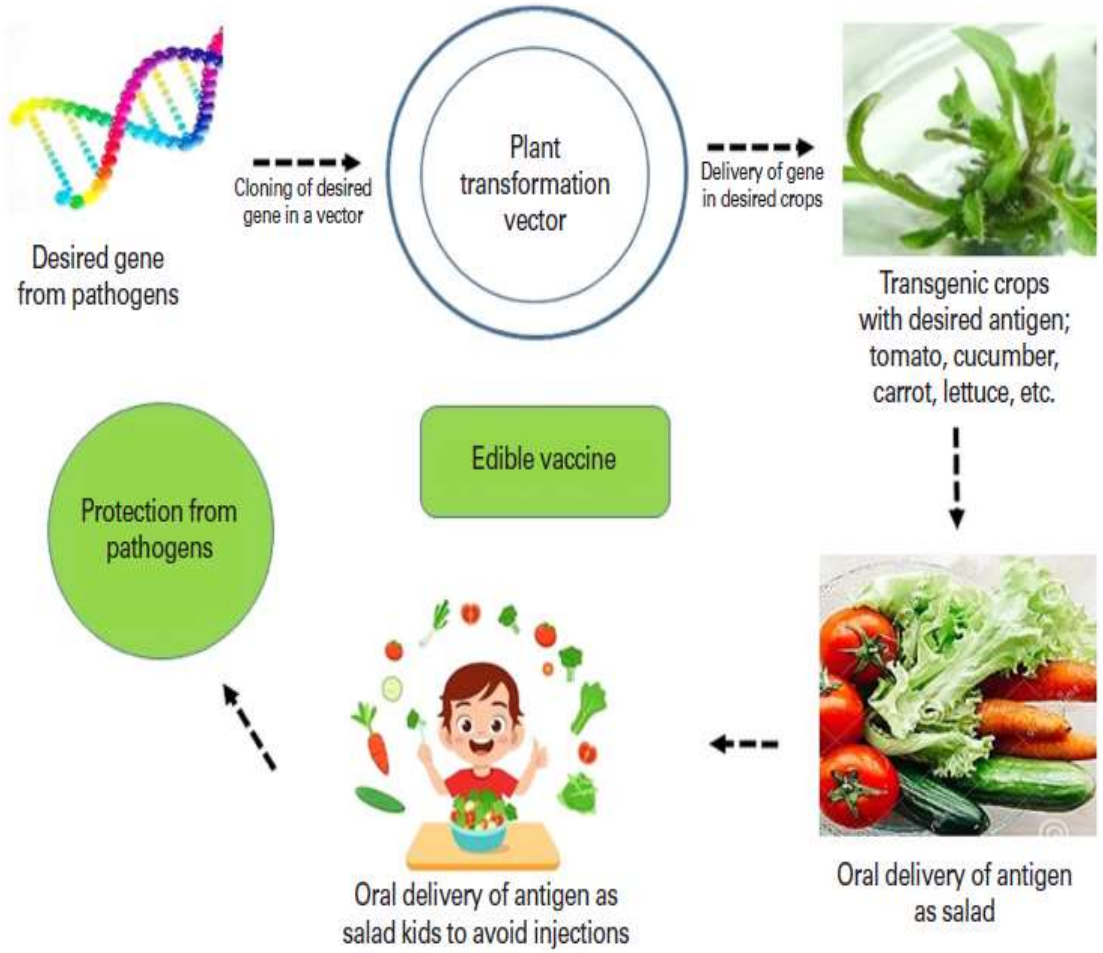


Design of delivery vehicles for oral vaccination has been focused on three different types of carriers: particle-based, adenoviral vectors, and lipid-based technologies to enhance the efficacy of the antigen upon its administration.

*Adv Drug Deliv Rev. 2017 May 15

Plant- based platform for vaccine (**edible vaccine**)

Hiatt and his colleagues firstly made attempt to produce vaccines using plants since 1989.



- ✓ Impossible of reverse virulence
- ✓ Costly effective
- ✓ No contamination
- ✓ Easily to expand production scale
- ✓ Easy for storage

Rabies virus G-protein – tomato
Norwalk virus-tobacco , potato
Vibrio cholera subunit B- potato

* Clin Exp Vaccine Res 2020;9:164-168 *Indian J Pediatr 2018;85(2)

Examples of needle free vaccines currently being developed for SARS-CoV-2

Type of Vaccine	Platform	Current Stage &Trial ID	Manufacturer
Microneedle patch (S1 subunit)	Protein subunit	Pre-clinical	University of Pittsburgh
DNA plasmid (**intraderma**l, followed by electroporation)	DNA	Phase 1/2 (NCT04447781) and (NCT04336410)	Inovio Pharmaceuticals & International Institute
Plasmid DNA (needle-free)	DNA	Pre-clinical	Immunomic Therapeutics, EpiVax and PharmaJet
Intranasal recombinant vaccine based on Influenza A virus, for SARS-Cov-2	Replicating viral vector	Pre-clinical	FBRI SRC VB VECTOR, Rospotrebnadzor and Koltsovo

* Pharmaceutics **2020**, 12, 945

Conclusion

Development of needle free vaccines is preferable to traditional injection for making immunization **safer** and **more effective**, **affordable**, **accessible**, and **acceptable for everyone**.

Microneedle patches, jet injection for cutaneous delivery and intranasal spray are the most promising strategies for the next generation vaccination.

The multitude of formulation possibilities and the simple handling devices simplify the logistics of delivery, especially during a pandemic and bioterrorism emergencies.

In addition to several marketed needle-free vaccine, many others candidate vaccines in development, preclinical and clinical studies show promising results. **Further works will be required to implement and commercialize these delivery systems**

Thank you for listening