The OptiNose Bi-directional Nasal Delivery Devices for Vaccines

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OptiNose AS
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DRUG DELIVERY DEVICES

Challenges for mass-vaccination

Natural Epidemics

Unsafe injection practices spread disease

Immunization Focus March 2001 SPECIAL FEAT

First, do no harm

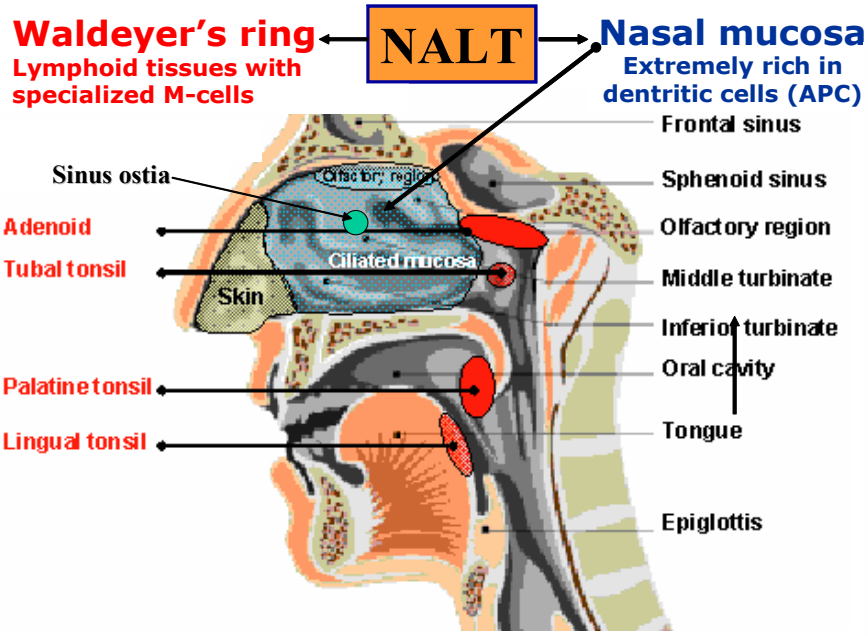
Hepatitis B: 8-16mill. Hepatitis C: 2,3-4,7mill.
HIV: 60 00-160 000

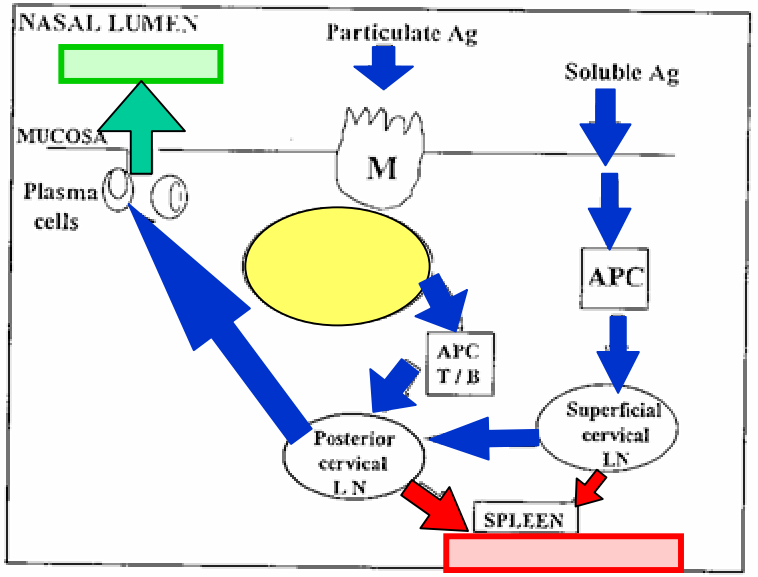
- **$ 540 mill.** – *Estimated annually expenses due to syringe related complication*
- **$ 200 mill.** - *Estimated annually expenses*
- *due to cold chain expenses/wastage*
- **WHO vaccination strategy**
- **Needle free devices**
- **Mucosal delivery**

Bio-terrorism

Why Intranasal Vaccination?
Facilitation of the immune response

- >80% of our immune system is concentrated to the mucosa
- 90% of the infectious agents reach our bodies via the mucosal surfaces

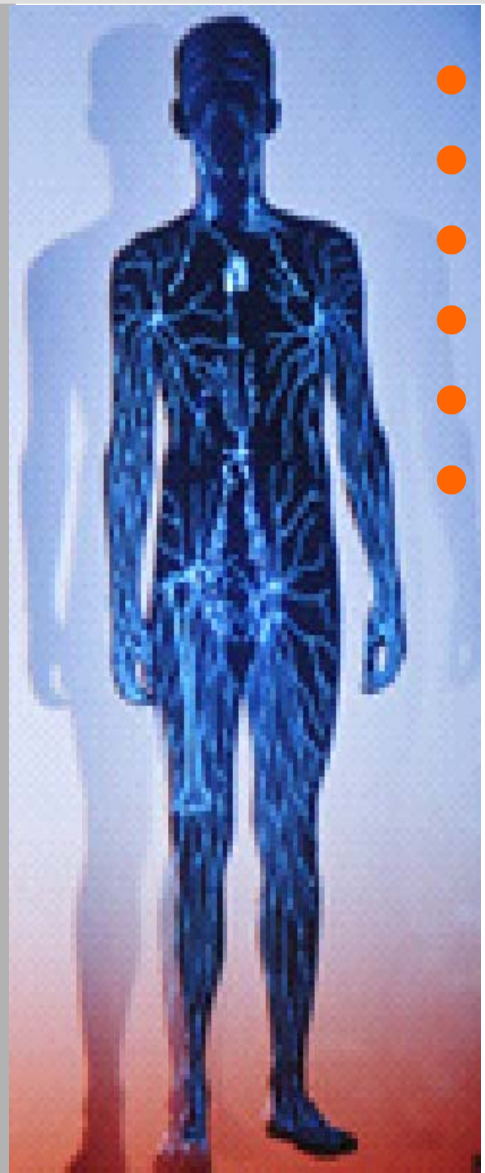




"Collectively, these results suggest that in order to obtain an enhanced immune response in the nasal mucosal, the vaccine should be targeted against topical DC's and/or M-cells of the NALT, perhaps particularly the adenoids.

Int. J. Med. Microbiol. 293, 3-15(2003) Professor Per Brandtzæg, University of Oslo, Norway

Intranasal versus other delivery methods



- **No mucosal response after injection**
- **Mucosal surfaces communicate**
- **Protection in other mucosal surfaces**
- **10 times more efficient than the oral**
- **Good systemic response**
- **Better cross-protection**

"Like natural infections, live topical vaccines or adequate combinations of inactivated vaccines and mucosal adjuvants give rise not only to SIgA antibodies, but also to longstanding Serum IgG and IgA responses, which is crucial to obtain complete protection.
The intranasal route of vaccine application appears particularly attractive to this end."
Int. J. Med. Microbiol. 293, 3-15(2003) - Professor Per Brandtzæg, University of Oslo, Norway

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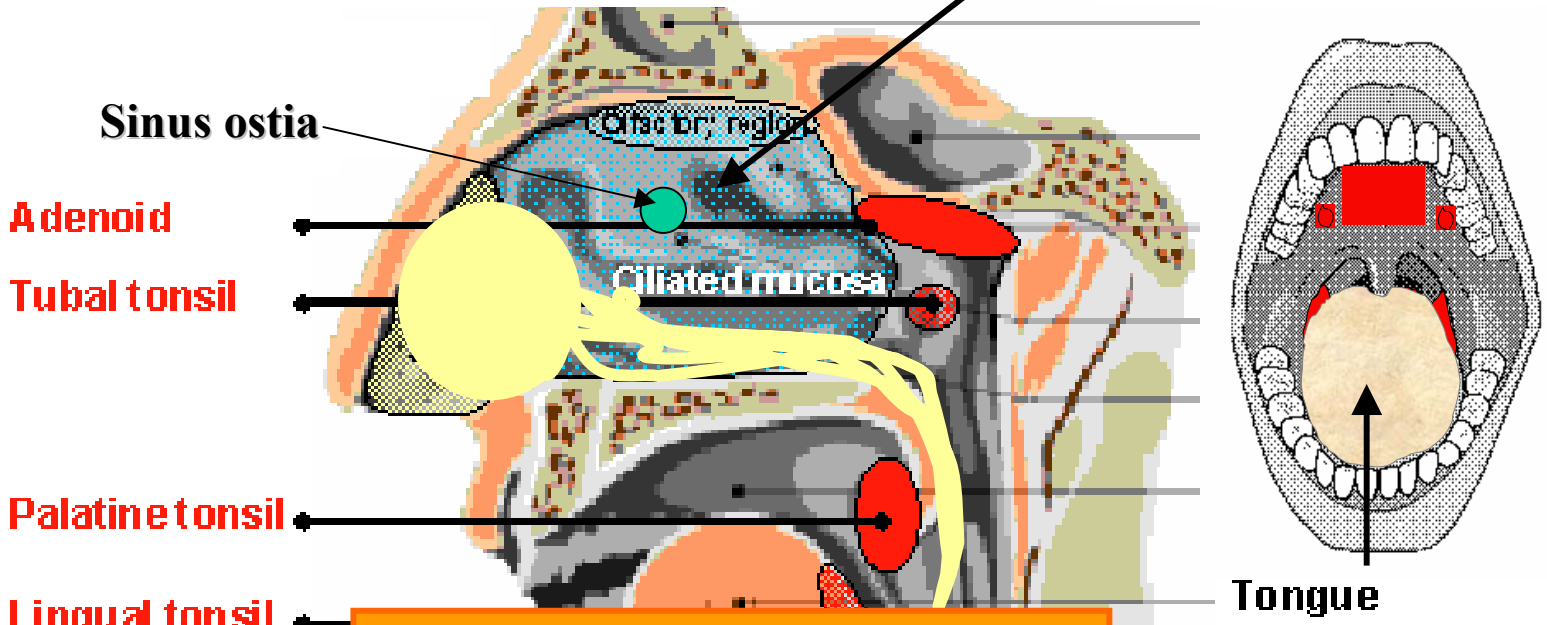
Intranasal vaccination- Why?

Waldeyer's ring
Lymphoid tissues with specialized M-cells

NALT

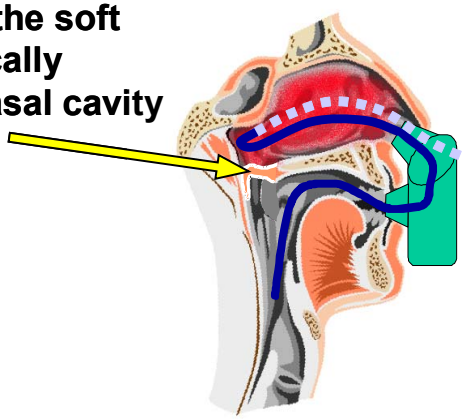
Nasal mucosa
Extremely rich in dentritic cells (APC)



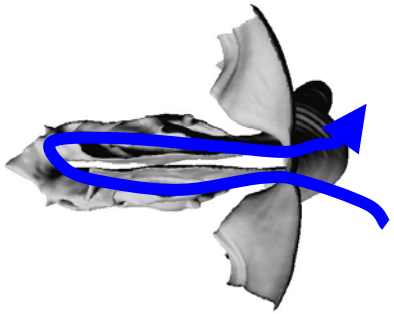
- Inadequate distribution
- Variable dosing
- Uncomfortable taste
- Irritation and nose bleeds
- New FDA guidelines

Bi-directional nasal delivery

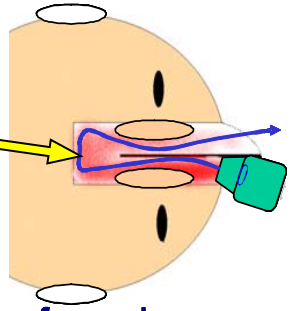
While exhaling, the soft palate automatically closes off the nasal cavity completely….



…exhaled air mixed with active substance enters the nose via a sealing nozzle…



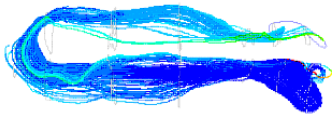
… passes through the communication posterior to the nasal septum



View from above

… and exits through the other nasal passage

Numerical flow simulations



Advantages of bi-directional nasal delivery

- Control of flow rate and particle size
- Two-point fixation of device
- Positive expanding pressure
- Targeted delivery possible
- Deposition to posterior surfaces
- Breath actuation possible
- Avoidance of lung inhalation
- Adaptable and flexible

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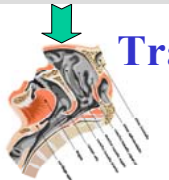
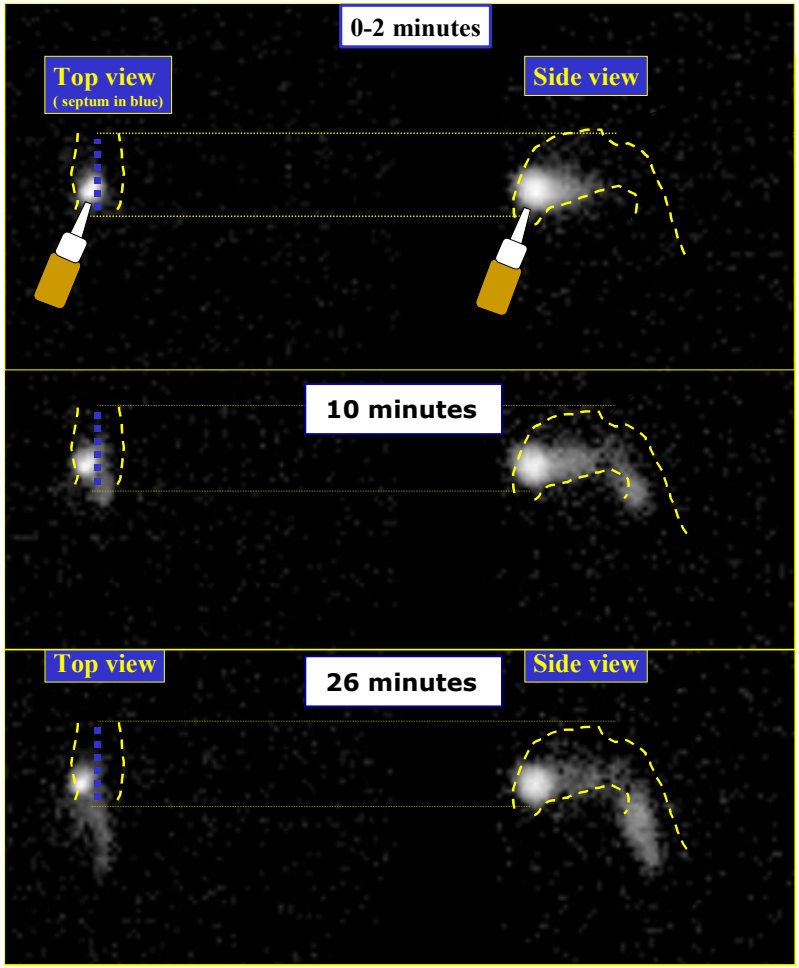
Trade. Spray vs. Bi-dir. nebulizer

Traditional hand actuated nasal spray pump

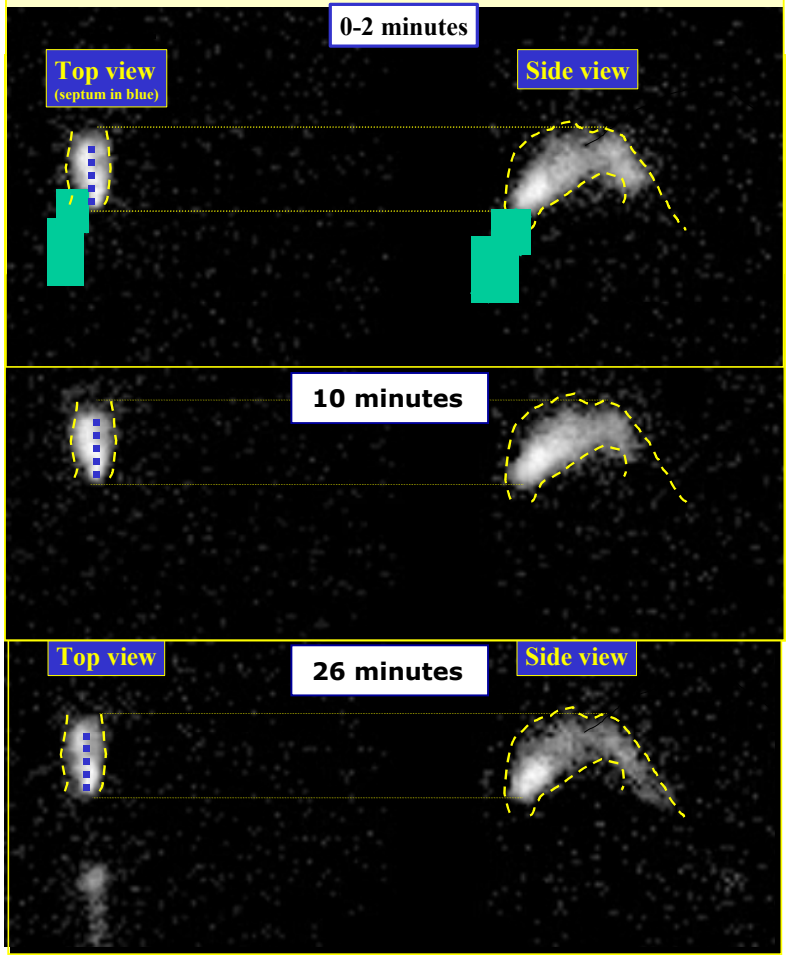


"State of the art" Gamma-scintigraphy with Technesium(Tc99)



"The OptiNose concept"

Opposite directed/bi-directional nasal drug delivery to the nasal passages in series



"Fly through the nose"

Video clip

Please contact the presenter for information regarding this video clip.

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OptiNose – Functional prototype

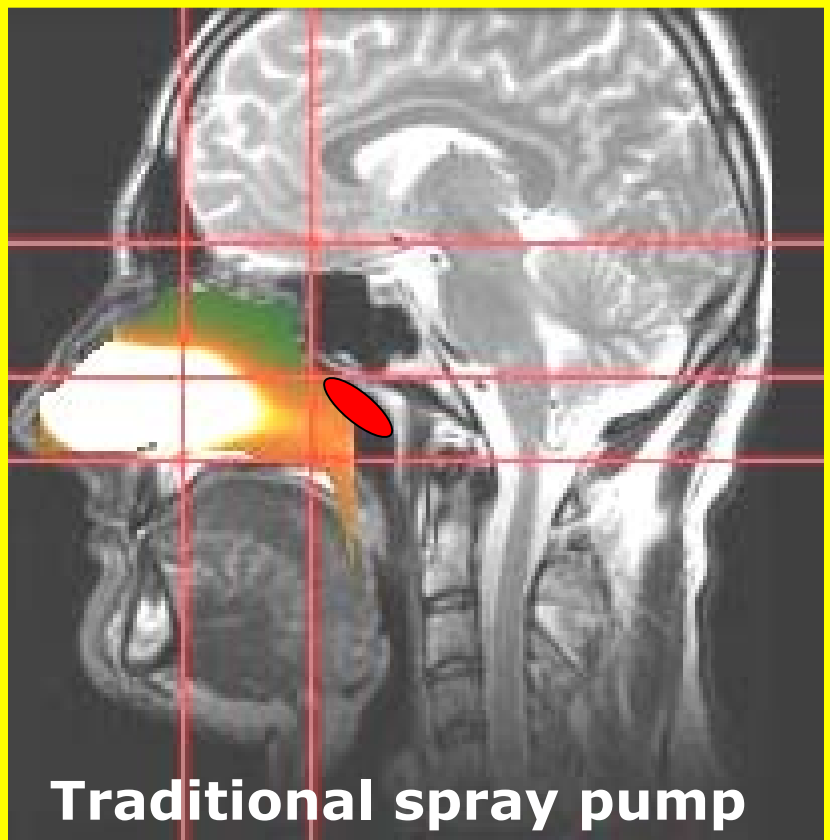
Video clip

Please contact the presenter for information regarding this video clip.

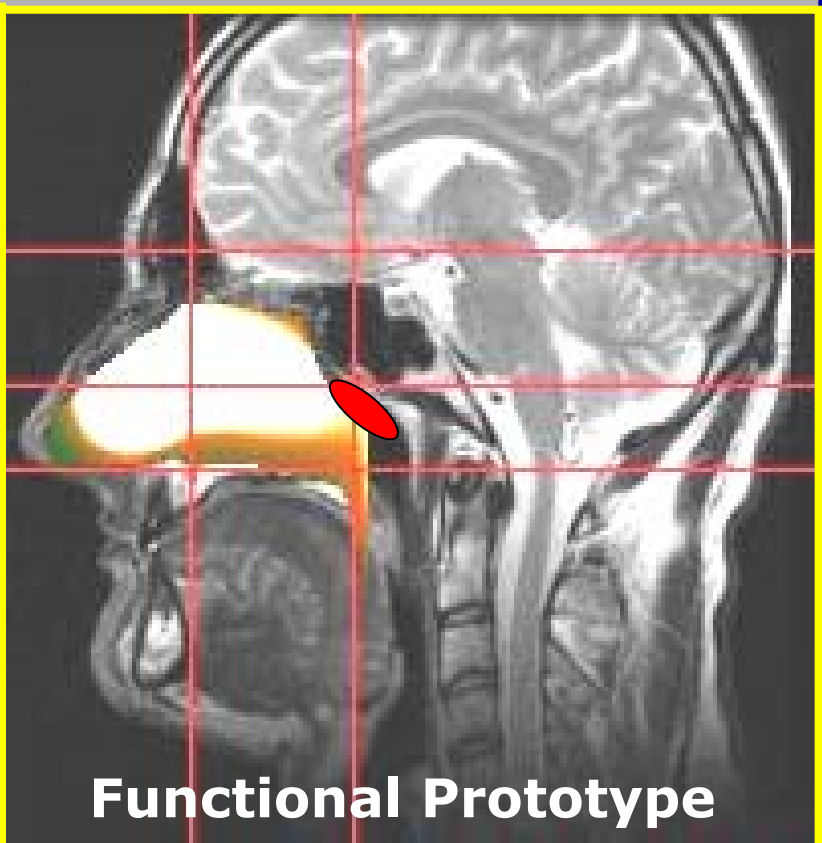
Gamma-scintigraphy (99Tc)

Cumulative distribution during 32 minutes

- White areas in the nose = 20% + of max. intensity
- Orange areas indicate = 0-20% of max intensity
- Green areas in the nose = No deposition



Traditional spray pump



Functional Prototype

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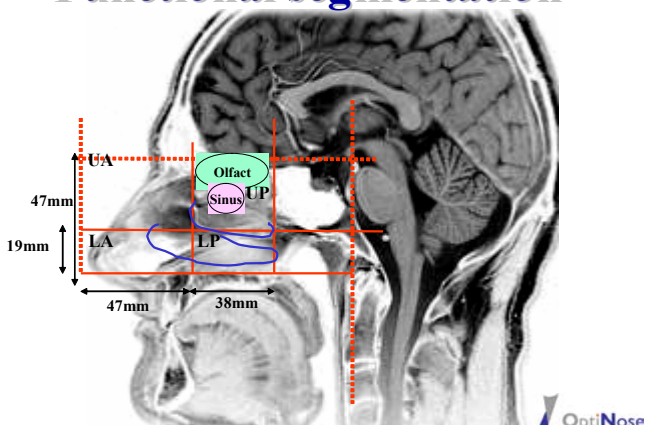
Cumulative nasal deposition

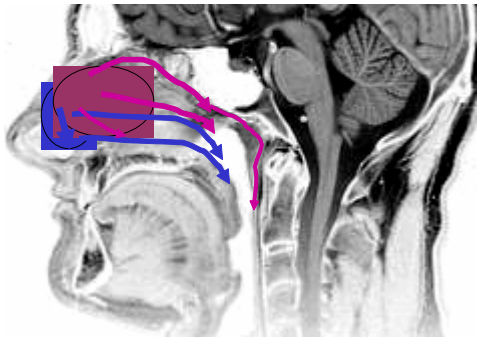
Reversed deposition pattern

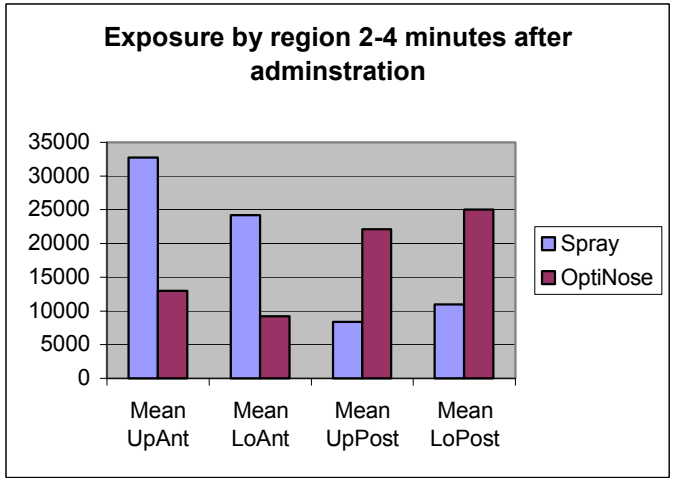
Functional segmentation

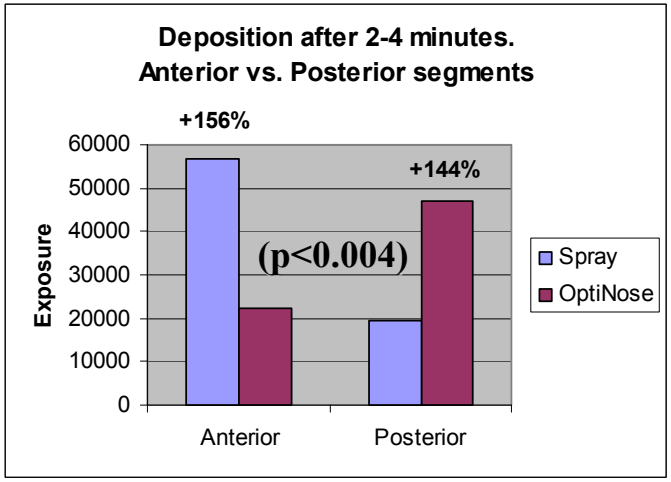


Suggested removal patterns

for traditional spray and
bi-directional nebulized aerosol







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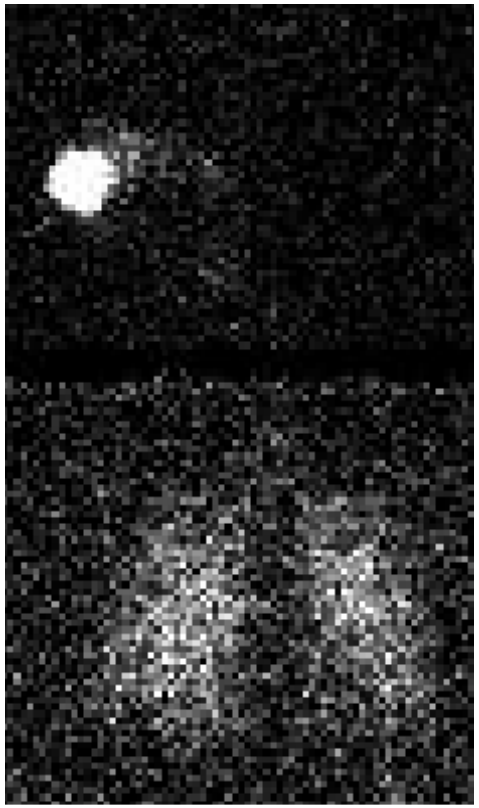
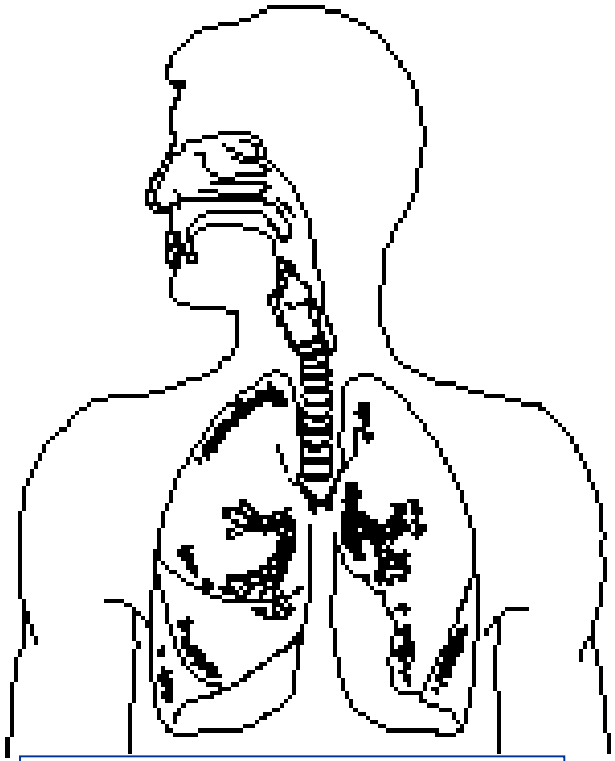
Minimal risk of inhalation to lungs

Nasal inhalation



27% of dose in lungs



Inhalation of 2-5 micron particles from PARI Nebulizer

Bi-dir. delivery

No radioactivity above backgr.

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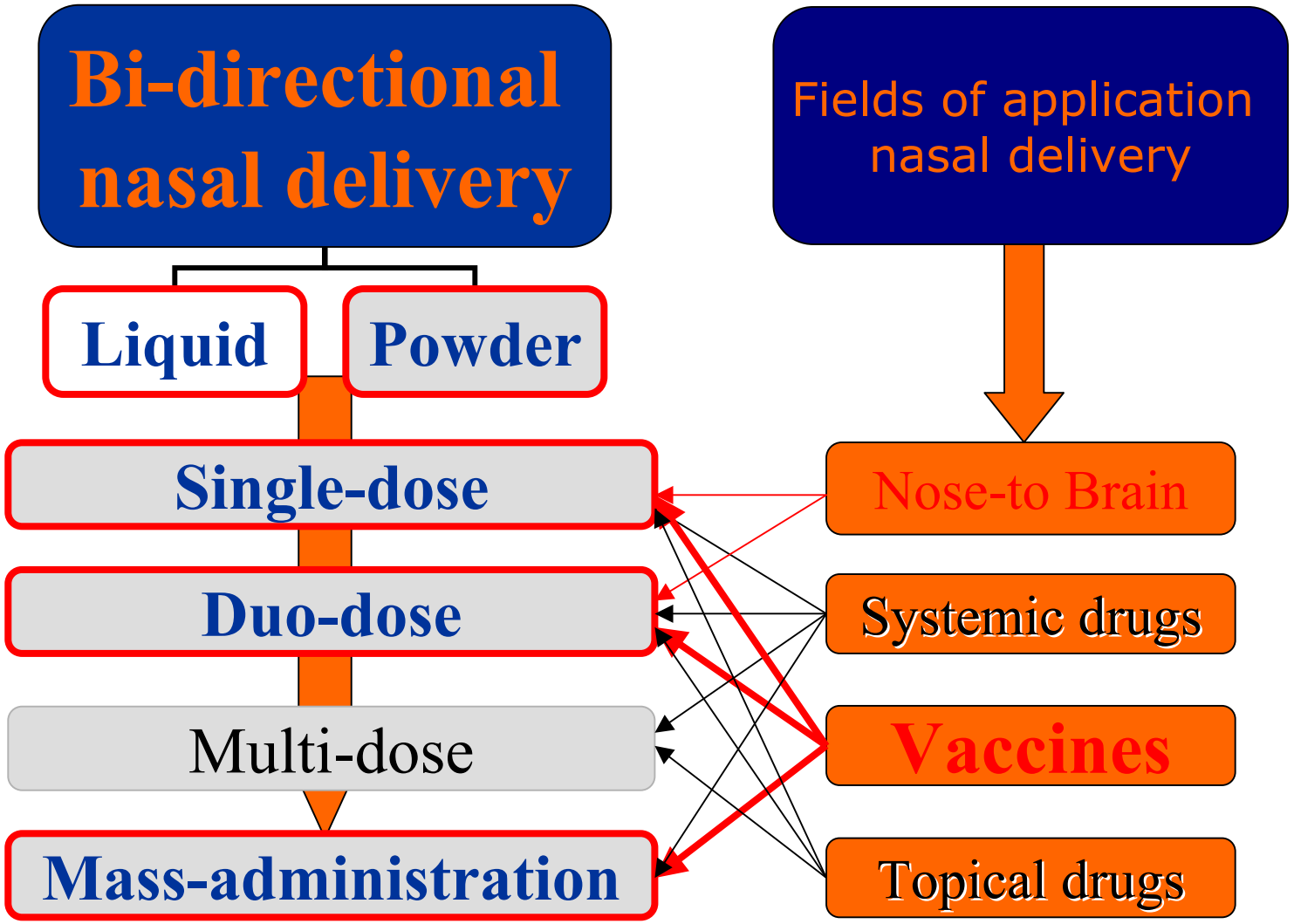
The adaptability of the technology

Versatility and flexibility



Independent Expert Opinion Report

Expert opinion by leading US University
Independent evaluation, April 2002

Overall opinion statements after review of scientific results from an extensive gamma-scintigraphy study conducted at the Norwegian Cancer Hospital

- **Examiner #1:**
  "Overall, my opinion is that the OptiNose technology has the potential to be a better nasal delivery device than what is currently available".

- **Examiner #2:**
  "Overall, the OptiNose technology has intriguing possibilities for improving nasal drug delivery".

- **Examiner #3:**
  Overall opinion of the technology: "Novel, intriguing"

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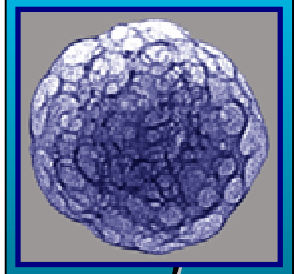
Need for antigen modifications or adjuvants

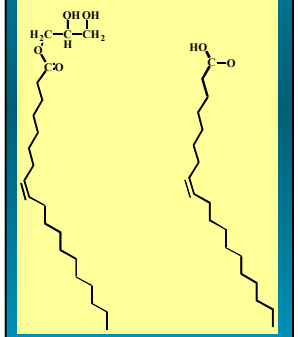
L3

Eurocine AB



Mono-olein

Oleic acid



Soy bean oil (Intralipid®)

Suspension – mix with antigen

Emulsion – formulate with antigen

The nature of vaccines

- Live attenuated vaccine - Adjuvant not required
  Potential problem with "nose-to brain" transport?
- Inactivated vaccines - Adjuvant required
- Sub.-unit vaccines - Adjuvant required
- Two doses seems required for primary vaccination

Adjuvants

- Toxin based (Chiron + others)
  Potential problem with "nose-to brain" transport? " The Berna-experience"
  But - *"Mutants of E-coli Heat –labile enterotoxin as safe and strong adjuvant for intranasal delivery of vaccines".* Peppoloni S. Expert rev. Vaccines 2(2), 285-293 (2003)
- Chitosan (West Pharmaceutical UK/US)
- Oleic acids - L3- Eurocine AB, Sweden
- Liposomes
- Others (NIPH, Norway)

Formulation issues

- Concentration issues (only 0,1-0,2 ml x 2 nasally)
- Receptor biding/Mucociliary clearance

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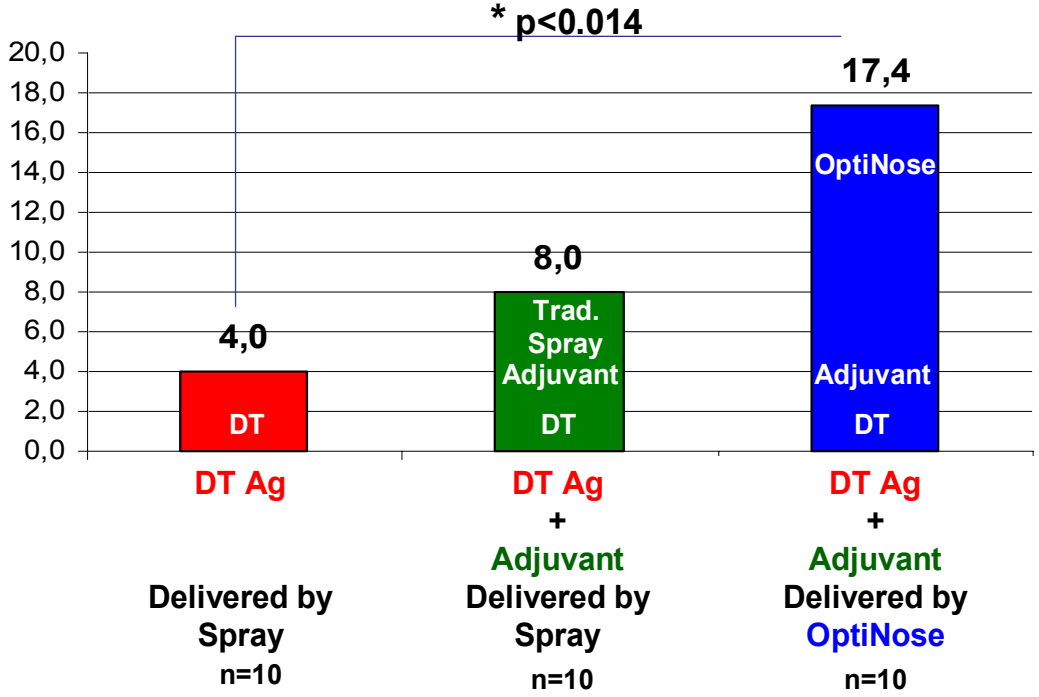
Human clinical experience
with nasal Diphtheria vaccine

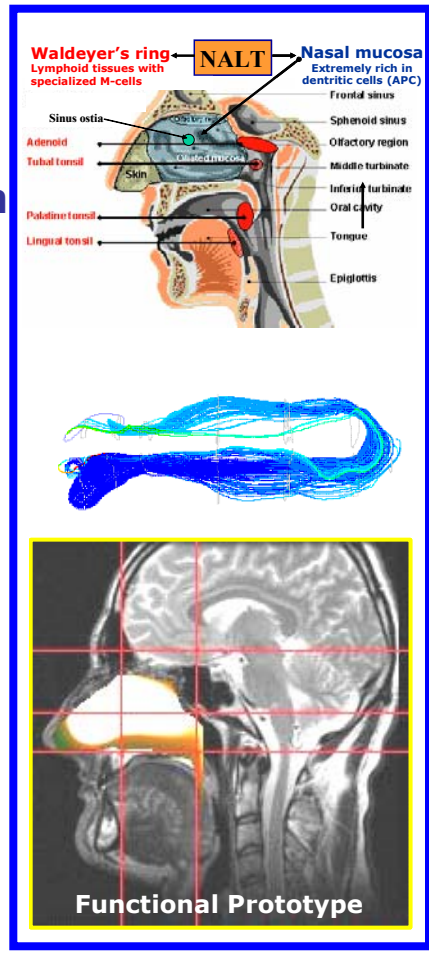
Nasal vaccination in humans

with Diphtheria Ag + Adjuvant + OptiNose Functional prototype

Preliminary data from Phase I safety study

Relative serum titer increases after single nasal vaccination





The preliminary results suggest that the improved vaccine distribution provided by the bi-directional delivery device may improve the immune response

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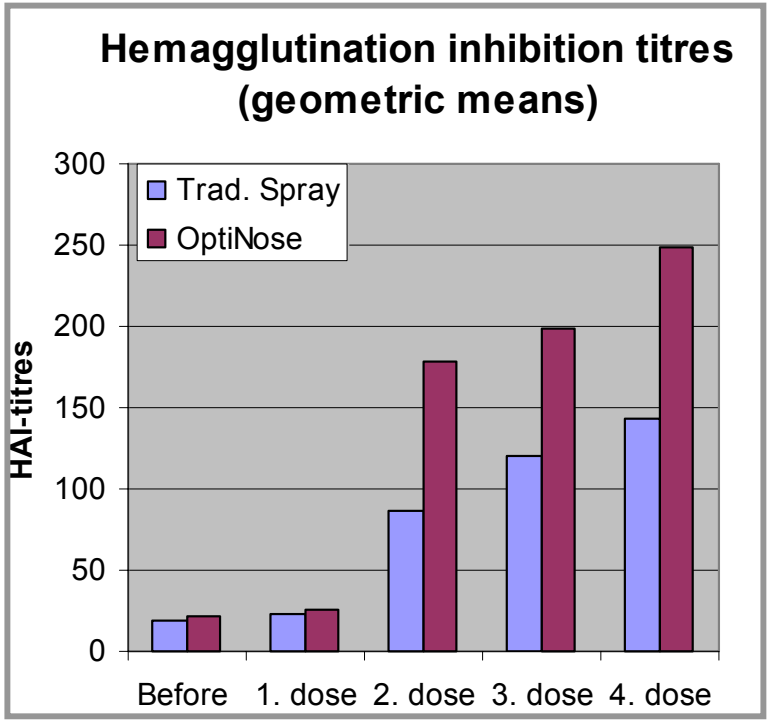
Human clinical experience
nasal influenza vaccine

Randomized study with inactivated Influenza virus vaccine without adjuvant
(19 subjects in each study group)

Collaboration between Norwegian Institute of Public Health, Vaccine company and OptiNose

		OptiNose	Nasal Spray
Protective AB levels	**HAI-titer > 40** + Significant increase after 2 doses	YES	YES
Protective AB levels	**HAI-titer > 40** **+** Sign. increase in 100% of subjects after 4 doses	YES	NO
Cellular immunity	**T-cell proliferation** (Periph.CD4+ T-lymfocytes) – Significant increase	YES	NO
Systemic immunity	**IgG in serum** (Vacc. spec. IgG-ab) - Significant increase	YES	YES
Mucosal immunity	**IgA in Nasal secretion** - Significant increase	YES	NO
Mucosal immunity	**IgA in Saliva** - Significant increase	YES	YES



These preliminary results suggest that the OptiNose bi-directional device may improve the immune response

Further details are confidentiality and/or for commercial reasons and not yet available

"A striking but unexpected observation was that antitoxin sIgA response was seen only after the second immunization and only in the vaccinated nostril".

Infection and Immunity, Feb 2003, Mills et al.

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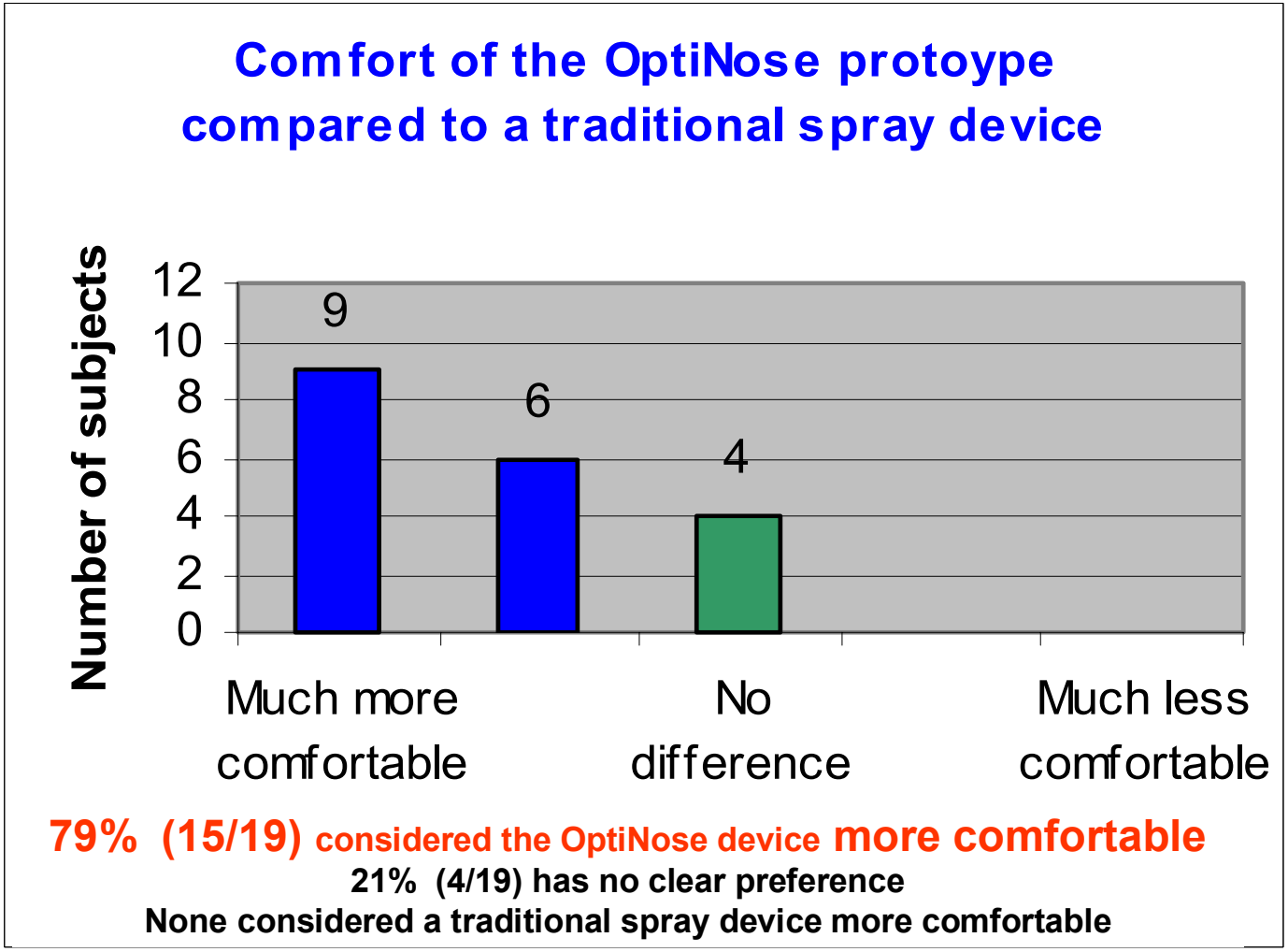
Human clinical experience
Subjective evaluation of prototype



79% (15/19) considered the OptiNose device more comfortable

21% (4/19) has no clear preference

None considered a traditional spray device more comfortable

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Reliability of use by nonprofessional staff

OptiNose bi-directional nasal vaccines delivery

- **Breath actuated**
- **User-friendly & intuitive**
- **Simple & inexpensive device**

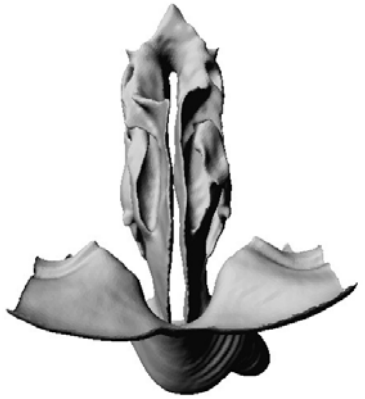
- **Adults/children:**
  Self-administration by the OptiNose – breath actuated delivery device
- **Infants/small children:**
  Assisted administration by parents or non-professionals using the OptiNose nasal device
- **Mass-vaccination**
  Mass-administration by Non-professionals using the OptiNose mass-vaccination concept or **Self-administration** by the OptiNose – breath actuated delivery device

Production & Regulatory issues

Self-administration

OptiNose breath actuated unit-dose devices

Cooperation for pilot-production of single dose device wit Pfeiffer (Germany, owned by Aptar Group, USA)



Small single dose vials in approved material (glass)

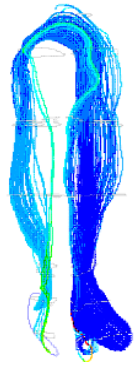
- Suitable for storage of vaccines in refrigerators
- Can be fitted into delivery device just before delivery

Approval process of breath actuated Single-dose device in progress (FDA and others)

Assisted Mass-vaccination

Mass-vaccination using multi-dose vials

- Suitable for storage in refrigerators
- Can be fitted into delivery device just before delivery



- **EU-support (CRAFT) –**
- **Research collaboration - Univ. of Oslo, CEVI and Karolinska Institute, Univ. of Stockholm, Sweden**
- **WHO – potential collaboration**
- **IAVI - potential collaboration**

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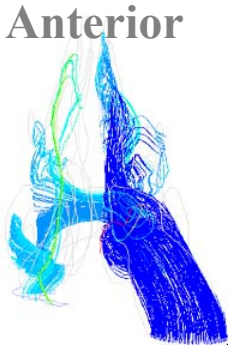
Summary

Bi-directional nasal delivery of vaccines

General features of nasal vaccination

- **Inactivated, subunit and live vaccines**
- **Adjuvants needed for most vaccines**
- **Dose reduction achievable**
- **Humoral, cellular and mucosal response**



Features of OptiNose nasal vaccination system

- **Unique patented bi-directional delivery**
- **Optimal distribution facilitates imm. response**
- **Can be adapted for powders and liquids**
- **Superior results in clinical studies/user-trials**
- **Using approved vials from market leader**
- **Regulatory approval process in progress**
- **Self-administration - simple, safe and intuitive**
- **Defense against epidemics and bio-terrorism**