A NEEDLE-FREE VISION

MEETING ON NEEDLE-FREE ADMINISTRATION SYSTEMS FOR VACCINES

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PUBLIC HEALTH IMMUNIZATION STRATEGIES & TARGETS, 2003

	USA	LDCs*
		* LDCs = Less Developed Countries
ROUTINE		
➢ pediatric	☯	☯
➢ elderly	☯	-
➢ special (travelers, pregnant F)	☯	☯
MASS CAMPAIGNS		
➢ disease control		
➢ epidemic (flu, mening, YF)	☯	☯
➢ endemic (polio, measles)	-	☯
➢ biodefense	☯	-

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ROUTINE vs. MASS CAMPAIGNS

ROUTINE IMMUNIZATIONS

- fixed care facilities
- outreach services (mobile teams)
- low or moderate workload
- vaccine supplies & logistics readily forecasted
- population typically needs to be motivated

MASS CAMPAIGNS

- more outreach
- high workload
- often strong consumer demand
- extra personnel required

EPI Unit in Health Center, Kangaba, Mali

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AN IDEAL VACCINE-- CHARACTERISTICS

- Safe in all ages & immunocompromised (e.g., tetanus toxoid)
- Efficacious in all ages (including young infants & elderly) & high risk groups (e.g., tetanus toxoid)
- Single-dose (e.g., 17D yellow fever, measles, rubella)
- Early onset of protection (e.g., CVD 103-HgR)
- Long-lived protection (e.g., 17D yellow fever, TT, Ty21a)
- ***Administrable without needle & syringe*** ***(e.g., OPV, Ty21a, FluMist, CVD 103-HgR)***
- Practical, simple formulation favors compliance
- Formulation resistant to high & low ambient temperatures (does not need a cold chain)

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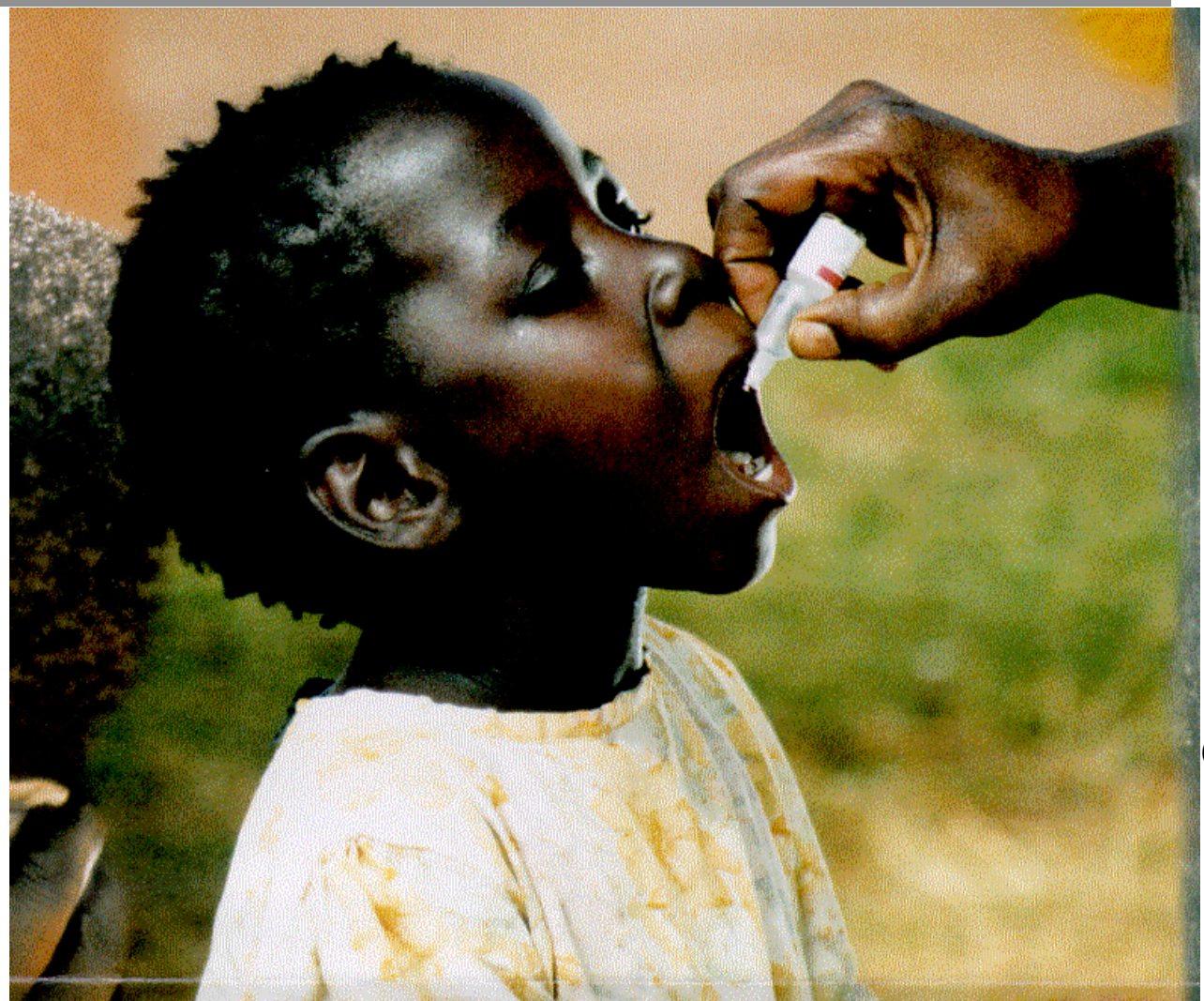
A WHY NEEDLE-FREE IMMUNIZATION IS DESIRABLE

SIMPLER

- More practical
- Less technical expertise required
- More suitable for mass campaigns



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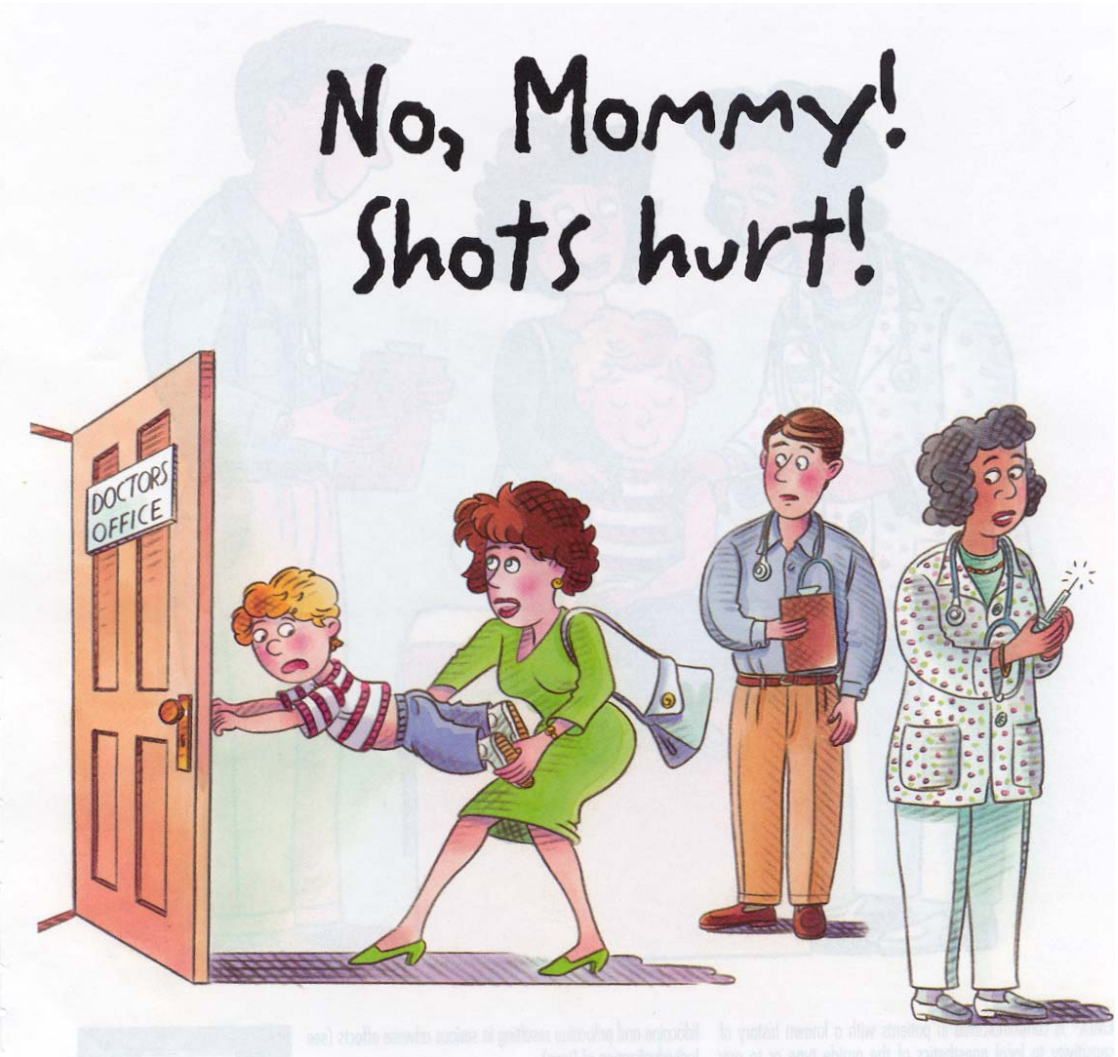
A WHY NEEDLE-FREE IMMUNIZATION IS DESIRABLE



PREFERRED

- Generally preferred over needles (increases compliance)

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WHY NEEDLE-FREE IMMUNIZATION IS DESIRABLE

SAFER

- Occupational safety (for health workers)
- Injection safety (for vaccinees)
- No infectious “sharps” waste

Infectious waste

Discarded infectious waste

INJECTION SAFETY IN DEVELOPING COUNTRIES

- Many cases of inadvertent transmission of HIV, HBV & HBC from re-use of non-sterile needles and syringes
- Vaccinations constitute ~ 10% of injections in developing countries
- Vaccination targets healthy subjects --- must be held to a higher standard
- Autodisposable (AD) syringes have helped
- AD syringes still constitute infectious waste that must be disposed of safely

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INJECTION SAFETY IN INDUSTRIALIZED COUNTRY MASS VACCINATION CAMPAIGNS

- Occupation health concern for vaccinators (needle sticks during high workload conditions)
- Disposal of infectious waste generated during high workload conditions

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3 STRATEGIES FOR NEEDLE-FREE IMMUNIZATION

- **MUCOSAL**
  - **Aerosol**
- **TRANSCUTANEOUS**
- **NEEDLE-FREE INJECTIONS**

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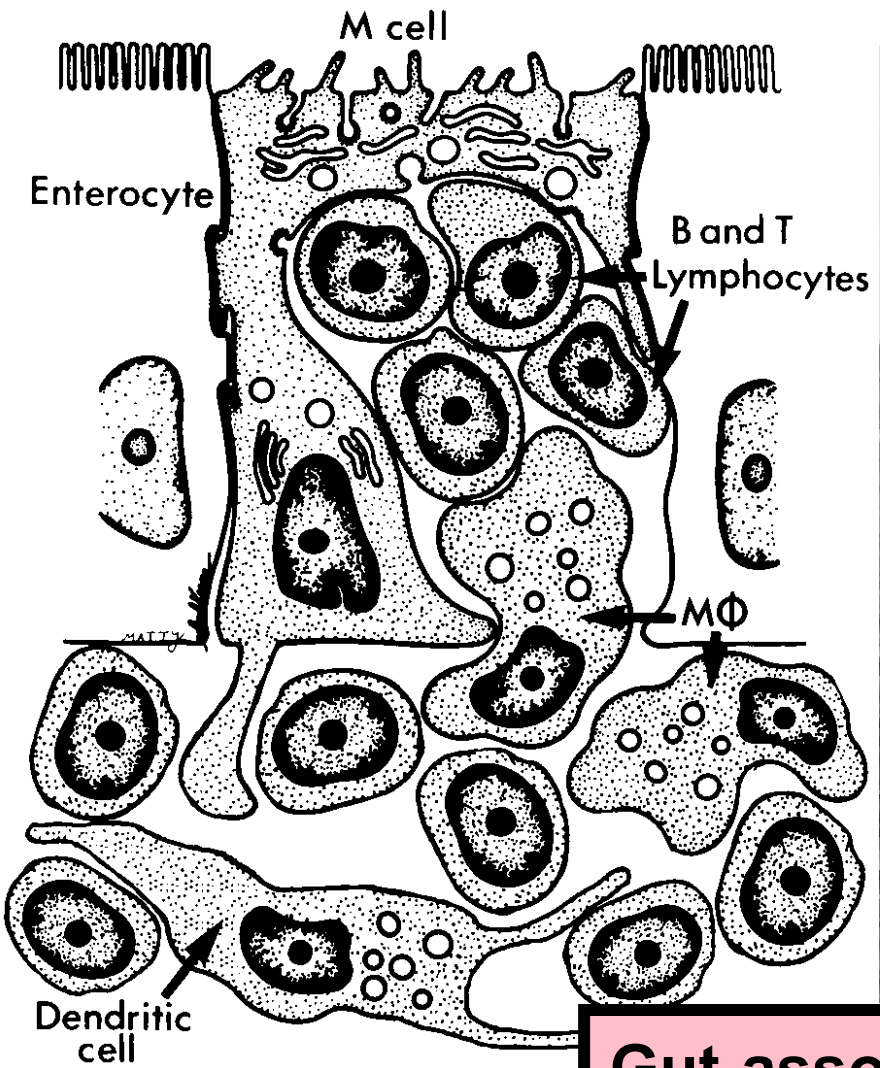
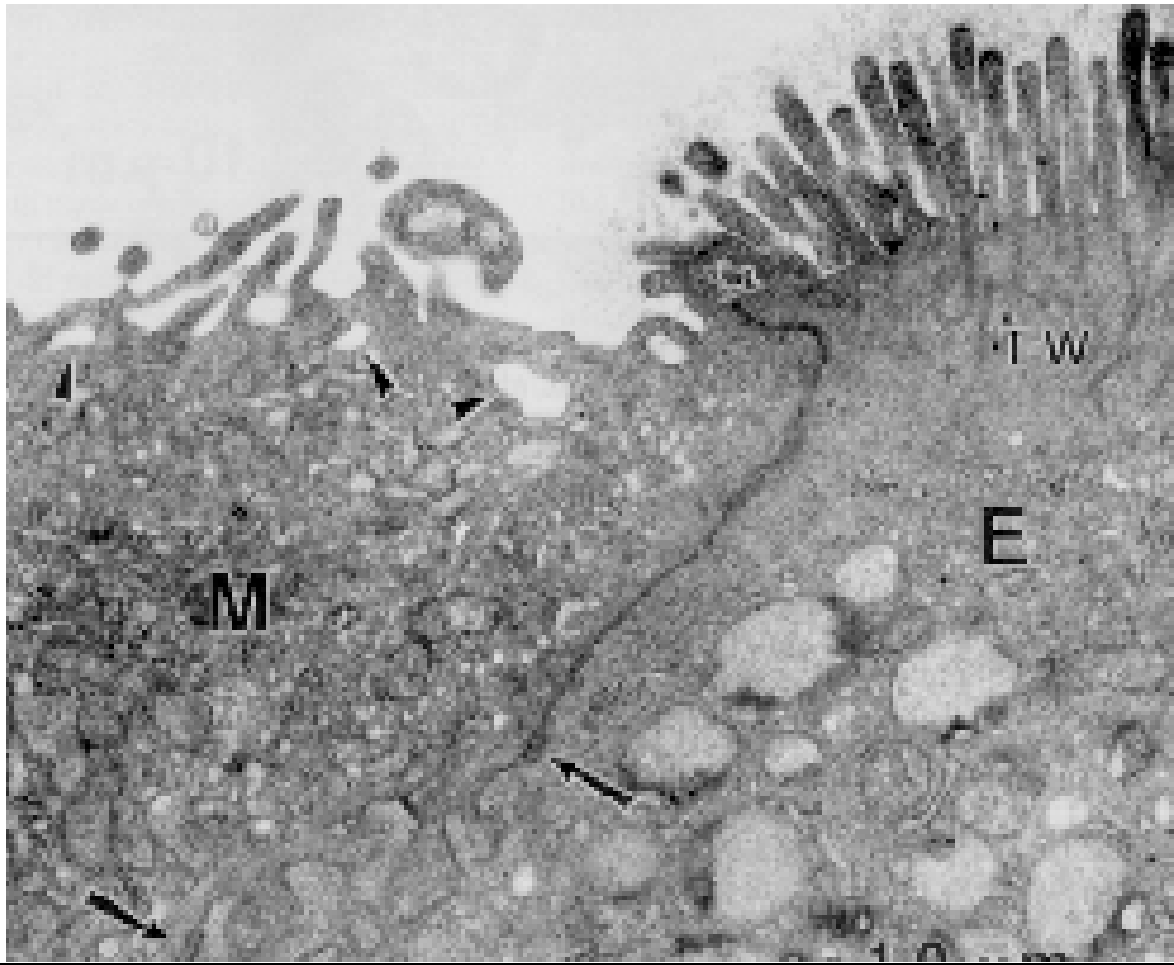
RATIONALE FOR ADMINISTERING VACCINES VIA MUCOSAL SURFACES

- Practical (e.g., Sabin oral polio vaccine)
- Preferred by parents & children over injections
- Avoids “injection safety” concerns in developing countries (inadvertent HBV, HCV, HIV transmission)
- Can stimulate all arms of the immune system (mucosal SIgA, serum antibodies, CMI [including CTL], ADCC)
- Preferred for mucosal pathogens
- Early defense for pathogens that invade via mucosa
- Some mucosal vaccines can elicit long-lived immunity (≥ 7 years)
- Some mucosal vaccines elicit rapid protection (day 8)

MUCOSAL LYMPHOID INDUCTIVE SITES





Gut-associated lymphoid tissue (GALT)
Bronchus-associated lymphoid tissue (BALT)
Nasal-associated lymphoid tissue (NALT)

MUCOSAL ROUTES OF IMMUNIZATION

ORAL

NASAL

Rectal

Vaginal

Conjunctival

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SOME MUCOSAL IMMUNIZATION STRATEGIES

- Live attenuated bacteria & viruses (Ty21a, CVD 103-HgR; cold adapted influenza virus, attenuated rotavirus)
- Live vectors (*Salmonella* Typhi, *Shigella*, adenovirus)
- Bacterial vectors delivering DNA vaccine
- Heterologous prime/boost

- Inactivated microbes (e.g., BS/WCV)
- Non-living antigen delivery systems (polylactide/polyglycolide microspheres; proteosomes, liposomes, cochleates, virus-like particles, virosomes, chitosan [polycationic polysaccharide] microspheres)
- “Edible vaccines” (transgenic plants)
- Mucosal adjuvants with non-living antigens (e.g., mutant LT or CT, CTA1-DD, cytokines, chitosan)
- DNA vaccines (e.g., given with chitosan)

LIVE ATTENUATED VACCINES

- Polio Eradication Initiative (Sabin OPV)
- Ty21a (Vivotif®) live oral typhoid vaccine
- CVD 103-HgR live oral cholera vaccine (Orochol®, Mutacol®, Orochol E®)
- Trivalent cold adapted influenza (FluMist®)

- New live rotavirus vaccines (GSK, Merck)
- Engineered attenuated *S.* Typhi live oral vaccines (CVD 908-*htrA*, ACAM948-CVD, Ty800, ZH9)
- Attenuated *Shigella* strains
- Attenuated *Shigella* expressing ETEC antigens

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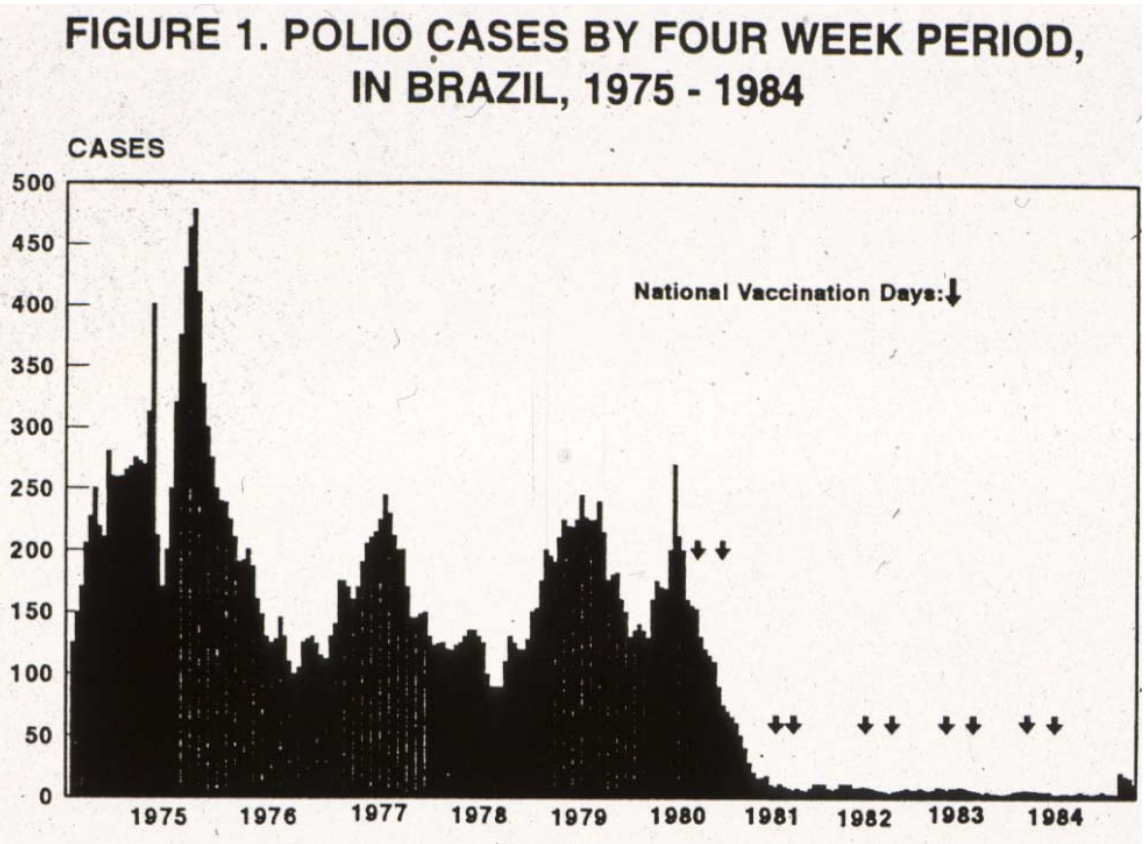
POLIO ERADICATION INITIATIVE

Mass immunization campaigns with Sabin OPV are the basis of the PEI



- ~ 35,000 polio cases in 1988
- 1,999 cases reported in 2002 (95% reduction)
- 7 polio-endemic countries
- 80% of all cases occur in India, Nigeria and Pakistan
- No type 2 wild poliovirus cases since 1999.

EFFICACY OF FLUMIST® TRIVALENT (H3N2, H1N1, B) COLD ADAPTED ATTENUATED INTRANASAL INFLUENZA VACCINE

Virus	Efficacy: Years 1 & 2
A (H3N2)	92%
B	91%
A or B	92%

Phase 3 field trial in the USA in 1,602 children, 15-71 months of age

Belshe et al NEJM 1998

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LONG-TERM PROTECTION FROM Ty21a LIVE ORAL TYPHOID VACCINE

Norte trial	Ty21a	Plbo	Efficacy
Years 1-3	N=22,170*	N=21,906	
Inc./10^5	104	310	67% (47-97%)+
Years 1-7			
Inc./10^5	226	598	62% (48-73%)
Suroriente trial			
Years 1-3	N=36,623**	N=10,602	
Inc./10^5	63	272	77% (60-87%)
Years 1-5			
Inc./10^5	93	417	78% (65-86%)

* 3 doses of enteric-coated formulation every other day

\+ (95% CI)

** 3 doses of "liquid" formulation every other day (Levine et al 1987, 1990 & 1999)

IMPORTANCE OF FORMULATION, EVEN FOR ORAL VACCINES

Chilean adolescents ingesting Ty21a in enteric capsule formulation

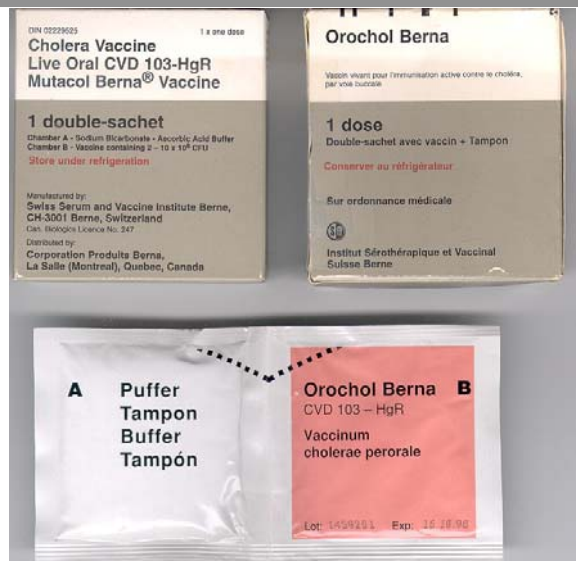
Mass immunization of Chilean adolescents with Ty21a in enteric capsules

8% of Chilean 6- & 7-year-olds could not swallow the enteric capsules.

100% of kids this age ingested a liquid formulation

CVD 103-HgR LIVE ORAL CHOLERA VACCINE

- Safety
- Immunogenicity
- Excretion of vaccine strain (minimal)
- Transmissibility (minimal)
- Environment (no introduction)
- Efficacy
- Effectiveness



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ASSESSMENT OF LIVE ORAL VACCINE EFFICACY, MICRONESIA OUTBREAK

- Retrospective cohort study of target population vaccinated
- Match between cholera case records & vaccination registries
- 47% of population vaccinated during mass campaign
- Cholera incidence 5x higher in non-vaccinees
- Estimated Vaccine Efficacy = 79% (CI, 72-85%)

Vaccine efficacy evaluation team led by Dr. Claire-Lise Chaignat, Global Task Force on Cholera Control, WHO

SINGLE-DOSE ORAL IMMUNIZATION OF YOUNG INFANTS IN A NON-INDUSTRIALIZED COUNTRY

- ~ 70% of Chilean infants were able to mount relevant immune (vibriocidal antibody) responses following administration of a single-dose of live oral vaccine CVD 103-HgR ($5x10^9$ CFU)
- Paves the way for studies with other single-dose oral vaccines

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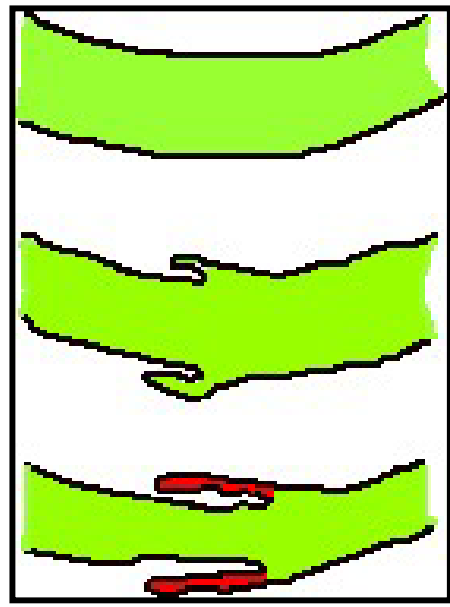
THE ROLLER COASTER "UPS" AND "DOWNS" OF MUCOSAL VACCINES, 1998-2003

LESSONS FROM ROTASHIELD®

- Licensed by FDA in 8/98 based on clinical acceptability, safety, & efficacy
- Routine infant immunization, USA, 10/98-7/99 (circa 1.8 million doses administered)
- VAERS detected cases of intussusception in relation to the first dose of Rotashield® vaccine
- Routine use discontinued in 8/99
- Product withdrawn from market
- Epidemiologic studies suggest risk of ~1 per 10,000 vaccinated infants
- Legacy -- large safety studies for new infant oral rotavirus vaccines



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ORAL VACCINES FOR WHICH IMMUNOGENICITY DIFFERS IN INDUSTRIALIZED VERSUS DEVELOPING WORLD POPULATIONS

- Sabin OPV
- RIT bovine rotavirus
- Tetravalent Rhesus rotavirus (10^4 PFU)
- CVD 103-HgR live oral cholera vaccine
- Non-living BS/WCV

- Competition by enteric viruses
- Bacterial competition
- "Environmental enteropathy"
  - Small bowel bacterial overgrowth
  - Blunted villi
  - Hypercellularity

A CAUTION FOR INTRANASAL ANTIGENS AND ADJUVANTS

- Intranasal influenza vaccine (virosomes plus wild type LT adjuvant) withdrawn from market because of possible association with Bell's Palsy
- Olfactory nerve fibers are present in the nasal mucosa
- Cribriform plate of the ethmoid bone separates nasal cavity from the anterior cranial cavity
- Olfactory nerve fibers perforate the cribriform plate and extend to the olfactory bulbs of the brain
- Some adjuvants (e.g., LT, CT and their mutants) and antigens that bind gangliosides on neurons can be transported centrally
- Animal models vary widely in their predictability

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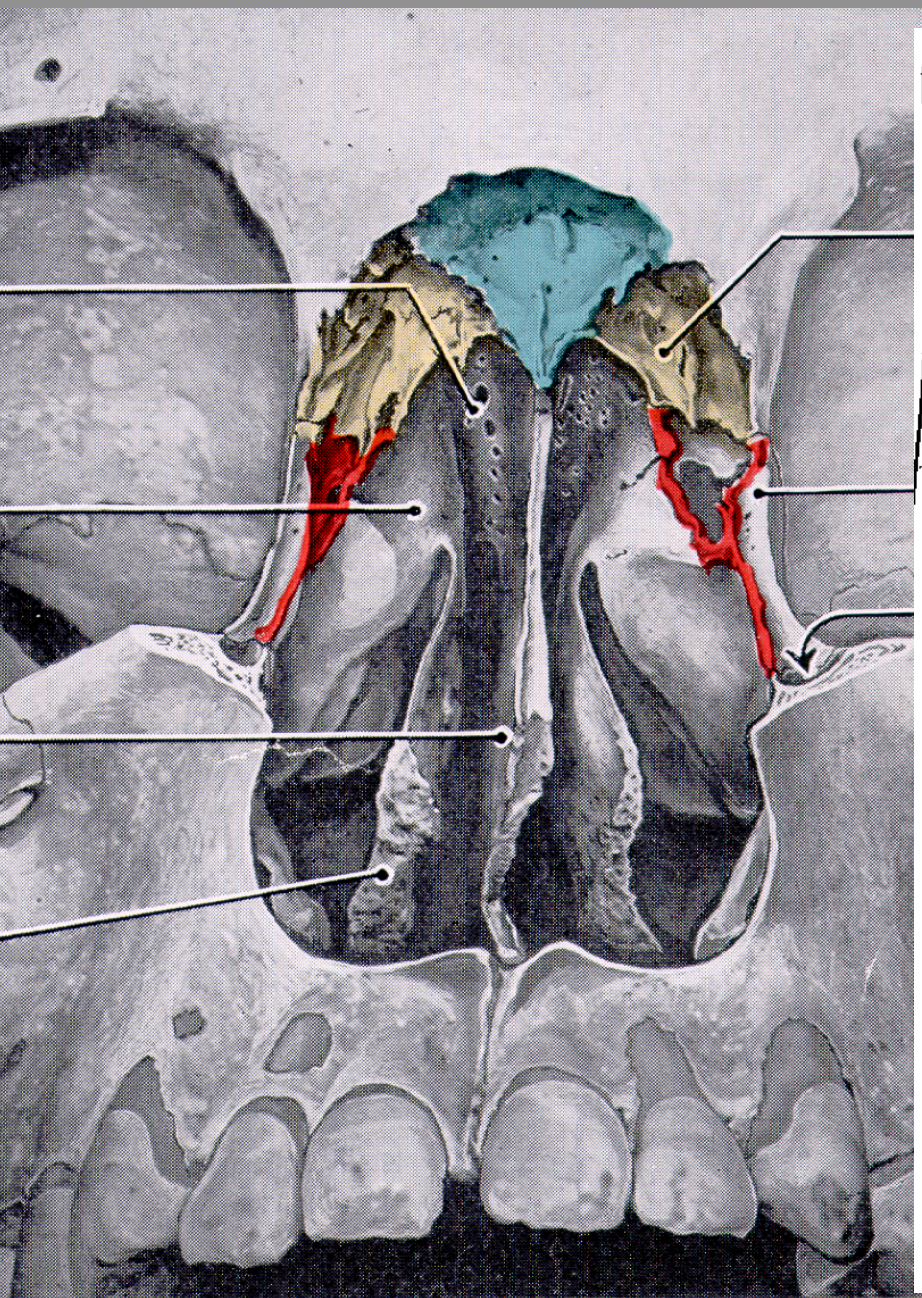
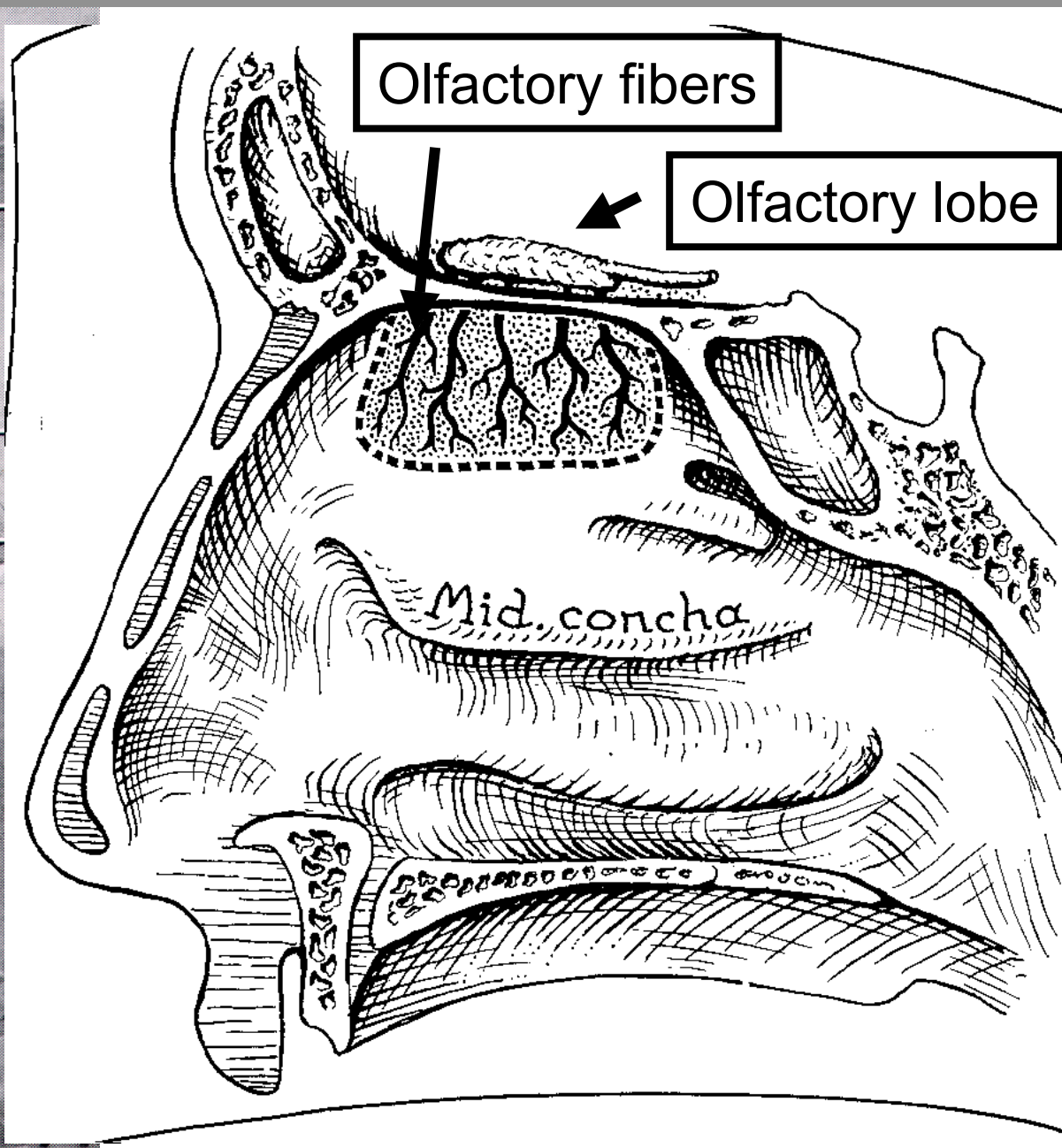
A CAUTION FOR INTRANASAL ANTIGENS AND ADJUVANTS

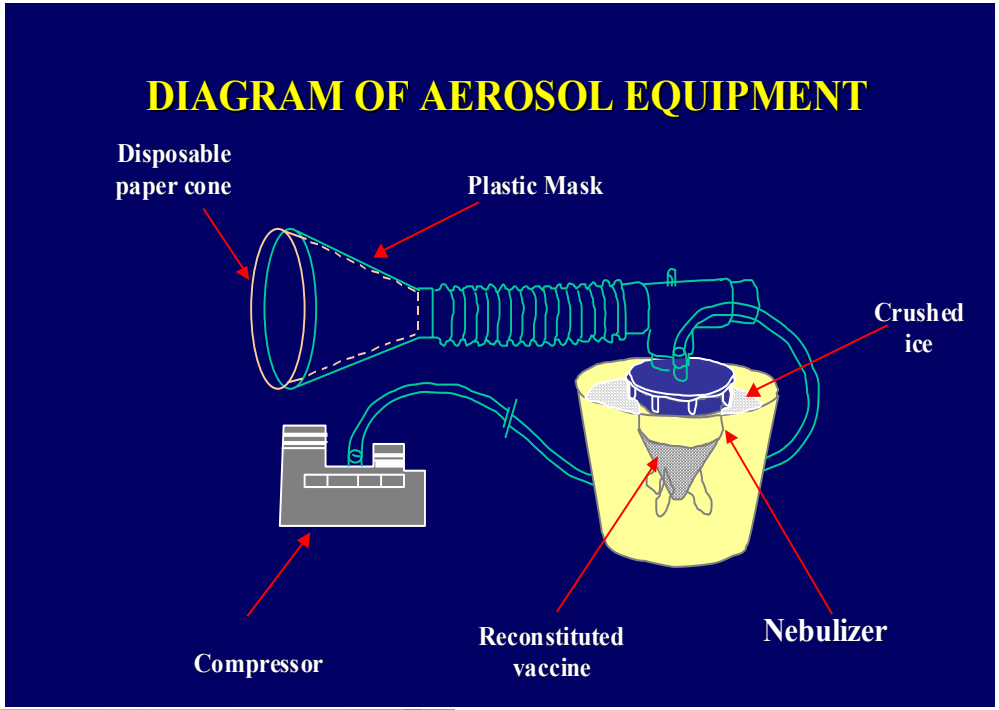




CONTROVERSY OVER TRANSGENIC PLANTS

AEROSOL MEASLES VACCINE

- Small particles (1-3 □) to reach alveoli
- "Classical Mexican" jet nebulizer
  - Huge experience (> 3 million children vaccinated); well tolerated & immunogenic
  - Efficient with E-Z strain
  - Bulky; needs ice & power
- Portable devices under development
  - CDC ultrasonic (piezoelectric) nebulizer
  - "Portable Mexican" device



"Classical Mexican" Jet Nebulizer

CDC Ultrasonic Nebulizer

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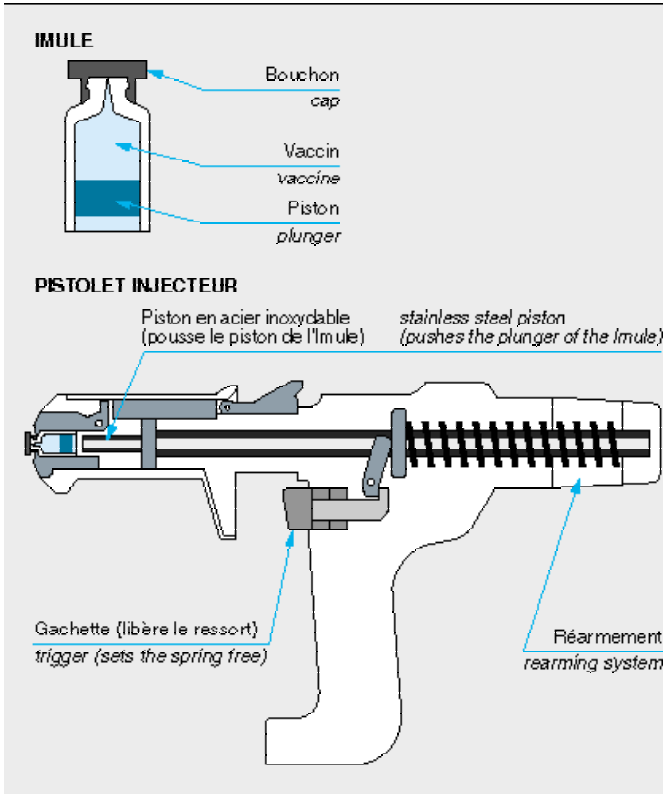
NEEDLE-FREE INJECTION DEVICES

"Universal Cartridge" Strategy

- Vaccines formulated in unidose "universal" cartridges of a standard size
- Cartridges fit needle-free injector devices
- Prototype -- Imule® cartridges and Mini-Imojet® hand-wound spring powered injector
- Premise -- all parenteral vaccines administrable by injection-free devices
- Practical obstacles
  - Cost of re-tooling production lines
  - Intellectual property issues
  - Need to agree on the "universal cartridge"



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“BIOJECT 2000®” NEEDLE-FREE INJECTION SYSTEM

“LECTRAJET ®” NEEDLE-FREE INJECTION SYSTEM

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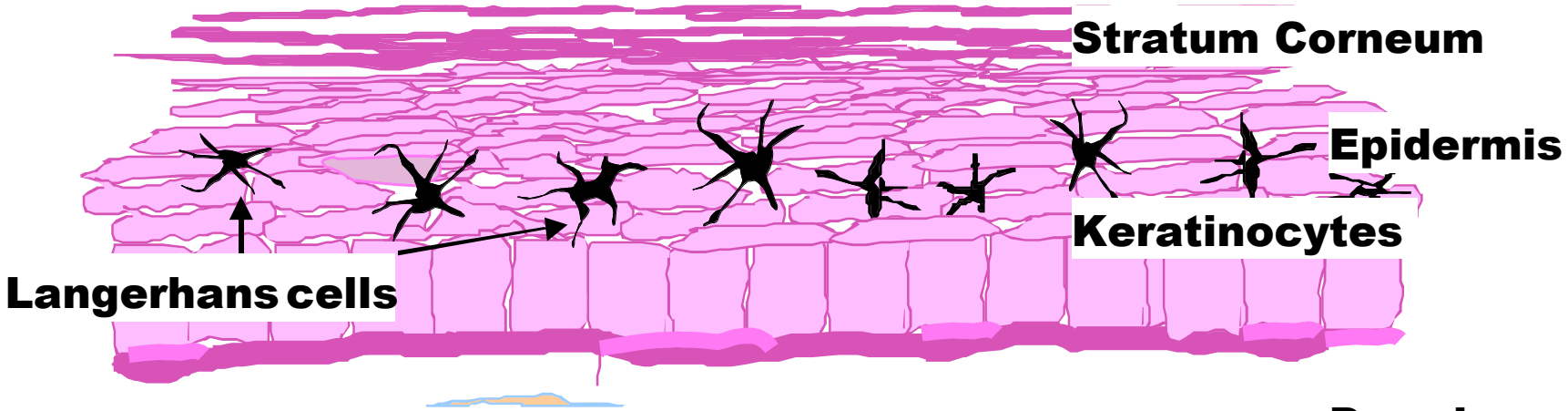
TRANSCUTANEOUS IMMUNIZATION



- Potent dendritic antigen presenting cells (APCs) reside in abundance in the epidermis (Langerhans cells)
- Make Stratum corneum permeable to antigen (hydration, abrasion, micron-scale silicon projections)
- Co-administer adjuvant (e.g., LT)

HUMAN TRIALS

- Safe
- Immunogenic

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Nasal immunization
- Specific vaccines
- Platform technologies

Oral immunization
- Specific vaccines
- Platform technologies

Small particle aerosols

Transcutaneous vaccination

Needle-free percutaneous jet injectors:
- High workload devices (for mass campaigns)
- Low work load devices

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SOME BARRIERS TO ACHIEVING THE VISION OF NEEDLE-FREE VACCINATION GLOBALLY

- Organizational and political
  - Need commitment to make this a priority
  - Agreement on universal standards (where relevant)
- Financial
  - Direct investment costs
  - Opportunity costs
- Paucity of clinical data on many technologies

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