FEASIBILITY OF AEROSOL VACCINATION IN HUMANS

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The feasibility of using aerosol vaccines to achieve mass and rapid immunization, especially in developing countries and disaster areas, is being assessed on the basis of current available information. The aerosol mode of vaccine introduction, which best follows the natural route of many infections, may first lead to development of immunity at the portal of entry, and may also induce a more generalized defense. The recommended optimal way of introducing an aerosol vaccine is nasal breathing, which is more suitable for geriatric and pediatric populations, permits use of greater antigen volumes, and allows easier monitoring of results. Technical requirements for ideal aerosol vaccines and delivery systems, possible adverse effects, and cost-effectiveness are other issues addressed. Several thousand human subjects have been aerosol-vaccinated over a period of many years in Russia with live-attenuated strains against many diseases. Extensive field trials in South America with aerosolized live-attenuated measles vaccine have also been successful, and excellent results have been reported with pilot projects employing inactivated or live-attenuated aerosol influenza A vaccine. We conclude that aerosol immunization seems a promising method of vaccination. Although some basic information is still lacking, this method has already been used successfully in large populations and has therefore passed the phase of initial feasibility evaluation.

KEY WORDS — aerosol, drug administration, immunization, nose.

INTRODUCTION

Mass and rapid vaccination is important, especially in developing countries and disaster areas. The common vaccine-preventable diseases are airborne (eg, measles, influenza, diphtheria, pertussis, and tuberculosis) or intestinal-contracted (eg, poliomyelitis and dysentery).

Aerosol vaccination is one possible way to rapidly immunize a population, inducing protection by exposure of the upper and lower airways to a vaccine. This mode of introduction, which best follows the natural route of infection, may lead to the development of immunity first at the portal of entry, and may also induce a more generalized defense elsewhere. It is the purpose of this study to overview some issues in aerosol immunization and to assess its feasibility.

MUCOSAL IMMUNIZATION

Mucous membranes are the portal of entry for several infectious agents. The respiratory and gastrointestinal mucosal tissues, as well as different levels of the upper and lower respiratory tracts, are immunologically linked and mutually stimulated.[1-4] Monitoring of immunization is difficult, since the usual serum parameters of humoral and cellular immunity may not reflect the true state of protection against challenge. Antibody levels in external secretions, eg, tears or saliva, correlate better with host resistance.[4-6] This correlation has been repeatedly demonstrated in chicken aerosol vaccination against Newcastle disease.[7,8] In other diseases (polio, typhoid, influenza A), it has been shown that mucosal immunization enhances systemic vaccination.[4]

Mucosal immunity does not undergo the age-associated changes seen in the systemic immune system.[4] The mucosal administration of vaccines might therefore be especially useful in the geriatric population. At the other end of the age spectrum, the persistence of maternal antibodies interferes with parenterally administered vaccines, but not with mucosal immunization, as has been demonstrated in polio and measles.[4]

Parenteral vaccine administration limits the number and amount of antigens that can be given in combination, while greater volumes can be administered by the mucosal route. Also, mucosal immunization efficacy and kinetics can be enhanced by absorption promoters (ie, microencapsulation), conjugation with adhesive antigens and with infective vectors (vaccinia, adenovirus, herpes simplex, *Escherichia coli*, lactobacilli), and the use of adjuvants.[4,6,9]

The goals of mucosal immunization include enhanced induction of both mucosal and systemic immune responses, priming for parenteral immunization and aiding booster administrations, and induc-

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TABLE 1. REQUIREMENTS FOR AEROSOL VACCINE

Live-attenuated virus
High antigenicity
Low incidence of side effects
Minimal storage restrictions
Stability and longevity in aerosol

TABLE 2. REQUIREMENTS FOR DELIVERY SYSTEM

Controlled (adjustable) aerosol airflow, particle size, temperature, and humidity
Adjustability of delivery parameters (nomograms) for varied settings, varied vaccines, and number of subjects
Aerosol stabilizing aids
Contamination-proof system
Easy operation and maintenance
Operability in difficult field situations

tion of "herd immunity" (as in polio).[10]

Local immunization of regions of the respiratory tract is still poorly understood, despite the more than 100-year-old history of inhalation vaccination.[11-13] Notwithstanding the scarcity of basic information, respiratory (mainly aerosol) immunization has been practiced in animals and humans.

AEROSOL VACCINATION IN ANIMALS

Aerosol vaccination is widely and effectively used throughout the world to immunize poultry against Newcastle disease.[7,14-16] There are several promising reports on successful immunization trials of fowls and pigs against fowlpox, infectious bronchitis, hog cholera, pseudorabies, erysipelas, gastroenteritis, pasteurellosis, and mycoplasmosis.[14,17-19]

Several research articles report the use of aerosol or respiratory (drops) immunization with different agents in the course of various immunologic studies in laboratory animals.[20-30]

AEROSOL VACCINES FOR HUMAN USE

Extensive experience with aerosol immunization exists in Eastern Europe, mainly in the former Soviet Union. Thousands of human subjects have been vaccinated in the past with live-attenuated strains against anthrax, plague, tularemia, and smallpox, as well as with tetanus and botulism toxoids. These comprehensive efforts involved also the development of polyvalent combined vaccines, aerosol, oral, and parenteral administration modes, and novel methods for mass immunization.[31-43]

In one impressive comparative study, 1,248 subjects were immunized against plague in a dynamic exposure chamber (48.5 m^3 room or tent) operated by 2 persons. During the same period of time (2 hours 40 minutes), only 150 subjects were immunized parenterally by a team of 6 medics.[44] Another large study on hundreds of children exposed in a classroom to measles vaccine for 30 minutes also demonstrated an excellent outcome.[45]

In the Western literature, extensive field trials with aerosolized live-attenuated measles vaccine were reported for more than 4 million Mexican children, with good results, high public acceptance, low cost, and fewer side effects as compared with the usual subcutaneous immunization.[10,46-52] Several limited studies have demonstrated excellent results with inactivated or live-attenuated aerosol influenza A vaccine.[49,53,54] This may well become the first vaccine to be widely used in aerosol administration. There are anecdotal reports of intranasal or aerosol vaccine trials against parainfluenza,[49,55,56] rhinovirus,[49,57] and respiratory syncytial virus,[49,58-60] with variable results. Intranasal aerosol delivery of passive immunization (antibodies) against various viral agents has also been tested.[61]

VACCINES AND DELIVERY SYSTEMS

The physical peculiarities of aerosol particles in the respiratory tract should be considered in studying their interactive host mechanisms, as well as the biological and immunologic interactions of the vaccinating agent with the respiratory cells and secretions.[62] Important features of aerosol biophysics involve the composition and state of aggregation of the inhaled aerosol and the effect of cultivation conditions, suspension liquid composition, and the pH, dispersion mode, moisture, and temperature of the environmental air. These factors affect the stability of the immunizing agent. Other physical issues consist of changes during lyophilization and reconstitution and dispersion in various regions of the upper and lower respiratory tracts.[11,12,63,64] Recognizing these issues, we summarize the requirements for ideal vaccines and their delivery systems in Tables 1 and 2, respectively.

Nasal administration is, in our opinion, the optimal way of introducing a vaccine. This would provide imitation of the most frequent route of infection and enable rapid interaction with and absorption through the highly vascular lining of the nose. The specific absorptive capability of the nasal lining is gaining popularity as a drug administration mode for several medications.[49,65] In the past it has been demonstrated that toxoids can be absorbed intranasally and induce a systemic response.[66-68] Nasal application of medication, in liquid drops or in aerosol, is relatively easy and better tolerated than direct tracheal/lung deposition, and although most of the vaccine is locally installed in the nose, some limited respiratory and gastrointestinal exposure is provided,

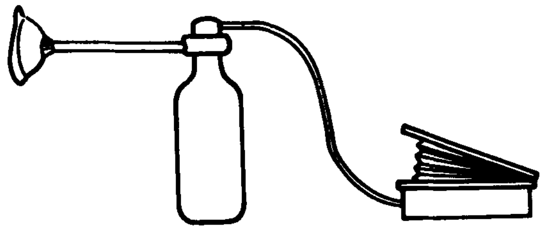

Fig 1. Personal aerosol generator.

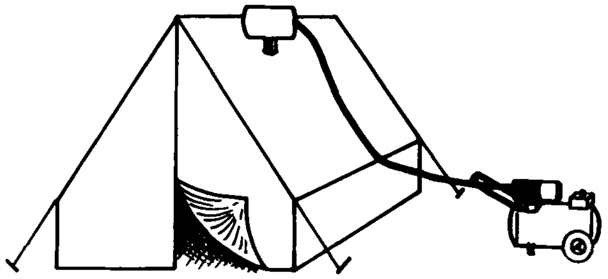

Fig 2. Exposure tent.

as well as possible direct brain exposure via the olfactory epithelium. In cases of live-attenuated agents, for safety reasons, prolonged infection for improved immunologic response is preferred in the nose and sinuses rather than in the lung. Monitoring (eg, secretions, cytology, absorption) is easier in the nose than in the lung. In the presence of nasal obstruction (acute infection, hypersecretion, anatomic deviations), oral breathing and lung deposition is always optional. This susceptibility of the nose may lead to variable results, as demonstrated in some limited studies with measles vaccine.[10,48]

While nasal drops, nasal spray, or a personal, metered-dose aerosol generator (Fig 1) may be convenient in a developed country,[10] we believe that the preferred induction mode is an exposure chamber (Fig 2), suitable for any situation, enabling either nasal or nasopulmonary deposition. Such a modality consists of a portable aerosol generator and nomogramic guidelines for vaccine administration in a designated tent, room, theater, or airplane hangar, temporarily sealed and with known dimensions. Ideally, this facility could be easily operated by minimally trained personnel, since those being immunized would require almost no instruction or preparation. This technique is most suitable when massive and rapid immunization is required.

ADVERSE EFFECTS

Regulation of the mucosal immune responses is poorly understood. Since the respiratory mucosa is constantly exposed to foreign antigens, dampening mechanisms exist to suppress excessive local inflammatory and immunologic responses that may damage the respiratory (mainly lung) tissues. These mechanisms may interfere with obtaining sufficient total antigenic exposure and necessitate prolonged duration of aerosol exposure or other effect-enhancing measures. Such mechanisms include the mucociliary system, alveolar macrophages, and surfactants.[12,69,70]

Lung deposition increases the reactions that depend on the number of particles, the virulence of the vaccine strain, adjuvant and other additives, and the health status of the host group. This health status is especially important in disaster scenarios and in underdeveloped areas.

Exposure to large antigen doses might lead to tolerance for subsequent subcutaneous booster immunization.[68]

The current available knowledge of possible side effects of aerosol vaccination in humans is scarce; increased incidence of febrile episodes was described in children receiving aerosol measles vaccination in one report,[51] but in another report,[48] there was no outstanding ratio of adverse effects. There is less-detailed Russian information that approximately 20% of adults receiving aerosol vaccines had adverse reactions (in most cases minor).[71,72]

PROPAGATION OF DISEASE AND IMMUNITY THROUGH OLFACTORY PATHWAY

A unique issue in aerosol inoculation, especially intranasal, is the potential exposure of the brain to the vaccinating agent. This factor, on one hand, may represent a cause for concern and possible adverse effects, and on the other hand may provide extension of the protection to the central nervous system.

The immunologic defense mechanisms of the central nervous system are as yet relatively unexplored. The brain is an immunologically privileged site that displays immune reactions similar to those of the rest of the body, but these are modified by the unique cellular environment of the central nervous system, primarily the blood-brain barrier.[73] As a result, there is a significantly diminished inflammatory response in the normal brain,[74] yet the brain is susceptible to infections, and abnormal inflammatory responses may nevertheless occur as well. In multiple sclerosis and subacute sclerosing panencephalitis, local measles virus–specific immunoglobulins are found in the brain.[75] One wonders what might be the implications for intranasal measles vaccination. Past experience has not revealed any risk, but given the rarity of those conditions, it would be difficult to investigate this event in a clinical study.[10]

Transport of infections to the brain via the olfactory region has been described in several animal models of aerogenic infections, mainly with neurotropic

TABLE 3. COST ANALYSIS OF MEASLES VACCINATION

	Cost of Delivery Systems	Cost of Vaccines*	Other Costs†	Cost of Total Operation	Duration of Operation (d)
Subcutaneous vaccination	$2,057,753‡	$587,929	$620,592	$3,266,274	30
Aerosol vaccination	$300,000§	$587,929 (same amount)	$620,592	$1,508,521	1
		$1,175,860 (double amount)		$2,096,450	

Data are from immunization campaign in Brazil involving 8,565,230 children.[51,52] Amounts are in US dollars.

*Including wastage. As stated in text, even if amount of vaccine purchased is doubled, there is still sizeable savings.

†For example, personnel (assumed same for both methods).

‡Disposable syringes and needles.

§Plastic foot or hand pressure (nonelectrical) pump and nebulizer (1 per vaccination center) and disposable personal face masks.

viruses: eastern equine encephalitis,[76] Venezuelan equine encephalitis,[77-84] Japanese encephalitis,[85] West Nile virus,[86] Semliki Forest virus,[87] herpes simplex virus,[88-91] and influenza.[92] This route is thought to be supplemental to the more common hematogenic infection, yet in some cases this may be a significant pathway, as with the intranasal administration of interferon, which successfully prevented the progression of mouse hepatitis virus to the central nervous system.[93]

The olfactory region may be a portal of entry to infection, even when the original spread occurs through peripheral viscera. Although intraperitoneal challenge of hamsters with St Louis encephalitis virus did not cause a high level of viremia, early in the course of infection, the virus was detected in the olfactory neuroepithelium.[94]

The induction of immunity in the nasal (olfactory) mucosa may have a special importance for protection of the central nervous system against certain infectious diseases. The spread of intracranial infection is a possible hazard specific to intranasal immunization, and merits further investigation.

COST-EFFECTIVENESS

By aerosol administration, sharp injection instruments are avoided, and health care givers are better protected (eg, from acquired immunodeficiency syndrome). Since this route of administration requires minimal patient cooperation and produces little if any discomfort, it is ideal for childhood inoculation and for mass immunization without the need for extensive educational programs. Oral or gastrointestinal administration, although seemingly convenient, inexpensive, and relatively safe as well, is inferior to aerosol, as it requires cooperation and individual attention.

The economic superiority of aerosol vaccination has been indisputably proven in avian medicine (Newcastle disease). Furthermore, parenteral therapy, which requires syringes, needles, disinfectants, individual sterile containers, and trained manpower, is more expensive than employing aerosol equipment. The latter could be used repeatedly for years, and requires only electrical, gas, or manual aerosol generators, tents, and nonprofessional community volunteers who can be easily trained to operate the equipment.

Financial advantages have been demonstrated by Sabin,[51,52] based on his experience with measles vaccination in Brazil (Table 3). This theoretical analysis clearly shows that even if the amount of vaccine purchased is doubled, there is still a sizeable savings. Further cost reduction is found when one takes into account the reduction of expenditure on personnel and lost workdays of subjects or parents.

CONCLUSIONS AND RECOMMENDATIONS

Aerosol immunization is a promising method of vaccination, especially suitable for pediatric and geriatric populations, in underdeveloped countries, and in disaster scenarios. Although some important basic information is still lacking, this method has already been used successfully in large populations and has therefore passed the phase of initial feasibility evaluation.

Certain requirements for the ideal aerosol vaccine and delivery system are also applicable to biological warfare assemblages; hence, great care should be applied to prevent misuse of such systems.

Physicians, public health officials, vaccine manufacturers, and patients should be educated about the potential of aerosol immunization, and increased efforts in research and development of common aerosol vaccines are now indicated.

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