Using Monoclonal Antibodies to Prevent Mucosal Transmission of Epidemic Infectious Diseases

Larry Zeitlin,* Richard A. Cone,*† and Kevin J. Whaley *†
*ReProtect, LLC, Baltimore, Maryland, USA; and †The Johns Hopkins University, Baltimore, Maryland, USA

Passive immunization with antibodies has been shown to prevent a wide variety of diseases. Recent advances in monoclonal antibody technology are enabling the development of new methods for passive immunization of mucosal surfaces. Human monoclonal antibodies, produced rapidly, inexpensively, and in large quantities, may help prevent respiratory, diarrheal, and sexually transmitted diseases on a public health scale.

In 1975, Köhler and Milstein noted that monoclonal antibodies (MAbs) "...could be valuable for medical and industrial use" (1). Since then, the use of MAbs has become routine in the research and diagnostic laboratory, but antibodies have yet to be used to their maximum potential in medical and public health applications. Two recent reviews of the therapeutic use of antibodies suggest that systemically administered antibodies may play an important role in treating infections by drug-resistant pathogens as well as pathogens for which no antimicrobial drugs are available (2,3). However, the greatest potential for MAbs probably lies in prevention since antibodies are in general more effective for prophylaxis than for therapy (3,4). From a public health perspective, prevention is especially important (5). In particular, direct application of MAbs to mucosal surfaces blocks the entry of pathogens into the body.

We review here the evidence of antibody efficacy in preventing disease and recent advances that have facilitated the development of MAbs for mucosal applications in humans. Finally, we consider the public health potential of topical delivery of MAbs for preventing mucosal transmission of infections.

Address for correspondence: Kevin Whaley, 3400 North Charles St. Jenkins Hall, Baltimore, MD 21218, USA; fax: 410-516-6597; e-mail: whale@jhu.edu.

Immunologic Strategies for Preventing Mucosal Transmission

Vaccines that stimulate systemic immunity can prevent systemic disease, but generally fail to prevent mucosal disease. Vaccines that stimulate active mucosal immunity have demonstrated good efficacy in animal models, but with few exceptions (polio and influenza vaccines), have not been as effective as they could be in humans. Some of the discrepancies between study results in animals and humans are probably due to a failure of studies in animals to model immune evasion strategies of pathogens (6) that occur in humans. These strategies include rapid evolution of variable strains (7), pathogens that coat themselves with host antigens (8), and pathogens that are transmitted to a new host by hiding inside cells shed by the infected host (cell vectors) (9). Furthermore, most vaccines successful in stimulating mucosal immunity in animals contain irritating adjuvants or attenuated pathogens, which are generally considered unacceptable for use in humans; vaccines with human-safe adjuvants have not generated high concentrations of protective antibody in the mucosa. Current research is investigating improved immunogens, delivery vehicles, and adjuvants, as well as exploring the best inductive sites for generating a protective mucosal immune response at a specific mucosal surface (10).

In contrast to vaccines, passive immunizations can deliver protective levels of antibodies immediately and directly to the susceptible mucosal surface (Figure 1-top). Also, with passive mucosal immunization, it may be possible to defeat some key immune evasion strategies by using antibodies directed against host cell vectors, host antigens that coat the pathogen, or receptors used by pathogens to enter target cells (11). In addition, new methods for the sustained release of antibodies offer the possibility of long-term protection (12).

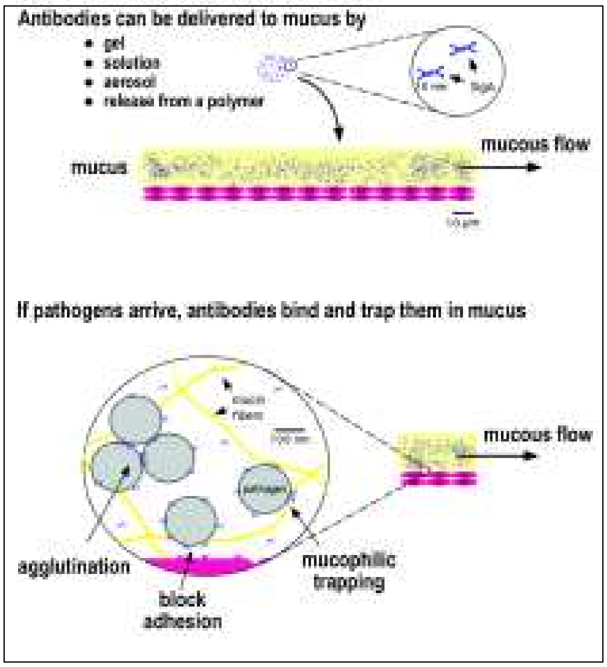

Figure 1. Topical delivery of pathogen-specific MAbs can protect the mucosal epithelium. (Top) Protective MAbs (in this figure, secretory immunoglobulin A; SIgA) can be topically applied to the mucosa in various ways. (Bottom) In mucus, MAbs are believed to act by a number of mechanisms to prevent penetration of the mucous layer and subsequent infection of target cells (62). MAbs can trap pathogens in the mucous gel by forming low affinity bonds with mucin fibers and can agglutinate pathogens into clusters too large to diffuse through the mucous gel.

Efficacy of Antibodies in Preventing Disease

The first use of immune serum for preventing disease by passive immunization was reported more than 100 years ago by von Behring and Kitasato (13). Subsequently, systemic passive immunization with antibodies has been proven effective in preventing many diseases. By binding to a pathogen, systemically delivered antibodies can inhibit attachment to and fusion with target cells, inhibit internalization by target cells, inhibit uncoating inside a cell, aggregate pathogens thereby preventing them from reaching target cells, interact with complement to lyse the pathogen, induce phagocytosis of the pathogen, and cause killer cells to lyse the pathogen by antibody-dependent cellular cytotoxicity (14). Table 1 lists the highest efficacy reported for systemically delivered antibodies in preventing disease in mammalian species and against a wide range of pathogens that infect humans. No antiviral treatments are available for most viruses listed in the table, yet antibodies can prevent the diseases caused by all of these viruses.

Although less studied than systemic passive immunization, the prophylactic use of mucosal antibodies predates the therapeutic use of immune sera. Antibodies delivered in mother's milk have been protecting the gastrointestinal tract of nursing infants since the mammary gland first evolved approximately 50 million years ago. Most infections begin in mucosal surfaces (approximately 400 m^2 in an adult human); supplementing the antibody repertoire in a mucous secretion (Figure 1-top) thus offers an effective method for protecting a mucosal surface against pathogens to which the host has not been exposed or become immune. In addition to the protective mechanisms described above, antibodies delivered to mucosal surfaces can trap pathogens in the mucous gel, make them mucophilic, and prevent their diffusion and motility (Figure 1-bottom); as a result, pathogens trapped in mucus are shed from the body with the normal flow of mucous secretions or are digested if these secretions enter the digestive tract (61-63). Topical passive immunization of mucosa can block transmission of bacteria, viruses, fungi, and parasites that infect humans (Table 2).

The predominant (and perhaps the most appropriate for mucosal delivery) antibody isotype on most human mucosal surfaces is secretory immunoglobulin A (SIgA); efficient methods for producing SIgA have been reported (82,83). SIgA, a tetravalent dimer of monomeric IgA associated with two polypeptides (joining chain and secretory component), is especially stable and well suited to function in the

Table 1: Examples of highly effective systemic passive immunization

Pathogen	Species[a]	Antibody[b]	Prevention (%)	DRS[c]	Ref.
Viruses					
Chikungunya	mou	p	100		(15)
Cytomegalovirus	hum	p	50	X	(16)
Dengue	mou	p	100		(17)
Ebola	bab	p	80		(18)
Hantavirus	mou	m	100		(19)
Herpes simplex (genital)	mou	m	100	X	(20)
(ocular)	mou	m	100		(21)
HIV	mou	m	100	X	(22)
Hepatitis A	hum	p	90		(23)
Hepatitis B	hum	p	92		(24)
Influenza	mou	m	100		(25)
Lassa	mon	p	100		(26)
Measles	mou	m	100		(27)
Polio	hum	p	58		(28)
Rabies	mou	m	100		(29)
Reovirus	mou	m	100		(30)
Rift Valley fever	ham	p	100		(31)
Respiratory syncytial	hum	m	100		(32)
		p	40		(33)
Rubella	hum	p	57		(34)
Varicella zoster	hum	p	100		(35)
Venezuelan equine encephalomyelitis	mou	p	100		(36)
Bacteria					
Borrelia burgdorferi	ham	p	100		(37)
Bordetella pertussis	mou	m	100	X	(38)
Chlamydia pneumoniae	mou	p	100		(39)
Chl. trachomatis	mou	m	90		(40)
Escherichia coli	rat	m	100	X	(41)
Francisella tularensis	mou	p	100		(42)
Group B *Streptococcus*	mou	m	100	X	(43)
Haemophilus influenzae	rat	p	100	X	(44)
Mycoplasma pneumoniae	ham	p	80		(45)
Neisseria meningitis	mou	m	90	X	(46)
Proteus mirabilis	mou	m	100	X	(47)
Pseudomonas aeruginosa	mou	p	100	X	(48)
Salmonella Typhimurium	mou	p	100	X	(49)
Shigella flexneri	rab	p	100	X	(50)
Staphylococcus aureus	rab	m	100	X	(51)
Streptococcus pneumoniae	mou	p	90	X	(52)
Treponema pallidum	ham	p	100		(53)
Yersinia pestis	mou	p	100		(54)
		m	NR[d]		(55)
Fungi					
Candida albicans	mou	p	> 67	X	(56)
Cryptococcus neoformans	mou	m	70	X	(57)
Parasites					
Plasmodium falciparum	mon	p	75	X	(58)
Toxoplasma gondii	mou	m	100		(59)

[a]Species: mou=mouse; hum=human; bab=baboon; mon=monkey; ham=hamster; rat= rat; rab=rabbit.
[b]Antibody: m=monoclonal; p=polyclonal.
[c]DRS=Drug-resistant strains reported (from Ref. 60).
[d]NR = not reported

Table 2: Examples of highly effective topical passive immunization of mucosa

Pathogen	Species[a]	Route[b]	Antibody[c]	Prevention	Ref.
Viruses					
Herpes simplex	mou	v	m	100%	(64,65)
		r	m	100%	(66)
Influenza	fer	o	p	100%	(67)
	mou	n	p	> 4[d]	(68)
Rotavirus	hum	o	p	100%	(69, 70)
Respiratory syncytial	mon	n	m	3-4[d]	(71)
Bacteria					
Chlamydia trachomatis	mou	v	m	90%	(72)
Clostridium difficule	ham	o	p	100%	(73)
Escherichia coli	hum	o	p	100%	(74)
Porphyromonas gingivalis	hum	o	m	100%	(75)
Shigella flexneri	hum	o	p	100%	(76)
Staphylococcus aureus	mou	n	p	3-4[e]	(77)
Streptococcus mutans	hum	o	m	100%	(78)
Vibrio cholerae	mou	o	m	100%	(79)
Fungi					
Candida albicans	mou	v	p	>50[f]	(80)
Parasites					
Cryptosporidium parvum	mou	o	m	77[g]	(81)

[a]Species tested in: mou=mouse; fer=ferret; hum=human; mon=monkey; ham=hamster.
[b]Delivery route of pathogen and antibody: v=vaginal; r=rectal; o=oral; n=nasal.
[c]Antibody: m=monoclonal; p=polyclonal.
[d] log_{10} reduction in virus titer.
[e] log_{10} reduction in cfu.
[f] % reduction in cfu.
[g] % reduction in number of parasites.

enzymatically hostile environment that prevails at mucosal surfaces (84). SIgA, the least phlogistic class of antibody (84), is the least likely to induce inflammatory responses that can make it easier for toxins and pathogens to breach the mucosal surface. Immune exclusion of antigens, enzymes, and toxins has been repeatedly demonstrated in vivo, and protection generally correlates with levels of SIgA antibodies in the relevant mucous secretions. Finally, the protective role of SIgA has been demonstrated in many systems (85).

Recent Advances in mAb Technology

Generating High-Affinity Human MAbs

Since the advent of cloning of human antibodies from combinatorial libraries constructed from seropositive persons (86,87), generation of fully human MAbs against human pathogens has become routine (Figure 2) (88). For example, from a single bone marrow donor, human MAbs were prepared against HIV, respiratory syncytial virus (RSV), cytomegalovirus, herpes simplex virus types 1 and 2, varicella zoster virus, and rubella virus (88). MAbs can even be obtained from naive libraries prepared from unexposed persons (if the library has a large enough repertoire) (89); therefore, antibodies against pathogens lethal to humans can be generated. Alternatively, human MAbs can be generated by traditional immunization of commercially available mice that have been genetically engineered to contain human immunoglobulin loci in their germline (Figure 2) (90,91).

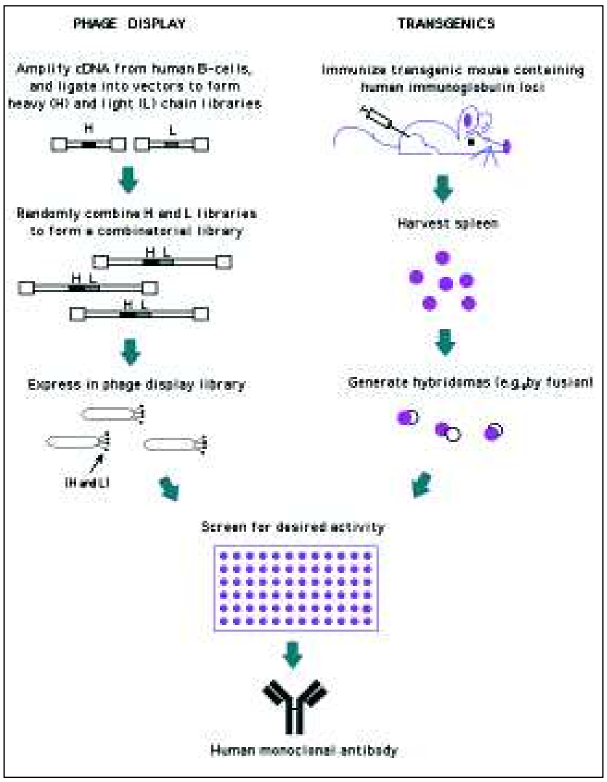

Figure 2. Generation of human monoclonal antibodies. (Phage display) Heavy and light chain cDNA isolated from human B-cells is used to generate a combinatorial library in which random heavy (H) and light chain (L) pairings are expressed on the surface of phage. These phage can then be screened for antigen binding by traditional techniques (e.g., ELISA). Since only the antigen binding region is used in the phage display process, the selected clone is then placed into an appropriate expression vector to produce a full antibody molecule.(Transgenics) Genetically manipulated mice have been produced with inactivated endogenous immunoglobulin genes, and with unrearranged human immunoglobulin gene segments introduced (90,91). These mice are then immunized with antigen, and hybridomas are produced by traditional routes. (See refs. 88, 89 for more technical information on these two methods and refs. 92, 93 for comparisons of these two methods).

Dramatic enhancement of the affinity of an mAb has been demonstrated by molecular biologic techniques in which mutants of an antibody are generated and then screened for higher affinity or higher neutralization activity (93-95). For example, the affinity of one anti-HIV mAb has been enhanced 420-fold, and this matured antibody neutralizes more HIV strains than the original mAb (94). Furthermore, expressing a mAb as a multivalent isotype, such as SIgA or IgM, can dramatically enhance the potency of an antibody by increasing the avidity (96) or agglutination activity (14). For example, an anti-*Escherichia coli* IgM was 1,000-fold more effective in protecting neonatal rats than its class-switched IgG (both in vitro and in vivo)(41). From a commercial standpoint, a 1,000-fold increase in avidity could translate into a 1,000-fold decrease in dose and subsequent cost. Also, a large dose of a highly potent mAb can substantially increase the duration of protection (97).

Production Systems

MAbs have traditionally been produced in cell culture and have been prohibitively expensive for most preventive uses. Over the years, however, the cost has continually dropped; MAbs are now being produced in cell culture for $200 to $1,000 per gram (98,99). Production of MAbs has recently been reported in both transgenic plants and animals (82,100,101). Both of these systems are expected to lower costs dramatically. Indeed, transgenic plants can be scaled up in agricultural fields to produce tons of “plantibody,” and plant-produced antibody is predicted to cost less than U.S. $1/g (102). The actual cost, however, will remain unknown until large-scale batches are produced, purified, and formulated in accordance with Good Manufacturing Practices.

Safety and Regulatory Status

More than 80 MAbs are now in clinical trials (most for cancer imaging or therapy) and more than one quarter of these are in phase III trials (103). Few safety problems have been reported for systemic applications; antibodies are now considered "biotechnology-derived pharmaceuticals" by the U.S. Food and Drug Administration (FDA)—enabling a more straightforward regulatory process than in the past (92,104). Even though MAbs have often been evaluated for systemic applications, only recently have they been evaluated in humans for mucosal applications. This new interest in mucosal antibodies may be partially due to the increasing recognition of the importance of mucosal immunity. Only two clinical trials have evaluated topically delivered MAbs: intranasally delivered anti-RSV in infants at high risk (105) and orally delivered anti-*Streptococcus mutans* in adults (106); no major adverse effects were reported in these studies.

Safety concerns, such as peptide and glycosylation immunogenicity, are important when MAbs are delivered systemically but are likely to be of less concern when MAbs are applied to the mucosa, a surface that has evolved to interact with the external environment. Indeed, antibodies delivered to the lumen of a mucosal surface have minimal interaction with circulating immune cells. Although proteins, and even antibodies, can be absorbed through mucosal surfaces (107,108), generally only small quantities are absorbed (109,110). The inability of SIgA to activate complement by the classic pathway is likely involved in maintaining the integrity of mucosal surfaces (63); therefore, SIgA may be preferable to IgG or IgM for many mucosal applications.

The FDA "Points to Consider" for characterization of antibodies produced in cell-culture and transgenic animals (111) are better defined than for characterization of antibodies produced in transgenic plants; however, plant-derived antibodies are free of animal viruses and may therefore not require rigorous viral inactivation processing steps. In addition, although glycosylation patterns of MAbs produced in mammalian cell-culture and transgenic animals are closer phylogenetically to humans than glycosylation patterns in plants, given our repeated exposure to plant sugars in food and personal care products, it is unlikely that any of these patterns are novel to human immune systems (112). In fact, in a recently completed clinical trial with repeated applications of plant-produced antibody for the prevention of oral colonization by *S. mutans*, no safety problems were encountered, nor were there any detectable human anti-plant antibody responses (113).

Selection for resistant organisms by widespread and repeated use of antibiotics is a serious health concern (60). Drug-resistant strains of a wide variety of pathogens have already been reported (Table 1). Antibiotic or antiviral treatment of infected persons in which pathogens are actively replicating provides a strong evolutionary selection process for developing drug-resistant pathogens. In contrast, MAbs are less likely to create resistant organisms when used in a preventive context at a mucosal surface against a pathogen that is not yet actively replicating. Even if a systemic infection does occur during topical use of MAbs, resistant organisms will likely not be created since the pathogen will not be replicating and evolving in the presence of the mAb applied to the mucosal surface. This is in marked contrast to the settings in which antibiotics and antiviral drugs select for resistant strains (60). If MAbs are used frequently on a population level, the risk of selecting for resistant organisms may increase. When the emergence of resistant strains is of particular concern, the tendency to select mAb-resistant organisms could be minimized by using cocktails of mucosal antibodies directed at multiple antigenic targets (2,114). Because new MAbs can be produced with a rapid turnaround time (discussed below), the emergence of an antibody-resistant strain could be countered by producing a new mAb directed toward the mutated epitope or another antigenic target of the resistant strain. Indeed, the flexibility of the antibody structure to create a virtually inexhaustible repertoire of antigen binding specificities suggests that immunoglobulins evolved in part as a means to cope rapidly with new pathogens.

Turnaround Time for Developing a New mAb

Since human MAbs can be identified quickly by cloning variable regions from specific antigen-binding human lymphocytes (115) or panning combinatorial libraries (87), antibodies could be used as a rapidly developed method for defending against new pathogens. The time required for collecting lymphocytes from a seropositive person, screening for an appropriate antibody, cloning, and expressing the antibody in culture in a well-equipped laboratory is 1 to 3 months; quantities sufficient for protecting persons at high risk or those at the focal point of an outbreak could be available in fewer than 6 months. High-capacity production in quantities sufficient for broad public health application could be available in several years, assuming that the safety of antibodies as a class of molecules is established and an infrastructure is in place for producing these antibodies. While in rare instances vaccines can be developed this quickly (e.g., the 1976 influenza vaccine [5]), new vaccines, antibiotics, and antiviral therapies usually take considerably longer to develop. Moreover, even though passive immunization may require repeated applications, MAbs delivered to a mucosal surface can provide immediate protection against infection.

Potential Preventive Uses for Topically Delivered MAbs

From a public health perspective, MAbs are most promising for preventing gastrointestinal, respiratory, and reproductive tract infections. These infections cause almost 11 million deaths annually worldwide, accounting for more than 50% of the deaths caused by communicable diseases and 22% of deaths by all causes (116). Sexually transmitted diseases (STDs) accounted for 87% of all cases reported among the top ten most frequently reported diseases in 1995 in the United States; more than 12 million Americans are infected with STDs each year at an estimated annual cost of more than $12 billion (117).

If a track record of safety and efficacy can be achieved, mucosal antibodies will probably be most useful as over-the-counter products that could reach populations not well integrated into the health-care system. The condom, a nonmedical over-the-counter personal protection product, has played an important preventive role in the HIV epidemic. Personal protection provided by over-the-counter antibody-based technology could play a similar role in future emerging disease epidemics.

Diarrheal Disease

Studies in animal models have demonstrated that orally delivered antibodies were 100% effective in preventing rotavirus (70) and cholera (79) infections. In humans, orally delivered bovine antibodies were 100% effective in preventing rotavirus (118), enterogenic *E. coli* (74), *Shigella* infection (76), and necrotizing enterocolitis (119).

For orally delivered MAbs, digestive degradation is a potential concern. However, significant levels of functional antibody survive treatment with pepsin at pH 2 or with a pool of pancreatic enzymes at pH 7.5 in vitro (120). In addition, most ingested IgA in milk survives passage through the gastrointestinal tract of infants (121); intact antibody delivered orally with an antacid survived passage through the gastrointestinal tract of adults (74,76). Assuming that a 10-mg dose of antibody is protective (i.e., assuming that the mAb is only 100-fold more potent than polyclonal preparations [118]), the production costs for the amount of plantibody needed for 100 days of protection could be approximately one cent (102).

Since diarrheal diseases are most prevalent in developing countries, preventive strategies must be extremely inexpensive; therefore, MAbs produced in plants or in the milk of animals are likely most suitable for these countries. Because of the speed with which MAbs pass through the gastrointestinal tract, antibodies delivered orally will need to be delivered frequently, perhaps more than once a day. In endemic-disease regions, MAbs could be delivered orally as a supplement with food or water.

Respiratory Disease

Animal studies have demonstrated the efficacy of nasal delivery of antibodies for the prevention of RSV infection (71) and influenza (68). In one study, topical application was approximately 100 times more effective than systemic delivery (122). Another study found an anti-RSV mAb (MEDI-493) to be approximately 100 times more effective than an equal quantity of a polyclonal preparation (32). These results suggest that 10,000 times less anti-RSV mAb would be required for topical applications than for systemically delivered polyclonal preparations. Protective systemic doses of MEDI-493 are approximately 100 mg (15 mg/kg) (32), so <1 mg might suffice for protection if this mAb were applied topically. Intranasally applied mAb has a residence half-time of a little under one day in the monkey (71), suggesting that once-a-day applications that deliver several-fold more than a protective dose can provide continuous protection. MAbs for protecting the respiratory tract could be delivered in nose drops or by aerosol once a day to those at particular risk (e.g., infants and the elderly during influenza season) or to everyone living near the epicenter of an epidemic.

STDs

With the exception of hepatitis B, no vaccines are available for the prevention of STDs (Table 3). Until effective and safe vaccines are developed, vaginal delivery of a cocktail of anti-STD pathogen MAbs might make an effective new method for broad spectrum protection against STDs (11). In animal models, MAbs have been shown to protect against transmission of *C. albicans*, *C. trachomatis*, HSV, HIV, and syphilis (Tables 1, 2) (11). Antibodies have been delivered experimentally to the vagina in solution, gels, and more recently, by sustained release devices for long-term delivery of protective MAbs (123,124). Antibodies were found to be stable when stored in seminal fluid or cervical mucus for 48 hours at 37°C (125); no significant inactivation occurred over the pH range of the human vagina (pH 4 to 7) for at least 24 hours at 37°C (Zeitlin et al., unpub. obs.). Since the effective half-life of antibodies applied topically depends on the turnover time of mucus, a single vaginal application may thus provide protection for at least 1 day, and probably several days (97). If so, passive immunization of the vagina may extend protection to the occasional days when the user forgets to apply the mAb. Considering there are an estimated 5 billion acts of sexual intercourse per year in the United States (11), large-scale production of MAbs in plants may offer the best system for the low costs needed for such a public health initiative. In addition, because the most common class of infection in the first month of life is primarily caused by STD pathogens present in the birth canal (126), the same mucosal antibodies could be used in a predelivery cervicovaginal lavage or applied to newborns' eyes for studies in the prevention of ophthalmia neonatorum. Indeed, in some cultures the mother's colostrum, a fluid rich in SIgA, is applied to the newborns' eyes (127).

Table 3: Preventive vaccines or cures for major sexually transmitted disease pathogens

Pathogen	Vaccine	Cure	DRS[a]
Chlamydia trachomatis	no	yes	
Haemophilus ducreyi	no	yes	X
Hepatitis B	yes	no	
Herpes simplex 1 and 2	no	no	X
HIV-1 and 2	no	no	X
Human papilloma virus (HPV)	no	yes[b]	
Neisseria gonorrhoeae	no	yes	X
Treponema pallidum	no	yes	
Trichomonas vaginalis	no	yes	X

[a]Drug-resistant strains reported.
[b]Surgical removal of HPV-infected tissue is performed. HPV-related cervical cancer identified early has a high cure rate; however, in the United States, for every three new cases, there is approximately one death (117).

Conclusions

In animal models and human studies, antibodies have been shown to prevent a wide variety of infectious human diseases. Recent advances allow development of a new era of mucosal mAb-based products. These advances include the development of combinatorial libraries for rapid selection of human MAbs, the ability to increase dramatically the potency of a specific mAb, and the marked reduction in the cost of cell-culture–produced MAbs as well as the ability to produce MAbs inexpensively and at high capacity in transgenic animals and plants. In addition, since MAbs can be developed considerably more rapidly than most vaccines and antimicrobial drugs, MAbs may prove useful for combating emerging pathogens. Mucosal infections account for a large percentage of infectious disease-related illness and deaths; hence topical passive immunization with MAbs may offer a new opportunity for improving public health. Finally, many of the remaining safety issues regarding the human use of mucosal MAbs are likely to be addressed by clinical trials now under way.

Acknowledgments

The authors thank the Rockefeller Foundation Bellagio Study and Conference Center and Drs. Polly F. Harrison, Mich B. Hein, and Thomas R. Moench for their review of drafts.

Dr. Zeitlin is a research scientist at ReProtect, LLC. His interests focus on the development of monoclonal antibodies for contraception and the prevention of sexually transmitted diseases.

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