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Medicine & Health
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Vaccination

A CME Issue

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Cover: Emerging Infectious Diseases," by Eric Avery, MD, Clinical Associate Professor of Psychiatry and Behavioral Sciences and Associate Member of The Institute for the Medical Humanities at The University of Texas Medical Branch, Galveston, Texas. For thirty years Dr. Avery has made prints. His social content prints explore human rights abuses, and social responses to disease (HIV and Emerging Infectious Diseases), death, sexuality and the body. e-mail: eavery@utmb.edu

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COMMENTARIES

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Guest Editors: **Anne S. De Groot, MD, and Leonard Moise, PhD**

COLUMNS

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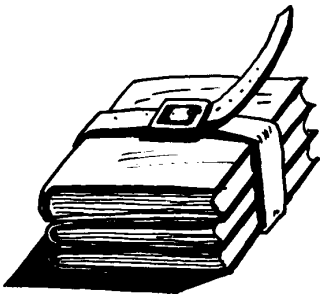
Commentaries



Feudalism or Futilism: Another Modest Proposal

I recently engaged in a debate with a bio-ethicist from the Cato Institute, a "think" tank based on the principle that the government that governs least governs best. I corresponded with her after the *Providence Journal* published an article she wrote.

Declining an embrace of anarchy, the institute members believe that people don't want, hence shouldn't be forced, to pay taxes, except for services that *everyone* desires, like "roads, military and police." The possibility that we may not "all" agree on military funding, or which roads should be built, is possibly too mundane a consideration in their ethereal, philosophical realm. (My father-in-law was a distinguished philosopher and my son may follow in his footsteps, but it's hard not to be a bit cynical here.)

This got me to thinking about adopting these principles to health care. With the exception of our current federal administration, everyone believes there is a health care crisis in this country. Of course, it has been going on for quite while, and those of us with reasonable incomes and medical insurance seem to be surviving it quite well, but we in health-care know that more than a few people are suffering out there. And our president, in a "what me worry?" approach that reflects the philosophical mood of the ruling elite, publicly remarked that anyone in the United States who needed care merely had to go to the local emergency room.

Luckily, in the US we presumably have a "safety net." We all agree that there should be one. Even the Cato Institute (I think). The only question is how fine to make the holes. We could make it very fine so that no one falls through, or we could loosen it a little bit so that only 47,000,000 people fall through. If we think of a safety net as being like a fishing net, we know that if the holes are too small, there is nothing left to feed the sharks and predator fish, and we wouldn't want to upset the ecological balance by too much. So there have to be some holes.

In Bill O'Reilly's categorization of conservatives as being "traditionalists" it makes eminent sense to consider times gone by in which health care was not in crisis, and people didn't depend on "handouts" and government dole. When bills couldn't be paid, there was always indentured servitude, back in the good old feudal days. And it seems that it is an idea whose time has come, again.

Only a couple of years ago, in preparation for the disaster of rapidly escalating mortgage bills facing the working poor and lower middle class, Congress made it virtually impossible for poor people to declare bankruptcy. Only corporations and wealthy people can escape their obligations. And now that the housing crisis has somehow managed to develop, forcing these people to lose their houses and still not escape their debt, the need for indentured servitude is clear.

Imagine someone needing an operation that will cost $20,000, and the patient has already maxed out his credit card, has no insurance and will become disabled without the operation. If someone, even the doctor, perhaps, picks up the tab, they might be able to have the person become a slave for some fixed period of time. The "owner" would be responsible for housing, feeding and clothing the person, paying for the medical care, but in return would have a slave who would be protected by government laws limiting work to perhaps 16 hours per day. Various limitations could be developed, by the local state authorities, explicating the minimum housing, clothing and food allowances. After all, that's better than what the homeless get now.

When someone first suggested feudalism to me as a solution to the healthcare miasma, I misunderstood and thought the suggestion was "futilism." After all, the health care crisis has been with us since before I started medical school, and it seems hopeless. I thought that the "futile" solution was mass extinction. It certainly seemed like an unpopular approach, but it would free up a lot of money if all the sick and uninsured simply died.

There are a number of economic approaches to comparing the two feudal/futile approaches. In each one, the outcome is improved efficiency, which is, after all, what our government is about. I haven't yet asked my bio-ethicist colleague at the Cato which solution would be closer to their philosophical foundations. I am pretty sure that they'd elect the first. Feudalism, when practiced the way it "should" be, free from external restraint, is another form of allowing freedom and nature to take its course, uncontaminated by any humanitarian tinkering that always throws a monkey wrench into the mix. After all, if someone invested in a slave, wouldn't that person try as hard as possible to keep that slave in tiptop shape? It makes a lot of sense. And it solves a lot of problems without the invasiveness and inherent bullying of forcing people to pay taxes.

It's time to stop trying futile approaches to health care. More money won't stanch the crisis. Only wise, cost-saving, effective approaches will do that. It's time to stop being futile and start thinking feudal.

And I haven't even seen "Sicko" yet!

– Joseph H. Friedman, MD

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A Sovereign Called Malaria: Humanity's Lethal Companion

Long before taxes there were fevers: fevers of the spirit, fevers of carnal passion, but especially, fevers of the body. The Mediterranean cultures knew fevers well and appreciated that all fevers were not the same; some were continuous and others, intermittent; some solitary and some recurrent; nor did they necessarily share the same ultimate fate. Thus, some fevers were transitory, gentle and brief while others were violent, with much sweating, rigors, even delirium and with a grievous prognosis.

The ancients created a taxonomy of fevers in five categories. There were the continuous fevers, unremitting and dangerous; then there were the periodic fevers, treacherous in their course; then quotidian [daily] fevers, tertian fevers [cyclic fevers, each separated by a day without fever] and quartan fevers [fevers separated by two days without fever.]

The Babylonians nominated Nergal, god of pestilence and devastation, as the creator of hectic fevers, especially the cyclic ones. Curiously, Nergal is depicted as an insect resembling a mosquito.

The Chinese were probably the first to declare that a relentless fever, particularly in their southern provinces, was associated with an enlarged spleen easily palpable by examining the left upper quadrant of the victim's abdomen. Sumerian texts, perhaps written 3,500 years ago, also note a close connection between an enlarged spleen [splenomegaly] and repeated attacks of periodic fevers. The Philistines knew of a fever so dangerous that they ascribed it to the evil intent of Beelzebub.

The Vedic scriptures of northern India refer to cyclic fevers associated with the early autumn, becoming epidemic in intensity after the autumnal rains.

Fever was fever, but malarial fever was probably the first of numberless fevers to be distinguishable as unique. And certainly malarial fever has molded the course of human history since antiquity. It was the first to be recognized by the profile of its pyretic character and predictable mortality rate [especially with children]; first to be recognized as both seasonal and geographic in distribution; and first to be given a name.

Malaria [meaning bad air] was closely associated with both tropical swamps and swarms of mosquitoes; but since the swamps were bigger and more menacing than the mosquitoes, it became natural to blame the disease on the swamps and their nebulous vapors. Athenian physicians believed that swamps produced some indefinable substance which, when inhaled or consumed, yielded the cyclic fevers of late summer. They believed that drinking of any stagnant water would produce the autumnal fevers. These physicians witnessed the slow emaciation of the fever-ridden patients while their spleens seem to enlarge. Their logic then presumed that the dissolving muscle fed the voracious spleen.

The Hippocratic physicians separated certain fevers, often arising during the time of the summer rains, and distinguished by a cyclic rhythmicity. Thus there were those with hectic fever for about a day, followed by a day without fever but with great exhaustion, followed then by a resumption of the fever associated with drenching sweats and shiverings. The Roman physicians called such fevers, ***febris tertiana,*** fevers which return on the third day [in English, tertian fever]. Then there were fevers with a non-febrile interval of two days, called ***febris quartana*** [in English, quartan fever] which were regarded as more serious, often with a fatal outcome.

When reliable knowledge is meager, speculation tends to be fertile. And now and then, either as inspired insight or by pure happenstance, someone's free-floating conjecture carries a small germ of the truth. Marcus Terentius Varro [116 – 27 BCE], a Roman archivist, when considering the fevers emanating from the swamps, wrote the following in his text on agricultural methods: "Certain animalcula which cannot be seen with the eyes and which we breathe through the nose and mouth into the body, where they cause grave maladies."

The histories of great wars, it is said, are written by the victorious leaders. And it would be unrealistic to expect that a winning general will ever write: "Of course the leadership of our armies displayed courage, daring and inventiveness but the crucial factor leading to our victory was the devastating malarial surge which selectively destroyed many of the enemy's battalions." Until recent years, indeed, pestilences such as malaria, smallpox, cholera and typhus were decisive factors in many if not most battles of historic significance.

Consider, for example, the role of malaria in the history of Roman independence during the first millennium of the current era. The king of the Goths, Alaric [310-410 CE], surrounded Rome, breached its defenses and entered triumphantly. But his victory was brief when he and many of his cohorts died of malaria within days. Attila's armies reached Rome in 452 CE but were decimated by malaria and then fled. Otto, king of the Germans, attacked Rome in 964 CE only to see his army disintegrate by the effects of malaria.

The Roman region was a swampy district known for its deadly malarial endemnicity. Certainly the enemies of Rome found this out during their attempts to conquer the city; but even the residents, both anonymous and illustrious, paid a heavy price to live in the Eternal City. At least five popes died of the fever called malaria [Gregory V, Damasus II, Leo X, Sixtus V and Urban VII].

In the lengthy history of *Homo sapiens*, no disease has wrought more damage or has adversely affected more people than malaria. And to this day, malaria looms as one of the prime killers of humans. In the year 2005, over 500 million new cases of malaria have been documented; and over two million people, mainly sub-Saharan children, have died of malaria.

– Stanley M. Aronson, MD

Disclosure of Financial Interests
Stanley M. Aronson, MD, has no financial interests to disclose.

Vaccine Renaissance — From Basic Research to Implementation

Anne S. De Groot, MD, and Leonard Moise, PhD

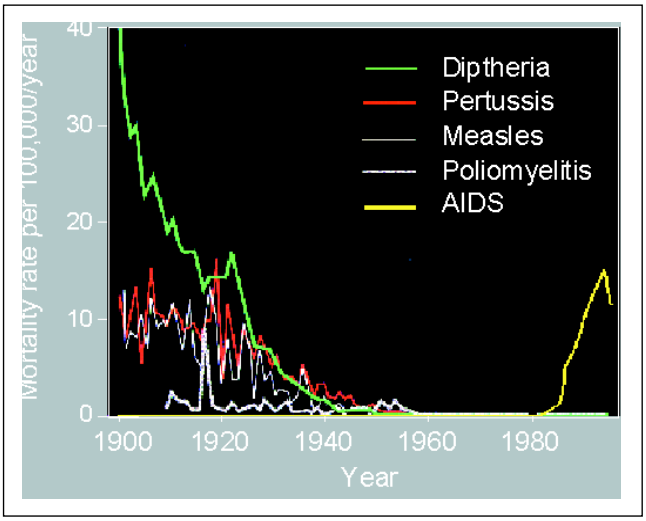
Disclosure of Financial Interests

Anne S. De Groot, MD. Major Stockholder: EpiVax, Inc.
Leonard Moise, PhD. Employee: EpiVax, Inc. Other Financial or material Interest: EpiVax, Inc.

Vaccines save an estimated 3 million lives and protect millions more adults and children from morbidity every year. In contrast to drug therapies, vaccines for infectious diseases prevent disease, can be administered in the field by minimally trained personnel, typically require only one to three doses, and have few side effects. Given the contributions of vaccines to human health, the fact that New England is home to vaccine giants and centers of excellence such as Novartis, Wyeth, Acambis, the New England Regional Center of Excellence at Harvard, the Tufts Grafton School of Veterinary Medicine and the University of Massachusetts Vaccine Center should be a point of regional pride. Rhode Islanders will have yet another reason to celebrate when the **Collaborative for Vaccine Research and Development (CVRD)**, an academic/industrial consortium based within the proposed "Center for Immunopharmacogenomics" at the University of Rhode Island, opens in October 2007. The URI CVRD will be devoted to development of safer, more effective vaccines for humans and animals, including vaccines for infectious diseases that are emerging or re-emerging in developing countries. This new academic research center will offer researchers all over the world access to tools emerging from the informatics revolution that are likely to accelerate development of new vaccines, enable the re-engineering of existing ones, and overcome traditional barriers to vaccine design. Finally, it will serve to train the next generation of vaccine researchers.

In honor of that occasion, this issue of *Medicine & Health/Rhode Island* reviews local vaccine research and development efforts. Five of the six articles were selected from presentations at the 2nd Annual Vaccine Renaissance Conference that took place on June 7-9, 2006, in Providence. The 2nd "Vax Ren" Conference brought more than 100 researchers and vaccine developers from a range of disciplines (animal and human vaccines, clinical vaccine trials and basic research) together for collaborative discussions in Providence, while offering regional biotechnology students exposure to this work. A 3rd Vaccine Renaissance is scheduled for Fall 2008.

Consistent with the goals of the CVRD and the Vaccine Renaissance, these articles bridge basic, pre-clinical research (on tuberculosis and tularemia vaccines) and vaccine trials (HIV, HPV and rotavirus) while also addressing the purported and unsubstantiated link between childhood vaccination and autism. These articles also address the development of new concepts, tools, and approaches that may accelerate vaccine development. The editors hope to inspire regional health care practitioners and researchers to engage in this expanding field by exposing them to the active research and clinical activity that is taking place within New England. There is no better time for a renaissance in the age-old art of vaccine development than now.



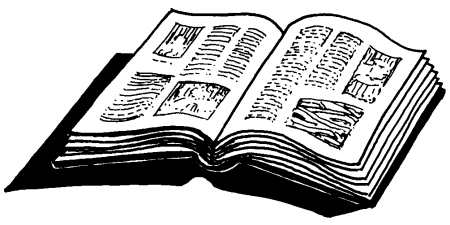
Source: Modified from Armstrong GL, Conn LA, Pinner RW. *JAMA* 1999;281:61-6. Trends in infectious disease mortality in the United States during the 20th century.

Legend: In addition to improved sanitation and public health interventions, vaccines against diphtheria, pertussis, measles and polio have contributed significantly to the decline of infectious mortality rates in the United States in the first eight decades of the 20th century. The emergence of HIV has led to an increased mortality rate, stimulating efforts to develop an HIV vaccine.

Leonard Moise, PhD, is Director of Vaccine Development at EpiVax, Inc.

Anne S. De Groot, MD, is President and CEO at EpiVax, and Associate Professor of Medicine, The Warren Alpert Medical School of Brown University.

CORRESPONDENCE:
Anne S. De Groot, MD
EpiVax, Inc.
146 Clifford Street
Providence RI 02903
phone: (401) 272 2123
E-mail: Admin@EpiVax.com



Progress Towards a Genome-derived, Epitope-driven Vaccine for Latent TB Infection

Leonard Moise, PhD, Julie McMurry, MPH, Daniel S. Rivera, E. Jane Carter, MD, Jinhee Lee, DVM, PhD, Hardy Kornfeld, MD, William D. Martin, and Anne S. De Groot, MD

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Every year, eight million people are infected with *Mycobacterium tuberculosis* (Mtb). Upon infection, the immune system isolates, but does not eradicate this bacterium. **Latent tuberculosis infection (LTBI)** leaves an individual vulnerable to develop the active form of the disease, and transmit the bacterium to other people. Indeed, one third of the world's population has LTBI, and each of these individuals has a 10% lifetime risk of developing active **tuberculosis disease (TB).** HIV co-infection increases the risk of developing TB within one year by 7-10%,[1] making TB the leading cause of death from AIDS.[2] As the global epidemic of HIV expands into countries with high rates of TB, more active TB cases can be expected. The TB pandemic has continued to worsen despite the use of **directly observed chemotherapy programs (DOTS).** The World Health Organization now reports that resistance to anti-TB medications (including those in the DOTS regimen) is as high as 40% in some countries,[3] with near complete resistance in parts of Russia and Eastern Europe to INH, the first line drug against Mtb.[4] To complicate matters further, it is likely that many individuals who have latent Mtb infection in the developing world have **multi-drug resistant (MDR)** LTBI. Continued expansion of the MDR TB pandemic underscores the urgent need for development of an improved TB vaccine.

Correlates of Immunity

Mtb infects individuals through the respiratory route. Alveolar macrophages engulf Mtb but it is able to survive and proliferate in the cell by inhibiting phagosome fusion with acidic lysosomes and thus avoid degradation. Infected macrophages migrate to nearby lymph nodes where a complex immune response involving T helper (CD4+) and killer (CD8+) T cells ensues, ultimately resulting in the formation of a granuloma.

Studies of TB in humans suggest that an effective TB vaccine must induce broad T cell-mediated immunity in general, and release of **T helper type 1 (Th1)** cytokines in particular.[5] These cytokines include interleukin (IL)-2, interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha and IL-12p40. The importance of CD4+ T cells in containment of LTBI is most clearly illustrated in HIV-infected individuals, who have lower than normal CD4+ T cell counts and increased rates of TB reactivation.[6] It is believed that reactivation is due to gradual HIV-mediated destruction of activated T cell clones specific for TB epitopes[7] By extension, the loss of TB-specific T cells appears to impair the host's ability to contain LTBI within the granuloma.[8]

On the other hand, T regulatory cells (CD4+/CD25+) produce Th1 suppressive cytokines, such as IL-10 and transforming growth factor (TGF)-beta; these cytokines are elevated in individuals diagnosed with active TB disease. A large cross-sectional study in Ethiopia found that patients with active TB disease have decreased levels of Th1 cytokines and increased levels of IL-10, when compared with individuals who are not infected or who are latently infected. This finding suggests that an effective TB vaccine may need to strongly induce Th1-dominant immune response that will prevail over the Th2 response of the host. This is supported by the finding that co-infection with other pathogens and stress are Th2 skewing factors that are common in areas where a TB vaccine is most needed.[9]

While Th1 cytokines are essential for protection, their levels of production do not alone explain the immunity/susceptibility dichotomy. CD8+ T cells exert cytotoxic lymphocyte (CTL, killing of infected cells) function and produce Th1 cytokines. CD8+ T cell responses are important in later phases of TB and have been shown to control Mtb replication in the human alveolar macrophage.[10] Indeed, Mtb-immune donors have been shown to have CD8+ T cells specific for Mtb antigens[11] and alveolar macrophages have been shown to be effective targets of CD8+ T cells.[12] Taken together, these data suggest that stimulation of Th1-biased and CD8+ T-cell responses to Mtb epitopes may control immune responses in latently-infected individuals.

The Existing Vaccine: BCG

Current vaccine development strategies focus on the prevention of Mtb infection. The only available licensed TB vaccine is bacille Calmette-Guérin (BCG), live attenuated *Mycobacterium bovis*. Approximately 115 million doses of BCG are administered each year, with a worldwide coverage rate of close to 80% of all infants.[13,14] While BCG reduces the incidence of childhood TB, meningeal TB, and leprosy,[15] it does not significantly impact the spread of TB because it does not reliably prevent adult pulmonary TB, the most common and most infectious form of the disease. This occurs for a number of possible reasons, including waning efficacy over time, differences between BCG sub-strains, deletion of protective antigens found in Mtb, and failure of BCG to stimulate adequate balanced CD4+ and CD8+ T-cell responses.

The safety of BCG vaccination of HIV-infected infants has also come under scrutiny. There are increasing reports of disseminated BCG infection in South Africa.[16] For this reason, the WHO has now officially contraindicated the use of BCG in HIV-infected children.[17] Prospective studies to investigate the use of BCG vaccination in the context of the HIV epidemic are required to more accurately

evaluate the safety and benefits of continuing universal BCG vaccination in areas of the world where HIV is endemic.

Development of a prophylactic vaccine with better efficacy and fewer safety concerns than BCG would aid in reducing the global burden of TB. However replacing BCG with a new TB vaccine is likely to be very difficult due to the strong protective effect of BCG against invasive TB in non HIV-infected children. Furthermore, demonstrating superiority of a new vaccine over BCG will also be difficult as a Phase III prevention study comparing BCG to a new vaccine will require a time frame of 10 – 20 years.

Alternatively, a vaccine targeting LTBI could significantly and economically reduce global TB infection rates.[18, 19] Furthermore, such a vaccine may also be compatible with BCG pre-immunization. In contrast to a new prophylactic TB vaccine, a therapeutic TB vaccine could be evaluated more simply and at lower risk; the trial participants would be LTBI and/or BCG pre-immunized adults at-risk for developing active infection. For these reasons, our collaborative team is developing a multi-epitope LTBI vaccine to (1) eradicate existing latent TB and to (2) boost BCG vaccine-induced immunity. Such a vaccine may also be useful as immunotherapy to shorten the course of TB chemotherapy, and/or to increase the cure rates of MDR TB.

Current TB Vaccine Development Strategies

Current TB vaccine development involves both live attenuated and subunit strategies. One live attenuated approach entails recombinant modification of BCG for overexpression of antigen 85B, an Mtb antigen demonstrated to be protective.[20,21] In animal challenge studies, this vaccine candidate, rBCG30, induced increased protection over BCG and is reported to be safe in a Phase I clinical trial.

A second approach involves design of endosome escape mutants to increase CD8+ T-cell responses. The rBCGΔUreC:Hly+ vaccine secretes listeriolysin to form pores in the endosomal membrane and escapes into the cytoplasm of infected cells. This vaccine demonstrated increased efficacy compared with the parental BCG strain in preclinical studies, and is currently in Phase I trials.[22] A vaccine that combines antigen overexpression and endosome escape approaches is scheduled for Phase I trials.[23] It uses perfringolysin instead of listeriolysin to enable endosomal escape and overexpresses 3 different antigens: Ag85A, Ag85B, and TB10.4.

Multiple antigen or epitope vaccinations could be one way to elicit the strong immune responses necessary to clear Mtb infections.

Several genes are missing from BCG but present in virulent Mtb. It is suspected that these missing genes may encode antigens required for full protection. In order to overcome this limitation, attempts have been made to make attenuated live Mtb vaccines. A mutant Mtb vaccine lacking only the PhoP virulence protein, for example, demonstrated diminished virulence and elicited immune responses similar to parental Mtb.[24] Auxotrophic Mtb mutants, such as the one produced by targeted deletion of the *panC*, *panD* and *lysA* genes, are also live vaccines that are infective but are replication deficient. The *panCpanDlysA* vaccine produced similar responses to that obtained by the BCG vaccine.[25] A similar *panCpanD* mutant with deletion of the RD1 region, which is thought to be partly responsible for attenuation of BCG, also produced responses comparable to BCG and is scheduled for Phase I trials.[26] While the live TB vaccine approach is reasonable, there are significant safety concerns about reverting mutations that may restore virulence.

Subunit vaccines represent a third approach, which involves vaccination with Mtb antigens proven to provide protection against TB in animal models. A number of immunogenic proteins have been identified by this approach such as Ag85A, Ag85B, ESAT6, TB10.4, Mtb9.9, Mtb39a-e, and Mtb41.[27] The antigens can be delivered in a range of delivery vehicles such as DNA vaccines, liposomes, **viral-like particles (VLPs)**, or as straightforward protein-in-adjuvant combinations. Subunit vaccines have a greater safety profile than live, killed or attenuated vaccines and the mechanism of protection can be more easily measured. This approach has been very successful for viruses such as Hepatitis B Virus and Human Papilloma Virus that express only a few proteins, but remains to be validated against more complex organisms like bacteria that are capable of expressing hundreds or thousands of proteins.

Using a unique strategy, our team is developing a T-cell epitope-based vaccine to boost BCG-specific immune responses. This approach combines the breadth of targets provided by the live vaccine approach with the safety benefits of the subunit strategy. During TB infection, the host processes over 4,000 Mtb proteins into millions of peptides and presents a specific subset of those to the immune system. By using computerized informatics algorithms we are able to accurately predict the peptides contained within that immunogenic subset. The selected peptides are further verified based on binding capacity to MHC molecules and immunogenicity as a vaccine. These computational strategies provide a rapid and more comprehensive alternative to biochemical and proteomics approaches aimed at identifying antigens to be used as subunit vaccines. Thus, our TB vaccine strategy is to include the most immunogenic T-cell epitopes from the entire Mtb genome with the aim of boosting and complementing an otherwise suboptimal T cell repertoire.

Progress to Date on an Epitope-driven Mtb Vaccine for Latent TB Infection

We have previously performed and published how we identified and validated immunogenic Mtb T-cell epitopes in human LTBI subjects using bioinformatics and experimental methods. The following paragraphs summarize our progress to date.

Epitopes from published Mtb antigens. Using our epitope mapping algorithm, EpiMer, we identified 23 epitopes from a set of nine Mtb antigens that were previously reported to induce a strong T cell response in both experimental animals and Mtb-immune individuals.[28] 22

of the 23 epitopes were validated in interferon-gamma enzyme-linked immunospot (ELISpot) assays using PBMCs from a limited number of Mtb-infected subjects (N=12).

Mtb genome alignment. Following this retrospective study, we aligned two Mtb genomes (lab strain H37Rv and clinical isolate CDC 1551 [29]) and analyzed both for new, potentially immunogenic T-cell epitopes. Two sets of proteins were analyzed:

Secreted antigens. This screen was directed at identifying epitopes from putative secreted protein antigens.[30] These proteins were chosen for analysis because they have been demonstrated to partially protect guinea pigs.[31] and mice[32] against challenge with Mtb. Protection in humans has also been associated with response to antigens secreted by Mtb in culture filtrate.[33,34] PBMC from 44 purified protein derivative (PPD) positive subjects and from ten PPD negative control subjects were stimulated with each of 17 putative epitopes derived from secreted Mtb proteins. Fifteen (88%) epitopes elicited an interferon-gamma response in ELISpot assays.

Upregulated antigens. In another genomic analysis, we mapped T-cell epitopes in proteins that were both deleted from BCG and expressed in a Mtb latent-like state.[35] 17 peptides were selected from this set of proteins. Each of the seventeen epitopes was tested with PBMCs from thirty-three PPD-positive subjects. Seventeen of seventeen (100%) epitopes elicited an interferon-gamma response, although each subject responded to a different subset of peptides. Individual peptide responses ranged from 5% to 33% of subjects. No epitope was recognized by every single subject in our study cohort, however, those peptides that were recognized by multiple subjects may be useful for a vaccine because they appear to be broadly recognized.

Conclusion

Future vaccine approaches for TB may need to move away from "whole" TB vaccines (based on BCG or attenuated Mtb) due to concerns of safety. Multiple antigen or epitope vaccinations could be one way to elicit the strong immune responses necessary to clear Mtb infections.

Our post-infection vaccine will be developed based on an ensemble of genome-derived epitopes that stimulate T cell responses in Mtb-immune individuals. Indeed, in studies not described here, we have also illustrated that these epitopes are immunogenic in wild-type and HLA transgenic mice (mice that express human MHC molecules). A major benefit of developing an epitope based rather than a subunit based vaccine is the ability to use immunogenic regions of many proteins. For TB this is especially important as function has been assigned to only 2,220 of the 4,203 proteins in the CDC-1551 genome. A lack in knowledge about the TB proteome and immunopathogenesis of TB need not impair our ability to develop a T-cell epitope vaccine for TB.

Given the enormous number of people affected by TB, the speed and adaptability of the epitope-driven vaccine approach promises to accelerate vaccine development.

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Leonard Moise, PhD, is Director of Vaccine Development at EpiVax, Inc.

Julie McMurry, MPH, is Senior Project Manager at EpiVax, Inc.

Daniel Rivera is Director of Molecular Biology at EpiVax

E. Jane Carter, MD, is Assistant Professor of Medicine, the Warren Alpert Medical School of Brown University.

Jinhee Lee, DVM, PhD, is Instructor, University of Massachusetts Medical School.

Hardy Kornfeld, MD, is Professor of Medicine, University of Massachusetts Medical School.

William Martin is CIO and Director of Bioinformatics at EpiVax.

Anne S. De Groot, MD, is President and CEO at EpiVax, and Associate Professor of Medicine, The Warren Alpert Medical School of Brown University.

Correspondence:

Anne S. De Groot, MD
EpiVax
146 Clifford Street,
Providence RI 02903
Phone: (401) 272 2123
E-mail: Admin@EpiVax.com

The New HPV Vaccine and the Prevention of Cervical Cancer

Michael A. Steller, MD

Disclosure of Financial Interests

Michael A. Steller, MD. Speaker's Bureau: Merck & Co, GlaxoSmithKline

Overwhelming epidemiologic, molecular, and clinical evidence indicates that cervical cancer is caused by a viral infection that can be prevented by an effective immunization. More than 99% of cervical cancers **harbor Human papillomavirus (HPV),**[1] and several recent clinical studies have demonstrated efficacious vaccinations to prevent HPV infection and subsequent cervical intraepithelial neoplasia.[2-4]

Cervical carcinoma is the second most common cause of cancer-related deaths in women worldwide.[5] Population-based cervical cytology screening programs have drastically reduced the incidence of cervical cancer in the United States and other developed countries, where it was the most common cause of cancer death in women in the 1940s. Before the introduction of screening programs, the incidence of cervical cancer in industrialized countries was similar to that of developing countries today.[6] Due to effective screening, only 2% of cervical cancers occur in the United States,[5,7] at an estimated annual cost of nearly $6 billion.[8] Conversely, 83% of cervical cancers occur in developing countries without the resources for effective screening.[5] In less developed countries, this disease is a leading cause of cancer related mortality among women, accounting for nearly 275,000 worldwide deaths annually.[5] Infection with HPV has been causally linked with the development of cervical cancer.[9] Although over 100 different HPV genotypes have been identified, only approximately 15 have been associated with the development of invasive cervical cancer, and HPV types 16 and 18 can be detected in approximately 70% of case.[10] In contrast, HPV types -6 and -11 are virtually never found in cancers, but are detected in over 90% of genital warts. HPV infection has also been linked to squamous cancers of the vulva, vagina, anus, and oropharanx.[11] Epidemiological data indicate that female genital HPV infection occurs commonly, with an estimated lifetime risk of HPV infection approximating 80% in some populations.[12,13] However, despite the prevalence of HPV infections in sexually active young women, the development of cervical cancer occurs in a minority of exposed women, even in unscreened populations. The host's immune response has an important role in the pathogenesis of HPV-associated cervical lesions. For instance, over 60% of HPV positive, mildly dysplastic lesions resolve spontaneously[14] and such factors as HIV infection and exposure to immunosuppressive agents have been strongly associated with HPV-induced carcinogenesis.[15,16] Also, the prevalence of genital HPV infections peaks soon after the onset of sexual activity in women and declines thereafter, suggesting that long-term protection is generally induced.[17]

Cervical cancer is one of only a few virally associated malignancies. Prophylactic vaccination is achieved by inducing anti-viral neutralizing antibodies prior to viral infection. Certain preventative vaccines have been spectacularly effective in preventing subsequent infection by other human viruses, including mumps, measles, rubella, polio, and hepatitis B. In contrast to the oral poliovirus vaccine, which is an attenuated form of the poliovirus, the development of attenuated HPV vaccine has been hampered by difficulties growing HPV in cultured cells. Because of the paucity of available tissue, the use of inactivated virus or crude viral extracts from infected humans has been impractical and has the theoretic disadvantage of exposing normal subjects to viral oncogenes encoded by HPV DNA. Accordingly, prophylactic vaccine development for HPV has focused on recombinant subunit preparations consisting of the L1 and L2 virion structural proteins. A similar strategy was used in the highly successful prophylactic vaccination program for hepatitis B virus.[18] This vaccine elicits the production of protective antibodies against the surface antigen of hepatitis B virus, prevents the subsequent transmission of this virus,[18] and has reduced the incidence of hepatitis B-associated hepatocellular carcinoma.[19]

Virus-like particles (VLP) have been successfully synthesized by expressing the L1 major capsid protein alone, or together with the L2 minor capsid protein. The L1 pentamers self-assemble VLP that are morphologically indistinguishable from the authentic virion, but lack any oncogenic DNA and are non-infectious. The VLP are effective in generating papillomavirus type-specific protection from viral challenge. During the past few years, several HPV VLP clinical trials have been conducted, all of which have consistently demonstrated that these vaccines are highly immunogenic. In humans, the initial "proof of principle" study involved the administration an HPV-16 L1 VLP.[2] A second large, randomized controlled study described the effectiveness of a bivalent vaccine incorporating HPV-16 and -18 L1 VLP.[4] Recently, a quadrivalent vaccine, containing L1 VLP of HPV types -16, -18, -6, and -11 was investigated.[3] All of theses studies demonstrate that the VLP-based vaccines confer type-specific protection from persistent genital HPV infection, from transient genital HPV infection, and from the development of HPV-associated preinvasive cervical neoplasia. After 2 years of extended follow-up, the quadrivalent vaccine has achieved 100% efficacy against vulvar, vaginal and cervical genital neoplasia. It also was 100% effective in preventing genital warts.[20]

The implementation of an effective, first generation HPV vaccine is anticipated to confer primary protection from the two most prevalent oncogenic HPV infections and will thereby reduce the incidence of abnormal cervical cytology tests during secondary screening to prevent cervical cancer. The first commercially available vaccine, recently released by Merck and named Gardasil, contains VLPs to HPV-16 and -18, which would theoretically prevent 70% of cervical cancers (Gardasil also contains VLPs to HPV-6 and -11). Later-generation vaccines hold the promise of expanding primary protection to include less prevalent oncogenic HPV infections.

Immunity to HPV is, for the most part, genotype specific[21] although divergent variants of HPV genotypes are serologically cross-reactive.[22] Therefore, a multivalent vaccine is a practical means to expand primary protection. In theory, in order to prevent 100% of cervical cancers, VLPs from all fifteen oncogenic HPV types would need to be included in a multivalent vaccine. In later generation vaccination protocols, inoculation with the L2 minor capsid protein, whose sequence is highly conserved across HPV genotypes, may yield broad-spectrum, cross-protective antibody responses against infection with multiple HPV types.[23] Such a strategy, consisting of a single antigen, would substantially reduce the complexity and expense of developing a broadly protective vaccine against the multiple oncogenic HPV types.

As impressive as VLPs appear to be for preventing papillomavirus infections and subsequent diseases, this technology's potential for also *treating* established lesions is potentially of surpassing importance.[24] To increase their therapeutic potential, polypeptides of the non-structural viral genes have been incorporated within the VLPs as a genetic fusion with either the major (L1) or minor (L2) capsid proteins. These chimeric VLPs, which are morphologically indistinguishable for their parental VLPs, induce cell-mediated immune responses to the fused polypeptides contained within it. Chimeric VLPs containing HPV-16 E7 polypeptides have been shown to induce potent cytotoxic T-lymphocyte responses and to induce the regression of established tumors.[25] The VLPs specifically bind to dendritic cells (antigen presenting cells) and induce their activation. [26] Chimeric VLPs may ultimately be developed as a combined prophylactic and therapeutic vaccine since they retain the conformational L1 surface epitopes required for inducing neutralizing antibodies. Non-HPV antigens can also be incorporated within the VLPs, raising the possibility that chimeric VLPs may be useful as vehicles for the delivery of antigens to treat non-HPV associated diseases.

Certain inexorable dilemmas will reflexively emerge following the successful clinical implementation of an effective HPV vaccine. In a population with an effective and organized cervical cancer screening program, the clinical impact of the first generation HPV vaccines will likely reduce, but not eliminate the incidence of disease. The cost of vaccination would be superimposed upon the existing cost of screening, which is formidable.[27] Improved cost-effectiveness has been projected in a scenario involving a combination of vaccination and both increasing the interval and the age of initial screening.[28, 29] An effective vaccination could also reduce the clinical morbidity associated with the management of abnormal screening results, including colposcopies, biopsies, and tissue ablation procedures, further reducing the economic burden of preventing HPV-associated malignancies.[29] Because about 50% of cervical cancers occur in unscreened women or those who do not undergo screening at prescribed intervals,[30] mass vaccination programs might prevent the majority of this population sector from subsequently developing disease.

Before mass vaccination initiatives can supplant organized screening programs, extensive long-term clinical data will be required that address the long-term effectiveness of vaccination, duration of immunity, and impact of type-specific vaccination on other HPV types. Indeed, screening programs will continue to be necessary for several years even if a universal vaccine program is successfully implemented since there will remain women already infected with HPV for whom the prophylactic vaccination is unlikely to protect. As pointed out by Franco:

> "…Policy makers are strongly cautioned to avoid scaling back cervical cancer screening. Any premature relaxation of cervical cancer control measures already in place will bring a resurgence of the disease to the unacceptable levels of the not too distant past"[31]

In developing countries that do not have the infrastructure to maintain organized screening clinics, an effective vaccine to prevent cervical cancer has the potential to dramatically reduce the incidence of this disease. Because it usually takes many years for cervical cancer to develop following incident genital HPV infection, it will take one or two decades for a widespread vaccination program to reduce the incidence of cervical cancer. For instance, in North American women, incident genital HPV infection usually occurs during the late-teen age years,[32] but the median age of cervical cancer in the United States is 47 years of age.[33] In contrast, screening programs can rapidly reduce morbidity and mortality.[34]

Reductions in disease incidence in developing countries must remain a high priority, for 83% of cases occur in these resource settings. Like screening programs, one limiting factor for implementing a vaccination program in developing countries is economic. Financial support through the generosity of philanthropic foundations, such as the Bill and Melinda Gates Foundation, may be indispensable. However, history teaches that the successful implementation of vaccines in developing countries is complicated and is impacted by other factors besides economics. For example, in the twenty years since universal hepatitis B vaccination programs were implemented in some nations, today more than 1/3 of countries still do not have a hepatitis B vaccination program, despite the high prevalence of hepatitis B infection in these countries and the dramatic reductions in the cost of the vaccine.[35] Even recommendations from the World Health Organization to include the hepatitis B vaccine in already established infant immunization programs have not succeeded in overcoming this problem.

History can teach us important lessons concerning the implementation of vaccine programs, both in developing countries and in Westernized nations. Consider the experience with the rubella vaccine. Several programs initially targeted susceptible women after pregnancy, women at special risk, and schoolgirls. Vaccine delivery was targeted at different age groups and sexes, and divergent vaccination policies were adopted in different countries.[36] This resulted in equally divergent epidemiologic consequences that conflicted with the vaccine's overarching purpose: to reduce or eliminate the incidence of rubella syndrome.[37] Rubella epidemics subsided only after mandatory inoculation policies were adopted to target *all* preschool-aged children, with booster doses provided to adolescent girls. Similarly, ineffective public health policy occurred in the United States when the hepatitis B vaccine was originally introduced.[38] Initially, the **Advisory Committee on Immunization Practices (ACIP)** recommended vaccination only for populations at high risk of contracting hepatitis

B infection. After several years, there was no reduction in the incidence of hepatitis B infection in the U.S., prompting the ACIP to change its vaccination policy to focus on universal childhood vaccination, prevention of perinatal transmission, and other target populations. Following this shift, hepatitis B infection rates fell dramatically, particularly in highly vaccinated populations. To eliminate viral transmission, the collective experience with immunoprophylactic vaccines overwhelmingly indicates that high vaccine coverage rates must be sustained among infants, children, and adolescents, as well as adults *of both genders* at high risk for infection.

Taking vaccination efficacy to its logical extreme, a vaccine conferring enduring immunity that is 100% effective against all oncogenic HPV genotypes would usher in another health policy challenge: assuring that an unscreened population has been vaccinated. Implicit in the prospective success of an HPV vaccine program is the availability of expanded funding for childhood vaccinations and the enactment of laws requiring vaccination of school children. In the U.S., it is the current policy that, once the ACIP makes a universal recommendation for a vaccine, it automatically provides for the vaccine to be covered under the **Vaccines for Children (VFC)** Program, a federally-funded entitlement program for the uninsured children of the US (under 19 years old.[39] For the insured, private payers usually cover or reimburse based upon the ACIP's recommendations. States generally have to fund the remaining "underinsured", comprising children who are not insured and not VFC-eligible. This amounts to about 10% of a state's population. It is this group that can benefit from legislation to appropriate funding for vaccination.

In the past, school immunization laws have had a remarkable impact on vaccine-preventable diseases in the United States, particularly in school-aged populations (40). These laws have helped to expand immunization coverage in large populations, which, compared to pre-vaccination era peaks, has resulted in a 97% reduction in vaccine-preventable diseases. However, because HPV is a sexually transmitted infection, it carries a stigma of unacceptable sexual behavior instead of a rare complication of a common infection.[41] Although this stigma may impede acceptance of the HPV vaccine, the sexual transmissibility of hepatitis B did not hinder universal vaccination efforts to prevent its infection. Historically, mandatory immunization programs, implemented primarily through school laws, have been well accepted, even in democratic societies.

Historically, mandatory immunization programs, implemented primarily through school laws, have been well accepted, even in democratic societies.

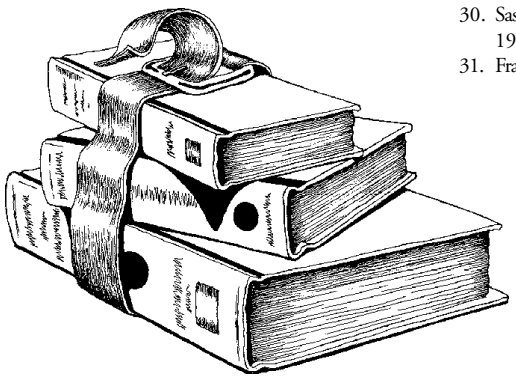
To optimally prevent HPV infection, vaccination should ideally be administered before women begin to engage in sexual behavior. According to the Centers for Disease Control and Prevention, sexual behavior is common among young people well before graduation from high school. In the United States, 7.4% of the population have had sexual intercourse for the first time before age 13 years, and an estimated that 33% of 9th graders and 62% of 12 graders have already engaged in sexual intercourse.[42] Accordingly, parental acceptance is a critical issue that will profoundly impact the potential effectiveness of a prophylactic HPV vaccine. Education of the public is paramount to inform that genital HPV infection is a sexually transmitted condition that is extremely common, and that there is a causal link between HPV and cervical cancer. Unfortunately, even in a well educated population, awareness and knowledge of HPV is poor.[43] However, acceptance of the HPV vaccine is very high among providers, parents, and young adults, particularly following a brief educational intervention.[44]

In addition to vaccinating pre-exposed children and adolescents, there may also be a role for administering "catch-up" inoculations to young adults who have already engaged in sexual activity. In one recent study, 75% of sexually active 16-26 year olds were clinically naïve to HPV 6, 11, 16, and 18,[45] and those who were already infected were generally infected with only a single HPV type. Vaccine efficacy against the other 3 types contained in the quadrivalent vaccine was unimpaired in this group of patients. "Catch-up" vaccinations among sexually active young women would augment efforts to achieve herd immunity by decreasing viral transmission rates and could potentially confer considerable cost-savings by reducing the incidence of HPV-associated neoplasias.

The ACIP recently recommended that the initial target population for Gardasil should be all women between the ages of 9 and 26 years, since it is this population that has the highest disease burden from HPV infection and has been the most rigorously studied thus far. In the near future, it is anticipated that vaccine efficacy data will become available for both younger and older women, as well as males. Although vaccine policies vary from country to country, Gardasil has already been approved for use in males in the nations of the European Union and in Australia, in spite of the fact that no published data yet confirm efficacy in males.

Similar to females, clinical experience inoculating males with a VLP-based HPV vaccine clearly demonstrates that potent neutralizing antibody responses can be safely and reliably elicited.[46] Unfortunately, all the clinical trials to date that assess the prevention of epithelial HPV infection have been limited to females. The recently reported success using the quadrivalent vaccine to prevent warts from developing on the vulva,[20] where the epithelium is keratinized similar to the penis, suggests that male vaccination may be efficacious. Productive infection in males commonly results in the development of genital warts, but compared to females, only rarely results in the development of a malignancy. Given the importance of the decision to include or exclude males in large-scale vaccination programs, research to elucidate the effectiveness of HPV vaccines in males should be accorded very high priority.[47] Assuming that vaccination of males proves efficacious in preventing genital warts, the inclusion of males in a universal vaccination program provides important advantages, including direct protection from developing genital warts and major contributions to achieving herd immunity by reducing the circulation of HPV in the general population.

The successful development of an effective HPV vaccine marks the dawn of a new era. Compared to all other cancers, only cervical cancer has been shown to have a necessary causal intermediate: HPV infection.[1,9] This necessary causal association far surpasses the associations of tobacco consumption with lung cancer and chronic hepatitis B infection with liver cancer, which are two of the strongest epidemiologic associations ever identified.[31] In an age when a preventive vaccine is now commercially available, the link between HPV and cervical cancer sets this malignancy apart as a vaccine-preventable disease. Historically, vaccines have been underutilized, in part because of underestimation of seriousness of vaccine-preventable diseases, underestimating the benefits of vaccination, and concerns regarding the side effects of vaccines.[48] In previous eras when vaccines were not available, the ravages of smallpox and polio were devastating both to individuals and to populations. Those who witnessed the successful implementation of vaccines to prevent these diseases viewed them as miracles. However, in modern times, few of us have experienced the devastation caused by these and other vaccine-preventable diseases. When there is no longer an imminent fear of contracting a disease, apathy about prevention can occur: the public forgets about the limitations of cures.[49] Therefore, a sense of urgency must be maintained as HPV vaccines make their way into the global healthcare arena.



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Michael A. Steller, MD, is Director, Division of Gynecologic Oncology, Caritas Christi Health Care System, and Clinical Professor of Obstetrics & Gynecology, Tufts University School of Medicine.

Correspondence:

Michael A. Steller, MD
St. Elizabeth's Medical Center
Division of Gynecologic Oncology
736 Cambridge Street
Boston, Massachusetts 02135-2997
phone: (617) 562-7406
e-mail: Michael_Steller@cchcs.org

Vaccines and Autism: An Update

Gita V. Harappanahally, MD, Christine L. Trask, PhD, and David E. Mandelbaum, MD, PhD

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Pervasive developmental disorders (PDD) or **Autistic Spectrum Disorders (ASD)** are characterized by qualitative impairment of social interaction, language and communication with restricted, repetitive and stereotyped patterns of behavior, interests and activities. In the past two decades, substantial attention has been focused on an apparent increase in the prevalence and incidence of ASD and questions have been raised about a possible role of vaccines in this purported increase.

Epidemiology

Prevalence is the proportion of individuals in a population who suffer from a defined disorder at a given time. Incidence is the number of new cases of a defined disorder occurring in a population during a time interval. Both prevalence and incidence estimates will increase when case definition is broadened and/or case ascertainment is improved.

In a 1943 paper Kanner described autism, yet offered no estimates of the number of people affected in the general population. In 1966, Lotter published the first paper to give the results of an epidemiological study of autistic conditions in the entire large population of children of all levels of intelligence living in a defined geographical area and found age-specific rates of 4.1 per 10,000 children aged 8-10 years. In 1993 Wing[1] reviewed sixteen published epidemiological studies of the prevalence of autism from 1966 to 1983. These studies were done in Europe, the USA and Japan and used different diagnostic criteria. The age-specific prevalence rates of ASD varied from 3.3 to 16.0 per 10,000. The age groups varied in all the studies, ranging from 0-20 years. Variation in the definition of ASD was one of the factors accounting for differences in the prevalence rates. There was evidence that immigration may have affected true prevalence and that greater knowledge of ASD increased the number of cases identified. The higher rates may also have resulted from the inclusion of both severely retarded and more able children.

A 1999 report by California's **Department of Developmental Services (DDS)** stating that the number of individuals served under the category of "autism" had increased by 273% between 1987 and 1998 has been widely quoted as evidence for an "epidemic" of autism. The fact that the report's figures applied to numbers rather than rates and failed to account for changes in the size and composition of the underlying population has fueled much speculation. The report also failed to consider changes in diagnostic concepts and definitions. Since autistic children have, of late, been diagnosed at a much earlier age, a decreasing mean age at diagnosis would necessarily result in an increased number of reported cases, even assuming a stable prevalence or incidence.[2]

With the exception of some influenza vaccines, Thimerosal has been removed from most vaccines since 2001.

Some have argued that diagnostic transfer may account for the increased prevalence rate of autism. Croen et al in 2002[3] found an increase in the number of children diagnosed with autism and a decrease in the number of children diagnosed with mental retardation. A similar pattern was seen with autism and developmental disorder: the incidence of autism increased with a corresponding decrease in other developmental disorders.[4]

Fombonne in 2003[5] reviewed 32 epidemiological surveys of pervasive developmental disorders, published from 1966-2001 and his findings point towards an increase in prevalence estimates in the last 15 years. These surveys were conducted in 13 countries. Prevalence estimates for autistic disorder ranged from 0.7 to 72.6 per 10,000 children. When surveys were combined in two groups according to the median year of publication, the median prevalence rate for 16 surveys published in the period 1966-1991 was 4.4 per 10,000 and the median rate for the 16 surveys published in the period 1992-2001 was 12.7 per 10,000. Prevalence rates above 7 per 10,000 were all published since 1987. Considering surveys strictly from 1987 on reveals prevalence estimates for autistic disorder that ranged from 2.5 to 30.8/10,000, with an average rate of 11.1 per 10,000 and a median rate of 9.5 per 10,000.

Prevalence estimates for combined PDD from epidemiological surveys done by Baird in 2000, Bertrand in 2001 and Chakrabarti in 2001 [6-8] ranged from 57.9 to 67.5 per 10,000 children. Gurney et al in 2003 [9] found that the prevalence of ASD had increased from 3 per 10,000 in 1991-1992 to 52 per 10,000 in 2001-2002 in children aged 6 to 11 years. They found that federal and state administrative changes favoring identification of ASD corresponded in time to the increasing trends. Unlike Croen et al, however, they did not find any corresponding decrease in any special educational disability category to suggest diagnostic substitution as an explanation for the increasing autism prevalence.

Few studies have been done to estimate incidence. Powell et al in 2000[10] and Kaye et al in 2001[11] showed an upward trend in incidence over short periods of time but failed to assess changes in diagnostic criteria. Smeeth et al in 2004[12] showed an increase in incidence of PDD from 1988 to 2001. Here again the increase could not be attributed to a true change in the incidence of PDD as opposed to an increased awareness of the disorder and a broadening of diagnostic criteria, two phenomena that were occurring at the same time. Chakrabarti and Fombonne [7,13] conducted two surveys in the same geographic area in 2001 and in 2005 to compare trends over time. They found prevalence rates of PDD of 62 per 10,000 and 59 per 10,000 children, respectively. The stability of the prevalence rates in the two periods indicates a stable incidence.

In 2000, in response to increasing public health concern regarding ASD, the **Centers for Disease Control and Prevention (CDC)** established the **Autism and Developmental Disabilities Monitoring (ADDM)** Network. A total of 1,252 children aged 8 years across 6 sites were identified as having ASD. The overall prevalence of ASD per 10,000 children ranged from 45 (West Virginia) to 99 (New Jersey).[14] In 2002, data were collected from 14 collaborative sites.[15] Of 407,578 children aged 8 years, 2,685 were identified as having ASD. Prevalence ranged from 33 (Alabama) to 106 (New Jersey) per 10,000. Higher prevalence was found in sites with access to health and education records compared to sites with health records only. Results from the second report of a US multi-site collaboration demonstrated consistency of prevalence in the majority of sites, with variation in two sites.

MMR Vaccine and Autism

Hypotheses have linked vaccinations to autism since 1998. The first hypothesis implicated the **measles-mumps-rubella (MMR)** vaccine, usually given to children between 12 and 15 months of age. This hypothesized linkage first received attention in 1998 following the publication of Wakefield et al.[16] Subsequent epidemiologic investigations, however, failed to establish an association between MMR and autism in cohort, case-control and ecological studies. Clinical studies have also failed to identify a clinical phenotype characterizing a smaller group of autistic children presumably at risk for MMR-induced autism.

Fombonne and Chakrabarti in 2001[17] found no evidence of a distinct syndrome of MMR-induced autism or "autistic enterocolitis." Three clinical samples were studied. One with a diagnosis of PDD in subjects born between 1992 and 1995 was compared with two other clinical samples: one with a diagnosis of PDD and believed to have received MMR vaccine, in subjects born between 1987 and 1996, and the second with a diagnosis of autism who were not given MMR vaccines, in subjects born between 1954 and 1979. There was no difference in the mean age of first parental concern between the two samples exposed to MMR (19.3 and 19.2 months) and the pre-MMR sample (19.5 months). There was also no increased frequency of Childhood Disintegrative Disorder in children receiving MMR vaccine.

Honda et al1[18] studied incidence of ASD up to age seven for children born from 1988-1996 in Yokohama, Japan. MMR vaccination rate in the city of Yokohama declined significantly in the birth cohorts between the years 1988-1992. Although not a single vaccine was administered in 1993 or thereafter, the cumulative incidence of ASD up to age seven increased significantly in the birth cohorts between the years 1988-1996. Hence, it was concluded that MMR vaccination is most unlikely to be a cause for ASD.

There is no scientific evidence implicating MMR vaccine or Thimerosal in the etiology of autism.

It has been suggested that MMR vaccine is a cause of regressive autism. This hypothesis could best be tested in Japan, because MMR vaccination was used in Japan only between 1989 and 1993. Uchiyama et al in 2007[19]analyzed data on 904 patients with ASD and did not find any difference in the incidence of regression between MMR-vaccinated children and non-vaccinated children. There was no increase in the rate of regression in ASD during the period when MMR was used as compared to the period prior to use of MMR and the period after the use of MMR as well as the two periods combined.

Recent reviews of the MMR hypothesis by an ad hoc committee of the Institute of Medicine and the Cochrane collaboration[20] concluded that the evidence favored the rejection of this hypothesis.

Thimerosal and Autism

Thimerosal is almost 50% ethyl mercury by weight, a form of organic mercury, used as a preservative in vaccines. Added in minute amounts to vaccines, it helped prevent bacterial contamination of multidose vials of vaccines. **Haemophilus influenzae b (Hib), Hepatitis B (HepB)** and **diphtheria-tetanus-pertussis (DTP/DTaP)** vaccines contained Thimerosal.

Most of the information we have about mercury toxicity is related to exposure to methyl mercury rather than ethyl mercury. The two compounds have different half-lives (50 days for methyl mercury versus 7 days for ethyl mercury). Unlike ethyl mercury, methyl mercury is actively transported across the blood brain barrier. Postnatal exposure to ethyl mercury causes patchy damage to the cerebellar granular layer, whereas methyl mercury causes diffuse abnormality[21]. Guidelines have been set by various international and national agencies to limit the cumulative exposure of mercury. The **Food and Drug Administration (FDA)** announced in 1999 that infants who had received multiple Thimerosal-containing vaccines might have been exposed to cumulative dose of mercury in excess of Federal safety guidelines. Despite lack of evidence that this level of ethyl mercury can cause harm, in 1999 the AAP and the Public Health Service, recommended the removal of Thimerosal from vaccines, as a precautionary measure. With the exception of some influenza vaccines, Thimerosal has been removed from most vaccines since 2001.

Bernard et al.[22] have reported more than 90 clinical features that they considered common to autism and mercury poisoning. Nelson and Bauman in 2003[23] compared the clinical manifestations of autism and mercury poisoning and did not come to the same conclusion. The motor findings in high-dose mercury poisoning include ataxia, dysarthria, tremor, muscle pain and weakness. In contrast, motor findings in autism include stereotypies such as hand flapping, spinning or rocking. Hypotonia and clumsiness may be seen in autism. Sensory findings in mercury poisoning include bilateral constriction of the visual fields, paresthesias and peripheral neuropathy. In autism, there is hyperacusis and decreased responsiveness to pain, which is not due to peripheral neuropathy. Other signs of chronic mercury toxicity include hypertension, skin eruption and thrombocytopenia, which are seldom seen in autism. Psychiatric symptoms include depression, anxiety, irritability and recent memory impairment with mild mercury poisoning. In autism, there is social impairment and restricted interests and insistence for sameness. Decreased head size is seen with prenatal or early childhood exposure to mercury, whereas patients with autism have a large head. Overall, clinically there are few similarities between the two conditions.

In 2001, the Institute of Medicine completed a review of the available scientific literature on the association between Thimerosal and autism. At that time, they concluded that there was insufficient evi-

dence to support a causal relationship between Thimerosal and autism.

In 2002, the WHO Strategic Advisory Group of Experts reported that the review of evidence of toxicity from Thimerosal-containing vaccines was not supported and that these vaccines should be used. In 2004, the Global Advisory Committee on vaccine safety established by WHO reported that several of the features associated with autism was not biologically consistent with an external toxic agent, such as mercury exposure.

Madsen et al in 2003[24] studied a total of 956 children, diagnosed with autism during the period 1971-2000. The discontinuation of Thimerosal-containing vaccines in Denmark in 1992 was followed by an increase in the incidence of autism. They concluded that their data did not support a correlation between Thimerosal-containing vaccines and the incidence of autism. Another study from Denmark by Hviid et al in 2003[25] found that the risk of autism and other autistic-spectrum disorders did not differ significantly between children vaccinated with Thimerosal-containing vaccine and children vaccinated with Thimerosal-free vaccine.

Fombonne et al in 2006[26] studied the prevalence of PDD in Montreal, Canada in cohorts born from 1987-1998 and evaluated the relationship of trends in PDD rates with changes in cumulative exposure to Thimerosal and trends in MMR vaccination use rates. They concluded that there was an increase in prevalence of PDD; however they ruled out an association between PDD and either high levels of ethyl mercury or MMR vaccinations.

Woo et al [27] investigated vaccine risk perception among reporters of autism to the **Vaccine Adverse Event Reporting System (VAERS)** from 1990 to 2001. A total of 124 parents were interviewed. Almost two-thirds (65.3%) of the VAERS reports listed MMR or its component vaccines. MMR was the only vaccine listed on 17.7% reports; on 47.6% of reports, it was listed in conjunction with other vaccines, the most common of which were Haemophilus influenzae type B, oral polio, DTaP and varicella. Respondents perceived vaccine-preventable diseases as less serious than did other parents from the general population. When questioned about the factors that may have contributed to the reported condition, 96% of the respondents stated that the ingredients of the vaccines played a very strong or moderate role. The vast majority of the respondents also said that the child received the vaccines at too early an age (95.2%), that the child received too many vaccines at one time (94.4%), and that Thimerosal or mercury in vaccines (86.3%) and the MMR vaccine (78.2%) played a very strong role or moderate role. Only 15% of respondents felt immunization was extremely important for children's health. Two-thirds withheld vaccines from their children.

Conclusion

The prevalence rate of PDD is higher than reported 15 years ago and is about 60 per 10,000. Most of the increase can be attributed to the change in case definition and case ascertainment. Improved funding and services also encourage diagnosis. There is, however, no evidence of an increase in the incidence.

No scientific evidence implicates MMR vaccine or Thimerosal in the etiology of autism. In fact, the stable incidence and rising prevalence figures for autism, in spite of the removal of Thimerosal from vaccines in 1999-2000, provide compelling evidence that there is no association. The persistence of this misconception is likely to lead to a reduction in the number of children who are vaccinated, thus potentially undermining one of the most successful public health successes in recent times.

In June, 2007 the US Court of Federal Claims in Washington, D.C., began hearings on this issue. Dr. Isabelle Rapin, a renowned autism expert, in an interview by *Neurology Today* about these proceedings stated, in her inimitable style: "There is abundant epidemiological evidence against both the measles virus and the Thimerosal hypotheses, and I do not understand why the public is unable to understand this relatively straightforward evidence."

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Gita V. Harappanahally, MD, is Clinical Assistant Professor of Medicine, The Warren Alpert Medical School of Brown University.

Christine L. Trask, PhD, is Clinical Assistant Professor of Medicine, The Warren Alpert Medical School of Brown University.

David E. Mandelbaum, MD, PhD, is Professor of Medicine, The Warren Alpert Medical School of Brown University.

Correspondence:
Gita V. Harappanahally, MD
110 Lockwood St.
Providence, RI 02903
Phone: (401) 444-4345
e-mail: gharappanahally@lifespan.org

Tularemia Vaccines – An Overview

Julie A. McMurry, MPH, Leonard Moise, PhD, Stephen H. Gregory, PhD, Anne S. De Groot, MD

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Julie McMurry, MPH. Employee: EpiVax, Inc. Other financial or material interest: EpiVax, Inc.

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Francisella tularensis is a zoonotic bacterium that infects a variety of human tissues including skin, lungs, pharynx, and lymph nodes. It is one of the most infectious pathogens; as few as 10 organisms can cause disease. Aerosolized *F. tularensis* represents a potentially dangerous biological weapon owing to its high degree of infectivity, ease of dissemination and capacity to cause severe illness. In the absence of prompt antibiotic therapy, inhalation of tularemia results in a high rate of severe pneumonia and a potential mortality of 60% if left untreated. *F. tularensis* is difficult to identify microscopically, and physicians can be unfamiliar with its presentation. Such factors can delay proper diagnosis and treatment.

There are four subspecies of *F. tularensis (tularensis, holarctica, mediasiatica, and novicida).* Subspecies *tularensis* "type A," found primarily in North America, is the most virulent form and most likely to be used as a bioweapon. Ssp *holarctica* or "type B," the less virulent type, is found primarily in Europe and Asia.

Despite several decades of research, no vaccine for tularemia is licensed for public use. **LVS, the Live Vaccine Strain**, is a derivative of subspecies *holarctica*. When administered via scarification, LVS protects well against exposure to a large systemic dose of *F. tularensis* subsp. *tularensis*, but is much less protective against a large aerosolized challenge (the likely route of exposure in a bioterrorist attack).[1] In animal models, LVS is more protective against respiratory challenge when administered by a mucosal route; inhaled or ingested LVS is quite virulent, however, creating a barrier to its licensure.

Developing an improved tularemia vaccine is important for several reasons:[1] A limited number of antibiotics are effective in treating tularemia; resistance to these antibiotics can be bioengineered.[2] Diagnosis takes time and thus antibiotic treatment is sometimes delayed.[3] The existence of an effective vaccine would dissuade those who seek to develop tularensis as a bioweapon.[4] If *F. tularensis* were used as a bioweapon, the event could easily exhaust antibiotics supplies and exceed the capacity of the healthcare infrastructure.

...a tularemia vaccine that stimulates CD4+ and CD8+ T cells responses and the production of IFN-γ, TNF-α, and IL-12 should protect against tularemia.

F. tularensis is an intracellular pathogen that infects macrophages, dendritic cells, neutrophils, and nonphagocytic cells including hepatocytes and endothelial cells.[2] Our understanding of its virulence mechanisms derives primarily from studies of macrophages infected *in vitro.*[3,4] Following uptake by macrophages, the bacteria reside in late phagosomes where acidification is blocked and the organisms survive.[3,4] Subsequently, the bacteria enter the cytoplasm and are eventually released from apoptotic cells thus permitting infection of new host cells.[5,6]

Correlates of Immunity

Neither innate nor adaptive immunity to tularemia is well-understood. Some studies suggest that *F. tularensis* is poorly recognized by the innate immune system allowing the bacterium to evade early recognition by the host.[7] In the absence of a robust innate response, it is the primary function of the adaptive immune system to respond to infection. Although some data suggest the possible role of humoral immunity, evidence gathered from both human and animal studies described in more detail below indicates that **cell-mediated immunity (CMI)** is required for protection.

Humoral immunity. The role of antibodies in resistance to tularemia is currently disputed. Passive transfer of serum from immune to naïve immuno-competent mice confers partial protection against LVS challenge.[8-10] These studies, however, demonstrated no protection against subspecies *tularensis*. Rather, it appears that CMI constitutes the major defense mechanism against *F. tularensis*, as it does for other intracellular bacterial pathogens.

Cell-mediated immunity. The obligate role of T cells in immunity to *F. tularensis* was largely demonstrated in animal models. Passive transfer of splenic T cells from immune mice to nonimmune recipients confers resistance to challenge with *F. tularensis.*[11,12]

The contributions of CD4+ and CD8+ T cells to host defenses depend upon the subspecies of *F. tularensis* studied. LVS-immunized, CD4 *or* CD8 T cell-depleted mice survive LVS challenge, but do not clear LVS infection.[12,13] In contrast, both CD4+ *and* CD8+ T cell populations are required to survive challenge with subspecies *tularensis*, particularly when the challenge is administered mucosally, the probable route of infection in the event of a deliberate dispersal.[12,13]

Interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) are essential factors in primary host defenses to systemic tularemia infections.[14,15] It is speculated that IFN-γ and TNF-α synergize to promote nitric oxide production and to regulate iron homeostasis and pH, thereby limiting *F. tularensis* survival within phagosomes.[15] In additional studies, both IFN-γ and IL-12 were strictly required for protection; mice deficient in IFN-γ or IL-12 succumbed to LVS doses that were sublethal for wild-type mice.[16] Thus, a tularemia vaccine that stimulates CD4+ and CD8+ T cell responses, and

the production of IFN-g, TNF-a, and IL-12 should protect against tularemia.

Existing Experimental Vaccines

Although an attenuated **Live Vaccine Strain (LVS)** (subspecies *holarctica)* exists, it is not licensed due to safety and manufacturing issues. The main concerns relate to the fact that the genetic nature of the attenuation, the identity of its protective antigens, and the immunological basis for its efficacy are largely unknown. Hence, the demand for a safer, better understood vaccine of equal or greater efficacy. Indeed, a licensable tularemia vaccine must have an extremely favorable risk to benefit ratio due to the low probability of pathogen exposure.

Three different approaches have been taken to developing a safe, effective tularemia vaccine: killed whole cell, live-attenuated and subunit vaccines.

Killed vaccines

Killed, whole-cell vaccines prepared as heat- or chemical-killed formulations afford insufficient levels of protection in humans, as well as in animal models.[17] No research on killed whole-cell vaccines has been reported in the past decade. Using a variation on this approach, Cerus Corporation is developing a vaccine against *F. tularensis* with its **Killed but Metabolically Active (KBMA)** vaccine platform, a technology that utilizes non-replicating bacteria to elicit an immune response. However, the KBMA platform has not been demonstrated safe in humans. Moreover, given the current state of vaccine research, good manufacturing practice standards would be difficult to implement and public acceptance of a killed vaccine seems highly unlikely.

Live Vaccines

Live attenuated vaccines have long been considered a reasonable prospect for a tularemia vaccine given the promise LVS showed in reducing laboratory-acquired infections.[18] An attenuated strain needs to demonstrate protective efficacy and the limited ability to survive, replicate, and cause disease. Like *holarctica*, subspecies *novicida* is a live vaccine candidate due to its demonstrated low virulence in humans. However, the sequences of *novicida* and *holarctica* differ significantly from the sequence of ssp *tularensis*, raising concerns about their ability to induce protective immunity against this, the most virulent of the subspecies.[19] Recent efforts to develop an attenuated vaccine have targeted virulence and metabolic genes to create weakened mutants. The challenge of this approach is in predicting the degree of attenuation that results from gene inactivation, that is, in obtaining the correct balance in an attenuated organism that can elicit protection, but not cause disease.

...a licensable tularemia vaccine must have an extremely favorable risk- benefit ratio due to the low probability of exposure to the pathogen.

Subunit Vaccines

A third approach to immunizing against *F. tularensis* involves the development of a subunit vaccine. Such vaccines usually depend upon a single antigen, or a set of antigens to provoke an immune response. Immunization with *F. tularensis* lipopolysaccharide or LPS , one of the few protective antigens identified, is ineffective in preventing infection by highly virulent strains.[20] Undoubtedly, this is due in part to the failure of LPS to induce the T cell-mediated immunity necessary for protection.[21] Antigens reactive with T cells derived from patients exposed to tularemia have been identified as potentially protective.[22,23,24] Only three of these antigens have been assayed for protection in mice; all were immunogenic, but none alone protected against challenge.[19, 25, 26]

Conceivably, no single antigen will provide sufficient protection against tularemia, necessitating the development of a subunit vaccine comprised of more than one antigen. Alternatively, it may be possible to construct a low cost subunit vaccine composed of many T cell epitopes thus utilizing the protective elements associated with a large number of antigens.

T-cell epitopes

T cell epitopes are critical mediators of cellular immunity derived from fragments of a pathogen's protein antigens. Two distinct antigen-processing pathways (MHC class I and class II) give rise to two different T cell responses: a CD4+ helper T cell response and a CD8+ cytotoxic T cell response. After initial exposure to the pathogen, memory T cells are generated that respond more rapidly and efficiently upon subsequent exposure.

Epitope-Driven Vaccines

Because epitopes provide the essential information needed to trigger a protective immune response, epitope-driven vaccines represent a logical approach to vaccine development. An epitope-based tularemia vaccine represents an appealing alternative in light of the difficulties associated with killed, attenuated, and whole-subunit approaches. Researchers carrying out epitope-driven vaccine studies in a variety of models have demonstrated protective immune responses in animals vaccinated with single peptide epitope.

Epitope-driven vaccines offer a distinct advantage over vaccines encoding whole protein antigens. That is, multiple epitopes derived from a panel of antigens can be packaged into a relatively small delivery vehicle.

Notably, the field of epitope-driven vaccines for infectious diseases is relatively young. Only a few epitope-driven vaccine constructs for microbial pathogens have reached Phase I or II clinical trials in humans. By contrast, a number of epitope-driven cancer vaccines have successfully passed preclinical testing and are currently in or are entering Phase I/II clinical trials.

There are a number of reasons that a given pathogen-directed, epitope-based vaccine might fail to reach clinical trials or protect humans: (1) the limited number of epitopes expressed by the vaccine (i.e., poor payload quantity); (2) limited conservation of epitopes (leading to limited coverage of variant clinical isolates) (3) the limited HLA population coverage (i.e., poor payload quality); (4) suboptimal vaccine delivery; and/or (5) the dearth of suitable animal models.

Epitope Mapping Methods

Immunoinformatics uses computational algorithms to efficiently analyze large datasets, such as whole genomes, to *a priori* identify immunogenic epitope sequences. A computational approach pro-

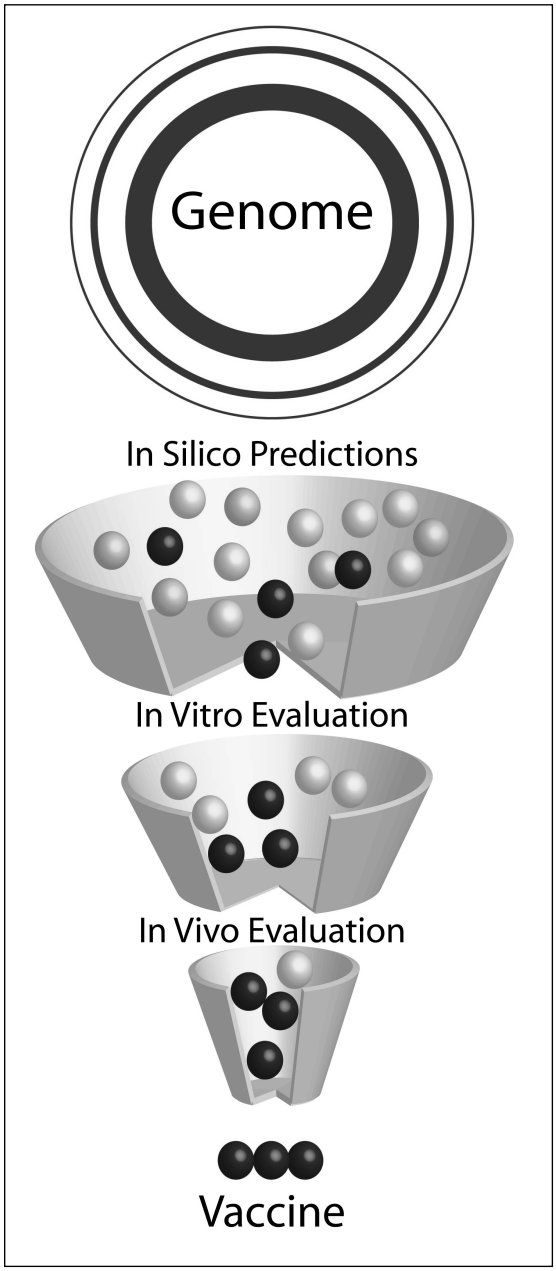

Figure 1. Steps to triaging sequences for inclusion in a genome-derived, epitope-driven vaccine. 1) Computational tools are used to identify genes that encode proteins with vaccine-suitable characteristics. 2) In silico. Immunoinformatics tools are then used to search protein sequences for short, linear putative T cell epitopes. 3) In vitro. Candidates are synthesized as peptides and evaluated for MHC binding and antigenicity. 4) In vivo. Prototype epitope based vaccines are evaluated for immunogenicity and protection in mice transgenic for human MHC.

vides an efficient and reliable alternative to conventional epitope mapping, which uses overlapping synthetic peptides.

Epitope Vaccine Formulation

DNA-based vaccination induces broad humoral and cellular immune responses in a number of preclinical models of disease. Immune responses to DNA vaccines in chimpanzees and humans have generally not been as robust as that seen in mice. Nevertheless, macaques have been successfully immunized against both *P. falciparum* and HIV.[27] DNA vaccination is a reasonable approach to developing a *F. tularensis* vaccine since it is a simple method to elicit both MHC class I and class II-restricted CMI responses to multiple epitopes. DNA vaccination is particularly effective against intracellular bacteria.[28] Large-scale synthesis, rapid scale up and long shelf-life are additional advantages to DNA vaccines.

Genomics & Antigen discovery for *F. tularensis*

We have been actively developing an epitope-based tularemia vaccine combining computational immunology with *in vitro* and *in vivo* validation. The starting point of our vaccine was the fully annotated *F. tularensis* subsp. *tularensis* genome published in by Larsson et al in 2005.[27]

The genome contains 1603 ORFs, 523 of which encode 'hypothetical proteins' with no known function. In addition, 20% of the genes are unique to *F. tularensis* and not found in related subspecies. To date, no group of proteins has been shown to protect against active tularensis infections. We chose to analyze proteins that were (1) putatively secreted or (2) that had vaccine-suitable characteristics. We predicted MHC class I and class II epitopes and confirmed that they were recognized by individuals previously infected with *F. tularensis*.[27]

Immunogenicity and Challenge studies

The genetic sequences that encode the MHC class II epitopes identified were incorporated into a multi-epitope DNA vaccine that was boosted with peptides formulated in liposomes. The immunogenicity and protective efficacy of this prime-boost vaccine was evaluated in an HLA transgenic mouse model. The vaccine was 57% protective against 5xLD50 *F. tularensis* LVS inoculated intratracheally. Given the requirement of CD8+ T cells for maximum immunity, it is remarkable that a vaccine comprised only of CD4 epitopes achieved this level of protection. Furthermore, LVS (ssp holarctica derivative) constitutes a heterologous challenge for these subspecies tularensis-derived vaccine epitopes. High virulence challenge (ssp tularensis) studies will begin in 2007. To provide increased protection, we will add CD8+ epitopes, and optimize both vaccine formulation and mucosal delivery.

Summary

F. tularensis is among of the most virulent pathogens known, yet it remains poorly understood. Correlates of protection involve robust CD4+ and CD8+ T cell responses, and the production of IFN-γ, TNF-α, and IL-12. Novel approaches may be required to develop a safe vaccine that achieves these correlates.

In contrast to other types of vaccines, epitope-based vaccines combine targeted biologic activity with the practical advantages of platform independence, scalable synthesis and manufacturing. These advantages, coupled with the proof of principle achieved with an epitope-based tularemia vaccine, suggest that this approach might be applied more widely to develop vaccines against other pathogens, intracellular bacteria most notably.

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Julie McMurry, MPH, is Senior Project Manager at EpiVax, Inc.

Leonard Moise, PhD, is Director of Vaccine Development at EpiVax, Inc.

Stephen H. Gregory, MD, is Associate Professor of Medicine, The Warren Alpert Medical School of Brown University.

Anne S. De Groot, MD, is President and CEO at EpiVax, and Associate Professor of Medicine, The Warren Alpert Medical School of Brown University.

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Correspondence:

Julie A. McMurry, MPH
EpiVax, Inc.
164 Clifford St.
Providence, RI 02903
Phone: (401) 272-2123
e-mail: jam@epivax.com

Artist: Eric Avery, MD

HIV Vaccine Update: Recent Developments and Current Trials

Michelle Lally, MD, MSci, Kaitlin Lemei, Kenneth Mayer, MD

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Kenneth Mayer, MD, has no financial interests to disclose.

Over 42 million people are living with HIV throughout the world. In the last decade, the prevalence of HIV infection worldwide among pregnant women rose from less than one percent to 25% in 2003.[1] Stover et al. predict at least 45 million new infections between 2002 and 2010.[2] This figure may be conservative; the National Intelligence Council estimates at least 50 million new cases by 2010 in only five countries – China, Ethiopia, India, Nigeria, and Russia.[3] Our best hope for controlling the HIV/AIDS epidemic is the development of an HIV vaccine.

What the HIV Vaccine Can and Cannot Do

Multiple HIV vaccine candidates are being tested in various phase clinical trials. All these candidates are man-made; there is no chance of developing an HIV infection from an HIV vaccine. Candidate vaccines tested to date all share favorable safety profiles. An HIV vaccine can cause a "false-positive" HIV test. That is, both a screening HIV ELISA and a confirmatory Western Blot can give the appearance of HIV infection due to the antibodies generated by the vaccine. A testing algorithm that may include HIV viral load assays is used to distinguish between vaccine-induced seropositivity and true HIV infection.

How an Initial HIV Vaccine May Work

An initial HIV vaccine will likely not prevent HIV infection. Instead, a person who is vaccinated against HIV might still become HIV-infected by sexual or blood exposure. It is thought that the vaccine will induce cellular immunity that will allow for a decreased viral load peak and/or set point, and will, therefore, significantly delay progression to AIDS. These concepts are being tested in ongoing/upcoming "proof-of-concept" trials. Within the next 5 years, at the conclusion of these trials, we will know whether an HIV vaccine can significantly alter the course of HIV infection. Concurrent scientific efforts are being devoted to the development of an HIV vaccine that will induce neutralizing antibodies in order to prevent initial HIV infection. A final HIV vaccine may work by stimulating both neutralizing antibody and cellular immunity.

An initial HIV vaccine will likely not prevent HIV infection.

Where HIV Vaccines are Being Tested

Multiple organizations are working together to develop an HIV vaccine. The **Partnership for AIDS Vaccine Evaluation (PAVE)** is a voluntary consortium of United States Government agencies and funded organizations that conducts HIV vaccine clinical trials.[4] PAVE includes the **HIV Vaccine Trials Network** (HVTN), the United States Military HIV Research Program (USMHRP), the **International AIDS Vaccine Initiative (IAVI),** and the **Centers for Disease Control and Prevention (CDC).**[5]

The HVTN, under Principal Investigator Dr. Larry Corey, is the largest clinical trial program participating in the development and testing of an HIV vaccine worldwide. Trial units are located in twenty-seven cities on four continents. HVTN is supported by the **National Institute of Allergy and Infectious Diseases (NIAID)** division of the United States **National Institutes of Health (NIH).**[6]

The **United States Military HIV Research Program (USMHRP)** is a multi-faceted research organization that not only conducts pre-clinical through Phase III efficacy trials, but also researches diagnostic and immunologic techniques critical for vaccine development. The USMHRP, under director Nelson Michael, M.D., Ph.D., is based at the Division of Retrovirology at the **Walter Reed Army Institute of Research (WRAIR), US Army Medical Research and Materiel Command (USAMRMC).** The USMHRP, partnered with the not-for-profit **Henry M. Jackson Foundation (HJF)** for the Advancement of Military Medicine (HJF), conducts research in Thailand, Kenya, Uganda, Tanzania, Cameroon, Nigeria, and other locations.[7]

IAVI is a global not-for-profit partnership founded in 1996 to accelerate the development of an HIV vaccine. IAVI is partnered with over 40 academic, biotechnology, pharmaceutical, and government institutions. IAVI trials are located primarily in Africa and India, and are often achieved through partnerships with the **Kenya AIDS Vaccine Initiative (KAVI),** Rwanda's Project San Francisco, the **Uganda Virus Research Institute (UVRI),** the **Indian Council of Medical Research (ICMR),** and the **Zambia Emory HIV Research Project (ZEHRP).**[8]

The CDC HIV Vaccine Unit, in the Epidemiology Branch of the Divisions of HIV/AIDS Prevention, works to develop new models for the evaluation of HIV vaccine candidates, as well as establish future HIV vaccine trial sites in Cameroon, Kenya, and Thailand. The CDC HIV Vaccine Unit joined the NIH, the Department of Defense, and HVTN in 2003 to form PAVE.[9]

Local Participation in HIV Vaccine Trials

Over the past decade, over 200 Rhode Islanders have participated in twenty Phase I and II HIV Vaccine Trials as listed in Table 1. These trials have collectively contributed to the scientific body of research informing HIV vaccine development.

Table 1: Rhode Island Participation in HIV Vaccine Trials

Trial	Funding Source	Years	Number Enrolled
Vaccine Prep Study	HIVNET	1994-1998	260 at-risk women
HIVNET	NIAID	1995-1997	12 at-risk women, 1 MSM
VAXGEN	VAXGEN	1999-2001	33 at-risk women, 22 MSM
HVTN 203	DAIDS	2001-2003	1 at-risk woman, 4 MSM
HVTN 039	DAIDS	2002-2004	4 women
HVTN 041	DAIDS	2002-2004	3 women
HVTN 048	DAIDS	2003-2005	2 women, 1 man
HVTN 052	DAIDS	2004-2005	1 woman, 1 man
HVTN 049	DAIDS	2004-2006	4 women, 2 men
HVTN 057	DAIDS	2005-2006	1 woman
HVTN 042	DAIDS	2004-2007	9 women, 2 men
HVTN 044	DAIDS	2004-2007	4 women, 4 men
HVTN 063	DAIDS	2005-ongoing	1 woman, 2 men
MERCK 007	MERCK	2001-ongoing	5 women, 11 men
HVTN 050/MERCK 018	DAIDS	2003-ongoing	3 women, 2 men
MERCK 016	MERCK	2003-ongoing	8 women, 8 men
MERCK 019	MERCK	2003-ongoing	4 women, 7 men
HVTN 204	DAIDS	2005-ongoing	4 women, 10 men
MERCK 022	MERCK	2005-ongoing	4 women, 5 men
MERCK 027	MERCK	2006-ongoing	5 women, 9 men
MERCK 001	MERCK	2005-ongoing	6 women, 3 men

Proof Of Concept Clinical Trials

At the forefront in HIV vaccine development is the Merck & Co./HVTN 502/503 "proof-of-concept" vaccine trial, a current Phase IIb trial, which began enrollment in December, 2004.[10] The Merck/HVTN trial is a multi-center, randomized, double-blind, and placebo-controlled study. The trial will enroll approximately 3,000 volunteers; over the span of approximately six months. Participants will receive three injections, either containing a placebo saline solution, or three doses of the investigational vaccine.[11] At each visit, individuals will receive risk-behavior counseling. Over the next four years or so, participants will be tested for HIV infection every six months.[12]

Due to the fact that the trial attempts to enroll high-risk individuals, it is expected that a portion of study participants will be exposed to, and contract HIV. Through frequent testing, the study will attempt to determine whether the study vaccine product helps to prevent infection and/or lowers the level of HIV in the blood of individuals compared to the placebo group.[12]

Inclusion criteria for participation includes HIV-negative adults between the ages of 18 and 45, considered to be "high-risk" for HIV infection as determined by reported sexual behavior.[10] Investigators are making special efforts to enroll high-risk women. Potential participants must meet medical and non-medical criteria for entry.

This proof-of-concept trial is designated Merck/HVTN 502 and 503 due to distinctions in the geographic areas in which the trial is taking place. In the United States (12 study sites), the trial is designated Merck/HVTN 502. The 503 trial is being conducted in Australia (1 study site), Canada (1 study site), the Dominican Republic (1 study site), Haiti (1 study site), Puerto Rico (1 study site), and Peru (2 study sites) and in early 2007, a new study site in South Africa was added.[13]

Addition of the 503 study sites has drawn attention to a possible obstacle to the efficacy of the vaccine product, namely the potential for the virus to evade immune responses because of the genetically distinct subtypes or clades that have arisen in different parts of the world. The vaccine product being tested is based on Clade B HIV.[13] In South Africa the predominant HIV subtype is Clade C. The inclusion of South Africa in this proof-of-concept trial will allow for examination of variable efficacy in Clade B and C geographic areas. The differing Clade types of the HIV virus is a universal challenge for HIV vaccine developers; it is not clear if cross-clade immunity will be achieved.

The Merck/HVTN 502/503 trial is a "proof-of-concept" trial.[14] The concept that the Merck/HVTN 502/503 trial attempts to prove is that through introduction of several HIV genes, the body's immune system can be trained to recognize and eliminate cells displaying signs of HIV infection. This recognition and destruction could potentially slow or prevent HIV infection.

The investigational vaccine being tested in the Merck/HVTN 502/503 trial is MRKAd5 HIV-1 gag/pol/nef. There are two parts to the vaccine product: the adenovirus vector that carries an HIV gene insert. The vector, adenovirus type 5 (Ad5), is non-replicative. The HIV genetic insert contains genes *gag*, *pol*, and *nef*. In Phase I studies the vaccine has been demonstrated to produce an immune response.[14]

Though promising, the Merck/HVTN 502/503 study vaccine product will not be enough to fight the HIV epidemic alone. "These cellular-immunity–producing vaccines are primarily blunting mechanisms to dampen the progression of infection," said Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Disease, "but if they do work, we will be scrambling to produce one in combination with a vaccine that would induce neutralizing antibodies to protect against infection. This should be seen as a first step rather than an end point. No one is relying on these vaccines alone."[15]

In a "proof-of-concept" trial similar to Merck/HVTN 502/503, PAVE is planning a Phase IIB study, (PAVE 100), that may begin enrollment as soon as late 2007. PAVE 100 will enroll approximately 8,500 volunteers across the Americas, and East and Southern Africa at study sites sponsored

by HVTN, the (USMHRP, the IAVI, and the CDC.[5] PAVE 100 will test whether the Vaccine Research Center DNA/rAd5 prime-boost vaccination regimen prevents HIV infection, or slows progression of the virus. The DNA/rAd5 study vaccine product is a recombinant adenoviral vector vaccine that serves as a booster to a primary multi-clade DNA plasma vaccine.[5] If effective, the PAVE 100 trial will provide researchers with immune correlates of protection using newly developed immune assays, improving HIV vaccine prospects across the board.[5]

Development of an HIV vaccine faces both scientific and economic difficulties. "HIV is astounding," says Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Disease. "Of the 60-million-plus people who have been infected with it, there's not a single documented case of someone who has ultimately cleared the infection from his or her body. The initial infection wipes out specific immune responses, the virus permanently integrates into the host cell's chromosome and establishes what appears to be a permanent reservoir of infected cells, and…the antigens that induce broadly reactive neutralizing antibodies do not appear to present themselves in a way that allows the host to elicit a protective immune response."[15] The development of an HIV vaccine struggles not only against multiple clade strains of the HIV virus and other scientific barriers, but also against inadequate funding. In 2005, Mitchell Warren, executive director of the AIDS Vaccine Advocacy Coalition in New York, stated: "Last year, about $680 million, primarily from the public sector but in smaller amounts from the private sector and philanthropy, went toward the development of AIDS vaccines—less than 1% of the total global spending on health product research and development."[15] In spite of these challenges, research continues locally, domestically, and internationally to find an HIV vaccine.

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Michelle Lally, MD, MSc, is Assistant Professor of Medicine, The Warren Alpert Medical School of Brown University.

Kaitlin Lemei, is a Research Assistant, The Miriam Hospital.

Kenneth Mayer, MD, is Professor of Medicine and Community Health, The Warren Alpert Medical School of Brown University.

Correspondence:
Michelle Lally, MD, MSc
The Miriam Hospital
164 Summit Avenue
Providence, RI 02906
Phone: (401) 793-4770
e-mail: mlally@lifespan.org

Artist: Eric Avery, MD

Rotavirus Vaccines – Success After Failure

Penelope H. Dennehy, MD

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Rotavirus is the most common cause of severe diarrhea disease in infants and young children worldwide. About 600,000 children die every year from rotavirus, primarily in developing countries in South Asia and sub-Saharan Africa.[1] Virtually all children worldwide have been infected by the time they reach 2 to 3 years of age. Most symptomatic episodes occur between 3 months and 2 years of age with a peak incidence between 7 and 15 months.

Rates of rotavirus illness among children in industrialized and less developed countries are similar, indicating that clean water supplies and good hygiene have little effect on virus transmission and further improvements in water or hygiene are, therefore, unlikely to prevent the disease.[2] In view of the high burden of rotavirus disease, safe and effective rotavirus vaccines are urgently needed, particularly in developing countries.

Virology

Seven rotavirus groups (A to G) are described; only groups A, B and C cause human infections. Group A rotaviruses are the most important causes of gastrointestinal infections in humans and are, thus, the most important from a public health perspective. They are targets for vaccine development.

The rotavirus particle is composed of three protein shells: an outer capsid, an inner capsid and an internal core that encases the 11 segments of double-stranded RNA. When mixed infections with different rotavirus strains occur, the gene segments may reassort independently, producing progeny virus of mixed parentage, which is a source of viral diversity.

Rotaviruses contain two structural outer capsid proteins: VP7, the glycoprotein (G protein), and VP4, the protease-cleaved protein (P protein). These two proteins define the serotype of the virus and are considered critical to vaccine development because they are targets for neutralizing antibodies which may provide protection.[3] Because the two gene segments that encode these proteins can segregate independently, a typing system consisting of both P and G types has been developed. It has been difficult to characterize the P types by traditional methods of virus neutralization, so molecular methods have been used to define genotype based on sequence analysis. Since these genotypes correlate well with known serotypes, the genotypes are tentatively designated in brackets (e.g., P1A [8]). Strains are generally designated by their G serotype specificity (serotypes G1-4, G9).

Human rotaviruses bearing VP7 G serotypes G1-G4 and G9 and VP4 P genotypes P1B[4], P2A[6] and P1A[8] are predominant worldwide.[4] P1A[8]G1 is the globally predominant strain, representing over 70% of rotavirus infections in North America, Europe and Australia, but only about 30% of the infections in South America and Asia, and 23% in Africa.[4] Other frequently isolated strains are P1A[8]G3, P1B[4]G2, and P1A[8]G4. G9 strains have been emerging since the late 1990s and now constitute the predominant strains in some parts of Asia and Africa. G8 strains are more frequent in Africa, and in South America, G5 strains have emerged. The distribution of the VP4 P2A[6] antigen varies according to region. P2A[6] strains now constitute over 50% of the circulating strains in Africa, whereas P1A[8] is associated with most rotavirus strains from the rest of the world.[5] The implementation of effective rotavirus vaccines will need to take into account the geographical variation of rotavirus strains.

Natural Protection

Longitudinal studies have demonstrated that naturally acquired rotavirus infections provide protection against rotavirus disease upon reinfection. This protection is greatest against the most severe disease outcomes. Although children can be infected with rotavirus several times during their lives, initial infection after age 3 months is most likely to cause severe diarrhea and dehydration. In a study in Mexican children a single natural infection, either symptomatic or asymptomatic, protected 40% of children against any subsequent infection with rotavirus, 75% against diarrhea caused by a subsequent rotavirus infection, and 88% against severe rotavirus diarrhea.[6] Second, third, and fourth infections conferred progressively greater protection. In this study no child with two previous infections subsequently developed severe rotavirus diarrhea.

Despite the ability of natural rotavirus infection to protect against subsequent severe disease, the immune correlates of protection from rotavirus infection and disease are not completely understood. Both serum and mucosal antibodies are probably associated with protection from disease. VP4 and VP7 were found to be independently capable of raising antibodies that neutralize virus infectivity *in vitro* and protect against rotavirus challenge *in vivo*. The first infection with rotavirus elicits a predominantly homotypic, serum-neutralizing antibody response to the virus and subsequent infections elicit a broader, heterotypic response. However, in vaccine studies, correlation between serum antibody and protection has been poor.[7] Because a reliable immune correlate of protection has not been found, each new vaccine candidate must be tested in large field trials for efficacy.

Goals for a Rotavirus Vaccine

A realistic goal for a rotavirus vaccine is to duplicate the degree of protection against disease that follows natural infection. Therefore, vaccine program objectives include the prevention of moderate to severe disease but not necessarily mild disease associated with rotavirus. An effective rotavirus vaccine will not only decrease the number of children admitted to the hospital with dehydration or seen in emergency departments but should also decrease the burden on the practicing primary care practitioner, by decreasing the number of office visits and telephone calls.

Rotavirus Vaccines

All licensed rotavirus vaccines are live, orally administered vaccines that aim to mimic the protection seen after naturally occurring rotavirus infection. Attenuation of rotaviruses for use as oral vaccines may be achieved in several ways. The most extensively evaluated approach is based on the ''Jennerian'' concept, involving immunization of infants with animal rotaviruses that are considered naturally attenuated for humans.[8] More recently, human rotaviruses attenuated by passage in cell culture have been developed and tested.[9] Finally, rotaviruses recovered from asymptomatic human neonates that may be naturally less virulent are being developed as oral vaccine candidates.[10]

Monovalent Animal Rotavirus Vaccines

Research to develop a safe, effective rotavirus vaccine began in the mid-1970s when investigators demonstrated that previous infection with animal rotavirus strains protected laboratory animals from experimental infection with human rotaviruses. Researchers thought that live animal strains which were naturally attenuated for humans, when given orally, might mimic the immune response to natural infection and protect children against disease. Three nonhuman rotavirus vaccines, two bovine rotavirus strains, RIT 4237 (P[1]G6) and WC3 (P[5]G6), and simian (rhesus) RRV strain (P[3]G3) were studied.[11-13] These vaccines demonstrated variable efficacy in field trials and gave particularly disappointing results in developing countries. Currently a lamb-derived monovalent (P[12]G10) live-attenuated oral vaccine, developed by the Lanzhou Institute of Biomedical Products, is licensed and used in China. The efficacy of this vaccine is not known as it has not been tested in a controlled phase III trial.

As a result of the inconsistency of protection from monovalent animal rotavirus-based vaccines, vaccine development efforts began using either naturally attenuated human rotavirus strains or reassortant rotavirus strains bearing a human rotavirus gene for the VP7 protein, together with the other 10 genes from an animal rotavirus strain.[14]

Live Reassortant Virus Vaccines

The next generation of vaccines was formulated to include more than one rotavirus G-serotype to provide heterotypic as well as homotypic immunity. The ability of rotaviruses to reassort during mixed infections *in vitro* allowed the production of reassortant vaccines, termed the ''modified Jennerian'' approach. Reassortant viruses contain some genes from the animal rotavirus parent and some genes from the human rotavirus parent. Because both VP4 and VP7 were thought to be important in protection, human-animal reassortant rotaviruses for use as vaccines include either human VP7 or VP4 genes to provide protective immune responses.

The US Food and Drug Administration licensed PRV in February 2006.

The first multivalent live oral reassortant vaccine developed, RRV-TV (Rotashield™), contained a mixture of 4 virus strains representing G types G1 to G4: three rhesus-human reassortant strains containing the VP7 genes of human serotype G1, G2 and G4 strains were substituted for the VP7 gene of the parent RRV, and the fourth strain comprised serotype G3 of RRV.[15] This vaccine was extensively evaluated in field trials in the US, Finland, and Venezuela and proved highly effective (80-100%) in preventing severe diarrhea due to rotavirus in each of these settings.[16-19] Due to the proven efficacy of the RRV-TV vaccine in preventing severe diarrhea and hospitalization caused by rotavirus, this vaccine was licensed in August 1998 for routine use in children in the United States at 2, 4 and 6 months of age.

After inclusion of this vaccine in the immunization schedule in the US, and immunization of over 600,000 infants in the first 9 months of the program, several cases of vaccine-associated intussusception were reported. The period of greatest risk of intussusception was shown to be 3 to 10 days after the first dose.[20] Although the true overall incidence of this adverse event proved difficult to assess, a group of international experts suggested a consensus rate of 1 per 10,000 vaccinated infants.[21] The pathogenic mechanisms involved in intussusception following vaccination are unknown.

As a consequence of this rare but potentially dangerous adverse effect, the manufacturer withdrew the vaccine from the US market nine months after its introduction. Unfortunately, the vaccine was not evaluated in terms of risk-benefit for children in developing countries, as the ongoing trials in Asia (Bangladesh and India) and Africa (Ghana and South Africa) were stopped at that time. Although still licensed, the vaccine has not been subsequently tested or licensed in other parts of the world.

Merck Research Co has developed a pentavalent human-bovine (WC3) reassortant (Gl, G2, G3, G4 and P1A[8]) live-attenuated, oral vaccine, RotaTeq™ It is administered in 3 doses at 1 to 2 month intervals beginning at 6 to12 weeks of age. This pentavalent vaccine (PRV) was tested in a Phase III trial in 11 countries, with the United States and Finland accounting for more than 80% of all enrolled subjects.[22] The trial included more than 70,000 children and was designed primarily to evaluate vaccine safety with respect to intussusception, but also to evaluate the efficacy of the vaccine with respect to the severity of illness and the number of hospitalizations or emergency department visits for rotavirus gastroenteritis.

During a 42-day period after each dose, there was no increase of intussusception among recipients of vaccine compared with placebo. Six vaccinated patients and five placebo recipients developed intussusception in this period, demonstrating no increased risk of intussusception in vaccinees. Among vaccine recipients, there were no confirmed cases of intussusception within the 42-day period after the first dose, which was the period of highest risk for the previously licensed RRV-TV vaccine. In addition, no evidence of clustering of cases of intussusception was observed within a 7- or 14-day window after immunization for any dose. The overall rate of intussusception was consistent with the expected background rate of intussusception.

The clinical efficacy of PRV against rotavirus gastroenteritis of any severity was 74%. Against severe rotavirus gastroenteri-

tis, however, the vaccine demonstrated efficacy of 98%. PRV also proved strongly efficacious in preventing rotavirus gastroenteritis of any severity caused by the predominant G1 serotype (75% efficacy) and the G2 serotype (63% efficacy). There was a trend toward efficacy for the remaining serotypes, but the number of subjects was too small to show statistical significance (G3 83 % efficacy, G4 48 % efficacy, and G9 65 % efficacy). The efficacy of PRV in reducing the number of office visits for rotavirus gastroenteritis and in reducing the number of emergency department visits and hospitalizations for rotavirus gastroenteritis was evaluated. PRV reduced the incidence of office visits by 86%, emergency department visits by 94%, and hospitalizations for rotavirus gastroenteritis by 96%.

The US **Food and Drug Administration (FDA)** licensed PRV in February 2006 by for use among US infants, is routinely recommended as a 3 dose schedule at 2, 4 and 6 months of age.[23] As of April 2007 applications for licensure have been filed in more than 100 countries including Europe and Latin America. Through its partnership with PATH, Merck plans to conduct clinical trials in Africa and Asia.

Another multivalent bovine-human reassortant vaccine has been independently developed by the National Institute of Allergy and Infectious Diseases. Phase II data showed a good immune response and no adverse interference with concomitantly administered childhood vaccines,[24] A non-exclusive license for production of the vaccine candidate is being negotiated with vaccine producers in Brazil, China and India.

Finally, two naturally occurring human-bovine, neonate-derived, reassortant strains (116E and 1321) are under development in India in a consortium with partners from the United States including CDC and the Children's Vaccine Program at PATH.[25] These strains have a P[10]G9 and P[11]G10 antigenic makeup, respectively.

Live Attenuated Human Rotavirus Vaccines

A live, attenuated human rotavirus G1, P1A, vaccine (strain 89-12) was originally developed in Cincinnati, OH, by tissue culture passage of a wild-type human rotavirus isolate.[9] This vaccine is a G1 P1A[8] strain and thus represents the most common human rotavirus strain seen worldwide. The vaccine was further developed by Avant Immunotherapeutics and licensed to GSK Biologicals, who have further modified the strain. The resulting vaccine RIX4414 (Rotarix®) underwent initial trials in Finland which showed safety, immunogenicity, and efficacy. The assessments revealed that RIX4414 was clinically more attenuated than the parent strain 89-12. A large scale, double blind, placebo-controlled trial of more than 63,000 infants enrolled in 11 Latin American countries and Finland was done to confirm that the vaccine did not cause intussusception.[26] The vaccine was administered at 2 and 4 months of age. During a 31-day period after each dose, there was no increase of intussusception among recipients of vaccine compared with placebo. Six vaccinated patients and seven placebo recipients developed intussusception in this period, confirming the lack of a causal association.

A subset of 20,000 infants in this large trial was followed for efficacy.[26] The results demonstrated a high protection rate (85%) against severe rotavirus gastroenteritis and 100% protection against the most severe dehydrating rotavirus gastroenteritis episodes. The vaccine also proved strongly efficacious in preventing rotavirus gastroenteritis of any severity caused by the predominant G1 serotype (92% efficacy) and for serotypes G3 G4 or G9 (88% efficacy). Efficacy against the G2 serotype was not significant in this large trial (41% efficacy).

Rotarix® was first licensed in Mexico and the Dominican Republic in 2004. As of April 2007, the vaccine is licensed in about 60 countries in Europe, Latin America, Africa, and Asia. A licensure application was submitted in the United States in August 2007. In addition, Phase II clinical trials have been started under the auspices of WHO in Bangladesh and South Africa to investigate issues pertinent to developing countries such as the safety and immunogenicity of the vaccine when given concomitantly with the oral polio vaccine (OPV), or when administered to HIV-infected infants.

Neonatal strains were initially explored as vaccine candidates because they appeared to be naturally attenuated and a natural-history study had shown that asymptomatically infected neonates subsequently had a reduced frequency and severity of rotavirus diarrhea. However, a neonatal strain failed to provide protection in a small efficacy study and this approach was temporarily abandoned.[27]

A human neonatal P[6]G3 strain, RV3, developed by Bishop and colleagues in Australia, was evaluated as an oral vaccine in 3-month-old infants and found to be safe and well tolerated. A small Phase II study with three doses of the vaccine indicated relatively low immunogenicity as measured by serum IgA. However, the vaccine recipients who developed an immune response were protected against clinical disease in the following year.[10] Phase II immunogenicity studies are being planned with a higher dose of the vaccine.

Other Vaccine Approaches

Other approaches to the development of rotavirus vaccines are being pursued. Rotavirus antigens for parenteral delivery have received some attention, as virus-like particles prepared in baculovirus, as well as expressed antigens, DNA vaccines, and killed virus. These novel approaches are being pursued in animal models.

Future Challenges

Post-marketing surveillance studies are needed to monitor the vaccine impact on circulating viral strains recovered from stools in order to not only test possible vaccine selection pressure and strain replacement but also to measure the extent of cross-protection against different rotavirus serotypes, including serotype G9, which is becoming increasingly important across Asia and Africa, and G8, which is also gaining prevalence in parts of Africa.

The World Health Organization has given high priority to the development and introduction of rotavirus vaccines for children in the developing countries. In addition, the **Global Alliance for Vaccines and Immunizations (GAVI)** is sponsoring a new public-private organization, the Rotavirus Vaccine Program at PATH, whose role is to accelerate the development and introduction of vaccines in developing countries.

Despite this support, implementation of rotavirus immunization programs in the developing world will require substantial input from the international donor community.

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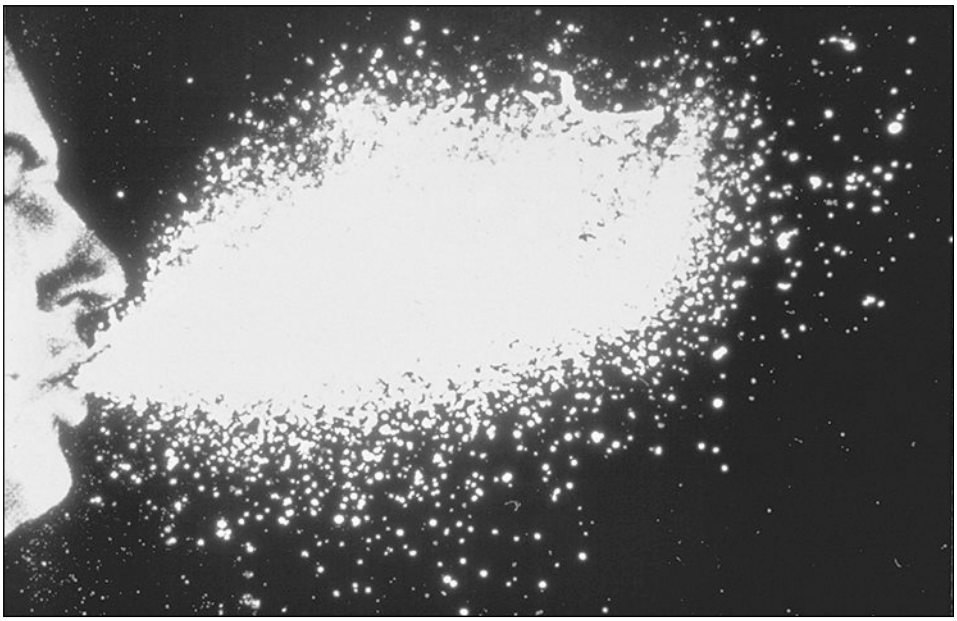
Penelope H. Dennehy, MD, is Professor of Medicine, The Warren Alpert Medical School of Brown University.

Correspondence:

Penelope H. Dennehy, MD
Division of Pediatric Infectious Diseases
Rhode Island Hospital
593 Eddy Street
Providence, RI 02903
phone: (401) 444-4298
E-mail: pdennehy@lifespan.org



CME Background Information

CME Background Information

This CME activity is sponsored by the Warren Alpert Medical School of Brown University.

Target Audience: This enduring material is designed for physicians licensed in Rhode Island.

Educational Objectives:

1) Readers will know the status of the development of a genome-derived, epitope-driven vaccine for latent tuberculosis infection.
2) Readers will describe the recent development and current trials for an HIV vaccine.
3) Readers will describe the recent HPV vaccine.
4) Readers will describe the advances in a rotavirus vaccine.
5) Readers will know recent research into the relationship of vaccines and autism..
6) Readers will know the recent advances in tularemia vaccines.

Needs Assessment/How was the need for this CME Journal determined?

Over the past four years, scientists and physicians have made startling advances in the development of vaccines. This issue will update readers on some of those advances.

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VACCINES: CME QUESTIONS

Please circle the single correct answer for each of the questions below:

1. Individuals bearing latent tuberculosis infection have a _____ chance of disease activation.
   a. 10%
   b. 15%
   c. 20%

2. The only licensed TB vaccine, BCG, reliably prevents _____.
   a. childhood TB
   b. adult pulmonary TB

3. An effective TB vaccine needs to elicit a strong T cell response.
   a. True
   b. False

4. The first HIV vaccine we have will most likely work by
   a. Preventing infection
   b. Delaying progression from HIV disease to AIDS

5. HIV Vaccine trial participants can have a false positive
   a. ELISA
   b. Western Blot
   c. HIV RNA viral load
   d. a & b
   e. All of the above

6. There is a small but significant risk of contracting HIV disease from an HIV vaccine.
   a. True
   b. False

7. The virus-like particle HPV vaccine is a _____ vaccine.
   a. live, attenuated
   b. killed, inactivated
   c. subunit

8. The licensed quadrivalent HPV vaccine is expected to prevent ____ of cervical cancers.
   a. 70%
   b. 80%
   c. 90%

9. Continued development of HPV vaccines is aimed at _____ HPV infection.
   a. preventing
   b. treating
   c. both preventing and treating

10. The goal of rotavirus vaccine program is _____.
    a. complete disease prevention
    b. prevention of mild disease
    c. prevention of moderate to severe disease

11. The adverse effect that led to withdrawal of the first licensed rotavirus vaccine from the market was _____.
    a. erythema
    b. intussusception
    c. anaphylaxis

12. The two rotavirus vaccines available on the world market today are _____ vaccines.
    a. Live
    b. killed
    c. subunit

13. PDD/ASD is defined by all except:
    a. Speech and language impairment
    b. Social impairment
    c. Mental retardation
    d. Stereotypic behavior

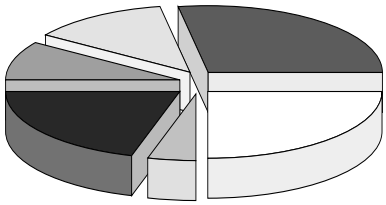
14. The increasing prevalence rates have been suggested to be due to:
    a. Decreasing mean age at diagnosis
    b. Broader case definition
    c. Improved case ascertainment
    d. All of the above

15. Thimerosal was used as a preservative in these vaccines except:
    a. Haemophilus influenzae type B
    b. MMR
    c. DTP/DTaP
    d. Hepatitis B

16. A vaccine against tularemia is commercially available.
    a. True
    b. False

17. Protection from F. tularensis requires _____ immunity.
    a. cell-mediated
    b. humoral

18. Tularemia vaccine development strategies include:
    a. killed, inactivated vaccine
    b. live, attenuated vaccine
    c. epitope-based vaccine
    d. all of the above



Health Insurance Update

Small Employer Health Insurance Availability Act – HEALTH*pact* Rhode Island

Patricia E. Huschle, MS

Health insurance premiums are rising to keep pace with medical costs at 10-13% per year. Small employers are particularly vulnerable to such increases, because they have no leverage or resources to negotiate benefit designs with insurers. In fact, small businesses on average pay 10% more in premium than larger employers. As a result, small employers face difficult choices with respect to their health insurance benefits: either increase employee cost-sharing or drop their employees' health insurance benefit entirely.

In 2006, the Rhode Island legislature amended the Small Employer Health Insurance Availability Act to begin to address the erosion of the small employer health insurance market. The Act requires health insurance carriers actively marketing in the small employer market to offer small employers (those with 50 or fewer employees) a more affordable plan option. Specifically, Blue Cross and Blue Shield of Rhode Island and UnitedHealthcare of New England, the two largest health insurance carriers in the state, were each required to develop, in conjunction with the Office of the Health Insurance Commissioner, a health plan that focused on wellness and charged average premiums of less than 10% of the annual statewide wage—about $314 per month. As a result, each carrier now offers a HEALTH*pact* plan.

HEALTH*pact*

HEALTH*pact* plans are an alternative to high deductibles or reduced coverage, helping employers and employees afford coverage and promote health and wellness at the same time.

HEALTH*pact* plans include cost savings incentives that advance the affordability principles as outlined in the Governor's health policy agenda and in statute. These principles include:

- A focus on primary care, prevention and wellness
- Active management of the chronically ill
- Use of least cost, most appropriate clinical setting
- Use of evidence based quality care.

The plan requirements were determined by the Wellness Advisory Committee, a group consisting of small employers, Direct Pay (individual) subscribers, employer organizations, health insurance brokers, consumer advocates and labor unions. Representatives from both Blue Cross and Blue Shield of Rhode Island and UnitedHealthcare of New England attended all the meetings. As a result of the committee's work, the HEALTH*pact* plans propose to achieve significant cost savings through financial incentives to enrollees to improve and maintain their health.

Advantage vs. Basic levels of Cost Sharing

HEALTH*pact* plans are unique in their design, having Advantage and Basic cost-sharing levels. Eligibility for the lower Advantage level deductibles, co-pays and out of pocket maximums depends on member commitment to five HEALTH*pact* principles:

- Selecting a primary care physician,
- Completing a health risk appraisal,
- Signing a pledge to remain at healthy weight or participate in a weight management program,
- Signing a pledge to remain smoke-free or to quit smoking, and
- Signing a pledge to participate in disease and case management programs if applicable.

HEALTH*pact* plans' two-tiered cost-sharing is unique in Rhode Island, offering comprehensive coverage and lower premiums by giving incentives to enrollees who commit to actively manage their health.

Part of the enrollee's commitment and pledge is the **Primary Care Physician (PCP)** Checklist, which must be submitted to the carrier within the first eight months of enrollment. The PCP Checklist, a requirement for Advantage level cost-sharing, addresses wellness activities related to smoking cessation and weight management programs in which the enrollee has agreed to participate. The PCP Checklist, as well as other features of the HEALTH*pact* plans that will be of interest to physicians, will be discussed in the next issue of *Medicine & Health/Rhode Island*.

Blue Cross and United began to offer these plans in August and September, with the first plans effective October 1, 2007.

Stemming the erosion of employer-based health insurance coverage in Rhode Island is critical to maintaining the integrity of the private health insurance market in this state. The small employer, HEALTH*pact* plans are a step in that direction.

For more information about the HEALTH*pact*, other regulatory developments and information about the efforts of the OHIC to ensure the fair treatment of the state's health care providers, please visit: www.dbr.state.ri.us/health_insurance.html.

Correspondence:
Patricia E. Huschle, MS
Office of the Health Insurance Commissioner,
233 Richmond Street
Providence, RI 02903
phone: (401) 222-5424
e-mail: phuschle@dbr.state.ri.us

Perinatal Depression in Rhode Island

Samara I. Viner-Brown, MS, Hyun (Hanna) K. Kim, PhD, and Rachel Cain

Research has shown that maternal psychological well-being during pregnancy has a significant influence on birth outcomes such as birth weight and length of gestation. Perinatal depression (before, during and after pregnancy) affects the mother and can negatively impact a child's development. Untreated major depression may lead to poor nutrition, smoking, drinking, premature labor, and low birth weights.[1] It has also been found that depressed women have higher levels of stress which can also adversely affect the fetus.[2] Although much national research has been conducted on perinatal depression, less is known about its relationship with maternal behavior and wellness in Rhode Island.

Methods

Data were analyzed from the Rhode Island **Pregnancy Risk Assessment Monitoring System survey** (**PRAMS**) of mothers who recently gave birth. The survey includes questions about behaviors and experiences before, during and after pregnancy. During 2004-5, a total of 3,991 women were sampled and 2,930 completed the survey, yielding a 75.3% weighted response rate. Maternal depression was examined during three periods: before, during and after pregnancy. Depression was indicated if there was a medical diagnosis before or during pregnancy or if there was self-reported depression after the baby's birth. The mother's experience during pregnancy was also considered. The following maternal behaviors, characteristics and psychosocial issues were analyzed in conjunction with maternal depression: unintended pregnancy, delayed prenatal care, cigarette smoking during pregnancy, alcohol use during pregnancy, domestic abuse during pregnancy, three or more stressors during the year before the baby's birth, activity limitation, breastfeeding, and fussy baby. Poor birth outcomes were measured by low birth weight (<2,500 grams), preterm birth (<37 weeks of gestational age) and **neonatal intensive care unit** (**NICU**) use. All analyses were performed using survey data analysis software that accounts for the complex sample survey design (SUDAAN). We employed chi-square tests to determine whether there is an association between mental health during pregnancy and maternal behaviors and birth outcomes. [Note: Because the overall number of respondents diagnosed with depression during pregnancy was relatively small (n = 226), we did not compare behaviors and birth outcomes for those who received treatment for their depression with those who did not receive treatment.]

Results

More than one in ten (11.0%) of respondents indicated they had been diagnosed with depression in the 12 months before pregnancy; 7.7% were diagnosed with depression during pregnancy; and 14.1% reported having postpartum depressive symptoms since their baby was born. More than one in five (21.6%) described their pregnancy as moderately hard, very hard or one of the worst times in their lives. (Figure 1)

Women were more likely to be diagnosed with depression during pregnancy if they were aged 20-24 (11.5%), were unmarried (12.2%), had less than a high school education (12.2%), had annual household incomes less than $25,000 (12.5%), had public health insurance (13.5%), or were enrolled in the **Women, Infants and Children** (**WIC**) Nutritional Program (12.5%). (Figure 2) The prevalence of depression did not differ significantly by race and ethnicity.

Compared to women without depression, women who were diagnosed with depression during pregnancy were significantly more likely to: report their pregnancy was unintended (50.6% vs 37.4%; p=0.0017); have delayed prenatal care (23.0% vs. 13.8%, p=0.0103); be obese before their pregnancy (29.0% vs 18.5%, p=0.0059); smoke during pregnancy (29.3% vs 10.0%, p<0.0001); experience domestic abuse during pregnancy (10.8% vs 1.9%, p = 0.0004); experience three or more stressors (62.2% vs 22.8%, p<0.0001); be limited in activities (22.8% vs 5.6%, p<0.0001); have a low birth weight baby (10.0% vs 6.7%, p<0.0001); deliver a preterm baby (13.3% vs 9.5%, p=0.0121); have their baby in the NICU (16.2% vs 9.6%, p=0.0158); and report difficulty calming their baby (14.3% vs. 7.3%, p = 0.0162). Women who were diagnosed with depression during pregnancy were also less likely to ever breastfeed compared to women who

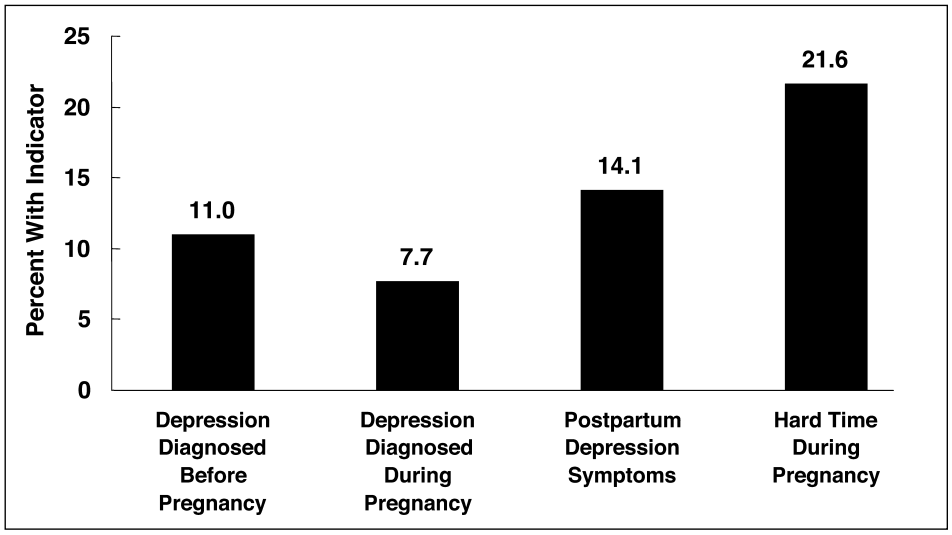


Figure 1. Selected indicators of maternal depression, Rhode Island, 2004-2005

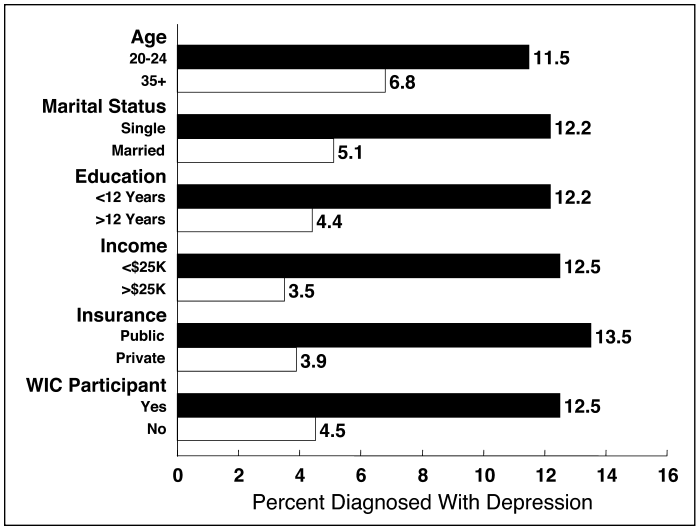


Figure 2. Women diagnosed with depression during pregnancy, by selected characteristics, Rhode Island, 2004-2005

were not diagnosed with depression (62.2% vs. 71.8%, p = 0.0207). The likelihood of drinking alcohol during the last three months of pregnancy was not significantly different for women with diagnosed depression (11.6%) compared to women who were not diagnosed with depression (9.4%). (Figure 3)

Similar results were seen among women who were diagnosed with depression before pregnancy, among women who described the time during their pregnancy as hard, and among women who reported symptoms of postpartum depression.

In terms of treatment, just over half (52.7%) of the 226 women who were diagnosed with depression during pregnancy reported taking prescription medications during their pregnancy, more than half of the respondents (55.3%) indicated they had received counseling for their depression during their pregnancy, and nearly three-fourths (74.6%) stated their health care provider had talked to them about the benefits and risks of taking antidepressants during pregnancy.

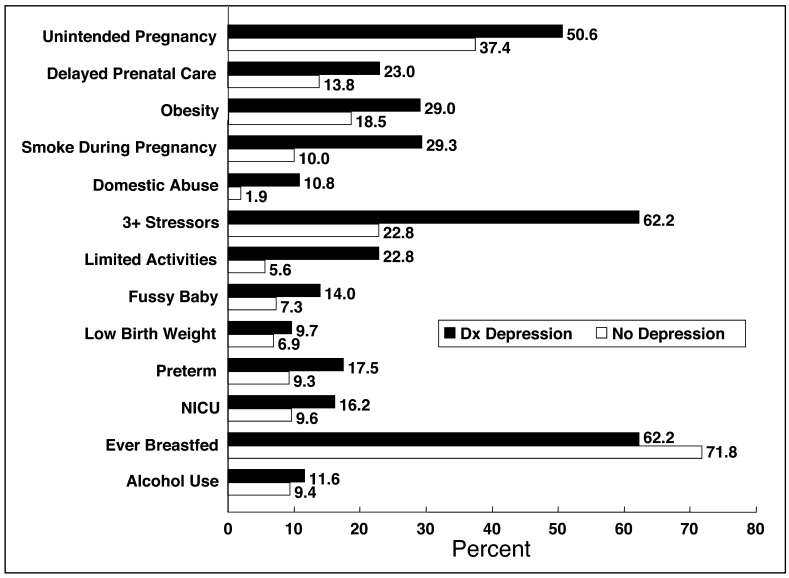


Figure 3. Depression during pregnancy by selected behaviors, characteristics and outcomes, Rhode Island, 2004-2005

Discussion

Maternal depression during pregnancy is a significant risk factor for poor birth outcomes and the well-being of mother and child. Many factors need to be taken into consideration when determining treatment for perinatal depression. For example, psychotherapy can help with milder symptoms, but antidepressant medications are often needed for more severe depression.[1] However, there are concerns about pregnant women using medications due to the possibility of harming the fetus. Rhode Island may want to consider implementing a toll-free number that links primary care physicians to psychiatrists and to information about medications to manage depression during and after pregnancy (which was implemented in Illinois).[3]

National recommendations for preconception health include screening for social and mental health concerns (e.g., depression, social support, domestic violence and major psychosocial stressors).[4,5] Women with identified risks should be offered counseling, testing and interventions. Other strategies to help assure that perinatal depression is identified and treated early include: providing outreach and education to the general public and health care providers; strengthening partnerships with mental health and social service agencies around perinatal health issues; and providing home visits and peer support for women with diagnosed depression.

Samara I. Viner-Brown, MS, is Chief, Data and Evaluation, Division of Family Health, Rhode Island Department of Health.

Hyun (Hanna) K. Kim, PhD, is Senior Public Health Epidemiologist, Division of Family Health, Rhode Island Department of Health.

Rachel Cain is Senior Health Promotion Specialist, Division of Family Health, Rhode Island Department of Health.

Disclosure of Financial Interests

Samara I. Viner-Brown, MD, Hyun K. Kim, PhD, and Rachel Cain have no financial interests to disclose.

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Geriatric Osteoporosis

Tom J. Wachtel, MD, FACP, CMD

DEFINITIONS

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, resulting in reduced bone strength and increased risk of fracture.

EPIDEMIOLOGY [1,2,3]

- 44 million adults in the US have abnormally low bone mass
- 40% of all women and 25% of all men will experience a fragility fracture in their lifetime.
- osteoporosis accounts for 800,000 vertebral compression fractures, 300,000 hip fractures and 250,000 wrist fractures annually.
- The consequences of those fractures are significant:
  - the mortality for hip fracture is 24% in the first 12 months; of those who survive, 50% fail to regain full ambulatory capability
  - vertebral fractures can be asymptomatic but they can also be associated with back pain, reduced activity, and increased mortality.
- Under-diagnosis and under-treatment are common

PRINCIPAL RISK FACTORS FOR OSTEOPOROSIS AND FRAGILITY FRACTURES

- Personal history of a prior fragility fracture is the strongest predictor of a subsequent fracture regardless of bone density[4]
- Low Weight
- Female gender
- Advancing age
- History of falls and unsteady gait

ETIOLOGY

- Primary osteoporosis is associated with many factors, including nutrition, low peak bone mass, genetics, low level of physical activity and early menopause. Postmenopausal osteoporosis is by far the most common form of osteoporosis. Bone remodeling is lifelong; however, increased bone resorption after age 30 results in net bone loss, most rapidly during the first 5 years following menopause.
- Secondary osteoporosis (Table 1)

SYMPTOMS

- Often silent. The prevalence of osteoporosis is 38% in white women aged 70 to 79 and 70% in those aged above 80. This means that osteoporosis should be presumed to exist in all elderly women until proven otherwise.[5]
- The most common sign of osteoporosis is height loss. Elderly patients should be measured yearly.
- Another sign is thoracic kyphosis (dowager's hump).
- Osteoporosis without fractures does not cause pain.

WORK-UP

- Diagnosis of osteoporosis is made by bone densitometry,[6,7] indicated in :
- all women 65+ and women under age 65 with osteoporosis risk factors
  - all adults with fragility fractures
  - anyone expected to be treated with glucocorticoids for longer than 3 months or with diseases associated with secondary osteoporosis
  - men 70 and older (controversial)

TECHNOLOGIES FOR MEASURING BONE MINERAL DENSITY (BMD)

- **Quantitative ultrasound** (QUS) should be used only for screening in low osteoporosis prevalence populations
- **Dual-energy x-ray absorptiometry** (DXA) is the "gold standard" because epidemiologic studies have correlated and standardized BMD data obtained by DXA with fracture risk. However, any dense structure between radiation source and film (e.g. osteophytes or vascular calcifications) will give a falsely high reading, because density is measured from a 2-dimensional image
- **Quantitative computed tomography** (QCT) measures the intended 3-dimensional targeted bone only

INTERPRETATION

All BMD results are measured in gm/cm^2, but expressed in T scores and Z scores. T scores are standard deviations (SDs) above or below values for young normal adults and Z scores are standard deviations above or below age-matched values. A T score more than 2 SDs below the mean 30-year-old BMD indicates an increased risk of fracture and should lead to therapy to prevent further bone loss. A Z score of more than 1 SD below the age-matched mean value signifies a BMD that is lower than expected for one's age and should prompt an evaluation for secondary causes of bone loss.

WORLD HEALTH ORGANIZATION CRITERIA FOR THE DIAGNOSIS OR OSTEOPOROSIS

	T-score
Normal	>-1
Osteopenia (or low bone mass)	-1 to –2.5
Osteoporosis	≤-2.5

The work-up for secondary causes of osteoporosis is presented in Table 1.

Table 1: Work-up for the Secondary Cause of Osteoporosis (Low Z Score)

Differential diagnosis	Screening	Positive Screen	Confirmatory Test
Endocrine/Metabolism			
• Hyperparathyroidism	Ca++, Phos	↑Ca++and/or ↓ Phos	Parathormone (PTH) level
• Low vitamin D state*	Ca++, Phos	Lowish Ca++and ↓ Phos	25-OH-vit D level
• Hypercortisolism	FBS, K+	↑ FBS, ↓ K+	overnight dexamethasome supression test
•			
• Hyperthyroidism	TSH	↓ TSH	TT_4, TT_3, T_3 RU
• Hypogonadism	Testosterone, FSH, LH in men; FSH, LH in premenopausal women	↓ testo, ↑ FSH, ↑LH ↑ FSH, ↑LH	
Neoplasia			
• Multiple myeloma	CBC, ESR, Ca++, creat	Anemia, ↑ ESR, ↑ CA ++ or ↑ crest	SPEP, UEP
• Lymphoma	CBC ? Imaging	Anemia, lymphadenopathy	More imaging
• Leukemia	CBC	↑ WBC	Bone marrow aspirate
• Metastatic cancer	N/A		
Chronic Illness			
• Hepatic failure	SGPT, Alk Phos, PT	Abn LFTs	Variable
• Renal failure	Creat	↑ Creat	Variable
• Rheumatoid arthritis	Steroid use (for longer than 3 months)		
Gastrointestinal			
• Malabsorption	CBC, PT, Carotene	Anemia, ↑ PT, ↓ carotene	-d xylose absorption anemia evaluation
Drugs	Medication History		
• Glucocorticoids			
• Thyroid hormone			
• Loop diuretics			
• Dilantin			

*in high risk populations (e.g. nursing home, northern latitude residence) a screening 25 OH vit D level is recommended

TREATMENT [8,9]

The goal of treatment is fracture prevention. The strongest predictors of fracture are previous fracture(s), fall(s), low BMD and advancing age.

Nonpharmacologic Management

- Resistive exercises
  -walking
  -rowing machine
  -weight lifting
- Fall prevention
  -assess gait and fall risk (e.g. "get up and go" test)
  -gait training
  -home safety evaluation
  -assistive devices as appropriate
- Hip protectors
- Supplements
  -calcium
  -provide 1,500 mg per day from diet and/or supplements
  -examples of dietary sources include:
    milk = 300 mg per 8 oz
    yogurt = 350 mg per cup
    broccoli = 100 mg per cup
    seaweed = >1000 mg per serving

  -supplements
    calcium carbonate
    calcium citrate

Vitamin D plays an important role in calcium homeostasis and bone metabolism. Low levels of vitamin D lead to inadequate intestinal calcium absorption and result in relative hypocalcemia triggering secretion of parathyroid hormone (PTH). PTH stimulates osteoclastic activity and calcium release from bone to maintain eucalcemia at a cost of loss in bone mass.[10,11]

To become biologically effective, nutritional vitamin D and skin-synthesized vitamin D must be hydroxylated twice: first in the liver to become 25 (OH) vit D, then in the kidney to become 1-25 (di-OH) vit D. Adequacy of vit D stores is best measured by the serum levels of 25 (OH) vit D, except in patients with renal failure in whom 1-25 (di-OH) vit D should be measured.

Vit D deficiency is defined by a level of 25 (OH) vit D < 10 ng/ml; however, secondary hyperparathyroidism occurs at a level of 25 (OH) vit D < 30 ng/ml (vit D insufficiency), which is the threshold for optimum bone health.

The prevalence of low vit D level is high; NHANESIII data show that 32% of Caucasians, 55% of Mexican-Americans and 67% of African-Americans over age 50 have 25 (OH) vit D level < 23 mg/ml. Such numbers could justify population-wide screening for vit D deficiency. Among patients with low UV-B sunlight exposure (e.g. nursing home patients), the prevalence of vit D deficiency is even higher.[12]

In addition to bone health, vit D deficiency has been associated with muscle weakness, falls, myalgias, fibromyalgia, several cancers (colon, breast, prostate), hypertension, rheumatoid arthritis and even type I diabetes mellitus.

The daily requirement of vit D in the geriatric population is at least 800 units per day. Vit D3 is more effective than D2, but either type will do the job. In patients whose level of 25 (OH) vit D is < 30 ng/ml, a weekly dose of vit D 50,000u orally for 2 months is appropriate. Once the 25 (OH) vit D level has been replenished to > 30 ng/ml, the daily requirement of 800 units should be prescribed indefinitely.[13] Note that all the trials of pharmacologic agents used to treat osteoporosis have been conducted in calcium and vit D replete subjects.

Pharmacologic Treatment

- Preventive treatment for osteoporosis and treatment of osteopenia are controversial, even though some drugs have FDA approval for prevention.
- Indication for treatment (according to the National Osteoporosis Foundation):
  1) T-score < -2.0 (by central DXA)
  2) T-score < -1.5 (by central DXA) plus at least one additional fracture risk factor
  3) Any prior history of fragility fracture: such patients should be treated even if a DXA is not available (e.g. nursing home residents).[14]
- Antiresorptive (i.e., anti-osteoclastic) treatments
  -estrogen: conjugated estrogen 0.625 mg daily is efficacious in preventing fractures; however, the overall risk outweighs the benefit. This treatment is no longer recommended for osteoporosis.[15]
  -selective estrogen receptor modulators (SERMs): raloxifen 60 mg daily is approved for the treatment (and prevention) of osteoporosis. It is efficacious in reducing the risk of vertebral fractures and reduces the risk of breast cancer. Side effects are hot flashes, leg cramps, and increased risk of deep vein thrombosis and endometrial cancer.[16]
  -calcitonin nasal spray 200 IU per day reduces the risk of vertebral fractures. The drug is well tolerated, but probably less effective than other agents.
  -biphosphonates

Three biphosphonates are widely used for the treatment or prevention of osteoporosis as first line agents. They are alendronate (70 mg p.o. weekly or 10 mg p.o. daily),[17,18] risedronate (35 mg p.o. weekly or 5 mg p.o. daily)[19,20] and ibandronate (150 mg once monthly or 2.5 mg daily). All three drugs are efficacious in reducing fractures. Side effects of these drugs include esophageal ulceration, musculoskeletal pain and diarrhea. Any co-administered substance (food or medication) binds to bisphonates which must be taken fasting with 8 oz of water and trunk upright. Nothing else should be taken orally for 45 minutes. Three bisphonates can be administered intravenously: pamidronate, ibandronate and zolendronate.

- bone building treatment (i.e., osteoblastic stimulant)

Recombinant human parathyroid hormone (rh-PTH or teriparatide) is a potent stimulant of osteoblastic cells when administered as pulse therapy.[21] Continuous exposure to parathormone, such as occurs in hyperparathyroidism stimulates osteoclasts more than osteoblasts and results in bone loss. Teriparatide is administered at the dose of 20 mcg, injected S.C. daily for up to 2 years, followed by antiresorptive treatment. The main concern with teriparatide is its potential to cause osteosarcoma at high doses in rats. It is also very expensive.

Monitoring patients with osteoporosis[22]

Most clinicians recommend a central DXA at baseline, at two years and at four years into treatment. Treatment success can be defined by improvement or no change in BMD over time and no fracture. However, a decline in BMD over time does not necessarily indicate failure. Treatment trials show efficacy in fracture reduction compared with placebo, even in subjects with declining BMD. Nonetheless, many clinicians consider declining BMD and/or fracture to be indicative of treatment failure and the need to change treatment. Combined treatment is not recommended.

Markers of bone turnover can be used to monitor treatment. The most common markers of bone resorption include hydroxyproline and N-telopeptide. The most common markers of bone formation are alkaline phosphatase and osteocalcin. Change in those markers often occurs within three months of effective treatment, but they correlate poorly with fracture risk.

Duration of Treatment

Treatment trials were not conducted for periods longer than 5 years. Some clinicians hesitate to treat for longer than 5 years (for lack of any evidence base), while others treat indefinitely because BMD declines after treatment withdrawal.

Osteoporosis in Men

Twenty percent of all osteoporotic persons in the US are men. Secondary causes (e.g., hypogonadism) are more likely than in women, who typically have primary osteoporosis. Biphosphonates, calcitonin and teriparatide are used to treat osteoporotic men.

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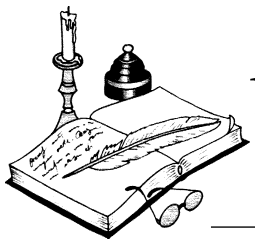

Physician's Lexicon

Forty Days in Limbo

The English medical vocabulary owes a great debt to the Italian language for many of its words including lazaretto, anemia, malaria, marijuana, influenza, belladonna, dengue and quarantine.

The word, *quarantina*, derived from the Italian term for forty [days], echoes man's lengthy preoccupation with the numeral forty. The Bible is replete with forties. For example, the reign of Solomon [I Kings 11:42] was forty years, as were the reigns of his predecessors, Saul and David [II Samuel 5:4]. Noah's flood lasted forty days; and Moses, at age 40, climbed Mount Sinai and remained isolated for forty days before resuming leadership of the wandering Israelites. The periodic faithlessness of these nomadic Israelites forced them to wander for forty years in the vast deserts of the Middle East before reaching their promised land.

Jesus endured forty days in the wilderness, emerging victorious over temptation [Matthew 4:2] and then preached for forty months. Both Muhammad and Buddha began their separate evangelic missions at age forty. The number forty appears in many of the funerary rituals of the Fulani of Africa. And in many African tribes, the final mourning taboos are lifted after forty days of grieving. In certain Asiatic tribes, a widow may seek a new husband but only after forty days of celibate mourning.

Forty, some anthropologists believe, represents an interval for the preparation of some inspired task or, alternatively, a cycle of days marking the end of one living event and the beginning of another. And, of course, there is the medical student's aphorism of those most likely to be victimized by gall bladder disease: "female, fair, fat and forty."

A *lazaretto* was the name given to hospices for the care of those with leprosy, the first bearing this name was established in Venice in 1403. The Bible [Luke 16:20] describes a certain beggar, with many sores, named Lazarus, who was apparently afflicted with leprosy. Though hungry, he was not fed by a rich man at whose gates Lazarus dwelt. The beggar died and "was carried by the angels into Abraham's bosom." And thus medieval sanctuaries for the lepers—and later, for patients with any contagious pestilence—were often called lazarettos.

– Stanley M. Aronson, MD

Rhode Island Department of Health
David Gifford, MD, MPH
Director of Health

Vital Statistics

Edited by Colleen Fontana, State Registrar

Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	October 2006	12 Months Ending with October 2006		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	210	2,728	255.0	3,099.5
Malignant Neoplasms	210	2,311	216.0	6,197.0
Cerebrovascular Diseases	34	401	37.5	465.0
Injuries (Accidents/Suicide/Homicde)	44	477	44.6	7,208.0
COPD	32	480	44.9	437.5

Vital Events	Reporting Period		
	April 2007	12 Months Ending with April 2007	
	Number	Number	Rates
Live Births	1,108	13,548	12.7*
Deaths	821	10,003	9.4*
Infant Deaths	(16)	(97)	7.2#
Neonatal Deaths	(15)	(67)	4.9#
Marriages	385	6,905	6.5*
Divorces	277	3,090	2.9*
Induced Terminations	329	4,741	349.9#
Spontaneous Fetal Deaths	46	952	70.3#
Under 20 weeks gestation	(40)	(884)	65.2#
20+ weeks gestation	(6)	(68)	5.0#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,067,610

(c) Years of Potential Life Lost (YPLL)

Note: *Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.*

* Rates per 1,000 estimated population

\# Rates per 1,000 live births

MEDICAL MALPRACTICE TOPICS

INFORMATION FOR RHODE ISLAND PHYSICIANS FROM BABCOCK & HELLIWELL

THE USE OF MEDICAL RECORDS IN LITIGATION

John Tickner, CPCU, President, Babcock & Helliwell

Whether facing a personal injury, medical malpractice, or wrongful death claim, one of the first things that lawyers do is request copies of medical records. Litigation brings to light the purpose of medical records, but can also show the dangers of poor record keeping.

There are several important uses for medical records:

- To document the patient's treatment, which allows for appropriate continued care.
- To allow hospital quality assurance or peer review committees to determine whether you provided the appropriate medical care.
- To form the basis for financial reimbursement (complete, accurate records speed the processes).
- To support litigation.

In litigation, the medical record can show the care provided and thus form the basis either for a malpractice claim or its defense. Think of your complete medical records as witnesses whose memory is never lost. However, if medical records are inaccurate or incomplete, your malpractice liability company's ability to successfully defend a malpractice case is compromised. The worst case scenario is that a jury is left to guess what level of care was provided because the "memory" is poorly recorded. Therefore, it is very important that records be accurate, complete, and legible and that the care be well documented.

The standard medical record includes four parts:

- a patient history;
- your observations of the patient;
- your diagnosis or summary; and
- the treatment plan.

Lawyers read the medical record to determine both the subjective and objective basis for the treatment provided, the conclusions reached by the medical providers, and what treatment the provider recommended to the patient.

The different parts of the medical records take on varying importance depending on the type of case. Most medical malpractice cases focus on the diagnosis (to see if something was missed) or whether the provider's proposed/actual treatment was reasonable in light of the subjective and objective information.

In the standard personal injury case, the history and observation take on a greater importance: when the patient has a subjective complaint with no objective basis, one must consider somatic issues or even malingering. The diagnosis is important in terms of legal causation—the injury must be of a kind caused by the accident. The plan is important for determining whether the patient/plaintiff is following orders and mitigating damages.

When it comes to the use of medical records in litigation, good, clear, complete, and accurate records provide the basis for a strong defense and could possibly preempt litigation against the provider. Ultimately, it is best for you and your patient to take the time to document his or her care as accurately and in as much detail as possible.

***John Tickner**, CPCU, is president of Babcock & Helliwell, a privately held independent insurance agency established in 1892 that provides professional insurance-related services of all kinds. Babcock & Helliwell is an agency for ProMutual Group, New England's largest medical malpractice insurance provider and the second-largest provider in Rhode Island. The views expressed are solely those of John Tickner, CPCU, and Babcock & Helliwell.*

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Ninety Years Ago, October 1917

Major Horace D. Arnold, MRC, US Army, read "Medical Officers' Reserve Corps" before the Rhode Island Medical Society on September 6, 1917. The Journal reprinted his talk. Speaking "personally and not officially," he traced the Medical Officers' Reserve Corps to the Spanish War: "The object of the MRC is to avoid the errors of the Spanish War and of other previous wars. The medical department was the first department of the army to inaugurate this plan…in time of peace, to be prepared for the demands of war. Even as late as the Spanish War there was no such provision, and when the war began they had to provide doctors for a suddenly increased army, and in the rush they had to take most anybody that would volunteer….in the Spanish War we had a great many incompetent men, who were accepted because of the hasty selection. The story of disease and death in our mobilization camps in that war under the care of such officers I consider a disgrace to the profession." He foresaw a draft army of 1,500,000, with the legal requirement of 7 physicians for every thousand soldiers—a requirement long considered inadequate (the Civil War ratio was 10 per thousand). He predicted that in time the army would need 5 million men, and, subsequently, 35,000 physicians.

D.N.Carpenter, US Navy, Medical Inspector, read "Organization of the Dispensary Services of the Second Naval District" at that same meeting. The second district went from Chatham to New London. There were 8 naval districts on the Gulf and Atlantic Coasts, each with a Naval Yard.

A review, of "Pulmonary Tuberculosis: A Handbook for Students, by E.O. Otis, MD, repeated Dr. Otis's admonition: "…pulmonary tuberculosis, which has been diagnosed by the physical signs alone, and is without symptoms, requires no treatment. Symptoms are the indication of active disease, and for active treatment."

Fifty Years Ago, October 1957

George W. Anderson, MD, Professor of Obstetrics, Johns Hopkins, presented "Investigations of Obstetrical Factors in Subsequent Neuropsychiatric Disorders in Children" at the 146th annual meeting of the Rhode Island Medical Society. The Journal reprinted his talk. He focused on cerebral palsy, mental deficiency, epilepsy, behavioral disorders, reading disorders, tics, hearing disorders and blindness, and found premature birth a major factor. Specifically, he linked prematurity to 71.4% of Rhode Island infant deaths (the national figure was 50.8%). He asserted that 20 to 35% of children with cerebral palsy were born premature, 13.7% of children with epilepsy were born premature, 17% of children with mental deficiency were born premature; and he linked prematurity to 90% of the cases of pediatric blindness.

Jane Desforges, MD, Assistant Professor of Medicine, Tufts University, contributed "Red Blood Disorders." She stressed the need for "knowledge of iron turnover" in a patient.

An Editorial, "Coronaries and Corn Oil," urged cautious skepticism before embracing the linkage between high fat diets and heart disease. The Editorial cited a *JAMA* report: "The hypothesis that dietary facts affect atherogenesis, however plausible and appealing, remains unproved." The Editorial urged readers not to "sway to every experimental breeze that blows our way."

Twenty-Five Years Ago, October 1982

Elizabeth S. McCormick, MSW, Doris S. Ware, AB, and Joseph M. Zucker, MD, contributed "Time-Limited Action-Oriented Psychotherapy in a General Hospital, with Focus on Separation." The authors followed up on 12 patients, from the Psychiatric Outpatient Department of Rhode Island Hospital, and concluded: "Short-term therapy was effective for two-thirds of those selected who accepted the treatment contract."

Manuel E. Soria, MD, in "Overview on the Competency to Stand Trial and Determining Criminal Responsibility," updated readers on the different standards for judging competency, in light of the increase in successful insanity pleas nationally.

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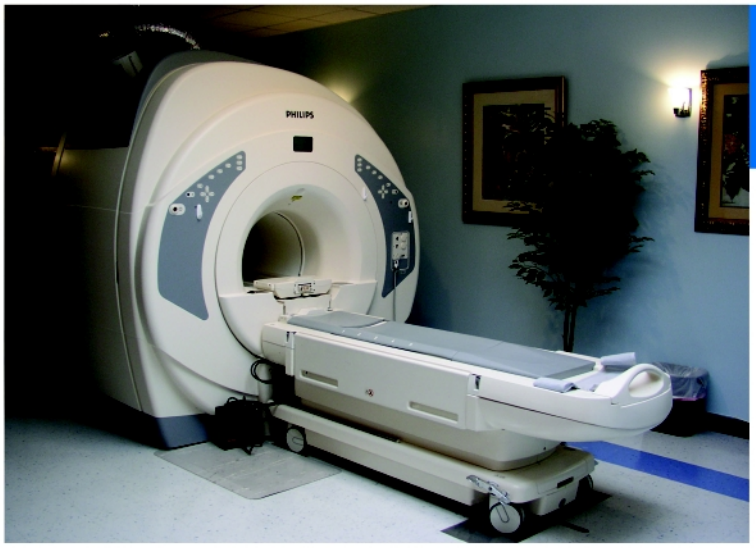

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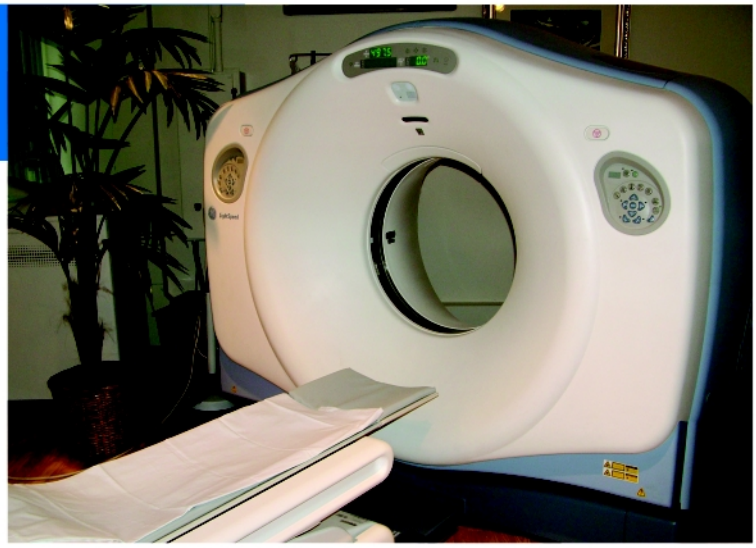

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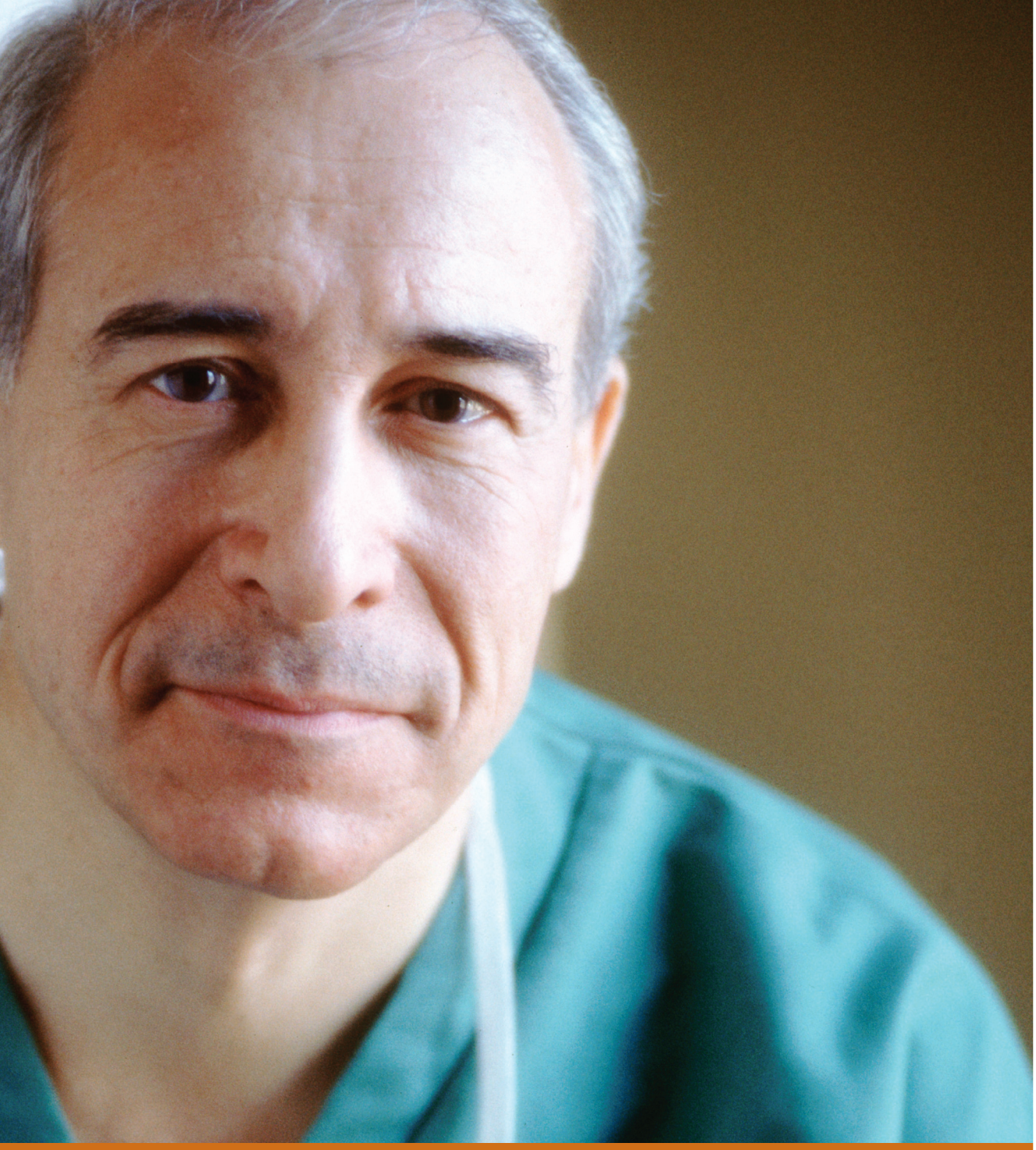

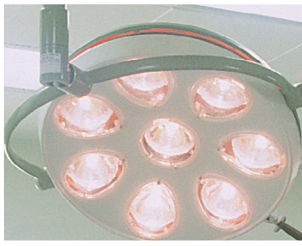

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