February 2013 Epidemics and AIDS Update

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New Study Sheds Light On Link Between Dairy Intake and Bone Health: Not All Dairy Products Are Equal

Feb. 1, 2013 — A study by researchers at the Institute for Aging Research (IFAR) at Hebrew SeniorLife, an affiliate of Harvard Medical School (HMS), has found that dairy intake—specifically milk and yogurt—is associated with higher bone mineral density (BMD) in the hip, but not the spine.
Cream, on the other hand, may be associated with lower BMD overall. Published February 1 in the journal *Archives of Osteoporosis*, these findings suggest that not all dairy products are equally beneficial in promoting bone strength.

"Dairy foods provide several important nutrients that are beneficial for bone health," says lead author Shivani Sahni, Ph.D., Musculoskeletal Research Team, IFAR. "However, cream and its products such as ice cream have lower levels of these nutrients and have higher levels of fat and sugar. In this study, 2.5–3 servings of milk and yogurt intake per day were associated with better bone density. More research is needed to examine the role of cheese intake (some of which can be high in fat and sodium), and whether individual dairy foods have a significant impact in reducing fractures."

IFAR researchers based their findings on data collected from a food frequency questionnaire completed by 3,212 participants from the Framingham Offspring study. They then compared participants’ dairy intake with BMD measurement, which revealed the benefits of milk and yogurt versus cream in largely middle-aged men and women. According to the study, nutrient composition varies among dairy foods. Choosing low-fat milk or yogurt over cream can increase intake of protein, calcium and vitamin D while limiting intake of saturated fats.

This study is an example of a growing area of research focused on the relationship between nutrition and bone health. Past studies suggest that dairy products contain more than one beneficial nutrient, and for this reason certain dairy products may contribute towards maintaining healthier bones.

Research like this supports the idea that proper nutrition can help combat osteoporosis and fractures. Osteoporosis is considered a major public health threat for an estimated 44 million Americans, or half of those aged 50 and older.

- An estimated 10 million in the U.S. already have the disease. Women are at higher risk than men.
- Another 34 million Americans have low bone density, putting them at increased risk for osteoporosis and fractures, especially of the hip, spine and wrist. About one-quarter of those who suffer a hip fracture die within a year of the injury.
- Osteoporosis-related fractures were responsible for an estimated $19 billion in health care costs in 2005, with that figure expected to increase to $25 billion by 2025.


**Imaging Unveils Temperature Distribution Inside Living Cells**
Feb. 1, 2013 — A research team in Japan exploring the functions of messenger ribonucleic acid (mRNA)—a molecule that encodes the chemical blueprint for protein synthesis—has discovered a way to take a close look at the temperature distribution inside living cells. This discovery may lead to a better understanding of diseases, such as cancer, which generate extraordinary intracellular heat.

This breakthrough is the first time anyone has been able to show the actual temperature distribution inside living cells. The team will present their findings at the 57th Annual Meeting of the Biophysical Society (BPS), held Feb. 2–6, 2013, in Philadelphia, Pa.

Conventional temperature imaging methods lack spatial resolution and sensitivity, which means these methods are incapable of imaging extremely tiny temperature differences inside living cells. To overcome these issues, the team developed a new imaging method that combines a highly sensitive thermometer with an incredibly accurate detection technique, enabling the creation of detailed intracellular temperature maps.

"Our imaging method allows us to clearly see the temperature inside living cells, and we found that the temperature differs greatly depending on the location in the cell," says Kohki Okabe, an assistant professor at the University of Tokyo’s Laboratory of Bioanalytical Chemistry, Graduate School of Pharmaceutical Science. "We discovered that the temperature difference is related to the various stages of the cell cycle."

This research provides a novel point of view: **Temperature not only regulates biological molecules, but it actually contributes to cellular functions.**

"By incorporating cellular temperature mapping into the analysis of any kind of cellular event, we can achieve a deeper understanding of cellular functions," Okabe explains. "It is our hope that by using this method of temperature imaging, the pathogenesis of diseases known to generate significant heat within cells, such as cancer, can be clarified. We believe this may help lead to future cures."
Next, Okabe and colleagues plan to explore how temperature contributes to cellular functions in even greater detail, as well as investigating differences in the intracellular temperatures of various living cells.

**Programming Cells: Importance of the Envelope**

Feb. 1, 2013 — In a project that began with the retinal cells of nocturnal animals and has led to fundamental insights into the organization of genomic DNA, researchers from Ludwig-Maximilians-Universitaet (LMU) in Munich show how the nuclear envelope affects nuclear architecture—and gene regulation.

The double-stranded DNA molecules that make up the genetic material are wrapped around protein complexes to form compacted "chromatin." The active portion of the genome is less densely packed, and thus more easily accessible, than the inactive fraction, and is referred to as euchromatin. Euchromatin is typically located in the inner regions of the cell nucleus, while much of the inactive DNA in "heterochromatin" is associated with the inner face of the nuclear envelope. This type of chromatin organization is found in almost all higher organisms and may have been invented 500 million years ago.

But there is a curious exception to this generalization. In the retinal cells of nocturnal animals, the heterochromation is localized in the central area of the nucleus, as a research group led by LMU biologists Dr. Irina Solovei and Dr. Boris Joffe showed in a previous study. "This got us interested in the mechanisms that control the distribution of chromatin," says Professor Heinrich Leonhardt of LMU’s Biozentrum. "How can the nuclear architecture in the rod cells of nocturnal animals be inverted in this way, and what determines the typical positioning of inactive chromatin on the outskirts of the nucleus in normal cells?" Leonhardt and his team have now completed an extensive study in search of the answers.

**A fundamental principle unveiled**

With the help of targeted genetic manipulations in the mouse, Joffe and Solovei together with their colleagues show for the first time that there are two independent mechanisms for fixing heterochromatin to the inner face of the nuclear envelope. These mechanisms make use of two different components of the inner nuclear membrane as clamps—lamin A/C, and the so-called lamin-B receptor (LBR), which itself binds to B type lamins.

Normally the two components are used sequentially for this purpose. "In the course of differentiation, there is a switch from the LBR to lamin A/C, and there is always a least one type of tether available for attachment of heterochromatin to the nuclear periphery. But if both are missing, the inactive heterochromatin recoils like a severed elastic band and collapses in the center of the nucleus," explains Leonhardt. Moreover, the switch seems to be a fundamental principle of genome organization and cell differentiation in mammalian cells, as the researchers concluded from the study of 39 species and the analysis of diverse tissue types in nine genetic strains of mice.

Prospects for targeted therapies Lamin proteins not only have a structural function but also have an impact on gene regulation. Thus LBR binds B type lamins and regulates stem-cell populations by promoting the expression of genes that are important for the proliferation of rapidly dividing stem cells. The lamin A/C gene on the other hand codes for a structural component of the nuclear envelope, and regulates cellular differentiation programs like e.g. the expression of muscle-specific genes in muscle cells. Mutations in this gene result in so-called laminopathies—rare genetic diseases that are associated with a broad spectrum of clinical symptoms, including muscular dystrophy and progeria, a premature aging syndrome.

Joffe and Solovei suspect that mutations in lamin A/C affect the expression of specific genes during the maturation and differentiation of cells, with deleterious results for their function and for tissue integrity. This notion could explain the highly diverse and complex symptoms seen in patients with mutations in the lamin A/C gene—and it could open routes to the design of targeted therapies for laminopathies.

The new findings thus yield fundamentally new insights into how each of the many differentiated cell types in the body arises as the result of the precisely regulated expression of a specific complement of genes appropriate to each. "In the end, we have been brought from studies of night vision and an odd quirk of nature to the discovery of a fundamental regulatory mechanism: The nuclear envelope has a major say in development, and what kind of envelope our genetic material comes in makes a great deal of difference to our fate," Leonhardt concludes.
Is Monitoring for CD4 Counts Still Needed for the Management of Patients With Long-Term HIV RNA Suppression?

Christoph Stephan, MD, Andrew Hill, PhD, Ning Xi, MSc, Yvon van Delft, MSc, Christiane Moecklinghoff, MD

It is unclear whether continued CD4 testing is necessary for patients with full HIV RNA suppression and high CD4 counts. In the MONET trial, 257 patients with HIV RNA less than 50 copies/mL at baseline received darunavir/ritonavir, with or without nucleoside analogues. During 144 weeks of treatment, of 208 patients with baseline CD4 counts more than 350 cells/μL, only one patient had a short-term reduction in CD4 count less than 200 cells/μL, which then rose back more than 350 cells/μL with no change in treatment. Monitoring based on HIV RNA only could save significant costs from large-scale treatment access programmes.

Since the first antiretrovirals were developed in the late 1980s, CD4 counts have been used to help decide which patients should be started on antiretroviral treatment. International HIV treatment guidelines documents include a CD4 threshold for the initiation of treatment of either less than 500 cells/μL or less than 350 cells/μL.[2]

During antiretroviral treatment, the CD4 count is a poor measure of success on treatment, with low sensitivity or specificity to detect virological failure or the emergence of drug resistance.[3,4] However, patients with CD4 counts less than 200 cells/μL are at higher risk of opportunistic infections—this correlation is consistent across different antiretroviral classes. If CD4 counts are close to or less than the threshold of 200 cells/μL, continued monitoring for CD4 counts can help to identify those needing prophylaxis for opportunistic infections.[5]

When the CD4 counts increase more than 350 cells/μL, after full HIV RNA suppression, the value of continuing CD4 counts may be limited. European and US treatment guidelines are now recommending less frequent monitoring for CD4 counts (every 6–12 months) if patients have full HIV RNA suppression.[6,7] Can we stop testing for CD4 counts for patients who have full HIV RNA suppression and high current CD4 counts?

In the PLATO cohort, patients with suppressed HIV RNA less than 10,000 copies/mL had no overall change in CD4 counts over time.[6] A previous analysis of the Frankfurt HIV cohort showed that patients with CD4 counts more than 350 cells/μL and HIV RNA suppression less than 50 copies/mL were very unlikely to show falls in CD4 count less than 350 cells/μL during long-term follow-up.[8]

We reanalyzed the MONET trial[6] to determine whether CD4 counts were maintained above safe thresholds for patients with HIV RNA suppression over 3 years. In this trial, 256 patients with HIV RNA less than 50 copies/mL at screening on current highly active antiretroviral therapy for at least 6 months and with no history of virological failure switched to darunavir/ritonavir 800/100 mg once daily, either as monotherapy (n = 127) or with 2 nucleoside analogues (n = 129). Patients were 81% male and 91% white with a median of 7 years prior treatment before the trial. CD4 counts were measured at a central laboratory at screening, at baseline, and then at visits every 12–16 weeks to week 144. As both arms did perform similarly in regard to virological suppression,[6] pooled data from both arms were now assessed for CD4-strata development. We divided the patients into subgroups according to the mean of their CD4 counts at screening and at baseline: <200, 200–350, 350–500, and more than 500 cells/μL. Then, using data from the 231 patients with at least 48 weeks of follow-up, we assessed the lowest CD4 count measured on at least 2 consecutive visits during the trial, in the same categories.

During the MONET trial, the mean CD4 count increased from 571 cells/μL at baseline to 732 cells/μL at week 144 in the DRV/r monotherapy arm and from 579 cells/μL at baseline to 747 cells/μL at week 144 in the triple therapy arm, with no significant differences between the treatment arms.

The combined data from the 2 treatment arms are shown in Table 1. The one patient with CD4 counts less than 200 cells/μL at screening/baseline also had CD4 counts in this range during the trial. Of the 22 patients with CD4 counts in the range of 200–350 cells/μL at screening/baseline, one patient (4.5%) had a fall in CD4 count to less than 200 cells/μL during the trial (triple therapy arm). Of the 60 patients with CD4 counts in the range of 350–500 cells/μL at screening/baseline, one patient (1.7%) had a fall in CD4
count to less than 200 cells/μL during the trial. None of the 148 patients with CD4 counts more than 500 cells/μL had a reduction to less than 200 cells/μL during the trial.

The 2 patients with reductions in CD4 counts less than 200 cells/μL during the trial were both in the triple therapy arm. The first patient had a baseline CD4 count of 433 cells/μL, with a level of 325 cells/μL at week 72. There was a fall to 191 and 92 cells/μL at the week 84–96 visits and then a rebound to 453 cells/μL by week 144. Suppressed HIV RNA levels remained less than 50 copies/mL throughout this time, and the CD4 percentage remained in the range of 24%–30% throughout the trial. The second patient had a baseline CD4 count of 307 cells/μL, which remained level at 278 cells/μL at week 48. There were then 2 CD4 counts of 168 and 192 cells/μL at weeks 60–72, followed by CD4 counts consistently more than 300 cells/μL from week 84 to week 144. There were no confirmed elevations in HIV RNA in this patient; the CD4 percentage was in the range of 22%–27% throughout the trial, except for a single result of 17% when the absolute CD4 count was also low.

These results from the MONE trial suggest that there is limited benefit from continued measurement of CD4 counts in patients who have achieved full HIV RNA suppression and have high current CD4 counts—in the range of or more than 350 cells/μL. The risk of sustained CD4 cell count declines to lower levels and at elevated risk for clinical disease, progression was very low.

Even if CD4 counts do fall despite full HIV RNA suppression, no randomized trial has shown that patients with low CD4 counts on one antiretroviral, despite full HIV RNA suppression, can show significant rises in CD4 counts after switching to an alternative antiretroviral. There have been reports of slightly different effects on CD4 counts between treatments—for example, raltegravir versus efavirenz in the STARMRK trial,[10] lopinavir/ritonavir versus efavirenz in the ACTG 5142-trial,[11] or maraviroc versus efavirenz in the MERIT trial.[12] However, these differences between antiretrovirals have generally been small—in the region of 20–40 cells/μL—and have not been correlated with different rates of clinical disease progression between antiretrovirals.

This analysis of the MONET trial could be repeated in larger cohort studies, to assess longer term results from a wide range of antiretroviral combinations. If confirmed, the results could justify a change in current monitoring of people with long-term HIV RNA suppression and CD4 counts more than 350 cells/μL. Continued full HIV RNA suppression could be used as an alternative surrogate marker for sufficient immunologic performance, up to the extent that CD4 cell monitoring is no longer necessary.

**Binding of HIV-1 gp120 to DC-SIGN Promotes ASK-1-Dependent Activation-Induced Apoptosis of Human Dendritic Cells**

**Author Summary**

HIV-1 infected individuals become increasingly immunocompromised and susceptible to opportunistic infection during disease progression, which is associated with significant reduction of the dendritic cell number in the peripheral blood or secondary lymphoid tissues. Because dendritic cells are the most powerful antigen-presenting cells, their survival is critical for host defence and inadequate dendritic cell number will fail to induce effective host immune responses. Here we describe a mechanism that may at least partly explain why dendritic cells become significantly depleted in chronic HIV-1 infection. We found that after binding of the HIV-1 envelope protein gp120 to the dendritic cell surface protein DC-SIGN, the subsequent activation by CD40 ligation, or by exposure to bacterial product lipopolysaccharide or pro-inflammatory cytokines such as TNF-α and IL-1β, will lead to overexpression of pro-apoptotic molecule ASK-1, resulting in excessive dendritic cell death. We also confirmed that DC-SIGN(+) dendritic cells in the blood of HIV-1 infected individuals have actually been pre-sensitized by viral gp120, which exists in vast amount in the blood, for activation-induced exorbitant death. Our study thus reveals a previously unknown pathway for dendritic cell depletion and provides clues for potential therapeutic approaches to prevent DC depletion in chronic HIV infection.

**Neglected Tropical Diseases of Oceania: Review of Their Prevalence, Distribution, and Opportunities for Control**

Kevin Kline, James S. McCarthy, Mark Pearson, Alex Loukas, Peter J. Hotez

**Abstract**

Among Oceania's population of 35 million people, the greatest number living in poverty currently live in Papua New Guinea (PNG), Fiji, Vanuatu, and the Solomon Islands. These impoverished populations are at high risk for selected NTDs, including *Necator americanus* hookworm infection, strongyloidiasis, lymphatic filariasis (LF), balantidiasis, yaws, trachoma, leprosy, and scabies, in addition to outbreaks of dengue and other arboviral infections including Japanese encephalitis virus infection. PNG stands out for having the largest number of cases and highest prevalence for most of these NTDs. However, Australia's Aboriginal population also suffers from a range of significant NTDs. Through the Pacific Programme to Eliminate Lymphatic Filariasis, enormous strides have been made in eliminating LF in Oceania through programs of mass drug administration (MDA), although LF remains widespread in PNG. There are opportunities to scale up MDA for PNG's major NTDs, which could be accomplished through an integrated package that combines albendazole, ivermectin, diethylcarbamazine, and azithromycin, in a program of national control. Australia's Aboriginal population may benefit from appropriately integrated MDA into primary health care systems. Several emerging viral NTDs remain important threats to the region.


**Introduction**

The neglected tropical diseases (NTDs) represent the most common infections of the world's poorest people, a group sometimes known as “the bottom billion” [1], [2]. These tropical infections trap people in poverty through their adverse effects on worker productivity, pregnancy outcomes, and child cognition and development [1], [2]. Recently, the World Health Organization (WHO) developed a list of 17 NTDs [3], with an expanded list of these conditions on the website of *PLOS Neglected Tropical Diseases* [4]. Since 2008, efforts have been made to review and describe the differences in the etiologies, prevalence, and disease burden of the major NTDs according to their regional distribution [5]–[12]. In this respect, the prevalence and distribution of the NTDs in the Americas [5]–[7], Europe [8], sub-Saharan Africa [9], China and East Asia [10], India and South Asia [11], Central Asia [12], and the Middle East and North Africa [13] have been previously reviewed. Here we summarize current knowledge on the prevalence and distribution of the NTDs in the region known as Oceania, which includes Australia, New Zealand, Melanesia, and the Polynesian and Micronesian islands of the Pacific. This review was conducted using the online database PubMed from 1997 to 2012 with the Medical Subject Headings, the specific diseases listed in the WHO's first report on NTDs, and the list from *PLOS Neglected Tropical Diseases* [3], [4], as well as the geographic regions and countries of Oceania. Reference lists of identified articles and reviews were also manually searched, as were databases from the WHO (http://www.who.int), including the *Weekly Epidemiological Record*.

**Poverty in Oceania**

Approximately 35 million people live in Oceania, a region of tropical and sub-tropical islands in the South Pacific Ocean (Figure 1). Almost two-thirds of the population (22.3 million) lives on the continent of Australia, followed in descending order by Papua New Guinea (6.8 million), New Zealand (4.4 million), Fiji (0.9 million), and the Solomon Islands (0.5 million) (Table 1). In all, of the dozens of island nations that comprise Oceania, more than 99% live in eight nations including those listed above, together with French Polynesia, New Caledonia, and Vanuatu. Despite their proximity to one another, the nations of Oceania represent a diverse array of economies. Australia and New Zealand each rank near the top of the United Nations human development indices (HDIs, 2nd and 5th, respectively) [14], whereas more than one-third of the population of Papua New Guinea (PNG) live below the World Bank poverty figure of US$1.25 per day [15]. PNG has an HDI of 153, placing it near the bottom of the global HDIs and is one of only four non-sub-Saharan countries (the others being Afghanistan, Haiti, and Yemen) with HDIs below 150 [14]. Fiji, Vanuatu, and the Solomon Islands also have HDIs of 100 or lower [14]. However, extremely impoverished indigenous groups are also found within the two wealthiest countries in the region, Australia and New Zealand. For instance, Aboriginal Australians, numbering nearly half a million, earn average incomes amounting to 62% of non-indigenous residents [16]. Within Australia, indigenous Australians reside in greatest numbers in New South Wales and Queensland, although the Northern Territory has the highest percentage of Aboriginal people [17].
Throughout the world’s low- and middle-income countries, and even among wealthy countries, the NTDs disproportionately affect people living in poverty, but especially those in extreme poverty [5]–[13]. Here we provide an overview of the major NTDs affecting people living in poverty in Oceania, with an emphasis on the eight nations with populations that exceed 200,000 and comprise more than 99% of the number of people living in this region.
Helminth Infections
Helminth infections may represent the most prevalent NTDs in Oceania, led by hookworm and lymphatic filariasis (LF; Tables 2 and 3), although significant numbers of cases of ascariasis, trichuriasis, strongyloidiasis, and hymenolepiasis are also present.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated Number of Cases in Oceania</th>
<th>Percentage of Global Disease Burden</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hookworm infection</td>
<td>5.5 million</td>
<td>1%</td>
<td>[18,129]</td>
</tr>
<tr>
<td>Lymphatic Filariasis</td>
<td>2.7 million</td>
<td>2%</td>
<td>[34,130]</td>
</tr>
<tr>
<td>Trichuriasis</td>
<td>1.2 million</td>
<td>&lt;1%</td>
<td>[18,129]</td>
</tr>
<tr>
<td>Ascarisiasis</td>
<td>1.2 million</td>
<td>&lt;1%</td>
<td>[18,129]</td>
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*Numbers for the hookworm infection, trichuriasis, and ascarisiasis were derived by multiplying the current population of each nation as reported in Table 1 by the percentage of people infected as reported in reference [18].

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<tbody>
<tr>
<td>Hookworm</td>
<td>Papua New Guinea (4.9 million)</td>
<td>Fiji (318,000)</td>
<td>Solomon Islands (192,000)</td>
<td>Vanuatu (88,000)</td>
<td>[18]</td>
</tr>
<tr>
<td>Trichuriasis</td>
<td>Fiji (541,000)</td>
<td>Solomon Islands (338,000)</td>
<td>Papua New Guinea (204,000)</td>
<td>Vanuatu (150,000)</td>
<td>[18]</td>
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<tr>
<td>Ascarisiasis</td>
<td>Papua New Guinea (748,000)</td>
<td>Fiji (215,000)</td>
<td>Solomon Islands (135,000)</td>
<td>Vanuatu (59,000)</td>
<td>[18]</td>
</tr>
<tr>
<td>Lymphatic Filariasis</td>
<td>Papua New Guinea (2.7 million)</td>
<td></td>
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doi:10.1371/journal.pntd.0001755.t003

Soil-Transmitted Helminth Infections
Hookworm infection is possibly the most prevalent NTD in Oceania, with an estimated 5.5 million cases, comprising roughly 1% of the world’s cases of hookworm infection [18]. Most of Oceania’s hookworm cases are concentrated in PNG, where according to some estimates three-quarters of the population is infected, followed by Fiji, the Solomon Islands, and Vanuatu [18]. Necator americanus is the predominant hookworm species in PNG, comprising 100% of the hookworms in some areas [19], [20] (Supplemental Table 1 in Text S1) It is not known whether Ancylostoma duodenale is also present in PNG, but during the Australian Hookworm Campaign of 1919–1924, PNG was also studied, and N. americanus was found to be virtually the only hookworm detected [21]. In contrast, both N. americanus and A. duodenale may have been present historically in Australia among both white and Aboriginal communities. Today, hookworm is found almost exclusively among Aboriginal Australians in Western Australia and the Northern Territory, where A. duodenale is believed to be the sole species [21]. During the 1990s, isolated Aboriginal populations in northwest Australia exhibited hookworm prevalence rates that exceeded 75% (with high rates of hookworm anemia) [22], but no recent published data are available. However, it is likely that mass drug administration (MDA), although provided inconsistently, has reduced the hookworm prevalence among selected communities [23]. A unique eosinophilic enteritis syndrome caused by the dog hookworm, Ancylostoma caninum, has also been reported from north Queensland, and elsewhere in Australia, although it is not considered a significant public health problem [24].

Among the other soil-transmitted helminth nematode infections, ascariasis and trichuriasis are much less common in Oceania. However, trichuriasis appears to be a common geohelminth in Fiji, accounting for almost one-half of the number of cases in Oceania, while large numbers of cases also appear in the Solomon Islands and Vanuatu [18]. PNG accounts for much of the ascariasis in Oceania [25], followed by Fiji, the Solomon Islands, and Vanuatu [18]. Strongyloidiasis is an important soil-transmitted helminth infection in Oceania, although no overall prevalence data are available. Among Aboriginal Australian populations, the high rates of Strongyloides stercoralis infection may partly reflect a high incidence of human T-cell lymphotropic virus type 1 (HTLV-1) infections, which predisposes to this parasite. Prevalence rates of S. stercoralis infection as high as 60% have been reported [26]. A high mortality from S. stercoralis and HTLV-1 co-infections can result because of Strongyloides hyperinfection [27]. In a study of Strongyloides hyperinfection in central Australia among Australian Aboriginals, 77% were found to be HTLV-1 positive [28]. In PNG, S. stercoralis infection also occurs [26], as well as a unique form of strongyloidiasis caused by S. fuelleborni kellyi [25]. This form of the infection can be vertically
transmitted, and has been associated with swollen belly syndrome in the Gulf and Madang provinces [25]. In one study, 27% of children tested positive for Strongyloides, with 81% of these children under the age of one [25]. Strongyloides-infected populations in both Australia and PNG may therefore benefit from MDA programs using ivermectin [26]. Outside of PNG, S. stercoralis infection has recently been described in medical volunteers in the Solomon Islands [29]. Sporadic cases of human Trichostrongyulus infections have also been reported [30–32].

Hymanolepis nana infection has been reported as a common soil-transmitted cestodiasis among Aboriginal communities in Australia and PNG [23], [33], although the overall prevalence is not known. In Australia’s Northern Territory, MDA with albendazole was found to be ineffective at reducing the prevalence of this infection [23].

Lymphatic Filariasis (LF)

Next to hookworm and possibly strongyloidiasis, LF is likely to be the most prevalent helminthic NTD in Oceania. Although LF is found throughout Oceania, PNG is the only nation with a published national prevalence estimate [34]. In 1997 it was estimated that approximately 2.7 million people were infected [34], accounting for more than 2% of the global disease burden. Since then, MDA has been implemented with diethylcarbamazine citrate (DEC) plus albendazole [35]. On Lihir Island, MDA in conjunction with vector control led to a 75% reduction in the seroprevalence of microfilarial antigenemia [36], [37] and evidence of reduced transmission [38]. Despite these measures, the WHO reported in 2010 that, of the 5.6 million people in PNG who would benefit from empirical chemotherapy for LF, only 6.3% had been covered nationally [39].

Throughout most of Oceania, LF elimination efforts through MDA are underway through the auspices of the Pacific Programme to Eliminate Lymphatic Filariasis (PacELF) [40]. MDA has now ceased in Vanuatu because the prevalence has dropped below the 1% threshold. Ongoing post-MDA surveillance will be required to certify elimination efforts in this country [40]. On Ouvea Island, New Caledonia, a survey indicated that approximately one-third of the population was antigenemic prior to launching their PacELF program [41]. As of 2010, mapping of LF is complete in New Caledonia, but no MDA program has been implemented [39]. Fiji and French Polynesia currently have active MDA programs underway with 100% coverage [36]. On Fiji’s Kadavi Island, DEC has reduced the percent testing positive for microfilaraemia by 90% [42]. In PNG, PacELF has not yet been implemented at a national level. The remaining countries—Australia, New Zealand, and Solomon Islands—are considered non-endemic [36]. Of interest, the Solomon Islands achieved elimination largely through a program of vector control rather than MDA [43].

Zoonotic Helminth Infections

Two emerging helminth zoonoses, cystic echinococcosis (hydatid disease) and cysticercosis, are of concern. While several eradication programs have been implemented on the mainland of Australia, Echinococcus granulosus remains widespread among sheep and macropods [44], [45]. In Tasmania, following a successful eradication program, only one echinococcosis case of mainland Australian origin has been reported since 1974 [46]. Although echinococcosis has been declared eliminated in New Zealand, reports of hydatid disease presentations have occurred in Auckland, likely through importation [46], [47]. Cysticercosis is not endemic in Australia, but it has occurred in recent immigrants and Australians traveling to endemic regions [48], [49]. In PNG, indigenous and West Papuan refugees living along the border were found to have asymptomatic Taenia solium infections, but more comprehensive studies are needed to recognize the true prevalence of infection [50]. Trichinella psuedospiralis infections have been isolated from humans in Tasmania [51].

Protozoan Infections

The major intestinal protozoan infections in Oceania are amebiasis, balantidiasis, cryptosporidiosis, and giardiasis (Supplemental Table 5). In Australia, these infections can disproportionately affect Aboriginal populations. However, no overall prevalence estimates are available. Among urban Australians, an analysis of seroprevalence of men who have sex with men (MSM) indicated that HIV+ MSM have a higher seroprevalence of Entamoeba sp. infection than HIV− MSM [52], [53]. It is uncertain whether this represents infection with the pathogenic species Entamoeba histolytica or the saprophyte Entamoeba dispar. In New Caledonia, E. histolytica was found among hospitalized patients with hepatic abscesses [54]. Epidemic foci of Balantidium coli infection have been reported from swine-producing areas of PNG, and an outbreak of balantidiasis was described after a typhoon on Truk resulted in contamination of ground and surface water with pig feces [55]. Giardiasis is also common among Aboriginal Australians and presumably other populations in Oceania [22]. Albendazole used for deworming these populations may also have had some activity against Giardia [56], [57]. Among non-Aboriginal communities,
exposure to this pathogen has been identified in waterborne outbreaks, and is believed to be common among children in daycare settings [58]–[60]. In New Zealand, Giardia parasites were found in some people presenting with acute gastrointestinal illness [61]. Chagas disease is not endemic in any of the nations in the Oceania region. However, immigration of over 80,000 immigrants from Latin America to Australia in 2006 is likely to have resulted in the importation of 1,000 or more cases [62]. When combining the permanent arrivals from Argentina, Brazil, Chile, El Salvador, and Uruguay, as well as the resident population of Latin American immigrants from Columbia and Peru, the potential number of infected individuals in this group has been estimated to be 16 per 1,000 in Australia [63].

**Bacterial and Fungal NTDs**

The major bacterial NTDs include the treponematoses, yaws, and congenital syphilis; intracellular bacterial infections including active trachoma, leprosy, Buruli ulcer, bartonellosis, bovine tuberculosis (TB), and brucellosis; and leptospirosis and cholera (Supplemental Tables 2–4, 6). Mycetoma is a fungal NTD in the region.

**Treponematoses**

Yaws has not been eliminated from Oceania despite its susceptibility to MDA with azithromycin, or azithromycin used together with DEC in programs of PacELF [64], [65] (Supplemental Table 6). While great strides have been made in eliminating yaws, this chronic infection remains endemic in PNG, the Solomon Islands, and Vanuatu, although advanced cases are rare [66]. Infections occur among schoolchildren in PNG, including a high proportion of cases in the secondary stage (46%) [67], while an unspecified number of cases have been serologically detected in the Solomon Islands and elsewhere [68], [69]. Studies on school children from the island of Tanna in Vanuatu have recently confirmed a resurgence of yaws [70]. As part of WHO’s elimination program for congenital syphilis, PNG, the Solomon Islands, and Fiji have reported surveillance data on this infection, with PNG exhibiting the highest prevalence [71]. A prior WHO report combined seven studies of maternal syphilis seroprevalence from 1997 to 2003 for Vanuatu. Studies of syphilis among pregnant women were also performed in New Caledonia with seroprevalence between 7% and 12.4% [72].

**Active Trachoma, Leprosy, and Other Intracellular Bacterial NTDs**

Trachoma infections occur in Australia, PNG, Fiji, Vanuatu, and the Solomon Islands (Supplemental Table 2). The most recent released data from the WHO in 2003 indicated the greatest number of active trachoma cases were in PNG (16,289), followed by Australia (8,800), Fiji (1,865), and the Solomon Islands (1,403) [73]. Additional data indicated that the prevalence of active trachoma in Fiji, the Solomon Islands, and Vanuatu are similar (22%–23%) [74]. Aboriginal Australians living in remote communities also suffer from high prevalence of trachoma [75]. The SAFE (surgery, antibiotics, facial cleanliness, and environmental control) program has been implemented among Aboriginal Australians communities, with some reductions in overall prevalence [76].

The prevalence of leprosy is again highest in PNG, with 281 reported new cases in 2010 in addition to an estimated 580 existing cases [77]. Among Aboriginal Australians in the early 1950s, the incidence of diagnosis of leprosy was 270 per 100,000, but had fallen to 4/100,000 in the Northern Territory by 1997 [78]. This decrease was attributed to widespread use of the BCG vaccine in Aboriginal populations since 1958 [78]. Buruli ulcer, another mycobacterial infection, is endemic in some specific locations in Southeastern Australia and Queensland, with focal outbreaks being reported [79], [80]. Bartonellosis caused by Bartonella henselae has been detected in blood donors from Australia and New Zealand, as well as in children with hepatic abscesses in New Caledonia [81]–[84]. Bovine TB is present New Zealand, but it represents a small proportion of the overall TB incidence in Oceania [85], [86]. There were also cases of bovine TB originating in PNG that were detected in Australia [86]. Brucellosis is reportable in Australia, with 32 cases documented in 2009 [87].

**Leptospirosis**

Leptospirosis is endemic in Oceania, with both sporadic cases and outbreaks being reported. In Australia, there has been a significant increase in the incidence of leptospirosis over the past decade, with the heaviest occupational burden among banana farmers and dairy workers [88]. In 2009, Australia reported 149 cases of leptospirosis nationally, with over 75% of the cases occurring in Queensland [87]. In New Zealand, 81 cases of leptospirosis were reported in 2010, with an elevated incidence in Ruapehu, the West Coast District, and Hawke’s Bay [89], [90]. In New Caledonia, an outbreak of leptospirosis occurred during heavy rainfalls and flooding attributed to La Nina [91], while American Samoa was found to have a high prevalence of the disease [92]. Previously in Fiji, Vanuatu, and French Polynesia, Leptospira icterohemorrhagiae was identified as the dominant species [93], [94].
Cholera
Cholera outbreaks have been noted in several nations of Oceania. In 2009, an outbreak occurred in PNG, eventually reaching 8,997 cases by the end of 2010, with the highest incidence in the Madang Province \[95\], \[96\]. In addition, an outbreak was reported from a resort in Fiji \[97\]. In Australia, four cases, all imported were reported in 2009.

Arboviral Infections
The major arboviral infections in Oceania are the flavivirus infections caused by dengue, Japanese encephalitis (JE), and Murray Valley encephalitis (MVE), as well as mosquito-transmitted alphavirus infections, Ross River virus (RRV) and Barmah Forest virus (BFV).

Overall, the incidence of dengue is underreported in Oceania. In Australia, dengue infection and associated mortality were first identified in Charters Towers in northern Queensland in 1897 \[98\]. There have been reports of dengue in Fiji, French Polynesia, New Caledonia, the Solomon Islands, and Vanuatu prior to 1950 \[99\]. In 2010, the Western Pacific Region of the WHO (WPRO) reported national incidence data for dengue in Australia, Fiji, French Polynesia, New Caledonia, New Zealand, and Vanuatu (Supplemental Table 4) \[100\]. French Polynesia, New Caledonia, Vanuatu, and Australia accounted for more than 90% of the reported cases within the Western Pacific subregion \[100\]. In Australia, North Queensland reports the greatest number of cases \[100\], which included an outbreak during the 2008–2009 wet season \[101\]. Dengue is not endemic in New Zealand, and in 2010 all 51 reported cases in New Zealand were of foreign origin, with Vanuatu accounting for 12% of those cases \[87\], \[100\]. In addition to WPRO surveillance, a seroprevalence study indicated that dengue has also emerged in the Solomon Islands \[102\]. The overall epidemiology of dengue is perhaps least understood in PNG, although evidence for the infection has been found in adults and children with febrile illness \[103\].

Within Oceania, JEV and MVE are found primarily in Australia and PNG. JE emerged during the 1990s in PNG and in the Torres Strait of Australia \[104\]. The reports of JE in the Torres Strait islands may have resulted from movement of migratory birds or wind-blown mosquitoes from PNG \[105\]. The JE isolates from PNG and Torres Strait share >99% sequence identity \[106\]. In Australia, MVE is endemic in north and southeastern Australia, with four cases reported 2009 \[87\], \[107\], while in PNG MVE was identified in mosquito isolates, but no human seroprevalence data are available \[106\].

In Australia, RRV infection has been reported periodically, but outbreaks have become more intense and frequent \[108\]. In 2009, 4,786 cases were reported in Australia, with nearly half in Queensland \[87\]. In PNG, no national prevalence data have been compiled, but in the Southern Highlands Province antibody prevalence for RRV was 59% \[109\]. After an apparent disappearance in the years following a 1979–1980 outbreak, RRV has reemerged in Fiji \[110\]. BFV is unique to Australia, and is distributed throughout the continent with the highest incidence in Queensland \[111\]. In 2008, the national incidence of BFV was found to have increased 34% over the mean rate of the previous 5 years \[111\]. Within Australia, RRV and BFV account for most of the reported arbovirus disease notifications \[101\].

Ectoparasitic Infections
Scabies is a major endemic ectoparasitic infection among Aboriginal Australians and in other Oceanic nations. In Australia, pre-treatment prevalence levels exceeded 30% among indigenous children in some communities \[112\], \[113\], with high rates of secondary infections of streptococcal pyoderma \[112\]–\[114\]. MDA treatment with ivermectin in a village in PNG was found to reduce scabies prevalence by two-thirds to 26% \[115\]. In the Solomon Islands, scabies prevalence among children was reduced with ivermectin treatment to 0.7% \[116\]. In two studies undertaken in Fiji, the burden of scabies in schoolchildren was between 18.5% and 32% \[117\], \[118\]. A study in Vanuatu demonstrated increased efficacy of ivermectin over benzyl benzoate in treating childhood scabies \[119\]. Myiasis has also been reported in New Zealand, acquired both in the country and internationally \[120\].

Discussion
Several important NTD trends have emerged in the Oceania region.

1. MDA. Proof of concept for achieving success in MDA in Oceania has been obtained through the PacELF with high levels of LF treatment coverage in Fiji, French Polynesia, and New Caledonia, and the possible elimination of LF in Vanuatu \[40\]. The Solomon Islands has previously eliminated LF through vector control \[43\]. As such successes have not yet extended to PNG, it remains the most endemic in Oceania \[36\], \[40\]. A concerted effort in PNG for LF elimination in the coming years would be consistent with efforts by the Global Programme to Eliminate LF’s to eliminate this disease as a public health problem globally by 2020 \[40\], \[121\]; there is an urgency to ensure that the government of PNG has the adequate human capital and technical support as well as sufficient funding to expand MDA and elimination efforts. Currently, there are no comprehensive post-MDA surveillance programs in place for
any LF-endemic country in the region. The development and implementation of surveillance plans for all countries will be important to monitor areas of persistent or re-emerging LF [40]. Additional targets for MDA in Oceania could include soil-transmitted helminth infections, which could be linked to LF elimination efforts through the addition of albendazole to DEC, as well yaws elimination through the addition of azithromycin to DEC [64], [65]. The recent finding by Mitja et al. that single-dose azithromycin is as effective as benzathine benzyl penicillin for the treatment of yaws in PNG is an important breakthrough on that front [64]. There are opportunities to scale up these options, especially in PNG [64].

2. **PNG.** More than any other nation in Oceania, PNG stands out with respect to having the largest number of cases and high prevalence of several key NTDs, including *N. americanus* hookworm infection, strongyloidiasis, hynemopleiiasi, LF, balantidiasis, yaws, trachoma, leprosy, and possibly scabies and dengue and other arboviral infections, as well as outbreaks of cholera [18], [25], [33], [34], [55], [64], [73], [77], [103], [115]. PNG could benefit enormously from a national control program of integrated MDA that simultaneously targets many of these NTDs using the drugs albendazole, ivermectin, DEC, and azithromycin. Therefore, there are opportunities to collect the safety data needed to determine the suitability of combining these medicines in an integrated MDA package, together with financial support for implementation linked to operational research.

3. **Aboriginal populations in Australia.** Australia’s Aboriginal population also suffers from disproportionately high rates of NTds, including strongyloidiasis, leprosy, and scabies, and possibly hookworm infection [26], [73], [112], [119]. There may be opportunities for integrating MDA packages as outlined above for PNG into programs of primary care for Australia’s Aboriginal populations.

4. **Arboviral infections.** The impact of arboviral infections, especially emerging dengue and RRV in PNG, is still not well understood [106]. Dengue, JE, and RRV could emerge as important NTD pathogens in Oceania in the coming decade. Malaria is endemic in regions of PNG, the Solomon Islands, and Vanuatu. In the Solomon Islands, malaria vector control was responsible for a substantial reduction of LF [122]. Current malaria programs implemented by the Pacific Malaria Initiative Support Centre (PacMISC) in Vanuatu and the Solomon Islands as well as the Global Fund in PNG are promising tools for reducing the burden of several mosquito-borne diseases, particularly in PNG, where *Anopheles* transmit both malaria and LF. Integration of monitoring and evaluation M&E in these programs and in non-endemic nations will provide assistance in controlling the rising threat of arboviral pathogens in the future. In summary, tremendous strides have been made in controlling and eliminating some of the major NTDs throughout the region but especially in PNG and among Aboriginal Australians.

**Learning Points**

- The efficacy of the Pacific Programme to Eliminate Lymphatic Filariasis (PacELF) has been demonstrated in Oceania, but enhanced efforts are still required in Papua New Guinea and New Caledonia.

- While proof of concept for NTD management in Oceania was shown by PacELF, novel MDA programs need to be crafted, especially in Papua New Guinea and Aboriginal Australia, in order to target specific NTDs indigenous to neglected populations in these regions, including hookworm, strongyloidiasis, and other soil-transmitted helminthiases, yaws, trachoma, and scabies.

- While the impact of emerging arboviral infections, including dengue, Japanese encephalitis, and Ross River virus infection, is still not well understood, these diseases could also emerge as important NTDs in the coming decade.

**Key Articles in the Field**


**National Borders Effectively Halt the Spread of Rabies: The Current Rabies Epidemic in China Is Dislocated from Cases in Neighboring Countries**

**Author Summary**

Rabies as a fatal zoonotic disease continues to be a public threat to global public health. After India, China reports the second highest number of human cases, with more than 117,500 deaths and three major epidemics since 1950. China remains in the middle of the third epidemic. In this work we investigate the impact of China on rabies in South East (SE) Asia. We collected nucleoprotein sequences from samples isolated throughout SE Asia and investigated their phylogenetic and geographic relationships. Our results indicate that clear geographic patterns exist within rabies virus in SE Asia, with isolates mainly clustered according to their geographic origin. While we found evidence of the sporadic exchange of strains between neighboring countries, the major strain responsible for the current Chinese epidemic does not appear to spread to neighboring countries. Our findings suggest that national geographical boundaries and border controls act as effective barriers to halt the spread of rabies from China into adjacent regions. We further investigated the geographic structure of Chinese sequences and found the current epidemic is dominated by variant strains that likely evolved from previous domestic epidemics. Our study provides valuable insight for rabies control and prevention in China and SE Asia.


**Results of TB vaccine trial give cause for optimism, say researchers**

Michael Carter
Published: 04 February 2013
Results of a trial have been praised for “providing hard evidence about protection against tuberculosis in human beings.” The MVA85A vaccine did not confer any additional protection against tuberculosis (TB) or infection with *Mycobacterium tuberculosis* to infants who had already been immunised with the BCG vaccine.

However, MVA85A was found to induce an anti-TB immune response and was safe. Investigators are hopeful that the study’s findings, which are published in *The Lancet*, will provide important insights in the quest for a new TB vaccine, and that the product may yet prove efficacious in adolescents and adults.

“MVA85A could potentially protect adolescents and adults against pulmonary tuberculosis, in view of the fact that immunologically immature infants do not respond as well to this vaccine as adults do,” write the authors.

TB is a global health problem. Key to the long-term control of the epidemic is the development of an effective vaccine. The existing BCG vaccine protects young children against disseminated TB, but its efficacy against pulmonary TB is highly variable. Moreover, its effectiveness against infection with *Mycobacterium tuberculosis* is questionable. There is therefore an urgent need for an improved infant TB vaccine regimen.

MVA85A has been developed as a booster for BCG. It has performed well in laboratory studies, and an early clinical trial in infants showed that it was well tolerated.

An international team of investigators wanted to find out more about the safety and efficacy of MVA85A.

They therefore designed a double-blind, placebo-controlled, phase 2b study involving 2797 South African infants. All were HIV-negative and had received the BCG vaccine soon after birth. On a 1:1 basis, the infants were randomised to receive MVA85A or a placebo. There were monitored for localised and systemic adverse events and were followed every three months for evidence of TB disease or infection with *Mycobacterium tuberculosis*.

The median duration of follow-up was a little under 25 months. More infants in the MVA85A arm developed a localised adverse event than patients in the control group (89% vs. 45%). “The high frequency of mild, self-limiting local reactions to MVA85A recipients is consistent with previous studies,” comment the investigations.

Systemic side-effects were common both study arms, occurring in 80% of MVA85A recipients and 76% of those in the placebo group.
A serious adverse event was observed in 18% of infants in each of the study arms. No serious adverse events was related to MVA85A.

MVA85A was found to induce a CD4 cell response. However, this did not appear to confer any additional protection against TB compared to that already provided by BCG vaccination.

A total of 32 (2%) of MVA85A recipients developed TB (incidence 1.15 per 100 person years), as did 39 infants (3%) in the placebo arm (incidence 1.39 per 100 person years). The 17% reduction in TB incidence associated with the investigational vaccine was not significant.

Infection with *Mycobacterium tuberculosis* occurred in 13% of infants in the MVA85A arm and 12% of patients in the control arm.

“MVA85A was well tolerated and immunogenic in healthy infants who had been previously vaccinated with BCG,” write the investigators. “We noted no significant efficacy tuberculosis or *Mycobacterium tuberculosis* infection.”

The study investigators and the authors of an accompanying editorial were upbeat about the findings of the research.

“Our study showed that a large efficacy trial of a new tuberculosis vaccine in a high-burden setting is feasible with a stringent and objective case definition,” comment the investigators.

The authors of the editorial believe that MVA85A may yet prove to be useful in the fight against TB. They note that the BCG vaccine already provides high levels of protection against TB disease to infants and additional efficacy may have been “asking too much of MVA85A.” The authors also suggest that further research should explore the use of the product as a BCG booster in adults, and they ask “might this vaccine work if administered to people infected with HIV?” Trials are currently testing the vaccine in HIV-positive adults in South Africa and Senegal.

Two trials of TB vaccines of a similar type to MVA85A, sub-unit boosting vaccines, are currently underway, one in infants in South Africa and an adult study of GSK M72, a vaccine being developed by GlaxoSmithKline.

Further research will also take place to identify immunological correlates of protection against TB infection in infants vaccinated in the MVA85A study; Christopher Dye of the World Health Organization and Paul Fine of the London School of Hygiene and Tropical Medicine comment: "The identification of of a valid measure of protective immunity against tuberculosis would be a discovery of overwhelming importance."

Reference


**Vaccine Group Funds Cervical Cancer Immunizations for Poor**

*Reuters,* (02.03.2013) Kate Kelland

The nonprofit GAVI Alliance, which funds bulk-buy vaccination programs for poor nations, will safeguard more than 180,000 girls from cervical cancer in eight countries across Africa and Asia by funding immunization projects with vaccines from GlaxoSmithKline (GSK) and Merck. The eight countries GAVI will support for cervical cancer protection pilot projects are Kenya, Ghana, Laos, Malawi, Madagascar, Niger, Sierra Leone, and Tanzania.

The world's only two approved shots are GSK's Cervarix and Merck's Gardasil vaccines, which are designed to protect against the sexually transmitted human papillomavirus (HPV) that causes the greatest share of cervical cancer cases. More than 85 percent of cervical cancer deaths occur in developing nations, and 275,000 women die of the disease each year. GAVI declares that, globally, cervical cancer now kills more women than childbirth, taking a life every two minutes. Experts have stated that if no action is taken to protect females from cervical cancer, the annual worldwide death rate could rise to 430,000 by 2030.

GAVI's vaccination efforts will receive backing from the World Health Organization, the Bill & Melinda Gates Foundation, the World Bank, UNICEF, donor governments, and others. These organizations have been working with the vaccine manufacturers to secure the most affordable price for the shots. These pilot projects will provide countries an opportunity to test whether they can put systems into place that are needed to offer HPV vaccines nationally.

Most vaccines are offered to infants and children under age five; however, HPV vaccines are to be given to girls aged nine to 13 to protect them before they become sexually active. A major challenge is that many developing countries do not provide routine health services for girls in this age group. GAVI does
point out that the initial experience in offering HPV vaccines through schools in Latin America, Asia, and Africa has been encouraging. GAVI states that it hopes to help more than 20 countries immunize approximately a million girls with HPV vaccines by 2015 via these pilot projects; by the year 2020, GAVI anticipates helping more than 30 million girls in more than 40 countries obtain the vaccine.

Researchers pioneer treatment for viral infection common in children

Researchers at Imperial College London have discovered a new way in which a very common childhood disease could be treated. In the first year of life, 65 per cent of babies get infected by Respiratory Syncytial Virus (RSV). This causes bronchiolitis, and is thought to kill nearly 200,000 children every year worldwide.

In 1966 and 1967, vaccines were tested for RSV. These had disastrous effects on the immune response, leading to a worsening of the disease and, in many cases, death. Scientists have so far not been able to fully explain this effect, which continues to hold back vaccine development.

Studying this effect in mice, Imperial’s Professor Peter Openshaw and his team developed a new technique which they hope might be used in tackling a wide range of other diseases including viral bronchiolitis.

In a paper published in the Proceedings of the National Academy of Sciences, the researchers examined how the RSV vaccine boosts white blood cells that respond to infection, making them flock to the lungs and blocking the tubes that supply oxygen. They found that the vaccine boosted the accumulation of these T cells, but also virtually eliminated the regulatory immune response in the lungs caused cells known as Tregs.

Professor Openshaw said: "The reason for the vaccine's failure has been a puzzle for over 40 years. To solve it, we tested out new ideas about how the immune system slows down inflammation. If it doesn't regulate itself properly, inflammation can run out of control. This vaccine seems to have locked the accelerator in the on position and to have disabled the brakes.

Next, the team tested the effects of chemokines, proteins which cause nearby cells to move from place to place in the body. They found that when vaccinated mice inhaled the chemokines, Tregs were attracted back into the lungs where they reduced inflammation and helped to fight infection.

Professor Openshaw added "This is a very important discovery—it represents an entirely new way to treat these inflammatory diseases." If this approach were to work in patients, it could be used in a wide range of conditions in which there is excessive inflammation such as arthritis or psoriasis as well as bronchiolitis.

Openshaw's group hope that by gaining a better understanding of RSV disease they may at last be able to understand why some babies get so seriously ill, whereas others make a quick recovery. This knowledge could lead progress in reducing RSV's global impact and in the development of safe, and effective vaccines.

"Defective immunoregulation in RSV vaccine-augmented viral lung disease restored by selective chemotraction of regulatory T cells" Proceedings of the National Academy of Sciences journal, published in print Monday 4 February 2013 Jens Loebbermann, Lydia Durant, Hannah Thornton, Cecilia Johansson, and Peter J. Openshaw Centre for Respiratory Infection, Department of Respiratory Medicine, National Heart and Lung Institute, Faculty of Medicine, Imperial College London, W2 1PG, UK

Scientists notch a win in war against antibiotic-resistant bacteria

Sophisticated modeling and biotechnology used to weaken cells by fouling their metabolic machinery

Boston, MA, February 4, 2013 – A team of scientists just won a battle in the war against antibiotic-resistant "superbugs"—and only time will tell if their feat is akin to the bacterial "Battle of Gettysburg" that turns the tide toward victory.

They won this particular battle, or at least gained some critical intelligence, not by designing a new antibiotic, but by interfering with the metabolism of the bacterial "bugs" – E. coli in this case – and rendering them weaker in the face of existing antibiotics, as reported today in Nature Biotechnology.

It’s the "kick 'em when they're down" style of fighting, and the team from Harvard's Wyss Institute for Biologically Inspired Engineering and Boston University used sophisticated computer modeling and biotechnology as their weapons of choice.

"We are in critical need for novel strategies to boost our antibiotic arsenal," said senior author and Wyss Core Faculty member Jim Collins, Ph.D., a pioneer of synthetic biology who is also the William F. Warren Distinguished Professor at Boston University, where he leads the Center for BioDynamics. "With
precious few new antibiotics in the pipeline, we are finding new ways to harness and exploit certain aspects of bacterial physiology."

In this case, the team targeted a little understood but key part of bacterial metabolism called ROS production.

ROS, or "reactive oxygen species," include molecules like superoxide and hydrogen peroxide that are natural byproducts of normal metabolic activity. Bacteria usually cope just fine with them, but too many can cause serious damage or even kill the cell. In fact, Collins' team revealed a few years ago the true antibiotic "modus operandi": they kill bacteria in part by ramping up ROS production.

The precise genetic mechanisms by which E. coli produces ROS remain elusive, Collins said, so his team adopted a standard computer model that maps out the way scientists currently understand E. coli metabolism. Collins' team began by adding to this "system-level" metabolic model hundreds of reactions that are known to increase ROS production. Then they deleted various genes to see which were involved in ROS production, honed in on the suspected targets after running thousands of computer simulations, and validated the model in the laboratory—achieving 80-90% agreement with the model-based predictions.

"The next challenge was to determine if increasing the ROS production by the cell itself would render it more susceptible to death by oxidative, ergo, antibiotic attack," Collins said—and it did. The team deleted a series of genes that led to increased ROS production in the cell, added different antibiotics and biocides such as bleach—known cell-killers by way of increasing ROS production—and the cells died at a much higher rate than the cells without the deleted genes. In short, by interfering with the bacterial metabolism, the antibiotics and biocides were even more lethal to the cells.

"There is no magic bullet for the global health crisis we're experiencing in terms of antibiotic-resistant bacteria," said Don Ingber, M.D., Ph.D., Wyss Founding Director, "and yet there is tremendous hope in the kinds of pioneering systems biology approaches Jim and his team are spearheading."

The team's next steps are to use molecular screening technologies to precisely identify molecules that boost ROS production, Collins said, and to test the approach used in this E. coli study on other kinds of bacteria—such as the mycobacteria responsible for tuberculosis, a potentially lethal lung disease.

In a Fight to the Finish, Research Aims Knockout Punch at Hepatitis B

Feb. 4, 2013 — In research published in the Jan. 24 edition of PLOS Pathogens, Saint Louis University investigators together with collaborators from the University of Missouri and the University of Pittsburgh report a breakthrough in the pursuit of new hepatitis B drugs that could help cure the virus. Researchers were able to measure and then block a previously unstudied enzyme to stop the virus from replicating, taking advantage of known similarities with another major pathogen, HIV.

John Tavis, Ph.D., study author and professor of molecular microbiology and immunology at SLU, says the finding may lead to drugs which, in combination with existing medications, could suppress the virus far enough to cure patients.

"Hepatitis B is the major cause of liver failure and liver cancer worldwide," Tavis said. "This would have an extremely positive effect on liver disease and liver cancer rates."

"If we can cure hepatitis B, we can eliminate the majority of liver cancer cases. This research is a step toward achieving that goal."

World health experts estimate that more than 350 million people are chronically infected with the hepatitis B virus. Several drugs are able to treat symptoms successfully, though they are not able to cure many patients. Of those infected with hepatitis B virus, up to 1.2 million die from liver failure and liver cancer each year.

A person who is infected with hepatitis B virus can have up to a billion viral copies per drop of blood. To cure a patient, a drug needs to reduce those levels to zero.

Not Quite a Cure

While existing medications are very powerful, they cannot quite deliver the knockout punch to hepatitis B. The drugs approved to treat the virus can reduce its numbers, make symptoms disappear for years and push it to the brink of extinction. But for most people, the medications can't kill the virus completely. And, as long as any virus remains, it can multiply and grow strong again.

And so, hepatitis B treatment usually spans decades, with costs of $400 to $600 a month, if patients can afford the medication. Expensive and beyond the means of many, some patients do not receive any treatment at all. As a compromise measure, some patients opt to take medication for a short time, staving off the damage the illness will cause for a few years.
A 19-Year Puzzle
Hepatitis B virus puts up a protracted fight in the lab, as well. For 19 years, Tavis has worked on a particular part of the virus's genetic puzzle, and until recently he had been, in his words, failing miserably.

The problem was a common one in the laboratory. Until scientists can measure a puzzle piece, they can't study it. And, until researchers have some small success, they don't know if they're on the right track or headed down a dead end.

This was the case for the particular enzyme Tavis believed held answers. Stumped, he returned to the puzzle again and again over the years.

"Until you see that first glimmer, all negatives look the same," Tavis said. "One of the biggest skills in this job is knowing when to give up. It's not obvious when you are wasting time and when you are giving up too early."

In Tavis's case, his instinct served him well, and two years ago, he saw the first glimmer of the answer he was searching for.

A Virus's Tactics
"Viruses are genomic suitcases," Tavis said. "They have many tactics for invading and taking over our cells, using their own DNA as the blueprints."

In the case of hepatitis B virus, and, — in what turned out to be a lucky break, HIV, as well — the virus replicates by reverse transcription. In this process, viral DNA is converted to RNA and then converted back to DNA by two viral enzymes, both of which are vital to the virus's replication.

The first of these enzymes, a DNA polymerase, has been well studied in the lab. The five most commonly used hepatitis B drugs are able to treat (but not cure) the illness by blocking this enzyme.

The second enzyme, ribonuclease H (RNaseH) had eluded investigators in the lab. With no means to measure it, researchers hit dead ends even though they believed the enzyme was a promising target, in theory.

So, with five approved drugs targeting the first enzyme and none aimed at the second, Tavis sparred with RNaseH for nearly two decades.

Search for an Assay
Tavis was searching for a yardstick, of sorts.

Though it made sense to target RNaseH, no method existed that allowed researchers to measure the enzyme's activity. Tavis was looking for an assay, a way to tell if a substance would block the enzyme's function.

After years of work, Tavis and his research team saw the first glimmer of activity and were able to develop an assay for RNaseH, allowing him to begin to study the enzyme and try out promising theories about how to block it.

Borrowing from HIV
Because the hepatitis B and HIV viruses both use reverse transcription, the mechanism by which they copy themselves in the body's cells, hepatitis B researchers have been able to benefit from advances in HIV research. Thanks to substantial funding, HIV research has made rapid progress since the virus's discovery. Several effective drugs for HIV treatment work by targeting the reverse transcription process also work against hepatitis B virus.

Though the viruses are quite different, Tavis and his colleagues Stefan Sarafianos, Ph.D. at the University of Missouri and Michael Parniak, Ph.D., at the University of Pittsburgh believed that the shared process suggested there should be some chemical similarities that could be exploited.

"Just as every car has tires and an engine, both of these viruses have pieces that serve similar functions. You can take an engine from one car and try it in the other. It might not be a perfect fit, but it should serve the same function."

Once the assay for the RNaseH was developed, Tavis and his team were able to try out this theory. "We found that what worked with the first enzyme worked with the second enzyme," Tavis said. "This is a proof of principle. We're on the right track."

Tavis now has a measuring tool and evidence that a number of the techniques that stopped HIV, including inhibitors of HIV RNaseH, could also inhibit the hepatitis B virus RNaseH, showing that the parallels held true. From there, Tavis and his team went on to prove that hepatitis B replication could in fact be stopped in cells with drugs that targeted the elusive second enzyme, RNaseH.

Hope on the Horizon
With these promising advances, researchers say that the search for anti-hepatitis B RNAseH drugs is now feasible and that using similar anti-HIV compounds as a guide is likely to have a high chance of success.
The research team’s next step will be to study several variations of hepatitis B virus, different genotypes of the virus, to be able to measure and study the RNaseH enzyme in all forms of the virus. Current findings demonstrated success in only some genotypes. Findings from the current study suggest some promising avenues as researchers will now attempt to block RNaseH in the two most common genotypes, B and C.

In addition, researchers will aim to improve the strength and speed of the RNaseH assay for high throughput screening, a process for rapidly screening many thousands of compounds. These developments will clear the way for full-scale antiviral drug discovery.

Investigators have reason to hope that combining a new anti-hepatitis B RNaseH drug with the existing drugs may suppress the virus far enough to cure patients with hepatitis B.

"I anticipate a new drug targeting the second enzyme would be used together with the existing drugs," Tavis said. "They jam different parts of the process.

"The drugs we have are very good drugs. They push the virus down, but they can't quite kill it. They'll still do the heavy lifting in the future, but with an additional drug I hope we'll be able to mop up the rest. Together, they may be able to do it. We don't have a big distance we need to travel to reach that point."

**Journal Reference:**
DOI: [10.1371/journal.ppat.1003125](http://10.1371/journal.ppat.1003125)

**Extra-couple HIV transmission a major driver of Africa’s HIV epidemic**
February 4, 2013 in HIV & AIDS New research suggests that heterosexual couples in long-term relationships who have sexual encounters outside their established partnership (extra-couple relationships) are one of the main drivers of the HIV epidemic in sub-Saharan Africa. The findings of the modelling study, published Online First in The Lancet, indicate that current HIV-prevention efforts, which chiefly target couples where one partner is HIV-positive and the other is not (serodiscordant couples), will be insufficient to bring about major reductions in HIV incidence in the general population.

"Because of the large contribution of extra-couple transmission (from outside partnerships) to new HIV infections, interventions should target the larger sexually active population and not just serodiscordant couples", explains Steve Bellan from the University of Texas, Austin, who led the research. "Pre-couple (prior to relationship), extra-couple, and within-couple transmission are all common, and HIV control policies that address all these routes are needed to stem the HIV epidemic in Africa."

In sub-Saharan Africa, where most new HIV infections occur, defining the most-at-risk groups is crucial to targeting intervention efforts effectively. But the proportion of heterosexual HIV transmissions that occur within couples—compared with the proportions that occur in single people or in people in extra-couple relationships—has been hotly debated. To help clarify HIV risk for African couples, the authors of this new study developed a sophisticated modelling system that, unlike previous models, combines serostatus and relationship data from Demographic and Health Surveys (DHS) with country-specific trends for the prevalence of HIV, and estimates of HIV survival times. They used the model to distinguish the specific routes by which individuals became infected in 27 201 cohabiting couples from 18 sub-Saharan African countries. The estimates suggest that 30% of all new HIV infections in men and 10% in women within stable partnerships are the result of extra-couple transmission. Other important findings to emerge were that transmission in couples occurs more from men to women than vice versa, and that women have a period of high infection risk before entering a cohabiting partnership—emphasising the continuing need for prevention strategies aimed at young women. The researchers believe that despite its expense and logistic demands, a test-and-treat strategy that targets all heterosexual routes of transmission could be key to fighting the HIV epidemic. Writing in a linked Comment, Connie Celum and Jared Baeten from the University of Washington say that the findings reinforce that, "HIV prevention for only HIV serodiscordant couples will not be enough to reverse the HIV epidemic completely." They add, "HIV prevention is at a crucial stage: strategies to deliver evidence-based combination prevention efficiently and effectively, targeted at high risk populations and with high coverage for those at risk, will maximise this incredible opportunity in the history of the HIV epidemic."
**Suboptimal Suppression with Maraviroc plus a Boosted Protease Inhibitor?**

**Until larger studies are done, such regimens are probably best avoided.**

A nucleoside reverse transcriptase inhibitor (NRTI) backbone remains standard in combination antiretroviral therapy, but there is ongoing interest in developing NRTI-sparing regimens to avoid the drugs’ short- and long-term toxicities.

In a recent multinational, open-label, manufacturer-sponsored trial, 121 treatment-naive HIV-infected individuals with confirmed CCR5-tropic virus were randomized to receive ritonavir-boosted atazanavir in combination with either tenofovir/FTC or maraviroc at the unusually low dose of 150 mg once daily.

At week 48, rates of virologic suppression (HIV RNA <50 copies/mL) were 75% in the maraviroc group and 84% in the tenofovir/FTC group. The median change from baseline in CD4-cell count was similar between groups (+173 and +187, respectively). Almost all patients in both arms reported treatment-related adverse effects — most commonly jaundice, diarrhea, or nausea. Grade 3 or 4 adverse effects were more common in the maraviroc group (48% vs. 30%); the two patients who had treatment-limiting adverse effects were both in that group. Pharmacokinetic analyses demonstrated adequate plasma concentrations of maraviroc with the dose used.

**Comment:** This trial was not powered to detect meaningful differences in treatment outcome, and the authors characterize it as a proof-of-concept study to show that an NRTI-sparing maraviroc/boosted–protease inhibitor (PI) regimen results in virologic suppression in the majority of patients.

However, readers should note that longer follow-up of the same patients, presented at the recent 2012 International AIDS conference, undercuts these results somewhat: At week 96, the maraviroc group continued to lag behind the tenofovir/FTC group in complete virologic suppression (68% vs. 82%); low-level virologic breakthroughs were also more frequent in the maraviroc group ([JW AIDS Clin Care Aug 20 2012](http://jwc.journals.org/cgi/content/full/23/8/355)). Thus, pending a suitably powered study, clinicians should probably avoid the maraviroc/boosted PI options unless there is really no better alternative.

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**Abigail Zuger, MD**

Citation(s): Mills A et al. Maraviroc once-daily nucleoside analog-sparing regimen in treatment-naive patients: Randomized, open-label pilot study. *J Acquir Immune Defic Syndr* 2013 Feb 1; 62:164.

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**Predicting Survival Among Those Aging with HIV Infection**

*Medical Xpress*, (01.29.2013)

Even with the use of antiretroviral therapy (ART), which can lead to viral suppression and reductions in AIDS-related deaths, researchers maintain that people with HIV infection have a higher mortality rate because chronic HIV infection intensifies age-related organ system injury.

The Veterans Aging Cohort Study (VACS) Index funded by the National Institutes of Health used older indices that measured HIV biomarkers, including CD4 cell count, HIV-1 RNA levels, and patient age, to ascertain mortality risk. The newer VACS Index uses other critical factors, including the increasing role of multi-organ system injury and hepatitis C infection as well as the decreasing role of other factors such as CD4 count.

In a collaborative study by Yale University, the VA Healthcare System, and the North American Cohort Collaboration, the researchers compared the accuracy of the VACS Index with that of the newer VACS. Data reviewed were from more than 5,000 veterans and more than 10,000 non-veterans, representing 14 separate cohorts of HIV-infected persons from around the country who had at least one year of ART. The researchers followed up with patients for a little more than three years.

Researchers found the new VACS Index was much more accurate and effective than the previous index, which used CD 4 count, HIV-1 RNA, and age. Dr. Amy Justice, professor of internal medicine at Yale School of Medicine, stated that the VACS Index accurately estimated risk of mortality among persons aging with HIV infection whether they live in Canada or the United States. She also found that the index was accurate among men and women, older or younger individuals, and white people or people of color. The team has created an app for use by patients and their providers.

It is available at [http://vacs.med.yale.edu/](http://vacs.med.yale.edu/).

New TB Vaccine Shows No Benefit in African Study


The first test of Aeras’s MVA85A TB vaccine has shown it to be ineffective in preventing new infections in infants and in stopping the progression of existing infections. The researchers studied 2,800 South African infants in the rural outskirts of Cape Town. The researchers immunized 2,797 infants aged 4 months. All infants received BCG vaccines; half then received MVA854A and half received a placebo. In the vaccine group, 13 percent became infected with the TB bacterium and 2 percent developed active disease; in the placebo group, 12 percent became infected and 3 percent developed active disease. These differences were not statistically significant.

In the vaccine group, 80 percent had at least one “systemic” side effect, as did 76 percent in the placebo group. Also, 18 percent of the children in each group had a serious adverse event, and seven from the vaccine group and four from the placebo group died during the study. None of the problems were believed to result from the vaccine.

Tom Evans, Aeras’s chief scientific officer, commented that the company is disappointed that the trial did not have a positive outcome, but it does not mean that this type of vaccine would not be useful in another population.

The study, “Safety and Efficacy of MVA85A, a New Tuberculosis Vaccine, in Infants Previously Vaccinated with BCG: A Randomised, Placebo-Controlled Phase 2b Trial,” was published online in the journal The Lancet (2013; doi:10.1016/S0140-6736(13)60477-4).

Antiabortion Activists Block Sexual Health Funding for At-Risk Teens

Salon, (01.29.2013) Katie McDonough

In 2012, two researchers at North Dakota State University (NDSU) received a $1.2 million grant from the US Department of Health and Human Services Administration for Children and Families to inaugurate a sexual health program for at-risk teens that would focus on preventing pregnancy and sexually transmitted diseases. However, the university had contracted with Planned Parenthood—a nationwide women’s health provider that also provides abortion services in many states, although not in North Dakota—to provide the services, and antiabortion activists complained about NDSU associating with the provider. Speaking on a local radio show, Rep. Bette Grande (R-Fargo) denounced both Planned Parenthood and NDSU, stating, “It is an overt abortion industry that we don’t want to be a part of.”

Due to the controversy, NDSU President Dean Bresciani said during a January 15 conservative radio talk show appearance that the university had decided to block the funds, since a “legal hang-up” prevented NDSU from working with Planned Parenthood. The school now says it is freezing the funding while it investigates whether a 1979 state law that prevents state money or federal money coming through the state from being used “as family planning funds by any person or public or private agency which performs, refers, or encourages abortion.”

In the meantime, faculty and local reproductive and sexual health advocates are critical of what they consider to be political interference with both research and public health service delivery. Sarah Stoesz, president of Planned Parenthood Minnesota, North Dakota, South Dakota stresses the teens who were to be the beneficiaries of the program—the at-risk youth who are homeless, in foster care, or in the juvenile justice system—lose the most, particularly in North Dakota where so little is available to them.
Injection-Free Vaccination Technique Could Address Global Vaccine Challenge for HIV, Malaria

Feb. 4, 2013 — Scientists at King’s College London have demonstrated the ability to deliver a dried live vaccine to the skin without a traditional needle, and shown for the first time that this technique is powerful enough to enable specialised immune cells in the skin to kick-start the immunising properties of the vaccine.

Funded by the Bill & Melinda Gates Foundation and published today in Proceedings of the National Academy of Sciences, researchers say although it is an early study this important technical advance offers a potential solution to the challenges of delivering live vaccines in resource-limited countries globally, without the need for refrigeration. A cheaper alternative to hypodermic needles, it would also remove safety risks from needle contamination and the pain-free administration could lead to more people taking up a vaccination. The researchers add that it could have an impact beyond infectious disease vaccination programmes, for example managing autoimmune and inflammatory conditions such as diabetes.

HIV, malaria and TB represent major global health challenges. Although promising research is underway to develop vaccines for these diseases, considerable stumbling blocks remain for countries where transporting and storing live vaccines in a continuously cold environment (around 2°C to 8°C or below) would not be possible. If a cold chain cannot be maintained for a live vaccine there is a high risk it could become unsafe and lose effectiveness.

The team at King’s used a silicone mould developed by US company TheraJect to create a microneedle array—a tiny disc with several micro-needles made of sugar which dissolve when inserted into the skin. The team formulated a dried version of a live modified adenovirus-based candidate HIV vaccine in sugar (sucrose) and used the mould to create the microneedle array. They found that the dried live vaccine remained stable and effective at room temperature.

To test the effectiveness of the microneedle array, they applied it to mice. Using imaging (in collaboration with Professor Frederic Geissmann, King’s College London) they observed how the vaccine dissolved in the skin and were able to identify for the first time exactly which specialised immune cells in the skin ‘pick up’ this type of vaccine and activate the immune system. The researchers found the first evidence that a sub-set of specialised dendritic cells in the skin were responsible for triggering this immune response.

When compared with a traditional needle vaccine method, the immune response generated by the dried microneedle vaccine (kept at room temperature) was equivalent to that induced by the same dose of injected liquid vaccine that had been preserved at -80°C.

Dr Linda Klavinskis from the Peter Gorer Department of Immunobiology at King’s College London, said: ‘We have shown that it is possible to maintain the effectiveness of a live vaccine by drying it in sugar and applying it to the skin using microneedles—a potentially painless alternative to hypodermic needles. We have also uncovered the role of specific cells in the skin which act as a surveillance system, picking up the vaccine by this delivery system and kick-starting the body’s immune processes.

‘This work opens up the exciting possibility of being able to deliver live vaccines in a global context, without the need for refrigeration. It could potentially reduce the cost of manufacturing and transportation, improve safety (as there would be no loss in potency), and avoids the need of hypodermic needle injection, reducing the risk of transmitting blood-borne disease from contaminated needles and syringes.'
This new technique represents a huge leap forward in overcoming the challenges of delivering a vaccination programme for diseases such as HIV and malaria. But these findings may also have wider implications for other infectious disease vaccination programmes, for example infant vaccinations, or even other inflammatory and autoimmune conditions such as diabetes.

Journal Reference:

Green Tea and Red Wine Extracts Interrupt Alzheimer's Disease Pathway in Cells
Feb. 5, 2013 — Natural chemicals found in green tea and red wine may disrupt a key step of the Alzheimer’s disease pathway, according to new research from the University of Leeds.

In early-stage laboratory experiments, the researchers identified the process which allows harmful clumps of protein to latch on to brain cells, causing them to die. They were able to interrupt this pathway using the purified extracts of EGCG from green tea and resveratrol from red wine.

The findings, published in the Journal of Biological Chemistry, offer potential new targets for developing drugs to treat Alzheimer’s disease, which affects some 800,000 people in the UK alone, and for which there is currently no cure.

"This is an important step in increasing our understanding of the cause and progression of Alzheimer’s disease," says lead researcher Professor Nigel Hooper of the University's Faculty of Biological Sciences. "It’s a misconception that Alzheimer’s is a natural part of aging; it’s a disease that we believe can ultimately be cured through finding new opportunities for drug targets like this."

Alzheimer’s disease is characterised by a distinct build-up of amyloid protein in the brain, which clumps together to form toxic, sticky balls of varying shapes. These amyloid balls latch on to the surface of nerve cells in the brain by attaching to proteins on the cell surface called prions, causing the nerve cells to malfunction and eventually die.

"We wanted to investigate whether the precise shape of the amyloid balls is essential for them to attach to the prion receptors, like the way a baseball fits snugly into its glove," says co-author Dr Jo Rushworth. "And if so, we wanted to see if we could prevent the amyloid balls binding to prion by altering their shape, as this would stop the cells from dying."

The team formed amyloid balls in a test tube and added them to human and animal brain cells. Professor Hooper said: "When we added the extracts from red wine and green tea, which recent research has shown to re-shape amyloid proteins, the amyloid balls no longer harmed the nerve cells. We saw that this was because their shape was distorted, so they could no longer bind to prion and disrupt cell function.

"We also showed, for the first time, that when amyloid balls stick to prion, it triggers the production of even more amyloid, in a deadly vicious cycle," he added.

Professor Hooper says that the team's next steps are to understand exactly how the amyloid-prion interaction kills off neurons.

"I'm certain that this will increase our understanding of Alzheimer’s disease even further, with the potential to reveal yet more drug targets," he said.

Dr Simon Ridley, Head of Research at Alzheimer's Research UK, the UK's leading dementia research charity, which part-funded the study, said: "Understanding the causes of Alzheimer’s is vital if we are to find a way of stopping the disease in its tracks. While these early-stage results should not be a signal for people to stock up on green tea and red wine, they could provide an important new lead in the search for new and effective treatments. With half a million people affected by Alzheimer’s in the UK, we urgently need treatments that can halt the disease—that means it's crucial to invest in research to take results like these from the lab bench to the clinic."

Journal Reference:
Temple Scientists Find Cervical Cancer Causing Virus in the Brain, Show Potential Connection to Epilepsy

Temple Health, (01.23.2013)

Researchers at Shriner’s Hospital Pediatric Research Center at Temple University School of Medicine and the University of Pennsylvania have found that the human papillomavirus 16 (HPV16), a common cause of cervical cancer, is linked to a common form of childhood epilepsy.

The researchers have found that HPV16 may be present in the human brain. When they added a viral protein to the brains of fetal mice, the mice showed developmental problems in the cerebral cortex associated with a type of epilepsy called focal cortical dysplasia type IIB (FCDIIB). FCDIIB is a developmental malformation in the cerebral cortex, the area of the brain that plays a key role in thought, perception, and memory. It is a common cause of pediatric and adult epilepsy and is thought to occur in the womb during early brain development. It is characterized by a disorganized cellular structure and enlarged balloon cells.

Dr. Peter Crino, professor of neurology at Temple University School of Medicine, a member of Shriner’s Hospital Pediatric Research Center, and the study’s senior author, hypothesized that the HPV protein may be detected in FCDIIB because of similarities between cervical dysplasia and focal cortical dysplasia. The investigators examined FCDIIB tissue samples from 50 patients for evidence of the HPV16 E6 protein. They found that all samples were positive for the protein in balloon cells, but not in areas without balloon cells or in 36 control samples from healthy individuals. They then examined the samples of genetic material to search for evidence of HPV16 E6 and compared findings to tissue from healthy controls. Tissue from patients with FCDIIB contained HPV16 E6 protein while control specimens and tissue from other types of dysplasia and conditions did not. The researchers introduced E6 protein into the brains of fetal mice, to determine whether the E6 protein was the cause of the dysplasia. The mice’s brains developed malformations. The researchers plan to investigate other forms of cortical dysplasia to see if HPV or other viral proteins can be found.

The researchers are not sure how the virus gets into the brain or the exact mechanism by which it might cause the malformation and epilepsy. Implications for therapeutic approaches for this type of epilepsy and other forms are discussed.


Opinion Pieces Recognize International Day For Zero Tolerance To Female Genital Mutilation

The International Day for Zero Tolerance to Female Genital Mutilation (FGM) was observed February 6. The following is a summary of opinion pieces and blog posts published in recognition of the day.

- Efua Dorkenoo, TrustLaw Blog: Dorkenoo, a Ghanaian campaigner against FGM, recaps progress made against the practice in the past year and writes, "Although there have been noteworthy successes on the African continent, huge challenges continue to exist in all countries where FGM is still prevalent." Adding that "a global movement for change is gathering pace," she continues, "A world without FGM is in sight, but we need to redouble our efforts to ensure that both worldwide legislative change takes place and that educational efforts are drastically increased" (2/6).

- Yasmeen Hassan, Huffington Post’s "Global Motherhood" blog: "The recent United Nations Global Ban, an African-led resolution calling on all member states to criminalize FGM, signals the aspiration for international consensus on ending FGM at the highest level," Hassan, the global director of Equity Now, writes. "While recognition of FGM as a violation of human rights at the highest levels is a big step in the right direction, ... [t]o make lasting change for girls, first, governments need the political will to match their words with action," she writes. "Second, the efforts of grassroots activists fighting against FGM must be supported"; and, "Third, efforts to end FGM must be rooted in the recognition that FGM arises due to gender inequality and the lower status of women in society," she adds (2/6).

- Sandra Jordan, USAID's "IMPACTblog": "Significant efforts have been made at the community, national, and international levels to address the issue of FGM/C," but "work still lies ahead," Jordan, senior technical adviser for external relations at USAID, writes and highlights a number of policies and initiatives aimed at eliminating the practice. "We must all work together—men, women, grandfathers, grandmothers, community and religious leaders, government, civil society, and multilateral organizations—to overturn deeply entrenched social norms that are not only harmful to women and girls, but to our communities and societies" (2/5).
Katherine Marshall, Huffington Post's "Religion" blog: Noting the U.N. resolution to ban FGM/C and the international day "to observe the commitment," Marshall, a senior fellow at the Berkley Center for Religion, Peace, and World Affairs at Georgetown University, writes, "What comes next? The U.N. resolution has a moral force but no legal teeth or enforcement capacity." She states, "Efforts to end FGC are at least a century old," adding, "[T]he issue has to stay on the top of the priority list or action will languish" (2/6).

Farahnaz Zahidi Moazza, Express Tribune's "Welcome to Pakistan" blog: "In Pakistan, female circumcision is practiced by a few communities along the Iran-Balochistan border, and a few isolated tribes, as well as the Dawoodi Bohra community," Moazza, a writer at the Express Tribune, writes. "While the 'elders' of the families often insist it be done, some women are now questioning the idea, including young women who have not yet gone under the knife," she notes. "Female genital mutilation is one of the best kept secrets ... But the time may have come to uncover the unspeakable. The time to talk about it may just have arrived," she states (2/6).

Ann-Marie Wilson, Huffington Post U.K.'s "Impact" blog: "There was good progress during 2012 towards raising the profile of FGM," but "[w]e are optimistic that even more can be done in 2013 to bring about the elimination of" the practice, Wilson, founder and director of 28 Too Many, writes. "It will not be easy to make progress but now is the time to build on what has already been achieved and accelerate the pace of change," she continues, adding, "My vision is for the world to be a place where every woman is safe, healthy and lives free from FGM. ... Let's help them end FGM in their lifetime" (6/2).

**Zinc helps against infection by tapping brakes in immune response**

COLUMBUS, Ohio – New research suggests that zinc helps control infections by gently tapping the brakes on the immune response in a way that prevents out-of-control inflammation that can be damaging and even deadly.

Scientists determined in human cell culture and animal studies that a protein lures zinc into key cells that are first-responders against infection. The zinc then interacts with a process that is vital to the fight against infection and by doing so helps balance the immune response.

This study revealed for the first time that zinc homes in on this pathway and helps shut it down, effectively ensuring that the immune response does not spiral out of control. The team led by Ohio State University researchers also found that if there is not enough zinc available at the time of infection, the consequences include excessive inflammation.

In this research, zinc’s activity was studied in the context of sepsis, a devastating systemic response to infection that is a common cause of death in intensive-care unit patients. But scientists say these findings might also help explain why taking zinc tablets at the start of a common cold appears to help stem the effects of the illness.

"We do believe that to some extent, these findings are going to be applicable to other important areas of disease beyond sepsis," said Daren Knoell, senior author of the study and a professor of pharmacy and internal medicine at Ohio State. "Without zinc on board to begin with, it could increase vulnerability to infection. But our work is focused on what happens once you get an infection — if you are deficient in zinc you are at a disadvantage because your defense system is amplified, and inappropriately so.

"The benefit to health is explicit: Zinc is beneficial because it stops the action of a protein, ultimately preventing excess inflammation."

While this study and previous work linking zinc deficiency to inflammation might suggest that supplementation could help very sick ICU patients, it’s still too early to make that leap.

"I think the question is whom to give zinc to, if anybody at all. We predict that not everybody in the ICU with sepsis needs zinc, but I anticipate that a proportion of them would," Knoell said. "Zinc is a critical element that we get from our diet, but we do not think we can give zinc and fix everything. Usually, if there is zinc deficiency, we would expect to see other nutrient deficiencies, too."

Zinc deficiency affects about 2 billion people worldwide, including an estimated 40 percent of the elderly in the United States — who are also among the most likely Americans to end up in an ICU.

The research is published in the journal Cell Reports.

Knoell’s lab previously showed that zinc-deficient mice developed overwhelming inflammation in response to sepsis compared to mice on a normal diet. Zinc supplementation improved outcomes in the zinc-deficient mice.

Until now, the beneficial effects of zinc in combating infection have not been fully understood at the molecular level. This is because zinc has numerous complex jobs in the body and interacts with thousands
of proteins to sustain human life. Of all the zinc contained in our bodies, only about 10 percent of it is readily accessible to help fight off an infection, said Knoell, also an investigator in Ohio State’s Davis Heart and Lung Research Institute.

"We believe that our findings help to narrow an important gap that has existed in our understanding of how this relatively simple metal helps us defend ourselves from infection," he said.

In this work, Knoell and colleagues sought to zero in on zinc’s role in preventing the inflammation that had led to such poor outcomes in the zinc-deficient mice.

In experiments using human monocytes – cells involved in the first line of defense against an invading pathogen – the researchers examined what happens when the immune response is launched.

When a pathogen is recognized, a series of molecules wake up from dormancy to create a process that activates the innate immune response. A major part of this process involves the NF-κB pathway, named for a highly active protein that is known to play an important role in the immune response to infection.

Once NF-κB is activated and enters the nucleus, a gene is expressed that produces a zinc transporter called ZIP8. The transporter then rapidly mobilizes to the cell’s wall, where it can then shuttle zinc from the bloodstream into the cell.

After cell entry, zinc is then directed to and binds to a different protein in the NF-κB pathway. When this happens, it halts any further activity in that process. The cumulative impact of this feedback loop is that it prevents excessive inflammation, which can be damaging to cells and the body.

"The immune system has to work under very strict balance, and this is a classic example of where more is not always better," Knoell said. "We want a robust inflammatory response, which is part of our natural programming to defend us against a bug. But if that is unchecked, and there is too much inflammation, then it not only attacks the pathogen but can also cause much more collateral damage."

The researchers knew from previously published experiments that if ZIP8 activation was prevented, zinc couldn’t come into the cell and the cells died. In the current study, collaborators who specialize in computational modeling of protein interactions helped identify the likely target of zinc once it enters the cell; specific binding sites on a protein called IKKB. When researchers allowed this protein to function unchecked in mice with zinc deficiency, the animals developed excessive inflammation in response to sepsis – confirmation that IKKB was zinc's target to turn off the inflammatory pathway.

"There are certainly other zinc targets in the cell, but we found evidence that zinc is brought in by ZIP8 to turn the pathway off by interacting with this protein at a specific region," Knoell said.

The recommended daily allowance for zinc ranges from 8 to 11 milligrams for most adults. Red meat and poultry provide the majority of zinc in the American diet, according to the National Institutes of Health. Other food sources include beans, nuts, some shellfish, whole grains, fortified cereals and dairy products. The nutrient is also available in supplement form. Knoell said it is possible but relatively uncommon to take in too much zinc to reach toxic levels.

His lab is continuing to study the NF-κB pathway, inflammation and zinc deficiency in other disease processes. And though zinc would be inexpensive and easy to take as a supplement, Knoell said many questions remain about whether zinc should be considered as an intervention for specific disorders.

"There might be therapeutic implications about giving supplemental zinc in a strategic manner to help improve some people with certain conditions. But also, could we learn from this so someday we can be more diagnostic about who it is that needs zinc? And if so, what dose and for how long?" he said.

Immune Systems of Healthy Adults 'Remember' Germs to Which They've Never Been Exposed
Feb. 7, 2013 — It’s established dogma that the immune system develops a "memory" of a microbial pathogen, with a correspondingly enhanced readiness to combat that microbe, only upon exposure to it—or to its components though a vaccine. But a discovery by Stanford University School of Medicine researchers casts doubt on that dogma.

In a path-breaking study published online Feb. 7 in Immunity, the investigators found that over the course of our lives, CD4 cells—key players circulating in blood and lymph whose ability to kick-start the immune response to viral, bacterial, protozoan and fungal pathogens can spell the difference between life and death—somehow acquire memory of microbes that have never entered our bodies.

Several implications flow from this discovery, said the study's senior author, Mark Davis, PhD, professor of microbiology and immunology and director of Stanford's Institute for Immunity, Transplantation and Infection. In the study, newborns' blood showed no signs of this enhanced memory, which could explain why young children are so much more vulnerable to infectious diseases than adults.
Moreover, the findings suggest a possible reason why vaccination against a single pathogen, measles, appears to have reduced overall mortality among African children more than can be attributed to the drop in measles deaths alone. And researchers may have to rethink the relevance of experiments conducted in squeaky-clean facilities on mice that have never been exposed to a single germ in their lives.

"It may even provide an evolutionary clue about why kids eat dirt," said Davis. "The pre-existing immune memory of dangerous pathogens our immune systems have never seen before might stem from our constant exposure to ubiquitous, mostly harmless micro-organisms in soil and food and on our skin, our doorknobs, our telephones and our iPod earbuds."

CD4 cells are members of the immune club known as T cells. CD4 cells hang out in our circulatory system, on the lookout for micro-organisms that have found their way into the blood or lymph tissue.

In order to be able to recognize and then coordinate a response to a particular pathogen without inciting a Midas-touch overreaction to anything a CD4 cell bumps into (including our own tissues), our bodies have to host immensely diverse inventories of CD4 cells, each with its own narrow capacity to recognize one single pathogenic "body part" or, to be more scientific, epitope—and, it’s been believed, only that epitope. Contact with that epitope can cause a CD4 to whirr into action, replicating rapidly and performing the immunological equivalent of posting bulletins, passing out bullets and bellowing attack orders through a bullhorn to other immune cells. This hyperactivity is vital to the immune response. (It is CD4 cells that are targeted and ultimately destroyed by HIV, the virus responsible for AIDS.)

In the early 1980s, Davis, now the Burt and Marion Avery Family Professor of Immunology at Stanford, unraveled the mystery of how organisms such as ourselves, equipped with only 20,000 or so genes, can possibly generate the billions of differing epitope-targeting capabilities represented in aggregate by T cells. He found that highly reshufflable "hot spots" in a rapidly dividing T cell's DNA trigger massive mix-and-match madness among these genetic components during cell division, so each resulting T cell sports its own unique variant of a crucial surface receptor and, therefore, is geared to recognizing a different epitope.

That variation accounts for our ability to mount an immune response to all kinds of microbial invaders, whether familiar or previously unseen. But it doesn't account for the phenomenon of immune memory. CD4 cells, like other T cells, can be divided into two groups: so-called "naïve" CD4s randomly targeting epitopes belonging to pathogens they haven't encountered yet; and CD4s that, having had an earlier run-in with one or another bug, have never forgotten it. These latter CD4 cells are exceptionally long-lived and ultra-responsive to any new encounter with the same pathogen.

"When a naïve CD4 cell comes across its target pathogen, it takes days or even weeks before the immune system is fully mobilized against that pathogen. But an activated-memory CD4 cell can cause the immune system to mount a full-blown response within hours," said William Petri, MD, PhD, chief of infectious diseases and international health at the University of Virginia.

That’s why Petri, who was not involved in the study, thinks the newfound abundance in healthy adults, and total absence in newborns, of memory CD4 cells targeting microbes those individuals have never encountered before is so important. For the past 20 years, he has led a team conducting medical interventions in an urban slum in Dacca, the capital of Bangladesh. There, the average infant experiences a half-dozen diarrhea-inducing infections and as many upper-respiratory-tract infections within the first year of life, many of them within the first few months. The consequence, Petri said, is rampant malnutrition, with corresponding cognitive deficits and high mortality—this, despite the fact that Petri’s group provides free health-care and education services and visits homes twice a week.

"If I had lived in such a slum as a kid, I probably would have died of infection," Petri said.

A sophisticated technique invented by Davis in 1996 and since refined in his and others' laboratories permitted the Stanford team to identify a single CD4 cell targeting a particular epitope out of millions. Using this method, his team exposed immune-cell-rich blood drawn from 26 healthy adults, as well as from two newborns' umbilical cords, to various epitopes from different viral strains. They were able to fish out, from among hundreds of millions of CD4 cells per sample, those responsive to each viral epitope.

Nearly all of the 26 adult blood samples contained cells responsive to HIV; to HSV, the virus that causes herpes; and to cytomegalovirus, a common infectious agent that often produces no symptoms but can be dangerous to immune-compromised people. This wasn’t surprising, given humans' exhaustive inventories of divergent CD4-cell affinities.

What was surprising was that, on average, about half of the virus-responsive CD4 cells in each adult sample bore unmistakable signs of being in the "memory" state: a characteristic cell-surface marker, gene activation patterns typical of memory T cells, and rapid secretion of signature biochemical signals, called
cytokines, that communicate with other immune cells—even though highly sensitive clinical tests showed that these individuals had never been exposed to any of these viruses in real life.

The newborns' blood contained similar frequencies of CD4 cells responsive to the same three viruses. However, all these cells were in the "naïve" rather than memory state. "This could explain, at least in part, why infants are so incredibly susceptible to disease," said the study's first author, Laura Su, MD, PhD, an instructor in immunology and rheumatology.

Another surprise: About one-fifth of the adult samples boasted "cross-reactive" memory CD4 cells responsive to other harmless environmental microbes. For example, CD4 cells selected specifically for their reactivity to HIV turned out to be able to recognize a large number of common environmental microbes, including three gut-colonizing bacteria, a soil-dwelling bacterial species and a species of ocean algae. Considering that the investigators tested only a negligible fraction of all the microbes a person might encounter, it's a sure bet that this measure of CD4-cell cross-reactivity was an underestimate.

Next, the researchers recruited two adults who hadn't been vaccinated for flu in five years or longer, and then vaccinated them. In these volunteers, memory CD4s proliferated and otherwise became activated in response to exposure to certain components of the influenza virus, but also to epitopes of several different bacterial and protozoan microbes.

This cross-reactivity could explain why exposure to common bugs in the dirt and in our homes renders us less susceptible to dangerous infectious agents.

Which raises another point. "We grow and use experimental lab mice in totally artificial, ultra-clean environments," Davis said. "That's nothing like the environment that we live in. The CD4 cells from adult mice in the lab environment are almost entirely in the naïve state. They may be more representative of newborns than of adults."

Petri described the new study as paradigm-shifting. "It was one of those rare, seminal findings that changes the way I think about the immune response," he said.

Davis' study offers hope that some of the immunity conferred by a vaccine extends beyond the specific microbe it targets, Petri said. "This adds support to the impetus to vaccinate infants in the developing world," he said. As many as 30 different pathogens can cause diarrhea, so vaccinating small children against all of them—even if those vaccines existed—would require so many separate injections as to be logistically hopeless. Understanding the mechanism by which cross-reactivity occurs might further allow immunologists to develop "wide-spectrum vaccines" that cover a number of infectious organisms.

**Journal Reference:**

**Sense of 'immunity' spreads HIV**
By Alex McKinnon on February 7, 2013
A new study has found that gay men with the highest risk of contracting HIV are more likely to consider themselves immune to infection than those who practise safe sex.

Conducted by the National Centre in HIV Social Research (NCHSR) at the University of New South Wales, the study charted the sexual practices of more than 1,500 gay men in Sydney to track how they perceived their risk of contracting HIV.

Surprisingly, the study found that for people more likely to think themselves immune to contracting HIV the riskier their sexual practices were. Men who had had unprotected anal sex with a casual partner in the last six months were even less likely to think themselves at risk of infection than men who always used condoms.

NCHSR Senior Research Fellow Dr Limin Mao said that while gay men had accurate knowledge of what practices were risky and how to avoid infection, they often valued their personal feelings over applying that knowledge to themselves when assessing their own levels of risk.

"It’s quite common to fall into this false sense of security – if someone has a slip-up they’re likely to think they’re somehow uniquely immune to infection because they’ve practised safe sex before. It’s the same thinking that convinces people they’ll be the one to win the lottery – that they alone can get the good things and avoid the bad things,” Mao said.

Mao said this mistaken sense of safety made serosorting, or unprotected sex between partners of the same HIV status, more risky if both parties had not been recently tested. Rates of unprotected sex between gay men in Australia have jumped more than 40 percent since 1996.
“Gay men thinking they’re immune means that many aren’t getting tests when they have an incident, and they can end up infecting casual partners in the mistaken belief that they’re still HIV-negative,” she said.

The findings come four months after a Kirby Institute study revealed that HIV infection rates jumped eight per cent in 2011 and 50 per cent over the last 10 years, prompting urgent calls for action from HIV/AIDS advocacy groups and health bodies.

The study also found that while HIV-positive men have become far more optimistic about treatment prospects, HIV-negative men had very little knowledge about recent advances in treatment or the realities of living with the disease.

Cervical cancer a major threat to HIV-positive women
Cervical cancer affects about 30 percent of women in the country
HARARE, 8 February 2013 (PlusNews)—HIV-positive women are living longer, but are now dying of cervical cancer. In Zimbabwe, cervical cancer is now the most common cancer among women, particularly those living with HIV. Activists are urging the government to step up efforts to prevent deaths related to the disease, accusing it of paying lip service to the problem.

According to the Zimbabwe National Cancer Registry, cervical cancer affects about 30 percent of women in the country. Cervical cancer is caused by the sexually transmitted human papilloma virus (HPV). Although condoms are said to lower the risk of getting HPV, they do not prevent the risk of acquiring this virus completely. About 1,900 women are diagnosed with the disease every year in Zimbabwe and 1,300 die, according to the UN World Health Organization.

Efforts poorly resourced
In October last year, the government registered a cervical cancer vaccine for the prevention of HPV and reported that by early this year the new vaccine would be available for women in the country. However, those plans have been scuppered by financial constraints.

A number of public health institutions in Zimbabwe, including Parirenyatwa Hospital, the country’s largest referral hospital, were supported by the UN Population Fund (UNFPA) to run free cervical cancer tests known as visual inspection with ascetic acid and cervicography. While this method is faster and cheaper than the traditional pap smears, the machines at Parirenyatwa Hospital are not enough to service the large number of women coming from around the country for the service. Women have been forced to wait for up to a month to get screened.

In addition, some women who had been screened and found to have cervical cancer have been waiting for up to three months for treatment. One woman at the hospital, who asked not to be identified, told IRIN/PlusNews that after waiting for three months to begin her treatment, she was told the radio therapy machines had broken down and had to wait again until the machines were repaired.

AIDS activist Promise Mthembu noted that research indicated that more women in sub-Saharan Africa are dying of cervical cancer than of maternal mortality-related deaths. She urged the Zimbabwean government to do more to address this growing crisis.

“Before HIV/AIDS, cervical cancer was a disease of older women, affecting women beyond reproductive age, and it was marginalized because of this. But now it is affecting younger women,” said Mthembu.

“It is important that we have a comprehensive package for women that addresses cervical cancer. What we have seen in HIV/AIDS policy is that policy has been promoting pap smears or screening for cervical cancer. While a pap smear is a means to an end, why should the government screen cervical cancer if it doesn’t have means to treat cervical cancer?”

Awareness needed
Oncologist and cancer-prevention activist Anna Nyakabau says it is unacceptable that a large number of women continue to die as a result of cervical cancer given the slow progression of cervical cancer in a person’s body.

According to Nyakabau, many women are dying in Zimbabwe because they present themselves to health facilities when it is too late to save their lives. She says the disease is evasive because symptoms only show when the disease is already at an advanced stage. She says it is important for the government and its partners to increase knowledge among the population about the dangers of cervical cancer and the importance of regular screening for the disease.

Minister of Health and Child Welfare Henry Madzorera admitted that lack of funds had stymied the roll-out a cervical cancer vaccine early this year, but said the government would be mobilizing funds from
donors to launch the vaccine in 2014. Meanwhile, he said, the government would focus on other strategies to reduce cervical cancer deaths in the country, such as screening and testing and treatment for those infected.

**HIV Associated with Nonresponse to HBV Vaccine**

*Healio,* (02.07.2013) E. Irungu

Researchers from the University of Washington and Kenyatta National Hospital in Nairobi, Kenya, conducted a prospective interventional study to investigate the response of adults with HIV to hepatitis B virus (HBV) vaccination. The 603 participants were members of the partners’ pre-exposure prophylaxis (PrEP) study, and 310 of them had HIV infection. Participants were screened for HBV, and those who were found to be susceptible received HBV vaccine.

Six months after receiving the vaccine, 111 of the participants (35.8 percent) with HIV infection did not have protective HBV surface antibody titers compared to 42 (14.3 percent) of the 293 patients without HIV. A multivariate analysis of the participants with HIV indicated that sex and CD4 counts were associated with nonresponse. Men and participants with CD4 counts lower than 500 cells/mcL were more likely to be nonresponders.

When 102 nonresponders with HIV infection were revaccinated, 72 of them developed a positive antibody response after the first dose and 16 developed antibody response after the third dose. This resulted in a cumulative response of 64.2 percent among participants with HIV after the initial series, 89 percent after the first revaccination dose, and 94.9 percent after the complete revaccination. Nonresponse after revaccination was associated with low BMI, HIV-1 RNA of more than 50,000 copies/mL at baseline, and longer time to revaccination.

Data show that adults in Kenya had similar response to HBV vaccine as patients from developed countries. The researchers suggest that the results may help guide policy on best practices for revaccinating persons with HIV-1 infection who do not respond to the HBV vaccine schedule.


**Nine Polio Workers Killed In Northern Nigeria**

"Nine female polio vaccinators have been killed in two shootings at health centers in northern Nigeria, police have told the BBC," the news agency reports. "In the first attack in Kano the polio vaccinators were shot dead by gunmen who drove up on a motor tricycle," and "[t]hirty minutes later gunmen targeted a clinic outside Kano city as the vaccinators prepared to start work," BBC News writes (2/8). "Islamist militant group Boko Haram—a sect which has condemned the use of Western medicine—has been blamed for carrying out a spate of assaults on security forces in the city in recent weeks," Reuters writes (2/8).

"Nigeria remains one of the few countries left in the world where polio remains endemic," the Associated Press notes, adding, "Several years ago religious clerics had some of their followers stop receiving the vaccines saying that it would sterilize their children" (Rabiu, 2/8).

**NGOs Document Thousands Of Cases Of Indian Women Undergoing Unnecessary Hysterectomies, C-Sections**

"Thousands [of women in India] are being given hysterectomies and caesareans that they do not need by doctors and hospitals that can make substantial sums of money out of the operations," Guardian health editor Sarah Boseley reports in her "Global Health Blog." The operations "leave women in pain, infirm, unable to work to earn a living and in horrendous debt," she writes, highlighting several cases documented by the non-governmental organization (NGO) Oxfam and its Indian partners (2/7). "Reports from a handful of Indian states, including Rajasthan, Bihar, Chhattisgarh and Andhra Pradesh, suggest that an extraordinarily high number of women are having their uteruses removed, including many below the age of 40," BBC News reports.

"Until recently, no data was kept on the number of hysterectomies performed, but anecdotal evidence suggests the operations have become much more prevalent in recent years," the news agency writes, adding, "This follows the rapid expansion of small private clinics and hospitals, especially in remote rural areas that are poorly served by the government health system." The BBC continues, "[I]n some states, critics say the [Indian government’s national health insurance scheme] appears to be encouraging unnecessary hysterectomies, as unethical private clinics exploit the vulnerable poor, using them as a means to tap into government funds" (McGivering, 2/5). "Oxfam is calling for the Indian government to
make health care for all a priority—and is urging international donors to support them and back regulation of the private health care sector in developing countries," the Guardian notes (2/7).

**Global Response To Possible H5N1 Flu Outbreak Could Affect Epidemic's Course**

"It's been a rough flu season this winter in the United States and Europe, but it could be worse. A lot worse," science writer Carl Zimmer states in National Geographic's "Phenomena: The Loom" blog. In other parts of the world, including Egypt, India and Cambodia, the H5N1 avian influenza strain is "lurking," and according to official estimates, the disease has a case-fatality rate of 59 percent, he notes, adding that "may be a serious overestimate." Zimmerman continues, "[E]ven if the true rate was only half as high, H5N1 would not be a virus you'd want to cross paths with," and notes that the Spanish flu outbreak of 1918 had a case-fatality rate of about two percent and killed 50 to 100 million people worldwide.

Though scientists cannot predict how many people would die if an H5N1 outbreak occurred, "they can say this: what we do when and if we face an H5N1 pandemic could alter the evolution of the virus itself. And thousands of lives could be saved or lost as a result," Zimmer writes. He explains the pathology of H5N1 and several laboratory experiments and mathematical models that try to predict how the virus might mutate to become more infectious. Zimmer describes how public health officials' employment of isolation as a control technique during an outbreak could make the influenza strain less virulent but more widespread. The scenario "help[s] to sharpen our senses to the potential H5N1 has to evolve into something new. Whether the surprise is pleasant or horrifying may be, in part, up to us," he concludes (2/7).

**Yeast we can! New report answers questions on microbiology and beer**

WASHINGTON, DC – February 5, 2013 – What do microbes have to do with beer? Everything! Because the master ingredient in beer is yeast – a microbe – and every step in the brewing process helps the yeast do its job better. A new freely-available report; FAQ: If the Yeast Ain't Happy, Ain't Nobody Happy: The Microbiology of Beer explores the synergy between microbiology and brewing beer.

"Every time someone brews a batch of beer, in a very real sense he or she is doing a microbiology experiment. If you brew beer at home, you're a microbiologist.' says Dr. Charles Bamforth of the University of California, Davis, a member of the steering committee that produced the report.

The American Academy of Microbiology brought together some of the world's leading experts on yeast, brewing and food science to explain how making great beer depends on creating the perfect conditions for yeast to work its magic. Keeping the yeast happy, it turns out, is what will make or break your beer batch.

FAQ: The Microbiology of Beer is based on the deliberations of 18 participants who convened for a day to discuss the relationship between microbiology and beer brewing.

The FAQ answers 6 common questions:

- What does microbiology have to do with beer?
- What's so special about brewer's yeast?
- Is all brewer's yeast the same?
- How is beer made?
- How does the yeast affect the beer?
- Is it really all about the yeast?

All of the answers are straightforward and limited to two pages each for easier understanding. Important terms and concepts are introduced as needed and fully explained. Sidebars on topics like yeast genealogy and fermentation round out the 12 page report.

FAQ: The Microbiology of Beer is part of a series of reports designed to provide easy to understand explanations about the roles microbes play in the world, from cleaning up oil spills to causing epidemics, to producing many useful products. The FAQ series reports are based on the deliberations of 15-20 microbiology experts who meet for a single day to develop answers to frequently asked questions about a specific topic.

**Forensic pathology: tracing the origin of the Usutu Virus**

It is generally a mystery how new diseases arise and how the pathogens that cause them first enter countries. However, clues may come from examination of specimens from similar outbreaks. This approach has recently been taken by scientists at the University of
Veterinary Medicine, Vienna to trace the origin of the virus that caused a sudden decrease in the number of blackbirds in Vienna in 2001. The results are published in the current issue of the journal “Emerging Infectious Diseases”.

The effects were dramatic: throughout Vienna it was impossible not to notice that the blackbirds were disappearing. Their melodious song no longer rang around the courtyards of the inner city nor woke tired partygoers in the outlying districts. The birds were simply no longer there. Thankfully, they gradually reappeared and a few years later their population had returned to its original levels. But the sudden crash in numbers was alarming and scientists rushed to find the cause.

It soon became apparent that the birds had died as a result of a new kind of viral infection. The culprit turned out to be the Usutu virus, which had previously been identified only in Africa and had only seldom been associated with mortality in animals or birds. It was widely assumed that the virus had crossed from Africa to central Europe with the help of migratory birds – the Barn swallow was generally fingered as the most likely transmitter – and that such sudden outbreaks would appear more frequently as the result of climate change. But these conclusions have been called into question by the latest findings from a team at the University of Veterinary Medicine, Vienna (Vetmeduni Vienna).

Although not widely reported at the time, a large number of birds, especially blackbirds, died in Tuscany, Italy in 1996, five years before the outbreak of Usutu virus in Vienna’s blackbirds. The causative agent was not identified but Giacomo Rossi of the University of Camerino had stored tissue samples from the dead birds. Herbert Weissenböck, Norbert Nowotny and colleagues in the Institute of Pathology and the Institute of Virology at the Vetmeduni Vienna recently became aware of the samples’ existence and were naturally keen to investigate them. Surprisingly, the researchers found that the Italian samples contained exactly the same strain of Usutu virus that was responsible for the Viennese cases. As in Vienna, the birds were almost wiped out by the virus but resistance soon developed and the population returned to normal levels.

As Weissenböck says, “We still do not fully understand how the virus reached Austria but we have at least uncovered one piece in the jigsaw. Rather than coming directly from Africa to Vienna, the Usutu virus seems to have been present in Italy for some time.” The powerful techniques of forensic pathology may be helpful in unravelling the origins of other emerging diseases: for example, we still do not know how the bluetongue virus reached northern Germany or the West Nile virus arrived in central Europe. The paper Usutu virus, Italy, 1996 by Herbert Weissenböck, Tamás Bakonyi, Giacomo Rossi, Paolo Mani and Norbert Nowotny has just been published in the Journal Emerging Infectious Diseases (Vol. 19(2), February 2013: 274-277).

Got to go? Harvard scientists figure out how you know

New research in the FASEB Journal shows that the epithelium layer in the bladder is able to sense bladder fullness through the activity of integrins

Bethesda, MD—If you have an overactive bladder or incontinence, help could be on the way. A new research report published online in the FASEB Journal, shows that the epithelium, a thin layer of cells which line the surface of the bladder, is able to sense how full the bladder is through the action of a family of proteins called integrins. As the bladder becomes full, the cells in the epithelium stretch and become thinner, which activates the integrins to send that information to nerves and other cells in the bladder. As a result of this new knowledge, researchers may one day be able to design drugs that target this mechanism to treat conditions like incontinence and overactive bladder, both of which are common, serious, problems affecting millions of people.

"I am very hopeful that as we learn more about how the bladder senses fullness and conveys that information to the nerves and the muscles which control our ability to urinate, that this greater understanding and knowledge will lead to new treatments," said Warren G. Hill, Ph.D., a researcher involved in the work from the Department of Medicine at Beth Israel Deaconess Medical Center and Harvard Medical School in Boston, MA. "It is extremely important that we do this as quickly as possible, since there are millions of people who suffer enormously from the anguish of bladder pain, incontinence and constant feelings of needing to go. I am optimistic these new insights into the role of integrins will begin the process of discovering important new drug targets which will dramatically improve the quality of life for many of these people."

To make this discovery, Hill and colleagues tested two groups of mice. The first were genetically modified to not have an important member of the integrin family present in the epithelium. The second group of mice was normal. The mice lacking the integrin protein had normal looking bladders but very little urinary control. The normal mice also had normal looking bladders, but as expected, had bladder control. Researchers then tested the bladders from the integrin knockout mice and found that their
bladders were constantly squeezing and very overactive. In addition, they overfilled their bladders and took much longer to urinate than the normal mice. Since most drug treatments for overactive bladder target proteins in the muscle surrounding the bladder, this study shows that it may be possible to design drugs that target sensory proteins in the epithelium.

"No one wants to pee in his or her pants," said Gerald Weissmann, M.D., Editor-in-Chief of the FASEB Journal, "but the reality is that bladder problems— incontinence, frequency and pain—affect more people than we realize. This report offers hope that new drugs targeting the bladder's epithelium will succeed when current drugs fail."


Villain stomach bug may have a sweet side
Virginia Tech researchers reveal how 'bad' gut bacteria may help control diabetes

A stomach bacterium believed to cause health problems such as gastritis, ulcers, and gastric cancer may play a dual role by balancing the stomach's ecosystem and controlling body weight and glucose tolerance, according to immunologists at the Virginia Bioinformatics Institute of Virginia Tech.

"H. pylori is the dominant member of the gastric microbiota and infects about half of the world population. While H. pylori infection can be associated with severe disease, it helps control chronic inflammatory, allergic, or autoimmune diseases," said Josep Bassaganya-Riera, director of the Nutritional Immunology and Molecular Medicine Laboratory and the Center for Modeling Immunity to Enteric Pathogens (MIEP) at Virginia Tech. "We demonstrated for the first time that gastric colonization with H. pylori exerts beneficial effects in mouse models of obesity and diabetes."

During the past 20 years, obesity in the United States has increased dramatically, according to the Centers for Disease Control and Prevention. About 36 percent of U.S. adults and approximately 17 percent of young people aged 2 to 19 years are obese. Obesity is the leading risk factor for type 2 diabetes and the rates of diabetes have increased in parallel with the rates of obesity.

Mice infected with H. pylori showed less insulin resistance than uninfected mice or other mice infected with a more virulent strain of H. pylori, according to the study, which was recently published in PLOS One. Researchers believe that whether the infection is harmful or beneficial depends on the interaction between the genetic makeup of H. pylori and the host's immune response.

H. pylori carrying the cytotoxin-associated gene pathogenicity island were harmful. But the bacteria with or without an atypical island may be integral to human stomach microbiota. Indeed, studies show that humans have been colonized by H. pylori for about 116,000 years.

The role of H. pylori as a pathogen does not provide an explanation as to why it has colonized the stomach of humans thousands of years. Our new findings suggest that H. pylori may provide important metabolic traits required to ameliorate diabetes that humans have not evolved on their own," Bassaganya-Riera said.

This suggests that the overuse of antibiotics for everything from misdiagnosed infections in humans to supplementary livestock feed may destroy beneficial bacteria and contribute directly to diseases such as obesity, allergies, inflammatory bowel disease, and asthma. It may be time for humans to reconsider how we can better co-exist with H. pylori and other microbes as a means of promoting health.

"This novel finding underscores the complex relationship between H. pylori and humans, with effects not limited to the stomach, but more broadly affecting systemic inflammation and metabolism," said Martin Blaser, the Frederick H. King Professor of Internal Medicine and chairman of the Department of Medicine, and professor of microbiology at New York University School of Medicine.

To better understand the complex relationship between H. pylori and the human host and to better predict health outcomes, the Center for Modeling Immunity to Enteric Pathogens has developed computer models of the mechanisms by which H. pylori interacts with the host and new tools for investigating such interactions," Bassaganya-Riera said.
Histone Modification Controls Development: Chemical Tags On Histones Regulate Gene Activity

Feb. 8, 2013 — Every gene in the nucleus of an animal or plant cell is packaged into a beads-on-a-string like structure called nucleosomes: the DNA of the gene forms the string and a complex of proteins called histones forms the beads around which the DNA is wrapped. Scientists of the Max Planck Institute of Biochemistry in Martinsried near Munich, Germany, have now established that adding chemical tags on histones is critical for regulating gene activity during animal development.

Studies over the past two decades revealed that many proteins that control the activity of genes are enzymes that add small chemical tags on histone proteins but also on a variety of other proteins. With their studies the researchers have now shown that it is the tags on the histones that control if genes are active or inactive.

Their results were published in the journal Science. Histone proteins can be modified by a number of different chemical tags at very specific sites. The researchers in the Research Group 'Chromatin Biology' of Jürg Müller focused on the histone tag that is added by an enzyme called Polycomb Repressive Complex 2 (PRC2). PRC2 is essential for a variety of different cell fate decisions in animals and plants. PRC2 functions to keep genes inactive in cells and at times where they should remain inactive.

Using the model organism Drosophila—the fruit fly—the scientists now generated animals with cells expressing an altered histone protein to which PRC2 can no longer add the tag. These cells cannot keep genes inactive anymore and many cell fate decisions go awry, exactly like in cells that lack the PRC2 enzyme.

"This observation demonstrates that the business end is the tag on the histone and not on some other protein" says Ana Pengelly, the PhD student who conducted the experiments. Her colleague Omer Copur adds: "The approach we used permits us to now also investigate the function of other tags on histone proteins that have a different chemical nature." The insight gained from the work on PRC2 provides a strong impetus to figure how this tag alters the beads-on-a-string structure of genes and thereby controls gene activity.

Journal Reference:

Bacteria Are Blowing in the Wind

New work shows that bacteria reach miles into the atmosphere, bolstering the notion that microbes can affect precipitation and cloud formation.

By Sabrina Richards | January 28, 2013

Ten kilometers (more than 6 miles) into the atmosphere, a plethora of microbes is thriving, possibly affecting cloud chemistry and playing a role in atmospheric conditions, according to new research published today (January 28) in Proceedings of the National Academy of Sciences.

"It's the most exciting paper I've seen published this year," said Jessica Green, a microbial ecologist at the University of Oregon, who was not involved in the research. "It contributes significantly to the hypothesis that the atmosphere is alive. . . . The possibility of microbes being metabolically active in the atmosphere transforms our understanding of global processes."

Previous research on snow and rainwater collected at high elevations had already established that bacteria in the air initiate moisture condensation that leads to precipitation. Some of these microbes secrete special proteins that allow them to initiate ice crystallization, which may affect weather by changing the temperature at which ice crystals form in the sky. But most microbe-rich precipitation was collected from the Earth, and may represent different bacterial communities than those in the atmosphere, which may have different properties for ice nucleation and cloud formation than those found
in rain water, explained senior author Konstantinos Konstantinidis, a microbial genomicist at Georgia Tech.

To get a better glimpse of bacteria in the atmosphere—before they’ve fallen to earth—Konstantinidis and collaborators teamed up with NASA to collect atmospheric microbes. GRIP planes collected air from 1 to 10 kilometers above the ocean in August and September 2010, when Hurricanes Karl and Earl were brewing. Using DNA sequencing, the researchers identified a wide variety of bacteria, more than 60 percent of which were still viable despite the inhospitable conditions. The researchers found that the composition of the bacterial communities in the clouds differed before and after the hurricanes, suggesting that the storms whipped up bacteria from the Earth’s surface. They also noted some species known to be ice nucleators.

Theoretically, ice-nucleating bacteria could affect the number of and size of ice crystals formed in the atmosphere, possibly impacting the lifetime of clouds and even global climate. “If bacteria could reduce the number of high level clouds, it would allow more heat to go into space,” explained senior author Athanasios Nenes, an atmospheric at Georgia Tech, possibly cooling the earth.

But clouds have an “ambiguous” effect on the Earth’s temperature, noted Anne-Marie Delort, an atmospheric chemist at the Institute of Chemistry of Clermont-Ferrand in France, who was not involved in the research. Clouds can make the planet colder by blocking the sun’s radiation, or can have a greenhouse effect by preventing the Earth’s heat from dissipating, so it’s not entirely clear whether bacteria would promote warming or cooling, she said.

More information about how the bacteria might be interacting with cloud chemistry—possibly by looking at gene expression—will be important to understand the ways in which atmospheric bacteria impact weather, said Delort. Many qualities, such as hydrophobicity and metabolic activity, affect how bacteria might interact with clouds.

Recreating the dynamic conditions of the rapidly dissipating and reforming cloud environment will be difficult, said Allan Konopka, a microbial ecologist at Pacific Northwest National Laboratories who was not involved in the research, but “the idea of addressing whether bacteria are metabolically active could really shift how atmospheric chemists think about [cloud] reactions.”


Catching the Cold (long)

Tracking the genetic diversity and evolution of rhinoviruses can lead to a better understanding of viral evolution, the common cold, and more dangerous infections.

By Fred Adler | February 1, 2013

The common cold is usually nothing more than a temporary nuisance. Except for people who are highly immunosuppressed or have other serious conditions, colds—most commonly caused by very small RNA viruses known as rhinoviruses—are usually restricted to the cells lining the upper respiratory tract and tend to be limited in duration and symptoms. Nevertheless, with a global population exceeding one billion trillion (10^21), rhinoviruses are arguably the most successful rapidly infecting viruses on Earth today.

Despite their abundance, rhinoviruses have been relatively understudied by virologists and largely ignored by epidemiologists and virus modelers. Many mathematical methods for studying virus evolution and spread have provided key insights into the control of epidemics, but these efforts have concentrated on viruses such as HIV and influenza, and cannot be directly applied to the study of rhinoviruses. Unlike these more dangerous viruses, rhinoviruses did not jump recently from other animals to humans. They are human specialists that almost certainly evolved several times from the equally specialized enteroviruses that infect the gut. This means that rhinoviruses are highly adapted to humans, possibly explaining their low virulence—because they have had a chance to evolve efficient ways of spreading to many individuals without harming their hosts—and their high abundance as a consequence of this efficiency.

Their expert ability to infect humans makes rhinoviruses a good model for understanding the process of adaptation. Indeed, a handful of recent studies of rhinovirus evolution have yielded insights into how the viruses manipulate the immune system and cause only limited damage to their hosts. Such information will not only help researchers understand one of the most common of all viral infections, but will also shed light on the emergence of deadly diseases that likely share rhinoviruses’ mechanisms of evolutionary change.
The evolving virus

Studying population dynamics and evolution in plants and animals can require many years. With viruses, everything happens fast. Mutation rates are roughly 100,000 times higher than in humans, and population sizes, as we have seen, can be enormous. These factors combine to make ecological and evolutionary timescales converge, such that major evolutionary changes can occur during a single season—or even a single infection.

Evolution in an RNA virus is also distinct from that of more traditionally studied organisms because of its tiny genome of single-stranded RNA. Rhinoviruses, for example, carry just 10 genes. Because viruses cannot survive and reproduce on their own, they are especially dependent on their environment, which for rhinoviruses is the epithelial cell of a host’s throat. This home provides not just resources and protection, but also an “extended genotype” of host genes that do most of the virus’s work for it.

These special characteristics of small RNA viruses have many consequences beyond speeding evolution. These viruses show an odd mix of carefulness and carelessness. They have tidy genomes with no “junk DNA,” and thus a much higher probability that mutations will have a noticeable effect. This high-stakes evolution, in which a single bad mutation can mean the end, is counterbalanced by huge populations that can tolerate many individual failures. A swarm of viruses probably explores more evolutionary space than any other evolving entity, as seen in the rapid evolution of resistance to antiviral therapies in patients with HIV. In fact, there may well be more viruses in a single common cold infection than there have been primates in the entire history of life on Earth.

Finally, the simplicity that stems from the small physical size of viruses also changes how we think about the process of evolution. A mutation in a virus, as in all organisms, changes one molecule. Understanding the fitness effects of a mutation requires understanding how the biochemical change translates into survival and reproduction. Because small viruses like rhinovirus are little more than a few molecules themselves, it is far simpler to track the consequences of mutation than those of, say, a single nucleotide change in a neurotransmitter in the brain of a large, intelligent social mammal. Rhinoviruses thus provide a tractable and quickly evolving system by which researchers can probe the evolution of host and pathogen—and the coevolution of the two.

The rhinovirus switch

The jump from enteroviruses, which cause acute infections in the human gut, to rhinoviruses that are specialized in attacking the upper respiratory tract involved a series of biochemical changes to the capsid proteins encasing the mature virion. These changes rendered the gut-resident viruses sensitive to the low pH of the digestive tract, most likely forcing the subset that became the rhinoviruses into a new niche. It is unclear when these transitions occurred, due to the viruses’ high mutation rates and the obvious lack of a fossil record even in preserved human remains. Indeed, how long rhinoviruses and their ancestors have been causing misery to humans is almost impossible to establish. It may be that rhinoviruses are a pathogen of civilization, previously unable to persist in the small and relatively isolated groups that predated agriculture and urbanization. Alternatively, rhinoviruses may have been infecting humans since the dawn of Homo sapiens sapiens.

There are roughly 100 different rhinovirus serotypes that, until a couple of years ago, were thought to comprise only two species: HRV-A and HRV-B. Recent genetic testing revealed a new species of rhinovirus, however, called HRV-C, which fails to grow in cell culture and thus could not be detected using earlier methods.

Rhinoviruses can also be categorized by the receptors they use to enter cells. The major group, which consists of about 90 members and includes all HRV-B and the majority of HRV-A serotypes, binds to the cell surface receptor ICAM-1 for entry, while the minor group, which consists of just 12 or so HRV-A viral serotypes, binds to the unrelated low density lipoprotein (LDL) receptor. (It is not yet known which receptors HRV-C viruses bind to enter host cells.) Minor-group viruses appear to have evolved from major-group viruses, and then diversified. Since this initial diversification, however, the number of minor-group serotypes and the frequency of minor-group virus infections has remained fairly constant over the decades. This is despite—or perhaps because of—the fact that minor-group viruses interact quite differently with the immune system. (See illustration below.)
In addition to the epithelial cells targeted by rhinoviruses, the ICAM-1 molecule used by major-group rhinoviruses is expressed on many other types of human cells, including macrophages and dendritic cells, which play critical roles in initiating, amplifying, and controlling the immune response. The major-group viruses don’t actually infect these host immune cells, but they can alter the cells’ behavior just by attaching to the ICAM-1 receptor, which is upregulated when the immune response begins.³ Viral attachment stimulates these immune cells to produce anti-inflammatory signals, and also makes them travel more slowly to the lymph nodes where they activate the T cells that fight the invaders. Major-group rhinoviruses thus delay a full-on immune attack. These viruses also create delayed and ambiguous signals, slowing and reducing the production of antibodies and memory B and T cells that protect the host against reinfection.

Minor-group rhinoviruses, on the other hand, do not, in any way that we know, suppress the immune system. On the contrary, infections with minor-group viruses involve a more enhanced immune response. For example, when we reanalyzed antibody levels recorded in 1985 by John Fox and colleagues at the University of Washington in Seattle 1 year after initial infection,⁴ we found that major-group viruses induced antibodies in only a fraction of infected individuals, while most patients produced antibodies in response to infections with minor-group viruses. By eliciting a stronger immune response, minor-group viruses should be at a distinct competitive disadvantage. The phylogeny indicates, however, that the minor-group strategy has arisen at least three times within the HRV-A species, indicating some counterintuitive selective advantage.

It’s possible that if multiple infections are sufficiently common, minor-group viruses might capitalize on the ability of major-group viruses to suppress the immune response. Alternatively, minor-group viruses may escape immune attacks by evolving more rapidly than major-group viruses. Indeed, amino-acid changes have occurred most commonly among minor-group serotypes, and often close to places in the genome that encode the regions of capsid receptor proteins where antibodies bind, presumably allowing the viruses to evade antibody detection.⁵

The common cold has proven stubbornly resistant to treatment and prevention. Furthermore, because the symptoms of infection are predominantly caused by the immune system’s reaction, rather than by the viruses themselves, the fact that minor-group viruses elicit a stronger immune response could mean they are more virulent. Although no data yet exist to examine this in detail, high virulence could lead to more effective transmission as a result of the damage inflicted on the host. One new approach to better understand viral infections is to model the experience from our own perspective—namely, the progression of symptoms—rather than that of the virus. To date, only a few models have attempted to predict the symptoms produced by acute upper respiratory tract viruses, and those have focused on influenza. Similar models of rhinovirus infections could quantify the components of host damage and the host immune system that lead to particular symptoms, and thus could pave the way to study a whole range of questions: How do partial immunity, coinfection, and prior infection alter symptoms? What treatments might be most effective in alleviating symptoms, and what effects might those treatments have on viral reproduction and transmission? Because they are so common, rhinovirus
infections could serve as a natural experiment to test these models, and could eventually inspire new treatments that direct the immune system into more effective response pathways.

**Swapping out receptors**

Rhinoviruses may also shed light on the sometimes shadowy link between microevolution and macroevolution. Some small changes, of perhaps a single amino acid in a viral protease, might do little more than alter the rate of viral replication. Others, like the target receptor change that characterizes the switch from major to minor group, alter the very way that viruses overcome one of their central challenges—entering a host cell. We have seen that all members of HRV-B bind the same ICAM-1 receptor, while minor group members of HRV-A bind the alternative LDL receptor. This is quite different from the rest of the enterovirus genus, which as a group uses a panoply of receptors.

Receptor usage plays a central role in determining the course of infection. Some members of the human enterovirus C species use the ICAM-1 receptor for entry, much like major-group rhinoviruses, and the two groups follow a similar course of infection despite their somewhat distant relationship. Other enteroviruses, such as the polioviruses, use the receptor CD155, which determines the type of cells these potentially deadly viruses are able to attack. It has been speculated that the eradication of polio could open up a niche, and favor one of the virus’s close relatives to make the same receptor switch. As we have seen with the minor-group rhinoviruses, receptor switches might provide opportunities for new adaptive radiations.

In addition to understanding how these particular viruses evolve to inhabit different regions of the human body, tracking changes in the viruses’ targeted receptors may also provide insight into how the virus switches species. Specialized as enteroviruses and rhinoviruses are today, changes in host surely occurred at some point in the distant past, and those jumps were likely supported by changes of the receptor to which the viruses bind. While host species switches are rare and isolated events, and thus notoriously difficult to study, receptor switches are relatively common events within the enterovirus family and appear to parallel host switches. Indeed, in both host and receptor switches, we expect some degree of initial maladaptation—first creating severe symptoms that in no way aid viral transmission. But should these viruses succeed in making the change, whether it be to a new host organism or a new target receptor, they will then rapidly adapt and diversify, possibly accruing changes in virulence.

**Where next?**

Although neglected in comparison with viruses causing more severe infections, such as influenza and HIV, rhinovirus infections do create a serious public-health burden, forcing people to miss work, leading to wrongly prescribed antibiotics, and occasionally resulting in medical complications. And in the modern era, the common cold has proven stubbornly resistant to treatment and prevention. In spite of vast changes in science and society, the frequency of colds has remained pretty much constant over the last half century.

The promising drug pleconaril, originally developed by the pharmaceutical company Sanofi-Aventis in 1995, caused a modest reduction in the duration of symptoms in rhinovirus and enterovirus patients during Phase II trials, but was not used widely after 2002 because of side effects and interactions with other drugs. Given rhinoviruses’ high diversity and low medical profile, developing a vaccine seems quixotic at best and dangerous at worst, because it has been speculated that rhinovirus infections early in life could play a role in inhibiting infection by more-severe upper respiratory tract viruses or in training the immune system.
Asthma is probably the most important clinical side effect of rhinovirus infection; the virus is implicated in two ways. First, severe rhinovirus infections that cause wheezing in infants predict later asthma, although the causal factor appears more likely to be allergic sensitivity, which may increase the risks of both infection and asthma. Second, rhinovirus infections trigger many asthma exacerbations in children. Patients with cystic fibrosis are also highly sensitive to rhinovirus infections. These patients suffer from chronic bacterial lung infections, and the immunosuppressive effects of rhinovirus could release the bacteria from control. In both cases, understanding the ways in which rhinovirus manipulates the immune system is crucial.

Modern genetic techniques are making it possible to sequence the entire rhinovirus genome from individual patients, and to link viral sequences with symptoms collected using Internet-based tools. In combination with mathematical models, this places us in a position to look in detail at the way small changes in the viral genome translate into consistent patterns of symptoms. If we can figure out which rhinovirus serotypes cause the most severe pathology, and link those to genetic mechanisms, we will have new targets for controlling the worst infections.

**Fred Adler is a professor of biology and mathematics at the University of Utah.**

**References**


**Stem Cells: Safe Haven For TB**

*Tuberculosis* bacteria find shelter from drugs and the body’s defenses in bone marrow stem cells.

By Nsikan Akpan | February 5, 2013

*Mycobacterium tuberculosis* (TB) hides out in stem cells deep within bone tissue, where it avoids detection from the immune system and drugs, according to a study published last week (January 30) in *Science Translational Medicine*.

“This is a very exciting story,” said Horacio Frydman, a microbiologist at Boston University who was not involved in the research. In 2006, Frydman and his Princeton University postdoc advisor, Nobel Laureate Eric Wieschaus, reported the first case of bacteria living in a stem cell niche, after observing *Wolbachia* invade the stem cells of the *Drosophila melanogaster* germline. "Hitching a ride in cells that are self-renewing is a great strategy for reinfecting tissues in the host", continued Frydman, “and we always assumed that other bacteria should also be doing the same.”

Ninety percent of TB infections are cleared by the body’s immune defenses or by taking anti-TB medication. In the remaining 10 percent of cases, however, TB persists as a dormant, non-replicating infection. Though latent TB infections do not cause symptoms, they can reactivate after years of hiding. An estimated one-third of the global population has latent TB, which accounts for 1.7 million deaths per year—more than any other bacterial pathogen on the planet.

During the early stages of the disease, active TB bacteria replicate inside human macrophages and dendritic cells. But there is no evidence these cells harbor dormant TB, and the location of the latent reservoir has remained a mystery.

Bikul Das, the study's first author and a postdoc at Stanford University, first stumbled across a possible reservoir 15 years ago, while working for the World Health Organization (WHO) in the Himalayan country of Bhutan, where TB is severely endemic. While conducting bone marrow biopsies of patients with unexplained pyrexia, or fever, Das became curious as to whether TB could inhabit the bone marrow. Given that active TB can sometimes circulate in the bloodstream, he reasoned, perhaps the bacterium also infects the bone marrow, which is highly vascularized. Sure enough, when he examined
surplus biopsy material, Das detected a surprising number of patients that harbored TB in their bone marrow.

Interestingly, much of the TB was observed in progenitor cells, suggesting TB might target bone marrow stem cells, but Das’s tenure in Bhutan ended before he could further explore the finding. Then, 4 years ago, he joined the Stanford University lab of Dean Felsher to revisit the topic. Das and Felsher started by collecting the bone marrow of healthy human volunteers, and exposing the cells in culture to virulent or avirulent strains of TB. The cultures were then treated with an antibiotic to kill any bacteria that hadn’t entered the cells.

Four days later, a subset of bone marrow mesenchymal stem cells (BM-MSCs)—those that expressed the cell surface receptor CD271—carried a remarkably heavy load of TB bacteria. In a follow-up experiment, the researchers tagged TB with a fluorescent marker and watched as the bacteria preferentially infected CD271-positive BM-MSCs. They also checked whether the bacteria could establish latent infections, and found that TB harvested from BM-MSCs up to 2 weeks after initial exposure could successfully grow active cultures.

To confirm the results, Das used a mouse model developed by Antonio Campos-Neto at the Forsyth Institute, where rodents are infected with a genetically modified TB strain whose replication can be switched off after 3 weeks without killing the bacteria. Six months later, Das uncovered viable, nonreplicating TB in the animals’ BM-MSCs. Transferring infected BM-MSCs into tail veins of naïve mice developed severe lung infections, which is indicative of a latent infection in mouse BM-MSCs.

Felsher believes that TB might select this hideout because “MSCs express genes that spit out a broad spectrum of drugs,” such that the bacteria would be sheltered from their anti-microbial activity. These stem cells also reside in an immunoprivileged niche within the bone marrow, where multiple mechanisms cooperate to prevent immune attack, such as an elevated density of immunosuppressive Treg cells and higher expression anti-inflammatory molecules.

Interestingly, the researchers found that differentiated BM-MSCs were less supportive of TB infection, with bacterial viability reduced four-fold, as measured by colony-forming assays. These findings raise the question: Does TB compel BM-MSCs to retain their stem cell properties? A recent study in Cell showed that Mycobacterium leprae—the agent of leprosy—reprograms Schwann cells so they adopt stem-cell like properties, which promotes infection.

Finally, the investigators returned to an endemic TB region—Arunachal Pradesh, India—to collect human bone marrow from nine patients who had contracted TB, but had been successfully treated with “DOTS”—a WHO-endorsed, multistep therapy. The researchers isolated CD271-positive BM-MSCs with magnetic sorting, and found that these cells were positive for TB DNA in 8 of the 9 patients. Furthermore, two of the TB-positive bone marrow samples yielded viable bacteria.

While previous studies have detected TB DNA in other cell types, including epithelial/endothelial, fibrocytes, adipocytes, this is the first demonstration of viable TB being isolated from patients with latent infection.

“It’s worth studying how TB gets into mesenchymal stem cells because, in theory, blocking [this interaction] might be a way of reducing dormancy and reoccurrence,” said Felsher.

Das et al., “CD271+ bone marrow mesenchymal stem cells may provide a niche for dormant Mycobacterium tuberculosis,” Science Translational Medicine, 5:170ra13, 2013.

**Bacteria Boost Vaccine Effectiveness**

**Researchers are looking to microbes to improve immune responses to a wide range of vaccines.**

By Sabrina Richards | February 10, 2013

Vaccines were created to protect us from pathogens ranging from influenza and measles to smallpox, polio, and diphtheria. But vaccines to some pathogens—like HIV and the herpes simplex virus (HSV)—have repeatedly failed in clinical trials. In the lone successful HIV vaccine trial to date, the vaccine only provided slight protection over the placebo. And GlaxoSmithKline (GSK) reported last year that its promising HSV2 vaccine against genital herpes sputtered in a large, late-stage trial.

Most vaccines provide the immune system with key pathogen-derived molecules to help it later recognize and attack the same intruder. But many of the molecules are, by themselves, “not really capable of provoking strong immune responses,” explained Dennis Klinman, an immunologist at the National Cancer Institute.

One way to boost the effectiveness of a vaccine is to include adjuvants—extra ingredients that prompt the immune system to take notice and elicit protection. The most commonly used adjuvants, first
approved for human use almost 80 years ago, are aluminum-based salts (alum salts), usually aluminum hydroxide or aluminum phosphate. But alum salts only effectively rouse certain types of immune cells. T cells that recognize and kill infect cells—important in clearing infections—are not well stimulated by alum.

Now, scientists are looking for new and better adjuvants to boost the effectiveness of novel vaccines—and give new life a few that have failed late stage trials, including GSK’s HSV vaccine. Specifically, researchers are turning to bacteria for their well-established role as immune stimulators. Different bacteria attack the body in different ways—and the immune system has evolved to distinguish infections and activate the most effective immune cells to fight the current invader. Adding appropriate bacterial components to vaccines for similarly infecting pathogens could be the answer vaccinologists have looked for, says Klinman. “[A bacterial-based adjuvant] tells the immune system it’s encountered something truly foreign and pathogenic,” stimulating a stronger immune response to provide better, longer-lasting protection against infection.

**Breaking it down**

The first bacterial-derived adjuvant, approved for use in human vaccines in 2009, is a subunit of lipopolysaccharide (LPS), a molecule expressed on gram-negative bacteria. LPS stimulates strong—sometimes deadly—immune responses, but a subunit called monophosphoryl lipid A (MPL) can induce an immune response with little toxicity. Developed by GlaxoSmithKline, MPL is currently being used in GSK’s hepatitis B and human papilloma vaccines, and is being clinically tested with a range of other vaccines.

Given MPL’s success, the University of Texas at Austin’s Stephen Trent and his graduate student Brittany Needham decided to tweak lipid A to create a variety of adjuvants capable of stimulating different immune responses. Needham took her cue from the diversity of the LPS molecules expressed by different bacteria. Knowing that slight structural changes to LPS could alter immune cells’ cytokine responses, she began engineering *Escherichia coli* lines to express modified versions of lipid A. Testing her derivative lipid A subunits on LPS-sensitive cultured human monocytes, Needham found that each stimulated drastically different cytokines.

This could be the first step toward “designer” adjuvants, said Trent. “If you knew enough about the disease you want to try to cure, and you knew what pathways gave protection,” it could theoretically be possible to design the right adjuvant to maximize vaccine effectiveness, he speculated.

**Bacteria’s dead giveaways**

In addition to surface lipids, a handful of other bacterial structures, including toxins, bacteria-specific DNA sequences, and even whole commensal microbes (probiotics), are showing promise in activating pathogen-specific immune responses that bolster vaccines’ strength and longevity. One group of candidate adjuvants is enterotoxins, toxins made by gut-infecting bacteria like *E. coli* and cholera. Researchers think alum salt adjuvants have proven ineffective at boosting mucosal vaccine protection because they get washed away too quickly. Enterotoxins, on the other hand, bind to mucosal cells and increase gut permeability, and these toxins stimulate just the right kind of antibodies to fight mucosal infections—IgA.

Of course, whole enterotoxins are dangerous. The fact that they bind to the body’s mucosa is the reason infections with enterotoxin-carrying bacteria are so painful. So researchers have to modify the toxins before administering them to patients.

Nils Lycke and his colleagues at the University of Gothenburg in Sweden, for example, have developed an adjuvant called CTA1-DD that is derived from *Vibrio cholerae*’s deadly cholera toxin (CT). They attached a CT subunit to another protein from *Staphylococcus aureus* to create a non-toxic molecule that could have the same antibody stimulating properties as CT. Sure enough, mice vaccinated with an intranasal influenza vaccine plus CTA1-DD adjuvant produced mucosal IgA antibodies and were protected against death after flu infection. Lycke is hoping to start clinical trials of a CTA1-DD-boosted pandemic influenza vaccine soon.

Another possible adjuvant is bacterial DNA. Unlike human DNA, in which most cytosine–guanine pairs are methylated, so-called Cpg sequences are often unmethylated in bacteria, tipping off the immune system to the presence of an invader. B cells and plasmacytoid dendritic cells, key fighters of viral infections, respond to Cpg DNA. Making synthetic mimics of Cpg DNA could thus stimulate these cells to launch an immune response. Furthermore, Cpg sequences are “fairly non-toxic, and used as adjuvants they tend to be safe,” said Dennis Klinman at the National Institutes of Health National Cancer Institute, who was one of the first to recognize Cpg DNA’s immunomodulatory properties.
Among CpG DNA’s promising qualities is its apparent ability to encourage development of long-lived memory B cells—the cells that produce antibodies to fight a repeat infection. “To date almost every vaccine works because it induces strong antibody responses,” noted Klinman, but these often fade after several years and booster shots are required to provide long-lasting protection. By activating long-lived memory B cells, CpG DNA could help stimulate long-term antibody production.

In a recent Phase I clinical trial, pairing a CpG DNA adjuvant with the anthrax vaccine boosted volunteers’ immune responses to the vaccine. Compared to volunteers who received the standard vaccine, people injected with the CpG DNA-assisted anthrax vaccine generated about 8 times more anti-anthrax toxin antibodies and produced the strong antibody response about 3 weeks earlier. Several early phase clinical trials are also in progress to examine CpG DNA as an immune booster in cancer vaccines.

Probiotic panacea

Some researchers are taking a more holistic approach to vaccine adjuvants. Probiotics—beneficial, not pathogenic, microbes—have become famous recently for their ability to help influence the immune system. Though many studies focus on probiotics’ ability to stave off an overactive immune response, it turns out they can also boost the immune system.

“Probiotics have a whole range of different effects,” including enhancing immune responses, noted Paul Licciardi, an immunologist and vaccinologist at Murdoch Children’s Research Institute in Australia. A 2011 trial of live attenuated influenza vaccine, for example, showed that more patients given a 28-day course of the patented probiotic Lactobacillus rhamnosus GG produced protective antibodies to seasonal flu than patients given the vaccine alone.

“It’s a bit early to really know how good probiotics are going to be,” said Licciardi, but it’s an enticingly easy solution: simply give infants probiotics in yogurt or water during their vaccine course. Probiotics could “enhance general immunity,” said Licciardi, who is planning a small, placebo-controlled pilot study to give children oral probiotic supplements during a course of the vaccine for pneumococcal infection, “but maybe also to target specific immune responses.”

Immune system protein in semen boosts HIV spread in female genital tissue

NIH study suggests virus uses protein to spread

An immune system protein normally found in semen appears to enhance the spread of HIV to tissue from the uterine cervix, according to researchers at the National Institutes of Health.

The protein interleukin 7 (IL-7) belongs to a family of proteins that regulate the immune response. IL-7 is present in normal semen, and occurs at especially high levels in the semen of men with HIV.

The researchers developed a culture system of small pieces of tissue from the cervix and used this system to simulate male-to-female transmission of HIV, which causes AIDS. They observed the spread of the virus in cervical tissue under controlled laboratory conditions. In the presence of IL-7 at levels typically found in semen of men with HIV, the virus spreads to the tissue more readily than it spreads to tissue not treated with IL-7.

According to the study authors, the finding raises the possibility that IL-7, alone or in combination with other molecules, can foster male-to-female transmission of HIV. Similarly, they note, it’s possible that the level of IL-7 in semen may determine how infectious a particular HIV-positive male is for a female sexual partner. Also, researchers may one day be able to prevent or delay the spread of HIV by blocking seminal IL-7.

The major targets for HIV infection are T cells, a type of immune cell that normally marshal the body’s defenses against disease-causing organisms. Generally, when these cells become infected with HIV, they quickly die before the virus can produce a large number of copies of itself. However, the researchers found that in isolated pieces of cervical tissue, HIV-infected T cells in the presence of IL-7 live longer and so continued to produce the virus. IL-7 also stimulated uninfected T cells to divide thus increasing their number. These new T-cells would provide additional targets for the virus, potentially increasing its spread.

Researchers have long known that biological interactions that take place in the laboratory may not always occur in the more complex environment of a living organism. For this reason, Dr. Margolis noted that additional studies would be needed to confirm what he and his coworkers observed in the laboratory. “These experiments show us again how vicious HIV is,” said senior author Leonid Margolis, Ph.D., head of the Section on Intercellular Interactions at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), where the research was conducted. “The virus is able to commandeer an immune protein for its own benefit.”
Injection-free vaccination
Posted on 02/02/2013
Injection-free vaccination technique could address global vaccine challenge for diseases such as HIV and malaria
Scientists at King’s College London have demonstrated the ability to deliver a dried live vaccine to the skin without a traditional needle, and shown for the first time that this technique is powerful enough to enable specialised immune cells in the skin to kick-start the immunising properties of the vaccine.

Funded by the Bill & Melinda Gates Foundation and published today in Proceedings of the National Academy of Sciences, researchers say although it is an early study this important technical advance offers a potential solution to the challenges of delivering live vaccines in resource-limited countries globally, without the need for refrigeration. A cheaper alternative to hypodermic needles, it would also remove safety risks from needle contamination and the pain-free administration could lead to more people taking up a vaccination. The researchers add that it could have an impact beyond infectious disease vaccination programmes, for example managing autoimmune and inflammatory conditions such as diabetes.

HIV, malaria and TB represent major global health challenges. Although promising research is underway to develop vaccines for these diseases, considerable stumbling blocks remain for countries where transporting and storing live vaccines in a continuously cold environment (around 2°C to 8°C or below) would not be possible. If a cold chain cannot be maintained for a live vaccine there is a high risk it could become unsafe and lose effectiveness.

The team at King’s used a silicone mould developed by US company TheraJect to create a microneedle array – a tiny disc with several micro-needles made of sugar which dissolve when inserted into the skin. The team formulated a dried version of a live modified adenovirus-based candidate HIV vaccine in sugar (sucrose) and used the mould to create the microneedle array. They found that the dried live vaccine remained stable and effective at room temperature.

To test the effectiveness of the microneedle array, they applied it to mice. Using imaging (in collaboration with Professor Frederic Geissmann, King’s College London) they observed how the vaccine dissolved in the skin and were able to identify for the first time exactly which specialised immune cells in the skin ‘pick up’ this type of vaccine and activate the immune system. The researchers found the first evidence that a sub-set of specialised dendritic cells in the skin were responsible for triggering this immune response.

When compared with a traditional needle vaccine method, the immune response generated by the dried microneedle vaccine (kept at room temperature) was equivalent to that induced by the same dose of injected liquid vaccine that had been preserved at -80°C.

Dr Linda Klavinskis from the Peter Gorer Department of Immunobiology at King’s College London, said: ‘We have shown that it is possible to maintain the effectiveness of a live vaccine by drying it in sugar and applying it to the skin using microneedles – a potentially painless alternative to hypodermic needles. We have also uncovered the role of specific cells in the skin which act as a surveillance system, picking up the vaccine by this delivery system and kick-starting the body’s immune processes.

‘This work opens up the exciting possibility of being able to deliver live vaccines in a global context, without the need for refrigeration. It could potentially reduce the cost of manufacturing and transportation, improve safety (as there would be no loss in potency), and avoids the need of hypodermic needle injection, reducing the risk of transmitting blood-borne disease from contaminated needles and syringes.

‘This new technique represents a huge leap forward in overcoming the challenges of delivering a vaccination programme for diseases such as HIV and malaria. But these findings may also have wider implications for other infectious disease vaccination programmes, for example infant vaccinations, or even other inflammatory and autoimmune conditions such as diabetes.’

Practicing Safe Sex Is Important for Seniors
Queens Chronicle, (02.07.2013) AnnMarie Costella
To help prevent older adults from contracting STDs, some New York City senior centers are providing free condoms and informational sessions to its members. According to an agency spokesperson, the city’s Department of Health (DOH) distributes both male and female condoms as well as lubricant to more than 3,500 sites through its NYC Condom Availability Program. In 2012, the program sent 245,000 condoms to senior centers in the five boroughs.
Jacqueline Eradiri, executive director of the Ridgewood Older Adult Center, explained that men are at a premium and some men are having sex with more than one partner. This may result in STD transmission. To create awareness of safe sex, Eradiri periodically invites healthcare professionals to the center to speak about safe sex and demonstrate how to put on a condom. She keeps condoms and an equal number of individual lubricant packets in her desk drawer. DOH provides 1,000 of each to the center; clients ask for them when they need them. However, not all centers function in this way. Judy Ascherman, assistant director of the Howard Beach Senior Center, stated that she does not feel comfortable distributing condoms to clients, so she does not accept the free condoms that DOH offers to the center.

To better educate seniors, an independent collective of professional sexuality educators, researchers, authors, trainers, and counselors have created the SaferSex4Seniors.org site to teach elders about protected intercourse.

Pat Bishop, the executive director at the Rockaway Boulevard Senior Center in South Ozone Park, noted that DOH does not provide condoms for her facility, but its parent group, Jamaica Service Program for Older Adults (JSPOA), has a grant-funded department with staffers who visit the location to talk about safe sex and HIV transmission. Betty DeBaptiste, a retired nurse and HIV coordinator with JSPOA, gives safe sex classes. She mentioned that the education sessions include a film in which elder adults discuss the topic as well as demonstrate how to use both male and female condoms. She explained that she usually notifies the audience that they may leave the room, if they feel uncomfortable during the demonstrations, but only one or two have ever left.

**Three North Korean Doctors Killed In Nigeria; Government, U.N. Agencies Condemn Murders Of Polio Workers**

"Three North Korean doctors have been killed in a pre-dawn attack in Nigeria’s northeastern town of Potiskum, police say," but "[t]he motive of Sunday's attack was not immediately clear," *Al Jazeera* reports (2/10). "The deaths ... of the doctors in Potiskum, a town in Yobe state long under attack by the sect known as Boko Haram, comes after gunmen killed at least nine women administering polio vaccines in Kano, the major city of Nigeria's predominantly Muslim north," the *Associated Press* notes, adding, "No group has yet claimed responsibility for that attack either, though it follows alleged Boko Haram attacks now focusing on softer targets, like lightly guarded mobile phone towers."

According to the news service, "In a statement Friday, President Goodluck Jonathan condemned the killings of the polio workers and promised that efforts to cut child mortality wouldn't be stopped by 'mindless acts of terrorism'" (Abubakar et al., 2/10). A U.N. joint statement issued on Friday said, "UNICEF and WHO join the Government of Nigeria in condemning attacks in Kano state, Nigeria, that have killed and injured health workers. Such attacks are a double tragedy; for the health workers and their families and for the children and vulnerable populations who are robbed of basic life-saving health interventions. These attacks are unacceptable under any circumstance" (2/8).

**Cholera Cases Confirmed In Northern Mozambique After Heavy Rains, Flooding**

"In the last 10 days, 22 cases of the waterborne disease cholera have been confirmed by laboratory testing in three areas in and around the northern Mozambique town of Pemba, in Cabo Delgado Province," *IRIN* reports. "Leonard Heyerdahl, project manager of Africhol—an initiative of Paris-based NGO Agence de Médecine Préventive that is working in cooperation with the government’s National Institute of Health (NIH)—told IRIN that from 30 January, 'samples started turning positive [for cholera],’" the news service writes, noting, "Prior to that, there were 366 cases of severe diarrhea caused by the salmonella bacteria."

"Heavy rains, flooding, displacement and poor access for humanitarian assistance are creating an ideal environment for the proliferation of cholera" in the country, according to IRIN, which notes a U.N. Office for the Coordination of Humanitarian Affairs (OCHA) situation report from February 8 "said about '213,000 people have been affected by floods in Mozambique since October 2012'” (2/8).

**Chagas Disease Costs $7B Annually Worldwide, According To Study**

Chagas disease, transmitted by a bloodsucking insect that bites the face and lips, "costs the world about $7 billion annually, says [an] analysis just published in the Lancet Infectious Diseases," *NPR's "Shots"* blog reports. "That's more than the global cost of cervical cancer or cholera," the blog notes, adding, "Most Chagas cases occur in Latin America, but the disease is spreading northward." However, the data presented in the study are "rough approximates based on computer models for how much it costs to treat Chagas and losses incurred when sick people can't work or die prematurely—two things that are really
tough to nail down," according to the blog. Bruce Lee of the University of Pittsburgh and lead author of the study said, "The main thing is to view the order of magnitude. ... The numbers are based on some assumptions, but we tried to be conservative and underestimate the costs" (Doucleff, 2/10).

In an accompanying commentary in the Lancet, Gabriel Schmunis, a consultant to the WHO Regional Office of the Americas, writes, "The report by Lee and colleagues draws attention to the high economic burden of the disorder, from the level of individuals to the global level, including endemic countries and those as the USA, where vector transmission to humans is very rare. The article is a call for action; for sustained support for prevention and control as well as treatment of the thousands of individuals who are infected. I hope that the relevant governments from Latin America and elsewhere hear the call" (2/8).

**Roots Of FGM Lie In Tribal Culture, Not Religion**

"Female genital mutilation has long survived, hidden under the cloak of religious, cultural, and tribal practices, but ... as we commemorate the International Day of Zero Tolerance to Female Genital Mutilation (FGM), it is time for every leader whether political or religious, whether male or female, to unequivocally stand in opposition to FGM," Ufuk Gokcen, ambassador and permanent representative of the Organization of Islamic Cooperation to the United Nations, writes in the Huffington Post's "Religion" blog. "We can no longer allow the ignorance surrounding women's rights and FGM to be perpetuated by traditions and rituals disguised as religious teachings," he adds. "As the Organization of Islamic Cooperation's (OIC) Ambassador to the United Nations, I personally find it important to combat any notion that FGM is in the true nature of Islam," Gokcen continues. He says "despite statements from political and religious leaders and studies such as the Frontiers Program report put out by USAID de-linking FGM from Islam, the practice continues at an alarming rate." The perpetuation of the practice "can be explained by the fact that the practice takes its roots primarily in tribal culture, not religion; though some misguided local religious scholars might contest otherwise," he states, adding, "From Muslim women activists who agree that FGM is incompatible with Islam to global or local religious leaders who are making a stand against this horrific act, we must not only support their message but also put power behind these statements" (2/8).

**Infant gut microbiota influenced by cesarean section and breastfeeding practices**

**Practices may affect health in later life**

Method of birth (vaginal birth s. cesarean delivery) and feeding practices (breastfeeding v. formula-feeding) influence the development of gut bacteria in newborns and thus may affect lifelong health, according to a new study in *CMAJ (Canadian Medical Association Journal).*

Bacteria in the gut play an important role in health, helping digest food, stimulating the development of the immune system, regulating bowels and protecting against infection. Disruption of the gut microbiota has been linked to a range of diseases, such as inflammatory bowel disease, allergies, asthma, cancer and others.

"Our study addresses an important knowledge gap, since the infant gut microbiota has rarely been characterized with sequencing methods that provide sufficient coverage of the entire bacterial community," writes Dr. Anita Kozyrskyj, University of Alberta, with coauthors. "Our findings are particularly timely given the recent affirmation of the gut microbiota as a "super organ" with diverse roles in health and disease, and the increasing concern over rising cesarean delivery and insufficient exclusive breastfeeding in Canada."

As little is known about the development of this gut microbiota, a team of Canadian researchers sought to understand how the gut microbiome is established during early life, and what factors might disrupt this process. They looked at data on 24 healthy infants as part of the larger Canadian Healthy Infant Longitudinal Development (CHILD) study. CHILD involves more than 10 000 people, including 3 500 infants in 4 provinces (British Columbia, Alberta, Manitoba and Ontario) born after 2010 as well as their parents. The sample was representative of the Canadian newborn population, with 25% born by cesarean delivery, and 42% breastfed exclusively at 4 months of age.

New DNA sequencing technology was used by the research team to better understand the infant gut microbiome. Previous studies of this type have been conducted on laboratory cultures, although they were limited, as about 80% of intestinal microbes cannot be grown in culture. The DNA-based methods used in this study allow detection of virtually all bacteria since laboratory culture is not required.

The researchers found that infants born by cesarean delivery were lacking a specific group of bacteria found in infants delivered vaginally, even if they were breastfed. Infants strictly formula-fed, compared
with babies that were exclusively or partially breastfed, also had significant differences in their gut bacteria.

"We want parents (and physicians) to realize that their decisions regarding c-section and breastfeeding can impact their infant's gut microbiome, and this can have potentially lifelong effects on the child's health," says postdoctoral student and first author Meghan Azad, University of Alberta.

"The potential long-term consequences of decisions regarding mode of delivery and infant diet are not to be underestimated," write the authors. "Infants born by cesarean delivery are at increased risk of asthma, obesity and type 1 diabetes, whereas breastfeeding is variably protective against these and other disorders."

Beginning before birth, CHILD collects a range of information on environmental exposures such as pets, air pollution, household cleaning products, maternal and infant diet and more, and child health outcomes (including biological samples and clinical assessments). The researchers will use this information to study the development of the gut microbiome and its relationship to conditions such as wheeze and allergies in future studies.

"Children born by cesarean delivery or fed with formula may be at increased risk of a variety of conditions later in life; both processes alter the gut microbiota in healthy infants, which could be the mechanism for the increased risk," writes Dr. Rob Knight, a Howard Hughes Medical Institute Early Career Scientist and an Associate Professor with the BioFrontiers Institute and Departments of Chemistry and Biochemistry and Computer Science, University of Colorado, Boulder, Colorado, United States, in a related commentary.

"These issues are of direct relevance to pregnant women and health practitioners and should be considered when choices such as elective cesarean delivery and other interventions are discussed," state the commentary authors.

**Exercise linked with reduced prostate cancer risk in Caucasians but not African-Americans**

A new study suggests that exercise may reduce Caucasian men's risk of developing prostate cancer. And among Caucasian men who do have prostate cancer, exercise may reduce their risk of having more serious forms of the disease. Unfortunately, the benefits do not seem to apply to African-American men. The study is published early online in *CANCER*, a peer-reviewed journal of the American Cancer Society. Previous research has linked exercise to a reduced risk of developing prostate cancer. Studies have also revealed that African-American men have an increased risk of developing prostate cancer and of dying from the disease compared with Caucasians. It is not clear if exercise as a function of race plays any role in these disparities.

To investigate, Lionel L. Bañez, MD, of the Durham Veterans Affairs Medical Center, and his colleagues asked 307 men (164 white; 143 black) undergoing a prostate biopsy to complete a survey that assessed their exercise amounts per week. The exercise categories included sedentary, mildly active, moderately active, and highly active. Among Caucasians, men who were moderately or highly active were 53% less likely to have biopsy results indicating that they had prostate cancer compared with men who were sedentary or mildly active. There was no association between exercise amount and prostate cancer among black men.

The investigators also looked to see if exercise influenced the grade of tumors that were detected in men who did develop prostate cancer. Among men with cancer, those who exercised had a 13% reduced risk of having high grade disease, meaning that their cancer cells looked particularly abnormal under a microscope and were likely to quickly grow and spread. When this relationship was further explored as a function of race, it remained significant in Caucasians but not in African Americans.

"These findings that African-American men may not benefit from exercise the way Caucasian men do could be a contributor to why African-American race is a risk factor for prostate cancer and aggressive prostate cancer. Further studies are needed to investigate the mechanism behind this racial disparity in deriving cancer-related benefits from exercise which disfavors African-American men," said Dr. Bañez.
Lack of energy an enemy to antibiotic-resistant microbes

*Rice University engineers seek strategy to control resistant genes in the environment*

HOUSTON – (Feb. 11, 2013) – Rice University researchers “cured” a strain of bacteria of its ability to resist an antibiotic in an experiment that has implications for a long-standing public health crisis.

Rice environmental engineer Pedro Alvarez and his team managed to remove the ability of the *Pseudomonas aeruginosa* microorganism to resist the antibiotic medication tetracycline by limiting its access to food and oxygen.

Over 120 generations, the starving bacteria chose to conserve valuable energy rather than use it to pass on the plasmid – a small and often transmissible DNA element – that allows it to resist tetracycline.

The researchers’ results, reported this month in the American Chemical Society journal *Environmental Science and Technology*, are the latest in a long effort to understand the environmental aspects of antibiotic resistance, which threatens decades of progress in fighting disease.

“The propagation of antibiotic resistance has been perceived as a medical or microbiology-related problem,” Alvarez said. “And it truly is a serious problem. But what many people miss is that it is also an environmental pollution problem. A lot of the antibiotic-resistant bacteria originate in animal agriculture, where there is overuse, misuse and abuse of antibiotics.”

Alvarez contended that confined animal feeding operations (CAFOs) are potential sources of environmental contamination by antibiotics and the associated antibiotic-resistant genes that find their way into the ground, water and ultimately the food supply.

“We started with the hypothesis that microbes don’t like to carry excess baggage,” he said. “That means they will drop genes they’re not using because there is a metabolic burden, a high energy cost, to keeping them.”

The Rice researchers tested their theory on two strains of bacteria, *P. aeruginosa*, which is found in soil, and *E. coli*, which carries resistant genes directly from animals through their feces into the environment.

By slowly starving them of nutrients and/or oxygen through successive generations, they found that in the absence of tetracycline, both microbes dumped the resistance plasmid, though not entirely in the case of *E. coli*. But *P. aeruginosa* completely shed the genetic element responsible for resistance, which made it susceptible once again to antibiotics. When a high level of tetracycline was present, both microbes retained a level of resistance.

One long-recognized problem with antibiotics is that they tend to snatch defeat from the jaws of victory. If any antibiotic-resistant bacteria are part of a biological mix, whether in a person, an animal or in the environment, the weak microbes will die and the resistant will survive and propagate; this process is known by biologists as “selective pressure.”

So there is incentive to eliminate the resistance plasmid from bacteria in the environment as close to the source as possible. The experiments point to possible remediation strategies, Alvarez said. “There are practical implications to what we did,” he said. “If we can put an anaerobic barrier at the point where a lagoon drains into the environment, we will essentially exert selective pressure for the loss of antibiotic-resistant genes and mitigate the propagation of these factors.”

An anaerobic barrier may be as cheap and simple as mulch in the drainage channel, he said. “If you have a CAFO draining through a channel, then put an anaerobic barrier in that channel. A mulch barrier will do.” He said a mulch barrier only a meter thick could contact slow-moving groundwater for more than a month. “That may not kill the bacteria, but it’s enough to have bacteria notice a deficiency in their ability to obtain energy from the environment and feel the stress to dump resistant genes.”

Alvarez has been chipping away at the problem since moving to Rice from the University of Iowa in 2004, even without American funding for research. His study of the Haihe River in China, funded by the Chinese government and published last year, found tetracycline resistance genes are common in the environment there as well. “We tested water and river sediment and couldn’t find a sample that didn’t have them,” he said.

“ Our philosophy in environmental engineering is that an ounce of prevention is worth more than a pound of remediation,” Alvarez said. “Prevention here is, basically, don’t let these genes proliferate. Don’t let them amplify in the environment. Stop them before they’re released. And one easy way is to put up an anaerobic barrier.”
Important Step in the Activation of T-Cells in the Immune System Explained

Feb. 7, 2013 — A team headed by Prof. Dr. Wolfgang Schamel from the Institute of Biology III of the University of Freiburg and Prof. Dr. Balbino Alarcón from the Center for Molecular Biology Severo Ochoa of the Autonomous University of Madrid, Spain, has succeeded in explaining an important step in the activation of the so-called T-cells in the immune system. In humans and mice, T-cells are responsible for deciding whether a defense reaction should be activated to combat foreign substances.

Scientists want to prevent the receptor of the T-cells (TCR) from mistakenly also identifying the body's own tissue as a foreign substance to be fended off, because this can lead to autoimmune diseases such as multiple sclerosis. In order to do so, it is first necessary to elucidate the individual steps of TCR activation. Alarcón and Schamel published their findings on the exposure of the proline-rich region, an amino acid sequence in the TCR, in the current issue of the Journal of Immunology.

As soon as foreign substances like bacteria or viruses engage with the TCR, this binding triggers the process of phosphorylation of the receptor, activating the immune defense. Scientists were previously unable to explain how the information that binding has taken place is transmitted into the inside of the TCR. Some time ago, Alarcón and Schamel already established that the receptor undergoes a change in structure as soon as a foreign substance from the outside binds: The proline-rich region is hidden inside of the TCR, and after a binding the lower area of the receptor opens, exposing the region. By studying the proline-rich region, the scientists have now succeeded in demonstrating that this exposure is important for phosphorylation.

The team led by Alarcón changed the receptors in mice by removing the proline-rich region. Dr. Aldo Borroto in Madrid and Dr. Elaine P. Dopfer in Freiburg determined that the TCR no longer functions correctly without this region, as it is no longer phosphorylated. In a receptor that has not been changed, however, the proline-rich region binds to the adapter protein Nck after the region has been exposed. Dopfer performed an in vitro reconstruction of this interaction, thus providing quantitative evidence for the study. This was done within the EU consortium SYBILLA "Systems biology on T-cell activation," where Schamel and Alarcón are partners.

Through their joint research, the scientists in Freiburg and Madrid verified that the presence and exposure of the proline-rich region is of fundamental significance for activating the TCR, and consequently the immune defense. This finding will enable scientists to reach a more complete understanding of the process, from the binding of a foreign substance to the response from the immune system. It will now be possible to elucidate the subsequent steps, which have not yet been analyzed.

Schamel is a member of the Freiburg Cluster of Excellence BIOSS Centre for Biological Signalling Studies, the Spemann Graduate School of Biology and Medicine, and the Center for Chronic Immune Deficiency at the Freiburg University Medical Center. He also serves as coordinator of the EU FP7 network SYBILLA.

Journal Reference:

Was higher viral load responsible for the African HIV epidemic?
Co-infections may have increased incidence, especially in low-risk groups

Gus Cairns
Published: 12 February 2013
Researchers from Cornell University in New York have found that the average HIV viral load of people not taking antiretroviral medication (ART) in Africa, and especially in southern and eastern Africa, is higher than the viral loads of untreated patients on other parts of the world. The so-called 'community viral load' (CVL) off treatment was nearly four times higher on average in sub-Saharan Africa as a whole, and 5.5 times higher in southern African countries excluding South Africa, than it was in North America.
Speculating that these higher viral loads might be the reason Africa has experienced a far more serious epidemic of HIV than other regions, and one that has spread into the general population, the researchers used a mathematical model to estimate that one-in-seven HIV infections in sub-Saharan Africa would not have happened if the CVL in untreated people had been the same as in richer regions. Their model found that this effect was especially marked in low-risk populations such as heterosexual people with few partners.

**Off-treatment viral load is higher in Africa**
The observed community viral loads were gathered from a number of cohort studies of people with HIV who were not on ART in various parts of the world. Viral loads from over 66,000 people in 39 different cohort groups were gathered and divided into four CD4 count ranges (under 200, 200 to 350, 350 to 500, and over 500 cells/mm³). There was a big geographical imbalance, with nearly half of all samples from Europe and under 400, from a single cohort study, from South America, limiting the precision of the CVL estimate from this region.

There were significant differences in average viral loads off treatment around the world. As expected, they were lower in people with the highest CD4 counts, where they ranged from approximately 5000 in the US to 15,000 in east Africa (3.65 to 4.18 logs); and they were highest in people with the lowest CD4 counts, ranging from 15,000 in South America to 220,000 in west Africa (4.17 to 5.33 logs).

Viral loads in west Africa, east Africa and southern Africa were consistently higher than viral loads elsewhere – they were twice (0.29 logs) as high in west Africa as in North America, and 5 and 5.5 times higher respectively (0.71 and 0.74 logs) in east and southern Africa. The community viral load was also significantly, but modestly, higher in Asia (about 40% or 0.14 logs higher). The country of South Africa itself was considered separately because of its relatively better health system than other countries in the area; there, the average viral load was about 50% or 1.9 logs higher than in the North America.

**Implications for HIV infection**
Putting these viral load data into a model using previous findings on the degree to which rising viral load increases infectiousness, and using population data from the epidemic in Kisumu, Kenya, the researchers calculated that by 2010 cumulative HIV prevalence in an untreated population was 13.9% greater than it would have been had untreated CVL been at the level seen in North America rather than in Africa; in other words one-in-seven HIV infections was directly attributable to the higher viral load.

However, raised viral load also skews demographics because it disproportionately affects people at lower risk of HIV (because people at higher risk would become infected even if CVL was lower, due to greater frequency of unprotected sex). This means that HIV prevalence in lower-risk heterosexuals was 22.5% higher than it otherwise would have been; nearly one-in-four infections in this group was directly attributable to higher CVL.

The researchers also calculated that a 34% decline in the frequency of sex (or a 51% increase in protected sex) would be needed to compensate for the viral load effect seen.

Their model showed that the effect of higher CVL would be particularly marked at the mid-point of the epidemic’s growth. Using an assumption that HIV prevalence first started to rise significantly in 1980, they found that, with the observed CVL, the steepest point in the epidemic’s growth occurred about 1988. If CVL had been the global average in Africa, this point would not have been reached till seven years later, leading to a modelled HIV prevalence of about 20% in the mid-90s rather than 8% – pretty close to what actually happened in southern Africa.

**Questions and conclusions**
The question these data beg, of course, is what is causing the excess viral load? The researchers speculate that the higher rate of untreated co-infections in Africa could be to blame, and cite a 2002 paper from Uganda that shows that a herpes attack can raise HIV viral load by 50%, active tuberculosis by 150%, and acute malaria by 370% (a nearly fivefold increase).

This fact has been known for some time, and although trials that attempt to reduce HIV incidence by treating other diseases such as herpes and inflammatory STIs have tended to produce negative results, the concept is not dead; a trial in Kenya is currently looking at the effect on HIV of treating worm infestations.

This study shows that raised viral load cannot be the entire explanation for south and east Africa’s dramatically larger HIV epidemics: a combination of factors ranging from it being HIV’s home continent to war and poverty contributed to its unique spread into the general population.

It does, however, show that higher viral load probably made a very significant contribution at a key point in the epidemic in Africa and underlines, as the researchers say, the idea that controlling HIV viral load with antiretrovirals is key to stopping further infection. It also suggests that, until universal ART
coverage is achieved, treating co-infections with the right cheaper therapies “may offer a complementary strategy for the control of HIV in sub-Saharan Africa”.

Reference

President’s AIDS council calls on feds and states to repeal HIV criminalization laws
By Todd Heywood
The Presidential Advisory Council on HIV/AIDS (PACHA) passed a resolution last week that calls for an end to federal and state HIV-specific criminal laws and prosecutions.

While the resolution is only advisory, it recommends that the departments of Justice and Health and Human Services issue guidance and offer incentives to state attorneys general and state health departments to eliminate HIV-specific laws. The advisory group also asks these federal agencies to develop guidelines for how to approach HIV within criminal and civil justice systems that are “consistent with the treatment of similar health and safety risks.”

As the resolution notes, 32 states and two territories have laws criminalizing people living with HIV.

In explaining the reason to repeal these laws, the resolution reads:

People living with HIV have been charged under aggravated assault, attempted murder, and even bioterrorism statutes, and they face more severe penalties because law enforcement, prosecutors, courts, and legislators continue to view and characterize people living with HIV and their bodily fluids as inherently dangerous, even as ‘deadly weapons. Punishments imposed for non-disclosure of HIV status, exposure, or HIV transmission are grossly out of proportion to the actual harm inflicted and reinforce the fear and stigma associated with HIV. Public health leaders and global policy makers agree that HIV criminalization is unjust, bad public health policy and is fueling the epidemic rather than reducing it.

PACHA is also requesting that state and federal authorities review the cases of persons convicted under such laws and overturn convictions if deemed appropriate. The group is calling on the Centers for Disease Control and Prevention to “issue a clear statement addressing the growing evidence that HIV criminalization and punishments are counterproductive and undermine current HIV testing and prevention priorities.”


“I join the President’s Advisory Council on AIDS in calling on the Department of Justice and the Centers of Disease Control and Prevention to issue clear guidance to states and public health departments on the counterproductive effects of HIV criminalization policies; we must end this clear discrimination against people living with HIV,” Lee continued. “Criminalization laws breed fear, discrimination, distrust and hatred, and we must end them.”

The White House declined to comment on the resolution, but the National HIV/AIDS Strategy adopted by the Obama administration in July 2010 does call for state legislatures to “consider reviewing HIV-specific criminal statutes to ensure that they are consistent with current knowledge of HIV transmission and support public health approaches to preventing and treating HIV.”

Policymakers at the state level also welcomed the resolution. Randy Mayer, chief of the Bureau of HIV, STD, and Hepatitis for the Iowa Department of Public Health, said the resolution was a new tool in advocates’ fight to repeal Iowa’s HIV-specific law.

“This resolution came at an excellent time for Iowa,” Mayer said in an email to The American Independent.

State activists and public health officials, including Mayer, have laid out a strategy to repeal the state’s law.

“The advocates in Iowa have also aligned their efforts with a public health perspective, so the resolution was a reinforcement of their justification,” Mayer said. “I think the more public health entities that weigh in on this discussion the better.”

But while policymakers praise the resolution, activists urge cautious optimism.

Sean Strub, executive director of the anti-HIV-criminalization organization Sero Project, said the resolution was appreciated, but the “real test will be in whether federal agencies and the administration responds with the necessary urgency.”
Catherine Hanssens, executive director of the Center for HIV Law and Policy, which runs the Positive Justice Project, echoed Strub’s sentiment, noting that while the resolution is important, Pacha “has no power to order anyone to do anything.”

“[HHS] Secretary [Kathleen] Sebelius and President Obama both have the discretion to ignore the resolution’s recommendations.”

Regardless, Hanssens said the resolution is an important milestone in the battle to repeal HIV criminal laws in the U.S.

“The work of advocates who pushed for passage of the resolution is not over,” she said. “But we have passed a major marker on the road to reform, and justice, for many people and communities affected by HIV.”

**U.N. Secretary General Condemns Violence Against Health Workers In Nigeria**

U.N. Secretary-General Ban Ki-moon on Monday “strongly condemned the killing in north-eastern Nigeria of three doctors from the Democratic People's Republic of Korea, calling the attack and other recent incidents of violence against health workers 'unacceptable,'” the U.N. News Centre reports (2/11). "Those killings came quickly after gunmen shot dead at least nine female polio vaccinators Friday in Kano, the most populous city of Nigeria's predominantly Muslim north," the Associated Press/Washington Post writes, adding, "The U.N. chief said these acts of 'outrageous violence' ... could have devastating effects in the fight to improve the health of people everywhere, [U.N. spokesperson Martin Nesirky] said."

"These recent attacks in northern Nigeria show the changing tactics of Islamic extremists here and continuing dangers facing Africa's most populous nation, despite a buildup of soldiers and police officers, door-to-door searches by security forces and mass arrests," the news service notes (2/11). "Police in northern Nigeria say they've arrested three radio journalists over the killings of at least nine female polio vaccinators, saying their on-air discussion about rumors around the vaccine sparked the attack," the AP reports in a separate article, adding, "Kano state police commissioner Ibrahim Idris said Tuesday that the journalists, who work for Wazobia FM, will be charged with culpable homicide over the killings Friday" (Rabiu, 2/12).

**Sex Diseases Cost $16 Billion a Year to Treat, CDC Says**

*Bloomberg, (02.14.2013)* Elizabeth Lopatto

CDC reported that it costs the United States $16 billion annually to treat eight STDs—HIV, syphilis, gonorrhea, hepatitis B, chlamydia, trichomoniasis, herpes, and human papillomavirus (HPV). CDC’s most recent comprehensive data (2008) estimates there are 19.7 million newly diagnosed sexually transmitted infections each year, and that half of these infections occur among young people ages 15 to 24. The most common diagnosis is HPV, which has been linked to throat, cervical, and penile cancers. The report estimates 110 million total sexually transmitted infections among US men and women of all ages.

CDC Epidemiologist Catherine Satterwhite, an author of one of the reports, stated that young people—especially young women—have always been disproportionately affected by STDs because many lack good insurance or easy healthcare access. Satterwhite noted that all STDs are preventable, most are curable, and all have existing treatments. Techniques for preventing STDs include abstinence, condom use, and mutual monogamy for couples. CDC recommends boys and girls have vaccination with Merck’s Gardasil to prevent HPV. In spite of increased incidence of HPV-related cancers, use of HPV vaccine remains low.

HIV is the most expensive STD because it requires life-long treatment. Curable STDs cost $742 million annually. The most common curable STD is chlamydia. To lower prevalence, Satterwhite recommended increased testing, especially for young women, and urged all sexually active people to be tested at least once for HIV.


**Pregnant Women with Sexually Transmitted Diseases Often Don’t Get Medication in ER, Finds Study by MSU Med Student**

*Michigan Live*, (02.08.2013) Sue Thoms

Michigan State University researchers report that pregnant women treated in emergency rooms (ERs) often do not receive needed care for chlamydia and gonorrhea because laboratory results are not available before the women leave. The study based its conclusions on the records of 735 STD-infected women who were treated in three Grand Rapids hospital ERs. Half of these women received antibiotics for chlamydia or gonorrhea in the ER, but ER physicians prescribed antibiotics for only 20 percent of the 179 pregnant women who had gonorrhea or chlamydia.

Although inexpensive and effective antibiotics are available for these STDs, hospital staff is frequently unable to contact women after they leave the ER and tell them their laboratory results show gonorrhea or chlamydia infection. Medical student Roman Krivochenitser stated that on-the-spot testing would help staff provide immediate treatment for STD-infected pregnant women who come to the ER.

Diagnosing chlamydia and gonorrhea in pregnant women in the ER can be difficult, according to Krivochenitser, because some degree of abdominal discomfort is common during pregnancy. However, a mother’s untreated STD increases the risk of low birth weight, pre-term delivery, and passing the infection along to the baby. Women with untreated STDs also rarely develop pelvic inflammatory disease.

CDC currently restricts antibiotic prescriptions to prevent the growth of drug-resistant bacteria. The Michigan study recommends more research on rapid testing for chlamydia and gonorrhea, improved contact and follow-up with ER patients, and permission for physicians to treat pregnant women with antibiotics based on a clinical assessment.


**The human pathogen Streptococcus pneumoniae shields foreign DNA derived from other bacteria to promote genetic diversity and vaccine evasion**

A new report demonstrates that the human pathogen *Streptococcus* (*S.*) *pneumoniae* (one of the known causes of bacterial pneumonia) possesses an unusual enzyme that protects foreign DNA taken up during transformation, allowing exchange of pathogenicity islands donated from other pathogenic bacteria. This study, published February 14 in the Open Access journal *PLOS Pathogens* by researchers from the Laboratory of Microbiology and Molecular Genetics (CNRS-Université Paul Sabatier, Toulouse, France), establishes a role for this enzyme in protecting internalized DNA from restriction, and simultaneously shows that *S. pneumoniae* uses transformation, for example by DNA picked up from other bacterial strains, specifically to promote genome diversification.

Exchange of pathogenicity islands is crucial for pneumococcal virulence, as illustrated by the impressive variability in the polysaccharide capsule, which is usually targeted by current vaccines. Acquisition of different capsule loci, by relying on this genetic transformation, thus allows for vaccine evasion. Natural genetic transformation is thought of as the bacterial equivalent of sexual reproduction, allowing intra- and inter-species genetic exchange. This process, involving uptake of foreign DNA as single-strands (ss) that leads to chromosomal integration, is transient in *S. pneumoniae*.

Restriction-modification (R-M) systems classically include a restrictase, which protects the host bacteria from attack by bacteriophage via the degradation of only the foreign double-stranded (ds) DNA, and a dsDNA methylase that methylates the host genome, providing self-immunity against this restrictase. Since they degrade only foreign DNA, R-M systems are proposed to antagonize transformation by DNA from other bacteria. The DpnII R-M system investigated in this study is present in around half of pneumococcal isolates tested and also possesses an unusual methylase of ssDNA, DpnA, which is specifically induced during the brief genetic transformation time window.

This study shows that DpnA gene is crucial for the exchange of pathogenicity islands when the foreign DNA is unmethylated (i.e., from a non-DpnII modified DNA donor). By methylating the internalized foreign ssDNA, DpnA protects the chromosome of those transformants that incorporate the foreign pathogenicity islands, such as the capsule locus. In the absence of this unique methylation, the novel transformant chromosomes would be degraded by the DpnII restrictase, thus forbidding the acceptance of the foreign DNA sequences.

The researchers found that the role of DpnA is to protect foreign DNA, allowing pathogenicity island exchange between bacteria. Jean-Pierre Claverys, Principal Investigator and senior author of the paper.
concludes that "this finding is the first evidence for a mechanism that actively promotes genetic diversity of S. pneumoniae through programmed protection and incorporation of foreign DNA."

**Gene invaders are stymied by a cell's genome defense**

Gene wars rage inside our cells, with invading DNA regularly threatening to subvert our human blueprint. Now, building on Nobel-Prize-winning findings, UC San Francisco researchers have discovered a molecular machine that helps protect a cell's genes against these DNA interlopers.

The machine, named SCANR, recognizes and targets foreign DNA. The UCSF team identified it in yeast, but given the similarity of yeast and human cells, comparable mechanisms might also be found in humans, where they might serve to lower the burden of inherited human disease and death, the researchers said.

The targets of SCANR are small stretches of DNA called transposons, a name that conjures images of alien scourges. But transposons are real, and to some newborns, life threatening. Found inside the genomes of organisms as simple as bacteria and as complex as humans, they are in a way alien — at some point, each was imported into its host's genome from another species.

Unlike an organism's native genes, which are reproduced a single time during cell division, transposons — also called jumping genes — replicate multiple times, and insert themselves at random places within the DNA of the host cell. When transposons insert themselves in the middle of an important gene, they may cause malfunction, disease or birth defects.

But just as the immune system has ways of distinguishing what is part of the body and what is foreign and does not belong, researchers led by UCSF's Hiten Madhani, MD, PhD, discovered in SCANR a novel way through which the genetic machinery within a cell's nucleus recognizes and targets transposons. The study was published online February 13 in the journal *Cell*.

"We've known that only a fraction of human inherited diseases are caused by these mobile genetic elements," Madhani said. "Now we've found that cells use a step in gene expression to distinguish 'self' from 'non-self' and to halt the spread of transposons."

**Gene Wars Span Eons**

Transposons have been barging into genomes and crossing species boundaries throughout evolution. Rapidly evolving bacterial species often use them to transmit antibiotic resistance to one another. Nearly half of the DNA in the human genome consists of transposons, and the percentage can potentially creep upward with every generation. That's because nearly 20 percent of transposons are capable of replicating in a way that is unconstrained by the normal rules of DNA replication during cell division — although through generations over time, most have become inactivated and no longer pose a threat.

While humans are riddled with transposons, compared to some organisms they've gotten off easy, according to Madhani, a professor of biochemistry and biophysics at UCSF. The water lily's genome is 99 percent derived from transposons. The lowly salamander has about the same number of genes as humans, but in some species the genome is nearly 40 times bigger, due to all the inserted, replicating transposons. To accommodate this DNA, a salamander's cells are large in comparison to a human's cells.

The scientists' discovery of SCANR and how it targets transposons in the yeast Cryptococcus neoformans builds upon the Nobel-Prize-winning discovery of jumping genes by maize geneticist Barbara McClintock, and the Nobel-prize-winning discovery by Richard Roberts and Phillip Sharp that parts of a single gene may be separated along chromosomes by intervening bits of DNA, called introns. Introns are transcribed into RNA from DNA but then are spliced out of the instructions for building proteins.

In the current study, the researchers discovered that the cell's splicing machinery stalls when it gets to transposon introns. SCANR recognizes this glitch and prevents transposon replication by triggering the production of "small interfering RNA" molecules, which neutralize the transposon RNA. The earlier discovery by Andrew Fire and Craig Mello of the phenomenon of RNA interference, a feature of this newly identified transposon targeting, also led to a Nobel Prize.

"Scientists might find that many of the peculiar ways in which genes are expressed differently in higher organisms are, like intron splicing in the case of SCANR, useful in distinguishing and defending 'self' genes from 'non-self' genes," Madhani said.

**Humans and chimps share genetic strategy in battle against pathogens**

A genome-wide analysis searching for evidence of long-lived balancing selection—where the evolutionary process acts not to select the single best adaptation but to maintain genetic variation in a population—has
uncovered at least six regions of the genome where humans and chimpanzees share the same combination of genetic variants.

The finding, to be published Feb. 14 in the journal *Science*, suggests that in these regions, human genetic variation dates back to a common ancestor with chimpanzees millions of years ago, before the species split. It also highlights the importance of the dynamic co-evolution of human hosts and their pathogens in maintaining genetic variation.

Balancing selection allows evolution to keep all hereditary options open. The classic human example is the persistence of two versions of the hemoglobin gene: a normal version and hemoglobin S, a mutation that distorts the shape and function of red blood cells. Those who inherit two normal hemoglobin genes are at high risk for malaria, a parasitic disease that infects more than 200 million people each year. Those who inherit one normal gene and one hemoglobin S. gene are partially protected from malaria—a potentially life-saving benefit. Those with two copies of the gene suffer from sickle-cell anemia, a serious and lifelong circulatory disease.

"When we looked for genetic clues pointing to other, more ancient, examples of balancing selection, we found strong evidence for at least six such regions and weaker evidence for another 119—many more than we expected," said study author Molly Przeworski, PhD, professor of human genetics and of ecology and evolution at the University of Chicago.

"We don’t yet know what their functions are," she said. None of the six regions codes for a protein. There are clues that they are involved in host-pathogen interactions, "but which pathogens, what immune processes," she said, "we don’t know."

The researchers used genetic data from 10 chimpanzees from Western Africa and 59 humans from sub-Saharan Africa who were part of the 1,000 Genomes Project.

The scientists looked for cases in which genetic variations that arose in the ancestor of humans and chimpanzees have been maintained through both lines. The fact that variation in these regions of the genome has persisted for so long argues that they "must have been functionally important over evolutionary time," said Ellen Leffler, a graduate student in Przeworski’s laboratory and first author of the study.

The researchers, from the University of Chicago and Oxford University, designed the study to be very conservative. "We wanted to find the cases we believed the most, rather than the most cases," Przeworski said.

Computers sorted snippets of the genetic data from humans and chimps into clusters depending on how similar the subjects were to each other. For almost every snippet, they found a cluster of humans and a separate cluster of chimpanzees, as expected. But there were a few segments of the genomes in which each cluster included both chimpanzees and humans; in those regions, some humans were more closely related to some chimpanzees than to other humans.

"Instances in which natural selection maintains genetic variation in a population over millions of years are thought to be extremely rare," the authors wrote. The oldest and best known example of balanced polymorphism shared between humans and chimpanzees is the major histocompatibility complex (MHC), a group of genes that help the immune system distinguish between the body and potential invaders, such as bacteria or viruses.

Last year, a team led by Przeworski found that humans and gibbons shared genetic variation related to the ABO blood-group system from a common ancestor.

The six new examples of balanced selection described in this study appear to play a role, like the MHC, in fending off infectious disease. This requires a variety of evolutionary tools, including balancing selection. When a population moves to a new environment—for example the exodus out of Africa to northern Europe—they face many one-time adjustments, such as adapting to less intense sunlight and decreased ultraviolet radiation. Over many generations, their offspring manage to decrease melanin production—a static adaptation for a static environment.

Fighting off pathogens is more dynamic, a constant arms race. Balancing selection may have enabled humans and chimps to retain multiple lines of defense that can be called on when a pathogen evolves new weapons.

"Our results imply that dynamic co-evolution of human hosts and their pathogens has played an important role in shaping human variation," Przeworski said. "This highlights the importance of a different kind of selection pressure in human evolution."
Scientists find calcium is the initial trigger in our immune response to healing

For the first time scientists studying the cellular processes underlying the body’s response to healing have revealed how a flash of calcium is the very first step in repairing damaged tissue. The findings, published in *Current Biology*, could lead to new therapies that speed up the healing process following injury or surgery.

Until recently, very little was known about how damaged tissue activates and attracts the first white blood cells to the wound — the first stage in the healing process. However, researchers from the University of Bristol's School of Biochemistry in collaboration with a team from the University of Bath, have shown that the very first trigger in this process is a flash of calcium which spreads like a wave back from the wound edge through gap junctions that connect all the cells.

This flash of calcium signal goes on to activate an enzyme known as DUOX that synthesises hydrogen peroxide, which, in turn, attracts the first white blood cells to the wound. This white blood cell invasion, which is initiated during our inflammatory responses, is needed to kill off invading microbes and stop the onset of septicemia following tissue damage.

The findings indicate that the wound-induced calcium flash represents the earliest identified signal following wounding and might therefore orchestrate the rapid recruitment of immune cells.

To assess the impact of a reduced calcium flash upon the inflammatory response the team used Drosophila (fruit fly) embryos because they are translucent which makes it easy to image the inflammatory response and because of their simple genetics. The team found that blocking the calcium flash inhibited H2O2 release at the wound site leading to a reduction in the number of immune cells migrating to the wound.

Paul Martin, Professor of Cell Biology and an expert in wound healing at the University, said: "White blood cells are a little like 'Jeckyll and Hyde' in that they help us heal but are also the reason behind why we scar so we really need to know how they are regulated at wounds in order to learn how to control their behaviours for future therapeutic intervention."

Will Razzell, the lead PhD researcher on this study, added: "We are more than ever understanding the pathways that lead to immune cell attraction to wounds. As calcium represents the immediate inflammatory signal, we now have a good foundation to investigate this complicated process further."

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Eco-Safe Antibacterial Fiber Discovered

Feb. 14, 2013 — Researchers at KTH Royal Institute of Technology in Stockholm have discovered an antibacterial polymer that can be used in everyday products such as sportswear, diapers and bandages, without causing resistant bacteria.

"We have managed to find an antibacterial polymer that attaches stably to cellulose and therefore cannot be released into the environment," says Josefin Illergård, a chemistry researcher at KTH. The discovery could be an important breakthrough in the search for environmentally-friendly ways to control bacteria while preventing antibiotic resistance and resistant bacteria.

Illergård says the team's discovery is based on cellulose fibres embedded in a polymer, which kills bacteria. Cellulose is the most common organic substance in nature and the primary structural component of plant cell walls. The active polymer is so strongly bonded to the fibres of the cellulose material that it does not loosen or leak into the environment via water.

Antibacterial agents such as triclosan and silver ions are commonly used in sportswear and shoes to remove unpleasant odors from bacteria formation. But such biocides leak into the environment when the treated garments or surfaces are washed, raising the risk that bacteria will gradually become resistant to their effect.

"If someone uses a cloth to wipe a countertop treated with antibacterial agents, and that cloth is rinsed in the sink, those substances are then spread further through the drain and into the environment where they can contaminate soil and water and give rise to bacterial resistance," Illergård says.

She says that bacteria must come in direct contact with the material for the antibacterial process to work.

Because polymer has a positive charge and bacteria a negative charge, the new material actually attracts bacteria, she says. The material does not contain large amounts of polymer; and only non-toxic nitrogen oxides remain after it is burned. Nevertheless, the team's goal for the future is to continue the research and try to replace the antibacterial polymer with an entirely renewable material.
"We know that this project is of international interest," Illergård says. "Our papers have been requested by companies abroad and we are getting a lot of feedback when we present our findings at conferences.

"In the future, I believe our material will be used in cleaning clothes, in sanitation for hospitals and in different kinds of water purification filters," she says.

Illergård says the material could be ideal for simple water treatment in the future. "What if water could be purified in an environmentally friendly manner by our material, instead of just strainers?" she asks. "Many lives would be saved, and the material could be placed directly on the fire and burned after use."

**Gene That Suppresses Herpesviruses Discovered**

*Cells infected with the KSHV virus fluoresce yellow. The KSHV virus remains dormant in more than 95 percent of infected patients. (Credit: UNC/Damania Lab)*

Feb. 13, 2013 — Kaposi’s sarcoma-associated herpesvirus (KSHV) and Epstein-Barr virus (EBV) hide within the worldwide human population. While dormant in the vast majority of those infected, these
active herpesviruses can develop into several forms of cancer. In an effort to understand and eventually develop treatments for these viruses, researchers at the University of North Carolina have identified a family of human genes known as Tousled-like kinases (TLKs) that play a key role in the suppression and activation of these viruses.

In a paper published by *Cell Host and Microbe* on Feb. 13, a research team led by Blossom Damania, PhD, of the Department of Microbiology and Immunology and member of the UNC Lineberger Comprehensive Cancer Center, found that suppressing the TLK enzyme causes the activation of the lytic cycle of both EBV and KSHV. During this active phase, these viruses begin to spread and replicate, and become vulnerable to anti-viral treatments.

"When TLK is present, these viruses stay latent, but when it is absent, these viruses can replicate" said Dr. Damania.

Patrick Dillon, a postdoctoral fellow in Dr. Damania's lab, led the study. Other co-authors included UNC Lineberger members Drs. Dirk Dittmer, Nancy Raab-Traub and Gary Johnson.

KSHV and EBV are blood-borne viruses that remain dormant in more than 95 percent of those infected, making treatment of these viruses difficult. Both viruses are associated with a number of different lymphomas, sarcomas, and carcinomas, and many patients with suppressed immune systems are at risk for these virus-associated cancers.

"The dormant state of these viruses is what makes it so hard to treat these infections and the cancers associated with these infections," said Dr. Damania.

Researchers have known that stimuli such as stress can activate the virus from dormancy, but they do not understand the molecular basis of the viral activation cycle. With the discovery of the link between these viruses and TLKs, Dr. Damania said that researchers can begin to look for the molecular actions triggered by events like stress, and how they lead to the suppression of the TLK enzymes.

"What exactly is stress at a molecular level? We don't really understand it fully," said Dr. Damania.

With the discovery that TLKs suppress these viruses, Dr. Damania said that the proteins can now be investigated as a possible drug target for these virus-associated cancers. In its normal function in the cell, TLKs play a role in the maintenance of the genome, repairing DNA and the assembly of the chromatin, but there is a lot more to learn about the function of the TLKs, said Dr. Damania. One avenue of her lab's future research will investigate how TLKs function in absence of the virus.

"If we prevent this protein from functioning, and we combine this with a drug that inhibits viral replication, then we could have a target to cure the cell of the virus. If the virus isn't there, the viral-associated cancers aren't present," said Dr. Damania.

**Journal Reference:**

**Vitamin C Is Beneficial Against the Common Cold, Review Suggests**

Feb. 13, 2013 — According to an updated Cochrane Review on vitamin C and the common cold, vitamin C seems to be particularly beneficial for people under heavy physical stress. In five randomized trials of participants with heavy short-term physical stress, vitamin C halved the incidence of the common cold. Three of the trials studied marathon runners, one studied Swiss school children in a skiing camp and one studied Canadian soldiers during a winter exercise. Furthermore, in a recent randomized trial carried out with adolescent competitive swimmers, vitamin C halved the duration of colds in males, although the vitamin had no effect on females.

Regular doses of vitamin C of one gram per day or higher have reduced the average duration of colds in adults by 8% and in children by 18%. Although these findings unambiguously show that vitamin C has a biological effect on colds, taking vitamin C every day to shorten infrequent colds does not seem reasonable. On average, adults have only a few common cold episodes per year and children have some half a dozen colds per year.

Few therapeutic trials, meaning trials in which vitamin C was given only after the first symptoms of a cold appeared, have been carried out and their results are not consistent. Nevertheless, given the consistent effect of vitamin C on the duration and severity of colds in the regular supplementation studies, and the safety and low cost of vitamin C, the authors consider that it may be worthwhile for individual common cold patients to test whether therapeutic vitamin C is beneficial for them.

**Journal Reference:**
Eradicating Bacteria Linked to Gastric Cancer

Feb. 12, 2013 — In an analysis of the results of interventions to eradicate the bacterium Helicobacter pylori (a risk factor for gastric cancer) in seven diverse community populations in Latin America, researchers found that geographic site, demographic factors, adherence to initial therapy and infection recurrence may be as important as the choice of antibiotic regimen in H pylori eradication interventions, according to a study appearing in the February 13 issue of JAMA.

"Gastric adenocarcinoma is the second leading cause of cancer death worldwide. Although gastric cancer rates are declining in some areas, the number of deaths is expected to increase over the coming decades due to growing and aging populations in high-incidence regions such as Latin America and eastern Asia. Helicobacter pylori infects more than half of the world’s adult population, and chronic infection with this bacterium is the dominant risk factor for gastric cancer, accounting for an estimated two-thirds of all cases globally," according to background information in the article. "The feasibility of large-scale programs is uncertain and success in specific populations will depend on the efficacy of the antibiotic regimen used and the risk of recurrent infection following eradication."

Douglas R. Morgan, M.D., M.P.H., of Vanderbilt Medical Center, Nashville, Tenn., and colleagues estimated risk of H pylori recurrence and assessed factors associated with successful eradication 1 year after treatment with one of three regimens. The study included 1,463 participants, 21 to 65 years of age from 7 Latin American communities, who were treated for H pylori and observed between September 2009 and July 2011. Potential participants were selected using a census of households (Colombia, Costa Rica, Nicaragua), a large public clinic registry (Chile), or household recruitment (Honduras and 2 sites in Mexico). Participants were randomized to 1 of 3 treatment groups: 14-day lansoprazole, amoxicillin, and clarithromycin (triple therapy); 5-day lansoprazole and amoxicillin followed by 5-day lansoprazole, clarithromycin, and metronidazole (sequential); or 5-day lansoprazole, amoxicillin, clarithromycin, and metronidazole (concomitant).

Of the 1,133 participants who were urea breath test (UBT; a diagnostic procedure used to identify the presence of H pylori) negative following initial treatment, 1,091 had a 1-year UBT result, of whom 125 had become UBT positive, a recurrence risk of 11.5 percent. The recurrence risk ranged from 6.8 percent in Costa Rica to 18.1 percent in Colombia. The researchers found that recurrence at 1 year was significantly associated with study site, number of children in the household, and nonadherence to therapy, but not with treatment assignment.

In the primary analysis of treatment effectiveness based on the 1,340 participants with definitive 1-year UBT results, the estimated 1-year eradication success rate was 80.4 percent for triple therapy, 79.8 percent for sequential therapy, and 77.8 percent for concomitant therapy. Overall effectiveness was 79.3 percent.

"In a single-treatment course analysis that ignored the effects of re-treatment, the percentage of UBT-negative results at 1 year was 72.4 percent and was significantly associated with study site, adherence to initial therapy, male sex, and age. One-year effectiveness among all 1,463 enrolled participants, considering all missing UBT results as positive, was 72.7 percent," the authors write.

"In our current study, adherence, study site, sex, and age were significantly associated with the probability of a successful 1-year outcome. From the public health perspective, a ‘one size fits all’ intervention strategy may not be optimal."

"Ongoing research initiatives are needed, given the expected increase in the gastric cancer burden in Latin America over the next 2 decades, evidence that H pylori infection is the dominant risk factor, and evidence that eradication reduces gastric cancer risk," the researchers conclude.

Journal Reference:

Updated HIV Treatment Guidelines Include Stronger Recommendation for Acute Infection

Published on Friday, 15 February 2013 00:00
Written by DHHS
On February 12, 2013, the U.S. Department of Health and Human Services antiretroviral therapy (ART) guidelines panel issued an update to the adult and adolescent HIV treatment guidelines. Among the key
changes are additional information about the most recently approved antiretroviral agents and a recommendation that newly infected people with HIV should be offered combination ART.

The guidelines continue to recommend treatment for all people with HIV, both to reduce the risk of disease progression and for the prevention of HIV transmission. However, the panel states, "Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence" and "Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors."

The full guidelines are available online. The document includes an introductory section that summarizes the latest changes.

Key additions and revisions include:

- Updated recommendation on integrase inhibitor resistance testing for people on a failing integrase inhibitor-based regimen.
- Guidance on use of a new genotypic HIV tropism assay to predict co-receptor (CCR5 or CXCR4) use, especially before starting a CCR5 antagonist such as maraviroc (Selzentry).
- Recommendation that the NNRTI rilpivirine (Edurant, also in the Complera coformulation) should only be used by people with pre-treatment viral load ≤100,000 copies/mL.
- Recommendation that the recently approved Striibld (elvitegravir/tenofovir/emtricitabine/cobicistat) single-tablet regimen is an alternative for ART-naive people with pre-treatment creatinine clearance >70 mL/min (an indicator of good kidney function).
- Strengthened recommendation that people with "early" HIV infection—meaning both acute (before seroconversion) and recent (within the first 6 months)—should be offered ART, along with evidence supporting this change.
- Updated recommendations on the use of efavirenz (Sustiva) during pregnancy and intravenous zidovudine (AZT; Retrovir) during labor, mirroring recent changes to the perinatal guidelines.
- New information in the drug-drug interaction section on use of ritonavir (Norvir) and cobicistat as pharmacokinetic enhancers to increase levels of other antiretroviral drugs.
- Updates to drug interaction tables, including the addition of known and predicted interactions involving elvitegravir/cobicistat and other drugs.

The guidelines panel will be accepting feedback on the revisions through February 26, 2013. Send comments to ContactUs@aidsinfo.nih.gov with the subject line "Comments on Adult and Adolescent ARV Guidelines." 2/15/13

Sources
DHHS. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Updated February 12, 2013.

**HIV/AIDS Study—Link to Rapid Advancement of HIV Virus Found in Semen: NIH**

*The Guardian Express* (02.09.2013)

Researchers from the National Institutes of Health (NIH) have found that a protein in seminal fluid speeds up the spread of HIV in uterine tissue. The protein, called interleukin 7 (IL-7), is from a family of proteins that regulate the immune response. IL-7 is found in normal semen, but is found at high levels in the semen of men with HIV infection.

The researchers created a culture system of small pieces of cervical tissue and used it to simulate male-to-female HIV transmission. They then observed the spread of the virus to tissue under controlled conditions at the laboratory. In tissue containing IL-7 at levels found in the semen of HIV-infected men, the virus spread more quickly than to tissue that was not treated with IL-7. The researchers suggest that IL-7 alone or along with other molecules foster male-to-female HIV transmission. Also, it is possible that the level of IL-7 in semen determines how infectious a specific HIV-infected male is for a female partner.

HIV targets T cells, a type of immune cell that helps organize the body's defenses against disease-causing organisms. The T cells die quickly when they are infected with HIV, before the virus can produce a large number of copies of itself. The researchers found that in isolated pieces of cervical tissue, HIV-infected T cells live longer in the presence of IL-7 and continue to produce the virus. IL-7 also stimulated uninfected T cells to divide, thus increasing their number. The new T cells are additional targets for the virus to enable it to increase its spread. Researchers believe that one day it may be possible to prevent or delay HIV transmission by blocking seminal IL-7. The researchers said that they need additional studies to confirm the observations.
AIDS-Free Generation Is Within Reach But Only With Fully-Funded Global Fund

In the Huffington Post’s "Impact" blog, ACTION Director Kolleen Bouchane highlights President Barack Obama’s mention of global development and global health in Tuesday’s State of the Union address, “So the United States will join with our allies to eradicate such extreme poverty in the next two decades, by connecting more people to the global economy, by empowering women, by giving our young and brightest minds new opportunities to serve and helping communities to feed and power and educate themselves, by saving the world's children from preventable deaths, and by realizing the promise of an AIDS-free generation, which is within our reach,” Obama said in the address, Bouchane writes, adding, "While there are many important nuggets (eradicating extreme poverty—yes please!) to ramble on about, for me, the promise of an AIDS-free generation is the biggest tangible opportunity right now.”

"An AIDS-free generation is within our reach—but the choice President Obama makes in the next few weeks on the budget he sends to Congress will be more than a signal—it has the potential to accelerate progress around the world in a serious way. Or not,” she continues. "As the president and his team head into the final weeks of deciding their budget, a decision on what to commit to the Global Fund to Fight AIDS, Tuberculosis, and Malaria will be made,” Bouchane writes, adding, "We will not realize an AIDS-free generation without a fully-funded Global Fund." She concludes, "We must all keep up the pressure, and remind President Obama that supporting the Global Fund is the first opportunity he will have to keep his promise of leading us to an AIDS-free generation" (2/14).

Not your conventional nucleic acids
Spherical nucleic acids have novel properties that are perfect for biomedical applications

Northwestern University’s Chad A. Mirkin, a world-renowned leader in nanotechnology research and its application, has invented and developed a powerful material that could revolutionize biomedicine: spherical nucleic acids (SNAs).

Mirkin will discuss SNAs and their applications in therapeutics and diagnostics in a talk titled "Nanostructures in Biology and Medicine" at the American Association for the Advancement of Science (AAAS) annual meeting in Boston. His presentation is part of the symposium "Convergence of Physical, Engineering, and Life Sciences: Next Innovation Economy" to be held from 1:30 to 4:30 p.m. Friday, Feb. 15.

Potential applications include using SNAs to carry nucleic acid-based therapeutics to the brain for the treatment of glioblastoma, the most aggressive form of brain cancer, as well as other neurological disorders such as Alzheimer's and Parkinson's diseases. Mirkin is aggressively pursuing treatments for such diseases with Alexander H. Stegh, an assistant professor of neurology at Northwestern's Feinberg School of Medicine.

"These structures are really quite spectacular and incredibly functional," Mirkin said. "People don’t typically think about DNA in spherical form, but this novel arrangement of nucleic acids imparts interesting chemical and physical properties that are very different from conventional nucleic acids."

Spherical nucleic acids consist of densely packed, highly oriented nucleic acids arranged on the surface of a nanoparticle, typically gold or silver. The tiny non-toxic balls, each roughly 15 nanometers in diameter, can do things the familiar but more cumbersome double helix can’t do:

- SNAs can naturally enter cells and effect gene knockdown, making SNAs a superior tool for treating genetic diseases using gene regulation technology.
- SNAs can easily cross formidable barriers in the human body, including the blood-brain barrier and the layers that make up skin.
- SNAs don’t elicit an immune response, and they resist degradation, resulting in longer lifetimes in the body.

"The field of medicine needs new constructs and strategies for treating disease," Mirkin said. "Many of the ways we treat disease are based on old methods and materials. Nanotechnology offers the ability to rapidly create new structures with properties that are very different from conventional forms of matter."

Mirkin is the George B. Rathmann Professor of Chemistry in the Weinberg College of Arts and Sciences and professor of medicine, chemical and biological engineering, biomedical engineering and materials science and engineering. He is director of Northwestern's International Institute for Nanotechnology (IIN).

Last year, Mirkin and Amy S. Paller, M.D., chair of dermatology and professor of pediatrics at Feinberg, were the first to demonstrate the use of commercial moisturizers to deliver gene regulation
technology for skin cancer therapy. The drug, consisting of SNAs, penetrated the skin’s layers and selectively targeted disease-causing genes while sparing normal genes.

"We now can go after a whole new set of diseases," Mirkin said. "Thanks to the Human Genome Project and all of the genomics research over the last two decades, we have an enormous number of known targets. And we can use the same tool for each, the spherical nucleic acid. We simply change the sequence to match the target gene. That’s the power of gene regulation technology."

**Novel herbal compound offers potential to prevent and treat Alzheimer's disease**

**Findings published in Restorative Neurology and Neuroscience**

Amsterdam, NL, February 15, 2013 – Administration of the active compound tetrahydroxystilbene glucoside (TSG) derived from the Chinese herbal medicine Polygonum multiflorum Thunb, reversed both overexpression of α-synuclein, a small protein found in the brain, and its accumulation using a mouse model of Alzheimer’s disease. These results, which may shed light on the neuropathology of AD and open up new avenues of treatment, are available in the current issue of *Restorative Neurology and Neuroscience*.

Aberrant accumulation of α-synuclein can form insoluble aggregates that have been implicated in several neurodegenerative diseases, including Parkinson’s disease, dementia with Lewy bodies, and Alzheimer’s disease (AD). Researchers have now found that overexpression of α-synuclein increases with age and have demonstrated that α-synuclein aggregates in the hippocampus of older mice compared to normal controls.

"Our results raise the possibility that TSG might be a novel compound for the treatment of AD and dementia with Lewy body," says co-lead investigator Lan Zhang, MD, PhD, Associate Professor, Key Laboratory for Neurodegenerative Diseases of Ministry of Education, Department of Pharmacology of Xuanwu Hospital of Capital Medical University in Beijing.

The study used an animal model of AD: APPV717I transgenic (Tg) mice with the London mutation. In previous work, the authors showed that these mice show cognitive impairments beginning at 4 months of age and develop amyloid plaques in the brain that are evident by 10 months.

In one series of experiments, 4 month old Tg mice were divided into 3 groups and received daily intragastric administration of distilled water (controls), low dose TSG (120 µmol/kg/d), or high dose TSG (240 µmol/kg/d). A fourth group consisted of age-matched non-Tg controls. The mice were treated until 10 months of age. In a second series of experiments, 10-month-old mice were divided into similar control and TSG-treated groups and were treated for 6 months.

The authors used a variety of techniques to hone in on what was happening in the brains of the Tg mice compared to age-matched controls: cDNA microarray analysis, reverse transcription PCR, western blotting, and immunochemistry. They found that α-synuclein messenger RNA (mRNA) and protein expression levels increase in a time-dependent manner in the hippocampus of Tg mice between ages 4 and 16 months and α-synuclein aggregation was noticeable at 16 months. Age-related increases in α-synuclein were also seen in the control mice but to a lesser degree.

"We suggest that, besides increased Aβ (beta-amyloid) and amyloid plaques, overexpression and aggregation of α-synuclein in the hippocampus might partially account for cognitive impairment in this Tg mouse model of AD," comments co-lead investigator Lin Li, MD, PhD, Professor and Director, Department of Pharmacology, Xuanwu Hospital of Capital Medical University in Beijing. She adds that "α-synuclein overexpression occurs even in the early phase of AD and may accelerate Aβ production and deposition, which further facilitates α-synuclein overexpression and accumulation."

Analysis of the TSG-treated groups showed that TSG-treatment from the age of 4 to 10 months significantly downregulated α-synuclein mRNA and protein overexpression in the hippocampus of the Tg mice, and the effect was stronger at the higher dose. This suggests that TSG may have a role in preventing the neurotoxic effects of α-synuclein on synaptic function and cell activity. In addition, the finding that Tg reduced α-synuclein overexpression in older animals (>10 months) may indicate that it has therapeutic potential even after neuropathologic changes have occurred.

In previous work, the authors found that TSG acts as a "cognitive enhancer" to improve learning and memory in both APP transgenic mice and aged rats. The authors emphasize that while it is not completely clear how TSG works, their findings open up a new area of research. "The role of α-synuclein, especially in the early phase of AD, and its interaction with Aβ should be considered when developing new therapeutic strategies to target AD pathogenesis," says Dr. Zhang.
Using transportation data to predict pandemics
New computational model demonstrates how disease spreads in a highly connected world

In a world of increasing global connections, predicting the spread of infectious diseases is more complicated than ever. Pandemics no longer follow the patterns they did centuries ago, when diseases swept through populations town by town; instead, they spread quickly and seemingly at random, spurred by the interactions of 3 billion air travelers per year.

A computational model developed by Northwestern University's Dirk Brockmann could provide better insight into how today's diseases might strike. Brockmann, an associate professor of engineering sciences and applied mathematics at the McCormick School of Engineering and Applied Science, uses transportation data to develop models that better pinpoint the source of an outbreak and help determine how a disease could spread.

Brockmann will discuss his research in a presentation titled "Are Pandemics Predictable?" at the American Association for the Advancement of Science (AAAS) annual meeting in Boston. His presentation is part of the symposium "Predictability: From Physical to Data Sciences" to be held from 8:30 to 11:30 a.m. on Saturday, Feb. 16.

The ability to pinpoint with certainty the location of a pandemic outbreak and to predict where and how quickly it will spread would give governments and clinicians an important—and potentially lifesaving—advantage in responding to the disease, but current prediction models are limited.

Previous pandemic models have been based on geographical distance, but geography provides an incomplete picture of a pandemic. For instance, New York City and London are geographically very far apart, but with approximately 10,000 people traveling between the cities each day, the cities are far more connected than, for instance, New York City and Milwaukee, which are geographically closer.

"Furthermore, cities with a very high level of connectedness, such as London, are important epicenters for tracking the spread of diseases," Brockmann said. "When a disease reaches these cities, it is likely to spread far and quickly."

Using network theory and official transportation data, Brockmann developed a model that can generate with high accuracy the origin of an outbreak and the predicted arrival times of a pandemic in specific locations. The model can generate these findings using only data about the geographical location and number of occurrences of the disease.

"Spatial disease dynamics become far more straightforward when viewed from the right perspective using our technique," Brockmann said.

Common Chemicals Linked to Osteoarthritis

Feb. 14, 2013 — A new study has linked exposure to two common perfluorinated chemicals (PFCs) with osteoarthritis. PFCs are used in more than 200 industrial processes and consumer products including certain stain- and water-resistant fabrics, grease-proof paper food containers, personal care products, and other items. Because of their persistence, PFCs have become ubiquitous contaminants of humans and wildlife. The study, published in Environmental Health Perspectives, is the first to look at the associations between perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), and osteoarthritis, in a study population representative of the United States.

"We found that PFOA and PFOS exposures are associated with higher prevalence of osteoarthritis, particularly in women, a group that is disproportionately impacted by this chronic disease," said Sarah Uhl, who authored the study along with Yale Professor Michelle L. Bell and Tamarra James-Todd, an epidemiologist at the Harvard Medical School and Brigham and Women's Hospital. The research was the focus of Uhl's Master's of Environmental Science Program at the Yale School of Forestry and Environmental Studies.

The authors analyzed data from six years of the National Health and Nutrition Examination Survey (NHANES, 2003-2008), which enabled them to account for factors such as age, income, and race/ethnicity. When the researchers looked at men and women separately, they found clear, strong associations for women, but not men. Women in the highest 25% of exposure to PFOA had about two times the odds of having osteoarthritis compared to those in the lowest 25% of exposure.

Although production and usage of PFOA and PFOS have declined due to safety concerns, human and environmental exposure to these chemicals remains widespread. Future studies are needed to establish temporality and shed light on possible biological mechanisms. Reasons for differences in these associations between men and women, if confirmed, also need further exploration. Better understanding
the health effects of these chemicals and identifying any susceptible subpopulations could help to inform public health policies aimed at reducing exposures or associated health impacts.

**Journal Reference:**

**Saudi health officials fired over HIV tainted blood**

Saudi Arabia’s Ministry of Health fired seven senior officials after a 13-year old girl was given HIV tainted blood in a transfusion, *Saudi Gazette* reported.

Those terminated include the director general, the medical director, the directors of the laboratory and blood bank and the technical supervisor of a blood bank at Jazan General Hospital, the newspaper reported.

A fine of SAR10,000 (US$2,666) was imposed on the director and the technical supervisor of the blood bank, the newspaper said.

The coordinator of the AIDS programme and the director of labs and blood banks in the Directorate General of Health Affairs in Jazan were also fired, while the license of the lab technician, directly involved in the tainted blood transfusion, was revoked, the newspaper reported, citing the ministry.

Reham al-Hakami, who suffers from sickle-cell anemia, was given the HIV tainted blood in a transfusion last week at Jazan General Hospital, the newspaper reported. She has been receiving transfusions for her illness since she was eight.

**Ancient teeth bacteria record disease evolution**

DNA preserved in calcified bacteria on the teeth of ancient human skeletons has shed light on the health consequences of the evolving diet and behaviour from the Stone Age to the modern day.

The ancient genetic record reveals the negative changes in oral bacteria brought about by the dietary shifts as humans became farmers, and later with the introduction of food manufacturing in the Industrial Revolution.

An international team, led by the University of Adelaide's Centre for Ancient DNA (ACAD) where the research was performed, has published the results in *Nature Genetics* today. Other team members include the Department of Archaeology at the University of Aberdeen and the Wellcome Trust Sanger Institute in Cambridge (UK).

"This is the first record of how our evolution over the last 7500 years has impacted the bacteria we carry with us, and the important health consequences," says study leader Professor Alan Cooper, ACAD Director.

"Oral bacteria in modern man are markedly less diverse than historic populations and this is thought to contribute to chronic oral and other disease in post-industrial lifestyles."

The researchers extracted DNA from tartar (calcified dental plaque) from 34 prehistoric northern European human skeletons, and traced changes in the nature of oral bacteria from the last hunter-gatherers, through the first farmers to the Bronze Age and Medieval times.

"Dental plaque represents the only easily accessible source of preserved human bacteria," says lead author Dr Christina Adler, who conducted the research while a PhD student at the University of Adelaide, now at the University of Sydney.

"Genetic analysis of plaque can create a powerful new record of dietary impacts, health changes and oral pathogen genomic evolution, deep into the past."

Professor Cooper says: "The composition of oral bacteria changed markedly with the introduction of farming, and again around 150 years ago. With the introduction of processed sugar and flour in the Industrial Revolution, we can see a dramatically decreased diversity in our oral bacteria, allowing domination by caries-causing strains. The modern mouth basically exists in a permanent disease state."

Professor Cooper has been working on the project with archaeologist and co-Leader Professor Keith Dobney, now at the University of Aberdeen, for the past 17 years. Professor Dobney says: "I had shown tartar deposits commonly found on ancient teeth were dense masses of solid calcified bacteria and food, but couldn’t identify the species of bacteria. Ancient DNA was the obvious answer."

However, the team was not able to sufficiently control background levels of bacterial contamination until 2007 when ACAD's ultra-clean laboratories and strict decontamination and authentication protocols became available. The research team is now expanding its studies through time, and around the world, including other species such as Neandertals.
**Natural Probiotic for Osteoporosis? Building Healthy Bones Takes Guts**
Feb. 14, 2013 — In what could be an early step toward new treatments for people with osteoporosis, scientists at Michigan State University report that a natural probiotic supplement can help male mice produce healthier bones.

Interestingly, the same can’t be said for female mice, the researchers report in the *Journal of Cellular Physiology*. "We know that inflammation in the gut can cause bone loss, though it’s unclear exactly why," said lead author Laura McCabe, a professor in MSU’s departments of Physiology and Radiology. "The neat thing we found is that a probiotic can enhance bone density."

Probiotics are microorganisms that can help balance the immune system. For the study, the researchers fed the mice *Lactobacillus reuteri*, a probiotic known to reduce inflammation, a sometimes harmful effect of the body’s immune response to infection.

"Through food fermentation, we’ve been eating bacteria that we classify as probiotics for thousands of years," said co-author Robert Britton, associate professor in the Department of Microbiology and Molecular Genetics. "There’s evidence that this bacterium as a species has co-evolved with humans. It’s indigenous to our intestinal tracts and is something that, if missing, might cause problems."

In the study, the male mice showed a significant increase in bone density after four weeks of treatment. There was no such effect when the researchers repeated the experiment with female mice, an anomaly they’re now investigating.

By 2020, half of all Americans over 50 are expected to have low bone density or osteoporosis, according to the National Osteoporosis Foundation. About one in two women and one in four men over 50 will break a bone due to osteoporosis.

Drugs to prevent bone loss in osteoporosis patients are already in wide use, but over the long term they can disrupt the natural remodeling of bone tissue and could potentially have negative side effects that include unusual bone fractures and joint and muscle pain.

McCabe and Britton are quick to point out that this line of research is in its early stages and that results in mice don’t always translate to humans. But they’re hopeful the new study could point the way toward osteoporosis drugs that aren’t saddled with such side effects, especially for people who lose bone density from an early age because of another chronic condition.

"People tend to think of osteoporosis as just affecting postmenopausal women, but what they don’t realize is that it can occur with other conditions such as inflammatory bowel disease and Type 1 diabetes," she said. "You don’t want to put your child on medications that reduce bone remodeling for the rest of their life, so something natural could be useful for long-term treatment of bone loss that begins at childhood."

**The Human Pathogen Streptococcus Pneumonia Shields Foreign DNA Derived from Other Bacteria to Promote Genetic Diversity and Vaccine Evasion**
Feb. 14, 2013 — A new report demonstrates that the human pathogen *Streptococcus* (S.) *pneumoniae* (one of the known causes of bacterial pneumonia) possesses an unusual enzyme that protects foreign DNA taken up during transformation, allowing exchange of pathogenicity islands donated from other pathogenic bacteria.

This study, published February 14 in the Open Access journal *PLOS Pathogens* by researchers from the Laboratory of Microbiology and Molecular Genetics (CNRS-Université Paul Sabatier, Toulouse, France), establishes a role for this enzyme in protecting internalized DNA from restriction, and simultaneously shows that *S. pneumoniae* uses transformation, for example by DNA picked up from other bacterial strains, specifically to promote genome diversification.

Exchange of pathogenicity islands is crucial for pneumococcal virulence, as illustrated by the impressive variability in the polysaccharide capsule, which is usually targeted by current vaccines. Acquisition of different capsule loci, by relying on this genetic transformation, thus allows for vaccine evasion. Natural genetic transformation is thought of as the bacterial equivalent of sexual reproduction, allowing intra- and inter-species genetic exchange. This process, involving uptake of foreign DNA as single-strands (ss) that leads to chromosomal integration, is transient in *S. pneumoniae*.

Restriction-modification (R-M) systems classically include a restrictase, which protects the host bacteria from attack by bacteriophage via the degradation of only the foreign double-stranded (ds) DNA, and a dsDNA methylase that methylates the host genome, providing self-immunity against this restrictase. Since they degrade only foreign DNA, R-M systems are proposed to antagonize transformation
by DNA from other bacteria. The DpnII R-M system investigated in this study is present in around half of pneumococcal isolates tested and also possesses an unusual methylase of ssDNA, DpnA, which is specifically induced during the brief genetic transformation time window.

This study shows that DpnA gene is crucial for the exchange of pathogenicity islands when the foreign DNA is unmethylated (i.e., from a non-DpnII modified DNA donor). By methylating the internalized foreign ssDNA, DpnA protects the chromosome of those transformants that incorporate the foreign pathogenicity islands, such as the capsule locus. In the absence of this unique methylation, the novel transformant chromosomes would be degraded by the DpnII restriction enzyme, thus forbidding the acceptance of the foreign DNA sequences.

The researchers found that the role of DpnA is to protect foreign DNA, allowing pathogenicity island exchange between bacteria. Jean-Pierre Claverys, Principal Investigator and senior author of the paper concludes that "this finding is the first evidence for a mechanism that actively promotes genetic diversity of S. pneumoniae through programmed protection and incorporation of foreign DNA."

**Journal Reference:**

**Triple Trouble: Infection with Hepatitis B Increases Risk of Death for People with HIV and Hepatitis C Co-infection**
AIDS ASSIST, (02.19.2013) Michael Carter
A Spanish research team reports that hepatitis B infection increases the risk of death by 75 percent for HIV/ hepatitis C co-infected people. Earlier studies have focused on HIV/ hepatitis C co-infection or HIV/hepatitis B co-infection, but not the consequences of co-infection with all three viruses. Transmission is similar for HIV, hepatitis B, and hepatitis C.

The study analyzed data from the VACH cohort, comprised of 6,342 HIV/hepatitis C-infected individuals. Six percent of the VACH cohort also had hepatitis B. Study participants who had all three viruses were likely to be older, male, have a lower CD4 count, and higher AST-to-platelet index than cohort members co-infected only with HIV and hepatitis C.

VACH data provided almost 26,000 person-years of follow-up with a total of 543 deaths and an average mortality rate of 2.1 per 100 person years. In contrast, co-infection with all three viruses increased the mortality rate per 100 person years to 3.78. Researchers initially concluded that co-infection with hepatitis B increased the mortality rate by 90 percent, but they revised their estimate to 75 percent when they factored in AIDS-defining illness, age, HIV and hepatitis C treatment, CD4 cell count, and viral load. Factors that increased mortality risk for HIV/hepatitis B/hepatitis C co-infected people included “detectable” viral load and older age. Higher CD4 cell count, HIV treatment, and tenofovir treatment regimen (effective against HIV, hepatitis B, and hepatitis C) comprised factors associated with a better outcome.

The study also indicated that HIV/hepatitis B/hepatitis C co-infection increases the risk of liver disease-related death. Researchers strongly recommended hepatitis B immunization for HIV-infected people and people at risk of HIV infection.

The full article, "Hepatitis B Virus Infection Predicts Mortality of HIV and Hepatitis C Virus Co-infected Patients" was published online in the journal AIDS 27 (2013; doi:10.1097/QAD.0b013e32835ecaf7).

**SARS-Linked Virus Well Adapted To Infect Humans, Could Be Treated With Drugs To Boost Immune System, Study Shows**
"A new virus that emerged in the Middle East last year and has killed five people is well adapted to infecting humans but could potentially be treated with drugs that boost the immune system, scientists said on Tuesday," Reuters reports, noting, "The virus, called novel coronavirus or NCoV, is from the same family as the common cold and as SARS, or Severe Acute Respiratory Syndrome." The news service writes, "In one of the first published studies about NCoV, which was unknown in humans until it was identified in September 2012, researchers said it could penetrate the lining of passageways in the lungs and evade the immune system as easily as a cold virus."

Volker Thiel of the Institute of Immunobiology at Kantonal Hospital in Switzerland, who led the study, "said that although the virus may have jumped from animals to humans very recently, his research showed it was just as well adapted to infecting the human respiratory tract as other coronaviruses like SARS and the common cold viruses," according to Reuters. "The study, published in mBio, an online
Scientists Create New Strain Of Polio To Protect Vaccine Factory Workers

"Scientists have created new strains of polio intended to protect workers in factories that make polio vaccine," the New York Times reports. "The new strains have the same ability to invoke an immune reaction as the live viruses now used to make vaccine do, but there is virtually no risk anyone will get polio if one of the new strains somehow escapes," the newspaper notes, adding, "The research team, at the State University of New York at Stonybrook, is led by Eckard A. F. Wimmer, a molecular geneticist who made headlines in 1991 when he synthesized polio virus in the lab from its chemical components, the first time a virus had been made outside of living cells."

"Currently, factories making the injectable Salk vaccine used in the United States and Europe start with the dangerous wild-type viruses known as Types 1, 2 and 3," the New York Times notes. "After growing a large batch, vaccine makers 'kill' the virus with formaldehyde and prepare it for syringes," the newspaper writes, adding, "The finished product is safe, but if the growing live viruses ever escaped 'because of a leak, an explosion, an earthquake, a tsunami, a flood,' Dr. Wimmer said, 'the spill could spread like wildfire'" (McNeil, 2/18).

Working Toward Polio Eradication In 2018

"Since the eradication of smallpox in the late 1970s, no other diseases have followed suit; the goal that has come closest so far is eradication of polio," a Lancet Infectious Diseases editorial states, noting that in 2012 only about 250 people were infected with polio worldwide. However, the recent murders of polio vaccinators "highlight how a threat that for many is thankfully a distant memory—or for younger generations in some developed countries unknown—remains a real and present danger." The editorial continues, "The disease remains entrenched in three countries—Afghanistan, Nigeria, and Pakistan—where social, political, and logistical factors prevent effective vaccination campaigns and lead to export of virus to countries that have previously been free of the disease."

"The Bill & Melinda Gates Foundation is one of the major contributors of financial aid to the polio eradication effort, and speaking recently in London at the Richard Dimbleby lecture, Bill Gates reiterated his commitment to wiping out the disease, highlighting the new eradication target of 2018," the editorial notes. "On January 23, the [Global Polio Eradication Initiative] published a draft Polio Eradication and Endgame Strategic Plan (2013-18)" (.pdf), the editorial writes, noting, "The milestones for the new strategic plan are for the last case of wild polio by 2014, withdrawal of type 2 oral polio vaccine by 2015-16, worldwide certification of polio eradication by the end of 2018, and cessation of bivalent oral polio vaccination during 2019." The editorial concludes, "2018 seems soon, but for some children it will not be soon enough. And for the vaccination workers who have lost their lives, eradication of polio within five years would be a tribute to their efforts" (March 2013).

Could an old antidepressant treat sickle cell disease?
Tests in mice & human blood cells look promising

ANN ARBOR, Mich. — An antidepressant drug used since the 1960s may also hold promise for treating sickle cell disease, according to a surprising new finding made in mice and human red blood cells by a team from the University of Michigan Medical School.

The discovery that tranylcypromine, or TCP, can essentially reverse the effects of sickle cell disease was made by U-M scientists who have spent more than three decades studying the basic biology of the condition, with funding from the National Institutes of Health.

The way for a clinical trial now being planned for adult patients who have the life-threatening
condition. The discovery may also lead to other treatments for the disease, which leads misshapen red blood cells to cause vascular damage and premature death.

But the researchers caution it is too soon for the drug to be used in routine treatment of sickle cell anemia, an inherited genetic disease that affects tens of thousands of Americans and millions of others worldwide.

The climax of a decade of discovery
In the new paper, the researchers describe a painstaking effort to test TCP’s effect on the body’s production of a particular form of hemoglobin – the key protein that allows red blood cells to carry oxygen.

The drug acts on a molecule inside red blood cells called LSD1, which is involved in blocking the production of the fetal form of hemoglobin. The U-M team zeroed in on the importance of LSD1 as a drug target after many years of research.

Then, they literally did a Google search to find drugs that act on LSD1. That’s how they found TCP, which since 1960 has been used to treat severe depression.

In the new paper, they describe how TCP blocked LSD1 and boosted the production of fetal hemoglobin—offsetting the devastating impact of the abnormal "adult" form of hemoglobin that sickle cell patients make.

"This is the first time that fetal hemoglobin synthesis was re-activated both in human blood cells and in mice to such a high level using a drug, and it demonstrates that once you understand the basic biological mechanism underlying a disease, you can develop drugs to treat it," says Doug Engel, Ph.D., senior author of the study and chair of U-M’s Department of Cell & Developmental Biology. "This grew out of an effort to discover the details of how hemoglobin is made during development, not with an immediate focus on curing sickle cell anemia, but just toward understanding it."

Engel credits the dedication and persistence of his team, including a former research assistant professor, Osamu Tanabe, M.D., Ph.D., now at Japan’s Tohoku University, U-M postdoctoral fellow, Lihong Shi, Ph.D., first author of the study, and research instructor Shuaiying Cui, Ph.D..

Together, they have identified LSD1’s crucial role, and its epigenetic interaction with two nuclear receptors in the nuclei of red blood cell precursors called TR2 and TR4. Working in tandem, they repress the expression of the gene that makes fetal hemoglobin — an effect called gene silencing. So, interfering with this repression allows the fetal hemoglobin subunits to be made.

Treatment with TCP caused fetal hemoglobin to be produced at such high abundance that it made up 30 percent of all hemoglobin in cultured human blood cells – a finding Engel called "startling." TCP is FDA-approved, though patients taking it need to follow strict dietary guidelines to avoid drug interactions with certain naturally occurring chemicals in some foods.

Boosting healthy hemoglobin
Sickle cell disease occurs when a person or animal inherits two defective copies of a gene that governs the production of the "adult" form of hemoglobin. James Neel, the first chair of the U-M Department of Human Genetics, co-discovered the genetic basis for the disease in the late 1940s.

People with just one copy of the mutated gene normally do not get sick, but if they have a child with another person who carries the same trait, there is a one in four chance the child will develop the disease. An estimated 2.5 million Americans — including one in every 12 African Americans and one in every 100 Latinos — carry one copy of the mutated globin gene.

In sickle cell disease, the body makes a form of adult hemoglobin that can aggregate to cause red blood cells to become C-shaped or "sickle" shaped, and stiff and sticky. Those cells clog small blood vessels in the limbs and internal organs, causing organ damage, pain, and raising the risk of infection. Life expectancy in these patients is greatly shortened.

In a very small number of sickle cell patients, the 'fetal' form of hemoglobin – which is usually only made in the womb and the first couple of months of life – keeps being produced throughout life. These patients have symptoms that are either far less severe or nonexistent.

The most common current sickle cell treatment, oral hydroxyurea, aims to boost fetal hemoglobin production. Others, including transfusions and stem cell (bone marrow) transplants from unrelated donors, aim to exchange the source of the overall red blood cell supply.

More study needed
Andrew Campbell, M.D., who directs the Pediatric Comprehensive Sickle Cell program at U-M’s C.S. Mott Children’s Hospital and has worked with Engel on previous research, finds the new findings are very exciting news for sickle cell patients, since there are not enough treatment options. But, he notes, more
Variations Within Influenza Strain May Explain Varying Patient Response
Feb. 18, 2013 — Just the mention of H1N1 can conjure up images of long lines of people waiting to be vaccinated, news reports of the severity of the pandemic and the count of the number of people who perished from the 2009-10 outbreak. However, some positives are coming forward.

Researchers at the University of Louisville have found variations within H1N1 patients who were hospitalized and identified those that most impacted patients. Their findings were published Feb. 18, 2013 on the PLOS ONE website.

"While all of the variants that we uncovered hijacked the body's usual system for fighting off foreign objects in the lungs, namely the white blood cells, their ability to fight appears to differ," said Colleen Jonsson, Ph.D., professor of microbiology and immunology at UofL and the director of the university's Center for Predictive Medicine. "We were able to take the strain variants from patients who were hospitalized during the pandemic, isolate those variants and determine how they functioned using a mouse model. Future studies will determine the impact of various treatment options.

"These results are very limited and preliminary," Jonsson warned. "This year's influenza outbreak is an opportunity for us to verify much of what we originally learned and to extend our understanding of the mechanisms involved."

Jonsson said that collaboration between physicians at University of Louisville Hospital and her team has been critical to the advances made thus far. She noted that being able to have the full continuum of disease that has manifested inpatients, taking it to bench and animal research, and then ultimately back to helping patients is the final goal of the work.

Journal Reference:

Blood Is Thicker Than Water – And Blood Plasma Is, Too
Feb. 18, 2013 — Blood flows differently than water. Anyone who has ever cut themselves knows that blood flows viscously and rather erratically. The similarity between blood and ketchup is something not only filmmakers are aware of. Experts refer to these materials as "non-Newtonian fluids," of which ketchup and blood are prime examples. These fluids have flow properties that change depending on conditions, with some becoming more viscous, while others become less viscous. Blood (like ketchup) is a "shear thinning fluid" that becomes less viscous with increasing pressure and it is this that allows blood to flow into the narrowest of capillaries. The flow properties of water are, in contrast, essentially constant.

Up until now it has been assumed that the special flow characteristics exhibited by blood were mainly due to the presence of the red blood cells, which account for about 45 percent of the blood's volume. Blood plasma was generally regarded simply as a spectator that played no active role. For decades, researchers have assumed that blood plasma flows like water. After all, plasma, the liquid in which the blood cells are suspended, consists to 92 percent of water. But results from researchers at Saarland University and at the University of Pennsylvania have now shown that plasma is a very special fluid that plays a crucial part in determining how blood flows. The results demonstrate that blood plasma is itself a non-Newtonian fluid.

According to the study's findings, the complex flow behavior of blood plasma could play a crucial role with respect to vascular wall deposits, aneurysms or blood clots. The results from this research may well help to improve computer simulations of this kind of pathological process.

The research team around experimental physicist Christian Wagner and engineer Paulo E. Arratia have studied the flow dynamics of blood experimentally. The work at Saarland University involved experiments in which the blood plasma was allowed to form drops inside a specially built apparatus
equipped with high-speed cameras fitted with high-resolution microscope lenses to analyze drop formation. "Our experiments showed that the blood plasma forms threads, that is, it exhibits an extensional viscosity, which is something we do not observe in water," explained Professor Wagner. The plasma shows "viscoelastic" properties, which means that it exhibits both viscous and elastic behavior when deformed, forming threads that are typical of non-Newtonian fluids.

The studies by Professor Arratia and his team at the University of Pennsylvania involved a microfluidic approach in which they developed a model of a microvascular system in order to study the flow properties of blood plasma. Their measurements showed that blood plasma exhibits a flow behavior different to that of water and that plasma can demonstrate a substantially higher flow resistance. "An important part of our study was developing microfluidic instruments sensitive enough to pick up the small differences in viscosity that are the signature of non-Newtonian fluids," explained Professor Arratia.

Experiments performed by Professor Wagner's team in Saarbrücken also showed that blood plasma influences the creation of vortices in flowing blood. These vortices may facilitate the formation of deposits on blood vessel walls which could influence blood clot formation. In one of their experiments, the research team let plasma flow through a narrow channel of the kind found in stenotic (constricted) arteries or in a stent (a medical implant inserted into constricted blood vessels). The vortical structures were detected at the end, but also at the entrance, of the narrow channel and their formation is a direct result of the viscoelastic flow properties of blood plasma.

Original publication:

Variations in genital shedding of HIV during menstrual cycle large enough to impact on risk of sexual transmission
Michael Carter
Published: 25 February 2013
Genital shedding of HIV varies considerably during the menstrual cycle, investigators report in the online edition of the Journal of Infectious Diseases. The difference between peak and nadir shedding was approximately 0.74 log₁₀, which the investigators believe would translate into a significant difference in the risk of sexual HIV transmission.

“We found a significant cyclic variation in mucosal HIV-1 shedding,” comment the authors. “The cyclic nature of HIV shedding in the female genital tract must be considered in studies examining HIV transmission and correlates to the risk of HIV transmission during heterosexual contact.”

Factors affecting the detection of HIV in the female genital tract are poorly understood. The impact of the menstrual cycle on viral shedding is especially unclear.

An international team of investigators therefore designed a prospective study examining the effect of the menstrual cycle on HIV shedding in the genital tract.

A total of 67 women co-infected with HIV and herpes simplex virus-2 (HSV-2) were recruited to the study. All were of childbearing age and none were taking antiretroviral therapy. The authors also examined the impact of aciclovir therapy for HSV-2 and hormonal contraception on genital shedding. The research was undertaken in Thailand and was a sub-study of a larger randomised trial examining the impact of aciclovir therapy on HIV shedding.

Participants in the study performed self-collected vaginal swabs over two menstrual cycles. For genital HIV shedding frequency calculations, the menstrual cycle was divided into three phases: around the time of ovulation (+/- 3 days, periovulatory); the luteal phase (end of periovulatory phases to onset of menses); and the follicular phase (end of menses to beginning of ovulation).

Median CD4 cell count was 366 cells/mm³ and median plasma viral load was approximately 40,000 copies/ml. During the study, 18 women reported the use of hormonal contraception and five women – including four using hormonal contraception – reported no menses.

Overall, shedding occurred in 60%, 48% and 54% of samples collected during the follicular, periovulatory and luteal phases respectively (p = 0.01).

Among women with detectable shedding, levels of HIV were highest immediately following menses and decreased through the remainder of the follicular phase before reaching a nadir at the date of ovulation. These changes were highly significant (p < 0.0001).
Genital HIV levels remained essentially steady during the luteal phase prior to menstruation. However, in women with a CD4 cell count below 350 cells/mm$^3$ the rate of shedding increased during the luteal phase ($p = 0.05$).

Aciclovir therapy was associated with a fall of 0.5 log$_{10}$ copy/swab ($p < 0.001$) and reduced frequency of shedding. However, aciclovir did not have an impact on the pattern of genital shedding during the menstrual cycle.

The overall findings of the study were unaffected when women without menses and those using hormonal contraception were excluded.

The authors believe that variations in HIV shedding during the menstrual cycle could affect the risk of transmission. They explain: “Shedding declined by 0.054 log$_{10}$ per day. Assuming a 14-day follicular phase, this corresponds to a 0.75 log$_{10}$ difference between peak and nadir shedding.” They estimate this could represent a 65% difference in the risk of female-to-male transmission.

Reference

23 February 2013 – 19H14

Malawi gets 1,000 new HIV infections a week: official

HIV positive Martha Makaramba, 35, rests outside Makaramba's hut in a small village close to Mulanje town, Malawi. AIDS-ravaged Malawi, where over a tenth of the population is HIV positive, records on average 1,000 new cases weekly, a top government official said Saturday.

"It's a great concern to us that despite efforts by government to prevent HIV and AIDS, the country continues to register about 1,000 new cases of HIV every week," Edith Mkawa, a senior health ministry secretary in charge of nutrition, HIV and AIDS, told reporters.

"The number is very high. It is frustrating the fight against HIV pandemic," she said.

Mkawa said Malawi, where 11.8 percent of the 14 million citizens are HIV positive, "needs urgent action to attain zero new HIV infections."

People "are not changing their behaviours. These behaviours are fuelling the spread of HIV at an alarming rate."

The southern African nation has 350,000 people receiving free anti-retroviral drugs, up from 5,000 in 2004.

Bipartisan Group Introduces Bill to End Ban on HIV Organ Donation

Edge News (Boston), (02.22.2013) Sergio N. Cândido

Sen. Barbara Boxer (D-Calif.) and Sen. Tom Coburn (R-Okla.) introduced a bill to allow research into organ donation among HIV-infected people, which has been banned since a 1988 law made it illegal to transplant organs from one HIV-infected person to another. The 1988 law also prohibited research into transplants between HIV-infected persons. Rep. Lois Capps (D-Calif.) will introduce the bill, the HIV Organ Policy Equity Act, in the U.S. House of Representatives.

According to HIV Plus magazine, the bill would allow researchers to determine the safety of organ transplants from HIV-infected donors to HIV-infected recipients. Demonstrated safety would clear the way for the U.S. Health and Human Services Administration to allow the Organ Procurement and Transportation Network to develop “safe procedures” for transplants.

The bill’s opponents fear that organs from HIV-infected people could be transplanted by mistake to non-HIV-infected patients, as reported in a 2011 New York Times story that alleged “erroneous transplants” transmitted HIV to as many as five people. However, Coburn, who is also a physician, stated that with greater scientific knowledge, HIV-infected people are now living longer, which increases the need for liver and kidney transplants. The bill’s introduction is the culmination of two years of advocacy by lawmakers and HIV activists.

South Africa reported successful transplantations from one HIV-infected person to another in 2010.

Injection-Free Vaccination Goes After HIV and Malaria Without the Needle

Mobile Magazine, (02.11.2013) Matt Sabs

On February 5, researchers at King’s College London announced the capability of delivering a dried live vaccine to a patient’s skin with an alternative to a traditional needle. Scientists at the university have
developed a tiny disc with several sugar micro-needles that dissolve when pressed into the skin. The discs potentially could be used in developing injection-free vaccinations for diseases such as HIV, malaria, and TB. The discs do not require refrigeration, which could lead to major reductions in manufacturing and shipping costs and eliminate the risk of transmitting blood-borne disease from contaminated needles and syringes.

**Families Of Haitian Cholera Victims React To U.N. Decision To Deny Compensation For Deaths**

"The United Nations has come under heavy political fire for its decision to deny compensation for thousands of victims of cholera in Haiti—a deadly disease spread by U.N. peacekeepers in the troubled Caribbean nation," [Inter Press Service](http://www.ipsnews.net) reports (Deen, 2/22). "More than 8,000 Haitians have died from the epidemic and 500,000 people, some five percent of the population, have fallen sick since the disease entered the impoverished Caribbean nation’s water system in October 2010," the [Independent](http://www.independent.co.uk) notes, adding, "The claims were filed on behalf of 5,000 victims in 2011 by the Institute for Justice and Democracy in Haiti, a Boston-based human rights group" (Popham, 2/23). "On Thursday, U.N. spokesman Martin Nesirky told reporters that the representatives of cholera victims have been advised that their 'claims are not receivable pursuant to Section 29 of the Convention on the Privileges and Immunities,'” IPS writes (2/22).

According to the Independent, the families of the victims "vowed to continue their fight to hold the U.N. to account after it rejected their claims for compensation, citing diplomatic immunity." The newspaper notes, "The U.N. initially denied all responsibility, but in 2012 released a report admitting 'the strains [of cholera] isolated in Nepal and Haiti were a perfect match,'" adding, "But the report went on to argue that 'a confluence of factors' was behind the epidemic, which was therefore 'not the fault, or deliberate action, of a particular individual'" (2/23). A video report from [Al Jazeera](http://www.aljazeera.com) examines the reactions of the families of some of those who have died in the epidemic (Levin, 2/23).

**U.N. Must Do More To Fight Cholera In Haiti**

Noting U.N. Secretary-General Ban Ki-moon last week cited diplomatic immunity in "reject[ing] a legal claim for compensation filed in 2011 on behalf of cholera victims in Haiti," Louise Ivers, a senior health and policy adviser at Partners In Health, writes in a [New York Times](http://www.nytimes.com) opinion piece, "Regardless of the merits of this argument, the United Nations has a moral, if not legal, obligation to help solve a crisis it inadvertently helped start." She continues, "The evidence shows that the United Nations was largely, though not wholly, responsible for an outbreak of cholera that has subsequently killed some 8,000 Haitians and sickened 646,000 more since October 2010. The United Nations has not acknowledged its culpability." She states, "The United Nations should immediately increase its financial support for the Haitian government's efforts to control the epidemic."

"The United Nations recently started a 10-year initiative to eliminate cholera in Haiti and the Dominican Republic, based on a plan that was developed with multiple partners, including the governments of both countries," Ivers notes, adding, "On Feb. 27, Haiti's minister of health will introduce one important component of this plan—an initiative to expand access to cholera vaccination." She says, "If the United Nations were to finance this initiative, along with the rest of the government's anti-cholera program, it could have a significant and immediate impact on stemming this epidemic. As of now, however, the United Nations plans to contribute just one percent of the cost. That is not enough." Ivers concludes, "It's time for the United Nations to rethink what true stabilization could be: preventing people from dying of a grueling, painful—and wholly preventable—disease is a good start" (2/22).

**Polio Eradication Strategy Must Be Adjusted For Local Contexts**

"It has been a particularly busy couple of months for the Global Polio Eradication Initiative (GPEI)," SciDev.Net Director Nick Ishmael Perkins writes in a [SciDev.Net](http://www.sci-dev.net) editorial. "The deadly attacks on vaccinators in Pakistan brought renewed global attention to the campaign, and then Bill Gates went public with his personal commitment to end polio," he states, adding, "The GPEI has responded with a strategy for what it calls the 'endgame.'" He writes the eradication of smallpox "is often cited by the polio eradication campaign as a model from which to learn" but notes "the context in which the GPEI operates suggests we can only learn so much from past success." He continues, "Indeed, the similarities between the two campaigns are striking," but "we shouldn't overstate similarities between the two campaigns," he
continues, noting "[a] 1988 report by the WHO that documents the eradication of smallpox reveals some
telling differences between the two campaigns."

"We now operate in a more multipolar world and influence, support or opposition can come from
more places. Global campaigns can no longer rely on centralized power structures," Perkins writes. "On
the one hand, global campaigns are keen to integrate with local health structures because a lack of
national ownership is a liability," he continues, adding, "On the other, health systems in developing
countries face critical challenges, around providing equal access to care and a reliance on treatment over
prevention." He concludes, "Resolving this dilemma is possible—but it is clear that the way forward will
require more sophisticated engagement with local health structures than we have seen so far. One word
which recurs throughout the polio endgame strategy is 'microplanning'" (2/22).

Scientists' findings disclose a new and much needed test for river blindness
infection
LA JOLLA, CA – February 25, 2013 – Scientists at The Scripps Research Institute (TSRI) have found a
telltale molecular marker for Onchocerciasis or "river blindness," a parasitic infection that affects tens of
millions of people in Africa, Latin America and other tropical regions. The newly discovered biomarker,
detectable in patients' urine, is secreted by *Onchocerca volvulus* worms during an active infection. The
biomarker could form the basis of a portable, field-ready test with significant advantages over current
diagnostic methods.

"There has been a need for an inexpensive, non-invasive test that can discriminate between active and
non-active river blindness infections during treatment campaigns," said Kim D. Janda, who is Professor
and Ely R. Callaway, Jr. Chair in Chemistry, member of the Skaggs Institute for Chemical Biology, and
director of the Worm Institute of Research and Medicine at TSRI. "We think that this new biomarker can
be the basis for such a test."

The work is described in an online Early Edition of the *Proceedings of the National Academy of
Sciences* during the week of February 25, 2013.

**Leading Cause of Vision Loss**
A leading cause of vision loss, Onchocerciasis infections are transmitted among humans by river-dwelling
blackflies in tropical regions. The vast majority of cases occur in sub-Saharan Africa, although pockets of
endemic infection exist in Yemen and in Central and South America. The major symptoms of the disease,
including blindness, result from the spread of *O. volvulus* "microfilariae"—early-stage larval worms—to
the eyes and other tissues, where they trigger damaging inflammatory reactions.

Mass treatment campaigns, begun in the 1990s, have used the anti-worm drug ivermectin, as well as
the antibiotic doxycycline, which kills a symbiotic bacterium within the worms. The World Health
Organization's African Programme for Onchocerciasis Control has set a target date of 2025 for the
eradication of the disease in that region. But Onchocerciasis treatment is seldom effective immediately
and often spares adult worms. The latter can remain in protected nodules under the skin of a patient and
secrete microfilaria for a decade or more. Health agencies need better diagnostic methods not only to
monitor the progress of Onchocerciasis treatment campaigns, but also to limit the use of ivermectin and
doxycycline to reduce the risk of resistance.

Current diagnostic methods include the painful cutting of "skin snips" from patients for microscopic
analysis and an ELISA antibody test for microfilariae, which may yield positive results even for non-active
infections. "You can still have circulating antibodies to a nematode antigen in your blood for a long time
after the infection is gone," said Janda.

**Looking for a Better Way**
A better diagnostic marker would be a metabolite of *O. volvulus* that appears only during an active,
microfilariae-producing infection and that could determine both the presence and the severity of disease.
In 2010, Janda’s laboratory demonstrated the feasibility of this approach by sifting through the small-
molecule metabolites within blood samples from river blindness patients—a technique called
"metabolome mining"—and finding a set linked to active onchocerciasis infection. For the new study, the
team sought a simpler set of biomarkers—or better yet, a single unique biomarker in urine.

Daniel Globisch, a postdoctoral fellow in the Janda laboratory, started with samples of urine from
onchocerciasis-infected and non-infected Africans. Using a powerful laboratory technique called liquid
chromatography mass spectrometry, he measured the concentrations of hundreds of small-molecule
metabolites in the samples. Excitingly, between the infected and non-infected urine samples, one
difference stood out clearly: "An unknown small molecule was highly elevated in the samples from infected individuals," said Globisch.

In a process akin to looking for the proverbial needle in the haystack, Globisch was able to purify the mysterious metabolite, and, using mass spectrometry, determine the chemical identities of its individual pieces. "The metabolite itself wasn't present in the databases, so I searched the literature for what is known about the biosynthesis and metabolic pathways in these nematodes," Globisch said. Ultimately, he was able to identify the metabolite as N-acetyltiramine-O,β-glucuronide. Remarkably, this molecule's inection can be traced to *O. volvulus* as a neurotransmitter molecule that is secreted by young, reproducing worms and then modified by the human body on its way to being excreted in urine.

"It's a spectacular find in terms of biomarkers as it does not occur naturally in humans," Globisch said. Levels of the metabolite in a non-infected North American control sample were near zero.

**Toward a Field Test**

In urine samples from Africans with active onchocerciasis infections, Globisch found that levels of the biomarker were on average four to six times higher than in samples from Africans with non-active infections. In a separate test, the team determined that a full course of doxycycline treatment, which sterilizes or kills infecting worms by destroying their symbiotic bacteria, also reduced levels of the biomarker to near-normal. "This biomarker appears to be specific for an active infection," Globisch said. The wide gap between biomarker levels in active and non-active infections suggests that a field test based on the biomarker would be robustly useful.

Such a diagnostic, said Janda, might ultimately be a simple urine dipstick test, much like a home pregnancy test, which would indicate the amount of the *O. volvulus* biomarker present in the sample. "Ultimately for this to be of value in Third World countries we will need to morph this biomarker into something that's inexpensive, simple to use, tolerant of extreme temperatures and portable—basically distilling our finding to a test that can be carted around in a backpack," Janda said.

Importantly, he adds that Globisch's metabolome-mining approach in theory should be applicable to the development of diagnostic tests for other worm diseases.

Other contributors to the study, "*Oncocercus volvulus* Neurotransmitter Tyramine is a Biomarker for River Blindness," were Amira Y. Moreno, Mark S. Hixon, Ashlee A. K. Nunes and Judith R. Denery of TSRI; and Sabine Specht and Achim Hoerauf of the University Hospital Bonn, Germany.

**‘Stressed’ Bacteria Become Resistant to Antibiotics**

Feb. 20, 2013 — Bacteria become resistant to antibiotics when stressed, finds research published in BioMed Central's open access journal BMC Evolutionary Biology. In particular *E. coli* grown at high temperatures become resistant to rifampicin.

It is generally thought that antibiotic resistance is costly to maintain, for example mutations which reduce antibiotic uptake also restrict the amount of nutrients entering the cell. Consequently in the absence of antibiotics non-resistant bacteria will out-compete the resistant ones. However researchers from UC Irvine and Faculté de Médecine Denis Diderot have discovered that by putting bacteria under stress, by growing them at a high temperature, the bacteria could spontaneously develop resistance to the antibiotic rifampicin.

The mutations responsible for rifampicin resistance had different effects in other strains of *E. coli*. In each type of bacteria tested the mutated subunit of the RNA polymerase rpoB allowed them to grow in the presence of rifampicin, but unlike the original test strain they did not necessarily have a growth advantage at high temperature.

Dr Olivier Tenaillon who led this study commented, "Our study shows that antibiotic resistance can occur even in the absence of antibiotics and that, depending on the type of bacteria, and growth conditions, rather than being costly to maintain can be highly beneficial. Given that rifampicin is used to treat serious bacterial infections such as tuberculosis, leprosy, Legionnaire's disease, and for prophylaxis in cases of meningococcal meningitis, this development has important implications for public health."

These bacteria provide strong evidence that the evolution of antibiotic resistance is governed by two properties of genes, pleiotropy and epistasis. Dr Arjan de Visser from Wageningen University explained, "Pleiotropy describes how the antibiotic resistance mutations affect other functions, hence their fate in other environments. Epistasis describes how well different mutations combine in their effect on resistance, and therefore determines which mutational pathway will be preferred by evolution when several mutations are needed for full resistance."

**Journal Reference:**

Changes to Students’ Vaccinations Before 2013-14 School Year

WBIW.com, (02.25.2013)

Indiana health officials have changed the vaccination requirements for school-age children. The state is requiring children entering kindergarten to have two measles vaccinations and recommending two hepatitis A vaccinations; they are also recommending a meningitis booster shot for all 11th and 12th grade students for the next school year.

For the 2014-2015 school year, students entering kindergarten will be required to have two vaccinations for chickenpox and hepatitis A, and the meningitis booster will be mandatory for 12th-grade students. A meningitis vaccination is already required for students in the sixth through 12th grades, but the state is now requiring a booster. If a student receives the booster in the 12th grade, the booster will last the student through college.

Parents can refuse to have their children vaccinated on account of a religious objection, but then it is up to each school system to decide whether to allow the student to attend without the mandatory vaccinations.

The list of vaccinations is as follows:

Kindergarten: Hepatitis B (three doses); diphtheria, tetanus, and pertussis (five doses); polio (four doses); measles, mumps, and rubella (two doses); chickenpox (two doses); recommended two doses of hepatitis A.

Grades 1 to 5: Hepatitis B (three doses); diphtheria, tetanus, and pertussis (five doses); polio (four doses); measles, mumps, and rubella (two doses); chickenpox (two doses).

Grades 6 to 10: Hepatitis B (three doses); diphtheria, tetanus, and pertussis (five doses); polio (four doses); measles, mumps, and rubella (two doses); chickenpox (two doses); tetanus and pertussis (one dose); meningitis (one dose).

Grades 11 and 12: Hepatitis B (three doses); diphtheria, tetanus, and pertussis (five doses); polio (four doses); measles, mumps, and rubella (two doses); chickenpox (two doses); tetanus and pertussis (one dose); meningitis (booster).

Natural Antibiotic from Sweat May Help Fight TB

Health24, (02.22.2013) EurekAlert

Researchers from the Universities of Edinburgh, Goettingen, Tuebingen, and Strasbourg have discovered how a natural antibiotic called dermcidin, produced by the skin when humans sweat, is a highly efficient germ-fighting tool. The scientists uncovered the atomic structure of the compound and were then able to determine what makes dermcidin such an efficient weapon against dangerous germs.

When the skin is injured by a cut, scratch, or insect sting, antibiotic agents secreted in sweat glands kill the germs. These natural substances, called antimicrobial peptides, are more effective than man-made antibiotics as germs are not able to quickly develop resistance against them. They attack the weak point in the germs, their cell walls, which cannot be changed quickly to resist the attack. Scientists already knew that dermcidin was activated in salty, slightly acidic sweat. This sweat then forms tiny channels perforating germs’ cell membranes, which are stabilized by charged zinc particles in sweat. The water and charged particles flow uncontrollably across the membrane, killing harmful bugs.

The researchers used a combination of techniques to discover the atomic structure of the molecular channel and found it to be unusually long, permeable, and adaptable, representing a new class of membrane protein. The team found that dermcidin can adapt to widely variable types of membrane. They believe this explains why dermcidin is such an efficient broad-spectrum antibiotic and can fight off bacteria and fungi simultaneously. Dermcidin is active against many well-known organisms such as Mycobacterium tuberculosis and Staphylococcus aureus. The researchers hope that this finding can contribute to developing a new class of antibiotics that can kill some of these dangerous germs.


Police Escort Of Polio Workers Killed In Northern Pakistan

"Health workers administering polio vaccinations to children came under attack in northern Pakistan on Tuesday, killing their police escort, authorities said," CNN reports. "Two women administering the shots entered a house on the outskirts of Mardan when two assailants on a motorbike opened fire on them, according to Danishwar Khan, a local police official," the news agency writes, noting, "The women were
"No one immediately claimed responsibility for the attack. In December, gunmen killed nine polio workers in similar attacks across Pakistan," according to the Associated Press (Khan, 2/26). "Along with Afghanistan and Nigeria, Pakistan is one of only three countries where polio is still endemic," BBC News notes (2/26).

**Examining Global Efforts Against Buruli Ulcer**

"During my visit to the Médecins Sans Frontières [MSF] Buruli ulcer ward in Cameroon it was wonderful to see the amazing care that the patients receive on a daily basis: antibiotics, state of the art dressings, physiotherapy to help prevent deformities, free food and medicines, and surgery when required," Daniel O'Brien, a specialist adviser with MSF-UK focusing on HIV/AIDS, tuberculosis and Buruli ulcer, writes in the BMJ Group Blogs. "However I was confronted by the same feeling that I have when treating young children with HIV where, yes they do well on treatment, but if their mothers had received adequate antenatal care, they would not have HIV in the first place," he continues. He writes that "if we can manage to detect, diagnose, and treat the infection early then the outcomes would be greatly improved," but he states "[t]here are many challenges to making this a reality." He notes some of these challenges and concludes, "The goals are clear, the path challenging, but the potential is inspiring and the outcome possible. Now let's put our heads, resources, and commitment together and make it happen" (2/25).

**Over a million pregnant women infected with syphilis world-wide**

Press release from PLOS Medicine

Syphilis still affects large numbers of pregnant women world-wide, causing serious health problems and even death to their babies, yet this infection could be prevented by early testing and treatment, according to a study by international researchers published in this week's PLOS Medicine.

Researchers, led by Lori Newman from the World Health Organization, estimate that in 2008, 1.4 million pregnant women around the world were infected with syphilis, 80% of whom had attended antenatal care services.

The researchers reached this figure by using information on the number of syphilis infections from 97 countries and on antenatal clinic attendance from 147 countries and then inputting this information into a model.

In consultation with experts, the authors used a realistic scenario to estimate the percentage of pregnant women tested for syphilis and adequately treated, ranging from 30% for Africa and the Mediterranean region to 70% for Europe. Based on this scenario, the authors estimate that in 2008, syphilis infections in pregnant women caused approximately 520,000 harmful outcomes, including 215,000 stillbirths, 90,000 neonatal (baby) deaths, 65,000 preterm or low birth-weight babies, and 150,000 babies with congenital infections.

The authors estimate that in 2008, testing and treating pregnant women for syphilis prevented a quarter of such harmful outcomes but worryingly, the authors found that about two-thirds of these harmful effects occurred in women who had attended antenatal care but were not treated or tested for syphilis.

The authors say: "This analysis indicates that syphilis continues to be an important cause of adverse outcomes of pregnancy, including substantial numbers of perinatal deaths and disabilities."

They continue: "Countries also need to ensure that quality-assured syphilis testing is available in all antenatal clinic settings, now possible even in remote care settings with the introduction of rapid point-of-care diagnostics."

The authors add: "In addition, efforts are needed to ensure universal access to early antenatal care, as well as improved quality of antenatal care so that all pregnant women receive an essential package of services that includes routine and early access to point-of-care testing and adequate treatment for syphilis if seropositive."

**Gut microbiota plays important role in functional bowel disorders**

Microbiota research opens up promising paths for improving diagnosis

(24 February 2013) An estimated 50 per cent of patients consulting a gastroenterologist suffer from functional bowel disorders (FBD), such as dyspepsia or irritable bowel syndrome (IBS). It is characteristic for these conditions that underlying physiological mechanisms are hard to be found. "However, recent research shows that the gut microbiota is a likely candidate for filling some of the gaps in the causal chain leading to FBD," says Professor Fernando Azpiroz, Chairman of the Gut Microbiota & Health Section of
the European Society of Neurogastroenterology & Motility (ESNM). Further information on this issue—one of three topics to be presented at Tuesday’s online press conference on the occasion of the 2nd World Summit “Gut Microbiota For Health” in Madrid, Spain—can be found at http://bit.ly/SUN24PR. World-leading experts will inform about the gut microbiota’s impact on health during an online press conference on Tuesday, 26 February 2013, 8 a.m. ET (14.00-5.30 h CET), moderated by UK media medic Dr Mark Porter, best known for his television and radio work for the BBC. The following questions will be dealt with:

- In what way does the gut microbiota influence functional bowel disorders?
  Speaker: Prof. Fernando Azpiroz, Barcelona, Spain
- Can faecal microbiota transplantation be used to treat recurrent Clostridium difficile infection?
  Speaker: Prof. Lawrence Brandt, New York, USA
- The gut–brain axis: can probiotics have a positive effect on mental health?
  Speaker: Prof. Emeran Mayer, Los Angeles, USA

**Attend the press conference from your office**
If you would like to attend, please write an email to gutmicrobiota@impressum.de. The online press conference will be held in English. Details on how to access the press conference will be sent to you after your registration.

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**3-D Atlas of the Human Heart Drawn Using Statistics**

Feb. 26, 2013 — Researchers at Pompeu Fabra University (Spain) have created a high resolution atlas of the heart with 3D images taken from 138 people. The study demonstrates that an average image of an organ along with its variations can be obtained for the purposes of comparing individual cases and differentiating healthy forms from pathologies.

"This atlas is a statistical description of how the heart and its components—such as the ventricles and the atrium—look," as explained by Corné Hoogendoorn, researcher at the CISTIB centre of the Pompeu Fabra University. Scientists from this university have managed to create a representation of the average shape of the heart and its variations with images from 138 fully functioning hearts taken using multislice computed tomography. This technique offers three-dimensional and high resolution X-ray.

"In our analysis the population group included 138 people but it could be applied to much larger populations," comments Hoogendoorn. "We demonstrated the feasibility of constructing this type of atlas using many subjects, with an acceptable level of manual parameter tuning, while still providing good numeric results."

To create this cardiac map the researchers have developed a statistical model capable of managing high quantities of information provided by individual images. It can also collect temporary variations, given that the heart is never motionless.

The level of detail and the possibility to extend the atlas give it "an advantage over the majority of cardiac models present to date." This is the case according to the conclusions of the study, which was published in the 'IEEE Transactions on Medical Imaging' journal.

The researchers believe that the study can be applied to medical image processing, especially when segmenting, or in other words, properly differentiating a structure to be analysed from the rest of the image.
“The statistics of the atlas offer a continuous range of exemplary heart shapes, which allows for the comparison of concrete cases as well as the calculation of probabilities of the latter belonging to the modelled population,” says Hoogendoorn.

The scientist also outlines that the method can be applied to the images of any other organ or structure. It has the advantage of providing the ability to classify and diagnose healthy shapes and pathologies as well as to differentiate between different illnesses and even establish grading amongst each.

In addition, computational simulations of the heart electrophysiology and mechanics (as well as the mechanics of other organs) can be based on the atlas, which can help to better plan treatment for patients.

This study is one more of others of its kind that highlight the increasing importance of the statistics in biomedical sciences, a mathematic discipline. What is more, 2013 is the International Year of Statistics.

Journal Reference:

Distinct Niches in Bone Marrow Nurture Blood Stem Cells
Feb. 24, 2013 — In research that could one day improve the success of stem cell transplants and chemotherapy, scientists have found that distinct niches exist in bone marrow to nurture different types of blood stem cells.

Stem cells in the blood are the precursors to infection-fighting white blood cells and oxygen-carrying red blood cells.

The research, by a team at Washington University School of Medicine in St. Louis, is reported Feb. 24 in the advance online edition of Nature.

The new findings, in mice, suggest that it may be possible to therapeutically target support cells in a particular niche. On the one hand, a drug that nourishes support cells could encourage blood stem cells to establish themselves in the bone marrow, enabling patients who have had stem cell transplants to more quickly rebuild their immune systems.

On the other, tumor cells are known to hide in the bone marrow, and a drug that disrupts the niche environment may drive cancer cells into the bloodstream, where they are more vulnerable to the damaging effects of chemotherapy.

“Our results offer hope for targeting these niches to treat specific cancers or to improve the success of stem cell transplants,” says senior author Daniel Link, MD, the Alan A. and Edith L. Wolff Professor of Medicine. “Already, we and others are leading clinical trials to evaluate whether it is possible to disrupt these niches in patients with leukemia or multiple myeloma.”

Working in the mice, the researchers selectively deleted a critical gene, CXCL12, which is known to be important for keeping blood stem cells healthy. Rather than knock out the gene in all of the support cells in a niche, the researchers deleted the gene in specific types of support cells. This led to the discovery that each niche holds only certain blood stem cells that are nourished by a unique set of support cells.

“What we found was rather surprising,” Link says. “There’s not just one niche for developing blood cells in the bone marrow. There’s a distinct niche for stem cells, which have the ability to become any

Distinct niches exist in bone marrow to nurture different types of blood stem cells, new research shows. In mice bone marrow, blood stem cells, highlighted in blue, are nurtured by support cells shown in red and yellow. (Credit: Daniel Link, M.D.)
blood cell in the body, and a separate niche for infection-fighting blood cells that are destined to become T cells and B cells.”

The findings provide a strong foundation for investigating whether disrupting these niches can improve the effectiveness of chemotherapy.

In a phase II pilot study led by Washington University medical oncologist Geoffrey Uy, MD, assistant professor of medicine, Link is evaluating whether the drug G-CSF can alter the stem cell niche in patients with acute lymphoblastic leukemia whose cancer has recurred or is resistant to treatment. The drug was approved by the Food and Drug Administration more than 20 years ago to stimulate production of white blood cells in patients undergoing chemotherapy, who often have weakened immune systems and are prone to infections.

But Uy and colleagues will evaluate the drug when it is given before chemotherapy. Patients enrolled in the trial at the Siteman Cancer Center will receive G-CSF for five days before chemotherapy, and the investigators will determine whether it can disrupt the protective environment of the bone marrow niche and make cancer cells more sensitive to chemotherapy.

While it’s too early to know whether the treatment approach will be successful, Link’s new research in mice is bolstered by a companion paper in the same issue of Nature. In that research, Sean Morrison, PhD, director of the Children's Medical Center Research Institute at the University of Texas Southwestern Medical Center in Dallas, used similar molecular methods to also discover distinct niches in the bone marrow for blood stem cells.

“There’s a lot of interest right now in trying to understand these niches,” Link adds. “Both of these studies add new information that will be important as we move forward. Next, we hope to understand how stem cell niches can be manipulated to help patients undergoing stem cell transplants.”

**Journal Reference:**

**Bacteria Boost Vaccine Effectiveness**

**Researchers are looking to microbes to improve immune responses to a wide range of vaccines.**

By Sabrina Richards | February 10, 2013

Vaccines were created to protect us from pathogens ranging from influenza and measles to smallpox, polio, and diphtheria. But vaccines to some pathogens—like HIV and the herpes simplex virus (HSV)—have repeatedly failed in clinical trials. In the lone **successful HIV vaccine trial** to date, the vaccine only provided slight protection over the placebo. And GlaxoSmithKline (GSK) reported last year that its promising HSV2 vaccine against genital herpes **sputtered** in a large, late-stage trial.

Most vaccines provide the immune system with key pathogen-derived molecules to help it later recognize and attack the same intruder. But many of the molecules are, by themselves, “not really capable of provoking strong immune responses,” explained **Dennis Klinman**, an immunologist at the National Cancer Institute.

One way to boost the effectiveness of a vaccine is to include adjuvants—extra ingredients that prompt the immune system to take notice and elicit protection. The most commonly used adjuvants, first approved for human use almost 80 years ago, are aluminum-based salts (alum salts), usually aluminum hydroxide or aluminum phosphate. But alum salts only effectively rouse certain types of immune cells. T cells that recognize and kill infect cells—important in clearing infections—are not well stimulated by alum.

Now, scientists are looking for new and better adjuvants to boost the effectiveness of novel vaccines—and give new life a few that have failed late stage trials, including GSK's HSV vaccine. Specifically, researchers are turning to bacteria for their well-established role as immune stimulators. Different bacteria attack the body in different ways—and the immune system has evolved to distinguish infections and activate the most effective immune cells to fight the current invader. Adding appropriate bacterial components to vaccines for similarly infecting pathogens could be the answer vaccinologists have looked for, says Klinman. “[A bacterial-based adjuvant] tells the immune system it’s encountered something truly foreign and pathogenic,” stimulating a stronger immune response to provide better, longer-lasting protection against infection.
**Breaking it down**
The first bacterial-derived adjuvant, approved for use in human vaccines in 2009, is a subunit of lipopolysaccharide (LPS), a molecule expressed on gram-negative bacteria. LPS stimulates strong—sometimes deadly—immune responses, but a subunit called monophosphoryl lipid A (MPL) can induce an immune response with little toxicity. Developed by GlaxoSmithKline, MPL is currently being used in GSK’s hepatitis B and human papilloma vaccines, and is being clinically tested with a range of other vaccines.

Given MPL’s success, the University of Texas at Austin’s Stephen Trent and his graduate student Brittany Needham decided to tweak lipid A to create a variety of adjuvants capable of stimulating different immune responses. Needham took her cue from the diversity of the LPS molecules expressed by different bacteria. Knowing that slight structural changes to LPS could alter immune cells’ cytokine responses, she began engineering *Escherichia coli* lines to express modified versions of lipid A. Testing her derivative lipid A subunits on LPS-sensitive cultured human monocytes, Needham found that each stimulated drastically different cytokines.

This could be the first step toward “designer” adjuvants, said Trent. “If you knew enough about the disease you want to try to cure, and you knew what pathways gave protection, it could theoretically be possible to design the right adjuvant to maximize vaccine effectiveness, he speculated.

**Bacteria’s dead giveaways**
In addition to surface lipids, a handful of other bacterial structures, including toxins, bacteria-specific DNA sequences, and even whole commensal microbes (probiotics), are showing promise in activating pathogen-specific immune responses that bolster vaccines’ strength and longevity. One group of candidate adjuvants is enterotoxins, toxins made by gut-infecting bacteria like *E. coli* and cholera. Researchers think alum salt adjuvants have proven ineffective at boosting mucosal vaccine protection because they get washed away too quickly. Enterotoxins, on the other hand, bind to mucosal cells and increase gut permeability, and these toxins stimulate just the right kind of antibodies to fight mucosal infections—IgA.

Of course, whole enterotoxins are dangerous. The fact that they bind to the body’s mucosa is the reason infections with enterotoxin-carrying bacteria are so painful. So researchers have to modify the toxins before administering them to patients.

Nils Lycke and his colleagues at the University of Gothenburg in Sweden, for example, have developed an adjuvant called CTA1-DD that is derived from *Vibrio cholerae’s* deadly cholera toxin (CT). They attached a CT subunit to another protein from *Staphylococcus aureus* to create a non-toxic molecule that could have the same antibody stimulating properties as CT. Sure enough, mice vaccinated with an intranasal influenza vaccine plus CTA1-DD adjuvant produced mucosal IgA antibodies and were protected against death after flu infection. Lycke is hoping to start clinical trials of a CTA1-DD-boosted pandemic influenza vaccine soon.

Another possible adjuvant is bacterial DNA. Unlike human DNA, in which most cytosine–guanine pairs are methylated, so-called CpG sequences are often unmethylated in bacteria, tipping off the immune system to the presence of an invader. B cells and plasmacytoid dendritic cells, key fighters of viral infections, respond to CpG DNA. Making synthetic mimics of CpG DNA could thus stimulate these cells to launch an immune response. Furthermore, CpG sequences are “fairly non-toxic, and used as adjuvants they tend to be safe,” said Dennis Klinman at the National Institutes of Health National Cancer Institute, who was one of the first to recognize CpG DNA’s immunomodulatory properties.

Among CpG DNA’s promising qualities is its apparent ability to encourage development of long-lived memory B cells—the cells that produce antibodies to fight a repeat infection. “To date almost every vaccine works because it induces strong antibody responses,” noted Klinman, but these often fade after several years and booster shots are required to provide long-lasting protection. By activating long-lived memory B cells, CpG DNA could help stimulate long-term antibody production.

In a recent Phase I clinical trial, pairing a CpG DNA adjuvant with the anthrax vaccine boosted volunteers’ immune responses to the vaccine. Compared to volunteers who received the standard vaccine, people injected with the CpG DNA-assisted anthrax vaccine generated about 8 times more anti-anthrax toxin antibodies and produced the strong antibody response about 3 weeks earlier. Several early phase clinical trials are also in progress to examine CpG DNA as an immune booster in cancer vaccines.

**Probiotic panacea**
Some researchers are taking a more holistic approach to vaccine adjuvants. Probiotics—beneficial, not pathogenic, microbes—have become famous recently for their ability to help influence the immune system to fight disease. Probiotics have become famous recently for their ability to help influence the immune system to fight disease. The first bacterial-derived adjuvant, approved for use in human vaccines in 2009, is a subunit of lipopolysaccharide (LPS), a molecule expressed on gram-negative bacteria. LPS stimulates strong—sometimes deadly—immune responses, but a subunit called monophosphoryl lipid A (MPL) can induce an immune response with little toxicity. Developed by GlaxoSmithKline, MPL is currently being used in GSK’s hepatitis B and human papilloma vaccines, and is being clinically tested with a range of other vaccines.
system. Though many studies focus on probiotics’ ability to stave off an overactive immune response, it turns out they can also boost the immune system.

“Probiotics have a whole range of different effects,” including enhancing immune responses, noted Paul Licciardi, an immunologist and vaccinologist at Murdoch Children’s Research Institute in Australia. A 2011 trial of live attenuated influenza vaccine, for example, showed that more patients given a 28-day course of the patented probiotic Lactobacillus rhamnosus GG produced protective antibodies to seasonal flu than patients given the vaccine alone.

“It’s a bit early to really know how good probiotics are going to be,” said Licciardi, but it’s an enticingly easy solution: simply give infants probiotics in yogurt or water during their vaccine course. Probiotics could “enhance general immunity,” said Licciardi, who is planning a small, placebo-controlled pilot study to give children oral probiotic supplements during a course of the vaccine for pneumococcal infection, “but maybe also to target specific immune responses.”

**Mitochondria Versus Nucleus**

Disruptions in the interaction between nuclear and mitochondrial DNA can lead to deficiencies in the mitochondrial energy-generating process, affecting fitness.

By Juliet Ash | February 15, 2013

Interactions between the nuclear genome and mitochondrial DNA are essential for proper cellular functioning, but incompatibilities between the two can lead to compromised development and fitness according to research published last month (January 31) in PLOS Genetics.

“The work is most important for its fine dissection of a mito-nuclear interaction and its consequences for phenotypic variation and fitness,” said marine biologist Ron Burton, who wasn’t involved in the study. “These results show that we can’t expect to understand mitochondrial diseases by associations with mitochondrial DNA variation alone.”

Despite having their own genomes, mitochondria don’t make many of their own proteins; most are synthesized in the cytosol by cellular equipment encoded in the nucleus. Thus, the interactions of mitochondrial and nuclear DNA are critical to cellular life. But there is some evidence that mutations can disrupt the smooth-running of the interactions, resulting in incompatibilities between the two genomes.

In the new study, Colin Meiklejohn and colleagues worked with Drosophila melanogaster hybrids. Each hybrid combined one of two different nuclear genomes with one of three types of mitochondrial DNA, making six strains altogether. Five of these six were healthy, but the strain with D. melanogaster OregonR nuclear genes and D. simulans simw501 mitochondrial DNA showed developmental, physiological, and reproductive problems. The researchers had discovered a mitochondrial-nuclear incompatibility, albeit a man-made one.

“The incompatibility is ‘artificial’ in the sense that the mitochondrial and nuclear genomes were matched from two sister species of fruit fly—in natural populations they would never naturally occur together,” evolutionary biologist Damian Dowling of Monash University, who didn’t participate in the work, told The Scientist in an email. “It is likely that these incompatibilities do, however, exist in nature, within the same species/populations, and we have some preliminary evidence for such incompatibilities.”

Finding the incompatibility was just the start, though. The researchers were able to use the mitochondrial-disease model they had developed to look for the underlying mechanisms.

Through genetic mapping, Meiklejohn and his colleagues localized the nuclear factor responsible for the incompatibility on chromosome two. Then, by concentrating just on the development delays in the fruit flies, they were able to further narrow the field to a region containing just nine genes: these genes, when combined with the D. simulans mitochondrial DNA, were entirely responsible for the delayed development.

Scouring these nine genes for differences from the compatible genomes, the researchers identified a single gene, which encodes a tyrosine tRNA synthetase, carrying a point mutation that caused a valine to be coded where an alanine should have been. The team also traced the mitochondrial mutation to a single nucleotide polymorphism in the tyrosine tRNA gene.

Neither mutation by itself affected fitness—those fly strains that carried either one were healthy. But having both mutations meant that the synthetase couldn’t properly attach tyrosine to the tRNA, and this resulted in disrupted translation.

Biochemical investigations backed up the genetic findings. Analyzing mitochondrial enzymes, the team discovered reduced activity in three OXPHOS complexes, proteins involved in the mitochondrial energy-generating process. And since around 90 percent of a cell’s ATP typically derives from the
OXPHOS metabolic pathway, the reduced function means less energy is available for cell growth and development.

“Reduced activity of all three OXPHOS complexes suggests compromised transcription or translation of mitochondrial DNA,” Burton said. “Reduced activities probably impact fitness in several ways.”

The results point to the importance of the mitochondria-nucleus interactions and may inform our understanding of human mitochondrial disorders, about half of which are caused by mitochondrial mutations in tRNA genes. Despite having identified many of these mutations, scientists have found little correlation with disease: different mutations can lead to similar symptoms, while the same mutations can promote very different diseases. And even more puzzling, not everyone with a pathological tRNA mutation becomes ill; some individuals remain healthy. The new research suggests that these inconsistent findings may stem from mitochondrion-nuclear interactions: the nuclear-encoded tRNA synthetase has to be compatible with its associated mitochondrial tRNA for fully functioning protein synthesis.

“If there is natural variation in human populations for the appropriate tRNA synthetase, the disease phenotype might only occur in specific mitonuclear genotypes,” said Burton. “The implications for human mitochondrial medicine are substantial.”


**Cholera Confusion, circa 1832**

As cholera first tore through the Europe in the mid-19th century, people tried anything to prevent the deadly disease. Then science stepped in.

By Dan Cossins | February 1, 2013

All the way from the Ganges River delta in India, an unwelcome visitor arrived in Europe in 1831. Its victims suffered violent cramps, vomiting, and diarrhea, along with dehydration so rapid and severe that their skin was rendered a deathly blue. Many died within hours of the first symptoms.

Cholera was one of the most devastating diseases to hit Europe in the 19th century, with a series of epidemics taking hundreds of thousands of lives. And because its cause was a mystery, people were prepared to take any measure to keep it at bay. “They tried all manner of things,” says Christopher Hamlin, a science historian at the University of Notre Dame in Indiana and author of *Cholera: The Biography*.

Leading theories at the time held that the disease was caught through exposure to foul or filthy air, so measures designed to repel cholera by purifying the air were particularly common, as depicted in this satirical cartoon of a woman extravagantly equipped with chlorinated lime, garlic, various herbs, and vinegar bags. “Anything that tended to change the quality of the air was plausible as a preventative measure,” says Hamlin.

But by the 1850s, this so-called “miasmatic” explanation for cholera had a challenger: the idea that the disease was caused by contaminated water. In 1854, in what is now feted as the dawn of epidemiology, British physician John Snow traced the source of an outbreak in Soho, London, to a water pump on Broad Street. When the pump handle was removed, cholera cases quickly disappeared.

The same year, Italian anatomist and germ theory pioneer Filippo Pacini identified a comma-shaped bacillus he named “*Vibrio*” while examining the intestinal mucosa of dead cholera victims under the microscope. His findings were largely ignored at the time, however, so it was left to the German physician-scientist Robert Koch to claim the credit for the discovery. He identified the same microbe in Egypt in 1884 and, working in India a few months later, reported that the bacilli were always found in patients with cholera, but never in those with diarrhea from other causes.

Koch’s findings did not immediately put an end to the use of air purification measures, as many still clung to the miasmatic explanation. But by the end of the 19th century, cholera was known to be caused by a microbe. The vinegar bags were on the way out, while improved sanitation and a vaccine—first developed for cholera by Waldemar Haffkine in 1892—were emerging as new methods for preventing this dreaded disease.