

Interventional Cardiology



Why children receiving GSK's pandemic flu vaccine are at an almost tenfold increased risk of narcolepsy

The Pandemrix investigation in Finland continues: understanding the results

In February 2011 Finland's National Institute for Health and Welfare (NIHW) presented an interim report suggesting that children administered GlaxoSmithKline's Pandemrix vaccine against the H1N1 pandemic flu were nine times more likely to suffer from the sleeping disorder narcolepsy within 8 months of inoculation, compared with those who did not get the jab.

Though results are yet to be confirmed, the preliminary research which was conducted by the Finnish national narcolepsy committee, illustrates a nearly tenfold increase in narcolepsy cases among 60 children and adolescents aged 4–19 years who had received the vaccine during 2009 and 2010. Of those who fell ill, 52 had received Pandemrix.

Hanna Nohynek, the NIHW's vaccine safety officer stated: "The baseline risk for narcolepsy in children aged between 4–19 years was less than one per 100,000 and the study found that among those who had the Pandemrix vaccine the risk rose to 8.1 per 100,000".

"The National Institute considers it probable that the Pandemrix vaccine was a contributing factor to this observed increase, and has called for further investigation of other co-factors that may be associated with the increased risk," the WHO claimed. "They consider it most likely that the Pandemrix vaccine increased the risk of narcolepsy in a joint effect in those genetically disposed with some other, still unknown, genetic and/or environmental factor."

Whilst researchers at the NIHW attribute the rise in narcolepsy to this combined effect of Pandemrix and other factors, the British drug maker GSK claim

it is too soon to draw any conclusions in an emailed statement: "This (Finnish) investigation is independent of a broader ongoing European Medicines Agency (EMA) investigation initiated in 2010. GSK is reviewing the report and believes it would be premature to draw any conclusions on a potential association between Pandemrix and narcolepsy until this European investigation has been completed."

Meanwhile in Finland, the genetics behind the increase in narcolepsy is being investigated by the Finnish National Narcolepsy Task Force. Their final report is planned to be released on the 31 August 2011 after further investigations into the epidemiologic, immunologic and genetic causes for the onset of narcolepsy post-vaccination are conducted.

To date, the (HLA) *DQB1*0602* genotype has been implicated in the increase risk of narcolepsy following inoculation. Patrick Zuber, WHO's top vaccine safety official highlights "approximately 30% of Finnish people have this particular genotype, compared with 15% in the rest of Europe".

Meanwhile, an EMA spokeswoman recently stated that the safety review was continuing. "There is really not enough data at this point in time to determine anything. For the time being, the benefit-risk balance of Pandemrix remains positive."

In accordance with GSK statistics, over 31 million doses of Pandemrix have been administered worldwide in 47 countries. Since January 31 2011, a total of 162 cases of narcolepsy have been reported, with 70% of those cases originating from Finland and Sweden.

Source: Statement from the National Institute for Health and Welfare of Finland of 1 February 2011: *WEBSITE ADDRESS NEEDED



Genomic research may provide insight into aggressive *Pseudomonas* infection in cystic fibrosis patients

DNA sequencing technology, working at a speed of 30 billion letters of DNA sequence per day, may reveal future therapeutic targets to treat an aggressive strain of *Pseudomonas aeruginosa*.

Chronic respiratory infection by *P. aeruginosa* contributes significantly to the morbidity and mortality associated with cystic fibrosis (CF). The Liverpool Endemic Strain (LES) of *P. aeruginosa* is widespread among CF patients in the UK and is a particularly aggressive strain. LES causes chronic infection in CF patients and is transmissible, not only to other patients, but to non-CF patients.

To provide insight as to why this strain is so pathogenic in CF patients, sputum and cough swab samples were taken from CF patients by researchers from Liverpool University's Institute of Infection and Global Health.

Their results displayed rapid mutation rates of LES *P. aeruginosa* and huge diversity between patients. Collaboration with the Centre for Genomic Research at Liverpool University, using rapid-speed DNA sequencing technology to reveal the genetic code of LES, the use may provide information into the diversity of infection and how it evolves.

“Using the latest DNA technology we have the unique opportunity to study the behavior of bacteria during chronic infection in real-time. This will allow us to get a clearer picture of how it adapts so efficiently to CF patients. If we can understand how and why it behaves the way that it does we may be able to target more effective treatments for the infection,” explains Craig Winstanley, member of the National Institute of Health Research Biomedical Research Centre at Liverpool.

Source: www.eurekalert.org/pub_releases/2011-2002/uol-sts022111.php*NEED TITLE OF WEBPAGE- WEBLINK DOESN'T WORK

Mutation in *Mycobacterium bovis* BCG improves its efficacy against TB

Researchers at VIB (Flanders, Belgium) and Ghent University (Belgium) have recently demonstrated the improved efficacy of a modified version of the Bacillus Calmette-Guérin (BCG) TB vaccine in mice. A third of the world's population is infected with *Mycobacterium tuberculosis*, the causative agent of TB, however, the BCG provides only limited protection against pulmonary TB. Owing to the increase in multidrug-resistant TB seen worldwide the need for effective vaccination is now seen as a

priority. After hypothesizing that the BCG ‘might have retained immunomodulatory properties from its pathogenic parent that limit its protective immunogenicity’ the Belgium-based group examined the effect that mutation in the 28 kDa nonspecific acid phosphatase of *M. tuberculosis*, SapM (which acts in a protective shield for the bacterium) had on the effectiveness of the vaccine. The group determined that the SapM mutant BCG vaccine was more effective than the parental vaccine

in inducing recruitment and activation of CD11c⁺ MHC-II^{int} CD40^{int} dendritic cells to draining lymph nodes and believe that application of this strategy to future TB vaccines could produce a vaccine that affords greater protection against disease.

Source: *Efficacy of tuberculosis vaccine enhanced by VIB scientists: VIB news* www.vib.be/en/news/Pages/Efficacy-of-tuberculosis-vaccine-enhanced-by-VIB-scientists.aspx

Tenofovir Gel applied topically to rectal tissue provides new promise in HIV prevention strategies

New research presented at the 18th Conference on Retroviruses and Opportunistic Infections in Boston February 27–March 2, 2011 (MA, USA) found that tenofovir gel, used as a rectal microbicide, significantly inhibited HIV during a clinical trial.

The gel was tested in a clinical trial named RMP-02/MTN-006; the first clinical study to test the safety of vaginal

tenofovir in the rectum.

Small biopsies were taken from the rectal lining of participants in the clinical study. The tissue samples were then exposed to HIV in the laboratory to determine how well the gel protected rectal tissue from infection. The researchers found that HIV was significantly inhibited in tissue samples from participants who used tenofovir gel daily for 1 week compared

with tissue from participants who used the placebo gel.

“We are very encouraged about these findings that indicate applying tenofovir gel topically to the rectum could be a promising approach to HIV prevention,” said Peter Anton, Professor of Medicine and Director of the Center for Prevention Research at the University of California, Los Angeles (UCLA), who led the study.



While the majority of men and women in the trial did not like the gel and some experienced gastrointestinal side effects, but 75% of participants said they would use the gel in the future.

“These results tell us that tenofovir gel was relatively safe to use in the rectum for most participants, but we need to address side effects to make it more acceptable to use. Even though three-quarters of the participants reported they didn’t like the gel, we are very encouraged that the majority would consider using such a product in the future.”

Tenofovir gel was initially developed as an HIV microbicide gel for vaginal use. The rectal epithelium is much thinner than the vaginal lining, so the original formulation of tenofovir gel may not be as safe nor as effective as a rectal microbicide.

A reformulated tenofovir gel has been developed, which contains a reduced glycerin concentration. Researchers are now testing the reformulated gel in an early Phase clinical trial in men and women.

Source: *Tenofovir gel provides high level of protection against HIV in rectal tissue, study suggests* www.sciencedaily.com/releases/2011/02/110228090206.htm

Airway flora can influence respiratory health

Novel methods have been used to show that the airway is colonized by a complex interacting group of microbes that may have a relationship with a patients’ susceptibility to asthma. Further studies are called for into this interesting phenomenon.

It is fairly well known that the GI tract is inhabited by a large number of bacterial species, which contribute to the overall health of the gut. Imbalances in this colonization have been shown to have influence in the development of a host of disease. However, there has been little research into relationships of this nature in the airways. A group of researchers led by Yvonne J. Huang at the University of California, San Francisco (CA, USA) have recently published a paper on the airway flora and the correlations that appear with

respiratory disease.

“We took an ecological approach, considering the bacteria in the context of their microbial neighborhoods to identify relationships between characteristics of these communities and features of the disease. This new approach will help us to better understand the microbiota-host relationships that define human health.” said senior study Susan Lynch, also from University of California San Francisco.

The study, published in the *Journal of Allergy and Clinical Immunology* describes samples taken from 65 asthmatic adults and ten healthy patients. These samples were then analyzed using specialist high-throughput molecular assay to determine the bacterial complement colonizing each sample. A greater number and a greater

diversity of bacteria were found in asthma patients when compared with healthy study participants, and increased bacterial load correlated with airway hypersensitivity.

This has implications for models of asthma pathogenesis, as it complicated the idea that asthma is solely based on inhaled toxins. The influence of the airway microbiota may provide increased protection or susceptibility to patients at risk of developing asthma. The authors stress that further studies are needed to elucidate these mechanisms and find the clinical implications of this relationship.

Source: *Huang YJ, Nelson CE, Brodie EL et al.; National Heart, Lung, and Blood Institute’s Asthma Clinical Research Network: Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma.*

Priority Paper Alerts

Fang W, Vega-Rodriguez J, Ghosh A, Jacobs-Lorena M, Kang A, St Leger R: Development of transgenic fungi that kill human malaria parasites in mosquitoes. *Science* 331(6020) 1074-1077 (2011).

A number of recombinant strains of the fungus *Metarhizium anisopliae*, which naturally infects mosquitoes, were produced that demonstrate promise as tools of vector control in malaria. *M. anisopliae* were engineered to express salivary gland and midgut peptide 1 (SM1), which prevents the malaria sporozoite from attaching to the mosquito salivary glands, an antibody that causes sporozoites to agglutinate, or the antimicrobial toxin scorpine. Mosquitoes were treated with the strains 11 days after taking a bloodmeal and subsequent sporozoite counts were taken. The fungi expressing SM1, agglutinating antibody and scorpine reduced sporozoite counts by 71, 85 and 90%, respectively. A modeling exercise demonstrated that, compared with a wild-type strain of the fungus (which is lethal to mosquitoes), the transgenic strains could reduce transmission to humans by up to fivefold.

Chen H, Li C, Huang J et al.: CD4+ T cells from elite controllers resist HIV-1 infection by selective upregulation of p21. *J. Clin. Invest.* DOI:10.1172/JCI44539 (2011) (Epub ahead of print).

Investigates the susceptibility of CD4+ T cells from HIV elite controllers compared with susceptibility of T cells from HIV negative individuals and progressors. An ex vivo infection assay of CD4+ T cells from elite controllers had significantly lower p24 antigen production, indicating reduced HIV replicative capacity in these cells. Further studies revealed that inhibition of replication occurs early in the infection process. This effect was attributed to the upregulation of p21, which was shown to interrupt both HIV reverse transcription and mRNA transcription from proviral DNA.



J. Allergy Clin. Immunol. 127(2), 372–381 (2011).