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Human Vaccines and Immunotherapeutics: News

Measles vaccination: Targeted and non-targeted benefits

A new study found that receipt of the live measles, mumps, and rubella (MMR) vaccine on schedule after vaccination for other common infections is associated with a lower rate of hospital admissions for any kind of infections, but particularly for lower respiratory tract infections.

Besides protecting children against targeted diseases, childhood vaccines have also been shown to have non-specific beneficial effects that reduce illness and death from non-targeted diseases, especially in low-income countries. The aim of the Danish study, recently published in the journal *JAMA*,[1] was to examine whether such non-specific effects might also be important for children in high-income settings, like Denmark. The authors looked at whether live MMR vaccine was associated with lower rates of hospital admissions for infections among Danish children.

The study included 495,987 children born 1997–2006. They were followed from ages 11 mo to 2 y. The recommended vaccination schedule was inactivated vaccine against diphtheria, tetanus, pertussis, polio, and *Hemophilus influenzae* type b (DTaP-IPV-Hib) administered at ages 3, 5, and 12 mo; and MMR at age 15 mo. The research team found that there were 56,889 hospital admissions for any type of infection among the children in the study. Receiving the live MMR vaccine after the inactivated DTaP-IPV-Hib vaccine was associated with a lower rate of hospital admissions for any infection. The association was particularly strong for lower respiratory tract infections and for hospital stays of longer duration. Children who received DTaP-IPV-Hib after MMR had a higher rate of infectious disease admission.

The study authors conclude that timely vaccination in the recommended sequence could avert a considerable number of hospital admissions for any infection between ages 16 and 24 mo.

In an accompanying editorial,[2] Drs David Goldblatt from the UCL Institute of Child Health and Great Ormond Street Children's Hospital (London,UK) and Elizabeth Miller of Public Health England (London, UK) discuss unexpected benefits of vaccination, such as the apparent effect of live vaccines (i.e., measles and BCG) on reducing mortality from infections other than measles or tuberculosis.

Looking at measles vaccination from the viewpoint of fighting and globally eliminating this viral disease, the World Health Organization (WHO) has recently reported promising numbers. Annual measles deaths have reached historic lows, dropping 78% from > 562 000 in 2000 to 122 000 in 2012. During this time period, an estimated 13.8 million deaths have been prevented by measles vaccination, and surveillance data showed that reported cases declined 77% from 853 480 to 226 722. More details were recently published in the *WHO Weekly Epidemiological Report*.[3]

These promising numbers are a result of global routine measles immunization coverage holding steady at 84% and 145 countries having introduced a routine second dose of measles vaccine to ensure immunity and prevent outbreaks. In addition to routine immunization, 145 million children were vaccinated during mass campaigns against measles in 2012, and more than 1 billion since 2000, with the support of the Measles and Rubella Initiative. This Initiative was launched in 2001 as a global partnership led by the American Red Cross, United Nations Foundation, US Centers for Disease Control and Prevention (CDC), UNICEF and WHO. The Measles and Rubella Initiative aims to ensure that no child dies from measles or is born with congenital rubella syndrome, to reduce measles deaths by 95% by 2015, and to achieve measles and rubella elimination in at least five of six WHO regions by 2020.

Refereces

1. Sørup S, et al. JAMA 2014; 311:826-35; PMID:24570246; http://dx.doi.org/10.1001/jama.2014.470
2. Goldblatt D, et al. JAMA 2014; 311:804-5; PMID:24570243; http://dx.doi.org/10.1001/jama.2014.471
3. WHO Weekly Epidemiological Report (http://www.who.int/wer/2014/wer8906.pdf?ua=1).

CDC reports: 2-dose regimen of chickenpox vaccine is a success

The Centers for Disease Control and Prevention (CDC) recently reported in its *Morbidity and Mortality Weekly Report* that switching from one dose to two doses of varicella (chickenpox) vaccine has been a success.[4]

The one-dose varicella vaccination program, implemented in 1996, resulted in 70–90% declines in varicella incidence, hospitalizations, and mortality. Nevertheless, immunized children continued to catch chickenpox. This led the Advisory Committee on Immunization Practices (ACIP) to recommend a second dose of varicella vaccine for children at age 4–6 y, in addition to the first dose given at age 12–15 mo. The CDC adopted the routine two-dose program in 2007 to further decrease varicella disease and control outbreaks. The ACIP also encouraged health agencies to develop and enforce policies that make proof of immunity against chickenpox a requirement for starting school.

In order to determine the extent of implementation of the routine two-dose varicella vaccination program, the number of states with an elementary school entry requirement in 2012 for two-dose varicella vaccination was compared with the number in 2007, and two-dose varicella vaccination coverage during 2006 was compared with coverage in 2012 among children aged seven years. The CDC researchers looked at data from six monitoring sites to assess the effect the policies have had on uptake of the two-dose regimen.

The researchers found that in 2007, only four states required all children entering elementary school to have received two doses of a varicella vaccine. Such policies were in place in 36 states by 2012. Two-dose varicella vaccination coverage levels among 7-y-olds increased from a range of 4–9% in 2006 to a range of 80–92% in 2012 and were approaching the levels of two-dose MMR coverage,

which had a range of 82–94% in 2012.

These increases show that there has been substantial progress in implementing the routine two-dose varicella vaccination program in the first six years since its recommendation by ACIP. Wider adoption of two-dose varicella vaccination school entry requirements might help progress toward the *Healthy People 2020* target of 95% of school beginners having completed the tw- dose varicella vaccine regimen.

While the latest CDC report did not look at effectiveness of the two-dose schedule, previous studies found that its implementation in 2007 has resulted in declines in varicella incidence and outbreaks of 67–76%.

Reference

4. Lopez AS, et al. MMWR Morb Mortal Wkly Rep 2014; 63:174-7; PMID:24572613

Positive preliminary results from the CAPiTA study

Pfizer has announced positive top-line results of the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA), evaluating efficacy of the pneumococcal polysaccharide conjugate vaccine Prevnar 13 in older subjects.

Pneumococcal disease refers to a group of illnesses caused by *Streptococcus pneumoniae* bacteria. Invasive pneumococcal disease (IPD) occurs when bacteria enter the bloodstream, or another site that is normally sterile. Non-invasive pneumococcal pneumonia occurs when the bacteria cause infection in the lungs but are not detected in the blood concurrently. Pneumonia is the most common presentation of pneumococcal disease in adults. While non-invasive forms of pneumococcal disease are typically more common, the invasive types of disease are generally more severe.

The CAPiTA study included approximately 85,000 adults 65 y of age and older, and is thus the largest double-blind, randomized, placebo-controlled vaccine efficacy trial ever conducted in adults. The primary objective of the study - to demonstrate efficacy of Prevenar 13 against a first episode of vaccine-type community-acquired pneumonia (CAP)—was achieved. The CAPiTA study also met both secondary objectives, which were efficacy against (1) a first episode of non-bacteremic/non-invasive vaccine-type CAP and (2) a first episode of vaccine-type IPD.

Vaccine-type CAP (VT-CAP) was defined as CAP caused by any *S. pneumoniae* serotype included in the vaccine. Non-bacteremic/non-invasive VT-CAP was defined as CAP in which vaccine-type *S. pneumoniae* caused the pneumonia, but was not detected concurrently in the bloodstream or any other normally sterile site. Vaccine-type IPD was defined as a case in which vaccine-type S. pneumoniae was present in the bloodstream or any other normally sterile site, with or without pneumonia.

"Pneumococcal pneumonia is a significant cause of illness and death in adults around the world, and the potential to reduce the burden of this disease through direct vaccination of adults represents a meaningful public health benefit," said Dr. Emilio Emini, senior vice president, Vaccine Research and Development, Pfizer.

Prevenar 13 was licensed by the Food and Drug Administration (FDA) under an accelerated approval process to address an unmet medical need in older adults. As a requirement of the accelerated approval pathway, Pfizer conducted CAPiTA to verify clinical benefit.

More details of the CAPiTA study should become available after the presentation of the results at the 9th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD) in March 2014.

Seasonal flu vaccine associate with reduced stroke risk

According to a recent study in the journal *Vaccine*,[5] seasonal influenza vaccination could reduce the risk of suffering a stroke by almost one quarter.

The British team of researchers from the University of Lincoln and The University of Nottingham had reported a similar link between influenza vaccination and reduced risk of heart attack.

For the current study, called IPVASTIA, the researchers analyzed records of more than 47 000 patients who had suffered a stroke or transient ischemic attack (TIA), also called a "mini stroke", between 2001 and 2009. The researchers looked for uptake of both influenza and pneumococcal vaccines. Data were drawn from the UK's national General Practice Research Database (now the Clinical Practice Research Datalink). The study used a matched case-control design. Actual cases of stroke were compared against "control" patients, adjusted for other factors that might explain the differences in risk associated with flu vaccination such as age, existing diseases and treatment history.

They found that influenza vaccination was associated with a 24% reduction in risk of stroke, with the strongest effects seen if the vaccination was given early in the flu season. They observed no significant change in risk of TIA in people who received a flu vaccine. Pneumococcal vaccination was not found to be associated with a reduced wisk of either stroke or TIA.

Study lead author Dr Niro Siriwardena, from the University of Lincoln said: "The causes of stroke are not fully understood. Classical risk factors like age, smoking and high blood pressure can account for just over half of all cases. We know that cardiovascular diseases tend to hit during winter and that the risks may be heightened by respiratory infections such as flu.

Our study showed a highly significant association between flu vaccination and reduced risk of stroke within the same flu season. The results were consistent with our previous research into heart attack risk."

In the UK the seasonal flu vaccination is recommended for everyone over 65 y of age and other at-risk groups. With 74% in people

over 65 y of age and around 52% in people under 65 y, uptake of the vaccine in 2011–2 across UK was lower than national targets. The findings of the current study reinforce the value of the UK's national flu vaccination program, with reduced risk of stroke appearing to be an added health benefit.

Reference

5. Siriwardena AN, et al. Vaccine 2014; 32:1354-61; PMID:24486370; http://dx.doi.org/10.1016/j.vaccine.2014.01.029

HPV vaccine shown to halve cervical abnormalities

According to a new study, Merck's human papilloma virus (HPV) vaccine Gardasil halves the risk of young women to develop high-grade cervical abnormalities.

A team of Australian researchers set out to measure the effectiveness of the quadrivalent HPV vaccine against cervical abnormalities four years after implementation of a nationally funded vaccination program in Queensland, Australia. The study included women eligible for free vaccination (aged 12–26 y in 2007) and attending for their first cervical smear test between April 2007 and March 2011. The researcher looked at the health records of over 100 000 young women. Pap smear results were compared with vaccination history to give an estimate of how effective Gardasil is at preventing precancerous lesions. High-grade cases were women with histologically confirmed high grade cervical abnormalities (n = 1062), and "other cases" were women with any other abnormality at cytology or histology (n = 10 887). Controls were women with normal cytology (n = 96 404).

The researchers found that women who had received three doses of the vaccine were 46% less likely to develop high-grade cervical abnormalities. The vaccine also offered 34% protection against other cervical abnormalities. Two doses of the vaccine resulted in a vaccine efficacy of 21% against high-grade lesions and other cases. Study results were published in the journal *BMJ*.[6]

"We would expect when we continue to monitor these women into the future that they're going to have lower rates of cancer. Cervical cancer usually takes 10 or 20 years to develop so we would expect once these women get into their 30s or 40s, we'll start to see really substantial declines of cancer," study co-author Dr David Whiteman told the Australian newspaper *The Courier-Mail*.

In conclusion, the quadrivalent HPV vaccine conferred statistically significant protection against cervical abnormalities in young women, particularly in those who had received three doses of the vaccine. The difference seen between the two schedules may partly be due to the two-dose regimen offering less protection, but also many of the partially vaccinated women were older and therefore more likely to have been infected with HPV prior to being immunized. More research is necessary to better understand the difference between the protection provided by the two- and three-dose regimens, especially since some countries have decided or are considering to switch to a two-dose schedule.

Reference

6. Crowe E, et al. BMJ 2014; 348:g1458; PMID:24594809; http://dx.doi.org/10.1136/bmj.g1458

Global prize for mobile mast vaccine storage project

The not-for-profit organization Energize the Chain (EtC) was recently named as the Best Mobile Health Product or Service at the Global Mobile Awards. The idea to use surplus energy from mobile phone masts to refrigerate vaccines in remote areas was chosen by the judges because it is „simple, extraordinarily clever and truly innovative." The awards took place at the Mobile World Congress in Barcelona, Spain.

"More than two million children under five years of age die every year from vaccine-preventable diseases, many due to disruption of the cold chain required to keep temperature-sensitive vaccines effective", Alice Conant, a founding member of the EtC. told SciDev.Net. "EtC not only prevents vaccine-preventable deaths, but it is also a huge benefit to the healthcare system because it saves money and makes the whole system more efficient."

The US-based organization EtC wants to boost vaccine availability in rural, off-grid locations by using the excess energy from power installations at cellphone towers to run refrigeration units. They work with Econet Wireless, an international telecommunications group, in Zimbabwe, and together they are working to expand across Africa. In addition, EtC works with the Karuna Trust in India and plans to launch a pilot there shortly. The award should give EtC greater recognition so it can expand its work.

"We partner the telecom sector with the health sector. The telecom industry's entire business model is based around having reliable, robust 24-hour energy at their cell tower sites. It turns out that they actually have excess energy and we partner with them to physically plug in vaccine refrigerators at the cell tower sites. Then you can visit once a month or once a week to bring the vaccines out for an immunization session," Conant explained.

Developmental pathway of potent HIV-neutralizing antibodies

A new study recently explained how the body's immune system makes a potent antibody that can block human immunodeficiency virus (HIV) infection. The findings, published in the journal *Nature*,[7] may be an important step in developing an HIV vaccine.

The induction of neutralizing antibodies is believed to be essential for an effective vaccine against HIV. Such potent antibodies

capable of neutralizing HIV-1 often target variable regions 1 and 2 (V1V2) of the HIV-1 envelope, but the mechanism of their elicitation has been unclear.

The new *Nature* study, led by scientists from the National Institute of Allergy and Infectious Diseases (NIAID), Columbia University, the Centre for the AIDS Programme of Research in South Africa (CAPRISA), and the National Institute for Communicable Diseases, Johannesburg, defined the developmental pathway by which such antibodies are generated and acquire the requisite molecular characteristics for neutralization. They identified an HIV-infected volunteer who naturally developed V1V2-directed HIV neutralizing antibodies (named CAP256-VRC26) after several months of infection. The researchers analyzed blood samples donated by the volunteer between 15 wk and 4 y after becoming infected. This enabled the scientists to determine the genetic make-up of the original form of the antibody; to identify and define the structures of a number of the intermediate forms taken as the antibody mutated toward its fullest breadth and potency; and to describe the interplay between virus and antibody that fostered the maturation of CAP256-VRC26 to its final, most powerful HIV-fighting form.

They found that each antibody contained the protruding tyrosine-sulphated, anionic antigen-binding loop (complementarity-determining region [CDR] H3) characteristic of this category of antibodies. Their unmutated ancestor emerged at weeks 30–38 post-infection with a 35-residue CDR H3, and neutralized the virus that superinfected this individual 15 weeks after initial infection. Improved neutralization breadth and potency occurred by week 59 with modest affinity maturation, and was preceded by extensive diversification of the virus population.

Thus, HIV-1 V1V2-directed neutralizing antibodies could develop relatively rapidly through initial selection of B cells with a long CDR H3, and limited subsequent somatic hypermutation. In other words, even the early intermediates of CAP256-VRC26 (after relatively few mutations) could neutralize a significant proportion of known HIV strains. This improves the chances that a V1V2-directed HIV vaccine developed based on the new findings would be effective, according to the study authors. They have begun to work on a set of vaccine components designed to elicit V1V2 neutralizing antibodies and guide their maturation.

Reference

7. Doria-Rose NA, et al. Nature 2014; PMID:24590074; http://dx.doi.org/10.1038/nature13036

Burkholderia vaccine: US Dep of Defense collaborates with Bavarian Nordic

Bavarian Nordic recently announced that its MVA-BN (Modified Vaccinia Ankara –Bavarian Nordic) vaccine platform technology has been selected by the Defense Threat Reduction Agency (DTRA), a part of the US Department of Defense, for the development of a vaccine against two potential biological threats to national security—*Burkholderia pseudomallei* and *Burkholderia mallei.*

The bacterial pathogen *B. pseudomallei* causes melioidosis, a human disease endemic in Southeast Asia and northern Australia. *B. mallei* causes glanders, a zoonotic disease primarily occurring in Africa, Asia, the Middle East, and Central/South America. There is significant interest in developing vaccines against these two pathogens, because of the lengthy antibiotic therapy required to treat melioidosis and glanders, the suboptimal clinical outcomes, possible biothreat applications, and public health implications.

Bavarian Nordic will use their MVA-BN vaccine platform to develop vaccines against B. pseudomallei and B. mallei. This robust and adaptable vaccine platform is suitable for addressing a wide variety of infectious diseases, but also numerous types of cancer. To date, more than 7300 individuals, nearly 1000 of whom are immunocompromised, have been vaccinated with MVA-BN-based vaccines, showing the platform displays high immunogenicity and a favorable safety profile.

DTRA is the fourth US Government agency to collaborate with Bavarian Nordic on the development of novel biodefense vaccines. They will supports the Burkholderia project with $0.5 million and if the contract yields a successful proof of concept, DTRA may support further development of the vaccine through a larger contract award.

"The award of this contract illustrates the strength of our MVA-BN vaccine platform technology, which has been developed through a decade-long partnership with the U.S. Department of Health and Human Services," said Dr Anders Hedegaard, President and CEO of Bavarian Nordic. "As part of our strategy to expand our biodefense business beyond smallpox, we are pleased to add DTRA to our list of government partners with whom we work to develop novel biodefense vaccines."

Other ongoing collaborations with US government agencies include the development of vaccines against smallpox, filoviruses (Ebola and Marburg) and foot-and-mouth disease.