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RSV Vaccination – Lessons From the Past

Announcer:
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Dr. Simoes:
My name is Eric Simoes. I'm a Professor of Pediatrics and Epidemiology at the University of Colorado and the Colorado School of Public Health. I'm going to discuss RSV Vaccination – Lessons from the Past.

Firstly, I'll start a discussion on the formalin-inactivated RSV vaccine. Why do we not have an RSV vaccine today, despite the fact that RSV was discovered over 50 years ago? Well, shortly after it was discovered in 1955, RSV vaccine development began in the 60s, and an FI RSV vaccine, FI standing for formalin inactivated, RSV vaccine was created by inactivating RSV. It was administered to infants and young children at four centers in the U.S., including Denver, Colorado, in a clinical trial at all four sites. Unfortunately, it caused severe lung inflammation in previously naïve infants during the next RSV season, and that was called vaccine enhanced respiratory disease, or ERD. In fact, four of the children in that trial died from severe RSV in the FI RSV vaccine group. There were no severe RSV infections in the control groups, and there were various control groups. It turned out that RSV – FI RSV produced antibodies that bound to the F glycoprotein with a deficiency in neutralizing antibodies. So there was non-neutralizing antibody produced, and it stimulated an unbalanced immune response in the T cells that was probably responsible for the formalin-inactivated disease.

Subsequent to that, there was a lacking in what happened with RSV, we didn't have RSV vaccines. And Bob Chanock and his group at the NIH started developing live attenuated vaccines, knowing that inactivated vaccines are going to be very difficult to develop for young infants. So live RSV vaccines had three potential advantages. They replicate in the upper tract, and therefore, could reduce local immunity. And with the live attenuated vaccines, we have not seen enhanced disease that was seen with the FI RSV vaccine. However, despite 40 odd years of development of live attenuated vaccines, either the various vaccines that were developed were too attenuated or not attenuated enough. Currently, clinical trials have been done and we've got a fine balance between the two. Current trials are directed at those rather than 6 months of age, not really the highest risk group; the highest risk group are in infants less than 6 months of age.

About 20-30 years ago, Pfizer developed an RSV subunit vaccine, it was called the PFP-2 vaccine. It was made by immunoaffinity purification of the RSV F protein. Because it was a subunit vaccine, of course no investigators and no companies would be willing to go into seronegative infants, knowing the experience with the FI RSV vaccine. So these were administered to seropositive infants. And they worked. They worked reasonably well in seropositive infants, but there were two problems. One, is it was difficult to purify enough protein to make it commercially available. These were immunoaffinity purified. And the second was that it was – it was only safe to be administered to seropositive infants. In home, the burden of disease really is not a major issue. It is a problem but not major. So we still needed to have vaccines that went towards protecting the youngest babies.

So an alternative to RSV vaccines was the development of passively administered immunoglobulin. We knew from studies that Paul Gleason did many years ago that antibodies protected against RSV disease, maternally transferred antibodies in particular. And he

showed in studies published in the early 80s, that babies - or babies born to mothers with high antibody titers of RSV neutralizing antibody had more much less severe disease or no disease at all, compared to those who had no antibody, who developed RSV, lower respiratory tract disease. That other studies in cotton rats that showed the safety of passively administered high titer RSV immunoglobulin, led to the development of RSV immunoglobulin, and that was developed by George Siber at Mass Public Health Labs, and it was called RSV hyper-immunoglobulin. And this was derived from - by plasmapheresis of high-titer donors mostly at our doctors and nurses of that came to Mass Public Health Labs. RSV hyper-immunoglobulin at that time in several studies was shown to be safe and efficacious in preventing lower respiratory tract disease in young infant when administered every 4 weeks during the RSV season; the half-life being 21 to 28 days. It needed to be administered monthly. The infusion itself of 750 milligram per kg took about 4 hours. As you can imagine, this was not a practical solution to prevention of RSV in full-term babies. It was used for high-risk babies until the development of monoclonal antibodies happened.

In 1998, trials had been completed for a monoclonal antibody, now called palivizumab, that was then made and licensed for use in infants less than 35 weeks gestation, and those with congenital heart disease. It was - could be administered once a month. It was safe and effective. But because of the high cost, the AAP has been increasingly restricting its use, and it's now used and a small group of babies currently to very high-risk babies, premature babies less than 28 weeks gestation, those with chronic lung disease on oxygen, and those with congenital heart disease requiring treatment.

That, in a nutshell outlines the development to date of preventive therapies from the early 1960s to currently. Thank you very much for your attention.

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