Infection & Immunity Utrecht

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VACCINE SYMPOSIUM

LESSONS LEARNT FROM COVID-19 VACCINATION

15 September 2022

Universiteit Utrecht

NWO WG VACCINES

UMC Utrecht

VACCINE SYMPOSIUM

15 SEPTEMBER 2022

09.30 **Cécile van Els**, RIVM & Biomolecular Health Sciences, Veterinary Medicine, UU
Welcome

09.40 **Rogier Sanders**, Medical Microbiology and Infection Prevention, Amsterdam UMC
"Structural Vaccine Design for Spike Protein-based vaccines"

10.20 **Rory de Vries**, Viroscience, Erasmus Medical Centre, Rotterdam
"Humoral and cellular immune mechanisms induced by COVID-19 vaccines: cross-reactivity against Variants of Concern?"

11.00 Break

11.20 **Corine Geurts van Kessel**, Viroscience, Erasmus Medical Centre, Rotterdam
"Switching of COVID-19 vaccines in prime-boost schedules: a practical solution or strategy to optimize effectiveness?"

12.00 Lunch

12.40 **Dinja Oosterhoff**, Intravacc, Bilthoven
"Improving COVID-19 vaccination: vaccine candidates inducing Mucosal Immunity"

13.20 **Daniel L. Hurdiss**, Biomolecular Health Sciences, Veterinary Medicine, UU
"Mapping vulnerable sites on the SARS-CoV-2 spike protein"

14.00 Break

SHORT TALKS

14.30 **Sophie Bots**, Utrecht Institute for Pharmaceutical Sciences, Utrecht University
"The art of rapid safety evaluation studies in the context of COVID-19 vaccines: balancing a need for speed with reliable and robust research"

14.45 **Mirte Pascha**, Section Virology, Veterinary Faculty, Utrecht University
"Mosaic N1 and N2 neuraminidase nanoparticles induce high antibody titers and potent protection from Influenza A virus H1N1 and H3N2 challenge"

15.00 **Linda van Oosten**, Laboratory of Virology, Wageningen University & Research
"A two-component S1-nanoparticle vaccine protects against SARS-CoV-2 challenge in K18-hACE2 mice"

15.15 **Sebastiaan de Graaf**, Bijvoet Center for Biomolecular Research, Utrecht University
"Exploring the human milk IgA1 response to SARS-CoV-2 vaccination at the clonal level"

Humoral and cellular immune mechanisms induced by COVID-19 vaccines: cross-reactivity against Variants of Concern?

Rory de Vries

Viroscience, Erasmus Medical Centre, Rotterdam

The rapid spread of the SARS-CoV-2 Omicron sub-lineage in a largely immune population raises concerns about immune escape. It is known that monovalent COVID-19 vaccines induce neutralizing antibodies that poorly cross-react with the circulating Omicron sub-lineage. Whereas only a handful of mutations in the receptor binding domain (RBD) of the spike (S) protein is sufficient to escape neutralizing antibodies, escape from Fc-mediated antibody effector functions or T-cell responses could be more complex. Here, we studied functional antibody and T-cell responses against SARS-CoV-2 variants up to Omicron BA.2 after homologous or heterologous prime-boost COVID-19 vaccination regimens.

Consistent cross-neutralization of the D614G (ancestral), Alpha, Beta and Delta variants was observed after completion of a primary vaccination regimen. Neutralization of Omicron BA.1 and BA.2 was significantly lower or even absent. A booster vaccination given 3-6 months after completion of the primary regimen partially restored neutralization of the Omicron sub-lineage, but responses were still significantly decreased compared to ancestral SARS-CoV-2. Similar observations were made for Fc-mediated antibody effector functions (antibody-dependent cellular cytotoxicity, phagocytosis, and complement deposition).

SARS-CoV-2-specific T-cells could be detected up to 6 months after completion of a primary vaccination regimen. In contrast to antibody responses, no significant difference was observed between the ancestral- and variant-specific polyclonal T-cell response, including the response against Omicron BA.1. However, isolation and characterization of several SARS-CoV-2-specific T-cell clones showed that reactivity with the Omicron sub-lineage can be lost, due to mutations in the minimal epitope. Strikingly, the magnitude and breadth of the T-cell response did not increase after booster vaccination.

Overall, these data show minimal SARS-CoV-2 evasion from vaccine-induced specific T-cell responses, while cross-reactivity of neutralizing antibodies with emerging variants is significantly impaired. We speculate that T-cell immunity balances the lack of neutralizing antibody cross-reactivity, thereby preventing or limiting severe COVID-19 after infection with a novel SARS-CoV-2 variant. Bivalent booster vaccines, containing an ancestral and Omicron BA.1 S, are thought to increase the breadth of the vaccine-induced immune response and further restore variant cross-neutralization by antibodies.

Switching of COVID-19 vaccines in prime-boost schedules: a practical solution or strategy to optimize effectiveness?

Corine Geurts van Kessel

Viroscience, Erasmus Medical Centre, Rotterdam

A variety of vaccination regimens are effective in preventing severe coronavirus disease-2019 (COVID-19). However, functionality and durability of immune responses after homologous or heterologous vaccination require further investigation. To understand which vaccination regimen provides the strongest, broadest and most durable functional antibodies to SARS-CoV-2 in both healthy individuals and patients with primary or secondary immunodeficiencies, we compared the immunogenicity of different vaccination approaches. Comparative studies were performed to analyze the functionality and breadth of humoral and cellular immune responses, in which participants were vaccinated and boosted with vector-based or mRNA-based vaccines, and combinations thereof.

Independent of priming, all regimens resulted in development of detectable antibody and T-cell responses over an extended time period. Prior to boost, approved regimens for vector-based vaccines (two shots for ChAdOx1-S, one shot for Ad26.COV2.S) resulted in less pronounced humoral and cellular responses compared to approved regimens with mRNA-based vaccines (two shots for mRNA-1273 and BNT162b2). Heterologous vaccination of Ad26.COV2.S-primed individuals with an mRNA-based vaccine resulted in higher responses compared to homologous regimens. Interestingly, the fraction of neutralizing and thus functional antibodies in these participants was increased.

Binding and neutralizing antibody levels in Ad26.COV2.S-vaccinated individuals remained stable up to six months after vaccination. In contrast, neutralizing antibody levels of individuals with homologous mRNA-based vaccination regimens clearly waned and became comparable to levels of Ad26.COV2.S-vaccinated participants six month after completion of the vaccination regimens. Booster vaccination resulted in equalization of binding antibodies between different vaccine groups, and boosting of T-cell responses.

Altogether, we show that homologous and heterologous vaccination regimens against COVID-19 resulted in durable and functional immune responses in healthy individuals, with regimens containing mRNA vaccines yielding the highest immunogenicity. Ad26.COV2.S-priming induced lower initial antibody responses, which were stable and relatively more functional. These data may have direct implications for future considerations concerning prime-boost strategies against viruses.

Improving COVID-19 vaccination: vaccine candidates inducing Mucosal Immunity

Dinja Oosterhoff

Intravacc, Bilthoven

The development of more effective, accessible, and easy to administer COVID-19 vaccines next to the currently marketed vaccines is essential to curtailing the SARS-CoV-2 pandemic as well as seasonal vaccination. A major concern is reduced vaccine-induced immune protection to emerging variants, and therefore booster vaccinations to broaden and strengthen the immune response might be required. Intranasal vaccines have the capacity to induce next to systemic immunity also local mucosal immunity, thereby targeting the primary port of entry of SARS-CoV-2 with the potential of blocking transmission.
We developed an intranasal COVID-19 subunit vaccine, based on outer membrane vesicles (OMV) from Neisseria meningitidis and a recombinant Wuhan Spike protein of SARS-CoV-2 (OMV-Spike). The immunogenicity of the vaccine was tested in mice, Syrian hamsters and rabbits via intranasal vaccination. Hamsters were also used to determine protective immunity based on a challenge study as well as to study the reduction of viral transmission, whereas rabbits were used for a GLP toxicology study of the OMV-Spike vaccine. Animal studies demonstrate that intranasal vaccination with OMV-Spike induced high levels of IgG and IgA antibodies in the nose and lungs of the mice and high levels of serum-neutralizing antibodies in all animals. Vaccinated hamsters that were challenged with SARS-CoV-2 were protected from weight loss and viral replication in the lungs compared to control groups, and no lung lesions were observed 7 days after challenge. A reduced viral load in throat and lungs and highly reduced lung lesions was observed in OMV-Spike vaccinated animals exposed to placebo vaccinated, challenged animals. The results of the GLP toxicology study demonstrated the safety and efficacy of the OMV-Spike vaccine. Altogether, the preclinical data are very promising and support further clinical testing of this novel non-replicating, needle-free OMV-Spike subunit vaccine. A Phase I clinical study is foreseen to start the coming months.

The art of rapid safety evaluation studies in the context of COVID-19 vaccines: balancing a need for speed with reliable and robust research

Sophie Bots[1], Judit Riera-Arnau[2,3], Anna Schultze[4], Davide Messina[5], Svetlana Belitser[1], Carlos E. Durán[2], Ema Alsina[2], Ian Douglas[4], Patricia Garcia[6], Rosa Gini[5], Ron M.C. Herings[7], Consuelo Huerta[6], Mar Martín-Pérez[6], Ivonne Martin[2], Jetty A. Overbeek[7], Olga Paoletti[5], Patrick Souverein[1], Karin M.A. Swart[7], Olaf H. Klungel[1], Miriam Sturkenboom[2]

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Knowledge about the safety of COVID-19 vaccines was limited to pre-licensure clinical trials at the time national vaccination programmes were initiated. Therefore, comprehensive surveillance of the real-world safety of these vaccines was essential to detect and rapidly evaluate any signals that warranted regulatory action. Due to the nature of post-marketing surveillance, vaccination roll-out and safety evaluation occur simultaneously. Consequently, any potential safety signal needs to be evaluated rapidly to inform regulatory agencies on post-approval benefit/risk assessment of vaccines. In short, time is of the essence. However, reliability is also key because findings will directly inform regulatory action. How to balance this need for speed with making sure findings are robust to bias, especially in a vaccination setting where such issues are likely to occur? And what about collecting sufficient events for meaningful analyses given the short timeframe? This talk will discuss lessons learned using work from the European Medicines Agency (EMA)-funded Covid Vaccine Monitoring project on myo- and pericarditis as a case study. In July 2021, myocarditis was raised as a potential adverse effect of mRNA-based COVID-19 vaccines, especially in younger men after the second dose. Combining real-world data from four European countries, we applied both a cohort and a nested self-controlled risk interval design to evaluate the effect of four EMA-approved COVID-19 vaccines on myo-/pericarditis risk. Only four months after the signal was first raised, we confirmed an increased incidence of myo-/pericarditis after the second dose of both mRNA vaccines, especially in individuals aged 12-29 years. This talk will present the project in real time, encouraging the audience to think along. The aim is to introduce the audience to safety evaluation study designs and methods and challenges surrounding observational COVID-19 vaccine safety research.

Mosaic N1 and N2 neuraminidase nanoparticles induce high antibody titers and potent protection from Influenza A virus H1N1 and H3N2 challenge

Mirte N. Pascha[1], Marlies Ballegeer[2,3], Irina C. Albulescu[1], Berend Jan Bosch[1], Frank J.M. van Kuppeveld[1], Xavier Saelens[2,3], Cornelis A.M. de Haan[1]

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Current Influenza A virus (IAV) vaccines predominantly induce antibody responses against variable epitopes of hemagglutinin and require frequent updates. As the second most abundant glycoprotein with an essential role in the viral life cycle, neuraminidase (NA) is an attractive target for development of novel vaccines. Multivalent display of vaccine antigens has been shown to induce higher antibody titers with potential for improved breadth of the response. Here we aimed to elicit a broadly protective immune response by vaccination with self-assembling protein nanoparticles presenting NA antigens of the N1 and N2 subtypes. The oligomeric and enzymatically active NA antigens were coupled to Mi3 nanoparticles using the SpyTag/SpyCatcher system. Immunization of mice with nanoparticle formulations resulted in 10-fold higher antibody titers and improved protection against lethal challenge over soluble formulations, particularly at low NA antigen doses. Immunization with a mix of N1 and N2 particles resulted in antigenic competition and reduced protection against IAV H1N1challenge. In contrast, immunisation with mosaic nanoparticles presenting N1 and N2 on the same particle did not result in antigenic competition and provided full protection against lethal IAV H1N1 and H3N2 challenges. Further investigation of the breadth of the response to these mosaic particles is required to determine their value as broadly protective vaccine candidates.

A two-component S1-nanoparticle vaccine protects against SARS-CoV-2 challenge in K18-hACE2 mice

Linda van Oosten

Laboratory of Virology, Wageningen University & Research

Vaccines pave the way out of the SARS-CoV-2 pandemic. Besides mRNA and adenoviral vector vaccines, effective protein-based vaccines are needed for immunization against current and emerging variants. We have developed a virus-like particle (VLP)-based vaccine using the baculovirus-insect cell expression system, a robust production platform known for its scalability, low cost, and safety. Baculoviruses were constructed encoding SARS-CoV-2 Spike protein S1 domain for conjugation to bacteriophage AP205 VLP nanoparticles using tag/catcher technology. The S1 yield in an insect-cell bioreactor was 11 mg/liter, and authentic protein folding, efficient glycosylation, partial trimerization, and ACE2 receptor binding was confirmed. Prime-boost immunization of balb/c mice with 0.5 ug S1-VLPs (formulated with Addavax adjuvant) showed potent neutralizing antibody responses against Wuhan and UK/B.1.1.7 SARS-CoV-2 variants, comparable to a receptor binding domain (RBD)-VLP vaccine that is currently in phase III clinical trials.

We have also undertaken a vaccination and challenge study in K18-hACE2 transgenic mice and show that two doses of 2 ug S1-VLP vaccine provides protective immunity against SARS-CoV-2 infection and disease, without a requirement for additional adjuvants. In this trial, the S1-VLP vaccine was also compared to S1 subunit vaccine and a licenced mRNA vaccine (BNT162b2, Pfizer-BioNTech). This VLP display platform should theoretically be readily amendable to any (or even multiple) SARS-CoV-2 variants of concern.

Part of this research was published in mBio, and recently accepted for publication in Journal of Virology:

van Oosten, L., Altenburg, J. J., Fougeroux, C., Geertsema, C., van den End, F., Evers, W. A., ... & Pijlman, G. P. (2021). Two-component nanoparticle vaccine displaying glycosylated spike S1 domain induces neutralizing antibody response against SARS-CoV-2 variants. mbio, 12(5), e01813-21. https://doi.org/10.1128/mBio.01813-21

van Oosten, L., Yan, K., Rawle D.J., Le, T. T., Altenburg, J. J., Fougeroux, C., ... & Pijlman, G.P., Suhrbier A. (2022). An S1-nanoparticle vaccine protects against SARS-CoV-2 challenge in K18-hACE2 mice. *Submitted to Journal of Virology.*

Exploring the human milk IgA1 response to SARS-CoV-2 vaccination at the clonal level

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Information regarding vaccine driven antibody evolution against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in lactating women is limited, as current methods like ELISA and neutralization assays only provide information regarding total amounts and functionality, respectively. Here we make use of a novel LC-MS technique to characterize the secretory immunoglobulin A1 (SIgA1) clonal response to one of four SARS-CoV-2 vaccines from 9 selected mothers. We quantitatively followed clones by their mass and retention time over 17 timepoints, starting from pre-vaccine to 70 days after the first dose. We observed a highly heterogenous population of vaccine induced clones with respect to maximum abundance, abundance over time, persistence, and response to either the first or second dose. We further investigated the clonal response to the first and second dose by classifying clones based on their first and last detected timepoints. The results showed that donors mount a unique response to the SARS-CoV-2 vaccinations in terms of total titer, (relative) abundance and clonality. The vaccine induced clones were dominated by persistent clones, which come up after the first dose and recur until after the second dose. However, we also observe transient clones which disappear before the second vaccination, delayed clones which only form shortly before the second dose, and clones that appear to be induced only by the second dose of the vaccine. These four SIgA1 antibody subpopulations were present regardless of mRNA or vector-based vaccination. Overall, through clonal profiling, we revealed that while individual donors have unique vaccine induced evolutions of SIgA1 in human milk. Through our profiling method we were able to identify the clones that make up the response and assign them into subpopulations which follow a common trend across regardless of donor or vaccines, leading to an understanding of how SIgA1s are affected by vaccines on a level that cannot be explored using more prevalent modern immunological assays.