Optimizing the beneficial non-specific effects of vaccines

Odense, Denmark **9-11 November 2022**

Abstract book

OPTIMMUNIZE 2022 CONFERENCE

Optimizing the beneficial non-specific effects (NSEs) of vaccines

Dear OPTIMMUNIZE conference participants,

We are delighted to welcome you to the second OPTIMMUNIZE 2022 conference, hosted by the Danish Institute for Advanced Study, in Odense, Denmark.

We last convened at UK's Wellcome Campus in February 2020, just before most of the world was shut down. COVID-19 was known to be circulating. At the meeting, the idea of using live vaccines to provide non-specific protection in the first phases of the pandemic was discussed among participants. Many trials were initiated and the idea to "bridge the gap" until specific vaccines had been manufactured gathered wide-spread interest. We were privileged to host an OPTIMMUNIZE Webinar in April 2022, where preliminary results from many trials were presented, and we will surely hear more in Odense.

At the OPTIMMUNIZE 2022 conference, we will focus on the research conducted since 2020. The sessions have diverse presentations focusing on epidemiological and immunological studies of non-specific effects against infectious and non-communicable diseases, and the potential role of maternal priming, sex, and age on the magnitude and direction of these non-specific effects. We will have two keynote presentations, by Professors Stanley Plotkin and Bali Pulendran.

This is an area of research that has matured tremendously over the last decade, where we are now at a point in time where some of these findings could influence global vaccination policies. In the final session, with stakeholders from the WHO and the FDA, we will ask "*Can we start using vaccines for their non-specific effects now?"* For example, with the accumulated evidence for the beneficial non-specific effects, is now the time to introduce the tuberculosis vaccine, BCG, as a vaccine against neonatal sepsis?

Organizing Committee

Christine Stabell Benn

Eleanor Fish

Frederik Schaltz-Buchholzer

Jorge Dominguez-Andres

Katie Flanagan

Sabra Klein

Tobias Kollmann

General information

Scientific Session Protocol

Photography, audio, or video recording of the scientific sessions is not permitted.

Oral Presentations

Please provide an electronic copy of your talk to a member of the conference's technical team, who will be present in the conference auditorium, by latest in the break before your presentation. If you prefer, you can also send your presentation to adiness@health.sdu.dk ahead of the conference.

Speakers will have 30 minutes (15 minutes for talks selected from abstracts) for their presentation and a few specific Q/As. Each session will be followed by a discussion of the totality of the evidence in the area.

Oral presentations abstracts are numbered **S1-S21**.

Poster presentations

There will be two poster sessions during the conference:

Session 1: **P1-P9** poster presentations take place on Wednesday (November 9), 18:00-19:00.

Session 2: **P10-P21** poster presentations take place on Thursday (November 10), at 17:45-18:45.

Your assigned poster number is indicated by the page number of your abstract in this abstract book.

At each session, all poster presenters are invited to do a 3-minute lightning talk in front of their poster.

Conference venue

The conference venue is Danish Institute for Advanced Study (DIAS), University of Southern Denmark. Address: Fioniavej 34, 5230 Odense M

Internet Access at the conference venue (DIAS)

Please connect to the Wi-Fi network "SDU visitor". A registration page should open in your browser, and after entering your email and a valid phone number, a username and password will be sent to you by SMS, providing access for 24 hours. After the 24 hours have passed, the same procedure is followed again to renew access. In addition, the "eduroam" network is also available for those that already have access.

Room temperature at the conference venue

Please note that the Danish Government has decided that due to the current energy crisis the room temperature in public buildings should not exceed 19 degrees Celsius. Bring an extra sweater!

Transport between CPH Airport and Odense city

There are direct train lines between CPH Airport and Odense Central Station. The trains depart once every hour, and the trip takes 1 hour and 40 minutes.

At CPH Airport, the train station is located underneath Terminal 3. The trains for Odense depart from Platform 2. Tickets can be bought at the DSB sales desk in Terminal 3, or from the vending machines near it and in the baggage reclaim area (using a debit or credit card at the vending machines).

Currency

Denmark uses Danish Crowns ("kroner"), 1 EUR or 1 USD ~ 7.5 DKK. Almost all places take credit cards. See also "Tipping".

Accommodation in Odense

Conference hotels, where most participants stay, are Hotel Odeon, two Milling Hotels and First Hotel Grand. They have given us a conference discount. If you did not receive this when booking, ask for it in the reception when you pay.
All of the hotels are comfortably within walking distance from Odense Station < 1km

Transport from Odense city to the conference venue

- **Optimmunize conference bus**

Each day, a bus will be driving to and from the conference venue at the university.
Wednesday 9 November:

- The bus drives from First Hotel Grand at **11.30** – arriving at the conference venue ~ at noon.
- The bus drives from the conference venue at **21.30** – arriving at First Hotel Grand ~21.50.

Thursday 10 November:

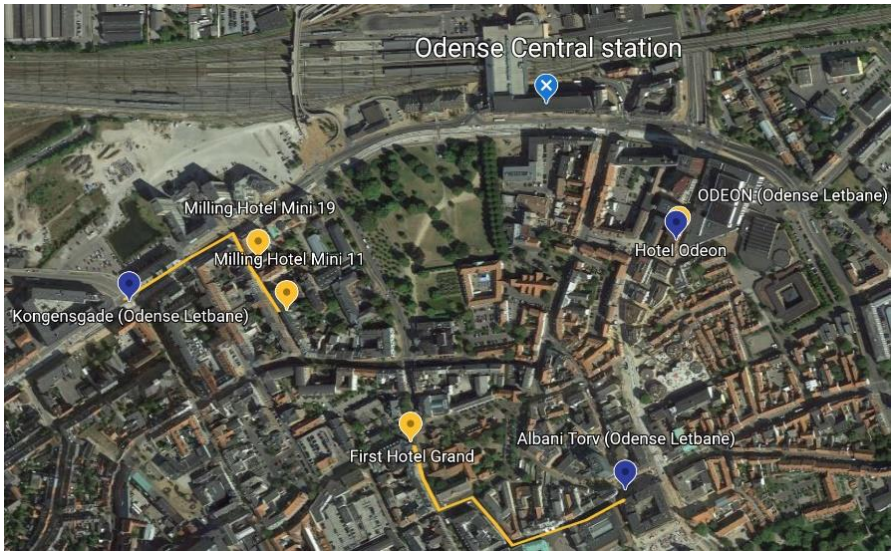
- The bus drives from First Hotel Grand at **8.20** – arriving at the conference venue ~ 8.50.
- The bus drives from the conference venue at **19.00** – dropping those not participating in the dinner in city, arriving at Restaurant NordAtlanten ~19.30.

Friday 11 November:

- The bus drives from First Hotel Grand at **8.20** – arriving at the conference venue ~ 8.50.
- The bus drives from the conference venue at **16.15** – arriving at First Hotel Grand ~16.40.

- **Odense City Tram ("Letbanen")**

If you need to go between city and the conference venue outside the conference bus hours, the easiest is to go with the tram ("Odense Letbane"). The location of the nearest tram station from the conference hotels is depicted in yellow below.



The trip from Odense Central to the SDU campus takes approx. 17 minutes. Count on an additional 5-10 minutes to walk from your hotel to the tram station, and 5-10 minutes to walk from the SDU campus tram station (station name: Campus Odense) to the conference venue marked with a red circle (700 meter):

Tram tickets: You can pick-up already-paid event tickets for the tram in the hotel receptions of Hotel Odeon and First Hotel Grand. The tickets are 3-day tickets for 2 trips on each of the 9th, 10th, and 11th November. Please hand in unused tickets as they can be reimbursed.

Taxis: There are several taxi-services available in Odense. Either ask the hotel reception to call a taxi for you or use the contact information provided below:

Taxa syd: +45 66154415. Dantaxi: +45 48484848. Odense taxi: +45 66122712

Rent or borrow a bike or electric scooter

Hotel Odeon, First Grand Hotel as well as Milling hotels all have bicycles that can be borrowed for free. If you would like to rent a bike or an electric scooter, while you are on the go, there are two options; Donkey Bike and TIER. Both services use apps to rent out bikes and electric scooters and are available on App Store as well as Google Play store. Downloading any of the apps will provide you with a map that shows the location of bikes and scooters nearby.

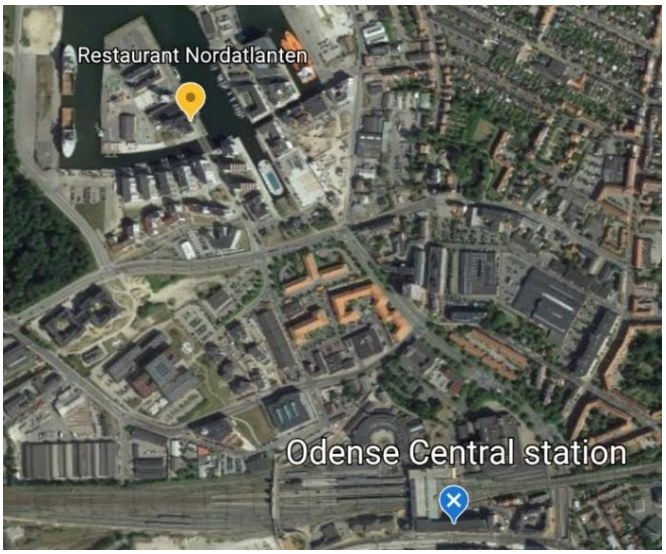
Conference dinners and social events

Early arrivers: On November 8, there is opportunity to participate in an informal event. At 16:30 we will meet in front of Hotel Odeon for a guided city tour in Odense, with the night watchman's round (more info in the appendix). Following the tour, which ends at around 17:45, we will go to Storm's Pakhus for an informal dinner. Here you can choose between food from >20 different stalls. There is no need to sign up - there is room for everybody. Christine's telephone number, if you get lost and need to find us again: (+45) 25883964, Frederik (+45) 42702170 (both also work on WhatsApp).

Conference dinner on Wednesday (day 1, November 9): At the end of the first day of the conference, there will be a conference dinner at the university, from 19:00-21:00. Before the dinner, we will be entertained by a small Hans Christian Andersen parade (Odense is his birth town).

Dinner at Restaurant NordAtlanten on Thursday (day 2, November 10): From 19:30-22:00, those who signed up during the registration process will participate in a dinner at Restaurant NordAtlanten. If signed up, there is a small star on your participant badge. The bus will take us form the conference venue to the restaurant. We anticipate that participants will take a leisure walk, back to the hotels, but taxis can be arranged for tired legs.

Address: Nordatlantisk Promenade 1, 5000 Odense. Location of the restaurant:



Tipping

In Denmark, we have progressive taxes, those earning most pay >60%, and we have good minimum wages and governmental subsidies for those in need. We usually do not tip in hotels taxis or in restaurants, unless on a table-cloth restaurant, if the service is very good.

COVID-19 protocol

We follow the guidance from the Danish Health Authorities at the time of the event, to mitigate any COVID-19 related risk. For entry into Denmark and participation at the conference, there are no rules or regulations regarding COVID-19 vaccination, recent PCR testing, or the use of face masks.

While there are thus no COVID-specific regulations in place in Denmark or at the conference, we encourage participants to respect anyone who chooses to wear a mask or that prefers social distancing to reduce the risk of infection.

Conference Sponsors

SDU D·IAS Projecto de Saúde BANDIM

Platinum sponsor

PARSEMUS FOUNDATION

Silver sponsor

AJVaccines

PROGRAM

Day 1

11:45 - 12:45	Registration and light lunch
12:45 - 13:00	12:45 - 12:50 - Opening by **Dean of Faculty of Health Sciences at University of Southern Denmark, Ole Skøtt** 12:50 - 13:00. Opening remarks by **WHO Director-General, Dr. Tedros Adhanom Ghebreyesus**
13:00 - 13:45	Keynote Lecture: **Stanley Plotkin**: State of the Vaccine World
13:45 - 15:15	**Session 1: Epidemiological studies of non-specific effects (NSEs): since 2020** **Chairs: Christine Stabell Benn & Frederik Schaltz-Buchholzer** 13:45 - 14:15. **Frank Shann**: Epidemiology of the non-specific effects of vaccines: new studies since 2020 14:15 - 14:45. **Peter Aaby**: Non-specific effects and their interactions 14:45 - 15:15. **Paul Welaga**: Studies of Oral Polio Vaccines from Africa and Asia
15:15 - 15:45	Coffee break
15:45 - 16:30	Session 1 (continued): 15:45 – 16:00. **Huong Le**: Non-specific benefit of pneumococcal conjugate vaccines on reducing risk of respiratory syncytial virus-hospitalisations in infants: an Australian population-based linked data cohort study (Short talk selected from submitted abstracts) 16:00 - 16:30. Discussion
16:30 - 18:00	**Session 2: Parental priming and pregnancy vaccination** **Chairs: Maria Yazdanbakhsh & Mike Berendsen** 16:30 - 17:00. **Christine Stabell Benn**: Maternal priming amplifies the beneficial NSEs of live vaccines in the offspring 17:00 - 17:15. **Tayyip Emre Kehribar**: Differential humoral and cellular immune response in pregnant and non-pregnant women upon vaccination against SARS-CoV-2 infection (Short talk selected from submitted abstracts) 17:15 - 18:00. Discussion
18:00 - 19:00	Poster Session 1 with "lightning talks"
19:00 - 21:30	Hans Christian Andersen performance followed by Conference dinner

Day 2

09:00 - 10:30	**Session 3: Using NSEs against COVID-19** **Chairs: Ofer Levy & Asimenia Angelidou** 09:00 - 09:30. **Nigel Curtis**: Results of the BRACE trial 09:30 - 09:45. **Carlos Del Fresno Sánchez**: The bacterial mucosal immunotherapy MV130 protects against viral respiratory infections and improves COVID-19 vaccines immunogenicity (Short talk selected from submitted abstracts) 09:45 - 10:00. **Büsranur Geckin**: The BNT162b2 mRNA vaccine against SARS-CoV-2 affects both adaptive and innate immune responses (Short talk selected from submitted abstracts) 10:00 - 10:30. Discussion
10:30 - 11:00	Coffee break
11:00 - 12:00	Keynote Lecture: **Bali Pulendran**. Systems biological analysis of immunity to COVID-19 infection and vaccination
12:00 - 13:00	Lunch
13:00 - 14:30	**Session 4: Immunological studies of NSEs: new studies since 2020** **Chairs: Jorge Dominguez-Andres & Nelly Amenyogbe** 13:00 - 13:30. **Carlos Martin**: MTBVAC entry in TB efficacy trials and exploring NSEs 13:30 - 14:00. **David Lynn**: Does immunization in pregnancy induce trained immunity in the offspring? 14:00 - 14:30. **Mihai Netea**: Trained immunity: from molecular mechanisms to vaccination
14:30 - 15:00	Coffee break
15:00 - 16:00	**Session 4 (continued): Immunological studies of NSEs: new studies since 2020** 15:00 – 15:15. **Gizem Kilic**: Exploring the immunological pathways induced by an unadjuvanted influenza vaccine and an adjuvanted herpes zoster vaccine in young and older adults (Short talk selected from submitted abstracts) 15:15 – 15:30. **Ozlem Bulut**: Resveratrol as a potential amplifier of BCG-induced trained immunity (Short talk selected from submitted abstracts) 15:30 – 16:00. Discussion
16:00 - 16:30	Coffee break
16:30 - 18:00	**Session 5: NSEs and non-communicable diseases** **Chairs: Sabra Klein & Joseph Hoffmann** 16:30 - 17:00. **Denise Faustman**: Mechanistic studies of BCG in US based adults with type 1 diabetes 17:00 - 17:30. **Annelise Barron**: BCG induction of LL-37 as a novel mechanism of neuroprotection against Alzheimer's Disease 17:30 – 18:00. Discussion
18:00 - 19:00	Poster Session 2 with "lightning talks"
19:30 - 22:00	Dinner at restaurant NordAtlanten in Odense City

Day 3

09:00 - 10:30	**Session 6: Sex and age differences in immunity and response to vaccines** **Chairs: Petra Arck & Dimitra Zazara** 09:00 – 09:30. **Sabra Klein**: Sex differential effects of aging on influenza and COVID-19 vaccine outcomes 09:30 – 10:00. **Katie Flanagan**: Sex differences in the immunological impact of influenza vaccination in younger and older Australian adults 10:00 – 10:15. **Inna Osvyannikova**: Sex-Based Differences in Immune Responses to Vaccination (Short talk selected from submitted abstracts) 10:15 - 10:30. Discussion
10:30 - 11:00	Coffee break
11:00 - 12:00	Session with Q/A from young researchers W/ Mike Berendsen, Maria Conti, Lise Gehrt, Joseph Hoffmann, Tayyip Kehribar, Yoanne Mouwenda, Puck Pelzer, Frederik Schaltz-Buchholzer, Natalie Stephens, Esther Taks, Bradley Whitehead, Martijn Zoodsma
12:00 - 13:00	Lunch
13:00 - 16:00	**Session 7: Policy implications, advocacy and impact - Can we start using vaccines for their NSEs now?** **Chairs: Eleanor Fish and Christine Stabell Benn** Panel members: **Kate O'Brien** (WHO), **Ulla Griffiths** (UNICEF), **Ofer Levy** (FDA), **Katie Flanagan** (Australian Technical Advisory Group on Immunisation), **Jaykumar Menon** (Open Source Pharma), **Annie Sparrow** (Mount Sinai) Can we start using vaccines for their NSEs now? If not, which studies are needed and who should do them? If yes, what are the steps from here? Closing remarks by **Marianne Holmer**, Director of Danish Institute for Advanced Study

Abstracts – Oral presentations

State of the vaccine world

Stanley Plotkin

The history of vaccination now goes back to the end of the 18th Century. From the first empirical efforts involving smallpox and rabies, inactivation was used to make vaccines against other pathogens, including toxin producing organisms. BCG became the first attenuated vaccine based on serial passage. Cell culture of viruses and genetic engineering led to a profusion of vaccines in the last 50 years, but now we are faced with biologically more difficult organisms. Nevertheless, real progress is being made against pathogens such as influenza, respiratory syncytial virus, dengue and SARS-2.

Epidemiological studies of the non-specific effects of vaccines: new studies since Optimmunize 2020

Frank Shann

Papers are identified here by their PubMed ID (PMID) number, google "PMID 12345678". Other speakers will discuss interactions (Aaby), parental priming (Benn), OPV (Welega), covid (Curtis) and non-communicable diseases (Faustman).
32645296 (Benn) is an outstanding review which lists the **key NSE epidemiological findings**: (1) Many live vaccines have beneficial NSE, (2) many non-live vaccines have harmful NSE, (3) the most recent vaccine has the strongest effect, (4) combinations of live and non-live vaccines have variable effects, (5) pre-existing immunity enhances the benefit of live vaccines, and (6) vaccines interact with other interventions such as vitamin A supplements.

Other NSE reviews. 34815120 (Arega) reviews veterinary vaccines, 34686866 (Joffe) reports a 2021 NIAID workshop, and 32185398 (Shann) suggests a live-vaccine-last schedule might save an extra million lives annually.
BCG NSE reviews: 33609459 (Aaby), 33857901 (Fisker), 34506734 (Lange), 34060492 (Singh).
BCG-RCTs. 33609457 (Prentice) Uganda, BCG-Denmark reduced 0-6wk infections. 34237262 (Glynn) Malawi, BCG-Glaxo revaccination no effect on 0-30yr mortality – but see commentary 34237263 (Netea). Schaltz-Buchholzer in Guinea-Bissau: 33893799 BCG trend to reduced hospital neonatal mortality, 31677386 BCG-Russia versus BCG-Denmark and BCG-Japan.
BCG-scar. 32301189 (Benn) and 32978212, 34226104, 35100521 (Schaltz-Buchholzer) reported improved survival with scar or TST reaction. 33474505 (Jensen) scar formation influenced by vaccination technique.
BCG-cohort. BCG improved immunity and reduced pertussis incidence (33711798, Broset) and reduced hospital admissions for infection (36096971, Nieminen). 32201619 (Jensen) BCG more beneficial in malaria season.
BCG-policy. Mathematical model (34344667, Thysen) reduced mortality if BCG always given, versus only if 10-12 children present.
Measles vaccine (MV) RCTs. 35747181 (Nielsen) Guinea-Bissau, MV at 4mo-and-9mo versus 9mo only did not reduce mortality unless maternal measles antibody in child or no OPV campaign. 35218356 (Berendsen) Guinea-Bissau, MV-revaccination at 18mo trend to fewer deaths-plus-admissions, attenuated when OPV campaigns. 33941513 (Byberg) Guinea-Bissau, MV for all (versus 6+ children present) reduced mortality only until MenAfriVac or OPV campaigns and increased Penta3.
MMR-cohort-studies. MMR revaccination reduced admissions for infection in Denmark individuals (29846533, Sorup) but not Denmark-Sweden populations (33518465, Sorup).
DTP-cohort-studies. Mortality reduced after OPV (33277047, Oland) and MV (32185375, Clipert-Jensen) but increased after DTP. Mortality not increased after DTP in Guinea-Bissau perhaps because of OPV campaigns (34217570, Sorensen) or Ghana-Tanzania but with severe survival bias (35618557, Quinn).
RTS,S non-live malaria vaccine. Approximately doubles mortality in girls, and unethical WHO Africa rollout of RTS,S (32102785, Doshi; 31980436, Aaby).
Non-live rabies vaccine RCTs. Increased mortality in female dogs (32178448, Arega; 33494967, Knobel) and no reduction in female pigs (33840563, Jensen); no effect on infection in veterinary students (34127294, Odita). These invalidate 28065475 (Gessner). See also Jensen response to 33568394 (Soentjens).
Other. 31949034 (Benn) suggests vitamin A supplements augment harm from DTP. 34806065 (Hviid) no harm from non-live papillomavirus vaccine in Danish cohort. 35610103 (Moller) suggests travel vaccines have NSE benefit – probable confounding.

What we learnt about interactions between health interventions

Peter Aaby and Christine Stabell Benn, Bandim Health Project, Bissau, Guinea-Bissau, and University of Southern Denmark

Identifying contradictions and resolving them by finding the interaction(s) which explained the contradiction has been the motor of development in the field of non-specific effects of vaccines.

We have found the following repeatable patterns: Measles vaccine and other live vaccines have beneficial NSEs as long as they are the most recent vaccination. The effect may be altered when new vaccine types are given. Thus, the sequence of vaccination turns out to be very important; a non-live vaccine like diphtheria-tetanus-pertussis vaccination (DTP) can reduce the beneficial effect of a live vaccine if given together with or after the live vaccine. It follows that a vaccine schedule that emphasizes "live-vaccine-last" would be optimal, so for example, if influenza vaccine is given after BCG given to reduce the severity of COVID-19 infection, this is likely to reduce the beneficial effect of BCG. The NSEs differ fundamentally for females and males. Revaccination with live vaccines have turned out to be far more important for child survival than usually anticipated. Maternal priming likewise seems to amplify the beneficial non-specific effects of the same vaccines in their offspring.

To secure that beneficial non-specific effects of some vaccines can be used in public health, we need systematically to identify and test these potential interactions which may affect the beneficial non-specific of some vaccines. A good way to identify and test potential interactions would be to monitor routine vaccinations and campaigns in demographic surveillance systems, and among children admitted to pediatric wards. For example, in this way we could identify that girls having received diphtheria-tetanus-pertussis vaccination after measles vaccination have a higher mortality or that if the mother of the child had no BCG scar her child had a higher risk of dying at the hospital.

Non-specific benefit of pneumococcal conjugate vaccines on reducing risk of respiratory syncytial virus-hospitalisations in infants: an Australian population-based linked data cohort study

Huong Le[1], Heather Gidding[5,6,7,8], Christopher C Blyth[1,2,3], Peter Richmond[1,2], Hannah C Moore[1,4]

[1] Wesfarmers Centre for Vaccines and Infectious Diseases, Telethon Kids Institute, University of Western Australia, Perth, Australia
[2] Perth Children's Hospital, Perth, Australia
[3] PathWest Laboratory Medicine, Perth, Australia
[4] School of Population Health, Curtin University, Perth, Australia
[5] The University of Sydney Northern Clinical School, St Leonards, NSW, Australia
[6] Women and Babies Research, Kolling Institute, Northern Sydney Local Health District, St Leonards NSW, Australia
[7] School of Population Health, UNSW Medicine, University of NSW, Sydney, NSW, Australia
[8] National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Sydney, NSW, Australia

Background: Pneumococcal conjugate vaccines (PCV) have been shown in randomised clinical trials to reduce the risk of respiratory syncytial virus (RSV). We aimed to assess the real-world effectiveness of PCV on RSV-hospitalisations among young Western Australian children using individual-level linked data.
Methods: We conducted a population-based cohort study of children born from 2000-2012 using probabilistic linkage of administrative health records including immunisation, hospitalisation, laboratory microbiology tests and perinatal records. Our outcome was the first RSV-confirmed hospitalisation in the first year of life and primary exposure was receipt of infant PCV doses. We performed Cox proportional hazard models with time varying exposure (vaccination) adjusted for multiple perinatal, infant and socio-demographic variables.
Results: Our cohort included 360,994 children. PCV coverage of at least 3 doses in Aboriginal children ranged from 40% in 2001 to 62% in 2004 when PCV was funded for Aboriginal children only. Since universal funding in 2005, PCV coverage has increased to approximately 90% for both Aboriginal and non-Aboriginal children. RSV-hospitalisation rates were highest in infants aged less than 6 months (22.5/1000) and were more than 2 times higher in Aboriginal infants than non-Aboriginal infants. Receipt of 3 or more PCV doses in the universal funded period was associated with 30% (95% CI: -6%-54%) reduction in RSV-hospitalisation in Aboriginal infants, and 21% (95% CI: 1%-37%) reduction in non-Aboriginal infants compared with unvaccinated infants. After further restricting the cohort to those with a prior history of hospitalisation or laboratory services to adjust for health seeking behaviour, VE point estimates increased (41% [95%CI: 5-63%] for Aboriginal infants; 28% [95% CI: 9-42%] for non-Aboriginal infants).
Implications: We showed a protective effect of PCV on RSV-hospitalisations in infants, highlighting the importance of epidemiological real-world studies to assess the non-specific beneficial effect of vaccines. Prior to the introduction of RSV vaccines, our study suggests that jurisdictions with universal childhood PCV vaccination programs may see a reduction in severe RSV infections in children, findings that may also have implications for countries who are yet to consider PCV programs.

Studies of the non-specific effects of campaigns with oral polio vaccine in Africa and Asia

Paul Welaga, Martin Kavao, Ahmed Hanifi, Peter Aaby and Sebastian Nielsen

Background: Most studies of the non-specific effects (NSEs) of vaccines have focused on BCG, measles vaccine (MV), and diphtheria-tetanus-pertussis (DTP) vaccine, as did the WHO in their review of the impact of NSEs on child survival under 5 years of age. However, it may have been oral polio vaccine (OPV) which have had the biggest effect on overall child survival. A randomised controlled trial (RCT) has documented that OPV-at-birth (OPV0) was associated with a 32% (0-55%) reduction in infant mortality before children received OPV during campaigns (C-OPV).

Methods: There has been conducted more than 2,500 national OPV campaigns since the 1990s. Presumably, because poliovirus infection rarely has affected child mortality in recent decades, there has been no attempt to evaluate the effect of C-OPVs on child survival. The INDEPTH-Optimunize network is in the process of evaluating the impact of the OPV campaigns within health and demographic surveillance systems (HDSS) where children have been followed in prospective population cohorts. With individual level survival information on children, it is possible to assess whether the mortality rates are different after vs before children received C-OPVs in Cox proportional hazards models. The primary analysis was of OPV administered alone, but also other health interventions were included, such as vitamin A supplementation (VAS) and MV campaigns.

Results: The first study conducted covered the Bandim Health Project HDSS, in urban Guinea-Bissau, between 2002-2014. C-OPV was associated with a 25% (95% confidence interval: 15-33%) reduction in the mortality rate for children from day 1 to 3 years of age. Interestingly, the beneficial effect increased by the number of C-OPVs the children had received, each campaign being associated with a 14% (8-19%) reduction in mortality. Other campaigns with VAS or MV did not have similar beneficial effect. In a similar analysis for Chakaria HDSS in southern Bangladesh, between 2004-2019, C-OPVs were associated with a 31% (10-%) reduction in mortality among children from day 1 to 3 years of age; furthermore, each campaign was associated with a 6% (-2-13%) reduction in mortality. Preliminary results from the Navrongo HDSS, in northern Ghana, and the Nairobi HDSS, Kenya, suggest that C-OPV may also have a beneficial effect on child survival.

Conclusion: These analyses indicate that the C-OPVs have contributed importantly to the marked declined in child mortality which has occurred since the 1990s when the C-OPVs started in low-income countries. The urgent question now is, what will happen with child health once poliovirus is eradicated and OPV is stopped?

Maternal priming amplifies the beneficial non-specific effects of live vaccines in the offspring

Christine Stabell Benn, Frederik Schaltz-Buchholzer, Peter Aaby

All: University of Southern Denmark

In a trial of early two-dose measles vaccination (MV), with the first dose being given before 9 months of age, we discovered that offspring vaccination in the presence of maternal antibody reduced mortality many-fold more than vaccination against measles provided in the absence of maternal measles antibody. We pursued this finding of maternal priming effects in other trials of MV and later also BCG vaccine.

In all studies of MV, we have found that children, who were measles vaccinated in the presence of maternal measles antibody, had lower all-cause mortality compared with children who were measles vaccinated in absence of measles antibody. In control groups not receiving measles vaccine, maternal measles antibody vs. no maternal measles antibody was not associated with lower mortality.

For BCG, we have likewise seen that previous maternal BCG vaccination and the presence of a maternal BCG scar is associated with stronger beneficial effects of BCG vaccine in the offspring. In addition, some data indicates that maternal BCG, identified by the presence of a maternal BCG scar, might have a beneficial effect for unvaccinated offspring.

Since maternal antibody levels are declining, it may be time to consider giving MV earlier and/or to provide MV to adolescent girls and/or women in the fertile age to boost antibody levels. Similarly, BCG to adolescent girls/women in the fertile age or to those without a BCG scar may be considered, to optimize the beneficial non-specific effects of BCG vaccine in their offspring.

Differential humoral and cellular immune response in pregnant and nonpregnant women upon vaccination against SARS-CoV-2 infection

Tayyip Emre Kehribar[1], Christopher Urbschat[1], Steven Schepanski[1,2], Felix Stahl[3], Luís Carlos Fonseca Brito[4], Kristin Thiele[1], Marylyn Martina Addo[4,5], Ina Annelies Stelzer[6], Anke Diemert[7,*] & Petra Clara Arck[1,*]

[1] Division of Experimental Feto-Maternal Medicine, Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2] Institute of Developmental Neurophysiology, Center for Molecular Neurobiology Hamburg (ZMNH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[3] Institute for Clinical Chemistry and Laboratory Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
[4] Institute for Infection Research and Vaccine Development, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
[5] Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany
[6] Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Palo Alto, CA,
USA
[7] Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[*] Equal supervision

Objective: The maternal immune adaptation to pregnancy ensures fetal development and survival. Concomitantly, this adaptation can interfere with the response to vaccinations. In our present study, we addressed this hypothesis by comparing vaccine-elicited immune responses between pregnant and non-pregnant women upon injection with the mRNA-based COVID-19 vaccine Comirnaty® following the same vaccination regimen and dosages. Blood was taken from all study participants 2-6 weeks after the second vaccination.
Method: Titers of SARS-CoV-2 immunoglobulin (Ig)G antibodies and IgG subclasses were determined using the DiaSorin® LIAISON immunoassay and the Milliplex® SARS-CoV-2 Antigen Panel respectively. Immune phenotyping of isolated peripheral blood mononuclear cells was performed by flow cytometry and Cytometry by time of flight (CyTOF). Cellular-mediated immunity was assessed by stimulating T cells with the SARS-CoV-2 spike protein (Prot_S; Miltenyi Biotec), IFN-γ release was subsequently measured using a chemiluminescence analyzer.
Results: Anti-SARS-CoV-2 IgG antibody levels were significantly lower in pregnant vaccinees compared to non-pregnant vaccinees. Moreover, a distinct reduction in IgG1 was observable. Flow cytometry analysis revealed a reduction of overall T and B cell frequencies in PBMCs of pregnant vaccinees. Additionally, we observed a decreased IFN-γ response upon stimulation of T cells with the spike protein in pregnant vaccinees, compared to non-pregnant vaccinees.
Summary: We here identified a blunted response to vaccination in pregnant women compared to nonpregnant women. Our findings highlight that vaccination schemes and dosages used to immunize pregnant women must be carefully revisited. The recommendations for vaccinations during pregnancy should encompass the unique immunological setting mounted during pregnancy.

BCG vaccination to Reduce the impAct of COVID-19 in hEalthcare workers (the BRACE Trial)

Nigel Curtis on behalf of: Laure F. Pittet, Nicole L. Messina, Francesca Orsini, Cecilia Moore, Veronica Abruzzo, Simone Barry, Rhian Bonnici, Marc Bonten, John Campbell, Julio Croda, Margareth Dalcolmo, Kaya Gardiner, Grace Gell, Susie Germano, Adriano Gomes-Silva, Casey Goodall, Amanda Gwee, Tenaya Jamieson, Bruno Jardim, Tobias R Kollman, Marcus V.G. Lacerda, Katherine J. Lee, Michaela Lucas, David J. Lynn, Laurens Manning, Helen S. Marshall, Ellie McDonald, Craig F. Munns, Suellen Nicholson, Abby O'Connell, Roberto D. de Oliveira, Susan Perlen, Kirsten P. Perrett, Cristina Prat-Aymerich, Peter C. Richmond, Jesus Rodriguez-Baño, Glauce dos Santos, Patricia V. da Silva, Jia Wei Teo, Paola Villanueva, Adilia Warris, Nicholas J. Wood, Andrew Davidson & the BRACE Trial Consortium Group.

In the BRACE randomised controlled trial (ClinicalTrials.gov NCT04327206), nearly 7000 healthcare workers were recruited in 36 sites in Australia, the Netherlands, Spain, UK and Brazil between March 2020 and April 2021. Participants were randomised in a 1:1 ratio to receive BCG-Denmark or a placebo saline vaccine, and followed up for 12 months. The primary outcomes of the trial were the incidence of Symptomatic COVID-19 and the incidence of Severe COVID-19 during the 6 months after randomisation. This talk will present and discuss the BRACE trial (and tribulations).

The bacterial mucosal immunotherapy MV130 protects against viral respiratory infections and improves COVID-19 vaccines immunogenicity

Carlos del Fresno, Hospital la Paz Institute for Health Research (IdiPAZ), Madrid, Spain

Paola Brandi, Spanish National Center for Cardiovascular Research (CNIC), Madrid, Spain
Laura Conejero, Inmunotek S.L., Alcalá de Henares, Spain
Juan García-Arriaza, Centro Nacional de Biotecnología (CNB), Madrid, Spain
Mariano Esteban, Centro Nacional de Biotecnología (CNB), Madrid, Spain
David Sancho, Spanish National Center for Cardiovascular Research (CNIC), Madrid, Spain
Miguel Casanovas, Inmunotek S.L., Alcalá de Henares, Spain
Jose Luis Subiza, Inmunotek S.L., Alcalá de Henares, Spain

MV130 is an inactivated polybacterial mucosal vaccine that confers protection gainst recurrent respiratory infections, including those of viral etiology as shown for wheezing in children in a previous clinical trial. This bacteria-virus heterologous protection is reminiscent of the trained immunity process, where a previous exposition of innate immune cells to certain stimuli generates a boosted immune response to a second challenge.

In here, we have experimentally addressed whether MV130 induces trained immunity. MV130-pretreated human monocytes showed enhanced cytokine responses, which were sensitive to epigenetic inhibitors and accompanied by transcriptomic and metabolic traits of trained immunity. In mice, mucosal administration of MV130 generated proinflammatory signatures in myeloid bone marrow progenitors, which gave rise to trained macrophages. All these data indicated that MV130 induces trained immunity.

We next addressed the relevance of this process against viral infections. We found that intranasal prophylaxis with MV130 modulates the lung immune landscape and provides long-term heterologous protection against viral respiratory infections such as Vaccinia and Influenza A, but also against SARS-CoV-2 in susceptible K18-hACE2 mice.

Considering the current need to achieve the greatest protection against COVID-19, we analyzed the impact of MV130 prophylaxis in the response to vaccines designed against de SARS-CoV-2 spike (S) protein. Independently of the two vaccine candidates tested and vaccination route (subcutaneous or intranasal), prophylaxis with MV130 boosted S-specific responses, including $CD8^+$-T cell activation and the production of S-specific mucosal IgA antibodies.

Therefore, the bacterial mucosal immunotherapy MV130 induces trained immunity, conferring protection against viral respiratory infections such as Influenza and SARS-CoV-2 infection, and improves COVID-19 vaccines immunogenicity. These data have prompted us to propose a clinical trial to define the clinical application of MV130 as a prophylactic intervention

The BNT162b2 mRNA vaccine against SARS-CoV-2 affects both adaptive and innate immune responses

F. Konstantin Föhse[1,*], Büsranur Geckin[1,*], Martijn Zoodsma[4,*], Gizem Kilic[1], Zhaoli Liu[4], Rutger J. Röring[1], Gijs J. Overheul[2], Josephine van de Maat[1], Ozlem Bulut[1], Jacobien Hoogerwerf[1], Jaap ten Oever[1], Elles Simonetti[3], Frank L. van de Veerdonk[1], Leo A.B. Joosten[1], Bart L. Haagmans[5], Reinout van Crevel[1], Ronald P. van Rij[2], Corine GeurtsvanKessel[5], Marien I. de Jonge[3], Yang Li[4], Jorge Domínguez-Andrés[1], Mihai G. Netea[1]

[1]Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands.
[2]Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, The Netherlands
[3]Section Pediatric Infectious Diseases, Laboratory of Medical Immunology, and Radboud Center for Infectious Diseases, Radboudumc, Nijmegen, The Netherlands
[4]Department of Computational Biology for Individualised Infection Medicine, Centre for Individualised Infection Medicine (CiiM) & TWINCORE, joint ventures between the Helmholtz-Centre for Infection Research (HZI) and the Hannover Medical School (MHH), Hannover, Germany
[5]Department of Viroscience, Erasmus MC, Rotterdam, The Netherlands
[*] These authors contributed equally.

The mRNA-based BNT162b2 vaccine, Comirnaty, from Pfizer/BioNTech is the first registered and FDA-approved COVID-19 vaccine and has been shown to be up to 95% effective in preventing SARS-CoV-2 infections. Little is known about the potential broad effects of the new mRNA vaccines, especially whether they have combined effects on innate and adaptive immune responses.

Here, we report that BNT162b2 vaccination induced effective humoral responses against SARS-CoV-2 and differences in cellular response against various stimuli in healthy individuals. We collected samples from the participants at baseline, three weeks after first dose (t1), two weeks after second dose (t2), six months after first dose (t3) and four weeks after booster shot (t4; a year after the core vaccination). We analysed plasma and serum for serology and neutralisation, respectively. We also performed RNA-seq and ELISA following *ex-vivo* stimulation of PBMCs with different stimuli to get a multi-dimensional picture for the effects of BNT162b2.
Fluorescent-bead-based-multiplex-immunoassay revealed that IgG concentrations elevated significantly following vaccination and booster shot in line with literature. Transcriptional analysis showed that the number of differentially expressed genes decrease through time points upon stimulation with viral stimuli: SARS-CoV-2, influenza and R848. In addition, cytokine production (IL-6, IL-1β and IL-1Ra) against SARS-CoV-2 and bacterial stimuli was measured. The results showed an oscillating pattern with a significant increase of cytokine production at t3 compared to baseline. For better understanding of the anti-viral responses, we also measured IFN-α and IFN-γ. While IFN-α presented a varying pattern, its level gradually decreased with time in response to SARS-CoV-2. Whereas IFN-γ secretion reflected the similar oscillation pattern as in other pro-inflammatory cytokines. The most distinctive observation was made regarding influenza response as the decrease at t1 and t3 were statistically significant when compared to baseline.

In conclusion, our data show that the BNT162b2 vaccine has an effect on both the adaptive and innate branch of immunity. Intriguingly, these observations can be linked to trained immunity phenomena as the BNT162b2 vaccine induces differential innate immune responses. This needs to be taken into account. A lesser innate immune response in combination with strong adaptive immune responses could contribute to a more balanced inflammatory reaction during COVID-19.

Keywords: Adjuvants and vaccines, Innate host defence, Innate immunity, Viral infections

Systems biological analysis of immunity to COVID-19 infection and vaccination.

Bali Pulendran, Violetta L. Horton professor of pathology, microbiology, and immunology at Stanford University.

Although the development of effective vaccines has saved countless lives from infectious diseases, the basic workings of the human immune system are complex and have required the development of animal models, such as inbred mice, to define mechanisms of immunity. More recently, systems biological approaches have been developed to directly explore the human immune system with unprecedented precision. I will discuss how these approaches are advancing our mechanistic understanding of the human system and its response to COVID-19 infections and vaccines.

MTBVAC entry in TB efficacy trials and exploring NSEs

Carlos Martin, on behalf of all collaborators and Team that support MTBVAC project

MTBVAC is a live attenuated TB vaccine candidate in clinical development constructed at the University of Zaragoza. MTBVAC was constructed from a clinical isolate of *M. tuberculosis* by the stable deletions in two major virulence genes, *phoP* and *fadD26* without antibiotic markers. Preclinical studies have shown the safety and protection of MTBVAC compared to present vaccine BCG (derived from *M. bovis*), in TB-relevant animal models conducted by independent collaborative-laboratories from mouse, guinea pigs to non-human primates. Biofabri is the partner responsible for Industrial and Clinical Development of MTBVAC for newborns and for adolescent/adults. From 2008-2012 Biofabri performed GMP development of freeze-dried MTBVAC and from 2012 until present: industrial development and scale-up production of MTBVAC. First-in-human Phase 1a of MTBVAC was performed in healthy adults in Lausanne, Switzerland (Spertini *et al* The Lancet Respir Med 2015). Successful Phase 1a completion leads to first-in-human Phase 1b evaluation of MTBVAC in newborns in Worcester, South Africa (SATVI) (Tameris *et al* The Lancet Respir Med 2019). Two Phase 2 dose-defining studies in healthy newborns (NCT03536117) and in adults (NCT02933281), which commenced in 2019 and were carried out by SATVI, are at their final completion stages. Safety and immunogenicity results of the two Phase 2 dose-defining trials, allowed the entry of MTBVAC into multi-center Phase 3 efficacy evaluation compared to BCG in newborns in South Africa, Madagascar and Senegal (NCT04975178). We propose to study MTBVAC Non Specific Effect assessment during the Phase 3 trial.

At the same time that the Clinical Development of MTBVAC is advancing we are exploring Non-Specific Effect of MTBVAC by our team of the University of Zaragoza.

We study the therapeutic effect of MTBVAC in the treatment of bladder cancer (Alvarez-Aguedas *et al* Trans Med 2018), and we found that intravesical treatment with MTBVAC increases the survival of tumor-bearing mice and in addition we found that MTBVAC can reject established bladder tumours in a preclinical orthotopic model which is unresponsive to BCG (Moreo *et al* J ImmunoTheraphy of Cancer 2022).

In collaboration with the team of Prof Netea we found that MTBVAC induce trained immunity by epigenetic reprograming human PBMCs (Tarancon *et al* Plos Pathogens 2000) in addition MTBVAC conferred protection against experimental lethal pneumonia in mice. We are interested in the study of the responsiveness of both live attenuated vaccines BCG and MTBVAC asthma in mice. In addition, we established a chronic mouse model induced by the egg protein OVA and by another relevant allergen such as House Dust Mite (Tarancon *et al* Ebiomedicine 2021). Results shown the NSEs of BCG and MTBVAC that, by intranasal vaccination, reverts established allergic airway responsiveness.

In addition, also we study the impact of BCG and MTBVAC vaccination on the immunization with DTaP vaccine: diphtheria, tetanus, and acellular pertussis. We found that BCG and MTBVAC triggered a higher Th1 Immune responses against DTaP and that humoral responses are enhanced by previous immunization with BCG or MTBVAC (Broset *et al* Ebiomedicine 2021). Human epidemiological data showed that pertussis incidence was10-fold lower in countries that use DTaP and BCG compared to countries that use only DTaP.

Does vaccination in pregnancy alter trained immune responses in the offspring?

Natalie Stevens[1,2], Alice Han[1], Anastasia Jasinski[1,2], Miriam Lynn[1,2], Marjolein van Wolfswinkel[1,3], Damon Tumes[4], David J. Lynn[1,2.]

[1]South Australian Health and Medical Research Institute, Adelaide, SA, Australia.
[2]College of Medicine and Public Health, Flinders University, Bedford Park, SA, Australia.
[3]University of Applied Sciences Leiden, 2333 CK Leiden, the Netherlands.
[4]Allergy And Cancer Immunology Laboratory, Centre for Cancer Biology, University of South Australia, Adelaide, SA, Australia.

Mounting data demonstrate that direct immunisation with certain vaccines can confer beneficial non-specific effects (NSE), leading to protection against subsequent unrelated infections. This phenomenon is explained, in part, by the induction of 'trained immunity' – an epigenetic and metabolic reprogramming of innate immune cells priming them for enhanced responses. Pregnant women are recommended to be immunized with the diphtheria-tetanus-acellular-pertussis (DTaP), influenza, and COVID-19 vaccines, however, whether vaccination during pregnancy can also induce trained immunity in the infant, is currently unknown.

To assess this in a preclinical model, pregnant mice (dams) were immunised s.c. with either the DTaP (Adacel®), FluQuadri™ inactivated influenza, or BNT162b2 COVID-19 mRNA vaccines. Another group of pregnant dams were administered saline as a control group. Offspring were humanely killed at 14 days of life. To assess the induction of trained immunity, splenocytes were stimulated with various immune agonists and cytokine production (TNFα and IL-6) was measured in several innate immune cell populations by flow cytometry analysis, as enhanced cytokine responses to secondary challenges/stimuli is a hallmark of trained immunity.

Immunisation in pregnancy did not alter the viability, average weight or sex distributions of the litters. Consistent with the induction of trained immunity in the offspring, mice born to dams immunised with either the influenza (mat-flu mice) or COVID-19 mRNA vaccine (mat-BNT mice) during pregnancy had significantly increased TNFα production by DCs, following stimulation with R848 and polyI:C, an agonist cocktail which mimics innate immune sensing of a viral pathogen. mat-BNT mice also had significantly enhanced production of TNFα and IL-6 by monocytes. There was no evidence for the induction of trained immunity in mice born to dams immunised in pregnancy with the DTaP vaccine.

Epidemiological data suggest that neonates born to mothers with a BCG scar have increased early-life survival, leading to speculation that maternal BCG immunisation may transfer beneficial NSE to the infant. We investigated this preclinically in mice born to dams immunised with BCG (Denmark). Maternal BCG immunisation was not associated with the induction of trained immune responses in the offspring, nor did it enhance trained immune responses or emergency granulopoiesis induced in these offspring following direct BCG immunisation. Future studies will characterise the mechanisms through which immunisation in pregnancy with influenza or COVID-19 vaccines induces trained immunity in the offspring, assess the potential consequences in disease models, and will investigate the induction of these responses in a human infant cohort.

Trained immunity: from basic mechanisms to vaccination

Mihai G. Netea, Department of Medicine, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands

The inability of innate immunity to build an immunological memory, considered one of the main characteristics differentiating it from adaptive immunity, has been recently challenged by studies in plants, invertebrates, and mammals. Long-term reprogramming of innate immunity, that induces adaptive traits and has been termed *trained immunity* characterizes prototypical innate immune cells such as natural killer cells and monocytes, and provides protection against reinfection in a T/B-cell-independent manner. In contrast, *trained immunity* has been shown to be able to induce protection against reinfection in a lymphocyte-independent manner. Non-specific protective effects dependent on *trained immunity* have also been shown to be induced after BCG vaccination in humans. Complex immunological and metabolic circuits link cell stimulation to long-term epigenetic reprogramming of the function of myeloid cells and their bone marrow progenitors. Several randomized clinical trials have also shown immunological and clinical effects of trained immunity-inducing vaccines on heterologous infections, including COVID19.

Exploring the immunological pathways induced by an unadjuvanted influenza vaccine and an adjuvanted herpes zoster vaccine in young and older adults

Gizem Kilic[1], Leonie Helder[1], Esther Taks[1], Elisabeth Dulfer[1], Yutaka Negishi[2], Mumin Ozturk[2], Jorge Dominguez-Andres[1], Jaap ten Oever[1], Musa Mhlanga[2], Mihai G. Netea[1]

[1]Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands

[2]Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands.

Aging causes dramatic changes in the immune system, making the elderly more susceptible to diseases. Immunoaging also decreases the efficacy of the vaccines, e.g., influenza. One of the exceptions, a recombinant adjuvanted shingles vaccine called Shingrix, has proven more than 90% efficacy in clinical trials in older adults, seeming to overcome the immunosenescence in the elderly. However, the mechanism and the immunological pathways induced by the Shingrix vaccine have not been known, thus the reason for the difference in vaccine efficacies.

To investigate this, we designed an open-labeled, partially randomized clinical study(n=140), in which young (18-35 years old) and elderly participants (≥60 years old) receive either an unadjuvanted influenza vaccine (Fluarix), an AS01-adjuvanted shingles vaccine (Shingrix) or a placebo to compare these two vaccines. We collect blood at the baseline, 1, 7, 60, and 120-days post-vaccination, and follow the participants up to 6 months after their last vaccination. The sample collection is still ongoing and is planned to be finalized in May-2023. Then, cytokine production following stimulation with heterologous pathogens will be measured, and flow cytometry, metabolomics, proteomics, transcriptomics, and epigenetic analyses will be performed.

Here, we hypothesized that the adjuvant AS01 improves the efficacy of the Shingrix vaccine against the specific antigen by engaging the innate and adaptive immune system and inducing trained immunity. Our preliminary results show that the Shingrix vaccine is safe and tolerable in both age groups, with more adverse effects in younger adults.

Whole blood measurements after blood collection show that Shingrix vaccination leads to a transient increase in monocytes and neutrophils in both young and older adults, but the monocyte numbers go back to the levels before vaccination within 7 days. On the other hand, neutrophil numbers stay higher in older adults for more than 7 days. Furthermore, lymphocyte numbers decrease 1-day post-vaccination and increase on day 7, being higher than the baseline levels. Influenza vaccination has less drastic effects on cell numbers in the blood. The experiments and analyses after sample collection will help us understand the differences in the immunological pathways induced by Shingrix and Fluarix and the reason for Shingrix's high efficacy.

Resveratrol as a potential amplifier of BCG-induced trained immunity

Ozlem Bulut[1], Ilayda Baydemir[1], Jorge Dominguez Andres[1], Mihai Netea[1]

[1] Department of Internal Medicine, Radboud University Medical Center, Nijmegen, Netherlands

Resveratrol is a phenolic anti-oxidant compound found in grapes and berries. Besides its protective role in plants during injury and infection, various cardioprotective, neuroprotective, and anti-aging effects were reported in model organisms with mixed results in humans. The primary identified target of resveratrol is the deacetylase Sirtuin 1, which regulates many immunological processes.
Certain pathogens, vaccines, or endogenous molecules reprogram innate immune cells epigenetically and metabolically to enhance responsiveness against a secondary insult. This phenomenon is called trained immunity. Genetic polymorphisms in the SIRT1 gene that codes for Sirtuin 1 were associated with altered trained immunity response in BCG-vaccinated humans. This study investigates resveratrol's effect on BCG-induced trained immunity.
Using an in-vitro model of trained immunity with monocytes obtained from healthy donors, we demonstrated that resveratrol boosts BCG-induced training up to 5-fold in terms of IL-6 and TNFα production after a secondary challenge with LPS. Although resveratrol did not improve and even limited glycolysis, oxidative phosphorylation, and reactive oxygen species production that are critical for trained immunity, it enhanced the permissive epigenetic mark H3K27Ac on IL-6 and TNFα promoters. Notably, in contrast to BCG training, resveratrol potently inhibited cytokine production after training with β-glucan, C. albicans, and oxidized low-density lipoprotein.
Further investigation is underway into how BCG training is potentiated by resveratrol while other modes of training are inhibited. Nonetheless, our results suggest that resveratrol might be helpful as an amplifier for the BCG vaccine. Future work will focus on detailing the mechanisms of the double-edged regulation of trained immunity by resveratrol, involvement of Sirtuin1 in these processes, and mouse models of BCG vaccination to explore the therapeutic possibilities.

Off-target effects of multi-dose BCG on diabetes

Denise L Faustman, professor of medicine at Harvard University and director of the Immunobiology Laboratory at Massachusetts General Hospital

Over the last 15 years we have studied the off-target effects of BCG on immune cells and metabolism in type 1 diabetes. With now over 536 human subjects enrolled in over 8 ongoing or finished clinical trials we have learned some important clinical lessons on what works for adult BCG dosing. The first lesson has been that BCG dosing in adults takes years from the vaccinations to the meaningful clinical effects – typically 2-3 years. Similar clinical data exists for dosing BCG in adults with multiple sclerosis. The second lesson has been multi-dosing of BCG works better than single dosing. Finally, we first clinically tried different strains of BCG and TICE neither works in mice nor humans but Pasteur and Tokyo BCG both work in mice and human clinical trials. Like tuberculosis, BCG can cause metabolic effects and immune effects. Metabolic effects of BCG is to convert the lymphoid system to aerobic glycolysis, a mechanism for the diabetic immune system to use sugar for aerobic glycolysis. This we discovered was an underlying defect in type 1 diabetes. This occurs by methylation changes in major glucose regulating pathways. Secondarily over 3 years, the Treg signature genes for immune suppression are also demethylated for enhanced protein expression and restoring of normal TCR signaling. We like to think BCG or its close relative tuberculosis, evolved with humans and even back to Neanderthals and this re-establishment of this precious host-microbe synergy is beneficial to human health. Our data supports with properly designed clinical trials, the health benefits of BCG at also making type 1 diabetics broadly resistant to infectious diseases.

BCG induction of LL-37 as a novel mechanism of neuroprotection against Alzheimer's Disease as well as Covid

Annelise E. Barron, Associate Professor of Bioengineering, Stanford University, School of Medicine
Co-authors*:* Jennifer S. Lin, John A. Fortkort, Josefine Eilsø Nielsen, Shirin Shamloo, Erwin Defensor

The increasing societal prevalence of Alzheimer's Disease (AD)—which should perhaps be called **Age-Related Immunodementia (ARID)**—is a growing health and economic crisis, especially with the Covid pandemic having contributed further to neurocognitive loss in many people. After 115 years of study, root causes for late-onset, sporadic AD—which is > 95% of AD—remain unclear. Since 2005, 425+ clinical trials of potential new drugs against AD failed. The approved AD drugs offer marginal if any benefit.

I discuss how NSEs of live vaccines, especially BCG, may prevent and treat AD **via the stable induction of human cathelicidin (LL-37) expression**. I will briefly explain my hypothesis for the etiology of sporadic / late-onset AD based on the growing knowledge that cerebral infection via pathogen invasion of lingual and olfactory neurons may be a key factor in many cases of dementia, and further, that an imbalance of expression between two innate immune peptides—Ab and LL-37—may well modulate the formation, stability, and clearance of AD-associated fibrils and plaques, as well as chronic polymicrobial infections.

The **human cathelicidin LL-37,** unique in our proteome, is an antiviral, antibacterial, and antifungal host defense peptide deployed by microglia, macrophages, neutrophils, epithelia, and endothelia, as well as T and NK cells that kill infected host cells. LL-37 is the factotum host defense peptide, necessary both for autophagy and for the maintenance of barrier integrity for the BBB and gut epithelia. LL-37's Vitamin D3-, RXR-agonist-, and butyrate-dependent expression is naturally stimulated by extracellular nucleic acids, as well as by infection, wounding, burning, exercise, and certain live vaccines (*e.g.*, BCG & OPV vaccines). Certain tenacious pathogens, e.g., *Porphyromonas gingivalis* and *Candida albicans*, release enzymatic virulence factors that degrade TNF-a and LL-37 and impair the innate immune response.

Degradation of LL-37 in particular may dysregulates the brain's defense, leading to neuroinflammation and neurodegeneration. In LL-37's absence, the essential innate immune process of macroautophagy is crippled. Alzheimer's-associated Ab is also a host defense peptide; brain infections by *Herpesviridae* or *P. gingivalis* stimulate Ab production, causing Ab accumulation in plaques co-located with pathogens.

In 2017, I and collaborators showed that LL-37 and Ab are both expressed in human brain and also bind to each other sequence-specifically, forming a non-toxic and non-inflammatory complex. LL-37/Ab binding prevents amyloid fibril formation and blocks Ab from adopting b-type secondary structure. Thus, LL-37's degradation and absence would allow Ab to accumulate.

Further, our *in vivo* studies indicate that cathelicidin induction in 5XFAD mice slows AD progression and improves 5XFAD cognition to match wildtype. We are working to tie this finding to infection-associated dementia or ARID. Degradation of LL-37 by pathogen-released virulence factors may be one cause of neurodegeneration leading to dementia, which can be prevented by early-life cathelicidin upregulation by the BCG vaccine, ideally followed by repeated BCG vaccination every 12 years or so throughout life. We show that the Tice BCG vaccine does upregulate the cathelicidin gene in serum, in wildtype mice.

Sex and gender differences in COVID-19 and influenza vaccine outcomes

Sabra L. Klein, PhD, Professor of Molecular Microbiology and Immunology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland USA

The COVID-19 pandemic has increased awareness about sex-specific differences in immunity and outcomes following respiratory virus infections and vaccination. Strong evidence of a female bias in COVID-19 and influenza vaccine-induced immunity and adverse events will be presented based on clinical data and preclinical animal models. Females possess immunological features that contribute to greater protection following vaccination. Both sex chromosome complement and related X-linked genes (e.g., *TLR7*) as well as sex steroids, including estrogens and androgens, play important roles in mediating the development of sex differences in immunity to vaccination. Aging as well as in utero exposure to viruses can impact the expression of sex differences in vaccine-induced immunity and protection, which will be presented

Sex differences in the immunological impact of influenza vaccination in younger and older Australian adults

Kirsty Wilson[1], Jennifer Boer[1], Iain Robertson[2], Kanta Subbarao[3], Kirsten Richardson[2,4], Ying Yi Lai[4], Alice Harper[2,4], Magdalena Plebanski[1,4], Katie Flanagan[1,2,4]

[1] Cancer, Ageing and Vaccines Laboratory, RMIT University, Melbourne, Victoria, Australia
[2] Tasmanian Vaccine Trial Centre, Clifford Craig Foundation, Launceston, Tasmania, Australia
[3] WHO Collaborating Centre for Reference and Research on Influenza, The Peter Doherty Institute for Infection and Immunity, University of Melbourne, Melbourne, Victoria, Australia
[4] School of Health Sciences, University of Tasmania, Launceston, Tasmania, Australia

Background

Vaccines have non-targeted immunological effects whereby they can modulate the immune system and impact immunity and susceptibility to non-targeted infections, cancer and allergy. These effects have mostly been studied in children who are the major target population for vaccination globally. However, aging adults also receive several vaccines to combat their increased disease susceptibility due to declining immunity with age. Cytomegalovirus (CMV) infection has been implicated in enhancing immunological aging and disease susceptibility. It is therefore important to consider the impact of non-targeted immunological effects of vaccination in older adults.

Methods

The Vaccine Immunomodulation Throughout the Aging Lifespan (VITAL) Trial is a prospective randomised trial investigating the immunomodulatory effects of diphtheria-tetanus-acellular pertussis and influenza vaccination in a cohort of young (20-50 years) and older (≥65 years) Australians. The dTap and influenza vaccines are either administered alone or given at the same time. Standard quadrivalent influenza vaccine (QIV) is administered to the younger cohort whereas the older cohort receive QIV or one of the augmented influenza vaccines – high-dose Fluzone or adjuvanted Fluad. Immunological analyses include vaccine antibodies, innate and adaptive cell subset analysis by flow cytometry, multiplex cytokine and chemokine analysis, bulk PBMC and single cell RNA sequencing, epigenetics and microbiome analysis. CMV serostatus is also determined.

Results

Recruitment is ongoing but preliminary analyses demonstrate sex and age differences in influenza antibody responses, cytokine and chemokine profiles, transcriptome profile and the impact of CMV infection.

Conclusion

Healthy aging is increasingly important since the global population of people over 60 years is anticipated to double by 2050. Immunity declines with age, a process called immunosenescence, and many older people develop low-grade chronic inflammation, so-called inflammaging. Vaccination offers an opportunity to protect against key infections in older people, but non-targeted effects of vaccination could also be harnessed to improve immunological health and restore homeostasis in aging individuals. This study provides evidence for sex-differential non-targeted immunological effects of immunisation with two key vaccines recommended for older adults. Understanding the broader immunological effects of vaccines administered to older people is key to developing strategies to use vaccines to enhance their immunity and slow immunological decline.

Sex-Based Differences in Immune Responses to Vaccination

Inna G. Ovsyannikova, Richard B. Kennedy, Gregory A. Poland

Mayo Clinic Vaccine Research Group, Mayo Clinic, Rochester, MN, USA

Data have shown sex-based differences in immune responses to many vaccines, leading to variations in protection across populations. The purpose of our study was to investigate whether biological sex contributes to inter-individual heterogeneity in immunity to MMR, seasonal influenza, and smallpox vaccines.

For the measles vaccine (n=2,872; 11-41 yo, 27% females), no differences were found for either neutralizing antibody (Ab, p=0.9) or IFNγ-Elispot (p=0.6) responses in males versus females.

For the mumps vaccine (n=346; 12-18 yo, 47% females), females demonstrated higher mumps Ab titers than males (median 876 vs 677 IU/mL, p=0.003), indicating sex-linked genetic differences in humoral immune response. We found no difference for LPA cellular responses (p=0.2) in males versus females.

For the rubella vaccine (n=1,145; 11-22 yo, 45% females), no sex-based differences were observed for rubella Ab (p=0.5). We found significant associations between rubella-specific IL-6 secretion and sex, with females demonstrating higher IL-6 secretion than males (median 3,616 vs 3,590 pg/mL, p=0.03).

For the influenza A/H1N1 vaccine (n=159; 50-74 yo, 61% females), the HAI titers show no associations with sex; however, memory B-cell-Elispot responses were higher in females (p=0.02) at Day28 post-vaccination. Females had higher TREC levels (p=0.0003) and an increased CD4+/CD8+ ratio (p=0.04). We found a sex-specific decrease in the % of CD3+T-cells (p=0.002) and naïve CD8+T-cells (p=0.03), and 20% and 27% increases in Treg (p=0.003) and NK (p=0.005) cells, respectively, in PBMCs from female subjects at baseline and Day28 post-vaccination.

For the Dryvax smallpox vaccine (n=1,071; 18-40 yo, 26% females), females had higher median ID_{50} vaccinia-specific Ab than males (159 [93, 256] vs 124 [75, 186]; p<0.0001). Men had higher IFNγ-Elispot responses (median 55 SFUs [27, 95]) than females (median 41 SFUs [17, 70], p<0.001) and higher secretion levels of the proinflammatory IL-1β (p<0.001), while females had higher vaccinia-specific IL-2 and IL-10 (p<0.001 and p=0.02, respectively).

By demonstrating a significant relationship between sex and immune response outcomes, our data suggest that vaccine-induced immune responses are influenced by the vaccinees'sex. Such knowledge may be used to design better vaccines that are optimally effective across gender and allow for a personalized approach to the practice of vaccinology.

Prevalence of Anti-SARS-CoV-2 antibodies among Health Care Workers (HCW) in hospitals from the islands of Santiago and São Vicente, Cabo Verde

Isabel Inês Araújo[1,2]; Kleidi Santos[1]; Tamar Monteiro[1]; Mérita Fidalgo[3]; Jacqueline Monteiro[1]; Ofélia Monteiro[4]; Janaína Vicente[5]; José Luis Spencer[3]; Isaquel Silva[6]; Elsi Ca[6]; Lidia Nhamussua[7]; Sebastian Nielsen[6,8]; Paulo Ferrinho[2]; Frederik Schaltz-Buchholzer[6,8,9]; Maria da Luz Lima[10]; António Pedro Delgado[1]; Pedro Aide[7]; Christine Benn[6,8,9]; Inês Fronteira[2]

[1]Faculdade de Ciências e Tecnologia, Universidade de Cabo Verde, Cabo Verde
[2]Global Health and Tropical Medicine, Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa, Portugal
[3]Hospital Central Dr. Baptista de Sousa, Ministério da Saúde de Cabo Verde, Cabo Verde
[4]Hospital Central Dr. Agostinho Neto, Ministério da Saúde de Cabo Verde, Cabo Verde
[5]Hospital Regional Santa Rita Vieira, Ministério da Saúde de Cabo Verde, Cabo Verde
[6]Bandim Health Project, Guinea-Bissau
[7]Centro de Investigação em Saúde de Manhiça
[8]Danish institute for Advanced Study, University of Southern Denmark
[9]OPEN, Department of Clinical Research, University of Southern Denmark, Denmark
[10]Instituto Nacional de Saúde Pública, Ministério da Saúde de Cabo Verde, Cabo Verde

Background: Cabo Verde is a small island country in West Africa, composed of 10 Islands, 9 of which are inhabited. The first COVID-19 case was reported on March 19, 2020. By October 13, 2020, all the inhabited islands had been affected by the pandemic. One year after the first confirmed case, the vaccination campaign started. HCW were the first to be vaccinated. At this time the country had 16,101 cumulative cases and 156 deaths (https://covid19.cv/boletim-semanal/). In the present study, we aimed to describe the presence and duration of anti-SARS-CoV-2 antibody among HCW, according to infection and vaccination status.
Methods: Within a case-control study to determine factors associated with transmission and dynamics of SARS-CoV-2 infection among HCW in hospitals on the islands of Santiago and São Vicente in Cape Verde, we identified 465 HCW, of which 46.7% (n=217) reported infection by SARS-CoV-2, the others were controls. The participants were enrolled between August 24th and October 8th, 2021. We tested them for IgG and IgM anti-SARS-CoV-2antibody (Ab) using the OnSite™ COVID-19 IgG/IgM Rapid Test.
Results: Of the 465 HCW, 388 (89%) were tested for Ab. The vast majority had been vaccinated against COVID-19 (n=362; 93%). Most had received the Pfizer BioNTech (BNT162b2) vaccine (n=237; 65%) while 117 (32%) had received the Oxford/AstraZeneca (ChAdOx1-S [recombinant] vaccine) vaccine. SARS-CoV-2 infection was reported after either the 1st or 2nd dose of vaccine in 15 (4%) HCW. Of tested HCW, 304/388 (78%) showed positivity for IgG, 60 (15%) for IgG and IgM, and one (0.3%) showed positivity for IgM only. Among vaccinated participants there was a highly significantly difference in the proportion with IgG and IgG+IgM between previously infected and previously uninfected; in previously infected, it was 69% and 28%, respectively, whereas in uninfected it was 89% and 6% ($p<0.001$). Among 9 presumably uninfected and uninfected HCW, 5 had IgG Ab.
Conclusion: These results confirm the presence of both IgG and IgM after vaccination and infection with SARS-CoV-2. A difference in the proportion with IgG+IgM between vaccinated infected and uninfected HCW was seen, for which we have no explanation. Very few CV HCW remain naïve to SARS-CoV2.

Implications of non-specific effects for testing, approving, and regulating vaccines

Christine Stabell Benn (1,2), Nelly Amenyogbe (3), Anders Björkman (4), Jorge Dominguez Andres (5), Eleanor Fish (6,7), Katie L. Flanagan (8,9,10), Sabra L. Klein (11), Tobias R. Kollmann (3), Kirsten Ohm Kyvik (12), Mihai G. Netea (5), Naja Hulvej Rod (13), Frederik Schaltz-Buchholzer (1), Frank Shann (14), Liisa Selin (15), Sanne M. Thysen (16), Peter Aaby (1,17)

1. Bandim Health Project, Open Patient Data Explorative Network (OPEN), Department of Clinical Research, Odense University Hospital and University of Southern Denmark, Odense, Denmark.
2. Danish Institute for Advanced Study, University of Southern Denmark, Copenhagen, Denmark.
3. Telethon Kids Institute, Perth, Western Australia, Australia.
4. Department of Global Public Health, Karolinska Institutet Stockholm Sweden.
5. Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center Nijmegen, The Netherlands.
6. Dept. Immunology, University of Toronto, Canada.
7. Toronto General Hospital Research Institute, University Health Network, Toronto, Canada.
8. Tasmanian Vaccine Trial Centre, Clifford Craig Foundation, Launceston General Hospital, Launceston, Tasmania, Australia.
9. School of Medicine, Faculty of Health Sciences, University of Tasmania, Launceston, Tasmania, Australia.
10. School of Health and Biomedical Sciences, RMIT University, Melbourne, Victoria, Australia.
11. W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland USA.
12. Department of Clinical Research, Odense University Hospital and University of Southern Denmark, Odense, Denmark.
13. Department of Public Health, University of Copenhagen, Denmark.
14. Department of Paediatrics, University of Melbourne, Parkville, Victoria 3052, Australia.
15. Department of Pathology, University of Massachusetts Medical School, Worcester, MA 01605, USA
16. Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark.
17. Bandim Health Project, Apartado 861, 1004 Bissau Codex, Guiné-Bissau

The current framework for testing and regulating vaccines was established before the realization that vaccines, in addition to their effect against the vaccine-specific disease, may also have "non-specific effects" affecting the risk of unrelated diseases.

Accumulating evidence from epidemiological studies shows that vaccines can affect all-cause mortality and morbidity in ways that are not explained by the prevention of the vaccine-targeted disease. Live attenuated vaccines have been associated with decreases in mortality and morbidity that are greater than anticipated. In contrast, some non-live vaccines have been associated with increases in all-cause mortality and morbidity in certain contexts. The non-specific effects are often greater for females than males. Immunological studies have provided several mechanisms that explain how vaccines modulate the immune response to unrelated pathogens, such as through trained innate immunity, emergency granulopoiesis, and heterologous T-cell immunity.

These insights suggest that the framework for the testing, approving, and regulating vaccines needs to be updated to accommodate non-specific effects. Currently, non-specific effects are not routinely captured in Phase I-III clinical trials or in the post-licensure safety surveillance. For instance, an infection with *Streptococcus pneumoniae* occurring months after a diphtheria-tetanus-pertussis vaccination would not be considered an effect of the vaccination, although evidence indicates it might well be for females. Here we propose a new framework that considers the non-specific effects of vaccines in both Phase III trials and post-licensure.

NON-SPECIFIC EFFECTS OF VACCINES: A RAPID REVIEW OF STUDIES CONDUCTED IN PORTUGUESE SPEAKING AFRICAN COUNTRIES

Ines Fronteira

Introduction: Some vaccines seem to have effects beyond those of targeted diseases. These are called non-specific effects.
Objective: to identify the studies conducted in PALOP on non-specific effects of human vaccines and summarize their main findings.
Methods: rapid review of experimental, cohort, case-control and cross-sectional studies indexed in Pubmed, Scopus or LILACS on i) non-specific effects of vaccines in ii) human populations from iii) Angola, Cape Verde, Guinea-Bissau, Equatorial Guinea, Mozambique and/or São Tomé and Príncipe. Qualitative synthesis of results.
Results: 421 studies retrieved; data collected on 67. 66 of these were conducted in Guinea-Bissau, were mainly cohort and experimental studies and most commonly included measles vaccine, BCG, DTP and OPV. The non-specific effects studied included mostly mortality and morbidity.
Discussion: Non-specific effects of vaccines are a relevant issue for global public health.

Vaccination against measles-mumps-rubella and non-targeted infectious disease hospitalisations among children below 2 years of age in Denmark, Finland, Norway, and Sweden

Lise Gehrt; Sören Möller; Hélène Englund; Ida Laake; Heta Nieminen; Berit Feiring; Arto A. Palmu; Lill Trogstad; Christine Stabell Benn; Signe Sørup

Background: The live vaccine against Measles-Mumps-Rubella (MMR) has been associated with decreased rates of non-targeted infectious disease hospitalisations in observational studies from high income countries. However, multiple differences in study designs and settings hamper comparability of results.

Aim: To investigate if having MMR as the most recent vaccine compared with three doses of DTaP is associated with a lower rate of infectious disease hospitalisations among children below two years of age in Denmark, Finland, Norway, and Sweden.
Setting: Denmark, Norway, and Sweden recommend a three-dose primary series of diphtheria, tetanus, and acellular pertussis containing vaccines (DTaP) followed by MMR. Finland recommends co-administration of the third dose of DTaP and MMR, but some children still receive MMR after DTaP.

Methods: The analyses were performed in each country separately using data from nationwide registries. Cox proportional hazards regressions with age as the underlying timescale were used to estimate crude, covariate-adjusted, and inverse probability of treatment weighted (IPTW) hazard ratios (HR) of infectious disease hospitalisations by time varying vaccination status (MMR vs. three doses of DTaP). Combined estimate was calculated using DerSimonian-Laird method for random-effects meta-analysis accounting for between study heterogeneity.

Results : A total of 1,397,027 children were included. MMR uptake was lower and more delayed in Denmark compared with the other countries. Having MMR after three doses of DTaP was associated with reduced rates of infectious disease hospitalisations in all countries: The adjusted HR and 95% confidence intervals were 0.86 (0.83 to 0.89) in Denmark, 0.71 (0.68 to 0.74) in Norway, 0.71 (0.65 to 0.77) in Sweden, and 0.70 (0.64 to 0.75) in Finland; the combined estimate across countries was 0.75 (0.65 to 0.84). Results were similar with the IPTW model.

Discussion: MMR was consistently associated with reduced rates of infectious disease hospitalisations across the Nordic countries. The effect estimate was closer to 1 in Denmark, where MMR- and DTaP-only vaccinated children may be more comparable due to more deviations from recommended MMR uptake, compared with the other countries. The results from Finland, where receiving MMR after DTaP only pertained to a subgroup deviating from recommendations, were similar to Norway and Sweden where this order was the policy. Bias attributable to deviations from recommendations may explain some of the observed association, especially in countries with high MMR uptake, but is unlikely to explain all of the protective associations consistently observed across countries with different underlying bias structures due to e.g. vaccination policy and MMR uptake.

Neonatal BCG vaccination to prevent early-life eczema: a systematic review and meta-analysis

Laure F. Pittet, MD, PhD[1,2,3,4,#], Lisbeth M. Thøstesen, MD, PhD [5,#], Peter Aaby, DMSc[6], Poul-Erik Kofoed, MD, DMSc[7], Nigel Curtis, FRCPCH, PhD [1,2,3,#], Christine S. Benn, MD, PhD.

*Infectious Diseases Group, Murdoch Children's Research Institute; †Department of Paediatrics, The University of Melbourne; ‡Infectious Diseases, The Royal Children's Hospital Melbourne, Australia; §Infectious Diseases Unit, Department of Paediatrics, Gynaecology and Obstetrics, Faculty of Medicine, University of Geneva, University Hospitals of Geneva, Switzerland; Department of Paediatrics and Adolescent Medicine, NIDO, Danmark, Gødstrup Hospital; ¶Bandim Health Project, Bissau, Guinea-Bissau; Department of Paediatrics and Adolescent Medicine, Lillebaelt Hospital, University Hospital of Southern Denmark; **Bandim Health Project, OPEN, Institute of Clinical Research, University of Southern Denmark; and ††Danish Institute for Advanced Study, University of Southern Denmark. L.F.P., L.M.T., N.C., and C.S.B. are joint first authors and joint last authors.

Increasing evidence suggests that early-life Bacillus Calmette-Guérin (BCG) vaccine could prevent atopic eczema through its beneficial off-target effects. In this meta-analysis, three randomised control trials with similar methods were included and enabled robust estimations with low heterogeneity, involving a total of 5655 children randomised to early-life BCG-Denmark (n=2832) or no BCG (n=2823). Meta-analyses suggest a beneficial effect of BCG to prevent eczema (risk ratio (RR) 0.89, 95%CI 0.82-0.98). In subgroup analyses, BCG was more beneficial in boys (0.84, 0.74-0.95) and in children born to two atopic parents (0.81, 0.68-0.97). The number-needed-to-treat to prevent one case of eczema among children of one or two atopic parent was 20 (95%CI 12-50). BCG-Denmark leads to an 11% reduction in the risk of eczema in early-life. A greater effect was observed with increasing predisposition. Given its well-established safety profile, neonatal BCG vaccination should be considered for children predisposed by virtue of atopic parents.

Comparing the effects of neonatal BCG-Japan versus BCG-Russia vaccination on overall mortality and morbidity: randomized controlled trial from Guinea-Bissau (BCGSTRAIN II)

Frederik Schaltz-Buchholzer (FSB)[1,2], Sebastian Nielsen (SN)[1,2], Marcus Kjær Sørensen (MKS)[1], Elise Brenno Stjernholm (EBS)[1], Rebecca Alison Fabricius (RAF)[1], Paulo Umbasse (PU)[1], Ivan Monteiro (IM)[1], Elsi Cá (EC), Peter Aaby (PA)[1], Christine Stabell Benn (CSB)[1,2,3]

[1] Bandim Health Project, INDEPTH Network, postal code 8611004, Bissau, Guinea-Bissau
FSB (MD, PhD), SN (Statistician, PhD Fellow), MKS (MD), EBS (MD), RAF (MD), PU (Senior data entry supervisor), IM (Senior trial supervisor), EC (MD), PA (Professor, DMSc), CSB (Professor, DMSc).
[2] Bandim Health Project, OPEN, Department of Clinical Research, Uni. Southern Denmark and Odense University Hospital, postal code 5230, Odense, Denmark FSB, SN, PA, CSB.
[3] Danish Institute of Advanced Study, Uni. Southern Denmark, postal code 5230, Odense, Denmark CSB.

Background:
Observational studies have found substantial reductions in infant mortality associated with Bacille Calmette-Guérin (BCG) scars, the scar size and having a tuberculin reaction. This prompted randomized controlled trials (RCTs) which has demonstrated pronounced reductions in overall neonatal mortality and morbidity after vaccination with BCG-Denmark. It is unknown whether these beneficial non-specific effects are similar for different BCG strains; two trials conducted in India that tested BCG-Russia vs no-BCG, provided to newborns admitted for intensive care, found no beneficial effect.

Methods:
RCT comparing BCG-Japan (n=8,754) vs BCG-Russia (n=8,752) for all-cause admission risk by six weeks (primary outcome) and six months of age. Secondary outcomes were in-hospital case-fatality risk (CFR), all-cause mortality at the same timepoints, and BCG skin reaction prevalence by 2 months of age. Participants were followed through telephone calls at six weeks and six months, with a subgroup also visited at home. Admission and mortality risk was assessed in Cox-models providing Incidence and Mortality Rate Ratios (IRRs, MRRs). CFR and skin reaction prevalence were assessed by binomial regression. We conducted all analyses overall and stratified by sex.

Results:
Overall, BCG strain was not associated with the overall risk of hospital admission, in-hospital CFR, or overall mortality risk. BCG-Japan produced more BCG skin reactions that were also larger, when compared to BCG-Russia.

Conclusion:
For mortality and morbidity outcomes, BCG-Japan and BCG-Russia had comparable effects. BCG-Japan was, however, associated with a higher prevalence of BCG scars that were also larger, which has been associated with reduced childhood mortality risk. Further trials comparing vaccine strains such as BCG-Denmark with BCG-Russia or BCG-Bulgaria are warranted.

SARS-COV-2 INFECTION VS VACCINATION IN PREGNANCY: IMPLICATIONS FOR MATERNAL AND INFANT IMMUNITY

Maria Giulia Conti[1], Sara Terreri[2], Gianluca Terrin[1], Fabio Natale[1], Carlo Pietrasanta[1], Roberto Brunelli[1], Vassiliki Papaevangelou[3], Fabio Midulla[1], Laura Petrarca[4], Rita Carsetti[2], Asimenia Angelidou[5]
[1] Sapienza University, Department of Maternal and Child Health, Rome, Italy
[2] Bambino Gesù Children's Hospital, Diagnostic Immunology Research Unit, Rome, Italy
[3] National and Kapodistrian University of Athens, Third Department of Pediatrics, Athens, Greece
[4] Sapienza University of Rome, Department of Translational and Precision Medicine, Rome, Italy
[5] Beth Israel Deaconess Medical Center, Harvard University, Department of Neonatology, Boston, United States of America

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been associated with adverse maternal and neonatal outcomes, yet uptake of SARS-CoV-2 vaccines during pregnancy and lactation has been slow. As a result, millions of pregnant and lactating women and their infants remain susceptible to the virus.

Methods: We measured spike-specific immunoglobulin G (anti-S IgG) and immunoglobulin A (anti-S IgA) in serum and breastmilk (BM) samples from 3 prospective mother-infant cohorts recruited in 2 academic medical centers. The primary aim was to determine the impact of maternal SARS-CoV-2 immunization vs infection and their timing on systemic and mucosal immunity.

Results: The study included 28 mothers infected with SARS-CoV-2 in late pregnancy (INF), 11 uninfected mothers who received 2 doses of the BNT162b2 vaccine in the latter half of pregnancy (VAX-P), and 12 uninfected mothers who received 2 doses of BNT162b2 during lactation. VAX dyads had significantly higher serum anti-S IgG compared to INF dyads ($P < .0001$), whereas INF mothers had higher BM:serum anti-S IgA ratios compared to VAX mothers ($P = .0001$). Median IgG placental transfer ratios were significantly higher in VAX-P compared to INF mothers ($P < .0001$). There was a significant positive correlation between maternal and neonatal serum anti-S IgG after vaccination ($r = 0.68$, $P = .013$), but not infection.

Conclusions: BNT161b2 vaccination in late pregnancy or lactation enhances systemic immunity through serum anti-S immunoglobulin, while SARS-CoV-2 infection induces mucosal over systemic immunity more efficiently through BM immunoglobulin production. Next-generation vaccines boosting mucosal immunity could provide additional protection to the mother-infant dyad. Future studies should focus on identifying the optimal timing of primary and/or booster maternal vaccination for maximal benefit.

Cord blood immune response differences between Europeans and malaria exposed Africans using mass cytometry

Yoanne D. Mouwenda[1,2], Madeleine E. Betouke Ongwe[1,2,3], Yabo J. Honkpehedji[1,2], Marion König[2], M. Massinga Loembe[1], P.G. Kremsner[4], Ayola A. Adegnika[1,2,4], S.P Jochems[2], M. Yazdanbakhsh[2]

Authors affiliations :
[1]Centre de Recherches Médicales de Lambaréné (CERMEL), Lambaréné, Gabon
[2]Department of Parasitology, Leiden University Medical Center (LUMC), Leiden, The Netherlands
[3]Centre National de la Recherche Scientifique et Technologique (IRET- CENAREST), Libreville, Gabon
[4]Institut für Tropenmedizin, Universität Tübingen and German Center for Infection Research, Tübingen, Germany

Besides genetic factors, environmental factors, have been shown to influence the immune response of adults and children living in different geographic areas. The question is, how early can this difference in immune response be detected? Using mass cytometry, we characterized the immunological profiles of newborns from Gabon and the Netherlands by examining the phenotype (ex vivo) of cord blood. We found differences in the expression of markers between the two populations, suggesting an enhanced maturational status of the neonatal immune system in Africans compared to Europeans. Indeed, increased $CD161^+$ CD4 or CD8 T cells were detected in Africans. Moreover, when assessed functionally, IFNg producing cells, in response to PMA/ionomycin are CD161+. Phenotypic differences in $CD34^+$ cells between the two populations were also examined. In general, $CD34^+$ cells were found to be abundant in Europeans, with $CD49f^+$ CD34 cells being more enriched in the cord blood of Europeans than of Africans. In the African population, some mothers tested positive for malaria during pregnancy. The data are currently being analyzed to assess the impact of malaria exposure in utero on the immune profile of African cord blood.

Keywords: Mass cytometry, cord blood, immunity at birth, hematopoietic stem cells, immune response, immunophenotyping.

Maternal BCG scars and mortality risk for male and female newborns in Guinea-Bissau

Frederik Schaltz-Buchholzer (FSB)[1,2], Sebastian Nielsen (SN)[1,2], Marcus Kjær Sørensen (MKS)[1], Elise Brenno Stjernholm (EBS)[1], Ivan Monteiro (IM)[1], Peter Aaby (PA)[1], Christine Stabell Benn (CSB)[1,2,3]
[1] **Bandim Health Project, INDEPTH Network, postal code 8611004, Bissau, Guinea-Bissau**
FSB (MD, PhD), SN (Statistician, PhD Fellow), MKS (MD), EBS (MD), IM (Senior trial supervisor), PA (Professor, DMSc), CSB (Professor, DMSc).
[2] **Bandim Health Project, OPEN, Department of Clinical Research, Uni. Southern Denmark and Odense University Hospital, postal code 5230, Odense, Denmark** FSB, SN, PA, CSB.
[3] **Danish Institute of Advanced Study, Uni. Southern Denmark, postal code 5230, Odense, Denmark** CSB**.**

Background:
Maternal priming with Bacille Calmette-Guérin (BCG) has been associated with reduced offspring mortality from all-causes. Among BCG-vaccinated newborns, a previous study has indicated that the presence of a maternal BCG scar is associated with reduced in-hospital mortality risk for males only. We investigated this association in a large cohort of healthy BCG-vaccinated neonates.

Methods:
Observational study within a randomized controlled trial (RCT) of BCG strains conducted in Guinea-Bissau from 2017-2020. As part of the trial inclusion procedures, which occurred on the day of discharge from the maternity ward, the maternal scar status was evaluated by visual inspection followed by BCG and oral polio vaccination of the newborn. Up to six weeks and six months of age, we assessed pediatric admission risk and all-cause mortality risk by maternal scar status in Cox Proportional Hazards models providing adjusted Incidence Rate Ratios and adjusted Mortality Rate Ratios (aMRRs). Case-fatality risk during admission was assessed by binomial regression providing aRRs. All estimates were adjusted for years of maternal schooling.

Results:
64% (11,070/17,275) of the mothers in the study had a BCG scar. For females and overall, maternal BCG scars were not associated with admission risk, admission severity or all-cause mortality. For males, being born to a mother with a BCG scar vs no maternal scar was associated with reduced case-fatality risk at both six weeks, the RR being 0.48 (0.26-0.89) and at six months of age, RR 0.59 (0.36-0.96). By six weeks of age, the maternal scar/no scar MRR was 0.87 (0.65-1.16); 0.73 (0.50-1.06) for males and 1.11 (0.71-1.75) for females (p for same effect=0.16). By six months of age, the maternal scar vs no scar all-cause aMRR was 0.86 (0.69-1.07); 0.74 (0.56-0.99) for males and 1.04 (0.74-1.47) for females (p for same effect=0.13).

Conclusion:
In males that received BCG shortly after birth, maternal BCG priming indicated by the presence of a maternal BCG scar, reduces the risk of death during infancy.

SPIKE SPECIFIC SALIVARY IgA2 IS NOT INDUCED OR BOOSTED BY BNT162B2 VACCINE IN CHILDREN

Maria Giulia Conti[1], Eva Piano Mortari[2], Raffaella Nenna[1], Alessandra Pierangeli[3], Leonardo Sorrentino[3], Federica Frasca[3], Laura Petrarca[1,4], Enrica Mancino[1,4], Greta Di Mattia [1,4], Giuseppe Oliveto[3], Carolina Scagnolari[3], Rita Carsetti[2]* and Fabio Midulla[1]

[1]Department of Maternal and Child Health, Sapienza University of Rome, Viale Regina Elena 324, 00161 Rome, Italy.
[2]B Cell Unit, Immunology Research Area, Bambino Gesù Children's Hospital, IRCCS, Viale di San Paolo, 00146 Rome, Italy.
[3]Department of Molecular Medicine, Laboratory of Virology, Sapienza University of Rome, Viale di Porta Tiburtina 28, 00185 Rome, Italy.
[4]Department of Translational and Precision Medicine, Sapienza University of Rome, Viale Regina Elena 324, 00161 Rome, Italy.

Children's mucosal immune response is highly dynamic. Salivary antibodies are an important tool for protection against respiratory infections. SARS-CoV-2 infected children develop a mild or asymptomatic disease compared to adults. The anti-COVD-19 vaccination induces a strong systemic but a week mucosal immune response in adults. Little is known about the mucosal immune response in children infected or vaccinated against SARS-CoV-2. We measured Spike-specific (S1) IgA and IgG in the saliva and serum of vaccinated children, before and after vaccination (VAX-C) and we compared them with those of infected children (INF-C). We found that 28% of VAX-C had detectable salivary IgA against SARS-CoV-2, mainly of IgA2 isotype before vaccination, indicating that in children SARS-CoV-2 infection may be undiagnosed. After complete vaccination, salivary specific IgA and IgG significantly increased ($p=0.0001$ and $p<0.0001$ respectively). Human IgA is produced in two isotypes: IgA1 which are more abundant in the serum (80%) and IgA2. IgA2 represents the classical mucosal neutralizing antibody, which is normally found in secreted fluids in a dimeric form. Vaccination led to a significant increase of RBD-specific IgA1 ($p=0.012$), but not IgA2. Conversely, INF-C had significantly higher salivary RBD-IgA2 compared to IgA1 ($p<0.0001$), indicating that natural infection but not vaccination induces a specific mucosal immune response. Finally, S1-IgA and IgG are significantly higher in the serum of vaccinated children compared to infected children ($p=0.008$ and $p<0.0001$ respectively), while S1 salivary IgA were higher, although not significantly, in infected versus vaccinated children.

TACTIC study: timing and sequence of vaccination against COVID-19 and Influenza

Elisabeth A. Dulfer[1,2], Büsranur Geçkin[1,2], Esther Taks[1,2], Corine H. GeurtsvanKessel[3], Helga Dijkstra[1,2], Liesbeth van Emst[1,2], Elles Simonetti[2,4], Djenolan van Mourik[3], Petra Koopmans[5], Jorge Domínguez-Andrés[1,2], Reinout van Crevel[1,2], Josephine S. van de Maat[1,2], Marien I. de Jonge[2,4], Mihai G. Netea[1,2,6]

[1]Department of Internal Medicine, Radboud university medical center, Nijmegen, the Netherlands
[2]Radboud Center for Infectious Diseases, Radboud university medical center, Nijmegen, the Netherlands
[3]Laboratory of Viroscience, Erasmus Medical Center, Rotterdam, the Netherlands
[4]Laboratory of Medical Immunology, Radboud university medical center, Nijmegen, the Netherlands
[5]Department of Biostatistics, Radboud university medical center, Nijmegen, the Netherlands
[6]Department for Immunology and Metabolism, Life and Medical Sciences Institute (LIMES), University of Bonn, Germany

Background

Novel mRNA-based vaccines have been used to protect against SARS-CoV-2, especially in vulnerable populations who also receive an annual influenza vaccination. The TACTIC study investigated potential immune interference between the mRNA COVID-19 booster vaccine and the quadrivalent influenza vaccine, and determined if concurrent administration would have effects on safety or immunogenicity.

Methods

TACTIC was a single-blind, placebo-controlled randomized clinical trial at the Radboud University Medical Centre, the Netherlands. Individuals ≥60 years, fully vaccinated against COVID-19 were eligible for participation and randomized into one of four study groups: 1) 0·5ml influenza vaccination Vaxigrip Tetra followed by 0·3ml BNT162b2 COVID-19 booster vaccination 21 days later, (2) COVID-19 booster vaccination followed by influenza vaccination, (3) influenza vaccination concurrent with the COVID-19 booster vaccination, and (4) COVID-19 booster vaccination only (reference group). Primary outcome was geometric mean concentration (GMC) of IgG against the spike (S)-protein of the SARS-CoV-2 virus, 21 days after booster vaccination. We performed a non-inferiority analysis of concurrent administration compared to booster vaccines alone. Secondary outcomes were virus neutralization capacity of the induced antibodies, antibody levels in mucosal lining fluid, and adverse events.

Findings

154 individuals participated from October, 4, 2021, until November, 5, 2021. Anti-S IgG GMCs for the co-administration and reference group were 1684 BAU/ml and 2435 BAU/ml, respectively. Concurrent vaccination did not meet the criteria for non-inferiority (estimate -0·1791, 95% CI -0·3364 to -0·02170) and antibodies showed significantly lower neutralization capacity compared to the reference group. Reported side-effects were mild and did not differ between study groups.

Interpretation

Although concurrent administration of both vaccines is safe, the quantitative and functional immunological responses were lower compared to booster vaccination alone. Lower protection against COVID-19 may be expected with concurrent administration of COVID-19 and influenza vaccination, which should be taken into consideration for public health decisions.

Non-specific effects of BNT162b2 vaccine in adolescents

Rimas Jankūnas[1,2]

[1] Institute of Physiology and Pharmacology, Medical Academy, Lithuanian University of Health Sciences, A. Mickevičiaus g. 9, LT-44307 Kaunas, Lithuania
[2] Institute of Health Law, Ulonų g. 5-303, LT-08240 Vilnius, Lithuania

An initial analysis of the pivot study of BNT162b2 in adolescents 12 to 15 years of age (representing a median follow-up of > 2 months after Dose 2) revealed no cases of symptomatic COVID-19 in 1,005 subjects of the BNT162b2 arm; 16 cases were reported in 978 (1.62%) subjects of a placebo arm. I.e., 1.62% of subjects got benefit from the vaccine (avoided mild to moderate symptomatic disease). [1]
However, more than 80% of subjects in the BNT162b2 arm had mild to moderate adverse events. Unfortunately, there is no update for this initial analysis. [1] Vaccination of the placebo group [2] decreases the scientific value of this study.
No cases of severe COVID-19 have been reported in either arm of the pivot study of BNT162b2 in adolescents 12 to 15 years of age. Serious adverse events (SAEs) were reported in 5 and 2 subjects in vaccine and placebo arms, respectively. Psychiatric SAEs were reported in 4 and 0 subjects, respectively. In addition, 2 adolescents originally randomized to receive a placebo had life-threatening SAEs after they were unblinded to receive BNT162b2. [2]
The assessment Report of the European Medicines Agency (EMA) insists that the frequency of SAEs in children is very low. [2] However, they occurred in 0.11% of subjects and should be classified as "uncommon" according to the Medical Dictionary for Regulatory Activities (MedDRA). The use of MedDRA is required by the guidelines of EMA. There is no "very low" category of frequency in the MedDRA. "Uncommon" is 100 times more frequent than "very rare". [3]
Furthermore, a subject of a pediatric study Maddie de Garay over the next 24 hours after Dose 2 experienced several adverse events and eventually lost feeling from the waist down, got muscle weakness, changes in vision, urinary retention, and loss of bladder control. Eventually, she got a nasogastric tube for nutrition. [4]
Known benefits of the BNT162b2 vaccine in 12 to 15 years old adolescents do not exceed potential risks. Long-term risks are unknown. [5]

Conclusion

Harm BNT162b2 in children due to non-specific effects may exceed the short-term benefit of protection against COVID-19.

References

1. European Commission. Union Register of Medicinal Products. Summary of Product Characteristics of Comirnaty. Available at https://ec.europa.eu/health/documents/community-register/2022/20220901156975/anx_156975_en.pdf [Accessed 11 September 2022
2. European Medicines Agency. Assessment Report of Committee for Medicinal Products for Human Use (CHMP, 28 May 2021 EMA/343389/2021). Available at https://www.ema.europa.eu/en/documents/variation-report/comirnaty-h-c-5735-ii-0030-epar-assessment-report-variation_en.pdf [Accessed 11 September 2022].
3. European Medicines Agency. Scientific Guidelines with SmPC Recommendations https://www.ema.europa.eu/en/documents/other/scientific-guidelines-summary-product-characteristics-recommendations_en.pdf [Accessed 11 September 2022]
4. Meeting of Senior United States Senator from Wisconsin Ronald Harold Johnson with Families on Adverse Reactions to COVID vaccine, FOX6 News Milwaukee. Available at https://www.youtube.com/watch?v=6mxqC9SiRh8&t=2159s [Accessed 11 September 2022].
5. Rimas Jankūnas, Rasa Jančiauskienė, Kristina Zamarytė Sakavičienė, Donatas Stakišaitis. Discrepancies of Pediatric Data of BNT162b2 mRNA Covid-19 Vaccine in the Assessment Report of the European Medicines Agency. Biomed J Sci & Tech Res 42(2)-2022. BJSTR. MS.ID.006711. Available at https://biomedres.us/pdfs/BJSTR.MS.ID.006711.pdf [Accessed 11 September 2022].

Changing from being amongst the countries with most successful pandemic management during one year to then becoming the least successful for three month is not rational.
But what if having the highest vaccination rate during these three month is behind of such a big change?

Juan M. Marqués

Montevideo, Uruguay

Have we evaluated effects of vaccines with respect to infections during the first days after dose administration such as differences in sensitivity to infections, viral loads and symptoms? Do our experimental models challenge during the period immediately after vaccination? In Uruguay and other parts of the World people were vaccinated with COVID-19 vaccines and then would have being exposed to viral infection. During March-June 2021 a link between vaccination rate and number of positive cases of covid by day can be observed in Uruguay. The peaks of vaccination rate curve by day correlate with the peaks of positives cases with a lag phase of 8 days. This can be observed during 3 months of high vaccination rate. A possible multiplier effect could be hypothesize due to vaccination during the pandemic in countries where lock down were not strictly applied, vaccination rate was near 1% of population per day, and virus was circulating at elevated rate when the vaccination program was implemented. There is a correlation between vaccination rate and positives cases per week at higher magnitude in many other countries. Based on recent preliminary results of experimental models not presented here, we hypothesized that adjuvant effects from vaccines “distract” innate immunity during the first hours/days after dose administration. This phenomenon could present a window of increased susceptibility to infection. Moreover, we hypothesize that this phenomenon could lead to higher viral loads in a diminished time in the case of SARS-CoV-2 infected people and this could lead to a higher spread of the virus, more if the proportion of asymptomatic patients is bigger. This could explain what was observed in Uruguay where even with measures to limit mobility and with an increasing fraction of protected vaccinated population since April, the number of new cases did not decrease until the end of June. There are publications, not studding this particular phenomenon, but which show evidence to sustain this hypothesis. Finally, I propose that simple measures such as quarantine for a short window of time after vaccination could be sufficient to avoid these effects.

Randomized clinical trial of BCG vaccine in patients with convalescent COVID-19: Clinical evolution, adverse events, and humoral immune response

Mehrsa Jalalizadeh [1], Keini Buosi [1], Franciele A V Dionato [1], Luciana S B Dal Col [1], Cristiane F Giacomelli [1], Karen L Ferrari [1], Ana Carolina Pagliarone [1], Patrícia A F Leme [1], Cristiane L Maia [1], Reza Yadollahvandmiandoab [1], Quoc-Dien Trinh [2], Kleber G Franchini [3], Marcio C Bajgelman [3], Leonardo O Reis [1, 2, 4 *]

[1]Department of UroScience, School of Medical Sciences, State University of Campinas-UNICAMP, Campinas, Brazil.

[2]Brigham and Women's Center for Surgery and Public Health, Harvard Medical School, Boston, Massachusetts, USA.

[3]Brazilian Center for Research in Energy and Materials, CNPEM, Brazilian Biosciences National Laboratory-LNBio, Campinas, Brazil.

[4]Center for Life Sciences, Pontifical Catholic University of Campinas, Campinas, Brazil.

* **Corresponding author/presenter:**

Background: The Bacillus Calmette-Guérin (BCG) vaccine may confer cross-protection against viral diseases in adults. This study evaluated BCG vaccine cross-protection in adults with convalescent coronavirus disease 2019 (COVID-19).

Method: This was a multicenter, prospective, randomized, placebo-controlled, double-blind phase III study (ClinicalTrials.gov: NCT04369794).

Setting: University Community Health Center and Municipal Outpatient Center in South America.

Patients: a total of 378 adult patients with convalescent COVID-19 were included.

Intervention: single intradermal BCG vaccine (n = 183) and placebo (n = 195).

Measurements: the primary outcome was clinical evolution. Other outcomes included adverse events and humoral immune responses for up to 6 months.

Results: A significantly higher proportion of BCG patients with anosmia and ageusia recovered at the 6-week follow-up visit than placebo (anosmia: 83.1% vs. 68.7% healed, p = 0.043, number needed to treat [NNT] = 6.9; ageusia: 81.2% vs. 63.4% healed, p = 0.032, NNT = 5.6). BCG also prevented the appearance of ageusia in the following weeks: seven in 113 (6.2%) BCG recipients versus 19 in 126 (15.1%) placebos, p = 0.036, NNT = 11.2. BCG did not induce any severe or systemic adverse effects. The most common and expected adverse effects were local vaccine lesions, erythema (n = 152; 86.4%), and papules (n = 111; 63.1%). Anti-severe acute respiratory syndrome coronavirus 2 humoral response measured by N protein immunoglobulin G titer and seroneutralization by interacting with the angiotensin-converting enzyme 2 receptor suggest that the serum of BCG-injected patients may neutralize the virus at lower specificity; however, the results were not statistically significant.

Conclusion: BCG vaccine is safe and offers cross-protection against COVID-19 with potential humoral response modulation.

Limitations: No severely ill patients were included.

Keywords: BCG; COVID-19; IgG; SARS-CoV-2; convalescence; immunomodulation; neutralization; safety.

Using BCG vaccination of Danish healthcare workers against COVID-19

Anne Marie Rosendahl Madsen[1], Frederik Schaltz-Buchholzer[1], Sebastian Nielsen[1], Peter Aaby[1], Christine Stabell Benn[1,2] and the BCG-DENMARK-COVID study-group[3].

[1] Bandim Health Project, Open Patient Data Explorative Network (OPEN), Department of Clinical Research, Odense University Hospital and University of Southern Denmark, Odense, Denmark.
[2] Danish Institute for Advanced Study, University of Southern Denmark, Copenhagen, Denmark.
[3] Madsen AMR, Schaltz-Buchholzer F, Benfield T, Bjerregaard-Andersen M, Dalgaard LS, Dam C, et al. Using BCG vaccine to enhance non-specific protection of health care workers during the COVID-19 pandemic: A structured summary of a study protocol for a randomised controlled trial in Denmark. **Trials 2020;21(1).**

Background:
Bacillus Calmette-Guérin (BCG) was developed as a vaccine against tuberculosis but has been shown to have non-specific effects on the immune system, which may provide protection against unrelated infections. In the beginning of the COVID-19 pandemic it was therefore hypothesised that BCG might convey temporary protection against COVID-19 to health care workers (HCWs), who faced an elevated risk of exposure to the novel coronavirus. The main objective of this study was to test whether BCG vaccination could reduce unplanned absenteeism (a proxy for the rate of transmission) among HCWs during the pandemic.

Methods:
A single-blinded randomised controlled trial. Between May 2020 and January 2021 HCWs were recruited at nine Danish hospitals. Participants were randomised 1:1 to standard dose BCG vaccination or placebo (saline injection) and followed for six months with weekly electronic questionnaires about their health. The primary outcome was days of unplanned absenteeism. Secondary outcomes included incidence of verified COVID-19, all-cause hospital admissions, and infectious disease episodes. Days of absenteeism was analysed using Bayesian negative binomial models yielding risk ratios (RR). Time-to-event outcomes were analysed using Cox proportional hazard models providing hazard ratios (HR).

Results:
The trial included 1,221 HCWs. There was no effect of BCG on unplanned absenteeism, the RR being 1.23 (95% Confidence Interval (CI) 0.98-1.53). BCG had no effect on incidence of COVID-19 or hospital admissions overall, but in subgroup analyses BCG was associated with a 147% higher incidence of COVID-19 (HR 2.47 (1.07-5.71)), as well as a 72% lower incidence of hospitalisation (HR 0.28 (0.09-0.86)) in subjects with a scar from previous BCG vaccination. The incidence of infectious disease episodes was similar between the groups (HR 1.09 (0.96-1.24)).

Conclusion:
In this relatively healthy cohort of HCWs there was no effect of BCG on any of the outcomes. In subgroup analyses, BCG re-vaccination was associated with increased risk of COVID-19 but also with significantly lower risk of hospitalisation.

Acknowledgments: We thank the participating hospitals for their help with advertising and recruitment.

The impact of recent BCG vaccination on the serological response after COVID-19 vaccination in a population of older European adults.

Esther Taks[1,2], Simone Moorlag[1,2], Konstantin Föhse[1,2], Elles Simonetti[2,3], Christa van der Gaast-de Jongh[2,3], Jaap ten Oever[1,2], Marien de Jonge[2,3], Mihai Netea[1,2,5], Janneke van de Wijgert[4]

[1]Department of Internal Medicine Radboud university medical center, Nijmegen, the Netherlands.
[2]Radboud Center for Infectious Diseases, Radboud university medical center, Nijmegen, the Netherlands.
[3]Department of Laboratory Medicine, Laboratory of Medical Immunology, Radboud Institute for Molecular Life Sciences, Radboud university medical center, Nijmegen, the Netherlands
[4]University Medical Center, Utrecht, the Netherlands
[5]Department for Immunology and Metabolism, Life and Medical Sciences Institute (LIMES), University of Bonn, Germany

Background. Earlier studies showed that individuals recently vaccinated with BCG have a better humoral response after vaccination with anti-COVID-19 specific vaccines. Similarly, in elderly we found an increased antibody response after COVID-19 infection if they were vaccinated with BCG. This study aims to assess the effect of BCG vaccination on the antibody responses induced by the COVID-19 vaccination in a population of older adults.
Methods. Serum was collected from 1555 participants of the BCG-CORONA-ELDERLY trial and analysed for anti-SARS-CoV-2 antibody concentration using a fluorescent-microsphere-based multiplex immunoassay. The BCG-CORONA-ELDERLY trial is a randomised controlled trial that assessed the efficacy of BCG vaccination against respiratory tract infections, including COVID-19, in adults aged 60 years or older. Only those who were fully vaccinated and had not tested positive for COVID-19 were used for further analyses. (n=945)
Results. Although there seemed to be a marginal increase in antibody responses in individuals vaccinated with BCG compared to placebo, none of the differences were statistically significant ($p>0.05$). Interestingly, women had a better antibody response compared to men ($p=0.0013$), especially in the age category 60-69 years of age. We also observed an inverse correlation between age and antibody concentration in those vaccinated with Bnt162b2 anti-COVID-19 vaccine ($p<0.0001$, $r(781) = -0.2243$).
Conclusions. BCG vaccination in the year prior to antiCOVID-19 vaccination did not significantly impact the serological response to SARS-CoV-2 vaccines in an older European population.

Investigating the modulation of metabolism to increase the efficacy of BCG vaccine

Ilayda Baydemir [1], Evelien Floor [1], Özlem Bulut [1], Marisol Báez-Magaña[1], Mihai G. Netea[1], Jorge Domínguez-Andrés [1]

1. Department of Internal Medicine and Radboud Center for Infectious Diseases (RCI), Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Trained immunity has been defined as the non-specific memory generated via metabolic and epigenetic reprogramming of innate immune cells after a primary stimulus such as infection or vaccination. BCG vaccine is one well-defined inducer of trained immunity. Several studies showed that BCG vaccination greatly reduced overall mortality in children and neonates, which could not be explained by the protection developed against tuberculosis alone. However, there is still room to improve the specific and non-specific protection provided by BCG. Our aim here is to define a metabolic component that can amplify the specific and non-specific immunoprotective effects of BCG vaccine. For this purpose, we aim to interfere with the acetylCoA metabolism of monocytes, by using CMS121, an inhibitor of acetyl-CoA carboxylase 1 (ACC1) enzyme. Cells trained with BCG in the presence or absence of CMS121 were subjected to secondary LPS stimulation, while RPMI was used as negative control. Our findings revealed that CMS121 further enhanced the ROS and secondary cytokine production induced by BCG training. However, CMS121 limits BCG's capacity to increase glycolysis and OXPHOS. Furthermore, changes in H3K9me3 and H3K27Ac levels induced by BCG were slightly reversed by CMS121. Overall, CMS121 enhanced BCG vaccine efficacy in terms of cytokine and ROS production, although this is likely not due to a metabolic shift in glycolysis and OXPHOS. Further investigation is necessary to understand the mechanisms underlying the effects of CMS121. Eventually, this compound might be utilized as an amplifier for BCG vaccine in humans

Fatty acid desaturation and lipoxygenase pathways support BCG induced trained immunity

Anaísa V. Ferreira[a,b]*, Juan Carlos Alarcon-Barrera[c]*, Jorge Domínguez-Andrés[a], Ozlem Bulut[a], Gizem Kilic[a], Priya A. Debisarun[a], Rutger J. Röring[a], Hatice N. Özhan[a], Athanasios Ziogas[a], Sarantos Kostidis[c], Vasiliki Matzaraki[a], George Renieris[d], Evangelos J Giamarellos-Bourboulis[d], Mihai G. Netea[a,e], Martin Giera[c]

[a] Department of Internal Medicine and Radboud Center for Infectious Diseases (RCI), Radboud University Nijmegen Medical Center, 6500HB Nijmegen, The Netherlands; [b] Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, 4050-313 Porto, Portugal; [c] Center for Proteomics and Metabolomics, Leiden University Medical Center, 2333ZA Leiden, the Netherlands; [d]4th Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, Athens, Greece; [e] Department for Immunology and Metabolism, Life and Medical Sciences Institute (LIMES), University of Bonn, 53115 Bonn, Germany

*These authors contributed equally

Infections and vaccinations can induce long-term enhanced responses of innate immune cells to heterologous stimuli, establishing a *de facto* innate immunological memory termed *trained immunity*. Monocytes exposed to the Bacillus Calmette-Guérin (BCG) vaccine, and to a lesser extent the fungal cell wall component β-glucan, have a trained immunity phenotype, characterized by an increased biosynthesis of different lipid mediators (LMs) derived from long-chain polyunsaturated fatty acids (PUFAs). Pharmacological and genetic approaches showed that long-chain PUFA synthesis and lipoxygenase (LOX)-derived LMs are crucial for the trained immunity responses of human monocytes. Furthermore, monocytes of healthy individuals vaccinated with BCG are enriched in 12-LOX products. The elucidation of the lipid metabolic pathways that promote innate immune memory contributes to our understanding of trained immunity and may help identify therapeutic tools and targets for the modulation of innate immune responses.

Randomized placebo-controlled trial to restore innate immune function in the elderly: First-in-class immunotherapy exploits the power of bugs as drugs

Authors: Shirin Kalyan (PhD)[1] & Hal Gunn (MD)[1]
[1]Qu Biologics Inc (Metro Vancouver, Canada)

Decline in innate immune function in the elderly is closely related to the development and progression of infections, inflammaging, metabolic dysfunction, and cancer. An important factor in susceptibility to morbidity and mortality in this age group is impaired innate immunity. Of note, age-related lung innate immune dysfunction results in increased susceptibility to serious lung infections, chronic lung diseases, and inflammatory disorders of the lung. This extreme vulnerability to infection in the elderly was made explicit by the COVID-19 pandemic, for which age is by far the greatest risk factor for COVID-19 morbidity and mortality. Even prior to COVID-19, the contribution of respiratory infections to all-cause mortality is known to be linked to increasing age. An early interferon (IFN) response, the production of which is primed by innate immune detection of viral infection, is a critical factor in the prevention of serious COVID-19 outcomes. In particular, impaired IFNγ production in the elderly is also linked to their poor response to vaccination and chronic viral infection.

A randomized placebo-controlled trial will assess the efficacy of a first-in-class immunotherapy (QBKPN SSI) to improve innate immunity in the elderly. QBKPN is a lung-directed Site-Specific Immunomodulator (SSI) that is formulated from a microbe that is ubiquitously endogenous in human lungs and a potential cause of lung infections. Proof-of-concept studies of QBKPN's pharmalogical effect in targeting lung innate immunity to overcome pathology has been demonstrated for lung cancer, peri-operative immune suppression resulting in lung metastasis, bacterial infection, viral infection, COPD, and asthma.[1-4] QBKPN's therapeutic effect has been shown to be particularly amplified in the context of impaired innate immune function, as is the case for aged animals, after surgical trauma, or cancer. The trial will assess changes in NK cell function, innate immune training, and interferon production in response to microbial stimulation. Respiratory tract and all-cause infection morbidity and mortality will be assessed. The elderly present a critically relevant clinical group for therapeutic targets that can improve innate immune function as they are at greatest risk for death and complications from infections, cancer, and chronic inflammatory diseases.

References

1. Kalyan, S., M. Bazett, H. P. Sham, M. Bosiljcic, B. Luk, S. Dhanji, A. M. Costa, et al. "Distinct Inactivated Bacterial-Based Immune Modulators Vary in Their Therapeutic Efficacies for Treating Disease Based on the Organ Site of Pathology." *Scientific Reports* 10, no. 1 (2020): 5901-z. https://doi.org/10.1038/s41598-020-62735-z.
2. Bazett, M., A. M. Costa, M. Bosiljcic, R. M. Anderson, M. P. Alexander, S. W. Y. Wong, S. Dhanji, et al. "Harnessing Innate Lung Anti-Cancer Effector Functions with a Novel Bacterial-Derived Immunotherapy." *OncoImmunology* 7, no. 3 (2017): e1398875. https://doi.org/10.1080/2162402X.2017.1398875.
3. Bazett, M., A. Biala, R. D. Huff, M. Bosiljcic, H. Gunn, S. Kalyan, and J. A. Hirota. "A Novel Microbe-Based Treatment That Attenuates the Inflammatory Profile in a Mouse Model of Allergic Airway Disease." *Scientific Reports* 6, no. Journal Article (2016): 35338. https://doi.org/10.1038/srep35338.
4. Bazett, M., A. Biala, R. D. Huff, M. R. Zeglinksi, P. M. Hansbro, M. Bosiljcic, H. Gunn, S. Kalyan, and J. A. Hirota. "Attenuating Immune Pathology Using a Microbial-Based Intervention in a Mouse Model of Cigarette Smoke-Induced Lung Inflammation." *Respiratory Research* 18, no. 1 (2017): 92-y. https://doi.org/10.1186/s12931-017-0577-y.

Sex hormones more than sex chromosomal complement predict sex differences in influenza vaccine-induced immunity and protection in mice

Kumba Seddu[1], Santosh Dhakal[1], Sabra L. Klein[1]
[1] W. Harry Feinstone Department of Molecular Microbiology and Immunology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: Following influenza vaccination, adult female mice have greater quantity and quality of antibodies than males, which significantly improves protection against live influenza virus challenge. Whether sex steroid hormone concentrations, sex chromosome complement, or both underlie greater immunity and protection following vaccination has yet to be determined.

Objective: To dissect the relative contribution of sex steroid hormones and sex chromosome complement on influenza vaccine-induced immunity and protection, we used the Four Core Genotype (FCG) mouse model to evaluate how gonadal sex (i.e., testes or ovaries) and sex chromosome complement (i.e., XX or XY) can independently or together contribute to sex differences in influenza immunity.

Methods: Adult (8-10 week old) FCG mice (n=20/genotype) were vaccinated and boosted intramuscularly with inactivated mouse-adapted A/California/04/09 (ma2009 H1N1). Blood samples were collected at several time points after vaccination to measure virus-specific IgG and neutralizing antibodies. Vaccinated mice were challenged intranasally with live ma2009 H1N1 drift variant virus and used to either measure lung virus replication kinetics or disease pathogenesis.

Results: Following vaccination, gonadal females (i.e., XXF and XYF), regardless of sex chromosome complement, produced greater antibody responses than gonadal males (i.e., XYM and XXM). After live virus challenge of vaccinated FCG mice, gonadal females had less pulmonary virus replication than gonadal males. Gonadal sex and sex chromosomal complement intersected to impact disease severity following live virus challenge, in which among gonadal females, XX females experienced less morbidity than XY females. In contrast, there was no effect of sex chromosome complement among gonadal males.

Conclusion: Sex steroid hormones more than sex chromosome complement underlie sex differences in influenza vaccine-induced immunity and protection. How hormones alter the activity of antibody-secreting B cells to differentially regulate responses to vaccination requires further investigation.

A systems immunology approach to understand the heterogeneous response to Influenza vaccination in the elderly.

Martijn Zoodsma[1,2*], Saumya D Kumar[1,2*], Nhan Nguyen[1,2], Stephanie Trittel[3], Peggy Riese[3], Cheng-Jian Xu[1,2,4], Frank Pessler[1,5], Carlos Guzmán[3], Yang Li[1,2,4]

1 Centre for Individualised Infection Medicine (CiiM), a joint venture between the Helmholtz Centre for Infection Research (HZI) and Hannover Medical School (MHH) Feodor-Lynen-Straße 7, 30625 Hannover, Germany.
2 TWINCORE, a joint venture between the Helmholtz-Centre for Infection Research (HZI) and the Hannover Medical School (MHH), Feodor-Lynen-Straße 7, 30625 Hannover, Germany.
3 Department Vaccinology and Applied Microbiology, HZI, Inhoffenstraße 7, 38124 Braunschweig, Germany
4 Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, Netherlands.
5 Research Group Biomarkers for Infectious Diseases, TWINCORE, Feodor-Lynen-Straße 7, 30625 Hannover, Germany

*Equal contribution

Vaccination has proven to be the most cost-effective approach to protect against seasonal Influenza infection. However, vaccine efficacy is greatly reduced in elderly individuals. Previous studies have associated ageing with reduced protection in response to the vaccine, but failed to identify the key molecular mechanisms that underlie the differences between responders and non-responders in the ageing population.

In the current study, we longitudinally examined the proteome and metabolome in a cohort of 234 elderly individuals (>65 years of age) across two separate seasons of the trivalent-inactivated Influenza vaccination.

Our results show distinct changes in both the proteome and metabolome over time in responders, while these changes are absent in non-responders. Systematic association of protein and metabolite levels to antibody titer fold-changes reveal three main sources of variation, dependent on: time, influenza strain and baseline immune status. These different sources of variation may obscure biologically relevant findings. Therefore, we examine the heterogeneity using various statistical methods (partial least squares regression (PLSR) and maximum residual after baseline adjustment (maxRBA)) to find the proteins and metabolites that are associated to increased protection in response to vaccination.

Results from this study highlight different sources of variation that need to be considered in systems immunology research. Statistically correcting for these variations to uncover the markers associated to increased protection will provide insight in the immunological processes that drive differential vaccine responsiveness in the ageing population. These results will assist in further stratification of vaccinees and drive development of more effective vaccines.

ABSTRACT for the panel discussion

Cleaning up an important mess: Addressing rigor in BCG research

Ofer Levy MD, PhD

Precision Vaccines Program, Boston Children's Hospital; Boston, MA, USA; Pediatrics, Harvard Medical School; Boston, MA, USA; Broad Institute of MIT & Harvard; Cambridge, MA, USA

Bacille Calmette-Guérin (BCG) is a live attenuated Mycobacterium bovis vaccine developed to protect against tuberculosis. BCG is a complex stimulus that engages multiple host innate immune pattern recognition receptors (PRRs) and is increasingly appreciated as having additional beneficial immunomodulatory effects including reduction of bacterial infection in early life via enhancement of granulopoiesis. Despite growing documentation of diverse beneficial effects of BCG beyond protecting against TB, including potential protection against certain auto-immune diseases, the BCG field remains unsettled with conflicting reports and lack of consensus in terminology and approach.

Challenges in optimizing clinical use of BCG include: (a) interchangeable use of diverse World Health Organization (WHO) pre-qualified BCG vaccine formulations (e.g., BCG-Bulgaria, BCG-Denmark, BCG-India (Pune), BCG-Japan, etc) that are distinct with respect to genetic sequence, mycobacterial viability and host innate immune activation, (b) production of most BCG vaccines via non-good manufacturing practice (GMP), limiting studies in many countries, (c) incomplete understanding of the mechanism of action (MOA) of BCG and a lack of a clear correlate of protection (CoP), and (d) inconsistent use of diverse terms to describe such effects ("off-target", "non-specific", "secondary" or "heterologous" effects, etc).

Approaches to increase rigor in translation of BCG's beneficial effects should include: (a) use of consistent, well-defined terms in describing BCG effects, (b) stating the specific BCG formulations used for each study in reporting results, (c) using standardized assays to define viability and innate immunogenicity of a particular lot used, (d) addressing potential sources of variability in study design, (e) inclusion of MOA and CoP sub-studies in all BCG clinical trials, (f) developing reliable sources of GMP-quality BCG vaccines to enable prospective clinical studies across the globe, (g) conducting studies comparing different BCG formulations head-to-head, (h) using best practices in data management principles, and (i) supporting research for non-live vaccines incorporating PRR agonists that may mimic BCG action as a more stable, practical, and scalable approach. BCG's potential in reducing non-TB infections and auto-immune diseases is such that efforts to enhance rigor in BCG research may lead to substantial public health benefit.

ABSTRACT for the panel discussion

Jaykumar Menon
Open Source Pharma Foundation

The science behind the non-specific effects (although we prefer a more positive phrasing, such as broad spectrum, ultra-broad spectrum, broadly protective, or universal) – of vaccines is indubitably strong enough to warrant vigorous, rapid, and well-funded explorations. The barriers to conducting such explorations are largely non-scientific. They include a dearth of funding (a lack of funding for health products for limited profit potential, even when the funding is coming from the government), and paradigm/narrative (a dominant story that says that vaccines can only be developed by large corporations using a proprietary model. The Open Source Pharma Foundation, a global pharma nonprofit which holds that health is a human right, with a presence in Bangalore, Paris, and New York, has been advocating on behalf of the NSE field, seeking to raise the field's profile and increase the firepower behind it. Those activities – e.g. procuring a long feature article in The New Yorker magazine on the subject, and working with the US Congress - shall be discussed, and group input shall be sought.

PARTICIPANTS

Peter Aaby
University of Southern Denmark
p.aaby@bandim.org

Nelly Amenyogbe
Telethon Kids Institute
n.akuvy@gmail.com

Asimenia Angelidou
Harvard Medical School
asimenia.angelidou@childrens.harvard.edu

Patrick Ansah
Navrongo Health research Centre
lonpoa2@gmail.com

Joann Arce
Boston Children's Hospital, Harvard Medical School
joann.arce@childrens.harvard.edu

Petra Arck
University Medical Center Hamburg
p.arck@uke.de

Annelise Barron
Stanford School of Medicine
aebarron@stanford.edu

Ilayda Baydemir
RadboudUMC
ilayda.baydemir1@gmail.com

Christine Stabell Benn
University of Southern Denmark
cbenn@health.sdu.dk

Mike Berendsen
Bandim Health Project
mike.berendsen.03@gmail.com

Ozlem Bulut
Radboudumc
ozlem.bulut@radboudumc.nl

Roy Burstein
Bill & Melinda Gates Foundation
roy.burstein@gatesfoundation.org

Ole Bæk
University of Copenhagen
ole.baek@sund.ku.dk

Laura Conejero
INMUNOTEK SL
lconejero@inmunotek.com

Maria Giulia Conti
Sapienza University of Rome
mariagiulia.conti@uniroma1.it

Nigel Curtis
University of Melbourne
nigel.curtis@rch.org.au

Mia Damhus
Center for Nutrition and Therapy
md@cetcenter.dk

Carlos Del Fresno Sánchez
Hospital la Paz Institute for Health Research (IdiPAZ)
carlos.delfresno.sanchez@idipaz.es

Lucy Denly
Jenner Institute, Oxford University
lucy.denly@sjc.ox.ac.uk

Arthur Diness
University of Southern Denmark
adiness@health.sdu.dk

Jorge Domínguez Andrés
Radboudumc
jorge.dominguezandres@radboudumc.nl

Elisabeth Dulfer
Radboudumc
elisabeth.dulfer@radboudumc.nl

Helene Englund
The Public Health Agency of Sweden
helene.englund@folkhalsomyndigheten.se

Denise Faustman
Harvard Medical School and Massachusetts General Hospital
dfaustman@mgh.harvard.edu

Anaisa Ferreira
Radboudumc
anaisa.validoferreira@radboudumc.nl

Eleanor Fish
University of Toronto
en.fish@utoronto.ca

Katie Flanagan
Launceston General Hospital
katie.flanagan@ths.tas.gov.au

Ines Fronteira
Universidade Nova de Lisboa
ifronteira@ihmt.unl.pt

Büsranur Geckin
Radboudumc
busranur.geckin@radboudumc.nl

Lise Gehrt
University of Southern Denmark
lgehrt@health.sdu.dk

Anastasios Giannou
University Medical Center Hamburg-Eppendorf
a.giannou@uke.de

Tessa Goetghebuer
Université libre de Bruxelles
tessa.goetghebuer@ulb.be

Ulla Griffiths
Unicef
ugriffiths@unicef.org

Joseph Hoffmann
Tulane University School of Medicine
jhoffm4@tulane.edu

Aliya Izumi
University of Toronto
aliya.izumi@gmail.com

Rimas Jankunas
Lithuanian University of Health Sciences
RimasJonas.Jankunas@lsmuni.lt

Andreas Møller Jensen
University of Southern Denmark
amoellerjensen@health.sdu.dk

Shirin Kalyan
QU BIOLOGICS
shirin@qubiologics.com

Martin Kavao Mutua
African Population and Health Research Center, Kenya
mkavao@aphrc.org

Tayyip Emre Kehribar
University Medical Center Hamburg-Eppendorf
t.kehribar@uke.de

Gizem Kilic
Radboud University Medical Center
gizem.kilic@radboudumc.nl

Myassa Kjaerem
AJ vaccines
MYEM@ajvaccines.com

Sabra Klein
Johns Hopkins University
sklein2@jhu.edu

Henrik Kloverpris
University of Copenhagen/Africa Health Research Institute
hkloverpris@sund.ku.dk

Hans-Henrik Kristensen
AJ Vaccines A/S
HHKR@ajvaccines.com

Huong Le
Telethon Kids Institute
Huong.Le@telethonkids.org.au

Ofer Levy
Precision Vaccines Program, Boston Children's Hospital
ofer.levy@childrens.harvard.edu

David Lynn
SAHMRI and Flinders University
david.lynn@sahmri.com

Anne Marie Rosendahl Madsen
University of Southern Denmark
arosendahl@health.sdu.dk

Arnaud Marchant
Université libre de Bruxelles
arnaud.marchant@ulb.be

Juan Martín Marqués
Universidad de Uruguay
jmarques@fcien.edu.uy

Carlos Martin
Universidad de Zaragoza
carlos@unizar.es

Anna Memborg Toft
Aarhus University
Anna-toft96@hotmail.com

Jaykumar Menon
Open Source Pharma Foundation
jaykumar@ospfound.org

Isabel Inês Monteiro De Pina Araújo
Universidade de Cabo Verde
iniza.araujo@adm.unicv.edu.cv

Yoanne Mouwenda
Leiden University Medical Center
Y.D.Mouwenda@lumc.nl

Line Møller Nanque
University of Southern Denmark
lmpedersen@health.sdu.dk

Peter Nejsum
Aarhus University
pn@clin.au.dk

Mihai Netea
Raboudumc
Mihai.Netea@radboudumc.nl

Duc Ninh Nguyen
University of Copenhagen
dnn@sund.ku.dk

Sebastian Nielsen
University of Southern Denmark
senielsen@health.sdu.dk

Kate O'Brien
World Health Organization
obrienk@who.int

Abraham Rexford Oduro
Ghana Health Service
aroduro@gmail.com

Inna Ovsyannikova
Mayo Clinic
ovsyannikova.inna@mayo.edu

Puck Pelzer
KNCV
puck.pelzer@kncvtbc.org

Stanley Plotkin
University of Pennsylvania
stanley.plotkin@vaxconsult.com

Bali Pulendran
Stanford University
bpulend@stanford.edu

Leonardo O. Reis
State University of Campinas (Unicamp)
reisleo@unicamp.br

Glaucia Reis
State University of Campinas (Unicamp)
reisleo@unicamp.br

Micha Roumiantzeff
Association Lyonnaise Coopeération Franco-Russe
micha.roumiantzeff@assolyon-russie-culturel-sanitaire.org

Jeanne Annette Rungby
Rungbyklinikken
jearungby@dadlnet.dk

Christine Rückert
Curevac SE
christine.rueckert@curevac.com

Frederik Schaltz-Buchholzer
University of Southern Denmark
buchholzer@gmail.com

Martin Schjødt Foged
Martinfoged@hotmail.com

Kumba Seddu
Johns Hopkins University
kseddu1@jhmi.edu

Frank Shann
University of Melbourne
shannf@netspace.net.au

Annie Sparrow
Mount Sinai
anniesparrow@icloud.com

Natalie Stevens
South Australian Health and Medical Research Institute
natalie.stevens@sahmri.com

Esther Taks
Radboudumc
Esther.Taks@radboudumc.nl

Paul Welaga
Navrongo Health Research Centre
pwelaga@yahoo.com

Bradley Whitehead
Aarhus University Hospital
bradley@clin.au.dk

Maria Yazdanbakhsh
Leiden University Medical Center
m.yazdanbakhsh@lumc.nl

Dimitra Zazara
Universitätsklinikum Hamburg-Eppendorf
di.zazara@uke.de

Martijn Zoodsma
Helmholtz Centre for Infection Research
martijn.zoodsma@helmholtz-hzi.de

Index

OPTIMMUNIZE 2022