Algemene gegevens / General Information

Programma / Programme	:	**COVID-19 Programma**
Subsidieronde / Subsidy round	:	**Bottom-up ronde COVID-19 aandachtsgebied 1**
Projecttitel / Project title	:	**Intranasal Administration of Hyperimmunglobulins against COVID-19**
Projecttaal / Project language	:	**Engels / English**
Geplande startdatum / Planned start date	:	**20-07-2020**
Geplande duur / Planned duration	:	**18 maanden / months**
Datum indienen / Date of application	:	**14-05-2020**
Projecttype / Project type	:	**Ontwikkelproject**
Vervolg eerder ZonMw-project / Continuation previously funded project ZonMw	:	**Nee / No**

Projectleden / Project members

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Projectgegevens / Project information

Aandachtsgebieden / Focus

1.1 Thema's aandachtsgebied 1
- Behandeling

1.3 Setting
- Anders

Samenvatting / Summary

ONDERZOEKSVRAAG
We will develop hyperimmune immunoglobulin (H-IG) immunoprophylaxis against COVID-19 through intranasal administration to ensure it is safe, easy to scale-up and targeted to the point of viral entry.
Aims:
(1) To determine which minimal dose of H-IG optimally prevents severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
(2) To confirm the safety and efficacy of IN H-IG to prevent viral replication in the respiratory tract in a non-human primate model.

URGENTIE
We propose to use H-IG as primary immunoprophylaxis to protect high-risk older adults with comorbidities using daily nose drops to reduce ICU admissions and restrict the size and duration of future outbreaks. In the current global health emergency, there is a race for prevention of SARS-CoV-2. H-IG is made from purified antibodies of convalescent plasma of patients who have recovered from disease. H-IG has shown clinical benefit by reducing mortality against SARS and severe influenza(1). Global production of H-IG was initiated because of the potential to be one of the fastest available and most promising interventions against COVID-19.

HYPOTHESE
We hypothesize that IN anti-SARS-CoV-2 H-IG blocks infection of the upper airways and thereby prevents COVID-19-like disease in non-human primates (bouncer hypothesis).

PLAN VAN AANPAK
We will use the international pool of H-IG developed by manufacturers of blood products. A dose-finding study will be

conducted in hamsters and confirmation of prevention of SARS-CoV-2 replication in the respiratory tract will occur in non-human primates.
Experiment 1: Proof-of-concept dose-finding study to determine the efficacy and optimal dose of prophylactic intranasal administration to prevent SARS-CoV-2 transmission and disease in hamsters in a golden Syrian hamster model
Experiment 2: To determine efficacy of prophylactic IN antibody to prevent replication of SARS-CoV-2 in the respiratory tract of cynomolgus macaques.

Trefwoorden / Keywords

mucosal immunity; targeted therapy, safety, prevention

Samenwerking / Collaboration

Samenwerking tussen onderzoek en praktijk / Cooperation between research and practice:

Ja / Yes

Organisaties

Erasmus Medical Centre
Viroscience

Harvard School of Public Health
Department of Epidemiology

Sanquin Research
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Inhoud / Content

Disciplines / Disciplines

- Infecties, parasitologie, virologie / Infections, parasitology, virology
- Immunologie, serologie / Immunology, serology
- Geneeskunde, overig / Medicine, other

Financiële gegevens / Financial data

ZonMw budget

	Jaar / Year								
Kostenpost	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	**Totaal / Total**
Personeel	5.1.1c								345.000
Materieel									125.000
Implementatie									10.000
Apparatuur									5.000
Overig									15.000
Totaal / Total	**333.000**	**167.000**	**0**	**0**	**0**	**0**	**0**	**0**	**500.000**

Co-financiering / Cofinancing

Naam co-financier / Name of cofinancier	Bedrag / Amount	Status

Bijzondere gegevens / Additional information

Vergunningen / Permits

	Verklaring nodig / Statement required?		Status verklaring / Statement status		
	Ja / Yes	Nee / No	Verkregen / Acquired	Aangevraagd / Applied	Nog niet aangevraagd / Not applied yet
METC		X			X
DEC	X		X		
WBO		X			

Onderschrijvingen / Assents

	Ja / Yes	Nee / No	N.v.t. / N.A.
Code biosecurity / Code Biosecurity			X
Code openheid dierproeven / Code Transparency of Animal Testing		X	

Andere vergunningen / Other permits

AANVRAAGFORMULIER PROJECTIDEE – BOTTOM-UP RONDE

COVID 19 programma

Deadline voor indiening: 14 mei 2020 (14:00 u)

LEES ALSTUBLIEFT ALLE INSTRUCTIES IN BIJLAGE ''TOELICHTING INDIENING PROJECTIDEE'' VAN DE OPROEPTEKST ZORGVULDIG!

Wanneer u het formulier heeft ingevuld:

1. **Zet het formulier om naar een PDF file en controleer de details**
2. **Upload het complete formulier als een bijlage bij uw indiening in Projectnet (Let op: dit zijn twee verschillende links, gebruik maar 1 van de 2!)**

ProjectNet: Aandachtsgebied 1 (voorspellende diagnostiek en behandeling)
ProjectNet: Aandachtsgebied 2 (zorg en preventie)

BASISGEGEVENS (voorpagina)

NAAM VAN DE HOOFDAANVRAGER:

5.1.2e

ORGANISATIE:

Wilhelmina Children's Hospital, University Medical Center Utrecht

PROJECTTITEL:

Intranasal Hyperimmune Immunoglobulins against COVID-19

DATASTEWARD:

Wie is de datasteward die de open science en FAIR data planning in uw project ondersteunt? Zie de webinars op de ZonMw website om de datastewards te informeren en ondersteunen.

☐ Ik betrek een datasteward bij mijn project:
Naam: Klik of tik om tekst in te voeren.
Instituut: Klik of tik om tekst in te voeren.
E-mail: Klik of tik om tekst in te voeren.
Was aanwezig bij de webinar: ☐ Ja ☐ Nee

☒ Ik heb nog geen datasteward.

ONDERZOEKSVOORSTEL **max 3 pagina's A4** (inclusief literatuurreferenties)	(voorpagina met basisgegevens niet meegerekend - font type Arial 10 pts)

1. PROBLEEMSTELLING EN DOELSTELLING(EN):

Background

We propose to use hyperimmune immunoglobulin (H-IG) against severe acute respiratory syndrome (SARS-CoV-2) as **primary immunoprophylaxis to protect high-risk populations with daily nose drops to reduce ICU admissions and restrict the size and duration of future outbreaks**. In the current global health emergency, there is a race for prevention of SARS-CoV-2 infection. H-IG is made from purified antibodies of convalescent plasma of patients who have recovered from disease. H-IG has shown clinical benefit by reducing mortality against SARS and severe influenza(1). Global production of H-IG was initiated because of the potential to be one of the fastest available and most promising interventions against COVID-19 disease.

For common respiratory viruses, passive administration of antibodies can effectively prevent infection, such as RSV-IVIG (polyclonal) and palivizumab (monoclonal) against respiratory syncytial virus (RSV). **Intranasal (IN) prevention administered at the site of infection, the upper airways, may be key to preventing disease and viral transmission.** In mice, we demonstrated that intranasal palivizumab provides full protection against RSV for at least a week after administration(2). We reformulated palivizumab as an investigational medicinal product in nose drop formulation. In a phase I double-blind RCT we showed that this formulation was safe in healthy adult volunteers (unpublished data). Currently a proof-of-concept phase IIb trial is being conducted in infants in 30 hospitals in the Netherlands (EUDRACT 2018-002742-37). **We propose to optimize H-IG immunoprophylaxis against COVID-19 through IN administration to ensure it is safe, easy to scale-up and targeted to the point of viral entry.** The advantage of polyclonal antibody preparation, as opposed to monoclonal, includes the fast production using established protocols(3), gaining knowledge of an effective humoral immune response against SARS-CoV-2, and the lower chance of escape mutants forming(4).

Improved Safety

We have shown IN administration of antibodies to be safe in healthy adults (unpublished data). We expect **local administration to be advantageous as it may avoid unwanted side effects**(5). Safety concerns of systemic H-IG administration include adverse events such as hypersensitivity reactions and transfusion-related acute lung injury(6). We expect local antibody administration to the upper airways to avoid antibody-dependent enhancement (ADE) which was previously found in SARS-CoV(7,8). The target population for this intervention, with a high comorbidity burden, is at an increased risk of transfusion-related adverse events with current systemic administration(10). Furthermore, extensive antibody characterization will guide avoidance of vaccine-associated enhanced respiratory disease (VAERD) associated with a high ratio of binding to neutralizing antibodies(9).

Scale Up to meet need

In contrast to the development of monoclonal antibodies, H-IG is especially promising as a prophylaxis because it can be made readily available by blood banks. The bottleneck of production is the collection of convalescent plasma from potential donors. Given an approximate 1000-fold reduction in the dose of neutralizing antibodies needed for nasal compared to systemic administration, **scaling up this prophylactic intervention will be sufficient to meet the need of the target population**. Furthermore, production of the IN formulation does not require sterilisation and can be made easily available by hospital pharmacies.

Targeted Prevention

Respiratory viruses such as RSV start as an upper respiratory infection and subsequently spread to the lower airways ("north-south route"). The currently proposed route of prophylactic administration for H-IG is mainly intramuscular, however, we hypothesize that administration to the upper airways will block SARS-CoV-2 at the point of entry (**Bouncer Hypothesis**). We showed that SARS-CoV-2 has viral tropism for the nasal mucosa, no viral RNA was detected in blood(11), and the virus can transmit to naïve animals by direct and indirect contact (unpublished data). IN H-IG will lead to abortive infection by prohibiting SARS-CoV-2 from early nasal replication. IN administration allows for **targeted prophylaxis at the point of viral entry** without massive product waste.

Aim

(1) To determine which minimal dose of H-IG optimally prevents SARS-CoV-2 infection in an animal model.

(2) To determine the safety and efficacy of IN H-IG to prevent viral replication in the respiratory tract in a non-human primate model. The goal of this study is to obtain proof of concept that IN administration of anti-SARS-CoV-2 H-IG protects against COVID-19 disease.
(3) To characterize isotypes and epitopes of H-IG antibodies that correlate with protection against infection and absence of ADE and VAERD.

2. PLAN VAN AANPAK:

Hypothesis
We hypothesize that IN anti-SARS-CoV-2 H-IG blocks infection of the upper airways and thereby prevents transmission and COVID-19-like disease in non-human primates.

Study Design
A dose-finding study will be conducted in hamsters and confirmation of prevention of SARS-CoV-2 replication in the respiratory tract will occur in non-human primates.

Experiment 1: Proof-of-concept dose-finding study to determine the efficacy and optimal dose of prophylactic IN compared to systemic administration (Intraperitoneal; IP) to prevent SARS-CoV-2 transmission and disease in hamsters.
Outcome: Area under the curve (AUC) for viral load through the 21st day after inoculation

Experiment 2: To determine efficacy of prophylactic IN antibody to prevent replication of SARS-CoV-2 in the respiratory tract of cynomolgus macaques.
Primary Outcome:
1. Area under the curve (AUC) for viral load through the 21st day after inoculation

Secondary Outcomes:
1. Time to non-detectability of the virus
2. Slope of viral load during the first 24-48 hours after the start of dosing
3. Maximum and timing of peak viral load
4. Half-life of anti-SARS-CoV-2 antibodies in nasal fluid
5. Local and systemic adverse events

Methods
IN anti-SARS-CoV-2 H-IG
We will use the international pool of H-IG developed by manufacturers of blood products. H-IG will be suspended in 0.9% saline nasal drops with the preservative benzalkonium chloride.

Dosage
We base our dose-finding studies on knowledge of RSV-IVIG(13). We have calculated the equivalent mass of H-IG needed for intranasal administration for a child of 5kg. RSV antibodies in bronchoalveolar lavage fluid (BALF) are, in the most conservative estimate 500-fold lower than plasma concentrations of antibody(12).

	RSV-IVIG (child, 5kg)	IN H-IG (adult)
Distribution volume blood/Epithelial Lining Fluid (mL)	400	1,6
Volume administered (mL)	15	0,1
Antibodies in product (mg/mL)	50	100
Specific IgG in product (ug/ml)	50	100
Mass administered (ug) (13)	3750	0,1*
Concentration in blood (ug/ml)	9,4	N/A
Concentration in ELF (ng/ml)	**18,8**	**59**

*1:100 dilution of IV formulation (1 ug/ml)
We found that the minimal effective concentration in ELF must be above 59 ng/ml based on RSV-IVIG dosing and propose to administer the following 3 experimental doses: (1) 1:10 dilution IV formulation; (2) 1:10 dilution of IM formulation, and (3) 1:100 dilution of IV formulation. Minimal effective dose is considered a dose that prevents viral replication on day 4.

Animal Models
We will use the golden Syrian hamster model which to date is the only animal model in which both transmission and disease of SARS-CoV-2 can be studied(14,15). In experiment 1 hamsters will receive IN H-IG in 3 predetermined experimental doses and will be compared to IP control and placebo. These animals are subsequently co-housed with SARS-CoV-2 infected hamsters to determine whether they are protected

against transmission and disease. Based on these results, a selection of the optimal dose can be made for testing in the non-human primate model (NHP).
NHP are considered the gold standard experimental animal models for highly pathogenic emerging viruses to test the efficacy and safety of countermeasures prior to use in humans. We have recently shown that SARS-CoV-2 replicates in the upper and lower airways of cynomolgus macaques and causes COVID-19 like illness (11). This animal model allows for the fastest transition and implementation in clinical trials. In experiment 2, eight aged macaques will be treated with the selected dose from experiment 1 of IN H-IG (Groups A, n=4), compared to 400ml of IV H-IG (group B; n=2), an IN placebo (Group C; n=2) (6). Six hours later, the macaques receive intranasal inoculation with 25ul of a SARS-CoV-2 strain (BetaCoV/Munich/BavPat1/2020) containing 2x10e5 infectious virus. Nasal and throat swabs will be collected from all macaques for RT-qPCR and viral culture at baseline and every other day from day 1 through 21 post-infection.

Laboratory Testing
Nasal and throat swabs will be tested for viral load using real-time quantitative PCR for detection of viral RNA and virus titration for detection of infectious virus. We will perform radioimmunoprecipitation and western blot against whole-virus. We plan to quantify RBD-binding antibodies, S1 and S2 specific antibodies of SARS-CoV-2 as well as seasonal coronaviruses by ELISA and a multiplex antigen array and perform isotype characterization. Additionally, we will perform neutralization and ADCC assays.

Statistical Analysis
The primary endpoint in both experiments will be assessed for each of the regimens as compared with IV/IP with the use of a mixed-effects model that includes a repeated-measures approach with baseline viral load as a covariate. An analysis-of-variance model will be used to detect differences between treatment groups.

Study team
We form a Dutch consortium with a broad range of expertise: (1) SARS-CoV-2 nonhuman primate model (Erasmus MC), (2) immunotherapy and preparation of H-IG (Sanquin), (3) translational research of monoclonal antibodies (Harvard School of Public Health), and (4) intranasal antibody formulations and clinical trials in respiratory diseases (UMC Utrecht).

3. HAALBAARHEID VAN HET PROJECT:

Reformulation of H-IG as a nose drop will occur in July 2020. Experiment 1 will be conducted from October 2020 to December 2020. Experiment 2 will occur from February 2021 to May 2021. First results are expected Q2-3 2021 which will allow rapid progression to first-in-human trials. We propose to use animal models that we currently have up-and-running (11) and H-IG for which global production was initiated March 2020.

4. RELEVANTIE VOOR DE PRAKTIJK:

The proposed target population of this clinical intervention is high risk individuals (elderly, those with comorbid conditions), health care workers and people with confirmed exposure to SARS-CoV-2. The project idea allows for a fast scale-up of H-IG production to prevent disease progression. By offering prophylaxis to healthcare workers they may be able to avoid quarantine and prevent potential collapse of the healthcare system in the Netherlands in periods of high viral circulation. In a mathematical model for SARS, **antibody prophylaxis has been shown to restrict the size and duration of a potential outbreak**(16).
We expect the intervention to have an impact in the short term as H-IG is currently the intervention projected with shortest time to market. We propose to increase safety, efficiency and worldwide availability of the product through intranasal administration. After the study in nonhuman primates has been completed, the next step is a confirmatory study in humans.

5. DEELNAME VAN DE STAKEHOLDER(S) (e.g. patiënten, zorgprofessionals, etc.):

Since the elderly population is disproportionately affected by SARS-CoV2 this population is important to involve in our research. From the RESCEU consortium, an IMI-funded study in elderly adults, we will involve past participants over 65 years of age to support us in preparing for clinical studies and implementation challenges. We will involve a general practitioner with interest in respiratory infection in the elderly (5.1.2e 5.1.2e to further facilitate clinical development and implementation of this product. We will ask scientific advice from EMA for this development plan, to ensure the study design and outcomes align with regulatory requirements, and may support registration, if the benefit-risk of the product is positive.

6. LITERATUURREFERENTIES (optioneel):

1. Mair-Jenkins, J Infect Dis 2014; 2. Jacobino, J Allergy Clin Immunol 2016; 3. Bull World Health Org 1982; 4. Ter Meulen PLoS Med 2006; 5. Jones, Crit Rev Biotechnol 2015; 6. Chun, Ann Lab Med 2016; 7. Wang ACS Infect Dis 2016; 8. Liu JCI Insight 2019; 9. Graham, Science 2020; 10. Piechotta, OSF registry 2020 (https://osf.io/dwf53); 11. Rockx, Science 2020; 12. Dall'Acqua, J Biol Chem 2006; 13. Infectious Diseases and Immunization Committee, Pediatr Child Health 1998; 14. Chan, Clin Infect Dis 2020; 15. Rogers preprint on BioxRxiv (https://doi.org/10.1101/2020.05.11.088674); 16; Bogaards, Travel Med Infect Dis 2007.