Protocol for the trial:

Oral polio vaccine as potential protection against COVID-19 A cluster-randomised trial in Guinea-Bissau

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Oral polio vaccine as potential protection against COVID-19

A cluster-randomised trial in Guinea-Bissau

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INTRODUCTION

We urgently need tools to mitigate the impact of the COVID-19 pandemic. The proposed cluster-randomised controlled trial may provide evidence regarding a safe and cheap tool, which is already at hand, namely the oral polio vaccine (OPV).

JUSTIFICATION

Oral polio vaccine (OPV) was developed in 1962 by Albert Sabin and consists of live attenuated polioviruses. Large-scale clinical studies of OPV for non-specific prevention of diseases were carried out in the 1960s-70s involving more than 60,000 subjects. The studies showed that OPV was effective against influenza virus infection, reducing the influenza incidence 3.8-fold on average(1, 2). More recent studies confirmed these observations on OPV. Data from a randomized controlled trial (RCT) of OPV in Guinea-Bissau, West Africa, showed that OPV-at-birth reduced infant mortality by ~32% (3). In addition, an analysis of the effect of annual / bi-annual national OPV immunization campaigns indicates that they reduce all-cause mortality by 19%, with each subsequent campaign adding a further 13% reduction(4). This means that repeated immunization has an additive effect despite protection induced by the first vaccination. Depending on initial age, it was necessary to give campaign OPV to between 68 and 230 children to prevent one death within the first 3 years of life(4). These observations were made in the complete absence of poliovirus circulation, emphasizing the non-specific nature of the broad protection induced by OPV.

In RCTs comparing OPV against Inactivated Polio Vaccine (IPV), it was found that OPV reduced the burden of bacterial diarrheal disease in infants in Bangladesh(5). In Finland, immunization with OPV was associated with less doctor-diagnosed acute otitis media than in the IPV-immunized group(6). Furthermore, a retrospective study from Denmark found that the use of OPV was associated with reduced hospital admissions for respiratory infections in children(7).

The duration of the non-specific protection induced by OPV is unknown, but long-term beneficial non-specific effects have been observed to last for many months to years after BCG vaccination(8).

We propose to assess the use of OPV to ameliorate or prevent COVID-19(2). Both polio- and coronavirus are positive-strand RNA viruses, therefore it is likely that they may induce and be affected by common innate immune mechanisms. There are multiple important advantages of OPV: a strong safety record, its low cost, and its ease of administration and availability. Over 1 billion doses of OPV is produced and used annually in more than 140 countries. A small fraction of OPV intended for the suspended polio eradication campaigns would be sufficient for the clinical trials, and provided a positive outcome, production could likely be scaled up quickly.

The risk of complications due to OPV is extremely low. Vaccine-associated paralytic polio (VAPP) develops in 1 per 3 million vaccine doses given to unimmunized individuals. Sequential use of IPV and OPV demonstrated that prior immunization eliminates the risk of VAPP. In populations with inadequate immunity OPV was also shown to generate circulating vaccine-derived polioviruses (cVDPV). However, in countries with sufficient vaccine coverage the risk is minimal: over 35 years of OPV use in the United States there was no documented case of cVDPV emergence.

An RCT of OPV against COVID-19 is currently being discussed in the US. This effort is acknowledged by the Global Polio Eradication Initiative(9).

The African population faces severe challenges due to COVID-19. As everywhere else, it is anticipated that not least the older part of the population will be at risk of severe COVID-19. Even though OPV is widely used in Africa, it is for children, and it seems unlikely that the older population have received OPV in childhood or will still benefit from any protection induced by their childhood vaccines. We therefore propose to test if a dose of OPV to older Africans above 50 years of age - presumably in the highest risk for severe COVID - may ameliorate or prevent COVID-19 and other infectious diseases. Even a partial protection could have enormous impact in a pandemic situation, while we are waiting for more specific vaccines and treatments to be invented.

If the results of RCTs with OPV are positive, OPV could be used to protect the most vulnerable populations globally (8).

OBJECTIVES

To test if OPV can reduce the risk of COVID-19 among adults aged 50 years and above in an urban African setting.

Primary outcome: Mortality and severe morbidity (hospitalisation or consultations for infections) during 6 months of follow-up.

METHODS

We will conduct a cluster-randomised trial of OPV vs. no OPV to 3400 adults aged 50 years and above in Bandim Health Project's study area. We will focus on the older individuals, because global figures show that they are at the highest risk for severe COVID-19, and because they will not have received OPV recently.

Setting: The Bandim Health Project's (BHP, *www.bandim.org*) Health and Demographic Surveillance System (HDSS) site follows a population of 102,000 individuals in six suburbs in Bissau, Guinea-Bissau, with home visits and through surveillance at the nearby national hospital. BHP has a long track record of conducting large-scale RCTs of vaccinations with infectious disease morbidity and mortality as outcomes. The six suburbs are divided into zones; within each zone, houses are given a unique number.

Design: The study will be a cluster-randomised trial of OPV. The main reason for choosing the cluster-randomised approach is to minimise the contact between the field assistant and the household.

Randomisation: The randomisation unit will be "house". Houses will be allocated randomly to intervention or control clusters by means of a randomly generated list of house numbers allocated to either group (https://www.random.org/sequences/ - for an example see Appendix 1; a new list will be generated for the purpose of the RCT).

Intervention: The intervention treatment will be bivalent OPV (GSK), given as two drops on a sugar lump, in addition to advice regarding how to protect oneself from COVID-19. The control persons will not receive OPV, but just similar advice.

Study population: Eligible for participation will be adults living in BHP study area.

Inclusion criteria: Living in a household which has had a census visit conducted after 1 January in 2017 or later. Age above 50.

Exclusion criteria: Previous adverse events to OPV; Previous documented COVID-19; Acute severe infection.

Study procedures: In each house, an assistant will come to the house, ask for oral consent, and provide OPV and advice or just advice to all household members above 50 years of age, who are registered in our registration system and who have consented orally and in writing to participate (for participant information and informed consent form, see Appendix 2a&b+3). Their name, age, sex and ID will be registered along with as many telephone numbers as possible. A short baseline questionnaire will be filled in regarding general health including chronic diseases (Appendix 4). To maintain social distancing, no physical examination will be carried out, but the field assistant will visually assess the participants weight using a validated tool (Appendix 5). Participants will be asked for consent to being followed for mortality, hospitalisation and consultations by monthly telephone calls and registration of consultations at the health centre for 6 months.

Follow up per telephone: Participants will be called monthly to ascertain their vital status and health (see follow-up questionnaire, Appendix 6). In the case that a participant reports acute severe illness during an interview, the participant will be advised to seek medical advice.

All individuals are also followed through the Bandim HDSS. For all registered deaths, we will conduct a verbal autopsy(10) seeking to establish the cause of death.

Follow-up on consultations: If a study participant is ill, he/she will can go to the Bandim Health Project (next to the Bandim Health Centre) between 8-12 in the morning to be registered and obtain a voucher for a free consultation at the Bandim Health Centre clinic. A BHP assistant will be present with a list of study participants, to verify participation in the study, register the person with name, study ID and main cause of the consultation, and to hand out the vouchers. The Bandim Health Centre will register the patient with a study ID, and the diagnoses and treatment. The health centre will be refunded on a regular basis for consultations held for study participants.

Outcomes:

Primary outcome: Composite outcome of the first of death, hospitalisation for infection and/or consultation for infection at the health centre

Secondary outcomes: Episodes with self-reported infectious disease morbidity. Episodes with self-reported infectious disease morbidity suspected to be caused by COVID (three or more of the following: fever, cough, sore thought, extreme fatigue, loss of smell/taste). Either of the components of the composite outcome described above included repeated events.

Statistical analysis: Data will be analysed in Cox proportional hazards models, with time since randomization as the underlying time, to provide hazard ratios (HRs) with 95% CIs for comparison of the intervention and control groups. With the exception of the primary outcome, data will be analysed as a multiple failure time data set. Age in groups of 5 years and suburb will be adjusted for. Clustering within houses will be adjusted for.

Sample size: The Bandim Health Project has purchased 1700 doses of OPV. The trial will include participants until the 1700 doses have been used. With a samples size of 3400, half getting OPV, the trial can show a reduction in the combined risk of mortality (which has been around 2% in this age group in our study area) and severe morbidity after 6 months of follow-up from a total of 10% to 7.2% (i.e. a 28%

reduction) with 80% power and alpha of 0.05. Since only individuals above the age of 50 years are eligible to enter the trial, only few houses will have several participants and we expect a very limited effect of clustering.

Explanation to participants: Participants will be given thorough information about Coronavirus, about precautions to be taken, and about the study (Appendix 2).

Timeline: A Gantt diagram is presented in Figure 1.

Ethical considerations

Based on previous experience the risk of side effects from OPV is extremely low. Very rarely, there may be vaccine associated paralysis in non-immune individuals (1 per 3 million vaccine doses given to unimmunized individuals), which we do not expect to encounter since most Guineans in this age group have had polio infection in childhood, they have been repeatedly exposed to vaccine viruses when campaigns have been conducted and polio vaccine is now recommended for all Guinean children. Adverse events are most often seen after the first dose in children. Individuals infected with human immunodeficiency virus (HIV), both asymptomatic and symptomatic, can be immunized with OPV(11).

All BHP contacts with families will be restricted to the minimum necessary and the recommended protective measures and physical distance will be accurately followed by field workers and household residents during essential contacts within the scope of the study.

The protocol has been approved by the Guinean Ethics Committee and will be submitted to the Danish Ethics committee for consultative approval. The trial will be registered at clinicaltrials.gov.

Dissemination of results

As soon as the data analysis has been completed, the study report will be made available to the Center for Health Emergency Operations in Guinea-Bissau for possible use of the results. The report will also be deposited in the library of the National Institute of Public Health. The data will be published in a scientific journal and may be used for graduate work. The results of the intervention will be widely disseminated to health personnel at all levels.

REFERENCES

1. Voroshilova MK. Potential use of nonpathogenic enteroviruses for control of human disease. Prog Med Virol. 1989;36:191-202.
2. Chumakov K, Benn CS, Aaby P, Kottilil S, Gallo R. Vaccines against other diseases for COVID-19 (In press). Science. 2020.
3. Lund N, Andersen A, Hansen AS, Jepsen FS, Barbosa A, Biering-Sorensen S, et al. The Effect of Oral Polio Vaccine at Birth on Infant Mortality: A Randomized Trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61(10):1504-11.
4. Andersen A, Fisker AB, Rodrigues A, Martins C, Ravn H, Lund N, et al. National Immunization Campaigns with Oral Polio Vaccine Reduce All-Cause Mortality: A Natural Experiment within Seven Randomized Trials. Frontiers in public health. 2018;6:13.
5. Upfill-Brown A, Taniuchi M, Platts-Mills JA, Kirkpatrick B, Burgess SL, Oberste MS, et al. Nonspecific Effects of Oral Polio Vaccine on Diarrheal Burden and Etiology Among Bangladeshi Infants. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;65(3):414-9.
6. Seppala E, Viskari H, Hoppu S, Honkanen H, Huhtala H, Simell O, et al. Viral interference induced by live attenuated virus vaccine (OPV) can prevent otitis media. Vaccine. 2011;29(47):8615-8.
7. Sorup S, Stensballe LG, Krause TG, Aaby P, Benn CS, Ravn H. Oral Polio Vaccination and Hospital Admissions With Non-Polio Infections in Denmark: Nationwide Retrospective Cohort Study. Open Forum Infect Dis. 2016;3(1):ofv204.
8. Rieckmann A, Villumsen M, Sorup S, Haugaard LK, Ravn H, Roth A, et al. Vaccinations against smallpox and tuberculosis are associated with better long-term survival: a Danish case-cohort study 1971-2010. Int J Epidemiol. 2017;46(2):695-705.
9. Initiative GPE. The use of oral polio vaccine (OPV) to prevent SARS-CoV2 2020 [Available from: http://polioeradication.org/wp-content/uploads/2020/03/Use-of-OPV-and-COVID-20200421.pdf.
10. INDEPTH network. Indepth Verbal Autopsy [Available from: http://www.indepth-network.org/index.php?option=com_content&task=view&id=96&Itemid=184.
11. Holubar M, Troy SB, Nathoo K, Stranix-Chibanda L, Musingwini G, Srinivas N, et al. Shedding of Oral Poliovirus Vaccine (OPV) by HIV-Infected and -Uninfected Mothers of OPV-Vaccinated Zimbabwean Infants. J Pediatric Infect Dis Soc. 2017;6(1):105-8.