

**COVID-19 Program**

**Application form**

**Oversterfte in Nederland 2020-2021**

**Deadline for submission: 30 September, 2022 (10:00 AM)**

**Instructions:**

1. Please read the call for proposals carefully before you start writing your proposal.
2. The proposal should be written according to the format on the next pages and should be written in English. Your application has a maximum of 10 pages, font size 10, excluding front page and references.
3. The proposal consists of the following parts:
   1. **Fill in all information in MijnZonMw** tabs, for example the title of your proposal and project group composition.
   2. **This application form**
   3. **Budget form**
   4. **Written motivation on your budget**
   5. **Optional:** 
      * Attachment with figures and tables (1 A4 max.)
      * If applicable: Letters of commitment of all co-financing partners (one per organisation)

**Submission of proposals (via MijnZonMw)**Proposals should be submitted online before **30 September 2022, 10:00 AM**. For technical assistance regarding MijnZonMw, please contact the servicedesk between 08.00-17.00 on +31 70 349 51 78 or by e-mail at [servicedesk@zonmw.nl](mailto:servicedesk@zonmw.nl).

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| **General information** |

1. **Name of main applicant** (This is the same main applicant as specified in MijnZonMw.)

Prof. dr. R. (Ronald) W.J. Meester

1. **Project Title**

Vaccinations as possible contributors towards excess mortality – a statistical analysis

1. **Summary (for public use)**

Max 200 words. Please keep in mind that this text may be used for a press release, website etc.

The excess mortality in the Netherlands and other countries in 2020, 2021 and also in 2022 is largely unexplained. In the scientific literature, many articles have appeared, peer-reviewed or not, in which a link is suggested or made between this excess mortality and the mRNA vaccinations. There are now also countless blogs available in which public data is used to say something about a possible statistical relationship. The purpose of this application is to categorize, evaluate, assess and, if necessary and if possible, evaluate all this information, in order to get an idea of whether we can draw reliable conclusions with the currently available data. Depending on the outcome, further research with better data will be needed. Furthermore, in this proposal we also investigate the so-called "test-negative-design" that is used in the statistical assessment of the various vaccines. We suspect that this design is unsuitable, but that needs to be investigated.

1. **Keywords** (max 5)

mRNA vaccinations; Statistical Analysis; Data: Excess mortality; Test-negative-design.

1. **Start date**

01-12-2022

1. **Duration of the project** (max 6 months)

6 months

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| **Problem definition, objectives and relevance**  Include relevant literature references (reference list must be placed at the end of the proposal and hence is not included in the word count) |

1. **Problem definition and objectives**
2. A literature and statistical study into the side effects of mRNA vaccines.

By now, many case reports and case series have been published in which the relationship between vaccinations and the occurrence of certain side effect is made plausible [8]. The most well-known side effects are of course the inflammation of the heart muscle and the pericardium. In any case, it is clear that side effects can occur in almost any organ system, can be very serious and can also be fatal, although for many publications the distinction between ‘after’ vaccination and ‘through’ vaccination cannot be clearly made. Moreover, the ‘post’ vaccination argument based on the sheer number of pre-vaccinations administered alone is the most likely explanation for the occurrence of common conditions.

But despite this, there is ample evidence that the mRNA vaccines can have serious side effects and can also lead to death, especially in people with underlying conditions [9]. The crucial question, however, is how often this happens and whether the various side effects reported are really as rare as certain publications claim.

In view of the fact that the individual data has not been made available for scientific research, the scientific community can only base its research on very limited data. Although the call is specifically about the excess mortality in The Netherlands in 2020 - 2021, any reasonable scientific inquiry will also use available data which is obtained abroad, and in addition also data from the year 2022. It would be strange and undefendable not to use available data that can help interpreting the excess mortality in 2020-2021 but also beyond.

In this proposal we seek possible relations between vaccinations and *all-cause* mortality. There are various reasons not to first subtract the registered COVID-19 death cases, and to try to explain the remaining ones – the method employed by the CBS in their investigations into the excess mortality. Indeed, first of all, the registration of mortality due to COVID-19 has proven to be unreliable in The Netherlands: certain publications of the CBS seem to contradict each other, and moreover many cases were reported as “suspected” COVID-19 deaths, without autopsy and even without a confirming PCR-test. We briefly elaborate on this issue.

On March 6, 2021, CBS published some death figures for COVID-19. Until December 2020, there were 17,463 confirmed COVID-19 deaths, and 2,675 suspected deaths, according to CBS. So a total of 20,138 deaths. On April 1, 2022, CBS published the COVID-19 death rates up to and including December 2021. According to CBS, there were 36,578 confirmed COVID-19 deaths up to and including December 2021, and 2,974 suspected deaths. Based on this, we conclude that in all of 2021, a suspected COVID-19 cause of death (code U07.2) was entered by doctors in 299 (namely 2,974 minus 2,675) deaths on the cause of death statement. However, on April 1, 2022, Ruben van Gaalen (CBS) tweeted that RIVM had reported a total of 21,049 COVID-19 deaths until December 2021, but CBS had reported 39,552. He concluded that this is 88 percent more. He stated in his tweet that the difference is caused by the fact that RIVM only counts confirmed (code U07.1) cases, but CBS also counts suspected cases (U07.2). That would mean we are talking a total of 39,552 minus 21,049 = 18,503 probable cases. But it cannot both be true that in one year we have 299 suspected cases, and a total of 18,503.

So, we do not really know what to subtract which makes this method flawed from the outset. Moreover, Martin Neil and Norman Fenton [12] showed that in the UK, deaths occurring after the first but before the second injection were reported as “unvaccinated”. It is unclear whether this applies to The Netherlands as well.

There are indications that vaccination at least temporally increases the all-cause mortality rate, especially between the first and second injection. Again, Martin Neil and Norman Fenton [12] were the first to show that there is a peak in death from non-covid causes in the first weeks after vaccination, which was higher for the 2nd shot than for the first.

There are other indications of a possible connection between vaccinations and all-cause mortality. Christian Kuhbandner's comprehensive analysis of the excess mortality in Germany [13] shows that there was hardly any excess mortality in the pandemic year 2020, but surprisingly shows a sharp increase in excess mortality in almost all age groups, except in the age groups 0 - 14 and the over-80s, which starts in April 2021. That is exactly the month the massive vaccination campaign against COVID-19 in Germany started. The peak in excess mortality for the age group from 0 to 29 years came a few months later, in June 2021 and that was also the time when most vaccinations were given in this age group. As the authors also state, a potentially life-saving treatment such as vaccination, to prevent an infectious disease that is new to the population, would at least expect a reduction in excess mortality, but of course even better a reduction in overall mortality. However, this study shows that the vaccination campaign against COVID-19 in Germany has not lived up to that expectation.

In The Netherlands there exist a large number of professional and non-professional statisticians and investigators, who have tried to interpret the overall vaccine volumes in relation to all-cause mortality, only making use of publicly available data, and who have published their sometimes conflicting views and conclusions in journals, blogs, preprints, articles on social media, et cetera. Indeed, this is made possible since the CBS publishes population data, detailed by age, gender and geography, and the RIVM publishes cumulative vaccination volumes. It is perfectly reasonable to investigate whether or not a relation between the various quantities can be established, dismissed or made believable, based on this publicly available data. Obviously, only with the full raw data, definitive claims could possibly be made, but in the current situation in which such data is not foreseen to become publicly available in the near future, we have to deal with the current data.

Some of the above mentioned publications were reassuring in the sense that they showed no visible relation between vaccinations volumes and all-cause mortality, but others certainly do. It has become increasingly difficult to make an overall assessment of all these publications, their interrelations and the bases of the various claims. This is partly due to the fact that the statistical methods used do not always seem optimal, or seem to be even clearly problematic in certain cases. Nevertheless it would be unwise not to use the data as collected and prepared by all these investigators. In the context of this proposal, this is simply all the data that we have.

Our proposal splits into three sub-projects. The first is an extensive search to obtain the best overview possible of data, approaches, methods and conclusions that are available in the above mentioned places. In the second phase we carry out our own statistical investigations. More precisely:

Research Phase 1. Carry out a literature and internet search for papers, preprints, essays and blogs concerning any relation between vaccination and all-cause mortality. Determine the statistical methods used, their assumptions and their restrictions, and discuss and assess their overall relevance and scope. The deliverable of this first phase is a comprehensive and complete list of papers, preprints and the like, together with an assessment of each individual contribution. This phase will be carried out by a research assistant under the guidance of the principle investigator of this project. We estimate that this phase will take approximately 3 months.

Research Phase 2. The first phase will result in a list of interesting data sets and corresponding statistical analyses that have been carried out. We will carry out our own analyses of these data sets, exploiting suitable statistical techniques, including Bayesian methods, frequentist methods, time series analysis and possibly other methods depending on the data and the precise questions asked. The deliverable of this second phase is an extensive and complete statistical picture - as far as the current data allows for – of any possible relation between vaccinations and all-cause mortality. Depending on the available data we may distinguish between first, second and booster shots, and type of vaccination. As we already mentioned, although we are aware of the fact that the call addresses the years 2020 and 2021, it is well known that the excess mortality continues to exist in 2022, and we see no reason not to use data of 2022. More data can only help. Carrying out Research Phases 1 and 2 should lead to a well-informed state of the art about what we can possibly say about side effects of (in particular) mRNA vaccinations based on the data that is at our disposal. This should inform a possible continuation of this research in a possible next phase, depending of course on the outcome of our research. This phase will be carried out in a cooperation between the principal investigator and Dr. Marc Jacobs, owner of *MJS Advies*. We have cooperated in earlier projects.

1. The test-negative design

In the discussion about the effectiveness and side effects of mass vaccination, it is difficult to assess how the various sub-topics of vaccines and vaccination interact. By this we mean that proponents and opponents of vaccination often zoom in on individual elements, but make no attempt to fit them into the bigger picture. It is then about the balance between the effectiveness of vaccination and how it is measured on the one hand, and the number of reported side effects and their seriousness on the other, and how the two are ultimately weighed against each other. That trade-off is important, because in this way it can be made clear whether the advantages outweigh the disadvantages, and perhaps more importantly, for whom the advantages outweigh the disadvantages. In any study concerning possible mortality as a side effect of vaccinations, one should be cautious and careful how to study the effect of vaccination

Anyone assessing studies that make a statement about the effect of vaccination must first ask themselves about which outcome measure the study actually reports. Does it concern the effect on mortality from the disease itself, the effect on total mortality, the effect on the number of IC or hospital admissions, the effect on symptomatic disease, or perhaps the effect of vaccination on the transmission of the virus? It is essential to make this distinction, as the reliability of measuring vaccine effectiveness varies widely for these different outcome measures. This perhaps requires further explanation.

The golden standard in vaccine effectiveness research is the randomized double-blind trial. Such trials have been conducted for both the Moderna and Pfizer/BioNTech vaccines, but in both studies the not very relevant outcome measure ‘symptomatic disease’ was used, and the studies were not suitable for reducing the number of hospital or ICU visits. Also, these studies were not designed to show a decrease in disease-specific mortality from COVID-19, or a decrease in all-cause mortality. And as may be assumed by now, the studies were also not suitable for demonstrating a reduction in the transmission of SARS-CoV-2.

Carrying out new randomized and double-blind trials with the mRNA vaccines is likely to be an overdue for several reasons which we do not further specify here but about which there is no controversy. Therefore, in more recent studies, a different study design has been used to investigate the effect of vaccination on different endpoints, the so-called ‘test-negative design’ [1, 2, 3]. This study design was originally designed to investigate the effectiveness of influenza vaccines in daily practice, but it is currently also used in the context of COVID-19. To be able to collect reliable and reproducible data using this method, several conditions must be met [4, 5]. For instance, it seems that the definition of the control group affects the outcome considerably.

This begs the question to which questions the test-negative design could possibly provide answers. This is not only relevant for the investigations into the COVID-19 vaccines, but has larger scientific relevance. In particular we are interested in the question to what extent this design can give information about side effects of the various vaccines and if it cannot, how we can possibly change the design.

Research Question 3. Investigate whether or not the test-negative design is suitable for applications in the context of COVID-19 vaccines, and formulate the questions to which research with this design can possibly provide answers. This is a more theoretical research question which will be carried out by the principal investigator, possibly in collaboration with national and international colleagues.

1. **Feasibility**

The proposed research seems highly relevant for the purpose of the call. There is no real guarantee that we will be able to cover the full relevant literature in research phases 1 and 2, but the proposal is an excellent opportunity to make optimal use of the available data – which may very well be all the data that will be available also in the future.

The biggest challenge is to find the best or most appropriate statistical analyses for the various datasets that we will encounter. Since the collection of this data is one of the deliverables of this application, we cannot further specify the types of statistical analyses that we will carry out.

The tentative timeline is as follows:

Research phase 1: months 1 -3

Research phase 2: months 4 -6

Research Question 3: parallel to the research phases mentioned above.

It is hard (as usual) to predict precise timelines, but based on my experience, I think that this give ample time to carry out the various stages of the project. I am afraid that this is about what there is to say about the feasibility within the given timeline. If it so happens that we encounter a shortage of time, then we can decide to focus on a part of the available data that we deem most interesting and/or informative. In any case we will be able to provide at least partial answers to the questions asked.

1. **Relevance**

We consider it self-evident that the proposed research is relevant for the programme and the grant call. In fact, we precisely address the question of interest, and do so by concentrating on one specific aspect about which there exists considerable societal disagreement, varying from a complete denial of any potential influence of vaccines for the excess mortality to the complete opposite. Therefore, the societal relevance and significance is beyond any doubt. The previous investigations of the CBS and RIVM have not led to a satisfactory answer, due to problems with the research design and the limited use of available data.

We have already commented on expected results. In fact, we have no expectation, in the sense that we are open for any outcome that the suggested research might give. But it will be - beyond doubt – the case that the proposed research will be informative. Depending on the outcomes, the result of our research may even play a role in helping to make the full individualized (but of course anonymous data to become available.

1. **Approach**

We already commented upon the fact that part of the research (phase 1) consists of gathering data which have been used in the literature (peer-reviewed or not), on various blogs online, or which is publicly available through the CBS. We are familiar with the various types of statistical analyses that can be carried out, and we will have to be flexible as to what method suits certain data best. Often it is even better to perform different analyses with the same dataset, and to also perform some sensitivity analysis, especially in cases where information is sparse.

It seems evident that this research meets the general relevance criteria of ZonMw as described in the call.

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| **Communication and implementation plan** |

1. **Communication and implementation plan**

We plan to produce an extensive report describing our findings, which we will communicate in various ways:

* as a report aimed at policy makers;
* as (a) scientific publication(s) in (a) suitable journal(s);
* as opinion papers and/or review articles in national newspapers or other places.

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| **Project group and stakeholders**  Please make sure that all project team members are also included in MijnZonMw. |

1. **Project group**

The project group consists of (1) a research assistant to carry out the first phase, (2) Dr. Marc Jacobs, owner of MSJ Advies, to carry out phase 2 of the project in collaboration of the principal investigator, and (3) the principle investigator which will be leading and guiding the project, and who will carry out research question 3 of the project.

1. **Stakeholders**

Apart from the project group, other stakeholders are the authors of the papers, essays and blogs that we are going to scrutinize. The CBS and RIVM are stakeholders, since we will be using public data from them. Furthermore, the policymakers in The Netherlands are stakeholders, since the result will possibly of great concern to them.

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| **Data management** |

1. **Data management**

* We use all publicly available data concerning vaccination volumes (RIVM) and demography (CBS) regarding age, mortality, geography, and gender.
* Permission of this data is not required and we do not need a further data steward. All further question here seem not to be relevant for our application.

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| **References** |

1. **Please provide a concise list of references**
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