NOVEMBER 2021
16TH ISSUE

EJM

ERASMUS JOURNAL OF MEDICINE

SCREENING FOR ABDOMINAL AORTIC ANEURYSM: THE SOLUTION FOR THE SILENT KILLER?

TRANSGENERATIONAL EFFECTS OF OBESITY ON THE HUMAN EPIGENOME

ANALYSIS OF A PUBLIC HEALTH PROBLEM: THE FIRST WAVE OF THE CORONA PANDEMIC IN THE NETHERLANDS

SHOULD THE GOVERNMENT MAKE INFLUENZA VACCINATION MANDATORY FOR HEALTHCARE WORKERS?

ERASMUS JOURNAL of MEDICINE
Erasmus MC
Universitair Medisch Centrum Rotterdam
• 2009 •

Colophon

The Erasmus Journal of Medicine (EJM) is a scientific magazine by and for students, especially students of Erasmus MC University Medical Center Rotterdam. It was initiated by the MFVR (the medical students' organization of Erasmus MC). We strive to release the journal twice a year. It is published on the EJM website (link below).

The main purpose EJM is to encourage medical and research master students to conduct research (empirical studies or systematic reviews), report on this research, and become acquainted with the professional publishing process either as authors, reviewers or editors. A secondary purpose is to make the results of excellent student-driven research known to others.
The Journal accepts articles describing original research, systematic reviews, extended abstracts (summaries of recently conducted studies), calls from research projects for students to participate, opinion papers written by students, editorial comments, case reports, clinical lessons, clinical images, and letters to the editor.
The Erasmus Journal of Medicine is funded by Erasmus MC, through an unrestricted grant.

Publisher
Erasmus University Medical Center Rotterdam.

Formatting & Printing
BladNL, Utrecht

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Website
www.eur.nl/erasmusmc/onderwijs/extracurriculair/erasmus-journal-medicine
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Foreword

Times change

Times change. Although the corona epidemic is still raging, fortunately the situation has improved, so that students are welcome again at Erasmus MC. We can well imagine that this leads to a great sense of relief among students after a period of mainly online education. The possibility to meet with each other sharpens the academic mind. That is why we as teachers are particularly looking forward to the face to face meetings and discussions with students, which we sadly missed for over a year and a half.

In the meantime, the editorial work of the Erasmus Journal of Medicine has continued. A large number of fine articles has been received, opinion statements as well as systematic reviews on various topics. Quite some work has been done by the student authors, -editors and -reviewers. We are therefore proud to present this 16th issue, with articles on transgenerational effects of obesity on the human epigenome, on influenza vaccination for healthcare workers, on the usefulness and necessity of systematic PSA testing in general practice, and more ... Take some time and read these contributions.

Times change. In the past years, 15 issues of Erasmus Journal of Medicine were printed on paper. The current edition is the first fully electronic version. By going paperless, we want to contribute to the long term sustainability of our planet. As such, we take our social responsibility, and we follow the trend that scientific journals started some time ago. At the same time, we updated the cover layout and the social media house style. We trust it will be appreciated.

Times change. Eric Boersma has been chair of the editorial board of Erasmus Journal of Medicine for five years. He now passes the baton to Kamran Ikram. Working with young, enthusiastic students - they are the bearers of the Journal - is a great pleasure and provides a lot of energy. Thank you students! Good luck with your education and scientific activities, the results of which will continue to be published in the Erasmus Journal of Medicine.

Maarten Frens, Prodean of Education
Kamran Ikram, incoming Chair

Eric Boersma, outgoing Chair

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Editorial comment

Analysis of a public health problem: the first wave of the Covid-19 pandemic in the Netherlands

Siem de Wit
Editorial board of the Erasmus Journal of Medicine

For the last year and a half, the COVID-19 pandemic might be the most discussed subject in healthcare with, as of September 14, close to two million cases and over 18 000 deaths in the Netherlands alone.[1] In this issue of Erasmus Journal of Medicine, an article by Ceuppens analyses the first wave of the COVID-19 pandemic in the Netherlands by discussing the infection numbers and mortality rate in the Netherlands from February 27, 2020 until May 11, 2020, compared to those of China and the United States.[2] Ceuppens has also written a determinants analysis, given an overview of the preventive measures taken by the Dutch government, discussed the consequences of the pandemic and has advised the government on areas that must be improved for the next pandemic.

Ceuppens reports 42788 cases with a hospital admission of 26.5% and a mortality rate of 12.8% between February 27, 2020 and May 11, 2020. However, as of September 14, 2021, these are 1.6% and 0.9% respectively. It is believed that these percentages vary so much because at the start of the pandemic, mostly people with severe COVID-19 symptoms were tested and less people who only experienced light COVID-19 symptoms were tested. Also, the lower rate of hospitalization and death may be attributed to the vaccine, which greatly reduces severe COVID-19 and leads to less hospitalisation and death.[3]

Ceuppens describes 3 major consequences of the pandemic, namely the homeless as a vulnerable group, students as an exposed group and the accessibility of healthcare, or the lack thereof. This subject is what makes this analysis more valuable than just a summary of statistics and measures as it does not only focus on COVID-19 related health issues, but also the mental health of individuals and addressing the effect of lack of healthcare for non-COVID patients and its effects. Ceuppens makes a compelling argument that the public health exceeds disease and death rates.

Ceuppens ends with some advice for the government on how to handle an epidemic of pandemic in the future. He makes some valid points which do have to be looked at to properly handle a pandemic like increasing the IC capacity and its staff, but this part begs the question whether the cost of doing so outweighs the benefit.

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Screening for Abdominal Aortic Aneurysm: The solution for the Silent Killer?

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Introduction

Abdominal aortic aneurysm

An abdominal aortic aneurysm (AAA) is an enlargement of the abdominal aorta of more or equal than 3.0 cm.[1] Most AAAs are asymptomatic until a rupture occurs. Because mortality rates are up to 80% in case of a rupture, AAA can be seen as a silent killer.[2] The prevalence of AAA is especially high among older men. For men aged 65 to 69 years, the prevalence in the population of Rotterdam was found to be 3.8% going up to 10.3% for men aged over 80 years. The prevalence was only 0.2% and 2.1% respectively for women in these age categories. [3] Because AAAs are almost always asymptomatic, they are mainly discovered by accident when an ultrasound or computed tomography (CT) is done for another reason.

Screening for AAA

Ultrasonographic surveillance provides early detection and thus treatment of AAAs in a non-acute setting.[1] This could be done by population-wide screening. The 4 randomized controlled trials of population-based screening for AAA in men age ≥ 64 years that have been performed, are included in meta-analyses with a follow-up of more than 13 years. One-time AAA screening reduces AAA-related mortality significantly. The relative risk reduction is in short term 43% and in long term 34%, with a reduction of 48% and 35% for AAA rupture rate respectively. Screening also significantly increases elective AAA-related surgeries and decreases emergency procedures. [4, 5] Moreover, a nationwide one-time screening for AAA in men of 65 years or older is already introduced in England and Sweden.[6, 7] The national screening in Sweden has created a reduction of AAA-related mortality of 4.0% per year.

In The Netherlands, there is no screening program for AAAs. On one hand, such a program could result in health improvement in people who are screened. On the other hand, screening also entails disadvantages such as overdiagnosis, overtreatment and costs for the Dutch society. Both sides will be discussed in this manuscript in order to answer the question whether a one-time screening for AAA in men aged 65 years or older should be introduced in the Netherlands. In other words, this paper will try to answer the question: Is the health benefit of screening for AAA proportional to the disadvantages?

Population-wide screening, Medical conditions

When introducing a population screening program, a number of conditions must be met that have been drawn up by the Health Council.[8] These conditions are based on the Wilson and Jungner criteria [9] and consist of both medical and ethical conditions. A number of these aspects will be discussed below.

AAA characteristics

The prevalence of AAA in the Netherlands among men increases with age from 3.8% (65-69 years) to 10.3% (>80 years), while it is low among women.[3] Risk factors for the development of AAA besides sex and age are hypertension, smoking and a positive family history for AAA.[10, 11]
The mortality rate in case of a rupture is over of 80%.[2] In a clinical setting, when an AAA between 30 and 54 mm is diagnosed, ultrasound surveillance is performed in combination with cardiovascular risk management and lifestyle advice. [1] Treatment of AAA with open repair or endovascular repair (EVAR) is only indicated when the aorta diameter reaches 55 mm.[1] The 30-day mortality rate is 1.4% for EVAR and 4.2 % for open repair. There is no difference in long-term mortality between both interventions.[12]

The usefulness of screening

The usefulness of AAA-screening is illustrated by studies showing that a one-time screening for AAA in men ≥ 65 years reduces AAA-related mortality. The relative risk reduction is in short term (3-5 years) 43% and in long term (>13 years) 34%. [4, 5] Also, it decreases the number of ruptured aneurysms and emergency operations, whilst increasing the number of elective procedures.[5] Besides, in long term follow-up, the AAA-screening reduces the all-cause mortality by 2%.[13]
However, the decrease in absolute risk of AAA-related mortality is small, namely 0.32% in a follow-up period of 13-15 years. This results in a Number Needed to Screen (NSS) of 311 to prevent 1 AAA-related death.[5]
It appears that screening women ≥ 65 years does not reduce AAA-related nor overall mortality.[14] All these data are derived from one-time screening. Only a small number of studies have been done on repeated screenings. One randomized study shows that after 10 years of follow-up, only in 4% of the screened population the aorta had progressed from a normal aorta (<3.0 cm) to an AAA. None of these AAAs were larger than 4.0 cm.[15]

Reliability and validity of the screening method

The screening method used in studies on AAA-screening is abdominal ultrasound. Ultrasound is a non-invasive and valid screening method for AAA with a sensitivity of 57.1 to 70.4% and specificity of 99.2 to 99.6%.[16] This means that the number of false-positive outcomes will be very low, but there will be some false-negative outcomes.

Efficient use of resources
In addition to efficacy, it is also important to look at the effectiveness of screening. A measure that has been used for effectiveness are the costs per Quality-adjusted life year (Qaly). In the Netherlands, we have set the limit for the costs of all forms of prevention at €20,000 per Qaly. This limit arose from a guideline for primary prevention of cardiovascular disease.[17] A meta-analysis showed that the costs per Qaly for AAA-screening are on average $16,854 (range $266 to $73,369). This is an average of €15,106 euros (range €238 - €65,758) based on the November 2017 currency year.[18]

Population-wide screening, Ethical aspects

Do well and don't harm
The one-time screening for AAA in men ≥ 65 years will promote the health of this screening population, representing the usefulness of screening. It provides a relative risk reduction in both short- and long-term AAA-related mortality.[4, 5, 13] It also decreases the number of ruptured aneurysms, which are associated with a high mortality.[5, 19] Additionally, surveillance of men with an AAA in combination with cardiovascular risk management and lifestyle advice improves the 5 year survival rates.[1] Given these points, the health of the at-risk population will be promoted, and the principle of beneficence will be met.[20]
However, the AAA-screening may also cause harm to the screened population. This would be against the principle of nonmaleficence.[20] The ultrasound is not 100% sensitive and specific.[16] This results in both false-positive and false-negative results. First, false-negative results lead to an AAA diagnoses to be missed in a number of men who then will not receive the desired treatment. Besides, this leads to unjustified reassurance. However, surgical treatment of an AAA is only indicated when the diameter exceeds 55 mm.[1] So, the chance that a person misses an important surgical treatment due to a false-negative result is small. Second, false-positive results can contribute to a temporary additional psychological burden for the screened population. However, the total number of false-positive results will be small due to the high specificity of the ultrasound.[16] Also, in case of a positive ultrasound result, these persons will be sent to the outpatient vascular surgery clinic. There, the ultrasound will be repeated or a CT-scan will be done. In case of a false-positive finding, soon it will be discovered that there was no AAA after all.
Finally, screening leads to the phenomena overdiagnosis and overtreatment. Overdiagnosis results from a screening program by identifying individuals that would otherwise not have been identified because the condition screened on would not have led to symptoms. Overdiagnosis can lower the mental Quality of Life (mQoL).[21] Studies have shown however, that the reduced mQoL normalizes after 12 months.[22] Overdiagnosis may result in overtreatment. Perhaps patients that are identified with an AAA greater than 55 mm are treated while they would have never ruptured. This is a phenomenon related to AAA treatment in general as it is a preventive procedure. Overtreatment can cause harm to individuals, since the 30-day mortality rate of EVAR and open repair are 1.4% and 4.2%, respectively.[12] Considering that the number of false positive and false negative results will be limited and that the phenomena overdiagnosis and overtreatment occurs in all forms of medical practice, the significant health gain of screening will be proportional to the limited harm the screening will cause.
Respect for autonomy
If screening for AAA will be introduced among all men ≥ 65 years, it will concern an entire population group of the Dutch society. The AAA screening is an active offer from the government to all men of the Dutch population. This offer is often without request from the individual. Due to the fact that the offer is provided by the government, people can initially feel compelled to participate. If screening would be mandatory, it could go against the will of the screening population which is against the principle of respect for autonomy.[20] A national screening for AAA can however comply with this principle by allowing every man to make a voluntary, well-considered decision. A screening population can only do this if they are sufficiently informed about the AAA screening.

Justice
The introduction of AAA-screening does not only involve the population to be screened, but also the entire Dutch society, because population screenings are nationally funded. In other words, everyone pays for it. The question that arises is whether screening for an AAA is cost-effective enough for it to be fair to pay for this screening program while possible other screening programs cannot be funded.
In the Netherlands, we have set the limit for the costs of prevention at €20,000 per Qaly and previous studies have shown that screening for AAA in men ≥ 65 years costs on average €15,106 per Qaly. However, there is a wide range of these costs from €338 to €65,758 per Qaly.[17, 18] This wide range does not provide a good basis for demonstrating the cost-effectiveness of AAA screening. Hence, it will not be fair to introduce this screening at the expense of other potential population-wide screening programs.

Discussion

The AAA screening fulfills most of the criteria used by the Health Council. AAA is not only a disease with a considerable prevalence in the Netherlands, but can also be associated with a high mortality rate. The screening is a great tool to reduce AAA-related and overall mortality in men aged over 65 years. Also, the detection of an AAA will warrant cardiovascular risk management and life style advice improving cardiovascular health. Additionally, the AAA screening includes a valid screening method and tends to be efficient in the sense of cost-effectiveness. Furthermore, the damage from the psychological burden, overdiagnosis and overtreatment is limited. Despite the slight reduction in absolute risk, the NNS is lower in comparison with other population screenings.[23] The advantages for the screened population outweigh the disadvantages for both the screened population and the Dutch society. This conclusion is in line with the recently revisited European Society for Vascular Surgery clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms, which recommends a population screening for AAA with a single ultrasound scan for all men at the age of 65.[1]
However, there are some preconditions when introducing AAA screening. It must be entirely voluntary and the screened population must be well-informed. Due to the wide range in costs per Qaly, further research should be conducted focusing on the effectiveness of AAA screening. This is necessary to justify the introduction into the Dutch society.

Conclusion

In my opinion, the health benefit of screening for AAA is proportional to the disadvantages and a one-time AAA-screen-

ing in men aged over 65 years should be implemented in the Netherlands.

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Opinion Paper

Early diagnostics by means of a PSA test: can a general practitioner refuse the request of a patient without prostate complaints?

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Introduction

With a prevalence of 82,144 diagnoses in 2017, prostate cancer is the most common form of cancer in men in the Netherlands. In addition, with 2,862 deaths in the same year, it constitutes 11.5% of all cancer deaths, making it the second cause of all cancer-related death in Dutch men.[1] The mortality of prostate cancer increases with age.[1-3] To diagnose prostate cancer at an early stage, in order to be able to start treatment earlier, there is the possibility of early diagnosis by means of a PSA test.[4] This test can be performed by a general practitioner at the request of a patient, even if there are no prostate complaints. Is it justified as a general practitioner to refuse such a request if the advantages of the test doesn't outweigh the disadvantages, despite neglecting the patient's autonomy?

Medical scientific overview

Prostate cancer or prostate carcinoma is a malignancy of the prostate and, therefore, only occurs in men. This type of malignancy grows slowly and generally does not present or presents late with symptoms.[2,5] Prostate cancer may have a high prevalence and constitutes a large share of overall cancer mortality in Dutch men, but having prostate cancer in most cases has no consequences for the individual's physical health. Research has shown that prostate cancer occurs in about 59% of men over 79 years, but that the chance of dying from prostate cancer is 'only' 3%.[6]

In view of the many occurrences, there is the possibility of early diagnosis with the help of the rectal examination and, if this is not abnormal, a PSA test.[7] PSA, or prostate-specific antigen, is a protein that is made by the prostate and can be measured in the blood. The higher the PSA value, the greater the chance that prostate cancer will be found.[4,6,8] Scientific guidelines have been drawn up containing cut-off values for the measured PSA level to determine whether and, if so, which follow-up diagnostics should be used. Possible follow-up examinations include ultrasound of the prostate and/or performing an MRI scan, including taking prostate biopsies, and possibly a bone scan. When a non-metastatic prostate carcinoma is diagnosed, depending on the Gleason score, a measure of the aggressiveness of the cancer, active monitoring, radical prostatectomy, external radiotherapy, brachytherapy and/or hormonal treatment can be chosen.[9]

Currently, there are no clear criteria for general practitioners on the basis of which they can determine which men should receive a PSA test. This also applies to men with a family history of prostate cancer. Different studies indicate that there is no clear relationship between family history and having more aggressive prostate cancer. Therefore, this difference shouldn't affect the decision.[10,11] However, various decision aids have been developed for men to make a proper assessment themselves.[12-15] This is because a PSA test has both advantages and disadvantages.

An important advantage of performing a PSA test is that prostate cancer can be diagnosed at an earlier stage. As a result, the patient can be spared further diagnostics and invasive therapy. For example, it has been shown that performing a PSA test is associated with a lower prostate cancer-specific mortality in the Netherlands.[4] In addition, a non-abnormal test result can also be reassuring for men.[16]

In contrast, performing a PSA test also has its drawbacks. First of all, the specificity of a PSA test is not 100%; in other words, a positive test result does not necessarily indicate the presence of a prostate carcinoma. In about 10-20% of cases, a PSA test gives a false positive result.[4,17] In addition, there are also other causes that can lead to an increased PSA level, such as prostatitis, benign prostatic hyperplasia (BPH) or a urinary tract infection (UTI).[6] A positive test result in these cases causes unnecessary stress for the patient. In addition, follow-up diagnostics are used based on the abnormal test result, which entails a higher risk of complications. For example, taking prostate biopsies can lead to infections, bleeding and problems with urination.[4,6,18-20] Also, an increased risk of hospitalization has been shown.[4,6,18-20] This while in about 60-80% of the men who take prostate biopsies, no prostate cancer is diagnosed [4]. Secondly, also the sensitivity of a PSA test is not 100%.[17] Thus a negative test result can be obtained in men with a prostate carcinoma, which means that these patients are wrongly reassured. This is the case in about 15% of men with a negative test result.[21] In addition to the consequences of specificity and sensitivity, there is a risk of overdiagnosis and overtreatment when performing a PSA test. The test also detects small indolent prostate carcinomas that would otherwise never have led to complaints or death.[2,4-6,8,18,19] This group makes up about 23-50% of prostate cancers detected.[6] These clinically irrelevant prostate carcinomas do qualify for major treatments with the associated risks, such as the development of urinary incontinence or sexual dysfunction.[4,6,18,19] These men also face psycho-

logical problems such as anxiety and insecurity throughout the process.[22] Another important point is that research shows that individual early diagnosis by means of a PSA test has no effect on the overall mortality, although in some studies a small decrease in prostate-specific mortality is found. [4-6,8,18,19,23] In addition, no increase in quality of life was found.[4,5] Finally, in addition to the consequences for the patient, the social consequences should also be considered. Both time and money are scarce health care resources, which are claimed by performing a PSA test. The average duration of a consultation with the GP is only 10 minutes, but a referral based on a positive test leads to one or more consultations with a urologist.[24] Besides, the administration of ultrasound-guided or MRI-guided biopsies or performing a bone scan can be needed, which takes about 20-30 minutes, 40 minutes or 4 hours respectively. It has not been shown that early diagnosis of prostate cancer by means of PSA testing is cost-effective, but the total healthcare costs incurred for prostate cancer in the Netherlands in 2017 amounted to about 381.7 million euros. [25,26]

Ethical aspects

As can be read earlier, prostate cancer is a common condition among men in the Netherlands and there is the possibility of early diagnosis using a PSA test.[1-3] This test has both advantages and disadvantages. The ultimate choice to have this test performed lies with the patient himself.[7] This raises the question: is it justifiable for a GP to reject the request if the test does more harm than good, despite ignoring the patient's wishes?

On the one hand, it may be argued in favour of refusing a request for a PSA test when a physician appeals to the ethical principles of "no harm" and "justice".[27,28] Every physician in the Netherlands has taken the Dutch Doctor's Oath, in which he/she promises not to harm a patient.[29] In the case of the PSA test, several harmful effects can be named: unnecessary anxiety and follow-up diagnostics due to false positive, false reassurance due to false negatives and overdiagnosis and overtreatment.[2,4-6,8,18,19] All this, while performing a PSA test is not associated with a decrease in overall all-cause mortality or an improvement in quality of life, makes that this damage can be considered disproportionate.[4-6,8,18,19,23] In addition, every physician has vowed to know his/her responsibility to society and to promote the availability and accessibility of healthcare.[29] Thus the physician has the task of guarding the claim on socially scarce resources such as time and money, by distributing them lawfully within healthcare. In the context of early diagnosis, this means that the option of refusing a PSA test can lead to less overdiagnosis and overtreatment. This will result in cost savings, freeing up money for other places in healthcare and/or society and savings in time so that urologists can help more other patients, for example.

On the other hand, it could be argued that refusing a request for a PSA test ignores the principles of "respect for autonomy" and "justice".[27,28] A competent adult in the Netherlands has the right to make choices for himself/herself that relate to his/her health. The danger of this when considering whether or not to have a PSA test performed is that it is difficult for a physician to estimate to what extent the patient is fully informed and is able to make a good choice in this regard. For example, it has been proven that men are not fully aware of all aspects of early diagnosis, value the information differently and do not always feel capable of making this decision themselves. [16,30,31] In addition, the question is to what extent you can let an individual make their own choice, when this choice also has social consequences. Thereby, there may be a risk of inequality between patients, as one physician may in a particular case refuse a request for a PSA test, while another physician would grant it. However, the question is whether this risk actually exists. Indeed, it appears that a variety of factors influence a physician's decision to honour a request or not.[32] By establishing clear criteria on the basis of which a physician can or cannot refuse a request for a PSA test, you reduce the influence of these factors and you may create, on the contrary, more equality between physicians.

Conclusion

A number of arguments have been discussed regarding whether or not it is justifiable to refuse a request for a PSA test in a patient without prostate complaints. On the one hand, it could be argued that a general practitioner should be allowed to refuse the request in order to avoid physical and psychological harm and to limit unnecessary claims on time and money in health care. On the other hand, a general practitioner does go against the autonomy of the patient and there may be a risk of unequal treatment between physicians. With regard to ignoring the patient's autonomy, it remains difficult for a physician to estimate whether a patient is actually able to make the choice for the request himself, men also indicate this themselves and the choice does not only relates to the individual but also has consequences for the society. In addition, it can be questioned whether the inequality is increasing; the effect could even be the opposite, because of the fact that the possibility of refusing a request for early diagnosis will be laid down in guidelines. The argument that a physician has a duty not to harm his patient weighs heavy. The negative consequences of performing a PSA test in men without prostate complaints can be enormous, while a physician can simply prevent this by refusing the request if there is no reason to perform the test. The part of the patient's autonomy that must be surrendered for this is not in proportion to the consequences that can be prevented. If all arguments are carefully weighed against each other, it can therefore be concluded that as a general practitioner it is justified to refuse a request for a PSA test in a patient without prostate complaints, if the advantages of the test doesn't outweigh the disadvantages, even though the patient's autonomy is hereby neglected. There are important preconditions to this. It is of great importance that clear guidelines are formed, which describe when physicians may or may not refuse a request; this is to prevent inequality between physicians. In addition, if the request is refused, a general practitioner must provide the patient with sufficient explanation in order to keep the relationship with the patient intact.[13]

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Analysis of a public health problem: the first wave of the Covid-19 pandemic in the Netherlands

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Epidemiological analysis

In December 2019 a new SARS-CoV-2 virus causes pneumonia-like symptoms when infecting patients. [1] Some of the patients end op on intensive care units where a significant part of these patients don't survive this new virus. Due to human-to-human transmission, the virus quickly spreads the city of Wuhan in China, where it originated. On March 11 2020, after the virus already infected more than 120,000 people in 114 countries, the World Health Organization (WHO) declared the coronacrisis a pandemic.[2] Meanwhile, the virus keeps spreading rapidly and uncontrollably with a disastrous effect on the world. Has the Dutch government made the right decisions during the first wave? In this paper the strategy of the government on handling the pandemic will be highlighted and an advice will be given out in order to be better prepared for future pandemics.

Figure 1 shows that from the first infections in the Netherlands on February 27 until May 11, 42788 cases were reported to the Gemeentelijke gezondheidsdienst (GGD), 11343 (26.5%) were admitted in the hospital and 5456 (12.8%) people died due to the coronavirus. More men (55.8%) than women died and the mortality rate is the highest among adults aged 70 or more (88.7%).[3] Figure 2 shows the incidende of infections in China compared to the United States. It shows that the peak of infections in China started much earlier, but also extinguishes to a minimal incidence on May 10. The total number of infections in China was 84450 people. In the United States it can be seen that the incidence starts later compared to China, which can be explained by the fact that the virus originated in China, but on May 10 it is still in full swing in the United States and a total of 1271645 Americans are infected.[4] The total number of infections worldwide is in reality much higher because not everyone who may be infected is also tested. When the WHO data is compared with the incidence in the Netherlands measured by the Rijksinstituut voor Volksgezondheid en Milieu (RIVM), there is underreporting of the WHO. As a result, the expectation is that the actual number of infections is higher than described by the WHO in China and the United States.
To compare coronavirus mortality rates with seasonal influenza mortality rates, mortality rates from 2010 to 2018 were compared with mortality rates due to corona until May 11 in the Netherlands, see Figure 3. It shows that the number of deaths due to coronavirus in the last 3 months is relatively much higher compared to influenza in the last 8 years with an actual effect size of 4.5.
The group of people aged over 70 has the highest mortality rate, suggesting that this is a risk factor for death. This is confirmed in a study by Wu et al.[5] In a systematic review of Yang et al.[6], hypertension, cardiovascular disease and chronic pulmonary disease were found as risk factors. This corresponds with the Dutch data: up to May 11, 614 patients under the age of 70 died in the Netherlands. Of these, 70.4% had an underlying disease such as cardiovascular disease (43.8%), diabetes (26.6%), chronic pulmonary disease (24.3%) or malignancy (15.0%).[3]

Determinants analysis

Origins

The origin of the pandemic is most likely due to the physical environment that served as its source. More than half of the first infected patients were linked to the Huanan Seafood Wholesale market.[7] Hence, the fish market was possibly the primary source of infection for the coronavirus. It could have started here as a zoonosis and later led to a pandemic through human-to-human transmission. Should this have been the cause, the political environment also had a considerable influence on the emergence of this pandemic. After the SARS outbreak in 2002 in China and the fierce criticism on the 'wet markets', little has been executed by Chinese politics to improve these kind of markets.[8]

Development

Chinese New Year at the end of January caused many Chinese to travel and in this way most likely contributed to the spread of the virus.[9] Because Wuhan has the largest airport in central China it contributes to a large flow of international air traffic, which may have been an important social determant for the cause of the spread. The spread of the virus in the Netherlands can most probably be traced back to the celebration of carnaval, which is an annual celebration in the southern provinces of the Netherlands, in view with the high number of infections in North Brabant. Moreover, another environmental determinant could be traced back to the different vacation periods in the Netherlands between south and north Holland. Around the period that the southern part of the Netherlands were on vacation, 1100 patients were reported in Italy, compared to 62 patients a week earlier when the northern part had a holiday week.[10] In addition, the virus presents mild symptoms in 81% of patients and is transmissible in asymptomatic patients.[11,12] These characteristics will most likely have contributed to the faster spread of the virus.

Seriousness

How the coronavirus could have eventually led to a global pandemic is strongly related to the attitude towards the virus. Because the Chines government probably withheld critical information about the virus in the first weeks of the outbreak

and the fact that they denied that human-to-human transmission could take place resulted in a longer period of time to take the virus serious.[13] As a result of this delay, it took longer for adjustments to be made in China, but the seriousness of this relatively unknown virus was also underestimated internationally.[14] This resulted in few changes in the environmental factors. The attitude in the beginning was that the virus was mainly innocent and that it would take a long time before it would reach the Netherlands due to the fact that there is no direct flight to Wuhan. This caused little change in the political environment. Even when the number of patients in Northern Italy increased, little or no adjustments were made to the travel advice to Italy and the rest of the world. The seriousness only became apparent when Italy's cry for help echoed across the rest of the world. It was too late when political measures were taken and the attitude towards the coronavirus changed extremely fast.

Prevention measures

In case of supra-regional infection outbreaks, the RIVM coordinates infection control instead of the local GGD. Since the Covid-19 outbreak, the RIVM has asked the Outbreak Management Team (OMT) several times for advice, which includes experts from various specialties. The RIVM then submits the advice to the Ministry of Public Health, Welfare and Sport. In the fight against infectious diseases, two phases can be distinguished to promote and protect public health. In the containment phase, efforts are made to contain the outbreak and prevent new infections by rapidly identifying and isolating patients. In addition, contact research takes place, carried out by the GGD, as soon as someone has tested positive for a virus, for example. If that does not succeed, a switch is made towards the mitigation phase. This phase tries to remain the capacity in hospitals for those who really need it. All measures aim to protect the elderly and vulnerable people. Some measures, however, return in both phases, because they can both slow down the spread of the virus and smooth out the peak of the outbreak. Communication in the transmission of measures is essential because there is always a part of the population that does not respond and a part that overreacts. Tables 1 and 2 describe the preventive measures.[15]

Consequences of the pandemic

Vulnerable groups: Homeless

Whereas staying inside is a relatively easy task for most people, this is an enormous obstacle for the homeless. Baggett et al. described that in a large shelter in Boston with 408 homeless people 147 Covid-19 infections were reported. Of these 147, 87.8% was asymptomatic.[19] In the Netherlands efforts are being made to prevent such outbreaks in homeless institutions. For example, the 1.5-metre rule in dormitories is strived for and hotels, cruise ships and sports halls are used as reserves to create overnight accommodation.[20] Furthermore, information is provided about Covid-19 and test are carried out on large scales in case of suspicion. This is extremely important since homeless people often have chronic underlying diseases and a poorer immune system. If they enter a shelter asymptomatically, they can also endanger other homeless people with underlying problems on a large scale.[21, 22] However, it is also a challenge to maintain an overview in this particular group due to the mobility of homeless people, which makes it a challenge to track down some and help those who need help.[23]

Exposed groups: Students

Where some would not describe students as exposed groups, a survey conducted by multiple Dutch universities stated otherwise. Since physical education has been replaced by online meetings and pre-recorded lectures, a decrease in mental health and an increase in general anxiety has been observed.[24] In this survey which was send in June 2020 with more than 8000 recipients, 56.3% found it harder to concentrate and 52.5% is more lonely. These results are specifically concerning given that the government is mostly interested in risk groups and the general population. Despite the lack of social involvement, which for most students is utterly important, future perspectives also seem to diminish.[25] Internships are cancelled and there are fewer job offers to which more people apply. Moreover, with the predicted upcoming recession, future perspectives are becoming darker and darker. It is therefore of importance to not only focus on the broad population but see it as it is: different groups requiring different approaches to solve this pandemic.

Accessibility of care

The result of the hard work to combat the coronavirus has led to a new problem: the delayed demand for regular healthcare. Throughout the Netherlands, regular care has disappeared to the background for the expected flow of Covid-19 patients and the high care these patients demand. Whereas the large flow of cases in the north of the country was not as high compared to the south, the regular care started again around June in this region. This creates inequality in care. Because non-corona care was put on hold for a longer period in different regions, the backlog was more present in these regions. This resulted in disproportionality of the years of life gained compared to the years lost due to the delayed healthcare. For example, an independent report by Gupta Strategists stated that, as a result of the postponement of regular care, there was a tenfold loss of healthy life years compared to the gain gained from the care for corona patients[26] In order to reduce the inequality of regular care, it should be more important that corona patients are evenly distributed among hospitals throughout the Netherlands.[27] In addition, the fear of going to the hospital and not the thought of not wanting to burden the GP causes postponing new diagnoses such as breast cancer.[27]

Advice to the government

In order to prepare the Netherlands for the next epidemic or pandemic, there are several areas for improvement that need to be implemented. First of all, the intensive care (IC) capacity needs to be increased. This is not only done by increasing the number of beds, but also by training enough staff. There is a shortage of IC nurses because they are well underpaid for the work they have to do.[28] As a result, there is little motivation for future and current nurses to stay in this specialization direction. Many nurses came back during the crisis to help in the IC, but as soon as that the peak has passed, they will leave again. However, the staff who will be left behind have no recovery time because all postponed surgeries will pick up again. It is therefore important in the long term to attract and retain enough trained people. In addition, an important lesson we must learn is that we are far too dependent on other continents when it comes to medical facilities. Companies such as DSM and Auping are now temporarily producing mouthpieces because there was no more supply from Asia. In order to cope with the next epidemic/pandemic, it is important to reduce this

dependency. The same applies to the test material, in case of mild complaints it was no longer possible to test due to a test shortage. The Netherlands was insufficiently prepared for a pandemic to test people and protect the medical personnel. Moreover, we have to ask ourselves whether we see profit in healthcare as a top priority. The Netherlands was very proud of the high occupancy rate of the IC beds, while in Germany, for example, this was a lot lower. As a result, during the first peak of the crisis, the Netherlands was able to take care of a much lower number of patients who were admitted on the IC, resulting in several Dutch patients being transported to Germany. Because there is always an insistence on keeping healthcare costs as low as possible, there is a narrow margin which makes it impossible to take care of large amounts of new patients in times of a pandemic. Saving the economy by the Dutch government as a result of the corona crisis by providing emergency funds may well cost a lot more than the profit that has been made by keeping the utilization rate so high in recent years. It is therefore important to look at whether the choices we have always seen as the best and only way should remain the choices for the future. The Netherlands should not remain so dependent on foreign countries and healthcare costs should be kept to a minimum now that we have seen what a pandemic can do to our country.

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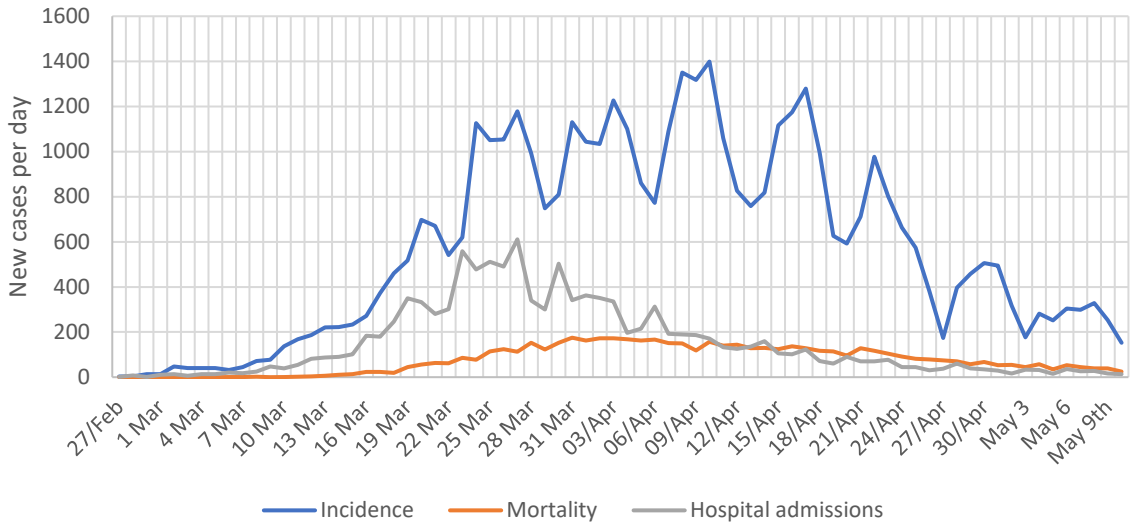


Figure 1: Epidemiological data in the Netherlands from February 27 to May 11 (incidence, mortality and hospitalizations)

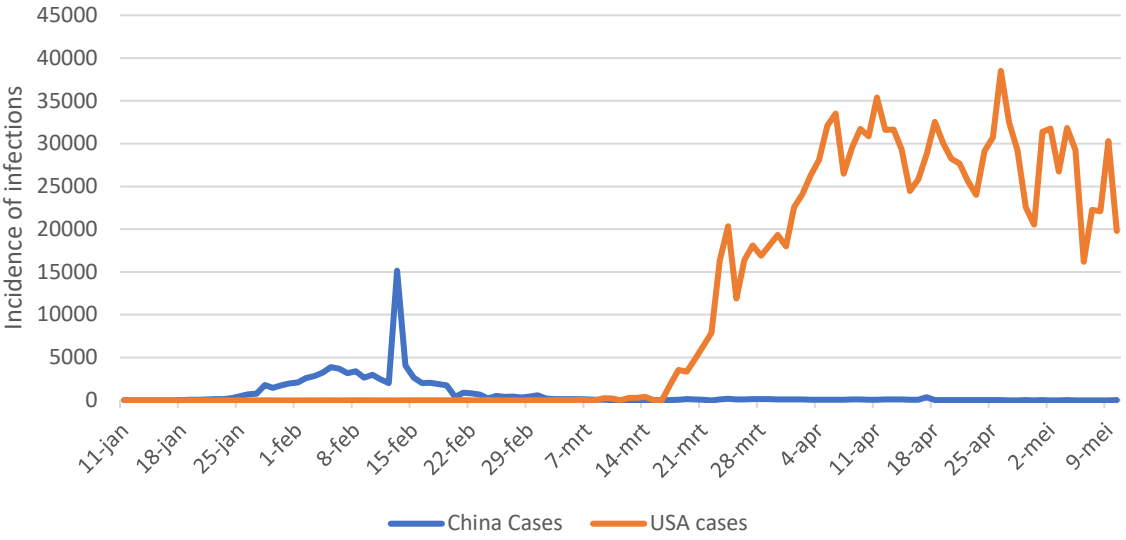
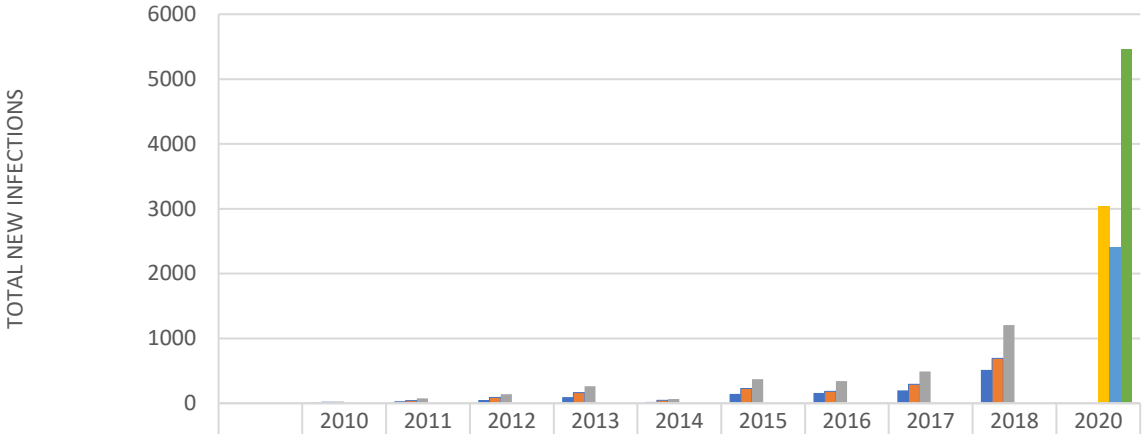


Figure 2: Epidemiological data in China and the United States (incidence)



		2010	2011	2012	2013	2014	2015	2016	2017	2018	2020
Men	0	10	31	51	96	23	143	157	198	513	
Woman Influenza	0	14	43	90	166	44	228	186	292	694	
Total Influenza	0	24	74	141	262	67	371	343	490	1207	
Men Corona	0										3044
Woman Corona	0										2412
Total Corona	0										5456

Figure 3: relative comparison of seasonal influenza mortality rates compared to the coronavirus in the Netherlands

Table 1: Prevention measures for the containment phase during the corona outbreak

Measure	Argument
Feb 27 – Feb 29: initiation of contact research by the GGD and mandatory notification when tested positive.	Contact research of the first positively tested corona patients in the Netherlands in order to control further spread.
March 4: Only necessary travel to Northern Italy.	This was the European epicenter of the virus.
March 6: Advice to stay at home for residents in Noord-Brabant with symptoms.	Most cases are in Noord-Brabant, by staying at home when having symptoms slows down further spreading of the disease.
March 9th: stop shaking hands and wash them well. Cough and sneeze in the inside of your elbow.	This significantly reduces the chance of spreading.[16]

Table 2: Prevention measures for the mitigation phase during the corona outbreak

Measure	Argument
March 12: Staying at home with symptoms applies for the whole country. Meetings with more than 100 people are canceled.	Not everyone is symptomatic and infectivity is high around the first symptoms. [17]
March 15: education and catering closes, sports are cancelled. People have to keep 1.5 meters distance between each other.	Closing schools, however is contradictory as children play a small role of dissemination.[18]
March 23: fines are handed out if measures are not complied with.	Because rules are not complied with, stricter action is taken in case of non-compliance.

Opinion Paper

Is a ban on hymenoplasty desirable in the Netherlands?

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Introduction

In February 2020, the Minister of Health, Welfare and Sport Hugo de Jonge and the Minister for Legal protection Sander Dekker, wrote in a letter to the House of Representatives (Tweede Kamer) that hymenoplasties, also known as hymen reconstruction surgery or hymenorrhapy [1], cannot be performed in the Netherlands anymore. If these surgeries still take place, a ban on these surgeries will be considered.[2] Women who are no longer virgin but wish to appear so for their partner or family, can undergo a hymenoplasty in the Netherlands.[1] In many cultures, women have to remain virgin before marriage, whereas this is not a requirement for men, causing a double standard.[3] In the Netherlands predominantly women from a migrant background go to hospitals or private clinics with the request for a hymenoplasty.[4] In 2018, 120 hymenoplasties were performed in the Netherlands, mostly in private clinics, according to research conducted by NOS (Nederlandse Omroep Stichting).[5]
The current policy regarding these surgeries, is that they are not performed unless no other option appears to be possible after counselling.[6] A prohibition of hymenoplasties will not solve the problem, according to gynaecologist Caroline Vos from the Dutch Association for Obstetrics and Gynaecology (NVOG).[7] She fears that when women will not be able to go to a physician to get a hymenoplasty, they will seek help somewhere else, without thorough counselling.[7] Dutch physicians can convince women through counselling not to undergo surgery, by proposing alternatives and by clarifying facts and myths about the hymen.[4,7] Hymenoplasty is not a type of surgery performed to treat a medical condition and preserves the myths and the double standard around virginity. On the other hand, performing this surgery can protect women against possible negative and sometimes life threatening consequences.[1] The question in this matter is: should hymenoplasties be banned by law in the Netherlands?

The myths concerning the hymen

Many people believe that the hymen is an actual membrane that breaks during the first sexual intercourse.[3] The Dutch term for hymen 'maagdenvlies', literally meaning 'virgin membrane', suggests that it is a membrane that is intact in virgins, although there is no correlation between the state of the hymen and a woman's prior sexual intercourse.[8] The hymen actually is a thin layer of mucosal tissue surrounding the vaginal opening or partly covering the vaginal opening [6], as seen in figure 1 [9], with few blood vessels that do not bleed much, when torn. Lacerations to the vaginal wall are more likely to cause bleeding during the first sexual intercourse, than the tearing of the hymen. These lacerations can be caused by forced penetration and lack of lubrication.[8] Bleeding can occur, but around 40% of women do not bleed during the first sexual intercourse.[10]
It is known that the hymen is a remnant of an embryological structure without a known physical function.[11] However, in many cultures, a perceived intact hymen is interpreted as proof of a woman's virginity.[12]
With a physical examination it is not possible to determine if a woman is a virgin or not.[8] Furthermore, an 'intact' hymen looks different in every woman regarding shape and size, but the hymen often has a circular or crescent shape.[11,13] The shape, size and flexibility also change during life.[8]

Culture and virginity

In some cultures, it is important that a woman marries as a virgin. Virginity of a woman before marriage is associated with an intact hymen.[12] In certain cultures, blood loss during the first coitus is seen as proof of a woman's virginity with blood-stained bedsheets as the ultimate proof. Although this belief occurs in a lot of predominantly Islamic countries, it is not a religious tradition within Islam, but rather a cultural tradition.[12] According to the Dutch government, hymenoplasties are an example of 'harmful practices', which also include forced marriage, female genital mutilation and honour-related violence.[2] Women who are no longer virgin, but wish to appear virgin, can undergo hymenoplasty.[1] In the Netherlands, predominantly women from migration backgrounds tend to request these surgeries, for example women with a Moroccan, Turkish, Afghan or Iraqi background.[4] When a woman cannot prove her virginity, it can have far-reaching consequences for her and her family which can vary from humiliation, shame, rejection or divorce to even death in some cases.[12,14]

Physician's methods in the Netherlands

According to the current guidelines of the NVOG, hymenoplasties should not be performed unless there is no other option possible after counselling.[6] Caroline Vos believes that current guidelines should be adjusted to create a clearer approach for doctors.[7] During counselling, gynaecologists and other specialists must explain facts and myths concerning the hymen, suggest other alternatives and eventually decide on a potential treatment with the woman in question for her specific situation.[7,12,13] Currently, there is no clear nationwide protocol [7], which causes approaches and methods to differ between doctors working in a hospital or a private clinic.[15] In one study, the approach from doctors from a hospital and a private clinic were compared. In the hospital, a step-by-step protocol was established by a few doctors, which included 3 consultations before surgery with a gynaecologist and a sexologist. During the third visit, the patient informs the doctor whether or not she wants to undergo surgery.
In the private clinic, patients often visit once and afterwards decide whether they want to proceed with the surgery or not. During this visit the patient can explain her reasons for wanting the surgery and a physical examination is often done

to determine if surgery is possible. Aside from the difference in consultation, hymenoplasty in a private clinic is also cheaper than in a hospital.[15] These two reasons might indicate why hymenoplasties are performed more in private clinics.
Alternatives proposed for a hymen reconstruction are often inspired by practices originating in the ancestral countries of the patients. Some examples include: a finger prick, inserting a capsule with red dye, or using the contraceptive pill and making sure the woman menstruates during the wedding night.[4]
When ultimately a hymenoplasty remains the only solution, two techniques are possible to perform this surgery. The 'small intervention' consists of stitching the hymen remnants, short before the wedding night. The 'large intervention' is a vaginoplasty, which should be performed further in advance before the wedding night.[6] These hymenoplasties are mainly done to make sure that a woman will bleed during the wedding night, to 'prove' her virginity.[12] Research has revealed that even after surgery not every woman bleeds during the first sexual intercourse. That is why physicians often recommend to keep the previously named alternatives as a backup, to ensure bleeding.[12,16]
Some women do not necessarily want to bleed but want to feel 'tight' for their spouses, so they can 'verify' their virginity.[4] To achieve 'tightness' without surgery, doctors can teach these women some pelvic floor exercises, but sometimes women ultimately still opt for a surgery.[12] Some women have to prove their virginity to their families (in-law), some only to their husbands.[15] Most women fear that their husband will feel that the women are no longer virgins.[4] In a few cases, women undergo hymenoplasty to find closure from sexual violations from the past.[15]
Knowledge about the female genital anatomy is absent in many women seeking consultation for hymenoplasties. This was shown in a research, where over 50% of women who went to these hymenoplasty counselling sessions, had very little knowledge about the female genital anatomy.[12] For this reason, anatomy is a field of attention during many consultations in hospitals.In some cases, women don't seek a hymenoplasty but ask for a so-called 'virginity certificate'. Physicians can 'declare' that after a professional physical examination, nothing indicated that the woman is no longer virgin.[17]

Medical ethical discussion

Different ethical aspects play a part in the discussion whether a ban on hymenoplasties is desirable in the Netherlands.
The Ministers who implemented the ban on hymenoplasties, believe that these surgeries are harmful.[2] On the one hand, the principle of nonmaleficence plays a role in this discussion, because hymen surgery is not medically necessary. The women undergoing this surgery are effectively being harmed, although not a lot is known about the complications that can occur after surgery. The surgery is relatively small with little known complications, like minor infections, dyspareunia, the formation of haematoma and haemorrhage. The absolute risk of complications is unknown, but is assumed to be small.[18,19] Aside from that, performing these surgeries preserves the myths surrounding virginity, namely that a woman should bleed during the first sexual intercourse. Furthermore, doctors contribute to misleading these partners and families. This is one of the reasons some doctors refuse to perform this type of surgery.[18,20] These can all be reasons to plead for a prohibition of hymenoplasties.
On the other hand, the principle of beneficence plays a role in this matter. Hymenoplasty can protect a woman from serious consequences she might encounter when her family or partner finds out she is no longer a virgin. These consequences can vary from humiliation, shame, rejection or divorce to even death in some cases.[12,14] Physicians can decide to perform a surgery in order to prevent harm. In this case, the possible complications could outweigh the risk of dangerous situations in the private environment of the woman. Research showed that physicians in Iran do not consider hymenoplasties to be unethical, because the consequences of finding out that a woman is no longer a virgin, can lead to violence and sometimes even death.[21] Hereby doctors can act in a paternalistic manner, by performing the relatively small surgery and therefore protecting the women from harm in their private environment.
Moreover, in the Netherlands, physicians conduct extensive counselling with women who seek hymenoplasty and after being informed about myths and other alternatives, many of these women do not choose to undergo surgery.[12] When hymenoplasties get banned, women who request this kind of surgery will not get these informative counselling sessions anymore through physicians. Women might choose to seek help in another country, where counselling might not be an important point of attention. Without thorough counselling, women do not get informed about the myths concerning the hymen and might not know of simpler alternatives that do not require surgery. Aside from that, the principle of respect for dignity applies in this case. Physicians must be respectful towards their patient's social, religious and cultural background and take this into account during consultation. This is also stated in the guideline of the Dutch Society of Obstetrics and Gynaecology concerning hymenoplasty.[6]
Another aspect in this discussion is whether the prohibition of hymenoplasties offer the possibility to break taboos regarding virginity or whether it sustains these taboos.
Informing women about the hymen and breaking the taboo concerning this matter, is very important, since many women and their future families and husbands have very little knowledge about the hymen and how this is connected to the virginity of a woman. Currently, this information is given during counselling sessions with women who seek to undergo a hymenoplasty. By banning this type of surgery by law, these informing counselling sessions do not take place anymore. If, for example the Ministry of Health, Welfare and Sport pays more attention to this matter, perhaps there will be a decrease in requests for hymenoplasties and a ban would not be needed.

Conclusion

In conclusion, a ban on hymenoplasties should not be applied in the Netherlands. When a ban on performing hymenoplasties is applied, Dutch physicians would not have to take part into this harmful practice, as the Dutch government called hymenoplasties. On the other hand, the prior successful counselling sessions would not take place anymore. This would mean that women do not get informed about the facts and myths around the hymen. Clearly, there is a lack of knowledge about virginity in women seeking advice and therefore gains are to be made in providing information. A ban on hymenoplasties will not end the ignorance and taboos around the hymen and female virginity, but might even maintain it.
There should be a clear general guideline for doctors in the Netherlands concerning counselling and intervention. Instead of a ban on hymenoplasties, the government could focus more on making taboos and myths discussable, through education.

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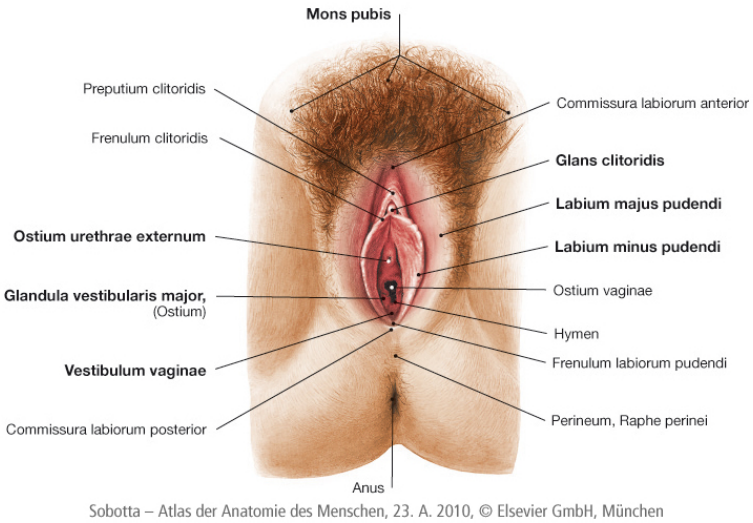

Figure 1: External female genitalia

Hypertonic saline or mannitol for the management of an elevated intracranial pressure in patients with traumatic brain injury: a systematic review and meta-analysis

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Abstract

Objective

Traumatic brain injury poses many problems, due to its high mortality and morbidity. The importance of an adequate therapy to minimalize the consequences of an elevated intracranial pressure (ICP) in patients with traumatic brain injury, is great. There are several hyperosmolar agents for the treatment of an elevated ICP. However, it is unclear which type of hyperosmolar therapy is most effective in lowering the ICP. Therefore, we sought to investigate whether hypertonic saline or Mannitol is the most effective therapy to lower the ICP in patients with traumatic brain injury.

Methods

We searched PubMed for studies comparing the use of hypertonic saline and Mannitol regarding the reduction of the ICP in adult patients with traumatic brain injury. The primary outcome was the mean change in ICP. The secondary outcomes were the treatment maintenance time and mortality. A meta-analysis was performed for all outcome measures.

Results

Seven studies were included in our meta-analysis. There was no statistically significant difference in mean change in ICP between treatment with hypertonic saline and treatment with Mannitol (mean difference = -0.744 mmHg, 95% CI -4.162 – 2.674; p = 0.051). None of the secondary outcomes showed a significant difference comparing treatment with hypertonic saline and treatment with Mannitol.

Conclusions

There is no significant difference in the effectiveness of treatment with hypertonic saline and Mannitol with regard to reducing the ICP in patients with traumatic brain injury. Further research is needed on the quality of survival, the adverse effects of both types of hyperosmolar therapy, and their effectivity in different subgroups of patients. Only then a formal recommendation can be made for either type of hyperosmolar therapy.

Introduction

Traumatic brain injury is a significant public health problem worldwide. The worldwide incidence of traumatic brain injury in the general population is estimated at 369 per 100.000 person-years.[1] In 2016, 27.082.033 people worldwide suffered from traumatic brain injury.[1] In addition to being relatively common, traumatic brain injuries can also have serious consequences. Traumatic brain injury is associated with high mortality and morbidity.[1,2] Traumatic brain injuries are a major burden for the affected patients and their families, as well as for the economy and healthcare. This has everything to do with the reduced productivity and high healthcare costs of these patients.[3] Traumatic brain injury itself is difficult to prevent, but its consequences can be minimalized through adequate treatment.[4]

Traumatic brain injury is often accompanied by an elevation of the intracranial pressure (ICP). An elevated ICP is associated with the development of secondary brain injury, which is associated with a poorer neurological outcome.[4] Therefore, lowering the ICP is an important part of the treatment of traumatic brain injury.[4] Hyperosmolar therapy is the cornerstone of the treatment of an elevated ICP in patients with traumatic brain injury. Regarding hyperosmolar therapy, Mannitol has long been the gold standard, until the use of hypertonic saline (HS) started gaining attention as an alternative to address concerns about the adverse effects of Mannitol.[5] Since then, there have been two main types of hyperosmolar therapy. There is, however, no consensus on the type of hyperosmolar therapy that should be used in lowering the ICP in patients with traumatic brain injury. The most recent guideline regarding the treatment of traumatic brain injury, published by the Brain Trauma Foundation, states that there is insufficient evidence to support a formal recommendation for either type of hyperosmolar therapy.[6] In conclusion, it is unclear which type of hyperosmolar therapy is most effective in lowering the ICP. Therefore, in this systematic review and meta-analysis, we sought to investigate whether hypertonic saline or Mannitol is the most effective therapy to lower the ICP in patients with traumatic brain injury with an elevated ICP.

Methods

Search strategy

We have searched the PubMed electronic database for eligible articles published up to and including September 2020 using the following search term: ((“saline solution, hypertonic”[MeSH Terms]) AND (“Mannitol”[MeSH Terms])) AND ((“Intracranial Pressure”[MeSH Terms]) OR (“Intracranial Hypertension”[MeSH Terms])). The last search for eligible articles was performed on September 22, 2020. Using the search term above, we have identified studies investigating the use of hypertonic saline versus the use of Mannitol in adult patients with an elevated ICP. In addition, the reference lists of the identified articles have been screened for additional studies missed by the PubMed search.

Study selection

The identification of potentially eligible studies was performed independently by the three authors. The studies were screened based on title and abstract. Hereinafter, the lists of potentially eligible studies were compared. In the event of a disagreement, the authors motivated their decisions, eventually leading to an agreement. In order to be included, studies had to compare the use of hypertonic saline and Mannitol in means of reducing the ICP in adult patients with an elevated ICP. Our search was aimed at randomized controlled trials (RCTs) and retrospective studies/analyses. Articles not written in English, articles not freely available or not available through the Erasmus MC license, articles concerning any cause of an elevated ICP other than trauma, data reviews, articles missing an analysis in which hypertonic saline and Mannitol were compared separately, Best Evidence Topic (BET) reports, articles investigating any form other than pure hypertonic saline and articles missing data on our outcome measures, were excluded.

Quality assessment

In order to assess the quality of the included studies, two different quality-assessment-scales were used. The Jadad scale was used to assess the quality of randomized controlled trials. The Newcastle Ottawa scale was used to assess the quality of case-control studies and retrospective studies. The Jadad scale examines the following terms: [1] randomization (yes = 2, unclear = 1, no = 0), [2] double-blind (yes = 2, unclear = 1, no = 0) and [3] withdrawals and dropouts (described = 1, undescribed = 0). The quality scale ranged from 0 to 5 points. A Jadad score ≤ 2 was considered as poor quality, and a Jadad score ≥ 3 was considered as good quality.[7] The quality of case-control studies and retrospective studies, assessed using the Newcastle Ottawa scale, was determined by converting the Newcastle Ottawa scale to the Agency for Healthcare Research and Quality (AHRQ) standard. Table 1 shows the terms on which the studies were assessed using the Newcastle Ottawa scale, and how the quality of the studies was defined according to the AHRQ standard.

Data extraction

A number of data has been extracted from the included studies. The study characteristics of the included studies (name of the first author, year of publication, country of origin, study design, study period, number of patients, number of patients per group, mean age, median or mean Glasgow Coma Scale at admission, definition of controlled ICP, formulation of Mannitol and formulation of hypertonic saline) have been used to create a table which gives an overview of the included studies. In addition, we have extracted data from the included studies to investigate whether hypertonic saline or Mannitol is the most effective therapy to lower the ICP in patients with traumatic brain injury with an elevated ICP.

The primary outcome was the mean change in ICP during treatment (measured from baseline to the end of the treatment) in mmHg. The secondary outcomes were the treatment maintenance time (defined as the time per day during which the ICP was under control, as defined by the individual studies) in hours, and the mortality (as a relative risk (RR), measured from hospital admission to the end of follow-up). In all outcome measures, a comparison was made between treatment with hypertonic saline and treatment with Mannitol. For these outcome measures, a meta-analysis was performed. For each outcome measure, the included studies were screened for data on this outcome measure. This data was either extracted from the text or from tables. For each outcome measure, the desired value (mmHg, hours, RR) with its corresponding 95% confidence interval (CI) and p-value was calculated for each eligible study. Hereinafter, the values of the various included studies were combined into a Forest plot. The ‘OpenMeta’ program was used to do so. The final outcomes of our systematic review were the pooled values with their corresponding 95% confidence intervals and p-values.

Statistical analysis

We have analyzed the pooled values and their corresponding 95% confidence intervals and p-values to determine the differences in the effectiveness of the hyperosmolar therapies at lowering the ICP. A p-value of $p < 0.05$ was considered as an indication for statistical significance. The I-square test was used to determine the heterogeneity between the studies. An I^2 greater than 60% was considered as an indication for significant heterogeneity between the studies. In the event of significant heterogeneity between the studies, a random-effects model was used. In the event of no significant heterogeneity between the studies, a fixed-effects model was used.

Results

Selection of the included studies

A total of 127 potentially eligible articles were identified through the PubMed search. The screening on title and abstract lead to the exclusion of 102 articles due to the absence of data on the use of hypertonic saline versus Mannitol in reducing the ICP in adult patients with an elevated ICP. After assessing the remaining 25 articles for eligibility, another 18 articles were excluded based on the exclusion criteria. After the application of these exclusion criteria, 7 eligible articles remained. These 7 studies have been included in our meta-analysis.[8-14] A detailed flow chart of the selection process described above is shown in Figure 1.

Characteristics of the included studies

The characteristics of the 7 included studies are shown in Table 2. The 7 studies consisted of five randomized controlled trials [8-10,13,14] and two retrospective studies.[11,12] The number of patients in the included studies ranged from 12 to 120, but the 7 included studies accounted for a total of 279 patients. The mean age of the patients ranged from 27 to 43. All studies concerned patients with severe traumatic brain injury. The severity of the trauma, reported as the median or mean Glasgow Coma Scale (GCS) at hospital admission, ranged from 3 to 7. The studies used different definitions of a controlled ICP.

Most studies considered the ICP to be under control when it was below 20 mmHg.[9-12] Almost all of the studies investigated a Mannitol concentration of 20%, with the exception of one study.[12] The investigated concentration of hypertonic saline varied between the studies, from 3% to 23.4%. In some studies, the amount of the administered hyperosmolar fluid was predetermined [9-14], and in others, the amount of the administered hyperosmolar fluid varied depending on the patient's course.[8] Of the 7 studies, 6 studies discussed the mean change in ICP [8-13], 3 studies discussed the treatment maintenance time [10,11,14], and 4 studies discussed mortality.[9,10,12,14]

Quality-assessment of the included studies
The results of the quality assessment of the included studies are shown in Table 3. This table shows, for each of the included studies, the study design, the used quality-assessment-scale, the achieved quality score and the final assessment of the quality of the study defined as good, fair or poor. The quality assessment showed that five of the seven studies were of good quality [8-10,13,14] and two of the seven studies were of fair quality.[11,12] All five of the RCTs were of good quality, each scoring 3/5 points on the Jadad scale. Four of these articles missed two points on the term 'double blind' [8-10,13] and one of these articles missed one point on the term 'randomization' and one point on the term 'double blind'.[14]

Mean change in ICP
The mean change in ICP was discussed in 6 of the 7 included studies.[8-13] The study by Vialet et al. did not report data on the mean change in ICP.[14] The pooled mean change in ICP following treatment with hypertonic saline was -8.899 mmHg (95% CI -11.632 – -6.166). The pooled mean change in ICP following treatment with Mannitol was -7.741 mmHg (95% CI -10.389 – -5.093). The pooled mean difference in the mean change in ICP comparing hypertonic saline to Mannitol was -0.744 mmHg (95% CI -4.162 – 2.674; p = 0.051). Concerning the mean change in ICP, there was no statistically significant difference between treatment with hypertonic saline and treatment with Mannitol. The Forest plot of the outcome measure of the mean change in ICP is shown in figure 2.

Treatment maintenance time
The treatment maintenance time was discussed in 3 of the 7 included studies.[10,11,14] The study by Jagannatha et al. did report data on the treatment maintenance times.[9] However, this data was presented as percentages, and could therefore not be used in the meta-analysis. The pooled mean treatment maintenance time of hypertonic saline was 12.909 hours (95% CI 1.534 – 24.283). The pooled mean treatment maintenance time of Mannitol was 11.766 hours (95% CI 0.196 – 23.337). The pooled mean difference in the treatment maintenance time comparing hypertonic saline to Mannitol was 0.995 hours (95% CI -0.786 – 2.776; p = 0.651). Concerning the treatment maintenance time, there was no statistically significant difference between treatment with hypertonic saline and treatment with Mannitol. The Forest plot of the outcome measure of the treatment maintenance time is shown in figure 3.

Mortality
Mortality was discussed in 4 of the 7 included studies. [9,10,12,14] Two of these articles reported the 6-month mortality [9,10], one of these articles reported the 90-day mortality [14] and one of these articles did not specify the timepoint of the measurement.[12] The pooled percentage of death following treatment with hypertonic saline was 30.216 percent (95% CI 18.854 – 41.577). The pooled percentage of death following treatment with Mannitol was 35.300 percent (95% CI 20.704 – 49.897). The pooled relative risk of death comparing hypertonic saline to Mannitol was 0.837 (95% CI 0.515 – 1.361; p = 0.857). Concerning mortality, there was no statistically significant difference between treatment with hypertonic saline and treatment with Mannitol. The Forest plot of the outcome measure of mortality is shown in figure 4.

Discussion

The importance of an adequate therapy to minimalize the consequences of an elevated ICP in patients with traumatic brain injury is great. There are several types of hyperosmolar therapy which can be used to lower an elevated ICP in patients with traumatic brain injury. However, it is unclear which type of hyperosmolar therapy is most effective in lowering the ICP. Therefore, in this systematic review and meta-analysis, we sought to investigate whether hypertonic saline or Mannitol is the most effective therapy to lower the ICP in patients with traumatic brain injury with an elevated ICP. Our meta-analysis showed that there was no significant difference regarding the mean change in ICP between treatment with hypertonic saline and Mannitol. There was also no significant difference regarding the treatment maintenance time and mortality comparing treatment with hypertonic saline and Mannitol. In conclusion, there is no significant difference in the effectiveness of treatment with hypertonic saline and Mannitol when it comes to lowering the ICP in patients with traumatic brain injury.
We have made an effort to conduct the best possible research, but some limitations of our study should be acknowledged. The results of this systematic review should be interpreted with said limitations in mind. The first and most major limitation of our study is the small number of patients that were investigated in the included studies. This small number of patients could have potentially lead to a larger risk of coincidental findings, as well as to a smaller chance of finding significant differences. Therefore, the small number of patients could have had an effect on our reported data. A second limitation of our study is the fact that the data from the included studies were not always equally comparable. For example, the included studies investigated different formulations (concentration and volume) of hypertonic saline and Mannitol. The number of administered boluses also differed between the studies. This means that in some studies, the patients received more boluses of a greater volume and concentration than patients in other studies. This may have affected the recorded effectiveness of the therapies. The studies also used different definitions of a controlled ICP. This may have affected our secondary outcome measure of the treatment maintenance time, as this outcome was defined as the number of hours during which the ICP was under control. These methodological differences between the studies limit the results of this systematic review. A third limitation of our study is the fact that we only included studies which were freely available or available through to Erasmus MC license. This may have led to exclusion of studies that could have been of value to our study. A fourth and final limitation of our study lies in the investigated study population. Our investigated study population turned out to be relatively young. This means, that our results might not be representative for all patients presenting with traumatic brain injury. This should be kept

in mind when interpreting, and possibly applying, the results of this systematic review. Despite the limitations mentioned above, we see no limitations with regard to the quality of the included studies, as the included studies were all of good to fair quality.

There have been a few systematic reviews with a study objective similar to this systematic review.[15-18] Our systematic review differs from these previous systematic reviews on a number of points. First of all, our systematic review investigated a unique combination of outcome measures that we believe are most important when it comes to determining the effectiveness of a hyperosmolar therapy in lowering the ICP. In addition, our systematic review only included studies in which a pure form of hypertonic saline was investigated. The systematic reviews by Gu et al., Burgess et al. and Rickard et al. have also included studies in which different forms of hypertonic saline were investigated.[16-18] We believe that this gives a distorted view of the effectiveness of treatment with hypertonic saline. When using hypertonic saline to which other substances have been added, it is unclear whether the effectiveness of the treatment is due to the hypertonic saline or due to the additional substances. For this reason, we have decided to exclude such studies. The previous systematic reviews concluded the following with regard to our investigated outcome measures. [15-18] The systematic review by Shi et al. found that both hypertonic saline and Mannitol can effectively reduce the intracranial pressure, but hypertonic saline has a more sustained effect (maintenance time) on the intracranial pressure.[15] The systematic review by Gu et al. found that hypertonic saline and Mannitol were close with regard to reducing the intracranial pressure and mortality.[16] Gu et al. concluded that hypertonic saline seems to be preferred.[16] The systematic review by Burgess et al. found no clinically important differences in mortality and ICP reduction between hypertonic saline and Mannitol.[17] The systematic review by Rickard et al. found that there is no statistically significant difference in the ability of hypertonic saline and Mannitol to effectively lower an elevated ICP in patients with traumatic brain injury.[18] In conclusion, we believe that for the methodological differences and the differences in the conclusions mentioned above, this systematic review provides new insights regarding the difference between the effectiveness of the hyperosmolar therapies.

Following our own study, a few recommendations for future studies came to mind. In the end, all that counts for the patient are survival and quality of survival. Our systematic review investigated the survival, but not the quality of the survival. It could be interesting for future research to focus on the quality of the survival, rather than just focusing on the survival as is. Therefore, we believe that further research should be done on the quality of survival. Our systematic review has found no evidence for differences in the effectiveness of treatment with hypertonic saline and Mannitol. However, the choice for either type of hyperosmolar therapy can not be made randomly, as there are more parameters to consider. First of all, hyperosmolar therapies also have certain additional effects besides lowering the ICP. These additional effects could be of beneficial effect. For example, some studies have shown that hypertonic saline leads to a better oxygenation of the brain.[19] Hypertonic saline also increases the serum sodium levels, and therefore has a less diuretic effect compared to Mannitol.[20] The additional effects can, however, also be of unbeneficial effect. For example, with the use of hypertonic saline, there is a risk of developing a hyperchloremic metabolic acidosis, and with the use of Mannitol, there is a risk of developing pulmonary edema, acidosis and renal failure leading to hypotension.[21] The choice for the type of hyperosmolar therapy should not only be based on the effectiveness of the therapy in means of reducing the ICP, but should also be based on the adverse effects of the therapy. Second of all, the underlying trauma mechanism of the traumatic brain injury might also be of importance when it comes to the choice for the type of hyperosmolar therapy. A certain type of hyperosmolar therapy might be more effective in certain types of underlying trauma mechanisms and their accompanying injuries. For example, patients with traumatic brain injury going through hypovolemic shock due to a major bleeding, could possibly benefit more from treatment with hypertonic saline than from treatment with Mannitol, as hypertonic saline has a less diuretic effect compared to Mannitol. [20] In conclusion, the adverse effects of hypertonic saline and Mannitol, and their effectiveness in different types of patients, play an important role in the choice for either type of hyperosmolar therapy. For this reason, we believe that further research should be done on the adverse effects of hypertonic saline and Mannitol, as well as on the effectivity of hypertonic saline and Mannitol in different subgroups of patients.

In summary, our systematic review demonstrated that there is no significant difference in the effectiveness of treatment with hypertonic saline and Mannitol with regard to lowering the ICP in patients with traumatic brain injury with an elevated ICP. Further research is needed on the quality of survival, the adverse effects of both types of hyperosmolar therapy, and their effectivity in different subgroups of patients. Only then a formal recommendation can be made for either type of hyperosmolar therapy.

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Tables

Table 1. Conversion of the Newcastle Ottawa Scale to the AHQR standard.

Quality	Conditions
Good	3 or 4 stars[a] in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome / exposure domain
Fair	2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome / exposure domain
Poor	0 or 1 stars in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome / exposure domain

[a] The Newcastle-Ottawa Scale has eight items for which one or two stars, depending on the domain, can be given.

Table 2. Characteristics of the studies included in the meta-analysis.

First author	Year of publ.	Country of origin	Study design	Study period	No. of patients	No. of patients per group [M/HS]	Age (mean) [M/HS]	GCS at admission [M/HS]	Definition of ICP control	M form.	HS form.
Patil	2019	India	Prospective RCT	2015 - 2017	120	40/40[a]	38.42 (± 15.5)[b]	5 (3 – 7) / 6 (3 – 8) (median)	< 15 mmHg	20% (variable)	3% (variable)
Jagannatha	2016	India	Prospective RCT	NA	38	20/18	31 (± 13) / 27 (± 8)	5 (4 – 6) / 4 (4 – 5) (median)	< 20 mmHg	20% (2.5 ml/kg)	3% (2.5 ml/kg)
Cottenceau	2011	France	Prospective RCT	NA	47	25/22	36.1 (± 16.8) / 42.7 (± 19.9)	7 (5 – 8) / 5 (4 – 7) (median)	< 20 mmHg	20% (4 ml/kg)	7.5% (2 ml/kg)
Kerwin	2009	USA	Retrospective analysis	NA	22	22/22	35.7 (± 15.1)	6.9 (± 3.99) (mean)	< 20 mmHg	20% (variable)	23.4% (30 ml)
Oddo	2009	USA	Retrospective study	2005 - 2006	12	12/12	36 (± 16)	3 (3 – 8) (median)	< 20 mmHg	25% (0.75 g/kg)	7.5% (250 ml)
Francony	2008	France	Parallel RCT	2002 - 2005	20	10/10	43 (± 11) / 37 (± 16)	NA	> 20% below baseline	20% (231 ml)	7.45% (100 ml)
Vialet	2003	France	Prospective RCT	NA	20	10/10	30.8 (± 19) / 35 (± 18)	5.4 (± 2.8) / 4.1 (± 1.6) (mean)	< 25 mmHg	20% (2 ml/kg)	7.5% (2 ml/kg)

[Publ.] publication, [No.] Number, [M] mannitol, [*HS]* hypertonic saline, *[GCS]* Glasgow Coma Scale, [*form.]* formulation [*RCT]* randomized controlled trial, [*NA]* not available.
[a] There was another group which received 10% mannitol + 10% glycerol. Said group was not used in our meta-analysis.
[b] This contains the mean age of all participants of the study, including the mentioned 10% mannitol + 10% glycerol group.

Table 3. Results of the quality-assessment of the included studies.

First author	Study design	Quality-assessment-scale	Score	Quality
Patil	Prospective RCT	Jadad Scale	3 / 5	Good
Jagannatha	Prospective RCT	Jadad Scale	3 / 5	Good
Cottenceau	Prospective RCT	Jadad Scale	3 / 5	Good
Kerwin	Retrospective analysis	Newcastle Ottawa Scale	6 / 9	Fair
Oddo	Retrospective study	Newcastle Ottawa Scale	5 / 9	Fair
Francony	Parallel RCT	Jadad Scale	3 / 5	Good
Vialet	Prospective RCT	Jadad Scale	3 / 5	Good

Figures

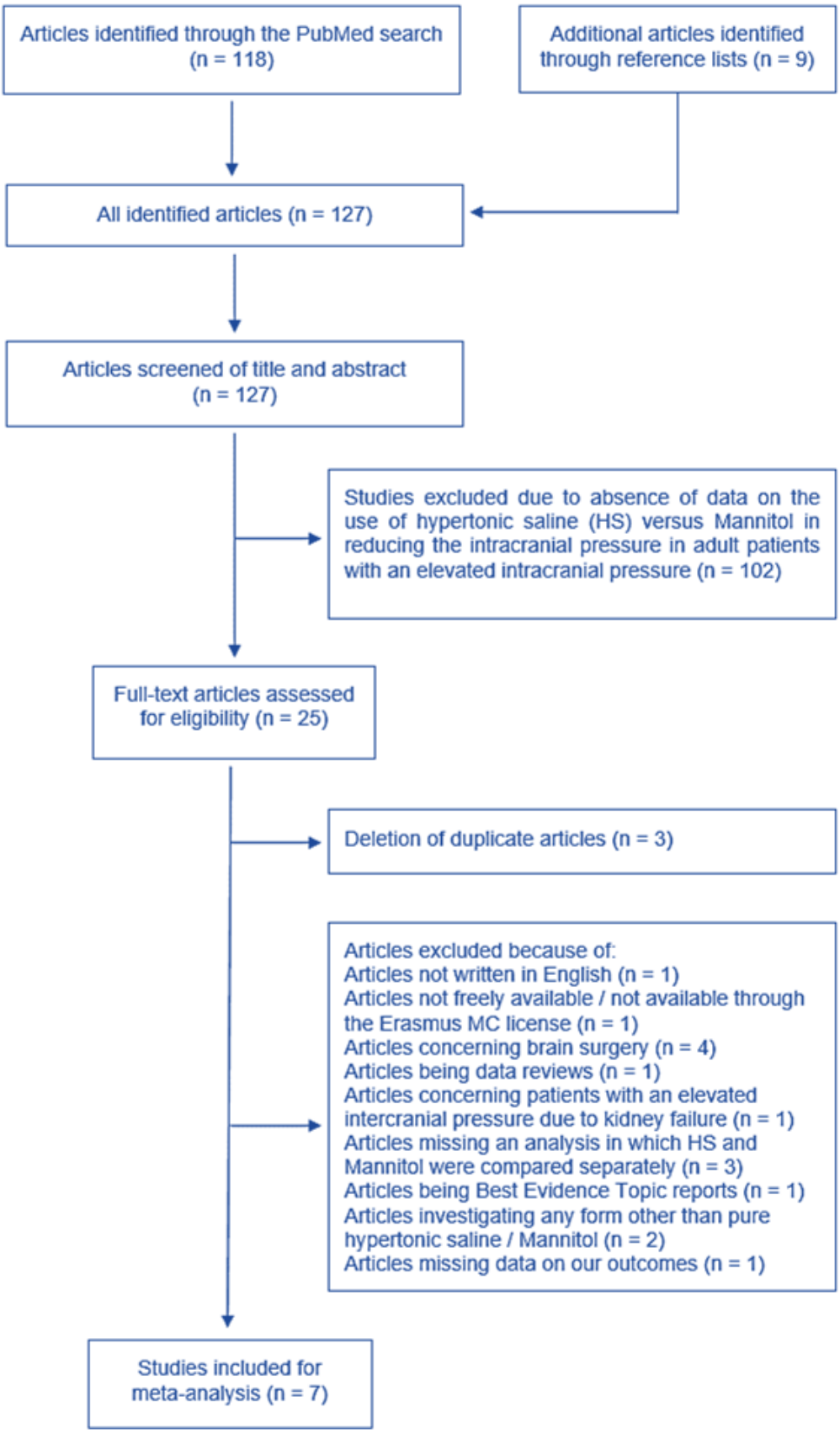

Figure 1. Flowchart of the selection process of the articles included in the meta-analysis.

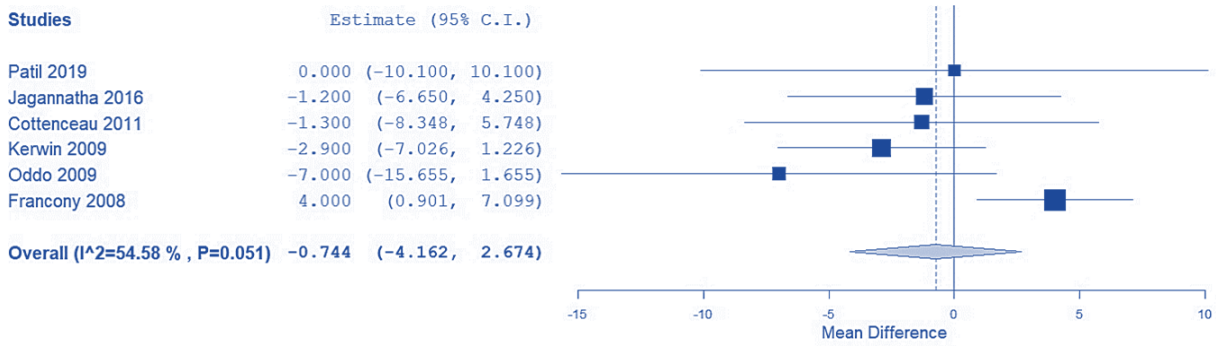

Figure 2. Forest plot demonstrating the mean difference between the mean change in intracranial pressure in mmHg following treatment with hypertonic saline versus treatment with Mannitol. Numbers below 0 correspond with a greater effect of hypertonic saline than of Mannitol.

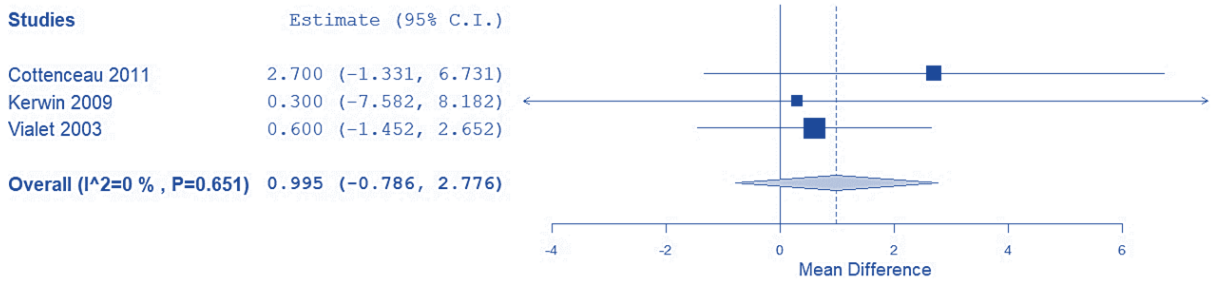

Figure 3. Forest plot demonstrating the mean difference in treatment maintenance time in hours following treatment with hypertonic saline versus treatment with Mannitol. Numbers above 0 correspond with a greater effect of hypertonic saline than of Mannitol.

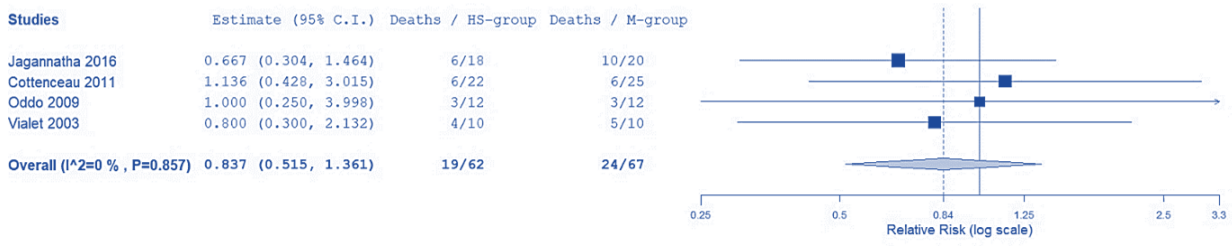

Figure 4. Forest plot demonstrating the relative risk of death following treatment with hypertonic saline versus treatment with Mannitol. Numbers below 1 correspond with a greater effect of hypertonic saline than of Mannitol.

The Potential Adverse Trans-generational Effects of (Mal)nutrition on the Human Epigenome

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Abstract

Nutrition impacts human health. Early studies suggest that dietary imbalances increase the transgenerational risk of chronic diseases through affecting the epigenome. The current literature review aims at specifically investigating the transgenerational epigenetic effects of (mal)nutrition. To explore various associations different study designs were used. Epigenome-wide association studies suggested that differential DNA methylation is a potential mechanism linking obesity to poorer health. Retrospective cohort studies show detrimental transgenerational effects of undernutrition on human health. Finally, animal models give evidence for adverse epigenetic effects of overfeeding across multiple generations. Taken all together, these findings provide evidence that malnutrition might increase the risk of chronic diseases through epigenetic dysregulation. These epigenetic risk factors are then inherited to subsequent generations. Studies on the effects of obesity on future generations are not yet available, since food abundance is a relatively new socio-economic challenge. Therefore, combining studies on related associations as of now only allows us to make estimations about possible health outcomes. Future longitudinal research is necessary to investigate the transgenerational effects of human malnutrition. Yet, this study highlights the importance of a balanced lifestyle in decreasing the disease risk of one's self and the subsequent future generations.

Introduction

That a poorly balanced diet can contribute to the development of chronic diseases, is a well-known fact.[1] Yet, for many of us it is difficult to comprehend that in 2017 "dietary risks" were globally responsible for more deaths than tobacco, alcohol or other lifestyle choices.[2] This, however, is the result of a large study by Afshin et al. who tracked dietary trends of several nutritional factors in 195 countries from 1990 to 2017.[2] The accelerating technological progress changes our environment at a rate that does not allow our bodies to grow accustomed to the new living standards. This is why the contemporary time of abundance and energy-dense diets result in a drastic increase in the prevalence of obesity.[3,4]

The importance of examining the impact of obesity, which is here defined as abnormal or excessive fat accumulation (based on body mass index = kg/m2 with BMI > 30), becomes evident when looking at related health outcomes. In a large body of research, overnutrition has been determined as a risk factor for the development of cancer, cardiovascular disease, diabetes and various chronic diseases, such as kidney disease and depression.[5] Understanding the causes and mechanisms underlying the association of dietary-intake and adverse health outcomes is of special interest because nutrition is one of the most strongly modifiable factors out of other environmental exposures.[6] Establishing these links is crucial to suggest new ways to prevent disease, not only in the individual, but also in subsequent generations.

One of the mechanisms linking the rapid change in dietary trends to observed obesity phenotypes is the altering effect of environmental factors on gene activity.[7] This connection between environment and gene expression can be regulated by epigenetics.[8] DNA methylation, one of the most important mechanisms of the epigenome, has been suggested to be a potential mediator between the environment and genes.[9] DNA methylation is a mechanism in which methyl groups are added to DNA nucleotides through enzymatic activity. CpG sites, namely cytosine-guanine dual base-pairs, are often located at gene promoter sequences. Therefore, differential DNA methylation has the potential to regulate gene expression without changing the DNA sequence. Prior studies have proposed that environmental exposures might alter DNA methylation levels, which are subsequently associated with poorer health.[9,10] Thus, hyper- or hypomethylation of these sites might lead to abnormal gene expression, or even repression of the gene transcription mechanism.[9]

While many lifestyle factors like physical activity, toxin exposure and drug abuse have been well studied as elements involved in altering gene expression[6], the field of nutritional epigenomics is relatively new but of growing interest.[11] Apart from clarifying mechanisms linking nutrition to the development of diseases in a single generation, examining effects on subsequent generations is crucial to understand how far-reaching the consequences of our individual lifestyle decisions might be. Research investigating transgenerational epigenomic inheritance suggests that malnutrition can cause genetic disorders and disease passed on to later generations.[12] Attempting to explain this observation, Hales and Barker (1992) proposed the Barker hypothesis.[13] This theory proposes "fetal programming" as a mechanism through which transgenerational effects of environmental exposure in utero cause certain phenotypes in the offspring. They describe that maternal nutrition impact the fetus mostly during the developmental phase. According to Hales and Barker, exposure to malnutrition during this critical period finally determines disease risk(s) in later life. These alterations might, in turn, result in permanent physiological and metabolic changes posing risks for multiple generations.[13] The Barker hypothesis is only one of many proposed theories trying to evaluate evidence for

transgenerational epigenetic inheritance. Understanding and intervening in these complex inheritance patterns is a promising attempt to stop the progression of diseases.
Discussing some of the previous studies about the association between lifestyle choices and health outcomes, the relevance of progressing research on this topic is evident. However, it becomes clear that only very few studies have so far investigated long-lasting effects of contemporary diet-trends on future generations. Therefore, the current literature review aims to establish the link between the effects of (mal)nutrition on both the epigenome and adverse health outcomes across several generations using three different study designs: epigenome-wide association studies (EWAS), historical cohort studies and animal models. More specifically, three subtopics are going to be discussed: general effects of obesity on the human epigenome, transgenerational effects of malnutrition on health outcomes, and evidence for potential transgenerational effects of overnutrition on the epigenome.

Methodology

The literature research was performed using PubMed Central in the days from September 21, 2020, up to and including October 6, 2020. A schematic overview of the research method is included in Figure 1. For the search, free text terms were used. This ensured that also articles could be found for which MeSH terms have not yet been assigned. No [tiab] field codes were specified so that automatic query creation was enabled. This Automatic term mapping allowed to cover all related concepts and explore less obvious links. The following strings were used for the screening phase of the first subtopic investigating the effect of obesity on the epigenome: ("Diet" OR "Obesity" OR "Overnutrition") AND ("Epigenome" OR "DNA methylation"). Sources covering the second subtopic on transgenerational effects of undernutrition in historical cohorts were identified using these terms: ("Undernutrition" OR "Famine") AND ("Transgenerational effect" OR "Epigenome" OR "DNA methylation"). Papers for the third subtopic on transgenerational effects of overnutrition in animal models were screened using the following strings: ("Overnutrition" OR "Diet" OR "High-Fat" OR "Obesity") AND ("Transgenerational inheritance" OR "Epigenome").
For all three subtopics, snowball sampling was applied as an efficient and effective strategy to discover pathways that were not obvious at the beginning of the study. This is how, for example, attention was drawn to famine studies as a way to explore the effects of undernutrition on the epigenome. This method was used based on articles with the most extensive description of the relevance of referred studies: Ling and Rönn[14], Kaspar et al.[15], Samblas et al. and Montalvo-Martínez et al.[10,12]
Sources were included based on the relevance of title, keywords and abstract. Relevance for this paper was determined by significant and biologically meaningful findings related to the research topic of the transgenerational effect of parental malnutrition on the offspring epigenome. Biologically meaningful was defined as demonstrating a functional consequence, thus affecting health or survival, for the individual. During the initial evaluation, articles that were in a language other than English or not freely accessible as well as non-empirical studies were excluded. Finally, remaining research articles and animal models were included and read completely. The papers were summarized and findings were evaluated based on their methodological quality and relevance.

Results

The Effect of Obesity on the Epigenome
Previous studies have shown that nutritional intake impacts health through changes in the epigenome.[7, 9, 11, 12] For this literature review, nine papers were selected for analysis. In the first section, epigenome-wide association studies (EWAS) investigating the effect of overnutrition on the epigenome were reviewed to evaluate evidence on possible underlying mechanisms.
Aiming to investigate whether differential DNA methylation variation is a common feature of obesity, Xu et al.[16] collected peripheral blood leukocyte samples from obese and lean participants of African-American ethnicity aged 14-20 years. Analyses were performed using the Illumina Infinium Human Methylation 450K Beadchip technology that allows for a comprehensive epigenome-wide profiling of DNA (~450,000 CpG sites, or methylated cytosines). Results suggest that several CpG sites can be associated with overnutrition. In total, 23,305 differentially methylated CpG sites and 28,653 differentially variable CpG sites (DVCs) were found. These CpG sites were located on 105 identified obesity genes, a finding in accordance with earlier genome-wide association studies.[17] Furthermore, 68.3% of the DVCs were more variable in obese participants, with about 9.45% of DVCs being driven by outliers. Hence, the obese group showed a larger variance of DNA methylation compared to the lean control group. This EWAS contributed by identifying relevant biomarkers of obesity and introducing a suitable statistical analysis based on means and variability to examine obesity-related methylation alterations.
In the following years, a large body of research has focused on analyzing specific CpG sites, in which differential DNA methylation has been associated with overnutrition in previous publications as well as the Genome-wide association studies (GWAS) catalog.[18] For example, Demerath et al.[19] identified 76 CpG sites associated with body mass index (BMI) and 164 CpG sites associated with waist circumference (WC) in adults between 47-70 years of age. Their results were replicated with samples from different ethnicities, thereby addressing one shortcoming of the aforementioned article by Xu et al.[16]
To clarify whether alterations in DNA methylation drive the development of obesity or vice versa, genetic association and Mendelian randomization are necessary. In the Mendelian randomization approach, genetic variants that have a well-established variation in genes of known biological function are used as proxies to investigate suspected effects of environmental factors on disease risk(s). This has the advantage that other physiological, behavioral or social factors can be ruled out as confounding variables.[20] Using this technique, Wahl et al.[21] analyzed DNA methylation variation in obese individuals, also using the Illumina 450K technology, and compared the results to normal-weight participants. They found that changes in blood DNA methylation are the consequence, rather than the cause, of adiposity at the majority of associated CpG sites. This result suggests that overnutrition might play a causal role in the development of metabolic, respiratory and cardiovascular diseases, amongst others. The obesity-related methylation variation in genes might act as pathways linking obesity to these clinical conditions.
Taken together, the discussed studies give concurring evidence for overnutrition being the cause for epigenetic dysregulation, which can be observed in the increased variability in specific obesity-related DNA methylation sites. Published findings provide new insights into mechanisms influenced by obesity,

which might be useful in risk stratification in developing novel prevention strategies of clinical consequences of adiposity.

Transgenerational Effects of Malnutrition on the Epigenome

After analyzing direct effects of obesity on the epigenome, transgenerational effects need to be explored to further establish the link between nutrition and transgenerational changes in the epigenome (see Figure 2). Therefore, longitudinal data of multiple generations is necessary. Since very limited data is available on long-lasting effects of food abundance, this section instead focuses on historical cohort studies examining transgenerational effects of malnutrition in general. For environmental effects to be transmitted, epigenetic reprogramming has to occur in the germline and persist in following generations. Therefore, it is crucial to study epigenetic changes during early germ cell development.[22]

One of the first studies to prove that malnutrition in early gestation can cause persistent epigenetic changes in future generations is based on data from famine in western parts of the Netherlands in 1944-45.[23] Known as the Dutch Hunger Winter, the food scarcity was a result of an embargo on food transport imposed by Germany at the end of World War II. During that time, daily caloric intake dropped to below 1,000 kcal compared to 2,000 kcal which is considered appropriate for an adult of healthy body weight (according to the World Health Organization).[31] Now, documented food rations and health care registries allow researchers assess potential long-term consequences of the event. Heijmans et al.[23] studied blood epigenome-wide profiles using a mass spectrometry-based method (Sequenom EpiTyper) in individuals who were prenatally exposed to the famine during the Dutch Hunger Winter. Same-sex siblings and unrelated participants who were born shortly before or after the famine were also recruited as controls. The main outcome of their study was the association between birth weight and differential methylation at the IGF2 locus. IGF2, or insulin-like growth factor II, is an epigenetically regulated locus involved in growth and development and is imprinted maternally. Their results showed that even six decades after the Dutch Hunger Winter, DNA methylation of IGF2 was significantly reduced in individuals exposed to the famine early in gestation compared to matched controls. This hypomethylation was not found in individuals exposed to the famine later in gestation. With this discovery, Heijmans et al.[23] were the first to provide evidence that temporary environmental conditions, affecting directly the mother and indirectly the embryo in early development, can result in persistent epigenetic changes throughout the offspring's life. However, their study did not assess the impact of epigenetic changes on the phenotype and possible health consequences to the individual.

Addressing the research gap regarding phenotypical effects, more studies have investigated transgenerational epigenetic changes induced by the Dutch Hunger Winter. For example, Veenendaal et al.[24] recruited adult offspring (F2) of men and women from the Dutch famine birth cohort (F1). Medical birth records and questionnaires about lifestyle, medication use and history of diseases were used for data collection and analysis. They found an association between maternal undernutrition during gestation and increased prevalence of metabolic and cardiovascular diseases in the F1 generation. Further investigations revealed higher rates of neonatal adiposity in the F2 offspring of F1 women who had experienced prenatal undernourishment themselves. Higher weight and BMI were also found in F2 offspring of F1 fathers who had been prenatally exposed to the famine. No such association was identified for offspring of prenatally unexposed fathers or prenatally exposed or unexposed mothers. Veenendaal et al. suggest this as evidence that transgenerational epigenomic changes are inherited mainly through the paternal line. No transgenerational effect on chronic disease was found among F2 offspring.

The articles discussed above were all limited to one cohort in the Netherlands, which greatly reduces their generalizability. That the established results are not specific to this sample, has been shown by Li et al.[25] who studied the effect of prenatal exposure to a famine that occurred from 1959 to 1961 in China. Participants included two consecutive generations (F1 and F2) for which health outcomes and transgenerational changes were examined. Instead of relying entirely on data acquired from questionnaires, this study additionally collected data on basic characteristics like sex, physical activity and food-frequency, and let participants complete a physical examination to determine health. Statistical analyses in this study revealed an increased frequency of type 2 diabetes and hyperglycemia in the exposed F1 generation compared to individuals born after the famine. An elevated risk for hyperglycemia was also found in the F2 generation with exposed parents, compared to offspring of nonexposed parents. These data support the idea that in utero nutrition might have a direct effect on the development of type 2 diabetes across consecutive generations. In conclusion, research based on historical records of individuals exposed to famine has shown that environmental exposure to undernutrition during early development in utero can result in transgenerational epigenetic changes leading to detrimental health outcomes in the offspring and subsequent generation.

Transgenerational Effects of Over-nutrition on the Epigenome

In the prior sections, direct and transgenerational effects of malnutrition on the epigenome have been explored. Attempting to analyze effects of obesity on subsequent generations, it became evident that, up to this date, no studies have demonstrated transgenerational effects of overnutrition on the human epigenome. However, animal studies suggest that certain dietary patterns and nutritional challenges may lead to persistent alterations in epigenetic marks with detrimental health outcomes.[26]

One of the studies investigating the transgenerational effects of maternal diet in mice is the paper by Pentinat et al.[27] They induced neonatal overfeeding in male mice offspring (F0) and observed the development of insulin resistance, obesity and glucose intolerance as a result of overgrowth. Although subsequent generations (F1 and F2) were not overfed, they showed phenotypic variation resulting in poorer health. By the age of 4 months (equivalent to around 26 years of human age), the F1 generation developed insulin resistance and glucose intolerance, but no obesity. The F2 generation only developed glucose intolerance, showing a more moderate phenotype. This research gives evidence that nutritional imbalances during early life might result in metabolic abnormalities that have the ability to affect subsequent generations.

Dunn and Bale[28] observed phenotype transmission throughout three generations to explore whether the epigenetic changes lead to stable programming. For this, the body size and insulin sensitivity of the F3 mouse offspring of parents exposed to a high-fat diet was analyzed. Results showed an increased body size phenotype exclusively in female F3 offspring. This effect was only passed on through the male lineage, which sup-

ports the notion of a non-genetic mode of inheritance. Using a quantitative TaqMan Array, Dunn and Bale detected potentially involved gene expressions from the paternal lineage in livers of F3 females. This indicated that the impact of paternal diet on r female mouse offspring might be the consequence of programming events at imprinted loci.
In subsequent research, Masuyama et al.[29] exposed mice to a high-fat diet and observed the effect on offspring over multiple generations. In agreement with the articles discussed above, metabolic abnormalities such as weight gain and insulin resistance were found. Negative metabolic effects of the high-fat diet diminished in F2 and completely disappeared after a normal diet for three generations. Although this research did not explain why the effects diminished in the following generations, it provided promising evidence for the possibility of reversing detrimental health effects in future generations caused by environmental exposure.
In summary, the animal models discussed above all replicate findings of metabolic abnormalities and increased body size in following generations of mice exposed to a high-fat diet in utero.

Discussion

The aim of this paper was to investigate the transgenerational effects of (mal)nutrition on the human epigenome. All three different study designs included in this paper provide distinctive insights accompanied by unique strengths and limitations, as discussed here.
EWAS enable a deeper understanding of underlying mechanisms responsible for the link between overnutrition and epigenomic dysregulation. Several CpG sites were found to be associated with obesity, and differential DNA methylation has been repeatedly suggested to mediate the effects.[16,19] Ultimately, methylation variation has been observed at loci involved in the development of several chronic diseases across different age groups and ethnicities.[21]
However, several limitations of the included EWAS must be taken into account. The study by Xu et al.[16] lacks in generalizability to other populations due to the strong link between age and DNA methylation and no control for other possible third variables such as environmental factors. Further, the cross-sectional design in the study by Demerath et al.[19] does not demonstrate the temporal relationship between BMI or WC and methylation. Another concern of the discussed epigenetic epidemiological studies is the use of blood as metabolically active tissue. Blood is often used for genomic analysis because methylation signals in leukocytes may be useful biomarkers of obesity-induced immunological activation due to the strong causal link between adiposity and immune reaction. However, unmeasured cell types in blood could have confounding effects[16], which could be solved by applying cell type composition corrections strategies such as the Houseman method.[30] Furthermore, to obtain biologically meaningful results, it is crucial to examine tissues specifically related to obesity such as adipose tissue. Caution is also needed when interpreting findings based on EWAS. Some EWAS, for example the study by Ling et al. [14], include combined cohorts to increase their sample size and power. However, this could increase the error variance due to differences in data analyses, which are often failed to be taken into account leading to an over- or underestimation of the true effect size. This could also result in over- or underrepresentation of specific cohorts or populations and should be addressed in the future.
In the second subtopic, historical cohort studies were reviewed to explore the transgenerational effects of malnutrition in a human sample. Studies discovered that maternal undernutrition during early gestation resulted in abnormal DNA methylation[23] and poorer health in the F1 generation.[25] These effects were passed on to subsequent generations (F2) through the paternal lineage.[24]
Nevertheless, it is important to note that the association analysis of chronic disease in the study by Veenendaal et al.[24] was based on self-report questionnaires, which is a poor measurement of health and limits statistical power. Also, the mean age of the sample was 37 years, although many chronic diseases are known to have a later onset. Hence, it is difficult to draw conclusions about general health indicators based on this data.
A point of caution when interpreting outcomes of the study by Li et al.[25] is the long duration of the Chinese famine. This resulted in findings of cumulative effects on metabolic risk over the entire intrauterine period. The long exposure complements the present paper's aim to investigate the influence of lasting lifestyle choices. Another limitation of historical cohort studies is their design, which only allows for conclusions about associations. The underlying mechanisms remain to be explored. Future research is necessary to replicate these studies also with individuals exposed to common contemporary factors like overnutrition. Additionally, clarifying the extent to which epigenetic marks are vulnerable to certain environmental exposures will help rule out possible third variables influencing the results.
Discussed animal models are congruent in their findings of metabolic abnormalities in the offspring of overfed mice. These permanent alterations seem to be caused by epigenetic modifications, concretely genomic imprinting, which is passed on through the male germline.[27,28] One limitation of the research by Pentinat et al.[27] is that the underlying mechanisms have not been examined. The progressive weakening of the phenotypes from F1 to F2 suggests that epigenetic modifications likely play a mediating role but continued investigation in this field is necessary. Interestingly, the study by Dunn and Bale[28] did not show reduced insulin sensitivity in the F3 offspring, which raised the question of whether adverse health effects caused by overnutrition can be reversed in consequent generations after returning to a normal diet. This has been addressed by Masuyama et al.[29] who found a weakening of the phenotypes in subsequent generations. The results suggest that adverse health outcomes caused by environmental effects might be reversible in future generations.[29]
Generally, one key advantage of animal studies is the shorter life cycle of animals (in this case mice) compared to humans. This allows us to study the effects of over-nutrition throughout the animals' life span together with several subsequent generations; therefore, to conclude transgenerational effects. Additionally, the influence of environmental factors and genetic background can be controlled much easier. However, one major drawback of studies based on homogenous animal populations is the limited generalizability to the heterogeneous human population. This highlights the importance of result replication in humans. More longitudinal data is needed to observe the effects of current nutritional trends on the health of subsequent generations in humans. Moreover, none of these studies was able to explain underlying mechanisms or demonstrate which specific tissues are involved in the process.
Altogether, the results of the discussed articles give evidence for possible threats of malnutrition on the human epigenome.

The literature is in line with the previous research and the early idea of the Barker hypothesis, suggesting that maternal malnutrition might have detrimental health consequences on the offspring when exposed in utero during early development. However, it is still unclear during what time window the critical period takes place. Future studies are necessary to determine the amount of exposure necessary to have direct effects on the epigenome and to clarify which food components or interactions play a role.

Apart from summarizing results and limitations of prior papers, the current review contributes to existing research by combining several study designs to suggest possible outcomes in a newly emerging field. Nevertheless, an important shortcoming of this paper is the small number of reviewed articles. Including all research that has been conducted to investigate each of the subtopics would be fundamental to create a complete overview but would go beyond the scope of this paper. Additionally, the snowballing method for the selection of articles should be avoided in such extended future work, as this might be subject to sampling bias. This method might also result in the selection of similar articles disregarding contradictory findings which are relevant for inclusive results.

Although longitudinal data is necessary to confirm direct links, the combined findings can be used to predict future outcomes of contemporary lifestyle trends. The fact that most of the reviewed articles revealed detrimental impacts of an unbalanced diet on health is highly alarming, considering the increasing prevalence of obesity. This highlights the urgent need to initiate more studies in the field of nutritional epigenomics. It is also crucial to prioritize nutritional education based on already known facts about a healthy diet, especially to mothers given the critical role of pregnancy highlighted in this review. Furthermore, the results should raise awareness about our modern environment in which food abundance, highly processed food and aggressive marketing of junk food makes living a healthy life a challenge. The phenomenon of poor health due to an unbalanced diet is intensified by the fact that not only the individual is adversely affected, but even future generations will have to suffer unhealthy life choices made by their parents. Luckily, animal models indicate that reversing these harmful effects might be possible by normalizing nutritional intake in subsequent generations.

Conclusion

In conclusion, this present literature review provided evidence for detrimental transgenerational effects of malnutrition on the human epigenome. Combining the results of different study designs investigating various links related to the topic allowed for making predictions regarding transgenerational health consequences of our current environment. In this study, malnutrition has been continuously associated with epigenetic dysregulation resulting in increased prevalence of metabolic and cardiovascular diseases. Some of these detrimental health outcomes have been shown to be transmissible to subsequent generations. Longitudinal studies are required to evaluate these predictions and determine further mechanisms linking nutrition to the epigenome. Research should also aim to identify which nutritional aspects play a key role and to clarify the developmental time window in which changes in the epigenome may occur. The extent to which life-style choices or limited in utero exposure have an impact on the health of later generations remains yet to be investigated.

Ultimately, more exploration of the field of nutritional epigenomics might help us prevent chronic diseases, improve treatment and allow us to intervene in complex transgenerational inheritance patterns.

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Figures

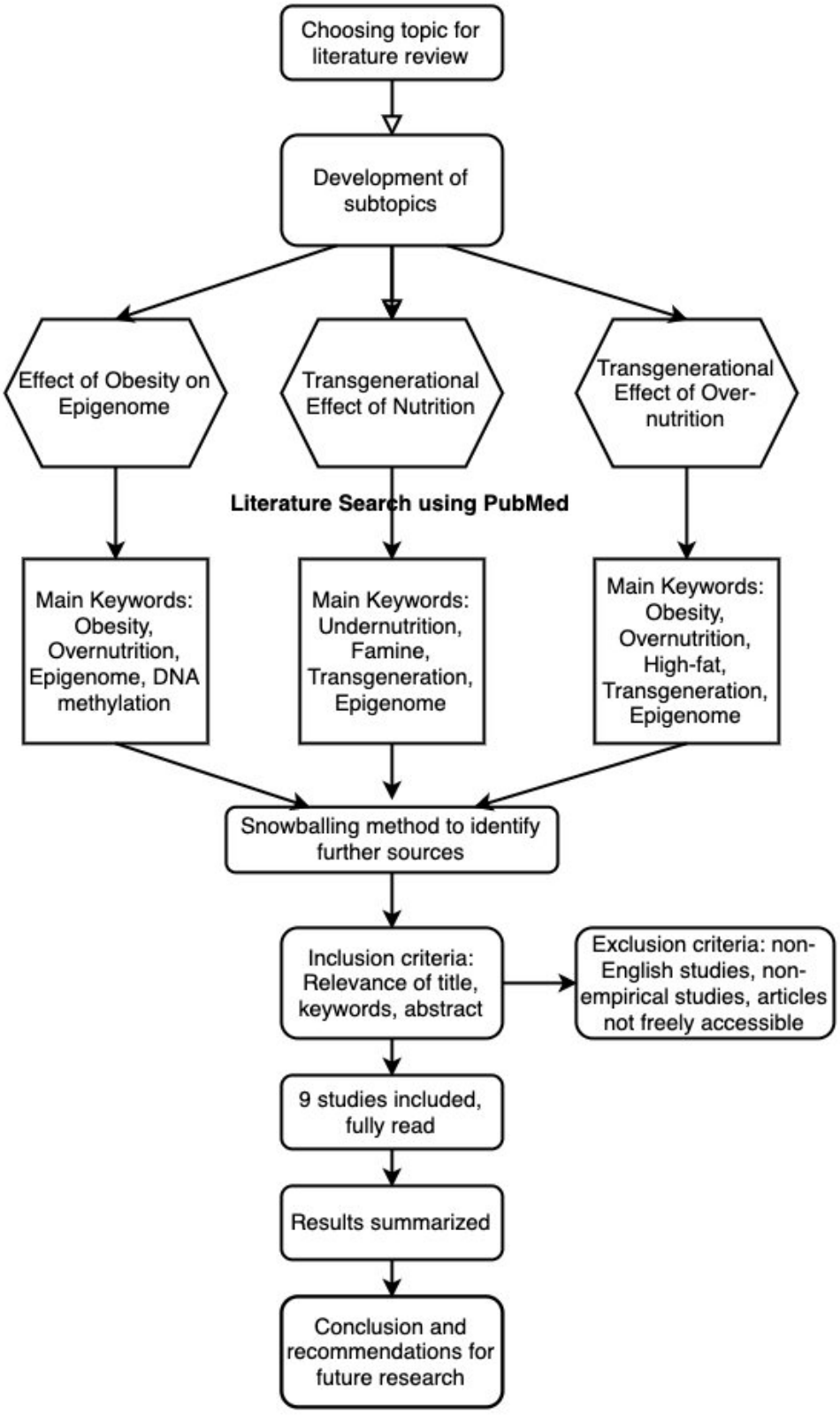

Figure 1. Schematic diagram of the research method.

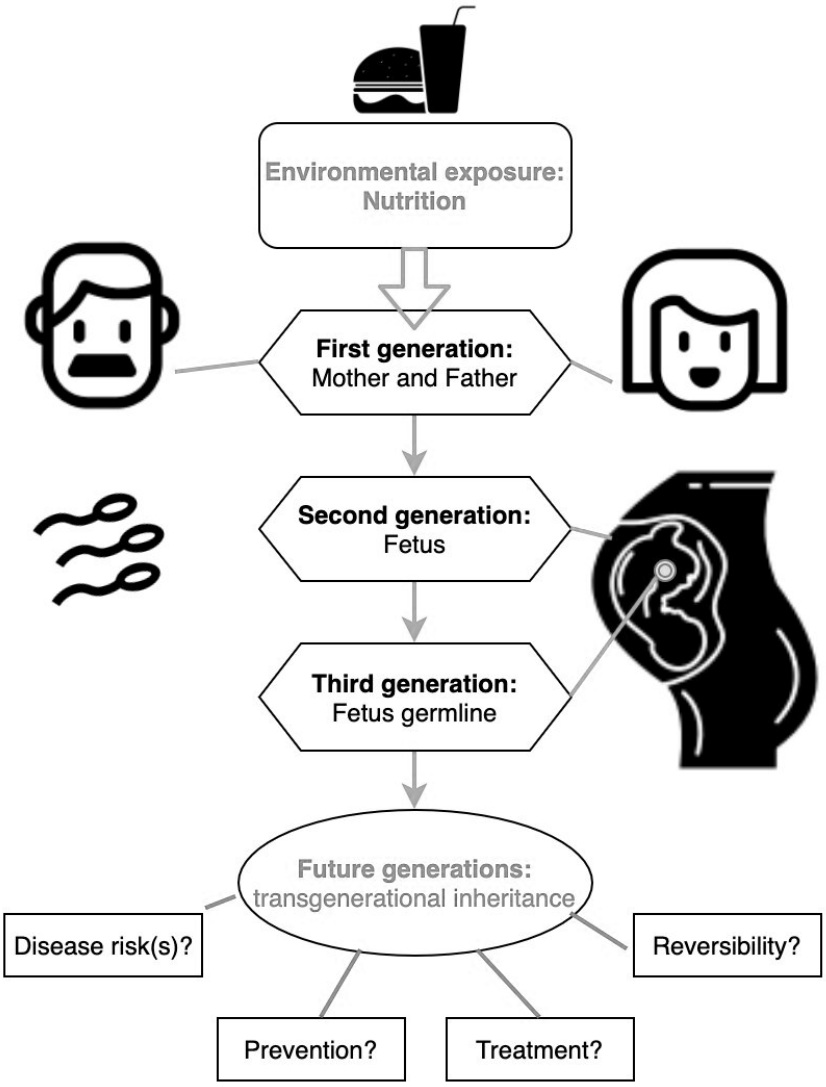

Figure 2. Mechanism and relevance of transgenerational epigenetic inheritance.

The government should make influenza vaccination mandatory for healthcare workers

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Introduction

The influenza vaccination rate among Dutch hospital employees is low: during the flu epidemic of 2012/2013, a study in 45 hospital showed that the median vaccination rate was only 13%, while the vaccination coverage ranged from 2 to 33%.[1] * For this reason, there is a lot of attention to increasing the influenza vaccination rate among healthcare workers. In 2018, the National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieuhygiëne or RIVM) advocated making influenza vaccination mandatory for healthcare providers.[3] However, in 2019 State Secretary Blokhuis for Public Health advised, on the basis of an exploratory study, not to make the flu vaccination compulsory. The conclusion of the study was that there is no legal basis, there are legal objections and there is little support from employers and employees for making influenza vaccination mandatory. Instead of making the vaccination compulsory he introduced other, non-mandatory, measures instead.[4]

The flu is caused by the influenza virus. The virus is secreted by an infected person through talking, sneezing or coughing; somebody else can then be contaminated by inhaling droplets or aerosols from the air, or by direct contact.[4] In the Netherlands, about 400,000 people were infected with the influenza virus during the relatively mild influenza epidemic of 2018/2019 and there were about 2,900 more deaths than usual during this period.[5]

Flu vaccination is available to prevent the flu. Flu viruses change every year, so everyone has to be vaccinated every year again.[6] In 2019/2020, a quadrivalent vaccine was used in the Netherlands[+] ; this protects against four influenza viruses.[7] The Health Council (Gezondheidsraad) [8] recommends that the elderly (people over 60 years of age), the chronically ill and healthcare workers should be vaccinated against influenza every year. The vaccination of healthcare providers has several goals: to protect healthcare providers themselves against the flu, to prevent the transmission of the influenza virus to patients and to maintain continuity of care.[3] Despite the goals of vaccination, vaccination coverage is low among healthcare providers: research shows that healthcare providers are sceptical about vaccination.[9] To increase vaccination coverage, the question is whether the government should make influenza vaccination a legal requirement for healthcare professionals. This question poses an ethical dilemma: do the health gains caused by influenza vaccination outweigh the legal restriction of freedom?

Medical-scientific insights

One of the three goals of influenza vaccination among healthcare workers is to protect them from influenza virus infection.[3] This is important because healthcare workers have a significantly higher risk of infection compared to non-healthcare providers [10], as they have a higher exposure to the influenza virus among infected patients. In addition, medical research shows that influenza vaccination prevents flu in both healthcare providers and non-healthcare providers. A recent meta-analysis [11] concluded that there were significantly fewer laboratory-confirmed influenza virus infections among vaccinated healthcare providers compared to non-vaccinated healthcare providers. In addition, a Cochrane review showed [12] that the risk of flu for healthy adults (16-65 years) without influenza vaccination is 2.3% and that the chance is lowered to 0.9% with influenza vaccination. Another Cochrane review [13], which examined the effectiveness of the flu shot in the elderly (persons of 65 years and older), indicated that the chance of getting the flu was reduced from 6% to 2.4% after flu vaccination. The flu shot thus prevents more than half of the flu cases among both healthy adults and the elderly.

Another goal of influenza vaccination of healthcare workers is to protect patients in healthcare facilities.[3] This is important because those patients are often immunocompromised, which implies that influenza virus infection can lead to severe morbidity and mortality.[14] However, there is no clear evidence that patients are protected from influenza when healthcare providers are vaccinated. In a 2016 Cochrane review [15], no significant difference was found in the number of influenza-positive patients (aged 60 years or older) who had contact with both vaccinated and non-vaccinated healthcare workers, although the authors emphasize that the studies used had a high bias risk[±]. A 2013 meta-analysis [16], which partly used the same studies as the 2016 Cochrane review, came to the same conclusion. A significant decrease was found in all-cause mortality and flu-like complaints in patients. However, the

* *The Dutch Hospital Association [2] claims that the vaccination rate among healthcare providers was 33% in 2019/2020. The research findings, however, have not been published.*
[+] *This essay uses data on inactivated flu vaccines, because these are used in the Netherlands [7].*
[±] *The most important causes for this were related to attrition, lack of blinding, cases of infection with the virus in the control groups and low rates of vaccination coverage in the intervention groups.*

quality of this evidence is low, because it could not be established that the deaths and complaints were actually caused by the influenza virus.

Overall, the evidence for protecting patients by vaccinating healthcare providers is inconclusive. A meta-analysis shows that influenza vaccination in children protects their immediate environment from influenza and the household against flu-like symptoms, and protects against death from influenza.[17] It is plausible that, if (almost) all healthcare workers are immune to the flu, and thus group immunity occurs, patients will be indirectly protected against the influenza virus. However, this is not certain, as influenza vaccination has been shown to be more effective among children [18] than among adults [12] (RR 0.36 and 0.41§, respectively).

The final goal of vaccinating healthcare professionals is to guarantee continuity of care during an influenza epidemic.[3] Not only patients, but also healthcare providers may contract an influenza virus infection during a flu epidemic. The increase in the number of patients and the greater dropout rate of healthcare providers can create problems for the capacity of hospitals.[3] Imai et al. [11] found that vaccinated caregivers have a significantly lower absenteeism due to influenza-like symptoms: on average, vaccinated caregivers' sick leave lasted 0.46 days shorter than that of non-vaccinated caregivers. This ensures that healthcare workers remain more available for their healthcare work.

Despite the evidence that influenza vaccination of healthcare professionals leads to fewer flu cases, only 13% of Dutch healthcare workers are vaccinated [1]. There are different views among healthcare providers about the flu and flu vaccination. For example, they fear possible side effects, do not believe they have an increased risk of influenza, consider it unlikely that they will transmit influenza to their patients, dispute the effectiveness of the vaccine, or feel that the effects of influenza are not serious. In contrast, vaccinated healthcare providers believe that vaccination is effective and that protecting their environment is their professional duty.[9]

Some healthcare workers fear the side effects of influenza vaccination. Ng et al. [19] concluded that most side effects were mild and not permanent. Local side effects that are significantly more common after flu vaccination compared to placebo vaccination are: a painful arm, and redness, hardening or swelling of the skin. In addition, systemic side effects were found, such as muscle pain, fever, fatigue and general malaise. [12] It is likely that most healthcare workers tolerate the vaccination well.

The most effective intervention to increase the flu vaccination rate of healthcare workers turned out to be mandatory vaccination [20,21]. Lytras et al. [21] concluded that rejection of vaccination should also have consequences. The most effective consequence turned out to be dismissal of the employee.

Ethical aspects

The advantages and disadvantages of influenza vaccination must be weighed before determining whether a legal obligation of influenza vaccination for healthcare workers is justified.

The medical-ethical principle of beneficence plays a role at two levels. Firstly, it concerns the relationship between the government and its citizens. The government has a moral duty to protect and promote the well-being and health of citizens, in this case healthcare professionals. Flu vaccination reduces the risk of influenza among citizens of all ages [12,13,18], including healthcare providers.[11] This is especially important for healthcare providers, as they have a significantly higher chance of getting the flu.[10]

Secondly, the principle of beneficence applies to the relationship between healthcare providers and patients: healthcare providers have a moral duty to prevent or remove harm to their patients.[22] Patients are often immunocompromised, which implies that the consequences of an influenza virus infection can be very serious and even lead to death.[14] Although there is no clear evidence that vaccinating healthcare providers leads to less laboratory-confirmed influenza in patients [15,16], patients are less likely to develop influenza-like symptoms and to die less frequently.[16] Moreover, healthcare workers protect their patients by getting vaccinated in two other ways. First, the flu vaccination prevents absenteeism from work [11], which means that healthcare providers can take longer and better care for their patients. Secondly, group immunity among health care providers, as described above, could indirectly protect the weaker population – the patients – from the flu.[17]

Yet, flu vaccination also has its disadvantages, because it can harm healthcare providers. This goes against the no-harm principle, i.e.: "above all, do not harm".[22] The flu vaccination can have side effects. These are both local side effects (a painful arm, and redness, hardening or swelling of the skin) and systemic side effects (muscle pain, fever, fatigue and general malaise).[12] Such side effects can be considered mild [19], making them tolerable for healthcare providers.

The arguments above show that the health benefits for healthcare providers outweigh the side effects. However, the benefits for patients cannot be demonstrated with certainty. It is clear, however, that they are not disadvantaged if healthcare providers are vaccinated. The literature [16] suggests that vaccination does provide health benefits and therefore it is also true that the benefits outweigh the disadvantages for patients.

When it comes to the ethical justification of compulsory influenza vaccination for healthcare providers, the medical-ethical principles of 'beneficence' and 'respect for autonomy' are at odds.

First, as mentioned above, the government must promote the well-being of citizens. Citizens include both the healthcare

§ *The abbreviation 'RR' stands for 'risk ratio'. This is calculated by dividing the absolute risk in the intervention group by the absolute risk in the control group. Here the intervention is the influenza vaccination, so the intervention group gets the vaccination and the control group does not. The risk of getting influenza is then calculated in both the group of adults and that of children. So the lower the RR, the lower the risk of getting the flu after vaccination compared to the group without vaccination. Using the RR one can therefore compare the effectiveness of the vaccination between adults and children.*

providers and the patients of the healthcare providers . It has previously been concluded that vaccinating healthcare workers improves the health of healthcare workers as well as that of patients. In order to protect as many healthcare providers and patients against influenza as possible, the flu vaccination rate among healthcare workers must be increased significantly, and the best way to achieve this is to make influenza vaccination compulsory.[20,21]

The principle of respect for autonomy points in a different direction than the argument related to beneficence. The Netherlands is a liberal society: individuals are, within certain limits, free to make their own choices, and thus to determine for themselves what is good for them.[22] Healthcare providers must therefore be able to decide for themselves whether they opt for the flu vaccination. Making influenza vaccination compulsory for healthcare providers is not in line with the values and standards of liberal society. However, healthcare workers have a special responsibility: they should take care not only of their own health, but also of their patients' health. In addition, healthcare providers have made the autonomous choice to work in the medical sector. This involves legal obligations and they must accept that influenza vaccination is part of this. The government may therefore act paternalistically and make influenza vaccination compulsory for healthcare providers: in this light, the personal choices of healthcare workers are of secondary importance.

The final medical ethical principle is the principle of justice. This principle implies that similar cases should be treated similarly.[22] Every patient should be considered equal and should be given equal opportunities. Every patient is entitled to an equal degree of protection against influenza and therefore to finding a vaccinated healthcare worker at the bedside. This means it would be unjust for patients if the flu vaccination is not mandatory.

Conclusion

This paper has reviewed a number of arguments related to mandatory influenza vaccination of healthcare providers. My conclusion is that the harm that health care providers experience from influenza vaccination is proportional. In addition, patients do not experience any harm from the vaccination but most likely benefit from it. The government would therefore act according to the principle of beneficence by making influenza vaccination compulsory. At the same time, the government must respect the autonomy of the care providers. All things considered, this medical-ethical principle weighs less heavily for the social group of healthcare workers, because they have a special responsibility for their patients. Finally, the principle of justice applies: every patient has an equal right to a vaccinated healthcare provider. In short, the health benefits outweigh the costs for the autonomy of healthcare workers. Flu vaccination for healthcare workers must therefore be made mandatory by the government.
This obligation must be qualified. The government must clearly explain its choice for mandatory vaccination and justify it to its citizens. The government must oblige healthcare institutions, which employ healthcare providers, to vaccinate all their employees, subject to the condition that vaccination is free. Healthcare institutions themselves must monitor whether vaccination actually happens and decide what consequences should follow the refusal of vaccination, varying from mild (conducting a conversation) to drastic (dismissal of the healthcare worker) penalties. However, the government must allow for exceptions, for example when the vaccination is a serious violation of moral or religious beliefs or when the health of the healthcare provider is threatened.

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A PSA test should not be refused, but discouraged

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Introduction

The prostate-specific antigen (PSA) test is a controversial subject within the field of Medicine. This blood test is used to screen for prostate cancer: an elevated PSA (≥3,0 ng/mL [1]) can reveal the presence of prostate cancer. Prostate cancer is the most common or second most common cancer amongst men and the second leading cause of cancer death in men in most parts of Europe and North America [2] and thus an important health issue. The aim of PSA-screening is to detect possible prostate cancer early and to save the patient from further harm that would have arisen if the cancer had not been discovered until it had become more advanced.[3] This concept sounds straightforward, but nothing is further from the truth.

The PSA test has become increasingly popular.[4] However, the test lacks convincing evidence of its proclaimed benefits, such as a decline in mortality and the burden of disease.[5] On top of that, the disadvantages such as overdiagnosis and overtreatment are considerable.[6] These are among other things reasons why general practitioners (GPs) and medical organisations are hesitant about the PSA test.[7] Therefore, when an asymptomatic man consults his GP and asks for a PSA test, the GP may not always consider this the right decision. However, could a GP decline the request for a PSA test?

Harms and benefits of the PSA test

In 2019 the results of two highly anticipated studies were published, which interestingly contrasted one another. The results of the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial [6], that included over 180.000 men across Europe, seemed impressive at first. In this randomised controlled trial, a 20% reduction in mortality was found in men aged 55-69 that were screened approximately every four years as opposed to the group that was not screened. The Prostate, Lung, Colon and Ovarian Cancer (PLCO) trial [8] is another randomised controlled trial performed in the United States that included over 75.000 men. They were randomised into either annual PSA testing and digital rectal examination or usual care. Contrastingly, this trial did not see a significant difference in mortality between the screened and non-screened group.

Upon closer inspection of the ERSPC trial, we find that the number of men that need to be screened in order to prevent one prostate cancer death, is 1410. Additionally, 48 prostate cancers would be discovered that would otherwise have remained asymptomatic for the rest of a person's life and would never have needed treatment.[6] This brings into question whether the prevention of one death due to prostate cancer is worth the unnecessary diagnosis of another 48 men with this disease. On the other hand, the ERSPC trial did show a 30% reduction in metastatic cancer after 12 years of follow-up, which decreases the burden of disease.[9]

Both studies mentioned above were analysed in a systematic review [5] together with three other randomised controlled trials, which concluded that PSA testing does not lead to a reduction in mortality. In addition to this, routine PSA testing reveals more prostate cancers than would have been found if there had never been tested.[6,8] The men who are diagnosed and treated feel relieved as they believe that they were saved by the PSA test. Yet, one should keep in mind that a significant percentage of the cancers would never have caused harm in the first place if the test had not been performed. In fact, the test did not need to save these individuals, as they would have never become symptomatic nor would they have died from prostate cancer in the first place. The amount of overdiagnoses from the PSA test is large: 23-42% of the prostate cancers would never have come to light without a test.[10] Since healthy men are classified as cancer patients due to the PSA test, the population faces a bigger burden of disease in the form of many additional prostate cancer cases and the need for extra treatment.

In addition, the treatment of prostate cancer is not without consequences as therapy may cause incontinence in up to 45% of patients and impotence in 88% of patients undergoing a prostatectomy.[11] Not treating in the form of watchful waiting, which entails that the tumour is monitored and one does not start treatment until symptoms arise, also has consequences. 36% of men following this treatment plan report a low to moderate psychological wellbeing and 45% reports a low to moderate quality of life.[12]

Furthermore, a positive PSA test does not always mean that a man has prostate cancer. An elevated PSA can be caused by different, usually harmless conditions.[13] Without an apparent reason for an elevated PSA, a man will be referred to a urologist for a prostate biopsy.[14] The ERSPC trial [6] concluded that after biopsy 75,9% of elevated PSA levels turned out to be false positives. These men however did all have a prostate biopsy, which can itself lead to complications. The PLCO trial [8,15] reported that in 2% of the biopsies infections or urinary problems arose. Along with this, a prostate biopsy generates stress: men with an elevated PSA but a negative biopsy are more worried about getting prostate cancer, visit a urologist more often and request more future PSA tests.[16]

Because of the controversial reduction in mortality, large number of overdiagnoses, overtreatment and psychological burden, the US Preventive Services Task Force (USPSTF) chose not to recommend PSA testing in asymptomatic men in 2012.[14,17] The Dutch Association for GP's (NHG) suggests that a GP should educate their patient about the possibility of finding a cancer that would have never become clinically apparent and that they can refer their patients to an online decision tool.[13]

The NHG however does not dictate what a GP should do if the patient, after having been informed about the advantages and disadvantages of a PSA test, still insists on taking the test.

The patient in the consulting room

The effects of PSA testing on the population as a whole are now presented above. However, one should also consider an individual patient in the consulting room, as statistics are hard to apply on an individual basis. Why is this man seeing his GP with this question at this point in time? Does he understand the possible consequences of taking a PSA test?

Patient characteristics can play a role in determining whether taking a PSA test is a good idea. Certain groups of men have a higher risk of prostate cancer, such as men who have a positive family history for prostate cancer as well as African-American men.[18] For these groups, a general practitioner may be more inclined to conduct a PSA test, despite the lack of symptoms.

Even though old age is a risk factor for prostate cancer, we should be careful when it comes to this matter. The NHG discourages testing men with a life expectancy of less than 10 years. They state that because of the indolent character of prostate cancer, the benefits of testing often will not outweigh the harms of treatment in this group.[13]

Furthermore, a patient is not always aware of the possible consequences of his request and is not always well informed. Therefore, it is important to explain to the patient what the possible harms and benefits of a PSA test are. GPs should ask the patient what he would do if his test came back positive and what he would do if he did in fact have cancer. A randomized controlled trial has shown that 55.2% of the men that were not asked these questions would take a PSA test against 34.3% that were asked these questions.[20] Thus asking these types of questions reduces the percentage of men that would still want to take a PSA test.

As it turns out, the wish to take a PSA test is heavily influenced by the attitude of the GP towards this test.[21] GPs that are in favour of PSA screening usually have this belief because of personal experiences and the fear of a lawsuit if they advised against screening a man that later turned out to have prostate cancer. GPs that are against routine PSA testing, often base their motivation on the existing evidence concerning the PSA test. However, an American and Australian study reported that none of these GPs would deny a PSA test to a patient if he is certain he wants it.[7,22]

Ethical aspects

From an ethical perspective much can be said about the PSA test. A GP wants the best for their patient, but this is complicated by the uncertainty of the test itself and the possible overdiagnosis and overtreatment.[5] Because of this, it is critical that the patient makes a well-considered decision in consultation with his GP about taking a PSA test and truly supports his own decision. In this way a feeling of guilt, regardless of the outcome, will be prevented in both parties.

The respect for autonomy plays an important part in this situation. This principle is sometimes wrongly interpreted as ‘the customer is king’, which is certainly not the case. The GP should not blindly adhere to the request of the patient to conduct a PSA test. When a patient poses this question, the GP however has the responsibility to provide that patient with the information they need to make a well-informed decision while respecting the patient’s norms and values.

The GP can decide to act paternalistically if the patient remains resolute in their request without being able to provide an understandable reason. This entails that one acts against the will of the patient and he is refused the test. Acting paternalistically is not always justified and we must ask ourselves whether restricting freedom of choice in this way is the right action. Are we even allowed to act paternalistically when it comes to something so uncertain as a PSA test?

Given the limited benefits and considerable risks of the PSA test, the principles of beneficence and non-maleficence can be conflicting.[23] On the one hand, one wants to reassure a worried man that he is fine or possibly give him the treatment that he needs, which is in line with the principle of beneficence. On the other hand, doing a PSA test may lead to diagnosing a cancer that would have otherwise never been discovered is in contrast with the principle of non-maleficence.[6] In addition to that, the treatment of prostate cancer is not without harm.[11,12] A consideration must be made here: which principle tips the scale? Perhaps it is better to determine this on an individual basis. Even if a GP is convinced that the principle of non-maleficence outweighs the principle of beneficence and they would rather not perform the test, they must actively discuss this with their patient. If the patient is indifferent to this discussion, we come back to the question whether acting paternalistically is justified in this case.

Conclusion

To conclude, there is little to no reduction in mortality of prostate cancer as a result of the PSA test. The test however does carry considerable harms, such as overdiagnosis and overtreatment and the physical and psychological consequences that go hand-in-hand with this. Furthermore, there are many false positive tests that cause stress. The PSA test is not just a harmless blood test: it could open the door to a strenuous path with serious consequences. Some men that will undergo this, will unfortunately have been diagnosed with prostate cancer unnecessarily.

Prostate cancer is a relatively innocent form of cancer and its diagnosis will lead to bigger harms than benefits in certain groups of men. Different guidelines therefore advise against PSA testing without probable cause. GPs should be cautious, as men do not always realize what the possible consequences are of this test.

A GP cannot deny an asymptomatic man a PSA test, as long as this man, regardless of age, understands what he might be getting himself into and he can motivate why he wants this test. By denying the test, GPs would be restricting someone’s freedom of choice. This test has been normalized to such a degree that denying it to a patient would cause resistance. A man would probably refrain from testing more easily when he realizes for himself that taking a PSA test is not necessarily a good idea, than when he is refused the test. Therefore, a GP refusing an asymptomatic patient a PSA test is not the way to go. Instead, the GP should inform the patient to ensure shared-decision making.

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Opinion Paper

Rotavirus vaccine should not be offered in the Dutch NIP to all children between 6 and 24/32 weeks old

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Introduction

The World Health Organization (WHO) recommends that rotavirus vaccines should be included in all national immunisation programmes.[1] The rotavirus can cause gastroenteritis which leads to fever, watery diarrhoea and vomiting.[2] However, the infection can be even more serious, resulting in dehydration, admission to the ICU and death.[3] In surrounding countries such as Belgium and Germany, the rotavirus vaccine is included in the national immunisation programme (NIP) for all children.[4] In the Netherlands, the rotavirus vaccine has been offered to all children with a medical risk factor (prematurity, dysmaturity and children with serious congenital abnormalities).[5] The reason for this is that children with a medical risk factor have an increased risk of a serious course of the infection [6] and rotavirus vaccination of children with a medical risk factor is cost-effective.[7]

Protecting health (beneficence), preventing harm (nonmaleficence) and equitable distribution of care (justice) are all relevant, but it is not immediately clear how this should be weighed up and what should ultimately be decisive. The question now is whether the rotavirus vaccine should be offered in the Dutch NIP to all children between 6 and 24/32 weeks (universal vaccination), instead of only to children with a medical risk factor (targeted vaccination).

Medical scientific overview

Below is a scientific overview of the most important aspects related to rotavirus infections and rotavirus vaccination.
First of all, it is useful to know something about rotavirus infection in general. The incubation period for rotavirus disease is 2.0 days (95% CI (confidence interval): 1.4-2.4).[8] An individual can become infected with the rotavirus multiple times, but the severity of the symptoms decreases with each new infection.[9] Compared to gastroenteritis caused by another pathogen, rotavirus gastroenteritis is more severe and causes dehydration 5.5 times more often.[10]
Secondly, an overview is given of information about the rotavirus in the Netherlands. The rotavirus causes 6.2% (95% CI: 5.3-7.3) of all hospital admissions of children in a general hospital in the Netherlands.[11] It is estimated that there are 4870 hospital admissions per year as a result of dehydration due to the rotavirus in the Netherlands.[11]
A Dutch observational study [6] shows that prematurity, low birth weight and congenital abnormalities are associated with a more serious course of the infection. Children with these medical risk factors have an increased risk of hospitalization (RR (relative risk): 1.6-4.4) and admission to the ICU (RR: 4.2-7.9).[6] In the Netherlands, death as a result of rotavirus infection almost exclusively occurs in children with a medical risk factor.[11]
In the Netherlands, a peak incidence of rotavirus infections is seen in winter and early spring. In recent years, the epidemiology of rotavirus infections in the Netherlands appears to have changed from an annual to a biennial pattern.[13,14]
A cause of this change in epidemiology could be relatively mild temperatures, but there are other unknown factors that play a role.[15]
Thirdly, the overview goes into more detail on the rotavirus vaccines and the effectiveness and side effects of these vaccines. The safety of the vaccine for premature children is also discussed.
The rotavirus vaccine Rotarix (RV1) or Rotateq (RV5) is offered in the NIP in 43% (84/194) of all countries and 36% (20/56) of high-income countries.[4] Both RV1[16] and RV5 [17] are efficacious and well tolerated when given concomitantly with other vaccinations from the NIP.
The recent Cochrane Database Systematic Review [18] shows that the vaccine RV1 and RV5 prevents respectively 82% (RR: 0.18 95% CI: 0.14-0.23) and 82% (RR: 0.18, 95% CI: 0.08-0.39) of the severe rotavirus diarrhoea in the first 2 years of life in low-mortality countries. Rotavirus vaccination prevents 90.6% (95% CI: 82.3-95.0) of severe diarrhoea caused by rotavirus in children under 5 years of age in developed countries.[19] In addition, rotavirus vaccination prevents 71.5% (95% CI: 53.4-82.9) of hospital admissions.[19]
The relative risk of hospital admissions of unvaccinated children due to rotavirus in populations with and without rotavirus vaccination is 0.75 (95% CI: 0.59-0.95).[20] This result shows that there is indirect effectiveness of the rotavirus vaccine (herd immunity). There is also other evidence for a herd immunity effect of rotavirus vaccine.[21,22] However, these studies [21,22] do indicate that more research into herd immunity is needed.
The recent Cochrane Database Systematic Review [18] shows that there is no increased risk of serious side effects after vaccination with RV1 and RV5. There are concerns that intussusception is a side effect of the rotavirus vaccine, especially after the first dose of the vaccine.[23-25] During an intussusception, the intestinal passage can become blocked, which can disrupt the blood supply and causes necrosis. Intussusceptions may disappear spontaneously, but a surgical procedure is performed in 56.5% of the cases and a resection in 4.4%.[26]
The baseline incidence of intussusception in children younger than 36 months is 21.2 per 100.000 person-years (95% CI: 12.5–34.3) in the Netherlands.[27] A systematic review with meta-analysis [28] shows that rotavirus vaccines are not associated with an increased risk of intussusception in neonates

and children within 31 days (RR: 1.14 95% CI: 0.49-2.64), 1 year (RR 0.84 95% CI: 0.53-1.32) and 2 years (RR 0.91, 95% CI: 0.55-1.52) after vaccination.
The safety of the rotavirus vaccine for premature children is the same as the safety of the vaccine for other children [29]. Furthermore, the medical scientific overview goes into more detail on cost-effectiveness of universal and targeted vaccination.
Targeted rotavirus vaccination of children with a medical risk factor is cost-effective in a high-income country with a relatively low rotavirus endemic setting.[7] The cost-effectiveness ratio for universal vaccination is 51.277 euros per QALY (Quality-Adjusted Life Year) when the vaccination price is 75 euros per child.[7] Compared to the widely used reference value of 20.000 per QALY, universal vaccination is not cost-effective.[7,20]
Universal vaccination is only cost-neutral if vaccination costs 32 euros per child [7], but it is already cost-effective in low- and middle-income countries.[30]
Finally, the support for rotavirus vaccination is discussed.
The intention of parents in the Netherlands to have their child vaccinated against, among other things, rotavirus gastroenteritis was investigated by sending an online questionnaire to 1500 parents with at least one child between 0-4 years.[31] 38% of parents intends to have their child vaccinated against the rotavirus if the vaccine should be offered in the NIP. 44% of parents believes that the disease caused by the rotavirus is not serious enough to vaccinate their child for it. A study from Italy [32] shows that public education programmes are needed to improve parent knowledge about rotavirus and rotavirus vaccinations so that more parents get their children vaccinated.

Medical ethical argumentation

The question now is whether the rotavirus vaccine should be offered to all children between 6 and 24/32 weeks. Various ethical aspects are important for this question, namely: protecting health (beneficence), preventing harm (non-maleficence) and equitable distribution of care (justice).
The government has a duty to protect its citizens and can do this by offering the rotavirus vaccine to all children between 6 and 24/32 weeks. Vaccination all children between 6 and 24/32 weeks with the rotavirus vaccine is effective in reducing the disease burden.
Firstly, the rotavirus vaccine prevents 90.6% of severe diarrhoea caused by the rotavirus in children in the first five years of life.[19] Secondly, the rotavirus vaccine prevents 71.5% of hospital admissions due to the rotavirus.[19] Finally, universal rotavirus vaccination prevents hospitalization of unvaccinated people.[20] This is because herd immunity can take place through rotavirus vaccination.[20-22]
However, vaccination of children against the rotavirus can also be stimulated in another way than through supply in the NIP (subsidiarity). For example, the rotavirus vaccine can be offered at their own expense to children without a medical risk factor in combination with a public education programme. This will increase awareness about the rotavirus and the rotavirus vaccine, so parents will be more willing to have their child vaccinated. In this way, the disease burden can be reduced without having to offer the vaccine in the Dutch NIP.

Universal vaccination against the rotavirus should be introduced because it provides health benefits. However, there is another way in which health benefits can be achieved.
The government can harm the child by offering the rotavirus vaccine because the rotavirus vaccine could have disadvantages for the child. However, there is no increased risk of serious side effects after vaccination with rotavirus vaccines.[18]
There are concerns that intussusception is a side effect of the rotavirus vaccine [23-25], but a systematic review shows that rotavirus vaccines are not associated with an increased risk of intussusception.[28]
The rotavirus vaccines are not associated with an increased risk of serious side effects, so the government should not harm the child by offering the rotavirus vaccine.
The government has a duty to distribute care equitably. By offering the rotavirus vaccine to all children between 6 and 24/32 weeks, there is no equitable distribution of care because the government does not use scarce resources equitably. This is because the cost-effectiveness of universal rotavirus vaccination is not favourable compared to the widely used reference value of 20.000 euros per QALY.[7]
Rotavirus vaccination of only children with a medical risk factor is equitable. Through targeted vaccination, the government uses scarce resources equitably. Firstly, children with a medical risk factor have a greater medical need than children without a medical risk factor. These children have an increased risk of a serious course of the disease and hospitalization.[6] In addition, mortality due to the rotavirus in the Netherlands occurs almost exclusively in children with a medical risk factor.[11] Secondly, the cost-effectiveness of targeted vaccination is favourable compared to the widely used reference value of 20.000 euros per QALY.[7]

Based on the principle of justice, the government should choose targeted vaccination instead of universal vaccination, because children with a medical risk factor have more medical needs and targeted vaccination is cost-effective.

Conclusion

A number of important elements have been discussed. First of all, the government can protect its citizens with universal rotavirus vaccination. The vaccine prevents severe diarrhoea and hospitalizations, and herd immunity can take place. However, making the vaccine available at their own expense in combination with a public education programme could also lead to health benefits. Secondly, the government should not harm children by offering the vaccine because the vaccine is not associated with an increased risk of serious side effects. Finally, there is no equitable distribution of care if universal vaccination is chosen, because universal vaccination is not cost-effective. On the other hand, targeted vaccination of children with a medical risk factor is equitable, because these children have a greater medical need and targeted vaccination is cost-effective.

The health benefits for the individual and population do not outweigh the side effects of the rotavirus vaccine and the unfavourable cost-effectiveness of universal vaccination. Offering the rotavirus vaccine to all children between 6 and 24/32 weeks is therefore not proportionate.

All things considered, I come to the conclusion that the rotavirus vaccine should not be offered in the Dutch National Immunisation Programme to all children between 6 and 24/32 weeks, but only to children with a medical risk factor.
There are some preconditions. Targeted vaccination was introduced in the Netherland in 2020. The effects of the introduc-

tion of this targeted vaccination should be evaluated. Targeted vaccination must be effective in reducing the burden of disease in children with a medical risk factor. For sufficient health benefits in this group, the attendance for targeted vaccination must be high. In addition, mortality due to rotavirus should no longer occur after the introduction of targeted vaccination. Furthermore, the cost-effectiveness of universal vaccination must still be unfavourable. If the price of the vaccine decreases, making the cost-effectiveness more favourable, a reconsideration should take place.

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The template for authors

Introduction

1. *What is the health-related problem that your research helps to solve?*

2. *What is your strategy to solve the problem?*

3. *What is your research question/hypothesis?*
   Whether a question or a hypothesis, state it in terms of 2 items:
   - variables: the measurable/observable independent and outcome variables that you measured/observed and
   - relationships: the relationships between those variables that your data analyses were designed to determine.

4. *The core concept of the methods you used to answer the research question*
   Briefly describe the core concept of the methods at the end of the Introduction section. This helps readers to understand the complex details that are then presented in the Methods section

Methods section

Organize the details of the Methods section under subheadings. Possible subheadings:

What was studied and study design (subheading)

Describe the details of
- what was studied: sample from a patient/animal population, and
- the design of the study: case-series, cohort study, case-control study, randomized trial, etc.

Data collection (subheading)

Describe the details of how the data was collected/observed

Note
Observable variables will be credible only if qualified observers and validated instruments were used to assess them. Examples of observable variables include patient symptoms, subject responses to open interviews/ questionnaires, ultrasound/MRI/CT images, assessments of articles in a literature review etc. In such cases, build credibility in the Methods section; report "who" observed and interpreted the data. For example, "An experienced radiologist interpreted the images."

Note
When reporting on decisions/judgments that were made, use the "we" form—take responsibility for what you did.

Note
The Methods section reports historical facts and must be in past tense.

Data analysis (subheading)

Results section

5. *The core concept of the Results*
   Briefly describe the core concept of the results in a short paragraph at the beginning of the Results section. This helps readers to understand the details that follow. Note just as in the Methods section, this section reports historical facts and must be in past tense.

Then organize the details of your Results under sub-headings, for example:

Patient/animal characteristics
Data
Statistical results

Discussion section

Structure your Discussion to focus on 4 core concepts [6, 7, 8, and 9 below).

6. *The answer to your research question*
   Present this right at the top of the Discussion section—the very first sentence, a present tense statement that expresses—to the best of your knowledge—how the world works as related to your research question/hypothesis. It is a direct answer to the question/hypothesis stated in the Introduction.

7. *Support that answer?*
   a) how your factual findings, (expressed in past tense), support your answer.
   b) relating the findings of others to your answer.
   c) theoretical considerations that support your answer.

Limitations (subheading)

8. *The limitations to that answer*
   Focus explicitly on limitations related to possible confounders:
   - sample size
   - specific locations/medical centers of your study,
   - possible ethnic/cultural variables,
   - uncontrolled patient/subject characteristics and
   - underlying assumptions.

Conclusions (subheading)

The Conclusion is not a summary, but should focus on the consequences of your work. Structure this subsection using separate paragraphs that state 2 main messages [9 and 10)

9. *What are the practical/theoretical consequences of your answer?*
   The value—relevance— of your work: how it helps to solve the problem described at the beginning of the Introduction.

10. *What is a next step to help solve the original problem?*
    - a new research question to be answered
    - a refinement of the present study to reduce limitations
    - a protocol to implement the findings in the clinic

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- Are the objectives appropriate and clearly stated?
- Are the data valid?
- Are the conclusions valid and properly supported?
- Is the already existing work described adequately?
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- Does abstract clearly convey meaning of the paper?
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- Are all sections really needed, or could they be shortened?
- Is the science reliable? Please, be aware of ethical issues such as plagiarism!

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