JOURNAL OF HEALTH POLICY AND ECONOMICS

Camille Bou, J. Sam Meyer. A Foreword by the Editors-In-Chief of the JOHPEC. Journal of Health Policy and Health Economics. 2021; 1(1).

A Foreword by the Editors-In-Chief of the JOHPEC

Camille Bou[1], J. Sam Meyer[1]

[1]LSE Department of Health Policy

Welcome to the inaugural issue of the Journal of Health Policy and Economics (JOHPEC): a student-led, peer-reviewed open access Journal of the LSE's Houghton Street Press, dedicated to publishing the work of LSE students and alumni in the diverse fields of health.

The JOHPEC was founded about a year ago, in April 2020, as health systems around the world faced the biggest challenge of their time: the COVID-19 pandemic. In a time when misinformation spread quickly, and public trust in expertise waned, the JOHPEC reminded its authors, readers, and developers the importance of centring policies around factual, evidence-based knowledge. Its rigorous guidelines and peer-review process has enabled us to publish papers of high quality, and our open access policy ensures those papers are always readily available to all.

More generally, the JOHPEC aims to give LSE students and alumni interested in health research an opportunity to understand the world of academia, by publishing the original papers they have written related to their coursework (or externally), build skills of peer-reviewing, and manage publications as an Editor. This learning platform would have never taken shape without the sponsorship of the LSE Department of Health Policy; we are most grateful for their continued support in the JOHPEC's mission. We are equally appreciative of the LSE Houghton Street Press team – Claire Delahunty, Lucy Lambe, and Emily Horsey – and Dr. Edgar Whitley for their help in developing the submission, peer-reviewing, and editing processes of the Journal.

The issue you read today is the product of a year's worth of collaborative, hard work. We would like to extend our gratitude to the Editorial Board of the JOHPEC, namely Nuha Bazeer, Kavyashree Satish, Ritesh Maharaj, Nilesh Raut, Marselia Tan, Leana Diekmann, and Diana Picon-Manyari, who have brilliantly managed the first influx of submissions whilst juggling their other scholarly responsibilities. Thank you as well to Amir Mohsenpour and Filippos Papadopoulos for creatively spearheading the JOHPEC's seminar series and communications strategy.

In this inaugural issue, you will find commentaries, original research, and policy briefs with topics ranging from Universal Health Coverage, to Cost-Effectiveness of Treatments, to Social Determinants of Health; this beautifully mirrors the impact of LSE students and alumni in a myriad of health fields. Thank you to the authors of the manuscripts populating our first Issue, for your dedication to finding answers to today's most pressing health questions, and for trusting the JOHPEC with the publication of your work.

Finally, an immense THANK YOU to our international pool of peer reviewers for their valuable input, for taking the time to carefully read through the submissions to provide formative feedback to authors. These contributions are, once more, a wonderful reflection of the commitment of the wider LSE community in delivering excellence in research:

Rosa Juarez Arriaga
Cameron Feil
Disha Patel
Nuha Bazeer
Ka Keat Lim
Jasmine Mah
Nilesh Raut
Sergio Nabais
Nurul Rahmayanti
Heidi Au
Srishti Acharya
Amitha Kapyur
Alison Mhazo
Arush Lal
Francis Ayomoh
Nada Kim
Debra Winberg
Simon Drees
Mary Bowman
Rafael Chaves
Chimba Sanga
Iqra Amin
Ramiro Gilardino
Kavyashree Satish
Krishnan Puri Puri Sudhir
Nicholas Ivin
Isabel Greaves
Carmen Lopez-Soto
Edmund Lodwick
Diana Picon-Manyari
Filippos Papadopoulos
Alexandra Schuster

Maura Reilly
Jessica Cook, and
Savvas Vlachos.

We hope you enjoy reading the works published in the JOHPEC, as much as we've enjoyed putting our inaugural issue together. Our call for submissions is always open, and we strongly encourage LSE students and alumni interested in health topics to submit their work to us and get involved as peer-reviewers for the Journal.

With best wishes,

J. Sam Meyer
Editor-In-Chief

Camille Bou
Deputy Editor-In-Chief

JOURNAL OF HEALTH POLICY AND ECONOMICS

Alistair McGuire. A Foreword by Professor McGuire, Head of the Department of Health Policy. Journal of Health Policy and Health Economics. 2021; 1(1).

A Foreword by Professor McGuire, Head of the Department of Health Policy

Alistair McGuire[1]

[1]LSE Department of Health Policy

It is my pleasure to give my wholehearted support, on behalf of the entire Department of Health Policy at the London School of Economics and Political Science (LSE), to the launch of the Journal of Health Policy and Economics (JOHPEC) through LSE's Houghton St Press. I would particularly like to congratulate the editorial board and all the students involved in putting together the Inaugural Edition, as well as alumni and staff involved in the publishing of the journal.

The aim of the journal is to publish the works of current and former students from the LSE Department of Health Policy, on topics ranging from cost-effective analyses of health care treatments, commentaries on the social determinants of health outcomes, mental health policy and much, much more. This first issue provides exactly that range of coverage and is truly a celebration of the department's interdisciplinary nature and bears the fruit of the academic rigor of the various degree programs offered by the department.

Moreover, the development of the Journal amidst a global pandemic - including the coordination of peer-review and publication workshops with our student body scattered across the globe - is a testament to our students' passion for their pursuit of knowledge and feeling of responsibility for engaging in the world's most pressing health questions. The founding of the JOHPEC was based on an editorial board working remotely from Singapore, to British Columbia, Tel Aviv, and Mumbai, and this equally represents the global spread of interests.

While our students receive the tools to apply to these issues during their LSE lectures, it is exciting to see the employment of these tools within the publications and their policy applications. I strongly encourage students to participate in the academic writing, publishing, and peer-reviewing process by sending articles inspired by the Department's various course offerings to the JOHPEC.

The whole LSE Department of Health Policy are very proud of this endeavour. We welcome the JOHPEC as a platform to further connect current and past students with the policy makers, leaders, and influencers that constitute our alumni community. The Department will continue to promote and support the initiatives of the Journal to ensure that the mandate to strengthen health systems around the world - shared by our students and staff alike – will not be confined to the classroom. We wish you all the success for the future!

JOURNAL OF HEALTH POLICY AND ECONOMICS

Amir Mohsenpour, Camille Bou. "How to Publish": The Journal of Health Policy and Economics' first seminar. Journal of Health Policy and Health Economics. 2021; 1(1).

"How to Publish": The Journal of Health Policy and Economics' first seminar

Amir Mohsenpour[1,2], Camille Bou[1]

[1] LSE Department of Health Policy
[2] London School of Hygiene and Tropical Medicine

First published in June 2021; Edited in Jan 2022 to reflect new link to seminar recording. The full recording can be found here.

On May 4th, 2021, the Journal of Health Policy and Economics (JOHPEC) held its first seminar, "*How to Publish*", coordinated and chaired by Amir Mohsenpour, an Assistant Editor of the JOHPEC.

The Seminar welcomed LSE guest speakers Dr. Edgar Whitley (Department of Management), Lucy Lambe (LSE Library, Houghton Street Press), and Hannah Boroudjou (LSE Library) for a 90 minute-seminar discussing the publishing cycle of academic papers in journals and the resources offered to LSE students and alumni to aid them throughout the publication process. The guest speaker presentations were then followed by an overview of the JOHPEC publishing cycle presented by Amir, with information on how prospective authors could prepare their article for submission to the JOHPEC.

Lucy started off the seminar by conceptualising publishing as a key tool in academia that allows the exchange of insights with a large audience worldwide, supporting the transfer and translation of evidence to other settings or countries.

Additionally, the results of publications enable other researchers and practitioners to read, critically appraise and give feedback to one's work, facilitating the overall advancement of knowledge in their discipline. This is especially important as a young researcher, as having a list of publications adds to their CV and improves their career prospects.

Finally, Lucy introduced the audience to key criteria that one should evaluate when deciding on a journal. This included the journal's readership, its rigour in peer-review and manuscript selection as well as the journal's reach, indexation in scientific databases and the articles' accessibility (e.g., by open access publication – giving everyone free access to the article).

Next, Hannah presented the importance of publishing concrete research data. Besides supporting the preservation of one's data in the long-term, and enabling replication studies to validate research findings, an increasing number of funders require such forms of data sharing. Data publication serves an ever more important role in ensuring a high quality, collaborative and open research environment while living up to modern ideas and responsibilities of publicly funded research.

In order to meet the different needs of researchers and their datasets, three levels of access are usually distinguished: "open", for data which are available to all and contain non-sensitive,

fully anonymised data; “safeguarded”, which translates to data published as part of larger repositories and thus available to all registered users; and finally, “controlled” accessibility for highly sensitive data which are only available on reasonable request through an application.

Last but not least, Edgar presented and discussed the behind-the-scenes of journals upon the submission of a manuscript. Firstly, the editors and review managers ensure the suitability of a manuscript for the journal’s scope of research as well as screen for questions of formatting and fundamental technical flaws. If this process does not lead to a so-called “desk rejection”, the manuscript is forwarded to appropriate researchers for the peer-review.

Peer-review serves an essential role in the publishing cycle. Every submission undergoes a review by fellow researchers knowledgeable in the manuscript’s research topic. This ensures quality publications of scientific validity and of high value to the journal’s readers. To achieve a smooth peer-review process and a successful collaboration with the editors, it is essential for authors to adhere to a journal’s guidelines for submission and ensure timely communication and responses to editors.

With consent from all speakers and attendees, the seminar was recorded. The full recording can be found here.

The JOHPEC would like to thank its guest speakers for helping make its first seminar a successful one, as well as the 79 registrants who expressed interest in the seminar, and the 44 attendees who tuned in on the day from around the world.

The JOHPEC accepts and reviews health-related manuscripts in the form of research articles, method articles, literature reviews, policy briefs and commentaries year-round. For more information about author submission guidelines, please click here.

We’re always looking to improve our events and expand the publishing knowledge of our prospective authors. If you have suggestions for future events, please fill in this form: https://forms.office.com/r/nN87zubviQ.

About the guest speakers:

Dr. Edgar Whitley is an Associate Professor (Reader) of Information Systems. He has a BSc (Econ) and PhD in Information Systems, both from the LSE. He is the co-editor of Information Technology and People, Senior Editor for the Journal of Information Technology and the AIS Transactions of Replication Research and an Associate Editor for the Journal of the AIS.

Lucy Lambe is the Scholarly Communications Officer at the LSE Library. She provides publishing support to research students and academics. This includes finding the right place to publish books and journal articles, queries around intellectual property, sharing their work online and using scholarly social networks (“Where Should I publish? Choosing and Evaluating Journal for Publication”) She is currently working on a project to implement a publishing platform for open access journals based at LSE.

Hannah Boroudjou is the Research Data Librarian. She joined LSE library in 2018 as part of the subscriptions team and has previously worked for City, University of London and in public libraries. She is also the Co-Founder and Co-Chair of EARLL, the professional network for Early career Librarians in Academic and Research Libraries in London. Hannah can offer help with data related enquiries including data management plans, data archiving, requests for secure data, and special data access agreements.

JOURNAL OF HEALTH POLICY AND ECONOMICS

Emily Trautner, Jina Kim, Adrian Rabe, Hari Thrivikramji. The Cost-Effectiveness of Immediate vs Routine Postpartum IUD Placement: a UK Perspective. Journal of Health Policy and Health Economics. 2021; 1(1)

The Cost-Effectiveness of Immediate vs Routine Postpartum IUD Placement: a UK Perspective

Emily Trautner[1], Jina Kim[2], Adrian Rabe[3], Hari Thrivikramji[4]

[1]Emory University, emily.trautner@emory.edu
[2]London School of Hygiene and Tropical Medicine, jina.elisa.kim@gmail.com
[3]Global Health Focus, adrianpaul.rabe@gmail.com
[4]NHS General Internal Medicine, hari.thrivikramji@nhs.net

Abstract

OBJECTIVES: Preventing pregnancy in the year after childbirth provides health benefits, and an intrauterine device (IUD) placed immediately after birth is a cost-effective tool to prevent pregnancy in the US. However, it is not known if this strategy is cost-effective in the UK. The objective of this study is to identify the cost-effectiveness of immediate compared to routine IUD placement strategies in the UK.

METHODS: A decision tree cost-effectiveness model was constructed using inputs from published literature including data and costs from the National Institute for Health and Care Excellence (NICE). The study population for this evaluation is women in the UK who desire a postpartum IUD and are eligible for placement at the time of delivery and at low risk for an STI. The perspective of the study is payer with a time horizon of one year. The outcome measure is incremental cost-effectiveness ratio (2018 Great British Pound per quality-adjusted life-year [QALY] gained), with a threshold of an ICER<20,000 considered cost effective.

RESULTS: The results of the analysis yielded an ICER of -£21,845, which is interpreted as a cost savings of £21,485 for every QALY gained with the immediate placement strategy. Our results and probabilistic sensitivity analysis both indicate that immediate placement is a consistently dominant strategy as compared to routine placement. Results are most sensitive to changes to the health utility assigned to pregnancy.

CONCLUSIONS: Immediate as compared to routine postpartum placement of an IUD is a dominant strategy and presents an opportunity for a cost saving policy. Budget impact analysis indicates that savings from the implementation of this strategy over a 5-year time horizon (2019-2023) would be over £15 million.

Keywords: Long-acting Reversible Contraceptive; Intrauterine Device; Cost-Effectiveness; Postpartum Contraception; Post-placental Contraception

Introduction

In the United Kingdom (UK), it is estimated that approximately 30% of pregnancies are unintended [1]. Unplanned pregnancies can adversely affect women's lives and are associated with a higher probability of adverse birth outcomes including low birth weight, pre-term and small for gestational age infants [2,3]. Furthermore, unplanned pregnancies cause additional health system costs, as they are associated with higher abortion rates, and with poorer health during childhood [3,4]. In England in 2010, the direct medical costs attributable to unintended pregnancies were estimated to be greater than £193 million [5].

There are negative health consequences for both mother and baby if a new pregnancy occurs within a short interval after a previous pregnancy. WHO recommends prevention of a subsequent pregnancy for two years after delivery of a child, based on evidence that short interval pregnancies (less than 18 months) are more frequently associated with adverse outcomes for both mother and child [6]. Specifically, there is increased maternal morbidity and likely maternal mortality risk if the interval is less than one year [6]. Furthermore, there is an increased risk of prematurity, fetal death, low birth weight and fetal growth restriction for birth intervals less than 18 months. While risks to the infant are higher among younger age women (20 to 34), maternal risks are higher among older women; though both age groups face higher risks if births occur at a short interval [7]. In a cohort of births in the United States (US), 35% were conceived in a short interval after a previous birth (less than 18 months). Of the short interval births, approximately one third were unintended, indicating a gap in knowledge and access to contraceptives. However, in women who initiated childbearing over the age of 30, those of higher socioeconomic status (SES) and white race were more likely to have a planned short interval pregnancy [8].

An intrauterine device (IUD) is a highly effective means of contraception with an efficacy rate greater than 99%. Approximately 4% of women of reproductive age in the UK use an IUD as their primary form of contraception [9,10]. An IUD can be placed immediately after the delivery of the placenta (within 10 minutes), which gives a woman an immediate and effective form of birth control [9,11]. This immediate form of birth control is important as ovulation may resume shortly after delivery of the child, and 41-57% of women may resume sexual intercourse before a postpartum visit [12-14]. Furthermore, since 20% of women in the UK fail to attend their planned postpartum visit [15], these women would not receive an IUD under routine practice.

It is also known that a certain number of IUDs placed will be expelled, which varies according to the timing of placement after birth. A worldwide meta-analysis showed that IUDs placed immediately (defined as within 10 minutes of delivery of the placenta after childbirth) have an expulsion rate of 10%. Expulsion rate rises to 29.7% when placed between 10 minutes to 4 weeks from delivery of the placenta after birth (defined as early placement). When placed at 4 weeks or later after birth (defined as interval or routine placement), the expulsion rate is 1.9% [16]. Given these data, immediate postpartum placement is superior to early placement because immediate placement allows for longer duration of pregnancy prevention with a higher likelihood of retention of the device. This study therefore compares only immediate to routine IUD placement.

Several analyses using US cost data have demonstrated that immediate postpartum LARC placement as compared to routine placement at the postpartum visit is highly cost effective [17-19]. Specifically immediate postpartum IUD placement as compared to delayed placement was demonstrated as a dominant strategy in a cost utility analysis of 1000 women with a cost

savings of $282,540 and a gain of 10 QALYs [17]. An analysis based on a retrospective cohort of uninsured patients demonstrated that the state would accrue $2.94 for every dollar spent on immediate postpartum IUD placement [18]. Another analysis of immediate postpartum IUD placement in the US estimated that delayed placement of an IUD resulted in a one year pregnancy rate of 24.6% as compared to pregnancy rates of 17.3% in a simulated vaginal birth cohort and 11.2% in a cesarean section cohort [19].

Given that the data support the immediate placement of an IUD as a safe and cost-effective means to prevent short-interval pregnancy, the American College of Obstetrics and Gynecology recommends immediate postpartum IUD placement for women desiring the method [11]. However UK guidelines indicate that an IUD should only be placed at a postpartum visit because there is no cost-effectiveness data in the UK for immediate postpartum IUD placement [20, 21].

This study seeks to determine whether immediate vs. routine placement of a postpartum IUD has a favorable incremental cost effectiveness ratio (ICER) in the UK context utilizing UK costs and quality adjusted life years (QALYs) associated with pregnancy outcomes. If the resulting ICER is favorable, the current guidelines should allow women who desire an IUD for birth control to elect for immediate placement instead of routine placement.

Methods

A review of the literature was conducted to determine if the central question of this paper had been answered previously. The PICO (population, intervention, comparison, outcome) construct was used to guide our search [22]. The population was women in the UK who desired IUD for birth control after delivery, who were eligible for immediate IUD placement, and who were considered low risk for STIs. The intervention was immediate IUD placement which was compared with routine placement. The outcome of interest was pregnancy rate. Combinations of search terms related to each of the PICO components were used to locate publications that addressed this topic. The main database used was Mendeley (Elsevier) with additional searches on PubMed, Medline, and Google Scholar. No publications were located that addressed this particular research question.

The population used in this study model is postpartum women in the UK who select an IUD as their primary form of contraception after delivery. The perspective of this analysis is that of a governmental payer, since the primary healthcare delivery model in the UK is the National Health Service (NHS) system. As such, the analysis is conducted in line with the National Institute for Health and Care Excellence (NICE) guidelines stipulating a 3.5% discount rate for costs and benefits of the intervention [23].

Model Design

The decision node of this model is the timing of placement of an IUD. The current standard of care in the UK is routine placement, which occurs 4 weeks or more after birth [10]. The comparator is the immediate placement of an IUD, which is defined as placement less than 10 minutes after delivery of the placenta [16]. Since the time frame of the cost effectiveness analysis is short (1 year) and events underlying the analysis are best represented as discrete decision points, a decision tree model was utilized. The full decision tree is displayed in Figure 1. Previous analyses of postpartum immediate vs delayed IUD placement have also used a decision tree format [17-19]. This model incorporated UK data for transition probabilities supplemented with other data as necessary.

Consistent with past cost-effectiveness models, a one-year time horizon was selected [19]. Furthermore, since IUD users in the UK context are older as compared to other contraceptive users [10], and older women are more likely to desire a short interval pregnancy [8], the assumption of desiring to delay pregnancy for a longer time horizon is less likely to be valid. Lastly, most of the differences between the costs and benefits of immediate vs. delayed treatment occur in the first year of placement, and IUD expulsion rates decrease with time since placement [24].

In order to construct this model, several assumptions were made about different branches of the decision tree and are summarized in Table 1 below.

Table 1: Assumptions by Branch of Decision Tree

Branch(es) of Decision Tree	Assumption(s)
Immediate placement, retained IUD at PP visit	Pregnancy rate is 0 [9,25,26]
Routine placement, lost to follow up	Use condoms for birth control
No IUD in place, not lost to follow up	Use mix of condoms and oral contraceptive pills based on UK average use [20]
Lost to follow up and average contraception arms	Pregnancy rates and cost based on forms of birth control used

Additionally, treatment costs for IUD side effects or rare adverse events (other than removal of IUD) are expected to be similar in both arms and minimal, and therefore such costs are not accounted for in the model [27,28]. Lastly NICE guidelines stipulate that gonorrhea and chlamydia tests should be completed before IUD insertion in high risk groups [10]. Accordingly, this model includes only low risk patients. It is estimated that 2.5% of the overall population would fall into the category of high risk based on a 95% CI. Furthermore, chlamydia and gonorrhea incidence is 1.5% and <0.1% respectively and is highest among people under 25 [29]. Since most chlamydia and gonorrhea infections are asymptomatic and thus would not prompt testing, the exclusion of 2.5% of the sample is likely a likely an overestimation of the high-risk proportion of postpartum women.

Utility

The primary outcome that is considered in this analysis is the disutility associated with pregnancy. The QALYs used in this model are the weighted outcomes of pregnancy, abortion, and miscarriage. The outcome of no pregnancy was given full utility of 1 [17]. The final product of analysis is the incremental cost effectiveness ratio (ICER), which is calculated by dividing the difference in costs between the standard of care arm (routine placement of IUD) and the comparator arm (immediate postpartum placement of IUD) by the difference in QALYs. The ICER threshold at which NICE will determine an intervention to be cost effective is £20,000 [30].

Cost

The costs data were taken from National Health Service (NHS) England as unit costs, mostly published in 2018. Older costs were adjusted using a price index to 2018 figures. The cost of unwanted pregnancy was calculated as a weighted average with proportions assigned to likely pregnancy outcomes including live birth, abortion, miscarriage and ectopic pregnancy. Table 2 summarizes the probabilities, utilities and costs used in the model.

Table 2: Model inputs

Probability	Base case	Sensitivity distribution
Postpartum (PP) visit attendance	0.80 [15]	Beta distribution
IUD placement at PP visit	0.605 [25]	Beta distribution
IUD expelled by PP visit[1]	0.116 [31,32]	Beta distribution
IUD retained at yr 1, immediate placement[2]	0.91 [33]	Beta distribution
IUD retained at yr 1, routine placement	0.87 [34]	Beta distribution
Pregnant at PP visit, no contraception	0.036 [25]	Beta distribution
Pregnant at PP visit, IUD expelled[3]	0.018 [25]	Beta distribution
Pregnant in yr 1, IUD in place	0.003 [26]	Beta distribution
Pregnant in yr 1, average contraception	0.15 [20]	Beta distribution
Pregnant in yr 1, lost to follow up no IUD[4]	0.17 [35]	Beta distribution
Pregnant in yr 1, lost to follow up with IUD[5]	0.02 [25,35]	Beta distribution
Utility		
Pregnant[6]	0.93 [36]	Beta distribution
Not Pregnant	1.00	
Cost		
Cost of IUD insertion	£ 187 [37]	Triangle, +/- 10%
Cost of average contraception (COC and condoms)[7]	£ 75 [38,39]	Triangle, +/- 10%
Cost of unintended pregnancy when on IUD[8]	£ 2,418 [37, 40-42]	Triangle, +/- 10%
Cost of unintended pregnancy on average contraception or male condom[8]	£ 2,436 [37-42]	Triangle, +/- 10%

[1] All clinical studies reviewed only reported expulsion events at PP visit, no removals
[2] This is a calculated conditional probability = [prob. retained at 1 yr]/[prob. of retention at PP visit]
[3] Probability is calculated based on the average of the probability of pregnancy at PP visit without contraception and the probability of pregnancy with IUD in place
[4] All patients lost to follow up were assumed to use condoms as their primary pregnancy prevention method. Their probability of having an unintended pregnancy with a year of childbirth was thus set at 17% (0.17) which is the failure rate of contraception with a male condom.
[5] This is a calculated probability based on the assumption that the same proportion of women lost to follow up will expel their IUD as was observed in clinical studies and will use condoms as their primary prevention method, the calculation is as follows: [prob expulsion]*[preg rate with condom use] + [prob retention]*[preg rate with IUD]
[6] This is a calculated weighted utility based on the probability of live birth, miscarriage, abortion, and ectopic pregnancies.
[7] It was assumed that 52 condoms were used annually based on the result of a Welsh survey of sexual practices.
[8] Costs of unintended pregnancy were calculated based on weighted proportion of possible pregnancy outcomes including live birth (normal delivery and C-section), abortion, miscarriage and ectopic pregnancy.

Sensitivity Analysis

A one-way deterministic and probabilistic sensitivity analyses were used to test the robustness of the results. In the one-way sensitivity analysis, a triangle distribution of ±10% for all costs values was used, since all cost data was based on published NHS costs. A beta distribution was used for the probability and utility inputs to the model. A tornado plot was generated to represent the outcome of the one-way sensitivity analysis. A probabilistic sensitivity analysis was performed with 1000 draws for costs and effects using the same distributions to generate a cost-effectiveness plane of values.

A cost-effectiveness acceptability curve was also generated using varying willingness to pay thresholds. Additionally, a threshold analysis was done for the cost of postpartum IUD placement, since this value is not known precisely.

Results

In the base case, we calculated an ICER of -£21,845. The ICER is negative because the immediate placement group offers a higher QALY and lower costs as compared to the routine placement group. The results are presented in the Table 3.

Table 3: Cost effectiveness analysis results

Placement timing	Costs	Incremental cost	Effect	Incremental effect	ICER: GBP per QALY
Routine	£414		0.9584		
Immediate	£288	-£126	0.9641	0.006	-£21,845

Sensitivity Analysis

The tornado diagram in Figure 2 represents the one-way sensitivity analysis. This indicates that the findings are robust to a range of inputs, since none of the resulting ICER values even cross zero to positive values. The most influential variable on the ICER is the utility of pregnancy.

Using a probabilistic sensitivity analysis varying the values of inputs simultaneously, the average ICER generated was -£23,540 per QALY. Figure 3 depicts a scatter plot of all ICERs generated.

The cost acceptability curve is displayed in Figure 4, which shows the probability of an intervention to be cost-effective at different willingness to pay thresholds. The probability of immediate placement yielding a cost-effective intervention is nearly 1 (100%) at every threshold evaluated.

A threshold analysis was also conducted for the cost of postplacental IUD placement, as the true costs of immediate postpartum insertion of an IUD is not known (not published under NHS tariffs). The cost of immediate placement was estimated to be £172, equal to the cost of routine placement. Given that placement cost has more uncertainty than the other inputs, the cost of immediate insertion was simulated at higher levels, and it was determined that any cost level under £304.74 would still result in a negative ICER, indicating higher QALYs at lower costs. At a cost of £428.24, the ICER will be £20,000/QALY gained, which is the threshold at which NICE will consider an intervention cost-effective.

Budget Impact Analysis

The budget impact analysis indicated that for the estimated 782,621 births in 2019 in the UK [43], 97.9% would occur in a hospital setting [44]. An estimated 4% of postpartum women are predicted to choose IUDs – the usage rate in reproductive age women [10]. Of all births, approximately 10% will be ineligible due to a uterine infection (1% - 4%) or a postpartum hemorrhage (6%) as these are contraindications to immediate placement [45, 46]. Furthermore 2.5% of women desiring postpartum IUD are considered high risk for STI infection and are therefore excluded in the budget impact analysis [29, 47]. Using these inputs, an estimated number of IUDs, QALYs and the corresponding savings was calculated. The rest of the budget impact analysis is provided in Table 4 and uses a 3.5% discount rate for subsequent years from the base year of 2019. The five-year cumulative cost savings for 2019-2023 is over £15 million (£15,683,206).

Table 4: Budget impact analysis

	2019	2020	2021	2022	2023
Predicted live births in the UK	782,621	780,584	777,068	773,372	770,163
Number of births in a hospital setting	766,969	764,972	761,527	757,905	754,760
No. of women who can receive IUD	671,098	669,351	666,336	663,166	660,415
No. of IUDs inserted	26,844	26,774	26,653	26,527	26,417
No. of QALYs gained from immediate IUD insertion	155	154	154	153	152
Savings if immediate IUD insertion (£)	3,380,431	3,371,633	3,356,446	3,340,481	3,326,620
Discount rate adjusted yearly savings (£)	3,380,431	3,257,616	3,133,278	3,012,923	2,898,958

Discussion

The results of this study indicate that providing immediate postpartum (defined as post-delivery of placenta or post-placental) IUD placement is a cost saving strategy. For every QALY gained, the NHS would save an estimated £21,845. This finding is robust to simulation of input variables across wide ranges. Given the uncertainty around the actual cost of a postpartum IUD placement, the costs could range up to £428 and the calculated ICER would still fall within the willingness to pay ICER threshold set by NICE. Since this value is more than double the cost of routine placement, it is highly unlikely that actual costs would make immediate postpartum IUD placement cost ineffective.

The most influential variable on the value of the ICER was the utility of pregnancy. The QALYs assigned to a pregnancy do not account for the intentionality of the outcome, as this is a standardized measure. Analyses comparing the utility of unintended to intended pregnancies suggests a lower utility associated with unintended pregnancies on a visual analog scale. However, time trade off and standard gamble approaches did not show a statistically significant difference between groups [48].

Although the findings of this study were robust and statistically significant in our analysis, there are several limitations to the findings. This model used many inputs from clinical studies mostly conducted in the US and other international settings. Although NICE also uses US-based studies as needed for decision-making, some of the studies may not be representative of UK populations. For example, if the UK has a much higher exclusive breastfeeding rate as compared to the study populations that determined the input parameters, then this study will overestimate the pregnancy rate and costs of pregnancy in the routine IUD placement arm. It is noted in the NICE LARC Guidelines that the IUD is more commonly used by older women, who thus have lower average fertility as compared to younger reproductive age women [10]. As a result of this usage pattern, this study may tend to overestimate the cost savings from IUD use after pregnancy, as these women may have lower than population average fertility. Another variable that may have significant variation is the proportion of women that attend a postpartum visit who receive an IUD during this visit, since the data used for this variable in this study was from the US. This may be a reasonable estimate because many general

practitioners who women follow-up with may not be IUD trained and women may need to seek another provider, which could lead to further drop-out. However, varying this proportion from the literature value of 0.605 up to 1 makes the ICER only slightly less negative at -£21,810, which indicates slightly lower cost savings, though it does not change the conclusion of the model.

There are also several costs that are not accounted for in this model that would make the ICER more negative, indicating more cost savings. The literature indicates that short interval pregnancies are more commonly associated with preterm birth and other adverse maternal outcomes [6], the costs of which are not accounted for in this model. If unintended pregnancy has a lower utility than that used in this study model, then this result is an underestimate of the benefit of immediate IUD placement [48]. Additionally, if the IUD is used beyond the one-year time horizon of this study, the benefit of the intervention may be underestimated since 60 percent of women who receive an IUD keep their IUD for 2 years or longer [49].

This model indicates that immediate postpartum IUD placement for women who desire a postpartum IUD should be clearly promoted as the preferred strategy. The calculated cost-saving finding is consistent with the results of past studies of cost effectiveness of immediate postpartum IUD placement conducted in the US [17-19]. However, it would be a worthwhile direction for future research to utilize more UK specific estimates based on NHS data, as this would give a better estimation of the expected ICER in the UK context. The authors hope that the NHS will consider repeating this analysis with UK specific data if it becomes available.

Conclusion

This study concludes that immediate postpartum IUD placement is cost saving. The next step is to train providers to place post-placental IUDs. A survey of UK community providers indicated willingness to better advertise post-placental IUDs and suggested post-placental IUD placement could be incorporated into the Royal College of Obstetricians Training [21].There are readily available training videos and descriptions of insertion methods, and training could be completed at a relatively minor cost for existing providers [50]. Midwives attend the majority of births in the UK and post-placental IUD training would need to be integrated into their curriculum (although this is not the subject of this study). In light of this study, the NHS should consider this potentially cost saving change to practice guidelines.

Acknowledgements

Thank you to Emily Lewis and Shuxuan Cheng for their assistance assembling and critiquing this work.

References

1. Fleissig A. Unintended pregnancies and the use of contraception: changes from 1984 to 1989. BMJ [Internet]. 1991 Jan 19 [cited 2019 Jan 8];302(6769):147. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1995134
2. Shah PS, Balkhair T, Ohlsson A, Beyene J, Scott F, Frick C. Intention to Become Pregnant and Low Birth Weight and Preterm Birth: A Systematic Review. Matern Child Health J [Internet]. 2011 Feb 10 [cited 2019 Jan 8];15(2):205–16. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/20012348
3. Mohllajee AP, Curtis KM, Morrow B, Marchbanks PA. Pregnancy Intention and Its Relationship to Birth and Maternal Outcomes. Obstet Gynecol [Internet]. 2007 Mar [cited 2019 Jan 8];109(3):678–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17329520
4. Gipson JD, Koenig MA, Hindin MJ. The effects of unintended pregnancy on infant, child, and parental health: a review of the literature. Stud Fam Plann [Internet]. 2008 Mar [cited 2019 Jan 8];39(1):18–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18540521
5. Montouchet C, Trussell J. Unintended pregnancies in England in 2010: Costs to the National Health Service (NHS). Contraception. 2013 Feb;87(2):149–53.
6. World Health Organization. Report of a WHO Technical Consultation on Birth Spacing Department of Making Pregnancy Safer (MPS) [Internet]. 2005 [cited 2019 Jan 8]. Available from: http://apps.who.int/iris/bitstream/handle/10665/69855/WHO_RHR_07.1_eng.pdf?sequence=1
7. Schummers L, Hutcheon JA, Hernandez-Diaz S, Williams PL, Hacker MR, VanderWeele TJ, et al. Association of Short Interpregnancy Interval With Pregnancy Outcomes According to Maternal Age. JAMA Intern Med [Internet]. 2018 [cited 2018 Nov 1]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2708196
8. Gemmill A, Lindberg LD. Short Interpregnancy Intervals in the United States. Obstet Gynecol [Internet]. 2013 [cited 2019 Jan 8];122(1):64. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749871/
9. Rowe P, Farley T, Peregoudov A, Piaggio G, Boccard S, Landoulsi S, et al. Safety and efficacy in parous women of a 52-mg levonorgestrel-medicated intrauterine device: a 7-year randomized comparative study with the TCu380A. Contraception [Internet]. 2016 Jun [cited 2019 Jan 8];93(6):498–506. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26916172
10. NICE. CG30 Long-acting reversible contraception: Full guideline [Internet]. NICE; 2014. Available from: www.rcog.org.uk%0Awww.rcog.org.uk
11. American College of Obstetricians and Gynecologists. Immediate Postpartum Long-Acting Reversible Contraception [Internet]. 2016 [cited 2019 Jan 8]. Available from: https://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co670.pdf?dmc=1&ts=20190108T2002353634
12. Mcdonald EA, Brown SJ. Does method of birth make a difference to when women resume sex after childbirth? BJOG [Internet]. 2013 [cited 2018 Dec 28];120:823– 830. Available from: www.bjog.org
13. Connolly A, Thorp J, Pahel L. Effects of pregnancy and childbirth on postpartum sexual function: a longitudinal prospective study. Int Urogynecol J [Internet]. 2005 Aug 19 [cited 2018 Dec 28];16(4):263–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15838587
14. Jackson E, Glasier A. Return of Ovulation and Menses in Postpartum Nonlactating Women. Obstet Gynecol [Internet]. 2011 Mar [cited 2019 Jan 8];117(3):657–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21343770
15. Smith, H, Saxena, S and Petersen, I. Postnatal checks and primary care consultations in the year following childbirth: an observational cohort study of 309 573 women in the UK, 2006–2016. BMJ Open, 2020; 10(11), p.e036835.
16. Jatlaoui TC, Whiteman MK, Jeng G, Tepper NK, Berry-bibee E, Jamieson DJ, et al. Intrauterine Device Expulsion After Postpartum Placement A Systematic Review and Meta-analysis. Obstet Gynecol. 2018;132(4):895–905.
17. Washington CI, Jamshidi R, Thung SF, Nayeri UA, Caughey AB, Werner EF. Timing

of postpartum intrauterine device placement: a cost-effectiveness analysis. Fertil Steril [Internet]. 2015 Jan [cited 2018 Oct 30];103(1):131–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0015028214022092
18. Rodriguez M, Caughey AB, Edelman A, Darney PD, Foster D. Cost – benefit analysis of state- and hospital-funded postpartum intrauterine contraception at a university hospital for recent immigrants to the United States. Contraception [Internet]. 2010;81(4):304–8. Available from: http://dx.doi.org/10.1016/j.contraception.2009.11.002
19. Sonalkar S, Hunter T, Gurney EP, McAllister A, Schreiber CA. A Decision Analysis Model of 1-Year Effectiveness of Intended Postplacental Compared With Intended Delayed Postpartum Intrauterine Device Insertion. Obstet Gynecol [Internet]. 2018;132(5):1211–21. Available from: http://insights.ovid.com/crossref?an=00006250-201811000-00018
20. Mavranezouli I. The cost-effectiveness of long-acting reversible contraceptive methods in the UK: Analysis based on a decision-analytic model developed for a National Institute for Health and Clinical Excellence (NICE) clinical practice guideline. Hum Reprod. 2008;23(6):1338–45.
21. Cooper M, Boydell N, Heller R, Cameron S. Community sexual health providers' views on immediate postpartum provision of intrauterine contraception. BMJ Sex Reprod Heal. 2018 Apr 1;44(2):97–102.
22. Training.cochrane.org. 2021. Chapter 2: Determining the scope of the review and the questions it will address. [online] Available at: <https://training.cochrane.org/handbook/current/chapter-02> [Accessed 8 February 2021].
23. National Institute for Health and Clinical Excellence. Discounting of health benefits in special circumstances [Internet]. 2011 [cited 2019 Jan 8]. Available from: https://www.nice.org.uk/guidance/ta235/resources/osteosarcoma-mifamurtide-discounting-of-health-benefits-in-special-circumstances2
24. Hatcher R. Contraceptive Technology. 17th ed. New York: Irvington Publishers; 1998.
25. Ogburn JA, Espey E, Stonehocker J. Barriers to intrauterine device insertion in postpartum women. Contraception [Internet]. 2005 Dec [cited 2018 Nov 25];72(6):426–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16307964
26. Çelen Ş, Möröy P, Sucak A, Aktulay A, Danışman N. Clinical outcomes of early postplacental insertion of intrauterine contraceptive devices. Contraception [Internet]. 2004 Apr [cited 2018 Nov 25];69(4):279–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15033401
27. Rowlands S, Oloto E, Horwell DH. Intrauterine devices and risk of uterine perforation: current perspectives. Open access J Contracept [Internet]. 2016 [cited 2019 Jan 8];7:19–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29386934
28. Welkovic S, Costa LO, Faúndes A, de Alencar Ximenes R, Costa CF. Post-partum bleeding and infection after post-placental IUD insertion. Contraception [Internet]. 2001 Mar [cited 2019 Jan 8];63(3):155–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11368989
29. Sonnenberg P, Clifton S, Beddows S, Field N, Soldan K, Tanton C, Mercer C, da Silva F, Alexander S, Copas A, Phelps A, Erens B, Prah P, Macdowall W, Wellings K, Ison C and Johnson A. Prevalence, risk factors, and uptake of interventions for sexually transmitted infections in Britain: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). The Lancet. 2013; 382(9907), pp.1795-1806.
30. NICE. Guide to the methods of technology appraisal 2013 | Guidance and guidelines [Internet]. NICE; 2013 [cited 2019 Jan 9]. Available from: https://www.nice.org.uk/process/pmg9/chapter/the-appraisal-of-the-evidence-and-structured-decision-making#decision-making

31. Colwill AC, Schreiber CA, Sammel MD, Sonalkar S. Six-week retention after postplacental copper intrauterine device placement. Contraception [Internet]. 2018 Mar [cited 2018 Nov 18];97(3):215–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29128372
32. Goldthwaite LM, Sheeder J, Hyer J, Tocce K, Teal SB. Postplacental intrauterine device expulsion by 12 weeks: a prospective cohort study. Am J Obstet Gynecol [Internet]. 2017 Dec [cited 2018 Nov 18];217(6):674.e1-674.e8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002937817309353
33. Sucak A, Ozcan S, Çelen Ş, Çağlar T, Göksu G, Danışman N. Immediate postplacental insertion of a copper intrauterine device: a pilot study to evaluate expulsion rate by mode of delivery. BMC Pregnancy Childbirth [Internet]. 2015 Dec 2 [cited 2018 Dec 4];15(1):202. Available from: http://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-015-0637-6
34. Rowe P, Farley T, Peregoudov A, Piaggio G, Boccard S, Landoulsi S, et al. Safety and efficacy in parous women of a 52-mg levonorgestrel-medicated intrauterine device: a 7-year randomized comparative study with the TCu380A. Contraception [Internet]. 2016 Jun [cited 2018 Dec 3];93(6):498–506. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26916172
35. Mosher WD, Jones J. Use of contraception in the United States: 1982-2008. Vital Health Stat 23 [Internet]. 2010 Aug [cited 2018 Dec 4];(29):1–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20939159
36. Sonnenberg FA, Burkman RT, Hagerty CG, Speroff L, Speroff T. Costs and net health effects of contraceptive methods. Contraception [Internet]. 2004 Jun [cited 2018 Dec 7];69(6):447–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15157789
37. NHS England. National schedule of reference costs 2017-2018. 2018.
38. Curtis L, Netten A. Unit Costs of Health and Social Care 2005 [Internet]. 2005 [cited 2019 Jan 10]. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2005/
39. Mercer CH, Tanton C, Prah P, Erens B, Sonnenberg P, Clifton S, et al. Changes in sexual attitudes and lifestyles in Britain through the life course and over time: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). Lancet [Internet]. 2013 Nov 30 [cited 2019 Jan 10];382(9907):1781–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24286784
40. Henshaw SK. Unintended pregnancy in the United States. Fam Plann Perspect [Internet]. 1998 [cited 2019 Jan 10];30(1):24–9, 46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9494812
41. Lakha F, Glasier A. Unintended pregnancy and use of emergency contraception among a large cohort of women attending for antenatal care or abortion in Scotland. Lancet [Internet]. 2006 Nov 18 [cited 2019 Jan 10];368(9549):1782–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17113427
42. Furlong L-A. Ectopic pregnancy risk when contraception fails. A review. J Reprod Med [Internet]. 2002 Nov [cited 2019 Jan 10];47(11):881–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12497674
43. US Census Bureau DIS. International Programs, International Data Base. 2018 [cited 2018 Dec 29]; Available from: https://www.census.gov/data-tools/demo/idb/region.php?N= Results &T=13&A=separate&RT=0&Y=2019&R=-1&C=UK
44. Office for National Statistics. Birth characteristics in England and Wales - 2017 [Internet]. 2019 [cited 2019 Jan 13]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthcharacteristicsinenglandandwales/2017

45. Gibbs R and Duff P. Progress in pathogenesis and management of clinical intraamniotic infection. American Journal of Obstetrics and Gynecology. 1991: 164(5), pp.1317-1326.
46. Carroli G, Cuesta C, Abalos E and Gulmezoglu A. Epidemiology of postpartum haemorrhage: a systematic review. Best Practice & Research Clinical Obstetrics & Gynaecology. 2008; 22(6), pp.999-1012.
47. ACOG.org. Immediate Postpartum Long-Acting Reversible Contraception. [online] Available at: <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2016/08/immediate-postpartum-long-acting-reversible-contraception#:~:text=postpartum%20follow%2Dup.-,Contraindications,of%20bleeding%20or%20infection%2028> [Accessed 8 February 2021]
48. Lundsberg LS, Xu X, Schwarz EB, Gariepy AM. Measuring health utility in varying pregnancy contexts among a diverse cohort of pregnant women. Contraception [Internet]. 2017 Dec [cited 2018 Oct 30];96(6):411–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0010782417303992
49. Diedrich JT, Madden T, Zhao Q, Peipert JF. Long-term utilization and continuation of intrauterine devices. Am J Obstet Gynecol [Internet]. 2015 Dec [cited 2018 Nov 1];213(6):822.e1-822.e6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26409157
50. Cwiak C, Cordes S. Postpartum intrauterine device placement: a patient-friendly option. Contracept Reprod Med [Internet]. 2018 [cited 2018 Nov 19];3:3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29686886

JOURNAL OF HEALTH POLICY AND ECONOMICS

Ivan Logrosan, Joy Silberschmidt, Rujuta Sanap, Giulia Brandolini d'Adda. Behavioural Aspects of the Use of Social Media and its Impact on Loneliness. Journal of Health Policy and Health Economics. 2021; 1(1)

Behavioural Aspects of the Use of Social Media and its Impact on Loneliness

Ivan Logrosan[1], Joy Silberschmidt[1], Rujuta Sanap[1], Giulia Brandolini d'Adda[1]

[1] Department of Health Policy, The London School of Economics and Political Science, <www.lse.ac.uk/health-policy>

Abstract

Loneliness is one of the most present issues in young adults, loneliness-related afflictions being more prevalent than in previous generations. Loneliness might be triggered by societal behavioural mechanisms such as social shaming and social compliance. This prevalence of loneliness has occurred simultaneously as the rise of social media. In this paper, we observe whether social media enhances the effect of social shaming and social compliance in young adults. To answer this question, we perform a qualitative and quantitative analysis using different datasets. In the first analysis, we use publicly available social media data in the state of Michigan, United States, between the years 2008 and 2012. This analysis shows mixed results regarding the impact of social media on the perception of loneliness. Although the number of loneliness-related conversations increases, half of the sample argues feeling less lonely when connected. In the second analysis, we use a dataset of 1,003 women aged 18 to 22 years, living in the state of Michigan, United States, within the same time frame, i.e., 2008-2012. The second analysis performed consists of several ordinary least squares (OLS) regressions based on a novel loneliness index. The results do not demonstrate any significant effect of social media on loneliness. Furthermore, data shows that social media nullifies the effects of social shaming on loneliness.

Keywords: Loneliness, Mental Health, Social Media, Behavioural Implications, Perceived Loneliness

1. Introduction

Loneliness represents a growing concern in the mental health field. Impacting individuals at first, the issue, by its reach, also has repercussions on societies and their healthcare systems. Eighty percent of the world's population below the age of eighteen years and almost forty percent of adults have experienced it at least once in their lives. Hawkley and Cacioppo (2010) define it as being "a distressing feeling that accompanies the perception that one's social needs are not being met by the quantity or the quality of one's social relationships" [1, p.218]. The feeling of loneliness relies on a perception of social isolation rather than on tangible metrics such as a small number of friends. Loneliness substantially impacts several human functions, e.g., cognition, emotion, behaviour, and, in broader terms, mental health. It leads to personality disorders, cognitive decline, anxiety, and low self-esteem, to diseases such as Alzheimer's or to suicide. Studies have also highlighted a strong link between loneliness and depressive symptoms, which can be accompanied by a high intake of alcoholic beverages [1]. Furthermore, there has been a growing body of evidence concerning the physiological effects loneliness has on individuals. It indeed is responsible for immune, autonomic and endocrine impairments, which in turn promote the development of cardiovascular diseases, cancer and other serious physical illnesses [2].

In the context of our research, we investigate the existence of a relationship between loneliness, peers' acceptance of an individual's behaviour, and the use of social media within a sample of young American women. More precisely, we aim at answering the following research questions: *Is there a statistical relationship between loneliness and the amount of social media use? Does social media amplify the effects of social shaming and social compliance in our sample?*

This study incorporates both qualitative and quantitative methods. It gathers specific psychological insights together with an empirical measurement of this effect. First, social media data is analysed to understand perspectives and behavioural patterns from unbiased and unprompted online data sources. Then quantitative analysis is conducted using survey data from Barber, Kusunoku & Gatny's (2012) study (henceforth Michigan Study), in which we apply the PICOT framework to understand the association between increased social media use and loneliness, and to measure the effect of social media on engaging in approved or non-approved behaviour (i.e., social compliance and social shaming, which can lead to a decrease or an increase in the perception of loneliness respectively [3]).

This paper is organised in 8 sections. Following the introduction, Section 2 sets the scene by providing an academic literature review on the current state of knowledge on the matter. Articles tackling the link between loneliness and behaviour are first introduced, followed by the ones tackling the link between loneliness and social media. Section 3 sheds light on the data used whereas Section 4 describes the methodology applied in both the qualitative and quantitative analyses. Section 5 exposes the results of our research. Finally, we discuss the conclusive findings, the corresponding health policy implications, and the limitations of our research in Sections 6, 7, and 8.

2. Literature Review

2.1 Loneliness and behaviour acceptance

First of all, it is important to note that very few studies have targeted our population segment, i.e., young women, and their relationship to loneliness. Despite a peak estimated age of 19

years old, loneliness has received greater attention when it comes to the elderly, children, and adolescents [4]. Similarly, few articles have focused on the relationship between loneliness and peers' acceptance of specific behaviours, e.g., social shaming and social compliance. The following paragraphs therefore refer to these closely intertwined topics, often relating to a slightly younger population segment.

According to Woodhouse, Dykas, and Cassidy (2011), studies highlight that loneliness due to peer relations includes factors such as social acceptance, friendship, and behaviour. Regarding social acceptance, a study among adolescents showed that the more negative peer acceptance is, the more likely the person is to feel lonely [5]. Pakaslahti, Karjalainen, and Keltikangas-Järvinen (2002) argue that peer nomination leads to positive feelings such as self-confidence, while peer rejection often leads to loneliness, depression, and other psychological issues [6].

Billy, Rodgers, and Udry (1984) shed light on the tendency that both adults and adolescents become friends with people sharing similar attitudinal and behavioural characteristics. They have demonstrated that similar attitudes, values, and behaviours explain the attraction, with greater rewards for individuals connecting with others when they 'approve' them and when they feel 'approved'. Such similarities indeed reduce the risk of potential conflicts and therefore the feeling of hostility [7].

According to scholars, there is salient evidence that sexual behaviour is linked to friendships in female adolescents, as sexual behaviour is a more sensitive topic among women than men according to the 'double sexual standard'. This phenomenon indeed emphasises the fact that men are usually praised by their peers for their engagement in sexual activities, while women tend to be stigmatised when adopting similar behaviours [8]. Hence, having sex is a friendship factor among women and therefore explains why non-experienced women are more likely to choose non-experienced women as friends, whereas this factor is less important among men. Accordingly, experienced women might prefer having experienced friends [7, 8]. Although loneliness cannot be directly related to the number of friendships an individual has, as it is a matter of perception, this study remains interesting in our case as loneliness can be felt by a non-experienced woman within a group of experienced women, and vice versa. Similar results were observed by Klein (1998), whose study highlights the strong correlation between loneliness variables, e.g., self-esteem, shyness and social support, and adolescent pregnancy. Pregnant teenagers indeed tend to feel lonelier when they do not receive social support during their pregnancy. However, teenagers who feel lonely are more likely to get involved in sexual behaviours and pregnancies in order to cope with this distressing feeling [9].

Finally, the academic literature outlines sociometric variables, e.g., being popular or neglected, and demographic variables as being a key-factor playing on loneliness. Woodhouse et al. (2011) explain that popular individuals, i.e., the ones receiving many positive nominations from their peers, usually feel less lonely than others. However, no causality relation could yet be established from these arguments [5]. Similarly, Shovestul, Han, Germine and Dodel-Feder (2020) suggest the household income to be a potential source of loneliness, richer individuals being less likely to feel lonely. However, evidence remains scarce [4].

2.2 Loneliness and social media

Mixed results stem from studies observing the link between loneliness and social media. On the one hand, scholars argue that an intense use of the Internet and social media is often correlated to a greater feeling of loneliness, with social loneliness distinguished from emotional loneliness Moody (2001). While face-to-face networking lowers both feelings of loneliness, the use of the Internet only reduces the feeling of social loneliness, leaving people emotionally unsatisfied [10]. Despite evidence of correlation, no causality relationship has yet been established between loneliness, the Internet use, and social media. Two models remain. Some researchers argue that the intensive use of the Internet and other derived products lead to social isolation. However, other researchers argue that this intensive use stems from the users' personality, meaning that the lonelier a person feels, the more likely he or she is to use the Internet and social media [11]. Hunt, Marx, Lipson, and Young (2018) indicate that limiting the use of social media results in a decrease in anxiety and fear of missing out, which directly decreases loneliness and depression [12]. This finding is sustained by Wang, Frison, Eggermont, and Vandenbosch (2018), who report that low to moderate users of social media, e.g., Facebook, decrease both their social and emotional loneliness when using the platform, whereas heavy users tend to increase their emotional loneliness when active on the platform [13].

On the other hand, observational evidence suggests that being active on social media, i.e., by posting and updating statuses can instead lead to a decrease in the feeling of loneliness. Deters and Mehl (2012) demonstrate in their study that social media posting allows individuals to feel connected to their peers on a daily basis, notably by enabling them to converse and share experiences on a diverse range of topics. However unidirectional online activities such as likes, does not have an effect on the feeling of loneliness [14]. Pittman and Reich (2016) suggest that social media brings some emotional benefit and that the higher the number of platforms a person uses, the less likely loneliness feelings are. The author reports that this phenomenon is optimal when the time spent on social media is moderate, i.e., from half an hour to an hour per day, with loneliness levels increasing, if the threshold is exceeded [15].

3. Data

3.1 Social media data analysis

Publicly available online data of 461 conversations from specified study populations (females, 18-22 years, Michigan) was collected from social media sources, ensuring compliance with the data privacy policies. Conversations that were public only were considered for interpretations and were anonymised at source. Specific searches on social media platforms were made using a comprehensive taxonomy of keywords related to "loneliness" and "social media use" using Boolean combinations. A quantitative and qualitative analysis of the data was performed to derive insights.

3.2 Michigan study data analysis

A database retrieved from the *Harvard dataverse* was used. This cross-sectional database consists of 1,003 women aged 18-22 and based in Genesee County (Michigan, United States)

from 2008 to 2012, a period in which social media use was extended but not dominant, thereby giving us the opportunity to study differences among users and non-users. This database comes from an extensive survey of relationship dynamics and social life [3].

3.2.1 Dependent variable

To develop a measurement of loneliness, a set of loneliness-defined variables was selected. These were the answers to the following questions: *'Do you feel that you lack companionship?'; 'Do you feel that you are close to people?'; 'Do you feel left out?'* and *'Do you feel that you have people you can turn to (in case of need)?'.* All these variables ranged from 1 to 5, based on recurrence. These variables were used to develop an index through the Principal Component Analysis (PCA) methodology [16]. To create it, we first checked through the Bartlett test of sphericity if the variables were intercorrelated. The results of the test were highly conclusive and positive, indicating unbiasedness and robustness. Then, we calculated the eigenvectors of the components and built, with them, the Index of Loneliness. This methodology gives an index that follows a normal distribution. The lower values of the index indicate higher isolation, while the higher values indicate greater socialisation.

3.2.2 Independent variables

The majority of the independent variables are dummy variables that indicate the absence or presence of certain behaviours or situations in individuals. These are used to study the social shaming and social compliance phenomena, apart from social network use. We selected behaviours with a high risk of affecting esteem-related sex due to the consequences of pregnancy, and the perceived notions of status and self-esteem around it, which are subject to peer evaluation.

The variables are: The use of social networks in general; the specific use of social networks (Twitter, Facebook, Myspace, etc.); having sex; having friends who engage in sexual behaviours; having friends who disapprove having sex; using birth control; having friends who use birth control and having friends who disapprove using birth control. The other variables acting as controls are the number of social networks used, which is discrete and used to evade forms of collinearity, and household income, which is reported in thousands of dollars per month and is proven to have a positive effect on loneliness [4].

Table 3.1: Descriptive Statistics for the Panel Dataset.

Income in thousands of dollars	3.457
	(3.821)
Feel there is People You Can Turn To (from 1 to 5)	4.295
	(0.940)
Feeling of being Left Out (from 1 to 5)	2.217
	(0.959)
Feel Close To People (from 1 to 5)	3.960
	(0.885)
Feel they Lack Companionship (from 1 to 5)	2.250
	(1.053)
Lonely Index (from 1 to 5)	4.230
	(0.992)
Use of any social media	0.947
	(0.223)
Number of social media sites used	1.481
	(0.796)
Use of MySpace	0.474
	(0.499)
Use of Facebook	0.835
	(0.370)
Use of Twitter	0.103
	(0.304)
Use of Other social media site	0.067
	(0.251)
Have Sex	0.762
	(0.426)
Use birth control	0.756
	(0.429)
Have regular Unprotected Sex	0.816
	(0.387)
Friends engage in sex	0.252
	(0.434)
Friends use birth control	0.620
	(0.485)
Friends have Unprotected Sex	0.583
	(0.493)
Have Friends who do not approve having sex	0.723
	(0.447)
Have Friends who do not approve birth control	0.296
	(0.456)
Have friends who do not approve unprotected sex	0.898
	(0.302)
Observations	1003

4. Methods

4.1 Social media data analysis

A taxonomy of synonyms of loneliness and social media-related keywords was created after the literature review. The data was disidentified and anonymised at the source to ensure compliance with data privacy policies. The dataset was filtered in order to retrieve conversations from females aged 18 to 22 years, and living in Michigan, United States, between 2008 and 2012. The retrospective data of five years was further analysed to generate quantitative analysis on volume trends, sentiments, and emotions at different time intervals.

The conversation volume trends indicate the increase or the decrease in awareness levels of loneliness amongst the population. It is also an unbiased measure between the number of online users being intrinsically motivated to be vocal about their condition on social media. The conversation trends were segregated by week and 24-hour daily windows to control for time effects. The sentiment of online conversations measured tonality and was considered as an indicator of positive or negative social media experience. Emotions expressed in social media conversations indicate the emotions of the users writing on social media at that point in time. The emotions analysis classified the emotions expressed in the comments on social media use and loneliness that elaborated on the positive or negative experience in further detail. The parameters used to measure social media connectedness included the number of connections, which was mapped with the individual online activity and social media experience to understand whether an increase in the number of social connections decreases loneliness and vice versa. The sample contained 15 users. The dataset was then manually analysed to derive qualitative insights on conversations' themes and interpreted for behavioural implications as well as effects on the perception of loneliness.

4.2 Michigan study data analysis

To estimate and measure the relationship between social network use, social shaming, and social compliance on loneliness several Ordinary Least Square regressions were computed using Stata15 [17]. The design of the Michigan survey enabled us to measure loneliness by combining several loneliness indicators using principal component analysis. Our PCA-generated Index of Loneliness is the dependent variable in the regressions. This approach of regressing using interactions between variables enabled us to robustly estimate the effects of external factors onto loneliness and represents a widely used approach in the field [4]. First, three regressions were computed to investigate social network effects on loneliness,

$$lonelyindex_i = \alpha_0 + \alpha_1 socialnetworkuse_i + \alpha_2 income_i + e_i \quad (1)$$

$$lonelyindex_i = \beta_0 + \beta_1 facebookuse_i + \beta_2 twitteruse_i + \beta_3 myspaceuse_i \beta_4 otheruse_i + \beta_5 income_i + e_i \quad (2)$$

$$lonelyindex_i = \theta_0 + \theta_1 n^o socialnetworkuse_i + \theta_2 income_i + e_i \quad (3)$$

where *i* represents the individuals, "*socialnetworkuse"* the use of social networks, and "*n°socialnetworkuse"* the number of social networks used. Variables "*facebookuse", "twitteruse", "myspaceuse",* and "*otheruse"* report the use of specific social networks. The variable *i5* is the control for income, which appears in all regressions. Equation (3) shows that

nºsocialnetworkuse is the most relevant control for the latter analysis. Then, regressions to investigate social shaming effects were performed,

$$lonelyindex_i = \gamma_0 + \gamma_1 sex_i + \gamma_2 percepcionX sex_i + \gamma_3 birth_i + \gamma_4 perceptionX birth_i + \gamma_5 income_i + e_i \quad (4)$$

$$lonelyindex_i = \gamma_0 + \gamma_1 sex_i + \gamma_2 percepcionX sex_i + \gamma_3 birth_i + \gamma_4 perceptionX birth_i + \gamma_5 income_i + \gamma_6 n^o socialnetworkuse_i + e_i \quad (5)$$

$$lonelyindex_i = \gamma_0 + \gamma_1 sex_i + \gamma_2 percepcionX sex_i + \gamma_3 snXperceptionX sex_i + \gamma_4 birth_i + \gamma_5 perceptionX birth_i + \gamma_6 snXperceptionX birth_i + \gamma_7 income_i + e_i \quad (6)$$

$$lonelyindex_i = \gamma_0 + \gamma_1 sex_i + \gamma_2 percepcionX sex_i + \gamma_3 snXperceptionX sex_i + \gamma_4 birth_i + \gamma_5 perceptionX birth_i + \gamma_6 snXperceptionX birth_i + \gamma_7 income_i + \gamma_8 n^o socialnetworkuse_i + e_i \quad (7)$$

where *sex* represents having sex, *birth* using birth control, and *perception* the disapproval from friends of the interacted behaviour. Variables "*snXperceptionXbehavior"* represent the interaction between the use of social networks, negative perception, and either having sex or using birth control. Variables *sex* and *birth* operate as controls, while we are interested in the signs and significance of the interactions. As can be seen, these regressions were performed twice, once with the variable "*nºsocialnetworkuse"* acting as a control, and once without.

Finally, econometric analyses to investigate social compliance effects were performed,

$$lonelyindex_i = \delta_0 + \delta_1 sex_i + \delta_2 engagementXsex_i + \delta_3 birth_i + \delta_4 engagementXbirth_i + \delta_5 income_i + e_i \quad (8)$$

$$lonelyindex_i = \delta_0 + \delta_1 sex_i + \delta_2 engagementXsex_i + \delta_3 birth_i + \delta_4 engagementXbirth_i + \delta_5 income_i + \delta_6 n^o socialnetworkuse_i + e_i \quad (9)$$

$$lonelyindex_i = \delta_0 + \delta_1 sex_i + \delta_2 engagementXsex_i + \delta_3 snXengagementXsex_i + \delta_4 birth_i + \delta_5 engagementXbirth_i + \delta_6 snXengagementXbirth_i + \delta_7 income_i + e_i \quad (10)$$

$$lonelyindex_i = \delta_0 + \delta_1 sex_i + \delta_2 engagementXsex_i + \delta_3 snXengagementXsex_i + \delta_4 birth_i + \delta_5 engagementXbirth_i + \delta_6 snXengagementXbirth_i + \delta_7 income_i + \delta_8 n^o socialnetworkuse_i + e_i \quad (11)$$

(12)

where *engagement* represents having friends engaging in the interacted behaviour, and "*snXengagementXbehaviors"* being the interaction between the use of social networks, friends' engagement in the behaviour, and either having sex or using birth control. As before, in this part we use the behaviours as controls, and we are interested in the signs of the interactions. Again, these regressions were performed twice, once with the variable n°*socialnetworkuse* acting as a control, and once without.

After performing all the above regressions, we looked at the significance and signs of the variables to determine if there was a relationship between the variables.

5. Results

5.1 Results from social media data analysis

The social media analysis provides mixed results on the relationship between the increasing use of social media and loneliness. Firstly, Figure 5.1 displaying the conversation volume on loneliness over the five-year period considered shows a rising trend in the social media usage to discuss loneliness, stagnating at its minimum in 2008 and reaching its maximum at the end of 2012. Figure 5.2 considers weekly trends and shows that users were discussing loneliness more often during the near end of the week (Thursday) and the beginning of the week (Monday) indicating that they felt lonelier during these periods. Based on the statistics of daily moments represented in Figure 5.3, the feeling of loneliness slowly increased during the evening hours, with some fluctuations, and peaked between 10 and 11pm, while being much lower during the early morning hours.

Figure 5.1. Trend in online conversation volume on ‘loneliness’ and ‘social media use’ (Michigan, 2008-2012)

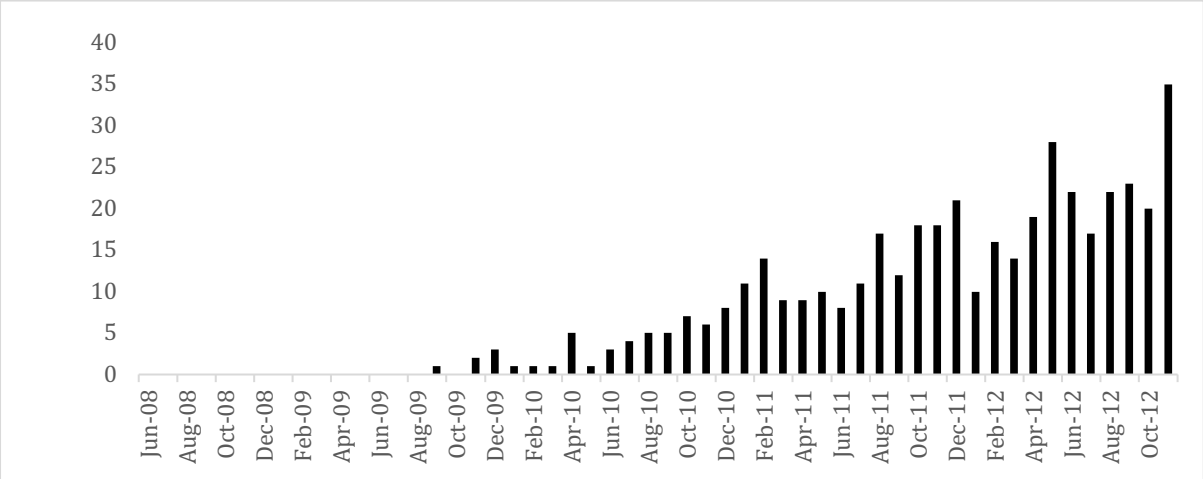


Figure 5.2. Weekly trend in online conversations on “loneliness”

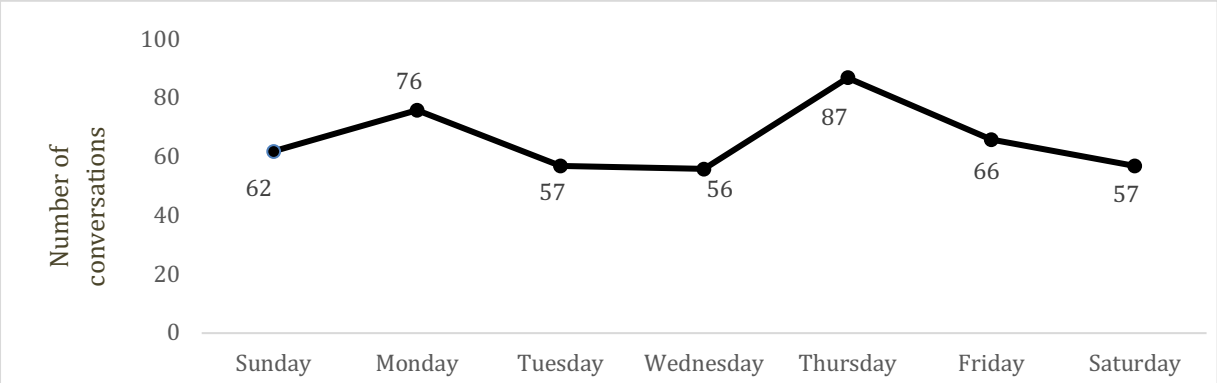


Figure 5.3. Daily moments of online conversations on “loneliness” within 24 hours

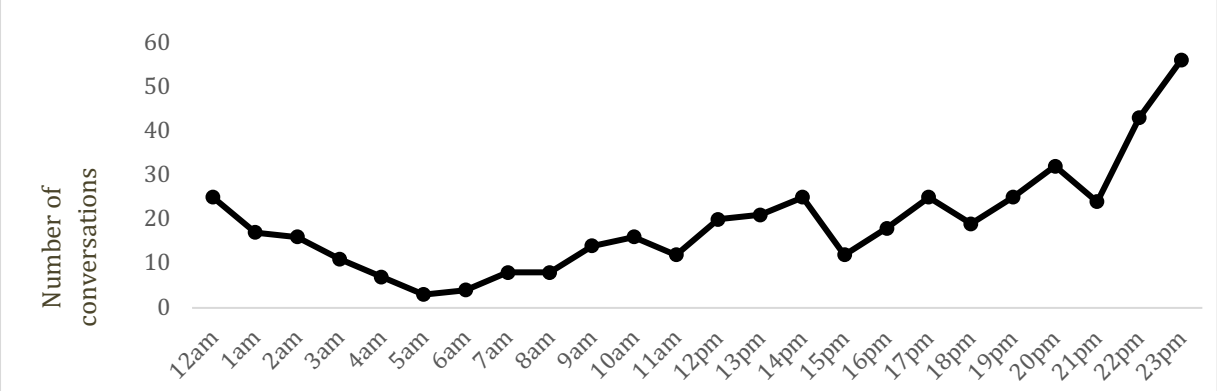


Figure 5.4. Trend in sentiment of online conversations on “loneliness” and “social media”

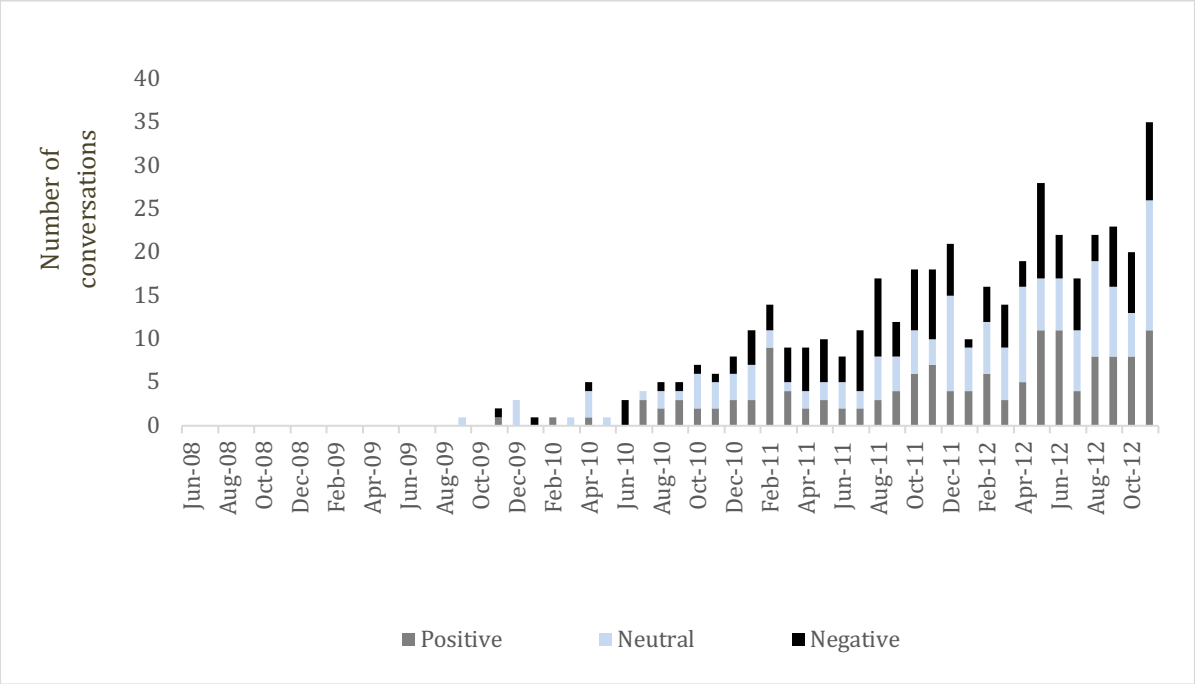
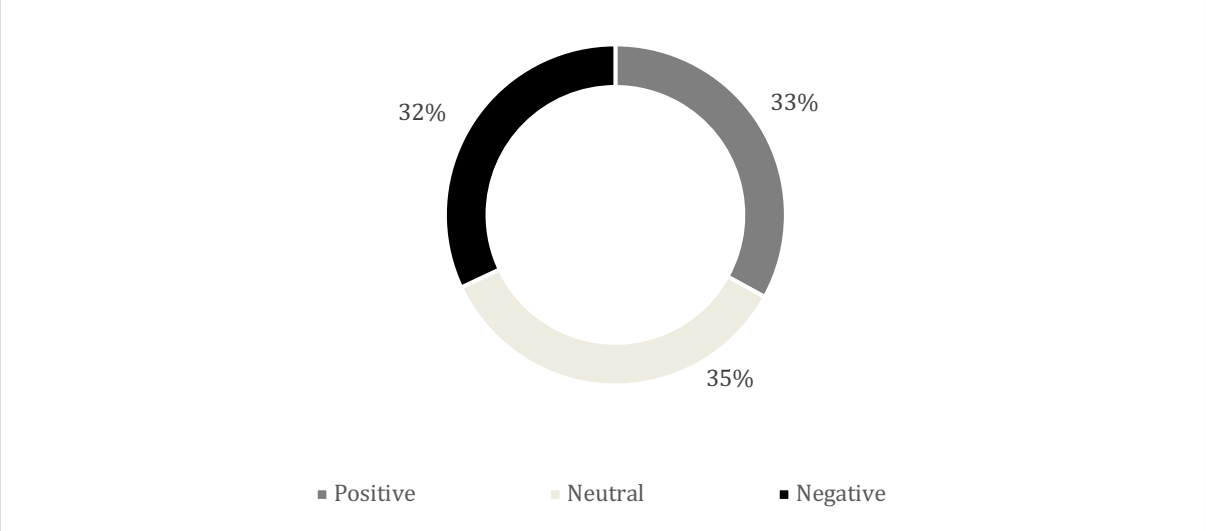


Figure 5.5. Sentiment analysis



Secondly, the automated sentiment analysis (Figure 5.4, 5.5) provides mixed results on the overall social media experience. The tonality of 32 percent of conversations was negative, suggesting perception of loneliness when using social media, compared to 33 percent of conversations having a positive tonality, hence suggesting happiness when using social media. Thirdly, despite equal percentages of positive and negative sentiments in social media use, the emotions analysis represented in Figure 5.6 and 5.7 shows that the predominant emotion expressed in 85 percent of conversations was sadness, followed by anger (8 percent) which suggests more loneliness in the population due to the increasing use of social media.

Figure 5.6. Emotions trend in online conversations on “loneliness” and “social media”

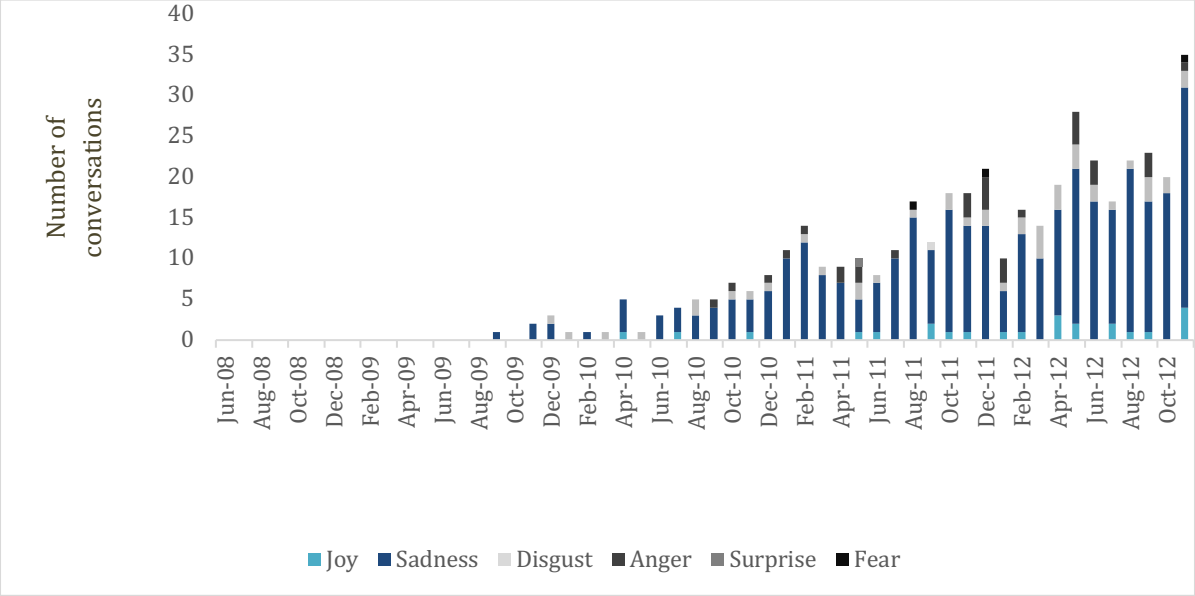
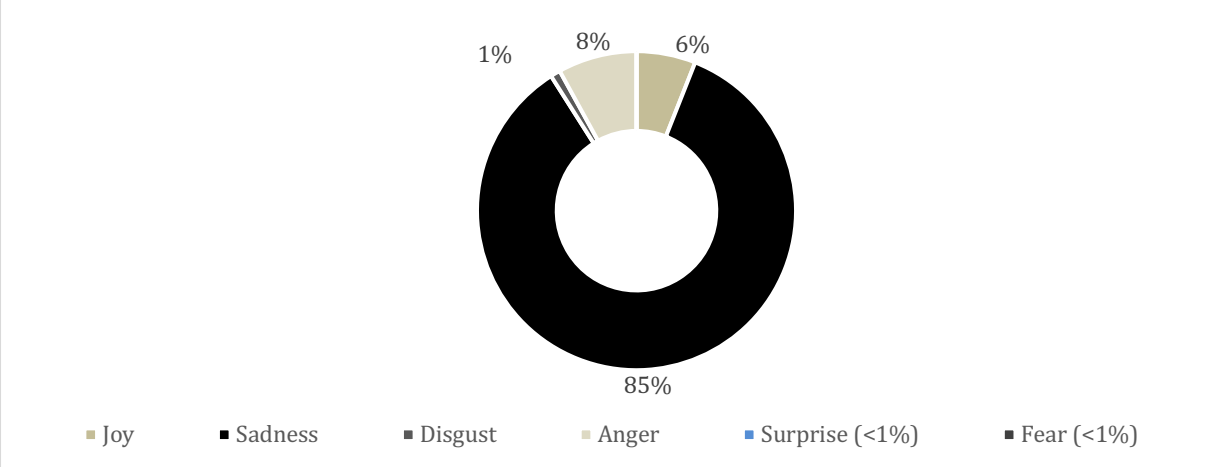
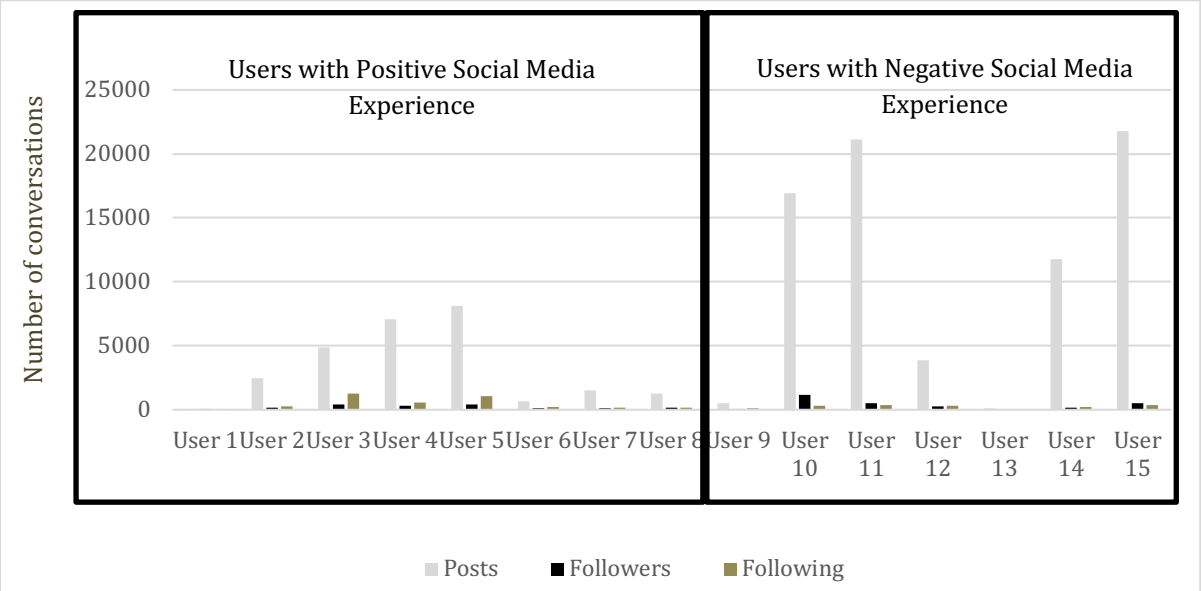


Figure 5.7. Emotions analysis



Fourthly, Figure 5.8 maps the online activity of 15 users who have expressed their positive or negative experiences on social media and shows interesting results. The users who felt less lonely when using social media and had a positive experience were comparatively less active online (number of posts ranging from 1,000 to 8,000). Whereas the users who felt lonelier on using social media and had a negative experience were starkly more active online (number of posts ranging from 3,000 to 22,000). This suggests that limited use of social media may significantly reduce the feeling of loneliness and increase the perception of being socially connected. In contrast, those who were extensively active on social media still felt lonely. Also, the number of connections was nearly similar in both groups of users and did not have any significant effect on the feeling of loneliness.

Figure 5.8. Social media activity and social connections of users with positive and negative experience



Finally, the qualitative analysis of social media data highlighted behavioural patterns as shown in Table 5. About 53 percent of the targeted population mentioned that social media makes them feel less lonely. This included those with positive online experiences. Nearly 13 percent of the online population felt more connected when using social media, and 21 percent mentioned that social media fulfils their social unmet need by making them feel more satisfied. However, this group expressed a need of being active on social media, which demonstrated signs of social media addiction. About 11 percent of the population also mentioned that being active on social media is a social norm and were thus adhering to socially compliance.

Furthermore, likes on Instagram and Facebook, as well as the number of replies to individual comments or posts appeared to be a source of instant gratification for 8 percent of the group, which made the individuals feel more satisfied due to identity payoffs, hence decreasing loneliness. On the contrary, 42 percent of the targeted population mentioned that social media made them feel lonelier. This group mostly included those with negative experiences. Nearly 18 percent of the online female population felt disconnected on social media, and 7 percent experienced loneliness by not receiving responses to their posts. A trend to engage or not in approved or non-approved behaviours by an individual's peers due to social media influence was also noticeable in the analysis. Almost 7 percent of the group reflected on social pretence, i.e., showing off extreme happiness or gaining sympathy by pretending to be lonelier. About 4 percent mentioned feeling envious of other people having relationships (partner or baby) and demonstrated a need of having a relationship for social conformity. Additionally, 6 percent of conversations consisted of commenting negatively on others' posts and indicated social shaming due to envy.

Table 5. Insights from qualitative analysis of social media data on 'loneliness' and 'use of social media'

Themes of conversations	Behavioural implication	Social media effect on loneliness	Number of conversations	Percentage of conversations
Feel connected on social media	Social connectedness	Decreases loneliness	58	13%
Relationship need	Social conformity	Increases loneliness	19	4%
Feel disconnected on social media	Loneliness	Increases loneliness	84	18%
Social media satisfies the unmet need	Social media addiction	Decreases loneliness	97	21%
No social acknowledgement (no response to posts)	Loneliness	Increases loneliness	32	7%
Social acknowledgement (replies/likes/comments)	Identity payoff	Decreases loneliness	39	8%
Social pretence (Show-off/gain sympathy)	Identity modulation, Identity loss	Increases loneliness	32	7%
More social media activity is sign of loneliness	Framing, Influencing behaviour	NA	19	4%
Being active on social media is a social norm	Social compliance	Decreases loneliness	52	11%
Social shaming due to envy	Engaging in negative behaviour, Identity loss	Increases loneliness	26	6%

5.2 Results from Michigan study data analysis

Regressions (1) to (3) studied the present estimates for different effects of social media over loneliness. As described above, there seems to be a correlation between social media use and loneliness. However, this does not seem to hold in the Michigan study. Results from regressions (1) and (2) (Table 5.1) show that no effect of social media on loneliness was found. Hence, neither the use of social media in general nor the use of a specific one makes an individual feel lonelier. However, regression (3) (Table 5.1) highlighted a relationship between the number of social media users and loneliness, which contradicts previous results.

Table 5.1: Regressions for social network use over loneliness.

	(1)	(2)	(3)
socialnetworkuse	-0.200		
	(0.129)		
myspaceuse		-0.135	
		(0.0836)	
facebookuse		0.142	
		(0.115)	
twitteruse		-0.248*	
		(0.144)	
otheruse		-0.259	
		(0.166)	
n°socialnetworkuse			-0.104**
			(0.0510)
Constant	4.411***	4.298***	4.458***
	(0.125)	(0.111)	(0.0886)
Observations	963	573	573
R^2	0.0027	0.0194	0.0072
Adjusted R^2	0.0007	0.0108	0.0037
F	1.396	2.169	2.087

Standard errors in parentheses
All models are controlled by income.
The Dependent variable is the lonely index.
Each column gives results for a different regression.
* p<0.10, ** p<0.05, *** p<0.01

Table 5.2 shows the coefficients of regressions (4) to (7), which looked at relationships between loneliness and social shaming, and the interaction between social shaming and the use of social media. In this correlation, we found that neither having sex nor using birth control are behaviours affected by social shaming. In the case of having sex, expectations were to find that engaging in sexual behaviours without peers' approval is a source of loneliness. Instead, we found out that having sex between the age of 18 and 22 is correlated to loneliness. Whether this is a way of coping or the source of it is yet to be determined. Results also showed that using birth control is a behaviour that makes you feel less lonely. Effects on sex and birth control were also found in regressions (8) to (11). Expectations for (4) to (7) were also that social shaming would be amplified when using social media. However, results showed that there is no effect altogether, which reveals that it takes no part in it on social shaming. This could be very well because of the taboo nature of the behaviours we study, as they are easy to conceal.

Table 5.2: Regressions for engagement in non approved behaviours over loneliness.

	(4)	(5)	(6)	(7)
n°socialnetworkuse		-0.107**		-0.135**
		(0.0511)		(0.0562)
sex	-0.417***	-0.304**	-0.413***	-0.295**
	(0.113)	(0.148)	(0.113)	(0.149)
badperceptionXsex	0.0421	-0.0321	-0.0702	-0.357
	(0.0819)	(0.110)	(0.234)	(0.253)
snXbadperceptionXsex			0.117	0.354
			(0.229)	(0.247)
birthcontrol	0.310***	0.379***	0.307***	0.372***
	(0.102)	(0.141)	(0.102)	(0.141)
badperceptionXbirthcontrol	-0.137	0.00373	0.395	0.332
	(0.0931)	(0.130)	(0.314)	(0.323)
snXbadperceptionXbirthcontrol			-0.554*	-0.354
			(0.324)	(0.343)
Observations	959	570	959	570
R^2	0.0172	0.0232	0.0188	0.0270
Adjusted R^2	0.0120	0.0128	0.0116	0.0132
F	3.591	2.088	2.985	1.942

Standard errors in parentheses. All models are controlled by income. Dependant variable is the created lonely index. Each column gives results for a different regressions.
* p<0.10, ** p<0.05, *** p<0.01

Table 5.3 shows the effects of social compliance on loneliness as well as the interaction between social media and social compliance on loneliness. Regressions (8) to (11) suggest that having sex when it is an approved behaviour is not a behaviour that makes you feel part of a group, and therefore has no effects on loneliness. So, having sex is not a behaviour that is part of the social compliance mechanism. Nevertheless, using birth control when your friends also do it appears to be a source of loneliness, which contradicts intuition, as using birth control does have the opposite significant effect in all regressions. This may be explained in different ways, e.g., the variable *having sex* when combined with birth control in a regression becomes a proxy for non-stable and stable relationships, which might explain why when their friends also use birth control they feel lonelier, as they have to share the time with friends with the time with their couple. Furthermore, no effects were found on the relationship between social media and social compliance. Therefore, the use of social media does not seem to have an effect on this social behaviour mechanism.

Table 5.3: Regressions for engagement of same behaviours over loneliness.

	(8)	(9)	(10)	(11)
n°socialnetworkuse		-0.113**		-0.115**
		(0.0512)		(0.0520)
sex	-0.382***	-0.301**	-0.397***	-0.317**
	(0.0967)	(0.124)	(0.108)	(0.138)
engagementXsex	0.0962	-0.0728	0.0947	-0.0756
	(0.0991)	(0.142)	(0.0992)	(0.142)
snXengagementXsex			0.0239	0.0275
			(0.0779)	(0.105)
birth	0.467***	0.539***	0.467***	0.538***
	(0.106)	(0.140)	(0.106)	(0.140)
engagementXbirth	-0.328***	-0.324***	-0.329***	-0.323***
	(0.0747)	(0.0988)	(0.0747)	(0.0992)
snXengagementXbirth			0	0
			(.)	(.)
Observations	959	570	959	570
R^2	0.0359	0.0442	0.0360	0.0444
Adjusted R^2	0.0309	0.0340	0.0300	0.0325
F	7.812	4.299	6.533	3.716

Standard errors in parentheses. All models are controlled by income. Dependant variable is the created lonely index. Each column gives results for a different regressions.
* p<0.10, ** p<0.05, *** p<0.01

6. Discussion

Increasing loneliness has become a concern in our society with the recurrence of loneliness incurred by an individual being associated with negative outcomes for this individual's mental and physical health. Consequently, phenomena such as isolation, depression, and self-harm have been reported in ever greater numbers. The latter has been found not only to be relevant to the elderly but also to young people. Today, a very young public is exposed to myriad ways of interacting with their peers and might affect the feeling of loneliness among this section of the population. The use of social media and its interplay with peer acceptance substantially contributes to mental health outcomes. This study highlights different findings concerning the use of social media, peer-accepted behaviours, and its effect on loneliness.

From the research carried out, it is argued that social media have a relatively limited impact on an individuals' feeling of loneliness, with the analysis demonstrating no significant effects of social media use on loneliness. The weak relationship between the use of social media and loneliness can be explained by considering that social media can also bring emotional benefits to individuals. It can also be argued that the use of social media makes people feel more interconnected and that it has become a coping tool for many. Notwithstanding, an opposing insight shows that there is a relationship between the number of social media outlets used and the feeling of loneliness. This highlights an important component, which is the approach that individuals have towards the use of social media. How social media is used by individuals,

such as the time spent on it and the number of platforms, does impact the feeling of loneliness perceived.

An important consideration brought forward by social media analysis is the individuals' perception of the role that the use of social media plays with regards to their loneliness. There has been growing concerns in mainstream media whether social media makes people feel less lonely. This might be because social media allows them to connect with each other and fulfil unmet social needs. It was also highlighted that the limited use of social media may have a significant reduction in loneliness, compared to those who extensively use social media, although the minority of the population felt that social media made them feel lonelier. This shows that individuals' perception is key to understanding whether the use of social media impacts the likelihood of feeling lonely.

Another contribution of the study concerns the relationship between social shaming and loneliness. Our quantitative study shows that social shaming is not amplified through the use of social media. In fact, it can be argued that social network usage cancels out the effects of social shaming related to loneliness, although this could be explained by the taboo nature of the variables used in the study. For instance, people that have specific interests and values, which can be considered to a certain extent as not peer-accepted behaviours, can connect with like-minded individuals through social media. This seems to have become prominent on social media platforms, where individuals participate in virtual communities where they can connect on the basis of their individual preferences, e.g., on blogs, forums, etc. Furthermore, we also studied the effect on social compliance behaviour of individuals. In this regard, no effect was found either. Societal behaviours towards identification with the group and adhesion to the beliefs of the group are not magnified by social media in our data.

7. Limitations

Firstly, the data considered in this study were derived from the publicly available datasets and therefore reflect the reality of the 2008-2012-time frame. However, we expect the use and proliferation of social media to have significantly increased since 2012, and we encourage further research to map more recent trends. Secondly, automated social media analysis was performed based on individual perceptions. The qualitative analysis adds an element of subjectivity to the results as it was based on individual interpretations from the online conversations. However, these inaccuracies were addressed through manual quality checks. Social media data demonstrate the magnitude of the perception of loneliness, but not necessarily the clinical loneliness per se. Finally, the study findings are limited to young females, aged 18 to 22, living in the state of Michigan, United States, and the behaviours studied are taboo behaviours that are easy to conceal from the group which might be exposed to confounding effects, thus diminishing the possible effect or concealing it. Further research with panels instead of cross-sectional data would be helpful in order to generalise the phenomenon, emphasise the divergences in trends, and better understand factors leading to loneliness**.**

8. Conclusion

Loneliness is a multi-faceted problem, one that is not resolved through the introduction of policies targeting a single specific cause. Although several initiatives are taken at the policy level for the elderly and adults, there are currently no policies targeting young adults and

adolescents in whom loneliness is equally or even more prevalent. It was shown by the study that inappropriate and excessive use of social media by individuals can create and enhance the feeling of loneliness. However, it was also demonstrated that social media can alleviate the phenomenon of social shaming. Hence, social media should be promoted as a tool that allows like-minded individuals to connect, and recommendations on how to use them healthily should be made publicly available. This study only investigates one potential factor explaining loneliness among young women, therefore it encourages further investigations to help understand the multiple factors that contribute to the increasing feeling of loneliness in the society and its repercussions on physical and mental health.

Competing interests: The authors have no competing interests to declare.

Authors' contributions: Authors contributed equally and jointly supervised the work.

References

1. **Hawkley LC, Cacioppo JT**. Loneliness Matters: A Theoretical and Empirical Review of Consequences and Mechanisms. Annals of Behavioral Medicine. 2010;40(2):218-227. DOI: https://dx.doi.org/10.1007/s12160-010-9210-8

2. **Hawkley LC, Cacioppo JT**. Loneliness and pathways to disease. Brain, Behavior and Immunity. 2003; 17(1): 98-105. DOI: https://dx.doi.org/10.1016/S0889-1591(02)00073-9

3. **Barber JS, Kusunoki Y, Gatny HH**. Relationship Dynamics and Social Life (RDSL) Study [Genesee County, Michigan], 2008-2012 [Public and Highly Restricted-Use]. Inter-university Consortium for Political and Social Research, 2016-10-20. DOI: https://dx.doi.org/10.3886/ICPSR34626.v5

4. **Shovestul B, Han J, Germine L, Dodell-Feder D**. Risk factors for loneliness: The high relative importance of age versus other factors. *PLoS One*. 2020;15(2):e0229087. DOI: https://dx.doi.org/10.1371/journal.pone.0229087

5. **Woodhouse SS, Dykas MJ, Cassidy J**. Loneliness and Peer Relations in Adolescence. Social Development. 2011;21(2):273-293. DOI: https://dx.doi.org/10.1111/j.1467-9507.2011.00611.x

6. **Pakaslahti L, Karjalainen A, Keltikangas-Järvinen L**. Relationships between adolescent prosocial problem-solving strategies, prosocial behaviour, and social acceptance. International Journal of Behavioral Development. 2002;26(2):137-144. DOI: https://dx.doi.org/10.1080/01650250042000681

7. **Billy JOG, Rodgers JL, Udry JR**. Adolescent Sexual Behavior and Friendship Choice. Social Forces. 1984;62(3):653. DOI:https://dx.doi.org/10.2307/2578705

8. **Kreager DA, Staff J**. The Sexual Double Standard and Adolescent Peer Acceptance. Social Psychology Quarterly. 2009; 72(2): 143-164. DOI: https://dx.doi.org/10.1177/019027250907200205

9. **Klein TM**. Adolescent Pregnancy and Loneliness. Public Health Nursing. 1998; 15(5): 338-347. DOI: https://dx.doi.org/10.1111/j.1525-1446.1998.tb00358.x

10. **Moody EJ**. Internet Use and Its Relationship to Loneliness. CyberPsychology & Behavior. 2001;4(3):393-401. DOI: https://dx.doi.org/10.1089/109493101300210303

11. **Amichai-Hamburger Y, Ben-Artzi E**. Loneliness and Internet use. Computers in Human Behavior. 2003;19(1):71-80. DOI: https://dx.doi.org/10.1016/S0747-5632(02)00014-6

12. **Hunt MG, Marx R, Lipson C, Young J**. No More FOMO: Limiting Social Media Decreases Loneliness and Depression. Journal of Social and Clinical Psychology. 2018;37(10):751-768. DOI: https://dx.doi.org/10.1521/jscp.2018.37.10.751

13. **Wang K, Frison E, Eggermont S, Vandenbosch L**. Active public Facebook use and adolescents' feelings of loneliness: Evidence for a curvilinear relationship. Journal of Adolescence. 2018; 67: 35-44. DOI: https://dx.doi.org/10.1016/j.adolescence.2018.05.008

14. **Deters FG, Mehl MR**. Does Posting Facebook Status Updates Increase or Decrease Loneliness? An Online Social Networking Experiment. Social Psychological and Personality Science. 2012; 4(5): 579-586. DOI: https://dx.doi.org./10.1177/1948550612469233

15. **Pittman M, Reich B**. Social media and loneliness: Why an Instagram picture may be worth more than a thousand Twitter words. Computers in Human Behavior. 2016;62:155-167. DOI: https://dx.doi.org/10.1016/j.chb.2016.03.084

16. **Bartholomew DJ, Steele F, Galbraith J, Moustaki I**. CHAPTER 5: Principal Components Analysis. In: Bartholomew DJ, Steele F, Galbraith J, Moustaki I. Analysis of Multivariate Social Science Data, Second Edition [Internet]. London: CRC Press LLC; 2011. [cited 2020 Dec 7]. p.117-144. Available from: https://ebookcentral.proquest.com/lib/londonschoolecons/reader.action?docID=1633250&ppg=130

17. **StataCorp**. Stata Statistical Software: Release 15. College Station, TX: Statacorp LLC. 2017

JOURNAL OF HEALTH POLICY AND ECONOMICS

Claudio Bernardini. Efficacy of Revefenacin in Treatment of Moderate-to-Very-Severe Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. Journal of Health Policy and Economics. 2021; 1(1)

Efficacy of Revefenacin in Treatment of Moderate-to-Very-Severe Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

Claudio Bernardini[1], Jacob Lang[1], Jina Kim[1], Marina Kousta[1], Audrey Jackson[1]

[1] Department of Health Policy, London School of Economics and Political Science, London, UK. Corresponding author: Claudio Bernardini, claudio_bernardini@yahoo.com

Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a major global health issue responsible for 5% of global deaths each year, and novel treatments are at a premium. Long acting-muscarinic antagonists are a standard treatment for COPD, and the recent approval of Revefenacin, a novel, once-daily, nebulized LAMA, prompts a need for a systematic review and meta-analysis of results.

Objectives: To assess the efficacy of Revefenacin, a novel, once-daily, nebulized LAMA in the treatment of moderate to very severe COPD.

Data Sources: MEDLINE (OVID), EMBASE, and CINAHL databases, as well as grey literature sources Clinicaltrials.gov and the International Clinical Trials Registry Portal.

Eligibility Criteria for Selecting Studies: Eligibility criteria for selecting studies: Populations: No age, geographical, contextual or other restrictions were imposed on populations. All human subjects diagnosed with moderate to severe Chronic Obstructive Pulmonary Disease (COPD) were eligible. Intervention: a novel bronchodilator (Revefenacin). Comparator: Placebo. Outcomes: the efficacy of Revefenacin, measured as the endpoint change in trough FEV1 from baseline. Study design: Randomised Controlled Trials (RCTs). Only studies written in English were considered.

Study Appraisal and Synthesis Methods: 1571 records were initially screened, with 27 being eligible for full text review. Eventually, 12 articles for 7 trials were included. A random-effects meta-analysis was conducted with the primary outcome of difference in means for change in trough FEV1 from baseline to study endpoint.

Results: 1472 patients were analysed, and the overall difference in means was an increase of 119.073 mL in change in trough FEV1 from baseline to study endpoint for the Revefenacin group compared to the placebo. This result was statistically significant, with a 95% confidence interval of 102.254 mL to 135.893 mL.

Limitations: Limitations of the study include possible risk of publication bias and placebo as the only comparator, relatively few trials (7), and a low generalizability of findings due to the specific nature of RCT populations excluding multi-morbid, and other complicated patients.

Conclusions: Revefenacin is an efficacious intervention when compared to placebo in the treatment of moderate to very severe COPD. Further research is needed in order to assess its efficacy compared to current standard of care, through RCTs or network meta-analysis.

Keywords: COPD; Revefenacin; Meta-analysis; Respiratory; Lungs; Pharmaceutical; Long-acting-muscarinic antagonist

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a significant global health issue affecting an estimated 328 million people worldwide and is projected to be the leading cause of death by 2030 (1–3). COPD refers to a larger group of chronic lung diseases that cause limitations in lung airflow, and is primarily caused by smoking tobacco, indoor air pollution, outdoor air pollution, and occupational dusts and chemicals (2). These factors can contribute to cause two of the most common conditions classified under COPD: emphysema, in which the alveoli at the end of the bronchioles are destroyed, and chronic bronchitis, which is characterized by inflammation of the lining of the bronchial tubes, which are responsible for transporting air to and from the alveoli (4). They lead to the most common symptoms of COPD, namely breathlessness, excessive sputum production, and chronic cough, as well as an increased risk of cardiovascular disease, lung cancer, depression, and premature death (2,4). COPD also carries a substantial economic burden, through both healthcare costs and productivity loss, and is also associated with a reduced quality of life (5,6).

COPD consists of four stages: mild, moderate, severe, and very severe. Each stage is calculated according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Staging System. The forced expiratory volume in one second (FEV1) measurement, derived from a pulmonary function test, is used to categorize the severity (7). The forced vital capacity (FVC) test which measures the amount of air an individual can forcefully and quickly exhale after taking a deep breath, is also an important in diagnosis. FEV1 shows the amount of air a person can forcefully exhale in one second of the FVC test. Generally, lower FEV1 signals more severe COPD (8). The breakdown of COPD stages and FEV1 cut-offs is presented in Table 1.

Stage	FEV_1	GOLD	Severity
I	≥ 80%	1	Mild
II	50% - 80%	2	Moderate
III	30% - 40%	3	Severe
IV	≤ 30%	4	Very Severe

Table 1. COPD Stages

Clinical consultation is usually sought once COPD progresses to the moderate stage, and it is in this stage that physicians usually begin to prescribe bronchodilators for treatment (8). A recent study found a prevalence of 10.1% in moderate-to-severe COPD worldwide – equivalent to GOLD 2 or higher (9). COPD cannot be cured, however, treatment and effective management can provide symptom relief, improved quality of life, and reduce the risk mortality (2). Long-acting muscarinic antagonists (LAMAs), a class of bronchodilator, have been shown to be an efficacious treatment option for patients with moderate to severe COPD. These are recommended as a maintenance therapy by the GOLD, but until recently, haven't been available in a once-daily nebulized form, easing their administration for patients.

Revefenacin, a novel LAMA produced by Theravance Biopharma, has recently been approved by the Food and Drug Administration (FDA) in the US due to its efficacy, safety, and tolerability profile (10,11). It acts as a long-acting muscarinic antagonist (LAMA) and only needs to be administered once-daily via a nebulizer (12). Revefenacin prevents bronchoconstriction and allows bronchodilation by inhibiting muscarinic M3 receptors in airway smooth muscles (13). There are five muscarinic receptors – M1 to M5 – which are all expressed in the lungs. Muscarinic antagonists that target M1 to M3 are used to treat lung diseases (14). The drug, being a competitive antagonist of M3 receptors, which mediate the contraction of the airway smooth muscle, suppresses the acetylcholine-evoked calcium mobilization and contractile responses in the airway tissue in order to regulate tone and patency (14,15). Despite the current variety of bronchodilators, Revefenacin becomes innovative in that it is the first approved once-daily sprayable LAMA compatible with common nebulizers (12).

The FDA approved Revefenacin on 8th November 2018 under the drug name YulperiTM (16). The agency, moreover, approved Theravane Biopharma Inc. and Mylan N.V.'s 'New Drug Application', making these the main companies behind the inhalation solution (17). However, this recent approval prompts the need for summative information on the effectiveness of revefenacin and serves as motivation for a systematic review and meta-analysis of the data regarding its efficacy for the treatment of patients with moderate to very severe COPD.

Objective

The objective of this systematic review and meta-analysis is to determine the clinical efficacy of Revefenacin, a novel nebulized LAMA, in the treatment of patients with moderate to very severe COPD (GOLD Stages 2 through 4), and any comparator. Eligible studies can have participants of any age, gender, and in any location. The primary outcome of interest is trough change in FEV1 from baseline to study endpoint, so studies were evaluated and excluded in full text review if this outcome was not present.

Methods

Protocol and Registration

The protocol for this systematic review and meta-analysis is registered on the PROSPERO international prospective register of systematic reviews, registration identification: CRD42019131334.

Inclusion Criteria – PICOS Framework

Population: Studies involving patients with moderate to very severe COPD of all ages were included as clinical diagnosis and prescription of bronchodilators usually occurs at the moderate stage (8).

Intervention: All studies including treatment with Revefenacin alone (of any dosage or dosing regimen) were included. Revefenacin is a novel, nebulized, once-daily LAMA used in the treatment of moderate to very severe COPD. All dosage levels were included in the meta-analysis.

Comparator: Any study with Revefenacin and comparator was included in the study, but placebo was the primary comparator for analysis, as it is the standard comparator for efficacy studies (18,19).

Outcome: The primary outcome of interest was Trough FEV1 change from baseline to study endpoint in mL. Outcomes do not determine eligibility in the initial screening, yet will be considered in the full text analysis in order to determine whether the study has sufficient information for final inclusion.

Study type: Randomised controlled trials (RCTs). RCTs are the most effective and least biased study design in evaluating the efficacy of a new treatment, as they use random allocation and comparison to a control in order to account for any confounders on the outcome of interest (18). Completed studies with results in English from any year were included.

Exclusion Criteria

Studies involving treatment with Revefenacin in patients with specific comorbidities in addition to, or in place of, COPD were excluded as the results of these studies could bias efficacy measures. Studies that included patients with unspecified stages of COPD were also excluded because of possible bias, along with studies that failed to measure FEV1, due to a lack of implication in the meta-analysis.

Information Sources and Search Strategy

We searched for eligible studies up to the 24th of February 2019, using MEDLINE (OVID), EMBASE, and CINAHL databases because of their breadth covering clinical research. Search strategies for the different databases using medical subject headings (MeSH) and free text keywords including ‘Revefenacin’, ‘chronic obstructive pulmonary disease’, ‘randomised control trial’ and more, were developed and are reproduced in Appendix A. We also searched the grey literature using ClinicalTrials.Gov and the International Clinical Trials Registry Portal for relevant clinical trials. Our search was restricted to studies with results in English.

Study Selection

Records from the search were stored using Mendeley Reference Management Software throughout the review. Titles and abstracts were initially screened by two independent reviewers to assess eligibility. Ineligible studies were then excluded, and those deemed eligible underwent full text review by two independent reviewers to determine final eligibility. Any discrepancies in eligibility determination were assessed by a third independent reviewer and discussion took place until consensus was achieved. Ineligible studies were removed and included studies entered the data collection process.

Data Collection and Items

Relevant study data was then extracted and compiled in a Microsoft Excel spreadsheet by five study team reviewers, with cross check for consensus. The form for data extraction included: authors, title, publication year, trial ID, study design, study duration, follow up duration, trial start year, country, number of participants, number of males, number of females, mean age, COPD stage (mean FEV1%), number of participants in intervention group, dosage, regimen, number of participants in control group, trough FEV1 change from baseline for placebo with standard deviation, trough FEV1 change from baseline for Revefenacin with standard deviation, and placebo-adjusted trough FEV1 change from baseline (if available) with standard deviation (Table 3). As all of the trials were multi-armed for different dosages of intervention, each dosage arm was treated as its own study and its standard error later adjusted for the unit-of analysis error and correlation between the shared placebo group using the exact adjustment method (Method 4) in Rucker et al., 2017 (See Appendix B) (20). Adjustment was performed in R statistical software, and the code can be found in Appendix C.

Risk of Bias in Individual Studies

Risk of bias in individual studies was measured at the study level by two independent reviewers with The Cochrane Collaboration's tool for assessing risk of bias in randomised controlled trials (21). This tool measures a range of sources of bias within individual studies, including: selection bias, through random sequence generation and allocation concealment; performance bias, through blinding of participants and personnel; detection bias, through blinding of outcome assessment; attrition bias, through incomplete outcome data; and reporting bias, through selective reporting (Table 2) (21). Each item in the tool was designated as low, unclear, or high risk of bias. Studies determined to have a high risk of bias will be excluded for sensitivity analysis. The risk of bias assessment within studies was created in Review Manager 5.3 (29).

No.	Bias Domain	Risk Judgment
I	Random Sequence Generation	Low
II	Allocation Concealment	
III	Blinding of Participants and Personnel	Moderate /
IV	Blinding of Outcome Assessment	Unclear
V	Incomplete Outcome Reporting	
VI	Selective Reporting	High

Table 2. Possible Biases

Principal Summary Measures

For our study, difference in means is the principal summary measure used, as measured by the change in trough FEV1 from baseline to study endpoint in mL, as this is the standard in evaluating efficacy of treatments in COPD interventions (22). Difference in means is used because of the same outcome and unit being measured in each of the included studies, as per the Cochrane Handbook (23).

Synthesis of Results

A random-effects pairwise meta-analysis was performed using Stata statistical software for a difference in means of change in trough FEV1 from baseline to study endpoint in mL between the Revefenacin intervention group and the placebo group. A random effects model was used because of the variation in dosages, study duration, and study design across the studies (24). As mentioned, adjusted standard errors were used in the pairwise meta-analysis in order to include information from multi-armed studies (20). The meta-analysis results were presented in difference in means (or mean difference) with the 95% confidence interval, and I2 was calculated as a measure of heterogeneity (25).

Risk of Bias Across Studies

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool was used to evaluate risk of bias, imprecision, inconsistency, indirectness, publication bias and confidence in cumulative evidence (Table 3) (26). Funnel plots with mean difference and standard error were used to assess possible bias across studies, as well as publication bias.

No.	GRADE Factor	Consequence on Quality
I	Limitations in study design or execution (risk of bias)	↓ 1 or 2 levels
II	Inconsistency of results	↓ 1 or 2 levels
III	Indirectness of evidence	↓ 1 or 2 levels
IV	Imprecision	↓ 1 or 2 levels
V	Publication bias	↓ 1 or 2 levels
VI	Large magnitude of effect	↑ 1 or 2 levels
VII	All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed	↑ 1 level
VI	Dose-response gradient	↑ 1 level

Table 3. GRADE Factors

Additional Analyses

Subgroup analysis was performed for study duration and drug dosage, which were both pre-specified, as well as study design (parallel or nonparallel), and study source (as results from the same trial are split into the different arms for analysis). Meta-regressions for drug dosage and study duration were performed for robustness. Sensitivity analysis was performed excluding studies with potential high risk of bias (27).

Results

Study Selection

We initially screened 1571 records from EMBASE, MEDLINE, and CINAHL databases, as well as 161 from the grey literature, and then removed 13 duplicates for a total of 1719 records. 27 records were assessed in full-text review, and eventually 13 full text articles containing information for 7 randomised controlled trials were included in the qualitative synthesis and meta-analysis (Figure 1). See Appendix C for full-text exclusions with reasons. Table 4 displays the authors and titles of the selected trials.

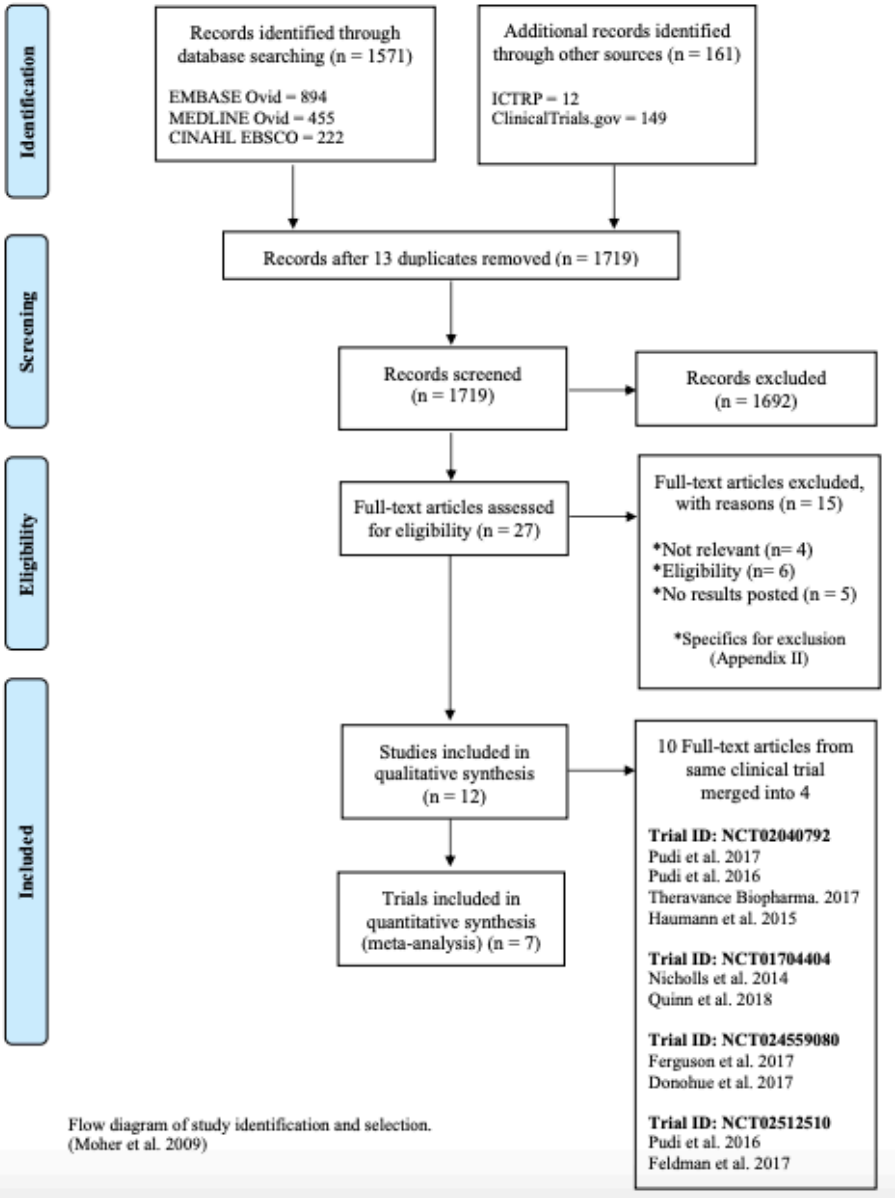


Figure 1. Study identification and selection flow diagram (28)

Author	**Title**
Pudi et al. 2017	A 28-day, randomized, double-blind, placebo-controlled, parallel group study of nebulized Revefenacin in patients with chronic obstructive pulmonary disease.
Nicholis et al. 2014	A Randomized, Crossover, 7-Day Study Of Once-Daily TD 4208, A Long-Acting Muscarinic Antagonist, In Subjects With COPD
Potgieter et al. 2012	A randomized, crossover study to examine the pharmacodynamics and safety of a new antimuscarinic (TD-4208) in COPD
Theravance Biopharma 2017	A 7-Day Cross-over Study of QD (Once Daily) and BID (Twice Daily) TD-4208 in Chronic Obstructive Pulmonary Disease (COPD)
Ferguson et al. 2017	Efficacy of Revefenacin , a Novel Once-Daily Nebulized Long-Acting Muscarinic Antagonist: Results of Two Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials in Participants with Moderate to Very Severe Chronic Obstructive Pulmonary Disease
Pudi et al. 2016	Trials in Progress: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials of a Nebulized Long-Acting Muscarinic Antagonist (Revefenacin) in Study Participants With Moderate to Very Severe COPD
Quinn et al. 2018	Pharmacodynamics, pharmacokinetics and safety of Revefenacin (TD- 4208), a long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD): Results of two randomized, double-blind, phase 2 studies

Table 4. Selected Trials

Study Characteristics

Study characteristics in the format of the Excel spreadsheet used for data extraction are presented in Table 5. The articles which were merged for singular trials are presented in the leftmost column and only represent

Risk of bias within studies

Details of risk of bias within studies are presented in Figure 2, with a summary in Figure 3. Studies could be measured as Low risk, unclear risk, or high risk. Pudi et al. presented the only section with a high risk of bias, in random sequence generation. This was due to a lack of information detailing how patients were randomised.

STUDY					METHODS			PARTICIPANTS AND SETTINGS								INTERVENTION			CONTROL	OUTCOME						
																				Placebo		Intervention			Pooled	
Author	Title	Publication Year	Study ID	Trial ID	Study Design	Total Duration (days)	Follow up Duration (days)	Trial Start Year	Country	No. of participants at start	No. of participants at end	No. of males	No. of females	Mean age	COPD Stage (mean FEV1 %)	Number	Dosage	Regimen	Number	FEV1 change from baseline	SE	Related dosage	FEV1 change from baseline	SE	FEV1 Placebo adjusted change	Pooled SE
Pudi KK et al.	A 28-day, randomized, double-blind, placebo-controlled, parallel group study of nebulized revefenacin in patients with chronic obstructive pulmonary disease.	2017	N/A	NCT02040792	PARALLEL	28	28	2014	United States	355	354	178	176	62	44%	68	44	Once Daily	70	-32.4	25.36	44	19.4	24.61	51.8	24.98781403
Pudi KK et al.	Nebulized Revefenacin Results in a Reduction in the Daily Use of Rescue Medication: Results From a 28-Day Study in Participants With COPD	2016	N/A													71	88					88	155	24.61	187.4	24.98781403
Theravance Biopharma	A Phase 2B, 28-Day, Randomized, Double-Blind Placebo-Controlled Parallel Group	2017	(0)117													71	175					175	134.2	25.07	166.6	25.21541691
Haumann BK et al.	Dose-Ranging Study of Once-Daily TD-4208, an Inhaled Long-Acting Muscarinic Antagonist (LAMA) in Patients with Chronic Obstructive Pulmonary Disease (COPD)	2015	N/A													74	350					350	138.2	24.38	170.6	24.87482663
Nicholis AJ et al.	A Randomized, Crossover, 7-Day Study Of Once-Daily TD 4208, A Long-Acting Muscarinic Antagonist, In Subjects With COPD	2014	(00)91	NCT01704404	NONPARALLEL	112	7	2014	United Kingdom	56	37	35	27	63.9	Moderate to severe COPD	37	22	Once Daily	56	37.8	16.93	22	91.2	19.21	53.4	18.10592444
Quinn D et al.	Pharmacodynamics, pharmacokinetics and safety of revefenacin (TD-4208), a long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD): Results of two randomized, double-blind, phase 2 studies.	2018	(00)91								32					32	44					44	92.8	20.25	55	18.66396796
											35					35	88					88	113.1	19.55	75.3	18.28698171
											33					33	175					175	151.9	19.99	114.1	18.52329614
											38					38	350					350	132.2	19.02	94.4	18.00535059
											35					35	700					700	119.4	19.54	81.6	18.28163696
Potgieter P et al.	A randomized, crossover study to examine the pharmacodynamics and safety of a new antimuscarinic (TD-4208) in COPD	2012	N/A	N/A	NONPARALLEL	1	1	N/A	United States New Zealand	32	32	N/A	N/A	60	Moderate to severe COPD	32	350	Once Daily	32	0	31.378	350	174	31.378	174	31.378
																32	700					700	169	31.378	169	31.378
Theravance Biopharma	A 7-Day Cross-over Study of QD (Once Daily) and BID (Twice Daily) TD-4208 in Chronic Obstructive Pulmonary Disease (COPD)	2017	(0)116	NCT02109172	NONPARALLEL	7	7	2014	United States	64	57	37	27	N/A	Moderate to severe COPD	64	44	Twice Daily	64	-14.4	15.29	44	90.2	15	104.6	15.14569411
																64	175	Once Daily				175	98.5	15.03	112.9	15.16055738
Ferguson G et al.	Efficacy of Revefenacin, a Novel Once-Daily Nebulized Long-Acting Muscarinic Antagonist: Results of Two Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials in Participants with Moderate to Very Severe Chronic Obstructive Pulmonary Disease	2017	(0)126	NCT024559080	PARALLEL	85	85	N/A	United States	619	477	317	302	64.1	54%	198	88	Once Daily	209	-19.41	16.108	88	59.81	15.095	79.22	15.60971955
Donohue J et al.	The 24-Hour Profile of FEV1 After 12-Weeks Treatment With Revefenacin, a Once Daily Long-Acting Muscarinic Receptor Antagonists for Nebulization: A Spirometry Substudy	2017	(0)126													212	175					175	126.85	15.389	146.26	15.75260272
Pudi KK et al.	Trials in Progress: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials of a Nebulized Long-Acting Muscarinic Antagonist (Revefenacin) in Study Participants With Moderate to Very Severe COPD	2016	(0)127	NCT02512510	PARALLEL	85	85	N/A	United States	610	482	302	308	63.4	54%	205	88	Once Daily	208	-44.92	18.841	88	115.58	18.637	160.5	18.7392776
Feldman G et al.	Safety and Tolerability of Revefenacin, a Novel Once-Daily Nebulized Long-Acting Muscarinic Antagonist: Results of Two 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials in Participants with Moderate to Very Severe Chronic Obstructive Pulmonary Disease	2017	(0)127													197	175					175	102.9	18.542	147.82	18.69209786
Quinn D et al.	Pharmacodynamics, pharmacokinetics and safety of revefenacin (TD-4208), a long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD): Results of two randomized, double-blind, phase 2 studies.	2018	(00)59	U1111-1120- 8290	NONPARALLEL	N/A	1	2011	South Africa New Zealand	32	32	22	10	62	35 - 80%	32	350	Once Daily	32	1533.8	22.4	350	1636.6	22.4	102.8	22.4
																32	700					700	1670.4	22.4	136.6	22.4

Table 5. Characteristics of Individual Studies(30–43)

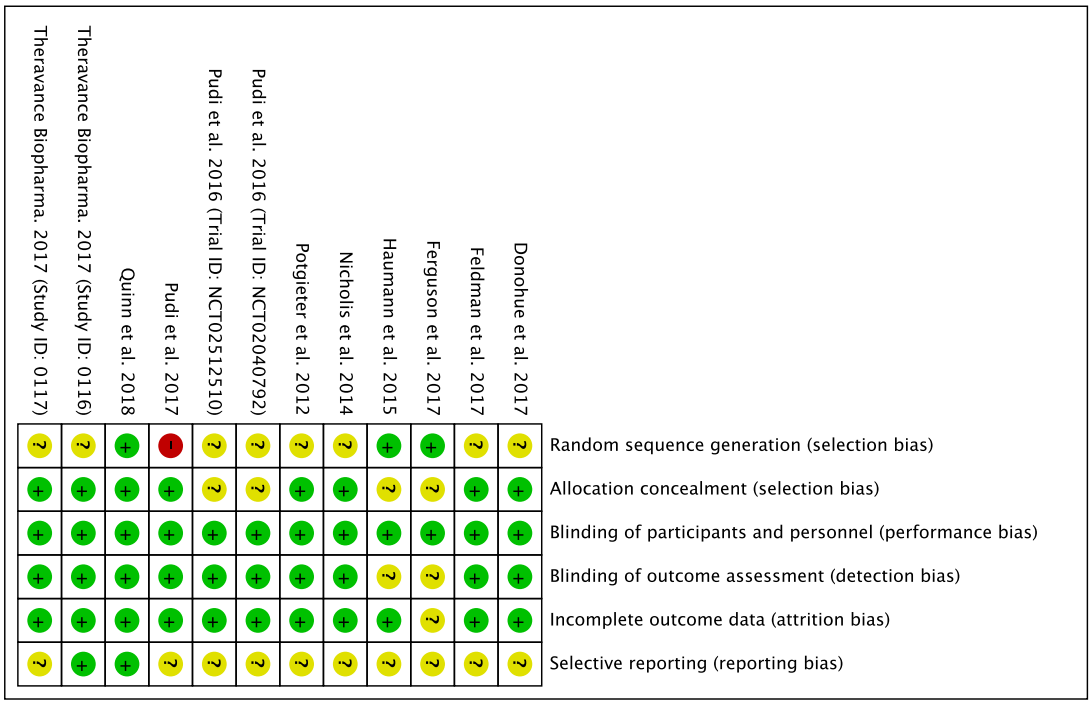


Figure 2. Risk of bias within studies

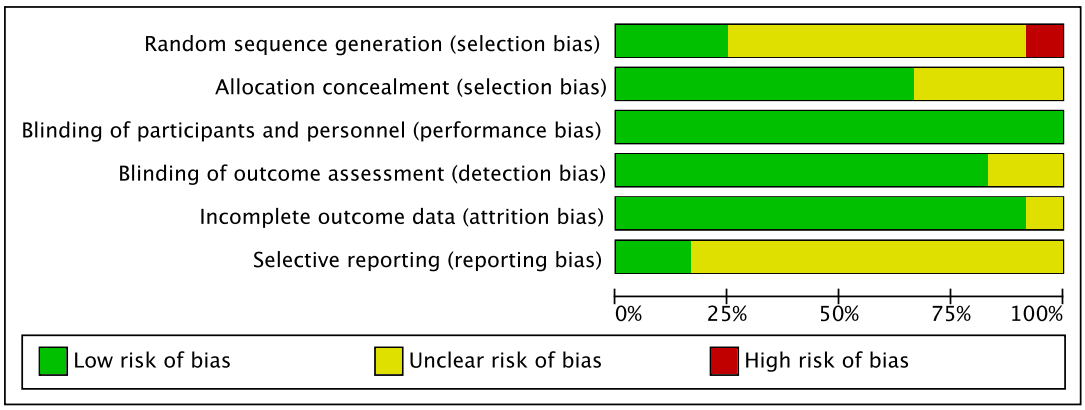


Figure 3. Summary of risk of bias within studies

Risk of Bias Across Studies

The GRADE tool was used to evaluate risk of bias, imprecision, inconsistency, indirectness, publication bias and confidence in cumulative evidence (26). The results are reproduced in the GRADE Summary of Findings (Figure 4). Funnel plots assessing possible bias across studies (Appendix E) and publication bias (Figure 5) demonstrate asymmetry and possible risk of publication bias, respectively. The possible risk of publication bias is due to all of the measured outcomes demonstrating statistical significance, as well the sponsorship by the manufacturer for all studies.

Efficacy of Revefenacin in the Treatment of Moderate to Very Severe COPD

Patient or population: the maintenance treatment of COPD
Setting: United States (n=4); United Kingdom (n=1); United States and New Zealand (n=1); South Africa and New Zealand (n=1)
Intervention: Revefenacin
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Revefenacin**				
Trough FEV1 change from baseline (0-24 hours) (FEV1) Assessed with: Spirometry Follow up range: 1 day to 85 days	N/A	N/A	**MD 119.073** (102.254 to 135.893)	1472 (7 RCTs)	⨁⨁⨁◯ MODERATE a,b,c,d,e	Revefenacin results in large increase in trough FEV1 change from baseline (0-24 hours). Note: Anticipated absolute effects of risk (95% CI) were not estimable.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Studies performed well in performance and attrition biases. Major unclarity has been reported for selection and reporting biases, result in a downgrading of the evidence.
b. Consistent estimates of the treatment effect across studies suggests no true differences in underlying treatment effect.
c. Head-to-head comparisons of Revefenacin and placebo.
d. 95% CI does not include null effect.
e. Visual assessment of the contour-enhanced funnel plot as an aid to differentiating asymmetry due to publication bias from that due to other factors, confirmed that all studies are plotted outside of the funnel, corresponds to p-values below 1% (p=0.01), making publication bias plausible (high risk of publication bias).

Figure 4. GRADE Summary of Findings

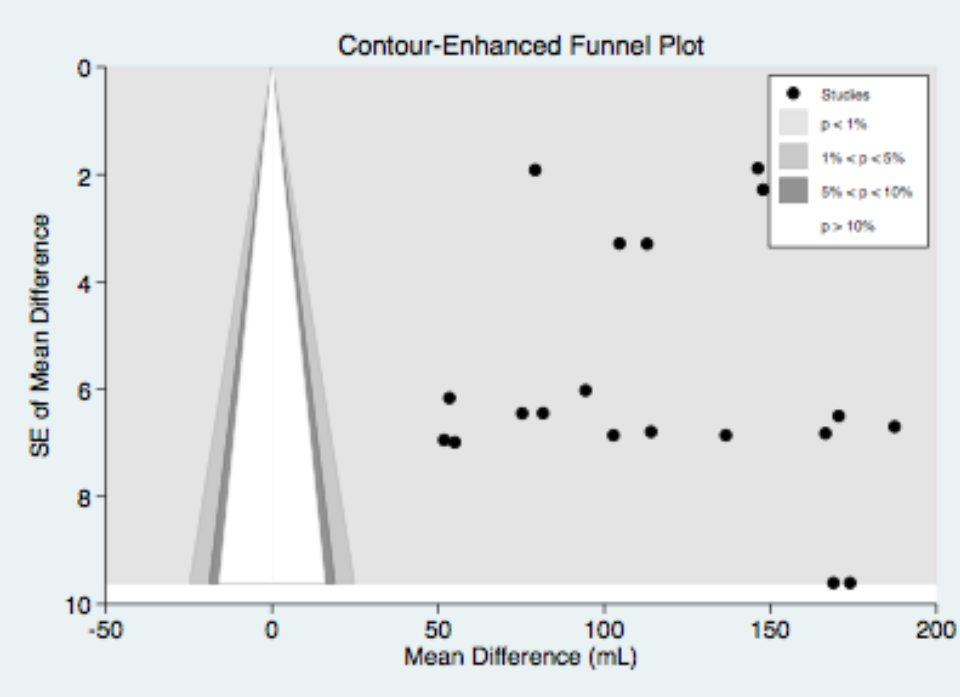


Figure 5. Contour-Enhanced Funnel Plot of Random-Effects Meta-Analysis

Results of Individual Studies

Results of individual studies and the random-effects meta-analysis are presented in Figure 6, along with the accompanying forest plot in Figure 7. For the pairwise, random-effects meta-analysis, 1472 patients were analysed, and the overall difference in means was an increase of 119.073 mL in change in trough FEV1 from baseline to study endpoint for the Revefenacin group compared to the placebo. This result was statistically significant, with a 95% confidence interval of 102.254 mL to 135.893 mL. The heterogeneity between studies was significant with a p value of 0.000, and the I2 measure of consistency was equal to 98.9%, which means that 98.9% of variation in the difference in means is attributable to heterogeneity, which can be interpreted as a high level of statistical heterogeneity.

Study	ES	[95% Conf.	Interval]	% Weight
Pudi 2017, 44{&mu}g	51.800	38.183	65.417	4.96
Pudi 2017, 88{&mu}g	187.400	174.271	200.529	4.97
Pudi 2017, 175{&mu}g	166.600	153.226	179.974	4.97
Pudi 2017, 350{&mu}g	170.600	157.860	183.340	4.98
Andrew 2014, 22{&mu}	53.400	41.317	65.483	5.00
Andrew 2014, 44{&mu}	55.000	41.304	68.696	4.96
Andrew 2014, 88{&mu}	75.300	62.656	87.944	4.99
Andrew 2014, 175{&mu	114.100	100.786	127.414	4.97
Andrew 2014, 350{&mu	94.400	82.595	106.205	5.00
Andrew 2014, 700{&mu	81.600	68.963	94.237	4.99
Potgieter 2012, 350{	174.000	155.170	192.830	4.82
Potgieter 2012, 700{	169.000	150.170	187.830	4.82
Theravance 2017, 44{	104.600	98.157	111.043	5.09
Theravance 2017, 175	112.900	106.444	119.356	5.09
Ferguson Site 1 2017	79.220	75.465	82.975	5.12
Ferguson Site 1 2017	146.260	142.560	149.960	5.12
Ferguson Site 2 2017	160.500	156.092	164.908	5.11
Ferguson Site 2 2017	147.820	143.346	152.294	5.11
Quinn 2017, 350{&mu}	102.800	89.357	116.243	4.97
Quinn 2017, 700{&mu}	136.600	123.157	150.043	4.97
D+L pooled ES	119.073	102.254	135.893	100.00

Heterogeneity chi-squared = **1808.46** (d.f. = **19**) p = **0.000**
I-squared (variation in ES attributable to heterogeneity) = **98.9%**
Estimate of between-study variance Tau-squared = **1.4e+03**

Test of ES=0 : z= **13.88** p = **0.000**

Figure 6. Results of Individual Studies and Overall Random-Effects Meta-Analysis

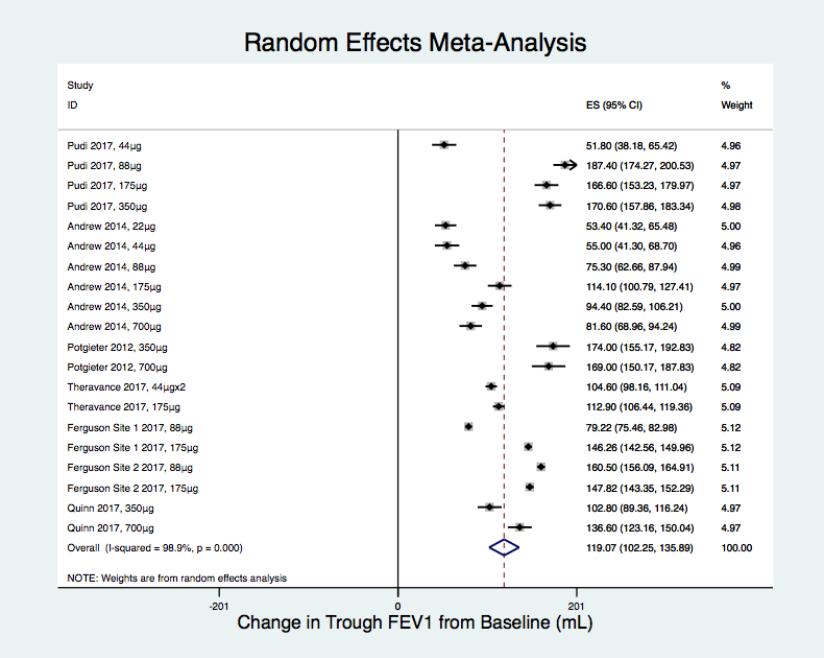


Figure 7. Forest plot of random-effects meta-analysis (Note that for Ferguson 2017 dosage was different per site)

Additional Analysis

Subgroup analysis

Subgroup analysis was performed for study duration (Figure 8), demonstrating significant difference for difference in means for 1 day versus 7 days only, as the 95% confidence interval for 1 day was higher and did not overlap with that of 7 days. There were non-significant differences amongst the rest of the groups by study duration. Subgroup analysis was also performed for dosage (Figure 9), yielding the highest overall difference in change in trough FEV1 from baseline to study endpoint for 175 μg, significantly higher than that of 22 and 44 μg. A dosage of 22 μg yielded a significantly lower difference than all but a dosage of 44 μg, with non-significant differences amongst the groupings of 44, 88, 350, and 700 μg, as well as 88, 175, 350, and 700 μg. Subgroup analysis of study design yielded no significant difference between parallel and nonparallel studies. Overall study is included to demonstrate the additive study effects if results were pooled, as the arms of each different study were split for analysis (Appendix F).

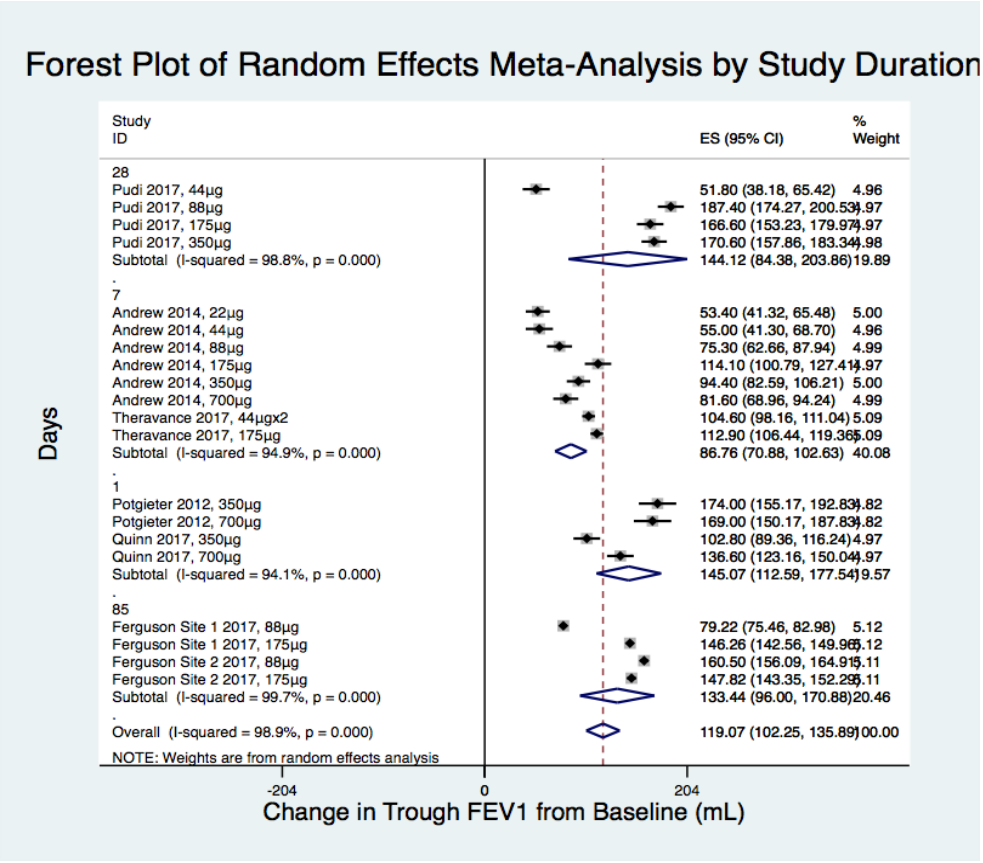


Figure 8. Random Effects Model Meta-analysis by Days

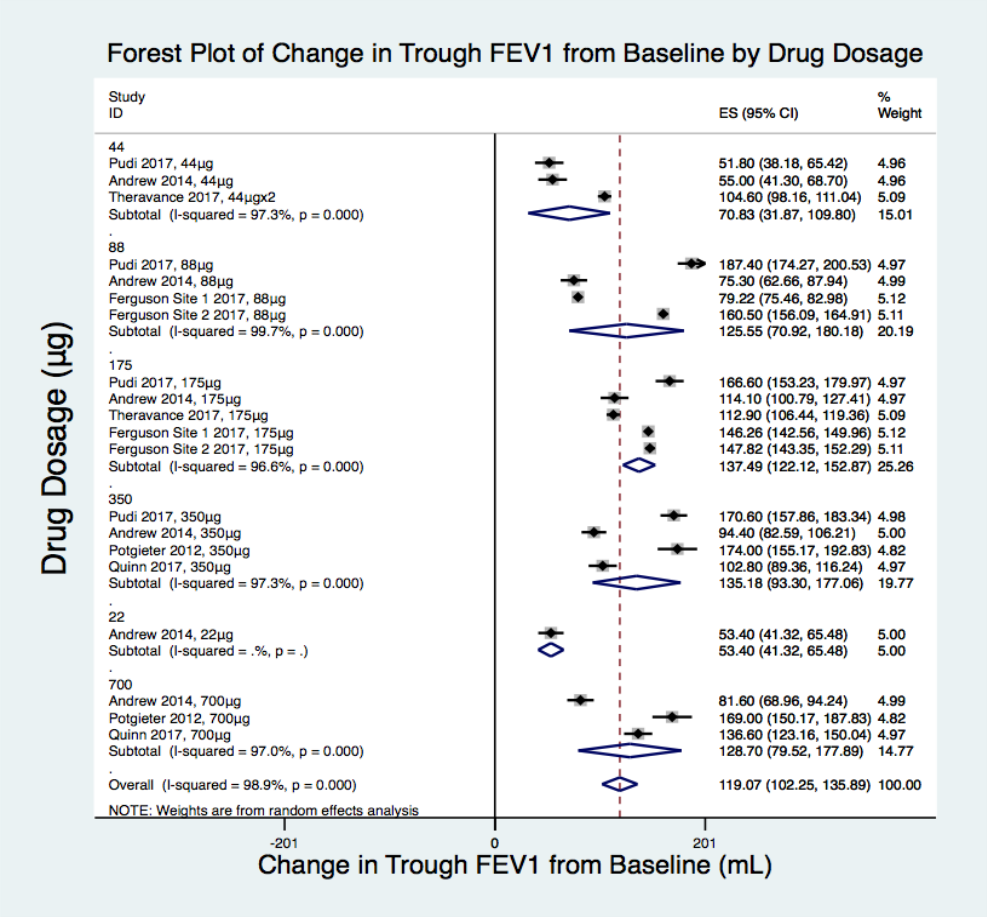


Figure 9. Random Effects Model Meta-analysis by Dosage

Meta-Regression

Meta-regression was performed for both study duration and dosages, yielding no significant correlation for either. Whilst meta-regression analysis for < 10 trials is not recommended, the precedent was unclear as we split the 7 trials into 20 intervention arms. Hence meta-regression was chosen to be robust (results in Appendix G).

Sensitivity Analysis

Sensitivity analysis included removing Pudi et al. from the analysis because of the high risk of bias in sequence of randomisation, resulting in a non-significant difference in difference in means before and after removal. The results of the sensitivity analysis are presented in Appendix H.

Discussion

Overall, through a systematic review and random-effects meta-analysis, 1472 patients were analysed from 7 RCTs. The difference in means in change in trough FEV1 from baseline to study endpoint between the Revefenacin intervention and the placebo comparator was significant, at an increase of 119.07 mL (95% CI 102.25, 135.89) demonstrating that Revefenacin is significantly more efficacious in treatment for moderate to very severe COPD compared to placebo. Subgroup analysis demonstrated 175 μg to potentially be the most efficacious dosage, in line with recommendations from the FDA.(44) Heterogeneity was detected across studies, but the I2 statistic must be interpreted cautiously as the seven individual studies were split into twenty intervention arms for analysis, inflating the heterogeneity between the arms as all studies used multiple dosages. The contour-enhanced funnel plot demonstrated high risk of publication bias, which could be due to industry sponsorship (funding bias), or comparison to placebo, so this must be taken into account with interpretation. It has been demonstrated that industry sponsored studies more frequently result in favourable efficacy outcomes, possibly hampering the validity of our own selected studies.(45) GRADE assessment concludes that Revefenacin results in a significant, large increase in change in trough FEV1 from baseline to study endpoint when compared to placebo, with moderate certainty of evidence. The results are also consistent with the 'time lag bias' in which simultaneous studies with negative results are published years after those with positive ones, which also must be taken into consideration.(21)

Implications of this meta-analysis include supporting evidence in approval of Revefenacin as a LAMA treatment for COPD, but further research into drug combinations with long-acting beta agonists and comparison to other LAMAs and COPD interventions is necessary to test its relative efficacy.(46) This study also used a recently developed method for including multi-armed trials in pairwise meta-analysis, allowing for dosage-specific subgroup analysis within the meta-analysis itself, a technique that will be useful in future drug intervention meta-analyses.(20) Some limitations of the study are that the main comparison was placebo, due to the lack of available studies with comparators. To address this, further research in clinical trials and a network meta-analysis of moderate to very severe COPD interventions including Revefenacin should be conducted. The study is also limited by a low number of RCTs (7), and an update as Revefenacin is compared to other interventions should occur sometime in the near future. Furthermore, the generalizability of the study is limited due to the nature of RCTs and their controlling for other factors affecting outcome, such as multimorbidities. Moreover, a geographical bias might be present with the majority of trials being performed in the US (n=4). This adds to the low number of studies which could severely impact the generalisability of results. Furthermore, despite proving that Revefenacin is efficacious against placebo, it is important to point out this systematic review and meta-analysis does not take into account safety and tolerability of the drug, which will need to be further assessed.

Conclusion

This paper's aim was to determine the clinical efficacy of Revefenacin in patients with moderate to severe COPD. Revefenacin has been determined to be an efficacious treatment for moderate to very severe COPD in comparison to placebo. Further research into whether it is efficacious in comparison to the current standard of care, through RCTs or network meta-analysis for the network of interventions to treat moderate to very severe COPD, is needed. This systematic-review and meta-analysis was limited by a small number of RCTs (n=7), and a larger body of evidence could provide further information on dosage gradients and duration of use. Moreover, being all the selected studies funded by Revefenacin 's manufacturer poses an important risk of publication bias which needs to be considered. There is also a need for further research into efficacy of Revefenacin in multi-morbid and other trial-excluded patient groups. However, this systematic review and meta-analysis provides a summary of the current evidence and demonstrates the efficacy of Revefenacin in comparison to placebo in its current setting.

References

1. Quaderi SA, Hurst JR. The unmet global burden of COPD. Glob Heal Epidemiol genomics [Internet]. 2018 [cited 2019 Feb 24];3:e4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29868229
2. World Health Organization. Chronic obstructive pulmonary disease (COPD) [Internet]. 2017. Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)
3. Mathers CD, Loncar D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. Samet J, editor. PLoS Med [Internet]. 2006 Nov 28 [cited 2019 Feb 24];3(11):e442. Available from: https://dx.plos.org/10.1371/journal.pmed.0030442
4. Mayo Clinic. COPD - Symptoms and causes - Mayo Clinic [Internet]. 2017 [cited 2019 Apr 30]. Available from: https://www.mayoclinic.org/diseases-conditions/copd/symptoms-causes/syc-20353679
5. May SM, Li JTC. Burden of chronic obstructive pulmonary disease: healthcare costs and beyond. Allergy asthma Proc [Internet]. 2015 [cited 2019 Feb 24];36(1):4–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25562549
6. Erdal M, Johannessen A, Askildsen JE, Eagan T, Gulsvik A, Grønseth R. Productivity losses in chronic obstructive pulmonary disease: a population-based survey. BMJ Open Respir Res [Internet]. 2014 Dec 1 [cited 2019 Feb 24];1(1):e000049. Available from: http://bmjopenrespres.bmj.com/lookup/doi/10.1136/bmjresp-2014-000049
7. BMJ Best Practice. Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [Internet]. BMJ Publ. Group; 2018 [cited 2019 Apr 30]. Available from: https://bestpractice.bmj.com/topics/en-gb/7/criteria
8. Lung Institute. Stages of COPD: Mild through End-Stage COPD | Lung Institute [Internet]. 2018 [cited 2019 Apr 30]. Available from: https://lunginstitute.com/blog/stages-of-copd-mild-through-end-stage/

9. Doucet M, Rochette L, Hamel D. Incidence, Prevalence, and Mortality Trends in Chronic Obstructive Pulmonary Disease over 2001 to 2011: A Public Health Point of View of the Burden. Can Respir J [Internet]. 2016 [cited 2019 Feb 24];2016:7518287. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27478397
10. AJMC. FDA Approves Revefenacin , a Once-a-Day Nebulized LAMA, for COPD [Internet]. 2018 [cited 2019 Feb 25]. Available from: https://www.ajmc.com/newsroom/fda-approves-Revefenacin -a-onceaday-nebulized-lama-for-copd
11. K. P, C. B, E. M, B. H. Nebulized Revefenacin results in a reduction in the daily use of rescue medication: Results from a 28-day study in participants with COPD. Chest [Internet]. 2016;150(4 Supplement 1):828A. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed17&NEWS=N&AN=613468950
12. Melao A. Revefenacin , Marketed as Yupelri, Approved by FDA to Treat COPD [Internet]. COPD News Today. [cited 2019 Jul 6]. Available from: https://copdnewstoday.com/2018/11/13/Revefenacin -marketed-as-yupelri-approved-by-fda-for-copd/
13. Heo Y-A. Revefenacin : First Global Approval. Drugs [Internet]. 2019 Jan 17 [cited 2019 Jul 6];79(1):85–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30560478
14. Buels KS, Fryer AD. Muscarinic receptor antagonists: effects on pulmonary function. Handb Exp Pharmacol [Internet]. 2012 [cited 2019 Jul 6];(208):317–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22222705
15. Hegde SS, Pulido-Rios MT, Luttmann MA, Foley JJ, Hunsberger GE, Steinfeld T, et al. Pharmacological properties of Revefenacin (TD-4208), a novel, nebulized long-acting, and lung selective muscarinic antagonist, at human recombinant muscarinic receptors and in rat, guinea pig, and human isolated airway tissues. Pharmacol Res Perspect [Internet]. 2018 [cited 2019 Jul 6];6(3):e00400. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29736245
16. FDA - US Food and Drug Administration. Novel Drug Approvals for 2018 | FDA [Internet]. [cited 2019 Jul 6]. Available from: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2018
17. Theravance Biopharma. Theravance Biopharma and Mylan Receive FDA Approval for YUPELRI™ (Revefenacin) in Adults with Chronic Obstructive Pulmonary Disease | Theravance Biopharma, Inc. [Internet]. 2018 [cited 2019 Jul 6]. Available from: https://investor.theravance.com/news-releases/news-release-details/theravance-biopharma-and-mylan-receive-fda-approval-yupelritm
18. Kabisch M, Ruckes C, Seibert-Grafe M, Blettner M. Randomized controlled trials: part 17 of a series on evaluation of scientific publications. Dtsch Arztebl Int [Internet]. 2011 Sep [cited 2019 Apr 30];108(39):663–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22013494
19. Sibbald B, Roland M. Understanding controlled trials: Why are randomised controlled trials important? BMJ [Internet]. 1998 Jan 17 [cited 2019 Apr 26];316(7126):201. Available from: https://www.bmj.com/content/316/7126/201
20. Rücker G, Cates CJ, Schwarzer G. Methods for including information from multi-arm

trials in pairwise meta-analysis. Res Synth Methods [Internet]. 2017 Dec [cited 2019 Apr 24];8(4):392–403. Available from: http://doi.wiley.com/10.1002/jrsm.1259
21. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ [Internet]. 2011 Oct 18 [cited 2019 Feb 25];343:d5928. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22008217
22. Glaab T, Vogelmeier C, Buhl R. Outcome measures in chronic obstructive pulmonary disease (COPD): strengths and limitations. Respir Res [Internet]. 2010 Dec 17 [cited 2019 Feb 25];11(1):79. Available from: http://respiratory-research.biomedcentral.com/articles/10.1186/1465-9921-11-79
23. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. 2011 [cited 2019 May 1]. Available from: https://handbook-5-1.cochrane.org/front_page.htm
24. Borenstein M, Hedges L V., Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods [Internet]. 2010 Apr 1 [cited 2019 May 1];1(2):97–111. Available from: http://doi.wiley.com/10.1002/jrsm.12
25. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med [Internet]. 2002 Jun 15 [cited 2019 May 1];21(11):1539–58. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12111919
26. Siemieniuk R, Guyatt G. What is GRADE? | BMJ Best Practice [Internet]. [cited 2019 Feb 25]. Available from: https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/
27. Bown MJ, Sutton AJ. Quality Control in Systematic Reviews and Meta-analyses. Eur J Vasc Endovasc Surg [Internet]. 2010 Nov [cited 2019 May 1];40(5):669–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20732826
28. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med [Internet]. 2009 Jul 21 [cited 2019 May 1];6(7):e1000097. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19621072
29. The Cochrane Collaboration. Review Manager (RevMan) Version 5.3 [Internet]. 2014 [cited 2019 May 1]. Available from: https://community.cochrane.org/help/tools-and-software/revman-5
30. Ferguson G, Pudi KK, Feldman G, Pendyala S, Barnes CN, Moran EJ, et al. Efficacy and safety of Revefenacin (REV), a long-acting muscarinic antagonist for nebulization: Results of replicate randomized, double-blind, placebo-controlled, parallelgroup phase 3 trials in participants with moderate to very severe COPD. Eur Respir J [Internet]. 2017;50(Supplement 61):PA1812. Available from: http://erj.ersjournals.com/content/50/suppl_61/PA1812
31. Haumann BK, Nicholls AJ, Barnes C, Bourdet DL. Dose-ranging study of once-daily TD-4208, an inhaled long-acting muscarinic antagonist (LAMA) in patients with chronic obstructive pulmonary disease (COPD). Am J Respir Crit Care Med [Internet]. 2015;191(MeetingAbstracts):A5750. Available from: http://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A5750

32. Potgieter P, Hopkins A, Liu P, Quinn D, Amburgey C. A randomized, crossover study to examine the pharmacodynamics and safety of a new antimuscarinic (TD-4208) in COPD. Eur Respir J [Internet]. 2012;40(SUPPL. 56):P2878. Available from: http://erj.ersjournals.com/content/40/Suppl_56/P2878.abstract?sid=fb221b1f-d72c-4ed1-bb7f-0ad2d9c4d084
33. Kerwin EM, Donohue JF, Sethi S, Haumann B, Pendyala S, Dean L, et al. Revefenacin , a once-daily, long-acting muscarinic antagonist for nebulized therapy of chronic obstructive pulmonary disease (COPD): Results of a 52-week safety and tolerability phase 3 trial in participants with moderate to very severe COPD. Am J Respir Crit Care Med [Internet]. 2018;197(MeetingAbstracts):A4239. Available from: http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A4239
34. Ferguson G, Barnes C, Pendyala S, Crater G. Efficacy and safety of Revefenacin , a long-acting muscarinic antagonist for nebulization from phase 3 trials in patients with moderate to very severe chronic obstructive pulmonary disease. JACCP J Am Coll Clin Pharm [Internet]. 2018;1(2):341. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexb&NEWS=N&AN=625879660
35. Quinn D, Barnes CN, Yates W, Bourdet DL, Moran EJ, Potgieter P, et al. Pharmacodynamics, pharmacokinetics and safety of Revefenacin (TD-4208), a long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD): Results of two randomized, double-blind, phase 2 studies. Pulm Pharmacol Ther [Internet]. 2018;48:71–9. Available from: http://www.elsevier.com/inca/publications/store/6/2/2/9/3/6/index.htt
36. Pudi K, Barnes C, Moran E, Haumann B. Nebulized Revefenacin results in a reduction in the daily use of rescue medication: Results from a 28-day study in participants with COPD. Chest [Internet]. 2016;150(4 Supplement 1):828A. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed17&NEWS=N&AN=613468950
37. Cazzola M, Rogliani P, Segreti A, Matera MG. An update on bronchodilators in Phase I and II clinical trials. Expert Opin Investig Drugs [Internet]. 2012;21(10):1489–501. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=22916733
38. Ferguson G, Barnes C, Pendyala S. Efficacy and safety of Revefenacin , a long-acting muscarinic antagonist for nebulization from phase 3 trials in patients with moderate to very severe chronic obstructive pulmonary disease. Consult Pharm [Internet]. 2018;33(10):600. Available from: c
39. Pudi KK, Barnes CN, Moran EJ, Haumann B, Kerwin E. A 28-day, randomized, double-blind, placebo-controlled, parallel group study of nebulized Revefenacin in patients with chronic obstructive pulmonary disease. Respir Res [Internet]. 2017;18(1):182. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med13&NEWS=N&AN=29096627
40. Ferguson GT, Pudi KK, Pendyala S, Barnes CN, Moran EJ, Haumann B. Efficacy of

Revefenacin , a novel once-daily nebulized long-acting muscarinic antagonist: Results of two randomized, double-blind, placebo-controlled, parallel-group phase 3 trials in participants with moderate to very severe chronic obstructive pulmonary. Am J Respir Crit Care Med [Internet]. 2017;195:A5474. Available from: http://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A5474

41. Donohue J, Pendyala S, Barnes C, Moran E. The 24-hour profile of FEV1 after 12-weeks treatment with Revefenacin , a once daily long-acting muscarinic receptor antagonists for nebulization: A spirometry substudy. Chest [Internet]. 2017;152(4 Supplement 1):A770. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed18&NEWS=N&AN=619296687
42. Nicholls AJ, Barnes C, Yates W, Moran EJ. A randomized, crossover, 7-day study of once-daily TD 4208, a long-acting muscarinic antagonist, in subjects with COPD. Am J Respir Crit Care Med [Internet]. 2014;189(MeetingAbstracts):A6003. Available from: http://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A6003
43. Pudi K, Pendyala S, Barnes C, Moran E, Haumann B, Kerwin E. Trials in Progress: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials of a Nebulized Long-Acting Muscarinic Antagonist (Revefenacin) in Study Participants With Moderate to Very Severe COPD. [Internet]. Vol. 150, Chest. Upstate Pharmaceutical Research, Greenville, SC: American College of Chest Physicians; 2016. p. 825A-825A. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=118540780&site=ehost-live
44. Li F, Yang J. Revefenacin for the treatment of chronic obstructive pulmonary disease. Expert Rev Clin Pharmacol [Internet]. 2019 Apr 3 [cited 2019 May 1];12(4):293–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30803279
45. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev [Internet]. 2017 Feb 16 [cited 2019 May 1];(2). Available from: http://doi.wiley.com/10.1002/14651858.MR000033.pub3

Appendix A: Search Strategies

MEDLINE (Ovid) - final ver.

1. lung diseases, obstructive/
2. exp pulmonary disease, chronic obstructive/
3. (copd or coad or cobd or aecb).tw.
4. emphysema*.tw.
5. (chronic* adj4 bronch*).tw.
6. (chronic* adj3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) adj3 obstruct*).tw.
7. (pulmonum adj4 (volumen or pneumatosis)).tw.
8. Pneumonectasia.tw.
9. *Dyspnea/
10. (chronic* adj3 (breath* or respirat*) adj3 (difficult* or labor* or labour* or problem* or short*)).tw.
11. (chronic* adj3 (dyspnea* or dyspnoea* or dyspneic or breathless*)).tw.
12. or/1-11
13. Muscarinic Antagonists/
14. (long act* adj4 muscarinic*).tw.
15. (muscarinic* adj1 antagonist*).tw.
16. LAMA*.tw.
17. Revefenacin .tw.
18. TD?4208.tw.
19. or/13-18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomi#ed.ab.
23. placebo.ab.
24. randomly.ab.
25. clinical trials as topic.sh.
26. trial.ab.
27. groups.ab.
28. or/20-27
29. 12 and 19 and 28

Clinicaltrials.gov final search

149 Results

Relevant RCTs will be searched using the following search strategy:

ClinicalTrials.Gov Advanced Search

- Condition or disease: Chronic Obstructive Pulmonary Disease OR Emphysema OR respiratory tract disease OR Bronchitis
- Study Type: Interventional Studies (Clinical Trials)
- Study Results: All Studies
- Status: Recruitment: Completed
- Sex: All
- Eligibility Criteria: Intervention/treatment: Muscarinic Antagonist OR TD-4208 OR Revefenacin OR LAMA

International Clinical Trials Registry Platform final search

8 results

RCTs searched in ICTRP

Look for trials with the exact phrase or contains:

- In the Title: (Chronic Obstructive Pulmonary Disease OR Emphysema OR respiratory tract disease OR Bronchitis) AND (Revefenacin OR TD-4208 OR LAMA OR Muscarinic Antagonist)
- In the Condition: Chronic Obstructive Pulmonary Disease OR Emphysema OR respiratory tract disease OR Bronchitis
- In the Intervention: Revefenacin OR TD-4208 OR LAMA OR Muscarinic Antagonist
- Recruitment Status: ALL
- In the Title AND In the Condition AND in the Intervention

CINHAL (EBSCO)
222 results

1. (MH "Lung Diseases, Obstructive+")
2. TX (copd or coad or cobd or aecb)
3. TX emphysema*
4. TX (chronic* N4 bronch*)
5. TX (chronic* N3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) N3 obstruct*)
6. TX (pulmonum N4 (volumen or pneumatosis))
7. TX Pneumonectasia
8. (MH “Respiratory Tract Diseases+”)
9. TX (chronic* N3 (breath* or respirat*) N3 (difficult* or labor* or labour* or problem* or short*))
10. TX (chronic* N3 (dyspnea* or dyspnoea* or dyspneic or breathless*))
11. Or/S1-S10
12. (MH "Muscarinic Antagonists+")
13. TX (“long act*” N4 muscarinic*)
14. TX (muscarinic* N1 antagonist*)
15. TX LAMA*
16. TX Revefenacin
17. TX “TD#4208”
18. Or/S12-S17
19. (pt "clinical trial") or (pt "randomized controlled trial")
20. ti (placebo* or random*) or ab (placebo* or random*)
21. ti (“single blind*” or “double blind*” or “treble blind*” or mask* or dummy* or singleblind* or doubleblind* or trebleblind*) or ab (“single blind*” or “double blind*” or “treble blind*” or mask* or dummy* or singleblind* or doubleblind* or trebleblind*)
22. ti (crossover or “cross over”) or ab (crossover or “cross over”)
23. ti clinical n2 trial* or ab clinical n2 trial*
24. (mh "crossover design") or (mh "placebos") or (mh "random assignment") or (mh "random sample")
25. (mh "clinical trials+")
26. Or/S19-25
27. S11 and S18 and S26

EMBASE (Ovid)
894 results
1. exp chronic obstructive lung disease/
2. (copd or coad or cobd or aecb).tw.

3. emphysema$.tw.
4. exp bronchitis/
5. (chronic$ adj4 bronch$).tw.
6. (chronic$ adj3 (airflow$ or airway$ or bronch$ or lung$ or respirat$ or pulmonary) adj3 obstruc$*).tw.
7. (pulmonum adj4 (volumen or pneumatosis)).tw.
8. pneumonectasia.tw.
9. dyspnea/
10. (chronic$ adj3 (breath$ or respirat$) adj3 (difficult$ or labor$ or labour$ or problem$ or short$)).tw.
11. (chronic$ adj3 (dyspnea$ or dyspnoea$ or dyspneic or breathless$)).tw.
12. Or/1-11
13. exp Revefenacin /
14. muscarinic receptor blocking agent/
15. (long act$ adj4 muscarinic$).tw.
16. (muscarinic$ adj1 antagonist$).tw.
17. LAMA*.tw.
18. Revefenacin .tw.
19. TD?4208.tw.
20. Or/13-19
21. randomized controlled trial/
22. controlled clinical trial/
23. randomi$ed.ab.
24. placebo.ab.
25. randomly.ab.
26. clinical trials as topic.sh.
27. trial.ab.
28. groups.ab.
29. Or/21-28
30. 12 and 20 and 29

Appendix B: *Exact adjustment method with R code*

This method of standard error adjustment to avoid unit of analysis error and account for correlation between groups using the same placebo comes from a paper titled *Methods for including information from multi-arm trials in pairwise meta-analysis*.(20) This method (Method 4) adjusts the standard errors within a study by exact inflation factors using a method similar to that of network meta-analysis, which also allows for multi-armed studies and accounts for the unit of analysis error and correlation between groups. The R code used for exact adjustment in our study is reproduced below.

Line	Code
1	pudi <- data.frame(study=rep("Pudi 2017", 5), id=c(1,2,3,4,5), treatment=c("placebo", "44", "88", "175", "350"), n=c(70,68,71,71,74), mean=c(-32.4,19.4,155,134.2,138.2), sd=c(25.36,24.98,24.61,25.07,24.38))
2	p1 <- pairwise(treat=treatment, n=n, mean=mean, sd=sd, , data=pudi, studlab=study)
3	nm <- netmeta(TE, seTE, treat1, treat2, studlab, data=p1)
4	as.data.frame(nm)[,1:6]
5	andrew <- data.frame(study=rep("Andrew", 7), id=c(1,2,3,4,5,6,7), treatment=c("placebo", "22", "44", "88", "175", "350", "700"), n=c(56,37,32,35,33,38,35), mean=c(37.8,91.2,92.8,113.1,151.9,132.2,119.4), sd=c(16.93,19.21,20.25,19.55,19.99,19.02,19.54))
6	p1 <- pairwise(treat=treatment, n=n, mean=mean, sd=sd, , data=andrew, studlab=study)
7	nm <- netmeta(TE, seTE, treat1, treat2, studlab, data=p1)
8	as.data.frame(nm)[,1:6]
9	potgieter <- data.frame(study=rep("Potgieter", 3), id=c(1,2,3), treatment=c("placebo", "350", "700"), n=c(32,32,32), mean=c(0,174,169), sd=c(31.378,31.378,31.378))
10	p1 <- pairwise(treat=treatment, n=n, mean=mean, sd=sd, , data=potgieter, studlab=study)
11	nm <- netmeta(TE, seTE, treat1, treat2, studlab, data=p1)
12	as.data.frame(nm)[,1:6]
13	theravance <- data.frame(study=rep("Theravance", 3), id=c(1,2,3), treatment=c("placebo", "44x2", "175"), n=c(64,64,64), mean=c(-14.4,90.2,98.5), sd=c(15.29,15,15.03))
14	p1 <- pairwise(treat=treatment, n=n, mean=mean, sd=sd, , data=theravance, studlab=study)
15	nm <- netmeta(TE, seTE, treat1, treat2, studlab, data=p1)
16	as.data.frame(nm)[,1:6]

Appendix C: Full-Text Excluded Studies with Reason for Exclusion

Authors	Title	Date	Reason for exclusion
Fura, A.,Obermeier, M., Tino, J., Burke, J., Marathe, P., Yang, Z.	Abstracts for the 9th American Conference on Pharmacometrics, ACoP	2018	Only pharmokinetics of the drug, not relevant
Donohue J., Pendyala, J., Barnes, C., Moran, E.	Improvements in health status with Revefenacin , a once-daily long-acting muscarinic antagonist for nebulization: Changes in St George's respiratory questionnaire and COPD assessment test in replicate 3-month studies	2017	Self-assessment and looks at qualitative aspects, not relevant for this research
Harris, E.	Industry update: What is new in the field of therapeutic delivery?	2018	Business focus with no clinical-relevant data
Mahler, D.A., Pendyala, S., Barnes, C.N.	Prevalence and characteristics of patients with COPD and low peak inspiratory flow rate recruited in a phase 3 development program for Revefenacin , a nebulized once-daily long-acting muscarinic antagonist	2017	No Revefenacin in the study
Borin, M., Barners, C., Darpo, B., Pendyala, S.	Revefenacin , a long-acting muscarinic antagonist (LAMA), does not prolong qt interval in healthy subjects: Results of a placebo-and positive-controlled thorough QT study	2018	Doesn't meet the elegibility criteria (healthy patinets for the RCT)
Baldwin, M., McConn, D., Potgieter, P., Steinfeld, T., Quinn, D.	Single-dose pharmacokinetics of TD-4208, a novel long-acting muscarinic antagonist, in patients with COPD	2013	Only pharmokinetics of the drug, not relevant
DeLaCruz, L., Pendyala, S., Barnes, C., Moran, E., Haumann, B., Feldman, G.	Trial in Progress: A 52-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trial to Evaluate the Safety and Tolerability of a Nebulized Long-Acting Muscarinic Antagonist (Revefenacin) in Study Participants With COPD.	2016	There is another treatment on the side. Moreover, only an update on an ongoing trial with no useable data
Theravance Biopharma	Revefenacin Peak Inspiratory Flow Rate (PIFR) Study in COPD	2018	Does not meet the eligibility criteria of moderate to severe COPD patients

Kerwin,E.M. , Donohue, J.F., Sethi, S., Haumann, B., Pendyala, S., Dean, L., Barnes, C.N., Moran, E.J., Crater, G.D.	Revefenacin , a Once-Daily, Long-Acting Muscarinic Antagonist for Nebulized Therapy of Chronic Obstructive Pulmonary Disease (COPD): Results of a 52-Week Safety and Tolerability Phase 3 Trial in Participants with Moderate to Very Severe COPD	2018	No results posted
Theravance Biopharma	Effects of TD-4208 on FEV1 in Subjects With Chronic Obstructive Pulmonary Disease (COPD)	2017	No results posted
Theravance Biopharma	A 52-Week Parallel Group Safety Study of TD-4208 in Chronic	2018	Does not meet the eligibility criteria of moderate to severe COPD patients
Theravance Biopharma	7 Days of TD−4208 in Subjects With Chronic Obstructive Pulmonary Disease	2017	Does not meet the eligibility criteria of moderate to severe COPD patients - has all levels of COPD patients
Theravance Biopharma	A 42-day Parallel Group Safety Study of Revefenacin and Formoterol, Administered in Sequence and as a Combination, in Subjects With COPD	2018	No results posted
Theravance Biopharma	A 42-day parallel group safety study of Revefenacin and formoterol, administered in sequence and as a combination, in subjects with COPD	2018	No results posted
Cazzola, M., Rogliani, P., Segreti, A., Matera, M. G.	An update on bronchodilators in Phase I and II clinical trials.	2012	No results in the text, this is an informative update
Feldman G., Barnes CN.., Moran E.J., et al.	Safety and tolerability of Revefenacin , a novel once-daily nebulized long-acting muscarinic antagonist: Results of two 12-week, randomized, double-blind, placebo-controlled, parallel-group phase 3 trials in participants with moderate to very severe COPD	2017	Looks only at saftey and tollerability

Appendix D: Risk of bias and interpretation

Risk of Bias	Interpretation	Within a Study	Across Studies
Low	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains **Quinn et al. 2018**	Most information is from studies at low risk of bias
Unclear	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains **Donohue et al. 2017** **Feldman et al. 2017** **Ferguson et al. 2017** **Haumann et al. 2015** **Nicholis et al. 2014** **Potgieter et al. 2012** **Pudi et al. 2016** **Pudi et al. 2016** **Theravance Biopharma. 2017** **Theravance Biopharma. 2017**	Most information is from studies at low or unclear risk of bias
High	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains **Pudi et al. 2017**	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results

JOURNAL OF HEALTH POLICY AND ECONOMICS

Francis Ifeanyi Ayomoh. The Rising Global Tide of Non-Communicable Diseases: A Call For Decisive Action. Journal of Health Policy and Economics. 2021; 1(1):

The Rising Global Tide of Non-Communicable Diseases: A Call For Decisive Action

Francis Ifeanyi Ayomoh MBBS, MSc[1]

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, United Kingdom. francis.ayomoh@phc.ox.ac.uk

Abstract

The prevalence of non-communicable diseases (NCDs) has been on the rise and led to numerous deaths globally. Although the burden of disease of NCDs is significantly high, healthcare expenditure on the prevention and control of NCDs in most countries does not match the prevalence of NCDs. In low-and-middle income countries (LMICs), most development assistance for health has not been focused on NCDs with most donor funds addressing communicable diseases such as HIV/AIDS, Malaria and Tuberculosis. NCDs have plunged households into poverty as a result of catastrophic health expenditure from out-of-pocket payments for the management of NCDs. The recent COVID-19 pandemic has further highlighted the global prevalence of NCDs and the need for all countries to prioritize the prevention and control of NCDs.

While some risk factors for NCDs are inherent and non-modifiable, exposure to other risk factors such as obesity, unhealthy diet, tobacco use and alcohol consumption can be curbed to reduce the incidence of NCDs. However, in most countries, especially in LMICs, the business interest of fast-food, tobacco and alcohol companies have hampered the implementation of prevention and control strategies for NCDs. Several cost-effective strategies for the prevention and control of NCDS have been outlined and have the potential to reduce the global prevalence of NCDs to the barest minimum if adopted and implemented by most countries. It is imperative that global and national stakeholders take decisive action and renew their commitment to tackle the rising tide of NCDs across the globe.

Keywords: NCDs; Health Policy; Healthcare Financing; Universal Health Coverage; COVID-19; Global Action

Executive Summary

Globally, despite the significant morbidity and mortality caused by NCDs, they have not received the requisite attention and funding that they deserve(1). In 2014, NCDs received only 2% of all overseas development assistance for health in contrast to 29% received by HIV. Ironically, that same year, NCDs represented half of the entire burden of disease globally and HIV made up only 4% of the global disease burden(2). Although early diagnosis and management of NCDs as well as limiting exposure to some major risk factors have proven

effective in tackling NCDs, most countries have failed to curb the menace of NCDs. This failure in the prevention and control of NCDs has been attributed to inadequate funding, ineffective policy implementation, and the vested interest of stakeholders in the tobacco, alcohol, and fast food industry(1). With the deaths from NCDs predicted to increase, it is pertinent that globally all stakeholders focus on effectively implementing policies to prevent and control NCDs(3).

Introduction

Non-communicable diseases (NCDs) have become the leading cause of death globally accounting for over 36 million deaths every year(4). The rising prevalence of NCDs gained global attention, leading member states of the United Nations to meet in 2011 and commit to the reduction of NCDs (particularly cardiovascular diseases, diabetes, cancer, and chronic respiratory diseases)(5). This commitment culminated in the inclusion of NCDs in the Sustainable Development Goals (SDGs) target 3.4 which aims to "by 2030, reduce by one-third, premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being"(6).

The prevalence of NCDs has been steadily increasing(7). In most developed countries, improved healthcare services have increased life expectancy and led to a resultantly higher prevalence of NCDs. In most low and middle-income countries (LMICs), NCDs have gradually overtaken infectious diseases as the leading causes of death(8),(9). Physical inactivity, tobacco use, unhealthy diet, and harmful use of alcohol are notable risk factors for NCDs which should be addressed(4). Despite the global commitment towards tackling NCDs, it appears that not much progress has been made to stem the tide and urgent action is needed to prevent a further rise in the morbidity and mortality associated with NCDs. This necessitates a review of strategies and policies employed so far to prevent and control NCDs.(10)

The aim of this brief is to remind stakeholders about the global scourge of NCDs and present key policy recommendations to be considered for accelerated progress towards curbing the rising global prevalence of NCDs. It is meant to serve as a concise overview of policy reforms necessary to build a national strategy to combat NCDs. It would focus on strategies to reduce the incidence of NCDs and mechanisms to improve access to care for people with NCDs. This policy brief is targeted at national governments, development agencies, civil society organizations, and non-governmental organizations implementing programmes focused on reducing the prevalence of NCDs.

Why Do NCDs Deserve Immediate Attention?

While NCDs have caused the death of millions of people worldwide, it appears that the worst is yet to come as the absolute number of deaths caused by NCDs has been predicted to rise if NCDs are not given immediate attention(7). The COVID-19 pandemic has further highlighted the magnitude of the global NCDs prevalence with COVID-19 infection having worse outcomes in people with NCDs. Globally, persons with NCDs have been noted to have a higher risk of severe COVID-19 infection and death when compared to those without pre-existing NCDs. A recent report from Italy showed that about 96.2% of patients who died from

COVID-19 had comorbidities, with hypertension, type 2 diabetes, ischaemic heart disease, chronic obstructive pulmonary disease, and cancer being the major pre-existing conditions noted(11).

Considerable resources are spent on dealing with NCDs and this contributes to rising total healthcare expenditure in most countries(8). This clearly indicates that the rising prevalence of NCDs has economic implications with NCDs estimated to gulp over $50 million from the global economy between 2011 and 2025(2). Thakur *et al* opined that NCDs caused recurrent out-of-pocket (OOP) spending and catastrophic healthcare expenditure which drove many households into poverty in India(12). Many LMICs have had similar experiences of catastrophic healthcare expenditure attributed to NCDs(2). Globally, the rising prevalence of NCDs could plunge over 150 million people into poverty as a result of catastrophic health expenditure from out-of-pocket spending on NCDs(13). It is clear that all nations should give NCDs the attention they deserve so as to place their citizens on the path to improved health outcomes and economic prosperity.

Determinants And Risk Factors Of NCDs

The incidence of NCDs has been shown to be determined by the interplay of underlying social determinants, lifestyle choices, and physiological risk factors. The major risk factors which have been associated with NCDs are tobacco consumption, alcohol use, physical inactivity, and unhealthy diet(14). Population aging, globalization, and urbanization as well as nutritional factors have also been identified as determinants of NCDs prevalence across the world. Additionally, inherent factors such as age, genetic predisposition, gender, and race have been shown to influence the incidence of NCDs(15).

While some risk factors of NCDs such as obesity, tobacco use, unhealthy diet, etc. are modifiable, other risk factors such as age, gender, and genetic factors cannot be easily modified to reduce the susceptibility of individuals to NCDs. To reduce the incidence of NCDs, policies to address the social determinants of NCDs and limit exposure to modifiable risk factors for NCDs need to be formulated and implemented(16). In a bid to advance their economic interests; big fast-food, tobacco, and alcohol companies have accelerated the rise of NCDs through their aggressive advertisements and influence on the implementation of NCDs prevention and control strategies, particularly in LMICs. Some tactics employed by these companies include influencing policymakers to water down the implementation of strategies to regulate the advertisement and sale of their products, sponsoring and influencing research that promotes their business interests, and financing front groups that counter public health recommendations for the prevention and control of NCDs(17).

Tackling NCDs: Which Policies Can Produce Results?

Although tackling the NCDs has been quite daunting over the past few decades, there is overwhelming evidence showing that reducing exposure to the modifiable risk factors for NCDs is an overarching strategy to reduce the incidence of NCDs. Economic analysis of programmes to prevent NCDs have elucidated that though these interventions may appear

expensive in the short run, they are indisputably more cost-effective in the long run(2). Early detection and requisite management of the NCDs have also been shown to be key strategies to reduce the morbidity and mortality associated with NCDs.

A recent study reported that only about 25 countries (mostly high-income economies), as well as the Western Pacific and European regions are on track to achieve the NCDs-related SDGs targets(18). This indicates that most countries of the world need to prioritize NCDs prevention and control and review their strategies towards achieving a global victory against the NCDs. Furthermore, global and national governance frameworks need to be instituted to limit the influence of big fast-food, tobacco, and alcohol companies to the barest minimum and ensure that regulations to prevent and control NCDs are effectively implemented(17). For the battle against NCDs to be won on a global scale, all countries must back their commitment to reduce the prevalence of NCDs with strategic policies and decisive actions(4).

To place most countries on track to effectively tackle the NCDs, the following policy reforms are recommended:

- Enactment and enforcement of tobacco and alcohol taxes with a concurrent ban on their advertisement; in a bid to discourage harmful alcohol and tobacco use(19).
- Integration of NCDs management into primary healthcare services. This is fundamental as evidence shows that it is a cost-effective, equitable, and affordable strategy for reducing the morbidity and mortality associated with NCDs(20).
- Innovative healthcare financing mechanisms to increase domestic funding for the prevention and control of NCDs should be considered to guarantee the sustainability of efforts at tackling NCDs(10).
- Engagement in mass media campaigns to educate the population about risk factors of NCDs such as tobacco use, alcohol abuse, unhealthy diet, and physical inactivity (21).
- Mobilization of resources to ensure that high-risk individuals access routine cancer screening and receive vaccination against hepatitis B and human papillomavirus to reduce their chances of having liver and cervical cancer respectively(22).

The policy suggestions outlined above are some of the “best-buy” strategies recommended by the World Health Organization (WHO) as cost-effective and reliable means through which NCDs can be curtailed at the national level(23). The successful implementation of these policies to prevent and control NCDs would require leadership and accountability from the government and all stakeholders involved(24).

Conclusion

Globally, most nations have not fared very well in the battle to prevent and control NCDs hence a concerted multilevel and multi-sectoral approach with strategic policy implementation is required(19). All countries should strive to adopt the “best-buy” policy recommendations and take active steps to implement them in the context of their unique settings. Universal health coverage with people-centred primary healthcare would make healthcare for NCDs more affordable and accessible, leading to a decline in the morbidity and mortality caused by

NCDs(22). Decisive action must be taken to stem the rising tide of NCDs in all countries, as the cost of inaction is astronomically greater than the cost of actions needed to tackle NCDs(4).

References

1. Kathirvel S, Thakur Rapporteurs J. Sustainable development goals and noncommunicable diseases: Roadmap till 2030 – A plenary session of world noncommunicable diseases congress 2017. Int J Noncommunicable Dis. 2018;3(1):3.

2. Allen LN. Financing national non-communicable disease responses. Glob Health Action. 2017 Jan;10(1):1326687.

3. WHO. Time to deliver: report of the WHO Independent High-level Commission on Noncommunicable Diseases. Geneva: World Health Organization; 2018. Licence: CC BY-NCSA 3.0 IGO. WHO. World Health Organization; 2018.

4. World Health Organization (WHO). Global Action Plan for the Prevention and Control of NCDs 2013-2020. WHO. World Health Organization; 2013.

5. Sivaramakrishnan K, Parker RG. The United Nations High Level Meeting on the Prevention and Control of Noncommunicable Diseases: A missed opportunity? Vol. 102, American Journal of Public Health. American Public Health Association; 2012. p. 2010–2.

6. Bennett JE, Stevens GA, Mathers CD, Bonita R, Rehm J, Kruk ME, et al. NCD Countdown 2030: worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4. Vol. 392, The Lancet. Elsevier; 2018. p. 1072–88.

7. Joshi A, Mohan K, Grin G, Perin DMP. Burden of Healthcare Utilization and Out-of-Pocket Costs Among Individuals with NCDs in an Indian Setting. J Community Health. 2013 Apr;38(2):320–7.

8. Muka T, Imo D, Jaspers L, Colpani V, Chaker L, van der Lee SJ, et al. The global impact of non-communicable diseases on healthcare spending and national income: a systematic review. Eur J Epidemiol. 2015 Apr;30(4):251–77.

9. Islam SMS, Purnat TD, Phuong NTA, Mwingira U, Schacht K, Fröschl G. Non Communicable Diseases (NCDs) in developing countries: A symposium report. Global Health. 2014 Dec;10(1):81.

10. Banatvala N, Akselrod S, Webb D, Sladden T, Hipgrave D, Schneidman M. Actions needed to prevent noncommunicable diseases and improve mental health. Bull World Health Organ. 2019 Feb;97(2):75-75A.

11. Kluge HHP, Wickramasinghe K, Rippin HL, Mendes R, Peters DH, Kontsevaya A, et al. Prevention and control of non-communicable diseases in the COVID-19 response. Vol. 395, The Lancet. Lancet Publishing Group; 2020. p. 1678–80.

12. Thakur J, Garg C, Menabde N, Prinja S, Mendis S. Social and Economic Implications of Noncommunicable diseases in India. Indian J Community Med. 2011 Dec;36(5):13.

13. Jakovljevic M, Jakab M, Gerdtham U, McDaid D, Ogura S, Varavikova E, et al.

Comparative financing analysis and political economy of noncommunicable diseases. Vol. 22, Journal of Medical Economics. Taylor and Francis Ltd; 2019. p. 722–7.

14. Islam SMS, Purnat TD, Phuong NTA, Mwingira U, Schacht K, Fröschl G. Non-communicable diseases (NCDs) in developing countries: a symposium report. Global Health. 2014 Dec;10:81.

15. Manning K, Senekal M, Harbron J. Non-communicable disease risk factors and treatment preference of obese patients in Cape Town. African J Prim Heal care Fam Med. 2016 Jun;8(1):e1–12.

16. Kim HC, Oh SM. Noncommunicable diseases: current status of major modifiable risk factors in Korea. J Prev Med Public Health. 2013 Jul;46(4):165–72.

17. Reeve B, Gostin LO. "Big" food, tobacco, and alcohol: Reducing industry influence on noncommunicable disease prevention laws and policies comment on "addressing ncds: Challenges from industry market promotion and interferences. Vol. 8, International Journal of Health Policy and Management. Kerman University of Medical Sciences; 2019. p. 450–4.

18. Martinez R, Lloyd-Sherlock P, Soliz P, Ebrahim S, Vega E, Ordunez P, et al. Trends in premature avertable mortality from non-communicable diseases for 195 countries and territories, 1990–2017: a population-based study. Lancet Glob Heal. 2020 Apr;8(4):e511–23.

19. Hunter DJ, Reddy KS. Noncommunicable Diseases. N Engl J Med. 2013 Oct;369(14):1336–43.

20. Varghese C, Nongkynrih B, Onakpoya I, McCall M, Barkley S, Collins TE. Better health and wellbeing for billion more people: Integrating non-communicable diseases in primary care. BMJ. 2019 Jan;364.

21. Tabassum R, Froeschl G, Cruz JP, Colet PC, Dey S, Islam SMS. Untapped aspects of mass media campaigns for changing health behaviour towards non-communicable diseases in Bangladesh. Vol. 14, Globalization and Health. BioMed Central Ltd.; 2018. p. 7.

22. Nugent R. Preventing and managing chronic diseases. BMJ. 2019 Jan;364:l459.

23. World Health Organization. Tackling NCDs: "best buys" and other recommended interventions for the prevention and control of noncommunicable diseases. Geneva PP - Geneva: World Health Organization; 2017.

24. Magnusson RS, McGrady B, Gostin L, Patterson D, Taleb HA. Legal capacities required for prevention and control of noncommunicable diseases. Bull World Health Organ. 2019 Feb;97(2):108.

JOURNAL OF HEALTH POLICY AND ECONOMICS

Nuha Bazeer. Only as Healthy as the Unhealthiest: how the COVID-19 pandemic has renewed the call for Global Health System Strengthening. Journal of Health Policy and Health Economics. 2021; 1(1)

Only as Healthy as the Unhealthiest: how the COVID-19 pandemic has renewed the call for Global Health System Strengthening

Nuha Bazeer, MSc[1,2]

[1] Department of Health Policy, London School of Economics and Political Science, London, UK, nuhabazeer@gmail.com
[2] London School of Hygiene and Tropical Medicine, London, UK

Executive Summary

- The geographic spread of the COVID-19 pandemic has had severe health, economic and political consequences, exposing the state of health systems across the globe.
- Progress in Health System Strengthening can lead to better health when health systems are responsive and resilient, such that they can absorb the shock of the current pandemic, and adapt to changing health needs.
- Global Governance for Health is urgently required given the disproportionate impact COVID-19 may have had on countries with poorer health systems with lower resilience and capacity.
- Sizeable vaccine purchases by wealthier OECD countries have exposed the divide between OECD countries and LMICs through inequitable vaccine distribution, prompting greater concern for global recovery.

Keywords: COVID-19; Health System Strengthening; Global Governance; Health Policy; Global Health; Vaccine Equity

Introduction

The shifting epicentre and subsequent geographic spread of the COVID-19 pandemic throughout 2020 raised international concern over a mainstay of national debate: the state of health systems. Comparisons between the rapid response and surveillance witnessed in the Far East, to the varied approaches of Europe (Italy, Spain, and Germany); and the somewhat tentative response of the UK and USA, have revealed more than just quantitative differences in national health systems (1).

Health System Strengthening (HSS) has predominantly been viewed as an agenda item for Low- and Middle- Income Countries (LMICs), defined by WHO as the identification and implementation of policies and initiatives to improve health system responsiveness, coverage, quality, access, and efficiency (2). Yet the unprecedented scale of the pandemic within High Income Countries (HICs) has exposed the true extent of health interdependence in our globalised society, from trade and migration, to education and investment. Just as the 2014-2016 Ebola epidemic demonstrated the consequences of health systems at their breaking

point, the COVID-19 pandemic has renewed calls for global HSS on the basis of three items: responsiveness and resilience; global governance for health; and equitable vaccine distribution.

Responsiveness and Resilience

Alongside health and financial fairness, WHO identifies responsiveness as a key objective of health systems; achieving better health by addressing the legitimate expectations of a population with appropriate responses (3). In 2014, the shock of the Ebola outbreak to existing inadequate health systems within West Africa (4) revealed the need for health systems resilience (5): the anticipation of, and adaptation to changing needs via effective interventions (6), and the ability to absorb such shocks. Following the COVID-19 outbreak, analysis of the International Health Regulations (IHR) State Party Annual Reporting (SPAR) tool found that as of 2018, 57% of 182 countries were operationally ready with the highest level of national health security capacity to prevent, detect, and control an infectious disease outbreak (7). Though this suggests possible effective responses to the current outbreak, the analysis also found that 76% of countries within the South East Asian and African WHO regions had low levels of operational readiness. Within OECD countries, concerns also exist over access and coverage: over a fifth of all OECD health care expenditure is in the form of out-of-pocket payments (OOPs), with over 28 million uninsured Americans (8) potentially foregoing timely health system interactions due to poor financial protection.

In the early months of 2020, many national health systems raced to prevent and mitigate the effects of large-scale community transmission as witnessed in China, Iran, Italy and Spain (9), mobilising high levels of health resources to detect and treat COVID-19 cases. The reallocation of resources has not been without an opportunity cost however, as health systems have struggled to balance the maintenance of essential services, exposing the finite nature of health system capacity. Globally, health systems have struggled with excess demand (diagnostics, hospitalisations, and critical care treatment) and limited supply (diagnostics, personal protective equipment, ventilators, fewer health workers due to infections, lower ward capacity). Long-term management of this surge in activity will require more than just swift public health measures of social distancing and handwashing, with varied policy responses for HSS across 4 fronts (Table 1).

Table 1 OECD Strategies for Health System Strengthening

Priority	Policy	Examples(8)
Access	► Waive user-charges for care and treatment related to COVID-19 to improve coverage and equity ► Emergency funds for health care systems to manage excess demands ► Legislation to reduce risk of infection and ensure long-term care	► US: Legislation passed on 18 March 2020 to provide COVID-19 diagnostic testing with no OOPs ► UK: £5bn emergency fund for NHS, social care and public services has been provided (albeit with few specifics) ► Germany: COVID-19 Hospital Relieve Act passed on 25 March 2020 for funding and liquidity of hospitals including subsidisation and compensatory payments
Supplies **(8)**	► Management and review of both national and international supply chains for diagnostics, ventilators and essential medicines	► European Commission: pre-existing Joint Procurement Agreement with Member states to enable joint purchasing

Staff **(8)**	► Provision of sufficient personal protection equipment (PPE), mental health support & child/social support ► Task-shifting of community workers and mobilisation of inactive/retired health workers & students nearing ends of studies ► Reallocation of health workers to more adversely affected areas	► France, Italy, Spain, UK: ensure health workers have sufficient/priority childcare options ► France: deploying the "sanitary reserve" ("réserve sanitaire") for temporary increase in staffing ► UK: mobilising retirees/inactive health workers for temporary increase in staffing
Space **(8)**	► Optimising healthcare facilities to increase critical care capacity ► Utilisation of telehealth or online triage as a first point-of-contact strategy and for better patient management ► Postponement of non-essential services.	► France, UK: repurposing of army camps and creation of temporary hospitals such as the NHS Nightingale Hospital ► Germany: daily online updates on available intensive care capacity to support doctors in identifying treatment availability. Use of a web-based application for patient assessment "CovApp" ► Italy, UK: delaying non-urgent (elective) care

Global Governance for Health

On 30th January 2020, WHO determined a Public Health Emergency of International Concern (PHEIC), bringing expectations of intensified preparedness with hopes for 'coordination, cooperation, and global solidarity' (10). What transpired since is perhaps less pleasant: from the distal erasure of almost all financial gain since the 2008 Financial Crisis, to the deserted cities and rising death tolls of neighbouring countries, and the proximate panic buying and empty supermarkets. At the height of these social distancing measures, the COVID-19 pandemic has offered a rather rude awakening to the extent of globalisation in our society and its fundamental reliance on strong and responsive health systems. Frenk *et a*l conceptualises Globalisation and Health as the international transfer of health risks; cross-border 'movements of people, products, resources, and lifestyles' (11). This presents 3 main governance challenges: sovereignty, accountability, and cross-sector interdependence. While in recent years, strong economic growth has emboldened inward-looking politics with enigmatic leaders arguing for protectionism, the political signal (10) of the PHEIC has transcended national health systems, echoing firmly that countries are only as healthy as the unhealthiest. Effective tackling of the pandemic will thus require global health system responses to demonstrate collective action via legitimate and monitored intergovernmental organisations, as well as consideration of the effects on interrelated policy areas, such as the environment, trade, migration and security.

The disproportionate effects of the COVID-19 pandemic have greatly emphasised the unequal distribution of wealth and health risks globally. Countries with less developed health systems, such as Mexico and Peru (12), have suffered higher levels of excess mortality as a result of weaker health infrastructure, lower health system capacity, and higher levels of respiratory infections (13). Countries with vulnerable populations and conflict zones – such as those the UN sought $2bn for – have also suffered rapid transmission due to overcrowding, scaled back humanitarian presence, and limited access to basic sanitation (14). However, health systems with limited capacity and ineffective policy responses are not only limited to those less developed, and in the face of rising infections and death tolls, the UK has joined South Africa and Brazil in recording a new, more transmissible variant (15). While the rapid launch of the COVID-19 Health System Response Monitor (HSRM) across the WHO European Region (9), in April 2020 is highly commendable, there must be intensified surveillance of health systems

evidence globally, so as to detect new variants, strengthen capacity and improve responsiveness accordingly.

Equitable Vaccine Distribution

As preliminary efficacy data trickled in by the end of November 2020 (16), the long-awaited news of COVID-19 vaccines and the promise of a return to normality soon arrived, manifesting in global stock market booms (17). Not soon after the release of this news from Pfizer/Biontech, Moderna, and Oxford/Astra Zeneca (18) however came the pertinent question: which populations would get vaccinated first? In much the same way that OECD countries demonstrated substantial financial responsiveness to the pandemic early on, their efforts in purchasing vaccine doses - sometimes pre-ordering over 3 doses per member of their population – has exposed stark differences amongst global health systems (16). Where wealthier countries have had the advantage of negotiating advance purchase agreements, low vaccine supplies are greater felt by LMICs, increasingly reliant on contributions from COVAX, a partnership between Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI) and WHO, tasked with equitable and fair vaccine distribution (18). In turn, COVAX relies on global collaboration to 'support the research, development and manufacturing of a wide range of COVID-19 vaccine candidates and negotiate their pricing' allowing LMICs to benefit from the collective purchasing power of two-thirds of the world (19).

Despite these aspirations, as of 8th January 2021, of the 42 countries who had rolled out national vaccine programs, HICs accounted for 36 while Low Income Countries (LICs) accounted for none (20). Such divergences could not come at a deadlier time, warned the WHO Director General, where the arrival of new variants demonstrate desperate survival attempts by the virus, coupled with the risk of vaccine nationalism threatening equitable vaccine distribution and jeopardising the safety of all countries (20). Though COVAX has estimated the cost of its vaccination target of 2 billion doses by the end of 2021 at US $5 billion, it has also estimated that the current pandemic has cost the global economy at least US $375 billion every month (19). Ultimately, the race to vaccinate populations will require a committed and equitable multilateral effort with clear recognition of the indirect protection afforded to national populations through international vaccination (18).

Limitations and Conclusions

The challenges and consequences of COVID-19 are unprecedented; with many wealthy nations implementing large-scale emergency domestic stimulus packages to cope with social and economic disruptions. The initial responsiveness of OECD health systems demonstrated through adaptative policies (Table 1) shed light on the disparities between countries with poorer infrastructure more exposed to the world trade cycle due to manufacturing and commodity-exporting economies than services. Though fears of insurmountable economic costs caused by the pandemic have often wrestled with appropriate health policy responses, countries who have been successful with the zero-COVID approach, such as New Zealand, have not had to endure high death tolls and periods of economic uncertainty. Improvements in responsiveness will require large financial support from intergovernmental organisations, such as the WHO COVID-19 Solidarity Fund or the releasing of approved grant funding to fight COVID-19 by the Global Fund (21). The efforts of the WHO, GAVI, and CEPI through COVAX in securing sufficient vaccine doses for equitable distribution are recognised as supporting Global HSS but is also reliant on pharmaceutical companies to make their vaccines available at affordable prices for greater vaccination impact in LMICs, as AstraZeneca has done (16).

While Global Governance for Health and robust health information management systems (HMIS) will play an increasing role in the detection of new variants, there also needs to be strong political will, advocacy, and stronger regulations to uphold responsibility and accountability within the field of public health. Differences in health stewardship (such as initial denial of the severity of the virus in the US in early 2020 and perpetuation of a false dichotomy between health and the economy) have shown deep disparities in approaches to health. Unequal distribution of wealth and health risks across the globe, alongside the unprecedented nature of this pandemic, suggest now more than ever, that Global HSS is fundamental in improving health systems within countries with weaker health infrastructure and thus ensuring stronger resilience against future outbreaks globally. Though mass vaccination programmes will also attest to the responsiveness and resilience of individual health systems, without equitable vaccine distribution and sustained efforts in Global HSS, none will be safe until all are.

References

1. Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. Coronavirus pandemic (COVID-19). Our world in data. 2020.
2. Organization WH. World Health Organization Health Systems Strengthening Glossary. 2011.
3. De Silva A, Valentine N. A framework for measuring responsiveness: World Health Organization Geneva; 2000.
4. Hanefeld J, Mayhew S, Legido-Quigley H, Martineau F, Karanikolos M, Blanchet K, et al. Towards an understanding of resilience: responding to health systems shocks. Health policy and planning. 2018;33(3):355-67.
5. Blanchet K. Thinking shift on health systems: from blueprint health programmes towards resilience of health systems Comment on "Constraints to applying systems thinking concepts in health systems: A regional perspective from surveying stakeholders in Eastern Mediterranean countries". International journal of health policy and management. 2015;4(5):307-9.
6. Mirzoev T, Kane S. What is health systems responsiveness? Review of existing knowledge and proposed conceptual framework. BMJ Global Health. 2017;2(4):e000486.
7. Kandel N, Chungong S, Omaar A, Xing J. Health security capacities in the context of COVID-19 outbreak: an analysis of International Health Regulations annual report data from 182 countries. The Lancet. 2020;395(10229):1047-53.
8. OECD. Beyond Containment: Health systems responses to COVID-19 in the OECD. OECD; 2020.
9. WHO European Region. Strengthening the health system response to COVID-19 - Recommendations for the WHO European Region - Policy brief Geneva: World Health Organisation; 2020.
10. Zarocostas J. What next for the coronavirus response? The Lancet. 2020;395(10222):401.
11. Frenk J, Moon S. Governance Challenges in Global Health. New England Journal of Medicine. 2013;368(10):936-42.
12. The Economist. Tracking covid-19 excess deaths across countries 2021 [Available from: https://www.economist.com/graphic-detail/coronavirus-excess-deaths-tracker.
13. The Economist. Tracking covid-19 excess deaths across countries 2020 [Available from: https://www.economist.com/graphic-detail/2020/07/15/tracking-covid-19-excess-deaths-across-countries.

14. United Nations. Funding the fight against COVID-19 in the world's poorest countries 2020 [Available from: https://www.un.org/en/un-coronavirus-communications-team/funding-fight-against-covid-19-world's-poorest-countries.
15. Mahase E. Covid-19: What new variants are emerging and how are they being investigated? BMJ. 2021;372:n158.
16. Mullard A. How COVID vaccines are being divvied up around the world 2020 [Available from: https://www.nature.com/articles/d41586-020-03370-6.
17. BBC. FTSE 100 and Dow Jones jump on second Covid vaccine hopes 2020 [Available from: https://www.bbc.co.uk/news/business-54959414.
18. Burki T. Equitable distribution of COVID-19 vaccines. The Lancet Infectious Diseases. 2021;21(1):33-4.
19. Berkley S. COVAX - explained 2020 [Available from: https://www.gavi.org/vaccineswork/covax-explained.
20. CNBC. WHO warns countries are helping Covid thrive through inequitable vaccine distribution 2021 [Available from: https://www.cnbc.com/2021/01/08/who-warns-inequitable-vaccine-distribution-helps-covid-thrive.html.
21. The Global Fund. COVID-19 Situation Report – 31 March 2020. The Global Fund; 2020.

JOURNAL OF HEALTH POLICY AND ECONOMICS

Jasmine Cassy Mah, Aparna Kulkarni, Rebecca Forman, Elias Mossialos. Social and Physical Environment Disparities Contribute to Mortality Outcomes during the COVID-19 Pandemic in the United States. Journal of Health Policy and Economics. 2021; 1(1).

Social and Physical Environment Disparities Contribute to Mortality Outcomes during the COVID-19 Pandemic in the United States

Jasmine Cassy Mah MD, MSc[1,3], Aparna Kulkarni MD MSc[2], Rebecca Forman MSc[3], Elias Mossialos MD PhD[3,4]

[1] Dalhousie University, QEII Health Sciences Centre, Halifax, NS, Canada;
[2] Zucker School of Medicine at Hofstra/ Northwell, Cohen Children's Medical Center, New York, USA;
[3] London School of Economics and Political Sciences, Department of Health Policy, London, UK;
[4] Institute of Global Health Innovation, Imperial College London, London, UK

Abstract

Demographic patterns suggest that fatalities from COVID-19 are disproportionately high in Black and Hispanic communities in the United States. This short commentary postulates that disparities in social & economic status and physical environment, with their resultant inequities, may also be contributing to high fatality rates. The top ten counties in the United States with the highest COVID-19 fatalities (as of January 1, 2021) from the Johns Hopkins University Coronavirus resource center were compared to county-level population size, racial demographics, socioeconomic status and physical environment factors. We conclude by recommending a multi-pronged response approach with coordination between health systems and local governments using county-level data to identify social disparity 'hotspots' where extra resources can be allocated and targeted interventions can be implemented.

Keywords: COVID-19; Social Determinants of Health; Socioeconomic Status; Physical Environment; Vulnerable Populations

Background

Numerous clinical factors are now recognized as risk factors for COVID-19 mortality. (1)(2) Concurrently, demographic patterns suggest that fatalities are disproportionately high in non-Hispanic Black and Hispanic (BH) communities in the United States (US). (3-5) We hypothesized that disparities in social & economic status (SES) and physical environment (PE), with their resultant inequities, may be contributing to the high fatalities. These factors have been known to contribute to the upstream determinants of many clinical outcomes in non-COVID-19 circumstances. Therefore, we performed a rapid analysis of the ten counties with the most COVID-19 deaths with their SES and PE rankings, population size and racial composition to test this proposition. (6)

Methods

We examined a total of ten US counties with the highest COVID-19 fatalities (as of January 1, 2021) from the Johns Hopkins University Coronavirus resource centre. (4) County-level population size, racial demographics, SES and PE factors from the publicly available Robert Wood Johnson Foundation (RWJF) County Health Rankings (5) were compared to fatality case numbers.

Results

Among the counties with high fatalities, Cook (IL), Harris (TX), Wayne (MI), Miami-Dade (FL), Bronx (NYS), Maricopa (CA), Kings (NY) and Los Angeles (CA) have the poorest SES or PE rankings in their respective states (Figure 1). All counties except one (Queens) are among the worst counties based on SES and PE ranking in their respective states (SES and PE scores >50). Between 44-86% of the populations in these counties are BH. Additionally, among all counties examined, these have the highest population size (Figure 2). Los Angeles, the county with the most deaths in the US, has both a high BH population percentage (57%) and the largest population (> 10 million) among all counties examined. While Queens and NY (Manhattan) have mid-range SES and PE scores (QU 37; 39 & NY 50; 52, respectively) they have some of the highest population sizes in New York State.

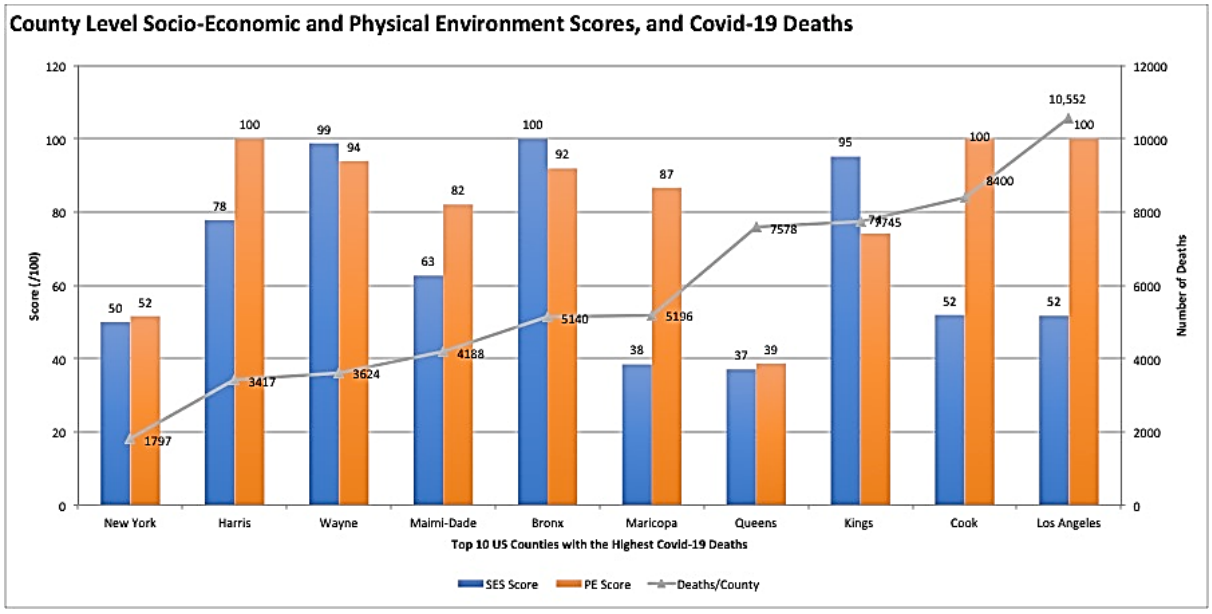


Figure 1: Social & Economic (SE) and Physical Environment Scores (PES) in Ten Counties with the Largest Numbers of COVID-19 Fatalities[1]

[1] All data is current as of January 1, 2021. In order to standardize county-level rankings between different states, their SES and PE scores were scaled from 0-100 (higher numbers indicating worse scores). The RWJF rankings use county-level measures from a variety of national and state data sources (such as US census bureau, state education department, etc.) and combines them with scientifically-informed weights.[6] Some metrics that contribute to the SES rankings include education level (high school/college), unemployment status, presence of income inequality, single parent households and social associations. The PE score is derived from factors such as air pollution, housing problems, long commute times and more. A score of >50 suggests a county's SES or PE is among the worst performing (bottom half in ranking) counties in the state for those factors; a score of 100 indicates the county is the worst ranking county in the state for SES or PE.

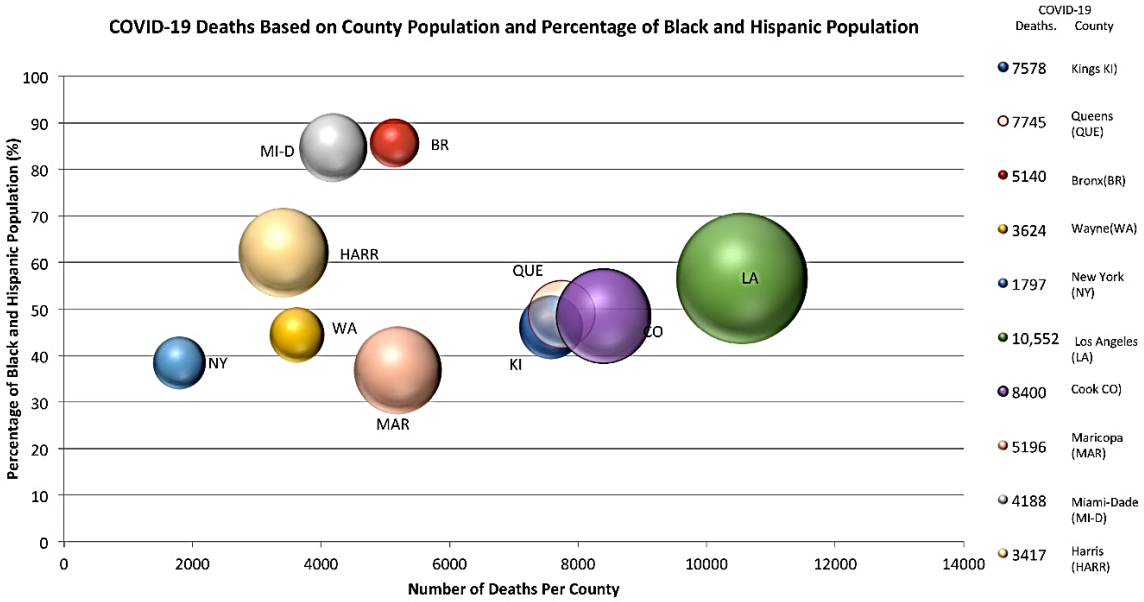


Figure 2: Total Number of COVID-19 Deaths/County against the Proportion of non-Hispanic Black and Hispanic Populations and the County Population in Ten US counties with the Largest Number of COVID-19 Deaths[2]

Discussion

- While this rapid analysis was limited by its ecological design and the unavailability of granular demographic data for COVID-19 fatalities, this evidence suggests that US counties with high COVID-19 fatalities have a combination of poor SES and PE factors, high populations and proportions of BH populations.

- SES and PE factors predispose communities to increased social vulnerability (decreased reserve to respond to a hazard) and higher rates of medical conditions, which in turn may make people more susceptible to COVID-19 mortality. It is likely that poorly-educated and non-English speaking communities have higher risks of being exposed to the illness if they lack sufficient knowledge about the pandemic. Large population sizes, poor physical environments and inter-generational living dwellings may also contribute to rapid spread of infection and subsequent death in these high-risk communities.

- A multi-pronged approach with coordination between health systems and local governments is needed. Electronic medical records can be used by health systems to identify patients with high-risk clinical factors and flag SES/PE risk factors. Local governments can simultaneously use census-level language and race data to pinpoint hotspots where resources should be re-directed. Measures such as aggressive door-to-door testing, contact tracing and education campaigns with appropriate language translation services by community and public health workers are needed. To help prevent

[2] Proportion of non-Hispanic Black and Hispanic Population in percentage of total county population. Size of bubble is proportionate to population size in the county.

delays in access to physicians in these high-risk communities, health systems could expand telehealth access through local vendors. At this moment, the SES and PE factors are impacting access to and uptake of effective vaccines and therapeutics and distribution to these high-risk communities should be prioritized.

- The COVID-19 pandemic presents an opportunity to address social inequities in high-risk communities to prevent further large-scale fatality and resurgence. Using county level data, local and state governments can identify social disparity 'hotspots' where they can allocate extra resources and implement targeted interventions for vaccine distribution. Targeted campaigns in these counties is a necessity to provide accurate public health messaging, designed to resonate with predominantly Black and Hispanic communities or communities with poor SES or PE scores. As granular fatality data becomes available, we can gain a greater insight into the contributing death factors and adjust interventions and policies accordingly.

References

1. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA : the journal of the American Medical Association* 2020 doi: 10.1001/jama.2020.5394 [published Online First: 2020/04/07]

2. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA : the journal of the American Medical Association* 2020 doi: 10.1001/jama.2020.6775 [published Online First: 2020/04/23]

3. Health NYSDo. NYS COVID19 tracker 2020 [cited 2020 April 19, 2020]. Available from: https://covid19tracker.health.ny.gov/views/NYS-COVID19-Tracker/NYSDOHCOVID-19Tracker-Fatalities?%3Aembed=yes&%3Atoolbar=no&%3Atabs=n accessed April 19 2020.

4. University JH. JHU Coronavirus US map 2020 [Available from: https://coronavirus.jhu.edu/us-map accessed April 19 2020.

5. Yancy CW. COVID-19 and African Americans. *JAMA : the journal of the American Medical Association* 2020 doi: 10.1001/jama.2020.6548 [published Online First: 2020/04/16]

6. Foundation RWJ. United States County Health Rankings 2020 [cited 2020 April 19, 2020]. Available from: https://www.countyhealthrankings.org accessed April 19 2020.

JOURNAL OF HEALTH POLICY AND ECONOMICS

J. Sam Meyer. Shouldering the Burden of Our Neighbours: How Exemptions in US Tax Law affect Global and Domestic Health Philanthropy. Journal of Health Policy and Economics. 2021; 1(1).

Shouldering the Burden of Our Neighbours: How Exemptions in US Tax Law affect Global and Domestic Health Philanthropy

J. Sam Meyer, MSc[1,2,3]

[1] Columbia University in the City of New York, New York, United States of America, j.sam.meyer@columbia.edu
[2] Department of Health Policy, London School of Economics and Political Science, London, UK
[3] Tel Aviv University School of Medicine, Tel Aviv, Israel

Abstract

Changes in healthcare have historically been driven by an equilibrium between two key institutional actors: the government and the private sector. This symbiotic relationship has offered advantages to both sides, as private foundations supplemented the resources and attention given to areas of public concern that were beyond the government's reach, and the government reciprocally exempted such charitable giving from taxes and afforded them the freedom to donate where they see fit. However, as the influence of private foundations only grows, their shift from a focus on domestic issues to global health may inevitably shift this equilibrium away from government benefit. Can upward trends in global health outcomes explain the downward trends in domestic ones, and if so, are tax exemptions on charitable donations responsible for the steep decline in US healthcare? In this paper, I will trace the tax exemptions in charitable giving that span from their roots in the autocratic rulers of 15th Century Europe, through their evolution to the democratic governments of today. I will analyse the public health effects of expanding tax-deductible status to organizations engaged in international rather than domestic activities. These tax exemptions are enabled by clause *501(c)(3),* a law enforced by the US Internal Revenue Service (IRS). As case studies, I will analyse the Ford Family and Bill Gates, two of today's key actors in global health, who divested from the corporations they founded through their charitable foundations. Despite a glaring decline in US health outcomes, both foundations continue to invest in projects outside the US. In light of current calls for reform, quintessential questions of biopolitics emerge, namely, should one prioritize human life differently within their borders than beyond them? Should these priorities be different for government versus private, non-state actors?

Keywords: Health Policy; Philanthropy; Tax Law; Politics; Global Health, US

"If, however, there is a needy person among you, one of your kinsmen in any of your settlements in the land that the LORD your God is giving you, do not harden your heart and shut your hand against your needy kinsman. Rather, you must open your hand and lend him sufficient for whatever he needs For there will never cease to be needy ones in your land, which is why I command you: open your hand to the poor and needy kinsman in your land."

-Deuteronomy 15. 7-8,11

Introduction

When Elizabeth Warren rolled out her Billionaire Wealth Tax Plan on her presidential campaign trail in 2020—a plan that would have placed a 2% tax on all assets worth over $50 billion—some billionaires panicked and most headed to their charities (1). As America approached federal elections in November 2020, candidates searched for means to fund progressive social issues such as education and housing programs and most prominently, national healthcare schemes. Increasingly, candidates have pointed to the modern-day titans of our economies to fund these programs, promising to reform tax codes and initiate systemic change.

Changes in healthcare have historically been driven by an equilibrium between two key institutional actors: the government and the private sector. This symbiotic relationship has offered advantages to both sides, as private foundations supplemented the resources and attention given to areas of public concern that were beyond the government's reach, and the government reciprocally exempted such charitable giving from taxes, and afforded them the freedom to donate where they see fit. However, as the influence of private foundations only grows, their shift from focus on domestic issues to global health may inevitably shift this equilibrium away from government benefit. Can upward trends in global health outcomes explain the downward trends in domestic ones, and if so, are tax exemptions on charitable donations responsible for the steep decline in US healthcare?

In this paper, I will trace the tax exemptions in charitable giving that span from their roots in the autocratic rulers of 15th Century Europe, through their evolution to the democratic governments of today. I will analyse the public health effects of expanding tax-deductible status to organizations engaged in international rather than domestic activities. These tax exemptions are enabled by clause 501(c)(3), a law enforced by the US Internal Revenue Service (IRS). As case studies, I will analyse the Ford Family and Bill Gates, two of today's key actors in global health, who divested from the corporations they founded through their charitable foundations.

Despite a glaring decline in US health outcomes, both foundations continue to invest in projects outside the US. In light of current calls for reform, quintessential questions of biopolitics emerge, namely, should one prioritize human life differently within their borders than beyond them? And, should these priorities be different for government versus private, non-state actors?

Charitable Tax Deductions: History and Law

The status of tax exemptions for philanthropies and charitable institutions in America today is an evolutionary product of hundreds of years of western tax law. As early as the 15th Century, English landowners bequeathed their land to trusts owned by the Church in order to avoid feudal tax. Under Queen Elizabeth I's reign at the turn of the 16th Century, British Parliament enacted a Charitable Corporation Act (1597) and the Statute of Charitable Uses (1601), which provided specific charitable institutions such as hospitals and poverty relief funds with exemptions from government charges, and allowed tax-free property transfers from individuals to various social service agencies (2).

These exemptions were exported across the Atlantic and adopted by colonists in various states in America and eventually enacted on a national level. In 1863, the US Treasury Department enacted the exemptions, declaring, "income of literary, scientific, or other charitable institutions, in the hands of trustees or others, is not subject to income tax" (2). This ruling was upheld in various cases brought before the Supreme Court who was guided by the general principle that funds used to provide services that would ultimately be of value to the State, were subject to tax exemptions because these services offset expenditures from government institutions on a dollar-for-dollar basis. These state-valued programs included philanthropic gifts to religious, educational, medical, and social welfare institutions (3).

The end of the Civil War and the ushering in of the Industrial Revolution saw the widening of economic gaps in America and an outburst of the philanthropic movement. Entrepreneurial tycoons such as J.P. Morgan, Andrew Carnegie, Andrew W. Mellon, and John

D. Rockefeller disproportionately controlled vast amounts of the US economy and established private charities from the fortunes of the Gilded Age to efficiently distribute their accumulating wealth. Concurrently, as the US faced mounting national debt at the onset of the Great War, Woodrow Wilson signed the Underwood Tariff Bill of 1913 and the War Revenue Act of 1917 to raise national funds to support the war effort (2). These laws effectively introduced tiered income taxes to redistribute the tax-burden, successfully alleviating national debt, while serving to fund the war machine and other domestic social services. However, the government was eager to avoid disincentivizing ultra-wealthy individuals from continuing their philanthropic endeavours, which provided services to the public that ultimately replaced and saved Government dollars. Now taxing their income at exponentially higher rates, Congress added 100 percent deductions for their charitable gifts (2).

Codified into law, the ultra-wealthy began utilizing these deductions to shelter profits and thus remain in lower tax brackets. Over the last century, these tax codes have morphed into a series of legal loopholes as shrewd accountants sought out ways to maximize deductibles and maintain the trillion-dollar philanthropic industry in the US. The US Tax Reform Act of 1969 re-affirmed the practice of transferring stock and real estate holdings as gifts to charitable trusts and organizations classified under the 501(c)(3) statute. Today, this gifting of 'non-cash items,' termed a 170(c)(1), allows individuals to avoid taxation on capital gains within one's lifetime, and reduces inheritance and estate tax after death. The gifts can also be classified as 'itemized deductions' and thus can be further subtracted from taxable income during the calendar year in which they are donated. Moreover, once these assets are transferred to a 501(c)(3), the profits gained from their appreciation are only nominally taxed, allowing endowments to grow for years (3).

When these private foundations were established, their founders sought to bring their own professional expertise to provide services to the public, or even optimize existing services, in areas where the government could not. Thus, a limited number of charities satisfied the criteria necessary to obtain a 501(c)(3) status. In order to be eligible for charitable deductions from federal tax, gifts and organizations had to directly discharge public functions from the government. However, the current state of the law calls into question whether these gifts aptly fulfil their original purpose of supplementing government responsibilities and spawning values of altruism and benevolence, or whether it has been tarnished and instead become a mechanism of tax evasion and libertarian bias, two by-products of Neoliberalism (4).[1]

Today, there are over 1.8 million registered IRS-recognized tax-exempt organizations, and questions of their efficacy and their alignment with national issues have begun to emerge (5). The long-debated question of whether private individuals provide public services and charitable efforts more efficiently than the government is outside the scope of this paper. However, it is worth acknowledging the enormity of their holdings and noting the potential that these diverted dollars could contribute to furthering government priorities. Amounting to $5.79 trillion in assets and $410.02 billion in annual giving as of 2017, the otherwise taxable funds diverted from public coffers to private organizations have drawn increasing scrutiny as figures continue to rise (6). Furthermore, an amendment to the tax code in 1971 extended 501(c)(3) status to any organization that "conducts a part or all of its charitable activities in a foreign country," as long as it is dispensed by a domestic corporation (7). Thus, the diversion of taxable dollars is especially noteworthy, as increasingly, many of the charitable organizations in the US do not only benefit domestic causes, but also serve as intermediaries through which private individuals fund and support international religious, medical, humanitarian, educational institutions.

Foreign Charity by Private Citizens

In order to demonstrate the way in which funds are diverted from domestic causes towards international development in the health sector, in this section, I will analyse the activities of two leading philanthropic institutions in the US: The Ford Foundation and the Bill & Melinda Gates Foundation. [2]

It is important to note the mathematical limitations of this study as the actual tax filings of private individuals are not public record. Furthermore, the US Tax Code is cumbersome and convoluted and has been interpreted and sometimes distorted countless times by 'tax planners.' Therefore, throughout the paper, the total calculations of diverted tax dollars reflect rudimentary calculations based off the crude tax rates on individuals and their holdings prior to deductions from other sources of wealth in accordance with US tax law. These numbers serve as a hypothetical framework in which democratically elected governments are the sole authority to determine priorities, allocate funds, and execute public services, thus removing

[1] It is often cited that Neoliberalism emerged in post-WWII America, as a reaction to national socialism and the heavy hand government placed on all aspects of the economy through Franklin Delano Roosevelt's (FDR) New Deal, both to fuel the war machine and emerge from the Great Depression (8). Neoliberalism sought to bring market freedom and liberate the tightly regulated American economy, thus shifting power from authority and government to the American consumers.

[2] The author concedes that utilizing case studies, rather than a systematic literature review, cannot provide an all-encompassing nor definitive review of the practices of all 501*(c)(3).* However, by specifically selecting institutions that are amongst the largest in financial size and global influence, the author argues that through examining their practices, industry standards at large can be extrapolated.

the philanthropy of the private individual and the deductibles available to them. I believe that the qualitative power and importance of performing this study deeply resonate despite its quantitative weaknesses, and further the argument that a more precise, and mathematically sound analysis must necessarily follow.

Ford Foundation

Facing the frightening possibility of losing family control of Ford Motor Company due to insurmountable taxes on inheritance, the Ford Family innovatively divested from its company through gifting, and thus evaded taxes that would have contributed to public services. By 1924, the newly enacted estate and revenue taxes from 1913 and 1916 had reached 40% on estates exceeding $10 million (7). An aging Henry Ford was aware of the unprecedented challenges that such taxes would pose to his family, who hoped to retain control of the Ford Motor Company, the largest privately owned company in America at the time. In anticipation of the largest estate tax in American history, Roosevelt enacted the 1935 Revenue Act which raised taxes on estates above $50 million to 70% (7). However, the act retained existing tax exemptions for charitable organizations. Therefore, had Henry Ford simply bequeathed the company to his family in his will, the astronomical taxes incurred by the transmission of the company to his children would have forced the family to sell most of the stock and likely leave them no choice but to surrender voting control over the business. While the law caps the amount of income that individuals and corporations can claim as tax deductible at 20% and 5%, respectively, an estate or trust can deduct without limitation (2). Thus, Ford reclassified the stock in his estate into two tiers, 90% non-voting and 10% voting. This non-voting stock would be donated to charity, 100% deductible as an estate, and offset the taxes of the 10% of voting shares upon his death (7).

With this, The Ford Foundation was established in 1936 by Edsel Ford, then President of Ford Motor Company. The foundation's mandate was to allocate resources towards "scientific, educational, and charitable purposes, all for the public welfare." With an initial gift of $25,000, the foundation worked locally in the city of Detroit and in the greater state of Michigan, notably funding the Henry Ford Hospital (9). However, with the death of Edsel Ford in 1943, and Henry Ford in 1947, the family's careful tax manoeuvring sparked the foundation's growth overnight, rerouting the organization's focus from local to international causes.

In 1951 the 90% non-voting shares of Ford Motor Company, valued at $417 million or roughly $4 billion today, officially transferred to the foundation, making it the largest philanthropic organization in the world (7). With this growth came seismic change to the foundation's focus and seismic focus to the foundation. The US Treasury was effectively denied $2,854,239,340.74 in inheritance taxes from the founder of the largest industry in the country.[3] This money, instead of going to the government, pushed the foundation to prove its philanthropic promise and spend its vast holdings under the guidelines set forth by the 1935 Revenue Act.

However, instead of continuing to pursue the local agenda Henry Ford had practiced in his lifetime, the Gaither Study Committee, commissioned by the board of trustees to assess the foundation's holdings, recommended that the foundation shift to "an international philanthropy dedicated to the advancement of human welfare through reducing poverty and promoting democratic values, peace, and educational opportunity." Thus began the transformation of this

[3] This is based on the aforementioned 1935 Revenue Act which raised taxes on estates above $50 million to 70%. Therefore 70% of $417 million is roughly $2,854,239,340.74.

local Detroit foundation to an international organization, shifting its offices from Detroit and opening its first field office in New Delhi, India in 1952, followed by Pakistan, Burma, and Beirut, shortly after (7).

In 1951, the first year following this transformation, the Ford Foundation dispersed $28,237,380. Of these grants, $12,755,000, or 45%, was sent overseas to “underdeveloped areas,” making it the foundation’s largest program (7). In the McCarthy Era, when fear of anti-American, and specifically Communist, values pervaded all aspects of American culture, these grants came under fire. In 1954, Gathier, the president of the foundation at the time, testified before the Reece Committee, the United States House Select Committee to Investigate Tax-Exempt Foundations and Comparable Organizations. He argued that although nearly $35 million had been spent abroad, these activities “served the interests of the American people” (Duquette). While shifts in the foundation’s leadership over the years prompted fluctuations in the amount of funding it has allocated to international programs, global development, specifically in the field of reproductive and sexual health, has emerged as a top focus.

In 1987, the Foundation began combating the global AIDS pandemic, and since then, their financial distributions have swelled to over $29 million in 2010 alone. From 2006 to 2019, the Ford Foundation gave 20,135 grants to 6,050 grantees, totalling $6.975 billion. These grants allocated $479 million to organizations outside the US, and $1.6 billion dollars to sexual and reproductive health rights in particular (10).

The Bill & Melinda Gates Foundation

Like the Ford Family, since 1996, Bill Gates has consistently reduced his stake in Microsoft, going from a 24% to a 1.3% shareholder (11). Bloomberg Financial Services reports that in total, this has amounted to $45.3 billion in pay-outs (12). These holdings are classified as long-term capital gains, or gains on assets held for over one year, and, Washington State, Gates’s state of residence, does not impose state tax on capital (13). Thus, at an average Federal capital gains tax rate of 23.8%, Gates would have owed the Federal Government roughly $10,781,376,000 over the course of that time (14). However, as of 2017, Gates has gifted $35 billion to the Bill and Melinda Gates Foundation, utilizing the aforementioned itemized deductions defined in the tax code 170(c)(1) to effectively avert federal taxes on most of this liquidation (15).

In 2018, the Bill and Melinda Gates Foundation distributed just over $5 billion. Of these funds, $2,962,930,000 was allocated towards Global Health causes outside the US such as polio, vaccinations, family planning, child health, nutrition, and hygiene. The Foundation donated only $493 million to the US, none of which was directly earmarked towards public health causes (16). Concurrently, in 2018, Bill Gates’s net worth increased from $86 billion to $90 billion. As a US citizen, this gain of $4 billion, technically taxed at a crude 37%, would amount to $1.48 billion in annual revenue tax in 2018 alone (17).

As of December 10, 2019, Bill Gates’s total net worth was estimated at $110 billion, making him at the time the richest man in the world, and he has claimed publicly that over his lifetime, he has paid over $10 billion in taxes (18). Although this amount is far from insignificant and some might argue that Gates earned the freedom to allocate his money as he sees fit, one might also argue that this prerogative should only come into effect once he has paid the full amount he would owe in tax-obligations if these exemptions did not exist. This would first

enable the government to fund healthcare projects in the US first, and then allow Gates to pursue global health efforts at his will.

Global Health vs US Healthcare

As the largest contributor to global health, the US spent over $10 billion in health official development assistance (ODA) in 2016, equal to half of the total health ODA provided by members in the OECD (19). In 2019, Congress increased this figure to $11 billion in order to fund major global health projects such as The President's Emergency Plan for AIDS Relief (PEPFAR), which contributes bilaterally to the Global Fund and the Joint United Nations Programme on HIV/AIDS (UNAIDS) (6).

Paradoxically, while the US is the greatest donor to Global Health concerns in the OECD, it also has the worst domestic health outcomes. According to a report published in JAMA in 2018, life expectancy in the US is 78.8 years, compared with a mean of 81.7 in other countries (20). The US also has the worst outcomes in reproductive health, with the highest infant, neonatal, and maternal mortality rates. The US has the fewest physicians and hospital beds, and falls below the mean in annual physician consultations, possibly contributing to the highest number of avoidable hospital admissions for diseases like asthma and diabetes. The US had the highest level of horizontal inequity, defined as inequities stemming from non-inherent qualities like income and race. People in the US care have the lowest self-reported satisfaction with their health system, with 10%, or 27 million people, remaining uninsured and lacking coverage for their basic health care needs (20).

These disparaging health statistics provide a clear explanation for why healthcare was such a defining issue in the 2020 US election, specifically in the democratic party primary race. The Kaiser Family Foundation (KFF), a non-profit organization focusing on national health issues, has used its Health Tracking Poll to monitor the prevalence of healthcare in the national debate. The tracking system identified that 1 in 4 democrats or democratically leaning Americans, believe healthcare to be the most important issue in the primary (21). However, reform is not cheap and current overhauls such as Medicare For All are estimated to cost $20.5 trillion over the next 10 years (22). While then candidates Elizabeth Warren and Bernie Sanders argued over the technical components of its funding, both agreed that a large sum would come from taxing the richest Americans at rates between 1-8% for assets above $32 million as well as taxing capital gains annually for the top 1% (23). According to their campaign economists, these taxes on solid assets would generate $3 trillion and prevent the 'ultra rich' from evading taxes by diverting liquid funds to charities. However, this notable tax increase could disincentivize philanthropists from giving altogether, both domestically and internationally, and thus inadvertently reduce the annual $4 billion in private donations to global health organizations (24).

Conclusion

The intervention of private foundations in global development work in general, and in global health in particular, has produced significant dividends for mankind. For example, in the field of vaccines, the Global Alliance for Vaccine Immunization (GAVI), led by the Rockefeller Foundation and the Gates Foundation, has reduced the burden of communicable disease globally (25). Foundations and private citizens, especially celebrities, have brought critical attention and funds to global diseases like HIV/AIDS, tuberculosis, and malaria. The 'doing

good and talking about it' model, as coined by Rushton and Williams, has undoubtedly increased altruistic behaviour amongst the wealthy as philanthropic contributions continue to rise (26).

Private profit-making individuals often engage in non-profit activities for various reasons. In order to diversify to new markets and improve their reputations, private citizens will engage in acts of corporate responsibility, which tend to bolster workplace satisfaction while often producing financial dividends. These actors apply corporate strategies, models, and metrics to their charitable giving and focus on inputs, outcomes, and impact. While the early philanthropists of the Industrial Era sought to simply dole out charity to alleviate the symptoms of poverty and provide social services to the public, today's givers focus on dissecting the root causes of a problem and introducing systemic change through science and technology (26).

With fewer stakeholders, less accountability, and more funds, private foundations have been able to set their own agendas and often bring more efficient and innovative responses to global health challenges. For example, the Gates Foundation's Malaria Atlas Project shifted from an approach which simply increased the volume of malaria drugs administered to African nations. Instead, they employed Microsoft technology to build road maps and identify malaria hot zones into distinguishable geographic treatment targets (26). Unlike governments, who are bound by a mandate to react immediately to outbreaks and disasters, private foundations have the luxury of taking a step back and looking at global health issues from a proactive, microscopic perspective. While the work of private foundations in global health has drawn criticism for its ability to exert power and set governmental agendas, these discussions are beyond the scope of this paper. However, it is worth questioning whether many US philanthropists and their foundations should have blanket freedom to tackle to the greater world's most pressing problems while ignoring, or underfunding, the significant domestic health crisis facing the US, especially when the funds used toward these projects comes from money that one could claim should have been paid in taxes to the United States government.

Whereas Biblical connotations have traditionally prioritized the needs of a person's neighbour above those outside of their geographic periphery, the current age of unprecedented globalization may be dissolving the lines between neighbour and outsider. Historically, even as recently as the McCarthy Era, loyalties belonged first and foremost to a citizen's government and fellow citizens. Yet, the globally-focused approach to healthcare discussed above may reflect a deeper change in the way the modern Western World has come to value human life. It is possible that wealthy American philanthropists consider themselves citizens of the world and of the US in equal parts, and wish to provide globally in order to compensate for the disparities their global neighbours face. Private foundations may value lives in and outside of the United States equally; however, given the widespread deficits in healthcare affecting hundreds of millions of people in the developing world, their apparent preference for donating to global causes is proportionate to metrics such as the Global Burden of Disease, and thus more cost effective. While we have demonstrated the failures of the US government to adequately provide for the health of its citizens, the gaps in the developing world are exponentially greater. A direct comparison of the unaddressed healthcare needs in the US versus these countries is warranted, but it would be impossible to determine that a life in one country is inherently more valuable than a life somewhere else. Although the government must undoubtedly prioritize the protection of its own constituents, particularly at the time of elections, citizens should have the prerogative to look beyond these borders. In light of this, perhaps a revaluation of the balance between the two is necessary to ensure an effective approach to tackling the needs of people both domestically and internationally.

References

1. Democratic Candidates' Wealth Tax Plans Would Shake Up Billionaire Philanthropy - WSJ [Internet]. [cited 2019 Dec 17]. Available from: https://www.wsj.com/articles/democratic-candidates-wealth-tax-plans-would-shake-up-billionaire-philanthropy-11573050551

2. Byrnes WH. the Private Foundation'S Topsy Turvy Road. Houst Bus Tax Law J. 2004;(4):498.

3. Arnsberger P, Ludlum M, Riley M, Stanton M. A History of the Tax-Exempt Sector: An SOI Perspective. Stat Income Bull [Internet]. 2008;501(Winter 2008):105–35. Available from: https://pdfs.semanticscholar.org/d736/4d73965f7c0e3255e1d81bdf74b2b8b37164.pdf

4. Bakija J. Tax policy and philanthropy: A primer on the empirical evidence for the United States and its implications. Soc Res (New York). 2013;80(2):557–84.

5. Should Hundreds Of New Nonprofits Be Created Each Year? [Internet]. [cited 2019 Dec 17]. Available from: https://bloomerang.co/blog/should-hundreds-of-new-nonprofits-be-created-each-year/

6. United Stated Global health | Donor Tracker [Internet]. Donor Tracker. [cited 2019 Dec 17]. Available from: https://donortracker.org/united-states/globalhealth

7. Duquette NJ. Founders' fortunes and philanthropy: A history of the U.S. Charitable-contribution deduction. Vol. 93, Business History Review. Cambridge University Press; 2019. p. 553–84.

8. Harvey D. A Brief History of Neoliberalism. Oxford University Press; 2007. 247 p.

9. Our origins / Ford Foundation [Internet]. [cited 2019 Dec 17]. Available from: https://www.fordfoundation.org/about/about-ford/our-origins/

10. Grants All / Ford Foundation [Internet]. [cited 2019 Dec 17]. Available from: https://www.fordfoundation.org/work/our-grants/grants-database/grants-all?subjects=%26SubjectIds%3D1%26SubjectIds%3D2%26SubjectIds%3D3%26SubjectIds%3D4%26SubjectIds%3D5%26SubjectIds%3D6%26SubjectIds%3D7%26SubjectIds%3D8%26SubjectIds%3D9%26SubjectIds%3D10%26SubjectIds%3D11%26SubjectIds%3D12&page=0&minyear=2006&maxyear=2019&originatingoffices=%26RegionIds%3D1&originatingoffices=%26RegionIds%3D2&originatingoffices=%26RegionIds%3D3&originatingoffices=%26RegionIds%3D4&originatingoffices=%26RegionIds%3D5&originatingoffices=%26RegionIds%3D6&originatingoffices=%26RegionIds%3D7&originatingoffices=%26RegionIds%3D8&originatingoffices=%26RegionIds%3D9&originatingoffices=%26RegionIds%3D11&originatingoffices=%26RegionIds%3D13#top

11. Hao K. Bill Gates will have no Microsoft (MSFT) shares by mid-2019 at his current rate — Quartz [Internet]. Quartz. 2017 [cited 2019 Dec 17]. Available from: https://qz.com/1054323/bill-gates-will-have-no-microsoft-msft-shares-by-mid-2019-at-his-current-rate/

12. Bloomberg. Bloomberg Billionaires Index - Bill Gates [Internet]. Bloomberg L.P. 2018 [cited 2019 Dec 17]. Available from: https://www.bloomberg.com/billionaires/profiles/william-h-gates/

13. Income tax | Washington Department of Revenue [Internet]. [cited 2019 Dec 17]. Available from: https://dor.wa.gov/find-taxes-rates/income-tax

14. 2019 Capital Gains Tax Calculator - See What You'll Owe | SmartAsset.com [Internet]. [cited 2019 Dec 17]. Available from: https://smartasset.com/investing/capital-gains-tax-calculator#XhnRsp9DWq

15. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Heal. 2020 Feb 1;8(2):e191–203.

16. History - Bill & Melinda Gates Foundation [Internet]. [cited 2019 Dec 17]. Available from: https://www.gatesfoundation.org/Who-We-Are/General-Information/History

17. Fiorillo S. Bill Gates Net Worth Timeline: How Much Money Does He Have? - Stock Market - Business News, Market Data, Stock Analysis - TheStreet [Internet]. The Street. 2018 [cited 2019 Dec 17]. Available from: https://www.thestreet.com/personal-finance/bill-gates-net-worth-14564023

18. Fortin J. Bill Gates Objects to Elizabeth Warren's Wealth Tax, and She Offers to Explain - The New York Times [Internet]. The New York Times. 2019 [cited 2019 Dec 17]. Available from: https://www.nytimes.com/2019/11/07/us/politics/bill-gates-elizabeth-warren-wealth-tax.html

19. IHME. Financing Global Health | IHME Viz Hub [Internet]. University of Washington. 2018 [cited 2019 Dec 17]. Available from: https://vizhub.healthdata.org/fgh/

20. Papanicolas I, Woskie LR, Jha AK. Health care spending in the United States and other high-income countries. Vol. 319, JAMA - Journal of the American Medical Association. American Medical Association; 2018. p. 1024–39.

21. Lopes L, Hamel L, Kearney A, Brodie M. KFF Health Tracking Poll – October 2019: Health Care In The Democratic Debates, Congress, And The Courts [Internet]. Kaiser Family Foundation. 2019 [cited 2019 Dec 17]. Available from: https://www.kff.org/health-reform/poll-finding/kff-health-tracking-poll-october-2019/

22. Warren E. Ending the Stranglehold of Health Care Costs on American Families | Elizabeth Warren [Internet]. 2019 [cited 2019 Dec 17]. Available from: https://elizabethwarren.com/plans/paying-for-m4a

23. Weissmann J. Warren v. Sanders: Whose wealth tax is harder on billionaires? [Internet]. Slate. 2019 [cited 2019 Dec 17]. Available from: https://slate.com/business/2019/11/warren-sanders-wealth-tax-ban-billionaires.html

24. Annual Report on Philanthropy. Giving Statistics : Charity Navigator [Internet]. [cited 2019 Dec 17]. Available from: https://www.charitynavigator.org/index.cfm?bay=content.view&cpid=42

25. Youde J. The Rockefeller and Gates Foundations in Global Health Governance. Glob Soc. 2013 Apr;27(2):139–58.

26. Rushton S, Williams OD. Partnerships and foundations in global health governance. Palgrave Macmillan; 2011. 308 p.

JOURNAL OF HEALTH POLICY AND ECONOMICS

Marselia Tan. Controversy over the Regulations of Infant Milk Formula Marketing from 1970s to 2000s: An Analysis on the Use of Evidence in Health Policymaking. Journal of Health Policy and Health Economics. 2021; 1(1).

Controversy over the Regulations of Infant Milk Formula Marketing from 1970s to 2000s: A Theoretical Analysis on the Use of Evidence in Health Policymaking

Marselia Tan[1]

[1]London School of Economics and Political Sciences, Department of Health Policy, London, UK, marseliatan@gmail.com

Introduction

Driven by the assumption that objective and scientifically sound evidence instead of values should inform policy decision-making, many politicians, academics, and professional bodies have supported the use of evidence-based policymaking in various public policy fields, including healthcare (1-3). However, an emerging view among scholars claims that the creation, selection, and interpretation of evidence related to public policies are inherently subjective and reflect the political interests of various stakeholders (2). Aligned with this view, this commentary focuses on how evidence has been used by different actors in the health system to influence the health policymaking process related to the marketing of infant milk formula (IMF). While the IMF industry's controversy has been studied before, the existing literature has focused on business ethics and corporate social responsibility implications of the policy-influencing activities of industry actors (4-6). Hence, past research had utilised analytical frameworks most relevant to the critical discourse on the IMF industry's corporate actors. While actors with substantial financial stakes in the industry –most notably the market leader Nestlé– have indeed defended their interests by strategically creating, selecting, and interpreting evidence, activists and other interest groups have also strategically utilised evidence to challenge the legitimacy of IMF companies and to promote stricter regulations on IMF marketing in the developing world (7,8).

By tracing controversial IMF cases that occurred worldwide from the 1970s to the 2000s (4,9,10) and using Kingdon's multiple streams model of policy change (11), this commentary argues that the strategic and agenda-driven use of evidence at crucial moments in the policymaking process has allowed both groups of actors to attain some success in influencing policy changes throughout the years. As this approach calls for analysing the IMF controversy in a chronological manner, Kingdon's multiple streams model is deemed the most appropriate framework as it "emphasises the time dimension in evidence use and recognises that evidence may influence policy at key moments or alternatively only after long periods of time." (2: p.26) The commentary concludes that the body of evidence involved in health policymaking on IMF products has grown and is likely to continue expanding, shaped by the intense contestations over values and ideologies between two diametrically opposed groups. The approach used in this commentary may be applied to analyse the strategic and political use of evidence in other ongoing health policy controversies.

A short description of Kindgon's multiple streams model

Kingdon argues that for a key change in policymaking to take place, three separate "streams" -problem stream, policy stream, and politics stream- must converge to enable a "window of opportunity" for influential policy change to open (11). In the *problem stream*, a particular policy issue receives the attention of policymakers, often due to how it is framed by interested stakeholders or due to an emerging focusing event or crisis around the problem, instead of solely due to any objective indicators. Certain groups of stakeholders may come into favour by capitalising on the crucial moment when a problem captures attention. The *policy stream* emerges with different policy entrepreneurs proposing viable policy solutions, developed in anticipation of certain problems receiving major attention. Lastly, in *politics stream,* policymakers are compelled by the national or international feedback on the particular problem's magnitude and the existence of policy proposals to address it, to select the policy solutions and enact the change (11).

The 1970s

Infant milk formula was developed in the 19th century as a substitute for breastfeeding (4), but only gained a wider market during the period after World War II. Journalists noticed that the widespread marketing campaigns by IMF companies had framed the product as a desired "status symbol" especially among lower-income women, misled consumers to perceive it as a "modern" replacement to natural breast milk, and created a false impression of doctors' endorsement (12,13). These campaigns were argued to contribute to the declining breastfeeding rate in both developed and less developed countries from the 1940s to the 1970s (9,14-16). In response to the allegations, IMF companies and their supporters explained that IMF's popularity was merely due to the increasing trend of women in Western countries entering the workforce without any mechanism in workplace to support them for exclusive breastfeeding (4,9,13,17). Thus, IMF products became an attractive and convenient infant feeding choice. This showcases how a strategic *interpretation of evidence* was utilised to shift the responsibility of in IMF product preference solely on a broader socioeconomic trend, instead of as a direct result of the companies' marketing activities.

In early 1970s, the dissidents of IMF marketing practices expressed their concerns more vocally. The Director of Carribean Food and Nutrition Institute at the time, Dr Jelliffe, was the first to claim in a public forum (12,18) that IMF companies' aggressive marketing tactics, such as offering free samples to mothers, over-incentivising doctors, and employing sales representatives dressed like nurses in maternity wards (7,12) were directly associated with the soaring rates of mortality and morbidity among infants in third-world countries (4,18). Other scientists subsequently presented studies indicating a link between IMF companies' aggressive marketing of IMF and infants' health problems in developing countries, where women lacked access to proper sanitary conditions, literacy, and financial means required to properly follow instructions about bottle-feeding their infants (6,12). Many third-world mothers used contaminated water to prepare IMF products or overly diluted the formula to make the expensive product last longer. These practices led to infants' malnutrition, diarrhoea, gastroenteritis, and deaths (19,20). Nestlé's countered these accusations by presenting a contrasting evidence implying a link between IMF consumption and the decrease in infant mortality rates, as observed in some countries from 1940 to 1970 (13). This claim provoked nutritionists and scientists to accuse Nestlé of a *technical bias in the interpretation of* the statistical evidence –the declining infant mortality in some countries at that period was more likely to be caused by a combination of systematic factors like the improved health care system, vaccination, and better standards of living rather than due to increased IMF consumption (21,22).

The movement against IMF companies at this juncture can be explained as a manifestation of an *advocacy coalition framework* (3), where individuals form coalitions to turn their beliefs into policies and to oppose the beliefs and policies of competing coalitions. Indeed, in calling for the establishment of an international health policy for IMF marketing, various actors such as religious groups (Interfaith Center on Corporate Responsibility (23), the U.S. Methodist Church (24)); activist groups (Infant Feeding Action Coalition (25)); International Baby Food Action Network (26)); paediatrics; nutritionists; and scientists coordinated to vigorously utilise and expand the body of evidence supporting their cause, guided by the same underlying *'policy core' belief* that "breast is best" (7,8). The controversy reached its tipping point and gained worldwide attention after the 1974 ground-breaking publication of "The Baby Killer" (27), an exposé of damages caused by IMF companies in the developing world. This sensationalist publication marks the coalition's exercise of power by framing evidence to discredit IMF companies, to the extent of "demonising" them (3). In response to the scathing pamphlet, Nestlé, the primary focus of the public's negative sentiment, sued the authors for libel and won (7,12). Capitalising on the public momentum from this lawsuit, the Infant Formula Action Coalition (INFACT) in 1977 launched a successful international boycott on Nestlé's products (4,12). To this day, the INFACT boycott continues to galvanise other boycotts by other NGOs and activists worldwide (28).

Pressured to react to these forces, IMF industry leaders employed various uses of evidence to maintain their legitimacy, such as creating the International Council of Infant Food Industries (ICIFI) in 1975, an industry association consisting of Wyeth, Ross-Abbott, Danone, Cow & Gate, four Japanese IMF companies, and Nestlé (12). The purported objective of this association was to be recognised as a self-regulatory body and to sponsor research studies in various areas, including topics such as infant feeding patterns and the extent to which breast milk alone can suffice an infant's needs (12,29,30). Such research topics can be construed as an attempt to orient the process of *creating new evidence* to favour the industry. The IMF industry also criticised its opponents for promoting the misconception on breastfeeding substitutes (12,17) and for campaigning to make IMF available only on medical prescription (29). The industry accused its opponents of *issue bias in their selection of evidence* (2) by neglecting some important social concerns, such as the benefits of IMF for women unable to naturally breastfeed and in preventing the use of less suitable alternatives like sweetened condensed milk or gruel for infants whose mothers were unable to breastfeed (17,29).

The 1980s to 1990s

The struggles between IMF industry and opposition groups culminated in 1981 with the establishment of the WHO International Code of Marketing Breast Milk Substitutes (the Code), a nonbinding code that restricts the promotional activities of IMF products (31). The events leading up to the creation of this Code can be analysed using multiple streams analysis (3,11). Kingdon captures the importance of time dimension in evidence use and posits that when *problem stream*, *policy stream,* and *politics stream* converge at the optimal time, a *window of opportunity* opens to enable a policy change (11). In the IMF controversy, a *problem stream* emerged as the evidence compiled in "The Baby Killer" and the worldwide attention it received made the issue of IMF marketing practices salient in agendas of policymakers such as the WHO and national governments. By the time the controversy reached its boiling point of Nestlé's lawsuit and the INFACT boycott, a *policy stream* had emerged, with a number of doctors, advocates of breastfeeding, and NGOs revealing proposals for restricting IMF companies' marketing practices especially among the vulnerable populations. Popular support for these proposals consequently enabled a *politics stream*, allowing policymakers to act in a

politically correct course. These three streams ultimately opened up a window of opportunity for the development of the WHO Code.

The Code was a result of 118 WHO member countries' positive votes and one negative vote from the United States, which was under the Reagan administration at the time (5) –an administration widely regarded to be protective of private sector's agendas (32,33). Echoing ICIFI's reasoning to oppose the Code, the U.S. rejected the WHO Code for its rigidity and incompatibility with the American values of "free speech and freedom of information" (9,34). However, this statement had neglected important research findings on the perils of the absence of IMF marketing standards in the U.S., such as recorded IMF misuse in low-income American cities (9). Disregarding this body of evidence reflects the U.S. government's *cognitive dissonance aversion* (2), as the idea of negative impact caused by private sector was incongruent to the pro-market ideology that thrived during the Reagan era (33). The negative vote also suggests a government's *issue bias in selection of evidence,* ignoring parts of a larger body of evidence about the social harms of unregulated marketing of IMF products.

In 1982, to end the prolonged boycott and to claim a commitment to Code compliance, Nestlé established the Nestlé Infant Formula Commission and the Nestlé Coordination Center for Nutrition to research on the level of compliance of its marketing activities to the WHO Code, as well as to expand the knowledge on artificial feeding for infants (12,19,35,36). Unsurprisingly, the commissioned research produced only favourable results for Nestlé (36), exemplifying how an influential industry player deliberately engaged in a *confirmatory bias* (2) by commissioning strategically designed research that produce evidence confirming the firm's existing hypothesis of its compliance to the Code. In contrast to the evidence produced by these research centres, in a manner befitting the *advocacy coalition framework*, WHO, UNICEF, and various influential NGOs like IBFAN, INFACT, and Baby Milk Action (BMA) found consistent evidence of the industry's continuous violations to the WHO Code as well as to various developing countries' national laws (4,37-39).

Throughout the years of global boycott implicating even Nestlé's non-IMF products, the public perception of Nestlé and the IMF industry has deteriorated (6). However, since 1985 onward, the industry found a new turning point. A growing number of studies showed that HIV/AIDS can be transmitted from mother to baby via breastfeeding (4,8,40). Rapidly reacting to this advantageous turn of events, IMF companies launched extensive campaigns publicising evidence on dangers of breastfeeding and benefits of IMF in preventing mother-to-baby HIV infections (8,41). In a strange twist, the IMF industry could then claim the moral high ground, accusing WHO and UNICEF of slow response to the crisis and of risking the lives of at-risk infants by limiting IMF access and availability to mothers (40,42). Nevertheless, the industry also showed an *issue bias in its selection of evidence*, by disregarding the existing concern that mothers in poor living conditions are not equipped to utilise IMF in the first place. On the other hand, the revelation HIV transmission risks from breastfeeding left anti-IMF groups baffled, confronted with the uncomfortable fact that once-decried IMF products could now be an effective tool for saving third-world children from AIDS (8). This hard-to-swallow evidence of the IMF's potential benefit destabilised the coalition's *policy core belief* (3) that "breast is best".

The 2000s

In the early 2000s, the mother-to-child HIV transmission issue reignited the waning debate of "breast versus bottle", enabling a *problem stream* that made IMF marketing regulations once again an attention-grabbing issue in the policymakers' agenda. IMF industry's continuous

effort to present various pieces of evidence and its emphasis on the moral imperative in making IMF available to HIV-infected mothers had even gained support from some of its past detractors, such as UNAIDS officials and doctors in developing countries (43). From the perspective of the multiple streams model, this acceptance from former "enemies" was crucial to enable a *politics stream* for a change in the WHO Code, as amendments could now be a politically correct response to the HIV crisis and might also appease breastfeeding advocates. Alongside Nestlé, Wyeth emerged as an enthusiastic *policy entrepreneur* (44), capitalising the developing body of evidence to propose a solution: donating free IMF products to HIV-infected mothers in Africa (42,43), explicitly violating part of the WHO Code prohibiting the distribution of free IMF samples (31). Ultimately, the convergence of the three streams resulted in a *window of opportunity* for a policy change favouring the IMF industry. After years of resistance, UNICEF relented to starting a pilot project to provide IMF to HIV-infected mothers in Africa (45). It commissioned a non-controversial French dairy cooperative to provide free, plain-packaged IMF products for HIV-positive mothers (40,45,46). Although the biggest companies were excluded as potential suppliers for UNICEF's programme, the pilot programme conferred back some legitimacy on the IMF products and brought hope to the wider IMF industry on possible future amendments to the Code.

In light of this seeming willingness of WHO and UNICEF to begin a cooperative relationship with the IMF industry, a strong advocacy coalition was re-established among the industry critics, consistently rejecting IMF companies' offers for donations and heavily relying on other evidence from emerging studies on breastfeeding's safety in HIV context (37,46-48) – particularly a pioneering study from South Africa that shows a reduction in risk of mother-to-infant HIV transmission when breastfeeding is combined with antiretroviral treatment (49). Other strategies employed by the activist groups since 2004 involve the *creation of evidence* through cataloguing IMF companies' Code violations. BMA and Interagency Group on Breastfeeding Monitoring, INFACT, and IBFAN continually monitor and report IMF companies' violations to the Code (4). In 2004, IBFAN released a report "Breaking the Rules, Stretching the Rules" (50), a documentation of purported evidence on how IMF companies idealised their products and downplayed the negative health impact of bottle-feeding. The document was put forward as evidence to the United Kingdom's House of Commons to demand the cessation of IMF marketing malpractice (42). To this day, opposition groups continue to develop the evidence base contesting the legitimacy of IMF companies by extensively cataloguing the industry's violations of the Code (4). One way Nestlé had reacted to this was by emphasising its "listed" status on the FTSE4Good Index (51) –an independent stock market instrument relied on by investors to measure corporate social responsibility performance of various companies–, framing it as impartial evidence of compliance to the Code and of its ethical operation (52). Nevertheless, critics scorned that Nestlé relied on its listing on the Index as evidence of its socially responsible activities, since the company had simultaneously pushed for the removal of Code compliance as a requirement for other companies to be included on the Index's listing (42,53).

Beyond the 2000s, the financial stake in the IMF industry continues to rise, as the global sales of IMF grow three times as quickly as the global economy (54). Given this economic incentive, it is unsurprising that IMF companies and its supporters continue to contend every World Health Assembly's resolution or amendment proposal to the WHO Code through various means. For instance, engaging in evidence creation, Nestlé sponsored a large-scale study on Chinese toddlers and found that they were lacking certain micronutrients in their diet. The company recommended that this deficiency could be supplemented with IMF products (55). Nestlé also framed the study's results as grounds to refuse further regulation on advertising on toddlers, arguing that further restriction on IMF advertisement may then increase the consumption of other less healthy, less restricted dietary alternatives such as Coca Cola (56).

Meanwhile, opposition groups have continued to present evidence on the industry's violations to the Code through new marketing channels. Save the Children cited several studies implying the IMF industry's exploit of the rise of social media for intensive behavioural targeting, for example by engaging social media influencers to promote IMF brands with a veneer of impartiality and non-sponsored endorsement (54).

Conclusion

In the long battle of "breast versus bottle", activists, scientists, physicians, and religious groups have fought in an "advocacy coalition" model to utilise evidence that advance their cause. Driven by a strong policy core belief that breastfeeding yields the best health outcomes for infants, the advocacy coalition insists that the IMF industry's values and intentions are inherently incompatible to public interests. Thus, it has continuously discredited the industry's legitimacy through persistent monitoring of its violations to the Code. While previous literature has critically examined mainly the IMF industry, by applying Kingdon's multiple streams analysis on some crucial moments in the history of IMF controversy, this commentary demonstrates that both the IMF industry and its opposing groups are capable of using evidence within ideal timeframes to allow three streams of problem, policy, and politics to converge into windows of opportunity for policy changes that suit their ideological, economic, or other interests.

As the debate on the IMF issue goes on, the body of evidence on breastfeeding and IMF continues to expand and evolve, reflecting the two polarised groups' interests, beliefs, and values. Future health policy analyses within the IMF topic may focus on the development of the controversy from 2010s onward, dissecting the roles of internet and social media as new devices of evidence creation, selection, and dissemination. As this commentary demonstrates, Kingdon's multiple streams model is suited for conducting a historical analysis on how intensely opposed groups of actors strategically influence the "evidence-based" policy making process. The model can be applied to understand actors' actions on other controversial, ideology-driven health policy cases that span across a substantial period of time, such as on the use of medical marijuana or mandatory childhood vaccinations.

References

1. Russell J, Greenhalgh T, Byrne E, Mcdonnell J. Recognizing rhetoric in health care policy analysis. Journal of Health Services Research & Policy. 2008;13(1):40–6.
2. Parkhurst JO. The politics of evidence: from evidence-based policy to the good governance of evidence. New York, NY: Routledge; 2017.
3. Cairney P. The Politics of Evidence-Based Policy Making. London: Palgrave Macmillan UK: Imprint: Palgrave Pivot; 2016.
4. Brady JP. Marketing breast milk substitutes: problems and perils throughout the world. Archives of Disease in Childhood. 2012;97(6):529–32.
5. Boyd C. The Nestlé Infant Formula Controversy and a Strange Web of Subsequent Business Scandals. Journal of Business Ethics. 2011;106(3):283–93.
6. Baker JC. The international infant formula controversy: A dilemma in corporate social responsibility. Journal of Business Ethics. 1985;4(3):181–90.
7. Beaver B, Silvester F. The Gall in Mothers Milk. International Journal of Advertising. 1982;1(1):1–10.

8. Meier B. In War Against AIDS, Battle Over Baby Formula Reignites [Internet]. The New York Times. The New York Times; 1997 [cited 2020Jan20]. Available from: https://www.nytimes.com/1997/06/08/business/in-war-against-aids-battle-over-baby-formula-reignites.html
9. Solomon S. THE CONTROVERSY OVER INFANT FORMULA [Internet]. The New York Times. The New York Times; 1981 [cited 2020Jan12]. Available from: https://www.nytimes.com/1981/12/06/magazine/the-controversy-over-infant-formula.html
10. Muller M. Nestlé baby milk scandal has grown up but not gone away [Internet]. The Guardian. Guardian News and Media; 2013 [cited 2020Jan10]. Available from: https://www.theguardian.com/sustainable-business/nestle-baby-milk-scandal-food-industry-standards
11. Kingdon JW. Agendas, alternatives, and public policies. Harlow: Pearson Education Limited; 2014.
12. Dobbing J, Geraldi G, McComas M. Infant feeding: anatomy of a controversy 1973-1984. Place of publication not identified: Springer; 2013.
13. Iatham MC. Bottles, Babies and Breast-Feeding: Debating the Nestle Boycott: Opinion: The Harvard Crimson [Internet]. Opinion | The Harvard Crimson. The Harvard Crimson; [cited 2019Dec11]. Available from: https://www.thecrimson.com/article/1978/11/7/bottles-babies-and-breast-feeding-debating-the/
14. Hirschman C, Hendershot GE. Trends in breast feeding among American mothers. Vital health and statistics. 1979;(3):1–39.
15. Millman S. Trends in Breastfeeding In a Dozen Developing Countries. International Family Planning Perspectives. 1986;12(3):91.
16. Wright AL, Schanler RJ. The Resurgence of Breastfeeding at the End of the Second Millennium. The Journal of Nutrition. 2001;131(2).
17. Summary Position Statement Re Proposed WHO International Code for the Marketing of Breast Milk Substitutes [Internet]. Archive.babymilkaction.org. 1981 [cited 2020Jan05]. Available from: http://archive.babymilkaction.org/pdfs/icifistatement81.pdf
18. Jelliffe DB, Jelliffe EFP. Feeding Young Infants in Developing Countries: Comments on the Current Situation and Future Needs. Studies in Family Planning. 1978;9(8):227.
19. Zelman NE, The Nestle Infant Formula Controversy: Restricting the Marketing Practices of Multinational Corporations in the Third World. The Transnational Law. 1990;3(2): 697-758.
20. Baer E, Marguiles L. Infant and Young Child Feeding: An Analysis of the WHO/UNICEF Meeting. Studies in Family Planning. 1980;11(2):72.
21. Krieger N, Rehkopf DH, Chen JT, Waterman PD, Marcelli E, Kennedy M. The Fall and Rise of US Inequities in Premature Mortality: 1960–2002. PLoS Medicine. 2008Feb26;5(2):227–41.
22. Francis DR. Why do Death Rates Decline? [Internet]. Why do Death Rates Decline? The National Bureau of Economic Research; [cited 2020Jan12]. Available from: https://www.nber.org/digest/mar02/w8556.html
23. Ermann, David M, Clements, H. W. Interfaith Center on Corporate Responsibility and its Campaign Against Marketing Infant Formula in the Third World * [Internet]. OUP Academic. Oxford University Press; 2014 [cited 2019Dec20]. Available from: https://academic.oup.com/socpro/article/32/2/185/1701773
24. Anderson DE. Nestle boycott gains support [Internet]. UPI. United Press International; 1988 [cited 2020Jan17]. Available from: https://www.upi.com/Archives/1988/11/29/Nestle-boycott-gains-support/4435596782800/

25. THE BABY MILK ISSUE - Ideas for Action [Internet]. New Internationalist. The New Internationalist; 1982 [cited 2020Jan21]. Available from: https://newint.org/features/1982/04/01/action
26. Küenzl J, Schwabenland C, Elmaco J, Hale S, Levi E, Chen M, et al. International Baby Food Action Network (IBFAN). International Encyclopedia of Civil Society. 2010;:880–1.
27. Muller M. The Baby Killer [Internet]. War on Want. War on Want; 2015 [cited 2020Dec23]. Available from: https://waronwant.org/resources/baby-killer
28. Puiu T. Why Nestle is one of the most hated companies in the world [Internet]. ZME Science. 2017 [cited 2020Jan21]. Available from: https://www.zmescience.com/science/nestle-company-pollution-children/
29. International Council Of Infant Food Industries. The Lancet. 1978Jun10;311(8076):1250–2.
30. Gerber J. Enforced Self-Regulation in the Infant Formula Industry: A Radical Extension of an "Impractical" Proposal. Social Justice. 1990;17(1):98–112.
31. International Code of Marketing of Breast-milk Substitutes [Internet]. Who.int. 1981 [cited 2020Jan11]. Available from: https://www.who.int/nutrition/publications/code_english.pdf
32. The Reagan Presidency [Internet]. The Reagan Presidency | Ronald Reagan Presidential Library - National Archives and Records Administration. Ronald Reagan Presidential Library and Museum; [cited 2020Jan21]. Available from: https://www.reaganlibrary.gov/sreference/the-reagan-presidency
33. The Second American Revolution: Reaganomics [Internet]. The Second American Revolution: Reaganomics | The Ronald Reagan Presidential Foundation & Institute. The Reagan Foundation; [cited 2020Jan21]. Available from: https://www.reaganfoundation.org/ronald-reagan/the-presidency/economic-policy/
34. Lusinchi V. U.S. IS A DISSENTER AS U.N. AGENCY VOTES BABY-FORMULA CODE [Internet]. The New York Times. The New York Times; 1981 [cited 2020Jan19]. Available from: https://www.nytimes.com/1981/05/21/world/us-is-a-dissenter-as-un-agency-votes-baby-formula-code.html
35. Duncan L. Nestle's Not 'Dumping' Formula, Panel Finds [Internet]. Los Angeles Times. Los Angeles Times; 1988 [cited 2020Jan18]. Available from: https://www.latimes.com/archives/la-xpm-1988-11-17-fi-88-story.html
36. Sethi SP. Nestle Infant Formula Audit Commission (NIFAC) a New Model for Gaining External Legitimacy for Corporate Actions. Issues in Business Ethics Multinational Corporations and the Impact of Public Advocacy on Corporate Strategy. 1994;:263–89.
37. Waterston T. Monitoring the marketing of infant formula feeds. Bmj. 2003Jan18;326(7381):113–4.
38. Bevin T. Breaking The Rules 1994: A worldwide report on Violations of the WHOIUNICEF International Code of Marketing of Breast-milk Substitutes. Journal of Human Lactation. 1995;11(1):61–61.
39. Taylor A. Violations of the international code of marketing of breast milk substitutes: prevalence in four countries. BMJ. 1998;316(7138):1117-1122.
40. Laurence J. Health Check: 'Aids has brought the makers of formula milk a marketing [Internet]. The Independent. 2004 [cited 2020Jan20]. Available from: https://www.independent.co.uk/life-style/health-and-families/health-news/health-check-aids-has-brought-the-makers-of-formula-milk-a-marketing-opportunity-to-die-for-563722.html
41. Nduati R, John G, Mbori-Ngacha D, Richardson B, Overbaugh J, Mwatha A, et al. Effect of Breastfeeding and Formula Feeding on Transmission of HIV-1: A Randomized Clinical Trial. Obstetrical & Gynecological Survey. 2000Mar;55(8):479–81.
42. Yamey G. The milk of human kindness. Western Journal of Medicine. 2001;174(3):165-166.

43. Freedman, Alix M., and Steve Stecklow. “Wyeth, Nestle Offer Free Tins to Stem Spread of AIDS; Children's Agency Balks.” The Wall Street Journal. Dow Jones & Company, December 5, 2000. https://www.wsj.com/articles/SB975978176677135549
44. Sætren H. From controversial policy idea to successful program implementation: the role of the policy entrepreneur, manipulation strategy, program design, institutions and open policy windows in relocating Norwegian central agencies. Policy Sciences. 2016;49(1):71-88.
45. de Wagt, Arjan, and David Clark. “UNICEFs Support to Free Infant Formula for Infants of HIV ...” World Alliance For Breastfeeding Action. World Alliance For Breastfeeding Action, April 2004. https://www.researchgate.net/publication/237326750_UNICEFs_Support_to_Free_Infant_Formula_for_Infants_of_HIV-infected_Mothers_in_Africa_A_Review_of_UNICEF_Experience
46. Moland K, de Paoli M, Sellen D, van Esterik P, Leshabari S, Blystad A. Breastfeeding and HIV: experiences from a decade of prevention of postnatal HIV transmission in sub-Saharan Africa. International Breastfeeding Journal. 2010;5(1):10.
47. Exclusive Breast-Feeding Is Safer Than Mixed Feeding For Infants Born to HIV-Positive Mothers [Internet]. Guttmacher Institute. 2007 [cited 19 January 2020]. Available from: https://www.guttmacher.org/journals/ipsrh/2007/06/exclusive-breast-feeding-safer-mixed-feeding-infants-born-hiv-positive
48. Dobson R. Breast is still best even when HIV prevalence is high, experts say. BMJ. 2002;324(7352): 1474.
49. Moodley, Dhayendre, Jagidesa Moodley, Hoosen Coovadia, Glenda Gray, James Mcintyre, Justus Hofmyer, Cheryl Nikodem, et al. “A Multicenter Randomized Controlled Trial of Nevirapine Versus a Combination of Zidovudine and Lamivudine to Reduce Intrapartum and Early Postpartum Mother-to-Child Transmission of Human Immunodeficiency Virus Type 1.” *The Journal of Infectious Diseases* 187, no. 5 (2003): 725–35. https://doi.org/10.1086/367898
50. Breaking the Rules 2004: Stretching the Rules Evidence of Violations of the International Code of Marketing of Breastmilk Substitutes and subsequent Resolutions [Internet]. International Baby Foods Action Network. 2004 [cited 2020Jan19]. Available from: http://ibfan.org/art/302-2.pdf
51. FTSE4Good Index Series [Internet]. Ftserussell.com. 2020 [cited 2020Jan21]. Available from: https://www.ftserussell.com/products/indices/ftse4good
52. The FTSE4Good Investment Index [Internet]. Nestlé Global. 2020 [cited 2020Jan21]. Available from: https://www.nestle.com/ask-nestle/health-nutrition/answers/what-is-ftse4good
53. Granheim SI, Engelhardt K, Rundall P, Bialous S, Iellamo A, Margetts B. Interference in public health policy: examples of how the baby food industry uses tobacco industry tactics. World Nutrition. 2017;:288–310.
54. Save the Children UK. Don’t Push It: Why the formula milk industry must clean up its act [Internet]. Save the Children UK. 2018 [cited 2020Dec29] p. 22–6. Available from: https://www.savethechildren.org.uk/content/dam/gb/reports/health/dont-push-it.pdf
55. Nestlé. Nestlé conducts first large scale study on young children’s diets in China [Internet]. Nestlé. 2015. Available from: https://www.nestle.com/media/news/nestle-ming-study-nutritional-imbalances-young-children-china
56. Plüss JD. Nestlé struggles to win over baby formula critics [Internet]. SWI swissinfo.ch. 2020. Available from: https://www.swissinfo.ch/eng/milk-for-older-babies_nestl%C3%A9-struggles-to-win-over-infant-formula-critics/45473338