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Τίτλος

Η στρατηγική Cocooning στον εμβολιασμό: παρελθόν, παρόν και μέλλον
Cocooning in vaccination: past, present and future

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Prologue - thanks

The current dissertation "Cocooning in vaccination: past, present and future" was conducted in the context of the MSc "Vaccinations and prevention of infectious diseases", in the University of Crete.

One of the most essential roles of a Paediatrician is to become the children's advocate, whose voice cannot always be heard due to their age or developmental stage. Through this study, I realised the importance of this role in every aspect of our care in order to make every vulnerable individual's voice heard.

This work could not be achieved without certain people's support that I would like to thank. The idea and inspiration came from the Professor Emmanouil Galanakis, who through his love about the cocooning idea intrigued me to study about it and through his encouragement, I intensified my effort. I also want to thank my Supervisor, Dr Eleni Vergadi, who listened to my thoughts, fears and she facilitated our contact despite the distance. Also, Dr Emmanouil Smyrnakis who helped me through his constructive feedback.

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CONTENTS

Περίληψη

Τίτλος εργασίας: Η στρατηγική Cocooning στον εμβολιασμό: παρελθόν, παρόν και μέλλον
Της: Στυλιανής Αλιφιεράκη
Επιβλέποντες: Ελένη Βεργαδή, Εμμανουήλ Γαλανάκης, Εμμανουήλ Σμυρνάκης
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Υπόβαθρο: Παρά την ιατρική πρόοδο και την ανάπτυξη αποτελεσματικών και ασφαλών εμβολίων, λοιμώδεις παράγοντες εξακολουθούν να απειλούν την δημόσια υγεία, υπαγορεύοντας την εφαρμογή περαιτέρω προληπτικών μέτρων. Το «Cocooning» είναι μία γνωστή εμβολιαστική πρακτική, στην οποία οι στενές επαφές ενός ευάλωτου ατόμου, το οποίο δεν μπορεί να εμβολιαστεί, εμβολιάζονται προκειμένου να δημιουργήσουν ένα περιβάλλον προστασίας, μέσω μείωσης της μετάδοσης του εκάστοτε λοιμώδους παράγοντα στο άτομο υψηλού κινδύνου.

Σκοπός: Σκοπός της παρούσας μελέτης είναι η χρονολογική ανασκόπηση της εμβολιαστικής στρατηγικής του cocooning, με επίκεντρο τις εφαρμογές, αποδοχή, περιορισμούς, οφέλη καθώς και τις μελλοντικές προεκτάσεις της στρατηγικής.

Μεθοδολογία: Πρόκειται για βιβλιογραφική ανασκόπηση στις ακόλουθες διεθνείς βάσεις ιατρικών δεδομένων: MEDLINE, Embase, Journals Ovid, AMED, Global Health, Cochrane library and Scopus. Οι λέξεις-κλειδιά που χρησιμοποιήθηκαν στην αναζήτηση ήταν: [Cocooning AND Vaccin*] OR [Cocooning AND Immun*]. Μόνο άρθρα στα Αγγλικά και όσα αφορούσαν στην εμβολιαστική στρατηγική του cocooning περιλήφθηκαν. Από την αναζήτηση αποκλείστηκαν άρθρα σε άλλες γλώσσες και εκείνα που αναφέρονταν σε άλλες χρήσεις του cocooning.

Αποτελέσματα: Η αναζωπύρωση του κοκκύτη από την δεκαετία του 1980 και η αυξημένη βαρύτητα στα βρέφη οδήγησαν στην δημιουργία της «Παγκόσμιας πρωτοβουλίας έναντι του κοκκύτη» το 2001. Ανάμεσα στις προτάσεις που τέθηκαν, η στρατηγική του cocooning πρόβαλε ως πολλά υποσχόμενη για την αντιμετώπιση του

προβλήματος και επίσημες συστάσεις από τον CDC/ACIP ακολούθησαν το 2006. Η στρατηγική ακολούθως επεκτάθηκε για την προστασία των βρεφών από τη γρίπη. Δεδομένα σχετικά με δυσκολίες στην εφαρμογή του cocooning, το υψηλό κόστος, χαμηλή πρόσληψη και αποτελεσματικότητα οδήγησαν στην αναθεώρηση των οδηγιών. Παράλληλα, άλλες εμβολιαστικές πρακτικές εξετάζονταν, μεταξύ άλλων ο μητρικός εμβολιασμός κατά την κύηση, ο οποίος κυριάρχησε ως ασφαλής και αποτελεσματικός χάρη στην επιπλέον προστασία που προσέφερε μέσω της μεταφοράς μητρικών αντισωμάτων και προστασίας από την γέννηση. Από το 2012, ο CDC/ACIP και ACOG προτείνουν τον εμβολιασμό με Tdap από το τέλος του β' τριμήνου κάθε κύησης. Το cocooning παραμένει μία σημαντική συμπληρωματική πρακτική στις περιπτώσεις που ο εμβολιασμός στην κύηση δεν έχει πραγματοποιηθεί.

Αξιολόγηση των δύο στρατηγικών αναδεικνύει αυξημένη αποτελεσματικότητα και χαμηλότερο κόστος του μητρικού εμβολιασμού αλλά μεγαλύτερο όφελος για την κοινωνία από το cocooning. Μέσα στα χρόνια, ο ρόλος του cocooning έχει επεκταθεί στην προστασία άλλων ευάλωτων ομάδων, με περισσότερες αλλά λιγότερο καλά εδραιωμένες συστάσεις.

Συμπεράσματα: Ο σημερινός ρόλος του cocooning είναι αμφισβητούμενος λόγω προγραμματικών δυσκολιών, κόστους και αμφίβολης αποτελεσματικότητας, περιορίζοντας την εφαρμογή του. Από την άλλη, τα οφέλη που προσφέρει για τα ευάλωτα άτομα – και τον περίγυρό τους- οι εκπαιδευτικές και κοινωνικές προεκτάσεις του, αναδεικνύουν την σημασία ενίσχυσής του. Αν συγκεκριμένα μέτρα εφαρμοστούν, η στρατηγική δύναται να έχει μεγάλη θέση στα μελλοντικά εμβολιαστικά προγράμματα και την προαγωγή της δημόσιας υγείας. Το γεγονός ότι νέες ασθένειες και εμβόλια συνεχώς εμφανίζονται σημαίνει ότι το cocooning θα συνεχίσει να έχει έναν πολύτιμο ρόλο ως συμπληρωματικό μέτρο στην πιο αποτελεσματική προστασία των ατόμων εκείνων, που δεν μπορούν να εμβολιαστούν ή να αναπτύξουν ικανή ανοσοπροστασία μετά τον εμβολιασμό.

Λέξεις κλειδιά: cocooning, εμβολιαστική στρατηγική, μητρικός εμβολιασμός, ανοσοκατεσταλμένοι, εμβολιαστικά κίνητρα

Abstract

Title: Cocooning in vaccination: past, present and future

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Background: Despite medical advances and the development of effective and safe vaccines, infective agents threaten public health necessitating further preventative measures to be implemented. Cocooning is a well-known vaccination strategy, in which the close contacts of a vulnerable individual, who is not able to be vaccinated, get immunised. This practice indirectly creates a protective environment for the "at-risk" individual through reduced transmission of the respective vaccine-preventable disease (VPD).

Objectives: Aim of the current study is to present a chronology of the cocooning vaccination strategy with main focus on the applications and uptake, limitations and benefits as well as the future implications of the strategy.

Methods: The methodology used for the conduction of the study was literature review on the following international medical databases: MEDLINE, Embase, Journals Ovid, AMED, Global Health, Cochrane library and Scopus. The keywords used for the search were: [Cocooning AND Vaccin*] OR [Cocooning AND Immun*]. Articles only in English and those referred to the cocooning vaccination strategy were included. Studies in other languages and the ones using cocooning as a shielding strategy were excluded.

Results: The pertussis resurgence since the 1980s and the significant burden of disease in young infants led to the development of the Global Pertussis Initiative in 2001, in order to combat the problem. Amongst the solutions suggested, cocooning was a well-promising strategy and official recommendations from CDC/ACIP followed in 2006. The strategy was subsequently used for the infantile protection against influenza. Increasing evidence around its implementation difficulties, the high cost and poor uptake and effectiveness gave rise to the revision of the guidelines. Simultaneously, other vaccination strategies for prevention of pertussis in infants were examined and maternal immunisation in pregnancy (MIP) dominated as a safe and effective strategy,

through the additional transplacental transmission of antibodies and protection since birth. Since 2012, CDC/ACIP and ACOG recommend the Tdap vaccination from the end of 2nd trimester in every pregnancy. Cocooning remains a complementary strategy in the cases where MIP has not been achieved.

Ongoing evaluation of the two strategies show a higher effectiveness and less cost of MIP but cocooning seems to be the most cost-saving strategy with higher benefit at a societal level. Through the years, the role of cocooning has expanded to the protection of other vulnerable groups (immunosuppressed, elderly) with further applications but less well-established recommendations.

Conclusion: The role of cocooning at present is debatable due to its numerous logistical challenges, cost and ambiguous effectiveness, which compromise its implementation. On the other hand, the public health benefits it confers for the most vulnerable individuals, the educational and ethical perspectives of this strategy call for further attention. If certain facilitators are encouraged, the strategy can have a significant impact on the future vaccination strategies. The fact that new diseases continuously emerge, and new vaccines make their appearance means that cocooning will have an ongoing role in the protection of the non-negligible portion of the population who still cannot be vaccinated or mount adequate responses by themselves.

Keywords: cocooning, vaccination strategy, immunisation strategy, maternal immunisation, immunosuppressed individuals, vaccination intentions

Abbreviations

COVID-19	Coronavirus Disease 2019
CDC	Centers for Disease Control and Prevention
ACIP	Advisory Committee on Immunization Practices
GPI	Global Pertussis Initiative
WHO	World Health Organisation
ACOG	American College of Obstetricians and Gynecologists
VPDs	Vaccine Preventable Diseases
NIP	National Immunisation Programme
RT-PCR	Real-time Polymerase Chain Reaction
wP	whole-cell pertussis vaccines
aP	acellular-pertussis vaccines
Tdap	Tetanus toxoid, reduced diptheria toxoid and acellular pertussis vaccine
DTP	Diptheria, tetanus, pertussis vaccine
Td	Tetanus, reduced diptheria vaccine
CCs	Close contacts
SAGE	Strategic Advisory Group of Experts
AAP	American Academy of Pediatrics
HCW	Healthcare workers
TIV	Trivalent inactivated vaccine
MIP	Maternal immunisation in pregnancy
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine effectiveness
CI	Confidence Intervals
IP	Immunosuppressed/immunocompromised population
AIDS	Acquired immunodeficiency syndrome
LAIV	Live-attenuated influenza vaccines
IIV	Inactivated influenza vaccines
MMR	Measles – Mumps – Rubella vaccine
ICU	Intensive Care Units
SOTR	Solid-organ transplant recipients
ILI	Influenza-like illness
IDSA	Infectious Diseases Society of America
SAGE	Strategic Advisory Group of Experts
IBD	Inflammatory bowel disease
CKD	Chronic kidney disease
ACG	American College of Gastroenterologists
RSV	Respiratory syncytial virus
GP	General Practitioner
HSCT	Haemopoietic stem cell transplant

1. INTRODUCTION

1.1 What is cocooning

Most healthcare professionals, have encountered the idea of cocooning in their practice and even encouraged it. It might have been in the form of a general practitioner asking their vulnerable elderly patients to stay at home during the current COVID-19 pandemic or an obstetrician advising the close contacts of the pregnant woman to be vaccinated against pertussis and influenza in order to protect the upcoming newborn infant.

The term cocooning comes from the noun cocoon, which refers to the silky envelop many insects create when on the chrysalis state. It derives from the French *coucon* or *cocon* (from the old French *coque)*, which means "shell". Similarly, in Latin encountered as *coccum* ("berry") and in Greek as *kokkos* ("berry, seed"). Cocoon was later used as a verb in the 1850s meaning "to form a cocoon" and the term extended since to mean to "to protect from dangerous environment" (1, 2).

In social science, the term was made popular in 1981 by Faith Popcorn, a marketing Consultant, when she used it to re-introduce the trend of staying inside one's home. The trend was initially created in Cold War, when people opted for recreational activities at home and was later applied broader after the 9/11 terrorist attack. Popcorn describes cocooning as "insulation and avoidance, peace and protection, coziness and control-a sort of hyper-nesting" (3-5).

Recently, the term has been used during the COVID-19 pandemic, as either "cocooning" or "shielding", to describe the measures to protect the vulnerable populations, such as elderly and people with chronic conditions by staying at home and minimising contacts (6).

In medicine, cocooning is a well-known vaccination strategy, in which close contacts of a vulnerable individual, who is not able to be vaccinated, get immunised. This practice indirectly creates a protective environment for the "at-risk" individual through reduced transmission of the referred vaccine-preventable disease. This vaccination strategy will consist the core of this review (1).

1.2 The conception of cocooning vaccination strategy

Despite pertussis vaccine availability since the late 1940s and high vaccine coverage, pertussis has started resurging since the 1980s mainly in developing countries, but epidemics have also occurred in developed parts of the world. In 2012, the USA faced the highest incidence since the pre-vaccine period with nearly 50,000 cases reported. WHO noted similar trends in the UK, France, Canada, Australia and Latin America and the worldwide cases from 500,000 (early 1980s) climbed to 2.2 millions in 2012 (7-11).

What became evident was the change in epidemiology with increased incidence amongst school-aged children, adolescents and adults whilst in the pre-vaccination era, pertussis used to be a disease of younger children (12). This change along with the inability to vaccinate young infants below 6 weeks of age and their inability to mount adequate immunological response before the second dose of DTwP/DTaP, account for the highest burden of pertussis in infants. The most vulnerable group with the greater morbidity and mortality is the group of infants less than 3 months old. According to USA national data, collected between 1993 and 2004, the majority of hospitalisations in the USA were amongst infants less than 2 months of age as 84% of infected neonates were hospitalised. In addition, 95% of infants requiring mechanical ventilation and all those who succumbed were less than 3 months old (1, 13). The estimated overall incidence of pertussis in the USA, the period from 2005 to 2010, was 117.7/100,000 amongst infants less than 12 months; that was 20 times higher compared to the general population and doubleof that reported in infants less than 3months old (247.7/100,000) (1, (14).

The resurgence of pertussis and the significant threat it has posed in infants led to the foundation of the Global Pertussis Initiative in 200, in an attempt to raise awareness and decide on the best strategies to implement to control the disease. The initial recommendations included reinforcement of the current immunisation programs, booster doses for preschool age children or adolescents and immunisation of the healthcare staff (15).

Despite the above suggestions, the pertussis incidence rise continued, hence additional measures were put in place in 2005, with first the adolescent booster in countries that could financially sustain it. Three other immunisation practices were considered: maternal vaccination, neonatal one and cocooning. Taking into account data from

simulation studies including various vaccination strategies, it was concluded that cocooning would be the most effective strategy to reduce pertussis incidence in infants <3months. (1, 16, 17). On that basis and in the absence of evidence supporting neonatal vaccination, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended cocooning in 2006 as the most effective strategy to combat infantile pertussis.

Cocooning refers to the practice of vaccinating all the household members and individuals who are anticipated to have close contact with an infant. The rationale behind this strategy is based on the fact that in the majority of cases the infection is acquired via the close contacts, hence the aim is to eliminate the transmission of *Bordetella pertussis* from these individuals to the at-risk infants (7, 18, 19). Indeed, it has been shown that parents or other family members are responsible for over 70% of the pertussis cases in infants (8).

1.3 What is our current knowledge of cocooning

Although the idea behind cocooning has a well-established rationale, it has not been widely implemented. The reasons are numerous, including logistic difficulties, as it should address a large number of people in order to be effective. This entails many practical obstacles, such as who will be responsible for the vaccination of people who are not under their direct care, who will reimburse them should any untoward side effects occur and who will pay for these vaccines? These practical difficulties in conjunction with the low education of the healthcare professionals and subsequently the individuals consisting the focus of the strategy have rendered the cocooning implementation unsuccessful. Other more effective strategies have emerged, conferring higher protection for the infants, such as the maternal immunisation during pregnancy, which is now suggested from ACIP/CDC and ACOG as the primary strategy. Cocooning is still recommended, mainly as a complementary strategy in cases where maternal immunisation was not performed. In the interim, other strategies, such as new pertussis vaccines and neonatal immunisation, are under research as still pertussis and influenza remain significant public health problems affecting not only the infants but other vulnerable populations too.

These other vulnerable groups, which include the elderly, people with chronic conditions and the immunosuppressed individuals, consist a large proportion of the population in need of protection from vaccine-preventable diseases (VPDs). Despite the existence of good vaccines, the natural immunosenescence and the use of immunomodulators or chemotherapy along with the frequent hospital visits, place these people at high risk of acquiring infections with potentially devastating consequences. Although, not universally recommended, cocooning has made its appearance as a strategy to consider or even included in the guidelines of some Associations or National Immunisation Programmes (NIPs) for protection of the elderly and people with chronic conditions but mainly against influenza. The role of cocooning is less well studied here but the potential benefits of its application would qualify further attention from the medical community.

The continuous advent of new vaccines, such as the ones against SARS-CoV-2, with unknown clinical effectiveness for populations such as pregnant women, children, the elderly and immunosuppressed, make cocooning consideration more valuable than ever. Cocooning is a more personalised way of protection of vulnerable people, who in most of the cases are either family members or our patients.

1.4 The aim of the study

The current review consists a chronology of the cocooning vaccination strategy with aim to unfold the various aspects of this practice from its outset till nowadays. This review will hopefully help to formulate a more holistic view of the current role of the cocooning vaccination strategy and its potential future implications. Are there still reasons to defend and promote this practice or is it time to abandon it? In a world where despite all the progress made in the immunisation field, VPDs remain a plague and especially for the not negligible population of infants, immunosuppressed and the elderly, alternative but sustainable solutions, is a priority to be sought. Till now, there is no review available gathering all the available evidence around this strategy and referring to all its aspects and applications. This study consists a review of the cocooning vaccination strategy from the past through the present, with inclusion of its future implications.

2. METHODOLOGY

This study has been conducted in the context of the Master's degree "Vaccinations and infection prevention" and consists a review of the cocooning vaccination strategy from the past through the present, with inclusion of its future implications.

A clear demarcation between the past and the present is not easy to be made, hence arbitrarily the time where cocooning transitions from the sole complementary vaccination strategy to its current role as a secondary complementary one, in 2012, will be used as the border.

Literature review on the following international electronic medical databases till the end of December 2020 was conducted: MEDLINE (1946-2020), Embase (1974-2020), Journals Ovid, AMED (1985-2020), Global Health (1973-2020), Cochrane library and Scopus. The keywords used for the search were the following: [Cocooning AND Vaccin*] OR [Cocooning AND Immun*]. For certain chapters, such as the cocooning definition, broader search was made in relevant websites using as key words [cocooning meaning] or [cocooning definition].

Inclusion criteria included articles in English and articles which referred to either the cocooning vaccination strategy or other strategies considered for the same purpose, in order to be compared with the cocooning. Amongst the exclusion criteria were articles published in languages other than English and articles referring to cocooning as a shielding and not vaccination strategy.

3. COCOONING: THE PAST

3.1 The roots of cocooning in vaccination

3.1.1. The problem: pertussis resurgence and the vulnerable infant

Pertussis, otherwise known as whooping cough, is a highly communicable respiratory infection caused by the Gram-negative bacteria, *Bordetella pertussis,* and less often *B. parapertussis* (20, 21).

In the first half of the 20th century, the annual pertussis cases in the USA were 100,000-265,000 with a peak of incidence in 1934 at 270,000 cases and 10,000 deaths against 250,000 deaths at a world level (9, 19).

Prior to the vaccine advent, pertussis was a disease of the infants and younger children with only 1-2% of cases occurring in adults. However, this probably consists underestimations as the disease presents mildly in this age group (12).

With the advent of whole-cell pertussis vaccines (wP) in the late 1940s, the incidence started declining reaching a nadir in early 1980s with <5,000 cases annually in the US (7, 9, 20). Despite the availability of the vaccine, the trend of pertussis incidence started rising since the late 1980s. What became evident in the post-vaccination era was that the incidence trend changed to older ages with more than 50% of the infected population to be school-age children, adolescents and adults (12).

3.1.2. The burden of pertussis in infants

Despite this change in the age of population affected, the overwhelming burden of the disease seemed to be amongst infants. On the one hand, vaccination is not allowed before the 6th week of life and practically, it is usually started in the 2nd month, as per most NIPs. Also, satisfactory immunity is not achieved until after the second dose, which leaves a susceptibility window in the first months of life.

The infantile cases from USA records went up 5 times from 26.4/100,000 population in 1991 to 103.5/100,000 in 2005 and 58% of infantile deaths in this interval occurred in <2 months infants (7, 10, 22, 23). Worldwide figures show an incidence of 117.7/100,000 person-years in infants<12 months and 247.7/100,000 in <3 months of life (14).

These high rates are also reflected in the cost for the healthcare systems. According to a study of Masseria et al, the hospitalisation and follow-up cost in infants <1year varied from $3772 to $18,781 in infants >7 months and neonates respectively (14).

3.1.3. The reasons behind the resurgence

Despite the advent of vaccines, the resurgence of pertussis is a fact. Although a clear explanation does not exist, a look into the suggested ones would give a better understanding of the solutions recommended.

Initial hypotheses of poor vaccination uptake have been disputed because worldwide data show a satisfactory uptake of the vaccine, with a proportion of >95% of toddlers having received the primary series in the USA, where significant epidemics occurred and similar cover is manifested in many countries, including Greece.

The increasing awareness along with the existence of more sensitive diagnostic tests, such as RT-PCR and notification of pertussis have contributed to the increased reporting of the disease. Additionally, in light of the selection pressure exerted by the vaccines, new *B. pertussis* strains are emerging. Some of them, such as the novel alleles ptxP3 and the variant of fimbriae fim3B seem to be more virulent and have been associated with epidemics in the USA, Europe, Asia and Australia. Some other strains seem to be capable of evading the immunity induced by the pertussis vaccines (10, 11, 21).

Besides the above, although the exact duration of induced immunity is not precisely known, it does not seem to last long. The estimated duration following natural infection is 4-20 years, whilst from vaccination 4-12 years. It has become known that immunity induced by the aP is shorter than the one following the wP vaccines. What seems to be responsible for this is the different immunological pathways in each case. T-helper (Th) 1/ Th17 responses following wP lead to more effective clearance of *B. pertussis* in contrast to the predominant Th2 response induced by aP. aP vaccines have progressively replaced wP in many parts of the world - where this was economically feasible due to concerns around the safety of the latter ones. Although the initial results from the clinical trials reported similar effectiveness, more recent studies showed an alarming drop of protection following aP, which seems to start 2-3 years later. Studies in baboons and mice showed hat although aP is efficient in the control of symptomatic disease, it was not successful in the reduction of infection and transmission (11, 19, 20).

3.1.4. The suggested solutions

Since the incidence of pertussis was and remains higher than any of the other VPDs, short-term and long-term solutions had to be sought (14).

The six strategies considered in the first years of the 21st century included cocooning as the predominant one, booster doses for adolescents and adults, reinforcement of the routine childhood vaccination programmes, neonatal vaccination and consideration of maternal vaccination as well as new vaccines. These strategies with the evidence around their expected impact on pertussis control are presented here (20).

3.2 Cocooning as the main complementary strategy: the recommendations

The Global Pertussis Initiative (GPI) was established in 2001 to raise awareness about the pertussis health crisis and make recommendations to reduce the burden of disease in infants. At that time three main vaccination strategies were taken into consideration: cocooning, neonatal and maternal immunisation (1).

In 2005, Tdap was first licensed in the US. On the one hand, there was lack of data supporting the neonatal and maternal immunisation in pregnancy and on the other hand, evidence from mathematical modelling studies was suggesting that the combination of cocooning with adolescent immunisation and the existing childhood NIPs would reduce the infantile pertussis by 50% (1, 24).

Taking into account the above, the ACIP of the CDC recommended officially in 2006 the cocooning as the preferred preventative strategy to combat infantile pertussis. Cocooning vaccination strategy entails the single administration of Tdap to all close contacts of a newborn, including the parents, siblings, grandparents and all their caregivers. An interval of two years from the last Td dose was considered as safe for Tdap. In order to be successful, all potential household contacts need to be vaccinated at least two weeks prior to the contact with the infant in order to timely create a “cocoon” of protection (18, 19, 23).

The rationale is simple and grounded on the idea that pertussis is transmitted to infants via a close contact. Hence, if the contact circle remains pertussis-free, then the infant should be protected. (8, 9)

In 2008, CDC published further recommendations for the protection of infants and their mother from pertussis and once more, cocooning was placed in the centre of these suggestions (25).

3.2.1. Sources of pertussis transmission

Although in many of the cases of infantile pertussis, the infection source is unknown, as shown in "Table 1", understanding of transmission dynamics is crucial in order to design the relevant preventative strategies. When the source is identified (40-78% of the cases), household members and mainly parents seem to be responsible with a variation between 15% and 76% in the majority of studies (7, 23, 26-32). In three other studies conducted in Canada, Netherlands and Australia (33-35), it was shown that siblings were responsible for the transmission in a greater proportion (41-53%) despite the complete vaccination of them with either wP or aP.

3.2.2. Implementation and uptake of cocooning

The suggestion for cocooning was predominantly made in the USA by ACIP/CDC in 2006. Amongst the countries that also adopted cocooning were France (since 2004) (36, 37), Germany and Australia from 2010 to 2015 (38, 39). Switzerland, Italy and Spain also followed (39, 40).

Despite the recommendations, the actual implementation and acceptance of the strategy has been challenging (28). From the various studies conducted in many parts of the world assessing the uptake of cocooning, the percentages remained low the first years after the recommendation.

Although the list is not exhaustive, "Table 2" shows the highly variable uptake by the close contacts (CCs). It is difficult to assess the complete cocooning but still the numbers for the partial cocooning are low. Where high uptake was achieved, such as in the two

studies of Healy et al (41, 42), significant resources were invested for HCW and maternal/CCs education as well as the organisation and staffing of the relevant clinics and the provision of Tdap. In the second study of Healy et al (42), the estimated cost of the maternal and three household contacts (based on the median number of CCs per newborn) vaccination with a target to vaccinate 86% of the CCs of the 5000 yearly deliveries was $800,000/year.

In other studies, conducted at population level the rates were similar. As per the National CDC Survey in 2008, only 5% of the adults who consisted close contacts of an infant had received Tdap. According to a Californian survey, before the introduction of free vaccines for the postpartum women, only 23% of the birth hospitals were offering the vaccine. However, even after the provision of free vaccines, only few hospitals were able to offer vaccines to other CCs due to the inability to vaccinate non-patients (43). In Switzerland, it was demonstrated that 23% of mothers and 17% of fathers were vaccinated and vaccination of all household contacts was achieved in only 7% of the families (40).

3.2.3. Effectiveness data

In order to decide whether a vaccine strategy can work, the knowledge around the effectiveness of the strategy is crucial. Data regarding the effectiveness of cocooning are limited and this is mainly down to the fact that it has been difficult to implement. In order to be considered effective, all the newborn contacts have to be vaccinated, ideally 2 weeks prior to the contact with the neonate. However, only rarely does this happen making the effectiveness assessment even more difficult (44).

Given the fact that the source of infantile pertussis is not always known in and in some studies this number approaches >50% (25), vaccinating all the known CCs seems as the minimal, yet difficult, goal that policy- makers should aim at (45).

Although there were studies showing some effectiveness of cocooning, these were mainly simulation studies conducted before the actual implementation of cocooning. As per the simulation study of van Rie and Hethcote, six vaccination strategies were compared. Three of them included cocooning either on its own or along with the children vaccination programme or with adolescent Tdap boosters. It was found that parental (not complete

cocooning) vaccination would lead to 70% reduction of pertussis in infants <3months and 65% reduction in 4-23 months infants (16, 7).

Data from effectiveness studies following the actual implementation of cocooning are minimal and conflicting. Amongst studies showing some effectiveness were two Australian case-control studies showing the VE (Vaccine Effectiveness) after Tdap vaccination of both parents. The first study showed reduction of pertussis by 51% in <4 months infants after the implementation of parental vaccination (46). The second one (47) demonstrated a VE of 77% and after adjustment for maternal education, number of siblings and primary series of immunisations went down to 64%. None of these results were statistically significant. Another Australian study assessing the effectiveness of cocooning in the pertussis incidence in <12months infants comparing the two periods (post-cocooning: 2009-2014 vs pre-cocooning: 2002-2007) showed a reduction of disease from 6.7% to 3.3% in the second interval (p=0.0067) (48).

On the other hand, in a cross-sectional study, no change in the pertussis incidence was demonstrated following the introduction of the strategy in postpartum women in a centre in Houston. Although 67% of women had been vaccinated prior to discharge, there was no effect in the pertussis incidence, which is partially explained by the fact that not all contacts were vaccinated (49). Healy et al compared the incidence of pertussis in three periods: pre-cocooning (May 2004-Dec 2007), during maternal postpartum vaccination (Jan 2008-May 2009) and cocooning (June 2009-Aug 2011). No difference in pertussis infections and hospitalisations were noted in the three periods for infants <6months (50). One more study assessing the impact of parental immunisation, in an area where free parental Tdap was offered, concluded that the pertussis incidence rate was similar between infants of vaccinated (1.9/1000) and unvaccinated (2.2/1000) parents (adjusted HR 0.91) (51).

Although most of the above studies do not refer to the complete cocooning and have their own limitations, it is shown that even in centers where cocooning was funded and offered to parents, its effectiveness was limited.

The SAGE (2010) and ACIP evaluation of cocooning (2011) concluded that the strategy was not functional at a national level as the Tdap uptake by the postpartum mothers and the other household members was minimal (8, 25). In addition, WHO concluded that

given the lack of data on the direct evaluation of cocooning efficacy, it is not able to make a formal recommendation around cocooning (1).

In light of the above, cocooning was considered a suboptimal strategy to control the burden of pertussis in infants (23). Other measures considered simultaneously for the prevention of pertussis morbidity and mortality in infants are elaborated afterwards.

3.3. Other measures to prevent pertussis

Realizing the problem of waning immunity with the pertussis vaccines, the ACIP recommended in 2006 the routine administration of **Tdap for adults aged 19 to 64 years**. Especially, for adults anticipating having contact with infants <12 months old, a single dose of Tdap is suggested with a minimum interval of 2 years from the previous Td (25, 52). In the revised 2008 ACIP recommendations, the age range expanded to: from 10-64 years, whilst in the 2011 ACIP recommendations, this was further expanded to adults above 65 years old. In addition, it was recommended that adolescents and young people 11-18 years after completion of their childhood program, to receive a single dose of Tdap ideally at 11-12 years of age (1, 10, 53).

The data regarding the impact of these strategies on infantile pertussis reduction were conflicting. Two studies conducted on adolescent immunisation concluded that it led to a reduction of pertussis cases in infants less than 6 and 12 months respectively (7, 46). On the other hand, WHO advised that there was insufficient data to support the effect of that measure in the protection of infants. This could be attributed to the suboptimal coverage, the reduced social contact of adolescents with infants but there was also evidence that this may be down to the incapacity of Tdap to prevent asymptomatic infection, hence transmission, which is the core of the cocooning strategy (8, 11).

In the absence of an effective strategy to protect infants from pertussis, other strategies had to be considered, amongst which was **maternal immunisation during pregnancy**. The rationale of passive transfer of maternal antibodies to the fetus and infant sounded an attractive alternative approach that would confer more direct protection to the newborn since birth (44, 46).

Amongst other strategies considered but not yet recommended as the evidence around it was conflicting, was **neonatal vaccination** (45). The idea is that neonates could be protected much earlier than the primary schedule which starts at 6-8 weeks and that was based on evidence of immune responses to pertussis in neonates (8, 19). However, the main concern was about blunting of subsequent immune responses to the primary schedule vaccinations that follow. This did not seem to be a problem when monovalent aP vaccines were given at birth (12, 22). Neonatal vaccination would theoretically be a promising strategy to reduce the burden of pertussis in infants. However, since a monovalent aP vaccine is not available and more evidence is required around the safety and interaction with other vaccines, this suggestion warrants further investigation (11).

Although pertussis resurgence is not attributed to low childhood vaccination coverage, the outbreaks around the world highlighted the need to **promote the existing primary vaccination series** and achieve maximal prevention in children.

Both first-generation wP and second-generation aP vaccines have resulted in pertussis disease and death reduction in children but they both have their limitations. It becomes evident that **newer vaccines**, which could overcome their shortcomings would be the best solution (20, 54). Additional antigens, different adjuvants and monovalent aP vaccines have been considered and live-attenuated intranasal vaccines are in trials (11, 12, 54, 55).

3.4. Healthcare workers immunisation

Cocooning in order to be effective should be complete and all close and potential contacts should be vaccinated timely. An often dismissed but crucial group in order to achieve this is the healthcare worker (HCW) body.

In an attempt to reduce the burden of pertussis in infants, ACIP/CDC in 2006 recommended the routine administration of Tdap for all HCWs having direct contact with patients. In 2011, this was further expanded to include all childcare providers (56). These recommendations were supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC) (25, 52). The USA, Australia and nine European countries adopted Tdap boosters for HCWs in order to prevent transmission of pertussis to infants (7, 57).

Despite the recommendations the vaccination coverage has remained at levels inadequate to offer protection to the vulnerable infants. As per CDC data, the Tdap coverage amongst HCWs in 2005-2010 was 20.3% and in high-income countries has been variable at 11-85% (7).

The Tdap coverage has been largely associated with mandatory application of the vaccine, which is not adopted though universally and there is a lot of debate around its pros and cons. Studies conducted in HCWs directly involved in patients' care show minimal knowledge of the need for Tdap boosters. According to a French study, only 13% of the Nurses and 22% of the Doctors were aware of the Tdap need (58). Another Dutch study demonstrated that around half of the HCWs had the intention to be vaccinated against pertussis (57). These studies reveal that knowledge gap and personal beliefs explain most of this trend. HCWs' education on vaccination and cocooning could act as a significant starting point to improve this picture than actually implement mandatory policies (59).

3.5. Cocooning and influenza

3.5.1. Burden of disease in infants

Influenza has been responsible for high morbidity and mortality rates in infants and especially those under 6 months old. Hospitalisation rates of healthy infants are comparable to those of high-risk adults and even higher for infants with underlying, and especially respiratory conditions (1, 44). Admission rates in the USA were five times higher in infants <5months compared to those 6-23months and the mortality rate in the first age group was 0.88cases/100,000 children population (60, 61).

3.5.2. The rationale of cocooning in influenza and the recommendations

Prevention of influenza in the vulnerable group of infants is of high importance. Since protection through vaccination is impossible in the <6 months infants given the poor immunogenicity in this age, the protection has largely relied upon the traditional preventative measures. These include hand and respiratory hygiene and contact avoidance

with individuals having influenza, which have recently been proven effective through their application for the COVID pandemic (62).

The idea for infantile cocooning against influenza emerged from the need to protect more effectively this group and it was based on data from the use of cocooning for pertussis. The rationale here is slightly different given the fact that infants < 6 months old are not eligible for vaccination due to suspected low immunogenicity and risks from side effects with the latter (1).

Despite inadequate data around its usefulness, cocooning has been suggested by CDC and AAP since 2011. Household contacts and caregivers of children < 5years and especially infants < 6months old were urged to receive influenza vaccine at least four weeks prior to the contact (1, 63) .

3.5.3. Role of maternal immunisation against infantile influenza

Infants born to unvaccinated against influenza mothers have little - if any - immunity against it. For this reason, cocooning has been recommended as a measure to create a cocoon of protection around the vulnerable infant. Compared to pertussis control, the idea of the MIP appeared much earlier for influenza.

Cumulative data from studies on women who received IIV during pregnancy were convincing of the protective role of antepartum vaccination for both the infant and the mother. Apart from the VE on infantile influenza reduction, other positive outcomes included protective effect against low birth weight and preterm birth (61).

A small randomised-trial conducted in 1990s (64), in pregnant women receiving TIV in the last trimester showed that their infants had even higher IgG antibodies than the mother at birth and at 2 months old. Other studies showed antibody persistence till the fifth month of life (71, 72). Reduction in the influenza incidence rates for infants <6months was estimated at 41-63% (65, 66), and for hospitalisation at 39-91.5% (65, 67, 68).

CDC/ACIP recommended MIP for influenza in 2004 and WHO recognised pregnant women as a high-risk group and reinforced the strategy in 2012 (69). Despite the official

recommendations, the uptake remained low (70). Prior to the 2009-2010 pandemic, the estimated coverage in the USA was <15%. Although the pandemic has urged more women to receive the vaccine, the coverage remained <50% and far beyond the goal of 80% made by the Healthy People 2020, necessitating other measures, such as cocooning (44, 71).

4. COCOONING: THE PRESENT

4.1. Cocooning in infants at present

4.1.1. Change in recommendations: cocooning as a secondary strategy

The recommendation for infantile cocooning against pertussis, made in 2006, remained the primary complementary protective method until 2011. Data regarding the rising pertussis incidence on the one hand, and the ambiguous effectiveness on the other hand, necessitated new measures imposition.

Vaccination with Tdap in pregnancy has gradually evolved as a promising, safe and effective strategy. For this reason, and in view of the cocooning limitations, this strategy is now recommended by many countries as the predominant complementary one in order to protect infants from pertussis (23).

Based on a CDC-decision analysis proving superiority of MIP, the ACIP revised its recommendation in **October 2011** by suggesting administration of Tdap in all unvaccinated pregnant women from the late 2nd trimester of pregnancy. In case of no Tdap receipt in pregnancy, postpartum maternal vaccination was suggested. In **March 2012**, the American College of Obstetricians and Gynecologists (ACOG), published the above recommendations made by ACIP/CDC. Following the USA epidemic of pertussis in 2012 and evidence supporting the quick waning of maternal antipertussis antibodies, the ACIP proceeded in revision of its recommendations in **October 2012**, to the ones valid till now. Tdap was recommended for all pregnant women between 27 and 36 weeks of gestation, in every pregnancy despite their previous vaccination status. This was further supported by ACOG and AAP (9, 18, 72).

Where pertussis remains still epidemic and when the mother has not been vaccinated during pregnancy or early enough, cocooning remains to consist a priority (71). However, the cocooning is now used more as an additional strategy to the maternal vaccination and not as the sole one against the protection from infantile pertussis (18).

4.2. Comparison of cocooning with maternal immunisation

In table 3, the accumulated data from various studies measuring the vaccine effectiveness (VE) of the MIP strategy are presented. Although it is difficult to compare these studies because of their different settings, it is evident that the VE is higher than the one for cocooning strategy in the section 3.2.3. The range of VE with maternal Tdap for infants < 3months of age is between 89% and 93%. Only one study showed suboptimal protection with reduction of cases in infants <6 months by 69% (73), whilst the protection against hospitalisation was at 94%, concluding that although severe pertussis disease was prevented efficiently, the prevention of milder disease was suboptimal.

Besides the physiological benefits of the two strategies, in order to decide whether a vaccination strategy should be promoted, economic parameters should be taken into account. Apart from the VE of each strategy, other factors considered are the benefit for the individuals which is calculated in quality-adjusted life-years (QALYs) gained and the expected reduction of the disease incidence. On the other hand, the cost of each strategy is estimated or the number of people needed to vaccinate (NNV) in order to prevent one case and whether there is any cost-benefit for the society.

In the tables 4-6, studies referring to economic parameters of cocooning, maternal vaccination or both are presented. The first study (74) was designed in Netherlands in order to compare the cost-effectiveness of three strategies (parental cocooning, MIP and neonatal vaccination, which is not presented here). The second study of Terranella et al (75), consists another simulation decision and cost-effectiveness analysis of three vaccination strategies, based on the 2009 US births and the study of Fernandez-Cano et al (76) took place in Spain based on epidemiological data of 2009-2011.

What is evident is that the estimated reduction of pertussis is higher with the MIP and the cost lower than the cocooning, which show the cost-effectiveness of MIP. From a payer's

perspective, cocooning was more costly in all but one study but when assessed from a societal perspective, parental cocooning was found as the most cost-saving strategy and it would lead to more QALYs gained as it also benefits the adults vaccinated (74).

Cocooning is cost-effective but less than the MIP strategy; it can benefit though more people. Although MIP is projected as the primary vaccination strategy in order to protect infants from pertussis, it is important that both strategies are encouraged as cocooning acts as an important complementary strategy for the cases of women that have not been vaccinated during pregnancy or women vaccinated but not timely in order to protect their newborn (38, 39, 77-79).

4.3. Cocooning and the immunosuppressed population

The immunosuppressed population (IP) consist a heterogenous group of individuals with various degrees of immunosuppression. It includes people with a primary immunodeficiency, such as B-cell, T-cell, combined, phagocyte or complement deficiency, or most commonly secondary immunodeficiency due to an acquired condition (e.g. haematological malignancy, HIV infection, solid organ/bone marrow transplantation, anatomic or functional asplenia), or immunosuppressive medications (e.g. steroids, chemotherapy, biologic agents). Although not strictly part of the IP, it is known that due to immunosenescence, the elderly population have reduced immune responses following vaccination and protein-malnourished people are also deemed to be immunosuppressed. The above list is not exhaustive and people with other chronic conditions have a degree of immunosuppression due to their underlying condition or medications they take, such as patients with chronic kidney disease, inflammatory bowel disease, diabetes mellitus, asthma on high dose of corticosteroids and autoimmune or rheumatological conditions, for which they are on immunosuppressants.

The importance of cocooning for these groups of individuals and the spectrum of diseases that is considered will be explored in the following sections (80).

4.3.1. Role of cocooning in the immunocompromised group

Vaccine-preventable diseases (VPDs) consist a significant cause of morbidity and mortality in the group of IP. Immunosuppression places them at a higher risk of severe presentation and complications from the acquired VPD. The immune system dysfunction leads to poor seroconversion following immunisation, which in most of the cases is still recommended especially for the inactivated vaccines (81). With regards to live-attenuated vaccines, except of special circumstances these are contraindicated. Even the inactivated vaccines cannot be given in patients with SCID or at least for six-months post-transplantation (80). Despite previous vaccination, the humoral immunity obtained might be compromised, especially in patients receiving chemotherapy and monoclonal antibody treatment, such as rituximab (82). Not only the number, but also the function and 'memory' of immune cells are affected compromising the post-immunisation protection. The frequent hospital visits is another risk factor as the exposure to VPDs is even higher for the group of IP (83). The poor vaccination uptake amongst this population also contributes to the increased vulnerability and this is mainly due to their limited knowledge and the side effects fear (84, 85).

4.3.2. Applicability of cocooning in the spectrum of diseases indicated

The cocooning vaccination strategy encourages the CCs of the IP to be vaccinated in order to reduce the possibility of transmission to the vulnerable person. This has been supported by relevant guidance published by IDSA in 2013, the CDC-ACIP as well as the NIPs of each country (86, 87).

Influenza

Influenza is responsible for significant morbidity and mortality in the IP. The hospitalisation and mortality rates in oncological patients and solid-organ transplant recipients (SOTR) are at least four times greater than the general population. Depending on the solid organ, the morbidity rates vary from 2.8/1000 persons/year in liver to 41.8/1000 cases in lung transplant recipients. Additionally, in this group, there is the risk of acute and chronic transplant rejection (85, 88).

The best way of influenza prevention is vaccination. The two types of vaccines are the live-attenuated influenza vaccines (LAIV), which are contra-indicated for the most immunocompromised individuals and the inactivated influenza vaccines (IIV). The latter ones are recommended for this group except of circumstances of severe immunodeficiency, such as intensive chemotherapy, monoclonal antibody therapy against B-cells or transplantation the previous 6 months (80).

Although IIV are recommended in the majority of IP and the elderly population as considered safe and offering a degree of protection, the immunogenicity conferred seems to be suboptimal (80). Low seroprotection has mainly been noted in patients with haematological malignancies on chemotherapy (89), but this has been reported in people with solid tumours too. In a study of people with neurological malignancies, the proportion of satisfactory antibody responses were equivalent to those in elderly people (23-37%) compared to the >70% responses in the general population (88). Similarly, lower rates (43-90%) are reported in SOTRs (85).

Another concern is that the immunisation rates in this group remain low, with <50% of oncological patients to be immunised against influenza (83, 88, 90, 91), 38-51% of SOTR (85) and 28% of patients with IBD in relevant studies (84).

The above underscore the importance of other measures in order to protect this vulnerable population from influenza and the cocooning offers an alternative and efficient way of protection.

The CDC and the IDSA reinforce cocooning through their recommendation of yearly vaccination with IIV of all close contacts of IP. If not available, LAIV can be administered alternatively but in this case contact for 1 week with the vaccinated individual should be avoided, especially in recipients of haemopoietic stem-cell transplant (HSCT), patients with graft-versus-host disease (GVHD) and those with severe combined immunodeficiency (SCID) (80, 85, 92). The American College of Gastroenterologists (ACG) also recommend the IIV vaccination of all household contacts of patients with IBD on immunosuppressants (84).

In the Greek NIP, other groups for which influenza vaccination is recommended, recognising the importance of cocooning are the following:

- chronic pulmonary disease and asthma
- severe cardiac conditions
- sickle cell disease and other haemoglobinopathies
- diabetes mellitus
- chronic kidney disease (CKD)
- neurologic and neuromascular conditions
- pregnant women
- morbid obesity
- children on chronic aspirin

Down Syndrome has also been included in the latest 2020-2021 recommendations (93). With regards to the elderly, the recommendation on the Greek NIP is people above the age of 60 years to be vaccinated with IIV, whilst in WHO the age limit has changed during the COVID-19 pandemic from 65 years in the 2012 guidance to 50 years old and above (62).

Apart from the CCs of the above groups, HCWs should be also vaccinated. It is not only for protection of themselves, but also to create a cocoon of protection for their patients. Especially, for clinicians coming into contact with the abovementioned vulnerable populations, there is a significant ethical dilemma how acceptable is to become the source of transmission of a VPD, with its devastating consequences (94). Recommendations of both the Greek NIP and WHO include the HCWs in their instructions. According to the latest WHO-SAGE instructions for the COVID-19 pandemic, the highest priority group for vaccination are the HCWs and the elderly. This is also to protect the high-risk individuals from COVID-19 disease and influenza as there seems to be increased burden with co-infection of the two (62).

In contrast to other VPDs, for influenza there are clear guidelines with regards to cocooning as shown in the IDSA, CDC and Greek NIP. Despite this, from the very few studies conducted, it seems that the awareness and uptake of IIV amongst CCs of the IP is suboptimal. In a study assessing (95), the influenza vaccination status and motivations of oncological patients and their escorts; the patients stated that 65% of their CCs were vaccinated. 72% of the actual caregivers reported to be vaccinated. What is surprising though is that two-thirds of the caregivers had motives other than their relative's illness

to be vaccinated. Another more recent study conducted in the USA amongst oncological population showed that 71% of patients' CCs were vaccinated with influenza and in the study of Rensink et al 44.9% of the CCs had received the flu vaccine. Similar to the first study, around one-third of the caregivers had taken into account the vulnerable status of their relative (90, 96).

Measles

Ambiguity about the MMR vaccine led to low vaccination rates resulting in measles epidemics around the world. Only 7 European countries achieved the WHO 95% immunisation target leading to epidemics such as the one of 2017- 2018. WHO and CDC estimate that 142,000 people died in 2018 from measles (82, 97). This above in association with the vulnerability of IP and inability to receive MMR as live-attenuated vaccine, points out the significance of other ways of protection, such as cocooning, which comes to play a pivotal role towards this attempt. Measles in the IP can lead to severe respiratory manifestations, but also disseminated disease and death even in people previously immunised (82, 98).

As per the IDSA (2013), CDC/ACIP and Greek NIP, all immunocompetent households of an immunocompromised person should receive the MMR. No special precautions are required and there have been no reported cases of contraction following vaccination (86). In the Greek NIP, HCW immunisation as well as of the non-immune women of reproductive age is suggested recognising the risk for the fetus too (99). Protection against measles, although not officially recommended, should be also offered to the CCs of other vulnerable individuals, such as patients with CKD or liver failure, in the verge of transplantation as they cannot receive live vaccines. The period following transplantation is also sensitive and re-initiation of live vaccines is recommended at least 2 years later. The uncertainty though surrounding this guidance and the HCW's and patients' fear leave them unprotected for much longer periods.

Varicella and herpes zoster

The varicella infection incidence amongst paediatric oncological patients is estimated 5% versus <0.5-2% in community. The risk of disease contraction and severe complications amongst the IP, prompts the establishment of additional measures, such as cocooning, in order to protect them from these viral infections (83).

As per the CDC and the IDSA, the household members of the immunosuppressed individuals are advised to receive the live-attenuated varicella (VAR) and herpes zoster (ZOS) vaccines. In the Greek NIP, immunisation of reproductive-age women is also suggested (99). The only precaution taken is in the case of skin lesions development in the vaccinated individuals, where contact should be avoided until these are healed (80). The varicella status of the immunocompromised individuals is important to be assessed and when time allows before the initiation of immunosuppressive therapy, VAR should be administered (84).

Assessment of cocooning for these infections is limited in research. In one study looking at patients with IBD, although 28% of them could not recall prior chickenpox infection, none of them, neither their children had been vaccinated (100).

Rotavirus infection

Rotavirus infection can lead to prolonged and generalised disease in the IP. The main way of protection is through common hygiene measures and vaccination of the infants in contact with the immunosuppressed individuals, as part of cocooning (100). As per IDSA guidelines, infants until the age of 7 months should be vaccinated and the severely immunosuppressed people should avoid contact with the infants' diapers for 4 weeks and all household members should wash their hands thoroughly after handling the diapers (80, 86). So far, no cases of rotavirus infection to the IP have been documented after infantile vaccination in the environment (101). The vaccination rates amongst CCs and effectiveness of cocooning against rotavirus have marginally been evaluated and in a study of the CCs of IBD patients, only 22% of their infants were vaccinated (100).

Hepatitis B

Apart from the risk of reactivation of Hepatitis B virus (HBV) infection amongst the IP (83), the higher rates of chronic infection, cirrhosis and hepatocellular carcinoma are another considerable risk (102). Due to the contamination risk through dialysis and blood transfusions, CKD patients are at high risk too (59). The low vaccination levels amongst these patients (84), prompts for reinforcement of the preventative measures for the protection of these populations. Apart from vaccination encouragement of the patients and the common hygiene measures, cocooning is another way of protection of these individuals from the risk of HBV and it is not routinely recommended for the environment of these patients. Further awareness is needed amongst HCWs and this information is crucial to be delivered to the families of high-risk groups.

Pneumococcal disease

In a Danish study the risk of invasive pneumococcal disease was 50 times higher amongst patients with haematological malignancies (83). The elderly is another group at risk of severe complications and high mortality. Other patients at risk, with possible suboptimal seroconversion upon immunisation are patients with HIV infection and those with Nephrotic Syndrome and CKD. Apart from the IDSA and NIPs recommendations on vaccination of the high-risk groups of pneumococcal infection, there is no official suggestion of vaccination of their CCs. This lies once more to the HCWs, who should make sure that the vaccination status of their patients and their CCs is updated.

Yellow fever and typhoid

Yellow fever and typhoid are endemic in certain areas and vaccination before travelling is essential. Both yellow fever and oral typhoid vaccines are live-attenuated, hence the IP cannot receive them except of special circumstances, such as HIV patients with minimal immunosuppression. The CCs of these individuals though are recommended to receive both vaccines depending on the risk of the country they travel to. Apart from the hand hygiene measures for typhoid and mosquito bites prevention for yellow fever, cocooning is recognised as an important strategy to protect these individuals. Although there is no

direct person-to-person transmission, the Aedes aegypti mosquitoes become infected when they bite a person who has yellow fever, hence prevention of the infection in the CCs is also important.

Cocooning applications amongst high-risk groups, such as the IP are numerous. The above list is not exhaustive but includes the commonly recommended vaccines and the ones to be considered. The cocooning vaccination strategy does not aim to replace the common hygiene measures and the vaccination of the patients, but it paves the way for the more complete and successful protection of these vulnerable individuals (92).

5. DISCUSSION

5.1.The pros and cons of cocooning

Cocooning vaccination strategy has been in place since 2006 and was firstly introduced for the protection of vulnerable infants. Its applications have expanded through the years to include protection of other susceptible populations too, revealing a significant role of this strategy within a large proportion of our population.

5.1.1. Limitations of cocooning

In practice, cocooning has not been widely implemented; the challenges of the strategy need to be considered in order to understand whether efforts for its promotion should continue or not. When cocooning was first recommended it had not been field-tested, which means that some of its limitations had been unrecognised (25).

Implementation difficulties

In order for cocooning to be successful, all CCs of the susceptible person should be vaccinated, which is easily said but not so easily done. The barriers here have to do with the recognition of all potential CCs of the vulnerable individual. Apart from the recognition, the vaccination should take place at least 2 weeks before the contact with the

infant for pertussis and 4 weeks prior for influenza. The reasonable question which arises is, who is responsible for prescribing and administering vaccinations for all these people? When it comes to infants, although the Paediatrician has traditionally the role to inform and vaccinate, this lies with the Obstetrician and Midwives who are the people caring for the pregnant women during the time that vaccination should take place (75). Obstetricians might also not be fully aware of the strategy and find it difficult to provide care beyond their scope (1, 23).

Usually, for the infantile cocooning, relevant units are established in maternity hospitals but even in this case the hospitals might be unable to provide vaccines to non-patients. In California, when cocooning was offered in hospitals, the main focus of the strategy remained the mother (43). These accessibility issues apply for the IP too, when the vaccination is not offered in the patients' visits (59, 84). In a study conducted to assess the immunisation attitudes of Paediatric transplant Hepatologists, in 85% of the centres, the HCWs were routinely asking about the vaccination status of the CCs, only 6% of them though were able to provide the vaccines (103). The above impracticalities transfer the responsibility to the Primary care and Paediatric Physicians, but similar challenges appear, such as the difficulty to approach the other family members and the busy schedules of adults.

A significant barrier for the IP's cocooning is that there is no clear guidance as to who provides their care. The immunosuppressed individuals often consider their Specialist Physician responsible, however that might not be so clear amongst HCWs. In a study, 65% of Gastroenterologists considered the Primary care Physician responsible for the vaccination recommendations and administration. Another survey revealed that only 29% of the Family Doctors were confident in making these recommendations for IBD patients (104).

The absence of clear guidelines is another reason for limited implementation. Although the IDSA and CDC have published relevant instructions for the IP and their CCs, for other vulnerable groups, such as transplant candidates or patients with CKD, specific evidence-based guidance seem to be lacking (59, 103).

Knowledge gap

Apart from the logistic challenges, one of the most well-recognised barriers of cocooning is the knowledge gap amongst the HCWs, which reflects to the patients and their families.

When cocooning was first recommended, the vaccination providers did not have the training required, compromising its implementation (1). In a recent study (105), assessing the paternal vaccination attitudes, although the majority of fathers had a positive attitude towards vaccination, only 40% of them showed interest in immunisation counselling and only 15% were updated with their vaccinations, revealing a knowledge gap and a lack of education interest.

In a survey assessing the vaccination knowledge of Gastroenterologists, one-third of them would give live vaccines to the IP and another third would withhold live vaccines from the immunocompetent patients and their families (84). In another study (100), the vaccination status of the children household contacts of patients with IBD was assessed in a Gastroenterology Department in Poland and only 40% of children were immunised with at least one of the recommended vaccinations. The main reason for the low uptake was that the patients did not consider immunisation necessary, which reveals a significant lack of knowledge (100). In the same note, the fact that the majority of the CCs of oncological patients in the studies of Price et al and Rensink et al did not include the vulnerability of their relative in their decision making reveals similarly this lack of knowledge (90, 95, 96).

Safety concerns consist other common misconceptions. Fear of disease exacerbation following vaccination has been expressed from both IBD patients and their Physicians despite the lack of evidence showing this association in several studies amongst rheumatological patients (84, 88, 89). Fear of influenza vaccine side effects has been expressed in various studies amongst IP and their CCs. The knowledge that this happens in a small proportion of patients (5.8% in a large Toronto study) is important to be delivered to the individuals involved (90).

Cost of strategy

Cocooning cost is a significant barrier in its successful implementation. This cost has to do with the funding for the CCs' vaccination as well as the creation of units for that purpose, staffing them and educating the staff (23). In a CDC analysis, the cost for just the parental and one grandparent cocooning was US $513.2 millions compared to US $171.2 millions for the MIP or postpartum maternal vaccination alone (75). The annual cost in a postpartum Unit in Houston was US $800,000 in order to vaccinate a mean of 4 people per newborn (42). What various studies conclude to is that in areas, where pertussis incidence is low and the vaccination coverage high, cocooning is inefficient and resource-intensive in the infantile pertussis prevention (12, 106-109).

Low effectiveness

The effectiveness of cocooning strategy varies and it does not seem to be higher than 77% (16) for infants against pertussis compared to 69%-93% with MIP (19, 110). However, the effectiveness studies are minimal, and they mainly assess partial cocooning, which is not the goal in order to have the best possible outcome.

In addition, what has been shown is that aP vaccines although effective in the prevention of symptomatic disease do not seem to reduce colonisation, hence asymptomatic transmission (19). This compromises the effectiveness of cocooning against pertussis, revealing that other strategies are needed. As new vaccines and neonatal vaccination are still not used in practice, in the interim, the most efficient-looking strategies, such as MIP, need to be promoted (23).

5.1.2. Benefits of cocooning

The limitations and implementation challenges of cocooning are numerous. Besides these though, there are other essential and not well-recognised benefits that merit the medical community's attention.

Effectiveness

From a payer's perspective, cocooning might not be the most cost-effective strategy, from a societal perspective though, it is the most beneficial strategy for the total of the population. In the neonatal vaccination, it is only the newborn benefited and in the MIP the mother too. When it comes to cocooning, however, all the people vaccinated are protected. That is why, it is presented as the strategy which leads to more QALYs gained and deemed to be cost-saving for the society (74, 111, 112).

Important as a complementary strategy and not only

Cocooning was initially introduced as the primary complementary strategy for the protection of infants against pertussis and following the evidence regarding MIP, it is nowadays considered the secondary complementary strategy for the protection of infants. Although complementary, it remains a very important one for the situations, where the traditional strategies do not suffice. Although MIP is considered superior for the protection of infants, the low vaccination rates amongst pregnant women, the ongoing safety concerns and the birth of preterm infants, underline the important role of this strategy in order to create a protective cocoon for the infant (75).

The applications of cocooning expand to essentially every individual at-risk of VPDs and in the core of this group are the IP and the elderly due to their limited immunogenicity and innate immunosenescence. Where their immunisation is possible, this should remain the priority. Although complementary, cocooning remains a crucial strategy for the complete protection of these individuals and in some cases the only way of protection. Post-SOTR, HSCT patients and people with SCID are not allowed to have any vaccine, in which case their protection from VPDs relies completely on their CCs (59).

Education promotion

Apart from the logistic barriers, another barrier is the suboptimal education of the people involved in the strategy. Cocooning can provide a unique opportunity for education around the vulnerability of some individuals and the devastating consequences that the

VPDs can have on them. Educational programmes would be of paramount importance for clinicians to understand their role in this chain of transmission and how to prevent it by getting vaccinated and also to transmit this knowledge to their patients and their families. Despite the abundance of information on the internet, the Doctor's role seems to be significant and when the information comes from a trustworthy source, then the likelihood of vaccine uptake is much higher (1, 59).

Encouragement of altruism

What cocooning adds compared to other vaccination strategies is an ethical perspective, which can act as a powerful incentive, potentially overcoming the well-known limitations of the strategy.

Cocooning introduces a different way of thinking beyond the self-interest, which dominates the other vaccination strategies. In altruistic vaccination, the primary motive is the desire to benefit someone else's health and this might entail risk for the vaccinated person (113). The encouragement of this aspect amongst families empowers them to become involved in their beloved person's care and also creates a more personalised approach. It also reminds the HCWs that caring for their vulnerable patients is another significant reason to get vaccinated themselves.

5.2. Future perspectives

Cocooning role as it has been outlined in this review seems to be controversial. Despite its limitations and challenges, its role as complementary vaccination strategy is a significant one and there is ongoing need for its presence in future. It is not only for the protection of the vulnerable individuals against diseases described in the previous sections but also due to the emergence of new threats, which continuously emerge and the strive for new vaccines is a fact. Despite the medical advances, the development of more immunogenic vaccines, the addition of adjuvants, natural constrains will demand other ways of protection for some individuals. Numerous vaccines against SARS-CoV2 are making their appearance in the last few months. The fact that certain individuals cannot mount significant responses and others cannot be vaccinated, amongst them

children (some of them immunocompromised) and pregnant women, is another reason to promote cocooning. The same applies for other infectious agents, for which vaccines are under development, for example the ones against the respiratory syncytial virus (RSV). Although MIP is predominantly proposed, in view of the high transmission rates of RSV from the household contacts and potential adverse events by directly vaccinating infants, cocooning is another consideration. In a modelling study, when cocooning of the eldest siblings and parents was used along with maternal vaccination was found to be highly efficient and led to >50% reduction in hospitalisation rates (114).

Cocooning and its underlying incentives, such as altruism can also be used in the promotion of other vaccination strategies. Reinforcing people's sense of caring for their beloved ones can be more powerful than the existing obstacles of hesitancy and free-riding.

5.3.Facilitators of cocooning

In order to make the most of cocooning, suitable promotion is needed. For that purpose, certain strategies should be applied.

5.3.1. Education of HCWs and patients: HCWs play the most pivotal role in the promotion of preventative strategies, such as cocooning. They are the main source of information and consist a significant part of the cocooning themselves. In order to be able to educate and motivate, they should be first themselves educated and motivated (105). In a study examining the vaccination behaviour amongst parents in Italy and Spain, the most frequent answer was the positive effect that information from HCWs would have on their decision (40). Women with negative vaccine attitudes were more likely to be vaccinated following a HCW recommendation rather than women with positive attitudes and no information, showing the significant impact of HCWs' guidance (78).

Educating the HCWs should be the priority and there is a lot to be done given the low perception and poor uptake they often have about vaccines. HCWs have as well their own hesitancy, as the general population. In a study examining the determinant factors of HCWs around acceptance of pertussis cocooning, attitude, decisional uncertainty and the

anticipated affect from non-acceptance were the most significant ones (57). It seems that there are two main powers driving the vaccination decisions, the one is related to the risk perception (either from the disease or the adverse effects of the vaccine) and the other has to do with caring. The main target of the educational campaigns should be to bring these forces in the same direction. The best starting point is at Medical School so that it starts early and includes all future Doctors. The one focus should be education around the risk perceptions, highlighting the infective risks and the risk to transmit these infections to their patients and families. It would also be helpful to disperse some common myths around the side effects and build confidence around the role of vaccines. On the other hand, education towards boosting pro-social values can have great impact on their behaviour, including the vaccination ones (115).

Ongoing and lifelong training is crucial for every Clinician so that they are educated and sensitised about the values of such preventative strategies and pass this knowledge to their patients (84). Regarding the immunosuppressed population, the advice might be even stronger when it comes from their Specialist Physician, whom they consider as their main Physician and see more often, hence special focus should be given on their education (90). The family training also should not be confined in the safety and effectiveness concerns around the vaccines but in the education around the vulnerability of their beloved family member and the important role they can play in the prevention of any potential devastating complications (59, 85, 100).

5.3.2. Expansion of responsibilities and better communication amongst HCWs: As large part of the infantile protection starts in pregnancy, educational campaigns should aim at the Obstetricians. What would also be helpful is that Midwives are also allowed to have this role as in many healthcare systems are the first port of call for the pregnant woman. Allowing them to educate and vaccinate would certainly contribute towards increased vaccination uptake amongst pregnant women and their family members (36, 71). Maternal education seems to play a crucial role in the acceptance amongst partners and other CCs, with significant likelihood of them being vaccinated when mother is and educates them accordingly (71, 77).

GPs who routinely care for adults should also be better educated, take a proper vaccination history and use every opportunity for vaccination encouragement. In a survey

within a pertussis epidemic area, only half of the GPs were checking the pertussis vaccination status (78).

Specialist doctors have a significant role too as the main co-ordinators of the IP's care. Where electronic record systems are in place, they can be used as a port of communication with the GPs, but even written information with clear instructions can be passed from the one team to the other (84).

5.3.3. Increasing accessibility of vaccines: In the systematic review of Hutchinson et al, the most efficient strategy to increase pertussis uptake amongst parents was to offer the vaccine in the maternal unit or in the postnatal visit and this was evident in other studies too when offered in NICU (40, 116). Provision of the vaccine in the Obstetric office would also be efficient and would provide vaccination of the pregnant woman and her family on time. Although 80% of Obstetricians in New York recommended Tdap, one-third of them were not administering it (78). Financial support along with training should be offered to Obstetricians in order to be able to administer the vaccines too. As a last resort - in view of the late initiation- should be the Paediatric office. In a low-income population, provision of cocooning in the 2-week infant's visit increased the vaccination uptake to 69% (10).

5.3.4. Certain proformas and vaccination platforms: Vaccination history taking should be routine for every Clinician and not just the Paediatrician. A helpful tool would the use of certain proformas, including the immunisation status of the patient and their immediate contacts too. When this was applied in practice proved to be effective (84).

Electronic health records of vaccination status is another very useful strategy to increase vaccination monitoring (9). Organised immunisation platforms, such as the ones increasingly built upon the COVID-19 vaccines circulation, would assist in the enhancement of other vaccinations too or in the concomitant administration of vaccines, such as influenza and pneumococcus (62).

5.3.5. Understanding vaccination intentions: In two studies examining the cocooning determinants amongst parents, 78% of them had a positive intention towards cocooning. The main intention factors were parental attitude, anticipated negative affect on acceptance or not and decisional uncertainty (117, 118). Other studies showed that the high perceived vaccination benefits had the greatest impact on influenza uptake (71). Understanding the vaccination motivations is helpful in the more efficient design of vaccination campaigns, such as cocooning. Although self-interest is presented as the main driver of vaccination decision, another motivation examined in the behavioural science but not so much used in vaccination is altruism. Understanding the relation between the self- and collective- interest and how this can affect individuals' decisions can have significant implications on public health policies (113).

In behavioural studies of "game theory", which hypothesises that people are driven by their self-interest in order to increase their personal payoffs, altruistic motivation in vaccination was examined. When a passive player was added to the game whose health was dependent on the other players' choices, the vaccination decisions shifted away from the self-interest to the collective one (119, 120).

This is a very interesting observation and gives a very powerful tool to the HCWs and policy-makers. At the small family-level, where cocooning targets, educating the family of the vulnerability of their beloved person and empowering them to protect him/her against any potential deterioration can have significant impact compared to merely obliging them to get vaccinated. It creates a personalised environment of care with great respect to the individual who needs it the most (59). This perspective can have a positive impact not only in the decision-making of the family members but of the HCWs too, reminding them of their role of caring.

Triggering altruistic motives can also be used by Health authorities to improve public health outcomes. It has been shown that having this sense of doing good takes priority over other considerations, such as vaccines cost and "free-riding", where people rely on the majority's vaccination status (115, 119).

Another pattern shown to be effective is highlighting how many other people have been vaccinated too. This positive message is another tool that Health authorities could use in order to create a more welcoming environment around vaccination (120).

5.4.Limitations of the current study

Although many studies have been conducted in the field of cocooning, they focus on certain aspects of the strategy. This is the first review which attempts to gather all the applications of cocooning since its very beginning, along with the benefits and barriers, and suggests future facilitators for the promotion of the strategy.

The main limitation of the study is that it was undertaken by only one Reviewer. Also, the conclusions drawn are based on the author's personal opinion and should be evaluated with an open mind.

Ongoing evaluation of the cocooning vaccination strategy, its effectiveness, limitations and expanding applications is required in order to better establish its role in the current and future vaccination programmes.

6. CONCLUSION

Despite the Medical advances, infectious agents continue to cause outbreaks and threaten public health. On the bright side, vaccinations consist the most effective and safe answer to this threat (113). They benefit not only the vaccinated individuals but also the ones around them. On this principle, cocooning vaccination strategy was created in order to protect vulnerable infants from the high morbidity and mortality of pertussis and then influenza.

Although the initial role of cocooning was as the predominant complementary strategy for infantile protection, accumulating evidence around its limited effectiveness and logistical barriers questioned its value. The need for other vaccination strategies was crucial and maternal immunisation in pregnancy, made its appearance. Increasing data on its safety and effectiveness established it as the predominant complementary strategy for the control of the abovementioned diseases.

None of these strategies have proved to confer the expected control on the burden of infantile disease, calling for more definitive solutions, such as new and more efficient

pertussis vaccines, which are under developmental (12, 22, 24, 121). Until then though, reinforcement of these two complementary strategies could lead to better outcomes.

The role of cocooning has expanded over the years to include protection of other vulnerable groups, such as the immunocompromised, the elderly and people with chronic conditions against diseases that they cannot be vaccinated for or have suboptimal immunogenicity. Although clear guidance does not always exist and the effectiveness of cocooning has not been evaluated for these individuals, its role is crucial in the protection of these people, who do not have other way to be protected, in many occasions, and rely on the vaccination of their CCs.

Via the evaluation of cocooning through the years, its debatable role becomes apparent. On the one hand, logistic challenges, high cost and ambiguity around its effectiveness restrict its implementation. On the other hand, its role as preventative vaccination strategy for the most vulnerable individuals and as an educational tool for the HCWs and the society as a whole, calls for a more serious consideration of the strategy.

It is the author's personal opinion that despite the numerous limitations, cocooning has a pivotal role to play in future. The reasons to support it derive from the kind role it serves, its various applications and the educational and ethical perspective it sets, which are promising not just for the promotion of the cocooning itself but for other vaccination strategies too and the public health benefit.

In the future, cocooning should certainly be encouraged for the protection of other groups, such as the immunocompromised, the elderly and pregnant women. As already described, it is not just a complementary strategy, but in some cases, it is the main protective way.

It is not just the benefit conferred for the susceptible individual, but the lessons learnt for the whole family and the sense that they assist in their beloved person's care. As Healthcare professionals, our focus in most of the occasions is how we treat our patients, forgetting that we have a tremendous tool in our kit. Cocooning comes to remind us that through education of ourselves and our patients and through caring, we can together have a significantly positive impact on the quality and span of life of the most vulnerable individuals of our population and along with them of all of us.

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8. TABLES

Table 1: *Sources of pertussis transmission to infants*

Resource	**Source identified in (%):**	**Household members (%)**	**Mother (%)**	**Father (%)**	**Siblings (%)**	**Non-household (%)**
Libster et al (7)	Unknown %	75%	33%			
Wendelboe et al (26) infants <6m	48-78%	76-83%	48-51%		16-21%	18-27%
Bisgard et al (27) infants <1y	43%	>70%	32%	15%	20%	26%
Carrico et al (28)			15-32%		8-20%	
Wiley et al (29)			39%	16%		
Halperin et al (33) infants <1y	40%		20%		53%	20%
Fedele et al (30)			49.1-56.4%			
Kowalzik et al(31) infants <1y PICU admissions		36%	63%	13%	21%	30%
Bonmarin et al (32)			55%		25%	12%
Blain et al (23)			23.1%	24.7%		
Bertilone et al (34) <6m (2008-12,					51.4%	

Perth, Australia)						
De Greeff et al (35) <6m (2006-8, Netherlands)		53%	38%	17%	41%	

Table 2: *Tdap uptake in cocooning vaccination programs*

Resource	**Period**	**Setting**	**Population**	**Cocooning uptake**
Blain et al (23)	1/1/2011-3/12/2011	Emerging Infections Program Network sites, USA Case-control study	42 infants with pertussis 154 matched controls 859 CCs (600 adults)	Complete cocooning in: - infants with pertussis:**4.8%** - infants-controls:**10%** (p=0.43) **43.7%** of households: **No** adult had Tdap
Camenga et al (122)		2w well-infant Clinic: Tdap in mothers and CCs, low-income area, USA	152 adult household contacts	**46% (70 adults)** of 152 vaccinated with Tdap
Healy et al (41)	7/01/2008-30/04/2008	Provision of Tdap through a standing order protocol in post-partum, uninsured women, Houston Hospital, USA	1570 post-partum uninsured women	**1129 (72%)** of 1570 women vaccinated

Healy et al (42)	**Phase 1:** 7/01/2008-31/01/2010 **Phase 2:** June 2009 – Jan 2010	Tdap through standing order protocol in post-partum, uninsured women and their CCs, Houston Hospital, USA	**Phase 1:** free provision of Tdap in post-partum women **Phase 2:** free provision of Tdap to mothers and CCs (3 per mother)	**Phase 1:** 8334 **(75%)** of 11,174 women received Tdap **Phase 2:** i)2969 **(86%)** of 3455 women vaccinated ii)2 contacts per mother vaccinated
Cohen et al (37)	2009-2014	French parents, online question-naire	300 mothers 200 fathers of infants <12m	**Maternal vaccination:** 86% (reported), **57%** (on vaccination records) 2009: **22%** → 2014: **61%** (p< 0.005) **Paternal vaccination:** 2010: **21%** 2013: **42%** (p 0.009) **Couples:** 26% fully vaccinated

Table 3: *Vaccine effectiveness of Tdap vaccine administration in pregnancy in the reduction of infantile pertussis cases*

Resource	**Setting**	**Population**	**VE**
Uriarte et al (123)	Bizkaia, Basque Country, Spain, 2015-2016	Infants <3 months old	<u><3 months:</u> **89%** (95% CI, 72% –96%)

Van Bellinghen et al (124)	Cross-sectional population model to assess the addition of MIP to the 2016 infantile program in Australia	Model included total Australian population	Neonates: **91%**
Saul et al (73)	Matched case-control study, 16/08/2015 to 17/08/2016, South Wales, Australia	117 cases and 117 infant controls	< 6 months old: **39%** (95% CI, -12% to 66%) <3 months old: **69%** (95% CI, 13%-89%) **VE against hospitalisation: 94%** (95% CI, 59%-99%)
Bellido-Blasco et al (125)	Case-control study, Valencian Community Spain, 1/03/2015 to 29/02/2016	22 cases, 66 infant controls, unvaccinated infants < 3 months old	**adjusted VE: 90.9%** (95% CI, 56.6% - 98.1%)
Baxter et al (126)	Retrospective cohort study of infants born at Kaiser Permanente Northern California (2010-2015)	148,981 newborns >37 weeks	<2 months: **91.4%** (95% CI 19.5% - 99.1%) 0-12 months: **69.0%** (95% CI, 43.6% - 82.9%)
Amirthalingam et al (110)	UK, monitoring of VE against laboratory-confirmed pertussis in the 3 years following its introduction (2012)	243 infants with pertussis <3 months	< 3 months: **91%** (95% CI, 88%–94%) <2months: **90%** (95% CI, 86%–93%) **VE against death: 95%** (95% CI, 79%–100%)

Dabrera et al (127)	Case-control study, England and Wales, (October 2012 - July 2013)	58 cases of pertussis in infants < 8 weeks and 55 control infants	0-12 months: **91%** (95% CI, 77%–97%) **Adjusted VE** for sex, geographical region and birth period: **93%** (95% CI, 81%–97%).

Abbreviations: VE= Vaccine effectiveness, CI= Confidence Intervals

Table 4: *Estimated reduction of pertussis cases in infants*

Immunisation of → **Study ↓**	**Mothers postpartum (partial cocooning)**	**Parents postpartum (partial cocooning)**	**Parents & 1 grandparent (partial cocooning**	**Mothers in pregnancy**
Westra et al (74)		↓ 47.6%		↓ **67.4%**
Terranella et al (75)	↓ 20%		↓ 32% ↓ 32% in hospitalisations ↓ 29% in deaths	↓ **33%** ↓ **38%** in hospitalisations ↓ **49%** in deaths
Fernandez-Cano et al (76)		↓ 27%		↓ **49%**

Table 5: *Estimated QALYs gained*

Immunisation of → **Study ↓**	**Mothers postpartum (partial cocooning)**	**Parents postpartum (partial cocooning)**	**Parents & 1 grandparent (partial cocooning**	**Mothers in pregnancy**

Westra et al (74)		**1975**		1166
Terranella et al (75)	253		253	**396**
Fernandez-Cano et al (76)		NA		NA

NA: Not applicable (not estimated)

Table 6: *Estimated cost of each strategy*

Immunisation of → / **Study ↓**	**Mothers postpartum (partial cocooning)**	**Parents postpartum (partial cocooning)**	**Parents & 1 grandparent (partial cocooning**	**Mothers in pregnancy**
Westra et al (74)		€ 4600 ($ 6400) / QALY		€ 3500 ($ 4900) / QALY
Lugner et al (111)	€ 89,000/ QALY or € 1.8 million/ y			€ 126,000 / QALY or € 3 millions / y
Terranella et al (75)			$ 513.2 millions/ year	$ 171.2 millions/ year
Fernandez-Cano et al (76)		NNV to prevent: • 1 hospitalisation: 4752 • 1 death: >900,000		NNV to prevent: • 1 admission: 1331 • 1 death: 200,000
Meregaglia et al (106)		NNV to prevent: • 1 hospitalisation: 5000 and cost: € >100,000		
Lim et al (107)		NNV to prevent:		

		• 1 case: 500 – 6,400 • 1 admission: 12,000-63,000 • 1 death: 1.1 - 12.8 millions		
Skowronski et al (108)		NNV to prevent: • 1 hospitalisation: >10,000 • 1 ICU admission: 100,000 • 1 death: 1 million		

NNV: Number needed to vaccinate