# Influenza Vaccination and Antimicrobial Resistance: Strategic Recommendations

Lotte van Heuvel, MSc
Saverio Caini, MD, PhD
Michel Dückers, PhD
John Paget, PhD

Nivel, Netherlands Institute for Health Services Research, Utrecht, The Netherlands

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On behalf of the Global Influenza Initiative (GII) Work Stream II Team

GII Work Stream II Team:

- Prof. H. Rogier van Doorn (Oxford University Clinical Research Unit, Hanoi, Vietnam)
- Prof. Masoud Mardani (Shahid Beheshti University of Medical Sciences, Iran)
- Prof. Susanna Esposito (University of Parma, Italy)
- Prof. Ann Falsey (University of Rochester, United States)
- Dr. Meral Akçay (Sanofi Pasteur, France)

Funding:

This study was funded by a research grant from Sanofi Pasteur.

June 1, 2021

+31 30 272 9700
nivel@nivel.nl
www.nivel.nl

# Target Audience

This report is aimed at supporting individuals and organizations who work in the field of vaccination and antimicrobial resistance (AMR):

- **Governments (e.g. Ministries of Health)** developing and implementing national action plans on AMR and influenza vaccination programs;

- **Policy makers** working on the development and implementation of public health interventions in the field of influenza and/or AMR;

- **Public health organizations** interested in influenza vaccination and AMR, who can share the messages and recommendations in this report with the public.

Results from this paper can also be used by **academic researchers** and **health care professionals** to strengthen future research in the field of vaccination against AMR and increase influenza vaccination coverage in practice.

# Summary

### Background
Antimicrobial resistance (AMR) is an increasing threat to global health. Vaccination has received heightened attention as an approach to combat antibiotic use and possibly AMR. Vaccination can prevent bacterial and viral infections that may otherwise be treated, sometimes inappropriately, with antimicrobial medicines. WHO has stated that increased uptake of influenza vaccines should be prioritized for its impact on antibiotic use and AMR. This reports aims to assess the association between influenza vaccination and AMR, and develop strategic recommendations regarding the implementation of influenza vaccination within a global strategy to combat AMR.

### Methods
We have performed a mixed-methods study, including a literature review (systematic literature review, review of public health reports, and review of national action plans on AMR) and interviews with experts in the field of influenza and/or AMR. The literature review formed the basis for the interview questions. The results of the literature review and expert interviews were used to develop strategic recommendations, targeting policy, research and practice.

### Results
The systematic review identified 18 RCTs and 16 observational studies on influenza vaccination and antibiotic use. These studies showed that influenza vaccination in children, adults and the elderly decreased the number of antibiotic courses (risk ratio 0.75 (95% CI: 0.62–0.90)) and the number of people receiving antibiotics (risk ratio 0.63 (95% CI: 0.51–0.79)). A total of 18 public health reports discussed the issue of vaccination and AMR, of which 8 specifically identified the association between influenza vaccination and AMR. Furthermore, the review of AMR national action plans revealed that 7/31 reports specified influenza vaccination as an approach to reduce AMR, while 20/31 plans included general information on vaccination.

Interviews with 12 experts (policy and public health experts, primary and hospital care physicians, and one expert from the pharmaceutical industry) presented diverse views and experiences regarding influenza vaccination and AMR. The main findings indicate that: (1) AMR is not seen as the primary argument for vaccination by primary care physicians or policy makers, (2) influenza vaccination should be mentioned in all AMR national action plans but these plans are frequently not implemented in practice, (3) there is a general need to focus efforts on increasing influenza vaccination coverage, and (4) COVID-19 can influence the attention to (influenza) vaccination but the effect is still unclear at the moment.

### Conclusion
Scientific evidence shows that influenza vaccination reduces antibiotic use. This may go on to reduce AMR and this intervention has received greater awareness in recent years, yet it is often not implemented at a policy level. To increase attention, it is advisable to: (1) gather high-quality data to, among others, produce a cost-benefit analysis to raise awareness regarding vaccination and AMR among policy makers, (2) increase influenza vaccination coverage rates among healthcare professionals, risk groups and the general public, (3) raise global awareness and understanding of influenza vaccination to reduce antibiotic use and include this topic in all AMR national action plans, and (4) build on the experiences of the COVID-19 pandemic to strengthen the importance of vaccination against viral respiratory pathogens.

# Contents

# 1 Introduction

## 1.1 Background

Antimicrobial resistance (AMR) is an increasing threat to global health [1, 2]. It has been projected that 10 million deaths a year will occur in 2050 due to drug-resistant bacteria [1]. AMR is driven by multiple factors, including the excessive and inappropriate use of antimicrobials in humans and animals, transmission of resistant pathogens in healthcare settings, and suboptimal (rapid) diagnostics to diagnose infections with resistant organisms [3]. Considering the development of new antibiotics is challenging and there is little to no economic incentive for companies to invest in this field, there is a need to identify alternative solutions to reduce AMR [4]. Holmes et al. (2016) and O'Neill (2016) have reported that complementary approaches are required to sustain access to antimicrobial medicines. These approaches include antimicrobial surveillance, infection prevention and control, awareness and understanding of AMR, and optimized use of antibiotics [1, 2].

In recent years, vaccination has been more frequently seen as an effective approach to reduce AMR. The World Health Organization (2015) was one of the first to acknowledge that "*vaccination, where appropriate as an infection prevention measure, should be encouraged*", as reported in the Global Action Plan on Antimicrobial Resistance. Figure 1 shows the impact of vaccines on AMR, with vaccination protecting individuals in several ways, for instance by: (1) preventing infectious diseases that are often inappropriately treated with antimicrobial medicines, and (2) decreasing infections and antibiotics use in the community through herd immunity [5].

The use of vaccines against viral diseases, such as influenza, may decrease antibiotic use through reductions in symptom-based antibiotic prescribing [6-9]. Influenza vaccination plays a major role in reducing respiratory symptoms. Respiratory infections are the most common reason for (inappropriate) antibiotic treatment [10], with excessive antibiotic use in the winter/influenza seasons [11]. Solid evidence suggests that influenza vaccination can reduce antibiotic use in different risk groups [5, 12] and the vaccine could help to prevent secondary bacterial infections which often require antibiotic treatment, such as *Streptococcus pneumoniae* and *Staphylococcus aureus* [5, 13]. In addition, indirect benefits to non-recipients, through herd immunity, may also decrease antibiotic use in the larger population [12]. WHO (2020) has therefore stated that increased uptake of influenza vaccines should be prioritized for its impact on antibiotic use and AMR.

Currently, vaccination coverage for seasonal influenza varies considerably among high risk-groups (e.g. adults >65 years and people with chronic diseases), ranging from <5% to >75% among the elderly [14, 15]. To enhance the contribution of vaccines to control AMR, strategic goals regarding influenza vaccination based on the WHO Action Framework [5, 16] would include: (1) expand the use of (licensed) influenza vaccines to maximize the impact on AMR, (2) develop influenza vaccines that contribute to the prevention of severe influenza disease, and (3) expand and share knowledge on the impact of influenza vaccines on AMR.

The use of influenza vaccines has expanded due to increased attention and demand for influenza vaccination following the COVID-19 pandemic [17]. Governments and experts have called for higher influenza vaccine uptake among high-risk groups and healthcare workers during the 2020-2021 influenza season in times of COVID [18-20]. This could have a significant impact on long-term influenza vaccination rates, antibiotic use and AMR after the pandemic is controlled.

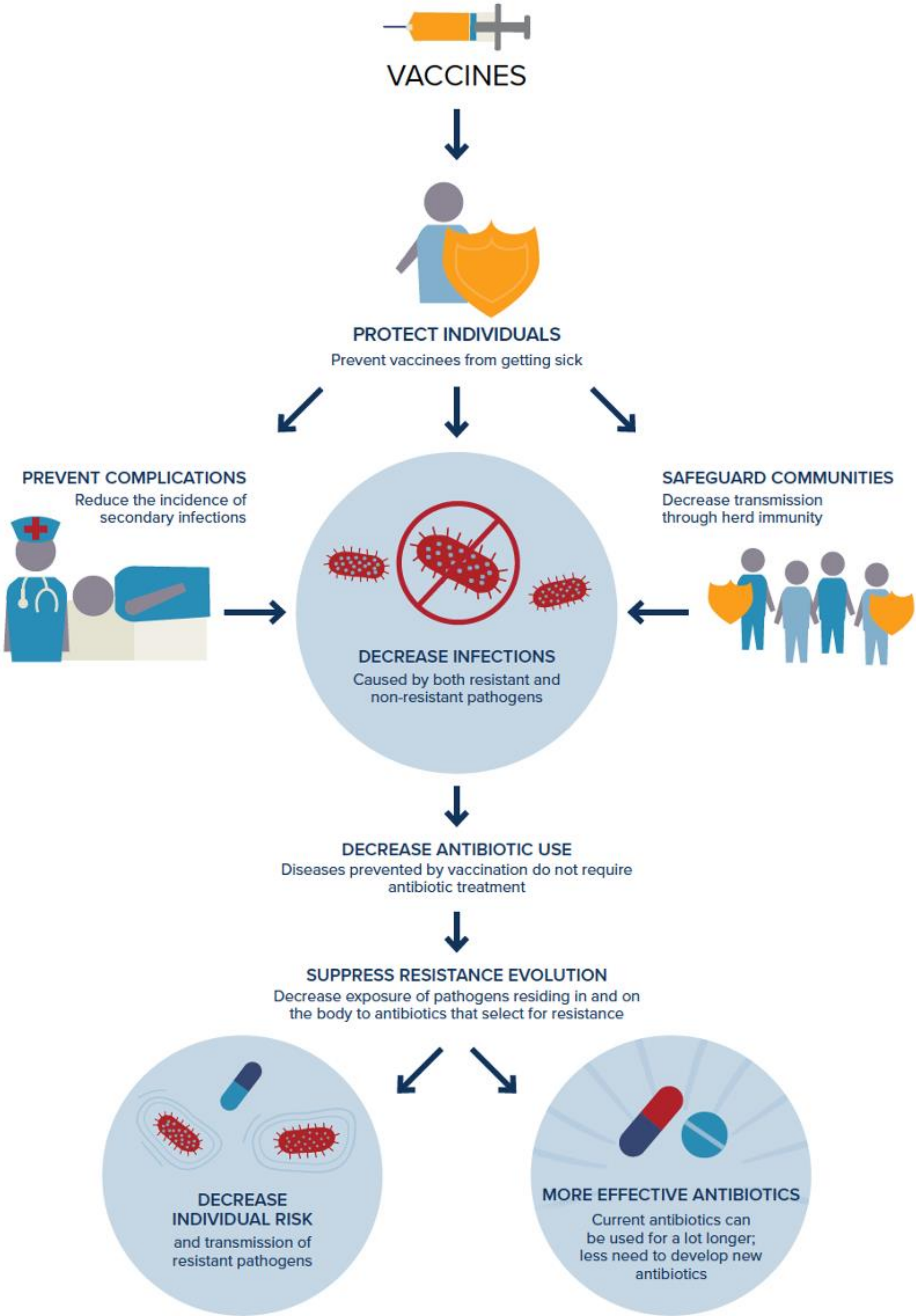


*Figure 1. A schematic pathway of the impact of vaccines on AMR (WHO Action Framework [5]).*

## 1.2 Global Influenza Initiative

This report has been written as part of the Global Influenza Initiative (GII). GII is an expert scientific forum of influenza experts composed of scientists, researchers and clinicians. One of the focus points (or Work Streams) of GII is the role of influenza prevention in AMR. The GII Work Stream II members (John Paget, Ann Falsey, Rogier van Doorn, Masoud Mardani, Susanna Esposito, and Meral Akçay) discussed and agreed that attention and research into influenza vaccination and AMR is swiftly developing and there is an urgent need to identify key topics, research priorities, data gaps and important areas of activity.

The aim of this mixed-methods study is to draw attention to this important public health issue and to develop strategic recommendations for governments, policy makers and public health organizations, to highlight influenza vaccination within a global strategy to combat AMR. The report presents an overview of the scientific literature, public health reports, national action plans on AMR and expert opinions on the impact of influenza vaccination on AMR.

# 2 Methods

This study used a mixed-methods approach including a literature review and qualitative interviews to examine the association between influenza vaccination and AMR (Figure 2). The literature study consisted of a systematic literature review, a review of public health reports, and an assessment of AMR national action plans. The interviews were conducted with experts in the field of influenza and/or AMR and included several members of the GII Work Stream II Team. Results from this exploratory research were used to develop strategic recommendations (Chapter 5). The time frame for this study was 8 months.

| Phases | Aims | Methods |
|---|---|---|
| **Phase I**<br>Literature Review | · Study the role of influenza vaccination on AMR | Review of:<br>· Scientific Literature<br>· Public Health Reports<br>· National Action Plans on AMR |
| **Phase II**<br>Expert Interviews | · Get insight in the global attention to influenza vaccination and AMR experienced by experts | Interviews with:<br>· GII Work Stream II Team<br>· International Experts |
| **Phase III**<br>Analysis and reporting | · Develop strategic recommendations to integrate influenza vaccination into the global AMR discussion | · Presentation at 7th ESWI Influenza Conference<br>· GII Report<br>· Scientific Article |

*Figure 2. Overview of the research methods.*

# 3 Results

## 3.1 Systematic Literature Review

The database search resulted in 563 articles (Figure 3). Duplicates were removed automatically using Endnote and manually to identify any missed duplicates, contributing to 450 unique articles. We assessed 16 full-text articles, of which 5 articles were included in analysis. Most of the articles (*n* = 414) were excluded because they did not contain information on both influenza vaccination and antibiotic use or AMR. A systematic review by Buckley et al. (2019) was identified regarding the impact of influenza vaccination on antibiotic use and updated with studies published after March 2018.

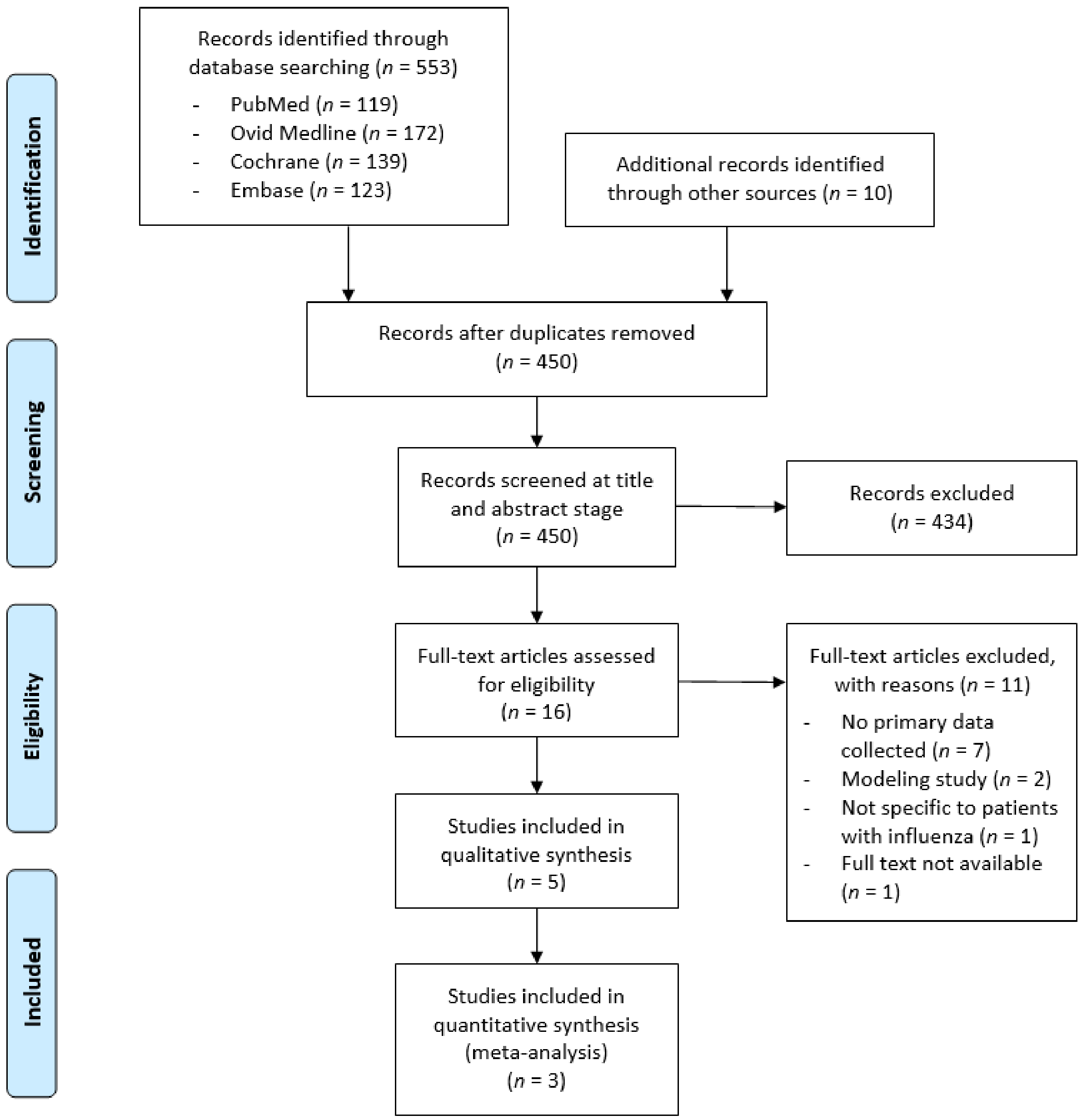


*Figure 3. Flow diagram of the results of the systematic literature review.*

For the meta-analysis, the study from Buckley et al. (2019) was updated with data from two newly identified RCTs (Table 1). We also identified two observational studies on influenza vaccination and antibiotic prescriptions (Table 2). Both studies reported a decrease of antibiotic prescriptions as a result of increased influenza vaccine uptake.

*Table 1. Characteristics of RCT studies included in the meta-analysis.*

| Study ID | Study Design, Country, Dates | Study Population | Intervention & Comparison groups | Study Outcomes |
|---|---|---|---|---|
| **Buckley 2019 [12]** | Systematic review of 16 RCTs on influenza vaccination * <br> United Kingdom, United States, Australia, Italy, China, Netherlands, Canada, Belgium, Finland, Israel, Spain <br> January 1998 - March 2018 | All ages <br> Total: *N* = 24.907 | Intervention: influenza vaccine <br> Comparison: placebo, unvaccinated, or hepatitis A vaccine | Antibiotic usage reported as prescription rate, clinician or self-report of antibiotic usage, antibiotic purchases, or number of antibiotic days/courses <br> Main outcome: high-certainty evidence that intranasal influenza virus vaccine in healthy adults resulted in a 28.1% reduction in the number of days taking antibiotics for febrile illness during an influenza outbreak period |
| **Pepin 2019 [21]** | RCT <br> Dominican Republic, Honduras, South Africa, Philippines, Romania, Spain, Greece, Italy <br> 2014 - 2016 | Children aged 6-35 months <br> *N* = 5.436 | Intervention: quadrivalent split-virion inactivated influenza vaccine (IIV4) <br> Comparison: placebo | Vaccine efficacy, healthcare use, antibiotic use, parental absenteeism from work <br> Main outcome: compared to placebo, IIV4 reduced the risk (95% CI) by 39.20% (26.89 – 56.24%) for antibiotic use |
| **Dbaibo 2020 [22]** | RCT <br> Europe, Asia-Pacific, Central America <br> 2011 - 2014 | Children aged 6-35 months <br> *N* = 12.018 | Intervention: inactivated quadrivalent influenza vaccine (IIV4) <br> Comparison: non-influenza control vaccines | Vaccine efficacy, healthcare utilization (antibiotic use) <br> Main Outcome: antibiotic use associated with influenza illness was reduced with IIV4 by 71% in Europe, 36% in Asia-Pacific and 59% in Central America |

* Annex II present an overview of the characteristics of the 16 RCTs included in Buckley. Of these, 13 RCTs are included in the meta-analysis.

*Table 2. Characteristics of observational studies on influenza vaccination.*

| Study ID | Study Design, Country, Dates | Study Population | Study Data | Main Study Outcome |
|---|---|---|---|---|
| **Hardelid 2018 [23]** | Self-Controlled Case Series (SCCS) Method<br>United Kingdom<br>2013 - 2015 | Children aged 2-4 years<br>*N* = 33.317 | Intervention: Live Attenuated Influenza Vaccine (LAIV) by The Health Improvement Network (THIN) database<br>Amoxicillin prescriptions in a 30 day period | Given a vaccine efficacy of 14.5%, amoxicillin prescribing could have been reduced by 5.6% if LAIV uptake in children aged 2-4 years increased to 50% |
| **Klein 2020 [24]** | Retrospective observational study<br>United States<br>2010 - 2017 | All ages<br>Pediatric (0-18 years), adult (19-64 years) and elderly (≥65 years) | Seasonal influenza vaccination by CDC FluVaxView database<br>Number of dispensed antibiotic prescriptions reported by retail pharmacies from IQVIA's Xponent database | A 10-percentage point increase in the influenza vaccination rate was associated with a 6.5% decrease in antibiotic use, equivalent to 14.2 (95% CI, 6.0-22.4; P = .001) fewer antibiotic prescriptions per 1000 individuals |

### 3.1.1 Meta-Analysis

We combined data from the meta-analysis from Buckley (13 RCTs) with two RCTs identified within this systematic review (Dbaibo [22] and Pepin [21]). Buckley et al. (2019) originally created two forest plots on antibiotic use following influenza vaccinations that included: (1) studies regarding the number of antibiotic courses or prescriptions per person, and (2) studies regarding the proportions of people receiving antibiotics.

Dbaibo et al. (2020) and Pepin et al. (2019) both studied the association between influenza vaccination and antibiotic use by analyzing the number of children using antibiotics, while no new study was found that examined the association between the influenza vaccine and the number of antibiotic courses. Figure 4 shows the original forest plot from Buckley et al. (2019) on influenza vaccination and the number of antibiotics courses (1). Study data from Dbaibo et al. (2020) and Pepin et al. (2019) have been added in Figure 5 to update this forest plot (2).

Buckley et al. (2019) reported an overall risk ratio of 0.79 (95% CI: 0.65–0.97) for the association between influenza vaccination and the proportion of people receiving antibiotics. After adding data from Pepin et al. (2019) and Dbabio et al. (2020), Figure 5 shows the overall association is made stronger by the inclusion of the new papers: risk ratio 0.63 (95% CI: 0.51–0.79).

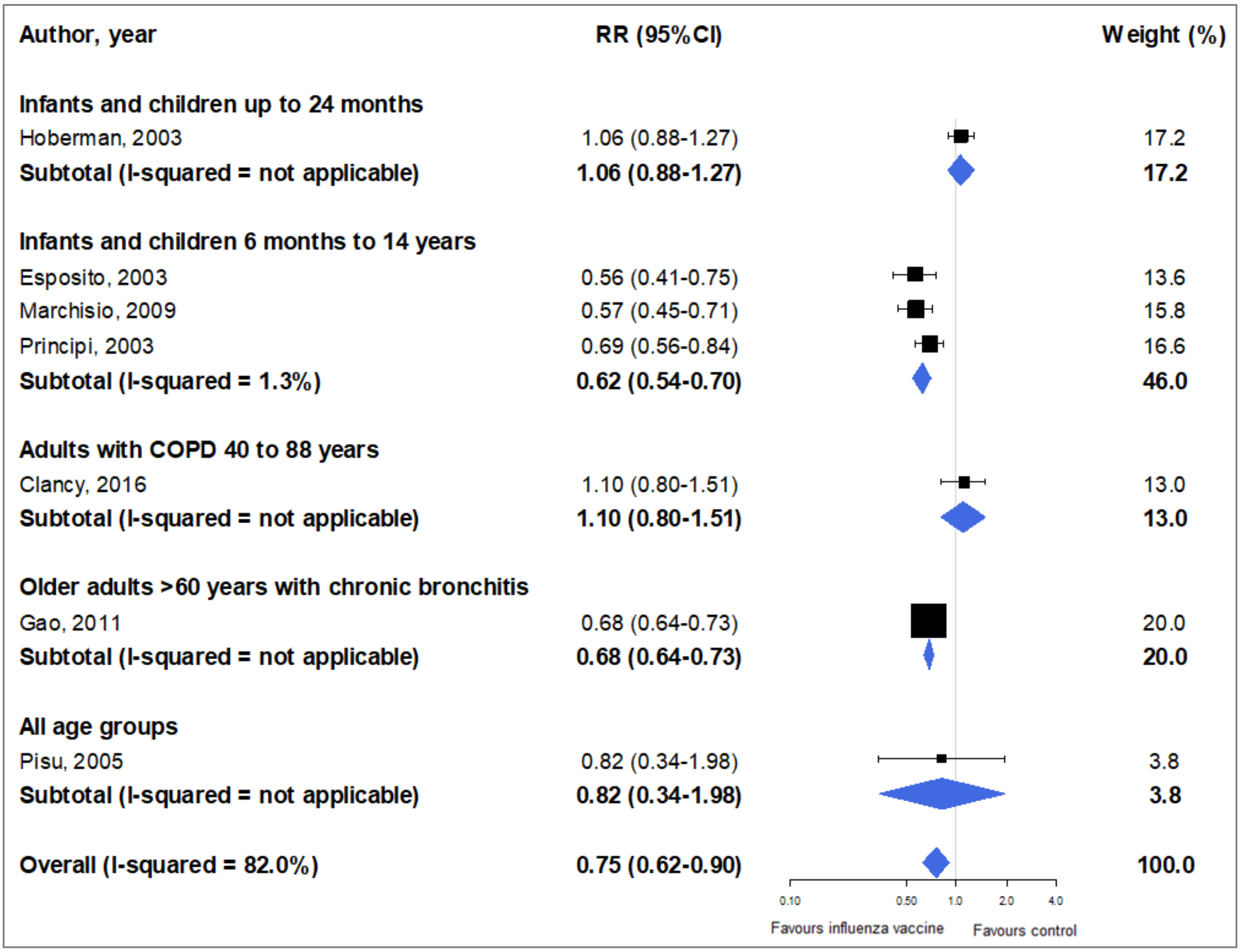


*Figure 4. Forest plot (1) for influenza vaccination and number of antibiotic courses or prescriptions [original Buckley et al. (2019) figure] – reproduced with permission from Buckley.*

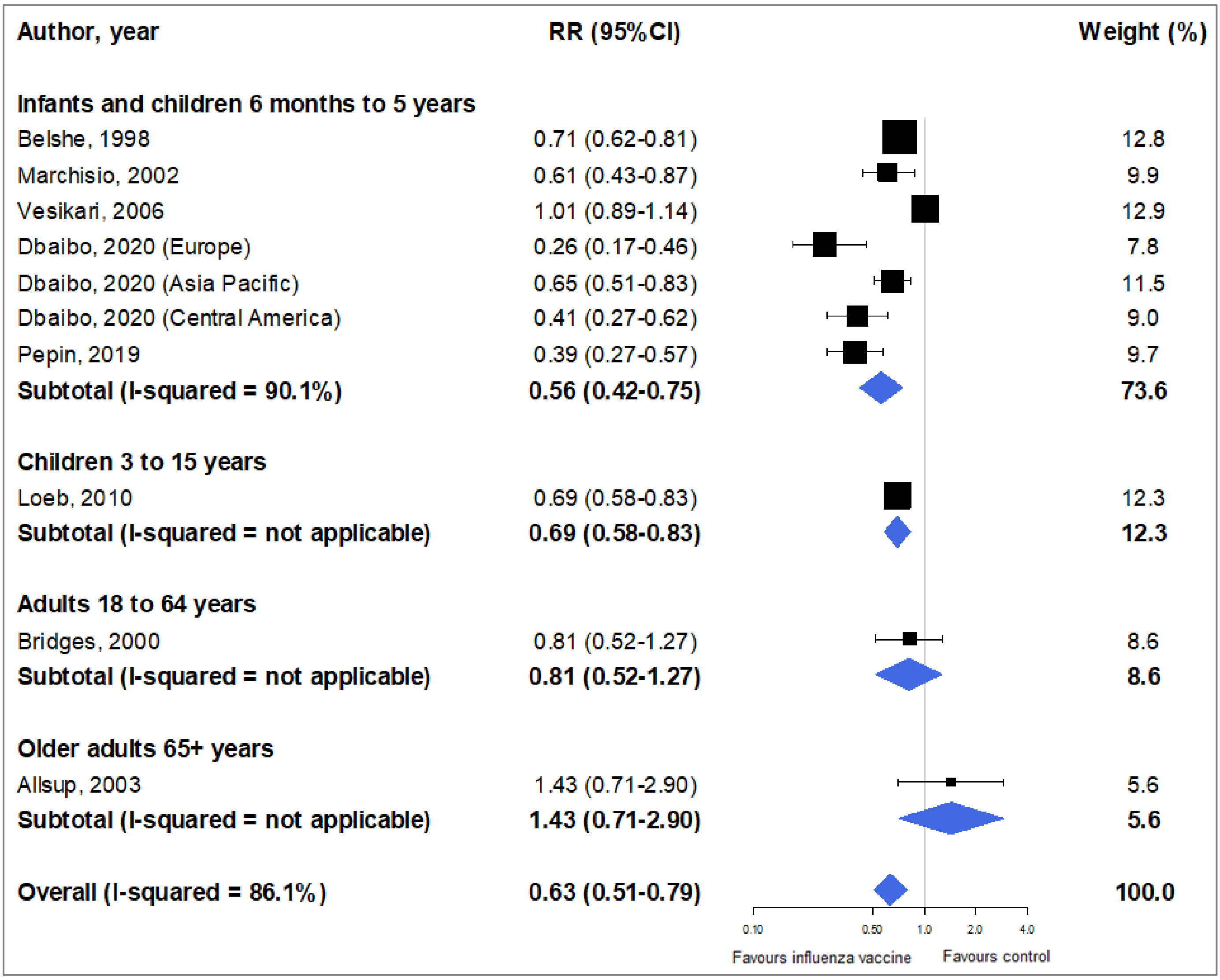


*Figure 5. Forest plot (2) for influenza vaccination and proportions of people receiving antibiotics [updated Buckley et al. (2019) figure] – reproduced with permission from Buckley.*

## 3.2 Public Health Reports

In total, we identified 47 public health reports on the subject of vaccination, AMR or influenza, of which 18 reports were included in the analysis. The other reports were excluded because of the subject, meaning these reports did not include information on both AMR and influenza vaccination but only on one of these subjects. The analysis includes 10 reports written by public health organizations: 6 studies published by WHO, 2 by World Bank Group and 2 by United Nations. The other 8 reports were published by independent organizations and the vaccine industry. Details of the reports are shown in Table 3.

### 3.2.1 Vaccination and AMR

The topic of influenza vaccination and AMR is not the main subject in most of the selected reports. All reports mention the possible effect of vaccination on AMR, however, influenza vaccination is mentioned in only 8 reports. The role of vaccination and immunization is often not discussed in detail and typically referenced in one or two sentences.

The selected public health reports generally discuss five topics: (1) increase the use of existing vaccines by routine immunization, (2) decrease the misuse and overuse of antimicrobials (by improving awareness of AMR), (3) develop new vaccines and alternative approaches through research and development (R&D), (4) strengthen vaccination systems and surveillance programs, and (5) improve infection prevention and control measures.

It is interesting that all analyzed reports mention that vaccines can prevent infections, reduce the need for and use of antibiotics, or slow the spread of AMR, even though only five reports substantiate these statements with scientific evidence. Vaccines Europe [25], Houses of Parliament [26], Chatham House [27], Wellcome [28], and WHO [5] validated their statements by referring to data from RCTs and observational scientific studies on the effect of influenza vaccination on antibiotic use. The reports refer to studies from Buckley [9], Klugman [37], Knight [17], Kwong [7], Nichol [24], and Wilby [29]. The other reports do not mention specific data on this subject.

The WHO action framework on vaccines and antimicrobial resistance refers to the systematic review by Buckley et al. (2019) as "*good evidence that influenza vaccination reduces antibiotic use by reducing misuse of antibiotics and treatment of secondary bacterial infections*". WHO mentions that influenza vaccination is one of the vaccines that should be prioritized for its impact on antibiotic use and AMR, and influenza vaccine coverage should be increased. This action framework also reports that countries should implement existing recommendations on vaccination provided in the global action plan on AMR.

### 3.2.2 Global Action Plan on AMR

The global action plan on antimicrobial resistance by WHO [2] is often referred to in the other reports. This action plan consists of 5 strategic objectives designed to reduce AMR. The importance of vaccination is mentioned in, among others, Objective 3: *'Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures'*. The report notes that "*vaccination, where appropriate as an infection prevention measure, should be encouraged.*" One argument for vaccination is that existing vaccines can prevent infectious diseases whose treatment would otherwise require antibiotics.

The global action plan on AMR provides a framework for countries to develop a national action plan to combat AMR. As a result, 78 WHO Member States have developed an AMR national action plan, available on February 2021 in the WHO library of national action plans [30]. The next section describes an evaluation of 31 national action plans on AMR.

*Table 3. Overview of relevant public health reports on vaccination and AMR.*

| | Study ID | Year | Organization | Information on Vaccination |
|---|---|---|---|---|
| **1** | Global action plan on antimicrobial resistance [2] | 2015 | World Health Organization | "Immunization can reduce antimicrobial resistance in three ways:<br>1. Existing vaccines can prevent infectious diseases whose treatment would require antimicrobial medicines;<br>2. Existing vaccines can reduce the prevalence of primary viral infections, which are often inappropriately treated with antibiotics, and which can also give rise to secondary infections that require antibiotic treatment;<br>3. Development and use of new or improved vaccines can prevent diseases that are becoming difficult to treat or are untreatable owing to antimicrobial resistance." |
| **2** | National action for global change on antimicrobial resistance [31] | 2016 | World Health Organization Western Pacific Region | "Vaccination can reduce the incidence of infectious disease and reduce the need for antibiotics." |
| **3** | Vaccines and alternative approaches: reducing our dependence on antimicrobials [32] | 2016 | Review on Antimicrobial Resistance | "Vaccines that prevent viral infections, **such as the flu**, can prevent infections and so reduce the need to use antibiotics." |
| **4** | Tackling drug-resistant infections globally: final report and recommendations [1] | 2016 | Review on Antimicrobial Resistance | "Vaccines can prevent infections and therefore lower the demand for therapeutic treatments, reducing use of antimicrobials and so slowing the rise of drug resistance." |
| **5** | The role of vaccination in reducing antimicrobial resistance (AMR) [25] | 2016 | Vaccines Europe | "For influenza, the most appropriate strategy for reducing the inappropriate use of antibiotics is vaccination. Several studies have demonstrated that antibiotic use for influenza related illnesses may decline by as much as 64% after **influenza vaccination** is introduced." |
| **6** | Evidence for action on antimicrobial resistance [33] | 2016 | Wellcome | "Similarly, greater use of vaccination could reduce infection levels and lower antibiotic usage (even vaccination against viruses could deliver AMR benefits, by reducing secondary bacterial infections and inappropriate antibiotic use to treat viral infections)." |
| **7** | Drug-resistant infections: a threat to our economic future [34] | 2017 | World Bank Group | "Services like vaccination, preventative care, and hygiene measures lower the need for antimicrobials and thus slow the spread of AMR." |
| **8** | The value of vaccines in the avoidance of antimicrobial resistance [35] | 2017 | Chatham House | "Meeting participants (vaccine experts etc.) prioritized financial investments in 15 possible vaccines for their |

| | | | | |
|---|---|---|---|---|
| | | | | impact on AMR: (1) TB, (2) Typhoid, (3) **Influenza**." |
| **9** | Monitoring global progress on addressing antimicrobial resistance [36] | 2018 | World Health Organization | "Substantial progress in addressing AMR is expected through measures such as immunization and infection prevention and control." |
| **10** | Antimicrobial resistance and immunisation [26] | 2018 | Houses of Parliament UK | "Immunization can reduce the AMR burden through preventing infections that avoid the need for treatment, so antimicrobial use is reduced." |
| **11** | Immunization strengthens the fight against antimicrobial resistance [37] | 2019 | World Health Organization Europe | "Preventing infections through vaccination helps reduce the need for and use of antibiotics." |
| **12** | Follow-up to the political declaration of the high-level meeting of the General Assembly on antimicrobial resistance [38] | 2019 | United Nations General Assembly | "Expanding the use of existing vaccines will reduce infections from pathogens that are typically treated with antibiotics, such as viral infections associated with inappropriate antibiotic use, **such as influenza**." |
| **13** | No time to wait: securing the world from drug-resistant infections [39] | 2019 | UN Interagency Coordination Group (IACG) on Antimicrobial Resistance | "Effective systems for vaccination avert infections in health care and reduce the future need for antimicrobials." |
| **14** | Pulling together to beat superbugs: knowledge and implementation gaps in addressing antimicrobial resistance [40] | 2019 | World Bank Group | "Higher vaccination rates against viruses can be an effective way to limit AMR through also reducing the need for antibiotics and subsequent selection pressure for the development of resistance." |
| **15** | Review of progress on antimicrobial resistance [27] | 2019 | Chatham House | "Vaccines that might have a particular impact on AMR by averting future antibiotic treatment include those for **seasonal influenza** and typhoid, as well as respiratory syncytial virus and Group A streptococcus." |
| **16** | Global influenza strategy 2019 - 2030: Prevent. Control. Prepare. [41] | 2019 | World Health Organization | "**Influenza** is also posing a challenge for other global health threats, including noncommunicable diseases, severe pneumonia and antimicrobial resistance." |
| **17** | Leveraging vaccines to reduce antibiotic use and prevent antimicrobial resistance: an action framework [5] | 2020 | World Health Organization | "Among available vaccines, increased uptake of Hib, PCV, TCV, and **influenza vaccines** should be prioritized for impact on antibiotic use and AMR." * |
| **18** | The global response to AMR: momentum, success, and critical gaps [28] | 2020 | Wellcome | "Multiple studies have observed indirect effects even of **influenza vaccination** on AMR, with antibiotic prescriptions decreasing by 13 to 50 per cent among those vaccinated compared to controls." |

* Hib = Haemophilus influenzae type b, PCV = pneumococcal conjugate vaccine, TCV = typhoid conjugate vaccine

## 3.3 National Action Plans on AMR

This analysis included 31 national action plans on AMR available from the WHO member states [30], including reports in English, Dutch, French, Italian, Spanish and Portuguese. Figure 6 presents an overview of the national action plans included from countries in different continents with diverse income levels (e.g. high-income (*n* = 11), upper-middle income (*n* = 10) and low/lower-middle income (*n* = 10)).

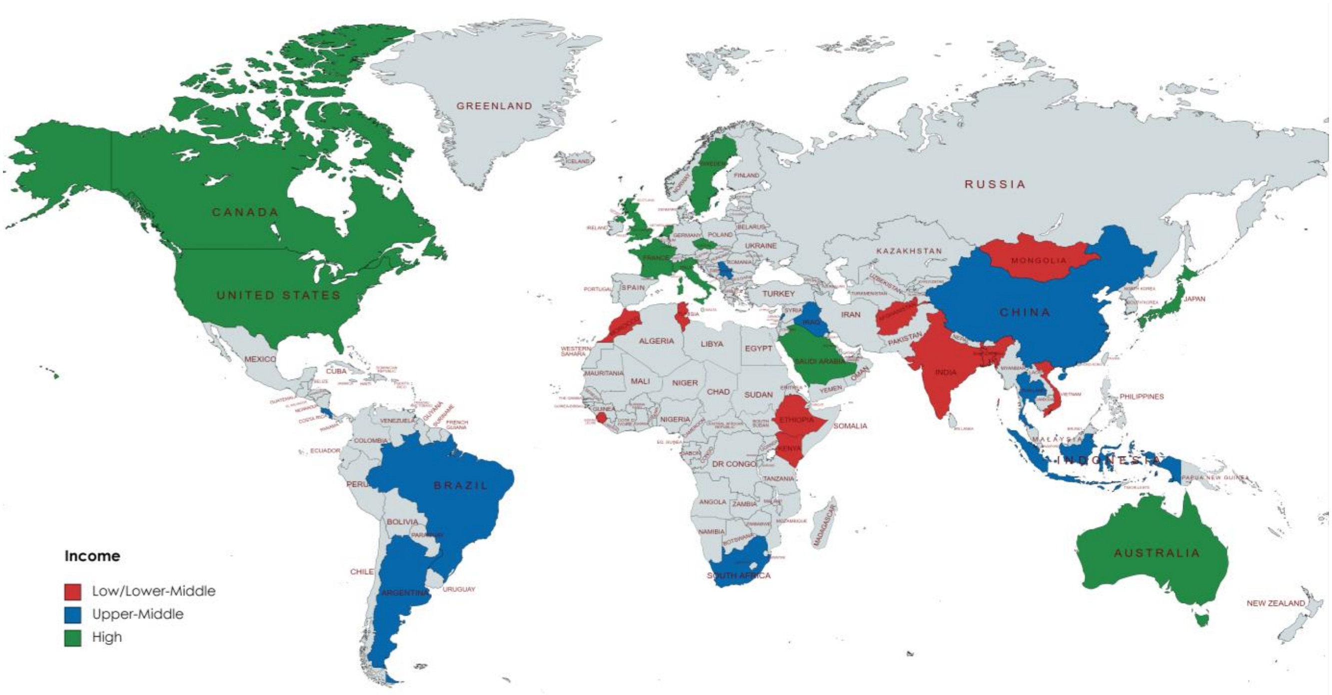


*Figure 6. Overview of the income level of countries whose AMR national action plans were selected for review.*

### 3.3.1 Main objectives

Most national action plans are extensive multi-year plans, ranging from 2 to 7 years in length. Each plan consists of multiple objectives or strategies to tackle AMR. These objectives are generally based on the global action plan on AMR, with additional country-specific objectives. The majority of the national action plans on AMR (*n* = 20) are similar to the global action plan on AMR.

Several objectives are recurring in the different AMR national action plans: (1) increase national awareness and understanding of AMR, (2) enhance national surveillance of AMR, (3) reduce the incidence of infections and contain the spread of antimicrobial-resistant organisms through effective infection prevention and control (e.g. sanitation and hygiene), (4) optimize the appropriate use of antimicrobials in humans, animals and agriculture, and (5) increase investment in research and development (R&D) for new antibiotics, vaccines, tools and other interventions. These 5 objectives are in line with the objectives of the global action plan on AMR.

The national action plans are usually drawn up by the Ministry of Health, Environment and/or Agriculture, while experts in the field of AMR or stakeholders can also be involved in this process. Most national action plans are extensive reports, however they do not include many references or evidence-based statements. The objectives in the plans are described in detail, yet implementation strategies are not mentioned in all reports. Twelve countries included an implementation and operational plan, though only five of these also covered costs and funding.

### 3.3.2 Attention to vaccination

Over half of the countries ($n$ = 20) mentioned vaccination or immunization in their AMR national action plan, with these often included as an objective. Of these, 7 countries specifically mentioned influenza vaccination (23%), mainly as an example of one type of vaccine to prevent infections (e.g. influenza, pneumococcal, Hib and typhoid vaccination). Influenza vaccination is discussed by Italy, Iran, Afghanistan, India, Japan, Australia and Tunisia (Figure 7).

Based on our review, Tunisia included the most extensive information on influenza vaccination in their national action plan on AMR. They describe vaccination in Objective 9: *'Improve the capacity of the national immunization program in a manner that covers all vaccination activities aimed at children and adults'*. Two sub-goals of Objective 9 are (1) to improve influenza vaccination in high-risk groups and (2) to evaluate the current influenza vaccination program. Tunisia aims to accomplish this by reducing the incidence of severe influenza infections and reducing viral infections treated with antibiotics. However, implementation of these objectives in practice is unclear.

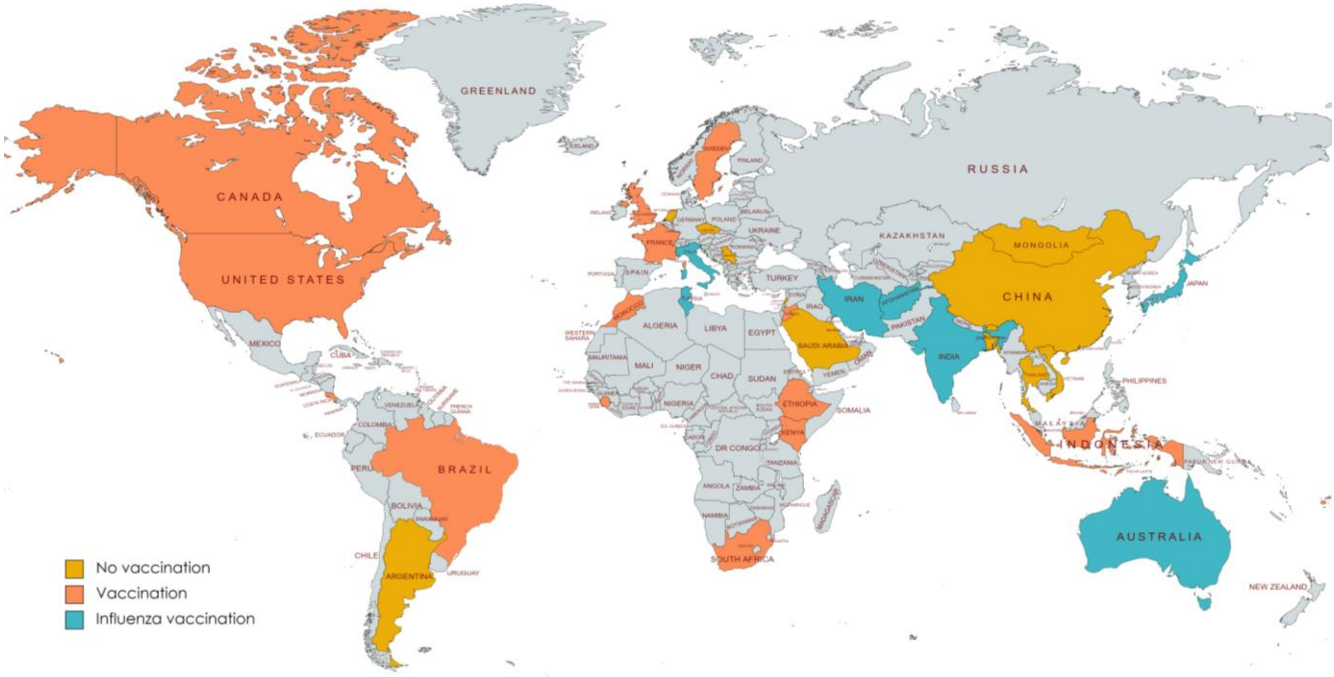


*Figure 7. Overview of the information on vaccination in countries' national action plan on AMR.*

### 3.3.3 Country comparison

No direct link was found between countries' income level and reporting vaccination in the national action plan. For instance, 6 high-income countries mentioned vaccination while 5 high-income countries have not. Vaccination is included in the action plan of 8 high-income, 5 middle-income and 7 low/lower-middle income countries, while influenza vaccination is discussed by 3 high-income countries, 1 country with an upper-middle income level, and 3 low/lower-middle income countries. Notably, more countries with upper-middle and low/lower-middle income economies have based their AMR national action plan on the global action plan on AMR. This is not the case for the high-income countries.

Table 4 presents a comparison of 31 national action plans included in this study.

*Table 4. Overview of 31 national action plans on antimicrobial resistance.*

| | Country | Income level | Year | Information on Vaccination |
|---|---|---|---|---|
| | **INCLUDE INFLUENZA VACCINATION IN NATIONAL ACTION PLAN** | | | |
| **1** | Australia | High | 2015 - 2019 | "Vaccines offer potential to reduce AMR in humans and animals by preventing infection, assisting in the eradication of some diseases and eliminating the need for some antibiotics. In human health, seasonal influenza has been shown to be a significant driver of inappropriate antibiotic prescribing. Efforts to improve immunization coverage and, in particular, increase the uptake of seasonal **influenza vaccine** among priority populations can help to reduce antibiotic usage." |
| **2** | Iran | Upper-Middle | 2016 - 2021 | "Promote vaccination (pneumococcal vaccine, Hib vaccine, and **influenza vaccine**) to prevent infections caused due to antimicrobial resistance." |
| **3** | Japan | High | 2016 – 2020 | "Promote vaccinations (pneumococcal vaccines, Hib vaccines, **influenza vaccines**, etc.) contributing to the prevention of antimicrobial-resistant infections." |
| **4** | Afghanistan | Low | 2017 – 2021 | "Develop strategies to improve efficacy and broaden coverage of existing vaccines and their usage, especially by at-risk populations e.g. Hib, **influenza**, pneumococcal and typhoid vaccines." |
| **5** | Italy | High | 2017 – 2020 | **Influenza vaccination** may play a role to contain AMR. |
| **6** | India | Lower-Middle | 2017 – 2021 | "Develop strategies to improve efficacy and broaden coverage of existing vaccines and their usage, especially by at-risk populations e.g. Hib, **influenza**, pneumococcal and typhoid vaccines." |
| **7** | Tunisia | Lower-Middle | 2019 – 2023 | Activities: (1) Promotion of **influenza vaccination** in high-risk groups; (2) Evaluation of the current **influenza vaccination** program and update of the program; and (3) Implement and update strategy of **influenza vaccination**. |

| | | | | |
|---|---|---|---|---|
| **INFLUENZA VACCINATION NOT INCLUDED IN NATIONAL ACTION PLAN** | | | | |
| **EUROPE** | | | | |
| **8** | Czech Republic | High | 2011 -2013 | None |
| **9** | France | High | 2011 - 2016 | General vaccination is a method of limiting the use of antibiotics. |
| **10** | Netherlands | High | 2015 - 2019 | None |
| **11** | Sweden | High | 2016 - 2020 | "The government expects a high level of compliance with vaccination and health programs to be maintained to keep people and animals as healthy as possible, thus reducing the need for antibiotics." |
| **12** | Serbia | Upper-Middle | 2019 - 2021 | No relevant information |
| **13** | United Kingdom | High | 2019 - 2024 | "Vaccines, for humans and animals alike, play a key role in tackling AMR; by promoting herd immunity and reducing the prevalence of infection, they reduce the need for antimicrobials." |
| **ASIA** | | | | |
| **14** | Vietnam | Lower-Middle | 2013 - 2020 | None |
| **15** | China | Upper-Middle | 2016 - 2020 | No relevant information |
| **16** | Saudi Arabia | High | 2017 | No relevant information |
| **17** | Indonesia | Upper-Middle | 2017 - 2019 | "Vaccination in humans and animals and biosecurity in food production systems are specific interventions that if implemented effectively, can result in better health outcomes and reduced risk of emergence of AMR." |
| **18** | Mongolia | Lower-Middle | 2017 - 2020 | None |
| **19** | Thailand | Upper-Middle | 2017 - 2021 | None |
| **20** | Bangladesh | Lower-Middle | 2017 - 2022 | None |
| **21** | Lebanon | Upper-Middle | 2019 | None |

| | | | | |
|---|---|---|---|---|
| | **AFRICA** | | | |
| **22** | Ethiopia | Low | 2015 - 2020 | "Strengthen vaccination programs in human and animal health to prevent infections." and "Ensure access to essential antimicrobials for therapeutic use and vaccines to prevent diseases and minimize the use of antimicrobials." |
| **23** | Kenya | Lower-Middle | 2017 - 2022 | "Research and investment in diagnostic tools and improved vaccines can contribute to the overall reduction in antimicrobial use." |
| **24** | Sierra Leone | Low | 2018 - 2022 | "The use of vaccines can reduce the infection rates and dependency on antimicrobial agents as well as the risk that antimicrobial resistant pathogens will develop and spread through food chain." |
| **25** | South Africa | Upper-Middle | 2018 - 2024 | "Prevention of infection through wide-reaching vaccination programs thereby preventing the need for antibiotic use is a key AMR prevention strategy. This will be implemented through primary prevention and promotion activities such as vaccination and awareness." |
| **26** | Morocco | Lower-Middle | 2019 - 2022 | Vaccination can reduce the weight of infections in society by preventing and controlling infections. |
| | **AMERICAS** | | | |
| **27** | United States of America | High | 2015 - 2020 | Activities to slow the emergence of resistant bacteria and prevent the spread of resistant infections include "the optimal use of vaccines to prevent infections, implementation of healthcare policies and antibiotic stewardship programs that improve patient outcomes, and efforts to minimize the development of resistance by ensuring that each patient receives the right antibiotic at the right time at the right dose for the right duration." |
| **28** | Canada | High | 2017 | "Research into standardized indicators, alternatives to antimicrobials (e.g. vaccines, good on-farm management practices), diagnostic tools, and into the behavioural and social aspects of antibiotic prescribing practices and use in human and animal health settings should be considered." |
| **29** | Costa Rica | Upper-Middle | 2018 - 2022 | Vaccines are a potential way to prevent AMR. |
| **30** | Brazil | Upper-Middle | 2018 - 2022 | Vaccines are a potential way to prevent AMR and investments should be made in this direction. |
| **31** | Argentina | Upper-Middle | 2018 - 2025 | None |

## 3.4 Expert Interviews

### 3.4.1 Overview of respondents

A total of 12 experts were interviewed with experience in the field of vaccination and/or AMR (including 3 members of the GII Work Stream II Team) during the COVID-19 pandemic. We interviewed 8 European experts, 3 Asian experts, and 1 expert from America (see Annex III). The experts worked in policy and public health organizations, research institutes, hospitals, universities and industry. Figure 8 shows an overview of the respondents.

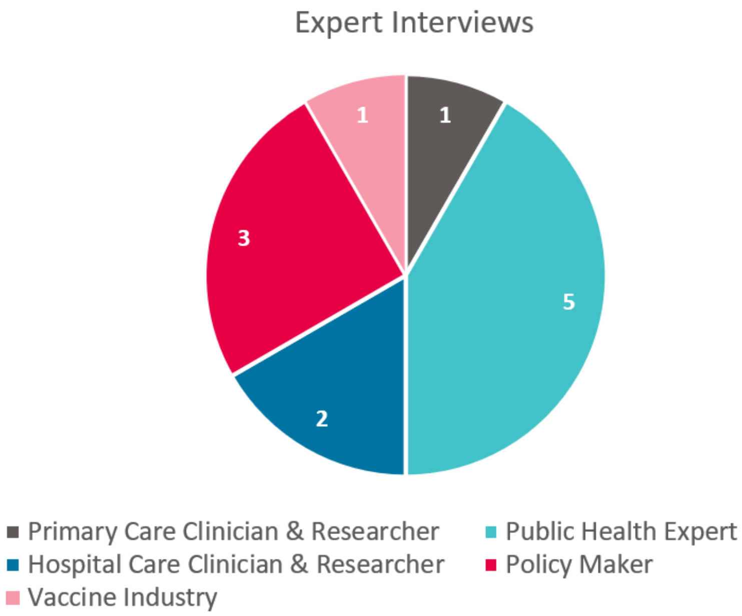


*Figure 8. Overview of 12 respondents participating in the interviews.*

### 3.4.2 Association between influenza vaccination and AMR

Several experts stated that respiratory infections, such as influenza, are one of the major drivers for prescribing antibiotics in primary care. Influenza vaccination can influence AMR in two ways: (1) by reducing the number of influenza cases, influenza vaccination reduces (inappropriate) prescribing of antibiotics and ultimately can lead to a decrease of AMR, and (2) by preventing secondary infections that require antibiotics. Five experts believe that this is an indirect association. They noted that we must be realistic about the effect of influenza vaccination on antibiotic use and AMR:

> *"There is very strong winter-associated antibiotics use. The use of influenza vaccines would reduce this partially, but I do not know if we would be able to actually get a significant reduction in overall antibiotics use."*

One advantage of influenza vaccination mentioned by the experts is that the influenza vaccine can reduce the pressure on healthcare systems by decreasing healthcare-seeking behavior, eventually decreasing antibiotic use. However, a primary care clinician indicated that reducing antibiotic use is not seen as a strong argument to promote influenza vaccination when talking to patients (it is seen as an indirect benefit of influenza vaccination). Preventing the illness and severe outcomes (secondary infections) is seen as the main arguments for promoting influenza vaccination among patients.

The interviews showed that a number of experts thought that the link between influenza vaccination and AMR is complex. There is a shared belief among experts that influenza vaccines helps to combat AMR, however, vaccines should be considered in the context of other interventions to decrease AMR (e.g. hospital hygiene, screening, prevention, a ban on selling antibiotics without a prescription, and antibiotic stewardship). Furthermore, AMR is often not used as an argument to increase influenza vaccination:

> *"I feel like this [AMR] is always going to be the 'cherry on the top'. It can boost the argument but it is not the main benefit that will determine whether or not countries decide to recommend a vaccine for specific age groups. It is going to be an added benefit."*

In conclusion, the experts recognize and acknowledge the benefits of influenza vaccination on antibiotic use, however the size of the effect of vaccination on AMR is still unclear.

### 3.4.3 Implementation of national action plans on AMR

The experts agree that influenza vaccination should be mentioned in national action plans on AMR as a preventive measure. However, experts with experience in developing these plans mentioned that this is a slow, bureaucratic process and it is not easy to introduce this point into the plans. Besides, they have noticed that not all countries implement their national action plans and take proper action:

> *"Many countries will simply take the global action plan [on AMR], in essence copy it, put a national label on it and then say we have a national plan. There is something written down but it is no operational plan and it does not get implemented."*

Different reasons explain the lack of interest in vaccination in AMR national action plans. The experts mentioned: (1) influenza is not seen as a priority pathogen in their country, (2) there is a lack of budget or financial resources, (3) bacteriologists involved in the national action plan are less interested in viral vaccines, and (4) experts believe that there is not enough scientific evidence to strongly articulate the role of influenza vaccines in preventing AMR.

A number of experts (*n* = 6) highlighted the role of WHO in raising interest in AMR and vaccination. Two important WHO documents were discussed: the global action plan on AMR [2] and the action framework on vaccines to reduce antibiotic use [5]:

> *"I think it is really important to have a clear endorsement by the WHO showing how important vaccines are in fighting AMR. The WHO will be listened to by more countries and have a broader audience. I think a lot of the value [of the action framework] will be in raising awareness."*

In short, influenza vaccination should be included in AMR national action plans and, with the help of WHO, attention needs to be paid to implementing these plans in practice.

### 3.4.4 Worldwide attention to influenza vaccination and AMR

In recent years, the experts have noticed increased interest and awareness regarding the use of viral vaccines against AMR. Organizations such as WHO, Wellcome, and Chatham House have recommended vaccination to reduce AMR. This effects policy makers, who now have greater awareness. However, 2 of the 12 experts said there still is a need for more attention to the subject. Worldwide there is no incentive to develop new antibiotics, so we need to look for new solutions like vaccination:

> *"I think the Americans call it the perfect storm: there are no new antibiotics, antibiotic resistance is rising and there is no means you can control it. It is going to be a catastrophe."*

The interest in influenza vaccination differs between countries and the experts have experienced national and regional differences as well. Importantly, an expert reported that there is very little interest in influenza vaccination in primary care, as a measure to address AMR. The primary care expert described that preventing influenza, pneumonia and secondary infections are the main arguments for influenza vaccination in this setting:

> *"I think it is more important for patients to explain to them that they can prevent severe pneumonia with influenza vaccination, rather than explaining I would prescribe them less antibiotics. Patients are more sensitive to the first argument. The second argument could be aimed towards physicians, but I do not think this will be effective."*

One problem recognized by the experts is that vaccination and AMR is often seen as two separate subjects. There is only a limited number of people interested in both areas. Two experts from Asia therefore emphasized the need to adapt our messages to different groups, such as policy makers, economists, patients, physicians and healthcare workers.

In summary, there is increased attention regarding influenza vaccination and the fight against AMR, but there is a need for increased interest concerning this subject among experts, especially in primary care.

### 3.4.5 Impact of COVID-19 on influenza vaccination

In light of the COVID-19 pandemic, 7 of the 12 experts reported that the general public is more interested in influenza vaccination. The experts noted that many governments (often in high-income countries) have highlighted the importance of influenza vaccination before the 2020/2021 winter season; this has also resulted in increased demand and problems surrounding the availability of the vaccine. Moreover, COVID-19 public health measures (e.g. social distancing and mask wearing) have strongly impacted the incidence of influenza. Two European experts suggested that the experiences of COVID-19 could be used to increase interest in AMR and vaccines against AMR:

> *"I would use COVID-19 to put AMR on the agenda. Show that COVID kills quickly, but AMR is also a killer, a 'slow killer'. The consequences of antimicrobial resistance are just as severe as COVID, because if we do not do anything the 'slow killer' will also create victims."*

Nonetheless, the effect of COVID-19 on (influenza) vaccination remains unclear in January 2021. Two Asian experts mentioned the effect will depend on the roll-out of COVID-19 vaccination and its experience among the public. In addition, the experts believe that the impact of social media and misinformation on people's willingness for vaccination should be taken into account. Overall, there was no clear consensus on the exact impact of COVID-19 on the future of influenza vaccination.

#### 3.4.6 Experts' recommendations to increase interest in influenza vaccination and AMR

The experts mentioned several recommendations regarding influenza vaccination and AMR: (1) raise advocacy and awareness, (2) increase research and development, (3) improve international collaboration, and (4) increase influenza vaccination coverage.

The first recommendation was made by two European experts who believe that we need more awareness regarding the role of non-bacterial pathogens, such as influenza, on AMR. The message should tackle different audiences, including healthcare workers and policy makers, and not only focus on researchers and academics. Three experts mentioned that community level healthcare workers are very influential in educating the public on vaccination:

> *"Healthcare workers are the 'informal voice' that a lot of people generally turn to. Even though people go to the internet for all kinds of information, once they get confused on these matters physicians are disproportionally influential."*

A second recommendation is to increase research and development in the field of vaccination and AMR. First, there is a need to strengthen the evidence and collect more high-quality data on influenza vaccines and AMR, to be able to perform a cost-benefit analysis. To address the subject among policy makers, it is important to present cost-effectiveness studies regarding influenza vaccination. One expert suggested the collection and presentation of antibiotic use data should be part of the standard protocol in vaccine trials. A second point made by 3 of the 12 experts is that rapid virological diagnostic tests (e.g. CRP tests) should be further developed and greater use of these tests would significantly help to reduce antibiotic prescribing in primary care:

> *"In practice, proper diagnosis before starting a therapy is a better instrument than influenza vaccination."*

A third recommendation, made by three experts, is that more collaboration between countries should be encouraged on this subject, for instance by developing a global coalition to combat infectious diseases and AMR. Collaboration between countries can also be improved by seminars and webinars.

Lastly, there is a need to focus on increasing influenza vaccination, instead of linking vaccination to AMR. The experts believe it should be easier for people to receive the influenza vaccine. For instance, vaccinate chronic patients at a healthcare center during routine visits. Vaccination strategies differ per country, but experts agree there should be no barriers for vaccination. Increasing influenza vaccination is therefore seen as a key issue:

> *"I think it goes back to the issue of increasing influenza vaccines. In that case, whether people see a linkage or not does not matter. It will have the effect that you want: the beneficial effect."*

# 4 Discussion

To our knowledge, this mixed-methods study is the first of its kind to fully explore all evidence on the association between influenza vaccination and AMR. The literature review has shown considerable evidence that influenza vaccination can reduce antibiotic use which could lead to decreased rates of AMR. This has received more attention since the publication of the WHO global action plan on AMR in 2015 and there is growing interest in influenza vaccination among experts. However, the potential of influenza vaccination against antibiotics is not fully utilized in all countries (i.e. influenza vaccination is not included in all AMR national action plans). Moreover, implementing influenza vaccination in order to tackle AMR is often difficult to accomplish. There is therefore a need to rethink the position of AMR on the global health agenda and take actions to increase worldwide attention to influenza vaccination and AMR.

Numerous studies have indicated that influenza vaccination can reduce antibiotic use [12]. The systematic literature review highlights that influenza vaccines reduce the number of antibiotic courses and the number of people receiving antibiotics, mainly in infants and children. However, the certainty of most scientific studies is low [12]: Buckley identified 12 of the 16 RCTs of low certainty using the GRADE approach. Hence there is a need for more high-quality studies and data. One solution mentioned during the expert interviews, as well as in the literature [12, 42, 43], is the development of a standard protocol for vaccine trials to collect and analyze data on antibiotic consumption. More of this high-quality data could help to fill a current research gap and support a cost-benefit analysis regarding influenza vaccination coverage rates and AMR [4, 44]. Standard cost-effectiveness analyses of vaccination programs have not yet taken into account the indirect consequences of vaccination such as the reduction of AMR [45]. These analyses could guide policy decisions and would significantly influence policy makers to include vaccination in their AMR national action plans and policies.

The analysis of 31 national action plans on AMR showed that only 7 of the countries acknowledge influenza vaccination as a way to reduce AMR. The implementation of these plans, however, is unclear as most countries lack an operational and implementation plan. This is supported by the expert interviews and literature [46-48]: countries experience problems with the operationalization of the plans because there is often no functioning coordination mechanism in place to address AMR. Notably, the global AMR discussion has not been translated into action in many low- and middle-income countries [46]. However, the inclusion of vaccines in AMR national action plans is likely to improve in the future, as the latest WHO action framework (2020) discussed that "*AMR national action plans and international organizations dedicated to AMR control should consistently include vaccines in the armamentarium of interventions planned for use against AMR*" [5].

The qualitative interviews revealed that COVID-19 could also trigger heightened awareness of AMR. This is crucial because the global spread of AMR could have significantly expanded through the extensive use of antibiotic treatment for hospitalized COVID-19 patients at the beginning of the pandemic [49]. In addition, the pandemic has also contributed to greater interest in influenza vaccination among the public. Berkley and Laxminarayan (2020) acknowledge that a similar collaborative approach seen with the development of COVID-19 vaccinations could help with the development of new vaccines and antimicrobials [49]. Over the last few years it has been a challenge to demonstrate the magnitude and value of AMR as a reason for policy makers to assign a higher priority to vaccine use and development [27]. This has been recognized by experts in a report by

Wellcome [28]. They have suggested that COVID-19 can give rise to new opportunities regarding AMR on a policy level, such as increased surveillance and a better understanding of infection prevention and control, but can also lead to risks including ineffective stewardship or decreased funding.

Healthcare workers are considered to be one of the groups that are the most influential in addressing vaccination among the general public. During the expert interviews, however, a general practitioner indicated that using AMR to promote influenza vaccination would only be used as a secondary argument. To our knowledge, no research is available regarding the perspectives of healthcare workers on the use of vaccines to control AMR. It is clear that coverage of seasonal influenza vaccination among healthcare professionals varies widely around the world. The coverage in many European countries is below 30% [50], while healthcare professionals' behavior can strongly influence parents' decisions to vaccinate their children [51]. Nonetheless, public health reports on vaccination against AMR are mainly focused on policy makers. Hence there is a need for more research among healthcare workers, since they are one of the priority groups for influenza vaccination.

Influenza vaccination is prioritized among healthcare workers and various risk groups, such as older adults and people with chronic medical conditions [52]. The systematic literature review showed that the effectiveness of influenza vaccination in reducing antibiotic use differs between population groups (e.g. children, adults (including healthcare professionals) and the elderly). When preparing recommendations for influenza vaccination this should all be taken into account. Influenza vaccination programs and arguments in favor of influenza vaccination should therefore be adapted to each population group. Secondary bacterial infections associated with influenza can become invasive in risk groups such as young children and the elderly and this would require antibiotic treatment [53]. By eliminating the antecedent viral infection (e.g. influenza), secondary bacterial infection can be prevented as would the need for antibiotics. These findings stress the importance of influenza vaccination.

Overall, influenza vaccination is seen as a driver that impacts antibiotic use and possibly AMR. In order to use the vaccine effectively against AMR, it is necessary to increase vaccine coverage rates [4]. This problem was also addressed during the expert interviews: there is a need to promote influenza vaccination coverage among the general public and specifically in high-risk population groups. The COVID-19 pandemic has shown an increased acceptance of influenza vaccination, for instance in the United Kingdom [17]. This momentum should be taken advantage of to increase the interest and awareness of influenza vaccination and AMR.

## 4.1 Strengths and Limitations

One strength of our study is the use of a mixed methods approach to include diverse perspectives on influenza vaccination and AMR, particularly the review of low, middle and high-income countries' national action plans. The development of strategic recommendations for policy, science and practice is another strength of this report.

The small number of expert interviews can be considered a limitation of this study. The COVID-19 pandemic and the limited time frame for the study (8 months) had an impact on the number of experts who could be included in the study. The interviews were mostly focused on Europe and we did not include enough healthcare professionals or experts from industry to reach data saturation, even though we felt there was saturation for the public health experts.

It is also worth noting that the strategic recommendations are based on various opinions from the experts and there was no consensus on all of the recommendations. The limited time frame also meant that we merely updated an existing systematic literature review (Buckley [12]) and only included 31 out of 78 AMR action plans. There is a lack of country context with regards to the review of national action plans, as it was not feasible to include country representatives' perspectives on vaccines as tools to combat AMR in the action plans.

The systematic literature review focused on observational studies and RCTs, whilst other non-randomized and population-based studies on the subject of influenza vaccination and antimicrobial prescriptions might also be of interest, for instance modeling studies [54-56]. Moreover, we did not include a systematic review by Doherty, Hausdorff and Kristinsson (2020) on the effect of vaccination on the use of antimicrobial agents [57]. This review was published online in September 2020, after we finished data collection. The review by Doherty does include one RCT not included in the review by Buckley et al. (2019): Hurwitz et al. (2000). This study found that after vaccinating day care children, there was an 80% reduction in the number of antimicrobial prescriptions for their 5-17 year old household contacts [58].

## Conclusion

This exploratory mixed methods study is a first contribution to assess the evidence on the association between influenza vaccination and AMR, and the interest and implementation of this subject in practice. While scientific evidence shows that influenza vaccination can reduce antibiotic use in children, adults and the elderly, vaccination as a measure to reduce AMR is often not yet common policy. There is therefore a need to raise global awareness on the importance of influenza vaccination in reducing antibiotic use, and increase influenza vaccination coverage worldwide. The COVID-19 pandemic has pointed a spotlight on the devastating effects of viral respiratory diseases, tremendous antibiotic overuse for viral infections and the value of vaccination. Lessons learned and momentum for vaccination can be gained to improve influenza vaccination coverage rates and reduce antibiotic use and AMR.

# 5 Strategic Recommendations

Recommendations following the review of the literature and expert interviews

## POLICY RECOMMENDATIONS

1. Increase influenza vaccination coverage rates in children, adults and high-risk populations, with a focus on vaccine equity, to reduce antibiotic use and indirect use among household members
2. Include influenza vaccination in all AMR national action plans and support the development of other guidelines on vaccine use and AMR, with a focus on the implementation of these plans
3. Periodically monitor the progress and development of national action plans on AMR with regards to vaccination, as well as the implementation of these plans
4. Build on the experience of COVID-19 to strengthen the importance of infection prevention and control measures (e.g. hand hygiene, social distancing, face masks) that help reduce influenza transmission and increase understanding of the importance of influenza vaccination
5. Adapt the AMR-influenza vaccination message to each different target population group to include in tailor-made influenza vaccination programs to change behavior towards influenza vaccination
6. Increase funding for R&D, including the development of new antibiotics, antimicrobials and universal influenza vaccines

## SCIENTIFIC RECOMMENDATIONS

1. Define the effect of influenza vaccination on AMR
2. Increase high-quality data on the association between influenza vaccination and antibiotic use by developing a guideline to collect antibiotic use data as part of a standard protocol in vaccine trials and other studies *
3. Prepare a cost-benefit analysis on the costs of influenza vaccination and the effect on AMR to share among policy makers, including data on the prevention of secondary infections and hospitalization rates
4. Review all available national action plans on AMR regarding influenza vaccination coverage to reduce AMR, with a focus on implementation, actionable information and pragmatic recommendations

* This could be achieved by creating a list of recommended endpoints for these studies (e.g. for RCTs, epidemiological studies etc.). Examples of measured outcomes include: antibiotic usage, prescription rate, dosage, days of therapy, and type of antibiotic.

# RECOMMENDATIONS FOR PRACTICE

1. Increase awareness and understanding among healthcare workers and the public regarding the association between influenza vaccination and AMR, through medical organizations, experts and public health agencies
2. The influenza vaccine should be easily accessible to healthcare personnel, risk groups and the general public
3. As addition to influenza vaccination, use and expand the use of rapid virological and bacteriological diagnostic tests (point-of-care testing) in primary care to decrease inappropriate antibiotic prescribing (e.g. CRP tests)
4. Include influenza vaccination in antimicrobial stewardship programs aimed towards healthcare workers (e.g. general practitioners) to reduce antibiotic prescribing in primary care

# 6 References


1. O'Neill, J., *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. 2016, Review on Antimicrobial Resistance.
2. World Health Organization, *Global Action Plan on Antimicrobial Resistance*. 2015.
3. Holmes, A.H., et al., *Understanding the mechanisms and drivers of antimicrobial resistance.* Lancet, 2016. **387**(10014): p. 176-87.
4. Buchy, P., et al., *Impact of vaccines on antimicrobial resistance.* Int J Infect Dis, 2020. **90**: p. 188-196.
5. World Health Organization, *Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: an Action Framework.* 2020.
6. von Gottberg, A., et al., *Effects of vaccination on invasive pneumococcal disease in South Africa.* N Engl J Med, 2014. **371**(20): p. 1889-99.
7. World Health Organization. *Why is vaccination important for addressing antibiotic resistance?* 2016; Available from: https://www.who.int/westernpacific/news/q-a-detail/why-is-vaccination-important-for-addressing-antibiotic-resistance.
8. Kwong, J.C., et al., *The effect of universal influenza immunization on antibiotic prescriptions: an ecological study.* Clin Infect Dis, 2009. **49**(5): p. 750-6.
9. Lipsitch, M. and G.R. Siber, *How Can Vaccines Contribute to Solving the Antimicrobial Resistance Problem?* mBio, 2016. **7**(3).
10. Petersen, I. and A.C. Hayward, *Antibacterial prescribing in primary care.* J Antimicrob Chemother, 2007. **60 Suppl 1**: p. i43-47.
11. Alsan, M., et al., *Antibiotic Use in Cold and Flu Season and Prescribing Quality: A Retrospective Cohort Study.* Medical care, 2015. **53**(12): p. 1066-1071.
12. Buckley, B.S., et al., *Impact of vaccination on antibiotic usage: a systematic review and meta-analysis.* Clin Microbiol Infect, 2019. **25**(10): p. 1213-1225.
13. Klein, E.Y., et al., *The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis.* Influenza Other Respir Viruses, 2016. **10**(5): p. 394-403.
14. World Health Organization. *Influenza vaccination coverage and effectiveness*. 2021; Available from: https://www.euro.who.int/en/health-topics/communicable-diseases/influenza/vaccination/influenza-vaccination-coverage-and-effectiveness
15. OECD. *Influenza vaccination rates (indicator).* 2021; Available from: https://data.oecd.org/healthcare/influenza-vaccination-rates.htm
16. Vekemans, J., et al., *Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: A World Health Organization Action Framework.* Clinical Infectious Diseases, 2021.
17. Bachtiger, P., et al., *The Impact of the Covid-19 Pandemic on Uptake of Influenza Vaccine: A UK-Wide Observational Study.* JMIR Public Health Surveill, 2021.
18. Richmond, H., et al., *Seasonal influenza vaccination during a pandemic.* Human vaccines & immunotherapeutics, 2020. **16**(9): p. 2219-2221.
19. Maltezou, H.C., K. Theodoridou, and G. Poland, *Influenza immunization and COVID-19.* Vaccine, 2020. **38**(39): p. 6078-6079.
20. Jaklevic, M., *Flu Vaccination Urged During COVID-19 Pandemic.* JAMA, 2020. **324**(10): p. 926-927.
21. Pepin, S., et al., *Impact of a quadrivalent inactivated influenza vaccine on influenza-associated complications and health care use in children aged 6 to 35 months: Analysis of data from a phase III trial in the Northern and Southern Hemispheres.* Vaccine, 2019. **37**(13): p. 1885-1888.

22. Dbaibo, G., et al., *Quadrivalent Influenza Vaccine Prevents Illness and Reduces Healthcare Utilization Across Diverse Geographic Regions During Five Influenza Seasons: a Randomized Clinical Trial.* Pediatric infectious disease journal, 2019.
23. Hardelid, P., et al., *Effectiveness of live attenuated influenza vaccine in preventing amoxicillin prescribing in preschool children: a self-controlled case series study.* J Antimicrob Chemother, 2018. **73**(3): p. 779-786.
24. Klein, E.Y., et al., *The Impact of Influenza Vaccination on Antibiotic Use in the United States, 2010–2017.* Open Forum Infectious Diseases, 2020. **7**(7).
25. Vaccines Europe, *The role of vaccination in reducing antimicrobial resistance (AMR).* 2016.
26. Houses of Parliament, *Antimicrobial Resistance and Immunisation.* 2018.
27. Clift, C., *Review of Progress on Antimicrobial Resistance*. 2019, Chatham House.
28. Wellcome, *The global response to AMR: momentum, success, and critical gaps*. 2020.
29. Wilby, K.J. and D. Werry, *A review of the effect of immunization programs on antimicrobial utilization.* Vaccine, 2012. **30**(46): p. 6509-14.
30. World Health Organization. *Library of national action plans*. 2020; Available from: https://www.who.int/antimicrobial-resistance/national-action-plans/library/en/.
31. World Health Organization, *National Action for Global Change on Antimicrobial Resistance.* 2016.
32. Review on Antimicrobial Resistance, *Vaccines and Alternative Approaches: Reducing our Dependence on Antimicrobials*. 2016.
33. Wellcome Trust, *Evidence for action on antimicrobial resistance*. 2016.
34. World Bank Group, *Drug-Resistant Infections: A Threat to our Economic Future*. 2017.
35. Chatham House, *The Value of Vaccines in the Avoidance of Antimicrobial Resistance*. 2017.
36. World Health Organization, *Monitoring Global Progress on Addressing Antimicrobial Resistance*. 2018.
37. World Health Organization, *Immunization strengthens the fight against Antimicrobial Resistance.* 2019.
38. United Nations General Assembly, *Follow-up to the political declaration of the high-level meeting of the General Assembly on antimicrobial resistance*. 2019.
39. IACG, *No Time To Wait: Securing the World from Drug-Resistant Infections*. 2019.
40. World Bank Group, *Pulling Together to Beat Superbugs: Knowledge and Implementation Gaps in Addressing Antimicrobial Resistance*. 2019.
41. World Health Organization, *Global Influenza Strategy 2019 - 2030: Prevent. Control. Prepare.* 2019.
42. Klugman, K.P. and S. Black, *Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects.* Proc Natl Acad Sci U S A, 2018. **115**(51): p. 12896-12901.
43. Malarski, M., et al., *Vaccine impact on antimicrobial resistance to inform Gavi, the Vaccine Alliance's 2018 Vaccine Investment Strategy: report from an expert survey.* F1000Res, 2019. **8**: p. 1685.
44. Sevilla, J.P., et al., *Toward economic evaluation of the value of vaccines and other health technologies in addressing AMR.* Proceedings of the National Academy of Sciences of the United States of America, 2018. **115**(51): p. 12911-12919.
45. Machado, A., et al., *Impact of influenza vaccination programmes among the elderly population on primary care, Portugal, Spain and the Netherlands: 2015/16 to 2017/18 influenza seasons.* Euro Surveill, 2019. **24**(45).
46. WHO, FAO, and OIE, *Monitoring global progress on addressing antimicrobial resistance: analysis report of the second round of results of AMR country self-assessment survey 2018*. 2018.
47. Wells, V., et al., *Implementing WHO, EU and UK AMR strategies and action plans: has the world lived up to the challenge?* 2017, APPG on Antibitiotics.
48. Wellcome Trust, *Sustaining global action on antimicrobial resistance*. 2017

49. Berkley, S., Laxminarayan, R., . *Any Delay in Ending COVID Could Spur a Different Pandemic*. 2020; Available from: https://www.scientificamerican.com/article/any-delay-in-ending-covid-could-spur-a-different-pandemic/
50. To, K.W., et al., *Increasing the coverage of influenza vaccination in healthcare workers: review of challenges and solutions.* J Hosp Infect, 2016. **94**(2): p. 133-42.
51. Smith, P.J., et al., *Association between health care providers' influence on parents who have concerns about vaccine safety and vaccination coverage.* Pediatrics, 2006. **118**(5): p. e1287-92.
52. ECDC. *Seasonal influenza vaccines*. 2018; Available from: https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/seasonal-influenza-vaccines
53. Morris, D.E., D.W. Cleary, and S.C. Clarke, *Secondary Bacterial Infections Associated with Influenza Pandemics.* Front Microbiol, 2017. **8**: p. 1041.
54. Knight, G.M., M. Clarkson, and T.I. de Silva, *Potential impact of influenza vaccine roll-out on antibiotic use in Africa.* J Antimicrob Chemother, 2018. **73**(8): p. 2197-2200.
55. Chae, C., et al., *Effect of Pediatric Influenza Vaccination on Antibiotic Resistance, England and Wales.* Emerging infectious diseases, 2020. **26**(1): p. 138-142.
56. Smith, E., et al., *Improving antibiotic prescribing in the ambulatory care setting-stewardship through influenza vaccination, us flu ve network 2013-2014 through 2017-2018.* Open Forum Infectious Diseases, 2019. **6**: p. S695.
57. Doherty, T.M., W.P. Hausdorff, and K.G. Kristinsson, *Effect of vaccination on the use of antimicrobial agents: a systematic literature review.* Annals of Medicine, 2020. **52**(6): p. 283-299.
58. Hurwitz, E.S., et al., *Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts.* Jama, 2000. **284**(13): p. 1677-82.
59. Ouzzani, M., et al., *Rayyan—a web and mobile app for systematic reviews.* Systematic Reviews, 2016. **5**(1): p. 210.
60. World Bank Group. *World Bank Country and Lending Groups*. 2020; Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519#High_income.

# Annex I: Methods

## 7.1 Systematic Literature Review

The quantitative phase of this study involved a literature review which analyzed the effect of influenza vaccination on antibiotic use. We built on the work of a systematic literature review published by Buckley et al. in 2019 regarding the impact of vaccination on antibiotic usage. This study assessed the effect of the pneumococcal vaccine, measles vaccine and influenza vaccine on antibiotic use, with the inclusion of randomized controlled trials (RCTs) and observational studies [12]. Buckley et al. (2019) included 16 RCTs and 14 observational studies on influenza vaccination, published from January 1998 to March 2018. They conducted a meta-analysis of the RCTs.

The Buckley review was updated with relevant scientific articles published after March 2018 with permission from the Buckley research team (e.g. updating the meta-analysis (RCTs) and providing an overview of new observational studies). The literature search was identical to Buckley et al. (2019) and therefore included articles from PubMed, Ovid Medline, Embase and Cochrane. The search involved four components: antimicrobials, resistance, influenza and vaccination. The analysis covers publications from April 2018 to July 2020, and was restricted to publications available in full-text, written in English, and involving human subjects. The last database search was conducted on July 15, 2020.

The process of study selection was performed by two researchers (LvH and SC) using the program Rayyan QCRI, a web application used to screen literature [59]. Beforehand, duplicates were removed automatically using Endnote and manually to identify any missed duplicates. The researchers identified articles as 'included', 'maybe' or 'excluded' based on title and abstract screening. They were in accordance with 96% of the articles selected. Full-text articles defined as 'included' or 'maybe' were analyzed by one of the researchers (LvH). Articles were included containing information on both influenza vaccination and antibiotic use or AMR.

## 7.2 Public Health Reports

Public health reports were included from different health organizations, institutions, NGOs and vaccine organizations. Reports were searched for by one researcher (LvH) on websites of public health organizations such as: World Health Organization (WHO) including the regional offices sites, United Nations (UN), World Bank Group, United States of America's Centers for Disease Control and Prevention (US CDC), European Centre for Disease Prevention and Control (ECDC), International Monetary Fund (IMF), Chatham House and Wellcome. All reports were written in English. A first selection of reports was based on title and summary. The reports were organized in categories according to the subject: (1) vaccination and AMR, (2) AMR in general, or (3) vaccination in general. All full-text reports in category 1 were analyzed by the researcher (LvH).

## 7.3 National Action Plans on AMR

The aim of this analysis was to include approximately 30 AMR national action plans from low-, middle- and high-income countries from all world regions, available in the WHO library of national action plans [30]. We used the World Bank Country Classification to evenly include low-, middle- and high-income countries from different regions worldwide [60]. The researchers agreed on a list of countries to be analyzed based on income level and continent (LvH, JP and MD). Information was extracted from the national action plans of these countries by three researchers (LvH, SC and JP). Each plan was analyzed using content analysis based on 9 factors: (1) information on vaccination, (2) structure and objectives, (3) extensiveness and details, (4) similarities with the global action plan on AMR, (5) implementation and operational plan, (6) monitoring and evaluation plan, (7) costs and budget, (8) involvement of experts, and (9) evidence-based references. National action plans available in English, Dutch, French, Italian, Spanish and Portuguese were analyzed.

## 7.4 Expert Interviews

To obtain a broad overview of the experiences and attention to influenza vaccination and AMR in different countries, the qualitative interview sample included international experts with different backgrounds in the field of influenza and/or AMR, including members of the GII Work Stream II Team. The 30-minute video interviews were conducted collectively online by two researchers (LvH and JP) using Zoom or GoToMeeting between the end of October 2020 and the beginning of January 2021. All interviews were audiotaped, transcribed and analyzed using MaxQDA 2020 by one of the researchers (LvH).

A combination of convenience and snowball sampling was employed to recruit respondents with help of the network of the GII Work Stream II Team. The respondent invitation contained an accompanying document including information about the GII research project and a list of interview questions. The semi-structured interview guide was devised from the literature review and focused on the following topics: impact of COVID-19 on influenza vaccination and AMR, association between influenza vaccination and AMR, global attention to influenza vaccination and AMR, AMR national action plans, and recommendations for research, policy and practice (see Annex III). Afterwards, the respondents were sent a draft version of this report for validation and commentary.

# Annex II: RCTs in Buckley et al. (2019)

| Study ID | Study Design, Country, Dates | Study Population | Intervention & Comparison groups | Study Outcomes |
|---|---|---|---|---|
| **Belshe 1998** | RCT<br><br>USA<br><br>August 1996 – March 1998 | Healthy children aged 15 – 71 months<br><br>*N* = 1602 | Intervention: Aviron intranasal live attenuated, cold-adapted, trivalent influenza vaccine.<br><br>Comparison: Placebo | Antibiotic-use data: parental self-report<br><br>Main Outcome: Risk ratio 0.71 (0.62–0.81) |
| **Nichol 1999 *** | RCT<br><br>USA<br><br>September 1997 – March 1998 | Adults aged 18–64 years working at least 30 hours per week outside the home<br><br>*N* = 4561 | Intervention: Live-attenuated influenza vaccine (FluMist, Aviron)<br><br>Comparison: Placebo | Antibiotic-use data: patient self-report<br><br>Main Outcome: Rate reduction 28.1% (16.6%–38.0%) |
| **Bridges 2000** | RCT<br><br>USA<br><br>October 1997 – March 1999 | Healthy working adults, median age 43–44 years<br><br>*N* = 2375 | Intervention: Trivalent inactivated influenza vaccine (FluShield, Wyeth-Lederle)<br><br>Comparison: Placebo | Antibiotic-use data: patient self-report<br><br>Main Outcome: Risk ratio 0.81 (0.52–1.27) |
| **Marchisio 2002** | RCT<br><br>Italy<br><br>November 1999 – July 2000 | Children aged 1–5 years with a history of acute otitis media<br><br>*N* = 133 | Intervention: Nasalflu intranasal, inactivated, virosomal subunit influenza vaccine (Berna Biotech)<br><br>Comparison: Unvaccinated | Antibiotic-use data: parental self-report<br><br>Main Outcome: Risk ratio 0.61 (00.43–0.87) |
| **Allsup 2003** | RCT<br><br>UK<br><br>September 1999 – May 2000 | Healthy individuals aged 65 – 74 years without risk factors for influenza<br><br>*N* = 729 | Intervention: Trivalent, split virion influenza vaccine (Wyeth Laboratories).<br><br>Comparison: Placebo | Antibiotic-use data: medical records<br><br>Main Outcome: Main outcome: Risk ratio 1.43 (0.71–2.90) |

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|---|---|---|---|---|
| **Esposito 2003** | RCT<br><br>Italy<br><br>December 2000 – April 2001 | Children aged 6 months to 9 years with history of recurrent respiratory tract infections<br><br>*N* = 127 | Intervention: Nasalflu intranasal influenza vaccine (Berna Biotech). Inactivated, trivalent, virosome-formulated subunit influenza vaccine.<br><br>Comparison: Placebo | Antibiotic-use data: parental self-report<br><br>Main Outcome: Ratio of means 0.56 (0.41–0.75) |
| **Hoberman 2003** | RCT<br><br>USA<br><br>October 1999 – March 2001 | Children aged 6–24 months<br><br>*N* = 793 | Intervention: Fluzone inactivated trivalent subvirion influenza vaccine<br><br>Comparison: Placebo | Antibiotic-use data: parental self-report<br><br>Main Outcome: Ratio of means 1.06 (0.88–1.27) |
| **Principi 2003** | RCT<br><br>Italy<br><br>2001 – 2002 | Healthy children aged 6 months to 5 years<br><br>*N* = 303 | Intervention: Inflexal V intramuscular virosomal influenza vaccine (Berna Biotech)<br><br>Comparison: Unvaccinated | Antibiotic-use data: parental self-report<br><br>Main Outcome: Ratio of means 0.69 (0.56–0.84) |
| **Pisu 2005** | RCT<br><br>USA<br><br>November 1996 – April 1999 | Families of children aged 2 to 5 years attending day care centres<br><br>*N* = 260 | Intervention: Inactivated influenza vaccine (Wyeth-Lederle)<br><br>Comparison: Hepatitis A vaccine | Antibiotic-use data: parental self-report<br><br>Main Outcome: Ratio of means 0.82 (0.34–1.98) |
| **Vesikari 2006** | RCT<br><br>Belgium, Finland, Israel, Spain, United Kingdom<br><br>October 2000 – May 2002 | Healthy children aged 6 to <36 months attending day care ≥12 hours/week<br><br>*N* = 1784 | Intervention: CAIV-T Cold-Adapted Influenza Vaccine-Trivalent (Wyeth Vaccines Research)<br><br>Comparison: Placebo | Antibiotic-use data: parental self-report<br><br>Main Outcome: Risk ratio 1.01 (0.89–1.14) |
| **Jansen 2008 *** | RCT<br><br>Netherlands<br><br>2003 – 2005 | Children aged 18–72 months with a previously diagnosed respiratory tract infection.<br><br>*N* = 579 | Intervention: Influvac (trivalent influenza vaccine) with placebo<br><br>Comparison: Recombinant HBV vaccine (Engerix-B Junior; GlaxoSmithKline) + placebo vaccination | Antibiotic-use data: parental self-report & clinician data collection form<br><br>Main Outcome: Incidence rate ratio 0.89 (0.50–1.61) |

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|---|---|---|---|---|
| **Marchisio 2009** | RCT<br><br>Italy<br><br>October 2006 – April 2007 | Children aged 1–5 years with a history of recurrent acute otitis media<br><br>*N* = 180 | Intervention: Inactivated virosomal-adjuvanted subunit influenza vaccine (Inflexal V, Berna Biotech)<br><br>Comparison: Unvaccinated | Antibiotic-use data: parental self-report<br><br>Main Outcome: Ratio of means 0.57 (0.45–0.71) |
| **Loeb 2010** | RCT<br><br>Canada<br><br>September 2008 – June 2009 | Children and adolescents aged 36 months to 15 years<br><br>*N* = 10985 person-seasons | Intervention: Inactivated seasonal influenza vaccine recommended for the 2008–2009 influenza season (Vaxigrip, Sanofi Pasteur)<br><br>Comparison: Hepatitis A vaccine (Avaxim-Pediatric, Sanofi Pasteur) | Antibiotic-use data: parental self-report<br><br>Main Outcome: Risk ratio 0.69 (0.58–0.83) |
| **Tandon 2010 *** | RCT<br><br>Australia<br><br>April 2006 – October 2006 | Adults aged 47–88 years with severe recurrent chronic obstructive pulmonary disease<br><br>*N* = 38 | Intervention: HI–164OV non-typeable Haemophilus influenzae enteric-coated tablets<br><br>Comparison: Placebo | Antibiotic-use data: patient self-report<br><br>Not estimable |
| **Gao 2011** | RCT<br><br>China<br><br>September 2008 – November 2009 | Patients ≥60 years of age with chronic bronchitis<br><br>*N* = 138 | Intervention: Influenza vaccine (Shanghai Institute of Biological Products)<br><br>Comparison: Unvaccinated | Antibiotic-use data: patient self-report<br><br>Main Outcome: Ratio of means 0.68 (0.64–0.73) |
| **Clancy 2016** | RCT<br><br>Australia<br><br>2011 | Adults aged 40–85 years with diagnosis of moderate–severe chronic obstructive pulmonary disease<br><br>*N* = 320 | Intervention: Oral non-typeable Haemophilus influenzae (NTHi) vaccine (HI–164OV) and 3 courses of HI–164OV enteric-coated tablets<br><br>Comparison: Placebo | Antibiotic-use data: patient self-report<br><br>Main Outcome: Ratio of means 1.10 (0.80–1.51) |

* Not included in the meta-analysis

# Annex III: Interviews

The interviews were organized according to the following research questions:

1. What do you think will be the impact of COVID-19 on vaccination, including influenza vaccination, and antimicrobial resistance?
2. What is your expert opinion about the association between influenza vaccination and antimicrobial resistance?
3. How do you experience the attention towards influenza vaccination and antimicrobial resistance in your work field?
    - Global
    - Regional (Europe, Africa, Asia or the Americas)
    - Country
4. We have noticed that vaccination, in particular influenza vaccination, is often not a detailed component of countries' National Action Plans on AMR. How do you think this can be explained?
5. Do you have recommendations on increasing the interest in influenza vaccination and antimicrobial resistance?
    - Scientific recommendations
    - Policy recommendations
    - Recommendations for practice (primary/secondary care)
6. How can we increase the attention for influenza vaccination and AMR on the global agenda?
7. Do you have any additions to the topic of influenza vaccination and antimicrobial resistance?

We would like to thank the following people for participating in the interviews:

- Prof. dr. H. Rogier van Doorn (Oxford University Clinical Research Unit (OUCRU), Hanoi, Vietnam)
- Prof. Masoud Mardani (Shahid Beheshti University of Medical Sciences, Iran)
- Prof. Susanna Esposito (University of Parma, Italy)
- Prof. dr. ir. Liset van Dijk (Nivel, Netherlands)
- Dr. Martin Friede (WHO, Geneva, Switzerland)
- Dr. Mateusz Hasso-Agopsowicz (WHO, Geneva, Switzerland)
- Dr. Barbara Michiels (University of Antwerp, Belgium)
- Prof. dr. Alex Friedrich (University of Groningen, Netherlands)
- Dr. Elizabeth Klemm (Wellcome, United Kingdom)
- Dr. Jan Poolman (Johnson & Johnson, Netherlands)
- Prof. Keiji Fukuda (School of Public Health, University of Hong Kong, China)
- Dr. Ramanan Laxminarayan (Centre for Disease Dynamics, Economics & Policy (CDDEP), United States & India)

# Acknowledgements

Special thanks to Mateusz Hasso-Agopsowicz [Disclaimer: The opinions expressed herein do not necessarily reflect the decisions of the World Health Organization], Elizabeth Klemm and Keiji Fukuda for providing specific comments to the report.

We would also like to thank the members of the GII Work Stream II for reviewing the report: Rogier van Doorn, Masoud Mardani, Susanna Esposito, Ann Falsey and Meral Akçay.

Finally, we would like to thank the members of the Sanofi Pasteur Innovation and Vaccine Value Team for the interesting discussions. When preparing the report, we received valuable comments and suggestions from the Sanofi Pasteur team. Special thanks to Marine Martin, Alireza Mafi, Michael Greenberg, David Greenberg, Margaux Deral, Amine Amiche, and Jean-Denis Shu.