OHE

The Socio-Economic Value of Adult Immunisation Programmes

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List of Acronyms

AMR – Antimicrobial resistance
BCA – Benefit-Cost Analysis
BCR – Benefit-Cost Ratio
CEA – Cost-Effectiveness Analysis
HICs - High-Income Countries
HTA – Health Technology Assessment
HZ – Herpes Zoster
LICs – Low-Income Countries
LMICs – Low- and Middle-income Countries
NB – Net Benefits
NIP – National Immunisation Programme
PD – Pneumococcal disease
VSL – Value of a Statistical Life
VSLY – Value of a Statistical Life Year
VZV - Varicella Zoster Vaccine
RSV – Respiratory Syncytial Virus
RZV – Recombinant Zoster
SDGs - Sustainable Development Goals
ZVL - live-attenuated Varicella Zoster Virus vaccines

Executive Summary

KEY TAKEAWAYS

- Global demographic changes and health challenges are putting ever-greater pressure on healthcare systems and society more broadly. Adult immunisation programmes are a potentially powerful tool for policymakers to ease those pressures.
- This report provides evidence for adult immunisation programmes across ten countries and four vaccines showing that adult immunisation programs offset their costs multiple times through benefits to individuals, the healthcare system, and wider society.
    - In particular, benefit-cost analysis of the same vaccines showed that adult vaccines can return up to 19 times their initial investment to society, when their significant benefits beyond the healthcare system are monetised.
    - This is the equivalent of billions of dollars in net monetary benefits to society, or more concretely, up to $4637 for one individual's full vaccination course.
- Despite increasing recognition of the broader value of vaccination, substantial evidence gaps remain, leading to underestimation of vaccine value and risking suboptimal policy decisions.
- Governments are recommended to adopt a prevention-first mindset to help ease increasing pressures on health systems and society, with adult immunisation playing a crucial role in enabling us to live longer, healthier, and more productive lives.

What is this report about?

Global Demographic Transitions and Health Challenges

The world is currently undergoing significant demographic shifts, with ageing populations as the dominant trend. For infectious diseases, such as shingles and pneumococcal disease, the incidence and severity of symptoms can increase with age and are associated with a substantial hospitalisation burden amongst this population. Healthcare resource use associated with noncommunicable diseases also increases with population ageing. This necessitates readiness of health and social care systems to meet these challenges. Concurrently, the "tripledemic" of COVID-19, influenza, and RSV, along with rising rates of chronic diseases among lower age groups, places immense pressure on healthcare systems already grappling with treatment backlogs and the growing challenges of antimicrobial resistance and other pandemic threats.

Shifting Focus to Prevention – Vaccination as a Tool

Addressing these challenges requires a paradigm shift from primarily treatment-focused healthcare interventions to preventive interventions, leveraging novel technology and innovations and including vaccination as a powerful tool. A prevention mindset is often adopted in other sectors beyond healthcare (e.g. road safety and workforce health and safety) to prevent harmful health outcomes

and productivity losses and promote societal well-being. Similarly, preventive public health interventions are recognised as essential in supporting healthcare systems, promoting healthier lives, and fostering productivity and societal well-being within societies. Vaccination stands as a fundamental preventive measure, integral to achieving global health goals like the UN Sustainable Development Goals (SDGs).

Adult Immunisation Gaps and WHO's Strategic Priority

While substantial progress has been made in childhood immunisation globally, the value of adult immunisation programmes often remains overlooked. Access to adult vaccinations is inconsistent across countries, with limited inclusion in routine immunisation schedules. The WHO's IA2030 aims to promote recommended immunisations throughout the life-course, emphasising the need to raise awareness of the benefits of adult immunisation and national strategies for life-course immunisation.

Overview of our report and methods

This report demonstrates the health and socioeconomic value of adult immunisation programmes against seasonal influenza (influenza), pneumococcal disease (PD), herpes zoster (HZ), and respiratory syncytial virus (RSV) in ten countries (Australia, Brazil, France, Germany, Italy, Japan, Poland, South Africa, Thailand, and the United States of America).

Results are based on:

1) A targeted literature review of the published evidence on the burden of these vaccine-preventable diseases in adults and the health, healthcare system, and societal benefits of immunisation.

2) Health economic modelling to estimate the benefit-cost ratios and net monetary benefits associated with adult immunisation programmes in a sample of up to 10 countries.

The findings support the critical role of robust adult immunisation programmes in addressing major health and societal challenges while aligning with and advancing critical global agendas such as the UN SDGs, the UN Decade of Healthy Ageing (2021–2030), and the WHO Immunisation Agenda 2030 (IA2030).

The Broader Value of Adult Immunisation

Our review found significant evidence for the value of adult immunisation, which included examples from across the three overarching domains of vaccine value: value for population health, value for healthcare systems, and value for society.

The Value of Adult Immunisation for Population Health

Vaccine-preventable diseases continue to impose a substantial burden on adult populations, causing mortality and severe health consequences. Evidence shows that adult immunisation is highly effective in preventing diseases, their sequelae, and mortality, particularly in older adults and those with chronic health conditions.

The Value of Adult Immunisation for Healthcare Systems

Infections caused by influenza virus, streptococcus pneumoniae, RSV, and reactivated VZV significantly contribute to healthcare resource utilisation and associated costs. Adult immunisation programmes are highly cost-effective and can result in net cost savings for healthcare systems. Recent studies have highlighted that these programmes not only offer health benefits but also yield financial gains by averting hospital inpatient and emergency care.

The Value of Adult Immunisation for Society

Vaccine-preventable diseases impact productivity and result in a significant socioeconomic burden. Expanding adult immunisation programmes and coverage can lead to substantial productivity gains by individuals and their caregivers and economic benefits for society. Additionally, adult immunisation programmes can contribute to health and economic equity within countries, particularly benefiting vulnerable populations and underserved communities.

The research also shows that many broader elements, for example societal-economic elements such as productivity value, are currently underrepresented in the academic literature. Without such evidence, the full value of immunisation programmes is likely underestimated by policy- and decision-makers, risking suboptimal investment decisions.

The Benefit-Cost Profile and Socioeconomic Impact of Adult Immunisation

Across the ten countries, our analysis of the four immunisation programmes demonstrates that adult immunisation programmes produce benefits likely large enough to offset their costs and generally outweigh them many times over. Across all countries and disease programs, these programmes return up to 19 times their initial investment when monetising the full spectrum of benefits using the most common valuation approach as applicable to each programme. This is the equivalent of billions of dollars in net monetary benefits to society and corresponds to about $4637 for one individual's full vaccination course.

Adult immunisation programmes can offset their costs multiple times

19x

Adult vaccines can return **up to 19 times their initial investment to society**, when their significant benefits beyond the healthcare system are monetised.

This 19x return is equivalent to billions of dollars in net benefits to society.
Or, more concretely, **up to $4637 per individual** full vaccination course.

up to **$4637**
per full vaccination course

These results, based on mostly conservative estimation methods and inputs, are proportionate with returns observed in childhood immunisation programmes – widely recognised as some of the most cost-effective interventions available to healthcare systems.

Discussion and Recommendations

The burden of vaccine-preventable diseases is projected to rise, underscoring the importance of robust adult immunisation programmes. Adult immunisation programmes produce value for society by averting death, serious disease, and productivity losses. They also support equity and the fight against antimicrobial resistance. Expanding access to a broader adult population can enhance overall cost-effectiveness and net cost savings for healthcare systems, as well as support healthcare system capacity and resilience.

However, there are significant gaps in evidence regarding the broader elements of the value of immunisation programmes, indicating a critical need for further research to prioritise and enhance adult immunisation programmes for the benefit of society and public health. Closing these knowledge gaps is vital for informed decision-making and targeted policy interventions that aim to optimise the value of adult immunisation programmes.

KEY RECOMMENDATIONS

1) **Adopt a prevention-first mindset and provide robust funding for adult vaccination programs**

   Now, more than ever, healthcare systems must invest in strategies to cope with unprecedented and growing demand. Prevention must be at the heart of such strategies, and robust adult immunisation programmes are a fundamental component of effective prevention.

2) **Implement and optimise adult immunisation programmes as part of a life course immunisation approach**

   The burden of vaccine-preventable diseases is projected to rise, underscoring the importance of robust adult immunisation programmes. Expanding access to a broader adult population can generate more value and higher net cost savings for healthcare systems and society. Adult immunisation programmes also present a great opportunity to help our societies age well and sustainably long into the future - and deliver an excellent return on investment in the process.

3) **Expand and develop the evidence base for the value of adult immunisation programmes**

   There are significant gaps in evidence regarding the broader elements of the value of immunisation programmes. Further research is needed to close these knowledge gaps, which is vital for informed decision-making and targeted policy interventions that aim to optimise the value of adult immunisation programmes. More robust data collection systems, widely accepted methods, and transparent/open data access would allow more accurate quantification of these values. It is especially important to close these information gaps in middle and lower income countries.

1 Introduction

1.1 Background

Global demographic transitions towards ageing populations are transforming the social and economic structures of countries worldwide. Between 2015 and 2050, the proportion of the world's population over 60 years old is projected to nearly double from 12% to 22% (WHO, 2022b). The global old-age dependency ratio (the number of people aged 65+ per 100 people aged 15 to 64) will double from 19 in 2020 to 38 in 2050 (UNDESA, 2019). Every country faces major challenges in ensuring that its health and social care systems are ready to respond to this demographic shift (WHO, 2022b). The UN and WHO are jointly championing a 'Decade of Ageing' to ensure that the Sustainable Development Goals (SDGs) are met for all segments of society with a particular focus on the most vulnerable — including older persons (UNDP, 2017). In parallel, growing rates of chronic disease amongst younger age groups (CDC, 2020; Gore et al., 2011; NCD Alliance, 2011) and the 'tripledemic' of COVID-19, flu, and RSV (Guido et al., 2023) are placing significant pressure on healthcare systems still dealing with major treatment backlogs (WHO, 2022a).

A shift in focus from treatment to prevention is increasingly recognised as essential for supporting healthcare systems to cope with unprecedented and growing levels of demand, for supporting people of all ages to live full and healthy lives, and for promoting productivity, equity and societal well-being in the broadest sense. Preventive public health interventions help achieve this while delivering substantial cost-savings to healthcare systems and society, offering a median return on investment of 34.2 to 1 (Masters et al., 2017).

Vaccination is well-recognised as a fundamental component of prevention and is critical for advancing global agendas, including the UN Sustainable Development Goals (SDGs), the UN Decade of Healthy Ageing (2021–2030), and the World Health Organisation (WHO) Immunisation Agenda 2030 (IA2030). The SDGs, for example, aim to prevent needless suffering from preventable diseases and to achieve access to safe, effective, quality and affordable essential medicines and vaccines for all by 2030 (UNICEF, 2023, p.3). Yet, whilst tremendous progress has been made in ensuring global access to childhood immunisation programmes, the value of adult immunisation programmes continues to be under-recognised in the academic literature and the decision-making frameworks used by healthcare systems worldwide (Cafiero-Fonseca et al., 2017; Beck et al., 2022; Postma et al., 2022).

Access to vaccinations is highly variable, and in many countries, adult vaccinations are not included in routine immunisation schedules (see Table 1). For example, the WHO recommends that all older adults receive a pneumococcal vaccine, but only 31 countries currently include any adult pneumococcal vaccinations in their schedules (World Health Organisation, 2023b; a). Moreover, coverage of adult immunisation programmes has been compromised by the COVID-19 pandemic: research estimates that 100 million adult vaccine doses were missed in 2021 and 2022, compared to what would have been expected based on pre-pandemic trends (IQVIA, 2023). Beyond immunisation schedules, vaccine hesitancy is a growing concern in many countries, which ultimately impacts the uptake of recommended vaccines (and subsequent arguments around immunisation programme effectiveness) (Figueiredo et al., 2020).

In recognition of this challenge, one of the strategic priorities of the WHO's IA2030 is to ensure that "[a]ll people benefit from recommended immunisations throughout the life-course, effectively integrated with other essential health services" (World Health Organisation, 2020). The IA2030 points to the need to raise awareness of the benefits of adult immunisation. This Report seeks to contribute to the policy discourse by synthesising evidence of the value adult immunisation programmes create for health, healthcare systems, and societies.

1.2 Report Overview

This report presents the results of two analyses which offer complementary perspectives on the socioeconomic value of adult immunisation programmes, focussing on programmes against seasonal influenza (influenza), pneumococcal disease (PD), herpes zoster (HZ) (caused by reactivated varicella-zoster virus, or VZV), and respiratory syncytial virus (RSV).

First, we describe a comprehensive targeted review of the value of adult immunisation programmes from 2017 onward. It synthesises evidence on the burden of these diseases and the health, healthcare system, and societal benefits of adult immunisation. The review is structured according to an existing conceptual framework for the value of immunisation programmes to ensure that the manifold dimensions of this value are comprehensively considered.

Second, we report estimates of the benefit-cost ratios and net monetary benefits associated with adult immunisation programmes, derived from benefit-cost analysis. Benefit-cost analysis is an established form of economic evaluation that models the monetised benefits and costs associated with different policies in order to compare their overall impact on societal welfare.

The objective of both analyses is to demonstrate the vital role of robust adult immunisation programmes in solving some of the greatest health and social care challenges of our time and achieving crucial global political agendas.

TABLE 1: ADULT VACCINATION RECOMMENDATIONS IN SELECTED COUNTRIES

Source: Data taken from https://vaccine-schedule.ecdc.europa.eu/ and https://immunizationdata.who.int/pages/schedule-by-country/; and specifically (CDC, 2024; EMA, 2023) for the emerging RSV vaccines. Where there is a discrepancy, the broader schedule is reported. Schedule data collected in Q3-Q4 2023.

Key: population groups recommended for immunisation

Recommended for all adults >18 years	Recommended for older adults and /or risk groups	Recommended for older adults but not funded by the healthcare system	Not included in the immunisation schedule

	Australia	Brazil	France	Germany	Italy	Japan	Poland	South Africa	Thailand	US
Influ-enza	65+ and at risk; >18 in some regions	60+ and at risk	65+ and at risk	60+	65+ and at risk	65+ and at risk	55+	65+ and at risk	65+ and at risk	18+
Pneum-ococcal	70+ and 50+ for indigenous communities		At risk	60+	65+	65+	50+			65+
Herpes Zoster	70-79		65-75	>60 and at risk >50	65+ and at risk >50	50+				50+ and at risk 19+
RSV				60+						60+

2 Review of Evidence for Adult Immunisation Programmes

2.1 Objectives

This chapter presents the results of a targeted literature review which sought to identify evidence on the burden of disease caused by infections due to flu, streptococcus pneumoniae, RSV and reactivated varicella zoster virus (VZV), and the value of the associated adult immunisation programmes (influenza, PD, RSV and HZ). We focus on ten countries selected to represent a diversity of immunisation schedules, healthcare systems, geographies, and demographic contexts. This includes seven high-income countries (Australia, France, Germany, Italy, Japan, Poland, and the United States of America (US)) and three upper-middle- income countries (Brazil, South Africa, and Thailand).

2.2 Methods

2.2.1 Approach

The results of the targeted literature review are structured according to the OHE Value of Vaccines framework. This is a tool for conceptualising the distinct elements of vaccines' value based on a synthesis of literature and schematics and has been validated by experts in the economic evaluation of vaccines (Bell, Neri and Steuten, 2021). A summary of our assessment of the strength of the evidence base per element of value for each immunisation programme and country is provided in section 2.3. A deep dive into the key findings from the evidence base is then presented in the three following sections reflecting the three overarching domains of value: value for population health (section 2.4), value for healthcare systems (section 2.5), and value for society (section 2.6). Within each section, we provide additional context through a summary of the disease burden and then present evidence for each individual value element. Our review was targeted and comprehensive, with the goal of highlighting high-quality evidence demonstrating the value of vaccines, in particular for under-recognised elements. This involves looking beyond the traditional criteria used to estimate the cost-effectiveness of drugs, which typically focus on 'narrow' health and healthcare system effects (Bell, Neri and Steuten, 2021; Postma et al., 2022; Hutubessy et al., 2023; Bloom, Cadarette and Ferranna, 2021).

2.2.2 Search strategy

The following search strategy was used in the PubMed database to identify relevant research: ((influenza[Title/Abstract]) OR (pneumo*[Title/Abstract]) OR (zoster[Title/Abstract]) OR (RSV[Title/Abstract]) OR (respiratory syncytial virus[Title/Abstract])) AND ((vaccin*[Title/Abstract]) OR (burden[Title/Abstract]) OR (impact[Title/Abstract])) AND ((australia) OR (brazil) OR (france) OR (germany) OR (italy) OR (japan) OR (poland) OR (south africa) OR (thailand) OR (united states))

Definitions of the study population, intervention, comparator and outcomes (PICO) are summarised in Table 2. We employed the following inclusion criteria: papers published from the 1st of January 2017 to the 31st of June 2023, results with full texts available, papers published in the English language, and studies that included adult populations over the age of 18. Our exclusion criteria comprised: studies published prior to 2017, studies including children only, results where only the

abstract was available, studies including animals and treatment guidelines, and studies considering vaccinations which have not yet been approved in any of our selected countries at the time of searching. Further, we reviewed the reference lists in the articles identified by the database search to capture additional relevant studies, including those that fall outside the time range but capture broader effects for which no other or more recent data were available.

TABLE 2: PICOS TABLE

Population	Adults >18 years
Intervention	Influenza, pneumococcal, HZ, and RSV vaccines; evidence on the burden caused by the diseases these vaccines target is also included.
Comparator	For vaccine intervention, no vaccine.
Outcomes	Any: e.g., health outcomes, societal economic outcomes

The search was restricted to evidence published since 2017 to prioritise the more recent literature showcasing the breadth of effects. Consideration of the broader benefits is more common and likely in more recent literature. The majority of studies of vaccines published prior to 2017 do not consider effects beyond health benefits to the individual, and the vast majority only consider health benefits and cost savings to healthcare systems – excluding, for example, population-level health benefits, productivity benefits, and other broader benefits (Cafiero-Fonseca et al., 2017).

All results presented are statistically significant with a confidence level of 95% or higher unless otherwise stated.

2.2.3 Value of Vaccines framework

Following Cafiero-Fonseca et al. (2017) and Bell et al. (2022), we assessed the strength of the evidence base for the value of adult immunisation programmes by reviewing the papers identified in our search to determine which elements of value have been evidenced for each focus vaccine and country. The elements of the OHE Value of Vaccines framework shown in Figure 1 were used to structure this assessment.

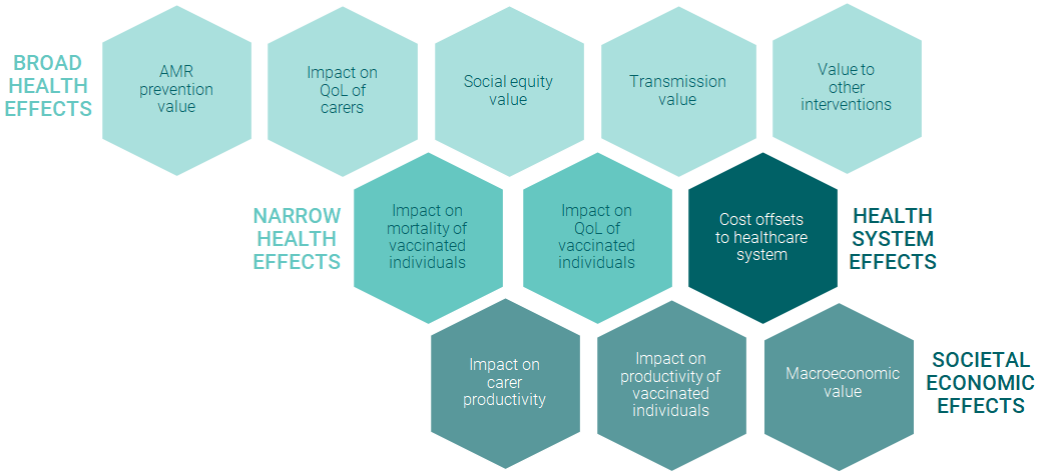

FIGURE 1: VALUE OF VACCINES FRAMEWORK.
Source: Adapted from Bell, Neri And Steuten (2021).

The definition and characterisation (broad/narrow) of each of the value elements of the framework are explained in Table 3. This framework is a tool for conceptualising the distinct elements of vaccines' value based on a synthesis of the value of vaccines literature and schematics and has been validated by experts in the economic evaluation of vaccines (Bell, Neri and Steuten, 2021). For this exercise, we analysed all search results relating to the value of adult vaccination but excluded evidence relating solely to the burden of disease[1].

TABLE 3: VALUE DOMAINS AND VALUE ELEMENTS, ACCORDING TO THE VALUE OF VACCINES FRAMEWORK

VALUE DOMAIN	VALUE ELEMENT	BROAD OR NARROW?	DEFINITION
Population health	Impact on quality of life of vaccinated	Narrow	Value of effects on the physical, mental, emotional, and social functioning of vaccinated individuals
	Impact on mortality of vaccinated	Narrow	Value of effects on life expectancy or life-years saved of vaccinated individuals
	Impact on quality of life of carers	Broad	Value of effects on the physical, mental, emotional, and social functioning of caregivers of vaccinated individuals
	Transmission value	Broad	Value of effects on disease transmission patterns and associated quality of life and mortality effects in non-vaccinated individuals
Healthcare systems	Cost offsets to the healthcare system	Narrow	Value of effects on net resource use by healthcare systems in providing care to vaccinated individuals,

[1] *In research assessing consideration of broader value by HTA agencies the Value of Vaccines framework also includes the element 'Burden of disease value', intended to reflect the prioritisation by some of these bodies of interventions impacting diseases with high disease burdens (Bell, Neri and Steuten, 2021; Brassel et al., 2021). As such, this element is not relevant for our purposes in this paper of assessing the consideration of the value of vaccines in research studies. We do however present background information on the current disease burden associated with selected vaccine-preventable diseases, across each domain of value.*

VALUE DOMAIN	VALUE ELEMENT	BROAD OR NARROW?	DEFINITION
			i.e., the value of resources spent on avoidable illness (opportunity cost)
	Value to other interventions	Broad	Value of increasing the cost-effectiveness of other non-vaccine interventions
Society	Impact on the productivity of vaccinated	Broad	Value of effects on net time spent at work/in informal care and the level of productivity of vaccinated individuals, and associated fiscal impact
	Impact on carer productivity	Broad	Value of effects on net time spent at work and the level of productivity at work of caregivers of vaccinated individuals
	Social equity value	Broad	Value of effects on disparities in the distribution of health across the population
	AMR prevention value	Broad	Value of slowing the rate of development and transmission of resistant bacterial, fungal, parasitic and viral infections and associated effects on quality of life and mortality
	Macroeconomic effects	Broad	Value of effects on the macroeconomy beyond productivity, e.g., effects on the value of trade during major outbreaks. Note: not predicted to be relevant for the selected vaccines.

2.3 Assessment of the evidence base for the value of adult immunisation programmes

The availability of evidence on the value of vaccines for each of the four target diseases, for each element of OHE's value framework, is shown in Table 4, providing the percentage of countries in our sample for which relevant evidence was identified on each value element and by vaccine. Tables showing results by country are presented in Appendix 1.

The results show that evidence availability is greatest for the so-called 'narrow' value elements: quality of life and mortality benefits to vaccinated individuals and cost-offsets to healthcare systems. Evidence of these value elements was identified across vaccines in each of our ten focus countries. For each vaccine, effects on the quality of life of vaccinated individuals were the value element most consistently evidenced across countries,[2] with at least 60% of our sample countries evidencing this element.

A substantial evidence base also exists on the value of vaccination for a range of some 'broader' value elements. Evidence on effects on productivity and transmission exists in the majority of countries in our sample and for the majority of vaccines considered. Productivity value was considered in at least one country for every vaccine except RSV, although we identified evidence of the productivity burden associated with RSV (Zhang et al., 2022). Evidence for impact on transmission exists for all vaccines expected to produce transmission value (i.e., influenza,

[2] *The definition of this value element in OHE Value of Vaccines' framework is the value of effects on the physical, mental, emotional, and social functioning of vaccinated individuals, and we include any outcomes relating to infections, morbidity and health-related quality of life within this definition.*

pneumococcal and RSV, but not HZ as there is limited transmissibility of VZV between adults), evidenced in up to 50% of our sample countries (for influenza).

However, there is a paucity of evidence relating to other 'broader' value elements. Some evidence for effects on the productivity of carers exists for all vaccines except RSV. 'There is evidence relating to one of the included vaccines in one country for equity and antimicrobial resistance effects (pneumococcal disease in the United States and influenza in Australia, respectively). No evidence was identified relating to macroeconomic effects, value to other interventions, or effects on the quality of life of caregivers in any country in our sample.

The value of influenza and pneumococcal vaccination was the most comprehensively evidenced, with evidence for seven value elements identified. Evidence of five value elements was identified for HZ vaccination and of four value elements for RSV vaccination.

The level of evidence availability differed across countries. The most comprehensive evidence was available in the US, where evidence of seven value elements was identified. The least comprehensive was in Poland and Thailand, where evidence of only two and three elements, respectively, was identified. For an overview of the country-specific availability of evidence, see the full heatmaps presented in Appendix 1.

It should be noted that consideration of a value element may be through outcomes which reflect only partial value. For example, whilst effects on patient productivity were considered in the majority of countries, this was often measured solely in terms of absenteeism, excluding effects on presenteeism and the value of informal activities (in particular by unemployed or retired adults).

In comparison to the studies of pneumococcal vaccination published between 2010 and 2016, reviewed by Cafiero Fonseca et al. (2017), recent academic estimates of the value of vaccination have become increasingly comprehensive. Cafiero-Fonseca et al.'s global systematic review identified evidence pertaining to six of the value elements in our framework: impact on quality of life of vaccinated; impact on mortality of vaccinated; transmission value; cost offsets to healthcare system; impact on productivity of vaccinated and impact on carer productivity. We additionally identified evidence relating to pneumococcal vaccination's social equity value and influenza vaccination's AMR prevention value.

The academic literature is increasingly recognising and evidencing the diverse elements of socio-economic value associated with adult vaccination, although the evidence base is nascent in places, and many gaps remain. We caution that the generalisability of these results is limited, as the magnitude of effects on transmission depends substantially on the circulation of the infectious disease, as well as the uptake of both adult and child immunisation programmes (Cafiero-Fonseca et al., 2017).

TABLE 4: PERCENTAGE OF SAMPLE FOR WHICH COUNTRY-SPECIFIC EVIDENCE OF POSITIVE IMPACT ON VALUE ELEMENT IDENTIFIED

Key: percentage of sample countries for which relevant evidence identified

100%	70-90%	40-60%	10-30%	No evidence

Value domain	Population health				Healthcare system		Society				
Value element	Impact on quality of life of vaccinated	Impact on mortality of vaccinated	Impact on quality of life of carers	Transmission value	Cost offsets to the healthcare system	Value to other interventions	Impact on the productivity of vaccinated	Impact on carer productivity	Social equity value	AMR prevention value	Macroeconomic effects
	NARROW	**NARROW**	**BROAD**	**BROAD**	**NARROW**	**BROAD**	**BROAD**	**BROAD**	**BROAD**	**BROAD**	**BROAD**
Influenza	100	100		50	80		60	20		10	
Pneumo-coccal	60	50		30	60		40	10	10		
RSV	60	10		10	10						
HZ	70	30		NA[3]	40		30	10			

NA= Not applicable; [3] There is limited transmissibility of VZV between adults.

2.4 The value of adult immunisation programmes for population health

This section summarises evidence on the value of vaccines for health. In the taxonomy of our value framework, we include evidence of the value of vaccination in terms of **quality** and **length of life in vaccinated populations**, as well as protecting unvaccinated populations by reducing **transmission**[4]. We disaggregate health value in vaccinated adult populations into two key sub-populations generally prioritised in vaccine schedules: older adults (most commonly defined as adults aged 65 and older, but sometimes including adults from the ages of 50 upwards) and adults with risk factors[5]. The majority of evidence on the value of adult vaccination relates to these sub-populations. However, it is important to recognise that vaccines can benefit the general adult population. Our search identified evidence of the productivity effects of vaccinating working-age adults, which is presented in section 2.6. First, however, we provide context by describing the current health burden in adults associated with influenza, streptococcus pneumoniae, RSV and VZV.

2.4.1 Context: the health burden of vaccine-preventable diseases

Vaccine-preventable diseases continue to produce substantial disease and mortality burdens in adult populations worldwide. Data from the Global Burden of Disease Study (see Table 5) shows that 1 in 50 deaths amongst adults aged 20-54 and almost 1 in 25 deaths in adults over 55 were attributable to lower respiratory infections – of which influenza, pneumococcal disease caused by streptococcus pneumoniae, and RSV are the three major causes in adults (Troeger et al., 2018), and HZ caused by VZV. These diseases were also responsible for over 1% of the global disease burden amongst 20–54-year-olds and 2% of the burden amongst adults over 55.

There is also evidence that the burden of vaccine-preventable lower-respiratory tract infections - like Influenza and RSV - is often underestimated (Savic et al., 2022; Maleki et al., 2023). For example, RSV diagnosis is often based on symptoms, and thus, RSV is often simply reported as an "Influenza-like illness". In the case of RSV, the lack of a uniform clinical case definition makes it difficult to detect cases without testing, as antigen-based testing is insufficiently specific, and PCR testing can be costly (Tin Tin Htar et al., 2020). In addition, when testing does occur, the choice of diagnostic test and clinical specimen used impacts the likelihood of the RSV infection being identified. For example, compared to the common clinical practice of using nasopharyngeal or nasal swabs alone, RSV detection increased by 52% when adding reverse transcription polymerase chain reaction (RT-PCR) of sputum, 28% when adding RT-PCR of oropharyngeal swabs, and 42% when adding serology testing of paired specimens (Li et al., 2023; McLaughlin et al., 2022).

[4] We did not identify any direct evidence of effects on the quality of life of carers or value to other interventions, and therefore exclude these from the narrative. For further discussion, see Chapter 6, Assessment of the evidence base for the value of vaccination.

[5] Risk factors are factors which are known to place adults at higher risk of severe disease and death from vaccine-preventable infections, specifically underlying chronic conditions and multi-morbidities (De Sarro et al., 2022).

TABLE 5: MORTALITY AND DISEASE BURDEN ATTRIBUTABLE TO SELECTED VACCINE-PREVENTABLE DISEASES
Source: Institute for Health Metrics and Evaluation (IHME, 2023). GBD Results. Available from https://vizhub.healthdata.org/gbd-results/.

Note: the GBD does not disaggregate between the causes of lower respiratory infections (LRIs).

	DEATHS ATTRIBUTABLE TO LOWER RESPIRATORY INFECTIONS – 2019						DISABILITY-ADJUSTED LIFE YEARS (DALYS) ATTRIBUTABLE TO LOWER RESPIRATORY INFECTIONS – 2019					
	Per 100,000 population		% deaths - communicable diseases		% deaths – all causes		Per 100,000 population		% DALYs – communicable diseases		% DALYs – all causes	
	POPULATION AGE (YEARS)											
	20-54	55+	20-54	55+	20-54	55+	20-54	55+	20-54	55+	20-54	55+
Global	5.7	110.5	11.9%	45.0%	2.2%	3.8%	275.9	846.5	9.4%	34.0%	1.2%	2.3%
Australia	1.0	59.6	51.2%	86.0%	0.9%	2.6%	46.7	281.6	17.1%	66.1%	0.3%	1.1%
Brazil	8.2	180.9	33.2%	79.0%	3.2%	7.1%	385.8	1,356.8	23.3%	63.2%	1.6%	4.0%
France	1.2	105.3	39.7%	84.5%	0.9%	4.1%	52.4	445.7	17.5%	69.3%	0.3%	1.8%
Germany	1.5	79.9	53.1%	79.7%	1.1%	2.7%	66.2	423.8	22.3%	63.5%	0.4%	1.5%
Italy	0.8	55.0	25.7%	82.8%	0.8%	2.0%	37.3	249.3	11.9%	64.0%	0.2%	1.0%
Japan	1.8	227.4	70.8%	92.1%	1.8%	8.8%	79.4	935.5	26.6%	85.5%	0.5%	4.4%
Poland	4.8	90.4	70.8%	92.2%	2.4%	3.0%	220.4	627.9	38.1%	75.6%	1.1%	1.9%
South Africa	24.5	231.4	5.2%	30.4%	3.3%	6.9%	1,228.7	2,212.5	4.7%	21.5%	2.4%	4.6%
Thailand	8.1	151.5	16.1%	59.0%	2.9%	7.2%	382.7	1,199.7	13.4%	46.4%	1.6%	4.1%
USA	2.7	80.0	39.3%	79.3%	1.3%	3.0%	124.4	491.8	20.1%	60.4%	0.5%	1.5%
	DEATHS ATTRIBUTABLE TO HZ – 2019						DISABILITY ADJUSTED LIFE YEARS (DALYS) ATTRIBUTABLE TO HZ – 2019					
	Per 100,000 population		% deaths - communicable diseases		% deaths – all causes		Per 100,000 population		% DALYs – communicable diseases		% DALYs – all causes	
	POPULATION AGE (YEARS)											
	20-54	55+	20-54	55+	20-54	55+	20-54	55+	20-54	55+	20-54	55+
Global	0.03	0.46	0.06%	0.13%	0.01%	0.02%	4.33	6.45	0.13%	0.19%	0.02%	0.02%
Australia	0.01	0.81	0.50%	0.63%	0.01%	0.04%	2.46	5.73	0.77%	0.81%	0.01%	0.02%
Brazil	0.03	0.24	0.10%	0.06%	0.01%	0.01%	4.08	5.01	0.20%	0.14%	0.02%	0.01%
France	0.01	0.84	0.21%	0.37%	0.01%	0.03%	3.77	6.96	1.07%	0.64%	0.02%	0.03%
Germany	*<0.01*	0.53	0.11%	0.30%	<0.01%	0.02%	3.31	5.80	0.91%	0.53%	0.02%	0.02%
Italy	0.01	0.27	0.15%	0.23%	0.01%	0.01%	3.28	4.35	0.93%	0.68%	0.02%	0.02%
Japan	*<0.01*	0.16	0.07%	0.03%	<0.01%	0.01%	3.71	4.01	0.98%	0.20%	0.02%	0.02%
Poland	<0.01	0.04	0.01%	0.02%	<0.01%	<0.01%	1.88	2.30	0.23%	0.16%	0.01%	0.01%
South Africa	0.04	0.76	0.01%	0.08%	<0.01%	0.02%	4.20	8.43	0.02%	0.07%	0.01%	0.02%
Thailand	0.01	0.30	0.02%	0.07%	<0.01%	0.01%	3.72	5.95	0.12%	0.16%	0.02%	0.02%
USA	0.01	0.30	0.14%	0.16%	0.01%	0.01%	3.33	4.96	0.45%	0.38%	0.01%	0.01%

The burden of disease is expected to increase in countries experiencing demographic shifts towards older populations. For example, the lifetime risk of developing HZ is estimated at about 1 in 3 and increases with age, whereas 1 in 2 of the population are expected to develop an episode of HZ by the age of 85 (Zorzoli et al., 2018; CDC, 2023). In the US, Talbird et al. (2021) estimate that the annual number of cases of influenza, pneumococcal disease and HZ will increase by 36%, 64%, and 31% over the next 30 years, driven primarily by cases in the population aged over 65 years.

2.4.2 The value of adult immunisation programmes for vaccinated populations

2.4.2.1 Health value in older adults

There is a strong body of evidence demonstrating the health value of adult immunisation programmes in older adults with respect to the prevention of disease, disease sequelae with major health consequences, and mortality. There is also evidence showing that adult vaccination can promote healthy ageing more broadly by preventing the exacerbation of co-morbidities such as cardiac and pulmonary disease and avoiding the acceleration of frailty, which can be associated with infectious diseases (Doherty, Del Giudice and Maggi, 2019). Many vaccines have been shown to be effective in even the oldest and frailest populations – which are also the populations where the consequences of vaccine-preventable diseases tend to be most severe (Curran et al., 2017; Cunningham et al., 2016; Buchy and Badur, 2020; Dos Santos, Tahrat and Bekkat-Berkani, 2018). Recent evidence on the effectiveness of vaccines used to populate the heatmap is summarised below, prioritising systematic review evidence where available. We recognise that there may be adverse health effects associated with some vaccinations and include those in our BCA.

INFLUENZA VACCINATION:

- **Prevention of disease:** A recent Cochrane systematic review and meta-analysis across influenza vaccines concluded that, for older adults, vaccination is likely to more than halve the risk of experiencing influenza in a single season, from 6.0% to 2.4% (Demicheli et al., 2018). This review was underpowered to detect effects on pneumonia and mortality.

- **Major health consequences:** A recent systematic review and meta-analysis found that receiving the influenza vaccine reduces the risk of having a stroke and subsequent hospitalisation in older adults by 16% (Tavabe et al., 2023). Cancer patients vaccinated with the influenza vaccine also had statistically significantly better survival outcomes, including longer progression-free survival rates and overall survival compared to unvaccinated patients (Lopez-Olivo et al., 2022).

- **Mortality:** A cohort study of adults aged 65 and over in Italy found that influenza vaccination decreased an individual's risk of all-cause mortality by 13% during the 2018/2019 winter season. When the analysis was restricted to adults registered with GPs, reporting vaccination coverage of at least 55% in individuals aged 65 and over, the effect increased to a 43% reduction in risk (Lapi et al., 2022).

PNEUMOCOCCAL VACCINATION:

- **Prevention of disease:** Recent systematic reviews of pneumococcal vaccines in the general adult population and in older adults conclude that pneumococcal vaccines are effective against invasive pneumococcal disease and pneumonia, including vaccine-type and community acquired pneumonia (Farrar et al., 2023; Berild et al., 2020).

- **Major health consequences**: A recent systematic review and meta-analysis concluded that pneumococcal vaccination was associated with a decline in the incidence of cardiovascular mortality and heart attacks (hazard ratios: 0.78 and 0.82, respectively) (Jaiswal et al., 2022).

- **Mortality:** The same study also concluded that vaccination was associated with a decrease in the risk of all-cause mortality among adults with established cardiovascular disease (hazard ratio: 0.71)) (Jaiswal et al., 2022).

RSV VACCINATION:

- **Prevention of disease:** The latest evidence from Phase III clinical trials of RSV vaccines approved at the time of writing indicates that vaccines have protective efficacy against RSV-related respiratory diseases of different severities. One trial reported vaccine efficacy against RSV-related lower respiratory disease of 82.6% and against severe lower respiratory disease of 94.1% in adults aged 60 and older (Papi et al., 2023). Another trial reported a vaccine efficacy against RSV-related lower respiratory illness with at least two signs or symptoms of 65.1%, and an efficacy of 88.9% against RSV-related lower respiratory illness with at least three signs or symptoms in adults aged 60 and older (Walsh et al., 2023).

- **Major health consequences:** Evidence is not yet available directly linking RSV vaccination with major health consequences, although there is evidence that individuals with RSV are significantly more likely than those with influenza to experience exacerbation of chronic obstructive pulmonary disease and all-cause mortality in the year following infection (Ackerson et al., 2019). Therefore, prevention of RSV infection might be expected to reduce these outcomes in vaccinated individuals. Similarly, given that an increased risk of cardiovascular outcomes has been seen with respiratory viruses like RSV, the cardioprotective effects of the influenza vaccine (reducing the risk of cardiovascular complications in older individuals) may also potentially extend to the RSV vaccine (Ivey, Edwards and Talbot, 2018).

- **Mortality:** Evidence is not yet available directly linking RSV vaccination with mortality reduction, as RSV vaccines only started to be approved in 2023.

HZ VACCINATION:

- **Prevention of disease:** A recent Cochrane systematic review and meta-analysis estimated that vaccination with recombinant zoster vaccines (RZV) was up to 94% effective against infection with HZ (Xia et al., 2022), and a long-term follow-up showed efficacy of up to 73% ten years post-vaccination (Strezova et al., 2022).

- **Major health consequences:** A large RCT found that vaccination against reactivated VZV with one type of HZ vaccine (RZV) led to a greater than 88% reduction in postherpetic neuralgia (PHN, defined as cases of HZ with pain lasting more than 90 days) in vaccinated adults aged 70 years and older experiencing breakthrough infections (Cunningham et al., 2016). A US retrospective case-control study found that HZ patients (average age 71) who had received any vaccination against HZ were significantly less likely to experience stroke in the 30 days following HZ infection (Parameswaran et al., 2023). One cohort study found that HZ vaccine recipients aged 50 and older had a 16% lower risk of COVID-19 diagnosis and a 32% lower risk of related hospitalisation (Bruxvoort et al., 2022).

- **Mortality:** HZ does not usually cause death, and most studies of vaccine efficacy do not consider this outcome. However, long-term follow-up studies and models have shown that HZ vaccination is associated with reduced HZ-related mortality (Curran et al., 2017; van Oorschot et al., 2021).

Vaccination in older adults may, in some cases, also promote healthy ageing more broadly. For example, although the mechanisms are not well understood, there are indications that influenza vaccination in older adults may be associated with reduced or delayed onset of dementia. A systematic review including studies following older adults free of dementia at baseline found that,

over a mean follow-up of 9 years, the influenza vaccination was associated with a reduced risk of dementia by 3% (RR=0.97, 95%CI: 0.94-1.00), or 29% after adjusting for nine potential confounders (RR=0.71; 95%CI: 0.60–0.94) (Veronese et al., 2022a). Another systematic review (and meta-analysis) of observational studies of older adults concluded that annual influenza vaccination was associated with a 26% decrease in the risk of dementia onset and HZ vaccination with a 31% decrease (hazard ratios of 0.74, 95% CI: 0.63-0.97 and 0.69, 95% CI: 0.58-0.82 respectively) (Wu et al., 2022).

The effects of vaccine-preventable diseases are particularly severe in the oldest populations. These diseases can also act in a 'vicious cycle', accelerating frailty, which in turn makes individuals more vulnerable to the health consequences of vaccine-preventable diseases (Veronese et al., 2022b; Vetrano et al., 2021). Frailty relates to vulnerability associated with the age-related decline of an individual's physical, psychological, and social functional status. In relation to infectious diseases, frailty is associated with increased susceptibility, a lower chance of complete recovery, and a higher likelihood of adverse outcomes and long-term consequences. For example, the risk of long-term neurological complications like PHN increases with age in HZ patients, which can increase the risk of falls and fractures, initiating a cycle of increasing frailty (Zorzoli et al., 2018). A well-functioning immune system (supported by adherence to vaccination schedules) can delay the acceleration of frailty to disability (Vetrano et al., 2021; Veronese et al., 2022b).

While there is some evidence that some vaccines may be less effective in the oldest populations due to the progressive decline of immunity with age, the severity of vaccine-preventable infections and their implications for the acceleration of frailty make vaccination of this sub-population particularly important. New strategies have been (and continue to be) developed to improve vaccine efficacy in the oldest age groups, for example, high-dose and adjuvanted influenza vaccines (Bell and Kutzler, 2022; Tregoning, Russell and Kinnear, 2018; Lee et al., 2018; Buchy and Badur, 2020). There is evidence of recently developed vaccines demonstrating protection against disease, even in the oldest populations. A multi-country RCT of HZ vaccination concluded 89.1% efficacy against HZ and 88.8% efficacy against PHN over a time horizon of 3 years in individuals aged >80 (Cunningham et al., 2016). For influenza, a prospective cohort study using propensity score matching concluded that influenza vaccination decreased the risk of mortality over the course of one year by 3.0 percentage points (from 23.9% to 20.9%) in adults aged 80 and over, 57.4% of whom had at least one chronic disease (Walzer et al., 2020). We did not identify evidence relating to pneumococcal vaccine efficacy or effectiveness in individuals aged >80, although immune response has been demonstrated[6].

2.4.2.2 Health value in adults with comorbidities

Adults with comorbidities are included in some vaccination schedules due to their increased vulnerability to severe disease outcomes and the exacerbation of co-morbidities from vaccine-preventable diseases. This section summarises evidence of the important protective effects of vaccination in adults with comorbidities such as diabetes or who are immunocompromised due to conditions such as autoimmune diseases and cancer.

INFLUENZA VACCINATION:

Evidence from systematic reviews and meta-analyses suggests that rates of overall hospitalisation, influenza or pneumonia hospitalisation and all-cause mortality among adults with diabetes mellitus are significantly lower in those vaccinated for influenza compared to those who are not vaccinated (Dicembrini et al., 2023; Bechini et al., 2020).

[6] The CAPiTA trial, a large-scale RCT, found that immunogenicity was slightly lower in adults ≥80 years of age compared to younger age groups, but that pneumococcal vaccination nonetheless induced robust immune responses that were significantly above baseline and supportive of clinical effectiveness (van Deursen et al., 2017). The trial was not powered to detect efficacy by age group, but van Deursen et al. (2017) note that, based on the observed immunogenicity, efficacy does not appear to be significantly influenced by increasing age or common comorbidities.

PNEUMOCOCCAL VACCINATION:

While immunocompromised adults are often included in pneumococcal vaccination schedules regardless of age, the ability of pneumococcal vaccination to prevent disease in immunocompromised adults younger than 50 has not been directly demonstrated. However, there is evidence that pneumococcal vaccine protection in immunocompromised older adults is comparable to that in the overall older adult population, and immune responses in younger adults are stronger or comparable to those in older adults. This evidence is generally extended to support the argument that the pneumococcal vaccine would have at least a similar effectiveness in preventing vaccine-type disease in immunocompromised younger adults (Isturiz et al., 2018).

RSV VACCINATION:

Evidence from phase III clinical trials demonstrates that RSV vaccine efficacy in older adults with comorbidities (including cardiorespiratory and endocrine/metabolic conditions) was 94.6% (Papi et al., 2023).

HZ VACCINATION:

Estimates from models and systematic reviews have demonstrated that vaccinating immunocompromised younger adults (e.g. due to cancer and hematologic malignancies) would result in significant declines in cases of HZ, PHN and non-PHN complications (Curran et al., 2023, 2017; Racine et al., 2020).

2.4.2.3 The value of adult immunisation programmes for reducing disease transmission

By reducing transmission, adult immunisation programmes can reduce the number of infections and the burden of disease in unvaccinated populations, particularly when combined with general public health measures. These protective effects can be challenging to measure because they look beyond the differences between vaccinated and unvaccinated individuals observed in typical clinical trials to protective effects on the wider community (referred to as 'herd effects'). However, there is a small body of literature exploring the effects of adult immunisation programmes on broader disease transmission dynamics, which provides some indication of how substantial these effects may be. Some studies which use dynamic transmission models report directly on the additional health benefits accrued to unvaccinated populations due to adult immunisation programmes. For example, we identified a study of the community effects of influenza vaccination in Australia and South Africa, which found that, compared to no vaccination, vaccination of 15% of the population (prioritising HIV-positive individuals, adults aged 65 and older, and young children) could decrease the annual rate of symptomatic infection by over 47% and deaths by over 55% in both communities (de Boer et al., 2018).

2.5 The value of adult immunisation programmes for healthcare systems

In the taxonomy of our value framework, the value of adult vaccination for healthcare systems refers to **cost-offsets** to the healthcare system. We consider this value both when healthcare systems are functioning 'normally' and when healthcare systems are under pressure from excess demand – for example, due to the treatment backlog following winter seasons and as evidenced in many countries following the COVID-19 pandemic. First, however, we provide some context by describing the current healthcare system burden associated with diseases preventable by our four target vaccines.

2.5.1 Context: the healthcare system burden of vaccine-preventable diseases

Although vaccines are effective at reducing the overall risk of hospitalisation, influenza, streptococcus pneumoniae, RSV and reactivated VZV infections amongst adults continue to be major causes of hospitalisations and other types of healthcare resource use. Indeed, without sufficient investment in vaccines and treatments, the 'triple-demic' of COVID-19, influenza and RSV threatens to overwhelm healthcare systems (Fairbank, 2022).

Estimating healthcare resource use across countries or over time is challenging. Heterogenous coding practices in hospital records limit comparability between countries (Johnson et al., 2021). Some recent estimates from systematic reviews and meta-analyses do exist, however, regarding hospitalisation rates[7] and absolute numbers of admissions.

For influenza, there is high cross-country and seasonal variation, but an overall hospitalisation rate of 40.5 per 100,000 individuals has been reported, increasing to 96.8 per 100,000 in adults older than 65 (Paget et al., 2023). In 2016, there were 5.7 million adult hospital admissions due to influenza (Lafond et al., 2021). We did not identify any cross-country estimates of hospitalisation rates or hospitalisations due to pneumococcal disease in adults. A recent systematic review and meta-analysis concluded that hospitalisation rates for pneumonia are higher amongst older populations, and there were an estimated 6.8 million hospitalisations in adults aged 65 and over due to pneumonia in 2015 (Shi et al., 2020b). Infectious pneumococcal disease is the majority cause of pneumonia (GBD 2016 Lower Respiratory Infections Collaborators, 2018). It is also the main cause of the morbidity and mortality associated with lower respiratory tract infections worldwide (Troeger et al., 2018). For RSV, the hospitalisation rate among adults over 65 is approximately 100 per 100,000 in 'industrialised' countries and 30 per 100,000 in 'developing' countries (Shi et al., 2020a). In 2015, 336,000 hospitalisations were reported among adults >65 (Shi et al., 2020a). Regarding (reactivated) VZV (or shingles), we did not identify cross-country estimates of hospitalisation rates or the number of hospitalisations at the population level. In the US, the CDC reports that an estimated 1% to 4% of people experiencing HZ infection are hospitalised for complications (CDC, 2023). Studies following patients experiencing HZ infection found that 3.4% of adults over 60 in Japan and 3-35.7% of immunosuppressed populations in Latin America subsequently required hospitalisation (Sato et al., 2017; Javier Balan et al., 2022).

The cost to healthcare systems due to these infections is substantial. A recent systematic review and meta-analysis estimated the cost per episode for acute respiratory infections in adults over 50[8], disaggregated by income level according to the World Banks' classification system (Zhang et al., 2022). For high-income countries, the weighted mean cost is €17,806 per inpatient episode and €142 per outpatient episode. For upper-middle-income countries, the weighted mean cost is €1,275 per

[7] *The number of hospital episodes in a given year in a defined population, divided by the size of that population.*
[8] *78.6% of the papers included reported empirical costs for pneumonia; 7.1% for influenza-like illness; 4.8% for RSV; and 9.5% for acute respiratory infections in general.*

inpatient episode and €141 per outpatient episode. For HZ, a systematic review of evidence from Latin America found costs of up to $4,178 per HZ patient with PHN (Javier Balan et al., 2022).

The costs per inpatient episode are also disaggregated by age group, as shown in Table 6. About 14% of the studies included in the meta-analysis incorporate productivity costs in addition to costs to the healthcare system. The authors note that, for adults 50-65, these productivity costs are substantial, constituting approximately 40% of the total costs. Total costs per disease episode are nonetheless highest in the oldest populations. Productivity costs are explored further in Section 2.6.

TABLE 6: AVERAGE COSTS PER ACUTE RESPIRATORY INFECTION INPATIENT EPISODE BY AGE GROUP (ZHANG ET AL., 2022)

AGE (YEARS)	>50: overall	>50: high income	>50: upper middle income	50-65	66-74	75-84	>85
INPATIENT COSTS, EUROS (2021 AVERAGE EXCHANGE RATE)	17,804	17,806	1,275	15,783	15,937	22,802	24,079

These figures are likely to underestimate the true scale of the burden of vaccine-preventable diseases on healthcare systems for several reasons. Constraints to testing may mean that healthcare resource usage is not correctly attributed to vaccine-preventable diseases, especially for lower respiratory infections like influenza and RSV, where diagnosis is otherwise challenging (Johnson et al., 2021; Sullivan and Cowling, 2019).

Also, estimates tend to rely only on primary diagnoses of vaccine-preventable disease (which constitute the main reason for admission), but evidence indicates that a secondary diagnosis of vaccine-preventable disease in patients with other primary diagnoses is associated with greater hospitalisation costs. Data from the US suggests that there are 2.8 times more hospitalisations in which vaccine-preventable disease is recorded as a secondary diagnosis compared to hospitalisations in which vaccine-preventable disease is the primary diagnosis (Doherty et al., 2022). Patients with a secondary vaccine-preventable disease diagnosis are likely to have longer stays in hospital and poorer discharge outcomes than comparable patients without a secondary vaccine-preventable disease diagnosis (Doherty et al., 2022).

Further, observed healthcare utilisation does not tell us about the unmet need of populations suffering from vaccine-preventable diseases but unable to access care due to a lack of healthcare system capacity. For example, a recent systematic review estimated that the hospitalisation rate for older adults for RSV (as a proportion of the older adult population) was three times higher in 'industrialised countries' than in more resource-constrained environments – even after controlling for differences in the age of populations (Shi et al., 2020a).

The scale of the burden is also expected to increase further with ageing populations. Healthcare resource utilisation and costs are generally higher amongst older patients, as well as patients with co-morbidities (Federici et al., 2018; Zhang et al., 2022). Consequently, the burden is expected to rise in countries experiencing demographic trends towards older populations with higher rates of co-morbidities. Talbird et al., (2021) estimate that, in the US, increases in the number of cases of influenza, pneumococcal disease and HZ over the next 30 years – driven primarily by cases in the over 65s – will translate to increases in annual direct medical costs of 49%, 61%, and 43% respectively.

2.5.2 Value to healthcare systems

There is good evidence that adult immunisation programmes avert substantial costs to healthcare systems and are highly cost-effective.

INFLUENZA VACCINATION:

Adult influenza immunisation programmes have been shown to avert substantial costs to healthcare systems, in particular secondary care costs, by reducing negative health outcomes that would require hospitalisation or medically attended visits.

A systematic review focussing on North America found that 56% of age-based adult influenza immunisation programmes resulted in net cost savings, and 100% of age-based adult influenza immunisation programmes reported a cost-per-QALY of less than $50,000[9] (Leidner et al., 2019). Recent studies from Australia and Germany have also indicated that immunisation programmes for older adults result in net cost savings to the healthcare system by averting hospital inpatient and emergency care (Darmaputra et al., 2021; Storch et al., 2022).

Evidence from the US suggests that interventions to increase the uptake of adult influenza (and pneumococcal) immunisation programmes are extremely cost-effective, with an estimated cost of $512/QALY (Smith et al., 2017).

There is also evidence that expanding influenza immunisation programmes could generate even greater value for healthcare systems. Hypothetical expansion of the national influenza immunisation programme in Australia to adults aged 50-64 years has been estimated to be cost-saving for the government, with cost-savings mostly averted due to reduced acute myocardial infarctions hospitalisations (Raj et al., 2019). A cost-effectiveness analysis of public health interventions against influenza in France found that universal vaccination targeting the general population was more cost-effective than the vaccination of priority groups alone, which were also considered to be cost-effective or cost-saving (Beresniak et al., 2019).

PNEUMOCOCCAL VACCINATION:

Systematic reviews have reported cost-savings associated with pneumococcal vaccination, with the cost of vaccination offset by reduced hospitalisation costs, improved quality of life and increased life expectancy (Nishikawa et al., 2018; Leidner et al., 2019). In North America, 31% of age-based adult pneumococcal immunisation programmes were found to result in net cost savings. 78% were cost-effective at a threshold of $50,000/QALY and 100% at $100,000/QALY (Leidner et al., 2019).

Increasing uptake of existing pneumococcal immunisation programmes is expected to generate additional value for healthcare systems. Increasing pneumococcal vaccination coverage from 50% to 100% of older adults in Australia was estimated to result in cost-savings to healthcare systems, primarily by reducing acute coronary syndrome in healthy older adults (Ren et al., 2021).

Expanding pneumococcal immunisation programmes (for example, to high-risk groups) may also be valuable for healthcare systems. Evidence from the US suggests that expanding current recommendations to include adults aged 50-64 with chronic kidney disease in pneumococcal immunisation programmes would be cost-effective at a cost-effectiveness threshold of $100,000 per QALY, with a cost-effectiveness ratio of $38,000/QALY compared to no vaccination (Ishigami et al., 2019).

[9] *A recent estimation exercise suggested that the cost-effectiveness threshold in the US is $95,958 in 2019 prices.*

RSV VACCINATION:

At the time of writing, there were only a few studies estimating the potential cost-effectiveness of a potential adult RSV immunisation programme. One study in the US estimates the potential value-based price (VBP) from a cost-effectiveness perspective of an RSV vaccine for adults aged 60 years and older, finding the vaccine is likely to be cost-effective at prices ranging from $73.54 to $298.79 per vaccination, depending on the epidemiology data used and the willingness-to-pay threshold considered (Herring et al., 2022). In a systematic review of global evidence, Treskova et al. (2021) present predictions that an RSV vaccine strategy for older adults could have cost-effectiveness ratios proportionate to those for the influenza vaccine. A recent analysis by the Centre for Disease Control also indicates that RSV immunisation programmes have the potential to be cost-effective (Ortega-Sanchez, 2023).

HZ VACCINATION:

A systematic review of evidence from the US concluded that 71% of HZ immunisation programmes using live-attenuated VZV vaccines (ZVL) (one type of HZ vaccines) reported a cost-per-QALY of less than $100,000 (Leidner et al., 2019). Another systematic review reported that RZV vaccines (one type of HZ vaccine) were cost-effective compared to no vaccination in 100% of the studies included (Meredith and Armstrong, 2022). Most recently, a literature review published by Giannelos, Ng and Curran (2023) found the RZV vaccination against HZ to be cost-effective in 15 out of the 18 included studies in comparison to either no vaccination or prior vaccination with ZVL.

Expanding HZ vaccination to wider populations is also likely to be valuable for healthcare systems. A study in the US found that HZ vaccination was cost-saving in adults aged 60 and over compared to no vaccination and cost-effective in adults aged 50 and over with a cost-per-QALY of $14,916 per QALY gained (Meredith and Armstrong, 2022; Curran et al., 2019). Another study in Germany, which considered recent data on the long-term efficacy of vaccination, estimated that vaccinating adults aged 50 and over was even more cost-effective than vaccinating adults aged 60 and over (Curran et al., 2021).

The evidence presented above demonstrates vaccines' value to healthcare systems in preventing disease and associated healthcare system resource use. It is increasingly realised that vaccines deliver additional value in maintaining regular healthcare services and clearing excess demand. Brassel et al., (2022) found that treating an acute vaccine-preventable disease is a suboptimal choice compared with treating elective patients - preventing a vaccine-preventable disease from blocking a hospital bed generates opportunity cost savings of approximately twice the direct costs saved by avoiding vaccine-preventable hospitalisations. We did not identify any literature which incorporated these additional opportunity costs in consideration of the value of influenza, pneumococcal, RSV or HZ vaccines to healthcare systems in our focus countries.

2.6 The value of adult immunisation programmes for society

This section summarises evidence on the value of vaccines for societies. In the taxonomy of our value framework, this refers to the **productivity** value[10] of vaccines, as well as their role in promoting **social equity** and preventing **anti-microbial resistance (AMR)**. First, however, we provide some

[10] Macroeconomic value due to external shocks, such as pandemic-induced effects on trade, are not expected to be relevant to our selected diseases, and our review did not identify any evidence of this value element. Hence, we exclude it from the narrative.

context by describing the current socio-economic burden associated with diseases preventable by our four target vaccines.

2.6.1 Context: the societal burden of vaccine-preventable diseases

Vaccine-preventable diseases produce a substantial economic and societal burden.

The productivity losses associated with influenza are substantial and comprise a large proportion of the overall economic burden of influenza on society. A recent systematic literature review of studies from Europe and North America on the economic burden of influenza in working-age populations (18-64) found that most studies reported between 30% and 36% of influenza patients taking sick leave (de Courville et al., 2022). In addition, productivity costs were estimated to comprise 88% of the total societal costs of influenza in this population, including costs to healthcare systems (de Courville et al., 2022). In South Africa, it has been estimated that the annual cost of mild and severe influenza across the population was over $270 million in 2015, of which 44% are productivity costs, 41% are costs to the healthcare system, and 15% are out-of-pocket costs for medical care and associated transport borne by patients and caregivers (Tempia et al., 2019). It has been estimated that in Italy, the annual tax and productivity costs of absence from work due to influenza are €160 million and €840 million, respectively (Ruggeri, Di Brino and Cicchetti, 2020).

Diseases caused by streptococcus pneumoniae and RSV have not been studied well. A recent systematic review of the costs of acute respiratory diseases in adults aged 50 or over-identified only two studies reporting indirect costs, which estimated that these costs represented between 30% and 41% of total costs per episode (Zhang et al., 2022). The tax and productivity costs of absence from work due to pneumococcal disease in Italy are estimated to total €148 million annually (Ruggeri, Di Brino and Cicchetti, 2020). In addition, an estimated 13% of Japanese adults suffering from pneumococcal disease episodes require support from caregivers, with a subsequent impact on productivity (Igarashi et al., 2021). Regarding HZ, data from a study of the Black adult population aged 60 and over in the US estimates that the average productivity cost associated with an episode of HZ is $2,350 per patient (Wingate et al., 2018).

Effects on the productivity of caregivers of infected individuals are also substantial. Systematic review evidence suggests that 50%-75% of employees miss work to provide care to family members suffering influenza or influenza-like illness (adult and child) annually (Zumofen, Frimpter and Hansen, 2023).

Another element of the societal burden of vaccine-preventable diseases is their inequitable distribution. In the US, for example, underserved minority populations are at higher risk for pneumococcal disease and are also more likely to have undiagnosed conditions, placing them at higher risk of pneumococcal disease (Wateska et al., 2022). Similarly, studies have identified ethnicity and socioeconomic status as having independent effects on the risk of influenza infection in the US (Zipfel, Colizza and Bansal, 2021).

Antibiotic resistance is a growing challenge in treating vaccine-preventable diseases and another important consideration with regard to their societal burden. In 2019, more than 1.27 million deaths globally were attributable to AMR, including 15.9% attributable to Streptococcus pneumoniae (Murray et al., 2022). Streptococcus pneumoniae multi-drug resistance rates of above 30% and a trend of increasing resistance have been reported in diverse geographical settings (Mohanty et al., 2023; Sharew et al., 2021; Larsson et al., 2021; Fong, Shlaes and Drlica, 2019).

2.6.2 The productivity value of adult immunisation programmes

2.6.2.1 Productivity value in immunised populations

There is evidence that vaccines avert major productivity losses and that expansions of vaccination coverage would produce net gains for governments as a result of both increased tax revenue and averted productivity losses. We focus on the evidence used to populate the heatmap on the value of vaccination while recognising that there may also be some productivity losses associated with time losses due to vaccination, which we include in our BCA in Chapter 3.

INFLUENZA VACCINATION:

A study estimating the effect of influenza immunisation programmes on communities in Australia and South Africa found that vaccinating 15% of the population (prioritising adults aged 65 and over, high-risk adults, and young children) could halve total productivity losses due to influenza across the community (de Boer et al., 2018). A modelling study in Italy estimated that a vaccination strategy resulting in a reduction of the number of infected people by 200,000 (10% of current levels) would reduce productivity losses by €111 million and increase tax revenue by nearly €18 million annually (Ruggeri, Di Brino and Cicchetti, 2020). Cost-benefit analysis suggested that investment in this strategy would yield average per capita benefits 11.1 times the value of the investment in terms of productivity impact and 1.8 times the value of the investment in terms of tax impact over the 1-year time horizon.

There is also evidence that influenza vaccination of healthy, working-age adults would produce net economic benefits. A real-world evaluation of healthy, working-age adults in Italy during the influenza season reported a 56.4% reduction in average sick leave days per person compared to unvaccinated individuals (Ferro, Bordin and Benacchio, 2020) and a net cost saving of €314 per person when considering the costs of vaccination and absenteeism.

PNEUMOCOCCAL VACCINATION:

A modelling study in Italy estimated that a vaccination strategy resulting in a reduction of the number of infected people by 9,000 (10% of current levels) would reduce productivity losses by €124 million and increase tax revenue by €24 million annually (Ruggeri, Di Brino and Cicchetti, 2020). Cost-benefit analysis suggested that investment in this strategy would yield average per capita benefits of 16.2 times the value of the investment in terms of productivity impact and 3.1 times the value of the investment in terms of tax impact over the 1-year time horizon.

RSV VACCINATION:

At the time of research, no peer-reviewed studies were available investigating the productivity value of adult RSV immunisation programmes.

HZ VACCINATION:

One study estimated that a vaccination strategy resulting in a reduction of the number of individuals infected with HZ from 6,400 to 6,000 and with PHN from 1,050 to 750 would result in a total annual reduction in productivity loss of EUR 640,000 and an increase in tax revenue of EUR 63,000 (Ruggeri, Di Brino and Cicchetti, 2020). Cost-benefit analysis suggested that investment in this strategy would yield average per capita benefits of 20.0 times the value of the investment in terms of productivity impact and 1.7 times the value of the investment in terms of tax impact.

It is important to note that these studies only consider the productivity impacts of absenteeism. However, the productivity effects of some vaccines on presenteeism, though challenging to measure,

may be substantial. Systematic review evidence indicates that 60%-80% of employees report working whilst experiencing influenza and influenza-like illness (Zumofen, Frimpter and Hansen, 2023). In addition, they do not consider productivity effects on informal care delivered by many adults, in particular older adults, which may be substantial. For example, estimates suggest that 25% of adults aged 50 and over in Europe provide informal care (Tur-Sinai et al., 2020).

2.6.2.2 Productivity value in caregivers

There is limited evidence of the productivity value of caregivers. Three studies reported results incorporating productivity effects on caregivers of adults. A cost-effectiveness analysis of influenza immunisation programmes in South Africa including adults aged over 65 reported productivity losses averted amongst their caregivers and found the programme to be cost-effective (Edoka et al., 2021). Similar analyses of pneumococcal and HZ immunisation programmes in adults aged 60 and over (some of whom had underlying conditions) in Japan reported productivity costs averted amongst caregivers and found the programmes cost-effective (Igarashi et al., 2021; Teng et al., 2022).

We did not identify any evidence valuing the productivity gains of vaccination amongst older adults in terms of the value of the informal care they themselves contribute (e.g., to grandchildren).

2.6.3 The social equity value of adult immunisation programmes

There is evidence that vaccine programmes contribute to improved health equity within countries, as well as a reduction in the financial risk associated with vaccine-preventable diseases, which are also inequitably distributed. A recent systematic review of 'equity-informative' economic evaluations[11] of vaccines concluded that both the introduction of vaccine programmes and expanded vaccine coverage resulted in mortality reductions and financial risk benefits, which were relatively larger in subpopulations with higher disease burdens and lower vaccination coverage – in particular, poorer income groups and those living in rural areas (Patikorn et al., 2023). A recent modelling study explored the expected equity effects of ten vaccines, including for influenza, pneumococcal disease, and rotavirus, in forty-one low- and middle-income countries between 2016 and 2030 (Chang et al., 2018). The study estimated that the largest effects on averted deaths and cases of medical impoverishment would be in the lowest income quartile of the population, across vaccines and countries, with well over half of the deaths prevented by influenza, pneumococcal disease and rotavirus would be in the poorest two quintiles.

Expanded vaccine coverage could further increase the equity value of vaccines, as well as their broader health and economic value to society. A modelling study in the US found that expanding the pneumococcal vaccination recommendation to all adults over the age of 50 (compared to the current recommendation of vaccination for adults aged 65 and older and high-risk adults) would reduce inequity in the pneumococcal disease burden between Black and non-Black populations (Wateska et al., 2022). This is because, in the US, Black populations aged 50 to 65 have a higher prevalence of risk factors, a higher probability of undiagnosed underlying medical conditions, and a greater risk of pneumococcal disease (Wateska et al., 2019). As such, the expanded recommendation (combined with an effective vaccine delivery system) could also produce greater overall health and economic benefits and be more cost-effective (Wateska et al., 2022).

Another US study estimated that if the Black population aged 60 to 84 were vaccinated at the same rate as the White population of the same age, over 34,500 additional cases of HZ would be prevented over the next 20 years and $180 million in direct and indirect costs averted (Wingate et al., 2018)). Additionally, a similar study estimated that if the Hispanic population aged 60 to 84 were vaccinated at the same rate and frequency as the White population of the same age, over 34,000 cases of HZ

[11] *I.e., evaluations which consider equity dimensions*

would be prevented over the next 20 years, and $172 million in direct and indirect costs averted (Wingate, Maneno and Ettienne, 2018).

2.6.4 The role of adult immunisation programmes in the fight against anti-microbial resistance

Vaccines can affect antimicrobial resistance both directly and indirectly: directly via a reduction in the organisms and strains carrying resistant genes specifically targeted by a vaccine and indirectly through a reduction in illnesses which require treatment with antibiotics. Evidence suggests that pneumococcal vaccines are associated with a direct and significant reduction in the number of antibiotic-resistant invasive pneumococcal disease episodes in vaccinated groups compared with unvaccinated controls (Buckley et al., 2019; Klugman and Black, 2018; Cafiero-Fonseca et al., 2017; Wang, Cravo Oliveira Hashiguchi and Cecchini, 2021). While antiviral vaccines (e.g., influenza and RSV) do not directly affect organisms causing antibiotic-resistant disease, they reduce the incidence of illnesses for which antibiotics are inaccurately prescribed, as well as the risk of secondary bacterial infections which require antibiotic treatment. Significant reductions (11-50%) in the use of antibiotics have been observed in influenza-vaccinated adults compared to controls (Klugman and Black, 2018). One case-control study in Australia, which assessed the effects of influenza vaccine on antibiotic prescription for influenza-like-illness, recorded a 22-23% reduction in the likelihood of antibiotic prescribing in low-risk adults (aged 40-64 years and without comorbidities) (He et al., 2022).

New vaccines targeting respiratory pathogens such as RSV would not only prevent the viral disease but could potentially curtail subsequent antibiotic use and, consequently, induced AMR (Jansen, Knirsch and Anderson, 2018). In the US, an estimated half of antibiotic prescriptions are inappropriately prescribed for viral respiratory illnesses like RSV (Johnson et al., 2021). The use of antibiotics is common among outpatients and inpatients with RSV, even when chest radiographs are clear (indicating no bacterial infection) (Walsh, 2017). Vaccination's impact on AMR is generally not captured in cost-effectiveness analyses, yet the reduction in complications of antibiotic-resistant infections and a decrease in antibiotic prescriptions may yield more favourable cost-effectiveness results (He et al., 2022). It is important for future research to capture this effect.

3 Benefit-Cost Analysis of Adult Immunisation Programmes

3.1 Objectives

This chapter aims to quantify the broader value of the four immunisation programmes across ten selected countries. Given the methodological challenges and data requirements to model each value element defined in section 2.2.3 separately, we decided to apply a Benefit-Cost Analysis (BCA) framework described in the Reference Case Guidelines for Benefit-Cost Analysis in Global Health and Development (Robinson et al., 2019). In comparison to the more commonly applied Cost-Effectiveness Analysis (CEA) that aims to inform decision-making with respect to reallocating limited health budgets to improve population health, BCA can be used to assess a policy's impact on overall welfare rather than solely on health (Robinson et al., 2019). The approach is explained further in section 3.2.1.

The BCA approach captures many but not all value elements, as depicted in Figure 2, due to limited data availability and evidence gaps as well as a lack of widely accepted methodology which can incorporate these elements in a single model.

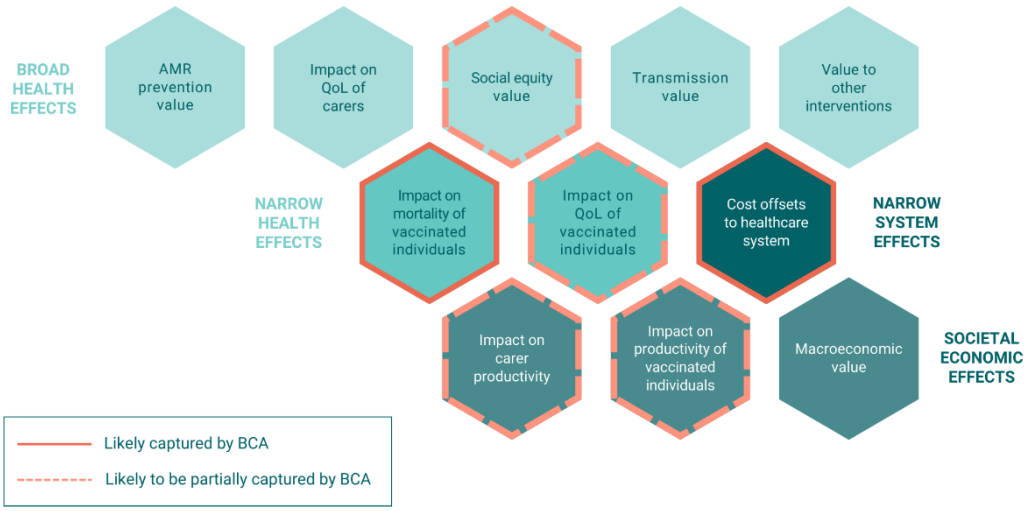

FIGURE 2: VALUE ELEMENTS LIKELY TO BE CAPTURED BY THE BCA FRAMEWORK.
Source: Own visualisation.

The BCA sought to estimate the societal value associated with a range of adult immunisation programmes within a sample of countries, compared to a state of the world where these programmes were not implemented at all.

BCA is a well-established form of economic evaluation that aims to compare policies in terms of their overall impact on societal welfare by estimating the monetised costs and benefits associated

with each course of action. It is especially useful when the policy question involves setting the health care budget or reallocating government resources as it allows policy options across different governmental departments to be compared. This aim differs from CEA, which is the most commonly used form of economic evaluation as part of Health Technology Assessment (HTA) that tends to focus more narrowly on the health system with the aim to maximise health given a constrained budget.

We provide full methodological details in relation to the BCA approach and a list of key input parameters within the technical Appendix 2

As in Chapter 1, our scope is influenza, PD, HZ and RSV programmes in ten countries: Australia, Brazil, France, Germany, Italy, Japan, Poland, South Africa, Thailand, and the US.

3.2 Methods

3.2.1 BCA framework overview

The methods used align with the Reference Case Guidelines for Benefit-Cost Analysis in Global Health and Development (Robinson et al., 2019), which distinguishes between a policy's inputs (e.g. cost of vaccine administration) and its monetised outputs (e.g. benefits of prevented mortality or improved health).

Within this framework, all benefits are captured within three outcome 'buckets', consisting of reductions in mortality risk, reductions in morbidity risk and changes in time use of the affected individuals. We aggregate all costs and benefits as specified in Figure 3 over the remaining life-time of each individual cohort and discount costs and benefits according to the national recommended rate in each respective country.

This approach follows the recommendations in Robinson et al. (2019) for all outcome buckets, except for adverse events, which, for pragmatic reasons, we consider as an addition to costs instead of an offset to the benefits. We also note that in the 'changes in time use' bucket, we only include averted formal productivity losses from averted sickness, but not those from averted premature mortality as this is accounted for in the monetisation approaches of fatal events, which are captured in the 'mortality risk reduction' bucket. We explain this further in section 3.2.2 and the technical appendix 2.

All aggregated cost and monetised benefits are then used to estimate two key outcome metrics for each programme within each country, the benefit-cost ratio (BCR) and the net benefits (NBs) per vaccination course as specified in equation (1) and (2):

$$BCR = \frac{Monetised\ Benefits}{Costs} \quad (1)$$

$$NB_{vaccination\ course} = \frac{Monetise\ Benefits - Costs}{Number\ of\ vaccinations} \quad (2)$$

BCRs over 1, therefore, indicate that a programme's benefits outweigh its costs, while a BCR between 0 and 1 indicates a partial offset of costs. This corresponds with the net benefit being either positive or negative. To obtain a single BCR and NB per vaccination course, all country and program-specific BCRs and NBs are then averaged. Our detailed approach to measuring and valuing benefits and costs is detailed in Appendix 2.

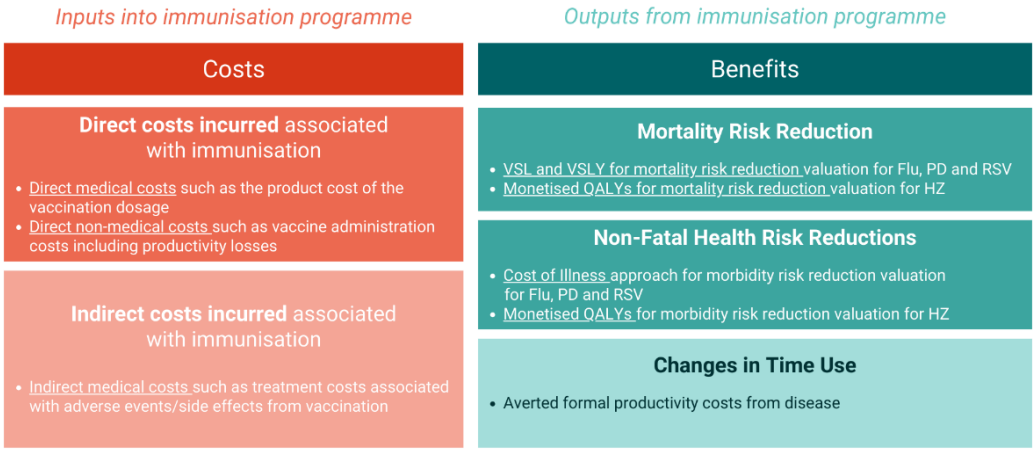

FIGURE 3: BENEFIT COST ANALYSIS FRAMEWORK.
Source: Adapted BCA framework based on Robinson et al. (2019).

Figure 3 shows the costs and benefits that we include in our BCA, which largely aligns with the reference case (Robinson et al., 2019). On the cost side (left-hand side in Figure 3), we deviate from the reference case as we do not include indirect non-medical costs such as productivity losses from long-term side effects of vaccination due to the lack of data availability and rarity of these side effects. On the benefits side (right-hand side in Figure 3), we do not explicitly include averted informal productivity costs of the vaccinated individual and caregiver productivity due to lack of data availability overall; however, these would be theoretically partly included in the valuation of mortality benefits through the VSL approach.

3.2.2 Disease models and immunisation programme specifications

We developed four static, deterministic disease models based on a life-table modelling approach, similar to the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) (Jit et al., 2014). We choose static over dynamic models for pragmatic reasons due to the number of countries and vaccination programs considered, and we acknowledge that the model choice does not capture the value that vaccines deliver to the unvaccinated population (transmission value). While each model is parameterised to reflect individual country settings where possible, our aim to produce results that are comparable across countries requires the prioritisation of consistency in modelling and outcome metrics, which leads to trade-offs with vaccine and country-specificity of our models.

One of the key methodological challenges while conducting a BCA is the valuation of non-monetary outcomes for different programmes. The vaccination programmes targeting influenza, PD and RSV differ from HZ, as the former prevents substantial risks of mortality, while the latter is rarely fatal but prevents substantial morbidity and sequalae with negative long-term impacts on quality of life.

The Reference Case Guidelines (Robinson et al., 2019) recommend a number of approaches to monetising health benefits, which vary in the comprehensiveness with which they reflect effects on mortality and morbidity, as well as in the associated data requirements. We therefore apply two different approaches included in the reference case, one for influenza, PD and RSV, and another for HZ, to calculate the respective lower and upper bound of monetised benefits.

PROGRAMME TYPE 1 - PROGRAMMES WHICH GENERATE HEALTH VALUE MOSTLY BY PREVENTING MORTALITY

- For vaccination programmes against the more fatal diseases of influenza, PD and RSV, we value each fatal case with the Value of a Statistical Life (VSL). The VSL provides a single monetary value for preventing the loss of a life, irrespective of the remaining life expectancy. In contrast, VSLY, which can be derived from the VSL, assigns a value to each additional year of life gained. VSL and VSLY valuations were therefore chosen to provide a reasonable lower (VSLY) and upper (VSL) bound of the value that society places on mortality risk reduction of influenza, PD and RSV programmes.

- The VSL is based on estimates of the average willingness to pay for a small reduction in mortality risk in a population and can be used to estimate the value society places on saving one life (Robinson et al., 2019). VSL values for 2022 were only available for the US (US Department of Transportation, 2023) and Australia (Australian Government, 2023). Values for other countries were computed through a value transfer approach to extrapolate the US VSL value to other countries. The approach follows the methodology recommended by Nandi et al., 2022, using GNI per capita values from the World Bank Open Data, 2023, assuming an income elasticity of one.

- The VSLY value can then be derived by dividing the VSL by the undiscounted future life expectancy at the average age of the country's adult population (Robinson, Hammitt and O'Keeffe, 2019).

- We pair both valuation approaches with a cost of illness (COI) approach to valuing non-fatal cases of these diseases, which primarily consists of medical costs to the healthcare system.

Programme Type 2 - Implemented national programmes which generate health value mostly by preventing morbidity

- For HZ, which largely impacts morbidity rather than mortality, we chose to value Quality Adjusted Life Years (QALYs) generated instead, as this better captures the vast amounts of value generated by preventing negative impacts on quality of life.

- The prevented QALY loss associated with HZ is valued using the VSLY value as our upper bound.

- For the lower bound we first value the QALY loss with different multiples of Gross Domestic Capital per Capita (GDP per capita) ranging from factors of 1 to 3 (Iino, Hashiguchi and Hori, 2022). We then average all GDP per capita valuations.

As a result, the analyses distinguish two types of programmes depending on whether they generate their health value mostly from averting morbidity or mortality. We further distinguish between whether the programmes are established (i.e. Flu, PD and HZ) or if they are rather emerging (i.e. RSV[12]).

For existing immunisation programmes (influenza, PD, and HZ), we include in our analysis all programmes where there is currently a formal general age-based recommendation, and we approximate the programme characteristics specified in this recommendation. We do not model specific risk populations such as pregnant adults or specific comorbidity populations that are likely

[12] *Recommendation of an adult RSV immunisation programme in the US and Germany commenced in 2023, but coverage rates and the final programme specification with respect to scheduling remain hypothetical at the time of writing.*

to have a better benefit-cost profile. Instead, we aim to take a general population view for our modelling to investigate the value of broader adult vaccination.

For RSV, we model emerging programmes based on the current recommendations in countries where there is a recommendation and a public price for both RSV vaccines, Arexvy and Abrysvo, that could be identified at the time of data collection. This is the case for the US, where the RSV program has already been initiated, and Germany, where both vaccines are approved and available in pharmacies. We reflect the most recent guidelines in the countries where we model a programme, aiming to estimate the value of these updated programmes against no vaccination. Due to the recency of some of the programme updates, we do use historical data as proxies for many of the parameters, such as using flu coverage rates for Germany where an intent analysis was not available like in the US, but we do use updated vaccine efficacy and other related parameters where possible.

Our specifications are intended to reflect the local reality per country while balancing consistency in the modelling approach. The specifications applied per immunisation and programme country are reported in Appendix 2, Chapter 4.

3.2.3 Model framework

We use disease-specific models applied consistently across countries and based on two archetypes:

- Archetype 1 models for single cohorts: PD and HZ are single cohort models and follow one age cohort, as outlined by a National Immunisation Programme (NIP), from the eligible vaccination age to the age of 100 or death. Both programmes assume that a vaccinated individual completes their immunisation in the base year, with the PD programme being based on a single dose, while HZ programmes may use one or two doses, depending on the vaccine used and the official NIP specification.

- Archetype 2 models for multi-cohort programmes (influenza and RSV) are multi-cohort models that capture all various eligible ages of vaccination of the general population in the base year[13]. They follow each age cohort at and above the vaccination age until the age of 100 or death. For RSV, we limit this to a two-year analysis for every eligible age cohort due to uncertainty around the longer-term protection of RSV vaccination beyond the initial two years.

The model structure for each immunisation programme is described in Appendix 2, Chapter 5.

Figure 4 provides a high-level overview of each disease model and programme type, specifying the modelling approach (single- or multi-cohort) and how the main outcome buckets are monetised using the BCA framework.

[13] *Please note that for the US, we use an age of 50 as the eligibility age following the approach in Talbird et al. (2021) instead of the offical age of 18.*

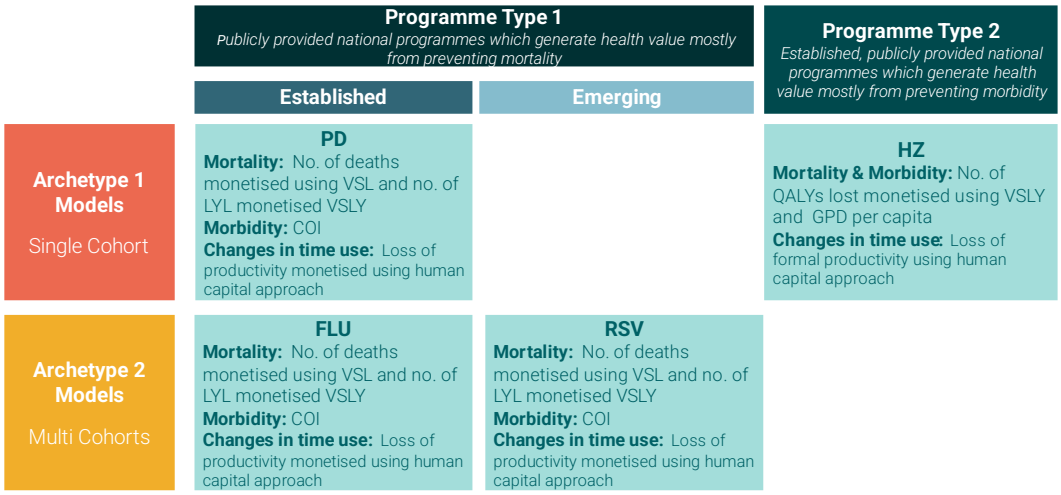

FIGURE 4: OVERVIEW OF VACCINATION PROGRAMME CHARACTERISATION, MODEL CHOICE AND MONETISING OF BENEFITS.
Source: Own visualisation.

3.3 Sensitivity analysis

For each vaccination programme modelled in each respective country, we applied a one-way sensitivity analysis to assess the impact of each individual parameter on the upper bound of the BCR. We varied each parameter relatively to its baseline value by +/-20% and capped the individual value where necessary (e.g. efficacy rates at 100%). Discount rates were varied by +/- 50%. Vaccination age was excluded.

3.4 Results

Across the ten countries, our analysis of the four immunisation programmes demonstrates that adult immunisation likely produces benefits large enough to offset their costs and generally outweigh them many times over.

The mean BCR across programs and countries based on the upper benefit valuation approaches (i.e. the valuation of fatal events using the VSL for influenza, RSV and PD and the valuation of QALYs using the VSLY for HZ) is 19. This means for each 1$ spent, $19 is returned in societal value. This corresponds to $4637 for one individual's full vaccination course.

Applying the lower benefit valuation approaches (i.e. the valuation of fatal events using the VSLY for influenza, RSV and PD and the valuation of QALYs using the mean of GPD multiples reaching from 1 to 3 for HZ), the average BCR across programs and countries is 5. This means for each 1$ spent, $5 is returned in societal value, which corresponds to $964 for one individual's full vaccination course.

Detailed results for each type of programme are provided in the subsequent sections.

3.4.1 Programmes which generate health value mostly by preventing mortality (Programme Type 1)

The established immunisation programmes against influenza and PD generate value mostly by preventing mortality. In every country assessed, the benefit-cost ratio is above 1 (Figure 5, Figure 6), and thus, the net benefits to society are always larger than zero (Table 7, Table 8), meaning that each programme's benefits to society, expressed in monetary units, outweigh its costs.

For the influenza programme, the returns to society are relatively consistent. On average, we capture the costs and benefits of the influenza programme over a time range of 38.5 years[14]. The mean BCR of the implemented influenza programmes within our country sample (n=10) is $5.6 (min: $1.3, max: $9.2) per $1 spent when valuing mortality using the VSLY approach (Figure 5). Applying the VSL approach to value mortality increases the mean BCR to $22.0 per $1 spent (min: $7.3 and max: $34.4), as shown in Figure 5. These BCRs correspond with mean net benefits per vaccination course of $1,682 (VSLY) to $7,412 (VSL) (Table 7).

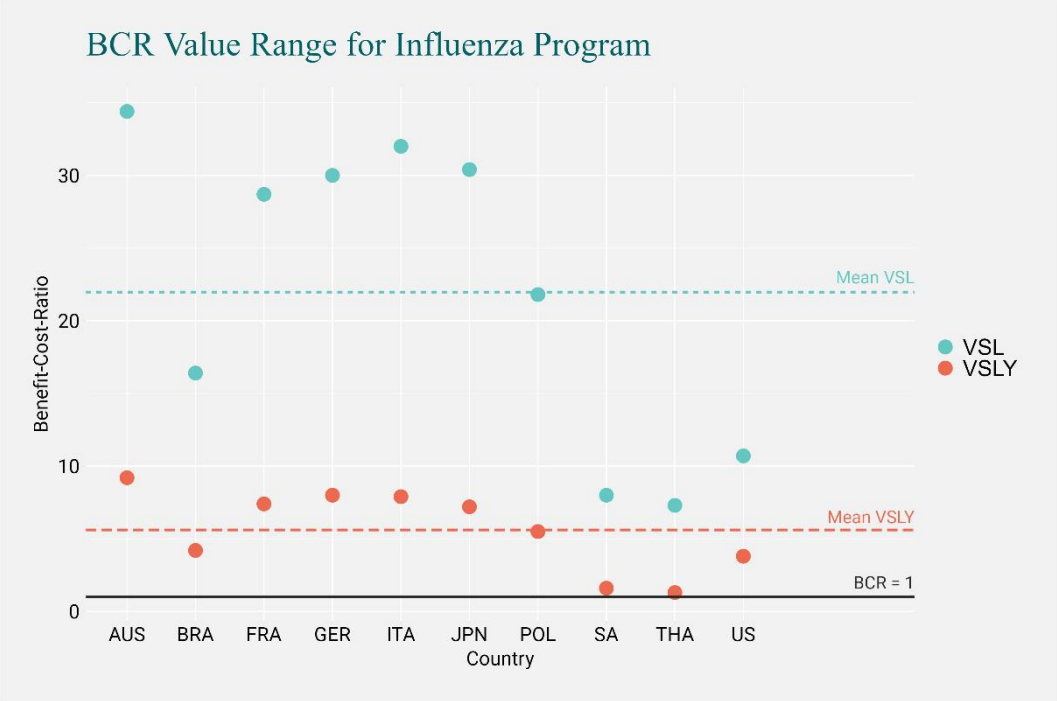

FIGURE 5: INFLUENZA IMMUNISATION: BENEFIT COST RATIOS OF ESTABLISHED PROGRAMMES.

The horizontal dotted lines indicate the mean value across all countries when the number of deaths is valued with the Value of a statistical life (VSL) or the number of life years lost is valued with the value of a statistical life Year (VSLY), respectively. The black line indicates cost neutrality as the benefit-cost ratio (BCR) equals 1.

[14] *The time frame is defined by the eligibility age within each country and the maximum age of the model (100 years).*

TABLE 7: INFLUENZA IMMUNISATION: NET BENEFITS PER VACCINATION COURSE FROM ESTABLISHED PROGRAMMES.

NUMBER OF COUNTRIES	NET MONETARY BENEFIT PER VACCINATION COURSE				
	VALUATION	MIN	MAX	MEAN	MEDIAN
10	VSL	$337	$17,590	$7,412	$6,478
10	VSLY	$30	$3,697	$1,682	$1,706

Publicly provided PD programmes that administer a vaccine once and provide a long duration of protection against disease that is often fatal deliver relatively large BCRs. The benefits are captured on average over a time range of 35 years. Within the five countries that implemented PD programmes, mean BCRs range from $14.9 (min: $8.0, max $20.4) when applying the VSLY approach to $33.3 (min: $22.2, max: $42.6) per $1 spent, as shown in Figure 6. The corresponding net benefits per vaccination course are substantial, with the mean per vaccination course ranging from $2,851 (VSLY) to $6,672 (VSL), as shown in Table 8.

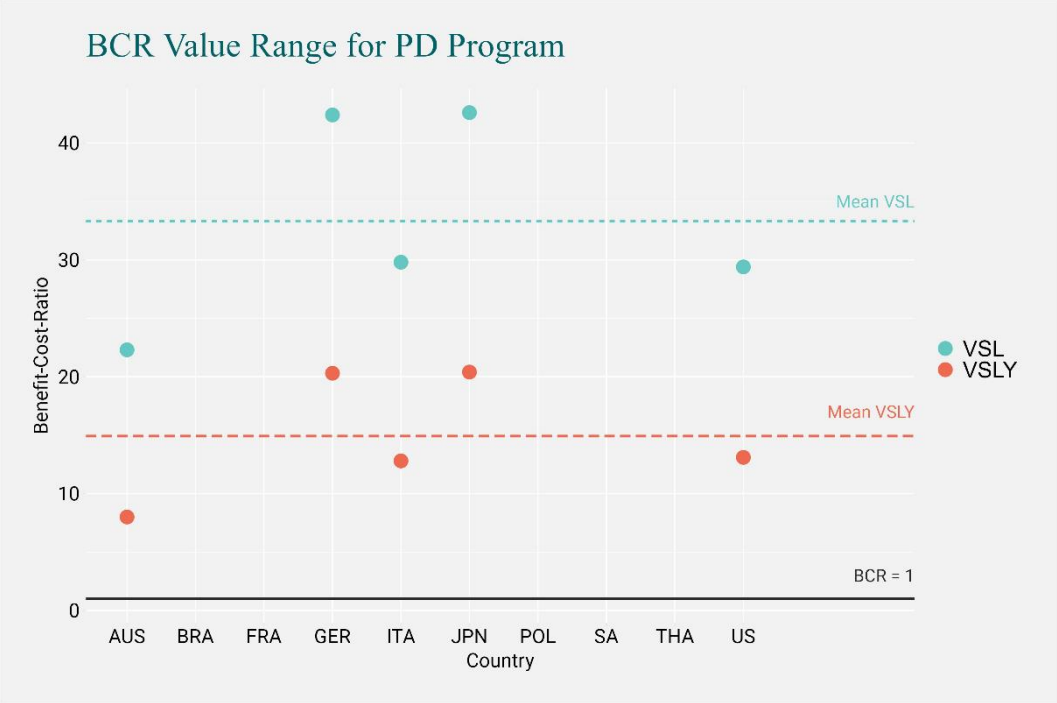

FIGURE 6: PD IMMUNISATION: BENEFIT COST RATIOS OF ESTABLISHED PROGRAMMES.
The horizontal dotted lines indicate the mean value across all countries when the number of deaths is valued with the Value of a statistical life (VSL) or the number of life years lost is valued with the value of a statistical life Year (VSLY), respectively. The black line indicates cost neutrality as the benefit-cost ratio (BCR) equals 1.

TABLE 8: PD IMMUNISATION: NET BENEFITS PER VACCINATION COURSE FROM ESTABLISHED PROGRAMMES.

NUMBER OF COUNTRIES	NET MONETARY BENEFIT PER VACCINATION COURSE				
	VALUATION	MIN	MAX	MEAN	MEDIAN
5	VSL	$1,893	$6,672	$3,970	$2,957
5	VSLY	$626	$2,851	$1,720	$1,375

Analysing the emerging RSV programs in the US and Germany, our results indicate that over a maximum time duration of 40 years, it may likely generate a positive return to society. Based on the model results in Germany and the US (Figure 7), the BCRs could range from $6.2 (VSLY) (min: $4.0, max: $8.4) to $16.0 (VSL) per $1 spent (min: $11.3, max: $20.8), corresponding to mean net benefits per vaccinated individual ranging from $1,260 (VSLY) to $3,646 (VSL).

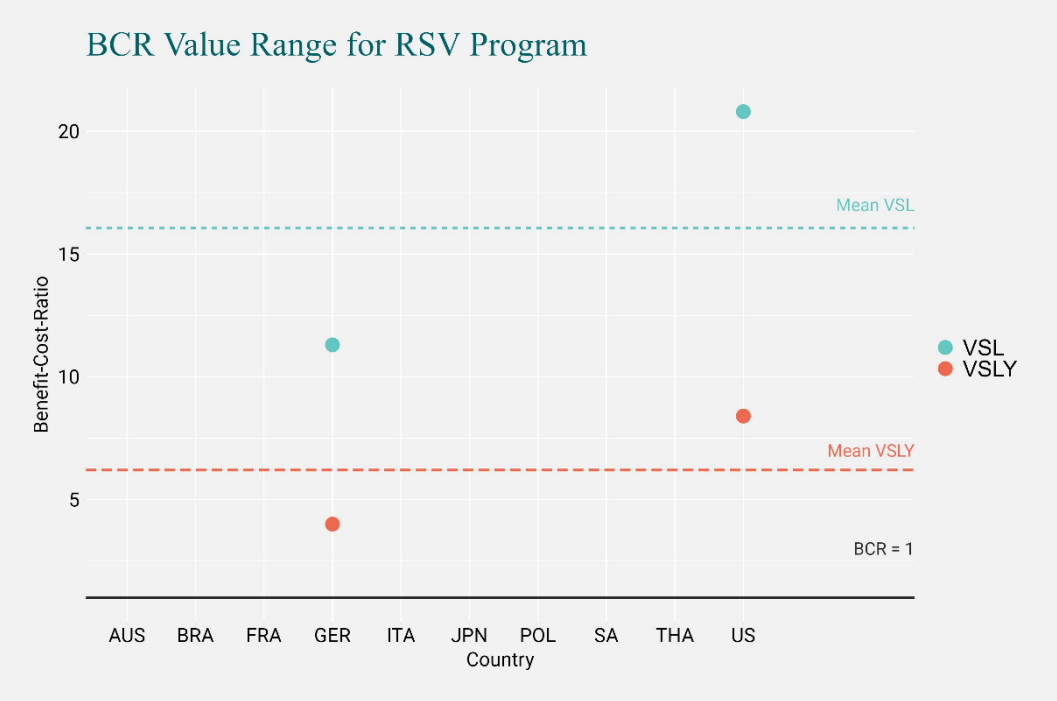

FIGURE 7: RSV IMMUNISATION: BENEFIT COST RATIOS OF EMERGING PROGRAMMES.
The horizontal dotted lines indicate the mean value across all countries when the number of deaths is valued with the Value of a statistical life (VSL) or the number of life years lost is valued with the value of a statistical life Year (VSLY), respectively. The black line indicates cost neutrality as the benefit-cost ratio (BCR) equals 1.

TABLE 9: RSV IMMUNISATION: NET BENEFITS PER VACCINATION COURSE FROM EMERGING PROGRAMMES.

NUMBER OF COUNTRIES	NET MONETARY BENEFIT PER VACCINATION COURSE				
	VALUATION	MIN	MAX	MEAN	MEDIAN
2	VSL	$2,408	$4,885	$3,646	$3,646
2	VSLY	$705	$1,815	$1,260	$1,260

3.4.2 Implemented national programmes which generate health value mostly by preventing morbidity (Programme Type 2)

The HZ programme prevents substantial short- and long-term morbidity, which is recognised over a maximum of 40 years when benefits are measured using QALYs and valued with VSLY or multiples of GDP per capita. Figure 8 shows that when averaging the different multiples of GDP per capita, preventing HZ in 6 countries generates an average return on investment of $1.9 per $1 spent (BCR min: $0.7, BCR max: $4.1). However, when valuing QALYs lost with their country-specific VSLY, the mean BCR increases to $3.6 per $1 spent (BCR min: $2.0 BCR max: $5.1). The corresponding net benefits per vaccination course are shown in Table 10 and range from $12 (GDP per capita) to $899 (VSLY).

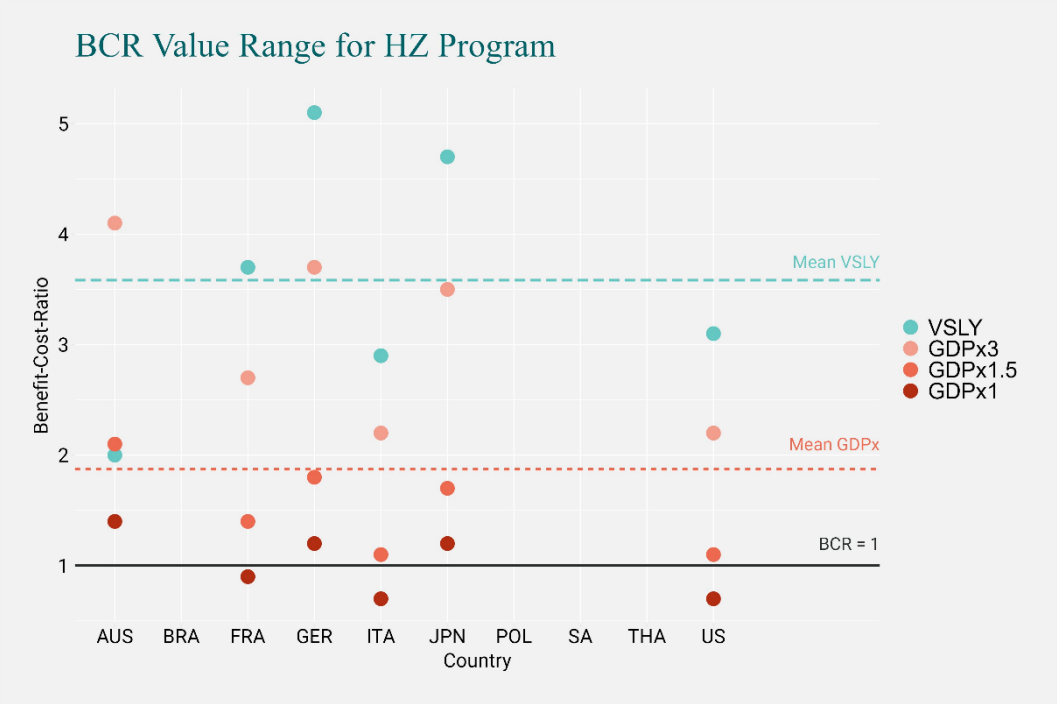

FIGURE 8: HZ IMMUNISATION: NET BENEFITS PER INDIVIDUAL VACCINATION COURSE FROM ESTABLISHED PROGRAMMES.

The horizontal dotted lines indicate the mean value across all countries when the averted QALYs lost are valued with the value of a statistical life year (VSLY) or the average of GDP Per Capita multipliers within the range recommended by WHO, respectively. The black line indicates cost neutrality as the benefit-cost ratio (BCR) equals 1.

TABLE 10: HZ IMMUNISATION: NET BENEFITS PER VACCINATION COURSE FROM ESTABLISHED PROGRAMMES.

NUMBER OF COUNTRIES	NET MONETARY BENEFIT PER VACCINATION COURSE				
	VALUATION	MIN	MAX	MEAN	MEDIAN
6	VSLY	$356	$1,693	$899	$860
6	GDP 3	$229	$1,390	$757	$676
6	GDP 1.5	$34	$474	$198	$144
6	GDP 1	-$117	$168	$12	$19

3.4.3 Results of the sensitivity analyses

The results of the most impactful parameters for each programme and country are presented in Appendix 3.

In general, the main drivers of the results can be categorized into three groups:

1. Parameters that relate to the underlying disease, mainly incidence rates and case fatality rates per outcome

2. Parameters that relate to the valuation approach of the non-monetary benefits (e.g. VSL or VSLY)

3. The cost/product price of the underlying vaccine

In addition, and as expected, the discount rate significantly impacts those programmes that incur most of the costs upfront while delivering benefits over a sustained period of years, i.e., the PD and the HZ programmes.

4 Realising the Value of Adult Immunisation Programmes

4.1 Discussion

Vaccine-preventable diseases continue to put a substantial burden on health, healthcare systems, and societies. While the value of vaccination is primarily discussed in the context of childhood immunisation programmes, adult immunisation is often overlooked. This research contributes to closing this gap, acknowledging the challenges from global demographic shifts towards older populations. Utilising a two-pronged approach through qualitative and quantitative research, we can paint a clearer picture of the evidence landscape associated with the four immunisation programmes in focus and the value they deliver.

The literature provides compelling evidence of the health economic value of adult vaccination.

Vaccine-preventable diseases continue to pose a major and increasing burden to healthcare systems. Infections caused by influenza virus, streptococcus pneumoniae, RSV, and reactivated VZV significantly contribute to healthcare resource utilisation and associated costs. An extensive evidence base shows that adult immunisation programmes are highly cost-effective, and programmes to expand uptake can also be very cost-effective given the relatively low variable costs compared to the fixed costs associated with delivering immunisation programmes (World Health Organization, 2019).

The value of adult immunisation programmes for the health of vaccinated individuals is well-recognised. All vaccine-preventable pathogens studied in this report generate a substantial disease burden, which is anticipated to rise in the coming decades as the world population ages. Each of our focus vaccines is effective in older adults and at-risk populations, with recent evidence demonstrating immune response and efficacy even in the frailest and most immunocompromised populations. Adult immunisation programmes also provide positive health externalities, e.g. by producing health benefits by protecting unvaccinated individuals.

Adult immunisation programmes provide significant societal value. Examples are the aversion of productivity losses by patients and carers or reducing antimicrobial resistance by avoiding the inappropriate prescribing of antibiotics in response to vaccine-preventable diseases (Klugman and Black, 2018). Additionally, as inequalities are an increasing concern (Nambiar et al., 2023), the benefits of adult immunisation programmes are concentrated in more socioeconomically disadvantaged sub-populations, and targeted expansion of adult vaccination schedules can reduce inequity in the distribution of vaccine-preventable diseases (Wateska et al., 2022, 2019).

The benefit-cost analyses demonstrate that investment in adult vaccination pays off.

The benefit-cost analyses provide novel quantitative evidence of some of the value that adult immunisation programmes deliver today and are expected to continue to deliver in the future. Using the recommended methodology within the Reference Case Guidelines for Benefit-Cost Analysis in Global Health and Development (Robinson et al., 2019) to value mortality and morbidity benefits, our assessment of the four immunisation programmes demonstrates that adult immunisation programmes produce benefits likely large enough to offset their costs and generally outweigh them many times over. On average, these returns are up to 19 times their initial investment when

monetising the full spectrum of benefits. This equals a societal return on investment of 1800% or a societal value of $4637 per individual vaccination course.

To our knowledge, this is the first quantitative assessment of the benefit-cost profiles of the selected adult immunisation programmes internationally. Our country selection includes ten diverse countries across regions, representing a range of healthcare systems, demographics, and vaccine schedules while acknowledging data availability requirements. Hence, we included some middle-income countries but did not include any lower-income countries, as multi-faceted obstacles an data availability often hinder the implementation or assessment of the programmes in focus (Hutubessy et al., 2023). Therefore, specific research and investment are needed to evaluate adult immunisation programmes in low-income countries and generate focused analyses.

There are limitations to our quantitative analysis. First and foremost, parameter uncertainty derives from very significant input data requirements for a project at this scale, which we address through a one-way sensitivity analysis of each input parameter. The second limitation relates to the reflection of the academic debate around how to value the non-monetary benefits within a BCA (Robinson, Hammitt and O'Keeffe, 2019). As the choice of monetisation method for mortality (in the case of influenza, PD and RSV) and morbidity (in the case of HZ) has maximum impact on the results, we are using the extremes of the different valuation approaches to adequately capture each programme type's societal value while acknowledging the uncertainty with the valuation of outcomes.

The value of life course vaccination is on par with other high-value healthcare interventions.

When compared to similar work, the order of magnitude of our results has face validity. It is similar to the returns associated with childhood immunisation programmes – widely recognised as some of the most cost-effective interventions available to healthcare systems. For example, a recent study by Sim et al. (2020) estimated the value of ten predominantly childhood immunisation programmes in ninety-four countries using the VSL and COI approach. On average, these programmes delivered a return on investment of $52 per $1 invested, compared to our estimate of $19 per $1 spent. Although the time horizon considered in Sim et al. (2020) is shorter than ours, their estimate is higher. However, this is expected given their focus on low- and middle-income countries and the high fatality rates that the diseases in focus have in those countries when vaccination is absent, as well as their focus on child populations.

The results also align with (and sometimes exceed) evidence of benefit-cost profiles from within and outside the health sector. Within the health sector, a systematic review found that public health interventions are associated with a median $14 return on investment, with *protective* public health interventions, including vaccines, providing a median return of $34 per $1 invested (Masters et al., 2017). According to the Benefit-Cost Results collated by the Washington State Institute for Public Policy (WSIPP), the benefit-cost profiles presented by our focus vaccines demonstrate higher returns than many healthcare interventions, including some behavioural and lifestyle interventions to prevent diabetes and reduce obesity, maternal and infant health interventions including variations of prenatal care and caesarean section reduction programmes, various adult mental health, smoking cessation, and substance use interventions (WSIPP, 2023). Outside of the health sector, evidence on public policies shows that our focus vaccines have better benefit-cost profiles than many interventions in areas like workforce development, lower and higher education, child welfare, and criminal justice (WSIPP, 2023).

The relative magnitude of BCRs between the immunisation programmes we included was as expected, considering the underlying diseases targeted and other factors. Compared to the other programmes, the BCR of HZ programmes was expected to be lower because the programme protects against non-fatal disease in a relatively old population. Our adjusted approach to capture

this quality of life loss through monetised QALYs might not capture this value accurately enough due to data limitations on the health-related quality of life estimates. Additionally, there are lower gains from averting formal productivity losses in that population, and we do not include informal productivity losses in our approach, which would be significant for elderly adults.

Despite this, HZ vaccination, on average, returns multiples of its costs back to society, and our evidence review demonstrated its value in relieving often extreme individual suffering and the burden to the healthcare system and society. It fits, therefore, global efforts to implement a life course immunisation strategy (Philip et al., 2018).

Data gaps and methodological challenges remain – and may result in the undervaluation of adult immunisation.

Whilst our evidence review shows growing evidence of the broad societal value of vaccination, it is also clear that many gaps remain. This can be explained in part by the methodological challenges involved in collecting and analysing evidence of broader value and in part by the 'narrow' decision-making frameworks which are typically used to evaluate immunisation programmes (Cafiero-Fonseca et al., 2017; Bell, Neri and Steuten, 2021; Beck et al., 2022; Postma et al., 2022).

Consequently, our benefit-cost analysis only captures some of the value elements. It includes the impact on mortality and cost-offsets to the health system and partly captures vaccines' impact on the quality of life of vaccinated individuals and productivity benefits to vaccinated individuals and their caregivers. This is due to the methodological and data challenges in systematically quantifying and including some of the broader value elements. Even for the narrow value element of population health, we do not incorporate the effects of vaccination on health problems beyond the disease of interest - which were identified for some of our focus vaccines in the literature review – due to methodological and data challenges.

Our analysis does not capture those elements relating to disease transmission, antimicrobial resistance, or social equity value. Further, we include adverse events in the denominator of the BCR, which has a larger impact on the results than treating it as offset to the benefits captured within the numerator. Finally, in some countries, we could not find baseline incidence rates to describe the state of the world where no immunisation programme is in place. As a result, the incidence rates in the comparator group (no vaccination) are often lower than they should be, leading to an underestimate of the estimated value of the vaccination programme. Despite this under-recognition, our results demonstrate a compelling investment opportunity with high returns on investment.

4.2 Conclusion

Without vaccination, the world would be very different, and our progress to date - especially in high-income countries - should not be taken for granted. History offers insights into the grim reality of a world without vaccines (CDC, 2012). Even more recently, the COVID-19 pandemic demonstrated that, beyond health, a social and economic argument should be made for vaccinations against outbreak-prone diseases (Bloom, Cadarette and Ferranna, 2021).

Under-recognition of the value of vaccination risks suboptimal decision-making. We have seen that while other public health preventative measures can also limit transmission of respiratory viruses, there are significant welfare consequences of interventions which require severe limitation of economic and social activities (Nasrullah et al., 2023; Camera and Gioffré, 2021; Bloom, Cadarette and Ferranna, 2021). Vaccines can prevent the need for drastic restrictive measures in a world already facing health system pressures and fiscal constraints beyond health. This value, in addition

to the inherent value that adult immunisation programs deliver to individuals, health systems, and society, can be substantial and delivers another argument to recognise the broader value of vaccines to optimise decision-making.

Prevention - and vaccination as a powerful tool for that- must be reimagined. Removing the various financial and non-financial barriers for adult vaccination programmes requires multi-stakeholder coordination and cooperation between policy makers from the health, finance, and social sectors. Ensuring their optimal implementation requires sufficient (earmarked) funding, a well-functioning vaccination delivery infrastructure, and addressing barriers that hinder equitable access and coverage, including vaccine hesitancy (Hutubessy et al., 2023; Badur et al., 2020; Baldwin, Tiro and Zimet, 2023). These collaborative efforts will be critical for achieving and advancing global agendas such as the UN Sustainable Development Goals (SDGs), the UN Decade of Healthy Ageing (2021 – 2030), and the WHO Immunisation Agenda 2030 (IA2030).

4.3 Policy recommendations

Adopt a prevention-first mindset and provide robust funding for adult vaccination programs.

Now, more than ever, healthcare systems must invest in strategies to cope with unprecedented and growing demand. Prevention must be at the heart of such strategies, and robust adult immunisation programmes, embedded in a well-functioning delivery infrastructure and supported by sustainable funding, are a fundamental component of effective prevention.

Implement and optimise adult immunisation programmes as part of a life course immunisation approach.

The burden of vaccine-preventable diseases is projected to rise, underscoring the importance of robust adult immunisation programmes. Expanding access to a broader adult population can generate more value and higher net cost savings for healthcare systems and society. Adult immunisation programmes also present a great opportunity to help our societies age well and sustainably long into the future - and deliver an excellent return on investment in the process.

Expand and develop the evidence base for the value of adult immunisation programmes.

There are significant gaps in evidence regarding the broader elements of the value of immunisation programmes. Further research is needed to close these knowledge gaps, which is vital for informed decision-making and targeted policy interventions that aim to optimise the value of adult immunisation programmes. More robust data collection systems, widely accepted methods, and transparent/open data access would allow more accurate quantification of these broader values to be incorporated into future economic evaluations to inform policy decisions.

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