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The Socio-Economic Value of Adult Immunisation Programmes

CONTRACT RESEARCH REPORT
DECEMBER 2023

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Report Amendments

Amendments were made to this report in February 2024 to incorporate results from additional literature.

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Executive Summary

What is this report about?

This report provides an in-depth review of adult immunisation programmes, focusing on seasonal influenza, pneumococcal disease, herpes zoster (HZ), and respiratory syncytial virus (RSV). It employs a structured literature review methodology, focusing on the value of adult immunisation programmes in ten countries from diverse geographies, synthesising evidence on disease burden and highlighting the health, healthcare system, and societal benefits of adult immunisation.

The evidence found supports the critical role of robust adult immunisation programmes in addressing major health and societal challenges while aligning with critical global agendas such as the UN Sustainable Development Goals (SDGs) and the WHO Immunisation Agenda 2030 (IA2030).

However, the research also clearly shows that many elements of the value of adult immunisation programmes 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.

Global Demographic Transitions and Health Challenges

The world is currently undergoing significant demographic shifts, with ageing populations emerging as a dominant trend. Infectious diseases such as shingles and pneumococcal disease can be more severe for older adults and are associated with a substantial hospitalisation burden amongst this population. Healthcare resource use associated with noncommunicable diseases also increases with population ageing. This demographic transformation necessitates proactive readiness of healthcare and social care systems to meet the emerging challenges. Concurrently, the "tripledemic" of COVID-19, seasonal influenza, and RSV, along with rising rates of chronic diseases among younger age groups, is placing 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 and Vaccination

Addressing these challenges requires a paradigm shift from treatment to prevention. Preventive public health interventions are recognised as essential in supporting healthcare systems, promoting healthier lives, and fostering productivity and societal well-being. Vaccination stands as a fundamental preventive measure, integral to achieving global health goals like the 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.

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 in Australia and Germany 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 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 Society

Vaccine-preventable diseases impact productivity and result in economic burdens. Expanding adult immunisation programmes and coverage can lead to substantial productivity gains 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.

Discussion and Recommendations

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 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.

We call on policy- and decision-makers to adopt a prevention-first mindset; implement and optimise robust adult immunisation programmes that are proven cost-effective; and (support research to) expand the evidence base for the broader value of adult immunisation.

Introduction

This report provides a comprehensive review of evidence on the value of adult immunisation programmes against seasonal influenza, pneumococcal disease, herpes zoster (HZ) (caused by reactivated varicella-zoster virus, or VZV), and respiratory syncytial virus (RSV). It synthesises evidence on the burden of these diseases and the health, healthcare system, and societal benefits of adult immunisation. The objective 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 political agendas, including the UN Sustainable Development Goals (SDGs) and World Health Organisation (WHO) Immunisation Agenda 2030 (IA2030).

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) and the 'tripledemic' of COVID-19, seasonal influenza, 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. 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). 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, and 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.

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/*; where there is a discrepancy, the broader schedule is reported[1].

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 healthcare system	Not included in immunisation schedule

	Australia	Brazil	France	Germany	Italy	Japan	Poland	South Africa	Thailand	US
Influenza	>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
Pneumococcal	>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

[1] *There is no defined RSV schedule at the time of writing, 1st September 2023.*

1. Methods

1.1 Approach

This paper presents the results of a structured literature review which sought to identify evidence on the burden of disease caused by infections due to seasonal influenza, streptococcus pneumoniae, RSV and varicella zoster virus (VZV), and the value of the associated adult immunisation programmes (seasonal influenza, pneumococcal disease, RSV and HZ). We focus on ten countries selected to represent a diversity of immunisation schedules, healthcare systems, geographies, and demographic contexts: Australia, Brazil, France, Germany, Italy, Japan, Poland, South Africa, Thailand, and the United States of America.

The results are structured according to the OHE Value of Vaccines framework. This is a tool for conceptualising the distinct elements of vaccines' value, based on 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 Chapter 2. A deep dive into the key findings from the evidence base are then presented in the three following chapters reflecting three overarching domains of value: value for population health (Chapter 3); value for healthcare systems (Chapter 4); and value for society (Chapter 5). Within each chapter, we provide additional context through a summary of the disease burden and then present evidence for each individual value element. Our goal is to highlight 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).

The report concludes with Chapter 6 which provides an overall summary of the evidence for each domain and provides policy recommendations.

1.2 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))

Our study design is summarised below in Table 2. We employed the following inclusion criteria: papers published from 2017 onwards, 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. Our results were supplemented using the snowballing approach, whereby articles citing potentially relevant research were also screened for inclusion.

The search was restricted to evidence published since 2017 to prioritise the more recent literature showcasing the breadth of effects. 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.

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 also included.
Comparator	For vaccine intervention, no vaccine.
Outcomes	Any: e.g., health outcomes, societal economic outcomes

1.3 Value of Vaccines framework

Following Cafiero-Fonseca et al. and Bell et al. (2017; 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 OHE Value of Vaccines framework shown in Figure 1 was used to structure this assessment. The definition and characterisation (broad/narrow) of each of the value elements of the framework are explained in Table 1. 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.

FIGURE 1: VALUE OF VACCINES FRAMEWORK

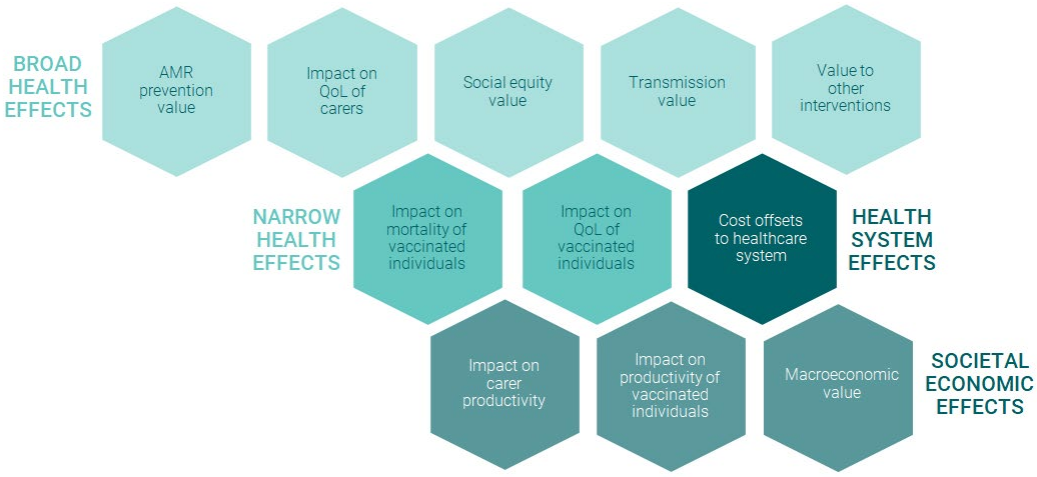

TABLE 1: VALUE DOMAINS AND VALUE ELEMENTS, ACCORDING TO THE VALUE OF VACCINES FRAMEWORK

VALUE DOMAIN	VALUE ELEMENT[2]	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 healthcare system	Narrow	Value of effects on net resource use by healthcare systems in providing care to vaccinated individuals, 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 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 focus vaccines.

[2] *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 information on the current disease burden associated with selected vaccine-preventable diseases, across each domain of value.*

2. Assessment of the evidence base for the value of adult immunisation programmes

The heatmap table below (Table 3) visualises the availability of evidence on the value of vaccines for each of the four target diseases, for each element of OHE's value framework. The heatmap also provides the percentage of countries in our sample for which relevant evidence was identified on each value element and by vaccine. Extended heatmaps, showing results by country, are presented in Appendix 1.

The results show that evidence availability is greatest for the 'narrow' benefits: 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 quality of life of vaccinated individuals was the value element most consistently evidenced across countries,[3] 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 other, '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, pneumococcal and RSV as there is limited transmissibility of VZV between adults), evidenced in 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 (in up to 20% of countries for influenza). For both effects on equity and antimicrobial resistance, there is evidence relating to one of the included vaccines, in one country (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 United States, where evidence of seven value elements was identified. The least comprehensive was in Poland and Thailand, where evidence of only two elements was identified. For an overview of the country-specific availability of evidence, see the full heatmaps presented in Appendix 1.

[3] 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.

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 depend 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 3: 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 healthcare system	Value to other interventions	Impact on 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[4]	40		30	10			

[4] *There is limited transmissibility of VZV between adults.*

3. 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**[5]. 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[6]. 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 6.2. First, however, we provide context by describing the current health burden in adults associated with influenza, streptococcus pneumoniae, RSV and VZV.

3.1 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 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, 2019) – 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 (see Table 4).

There is also evidence that the RSV burden is often underestimated (Savic et al., 2022). RSV diagnosis is often based on symptoms, and thus RSV is often simply reported as an "Influenza-like illness". The lack of a uniform clinical case definition makes it difficult to detect cases without testing, but 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).

[5] 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.

[6] 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 4: 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 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 United States, 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.

3.2 The value of adult immunisation programmes for vaccinated populations

3.2.1 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 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). Recent evidence is summarised below, prioritising systematic review evidence where available.

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, 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 currently available RSV vaccines indicates that vaccines have protective efficacy against RSV-related respiratory disease 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 we know 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 also 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 be benefits of the RSV vaccine (Ivey, Edwards and Talbot, 2018).

- **Mortality:** Evidence is not yet available directly linking RSV vaccination with mortality reduction.

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 VZV with 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 also promote healthy ageing more broadly. For example, although the mechanisms are not well understood, there are indications that 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). A 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).

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 individuals' physical, psychological, and social functional status. In relation to infectious diseases, frailty is associated with increased susceptibility, 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 makes vaccination of this sub-population particularly important. New strategies are being developed to improve vaccine efficacy in the adults aged 80 and over (Bell and Kutzler, 2022). There is also evidence of recently developed vaccines demonstrating protection against disease even in the oldest populations. An RCT including frail individuals aged 50 and above found that HZ vaccination was more than 90% efficacious against infection in all sub-populations, including adults aged 80 and over (Curran et al., 2017). 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). 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). We did not identify evidence relating to pneumococcal vaccine efficacy or effectiveness in individuals aged >80, although immune response has been demonstrated[7].

3.2.2 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 disease 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).

[7] *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 older adults. This evidence is generally extended to support the argument that 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).

3.2.3 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. 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 provide some indication of how substantial these effects may be. We identified two studies which reported directly on the additional health benefits accrued to unvaccinated populations due to adult immunisation programmes. A study of the community effects of influenza vaccination in Australia and South Africa 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).

4. 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 COVID-19. First, however, we provide some context, by describing the current healthcare system burden associated with diseases preventable by our four target vaccines.

4.1 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 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[8] and absolute numbers of admissions.

For influenza, there is high cross-country 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 lower respiratory tract infections worldwide (GBD 2016 Lower Respiratory Infections Collaborators, 2018). For RSV, the hospitalisation rate amongst adults over 65s 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 amongst adults >65 (Shi et al., 2020a). Regarding (reactivated) VZV, we did not identify cross-country estimates of hospitalisation rates or number of hospitalisations at the population level for reactivated VZV (or shingles). 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

[8] *The number of hospital episodes in a given year in a defined population, divided by the size of that population.*

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 of these infections is substantial. A recent systematic review and meta-analysis estimated the cost per episode for acute respiratory infections in adults over 50[9], 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 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 5. 14.3% 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, i.e., 'working age' adults, 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 Chapter 5.

TABLE 5: 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 estimates 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 of 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 there is evidence indicating 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 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

[9] *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.*

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 United States, 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.

4.2 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[10] (Leidner et al., 2019). Recent studies from Australia and Germany have also indicated that immunisation programmes of 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 uptake of adult 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).

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

Expanding pneumococcal immunisation programmes 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).

RSV VACCINATION:

At the time of writing, there was one study estimating the potential cost-effectiveness of a potential adult RSV immunisation programme in the US. The study 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) find predictions that an RSV vaccine strategy for older adults could have cost-effectiveness ratios similar to those for 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) reported a cost-per-QALY of less than $100,000 (Leidner et al., 2019). Another systematic review reported that RZV 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 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, and cost-effective in adults aged 50 and over with a cost-per-QALY of $14,916 per QALY gained (Meredith and Armstrong, 2022). 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, in addition to this, vaccines deliver 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.

5. 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[11] of vaccines, as well as their role in promoting **social equity** and preventing **anti-microbial resistance (AMR)**. First, however, we provide some context, by describing the current socio-economic burden associated with diseases preventable by our four target vaccines.

5.1 Context: the societal burden of vaccine-preventable diseases

Vaccine-preventable diseases produce a substantial economic burden, due to their effect on productivity.

The productivity losses associated with influenza are substantial and comprise a large proportion of the overall economic burden of influenza to society. A recent systematic literature review of studies from Europe and North America on the economic burden of influenza in working ageing 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).

Disease caused by streptococcus pneumoniae and RSV is less well studied. 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 pneumococcal disease episodes require support from caregivers, with subsequent impact on productivity (Igarashi et al., 2021). Regarding HZ, data from studies of working age adults from the US estimates that the average productivity cost associated with an episode of $2,350 per HZ 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).

[11] 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.

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 to have independent effects on the risk of RSV hospitalisation and the risk of influenza infection in the US (Prasad et al., 2020; 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).

5.2 The productivity value of adult immunisation programmes

5.2.1 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.

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 writing, there are no peer-reviewed studies available investigating productivity value in of adult RSV immunisation programmes.

HZ VACCINATION:

The same 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, like pneumococcal vaccination, 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. Estimates suggest that 25% of adults aged 50 and over in Europe provide informal care (Tur-Sinai et al., 2020).

5.2.2 Productivity value in caregivers

There is limited evidence of the productivity value of caregivers. Three studies reported results incorporating productivity effects on caregivers. 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).

5.3 The social equity value of adult immunisation programmes

There is evidence that vaccine programmes contribute to improved health equity within countries, as well as reduction in the financial risk associated with vaccine-preventable diseases, which are also inequitably distributed. A recent systematic review of 'equity-informative' economic evaluations[12] of vaccines concluded that both 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

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

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

5.4 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 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 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.

6. Discussion and policy recommendations: realising the value of adult immunisation programmes

Discussion

Our results show that vaccine-preventable diseases continue to generate a substantial burden on health, healthcare systems, and societies. This burden is projected to increase in line with demographic trends towards ageing populations. There is also clear evidence that adult immunisation programmes generate tremendous value. Expanding access to a greater share of the adult population generates additional value and can result in even higher overall cost-effectiveness and net cost savings for healthcare systems.

The value of adult immunisation programmes for population health: Our results show that adult immunisation programmes are essential for protecting the health of older adults and adults with risk factors. All vaccine-preventable pathogens studied in this report generate a substantial disease burden, which is anticipated to rise in the coming decades in countries with ageing populations (Zorzoli et al., 2018; Talbird et al., 2021). Each of our focus vaccines are effective in older adults and at-risk populations, with recent evidence demonstrating immune response and efficacy even in the frailest and most immunocompromised populations (Curran et al., 2017; Walzer et al., 2020; van Deursen et al., 2017). There is also evidence that adult immunisation programmes produce health benefits by protecting unvaccinated individuals (de Boer et al., 2018).

The value of adult immunisation programmes for healthcare systems: Vaccine-preventable diseases continue to pose a major and increasing burden to healthcare systems (Talbird et al., 2021). There is an extensive evidence base showing that adult immunisation programmes are highly cost-effective (Leidner et al., 2019; Meredith and Armstrong, 2022; Treskova et al., 2021). Indeed, recent studies of influenza and pneumococcal immunisation programmes in Australia and Germany have indicated that these programmes result in net cost savings to the healthcare system by averting hospital inpatient and emergency care (Darmaputra et al., 2021; Storch et al., 2022; Ren et al., 2021). Programmes to expand uptake can also be very cost-effective (Smith et al., 2017), which is intuitive given the relatively low variable costs compared to the fixed costs associated with delivering immunisation programmes (World Health Organization, 2019). Evidence from Germany and France indicates expanding adult immunisation programmes may increase their overall cost-effectiveness, perhaps as a result of economies of scale (Curran et al., 2021; Beresniak et al., 2019).

The value of adult immunisation programmes for society: Vaccine preventable diseases are associated with a large productivity cost in formal labour markets and the informal care provided by retired adults. There is evidence that adult immunisation programmes provide a positive return on investment in the form of both increased tax revenues and productivity, which outweighs the costs of the programmes to governments many times over (Ruggeri, Di Brino and Cicchetti, 2020). Workplace influenza immunisation programmes have also been shown to be cost saving to the employer (Ferro, Bordin and Benacchio, 2020).

There is evidence that the benefits of adult immunisation programmes are particularly concentrated in more socioeconomically disadvantaged sub-populations (Patikorn et al., 2023; Chang et al., 2018; Wateska et al., 2019). There is also evidence that expanding adult vaccination schedules to include younger adults can reduce inequity in the distribution of vaccine-preventable diseases (Wateska et al., 2022, 2019).

Additionally, evidence shows that adult immunisation programmes can reduce the prevalence of inappropriate prescribing of antibiotics (Wang, Cravo Oliveira Hashiguchi and Cecchini, 2021; He et al., 2022). Investment in the development of novel antimicrobial vaccines will also help to protect against the progression of AMR (Klugman and Black, 2018).

Gaps in recognition of the value of adult immunisation programmes: Whilst our results show that there is 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 (Beck et al., 2022; Bell, Neri and Steuten, 2021; Cafiero-Fonseca et al., 2017; Postma et al., 2022).

Policy recommendations

Adopt a prevention-first mindset: 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.

Implement and optimise robust adult immunisation programmes: 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. Adult immunisation programmes also present a tremendous opportunity to help our societies age well and sustainably long into the future - and deliver excellent return on investment in the process.

Expand the evidence base for the value of adult immunisation programmes: 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. Further research to close these knowledge gaps is vital for informed decision-making and targeted policy interventions that aim to optimise the value of adult immunisation programmes.

Appendix 1: Country heatmaps of evidence for the value of adult immunisation programmes

TABLE A1: AUSTRALIA

Key

X = Evidence available	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 healthcare system	Value to other interventions	Impact on productivity of vaccinated	Impact on carer productivity	Social equity value	AMR prevention value	Macroeconomic effects
Influenza	X	X		X	X		X			X	
Pneumococcal	X	X		X	X						
RSV	X										
HZ	X										
All vaccines	X	X		X	X		X			X	

TABLE A2: BRAZIL

Key

X = Evidence available	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 healthcare system	Value to other interventions	Impact on productivity of vaccinated	Impact on carer productivity	Social equity value	AMR prevention value	Macroeconomic effects
Influenza	X	X			X		X				
Pneumococcal											
RSV	X										
HZ	X										
All vaccines	X	X			X		X				

TABLE A3: FRANCE

Key

X = Evidence available	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 healthcare system	Value to other interventions	Impact on productivity of vaccinated	Impact on carer productivity	Social equity value	AMR prevention value	Macroeconomic effects
Influenza	X	X		X	X						
Pneumococcal	X			X							
RSV											
HZ	X										
All vaccines	X	X		X	X						

TABLE A4: GERMANY

Key

X = Evidence available	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 healthcare system	Value to other interventions	Impact on productivity of vaccinated	Impact on carer productivity	Social equity value	AMR prevention value	Macroeconomic effects
Influenza	X	X			X		X				
Pneumococcal	X	X		X	X		X				
RSV	X										
HZ	X	X			X						
All vaccines	X	X		X	X		X				

TABLE A5: ITALY

Key

X = Evidence available	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 healthcare system	Value to other interventions	Impact on productivity of vaccinated	Impact on carer productivity	Social equity value	AMR prevention value	Macroeconomic effects
Influenza	X	X			X		X				
Pneumococcal					X		X				
RSV	X										
HZ	X				X		X				
All vaccines	X	X			X		X				

TABLE A6: JAPAN

Key

X = Evidence available	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 healthcare system	Value to other interventions	Impact on productivity of vaccinated	Impact on carer productivity	Social equity value	AMR prevention value	Macroeconomic effects
Influenza	X	X		X	X		X				
Pneumococcal	X	X			X		X	X			
RSV	X										
HZ	X	X			X		X	X			
All vaccines	X	X		X	X		X	X			

TABLE A7: POLAND

Key

X = Evidence available	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 healthcare system	Value to other interventions	Impact on productivity of vaccinated	Impact on carer productivity	Social equity value	AMR prevention value	Macroeconomic effects
Influenza	X	X									
Pneumococcal											
RSV											
HZ											
All vaccines	X	X									

TABLE A8: SOUTH AFRICA

Key

X = Evidence available	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 healthcare system	Value to other interventions	Impact on productivity of vaccinated	Impact on carer productivity	Social equity value	AMR prevention value	Macroeconomic effects
Influenza	X	X		X	X		X	X			
Pneumococcal	X	X			X		X				
RSV	X										
HZ											
All vaccines	X	X		X	X		X	X			

TABLE A9: THAILAND

Key

X = Evidence available	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 healthcare system	Value to other interventions	Impact on productivity of vaccinated	Impact on carer productivity	Social equity value	AMR prevention value	Macroeconomic effects
Influenza	X	X									
Pneumococcal											
RSV											
HZ											
All vaccines	X	X									

TABLE A10: UNITED STATES

Key

X = Evidence available	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 healthcare system	Value to other interventions	Impact on productivity of vaccinated	Impact on carer productivity	Social equity value	AMR prevention value	Macroeconomic effects
Influenza	X	X		X	X		X	X			
Pneumococcal	X	X			X				X		
RSV	X	X		X	X						
HZ	X	X			X		X				
All vaccines	X	X		X	X		X	X	X		

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