Assessing the health burden of vaccine preventable infections in European adults: challenges and opportunities translated into action

Meeting Report

AIB technical Meeting, April 20 -21, Antwerp, Belgium

University of Antwerp and University of Florence

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Abbreviations list

AIB	Adult Immunization Board
ARI	Acute Respiratory Infection
ARTI	Acute Respiratory Tract Infection
BCoDE	Burden of Communicable Diseases in Europe
BoD	Burden of Disease
CDC	Centers of Disease Control and Prevention
CFR	Case-Fatality Rate
DALY	Disability-Adjusted Life Year
ECDC	European Centre for Disease Control
EHDS	European Health Data Space
EU	European Union
EEA	European Economic Area
GBD	Global Burden of Disease Study
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HPV	Human Papilloma Virus
HZ	Herpes Zoster
IA 2030	Immunization Agenda 2030
IC	Immunocompromised
IPD	Invasive Pneumococcal Disease
IMI2	Innovative Medicines Initiative 2
JE	Japanese encephalitis
MMR	Measles Mumps Rubella
MMR-V	Measles Mumps Rubella - Varicella
NITAG	National Immunization Technical Advisory Groups
N/A	Not applicable
PCR	Polymerase Chain Reaction
PHN	Post Herpetic Neuralgia
RCT	Randomized Clinical Trials
RZV	Recombinant Zoster Vaccine
RESCUE	REspiratory Syncytial Virus Consortium in Europe
RIVM	Rijksinstituut voor Volksgezondheid en Milieu[1]
RSV	Respiratory Syncytial Virus
QoL	Quality of Life
SMPH	Summary Measures of Population Health
SP	Strategic Priority
TdaP	Tetanus diphtheria acellular Pertussis
VHPB	Viral Hepatitis Prevention Board
VITAL	Vaccines and InfecTious Diseases in the Ageing popuLation
VMA	Vaccine Market Access
VPDs	Vaccine-Preventable Diseases
VPIs	Vaccine--Preventable Infections
WHO	World Health Organization
YF	Yellow fever
YLD	Years Lived with Disability
YLL	Years of Life Lost
ZVL	Zoster Vaccine Life

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1. Introduction

The Adult Immunization Board (AIB) (www.adultimmunizationboard.org) is a new independent multidisciplinary advisory board, created in November 2022. The purpose of the AIB is to contribute to the reduction of mortality and morbidity from vaccine-preventable infections and diseases in European adults by providing evidence-based guidance on fundamental technical and strategic issues, while monitoring the progress of adult immunization programmes at regional, national and European levels.

The AIB comprises a group of prominent experts from various fields of adult immunization and representing different European regions. Board members come from a broad array of adult immunization stakeholders (academia, public health, and international organisations) but act in their personal capacity for the board. The AIB is supported by an unrestricted grant from Vaccines Europe (www.vaccineseurope.eu) and applies the ethical rules of its hosting universities, the University of Antwerp and the University of Florence, to guarantee strict operational and scientific independence throughout its activities. The AIB and its board members pledge to work independently, transparently and collaboratively.

The AIB leverages the long-standing experience of the Viral Hepatitis Prevention Board (VHPB, created in 1992; www.vhpb.org) and the HPV Prevention and Control Board (HPV Board, created in 2015; www.hpvboard.org). In line with the *modus operandi* of the VHPB and HPV Board, the AIB organises two live meetings per year: a technical meeting to discuss specific technical aspects on adult immunization with subject-matter experts and a country meeting to discuss country/region-specific issues on adult immunization together with local experts.

This report covers the first AIB technical meeting, which took place in Antwerp, Belgium, on April 21-22, 2023. The meeting, with 50 participants, was a unique gathering of experts in research on the health burden of vaccine-preventable infections (VPIs). The purpose of this meeting was to identify and discuss the challenges and opportunities when assessing the health burden of VPIs. The meeting objectives were four-fold:

(1) to provide an overview of current VPIs in the adult population
(2) to discuss the methodology and challenges in assessing the health burden of adult VPIs with a particular focus on Europe
(3) to understand how health burden estimates of adult VPIs shape national vaccination policies and practices and inform public health priorities
(4) to evaluate current VPIs' health burden evidence to provide a convincing case for strengthening adult vaccination in Europe.

Meeting presentations, discussions and lessons learnt are summarised in this report. The meeting slides are available on the AIB website (www.adultimmunizationboard.org).

2. Overview of current vaccine-preventable infections in the adult population

A wide range of VPIs affects the adult population. Table 1 summarises the vaccines available for adult immunizations against VPIs. Adult vaccine types and recommendations differ between and/or within European countries. An overview of recommended vaccines in each EU/EEA country can be found in the vaccine scheduler on the European Centre for Disease Control (ECDC) website (https://vaccine-schedule.ecdc.europa.eu/) and on official national public health websites (1).

3. Methodology and challenges in calculating the health burden of adult vaccine-preventable infections

3.1. Definition and calculation of the health burden of disease

Ranking diseases in terms of their impact is essential to guide policymakers and help prioritise interventions and the use of available resources. Diseases impact multiple domains of life, including health, socio-economic and psycho-social well-being (of individuals, their caregivers, and/or the public). Burden of disease (BoD) is the comparative quantification of disease impact on one or more domains of life. The focus of the AIB technical meeting is on health BoD.

Health BoD may be calculated using multiple measures, ranging from case numbers to indicators of disease severity (e.g., disease duration, reduction of quality of life) and death, (e.g., residual life expectancy). Depending on the selected measure, the ranking of diseases will be considerably different. For example, a highly contagious pathogen causing mild and self-limited disease will rank high when using incidence as the measure of burden but low when using severity. Therefore, to obtain comparative BoD metrics, summary measures of population health (SMPH) that integrate multiple outcome measures are warranted. The most used SMPH are summarised in Table 2.

Table 1. Overview of current adult vaccines used in Europe (>18-years-old). The list covers adult vaccines up to September 2023

Overview of current adult vaccines used in Europe (>18-years-old)					
Vaccine	**(Age-dependent) routine vaccines**	**Catch-up missed child/ adolescence vaccines**	**Individual risk-based vaccines (e.g pregnancy, lifestyle, medical condition)**	**Travel-related vaccines**	**Occupational activity-related vaccines (e.g. HCP, CCW, people who work with animals, etc.)****
Anthrax			x		x
Cholera				x	
COVID-19	x		x	x	x
Dengue				x	
Ebola					x
Hepatitis A		x*	x	x	x
Hepatitis B		x	x	x	x
Hib			x		
HPV		x	x		
HZ	x		x		
S. Influenza	x		x	x	x
Pneumococcus	x	x	x		
JE				x	
MenACWY		x	x	x	
MenB		x	x	x	
MMR(V)		x			
Mpox			x		
Polio		x		x	
Rabies				x	x
RSV	x		x		
TB			x		x
TBE	x	x*	x	x	x
Tdap	x	x	x		
Typhoid fever				x	
Yellow fever				x	

Hepatitis E and Q-fever vaccines are not included, as these vaccines are not licensed in Europe. Abbreviations: CCW, child care workers; HCP, health care providers; Hib, Haemophilus influenzae b; HPV, Human Papilloma Virus; HZ: Herpes Zoster; S. Influenza: Seasonal Influenza; JE, Japanese Encephalitis; Men, Meningococcal; MMR(V): Measles Mumps Rubella Varicella; RSV, Respiratory Syncytial Virus; TB, tuberculosis; TBE, Tick-Borne Encephalitis; Tdap, Tetanus diphtheria acellular Pertussis; * Depends whether there is universal vaccination at (sub)national level. ** All vaccines can be given to lab workers working with these pathogens

Table 2. Summary measures of population health Courtesy of Dr Brecht Devleesschauwer

	Health Experience	Health Loss
Mortality	Life Expectancy	Potential Years of Life Lost (Years of Potential Life Lost) Standard Expected Years of Life Lost
Morbidity	Quality-Adjusted Life Year	Years Lived with Disability
Morbidity **+ Mortality**	Active Life Expectancy Disability-Free Life Expectancy Healthy Life Years Quality-Adjusted Life Expectancy Disability-Adjusted Life Expectancy	Disability-Adjusted Life Year

To understand the methodological considerations and challenges of calculating SMPH, Disability-Adjusted Life Year (DALY) can be used as an illustrative example. DALY is a commonly used health loss measure capturing both morbidity and mortality (2).

DALY is the sum of Years Lived with Disability (YLD) and the standard expected Years of Life Lost (YLL). One DALY equals one healthy life year lost.

DALY = YLD (N of incident cases x Duration x Disability weight)*
+ YLL (N of deaths x Residual Life Expectancy)

** Disability weight = relative reduction in QoL associated to the health state, ranging from 0 (perfect health) to 1 (death).*

Despite a standardised calculation, DALY estimates may vary according to:

- Data sources: Method for data collection, processing and management.
- Incidence vs. Prevalence-based approach: The incidence-based approach quantifies future health losses due to current exposures and is therefore useful for disease prevention and control. The prevalence approach quantifies current health losses due to past exposures and finds its application in estimates of healthcare burden.
- Normative assumptions: residual life expectancy and/or disability weights used in the calculation may differ depending on the data source or derivative method applied.
- Disease progression models (outcome trees): these models are schematic representations of health states that include the multiple outcomes of a disease (acute and chronic stages, complications, death) and quantify their transition probabilities and durations (Figure 1). Within each model, different points of interest allow for BoD estimates: hazard- or pathogen-based, outcome-based and risk-factor based. The pathogen-based approach allows to link sequelae to their infectious causes.

- Multiplication factors: multiplication factors are used to correct for under–ascertainment and under-reporting of disease (Figure 2). Under-ascertained infections are those occurring in individuals that do not seek healthcare, and therefore cannot be captured by the surveillance systems (e.g., asymptomatic infections, mild or self-limited disease, infections in individuals with no or limited access to healthcare). Underreported infections are those that occur in individuals that do seek healthcare, but the event is not captured by the surveillance system in place (e.g., undiagnosed or misdiagnosed, absence of reporting or notification).
- Study level: DALYs are typically calculated at the population level but can also be calculated at the individual level depending on the data available.
- Outcome measure: may differ depending on the specific interests of the organisations involved in data collection and analysis.

The different methodological designs may affect the comparability and the interpretation of results, highlighting the importance of transparency and standardisation of practices.

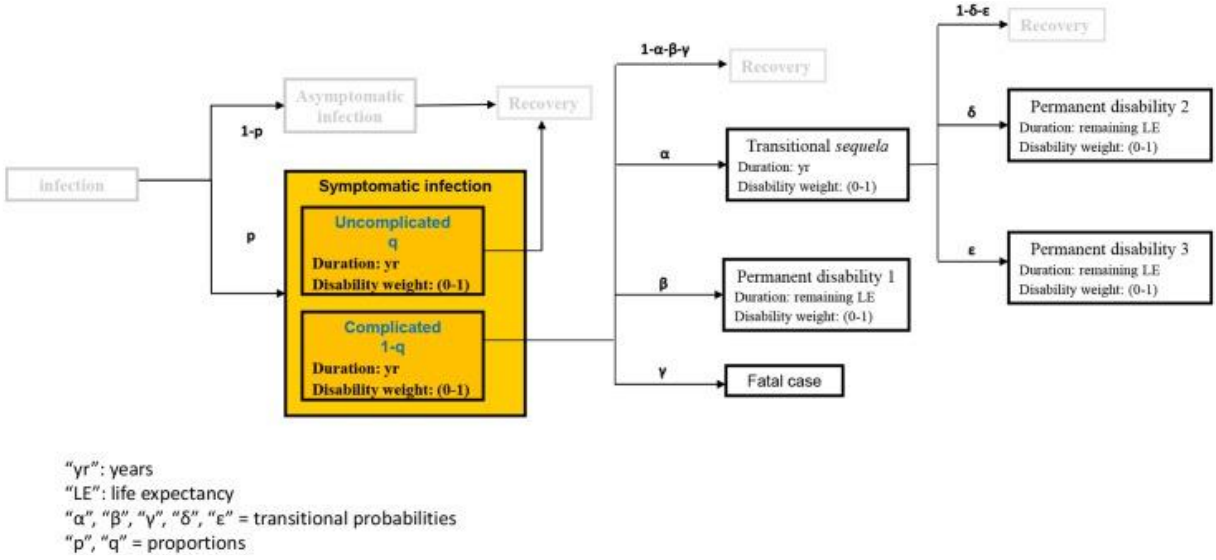

Figure 1 A disease outcome tree linking infection and all sequelae. Source: Colzani E et al, PLoS One 2017 (3)

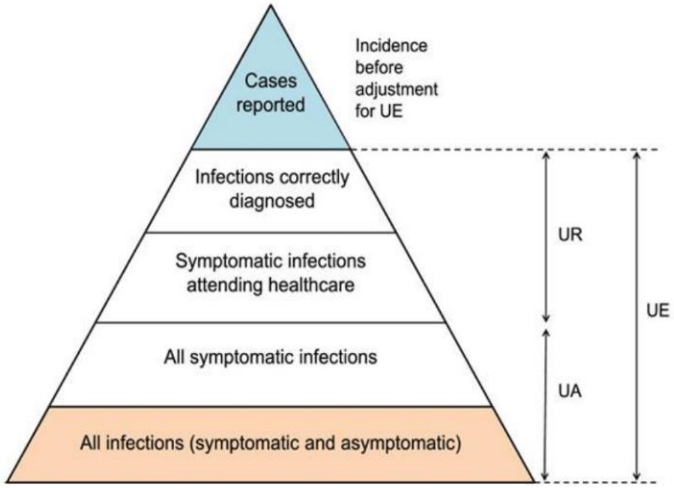

Figure 2 Underreporting and under-ascertainment of disease. Source: Gibbons et al. BMC Public Health. 2014 (4)

Abbreviations: UA, under ascertained; UR, underreported; UE, underestimated

3.2. Health burden of infectious diseases initiatives (focus on Europe)

The health burden of infectious disease evaluation initiatives, including dedicated research, networks, guidance and data sources, exist at the (sub) national, regional and global levels.

National and sub-national initiatives

A systematic review to identify the burden of infectious disease studies in Europe and the United Kingdom was published by Charalampous et al. in 2022. Studies estimating burden in terms of YLL, YLD and/or DALY and using their own national or sub-national data were included (5). Overall, 105 studies were identified with publication dates between 2000 and 2022, including 83 single-country studies. The Netherlands produced the highest number of studies (n=46) while certain countries had low, or no burden of infectious disease studies identified (France, Greece, Belarus, Croatia and Cyprus). Twenty-five studies elaborated on the burden of VPIs. The most frequently studied VPIs/VPDs were COVID-19 (n=14), influenza, tick-borne encephalitis (TBE), measles, hepatitis B virus (HBV), pertussis, invasive pneumococcal disease (IPD) and herpes zoster (HZ). In line with other reviews, DALY methodological choices varied across European-based burden of infectious disease studies (5-7).

European initiatives

European burden of (infectious) disease initiatives that were presented at the meeting include: BCoDE (Burden of COmmunicable Diseases in Europe), the European Burden of Disease Network and VITAL (Vaccines and InfecTious Diseases in the Ageing popuLation). Also the European Health Data Space (EHDS), who could potentially increase the quality of BoD in Europe, presented their project.

BCoDE is an ECDC funded project, led by the Dutch National Institute for Public Health and the Environment (RIVM) and implemented in collaboration with a European consortium of

academic and national health institutes. The project ran from 2009 to 2013 with the aim to generate comparable BoD estimates for communicable diseases in the EU/EEA using a standardised methodology. Incidence and pathogen based DALYs were used, calculated from centrally collected ECDC surveillance data. The project allowed for the publication of baseline average annual DALY estimates of selected infectious diseases (Figure 3) (8) and the development of the BCoDE toolkit (www.ecdc.europa.eu/en/publications-data/toolkit-application-calculate-dalys), a stand-alone downloadable software allowing the calculation of age-group and sex-specific DALYs for 32 infectious diseases and six healthcare-associated syndromes.

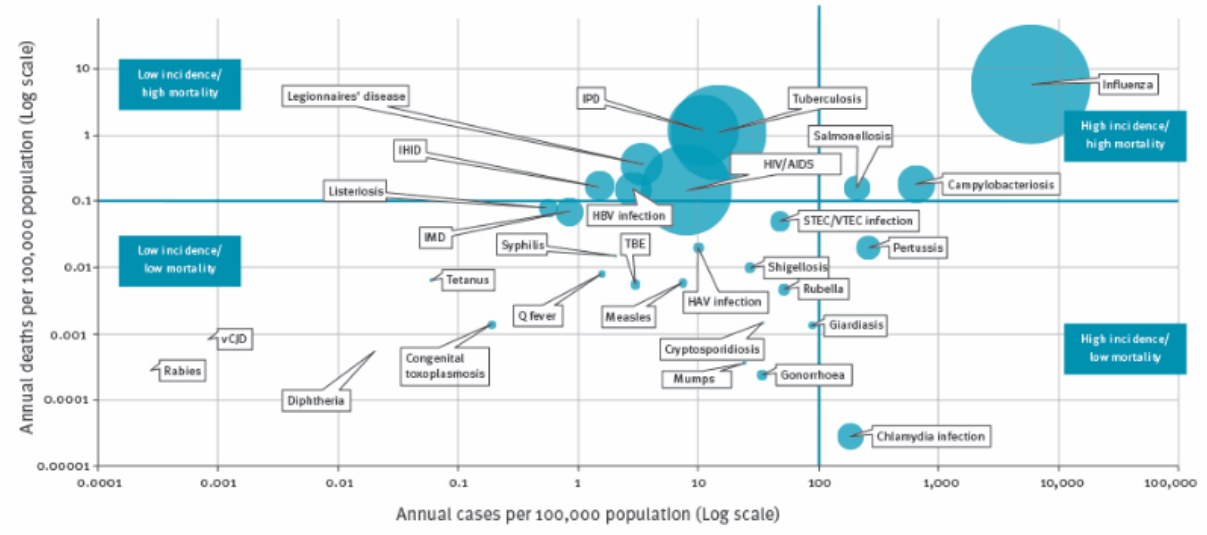

Figure 3 Bubble chart of the burden of selected infectious diseases in terms of mortality and incidence, EU/EEA countries, 2009–2013. Source Cassini et al. Eurosurveillance. 2018 (8)

The diameter of the bubble reflects the number of DALYs per 100,000 population per year. Abbreviations: EU/EEA: European Union/European Economic Area; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HIV/AIDS: Human immunodeficiency virus infection; IHID: Invasive Haemophilus influenzae disease; IMD: Invasive meningococcal disease; IPD: Invasive pneumococcal disease; STEC/VTEC: Shiga toxin/verocytotoxin-producing Escherichia coli; TBE: Tick-borne encephalitis; vCJD: variant Creutzfeldt–Jakob disease

Although the BCoDE project was terminated in 2013, multiple spin-off projects and studies have used its toolkit. These include Dutch national studies investigating the burden of infectious diseases, exploring the effects of an ageing population on the burden of VPIs/VPDs, or evaluating vaccine programme impacts on BoD (9-13). The toolkit has also been used beyond Europe. For example, the Australian Institute of Health and Welfare adapted the toolkit to its local specificities and included HPV as an additional pathogen of interest. Using incidence-based DALYs, the institute successfully showed the impact of the country's various vaccine programmes, including an overall decrease in VPD burden of 31% between 2005 and 2015, a reduction in IPD and HPV burden, and an increase in VPDs among older people principally attributed to influenza and shingles (14).

The European Burden of Disease Network (COST Action CA18218; www.burden-eu.net/) is a technical platform aiming to integrate and strengthen capacity in BoD assessment across Europe and beyond, including the development of guidelines for conducting standardised BoD studies. This COST Action is composed of several pillars, with Working Group 2 dedicated to BoD of infectious diseases. During the SARS-CoV-2 pandemic, the Network set up a COVID-19 Task Force that successfully published a protocol for COVID-19 BoD studies (www.burden-eu.net/outputs/covid-19), including data requirements, suggestion for standard methods and how to communicate results. This protocol has been used for multiple national COVID-19 BoD studies, allowing standardisation of methods and comparability (see Section *Burden of VPIs in a pandemic situation: COVID-19*).

VITAL is an Innovative Medicines Initiative 2 (IMI2) project set up to address current challenges of VPIs/VPDs in ageing adults and to provide knowledge on possible specific vaccination strategies to enhance healthy ageing (www.vital-imi.eu). The objective of its Work Package 1 (WP1) is to quantify the direct burden of infectious diseases in an ageing population across European countries. A VITAL WP1 pilot study is currently ongoing in two European regions/countries, Valencia (Spain) and Denmark, to estimate the BoD of two pre-selected (potentially) VPDs in the 50-year and older population: extra-intestinal pathogenic Escherichia coli (ExPEC) and pneumococcal pneumonia. These diseases were selected through a priority exercise assessing relevance, vaccine availability and data gaps through expert consultation and literature review (15). The pilot regions were selected based on their high potential of capturing a near-complete picture of the infectious disease burden at the individual level. However, the regions differ significantly in terms of data sources, linkage mechanisms, case definition (e.g., regional variations in ICD-10 codes), geographical and socio-economical settings, as well as healthcare organisation and clinical practices (e.g., antibiotic use, diagnostic approach). Building on this initial experience, the applicability of the pilot programme to different environments and VPIs/VPDs across Europe will be explored.

EHDS is an electronic cross-border health service proposal by the European Commission, with ongoing regulatory set-up (https://health.ec.europa.eu/ehealth-digital-health-and-care/european-health-data-space_en). The primary use of the EHDS would be for patient care: the EHDS aims to empower patients to have access and control over their personal health data and facilitate the sharing of this data with health professionals across the EU in a secure and safe environment to ensure cross-border continuity of care. The secondary use of the electronic health data would be, with the patient's consent, for healthcare, research purposes, innovation and public policymaking. The proposed regulation for the EHDS sets out common standards, infrastructures and a governance framework. The European electronic health record format to be used is to include a patient summary (which is recommended to contain immunization data), electronic prescriptions and dispensations, medical images and image reports, laboratory results and discharge reports.

Global initiatives

Two global initiatives related to health BoD were presented during the technical meeting: the Global Burden of Disease Study (GBD) and the World Health Organization (WHO)'s Immunization Agenda 2030 (IA 2030).

GBD has existed and grown for over 30 years, now providing yearly BoD data on 371 diseases and injuries, across 204 countries and territories (16). Ten major lessons learnt in the GBD's three decades of experience are translatable to other BoD initiatives:

- the importance of standardisation
- the value of data sources
- the role of modelling
- the importance of uncertainty
- the value of transparency
- the impact of interventions
- the need for regional/country level analysis
- the multidisciplinary collaboration
- the role of advocacy
- the need for continuous improvement

GBD has produced BoD results for multiple VPIs/VPDs, including *Str. Pneumoniae*, *N. Meningitidis*, varicella and HZ, HPV, and HBV. The data has been used for vaccine coverage (17, 18), vaccine cost-effectiveness studies (19, 20), as well a study assessing antibiotic microbial resistance burden avertable by vaccination (pre-print) having previously identified several bacterial VPIs amongst the highest-ranking pathogens with AMR-attributable deaths (21).

WHO's IA 2030 proposes a strategic framework, build upon four core principles of action (people centered, country owned, partnership based, *data guided*) and seven strategic priorities (SP) (www.who.int/teams/immunization-vaccines-and-biologicals/strategies/ia2030). VPD surveillance is embedded within SP1-Immunization programmes for primary health care and universal health coverage and SP5-Outbreaks and Emergencies. The IA 2030's vision is a WHO-supported global system of comprehensive VPD surveillance across Member States, where all countries have sustainable high-quality VPD surveillance systems that detect/confirm cases and outbreaks and generate the necessary data to guide outbreak prevention and response, immunization programme management and vaccine policy. VPD surveillance is, therefore, to evolve from the historical vertical pathogen-based programmes (e.g., eradication of poliomyelitis, elimination of measles and rubella) involving separate departments in country systems as well as within the WHO, to a coordinated comprehensive VPD surveillance. As shown in Figure 4, comprehensive surveillance encompasses multiple surveillance mechanisms for different end objectives (e.g., global national case-based surveillance for pathogens with eradication and elimination goals; sentinel-site surveillance in designated countries for selected VPDs; notifiable and event surveillance for early outbreak detection and management) sharing key support functions.

Global norms and minimum VPD surveillance standards have been defined in the WHO Recommended Surveillance Standards (https://www.who.int/publications/i/item/who-recommended-surveillance-standards). These surveillance standards are to be tailored to country and pathogen-specificities.

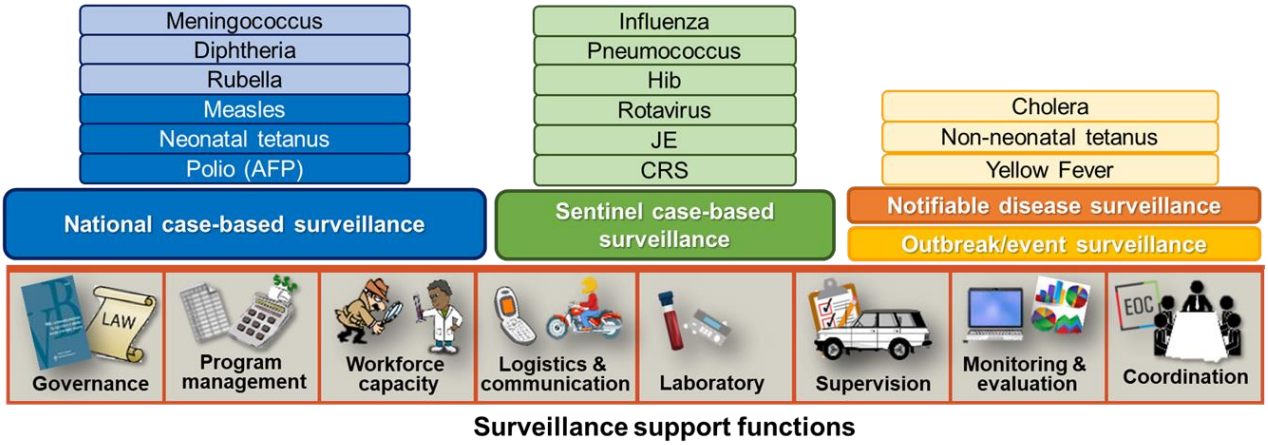

Figure 4. WHO's comprehensive VPD surveillance. Source: adapted from WHO – IA2030 – Global Strategy On Comprehensive Vaccine-preventable disease surveillance, publication 19 June 2020 (Courtesy of Dr Anindya S Bose).

3.3. Epidemiology and health burden of selected adult VPIs

VPIs have been identified among the highest-ranking infectious diseases in several BoD studies (22, 23), yet BoD studies that are specifically dedicated to VPIs remain scarce in Europe (5). To further explore the data and its availability, the AIB reviewed the epidemiology and health BoD of pre-selected adult VPIs, in specific situations (e.g., pandemic) and risk groups (e.g., elderly, immunocompromised, travellers).

Burden of VPIs in a pandemic situation: COVID-19

COVID-19 disease is an infectious disease caused by SARS-CoV-2, a novel coronavirus first detected in December 2019 in an outbreak in Wuhan City, China. The virus rapidly spread across borders, and a global pandemic was declared by the WHO on 12 March 2020. In the 3 years of pandemic, more than 275 million COVID-19 cases and 2.2 million COVID-19 deaths were recorded in the WHO European region (www.who.int/europe/emergencies/situations/covid-19). As the pandemic progressively evolves to SARS-CoV-2 endemicity, disease burden is expected to persist[2]. Risk of severe disease and death is higher in older adults (e.g., above 60 years of age), immunocompromised

[2] The end of global emergency status of COVID-19 was declared shortly after the AIB technical meeting, on 5 May 2023.

individuals, individuals with underlying medical conditions regardless of age, and pregnant women.

Building BoD studies during a pandemic presented multiple challenges, including the lack of data on the full spectrum of health effects of the emerging new virus. Nevertheless, it was an unprecedented opportunity regarding the abundance of surveillance data available and the chance to apply a harmonised methodology across countries.

COVID-19 BoD studies applying the European Burden of Disease Network protocol (see Section *European initiatives*) have been currently carried out in ten EU countries and Australia (24). Results are shown in Table 3. BoD estimates have varied widely, ranging from 32 to nearly 2000 DALYs per 100,000 inhabitants. Differences may reflect variations in population age structure and risk profile, pandemic response but also data management, data collection, degree of ascertainment of the true incidence of infection, case or mortality definitions. Notably, mortality was consistently found to be a major contributor to COVID-19 BoD across the different studies (95% - 99%) as was found in another multi-country initiative (25). For a same country, results obtained based on aggregated datasets (e.g., ECDC or WHO datasets) as done for these studies, may differ from those obtained from more detailed national datasets. COVID-19 BoD estimates based on the latter, have tended to yield higher BoD estimates than those based on European aggregated data (26).

As knowledge of COVID-19 evolved, so has the BoD COVID-19 disease model and disability weights of the European Burden of Disease Network protocol. To better assess the overall impact of COVID-19, BoD studies are now expanding to include long COVID-19. In addition, BoD studies measuring the effect of interventions and that unravel the indirect health impact of the COVID-19 crisis are needed and will contribute to future COVID-19 management and pandemic preparedness.

Table 3. BoD COVID-19 Studies; Source: Pires et al. Front Public Health 2022 (last updated: April 2023)

Country	Period of analysis	Long COVID included	DALY/100,000	% YLD
Australia	1 Jan - 31 Dec 2020	Yes, estimated	32.7	3.5%
Belgium	Mar 2020 - 31 Dec 2021	Yes	1,968	5%
Cyprus	9 March 2020 - 8 March 2021	N/A	1,881 YLL	NA
Denmark	28 Feb 2020 - 28 Feb 2021	No	520	1.6%
France	Jan - Dec 2020	Yes, limited	1,472	1%
Germany	1 Jan - 31 Dec 2020	No	368	0.7%
Ireland	1 Mar 2020 - 28 Feb 2021	Yes, estimated	1,033	1.3%
Malta	7 Mar 2020-31 Mar 2021	Yes, limited	1,086	5%
Netherlands	1 Jan-31 Dec 2020	No	1,570	1%
Scotland	1 Jan-31 Dec 2020	Yes, limited	1,770- 1,980	2%
Sweden	Mar 2020- Oct 2021	Yes	1,418	0.7%

Abbreviations: DALY, Disability-Adjusted Life Years; N/A, not applicable; YLD, Years Lived with Disability

Burden of VPIs in older adults: RSV

When considering the burden of infectious diseases in older adults, the heterogeneity of this sub-population must be acknowledged. Indeed, 'older adult' comprise individuals from a large age group with a heterogeneous risk profile and a broad frailty spectrum, from physical independence to institutionalisation.

RSV is a globally prevalent cause of respiratory tract infection. BoD data on RSV in adults are scarce compared to what is available for infants. Many cases, especially in primary care, may go undiagnosed due to a lack of incentive to diagnose RSV in the absence of specific treatments, the high cost of Polymerase Chain Reaction (PCR) testing, and the small window of opportunity for testing as viral loads rapidly drop. Moreover, the use of classical surveillance case definitions to capture cases (e.g., acute respiratory infection (ARI)) may lead to an underestimation of RSV burden in older, frail patients. Indeed, these patients often present with atypical symptoms, such as blunted or no fever, delirium, functional decline or falls rather than the classical clinical signs that are included in the case definitions.

Although RSV infections are often milder in the elderly compared to primary childhood infections, the virus can cause severe respiratory disease. Severe respiratory disease occurs in the most vulnerable, in those with increased frailty and immunosenescence, and/or with underlying comorbidities (chronic cardio-pulmonary disease, diabetes, severe immunosuppression). RSV-ARI incidence and hospitalisation rates are four-fold higher in older adults with comorbidities than in those without comorbidities, and the majority of RSV mortality in industrialised countries is found in those 65 years old and older (27).

Several RSV vaccines are now in phase 3 clinical trials, with first approvals expected in 2023 for the vaccination of older adults[3]. A snapshot of the RSV vaccine and monoclonal antibodies pipeline is available at www.path.org/resources/rsv-vaccine-and-mab-snapshot. With the arrival of these new RSV vaccines, RSV BoD research has been prompted. RESCUE (https://resc-eu.org/) is a public-private partnership, aiming to provide greater insights into the impact of RSV on health systems and societies throughout Europe. Amongst RESCUE's works, an international prospective study cohort to assess the community burden of RSV in older adults of 60 years and older was set up. Among 1040 participants with acute respiratory tract infection (ARTI) recruited across two seasons from three EU countries (2017-2018 and 2018-2019), 36 PCR-confirmed RSV infections were detected, with no death or hospitalisation among the confirmed cases (28). Authors concluded that RSV is prevalent in community-dwelling older adults and rarely causes severe disease. The same cohort was used to estimate average costs (29). Mean costs were lower per RSV episode than per influenza episode, but interquartile ranges largely overlapped and no formal statistical comparisons were made due to the small sample size. According to another RESCUE study, an average of 158229 (95%CI:140865-175592) RSV-associated hospitalisations occur each year among adults in the

[3] Since the Technical meeting, the first RSV vaccine has received FDA approval for use in adults 60 years and older https://www.fda.gov/news-events/press-announcements/fda-approves-first-respiratory-syncytial-virus-rsv-vaccine

EU - an estimation based on an extrapolation of data from six countries- with 92% occurring in adults ≥65years (30).

Several systematic literature reviews (SLRs) investigating the burden of RSV in older adults living in high-income countries have also been made in recent years. In a study by Nguyen-Van-Tam et al., RSV in adults 60 years and older caused 4.66% (95%CI 3.34-6.48%) of symptomatic ARI in annual studies and 7.80% (95% CI 5.77–10.45%) in seasonal studies (31). RSV-related case-fatality proportion was estimated at 8.18% (95% CI 5.54–11.94%), increasing to 9.88% (95% CI 6.66–14.43%) in high-risk groups. In a study by Savic et al., other measures of burden were used: RSV-ARI attack rates (1.62% [95% CI 0.84-3.08]), hospitalisation attack rates (0.15% [95% CI 0.09-0.22]) and hospital case-fatality rates (CFR) (7.13% [95% CI 5.40-9.36]) (32). In an SLR performed by Maggi et al., hospitalisation and mortality rates were similar between RSV and influenza, for which a high burden in older adults is well established (33). Other SLRs that have investigated RSV-associated hospital burden further differ in methods and measures, including case definitions, inclusion criteria, population, and statistical methods (e.g., adjustment for under-ascertainment), impeding comparisons between studies and making it still difficult to reach a comprehensive understanding of RSV burden in older adults (27, 34, 35).

Overall, although RSV burden in older adults is increasingly recognised, further BoD data and vaccine cost-effectiveness studies are needed.

Burden of VPIs in older adults: HZ

Varicella zoster virus (VZV) or HHV3 is a highly infectious herpes virus. Primary infection causes varicella, followed by lifelong viral latency within the host nerve ganglia. Reactivation of latent infection causes HZ disease or shingles. HZ can cause multiple complications, including post-herpetic neuralgia (PHN), a painful disease with a prolonged impact on QoL. Other complications include Bell's palsy, Ramsey-Hunt Syndrome, transverse myelitis, meningitis, encephalitis and ophthalmic involvement (36). HZ burden may go beyond acute disease complications and PHN, with evidence of increased risk of cardiovascular disease and stroke in the year following the disease (37-39). With the ageing of the population, the longer life expectancy and a parallel increase in the number of subjects with chronic diseases and immunosuppression, the burden of HZ is expected to increase. Currently, the lifetime risk of HZ in Europe is estimated between 23 and 30%, increasing to 50% in persons 85 years and older.

Two HZ vaccines are available: a live-attenuated herpes zoster vaccine (ZVL) and an adjuvanted recombinant zoster vaccine (RZV). ZVL has been evaluated as offering insufficient protection by several European NITAGs. In contrast, high efficacy of RZV has been demonstrated in two randomized clinical trials (RCTs), ZOE-50 and ZOE-70, with pooled-estimates of 91.3% efficacy against HZ in adults 70 years old and above and 88.8% against PHN. Long-term follow-up has confirmed safety and shown 84% efficacy against HZ five to seven years after the recommended two-dose vaccination schedule (40, 41). Multiple post-

marketing studies have since confirmed high vaccine effectiveness and a good safety profile other than short-term reactogenicity (42, 43). Additionally, a lower but substantial HZ vaccine efficacy estimated between 42.5 and 82.5% across underlying diseases was found in the RCT ZOE-HSCT for IC patients (autologous haematopoietic stem cell transplant recipients) [57]. Despite these results, only ten European countries have implemented HZ vaccination according to the ECDC vaccine tracker (Austria, Czech Republic, Estonia, France, Germany, Greece, Italy, Liechtenstein, Luxemburg, Spain), and not all offer national health system funding. The Dutch NITAG has also given positive advice for RZV based on local BoD studies (9, 12), high vaccine effectivity, cost-effectiveness and safety profile, but financial issues related to the high initial costs of catch-up campaigns have prevented its implementation so far.

In Italy, active and free offer of HZ vaccination for all 65-year-olds and for all 50- to 64-year-olds (in some regions from 18 year) with specific risk factors or comorbidities has been implemented. BoD data contributed to this policy. Based on outpatient data collected by a network of general practitioners from four regions, pre-vaccination HZ incidence in persons 50 years and above was estimated at 6.42/1000 person-year, with 75% of these patients having comorbidities. Rates of PHN were 22%, 12% and 2% respectively at one month, three months and one year after disease, comparable to other studies (44). Hospitalisation rates showed a 20-fold higher risk among subjects aged over 80 years and an 11-fold higher risk among 70-79-year-old subjects with respect to those aged less than 50 years (45). Additionally, the BoD of HZ in Italy was estimated at 49 million euros per year when considering both direct and indirect costs (46). So far, Italy's HZ vaccine programme impact on hospitalisation rates has been shown in the three-pilot regions where the programme was initially rolled out (47). Although clear vaccine coverage targets were set (50% by 2020), no national vaccine coverage results are available to date and increased awareness is warranted. In December 2023, the first AIB country meeting will take place in Italy where this and other adult immunization related topics will be discussed.

Burden of VPIs in younger adults: HPV

The Human Papilloma Virus (HPV) is the most widespread sexually transmitted infection. HPV infection causes a broad spectrum of disease, from asymptomatic infection to ano-genital warts, Juvenile Onset Recurrent Respiratory Papillomatosis (mother-to-child transmission), and cancers. HPV infection has one of the strongest associations with cancer, exceeding a relative risk of 500 between HPV and cervical cancer. The prevalence of HPV DNA in cervical cancer biopsies is as high as 99%, and HPV oncogenic types 16 and 18 are responsible for 70% of cervical cancer cases worldwide. Although cervical cancer is a rare outcome of extremely frequent HPV infection, it ranks as the fourth most common cancer in females, with a peak at 40 to 50 years old. HPV is also a relevant factor in other ano-genital cancers (anal, vaginal, penile and vulvar) and in 26% of oro-pharyngeal cancers.

Most burden of HPV infection and disease data are derived from the *Human Papillomavirus and Related Disease Report* of the Global Cancer Observatory (48). The report gathers country-

specific incidence and mortality rates. Importantly, coverage, methodology and quality of the data are highly variable across countries. Nonetheless, results show major health inequalities in terms of incidence and mortality of cervical cancer, with most cases occurring in low- and middle-income countries. Health inequalities are also found within Europe, with higher age-standardised incidence and mortality rates of cervical cancers in Eastern Europe than in Western Europe. Discrepancies in HPV prevention strategies such as cervical cancer screening and vaccination, are also present in the region. In 2018-2019, 87% of WHO Europe countries had an HPV national immunization programme, but with differences in recommendations, reimbursement and vaccine programme logistics. Seventeen countries had either no national recommendations or funding. Vaccine coverage rates varied from 4.3 to 99% (49).

The European region will have to considerably improve if we are to reach the targets set by the WHO Global Strategy towards the Elimination of Cervical Cancer (https://www.who.int/publications/i/item/9789240014107). Control targets for the year 2030 are threefold: 90% of girls fully vaccinated with the HPV vaccine by 15 years of age, 70 % of women screened with a high precision test at 35 to 45 years of age, and 90% of women identified with cervical disease receive treatment and care. These targets are set to ultimately reach 30% reduction in cervical cancer mortality.

The non-implementation and/or poor HPV vaccine coverage in certain European countries is striking when the positive impact of immunization on BoD both at the population and individual levels are now well established. Real-world evidence from Sweden has confirmed a substantial risk reduction of invasive cervical cancer at the population level after the introduction of national HPV immunization programme targeting adolescents (50). Inversely, the cost of HPV prevention inaction was shown in Japan, where a prolonged vaccine confidence crisis resulted in extremely poor vaccine coverage. The BoD consequences of this crisis have been modelled, and the 2013 to 2019 crisis is predicted to result in an additional HPV-related 5000 to 5700 deaths over the lifetime of cohorts born between 1994 and 2007.

Finally, the utility of the HPV vaccine may go beyond pre-exposure primary prevention. Benefits in sexually active women have now also been identified, such as the primary protection against HPV types not yet encountered and an increase in herd immunity. This has led to the Center for Disease Control and Prevention (CDC) extending its HPV vaccine recommendation from young adolescents to all individuals up to 26 years of age (https://www.cdc.gov/vaccines/vpd/hpv/hcp/recommendations.html). HPV vaccine has also been shown to have 80% clinical effectiveness in disease relapse prevention as an adjuvant additional to conisation for pre-cancerous lesions (51).

Burden of VPIs in travellers

In a recent SLR, the quality of VPI/VPD data in travellers residing in industrialised countries was rated as moderate (for high-incidence diseases) to low and very low, using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework (52). Indeed, there are many gaps in travel related VPI/VPD burden data, with no or limited data

on disease incidence and their denominators (abroad and upon return), on their outcomes (e.g. CFRs), and on vaccine coverage.

Faced with these gaps in data, the calculation of composite measures such as DALY or other SMPH is currently challenging, and selection of the most representative individual outcome measures to estimate burden is key. For example, the burden of rabies may be considered low if considering cases and mortality, with less than three rabies cases per year (53). Yet the number of potential rabies exposures, based on the number of post-exposure prophylaxis required (PEP), reflects a much larger health burden. Indeed, an average 474 PEP per year were recorded by the GeoSentinel network[4] between 2007 and 2018 (54), compared to 40 Typhoid fever cases and 21 Hepatitis A infections in the same period (55).

In a recent study by Steffen et al, COVID-19, influenza, dengue, yellow fever and rabies PEP were identified as the VPIs with the highest incidence rates in non-immune travellers. The VPIs with the highest CFRs included yellow fever, Japanese encephalitis, rabies, meningococcal disease, diphtheria, poliomyelitis and tetanus. Combining both measures, the current South American yellow fever outbreak presents a particularly large BoD (56).

Importantly, pre-travel immunization visits are a unique opportunity for catch-up of routine immunization in the EU, where Required (e.g., MenACYW for Hadj), Routine (e.g., DTaP, MMR or HPV) and Recommended vaccines are administered. Recommended vaccines will be based on four key criteria, in addition to special host factors: VPI's incidence rate abroad (incremental risk compared to home, estimated cumulative exposure), impact (death and sequelae; outbreak potential), financial aspects and legal aspects. However, a major challenge for the vaccination of travellers is the lack of uniform travel vaccine recommendations, with most countries using their own national recommendations. Differences in immunization practices may result from travellers' lack of confidence in the vaccines and their use, and public awareness regarding VPIs in travellers remains crucial.

Burden of VPIs in immunocompromised populations

The number of immunocompromised (IC) individuals residing in the EU is estimated at 14.5 million, and is constantly increasing (57). This population is an extremely heterogenous group, with multiple different causes of the immunocompromised state (inherited, acquired, treatment-related), and levels of immunosuppression that will vary over time (e.g., treatment modifications, disease progression). Immunocompromised hosts are at increased risk of contracting infectious diseases, of reactivation of latent infections, and most are at increased risk of severe infections. In addition, this population often cumulates other VPI risk factors such as multi-morbidity.

As with other populations, the choice of vaccinating an IC individual will be based on a positive benefit-risk balance assessment, that must consider the individual's risk of severe disease, the

[4] The GeoSentinel Surveillance Network (https://geosentinel.org/about) is an international clinician-based sentinel surveillance system, with a network of 71 specialized travel and tropical medicine sites across six continents, monitoring travel-related illness among international travellers and migrants.

person's expected vaccine response and protective effect, and any risks related to the vaccine. If toxicity data of vaccines in IC are quite robust, near to no 'real' vaccine efficacy data are available as this risk group is generally excluded from clinical trials. Vaccine efficacy in IC persons is generally extrapolated from surrogate endpoints, such as immune responses, and effectiveness is derived from real-world cohort studies.

Regarding safety, inactivated vaccines are considered safe, with no evident major risk of direct effects other than usual local and systemic side effects. Existing data suggest that the risk of immune-activation-related complications, such as graft rejection, graft versus host disease (GVHD), or exacerbation of autoimmune disease are very low with the exception of mRNA vaccines against COVID-19 for which several studies have shown a risk for development or worsening of GVHD (58-60). In contrast, live vaccines are generally contraindicated in IC persons, due to a risk, albeit low, of severe vaccine-induced disease, especially in patients with suppressed T-cell immunity.

VPIs/VPDs with the highest burden among IC patients are IPD (with a 4- to 20-fold higher risk in IC patients compared to immunocompetent persons (61)), Influenza, HZ and HPV. IC persons are at greater risk of severe influenza disease. In a large US cohort study of adults hospitalised with laboratory-confirmed influenza, IC patients had higher mortality, were more likely to require mechanical ventilation, and had a longer length of stay (62). Cohort studies have shown the benefits of influenza vaccination with a reduction in risks of infection and severity (progression to pneumoniae, ICU admission) in haematopoietic cell and solid organ transplant recipients (63-65).

With COVID-19, high mortality in IC patients was identified early in the SARS-CoV-2 pandemic, and IC patients received high priority for vaccination. Although T-cell responses could usually be mounted, decreased antibody responses to COVID-19 vaccines were found in IC patients, and an adapted primary COVID-19 mRNA vaccine schedule with an additional dose was recommended in many countries. In time, a reduction in COVID-19 morbidity and mortality has been observed in IC patients, probably due to multiple factors (variants, vaccination, therapeutic interventions) (66).

Despite the high burden of VPIs in IC patients, vaccine coverage remains strikingly low, and raising awareness and promoting vaccination among both patients and their caregivers is essential to reduce this immunity gap (67, 68).

4. How health burden estimates of adult vaccine-preventable infections shape national vaccination policies and practices and inform public health priorities

4.1. The translation of knowledge into action

Going from knowledge to action is a process to make research finding useful and accessible to the users. Each knowledge creation cycle is a comprehensive process, aiming to bridge the gap between the knowledge generator and the knowledge user. In the field of public health, knowledge translation is of particular importance, where research results are to be translated to multiple users (policymakers, general public, healthcare workers etc), with the final objective of reducing BoD.

When examining knowledge translation in the field of VPI/VPD burden, it may surprise that countries across the world make different vaccination decisions and implementation choices after reviewing similar data, as was exemplified by the COVID-19 pandemic. Using a mixed-method approach combining literature review and key informant interviews, Privor-Dumm et al. performed an archetype analysis of older adult immunization decision-making and implementation in 34 countries (69). The study investigated five domains of data collection: country characteristics, policies/decision-making, health/immunization systems, vaccination uptake, and stakeholders. Results showed that, although BoD data are central in decision-making processes, they are not necessarily the main drivers. Indeed, adult vaccine recommendations are driven by strong surveillance systems, economic data, health security issues, the existence of national healthy ageing policies and vaccine strategies for older adults, the presence of experts in adult immunization within the NITAG and the lack of stringent requirements for adoption. With regard to adult vaccine programme implementation and uptake, the identified facilitators were advocacy/influence of champions, vaccine access/reimbursement, centralised health system /vaccine delivery, equity focus, and use of vaccine coverage data/targets. The analysis concluded in four different country archetypes (Figure 5): (1) ***Disease-prevention focus*** **countries**, where local burden/impact data and processes are valued for decision-making (e.g., France, Germany, Netherlands), (2) ***Health security focus*** **countries**, where outbreaks, VPD threats and natural disasters are important drivers of country action (e.g., Italy, Greece),(3) ***Evolving adult focus*** **countries**, that share similarities with the disease-prevention focus countries but have weak to moderate decision-making processes (e.g., Belgium, Ireland, Spain) and (4) ***Child-focused and cost-sensitive*** **countries**, where no prioritised adult immunization programmes are currently implemented (e.g., Switzerland).

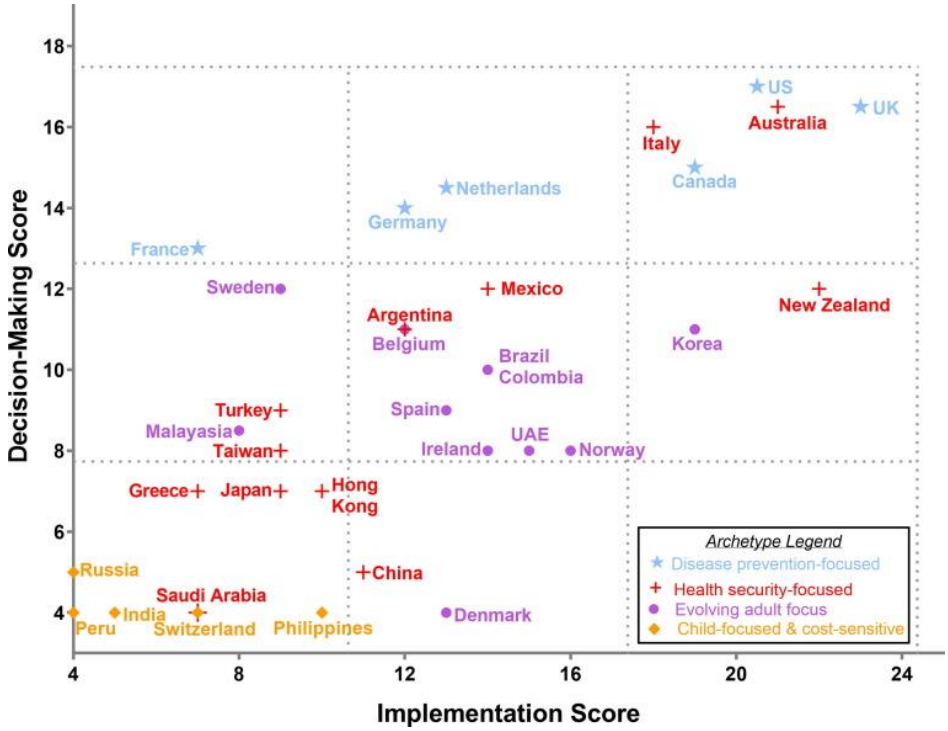

Figure 5 Country Score Plot and Adult Vaccine archetypes. Source: Privor-Dumm et al. Vaccine. 2020 (69)

Vaccine market access (VMA) frameworks also differ across countries, with different processes and stakeholders. Laigle et al. recently performed a comprehensive evaluation of the VMA pathways across EU27 and the United Kingdom, applying a mixed-method approach that combined literature review and expert stakeholder interviews (70). Key VMA steps identified were horizon scanning, NITAG recommendation, health technology assessment, final decision and procurement. Noticeably, time from licensure to population access was less than two years in seven countries, two to six years for ten countries and more than six years in nine countries. The main drivers of rapid VMA were BoD and vaccine benefit data (efficacy/effectiveness, safety, health economics), whilst barriers included budget limitations and complexity or unclarity of the VMA process. Proposed actions to improve VMA were identified by non-industry experts and are summarised in

Table 4 below. Overall, being timely, inclusive, consistent and transparent are the core principles for enhancing vaccine assessment and decision-making pathways, and there is a significant potential for alignment, collaboration, and improvement of VMA across the EU.

Table 4. Initiatives or actions to improve VMA. Source: Laigle et al. Vaccine. 2021 (70)

EU level • Improved collaboration to avoid duplication of effort and reduce time to vaccine access for local populations • Enhanced scientific activities and information sharing (e.g., literature reviews) • Joint HTA/clinical assessment and development of framework guidelines • Initiatives to address barriers such as limited research funding and lack of political or health authority support
Targeting NITAGs • Provision of formal early advice • Input of appropriate vaccine expertise • Formalisation of horizon scanning, definition of recommendation timelines, and prioritisation criteria to select in dossier
Targeting NITAGs and HTABs • Definition and standardisation of NITAG and HTAB roles and decision-making processes • Greater transparency in assessment and decision-making processes • Consideration of vaccination demographic effects, equity, country macroeconomic development, and increases in the cost-effectiveness thresholds for vaccines • Establishment of national public HTABs in charge of independent vaccine evaluations
Targeting vaccine industry/manufacturers • Early company engagement with vaccine assessment authorities • Early generation of evidence of vaccine effectiveness • Securing supply and stocks to avoid delay in the implementation of vaccination programmes following the final/local coverage decisions

Abbreviations: HTAB, health technology assessment body; NITAG, National Immunization Technical Advisory Group.

4.2. National Immunization Technical Advisory Groups

National Immunization Technical Advisory Groups (NITAGs) are national technical advisory bodies supplying guidance to national policymakers and programme managers on evidence-based immunization-related policy and programme decisions (71).

During the AIB technical meeting, representatives from four European NITAGs of different European subregions (Finland, Czech Republic, Germany, and Greece) described respective recommendation processes and how health burden estimates are used.

In Finland, the vaccination programme is national and centralised. Vaccinations within this programme are free-of-charge and voluntary. The Finnish NITAG uses a four-step approach when evaluating whether a vaccine should be introduced into the national vaccination programme: safety of the vaccine at individual level, safety effects on population level, expected public health benefit, and cost-effectiveness. Health burden estimates are needed for the assessment of the latter two steps. The current vaccines included in the Finnish vaccine programme can be found at https://thl.fi/en/web/infectious-diseases-and-vaccinations/information-about-vaccinations/vaccination-programme-for-children-and-adults. These vaccines are funded by taxes and procured through public tenders. An illustrative example of the importance of BoD monitoring, not only to guide recommendations for the implementation of a vaccine but also to monitor the programme's impact, is the

Finnish experience with pneumococcal vaccination. The successful introduction of the infant PCV10 vaccine programme in 2010 led to the near disappearance of vaccine serotypes, through direct and indirect vaccine effects (decrease of vaccine type naso-pharyngeal carriage, leading to the protection of unvaccinated children and herd immunity). However, as in other countries, vaccination pressure has resulted in pneumococcal serotype replacement, reducing vaccine effectiveness. In Finland, the burden of serotype replacement has been the highest in adults, particularly affecting the elderly population (72). With the availability and/or arrival of multiple PCV multi-valent vaccines (PCV10, PCV13, PCV15, PCV20), surveillance data on serotype distribution and serotype-specific invasiveness is crucial to guide and monitor PCV vaccination programmes.

The **Czech Republic's** NITAG was established in 2010. The exhaustive list of recommended vaccines can be found at https://szu.cz/tema/vakciny-a-ockovani/ockovaci-kalendar-v-cr/. Although many vaccines are recommended, not all are implemented into vaccine programmes. All mandatory vaccines but only certain voluntary vaccines are reimbursed. Currently, 11 vaccinations are fully reimbursed for all or at-risk adult populations: TBE, Tetanus, Flu, Pneumococcal, MMR, Men B, Men ACWY, Hib, rabies, and HBV. Local active and passive infectious disease surveillance systems are a base for the NITAG's decision-making processes. An illustrative example is TBE. Over the past decades, an increasing number of TBE cases have been recorded in the Czech Republic (73). The country is now one of the most affected in Europe, and the disease is considered endemic. Notably, TBE severity increases with age. So far, despite its recommendation in all age groups, TBE vaccination rate and adherence to the complete vaccine schedule has been low (38% in 2022, of which only 27% completed the recommended primary schedule and booster dose). In response to the growing epidemic, reimbursement of TBE vaccination in adults 50 years and older was introduced in 2022. Surveillance will show whether this policy will increase vaccine coverage and impact on the country's burden of TBE.

Germany's NITAG, STIKO, has a well-established methodology. Based on patient-relevant endpoints with regard to efficacy and safety, SLRs to gather evidence are performed using the PICO (Population, Intervention, Comparison and Outcome) approach and the quality of evidence is assessed using the GRADE framework. A risk-benefit analysis based on the overall quality of the vaccine efficacy and safety identified is made, taking also into consideration the burden of illness, population effects, cost-effectiveness, vaccine acceptance and modalities of integration into the vaccine calendar. Cost recovery is mandatory for a vaccine to be recommended, meaning that STIKO's recommendations result in reimbursed vaccine programmes. STIKO is composed of multidisciplinary honorary members that convene after vaccine licensure, and members with close relation to the product or industry are excluded from the vaccine decision-making process to ensure independent decision-making. This well-defined process with clear standard operating procedures has many strengths and allows yearly updated vaccine recommendations (STIKO website). It is, however, a high resource and time-consuming process, and some key VPIs are still lacking recommendations (Men B and

new PCV vaccines). STIKO's HZ vaccine recommendation is a good example on how BoD contributes to the recommendation process. RZV was introduced in Germany in December 2018, in all persons 60 years and above, and in persons 50 years and above with underlying comorbidities. This decision was based on national HZ incidence data showing an increasing trend in time and with age, on the estimated relative risk of HZ by comorbidity in Germany, on a modelling exercise showing a positive impact of vaccination on the HZ burden in Germany, and a cost-effectiveness assessment.

The example of implementation of the HZ vaccine recommendations was also used to illustrate the NITAG process in **Greece**. Limited local HZ disease burden data were available (one tertiary care cross-sectional study from 1955 -2002, a 2 year prospective surveillance study by a GP surveillance network on the island of Crete and a study of HZ incidence in post -kidney transplant recipients (74-76)). This data was complemented with a literature review of vaccine effectiveness and safety studies, the immunization guidance of neighbouring countries and various cost-effectiveness assessment including STIKO's, showing the possible support of smaller NITAGs by larger structures. RZV was recommended in IC patients of 60 years and above, as well as in IC patients of 18 years and above with recurrent episodes of HZ. ZVL was recommended in other patients. These NITAG recommendations were later challenged for not being fully in line with the American ACIP/CDC guidance, illustrating one of the obstacles to the adoption of national-based recommendations (77).

5. Current vaccine-preventable infection health burden evidence to provide a convincing case for strengthening adult vaccination in Europe

VPI and VPD health burden evidence is being generated in Europe and used to shape and strengthen adult vaccination strategies. Moreover, initiatives for standardisation of methods, resource sharing and collaborations are ongoing. Yet data gaps remain, particularly for certain pathogens, risk groups, and/or subregions. Burden of disease opportunities, challenges and strategies to move forward, as identified during the meeting's presentations, exchanges, and focused group discussions, are summarised in

Table 5 below.

Table 5. Health burden of VPI and diseases: challenges, opportunities, and improvement strategies identified by the AIB

BoD Opportunities	BoD Challenges	Improvement strategies and ongoing initiatives
Ranking diseases in terms of their burden can guide national policymakers and help prioritise and evaluate interventions (e.g. vaccination programmes). **Collection of high-quality BoD data can increase our actionable knowledge.**	**Lack of standardisation** of methods in BoD studies limits **comparability and interpretation** of results.	**Harmonisation** of methodologies and use of **standard protocols and reporting guidelines.** Standardisation initiatives are ongoing by the European Network of Burden of Disease.
Summary measures of population health such as DALYs integrate multiple outcome measures.	**Extensive data requirements and important resources needed** (funding and capacity). Current BOD estimates have wide uncertainty intervals. **Not all BoD can be accounted for** (e.g., loss of independence in older adults) and focus on health dimension has its limitations.	**Collaborative and comprehensive platforms** to build on existing initiatives, with capacity building and resource sharing, and prevention of parallel and overlapping initiatives. Collaborative platforms and initiatives include BCoDE (currently inactive) and VITAL.
BoD indicators can be useful for monitoring within and across-country public health in both non-pandemic and pandemic situations.	**Differences across European countries** (data sources, data collection, case definitions, geographical and socio-economical settings, healthcare organisation and clinical practices) make comparable burden estimates challenging to generate.	European strategies, albeit adapted to the country's reality, to standardise and harmonise data collection and analysis methods. Surveillance standards have been published by the WHO and harmonised protocols and case definitions are proposed by the ECDC.
BoD estimates are used to generate VPI epidemiology, vaccine effectiveness and vaccine cost-effectiveness data that inform NITAGs and the decision-making process and ultimately vaccine market.	**Sub-optimal registration records and surveillance of infectious diseases**, including underreporting, under-ascertainment and insufficient data quality and processing, exists in many countries. **BoD data gaps for key pathogen (e.g., RSV)** and risk groups (e.g., older adults, IC, travellers). **Lack of vaccine coverage data and/or targets** in vaccine programmes.	**Improve routine registration records and surveillance of infectious diseases**. Develop studies to correct for underreporting of targeted VPIs. Raise awareness among policymakers of the potential of BoD studies and emphasise pandemic preparedness. Leverage COVID-19 capacities. Investment in data linking (e.g. EHDS).
To make a convincing case for adult vaccination, BoD results are to be effectively translated into policymaking.	BoD data are **complex to communicate** to a broad array of stakeholders. BoD are **not the only driver in the decision-making process** nor vaccine recommendation.	**Improve result delivery to the political pathway** and connect with political agenda. Adapt BoD translation and communication to the data user (e.g., Ministry, NITAGs). Integrate with other policymaking drivers (e.g., Health economics).

Abbreviations: BoD, Burden of Disease; BCoDE, Burden of Communicable Diseases in Europe; DALY, Disability-Adjusted Life Year; ECDC, European Centre for Disease Control; EHDS: European health data space; IC, immunocompromised. NITAGs, National Immunization Technical Advisory Group; RSV, Respiratory Syncytial Virus; SMPH, Summary Measures of Population Health; VITAL, Vaccines and InfecTious Diseases in the Ageing population; VPI, vaccine-preventable infections; WHO, World Health Organization.

6. Conclusions

High-quality burden of VPI data is key for evidence-based vaccine-policymaking and help prioritise and evaluate interventions. Ideally, SMPH such as DALYs, that integrate multiple measures are to be used. However, these comprehensive measures require extensive data collection with standardised methodology and, consequently, important human and financial resources.

Several European initiatives promote health BoD standardised methodologies and/or capacity building collaborations that are to be further built upon. Nevertheless, BoD estimates will only be as good as the data inserted into the models. As such, efforts to harmonize and improve the quality of Europe's underlying VPI surveillance are equally fundamental. Political support will be needed to move forward on this path and raising awareness on the full potential of independent health BoD data and its core value for pandemic preparedness, is required.

The improvement of the quality of data sources and BoD estimates is a continuous process. Meanwhile, the absence of national high-quality BoD data should never hinder the endorsement of immunization/vaccines. Although country-specific data are best to underpin national recommendations, BoD evidence from similar demographic or socioeconomic conditions and/or mathematical models may be used as proxy evidence (78). These alternative data sources should be accorded significant importance, outweighing the absence of certain data and erasing any justification for postponement.

Importantly, even high-quality BoD estimates will have limitations that are to be considered when interpreting results. The comprehensive interpretation of BoD estimates always requires strong knowledge of the methodology, the study setting, and the surveillance systems behind the data-sources. An illustrative example is the implementation of an improved or broader surveillance system after the initiation of a vaccine programme. This may lead to an increase in BoD related to better case-detection, masking the true impact of the vaccine introduction.

Historically, vaccine programmes have focused on preventing disease in children. Now, the paradigm is changing, and vaccine programmes are evolving into lifelong strategies, with vaccines specifically indicated in adults. Nonetheless, the availability and quality of adult BoD and vaccine coverage data varies by pathogen (e.g., RSV) and adult sub-population (e.g., IC and travellers), with remaining gaps and major geographical differences.

Geographical differences and inequalities are found at all levels of adult immunization in Europe. Differences exist in surveillance strategies, recommendations, decision-making processes, vaccine implementation strategies and funding, and ultimately vaccine uptake. Moreover, lack of clarity around the rationale for inter-country differences in vaccine recommendations may in turn affect vaccine confidence. Therefore, despite intrinsic differences, standardization of approaches and/or improved education and communication

strategies would be highly valuable and could increase public confidence in local vaccine recommendations.

Finally, to strengthen adult vaccination in Europe, BoD must be effectively translated into action. Communication tailored to the different stakeholders is needed, with improved delivery of results and connection to the political pathway and agenda. A comprehensive strategy, using both BoD and other drivers of decision-making (e.g., economic data) is necessary if we are to provide a convincing case for adult vaccination.

Key points

- Health BoD data is essential for evidence-based vaccine-policy decision-making and for the monitoring of interventions (e.g., vaccination programmes).
- Harmonization of BoD methods is necessary to allow comparability and interpretation of results across studies.
- Health burden studies are resource demanding and require extensive high-quality data: efforts to improve Europe's infectious disease surveillance and collaborations offering both capacity building and cost-sharing should be further promoted.
- Geographical differences and inequalities are found at all levels of adult immunization in Europe (e.g., in surveillance strategies and data collection, data quality, vaccine recommendations and uptake) and are to be considered when interpreting BoD results.
- The communication of VPI health BoD is to be tailored to each stakeholder (ministry of health, NITAG, healthcare workers, general population) and combined with other drivers of political decisions (e.g., health economics) to ensure effective translation into vaccine policy.

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