



Assessing the health burden of vaccine preventable infections in European Adults: challenges and opportunities

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DISCLAIMER

“If you want me to give you a two-hour presentation,

I am ready today.

If you want only a five-minute speech,

it will take me two weeks to prepare.”

Mark Twain

Meeting objectives

1. To discuss the methodology and challenges in calculating the health burden of adult VPIs (focus on Europe)
2. To provide an overview of current vaccine-preventable infections (VPIs) in the adult population (≥ 18 years of age)
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



1. To discuss the methodology and challenges in calculating the health burden of adult VPIs (focus on Europe)

Methodology in calculating the health burden

Burden of Disease

- **Hundreds of Infectious diseases are relevant to (adult) health**
 - Ranking required, for policy making and prioritization of interventions, based on “impact/importance”
- **How to define the “Impact/importance” of the disease?**
 - Many ways to look at this question, surprisingly complicated answer
 - Multiple dimensions: physical state, psycho-social well being, socio-economic
 - The selected dimension will influence your conclusions

Health Burden of disease

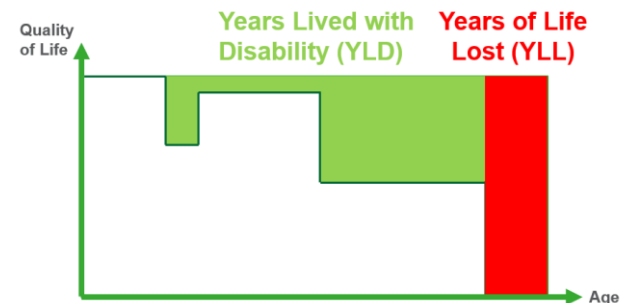
- **Multiple measures:**
 - n° cases, n° of deaths, severity (QoL, sequelae, residual life expectancy)
 - Infectious diseases have heterogeneous clinical courses (e.g. Norovirus versus Listeria)
- **Need for summary measures:** Summary measures of population health (e.g. DALY)

Summary measures of population health

	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

Disability-Adjusted Life Years (DALY) : 1 DALY = 1 healthy life year lost

- Morbidity + mortality; disease severity + occurrence
- Years Lived with Disability (YLD) + Years of Life Lost (YLL)
- Population level DALY and Individual DALY



Summary measures of population health

(DALY) Methodological considerations / challenges:

- **Incidence-based (future health loss due to current exposure; approach for disease prevention/control)** vs. prevalence- based (current health loss due to past exposures ; health care burden)
- **Normative assumptions** (e.g. disability weights, life expectancy)
- **Disease model :**
 - Outcome trees: schematic representation, includes acute disease and sequelae, distinguishes health states, quantify transition probabilities and durations
 - Points of interests: **Hazard-based, pathogen-based** (vs outcome-based; risk factor based);
- **Multiplication factors** for *underreporting* and *under-ascertainment*
 - *Importance of transparency on data + methodology choices made and standardization to compare results*

Burden of disease: initiatives in Europe

BoD studies in WHO European Region *M Donovan (unpublished)*

- Combination of 4 papers on BoD → 428 papers (1997-2022)
- 128 were multi-country; 104 in the Netherlands
- Variety in methodological choices: 89% use DALYS, 73% do own BoD calculations, secondary GBD results are increasing in time

Systematic (literature) review *Charalampous et al. Epidemiol Infect. 2023*

- 105 Burden of infectious disease studies identified in Europe and the UK (2000 to 2022)
- Most studied Food and Waterborne infectious diseases
- BoD of VPIs : **only 11 studies** (Netherlands n=7) (*COVID-19 was separate category*)
 - Most frequently: Influenza, TBE, measles, hepatitis B, pertussis, IPD, HZ
 - Few studies have estimated the burden of VPD among (young) adults
- 97% used incidence- and pathogen- based approach; but notable differences in methods regarding disability weights and life tables

Need for guidelines →



Burden of disease: initiatives in Europe



European Burden of Disease Network (COST action)

- **Publication of protocol** for COVID-19 BoD country studies: data requirements, standard methods and how to communicate results
- BoD COVID-19 studies in 10 EU countries → comparable estimates thanks to network
- High heterogeneity despite standard methodology :
National burden from 32 to 2000 DALYs/100 000 inhabitants
 - Reflects local (data) management → Standardize method but also know the data you use
- Consistent large contribution of mortality to the COVID-19 burden (between 95 and 99%)

Burden of COmmunicable Diseases in Europe project (BCoDE; RIVM, ECDC, ...)

Tool-kit : *Computational model that brings together the different outcome trees*

- DALY, incidence-based approach, disability weights assessed in 4 European countries (ECDC and IHME funded project)
- 31 EU+EEA countries, 32 infectious diseases + 6 healthcare associated syndroms
- Input: Incidence, multiplication factor ; Outputs : DALY, ranking of diseases, uncertainty bound
- Runtime 2009-2013, spin-offs continue: National annual updates and reports in Netherlands; publications on burden before and after vaccination programs

Burden of disease: initiatives in Europe

VITAL : Vaccines and Infectious Diseases in the ageing population



- IMI project. WP-1 Burden of diseases in aging adults (50+)
- **Which infections to study?** Short list (WHO summary, relevance, vaccine at least in Phase II)
→ Data gaps (survey to participating country experts and literature review on BoD and AMR to identify) → **ExPEC and Pneumococcal pneumonia**
- **Next Objective:** Estimate the burden of these 2 pathogens using composite measure of Burden : DALYs. **Pilot :** Denmark + Valencia - experience in real world data studies and quality health registries **Retrospective cohort study, 50y+ in region, 2010-2018**
- **Epidemiological challenges :** Case definition (Regional variations in ICD-10 codes), differences in clinical practice and Health care organization

European Health Data Space (EHDS) :

- Neutral, not for profit body, bringing stakeholders together to co-create solutions for:
 - the capture and sharing of better-quality health data
 - its trustworthy use for smarter health care and efficient research
- Primary use (patient care): data quality, citizen right to request and receive a consolidated view of their health- then secondary data use at EU level (PH) with patient consent

Burden of disease initiatives: beyond Europe

Global Burden of Disease

- 30 years experience, core principles
- Dataverse
- Main lessons learned →

Ten big lessons learned during 30 years of GBD

- 1 The importance of standardization
- 2 The value of data sources
- 3 The role of modelling
- 4 The importance of uncertainty
- 5 The value of transparency
- 6 The impact of interventions
- 7 The need for regional/country-level analyses
- 8 The strength of multidisciplinary collaboration
- 9 The role of advocacy
- 10 The need for continuous improvement



Trends in VPIs in WHO European region:

- Still substantial burden of HPV; Increasing trends in Herpes Zoster
- Reduction in burden of pneumococcal, meningococcal and hepatitis B
- Differences between Eastern, Central and Western Europe

AMR in WHO European region:

- Deaths associated and attributable to AMR: Str. Pneumoniae was in 4th place
- Correlation between existence of National AMR action plans and lower burden of AMR
- Estimating BoD by pathogen : combining approaches – GBD (based on underlying cause of death) and AMR (pathway to death framework – events included if pathogen on pathway to death)

Burden of disease initiatives: beyond Europe

BVPF project: Burden of Preventable Diseases, Australia

- *Burden of 17 VPIs (+ RSV and Q Fever);* incidence-based approach, BCoDE, models adapted to suit Australia
- From 2005 to 2015: drop in BoD of VPIs : TOP 5 remain the same but change in ranking: HPV, pneumo, meningo, shingles, Influenza (lead in 2015, low VC)
- **Impacts related to vaccine programs**
 - **HPV, IPD and rotavirus:** drop in BoD in vaccine targeted groups
 - **Zoster:** burden increase since 2005, mainly in elderly → 2016 : drop in burden in 70y+ since vaccine introduction
 - **Influenza:** Burden varies substantially depending on seasonal subtype. Increase may be linked to changes in reporting in testing strategy

ONBOIDS: Ontario Burden of Infectious Disease Study, Canada

- 51 distinct pathogens, 16 syndromes, 10 disease groups (using data 2005-2007)
- HALYs (health-adjusted life years); in-house severity weights
- TOP 5 pathogens (3 VPIs; 3 Cancer-causing) : HCV, Str. pneumoniae, HPV, HBV, E. Coli
- Sensitivity analysis with DALY: Overall ranking similar. Proportion attributable to death (YLL) was different - 82% for HALYs and 48% using DALYs → **importance of method used**

Burden of disease : Challenges

- A DALY is not a DALY :
 - Different methodological approaches affect comparability and interpretation of results
- Huge data requirements :
 - “One BoD study is enough in a lifetime”
 - Know your data
- Pathogen/infectious disease-specific challenges
 - E.g., HPV infection largely asymptomatic. Incidences underreported
 - E.g., Seasonal Influenza change BoD
 - E.g., COVID-19 or Str. Pneumoniae: differences in local (data) management
- Other challenges :
 - Not all BoD can be accounted for e.g., loss of independence in elderly
 - Exclusively looking at health-dimension



2. To provide an overview of current vaccine-preventable infections (VPIs) in the adult population (≥ 18 years of age)

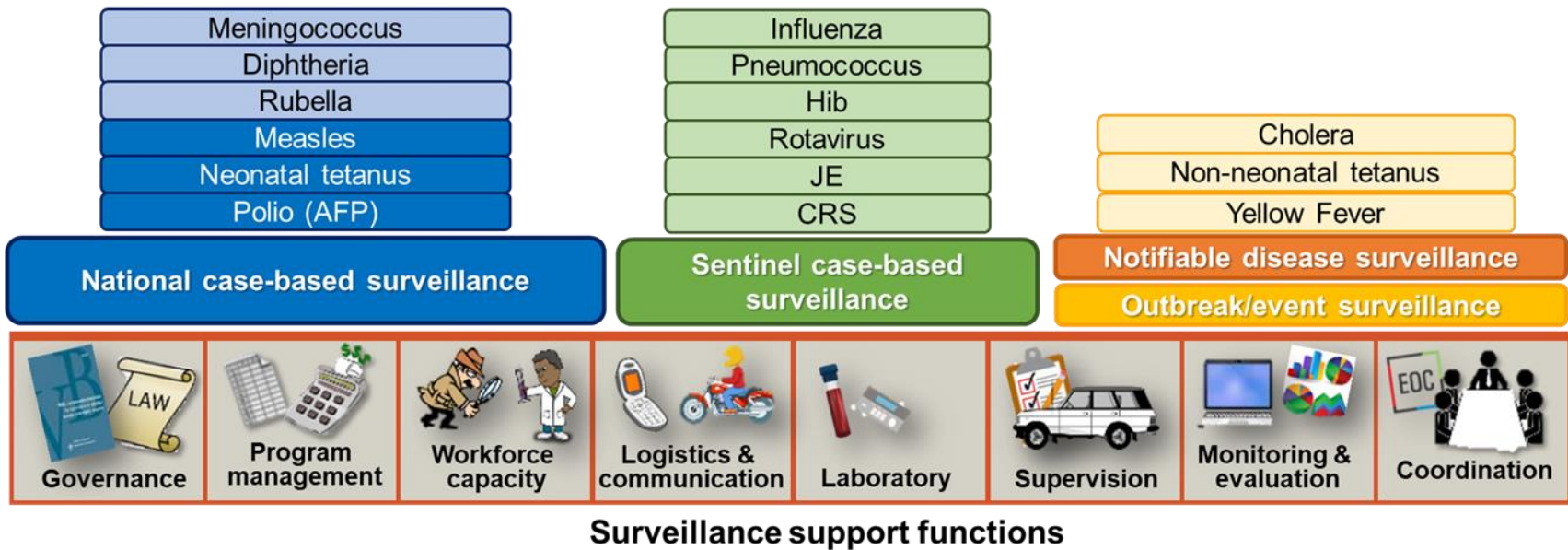
Overview of current adult vaccines (Europe)

Overview of current adult vaccines (>18y)	
Vaccines for adults who meet age requirement	COVID-19
	Influenza
	Pneumococcus
	RSV (<i>if licensed</i>)
	Tdap
	Zoster
Missed vaccines (e.g. childhood/adolescence)	e.g. HPV, MMR(V)
Personal risk-based vaccines*	e.g. Ebola, HBV, Hib, HPV, Influenza, MenACWY, MenB, Mpox, pneumo, TBE, Zoster
Travel-based vaccines	e.g. Cholera, Dengue, HBV, JE, MenACWY, MenB, Polio, Rabies, TBE, Typhoid, YF
Occupational-based vaccines	e.g. HAV, HBV, Influenza, TBE, HAV

Personal additional risks can be due to for example: life style, medical conditions and other indications
Please note that the vaccine landscape is dynamic (situation May 2023) and that this is a DRAFT overview - a final version will be published in the meeting report

Immunization Agenda 2023 : WHO surveillance guidelines

- IA 2030 envisions WHO supporting a global system of **comprehensive** VPD surveillance (VPDS) across Member States ; evolving from a historical vertical programs (polio, measles)
- To help countries generate data (for action) and monitor VPD trends globally
- To set (minimum) VPD surveillance standards. Tailored to pathogen and country



Epidemiology and health burden of selected adult VPIs

RSV vs INFLUENZA BURDEN

- Several RSV vaccines in phase 3, expected FDA approval in Q2 2023 for first vaccines in elderly
- Heterogeneity of older individuals (frailty spectrum) and risk of underestimated ILI rates (atypical first symptoms e.g., delirium; fall with fracture)
- **RSV 4-fold higher incidence and hospitalisation** in adults with comorbidities → RSV affects the most vulnerable, highest risk of severe disease in frail patients
- **BoD of RSV in adults? Systematic literature reviews : RESCEU, JnJ, GSK, Pfizer ...**
 - Different terminologies, different measures (attack rates vs ARI incidence; hCFR vs case fatality proportion; additional adjusting) → BoD is thus still unclear in adults + almost no data in pregnancy
 - **Prospective RESCEU cohort:** 3 EU countries and 2 seasons : Mean costs lower for RSV than Influenza, but IQR overlap (N=36 RSV; 59 Influenza) ; Health-related quality of life: QoL impact may be lower for RSV, to be confirmed
 - **Maggi et al Vaccines 2022** . Concluded that rates of hospitalization and mortality is similar between RSV and influenza in older adults

Epidemiology and health burden of selected adult VPIs

Herpes Zoster *(*only recommended by 8 EU/EEA countries, of which 2 without NHS funding)*

ITALY :

Outpatient, 50y+ : 6.42/1000 person-years; **75%** had comorbidities ; **PHN** at 1m 22%

Hospital data 2003-2018 : Decreasing trend over time in hospitalization rates, but increase in case fatality rates and length of stay → restriction in hosp. criteria rather than reduced BoD

Context : 99% population is VZV seropositive = at risk for HZ; ageing population (47.4% are 50y+)

- HZ vaccine* recommended and free of charge in 65+ since NIP 2017-2019; special risk groups 50-64y
- Autonomous regions handle vaccinations, with adapted indications
- Vaccine coverage currently unavailable (targets are set). Increased awareness required

Epidemiology and health burden of selected adult VPIs

HPV

- Most widespread STI - RR >500 with cancer – one of the strongest associations in Epidemiology
- Cervical cancer is a rare outcome of HPV infection - HPV cervical cancer: remains 3rd in young adults in Europe (Peak 40-50y), inequalities across the global incidences and mortality (Health inequalities)
- HPV and Related Disease Report (Global Cancer Observatory) : country-specific; limited coverage and accuracy of cancer data in LMIC: Methods are diverse > Quality of data varies from one country to another
- Proof of effectiveness e.g., data from Sweden: incidence rate ratio: VE 88% prevention of cervical cancer
- HPV immunization in EU: recommendations in 87% of countries (some only in girls, funding discrepancies). Western vs Eastern Europe
- Global strategy for elimination of cervical cancer : 2030 - 90% vaccinated, 30% reduction in cervical cancer
- Catch-up programs: WHO: Support Extension of vaccination to 26y
- Vaccination after treatment → Disease relapse prevention?
- **Cost of Inaction** - Japan : crisis in vaccine confidence -rumors-coverage dropped to 0% in 2000 cohort- BoD consequences

Epidemiology and health burden of selected adult VPIs

Specific groups

- Travelers:
 - GRADE assessments: moderate to low levels for incidence, indication of vaccines
 - Lack of data: what happens abroad, what occurs when they return? Underreporting? Outcomes? Cohort studies are illusionary
 - Health BoD in travelers: high for COVID-19, influenza, dengue and YF (Now outbreak Brazil); Hep A + Typhoid fever went down (hygienic conditions)
 - Impact of VPIs : Japanese encephalitis, Rabies, meningo, polio, dengue
 - Opportunity for routine immunization : catch up MMR, HPV or TBE (EU specificity vs USA focus on travel vaccines)
 - Lack of uniform travel vaccine recommendations → may lead to lack in confidence

Epidemiology and health burden of selected adult VPIs

Specific groups: Immunocompromised

- Approx. 8 million in EU, **increasing, heterogenous group**, varies over time, multimorbidity
- Increase risk in contracting ID, reactivation of latent infections, increase of severe infections
- **Almost no true efficacy data in IC** (*excluded from clinical trials*)
- Safety: Live vaccines: contraindicated; Inactivated = safe (local and systemic side effects may be lower in ID; risk of immune activation complications?? (graft rejection, exacerbation of AI disease)
- **Challenge - Compliance! Vaccine coverage low in immunocompromised**
- Most important VPI:
 - **Influenza:** higher mortality, longer mechanical ventilation, longer loss. Vaccine efficacy-data limited, but clinical protection despite poorer immune response (cell-mediated immunity?)
 - **Pneumococcal:** 4-20 fold increase
 - **COVID-19:** few clinical trials (often excluded) – less Ab response but vigorous T-cell response; reduction in morbidity and mortality in these patients (variants, vaccination, therapeutic)
 - **ZV:** Recombinant zoster vaccine: Randomized Clinical Trial; with VE in IC, but breakthrough infections
 - **HPV:** immunization of serological positive patients for prevention of cancer?



3. For theory to practice: how health burden estimates of adult VPIs shape policies, practices and inform public health priorities

How health BoD estimates of adult VPIs shape policies, practices and inform public health priorities

- **Knowledge Translation** : process to make research finding useful and accessible to the users → knowledge creation cycle needs to be looked as a whole, bridge the gap between knowledge generator and the knowledge user → key in Public Health, objective of reducing BoD

- **Archetype analysis of older adult immunization decision-making & implementation:**
Countries look at similar data yet end up with very different results/implementation

- Analysis across 34 countries for Influenza, pneumococcus and HZ, in 50y, across 5 domains
- 4 Archetypes - Focus: disease-prevention, health security, evolving adult, child/cost-sensitive
- Countries **make decisions differently** (politics and competing priorities); **Uptake** is influenced by public knowledge and perceptions, acceptance of mandates, AND access; **Financing** makes a difference – where vaccines are publicly funded, uptake is higher

- **Vaccine Market access** : see later “challenges”

NITAGs :

The Netherlands: Health Council: 2nd advice requested for recombinant zoster vaccine

- For their advice, **disease burden** (PNH), **high vaccine effectivity** (efficacy and including in immunocompromised and in longer term), **safety** (short term side effects; communication), acceptability, **Cost-effectiveness** (Study from Netherlands, review of publications in past 5y)
- Conclusions: positive advice in 2019 by Health Council: 60+ and catch-up campaign, but implementation still pending (COVID-19 pandemic, cost of catch-up vaccinations → >60y)

Finland:

- Centralized decision, Public tenders, Vaccine free of charge
- 4 most important decision: Expected PH benefit : BoD + VE, Assess safety : individual and population level, Cost-effectiveness : limited resources in health care
- Health BoD: key in decision of benefit → Register-based surveillance – THL
- E.g., Pneumococcal: in Finland, the childhood vaccination program impacts elderly (serotype replacement!)

NITAGs :

Republic Czech Rep :

- TBE, Pertussis, pneumococcal, meningo and HZ: BoD and changing epidemiology impact NITAG recommendations
- TBE: increase number of cases in time, Increasing severity with age. Now one of most affected in EU, endemic. But low coverage around 38% (even lower for complete vaccination). Since Jan 2022, reimbursement - impact to be seen

Germany

- STIKO methodology described, strengths and some limitations highlighted
- E.g. of Herpes Zoster: BoD and German epidemiology data: increasing trend in time, and with age; calculations of RR by comorbidity based on German data to identify risk groups; needed for modelling of impact of vaccine

Greece

- Challenge for local data
- Use of neighboring country outputs e.g. Cost effectiveness STIKO



4. To evaluate current VPIs health burden evidence to provide a convincing case for strengthening adult vaccination in Europe

Challenges related to VPIs and their vaccines (adults)

Differences across Europe

- In **epidemiology and surveillance strategies**
 - e.g. HPV-related cancer
- In **recommendations (adults, travel)**
 - loss in confidence
- In **decision-making process**
 - different archetypes; process vs adult vs health security vs economical driven)
 - how data is used
- In **implementation, funding/reimbursement, vaccine registries**
 - sub-national differences
- In **vaccine coverage (booster COVID-19)**
 - multifactorial : individual communication, “tradition”, literacy, trust, logistics, financial
 - importance of transparency, trust, champion, community outreach
- In **vaccine market access**
 - time from authorization to NITAG, from NITAG to funding and to population access
 - time to population access : 9 countries > 6y

Challenges related to VPIs and their vaccines (adults)

- **Need for more comprehensive approaches for life-long vaccination**
- **Persisting low vaccine coverage:** MMR (dose 2); Influenza ; programs disrupted by COVID-19 ; Immunocompromised; Pertussis in pregnancy; TBE in endemic setting
- **Gaps in data:** Disease-specific (e.g. RSV in adults); risk groups (e.g. pregnancy, immunocompromised, travelers)
- **Need for better vaccines:** e.g. Influenza
- **COVID-19 tools, will they be leveraged?**
- **Blind spots:** education, communication, digital → Knowledge to Action: make research finding useful and accessible to the users
- **Political support**
- **Budget unavailability, lack of specific research funding**

The way forward

- Use of the group discussion outputs
- Objective 4: “To evaluate current VPIs health burden evidence to provide a convincing case for strengthening adult vaccination in Europe”: still work to do to meet this objective

What are the 3 key challenges in calculating the health burden of vaccine-preventable infections in adults?

1. There is a need for a consensus on which data to use to calculate BoD, which measures of BoD should be used and which methods we should use to calculate them. This also apply to specific settings (e.g. nursing homes) or specific age groups.
2. Lack of centralization and resources (e.g. budgeting) for all the European countries
3. Lack of collection and access to high quality data

Working group 1 **What are the 3 possible strategies to address these challenges at (sub)national and European level?**

- Set up European strategies (adapted to the country reality, when possible) to standardize and harmonize data collection and analysis methods to allow comparisons within and between countries, to be then used by each country/NITAGS for specific calculations. It should be clear and stated what the data will be used for. This could be centralized by ECDC as an example.
- Good routine surveillance and follow-up should be integrated
- Find a specific platform (build on what already exists e.g. temporary projects) for experts to interact and share experiences in order to avoid repetition of exercises and therefore join forces

Working group 2

What are the **3 key challenges** in calculating the health burden of vaccine-preventable infections in adults?
What are the **3 possible strategies** to address these challenges at (sub)national and European level?

Challenges

1. Suboptimal surveillance

- Paucity of surveillance data or/and syndrome data, particular LMIC
- Lack of data to compare vaccinated and non-vaccinated populations
- No real-time surveillance

2. Underreporting of specific diseases

3. Lack of advocacy strategy to policymakers – reflected in lack of funding and capacity to conduct BoD studies

Strategies

1. Improving surveillance

- Develop studies to correct for underreporting for targeted VPIs (e.g. RSV)
- Link databases (e.g., vaccinated, non-vaccinated; different sources)

2. Standardized protocol for BoD calculations

3. Raise awareness to the potential of BoD estimates- present it as a win-win situation for policy makers

Working group 3



What are the **3 key challenges** in translating the health burden of adult VPDs into shaping adult vaccination programme?

What are **3 possible strategies** to address these challenges at sub(national) and European Level?

Lack of reliable data

Nationally need to priorities local data collection to support local decision makers : healthcare utilization, consequences etc

Quality reporting/surveillance system and analysis capabilities

Building modelling capabilities to show local impact



Need for different decision making processes locally

Some consistency on factors NITAGs consider e.g. burden of disease and effectiveness of vaccine while recognizing differences needed

Consider direct and indirect costs (can be difficult to quantify but think broader on society/ impact on frailty in OA)

Tailored strategies to local need e.g. tackling vaccine hesitancy



Fractured /regional differences on key areas

Coordinated regional capabilities (e.g. analytic capabilities) lead by centers of excellence

Coordinated vaccine procurement- equitable prices and access

EU funding for implementation studies- building the evidence base on effectiveness and impact – expand to other VPD beyond respiratory

Working group 4

What are the **3 key challenges** in translating the health burden of adult VPDs into shaping adult vaccination programme?

What are **3 possible strategies** to address these challenges at sub(national) and European Level?

Challenges

1. Dissemination of information/Communication :

- must be delivered and implemented in different ways depending on the group you are talking to : focus adapted when addressing NITAGs , Ministry or Public (and its subgroups)

2. Lack of support to decision-making groups (e.g. NITAG)

- e.g. strengthened surveillance needed

3. Implementation and operational pathway

Strategies

Work on decision-making groups :

1. Pressure for vaccine introduction

2. Emphasize on preparedness

3. Increase vaccine acceptance

- studies to identify vaccine acceptance barriers
- Deliver results to political pathway and connect with political agenda



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Feedback welcome!

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