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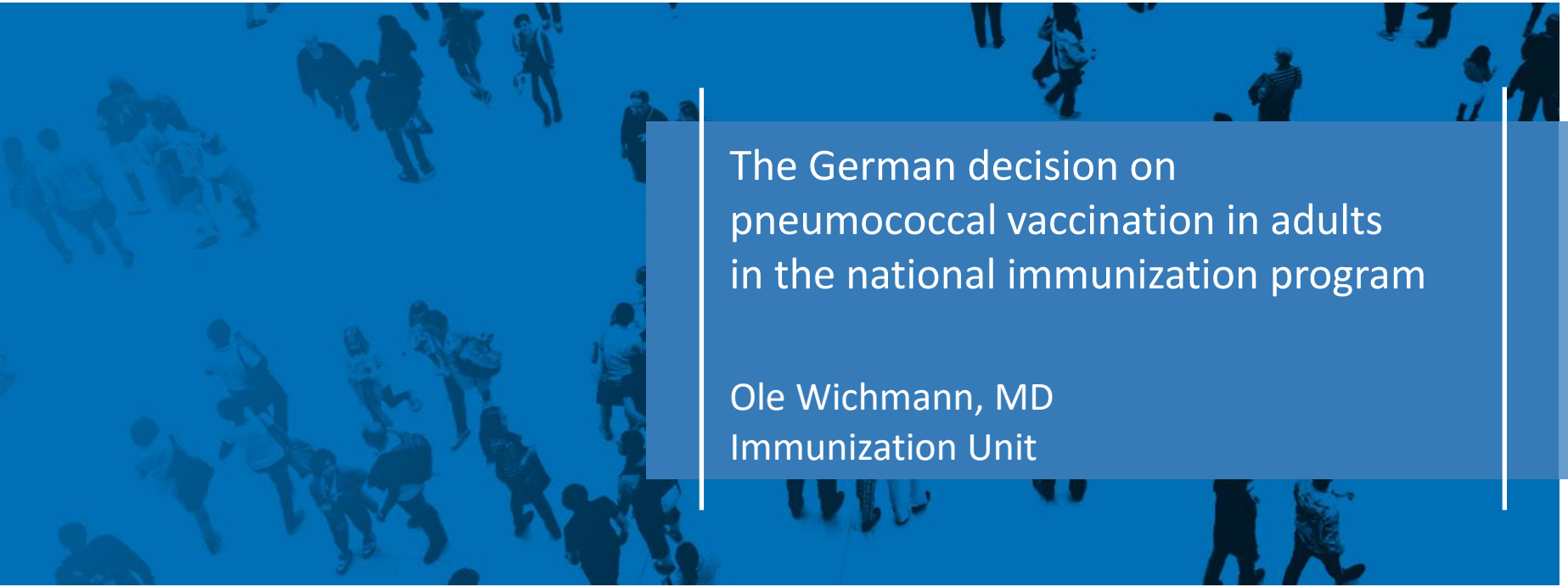

The German decision on pneumococcal vaccination in adults in the national immunization program

Ole Wichmann, MD
Immunization Unit

Adult Immunization Board (AIB) Technical meeting, 18 – 19 April 2024

The German immunization system and NITAG

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- Decentralized healthcare system
  - under the responsibility of 16 federal states
  - but: one national vaccination directive, based on recommendations of STIKO
- Funding through health insurance funds
  - all STIKO-recommended vaccines free of charge
- STIKO = National Immunization Technical Advisory Board
  - Established in 1972
  - 16-22 members, appointed by MoH for 3 years, executive secretariat hosted by RKI
  - Disciplines of the members: Pediatrics; General Medicine; Gynecology; Geriatrics, Occupational Medicine, Epidemiology; Virology; Microbiology; Public Health; EBM
- “Private vaccine market”
  - no governmental/central procurement
  - delivery: private physicians (~90%), company physicians, pharmacies (COVID19/flu)

Development of a STIKO recommendation

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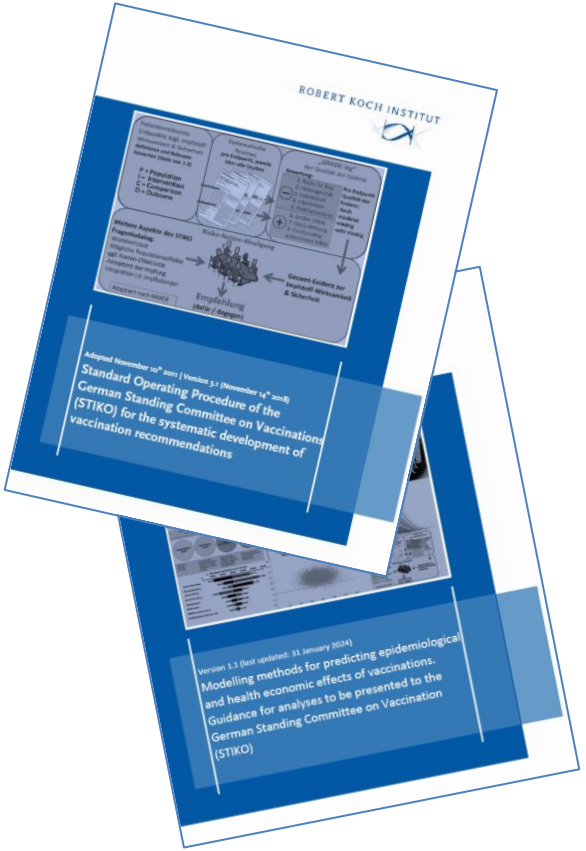
- Priorization procedure
- Goal of vaccination
- PICO Questions (for efficacy/effectiveness and safety)
- Systematic review
- GRADE for bodies of evidence
- Other questions (e.g. impact, feasibility, equity)
- Decision-making process (EtD-tool)
- Recommendation



STIKO's recommendations on pneumococcal vaccination

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Previous recommendation

-routine childhood vaccination: PCV13

-individuals with congenital or aquired immunodeficiency: PCV13+PPSV23

-individuals with other chronic diseases (age 16+ yrs): **PPSV23**

-age 60+ yrs: **PPSV23**

As of September 2023

-routine childhood vaccination: PCV13 or **PCV15**

-individuals with chronic diseases (age 2-17 yrs): PCV13/**15**+PPSV23

-individuals with chronic diseases (age 18+ yrs): **PCV20**

-age 60+ yrs: **PCV20**

References

1. **Background Paper** to the STIKO recommendation on PCV20 in adults. Epidemiological Bulletin 39, 28th September 2023 (in German): https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2023/Ausgaben/39_23.pdf?__blob=publicationFile

2. **Attachment** to the Background Paper (partially in English): Flow diagram, list of excluded studies, **GRADE tables**, **Evidence-to-Decision-Table** https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2023/Ausgaben/39_23_Anhang.pdf?__blob=publicationFile

3. **Dynamic transmission model** evaluating the impact of different vaccination strategies against pneumococcal disease in adults in Germany (PCV20 vs. PPSV23) (in German): https://www.rki.de/DE/Content/Infekt/Impfen/Forschungsprojekte/abgeschlossene_Projekte/Pneumokokken-Impfstrategie/Projektbericht.pdf?__blob=publicationFile

(I) Systematic Review on the safety/effectiveness of PCV20

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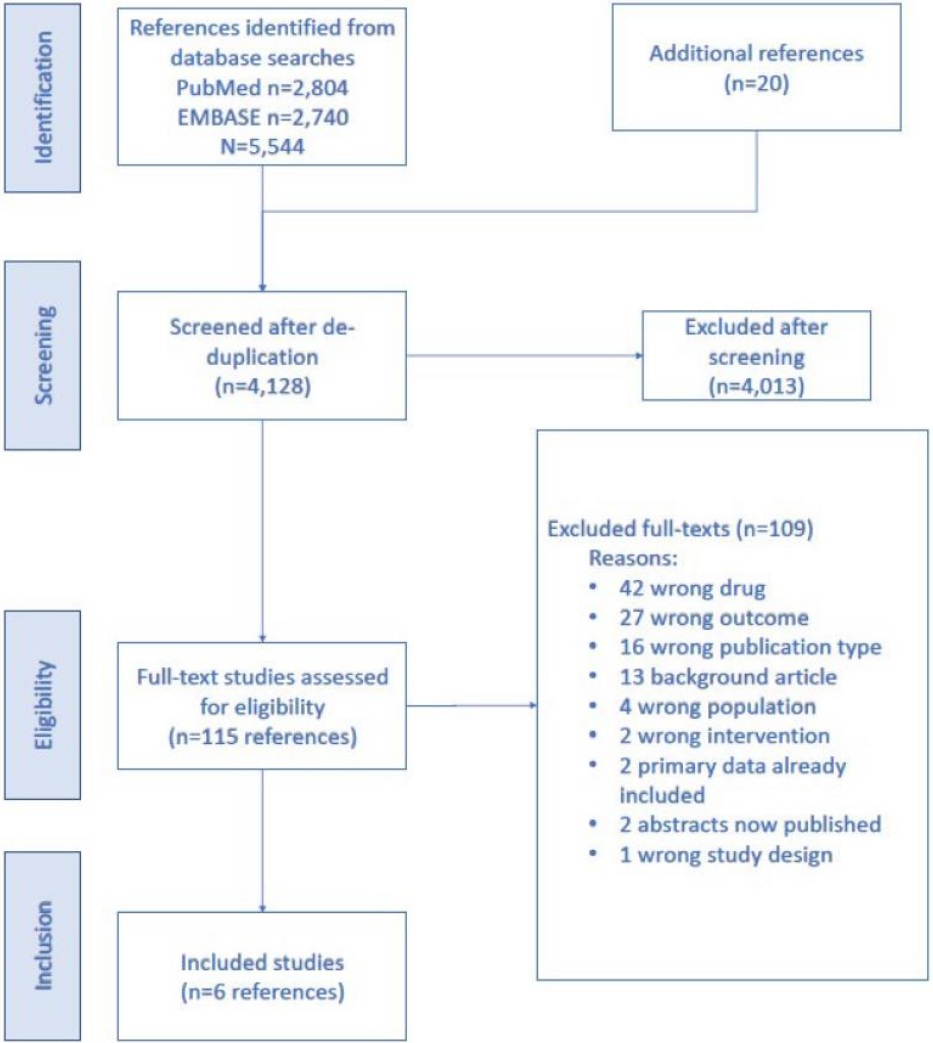
Population	60+ year-old individuals 18+ year-old individuals with underlying chronic disease
Intervention	PCV20 PCV20 + PPSV23
Control	PPSV23 and/or PCV13 Other non-pneumococcal vaccines Placebo No vaccination
Outcome	Invasive pneumococcal disease (IPD) Pneumococcal pneumonia (PP) Death due to IPD or PP Immunogenicity (OPA, GMR) Duration of protection Safety
(Study design)	Randomized controlled trials, observational studies with reference group



Flow diagram

Search was performed in *PubMed a*nd *Embase as of 17 January 2023*

Characteristics of included studies

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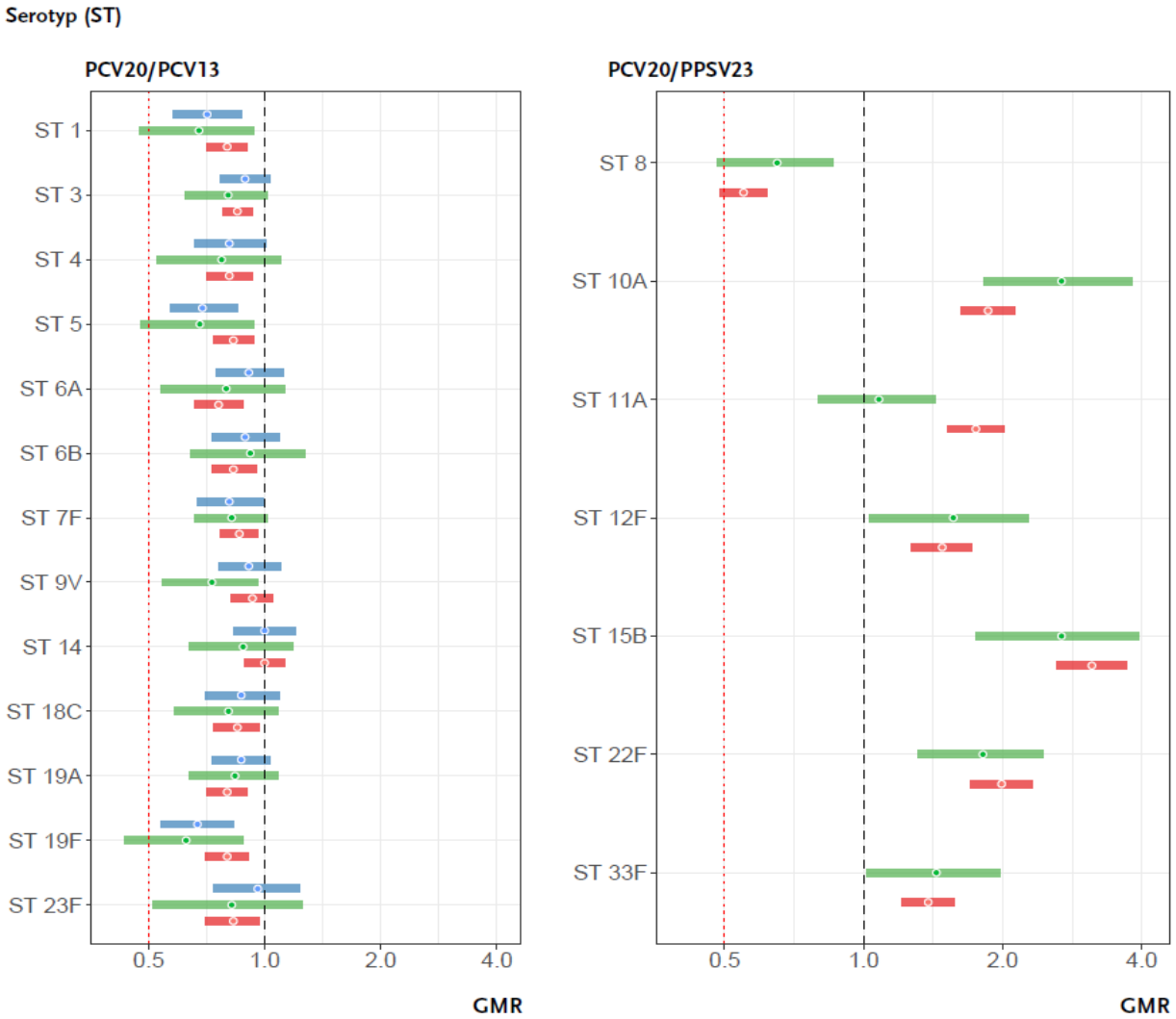
Study	Study design	Country	Funding	Population	N	Mean age (SD)	Endpoint	Comparator
Cannon 2021	RCT, open-label **Phase 3**	USA, Sweden	Pfizer	**Age 65+ yrs** with previous pneumococcal vaccination (PV)	875	70.3 (4.84)	Safety, immunogenicity	PCV13 or PPSV23
Essink 2021	RCT, blinded **Phase 3**	USA, Sweden	Pfizer	Age 18+ yrs (18-49, 50-59, **60+**) without previous PV	3,889	60.0 (11.15)	Safety, immunogenicity	PCV13 or PCV13+PPSV23
Klein 2021	RCT, blinded **Phase 3**	USA	Pfizer	Age 18-49 yrs without previous PV	1,708	35.3 (9.03)	Safety, immunogenicity	PCV13
Hurley 2020	RCT, blinded Phase 2	USA	Pfizer	Age **60-64** yrs without previous PV	443	62.0 (1.41)	Safety, immunogenicity	PCV13+PPSV23
Fitz-Patrick 2021	RCT, blinded Phase 1	USA	Pfizer	Age 18–49 yrs, healthy Without previous PV	103	31.3 (10.12)	Safety, immunogenicity	PCV7 or PCV13
Thompson 2019	RCT, blinded Phase 1	USA	Pfizer	Age 18–49 yrs, healthy without previous PV	66	32,1 (8,3)	Safety, immunogenicity	Tdap

→ no study with clinical endpoints (IPD, PP)

→ no study included immunocompromized patients



Immunogenicity

PCV20 vs. PCV13
and
PCV20 vs. PPSV23

Geometric mean ratio (GMR)
Non-inferiority: 0.5

Summary of findings, age 60+

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Endpoints	Estimated absolute effect		Relative effect (95% CI)	Number of Participants (studies)	Quality of Evidence (GRADE)
	Risk with PCV13/PPSV23	Risk with PCV20			
Severe adverse event (SAEs)	22 / 1,000	25 / 1,000 (7-37)	RR 1,1 (0.74-1.64)	4188 (3 RCTs)	Moderate[a]
Fever >38°C	8 / 1,000	7 / 1,000 (3-16)	RR 0.96 (0.44-2.08)	4175 (3 RCTs)	High
Headache	230 / 1,000	207 / 1,000 (184-232)	RR 0.90 (0.80-1.01)	4175 (3 RCTs)	High
Immunogenicity (OPA GMR), after 1 months				3273 (2 RCTs)	Low[b,c]

a) Sample size too small to detect rare or very rare events
b) High proportion of missing data related to OPA-results for some serotypes
c) Immunogenicity as a surrogate marker without defined threshold

(II) Dynamic compartment model (differential equations)

- Scenario continuation of PCV13 childhood vaccination

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Vaccination of 30% of all persons, who reach the vaccination age of 60 years in the years 2024 - 2033

	PPSV23	PCV20	PCV20 +PPSV23
comparator	No vaccination	No vaccination	PCV20
averted IPD cases	1,795	3,556	322
averted hospitalized NPBB cases	3,255	8,889	602
averted deaths	632	1,625	117
NNV to avoid one hospitalisation	742	301	4,046
NNV to avoid one death	5,935	2,308	31,900
Additional societal cost [€] per QALY gained	10,690	12,281	76,655

(III) Other questions - Evidence-to-Decision (EtD) table

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Shall PCV20 replace PPSV23 for people aged ≥ 60 years?

Goal of vaccination: Reduction of burden of IPD and its consequences such as hospitalization, disability and death in people aged ≥ 60 years

<table>
<tr><th colspan="2">Criteria</th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is the problem a priority?</td><td>o No
o Probably no
o Uncertain
o Probably yes
o Yes
o Varies</td><td>National office of statistic data (destatis)
-Hospitalizations due to pneumococcal pneumonia:
-Annual mean 2007-2019: N=2,674
-Annual mean age standardized incidence: 3.2/100.000 inhabitants.
-Highest incidence in elderly population
-Hospitalizations due to pneumococcal sepsis:
-Annual mean 2007-2019: N=2,417;
-Annual mean age standardized incidence: 2.9/100.000 inhabitants
-Highest incidence in elderly population
-Deaths due to pneumococcal pneumonia/sepsis/ meningitis: annual mean 2007-19: N= 130. From age 55 rise in mortality, most death occur in people aged ≥ 60 years</td><td>-Degree of underestimation of IPD and death due to IPD in National office of statistic data unknown
-for Germany no nationwide data on non-hospitalized cases available
-mandatory notification of invasive pneumococcal disease in Germany was issued in March 2020; implementation is ongoing</td></tr>
<tr><td>Benefits and harms of the options</td><td>What is the overall certainty of this evidence?</td><td>o No included studies
o Very low
o Low
o Moderate
o High</td><td>
<table>
<tr><th>Outcome</th><th>Relative importance</th><th>GRADE</th></tr>
<tr><td>VE</td><td></td><td></td></tr>
<tr><td>Prevention of IPD</td><td>critical</td><td rowspan="3">No evidence available</td></tr>
<tr><td>Prevention of pneumococcal pneumonia</td><td>critical</td></tr>
<tr><td>Prevention of deaths due to IPD</td><td>critical</td></tr>
<tr><td>Immunogenicity[1]</td><td>critical</td><td>Low</td></tr>
<tr><td>Safety</td><td></td><td></td></tr>
<tr><td>Fever</td><td>important</td><td>High</td></tr>
</table>
</td><td>-PCV20 Studies provide data on people aged ≥ 60 and 18-59 years separately</td></tr>
</table>

Criteria		Judgement	Research evidence	Additional considerations
Equity	What would be the impact on health inequities?	○ Increased ○ Probably increased ○ reduced ○ Probably reduced ○ Varies	-Vaccination with both vaccines are covered by health insurance. -PCV20 confers better protection of vulnerable group (elderly) thus it improves equity	
Acceptability	Is the option acceptable to key stakeholders?	o No o Probably no o Uncertain o Probably yes o Yes o Varies	-Current recommendation not well implemented: low vaccination coverage (2022): -Age 60 years: 3.2% -Age 60-74 years: 23.3% -Age 74 years: 41.9% -Vaccination coverage in elderly also low for other vaccines. -Anticipated improvement of acceptability by doctors due to simpler recommendation (same vaccine for all) and preference of doctors for conjugate vaccines	-what can be done to improve compliance?
Feasibility	Is the option feasible to implement?	o No o Probably no o Uncertain o Probably yes o Yes o Varies	-Coadministration with adjuvanted influenza vaccine and mRNA-covid-19 vaccines possible -No data on coadministration with influenza high dose vaccine -Use of only 1 vaccine for all makes communication and implementation easier (storage of only one vaccine type)	

Recommendation, justification, implementation (EtD-table)

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Recommendation	Vaccination with PCV20 as standard vaccination for people aged ≥ 60 years
Justification	Mathematical modelling suggests that vaccination with PCV20 prevents more IPD cases and deaths than vaccination with PPSV23 in the elderly while having a similar safety profile

Subgroup considerations	-In case of a shortage, vaccination with PCV20 should be postponed -Depending on the duration and the patient's risk profile, it may make sense not to wait but to use PPSV23 or PCV15. In both cases, if PCV20 is again available, sequential vaccination at a minimum interval of 1 year should be considered. -Persons aged ≥ 60 years, who have already received PPSV23, should receive PCV20 earliest 6 years after PPSV23 -No information can currently be given on the need for repeat vaccinations after PCV20
Implementation consideration	Coadministration with COVID-19 mRNA vaccines or influenza vaccines is possible
Monitoring & evaluation	-PCV coverage is regularly analyzed by “RKI Impfsurveillance” in people ≥ 60 years -Use of national surveillance data to measure impact of recommendation on IPD incidence -Surveillance of Pau-Ehrlich-Institute (PEI) for safety signals of PCV20 -Close monitoring of serotype distribution and replacement effects on a national/international level
Research priorities	-Studies investigating duration of protection of PCV20 -Clinical vaccine effectiveness studies -Further development of pneumococcal vaccines to provide better protection from serotype 3 or serotype independent protection

Acknowledgements

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