

# SYSTEMATIC LITERATURE REVIEW OF HERPES ZOSTER INCIDENCE WORLDWIDE

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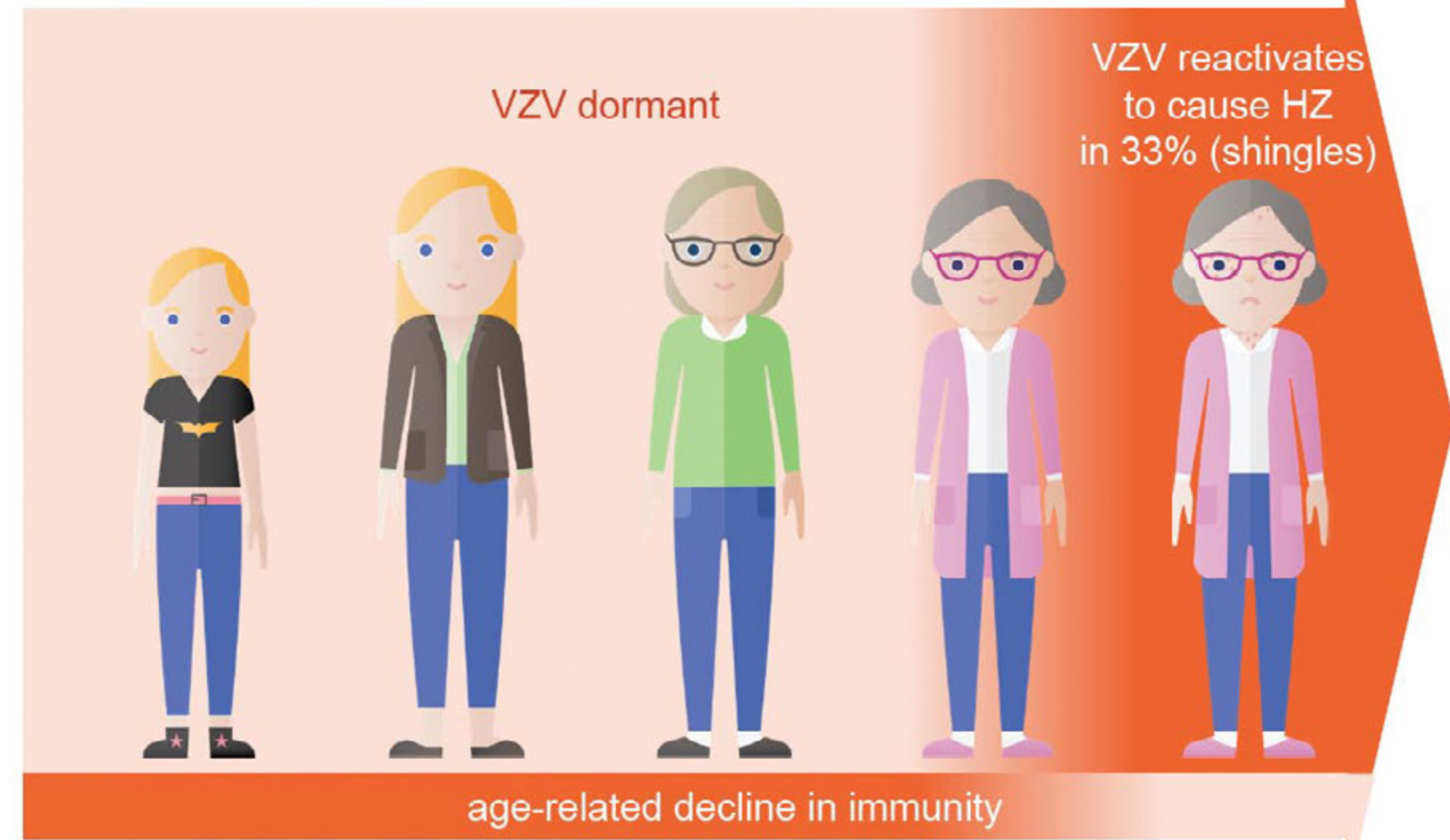
## OBJECTIVE

Primary infection with the varicella zoster virus (VZV) may lead to acute varicella (or chickenpox). The reactivation of VZV during later stages of life results in herpes zoster (HZ, or shingles), particularly in older individuals.<sup>1</sup>

Primary VZV infection may lead to acute varicella (or chickenpox)



≥50-year-old population: 99% infected with VZV



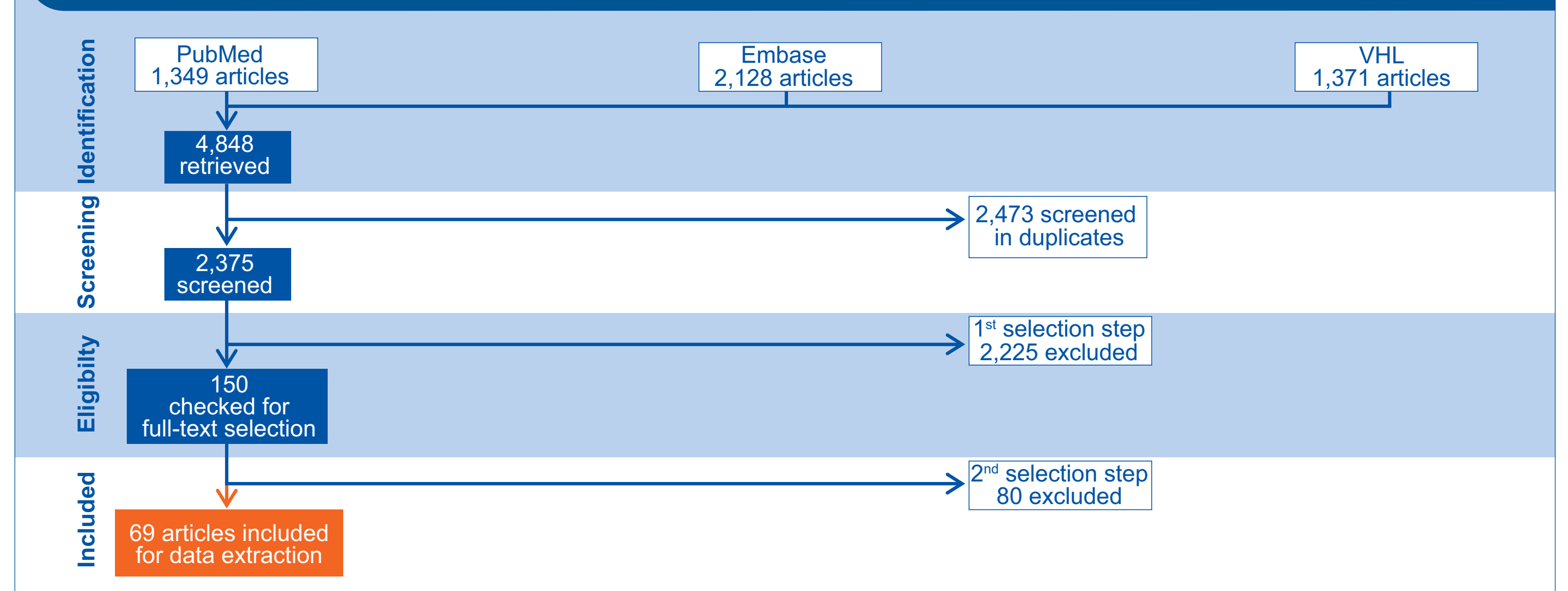
This systematic literature review (SLR) was performed to ascertain the global incidence of HZ in the general population comprising individuals ≥50 years of age (YOA).

## METHODS

From this SLR, data on HZ incidence (general population ≥50 YOA and stratified by geographic region, country, gender and age) is reported as:

- Incidence rate: Number of new HZ cases per 1,000 person-years or,
- Cumulative incidence: Number of new HZ cases per 1,000 of the population.

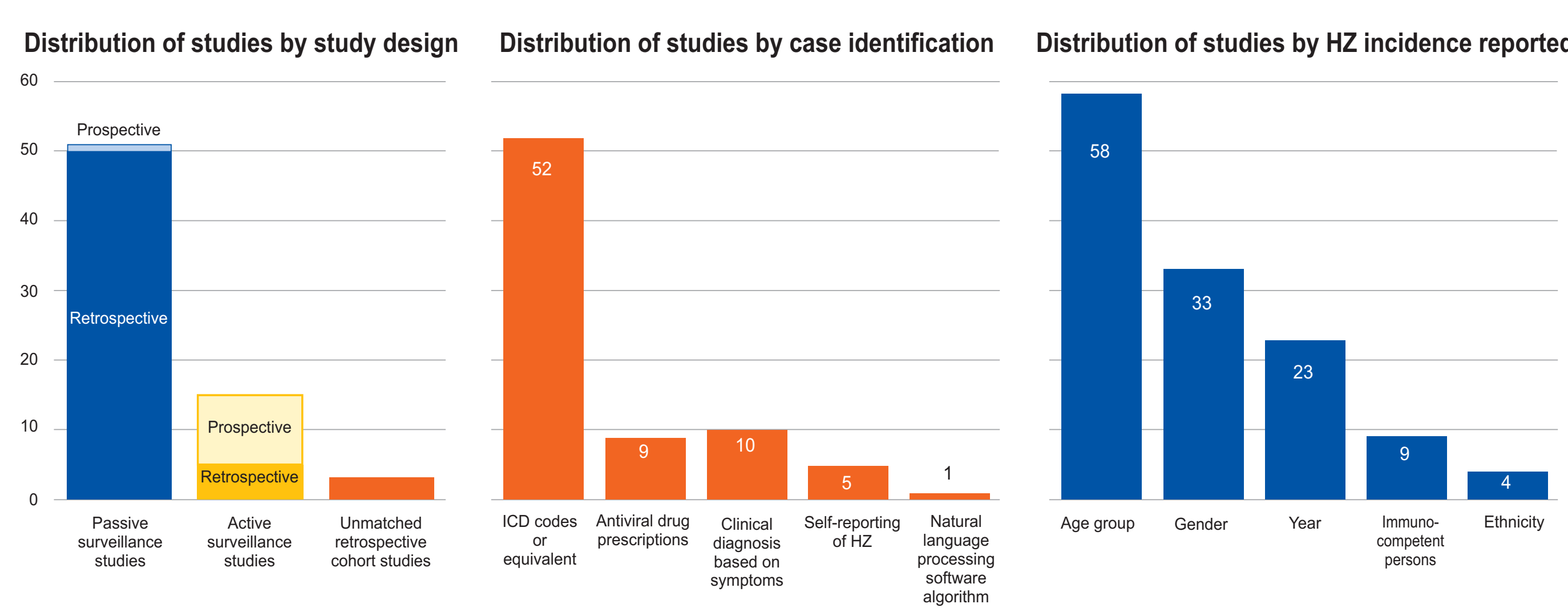
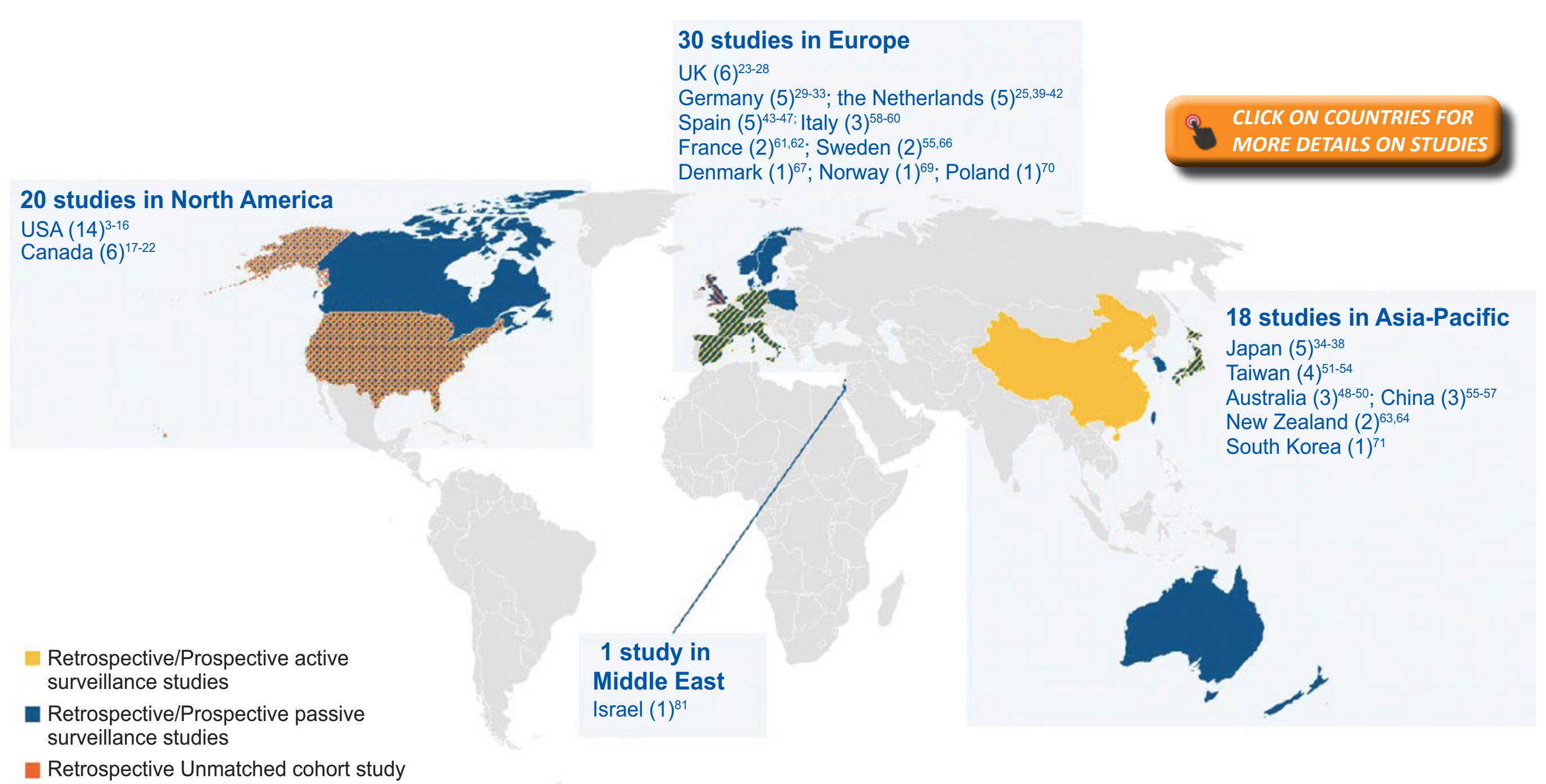
An SLR on HZ incidence was conducted in PubMed, Embase and the Virtual Health Library (VHL) from January 2002 until December 2018. Overall, 69 studies were included\*.



HZ, herpes zoster; SLR, systematic literature review. \*Additional details provided in Supplementary materials.

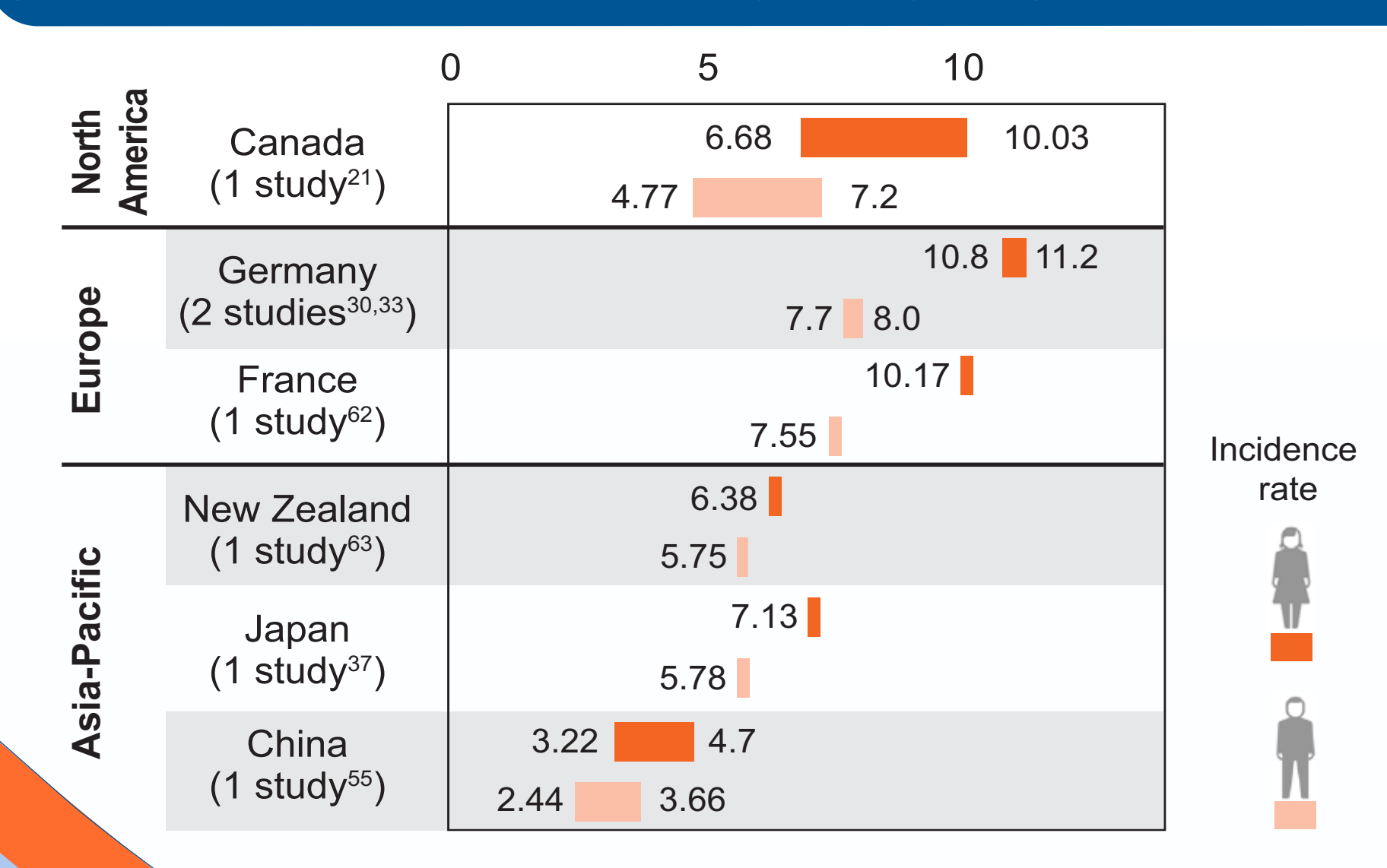
## RESULTS

Study characteristics\* reveal a good representation of studies in North America, Europe and Asia-Pacific. More than half the studies were nationwide studies. There were considerable methodological differences in the way HZ cases were identified.



HZ, herpes zoster; ICD, international classification of diseases; USA, United States of America; UK, United Kingdom. \*Additional details provided in Supplementary materials.

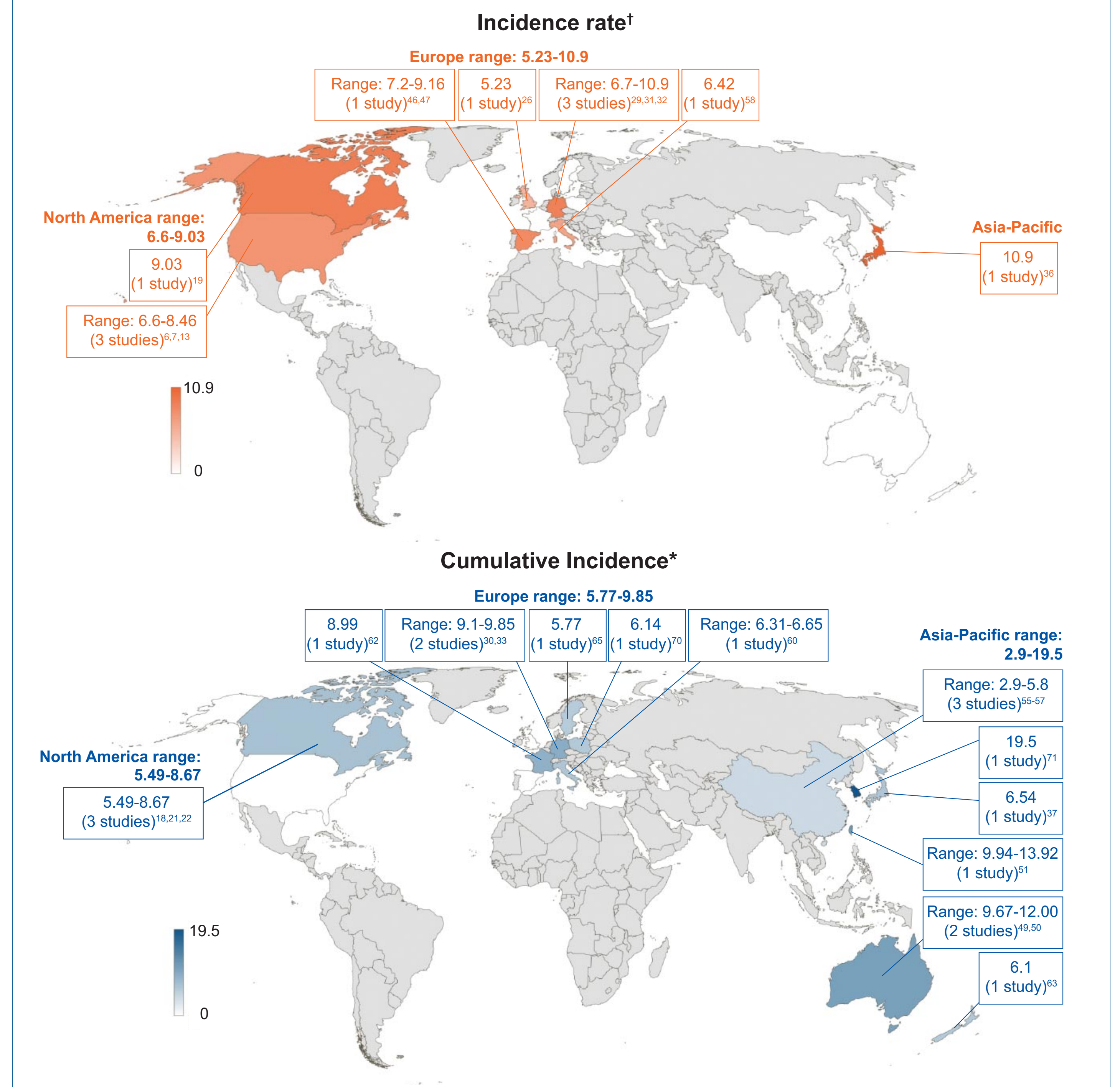
Higher HZ incidence\* for females compared to males was observed in the general population ≥50 YOA stratified by country and gender.



HZ, herpes zoster; USA, United States of America.

\*14 studies provided data on gender differences and HZ incidence. Only incidence rate data reported in the figure here shown. Cumulative incidence data provided in Supplementary materials.

Overall, HZ incidence rate ranged from 5.23 to 10.9 cases per 1,000 person-years and the cumulative incidence of HZ from 2.9 to 19.5 cases per 1,000 population ≥50 YOA. When comparing the geographical regions, the highest incidences were mostly reported in Asian-Pacific countries. (30 studies)



HZ, herpes zoster; YOA, years of age. †Number of new HZ cases per 1,000 person-years; \*Number of new HZ cases per 1,000 population.



## Plain Language Summary

Herpes zoster is known to affect older individuals because of the reactivation of the chickenpox virus in the later stages of life, especially at ≥50 years of age, due to age-related decline in immunity. This review shows that the worldwide incidence of herpes zoster is high in individuals ≥50 years of age with little variation in the different regions of the world. However, the incidence of herpes zoster is higher in females compared to males. In the context of the world's ageing population, the occurrence of herpes zoster is expected to place an additional burden especially in older patients who already have health problems to cope with in everyday life.

## CONCLUSIONS

- This SLR showed that HZ incidence in adults ≥50 YOA is similar across the geographic regions included.
- Most studies were conducted in North America, Europe and Asia-Pacific reflecting a paucity of data for South America and Africa.
- Future research in this field could benefit from a standard methodology to identify HZ cases, assess HZ incidence and better define the populations studied.

## Funding

GlaxoSmithKline Biologicals SA (GSK study identifier: HO-18-19810)

Scan for interactive Handout with Supplementary Materials, Disclosures and References



## Systematic literature review

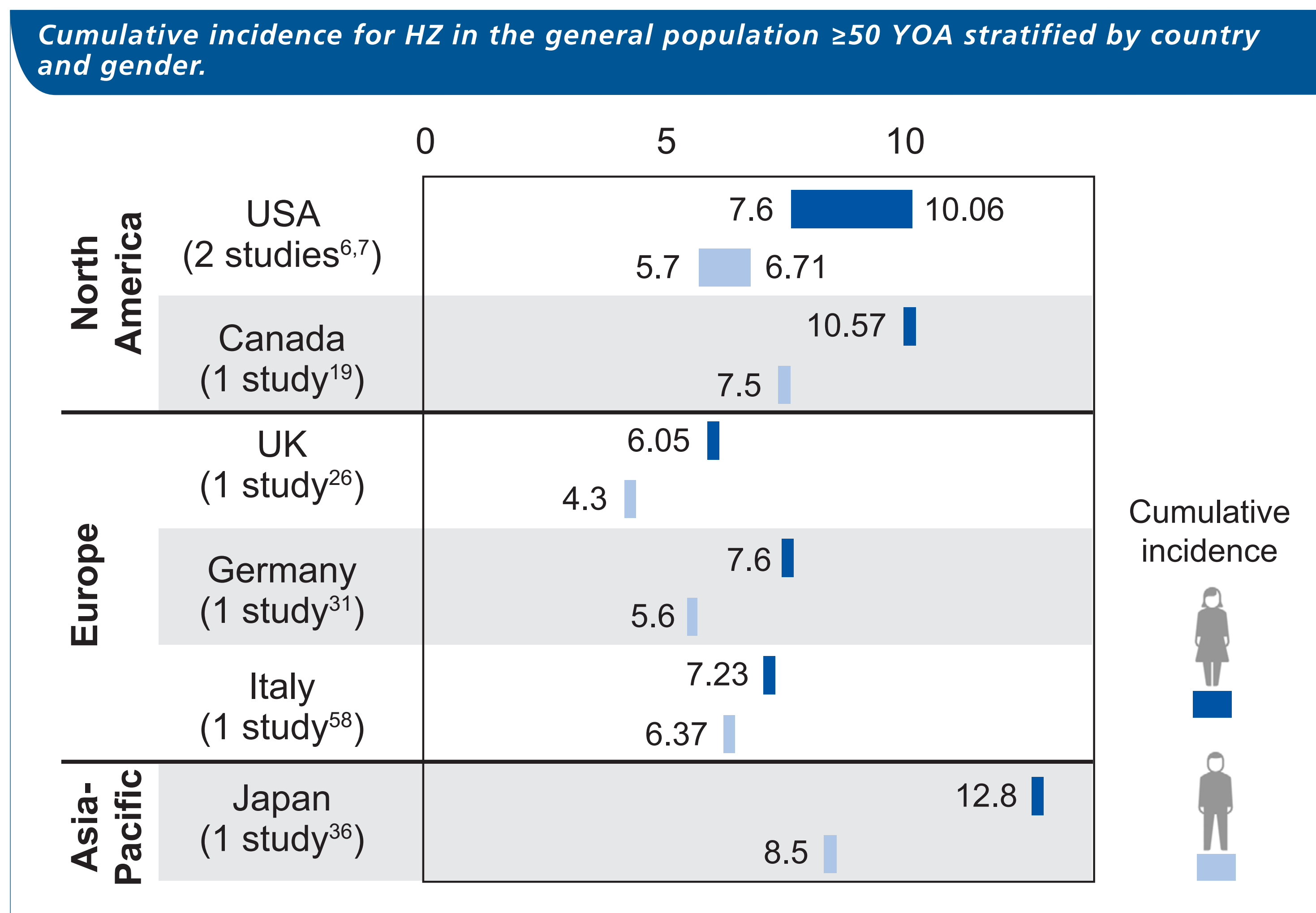
- ➔ The SLR was conducted according to guidelines specified in the Cochrane Handbook for Systematic Reviews of Interventions<sup>72</sup> and the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA).<sup>2</sup>
- ➔ SLR screening: the first 10% of full text articles were checked for relevance in duplicate by two reviewers using the inclusion and exclusion criteria.

Inclusion and exclusion criteria.		
	Inclusion criteria	Exclusion criteria
<b>Population</b>	• Studies in persons ≥50 YOA	• All other age groups • Non-representative population (e.g. military personnel)
<b>Intervention</b>	• Not limited by intervention	• NA
<b>Comparator</b>	• Not limited by comparator	• NA
<b>Outcome</b>	• Incidence of HZ	• HZ incidence in patients with another condition (e.g. immunocompromised persons). In case a study compared the incidence in a population with and without a certain condition, the full text was checked to see whether an overall incidence could be calculated for both groups combined. • All other topics besides incidence
<b>Study design</b>	• Primary research - Observational studies (cohort studies, case-control studies, pre-/post-vaccine introduction time series) • Surveillance reports (unpublished and published) • Publications/reports from global, regional and local published and unpublished data (if possible)	• Non-primary research - Reviews* - Narrative reviews (without methods) - Meta-analysis* - Public health programs or recommendations - Transmission modeling studies - Cost-effectiveness or health economics studies • Case reports • Meta-analysis • Letter to editor • Newspaper • Editorial • Comment • Opinion paper • Phase I/II/III trials • Molecular studies • Studies with insufficient methodological details
<b>Limits</b>		
<b>Publication date</b>	January 2002 – December 2018	Articles published outside of dates considered eligible for inclusion
<b>Geographic scope</b>	Worldwide	None
<b>Language</b>	English, German, Dutch, French, Spanish and Italian	Articles published in any other language besides those considered eligible for inclusion
<small>HZ, herpes zoster; NA, not applicable *Systematic literature review articles and meta-analysis articles from the search were excluded in the full text selection step but included articles in these reviews were manually screened for additional relevant original articles.</small>		

- ➔ 2<sup>nd</sup> selection step exclusion: Conference abstract (N=1), data already presented in another article (N=7), insufficient description of results (N=3), modeling study (N=3), narrative review (N=9), no HZ incidence data reported (N=13), no older adults data reported (N=13), no representative population (N=9), other language (N=1), relevant data only in a figure (N=6; the authors were contacted to retrieve the underlying data [numerators and denominators] of these figures), systematic review/meta-analysis (N=15; systematic reviews/meta-analyses were checked for possibly missed relevant original articles), no full text available (N=5).

## Study characteristics

- ➔ Retrospective studies conducted in all countries. Prospective studies were only conducted in Australia, France, Germany, Italy, Japan, the Netherlands and Spain.
- ➔ One study presented data for the Netherlands and the UK separately<sup>25</sup>; this study is captured within the individual countries.
- ➔ Thirty-six of the studies were nationwide studies or claimed to be representative of the national population<sup>3-7,9-11,13,16,23-29,33,34,39-41,43,51-54,61,62,65,67-69,71</sup>, while the remaining studies were conducted in one or several region(s). Study periods varied, with the oldest data reported for the period 1980-1989<sup>8</sup> and the most recent data for the year 2017<sup>38</sup>.



HZ, herpes zoster; UK, United Kingdom; USA, United States of America; YOA, years of age.

# DISCLOSURES

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# CHARACTERISTICS OF INCLUDED STUDIES

## North America

USA										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Chaves, 2007 <sup>2</sup>	USA	Retrospective active surveillance study	2 February 2004 – 27 May 2004	National Adult Immunization Survey	≥55	Self-report	Outpatients	PP	Age, ethnicity, gender	
Chen, 2014 <sup>4</sup>	USA	Retrospective passive surveillance study	1 January 2005 – 31 December 2009	Commercially insured, Medicare and Medicaid administrative medical and pharmacy claims databases	≥50	ICD codes	Inpatients and outpatients	PY	Age	
Hales, 2013 <sup>9</sup>	USA	Retrospective passive surveillance study	1 January 1992 – 31 December 2010	Medicare, a national health insurance program	>65	ICD codes	Inpatients and outpatients	PY	Age, ethnicity, gender, year	
Harpaz, 2018 <sup>16</sup>	USA	Retrospective passive surveillance study	1 January 1998 – 31 December 2016	Two Medstat MarketScan databases: Commercial Claims and Encounters, and Medicare Supplemental and Coordination of Benefits	≥45	ICD codes	Outpatients	PP	Age, year	
Insinga, 2005 <sup>5</sup>	USA	Retrospective passive surveillance study	1 July 2000 – 30 June 2001	Medstat MarketScan database	≥50	ICD codes	Inpatients and outpatients	PY	Age, gender, population (general population and IC only)	
Johnson, 2015 <sup>15</sup>	USA	Retrospective passive surveillance study	1 January 2011 – 31 December 2011	Two Medstat MarketScan databases: Commercial Claims and Encounters, and Medicare Supplemental and Coordination of Benefits	≥50	ICD codes	Inpatients and outpatients	PY	Age, gender	
Krishnarajah, 2014 <sup>7</sup>	USA	Retrospective passive surveillance study	1 January 2006 – 31 December 2010	MarketScan Medicaid database	50-64	ICD codes	Inpatients and outpatients	PP	Age, gender, year	
Langan, 2013 <sup>10</sup>	USA	Unmatched retrospective cohort study	1 January 2007 – 31 December 2009	Medicare, a national health insurance program	≥65	ICD codes and/or drug prescription	Inpatients and outpatients	PY	Age, ethnicity, gender, population (general population and IC only), case definition (with or without antiviral prescriptions)	
Leung, 2011 <sup>11</sup>	USA	Retrospective passive surveillance study	1 January 1993 – 31 December 2006	Two Medstat MarketScan databases: Commercial Claims and Encounters, and Medicare Supplemental and Coordination of Benefits	≥45	ICD codes	Outpatients	PP	Age, gender, year	
Mullooly, 2005 <sup>12</sup>	USA	Retrospective passive surveillance study	1 January 1997 – 31 December 2002	Kaiser Permanente North-West California	≥45	ICD codes x estimated % of probable HZ	Inpatients and outpatients	PY	Age, gender, year	
Suaya, 2014 <sup>13</sup>	USA	Unmatched retrospective cohort study	1 January 2005 – 31 December 2009	Three MarketScan databases: Commercial, Medicare and Medicaid databases	≥50	ICD codes	Inpatients and outpatients	PY	Age, population (general population and IC only)	
Yawn, 2007 <sup>14</sup>	USA	Retrospective passive surveillance study	1 January 1996 – 31 December 2001	Rochester Epidemiology Project, conducted in Olmsted County, Minnesota	≥50	ICD codes	Inpatients and outpatients	PY	Age, gender	
Yih, 2005 <sup>15</sup>	USA	Retrospective active surveillance study	1 January 1999 – 31 December 2003	Behavioral Risk Factor Surveillance System survey, Massachusetts	≥45	Self-report	Inpatients and outpatients	PP	Age, year	

USA, United states of America; ICD, international classification of diseases; HZ, herpes zoster; PP, per 1000 population; PY, per 1000 person-years; IC, immunocompetent.

Canada										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Edgar, 2007 <sup>17</sup>	Canada	Retrospective passive surveillance study	1 January 1994 – 31 December 2003	British Columbia Ministry of Health Medical Services Plan database (physician billing data)	≥65	ICD codes	Outpatients	PP	-	
Marra, 2016 <sup>18</sup>	Canada	Retrospective passive surveillance study	1 January 1997 – 31 December 2012	Population-DataBC Medical Services Plan and Discharge Abstract Database, linked to the outpatient prescription database PharmaNet; British Columbia	≥50	ICD codes	Inpatients and outpatients	PP	Age, year	
McDonald, 2017 <sup>19</sup>	Canada	Retrospective passive surveillance study	1 November 2009 – 31 October 2015	Alberta Health Care Insurance Plan Registry, an Alberta health insurance	≥50	ICD codes	Inpatients and outpatients	PY	Age, gender	
Russel, 2007 <sup>21</sup>	Canada	Retrospective passive surveillance study	1 January 1990 – 31 December 2002	Hospital Morbidity Inpatient database and the Alberta Health Care Insurance Plan Registry; Alberta Province	≥50	ICD codes	Inpatients and outpatients	PP	Age, gender, year	
Russel, 2014 <sup>20</sup>	Canada	Retrospective passive surveillance study	1 January 1994 – 31 December 2010	Alberta's universal, publicly funded healthcare insurance system databases	≥50	ICD codes	Inpatients and outpatients	PP	Age, year	
Tanuseputro, 2011 <sup>22</sup>	Canada	Retrospective passive surveillance study	1 April 1992 – 31 March 2010	Canadian Institute of Health Information Discharge Abstract Database (Ontario) and Ontario Health Insurance Plan	≥50	ICD codes	Inpatients and outpatients	PP	Age, year	
Edgar, 2007 <sup>17</sup>	Canada	Retrospective passive surveillance study	1 January 1994 – 31 December 2003	British Columbia Ministry of Health Medical Services Plan database (physician billing data)	≥65	ICD codes	Outpatients	PP	-	

ICD, international classification of diseases; PP, per 1000 population; PY, per 1000 person-years.

## Asia-Pacific

Japan										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Imafuku, 2018 <sup>34</sup>	Japan	Retrospective passive surveillance study	1 January 2005 – 31 December 2014	Japan Medical Data Center-Claims Database, a national health insurance database	50-74	ICD codes and drug prescription	Inpatients and outpatients	PY	Age, gender	
Shiraki, 2017 <sup>35</sup>	Japan	Prospective active surveillance study	1 June 2009 – 30 November 2015	36 dermatology clinics and dermatology departments of 7 flagship general hospitals belonging to the Miyazaki Dermatologist Society, Miyazaki Prefecture	70-79	Clinical	Outpatients	PP	Gender	
Takao, 2015 <sup>38</sup>	Japan	Prospective active surveillance study	1 December 2008 – 30 November 2012	Shozu County, Kagawa Prefecture, Japan	≥50	Clinical Inpatients and outpatients	PY	Age, gender		
Toyama, 2009 <sup>37</sup>	Japan	Prospective active surveillance study	1 January 1997 – 31 December 2006	39 dermatology clinics and dermatology departments of 7 flagship general hospitals associated with the Miyazaki Dermatologist Society, in Miyazaki Prefecture	≥50	Clinical Outpatients	PP	Age, gender		
Toyama, 2018 <sup>38</sup>	Japan	Prospective active surveillance study	1 January 1997 – 31 December 2017	33 dermatology clinics and dermatology departments of 10 flagship general hospitals associated with the Miyazaki Dermatologist Society, in Miyazaki Prefecture	≥60	Clinical Outpatients	PP	Year		

ICD, international classification of diseases; PP, per 1000 population; PY, per 1000 person-years.

Taiwan										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Chao, 2011 <sup>31</sup>	Taiwan	Retrospective passive surveillance study	1 January 2000 – 31 December 2008	NHIRD	≥50	ICD codes	Outpatients	PP	Age, year	
Jih, 2009 <sup>32</sup>	Taiwan	Retrospective passive surveillance study	1 January 2000 – 31 December 2006	NHIRD	>80	ICD codes	Inpatients and outpatients	PY	-	
Lin, 2010 <sup>33</sup>	Taiwan	Retrospective passive surveillance study	1 January 2000 – 31 December 2005	NHIRD	≥50	ICD codes	Inpatients and outpatients	PP	Age	
Lu, 2018 <sup>34</sup>	Taiwan	Retrospective passive surveillance study	1 January 2004 – 31 December 2008	NHIRD	≥50	ICD codes	Inpatients and outpatients	PP	Age, year	

ICD, international classification of diseases; PP, per 1000 population; PY, per 1000 person-years; NHIRD, national health insurance research database.

South Korea										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Kim, 2014 <sup>71</sup>	South Korea	Retrospective passive surveillance study	1 January 2011 – 31 December 2011	National Health Insurance Service database	≥50	ICD codes	Inpatients and outpatients	PP	Age	

ICD, international classification of diseases; PP, per 1000 population.

Australia										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Liu, 2015 <sup>6</sup>	Australia	Prospective passive surveillance study	1 January 2006 – 31 December 2009	The 45 and Up Study in New South Wales	≥45	Drug prescription or ICD codes (inpatients only)	Inpatients and outpatients	PY	Age	
Machtyre, 2015 <sup>69</sup>	Australia	Retrospective passive surveillance study	1 July 2006 – 31 March 2013	6302 GPs captured in the Bettering the Evaluation of Care and Health database, and the (Re)atriation) Pharmaceutical Benefits Scheme database	≥50	ICPC codes or drug prescription	Outpatients	PP	Age, case definition (GP visits or antiviral prescriptions)	
Stein, 2009 <sup>68</sup>	Australia	Retrospective passive surveillance study	1 April 2000 – 30 September 2006	6460 GPs captured in the Bettering the Evaluation of Care and Health database, and the (Re)atriation) Pharmaceutical Benefits Scheme database	≥50	ICPC codes or drug prescription	Outpatients	PP	Age, case definition (GP visits or antiviral prescriptions)	

ICD, international classification of diseases; PP, per 1000 population; PY, per 1000 person-years; IC, immunocompetent; GP, general practitioner; ICPC, international classification of primary care.

China										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Li, 2016 <sup>85</sup>	China	Retrospective active surveillance study	May 2013 – May 2014	One rural township each in Jiangsu, Jiangxi, Heilongjiang and Hebei and one community from Shanghai	≥50	Self-report	Inpatients and outpatients	PP	Age, gender, year	
Lu, 2018 <sup>86</sup>	China	Retrospective active surveillance study	December 2012 – March 2013	52 communities/villages in three districts of Beijing (Xicheng, Changping and Miyun)	≥50	Self-report	Outpatients	PP	Age, gender	
Zhu, 2015 <sup>87</sup>	China	Retrospective active surveillance study	28 October 2013 – NR	34 of the 126 counties/districts in Guangdong Province, selected using random sampling	≥50	Self-report	Outpatients	PP	Year	

PP, per 1000 population.

New Zealand										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Reid, 2014 <sup>69</sup>	New Zealand	Retrospective passive surveillance study	1 January 2009 – 31 December 2013	A large group practice in Lower Hutt	≥51	Coding (NR) or drug prescription	Outpatients	PP	Age, gender	
Turner, 2018 <sup>88</sup>	New Zealand	Retrospective passive surveillance study	1 January 2005 – 31 December 2015	39 consenting general practices from two primary health organizations in lower North Island	≥50	natural language processing software algorithm	Outpatients	PY	Age, year	

PP, per 1000 population; PY, per 1000 person-years; NR, not reported.

## Europe

UK										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Amrithalingam, 2018 <sup>9</sup>	England	Retrospective unmatched cohort study	1 October 2005 – 30 September 2016	164 Royal College of General Practitioners - Research and Surveillance Centre practices across England	60-89	READ codes	Outpatients PY	Age,	gender, year	
Brisson, 2003 <sup>24</sup>	UK	Retrospective passive surveillance study	1 January 1991 – 31 December 2000	89 Royal College of General Practitioners practices across England and Wales and participating GPs in the National Survey of Morbidity in General Practice database	≥45	ICD codes	Inpatients and outpatients	PP	Age	
Fleming, 2004 <sup>25</sup>	UK & NL	Retrospective passive surveillance study	1 January 1994 – 31 December 2001	Weekly Returns Service of the Royal College of General Practitioners in England and Wales and Dutch Sentinel practice network (number of GPs NR)	≥45	Clinical	Outpatients	PP	Age, gender (no both genders data)	
Gauthier, 2009 <sup>26</sup>	UK	Retrospective passive surveillance study	1 January 2000 – 31 March 2006	603 General Practice Research Datalink practices the UK	≥50	GPRD codes	Outpatients	PY	Age, gender	
Jain, 2018 <sup>27</sup>	England	Retrospective passive surveillance study	1 September 2003 – 31 August 2013	385 Clinical Practice Research Datalink practices across England	≥65	CPRD codes ICD codes (inpatients only)	Inpatients and outpatients	PY	Age, ethnicity, gender	
Walker, 2018 <sup>28</sup>	UK	Retrospective passive surveillance study	1 September 2013 – 31 August 2016	Clinical Practice Research Datalink practices across the UK (number of practices NR)	68-79	ICD codes	Inpatients and outpatients	PY	Gender	

UK, United Kingdom; NL, the Netherlands; GP, general practitioner; NR, not reported; ICD, international classification of diseases; PP, per 1000 population; PY, per 1000 person-years; GPRD, general practice research database; CPRD, clinical practice research datalink.

Germany										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Hillebrand, 2015 <sup>29</sup>	Germany	Retrospective passive surveillance study	1 January 2005 – 31 December 2009	German Pharmacoepidemiological Research Database, a national database	≥50	ICD codes	Inpatients and outpatients	PY	Year	
Schiffner-Rohe, 2010 <sup>30</sup>	Germany	Retrospective passive surveillance study	1 January 2003 – 31 December 2004	An insurance database (Allgemeine Ortskrankenkasse Hessen/KV Hessen)	≥50	ICD codes	Inpatients and outpatients	PP	Age, gender, population (general population and IC only)	
Schmidt-Ott, 2018 <sup>31</sup>	Germany	Prospective active surveillance study	November 2010 – December 2014	3 German regions (Fulda, Leverkusen and Mar) GPs, dermatologists and ophthalmologists in	≥50	Clinical	Outpatients	PY	Age, gender	
Ullsch, 2011 <sup>32</sup>	Germany	Retrospective passive surveillance study	1 January 2007 – 31 December 2008	Association of Statutory Health Insurance Physicians database	≥50	ICD codes	Outpatients	PP	Age, gender, year	
Ullsch, 2013 <sup>33</sup>	Germany	Retrospective passive surveillance study	1 January 2005 – 31 December 2008	German Statutory Health Insurance System Allgemeine Ortskrankenkasse and Regional Association of SHI-Accredited Physicians (KV) in Hessen	≥50	ICD codes	Inpatients and outpatients	PY	Age	

ICD, international classification of diseases; PP, per 1000 population; PY, per 1000 person-years; IC, immunocompetent; SHI, Statutory Health Insurance; GP, general practitioner.

The Netherlands										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Fleming, 2004 <sup>25</sup>	UK & NL	Retrospective passive surveillance study	1 January 1994 – 31 December 2001	Weekly Returns Service of the Royal College of General Practitioners in England and Wales and Dutch Sentinel practice network (number of GPs NR)	≥45	Clinical	Outpatients	PP	Age, gender (no both genders data)	
Opstelten, 2002 <sup>38</sup>	NL	Retrospective passive surveillance study	1 August 1994 – 31 July 1999	Huisartsen Netwerk Utrecht, a general practice research database in the province of Utrecht; 22 GPs in 6 locations	≥45	ICPC codes	Outpatients	PY	Age	
Opstelten, 2005 <sup>39</sup>	NL	Prospective active surveillance study	1 January – 31 December 2001	Second Dutch National Survey of General Practice; 186 GPs in 90 practices nationwide	≥65	ICPC codes	Outpatients	PP	-	
Opstelten, 2006 <sup>40</sup>	NL	Prospective active surveillance study	1 January – 31 December 2001	Second Dutch National Survey of General Practice; 186 GPs in 90 practices nationwide	≥45	ICPC codes	Outpatients	PP	Age, gender (no both genders data)	
Pierik, 2012 <sup>42</sup>	NL	Retrospective passive surveillance study	1 January 2004 – 31 December 2008	ZorgGroep Almere, a database of 22 GPs in Almere	≥60	ICPC codes	Outpatients	PP	Age	

UK, United Kingdom; NL, the Netherlands; PP, per 1000 population; PY, per 1000 person-years; ICPC, international classification of primary care; NR, not reported; GP, general practitioner.

Spain										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Cebrian-Cuenca, 2010 <sup>43</sup>	Spain	Prospective active surveillance study	1 December 2006 – 30 November 2007	24 GP offices of the public healthcare system of the Autonomous Community of Valencia	≥50	Clinical	Outpatients	PP	Age	
Esteban-Vasallo, 2014 <sup>44</sup>	Spain	Retrospective passive surveillance study	1 January 2005 – 31 December 2012	Madrid regional public health system	≥45	ICPC codes	Outpatients	PP	Age, gender, year	
Garcia-Cenoz, 2008 <sup>45</sup>	Spain	Retrospective passive surveillance study	1 January 2005 – 31 December 2006	"La base de datos de la historia clinica informaticizada de atencion primaria", Navarra	≥50	ICPC codes	Outpatients	PP	Age	
Morant-Talamante, 2013 <sup>46</sup>	Spain	Retrospective passive surveillance study	1 January 2007 – 20 December 2010	Abucasis electronic medical database and the Hospital Data Surveillance System, in the Valencian community	≥50	ICD codes	Inpatients and outpatients	PY	Age, gender, year	
Muñoz-Quiles, 2017 <sup>47</sup>	Spain	Retrospective passive surveillance study	1 January 2009 – 31 December 2014	SIA (not defined) database and Hospitalization Minimum Data Set, Valencian Region	≥50	ICD codes	Inpatients and outpatients	PY	-	

ICD, international classification of diseases; PP, per 1000 population; PY, per 1000 person-years; ICPC, international classification of primary care; GP, general practitioner.

Italy										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Alicino, 2017 <sup>48</sup>	Italy	Retrospective passive surveillance study	1 January 2013 – 31 December 2015	56 GPs in Liguria, Puglia, Toscana and Veneto	≥50	ICD codes or drug prescription	Outpatients	PY	Age, gender	
Di Legami, 2007 <sup>49</sup>	Italy	Prospective active surveillance study	1 January 2004 – 31 December 2004	All 24 GPs working in Torino and Cuornè, Piemonte	≥45	Clinical	Outpatients	PP	Age	
Gialloreti, 2010 <sup>50</sup>	Italy	Retrospective passive surveillance study	1 January 2003 – 31 December 2005	342 GPs reporting in the Health Search Database of the Società Italiana Medici Generali, from Northern, Central and Southern Italy	≥50	ICD codes	Outpatients	PP	Age, population (general population and IC only)	

ICD, international classification of diseases; PP, per 1000 population; PY, per 1000 person-years; IC, immunocompetent; GP, general practitioner.

France										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Gonzalez Chiaupe, 2010 <sup>51</sup>	France	Retrospective passive surveillance study	1 January 2000 – 31 December 2008	~1200 GPs reporting to the French general practitioners' Sentinelles electronic surveillance network	≥45	Clinical	Outpatients	PP	Age	
Mick, 2010 <sup>52</sup>	France	Prospective active surveillance study	1 January 2005 – 31 December 2005	225 GPs, 36 dermatologists, 15 neurologists and 5 physicians in pain clinics from a random sample of these physician types	≥50	Clinical	Outpatients	PP	Age, gender	

PP, per 1000 population; GP, general practitioner.

Sweden										
Author, year	Country	Study design	Study period	Setting	Age (years)	Case definition	Patient type	Denominator	Stratifications	
Nilsson, 2015 <sup>53</sup>	Sweden	Retrospective passive surveillance study	1 January – 31 December 2011	Swedish National Pharmacy Register	≥50	Drug prescription	Inpatients and outpatients	PP	Age	