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2 **Proportion of laboratory-confirmed seasonal influenza in people with**
3 **medically-attended, acute respiratory illness in Europe: A meta-analysis.**
4

5 **Abstract**

6 **Background:** Across the WHO European Region, there are few estimates of the proportion
7 of people seeking medical care for influenza-like illness or acute respiratory infections and
8 who have confirmed seasonal influenza infection when tested for respiratory viruses.

9 **Methods:** We conducted meta-analyses of data extracted from a) literature review of
10 studies published between 2004 and 2017; b) sentinel data from the European surveillance
11 system (TESSy), pooling within-season estimates by influenza type/subtype, setting
12 (outpatient/inpatient) and age-group, to estimate the proportion of people tested who have
13 laboratory-confirmed medically-attended seasonal influenza in Europe.

14 **Results:** In the literature review, the pooled proportion for all influenza was 33% (95% CI,
15 30%-36%), and higher among outpatients (36% [33-40%]) than inpatients (24% [20-29%]).
16 Pooled estimates for all influenza by age group were: 0-17 years, 26% (22-31); 18-64 years,
17 41% (32-50); ≥65 years, 33% (27-40%). From TESSY data, 33% (31-24%) of outpatients and
18 24% (21-27%) of inpatients were positive. The highest proportion of influenza A overall was
19 in people aged 18-64 years (22% [16-29%]). By subtype, influenza A(H1N1)pdm09 was
20 highest in 18-64 year-olds (16% [11-21%]) whereas influenza A(H3N2) was highest in those
21 ≥65 years (10% [2-22%]). For influenza B, the highest proportion of infections was those
22 aged 18-64 years (15% [9-24%]). Estimated proportions of confirmed influenza varied across
23 seasons and across countries.

24 **Conclusions:** Both the literature review and TESSy analyses showed a higher proportion of
25 laboratory-confirmed influenza in non-hospitalised patients, with further variation by
26 influenza type, age-group, country and season.

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1 Introduction

2 Seasonal and pandemic influenza are global public health problems associated with
3 significant clinical burden [1]. However, seasonal influenza causes higher cumulative
4 morbidity and mortality, as it affects populations on an annual basis [1, 2]. The
5 epidemiological impact of influenza varies from season to season, between geographic
6 areas and according to the circulating antigenic variants of the main influenza types, A and B
7 [2-6]. Within a population, the clinical impact in subgroups considered at-risk for the
8 development of serious influenza-related complications (the very young and the elderly,
9 pregnant women and people with underlying co-morbidities) is greater than in those not in
10 risk groups [2].

11
12 Influenza infection is very common; asymptomatic infections may account for between 16%
13 and 85% of seasonal influenza infections, depending upon study design and testing method
14 [1, 7], and most symptomatic individuals infected experience only mild and self-limiting
15 illness [2, 3]. In people seeking medical care, accurately diagnosing influenza A or B solely on
16 the basis of clinical criteria is difficult as the signs and symptoms of influenza overlap with
17 those of many other respiratory viral pathogens which co-circulate with influenza every
18 winter in temperate regions of the world. Laboratory-testing identifies the specific causative
19 virus but in clinical practice few patients presenting with signs and symptoms suggestive of
20 influenza are tested due to timeliness and cost; thus, the actual contribution of influenza
21 viruses to total respiratory illness in the population remains relatively uncertain, especially
22 in primary care settings where laboratory testing is extremely rarely undertaken.

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1 Since the early 2000s, large investments by the United States and others have supported
2 development of the global capacity for influenza surveillance, and many networks for
3 influenza surveillance now exist globally and in the European region specifically [8-11],
4 where the WHO Regional Office for Europe (WHO/Europe) and European Centre for Disease
5 Prevention and Control (ECDC) co-ordinate the collection and analysis of surveillance data
6 provided by Member States (European Surveillance System (TESSy)). These data provide a
7 source for estimating the frequency of influenza within countries. In 2015, we conducted a
8 scoping literature review on the burden of influenza within the WHO European Region
9 which provided an overview of the general burden caused by seasonal influenza and
10 highlighted the lack of data from eastern European countries (*author*, unpublished data).
11 However, some of the estimates provided were derived from symptom-based endpoints
12 (e.g., influenza-like illness [ILI] or severe acute respiratory infection [SARI]) which made it
13 impossible to compare the clinical burden of laboratory-confirmed influenza between
14 countries.

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16 In this study we aim to estimate the proportion of laboratory-confirmed influenza in the
17 WHO European region in people seeking medical care with clinically diagnosed acute
18 respiratory infection (ARI) or ILI and who are tested for respiratory viruses, including
19 influenza. Two methods are presented: a review and meta-analysis of data published in the
20 literature from 2004 to 2017; a meta-analysis of seasonal influenza data from the European
21 Surveillance System (TESSy).

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1 **Methods**

2 [Literature Review](#)

3 The study was conducted according to Preferred Reporting Items for Systematic Reviews
4 and Meta-Analyses (PRISMA) guidelines [12]. We identified articles which reported
5 quantitative data on laboratory-confirmed influenza infections in people seeking medical
6 attention for ILI/ARI, as defined by individual studies, in the WHO European Region.
7 MEDLINE was searched in September 2017 using a search strategy devised by one author
8 (Appendix A, Supplementary material). The strategy sought studies of any design, published
9 in English between 2004 and 2017 (influenza seasons up until 2016–2017 but excluding data
10 from the pandemic year, 2009-2010) which were conducted in countries within the WHO
11 European Region [13]. Studies were included which offered within-season influenza
12 positivity data for at least one full influenza season (from October through May of the
13 following year) on symptomatic and medically-attended acute respiratory illness in patients
14 of any age, and in whom influenza virus infection was confirmed by culture or reverse
15 transcription polymerase chain reaction (RT-PCR). Additionally, we searched the reference
16 lists of included studies and relevant systematic reviews [14-18] and the references included
17 in a literature review we conducted previously that looked at studies conducted between
18 the years 2004-2015 (*author*, personal communication). We included study populations of
19 all ages or in stratified age groups, and all healthcare settings including primary
20 care/ambulatory outpatients (OP) and hospitalised in-patients (IP).

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22 Studies were excluded if the total number of specimens tested each year was less than 50,
23 or were outbreak reports from closed or semi-closed communities (e.g., nursing homes,
24 army bases, or religious groups), in which the results would not be representative of the

1 wider population. Studies were also excluded if data presented were combined for more
2 than one season or more than one pathogen with no separate influenza data. We also
3 excluded studies in which there was no clear sampling strategy or in which participants
4 were sampled at the discretion of the treating clinician, which could introduce bias.

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6 One of the authors screened the titles and abstracts of all the identified literature for
7 relevance, then conducted a full review of papers. We extracted the following variables:
8 influenza season, country, age group, laboratory testing method, healthcare setting, case
9 definition, total number of symptomatic subjects tested and number of subjects positive for
10 influenza. If data for separate influenza types and subtypes were presented, the number of
11 positive subjects for each were also extracted. The percentage of positive subjects was
12 calculated based on number of subjects tested as a denominator, and number of positive
13 subjects as a numerator (aggregated influenza, types and subtypes according to the data
14 presented in each study).

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16 For quality assessment, we used a modified version of the Newcastle-Ottawa assessment
17 scale for cohort studies [19]. Indicators used to assess quality were the following:
18 representativeness (geographic, age and general representativeness) of the subjects tested,
19 assessment of the outcome (sensitivity of symptoms prompting laboratory testing such as
20 number of symptoms and having a clear case definition), and laboratory method. Some
21 indicators were not applicable and excluded (i.e., representativeness of exposed cohort,
22 ascertainment of exposure and demonstration that outcome was not present at the start of
23 the study). Other indicators (comparability of cohorts and adequacy and length of follow up)

1 were also excluded since we only included studies that had at least one complete season of
2 data.

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4 [The European Surveillance System \(TESSy\) data](#)

5 We retrospectively analysed laboratory-confirmed influenza detection data reported to the
6 European Surveillance System (TESSy; hosted by the European Centre for Disease
7 Prevention and Control [ECDC]) as a part of the surveillance of influenza in the WHO
8 European Region, which is jointly coordinated by WHO/Europe and ECDC. Sentinel influenza
9 surveillance is conducted in a representative subset of sites and co-ordinated by national or
10 sub-national networks, with systematic sampling of patients meeting pre-defined case
11 definitions. Data were provided by Albania, Armenia, Austria, Azerbaijan, Belarus, Belgium,
12 Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany,
13 Greece, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, North Macedonia,
14 Malta, Republic of Moldova, Netherlands, Norway, Poland, Portugal, Kazakhstan,
15 Kyrgyzstan, Portugal, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Spain,
16 Sweden, Switzerland, Tajikistan, Turkey, United Kingdom, Ukraine and Uzbekistan, and
17 released by ECDC. Data on the duration of participation of these countries are listed in
18 Appendix B (Supplementary Data). Data submitted by week and country for the period 2004
19 to 2018 (weeks 40 to 20) were extracted from TESSy on 29 August 2018. Separately, the
20 total number of specimens collected from patients presenting to sentinel primary care sites
21 and meeting the influenza-like illness (ILI) or ARI case definitions and hospitalised patients
22 meeting the case definition for SARI were calculated by country and influenza season
23 (International Organization for Standardization [ISO] week 40 in a given year to week 20 in

1 the following year) for the 2004-2005 to 2017-2018 seasons, as were the corresponding
2 total number of detections by influenza virus type and subtype (for influenza A) . Country-
3 seasons were excluded if there were fewer than 50 specimens or less than 20 weeks of data
4 submitted to TESSy. The proportion of sampled patients that tested positive for any
5 influenza virus, influenza A virus and influenza B virus were calculated by country-season.

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7 [Data extraction and analysis](#)

8 Data from the literature review and those derived from the TESSy dataset were extracted to
9 a Microsoft® Office Excel® 2013 spreadsheet (Microsoft Corporation, Richmond, VA, USA).
10 As we anticipated a degree of heterogeneity due to the observational nature of the included
11 studies, we used a generic variance approach based on a random effects model
12 (DerSimonian-Laird weights method)[20] to estimate the pooled proportion of laboratory-
13 confirmed influenza virus identified in tested patients,, stabilising the variances using the
14 Freeman-Tukey double arcsine transformation so that studies with proportions close to 0%
15 or 100% were appropriately estimated [21]. Exact binomial confidence intervals (CIs) were
16 computed for outcomes. The main outcome was the proportion (and 95% CI) of laboratory-
17 confirmed influenza in people with ARI or ILI symptoms who sought medical care and were
18 tested for influenza (the denominator). Data from the literature review and TESSY were
19 analysed separately. For analysis of the TESSy data, people with ARI/ILI were classified as
20 outpatients as the data were derived from primary care surveillance of mild influenza
21 disease due to influenza, and those with SARI were classified as hospitalised as data
22 originated from sentinel surveillance of hospitalised cases presenting with severe disease
23 [22]. The denominator in the latter was the number of people with SARI who were tested
24 for influenza. Heterogeneity between the studies was assessed using the I^2 statistic.

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The initial analysis was for all types of influenza (aggregated influenza) and for all ages. To investigate potential sources of heterogeneity, we performed subgroup analyses by influenza virus type and subtype [influenza A, influenza A(H1N1), influenza A (H3N2) and influenza B], age group, healthcare setting (OP versus IP), and requirement for fever in the case definition. To further investigate high heterogeneity, we undertook an I²sensitivity analysis by excluding datasets in which the estimated proportion was furthest from the overall estimated pooled proportion. We excluded data collected during the 2009 pandemic; influenza A(H1N1) was stratified by pre-pandemic seasons [A(H1N1), up to and including the 2008-2009 season] and post-pandemic seasons [A(H1N1)pdm09, 2010-2011 onwards] and analysed separately because population susceptibility to these two viruses will have been markedly different. Age groups in studies included were not uniform, so for the purpose of this analysis we created the following categories to best fit the majority of the data: 0-17 years, 18-65 years, and ≥65 years. All analyses were conducted using the *metaprop* command in Stata (SE 16, StataCorp, College Station, Texas, USA).

[Ethical Statement](#)

Ethical approval was not required; the review of the literature is based on secondary data with no personally identifiable information. ECDC has a legal basis to collect surveillance data (DECISION No 1082/2013/EU).

1 **Results**

2 [Literature Review](#)

3 The Medline database search identified 9316 manuscripts. In total, 9496 were screened by
4 title and abstract, 176 were fully reviewed, and 38 met the inclusion criteria Figure 1 and
5 Appendix C [Supplementary Material]).

6 *Figure 1 Flow chart displaying number of articles identified and screened at each stage of*
7 *the literature review*

8 **Study Characteristics**

10 Studies reported data from 25 European countries (Albania, Armenia, Austria, Belarus,
11 Bulgaria, Czech Republic, Finland, France, Georgia, Germany, Greece, Italy, Kazakhstan,
12 Kyrgyzstan, Netherlands, Portugal, Romania, Russian Federation, Slovenia, Spain, Sweden,
13 Switzerland, Turkey, United Kingdom and Ukraine). The greatest number of studies were six
14 each from Italy and the United Kingdom, the lowest was one (from each of Albania,
15 Armenia, Georgia, Kazakhstan, Romania, Belarus, Ukraine and Kyrgyzstan). Five studies
16 reported data from multiple countries.

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18 The studies included covered influenza seasons from 1996-1997 to 2014-2015. Of the 38, all
19 study designs were cross sectional except for two (case-control and randomized control
20 trial). Detection of influenza viruses was achieved by RT-PCR with or without culture in 32
21 studies and by culture alone in six. A sensitivity analysis was conducted excluding the
22 culture-only studies (Supplemental Table 1), however this had a negligible effect on the
23 pooled estimates. Ten studies were conducted among IPs while the remainder were among
24 OPs.

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1 **Risk of Bias assessment**

2 Of the 38 studies, the quality assessment was high or intermediate in 24 (63%) for
3 geographical representativeness, in 29 (76%) for age representativeness, in 38 (100%) for
4 general representativeness, in 31 (82%) for sensitivity of symptoms, and in 38 (100%) for
5 laboratory methods (Supplementary tables 2 and 3). Age representation was rated as low in
6 10 (26%) because data were presented for all ages, and sensitivity of symptoms was rated
7 low in seven (18%) as they required two or more specific symptoms for inclusion of subjects
8 in study.

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10 **Meta-analysis**

11 Over the influenza seasons included, the pooled estimates of the proportion of people of
12 any age who were tested and who were positive for any type of influenza were 36% (95% CI
13 33%-40%, $I^2=99.5%$, 9 studies, 47 datasets) for OPs, and 24% (95% CI 20-29, $I^2=98.4%$, 5
14 studies, 16 datasets) for IPs (Figure 2). Proportions by influenza types and subtypes are
15 presented in Table 1. I-squared sensitivity analysis in which 10 datasets where the
16 proportion of positivity was <5% or >50% were excluded slightly reduced the estimated
17 estimates but did not significantly decrease the observed heterogeneity (33% [95% CI 30-37,
18 $I^2=99.34%$] and 23% [95% CI 19-27, $I^2=97.76%$] for OPs and IPs respectively).

19

20 *Figure 2: Forest plot (studies from literature review) showing proportion of all influenza viruses*
21 *grouped by healthcare setting (outpatient or inpatient) in Europe*

22 *Key: ES effect size; CI confidence intervals; IP inpatient; OP outpatient*

23 *Note: Many studies reported findings for more than one season and more than one country.*

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1 Table 1. Pooled estimates of the proportion of medically-attended people with ARI/ILI testing positive
 2 for influenza viruses, overall and by age group from literature review meta-analysis.

Influenza virus	Proportion positive %	95% CI, number of studies	Proportion positive by age group (%) (95% CI, number of studies)		
			0-17yrs	18-64yrs	≥65yrs
Any influenza virus Overall	33	30-36, 14	26 (22-31), 21	41 (32-50), 4	33 (27-40), 5
Outpatient	36	33-40, 9	26 (21-31), 18	41 (32-50), 4	33 (27-40), 5
Inpatient	24	20-29, 5	9 (6-12), 3	-	-
Influenza A Overall	24	21-26, 11	12 (9-15), 12	22 (16-29), 4	18 (8-31), 4
Outpatient	24	21-28, 8	14 (11-18), 9	22 (16-29), 4	18 (14-31), 4
Inpatient	26	16-26, 3	6(4-9), 3	-	-
Influenza B Overall	7	6-10, 16	6 (3-8), 17	15 (9-24), 4	10 (3-19), 5
Outpatient	9	6-12, 10	9 (5-14), 13	15 (9-24), 4	10 (3-19), 5
Inpatient	5	3-8, 6	3(1-5), 4	-	-
Influenza A(H1N1): pre 2009 pandemic					
Outpatient	3	1-5, 2	3 (1-6), 4	-	-
Inpatient	-	-	-	-	-
Influenza A(H1N1): post 2009 pandemic Overall	12	8-16, 7	6 (4-8), 4	16 (11-22), 2	4 (1-8), 2
Outpatient	11	7-15, 3	8 (5-10), 2	16 (10-22), 2	4 (1-8), 2
Inpatient	14	5-26, 4	2 (1-5), 1	-	-
Influenza A(H3N2) Overall	11	8-14, 11	7 (4-9), 11	8 (4-12), 3	10 (2-22), 4
Outpatient	13	9-17, 6	10 (7-13), 10	8 (4-12), 3	10 (2-22), 4
Inpatient	9	5-14, 5	4(1-8) 1	-	-

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3 For OPs, the following pooled estimates of proportion influenza positive patients were
4 noted from studies which reported by age groups: 0-17 years, 26% (95% CI 21-31, 18
5 studies, 32 datasets); 18-64 years 41% (32-50, 4 studies, 14 datasets); and ≥ 65 years, 33%
6 (95% CI 27-40, 5 studies, 16 datasets)(Supplemental figure 1). For IPs, data were only
7 available for the age group 0-17 years, 9% (95% CI 6-12, 3 studies, 3 studies, 9 datasets)
8 (Supplemental figure 2).

9
10 Table 1 shows the proportions of influenza A, subdivided into pre-pandemic A(H1N1), post-
11 pandemic A(H1N1)pdm09, and A(H3N2) viruses and influenza B in OPs and IPs across the
12 different age groups. The highest proportion of influenza A infections was seen in the 18-65
13 year age group with a pooled proportion estimate of 22% (95% CI 16-29, 4 studies, 12
14 datasets), followed by the ≥ 65 years age group (18% [95% CI 14-31, 4 studies, 13 datasets]).
15 Similar to influenza A overall, the proportion infected with A(H1N1)pdm09 virus was highest
16 in the age group 18-64-65 years at 16% (95% CI 11-22, 2 studies, 10 datasets) in OPs. The
17 highest proportion of influenza A(H3N2) virus was noted in the ≥ 65 years age group (10%
18 [95% CI 2-22, 4 studies]). For influenza B, the highest proportion of confirmed patients were
19 in the 18-64 year group (15% [95% CI 9-24, 4 studies]), 12 datasets (Supplemental Figures 3-
20 14).

21
22 Pooled estimates of the proportion of confirmed influenza stratified according to influenza
23 season ranged from 19% in 2011-12 (95% CI 9-31, 2 studies) and in 2013-14 (95% CI 14-24, 2
24 studies, 5 datasets) to 48% (95% CI 46 to 49, 2 studies) in 2002-03. When stratified by
25 country, pooled estimates of confirmed influenza ranged from 9% (2 studies) to 65% (1

1 study). Stratification by the requirement for fever in the case definition of ILI/ARI in
2 individual studies, did not reveal a significant difference in the pooled proportion of
3 influenza positivity between studies specifying the presence of fever and those in which it
4 was not mandatory (32% [95% CI 25-39, 8 studies] versus 31% [95% CI 28-35, 3 studies
5 respectively], $p=0.82$). Heterogeneity was high ($I^2>90\%$) in all the meta-analyses.

7 [The European Surveillance System \(TESSy\) data](#)

8 ILI/ARI data were collected from 44 countries and SARI data from 15 countries. Both
9 datasets presented findings from persons of all ages only. The pooled estimate for all
10 influenza in tested patients seeking medical attention from the ILI/ARI dataset was 33%
11 (95% CI 31-34, $I^2=99.35\%$), and for SARI the proportion was 24% (95% CI 21-27, $I^2=98.75\%$).
12 Table 2 shows the proportions of detections of influenza A, B, A(H1N1), A(H1N1)pdm09 and
13 A(H3N2) viruses by case definition in TESSy.

14
15 Pooled estimates of the proportion of confirmed influenza in tested ARI patients for seasons
16 between 2004-05 and 2017-18, ranged from 22% (95% CI 18-27) in 2013-14 to 39% (95% CI
17 34-44) in 2012-13 and in 2017-18. The highest estimated proportions of confirmed
18 infections were noted in 2016-2017 for influenza A (32% [95% CI 28-37]), in 2015-2016 for
19 influenza A(H1N1)pdm09, excluding 2009-2010 (17% [95% CI 14-20]), in 2016-2017 for
20 influenza A(H3N2) (27% [95% CI 22-32]) and in 2012-2013 for influenza B (17% [95% CI 13-
21 21]) (Figure 3).

22 *Figure 3: Influenza positivity as a proportion of all ILI/ARI tested by influenza season: all influenza and*
23 *by type and subtype (TESSy data)*

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1 The pooled estimated proportion of confirmed influenza varied across countries, ranging
 2 from 6% (95% CI 2-10, 8 seasons) to 78% (1 season) for ARI, and from 8% (1 season) to 76%
 3 (1 season) for SARI.

4 *Table 2 . Pooled proportions of medically-attending patients with ARI/ILI/SARI testing positive for*
 5 *influenza from TESSy data; by all influenza types and by influenza subtypes*
 6

	Pooled proportion % of influenza positive (95% CI)	
	ILI/ARI [OP:Total tested 609,368] ^a	SARI [IP: Total tested 61,182] ^b
All influenza	33 (31-34)	24 (21-27)
Influenza A	21 (20-22)	16 (13-18)
Influenza B	8 (7-9)	6 (4-8)
Influenza A(H1N1) Pre-pandemic	3 (2-3)	-
Post-pandemic	6 (5-7)	5 (3-7)
Influenza A(H3N2)	8 (7-9)	5 (3-7)

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 8 ^a44 countries, 558 country-years
 9 ^b15 countries, 87 country-years
 10 Denominator = number of specimens tested from patients with ARI/ILI/SARI
 11 ARI acute respiratory infection
 12 CI Confidence intervals
 13 ILI influenza-like illness
 14 IP inpatients
 15 OP outpatients
 16 SARI severe acute respiratory infection
 17

18 Discussion

19 To our knowledge, these are the most comprehensive data assembled to date on the
 20 proportion of laboratory-confirmed influenza in people across the WHO European Region
 21 presenting for medical care and with clinically-diagnosed ARI or ILI. We used two
 22 approaches: a literature review and a review of surveillance data reported to WHO, to
 23 estimate the prevalence of within-season influenza in Europe. Both methods produced
 24 findings in all ages and for inpatients and hospitalised patients. The proportion of seasonal

1 influenza from the literature review data in outpatients was 36% and 24% for inpatients.
2 From the TESSy data ILI/ARI proportion for all influenza was 33%, while the SARI proportion
3 of all influenza was 24%. The 95% CIs for the TESSy ARI and SARI data were narrower
4 reflecting the larger number of samples. The lower proportion of laboratory-confirmed
5 influenza in hospitalised patients compared to patients seeking outpatient care has been
6 found in other parts of the world [23-26]. Diagnostic tests for influenza perform best when
7 specimens are collected as close to the onset of symptoms as possible, ideally within 72
8 hours [27]; hospitalised patients may experience symptoms for some time prior to
9 admission and being swabbed which may decrease detection rate. The observation may also
10 be a reflection of different characteristics of the outpatient and inpatient populations, and
11 neither the ILI nor the SARI case definition is specific to influenza.

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13 Our pooled analyses of the proportion of confirmed influenza using both the literature
14 review data and the TESSy data are somewhat higher than those that have been estimated
15 in the United States. A study pooling data from the North American literature estimated an
16 influenza incidence in children under 18 years of 12% (95% CI 4.6 to 14.7%) and 6.1% (95%
17 CI 4.3 to 7.9%) in adults over several seasons when influenza severity was moderate [28].

18 However, there is some evidence that the situation in Europe may be different. In a meta-
19 analysis examining the contribution of influenza to medically-attended ARI in children over
20 several seasons in high-income countries, the proportion of influenza positive patients
21 ranged from 18% (95% CI 12 to 25%) in the United States to 29% (95% CI 21 to 37%) in
22 Europe, which is closer to the results we obtained [14]. This may be partly explained by
23 differences in influenza vaccine recommendations in Europe and the United States.

24 Although most countries in the European Union and European Economic Area have policies

1 in place for seasonal influenza vaccination of people in high-risk groups, not all countries
2 target children and vaccination coverage rates vary widely across the groups recommended
3 for vaccination [29]. In the United States however, seasonal influenza vaccination is
4 recommended for everyone aged 6 months and over unless contraindicated [30].
5 Additionally, there may be differences between healthcare-seeking behaviour for ILI in
6 different parts of the world, with some countries having a higher threshold than others [31].

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8 The proportion of positive influenza tests varied from season to season in both the
9 literature review and analysis of the TESSy data. Over the totality of included seasons,
10 influenza A accounted for a greater proportion of laboratory-confirmed influenza infections
11 than influenza B. Since the 2009 pandemic, influenza A viruses have been dominant or co-
12 dominant in seven of eight seasons across the European Region with influenza B dominant
13 seasons occurring only infrequently, most recently in 2017-2018 [32]. Our literature review
14 data of five seasons since the 2009 pandemic mirror these findings, with influenza A virus
15 accounting for the greatest proportion of confirmed influenza in 2010-11, 2011-2012, 2013-
16 2014 and 2014-2015, and similar proportions of confirmed influenza A and influenza B in
17 2012-2013, a season when the influenza A and B were co-dominant. Over the ten year
18 period between 1999 and the 2009 pandemic, seven influenza seasons in Europe were
19 dominated by influenza A(H3N2), with or without co-circulation of influenza B, with
20 significant circulation of pre-pandemic H1N1 in only two of these seasons in 2000-2001 and
21 2007-2008 [33-36], which is in accordance with the data from both our literature review and
22 the TESSY analysis.

23

1 We acknowledge that our study has a number of important limitations. Differences in
2 estimated proportions between age groups may be genuine, but such differences may also
3 arise through variation in health-care seeking behaviour according to age. There is evidence
4 that younger working age adults are less likely to seek healthcare than children and even
5 then only when they are very unwell, so the denominator may be smaller in this age group
6 which could lead to increased overall positivity in accordance with our findings [[37].

7 Observed differences in the proportions of influenza positive patients between the age
8 groups should be interpreted with caution. We were only able to collect age group data
9 from the literature review, and the papers identified varied in how age was categorised.
10 There were very few studies that reported on children who were under 3 years old; the
11 largest number of the papers reported the age group ranging from 0-17 years, and hence it
12 is possible that older children have been over-represented in our meta-analysis.

13 Furthermore, although we did not include data for the 2009 pandemic, it is possible that
14 health-seeking behaviour may have increased in some age groups in the seasons
15 immediately following the pandemic and this may have affected our findings.

16

17 We defined influenza burden as the percentage of patients with an ARI or ILI seeking
18 medical care and tested for respiratory viruses, who are positive for laboratory-confirmed
19 influenza. We are unable to comment on the burden of laboratory-confirmed influenza in
20 people who get ARI or ILI and who seek care but are not tested, nor in those who develop
21 symptoms but do not seek medical care. The proportion of true influenza in each of these
22 populations may well be lower than our estimates. A study from the United States
23 estimated that 38% of people with influenza present for medical care, less than the
24 proportion of people with RSV or adenovirus infections but greater than in those with

1 rhinovirus, coronavirus, parainfluenza virus and other respiratory viral infections [38]. A
2 FluWatch cohort study over five seasons from the UK found that only 17% of those with
3 PCR-confirmed influenza had medically-attended illness [1]. Other studies from Europe have
4 shown that the majority of people with ARI or ILI do not seek medical care, but with much
5 variation between countries and between northern and southern Europe, suggesting
6 regional cultural differences [31]. Healthcare seeking behaviour and clinician behaviour are
7 complex issues and decisions made at different points of the clinical interaction may affect
8 the overall composition of the sampled population in terms of severity of illness. Even if
9 influenza attack-rates and healthcare seeking behaviour are similar between countries, if
10 the propensity of clinicians to test patients, refer them to hospital and to admit them differs
11 across countries, the resulting hospitalised populations will vary in the severity of their
12 illness. Our estimates from the literature review and from TESSy were within-season
13 estimates as influenza shows clear seasonality in temperate regions, so the positivity
14 estimates will not apply to respiratory illnesses occurring outside the influenza season. This
15 also limits direct comparability to existing influenza burden estimates, including multiplier-
16 based burden analyses and global burden estimates, which use annualised estimates and
17 may thus have lower influenza positivity [39-41]. However, within-season estimates have
18 more relevance for public health planning in countries with defined influenza seasons.

19

20 In the literature review, one person reviewed the references and extracted the data, so it is
21 possible that some studies were missed. Additionally, there was greater representation of
22 countries in the western part of Europe in the published literature and although we did not
23 exclude non-English language studies, it is likely that the database searched was less likely
24 to include studies from countries in Eastern Europe. We did not search Russian language

1 databases in our literature review which may have added more data from eastern European
2 countries.

3

4 Heterogeneity was very high in the meta-analyses but as our outcomes were absolute
5 measures rather than ratio measures which tend to be more stable across studies, this was
6 not unexpected [42]. Multiple factors are also likely to cause such heterogeneity, including
7 differences in healthcare systems, case definitions, age groups, climate, vaccination
8 coverage and general health, which makes comparisons challenging. It is also likely that
9 there are cultural differences between countries in terms of the healthcare seeking
10 behaviour of citizens. We included papers reporting ARI or ILI as defined by the individual
11 studies rather than standardised definitions so this is a potential source of heterogeneity. In
12 2011 the WHO revised the clinical case definition of ILI to enhance its specificity without
13 greatly compromising its sensitivity, such that the requirement for 'sore throat' and
14 'absence of another diagnosis' were omitted and 'sudden onset of fever' was replaced by
15 'acute respiratory illness'. The case definition of an ARI does not require fever to be present
16 so is less specific for detecting influenza than the revised ILI definition [43]. We explored
17 potential sources of heterogeneity through stratification and sensitivity analyses, yet
18 considerable heterogeneity remained and the results should be interpreted taking this
19 unexplained heterogeneity into consideration.

20

21 Notwithstanding, we believe that this study adds to the knowledge base on the contribution
22 of seasonal influenza virus infections to respiratory illness across the region. Estimates of
23 influenza positivity can help with appropriate allocation of limited health resources among
24 competing disease priorities, establish epidemic thresholds for comparison of disease

1 severity between seasons and localities, and provide a platform for the evaluation of the
2 effectiveness of vaccines and other intervention [44]. Particular strengths of this study
3 include the use of viral culture or RT-PCR, which is the gold standard for influenza diagnosis
4 because of its superior analytic and clinical sensitivity [45]. In the literature review we used
5 a comprehensive search strategy, careful inclusion criteria and used an adaptation of an
6 accepted quality assessment scale. Additionally, we relied on data collected individually
7 within a full season which strengthens the validity of our results.

8

9 In conclusion, this analysis estimated the proportion of laboratory-confirmed seasonal
10 influenza in symptomatic people who presented for health care with ARI and were
11 subsequently tested for influenza viruses in the European region across the influenza
12 seasons between 1996 and 2017. The estimated proportion of positive tests was shown to
13 be greater in outpatients than in hospitalised patients by both methods, with differences
14 according to influenza subtype and across different age groups. Overall, in Europe
15 laboratory-confirmed influenza accounts for around one third of all acute respiratory
16 infections for which medical care is sought during the influenza season and where
17 laboratory testing for influenza is undertaken. The effect of the ongoing COVID-19 pandemic
18 on healthcare-seeking behaviour for ILI, and changes in countries' testing priorities and
19 capacities may potentially affect estimates of influenza positivity in future seasons and this
20 should be taken into account when comparing our results and will require further
21 investigation in forthcoming influenza seasons.

22

23

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