Information and Communication Technologies

EPIWORK

Developing the Framework for an Epidemic Forecast Infrastructure

http://www.epiwork.eu

Project no. 231807

D6.4 A digitalized set of data from the concurrent deployment of population-based (PBA) and Internet-based voluntary monitoring (IMS) systems for infectious disease surveillance, a formal validation study of the PBA system, and a preliminary comparison between the PBA and IMS systems.

Period covered: Month 25th-36th
Start date of project: February 1st, 2009
Due date of deliverable: Month 36
Distribution: public
Date of preparation: 01-31-12
Duration: 12 Months
Actual submission date: 02-14-12
Status: Final draft

Project Coordinator: Alessandro Vespignani
Project Coordinator Organization Name: ISI Foundation
Lead contractor for this deliverable: SMI

Table of Contents

1. Background

1.1. Overall objective of WP6

The overall objective of the work produced within Work Package 6 (WP6) is to provide a comparative analysis of three systems for disease surveillance in Sweden: (1) the existing general practice-based sentinel system of influenza surveillance with the (2) new Internet monitoring system (IMS/*Influenzanet* or *Influensakoll*) that is implemented within the framework of Work Package 5 (WP5), and (3) a population-based approach (PBA, *Sjukrapport*), recently developed at the Swedish Institute for Communicable Disease Control (Smittskyddsinstitutet, SMI).

1.2. Overview of activities related to Deliverable 6.4

Recruitment of PBA cohort

The population-based infectious disease surveillance system (PBA), known as *Sjukrapport*, based on passive follow-up in representative general population cohorts, has now been deployed for several seasons. In collaboration with Statistics Sweden, a new cohort of approximately 2,500 men and women, 3 months to 95 years of age, was recruited in September 2011. The *Sjukrapport* system has generated incidence data in close to real time ever since. The procedures for population sampling and recruitment were elaborated in Deliverables 6.1 and 6.3 together with an investigation into the selection forces involved in the establishment of the general population cohorts. An account of the most recent sampling/recruitment is given under section 2.1.

Preparation and Launching of the IMS system

The Internet-based voluntary system was established already in February 2011, but due to technical problems associated with the change of platform, a public launch was impossible until November 17, 2011. The reason for the delay was technical bugs in and difficulties with the original system, which was developed in Holland. In the spring of 2011, a second Dutch subcontractor was engaged in the development and implementation work, and this – combined with huge efforts from all partners in WP5 – ultimately made the last-minute launch possible.

The reasons for the delay have been out of our control, but the consequences were aggravated by the fact that Sweden was the first country to join Influenzanet after the total re-make of the platform architecture. Since testing, de-bugging and accumulation of a sufficiently large stock of users of the website require considerable time and major marketing efforts, our original intention was to establish the Influenzanet website already in the fall of 2010, but this aim could not be realized.

Nonetheless, we were rather successful in drawing public attention to the November 17 launch, and we rapidly gained more than 1,000 participants. In relation to the total population, this figure compares well with those of the other Influenzanet partners, Holland excepted. It is notable that the launch was done in the aftermath of a wave of critique of health authorities' handling of the influenza A(H1N1) pandemic. There has been a general weariness among the public in regard to measures against influenza, reflected by lower vaccination rates, lower participation rates in our PBA system, and decreased participation in the established Influenzanet systems run by our WP5 partners.

The number of participants in the Swedish IMS system is still far below our own goal of 10,000 participants, which was set to ensure a fair comparison between PBA and IMS systems. Luckily, the influenza activity has been unusually low in Sweden, and this season's influenza peak is yet to come. We intend to continue the full operation of both systems (and of the regular sentinel reporting system) throughout the present season, and possibly in the 2012-2013 season.

1.3. Layout of the Deliverable 6.4

In this report, Deliverable 6.4, we first discuss the results of the PBA (*Sjukrapport*) and the IMS (*Influensakoll*), which WP6 strives to compare. Then we present the results of our preliminary comparison between the two systems using the data from the first 9 weeks of the 2011-2012 influenza season. Finally, we discuss next steps within WP6.

2. The Population-based Approach (*Sjukrapport*)

2.1. Recruitment of PBA cohort

For the past five influenza seasons, SMI has recruited between 12,000 and 15,000 people living in Stockholm to be a part of the PBA surveillance system, *Sjukrapport*. During the 2011-2012 season, we invited 14,022 people in a random sample of Stockholm's population between the ages of 3 months and 95 years to participate. The methodology was described in Deliverable 6.1. *Sjukrapport* has 2,556 participants during this season. Participants were recruited in September 2011 and data began to be used in surveillance starting week 40 (week of October 3) of 2011.

Figure 1 shows the breakdown of *Sjukrapport* participants by sex, with 59 percent being women and 41 percent being men. This matches rather closely to the sex distribution among participants of *Influensakoll*.

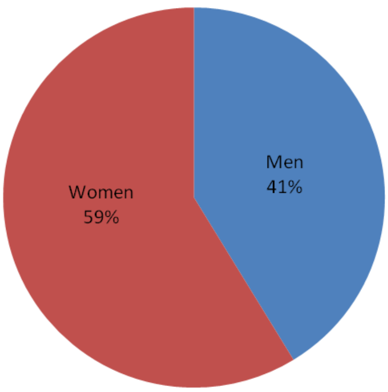

Figure 1. Sjukrapport participants by sex

Figure 2 shows the age distribution in Stockholm County population (in blue), the sample selected to receive invitations (in red), and in the final participant cohort of *Sjukrapport* (in green). As can be seen, we oversampled in the 15-39 years age group and under-sampled in the older age groups to account for expected age group-specific differences in participation rates.

Further, we intentionally refrained from under-sampling in the 0-14 years age group in order to get better resolution in this group, which accounts for a large part of infectious disease spreading in the community. Apart from this intentional over-representation of children (which requires weighting when all-age incidence rates are calculated), the age distribution among participants matches well with that in the underlying population.

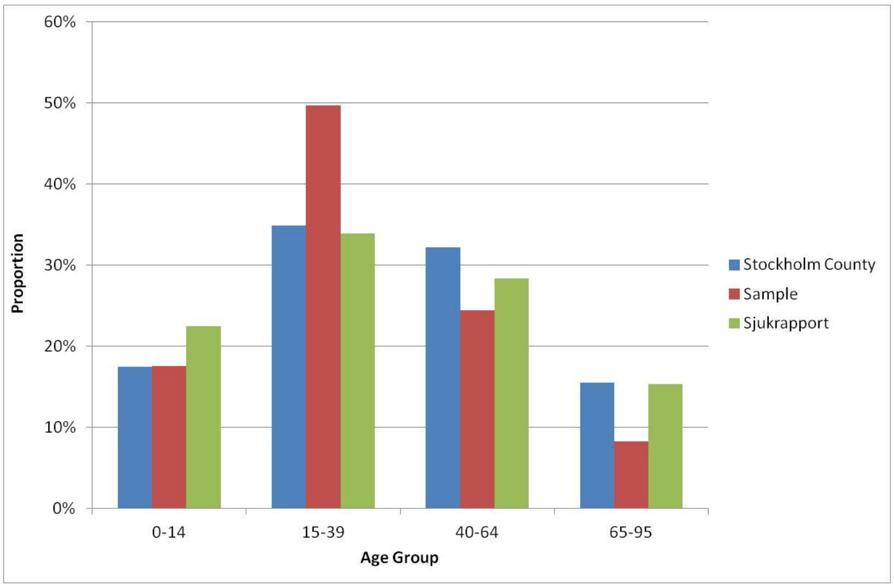

Figure 2. Age distribution of Stockholm County population, sample, and Sjukrapport participants

2.2. Validity of self-reports in the PBA surveillance system (Sjukrapport)

As part of the development of the PBA system, *Sjukrapport*, we conducted a validation study to determine how well the system captures ongoing disease status in the population. The following section describes the methods used, presents the results of the validation, and summarizes the discussion surrounding these results. These validation results are otherwise unpublished and should not be shared outside of the EPIWORK project.

2.2.1. *Sjukrapport* validation methods

The validation effort took place during ongoing surveillance in two consecutive *Sjukrapport* participant cohorts between January 14 and March 9, 2008, as well as between January 26 and March 22, 2009. The restriction in time was primarily to contain costs.

Although not a perfect gold standard, we used one-week recall questionnaires as a reference method. These questionnaires were distributed via e-mail when possible, otherwise by regular mail, and consisted of two questions: 1. Did you have a cold or fever last week [exact dates specified]? 2. If yes, did you fall ill last week? (The validation week was always Monday-Sunday the preceding week.) All cohort members in both periods received questionnaires, except for approximately 1,000 randomly selected cohort members per period who were left undisturbed. The latter groups enabled us to assess if the validation study affected the event-driven reporting of illness (reactivity).

We compared the reported absence or presence of fever or cold in the one-week recall reference method, with the absence or presence of an event-driven report consistent with fever or an acute upper respiratory tract infection (ARI) with onset in the specified week. The main result measures were *false negative proportion* (1–sensitivity, i.e., failure to report disease episodes ascertained with the reference method), *false positive proportion* (1–specificity, i.e., reports of episodes not confirmed by the reference method), *positive predictive value* (the probability of disease according to the reference method given an event-driven report of disease), *negative predictive value* (the probability of being disease-free according to the reference method given the absence of an event-driven report). Confidence intervals (CI) were calculated with the exact binomial method.

To avoid the problem of dependency of reports within the same individual, only the first validation week of each participant was included in the main analysis. A supplementary analysis included all validation weeks, and a second supplementary analysis included event-driven reports also in the *two* weeks preceding the validation week, to allow for possible telescoping bias, i.e., the incorrect inclusion, in the reference measurements, of infections that started *before* the retrospective one-week time window that was to be recalled.

The validity measures were calculated separately for each season, by age group and by validation week. To compare validation weeks (participants' first versus second and third), we calculated risk ratios and tested with the Wald test. Based on the prospective event-driven reporting, incidence rates with 95% CI were calculated for the entire 2007-2008 season, and for 2008-2009 by dividing the number of reported episodes with fever or ARI by the total person-time accrued. Incidence rates among cohort members selected for the validation effort were compared with the corresponding rates among the cohort members who were left undisturbed. The rate ratios were tested using the Wald test.

Regression modeling identified factors associated with failure to report ARI or fever occurrence when responses in the reference questionnaire indicated onset of cold or fever (henceforth referred to as "false negatives"). The modeling was restricted to the 2007-2008 cohort, for which we had information on the individuals' education level, marital status, household size, and household income, collected from registers held by Statistics Sweden. We considered gender, age (0-14; 15-39; 40-64; ≥65 years), length of education (for children, the reporting guardian's length of education) (≤9; 10-14; ≥15 years; missing data), household size (1; 2; 3; 4; ≥5 persons; missing data), household income in 2006 (≤226,810; 226,811-340,466; 340,467-473,903; ≥473,904 SEK; missing data), time from invitation to registration (<2 weeks; ≥2 weeks), mode of registration (Internet; telephone), first event-driven disease report within 24 hours of registration (yes; no). Trends among ordinal data were assessed by assigning integers to ordered categories and analyzing the integers as continuous variables. A generalized estimating equation (GEE) Poisson model was fitted with log link and robust standard errors to account for dependency between reports from the same individual. From the model we obtained risk ratios and 95% Wald CI.

We further compared the epidemic curves for ILI generated from the event-driven reporting during the first 5 months of 2008 and 2009 with curves from the Swedish routine sentinel influenza surveillance system (based on general practitioners) using cross-correlation with varying lag times.

At the end of follow-up in May 2008, we further distributed a postal questionnaire asking all who had been invited about the number of colds and fever episodes experienced between October 1, 2007 and May 25, 2008. We compared each cohort member's total number of disease episodes based on the event-driven reports in this period to the number retrospectively reported in the end-of-study questionnaire using weighted kappa.

2.2.2. *Sjukrapport* validation results

In both the 2007-2008 and 2008-2009 seasons, over 80% of those selected for validation returned at least one one-week recall questionnaire. Descriptive statistics can be seen in Table 1 below.

TABLE 1. Characteristics of individuals selected for and included in the validation of the event-driven reporting in *Sjukrapport*, 2008 and 2009

		2008						2009					
		Selected (n=2376)			Included in analysis[a] (n=2039)			Selected (n=2514)			Included in analysis[a] (n=2134)		
		No.	%	SD	No.	%	SD	No.	%	SD	No.	%	SD
Men		1040	44		888	44		1074	43		872	41	
Mean age, years		42		24	43		24	46		24	48		24
Age groups, years	≤14	464	20		374	18		413	16		313	15	
	15-39	562	24		454	22		530	21		406	19	
	40-64	895	38		782	38		924	37		815	38	
	65-95	455	19		429	21		647	26		600	28	
Dependent children		495	21		397	19		448	18		339	16	
Educational level, years	≥15	564	24		492	24							
	10-14	921	39		799	39							
	≤9	180	8		150	7							
	Missing[b]	711	30		598	29							
Marital status	Single	1075	45		894	44							
	Married[c]	924	39		813	40							
	Divorced	233	10		206	10							
	Widowed	96	4		91	4							
	Missing	48	2		35	2							
Household size	1	634	27		557	27							
	2	605	25		550	27							
	3-4	866	36		713	35							
	≥5	229	10		186	9							
	Missing	42	2		33	2							
Subjects with at least one event-report		1042	44		934	46		993	39		910	43	
Total number of complete event-reports		1486			1365			1183			1085		

[a] Included in the analysis were defined as selected individuals who returned at least one validation questionnaire with interpretable answers, inconsistent reports excluded.
[b] The "Missing" category included children who had not yet finished school, selected children n=495, included children n=397.
[c] The "Married" category included individuals in registered partnerships.

While the false positive proportion was no more than 1% in both seasons (upper bound of the 95% CI ≤2%), the false negative proportion (failure to report) was 60% (95% CI 52%-67%) in the first season and 60% (95% CI 52%-67%) in the second (Table 2). The lowest false negative proportion was observed for children, but with few exceptions the variation between age groups was small. Using all observations (i.e., more than 1 validation week per participant) yielded similar results; the false positive proportion was 1% in both seasons, while the false negative proportion was 66% (95% CI 61%-70%) and 60% (95% CI 54%-65%) in the first and second season, respectively. The negative predictive values (94% for the first and second season) were higher than the positive predictive values (79% and 88%, Table 2).

TABLE 2. Observed false negative proportion, false positive proportion and predictive values in the 2008 and 2009 validation divided by age group and overall

	Age group	2008		2009	
		%	95% CI	%	95% CI
False negative proportion	0-14	56%	(43-69)	55%	(40-69)
	15-39	61%	(45-75)	58%	(39-75)
	40-64	62%	(48-75)	58%	(44-71)
	≥65	61%	(36-83)	72%	(53-86)
	Total	60%	(52-67)	60%	(52-67)
False positive proportion	0-14	1%	(0-4)	1%	(0-4)
	15-39	1%	(0-3)	1%	(0-3)
	40-64	1%	(1-3)	0%	(0-1)
	≥65	0%	(0-1)	0%	(0-2)
	Total	1%	(1-2)	1%	(0-1)
Positive predictive value	0-14	88%	(71-96)	88%	(70-98)
	15-39	78%	(56-93)	82%	(57-96)
	40-64	67%	(47-83)	92%	(75-99)
	≥65	100%	(59-100)	82%	(48-98)
	Total	79%	(70-87)	88%	(78-94)
Negative predictive value	0-14	88%	(84-92)	88%	(84-92)
	15-39	92%	(89-95)	94%	(91-96)
	40-64	95%	(93-97)	95%	(93-97)
	≥65	97%	(95-99)	95%	(93-97)
	Total	94%	(93-95)	94%	(93-95)

Extending the time window for the event-driven reporting to 3 weeks (thus allowing for possible telescoping bias in the reference measures) reduced the false negative proportion to 51% (95% CI 44%-59%) in 2008 and to 48% (95% CI 39%-56%) in 2009, with only minor increases in the false positive proportions (5% in 2008 and 7% in 2009).

Validity did not change consistently with time. In 2008 the false negative proportion increased from 60% (95% CI 52%-67%) in the first validation week to 69% (95% CI 61%-76%) in the second and 75% (95% CI 63%-85%) in the third ($p=0.03$ for the third versus the first week). The false positive proportions in the corresponding weeks were 1% (95% CI 1%-2%), 1% (95% CI 0%-1%), and 0% (95% CI 0%-1%). In 2009, when reminders were more frequent, the false negative proportions remained unchanged (first validation week 60%, [95% CI 52%-67%]; second validation week 60%, [95% CI 51%-68%]). The false positive proportions were 1% (95% CI 0%-1%) in both weeks.

In 2008, Poisson modelling disclosed male gender and low education as independent risk indicators for failure to report (Table 3). Children (for whom a guardian did the reporting) had lower risk for false negatives than participants aged 40-64 years, and there was a general trend for increasing risk with increasing age (Table 3). A decreased risk for false negatives was noted among those who registered promptly after the invitation, while cohort members who reported disease within 24 hours after registration showed no evidence of being more negligent than the others.

TABLE 3. Generalized estimating equation Poisson model with loglink and robust standard errors of the risk of false negative reporting (i.e., no report through the population-based, event-driven surveillance system when the reference method – one-week recall questionnaires – signalled onset of disease) in 2008, n=396

		RR	95% CI	P-value for trend[a]
Gender				
	Women[b]	1.00		
	Men	1.24	(1.07-1.44)	
Age group, years				
	0-14	0.77	(0.63-0.97)	
	15-39	0.94	(0.78-1.13)	0.02
	40-64[b]	1.00		
	≥65	1.11	(0.82-1.51)	
Educational level, years[c]				
	≤9[b]	1.00		
	10-14	0.75	(0.62-0.89)	0.05
	≥15	0.75	(0.61-0.91)	
	Missing	0.77	(0.51-1.19)	
Household size				
	1[b]	1.00		
	2	0.93	(0.73-1.19)	
	3	1.23	(0.95-1.58)	0.24
	4	1.08	(0.82-1.41)	
	≥5	1.17	(0.88-1.56)	
	Missing	1.06	(0.57-1.94)	
Household income group[d]				
	Low & Middle/low[b]	1.00		
	Middle	1.17	(0.94-1.47)	
	Middle/high	1.07	(0.83-1.38)	0.33
	High	0.92	(0.72-1.17)	
	Missing	1.31	(0.94-1.84)	
Time from invitation to registration				
	≥2 weeks[b]	1.00		
	<2 weeks	0.84	(0.73-0.96)	
Mode of registration				
	Telephone[b]	1.00		
	Internet	0.94	(0.80-1.11)	
First event-driven disease report within 24 hours of registration	No[b]	1.00		
	Yes	0.96	(0.81-1.14)	

[a] Excluding missing values.
[b] Reference category.
[c] Education is the guardians' highest education if child.
[d] Low & Middle/low≤226 810; Middle=226 811-340 466; Middle/high=340 467-473 903; High≥473 904 in SEK in 2006.

ILI epidemic curves compared well with routine Swedish sentinel surveillance curves in terms of shape, timing of the peak, and year-to-year variation (Figure 3). Cross-correlation analysis showed that maximum correlation was attained when no lag time was applied. In 2008 the cross-correlation was 0.76 and in 2009, 0.88 ($p<0.05$ for both).

In May 2008, 2,676 (78%) cohort members answered the end-of-study questionnaire, which indicated that the incidence of ARI or fever had been 41 per 1000 person-weeks. Prospective event-driven report data for the same season showed an incidence of 24 per 1000 person-weeks (95% CI 23-25) for cohort members selected for the validation and 22 per 1000 person-weeks (95% CI 20-24) for those not selected ($p=0.07$). In 2009 the corresponding rates were 24 and 20 per 1000 person-weeks ($p=0.0001$) in those two groups. The agreement between event-driven prospective reporting and retrospective end-of-study reports was fair (weighted kappa=0.31), Table 4.

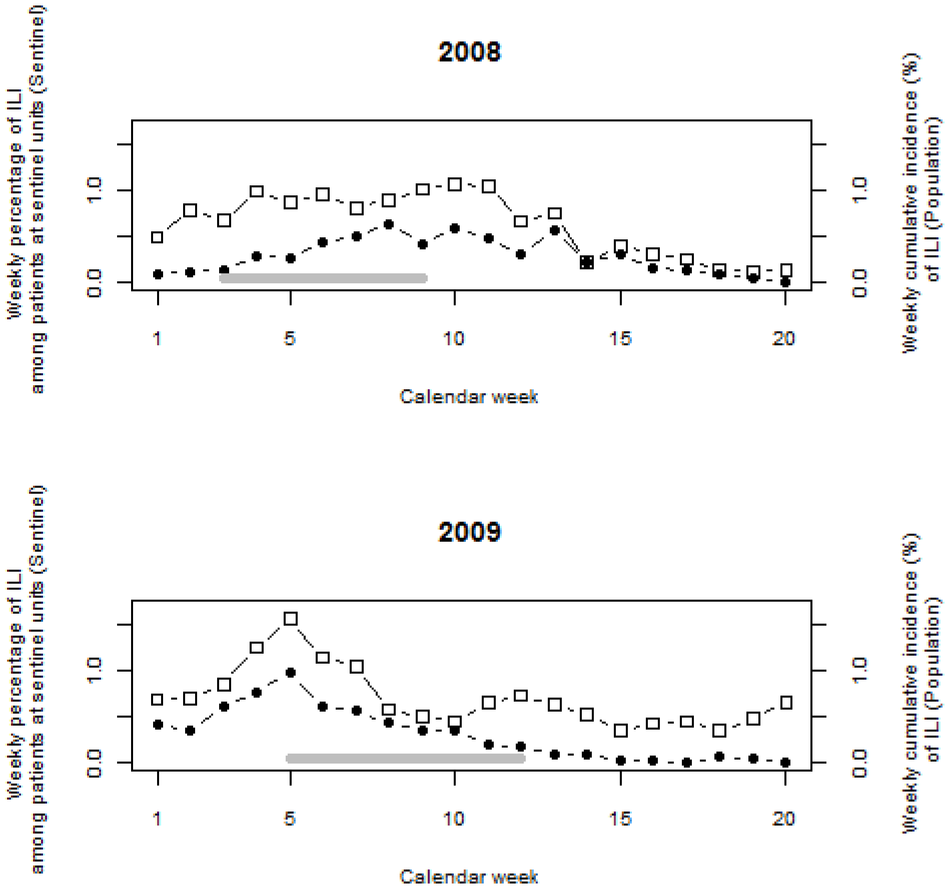

Figure 3. Epidemic curves for influenza-like illness (ILI) derived from the sentinel surveillance system in Sweden (filled circles) and the passive follow-up with self-initiated, event-driven outcome reporting in Sjukrapport (hollow squares)*. The upper graph represents 2008, the lower one 2009. The solid gray horizontal lines indicate start and end of the validation efforts. Week 10 and 11 of 2008 were excluded from analyses because they coincided with a reminder that was sent to all cohort members.*

TABLE 4. Comparison of number of illness episodes in the end-of-study questionnaire and the event-driven surveillance reports in the 2007-2008 season. Weighted kappa 0.31

		Event-driven surveillance reports of illness, No.					
		0	**1**	**2**	**3**	**4**	**≥5**
End-of-study questionnaire illness episodes, No.	0	727	81	7	0	0	0
	1	425	292	28	0	0	0
	2	225	200	105	15	3	0
	3	84	77	49	14	2	0
	4	18	31	24	13	8	2
	≥5	22	16	15	6	12	9

2.2.3. Discussion of the validation of *Sjukrapport*

The interpretation of discrepancies in relation to an imperfect reference is uncertain, but there is little doubt that passive follow-up for common respiratory infections relying on event-driven reporting suffers from underascertainment. The retrospective nature of the reference methods and the associated possibilities for biased reference data leaves some uncertainty as to the magnitude of the underascertainment. However, the false negative rate was remarkably constant over time and across seasons, but varied slightly with age, sex and educational level, as well as with the promptness with which the participant responded to the invitation.

Notwithstanding underreporting and virtual absence of false positive event-driven reports, the weekly cumulative incidence (incidence proportion) of ILI was orders of magnitude higher than the weekly cumulative incidence estimates for the population recalculated by the European Influenza Surveillance Scheme (EISS) based on Swedish sentinel data. Still, the event-driven reporting showed good correlation with the sentinel surveillance in terms of shape and timing of the peak. This similarity indirectly provides additional support to the notion that the error in event-driven reporting is fairly constant within and between seasons. Thus, with information about sex, age, education level, and time from invitation to registration, and using the stratum-specific misclassification data provided in our validation study, the underreporting is potentially correctable.

3. The Internet Monitoring System (*Influensakoll*)

3.1. Recruitment and outreach activities

Although somewhat unpredictable in time, the launch of the IMS system, *Influensakoll*, in Sweden had been carefully prepared long in advance. However, as events that could have served as natural springboards for media attention (launch of the national influenza vaccination campaign; the first recorded influenza case) passed before the IT platform was ready, we had to adapt and improvise. An elaborate alternative media strategy was developed that included targeting of local media with press releases throughout Sweden as influenza spread (November 17: National press release, area-specific press releases for Gothenburg and Örebro; Nov 29th: Area-specific press-releases for Norrland, Stockholm, and Värmland).

We sought assistance from the County Medical Officers, who are responsible for infectious disease control in the respective counties in Sweden, and who typically have good relations with the local press. We emphasized that the IMS system could become a valuable tool in their infectious disease control work if they could only summon sufficiently large numbers of participants in their own counties. Moreover, we were given the opportunity to post links on several well-known websites for medical advice (1177, Vårdguiden, County Medical Officers), the Swedish Science Council, etc.

We were fortunate to be quite successful in reaching out via media. Local newspapers throughout Sweden took up our news. Through our media monitoring system we know of approximately 30 articles and blurbs online, not counting articles in print-only papers, which we are unable to track. Therefore, we believe that this is an underestimate of the media coverage we received. *Influensakoll* was highlighted in four radio interviews and one local TV spot in Stockholm.

Further, *Influensakoll* is on both Facebook and Twitter. A search on Google for 'Influensakoll' (February 1, 2012) yielded 7,630 hits.

Influensakoll in the media

These outreach activities have resulted in a rather rapid accrual of participants.

Figure 4 shows the daily number of registrations of new participants between November 14th, 2011 and January 20th, 2011. The number of participants joining during the first ten days was high. This was followed by a period of reducing activity, followed by a low level of new participation during the holiday season. In January, when most Swedes came back to work and school after the holidays, participation again increased. An uncertain flux in influenza activity during this period may also have contributed to interest in *Influensakoll*.

Influensakoll's Facebook page

It is notable that the registrations consistently went down during weekends, suggesting that most registrations were done from computers at people's workplaces.

This might have implications for the disease reporting; if the e-mail reminders are sent to e-mail addresses at work, they may not reach participants who are on sick-leave until they are back to work again.

Influensakoll on Twitter

Figure 5 shows the cumulative number of registered participants. This number exceeded 1000 by the turn of the year, and *Influensakoll* presently (February 10, 2012) has approximately 1450 registered participants.

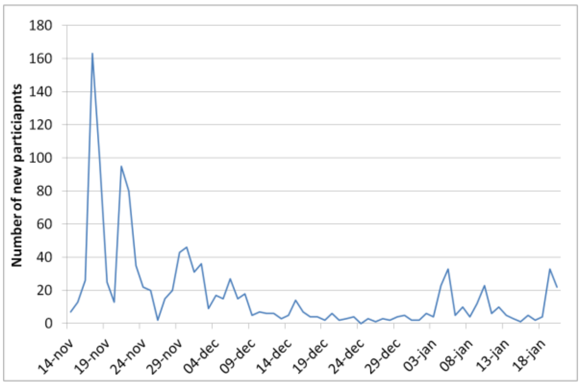

Figure 4. New Influensakoll participants per day

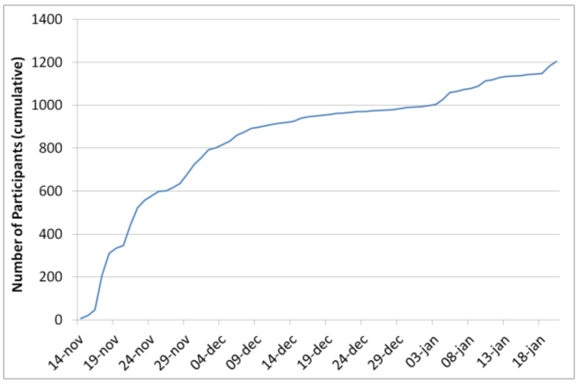

Figure 5. Cumulative participation, Influensakoll

3.2. Demographic characteristics

As part of this report, we have analyzed the demographic variables provided by those *Influensakoll* participants who joined during the first nine weeks that the system was operational in Sweden during the 2011-2012 season. Figure 6 shows the breakdown of participants by sex. As can be seen, nearly twice as many women as men have joined *Influensakoll*. Interestingly, the female predominance was only slightly less in the PBA cohort.

Figure 7 shows the breakdown of *Influensakoll* participants by age group. We were surprised to see a significant number of profiles being set up for children, although this matches well with our experience from the PBA system, *Sjukrapport*. That system has consistently shown that parents are some of the most active reporters and are more likely to join upon invitation. In *Influensakoll*, children (aged 0-18) make up 13 percent of participants.

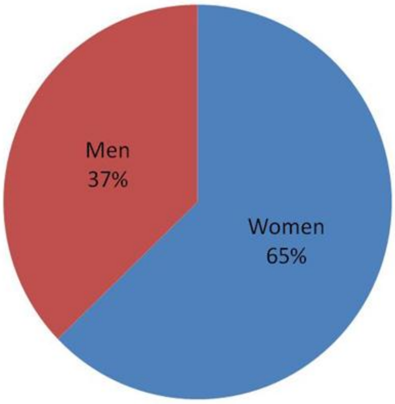

Figure 6. Influensakoll participants by sex

The breakdown among the adult age groups generally matches our expectations. The 25-34 age group seems to show considerably more activity in this system than they have historically shown through *Sjukrapport*. It is likely that the online nature of the *Influensakoll* system means it is easier to reach this otherwise difficult to reach group. The 18-24 age group seems harder to reach. Those above the age of 84 appear to be nearly impossible to reach through this system, whereas the *Sjukrapport* system recruits participants up to age 95.

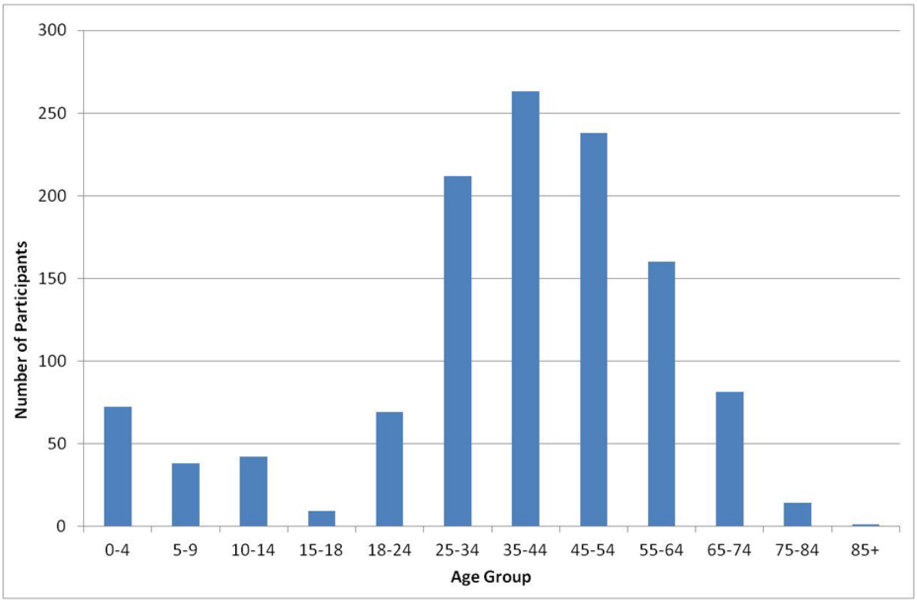

Figure 7. Influensakoll participants by age group

Part of the explanation for the success with age group 25-44 is given in Figure 8, which shows the level of education reported by participants. As shown, a high proportion of participants (48 percent) have a university or college degree of more than 3 years. Another 13 percent have attended university or college for less than 3 years, while about 16 percent are secondary school graduates. Only 4 percent of participants indicated their highest level of education was one of the three levels of primary school.

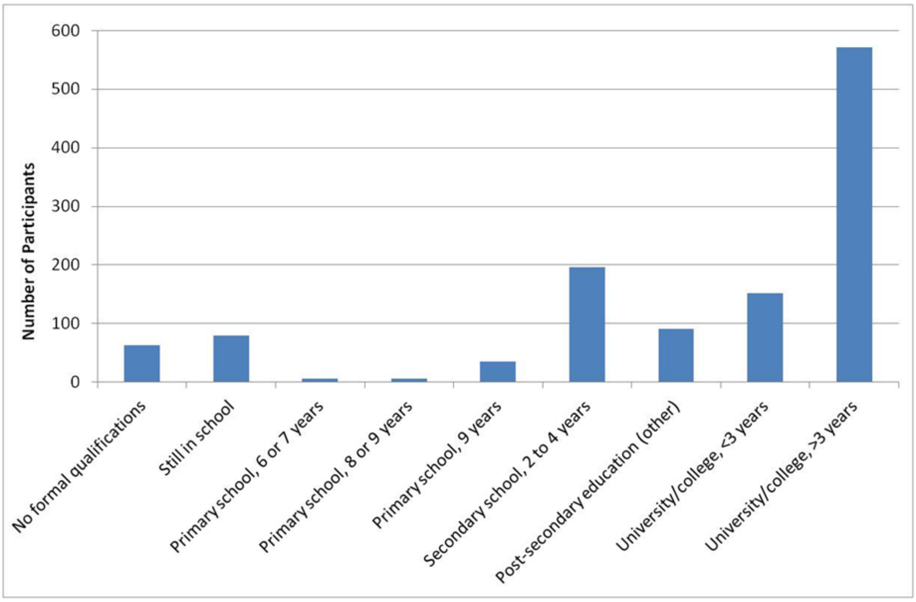

Figure 8. Influensakoll participants by level of education

Figure note: A variety of primary school institutions have existed in Sweden since the 1940s. The following educational levels of primary school were used: Folkskola (Primary school, 6 or 7 years), Realskola (Primary school, 8 or 9 years), and Grundskola (Primary school, 9 years).

The invitation to join *Influensakoll* has evidently appealed to the well-educated. Among *Influensakoll* participants who have finished school, those with a post-secondary school education, including a university education, constitute no less than

73 percent. The corresponding figure for the entire Swedish population above age 16 is 31 percent (Figure 9). Since a university education is particularly common among young adults, this explains their unexpectedly high representation.

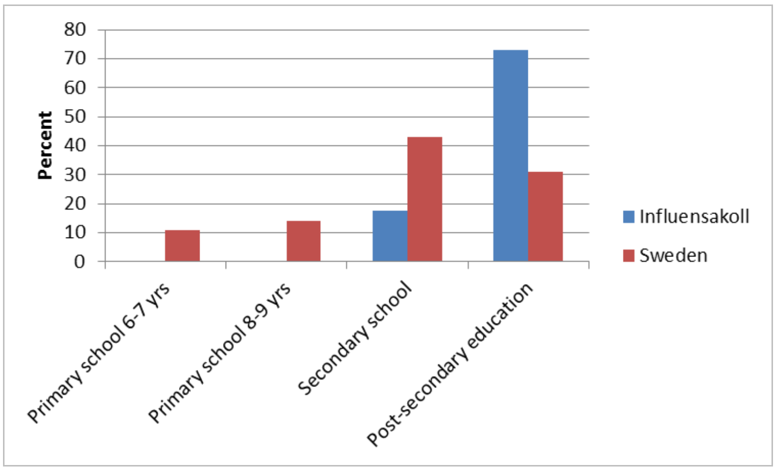

Figure 9. Highest finished education among Influensakoll participants and in the general Swedish adult population in 2010, according to Statistics Sweden (http://www.scb.se/Pages/ProductTables____9575.aspx)

As part of the *Influensakoll* background survey, participants also indicate what their "main activity" is. Figure 10 shows the breakdown of participants by activity type. More than half (52 percent) of participants describe themselves as employed full time. Those who are in school make up 15 percent of participants, which likely includes a good deal of the participating children.

Retirees make up 9 percent of participants, while part-time employment is indicated by 8 percent of participants. Remaining categories constitute between 1 and 5 percent.

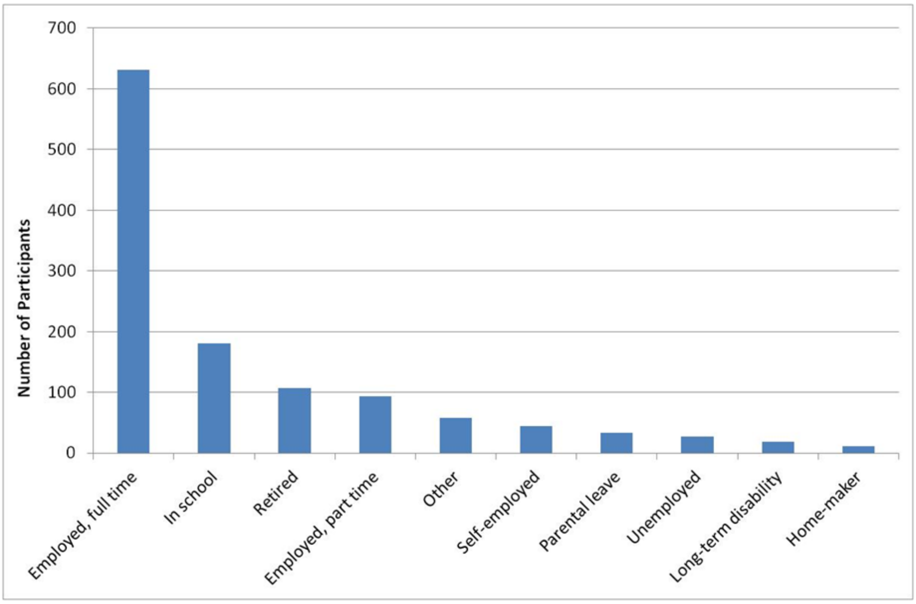

Figure 10. Influensakoll participants by main activity

Those participants who indicated that their main activity was employment, whether full-time, part-time or self-employment, were also asked to indicate their work category. Figure 11 shows the percentage of participants per job category. Most participants are professionals (67 percent) or office workers (18 percent), while only 3.5 percent indicate they do skilled manual labour of any kind and only 1.6 percent indicated that they work as unskilled labour. This demographic makeup is indicative of a selection bias and may skew the system's results.

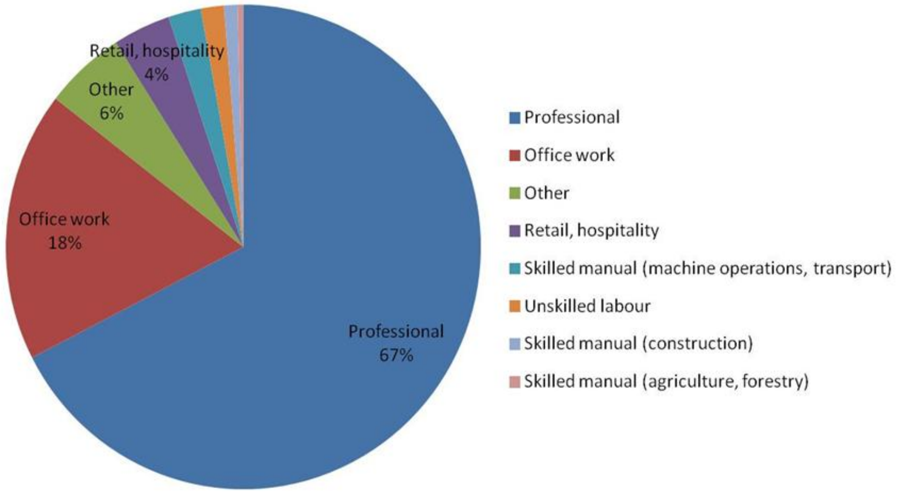

Figure 11. Job category among employed and self-employed Influensakoll participants

3.3. Geographic distribution

Participation in *Influensakoll* varies geographically. Figure 12 shows the number of registered participants (January 20, 2011) by county in falling order (blue line), while the total population counts in the corresponding counties are shown as red bars. As shown, almost half of the participants come from Stockholm County, the population of which constitutes only slightly more than 20% of the national population. The participation in other large counties that also include large cities (Västra Götaland County and Skåne County, where Gothenburg and Malmö are located, respectively) is much less impressive.

Figure 13 shows the participation rate per 100,000 population on January 20, 2011. Stockholm County exhibits the best participation rate (24.6 per 100,000), but surrounding counties also show a satisfactory uptake. However, other large counties with large cities mentioned above lag behind. Interestingly, counties whose newspapers were especially targeted in our outreach activities described earlier (Värmland, Örebro) are found in the bottom of the list. On January 20, 2012, the participation ranged between 24.6 per 100,000 (Stockholm County) and 4 per 100,000 (Blekinge County) with a weighted mean of 12.8 per 100,000 for all of Sweden.

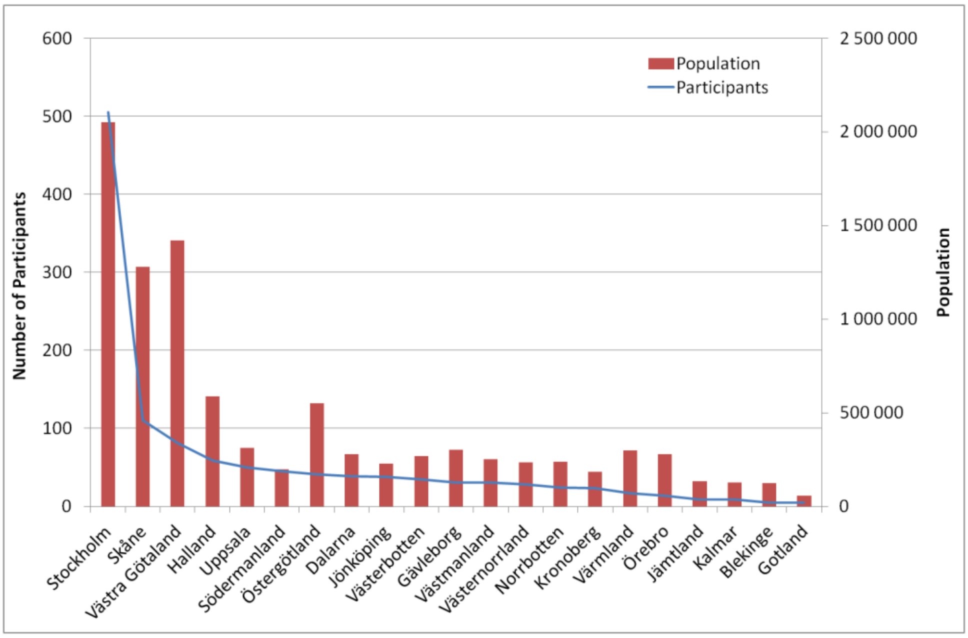

Figure 12. Number of participants and inhabitants per county

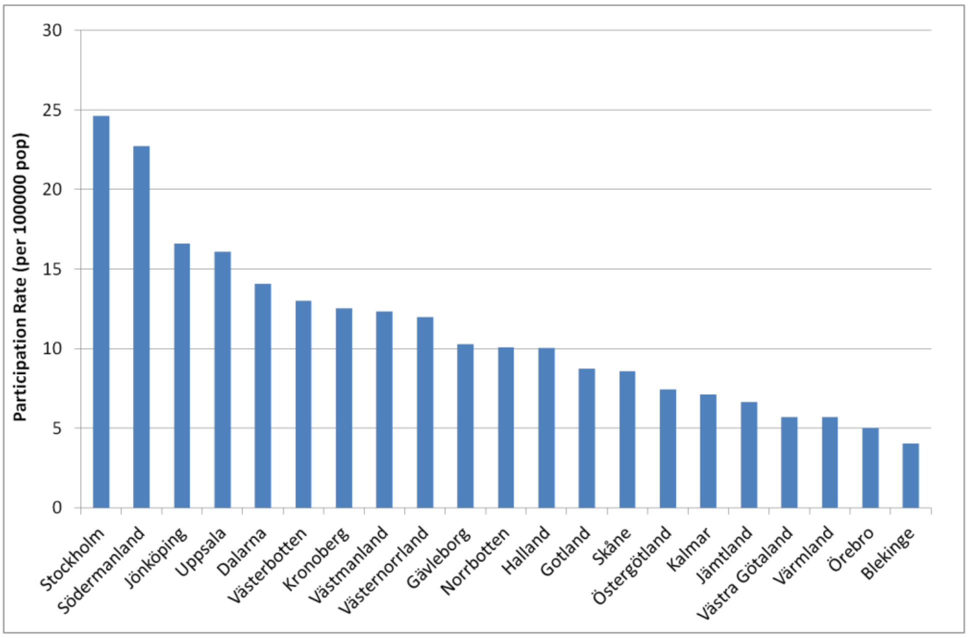

Figure 13. Participation rate (per 100,000 population) per county

In summary, we found indications of substantial misrepresentation of the Swedish population among the *Influensakoll* participants. There was some bias towards more women, greater bias towards people residing in Stockholm and surrounding counties, and heavy bias towards well-educated professionals.

3.4. Participant reporting in Influensakoll

3.4.1. Descriptive data

Our initial analysis indicates that anywhere from half to more than all participants report any given week, with an average during this start-up phase of 70 percent reporting. This includes very high reporting rates of 112 and 98 percent during the first two weeks. We can only assume that participants were testing the system and "playing" with the reporting survey during this period. After the first two weeks, we see a more stable proportion of reporters at around 60 percent each week, with a dip during the holidays.

TABLE 5. Number of reports and participants as well as percentage reporting per week

Week	Number of Reports	Number of Participants (cumulative)	Percentage Reporting
2011-46	387	347	112%
2011-47	605	616	98%
2011-48	618	818	76%
2011-49	598	911	66%
2011-50	575	954	60%
2011-51	469	974	48%
2011-52	541	993	55%
2012-01	558	1,078	52%
2012-02	739	1,138	65%
Total	**5,090**	**1,138**	**Average: 70%**

A measure indicating that participants report more than just once is Figure 12, which shows the number of participants who have reported once, twice, three times, and so forth, up to an ambitious 15. Considering that the reporting period only spans at most 9 weeks and no more than one report per week is expected, there does seem to have been some "playing" going on.

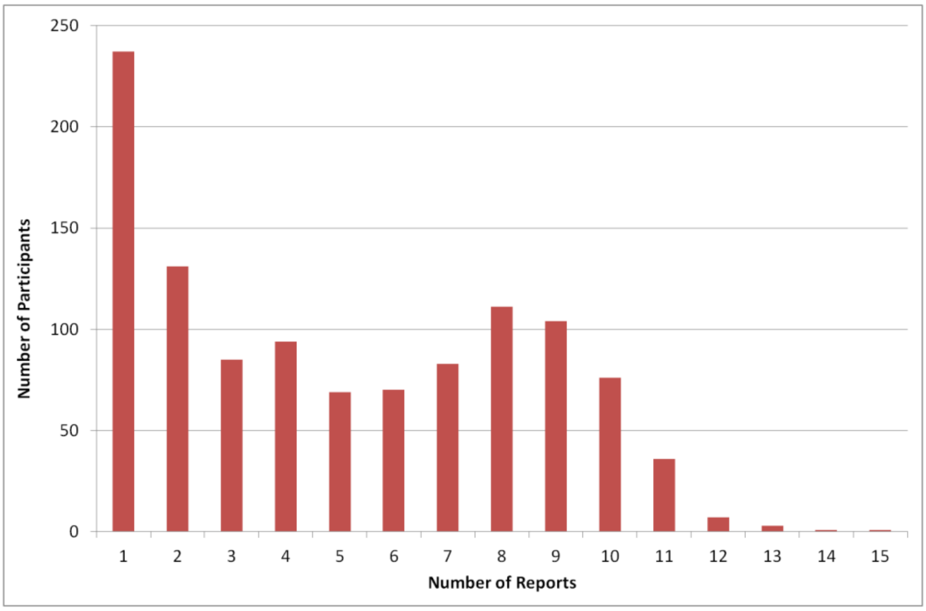

Figure 14. Number of participants by the number of reports registered, Influensakoll

3.4.2. Interpreting weekly reports

Because people with on-going infections are more likely to join *Influensakoll* – and to respond to the weekly reminders to report – than those without, selection bias is a constant threat to the validity of the system. To minimize such selection bias, which would otherwise lead to overestimation of the proportion of infected people in the population, participants must first prove to be faithful reporters even in the absence of disease to be considered *active*. Accordingly, they have to have submitted a number of negative reports in sequence before their reports can be used in the analyses.

As the criteria are still being developed by WP5, we did not apply rigorous criteria to participants to determine whether they are *active* for the purposes of this preliminary analysis. Instead, we have used two simplified weekly measures: (i) the number of positive disease reports per all registered participants *up to* (and including) the week in question; and (ii) the number of positive disease reports per all reporting participants (or more specifically the total number of submitted reports) *during* the week in question. As registered participants may discontinue their participation – permanently or temporarily – the number of participants who report in any given week will be smaller than the total number of people who have once registered as participants. Therefore, the first measure (with an overestimated denominator) will generate a lower estimate of the occurrence of disease in the population than the second measure (which has a smaller denominator).

In the following three graphs, we show both measures on the left vertical axis (the weekly number of positive disease reports per all registered participants up to the week in question – lilac line; the weekly number of positive disease reports per all reports submitted during the week in question – green line) for influenza-like illness (ILI – Figure 15), acute respiratory infection (ARI – Figure 16), and gastroenteritis (Figure 17).[1] With the reservation that selection bias might still be substantial, the best estimate of disease occurrence is likely to fall between the lilac and the green lines. Shown in the graphs using the right vertical axis is also the total number of reports – both positive and negative – per week (dark blue shaded area) and the cumulative number of registered participants (light blue shaded area). Please note the differences in left vertical axis scale between the three graphs.

It is notable that the proportions reporting were unrealistically high during the first couple of weeks. More than one third of the participants reported at least one of the three disease categories during these weeks. Moreover, in the first one or two weeks, the number of positive reports per all registered participants was consistently higher – for all three diseases – than the number of positive reports divided by the total number of reports during the week in question. This was because the number of weekly reports exceeded the number of participants. As mentioned, some participants incorrectly submitted more than one report per week (see Table 5 and Figure 14 above). We interpret the high proportions of participants with on-going disease as due to a combination of selection bias and incorrect use of the reporting system.

[1] ILI was defined as rapid onset AND (fever OR headache OR muscle/joint aches OR exhaustion/fatigue) AND (sore throat OR cough OR difficulty breathing). ARI was defined as non-rapid onset AND (sneezing OR sore throat OR cough OR difficulty breathing). Gastroenteritis was defined as (nausea OR vomiting OR diarrhoea OR abdominal pain). Cases with symptoms that were consistent with both gastroenteritis and either of ARI or ILI were classified as having ARI or ILI, because gastrointestinal symptoms are common in respiratory tract infections.

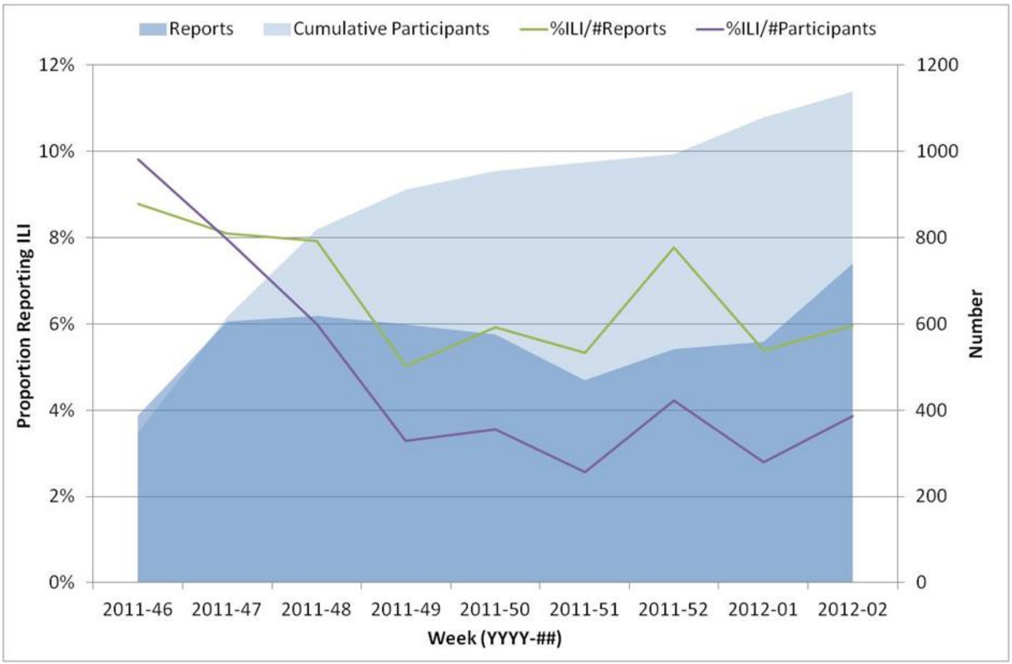

Figure 15. Reports of influenza-like illness (ILI) as a proportion of reports and of participants and number of reports and participants, Influensakoll

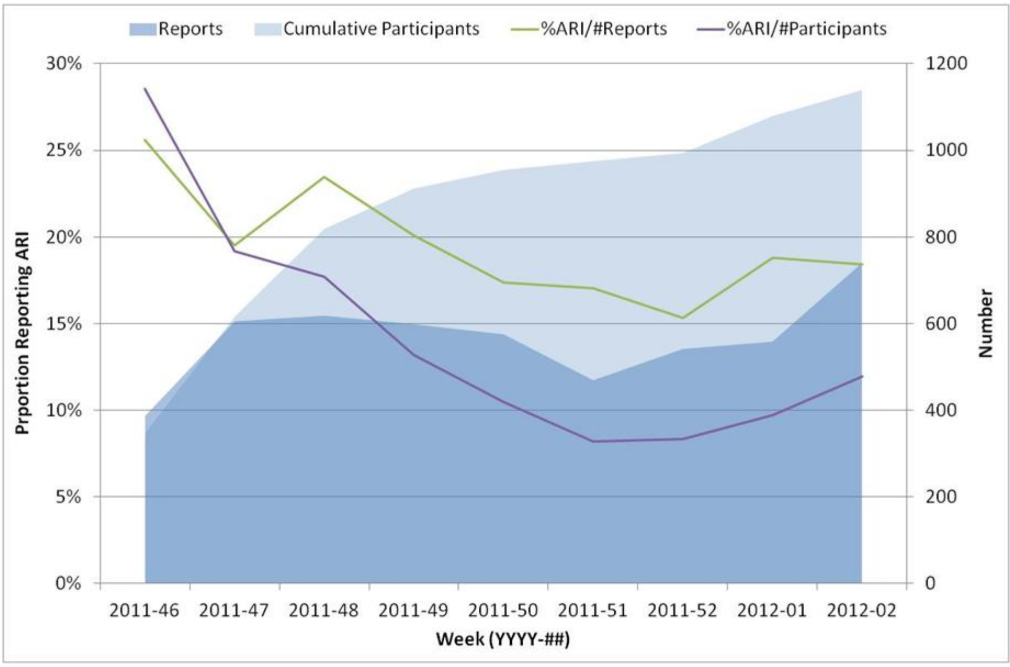

Figure 16. Reports of acute respiratory infection (ARI) as a proportion of reports and of participants and number of reports and participants, Influensakoll

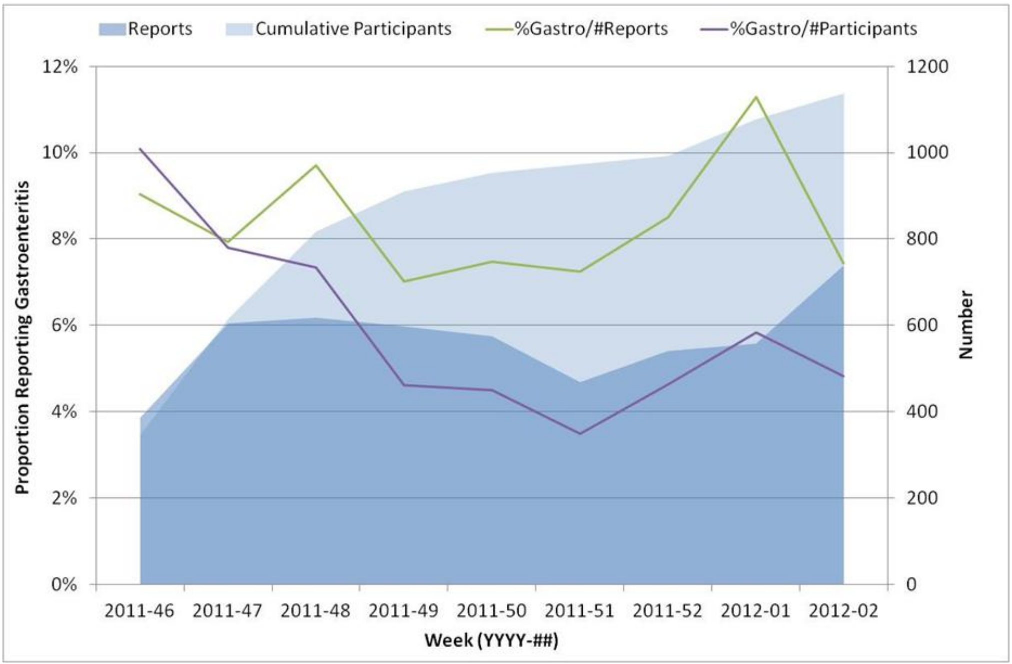

Figure 17. Reports of gastroenteritis as proportion of reports and of participants and number of reports and participants, Influensakoll

4. Comparison of *Influensakoll* and *Sjukrapport* results

Below we discuss the results of our preliminary comparison of the first 9 weeks of reported data for *Influensakoll* and *Sjukrapport* from the 2011-2012 influenza season.

4.1. Data analysis and results

To increase the comparability of *Influensakoll* and *Sjukrapport*, we re-analysed *Sjukrapport* data as number of positive disease reports per week divided by the number of participants during the week in question. This is a simplification of the regular analytic procedure, which is otherwise based on a person-time approach with possibilities for censoring on any day, and estimation of week-wise cumulative incidence (incidence proportion). Moreover, when overall cumulative incidence is calculated in *Sjukrapport*, age-specific data are normally merged in a weighted fashion to compensate for the deliberate overrepresentation of children (*see section 2.1.*). Such weighting was not done in this preliminary analysis.

To further align the data from the two surveillance systems, we applied the *Sjukrapport* disease definition for ILI and ARI, so that ARI also includes ILI.[2] We did not age-standardize the data. We restricted the comparison to ILI and ARI data, and to data emanating from Stockholm County (because the *Sjukrapport* scheme is presently confined to this county).

Panel A (upper left) of Figure 18 shows the ARI (brown) and ILI (dark grey) curves derived from the Stockholm component of *Influensakoll* (only the 505 participants

[2] The Sjukrapport case definitions are, for ARI: Cough OR Sore throat OR Shortness of breath OR Coryza/runny nose), and for ILI: Sudden onset AND (Cough OR Sore throat OR Shortness of breath OR Coryza/runny nose) AND (Fever OR Headache OR Myalgia/muscle aches).

residing in Stockholm County) during the nine weeks from November 17, 2011, until January 20, 2012. The curves from Stockholm County look very similar to those emanating from all of Sweden (displayed in Figure 15 and 16). Panel B (upper right) presents the corresponding curves derived from *Sjukrapport*.

Both panels have the same scale on the Y-axis. Due to the implausibly high proportions with ARI and ILI in the first 3 weeks among *Influensakoll* participants, with figures reaching above 40 percent, the scale is really out of range for *Sjukrapport* data, and the ARI and ILI curves look almost like 2 straight lines. Panel C (bottom left) displays the *Sjukrapport* data with a more appropriate Y-axis scale that permits a better resolution of the changes over time.

Not even after correction for the predictable underascertainment revealed in the validation of *Sjukrapport* (see *section 2.2.2.*) will the latter reach the levels observed in *Influensakoll*. However, the ILI curves show some resemblance as far as the shape is concerned. According to *Influensakoll*, there is an ILI peak in week 52, while a peak, albeit much smaller, appears during week 50 in *Sjukrapport*.

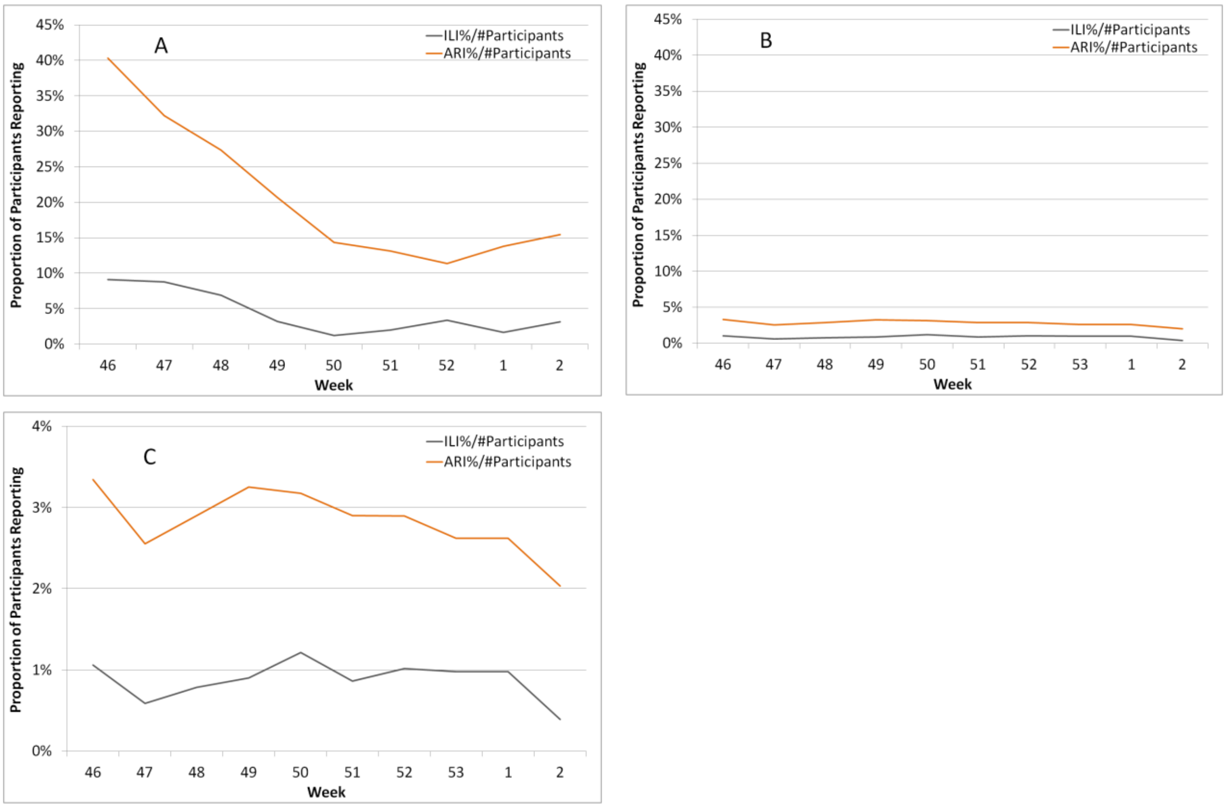

Figure 18. Curves portraying the week-wise number of disease occurrences (Stockholm County) divided by the number of registered participants up to the week in question (Influensakoll) or the number of people who participate during this week (Sjukrapport). The orange curves represent acute respiratory infection (ARI) and the dark grey influenza-like illness (ILI). Panel A (upper left) shows data derived from Influensakoll and Panel B (upper right) corresponding data from Sjukrapport. Panel C (lower left) shows the same data as Panel B but with a blown-up Y-axis scale, which allows a better resolution of time trends in Sjukrapport data.

Figure 19 shows ILI curves that are published by the Swedish Institute for Communicable Disease Control, and derived from the general practitioner-based sentinel reporting system (all of Sweden). The red-brown curve represents the 2011-2012 season. Overall, the influenza activity has been low in comparison with previous seasons (blue and yellow curves). A small peak occurred in week 50, coinciding with the peak in *Sjukrapport*, but less well with the week 52 peak in *Influensakoll*. The similarity between data from the sentinel and *Sjukrapport* surveillance systems with regard to the shape of the curves and timing of the peak becomes even more obvious when the *Sjukrapport* data are analysed according to our regular analysis plan described above, as shown in Figure 20.

Since the comparison between *Influensakoll* and *Sjukrapport* was confined to Stockholm County, it would be more appropriate to compare our surveillance data with sentinel data from Stockholm County. However, during the period in question, no more than 32 ILI cases were noted by the sentinel surveillance in Stockholm County, so the data are very unstable. The distribution of the cases over time is shown in Figure 21. It is notable that the denominator (number of persons listed) might have varied across the period because of holidays during part of the period. Nonetheless, the curve suggests that a small peak occurred in Stockholm during week 50.

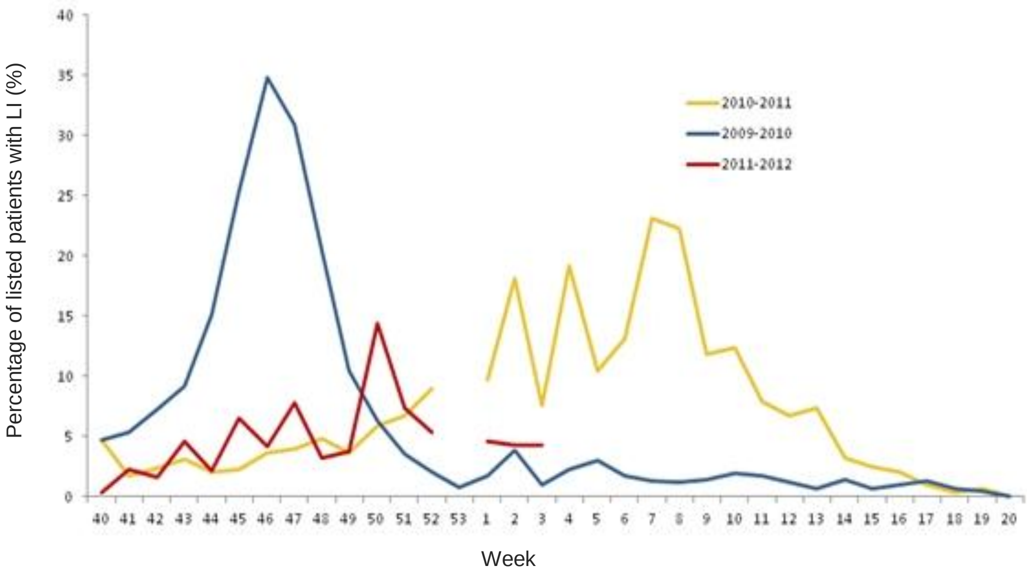

Figure 19. General practitioner-based sentinel data of ILI occurrence (all of Sweden), published by SMI (http://www.smittskyddsinstitutet.se/publikationer/veckorapporter/influensarapporter/sasongen-20112012/influensarapport-vecka-3-161---221--2012/). The red-brown curve represents data for the 2011/2012 season. The activity is low, but a small peak is seen in week 50.

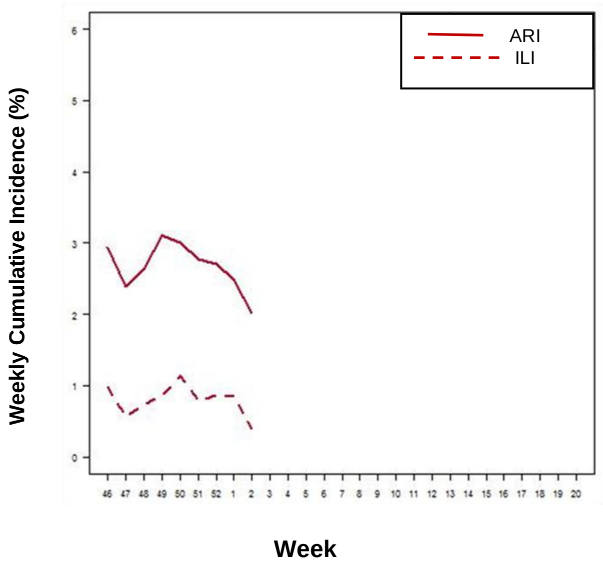

Figure 20. Curves depicting the weekly cumulative incidence of ARI (continuous line) and ILI (dashed line) in Stockholm County during week 46, 2011, through week 2, 2012, according to Sjukrapport. Compared to Figure 18, incidence rates are calculated according to the regular and more stringent analysis plan.

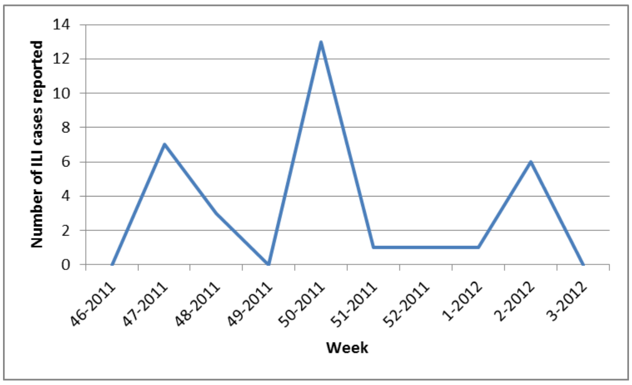

Figure 21. Number of ILI cases reported by the sentinel units in Stockholm County during week 46, 2011 through week 3, 2012.

4.2. Summary and conclusion

In summary, the *Sjukrapport* surveillance system produces underestimated but otherwise trustworthy ARI and ILI incidence rates. Because the underestimation is surprisingly constant over time and across seasons, the rates are, in principle, correctable through the multiplication by a factor of 2-2.5 (the uncertainty derives from the probable overestimation of rates by the retrospective reference method in the validation study). But even after such correction, the proportion of people with on-going ARI or ILI, based on *Influensakoll* reporting during the nine weeks under surveillance, is clearly above the level predicted by *Sjukrapport*.

Community-based data from Australia indicate that the incidence of ARI is of the order of 2 per person-year (Leder K, *et al*. Aust N Z J Public Health 2003;27:399-404). If the present *Influensakoll* proportions would be approximated as incidence rates (i.e., 10 per 100 person-weeks, as in the second half of the period we looked at), and it is assumed that the observed rate is representative of the all-year incidence (and except for an unusually high number of mycoplasma infections and an unusually low influenza activity, we have no indications to the contrary), this would correspond to an incidence of around 5 per person-year. This is likely an overestimation.

We had strong indications that our estimates of the proportion of people with on-going infections were considerably inflated during the first 2-3 weeks of registration in *Influensakoll*, most likely due to a combination of selection bias and incorrect reporting. A similar phenomenon is also observed in *Sjukrapport*. Therefore, we have long since routinely discarded the first 3 weeks of reporting data for each *Sjukrapport* participant (from when they join *Sjukrapport*). However, since the participation trajectory for many *Influensakoll* participants is substantially shorter than the 9 months that is standard in *Sjukrapport*, exclusion of 3 weeks' registration after entry and after each temporary pause takes a heavy toll.

Since the evaluation period was no more than 9 weeks in total, due to the delayed launch of *Influensakoll*, we were unable to apply rigorous criteria for who to consider active participants. The two systems will continue to operate in parallel throughout the present season, and the participation in *Influensakoll* will hopefully continue to grow. This might provide the necessary basis for more in-depth analyses.

To estimate the magnitude of the impact of selection bias that might occur through temporary interruptions and resumptions that are differential in relation to disease status, we made a series of simulations. We assumed (1) that the true weekly proportion with ARI among all participants would be 4%; (2) that each disease episode would last for only one week and would not spill over to the next; (3) that 30% of the participants would skip the reporting each week. We also assumed (4) that the risk of skipping the reporting among those who reported the previous week would be 5 times as great if they were healthy than if they were sick, and (5) that the risk of skipping the reporting among those who also skipped reporting in the previous week would be 10-fold higher if they were healthy than if they were sick. With these rather severe – although not inconceivable – assumptions, the proportion with on-going ARI among participants who report during the week in question would increase from 4% to 5.4%, corresponding to an overestimation by 35%. Thus, it is unlikely that selection bias alone would explain the high rates observed in *Influensakoll* during this period of evaluation.

5. Next steps in WP6

Clearly, the reporting in *Influensakoll* has not yet stabilized, and the data volume remains insufficient for adequate analysis. Furthermore, there has been an unusually low level of influenza activity in Sweden so far this season. Therefore, the prerequisites for a fair comparison between *Influensakoll* and *Sjukrapport* are not yet at hand. Then again, since this season's epidemic will likely start shortly, we are lucky to still be able to document all phases within the framework of this evaluation and WP6. Hence, we will continue to run both systems, and the final analysis scheduled for Deliverable 6.5 will be based on data from November 2011 through May 2012.

Attachments: Digitalized datasets from the concurrent use of *Sjukrapport* and *Influensakoll*

The anonymized and condensed datasets are delivered separately in encrypted form. Attached as Excel files are variable lists (metadata) for *Sjukrapport* and *Influensakoll*, along with raw data used for estimation of the respective epidemic curves shown in this evaluation.

The following files are attached:

- Metadata_IMS_Influensakoll
- Metadata_PBA_Sjukrapport
- DataforGraph_IMS_Influensakoll
- DataforGraph_PBA_Sjukrapport

The following files will be sent separately and encrypted:

- Dataset_IMS_Influensakoll
- Dataset_PBA_Sjukrapport