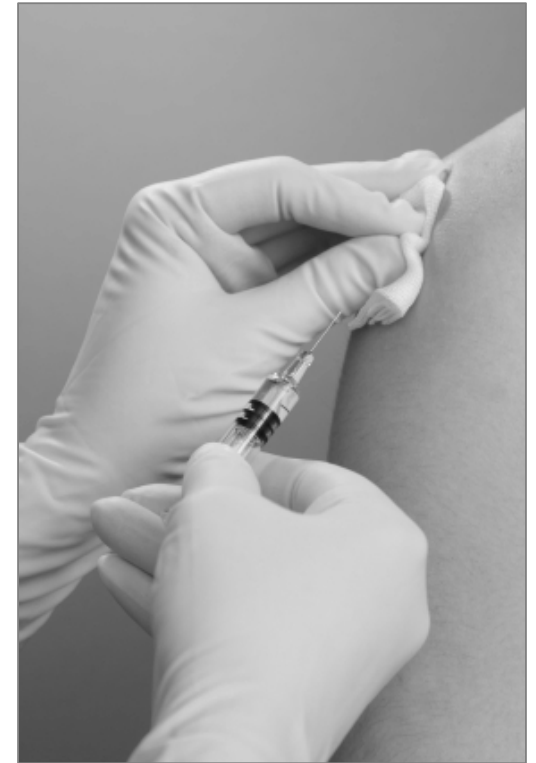# H1N1 Vaccine Surveillance

03 December 2009

Background – The H1N1 Vaccine

- H1N1 vaccine became available in the U.S. ~mid-October 2009

- The H1N1 vaccine is based on mock-ups, plus limited clinical trial information

  - As a result, there is limited safety information for this vaccine

  - Yet there will be substantial exposure across a variety of populations, including populations not evaluated in clinical trials

- This necessitates an urgent requirement for aggressive post-approval safety surveillance to identify and evaluate safety signals proactively to continuously monitor the risk-benefit balance of each vaccine and take action as appropriate.

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Regulatory Considerations

- In June and again in Sept 2009, EMEA updated their pandemic influenza vaccine risk management guidance

  – Includes substantial post-market safety surveillance requirements

- In July 2009, FDA published a briefing document regarding considerations for use of H1N1 vaccines from the Vaccines and Related Biological Products Advisory Committee.

  – The expectation is to collect additional safety and effectiveness data post-approval

  – FDA and CDC plan to (and are) conducting enhanced surveillance during early use of the vaccine; and in collaboration with other agencies in DHHS, are working to strengthen their ability to rapidly identify and evaluate potential safety signals following administration of H1N1 vaccines. DHHS is coordinating these activities.

Regulatory Considerations

- EMEA guidance requests a pharmacovigilance plan that specifically includes
  - Monitoring of both immunocompromised subjects and pregnant women receiving the vaccine
  - Surveillance of Adverse Events of Special Interest (AESIs)
    - Guillain-Barré Syndrome
    - Neuritis
    - Convulsions
    - Anaphylaxis
    - Encephalitis
    - Vasculitis
    - Bell's Palsy
    - Demyelinating disorders
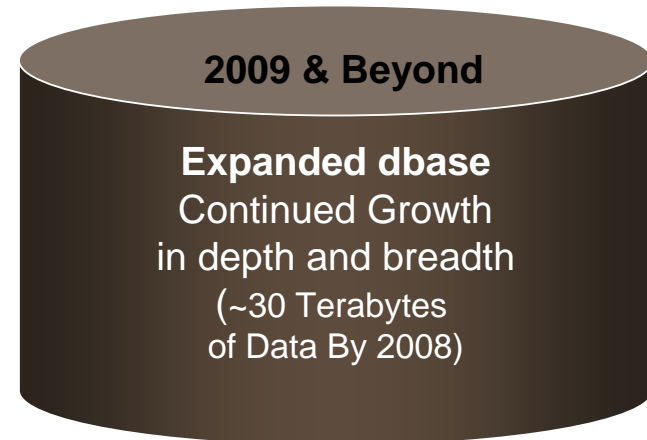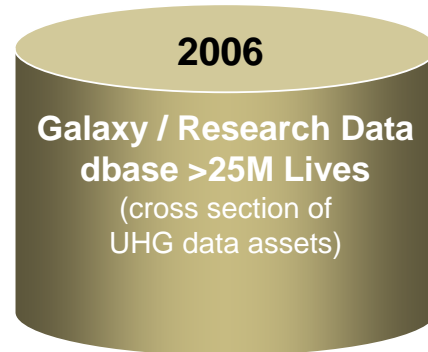   - Laboratory-confirmed vaccine failure

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Comprehensive Surveillance Program for the U.S. Leveraging i3 Drug Safety, Ingenix, and UnitedHealth Group Expertise and Data Assets

- Ingenix research database

- i3 Drug Safety's pharmacoepidemiologic scientists and expertise designing and conducting safety surveillance studies

- i3 Drug Safety's technology tools that facilitate comprehensive safety surveillance and risk management systems

  - i3 STORK (Systematic Tracking of Real Kids)
    - With over 100,000 deliveries each year, enables proactive monitoring of pregnancy outcomes to ascertain risks associated with exposure during pregnancy at a fraction of the cost associated with a more traditional pregnancy registry approach
  - i3 Rapid Cycle Surveillance System
    - Facilitates early identification and assessment of targeted safety issues of concern such as AESIs for influenza vaccination
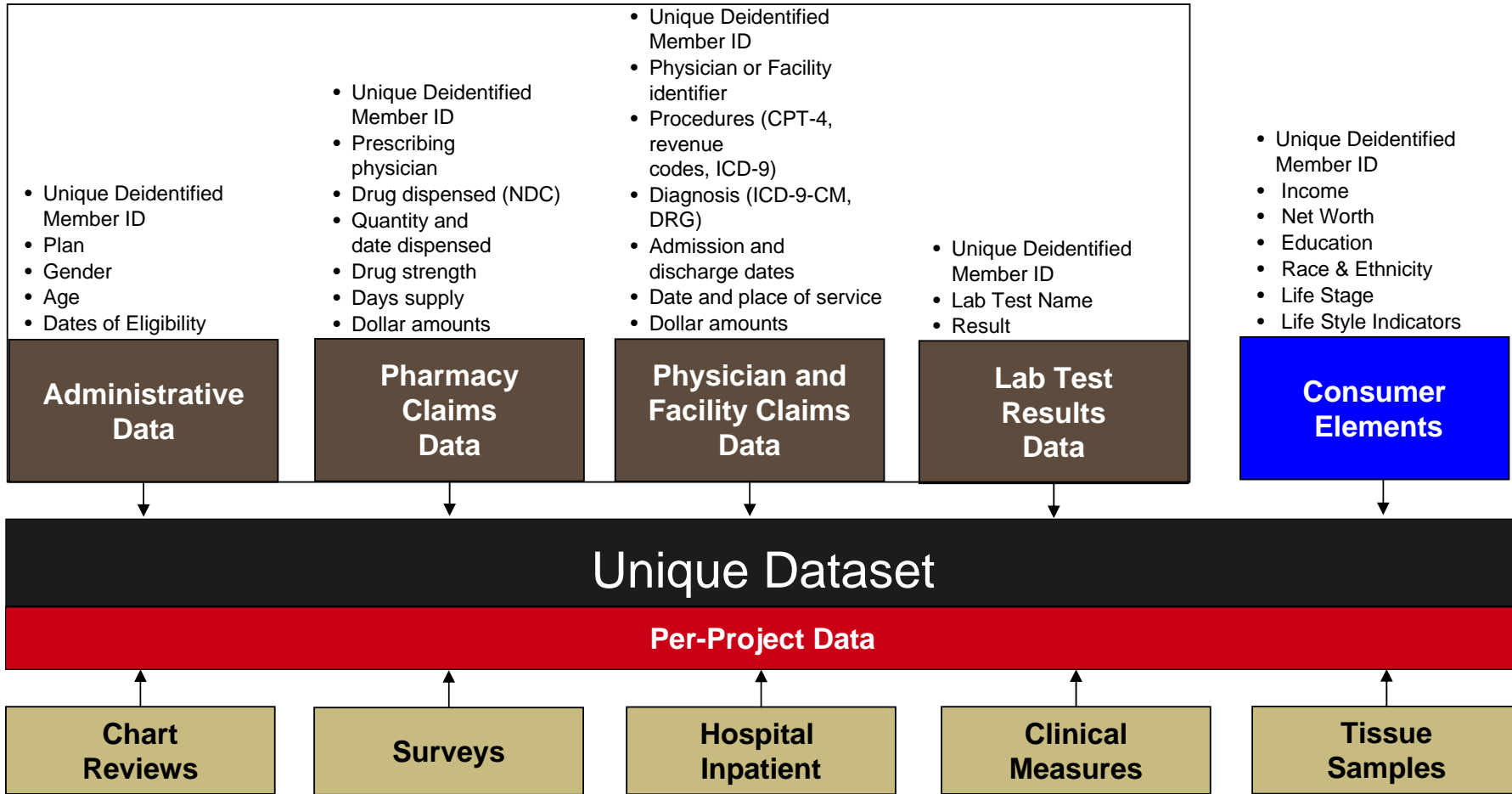
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Ingenix Data and Analytic Assets

- Largest linked claims/laboratory/consumer information database

- Claims data extracted from adjudicated physician, facility and pharmacy claims

- Longitudinal data on >97 million covered lives

- Geographically dispersed

- Medicaid and Medicare

The individuals in this system are all active with prescriptions

2006

Galaxy / Research Data dbase >25M Lives
(cross section of UHG data assets)

2009 & Beyond

Expanded dbase
Continued Growth
in depth and breadth
(~30 Terabytes
of Data By 2008)

Data Elements in Research Database

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- Unique Deidentified Member ID
- Plan
- Gender
- Age
- Dates of Eligibility

Administrative Data

- Unique Deidentified Member ID
- Prescribing physician
- Drug dispensed (NDC)
- Quantity and date dispensed
- Drug strength
- Days supply
- Dollar amounts

Pharmacy Claims Data

- Unique Deidentified Member ID
- Physician or Facility identifier
- Procedures (CPT-4, revenue codes, ICD-9)
- Diagnosis (ICD-9-CM, DRG)
- Admission and discharge dates
- Date and place of service
- Dollar amounts

Physician and Facility Claims Data

- Unique Deidentified Member ID
- Lab Test Name
- Result

Lab Test Results Data

- Unique Deidentified Member ID
- Income
- Net Worth
- Education
- Race & Ethnicity
- Life Stage
- Life Style Indicators

Consumer Elements

Unique Dataset

Per-Project Data

| Chart Reviews | Surveys | Hospital Inpatient | Clinical Measures | Tissue Samples |

Rapid Cycle Surveillance (RCS) System

- Information from large source population
  - Information ultimately feeds the Research Database

- Comprehensive
  - Essentially the same elements as in our Research Database

- With very short "lag"
  - Days/weeks from the patient encounter with the health care provider that generated the claim

- Implement i3's RCS System for the surveillance of AESIs for H1N1 vaccination in the US
  - Using RCS, can we really accrue vaccinated subjects in a very rapid fashion?
  - What's the correlation between information in RCS and the Research Database?
  - What's the PPV of an outcome in RCS?

Some Protocol Highlights

- Summary

  - Monitor the safety of the H1N1 vaccine with regard to specific Designated Medical Events (DMEs) during the 2009/10 influenza season within a large U.S. health insurance plan

- Selected methods and objectives

  - Identify recipients of both H1N1 vaccine and regular seasonal influenza vaccine on a daily basis using i3's RCS System

  - Follow vaccinees for 84 days and identify claims with diagnosis codes for the specific DMEs on a daily basis using i3's RCS System

    - DMEs include EMEAs AESI list

  - Compare the frequency of these DMEs among H1N1 vaccine recipients to the frequency among seasonal influenza vaccine recipients using maxSPRT analysis

    - Concurrently, and using historical data from the previous 4 influenza seasons

- IRB and Privacy Board approval received 9 October 2009

Identifying Pregnancy Women

- Pregnant women were identified in the RCS System by the occurrence of ICD-9 diagnosis codes related to pregnancy
  - V22: Normal pregnancy
  - V23: Supervision of high risk pregnancy
  - 630-677: Complications of pregnancy, childbirth, and the puerperium

Codes Used in the RCS System to Identify Selected Outcomes

- Guillain-Barré Syndrome
  - GBS was defined with ICD-9 diagnosis code
    - 357.0: Acute infective polyneuritis.

- Anaphylaxis
  - Anaphylaxis was defined with ICD-9 diagnosis codes
    - 995.0: Other anaphylactic shock
    - 999.4: Anaphylactic shock due to serum

- Urticaria, angioneurotic edema, and allergic reactions
  - The ICD-9 diagnosis codes used to define these outcomes were
    - 995.1: Angioneurotic edema
    - 995.3: Allergy, unspecified
    - 708.0: Allergic urticaria
    - 708.1: Idiopathic urticaria
    - 708.9: Urticaria, unspecified

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**Fall 2009 U.S. Influenza Season
Cumulative Number of Vaccinations**
Source: i3 Drug Safety's RCS
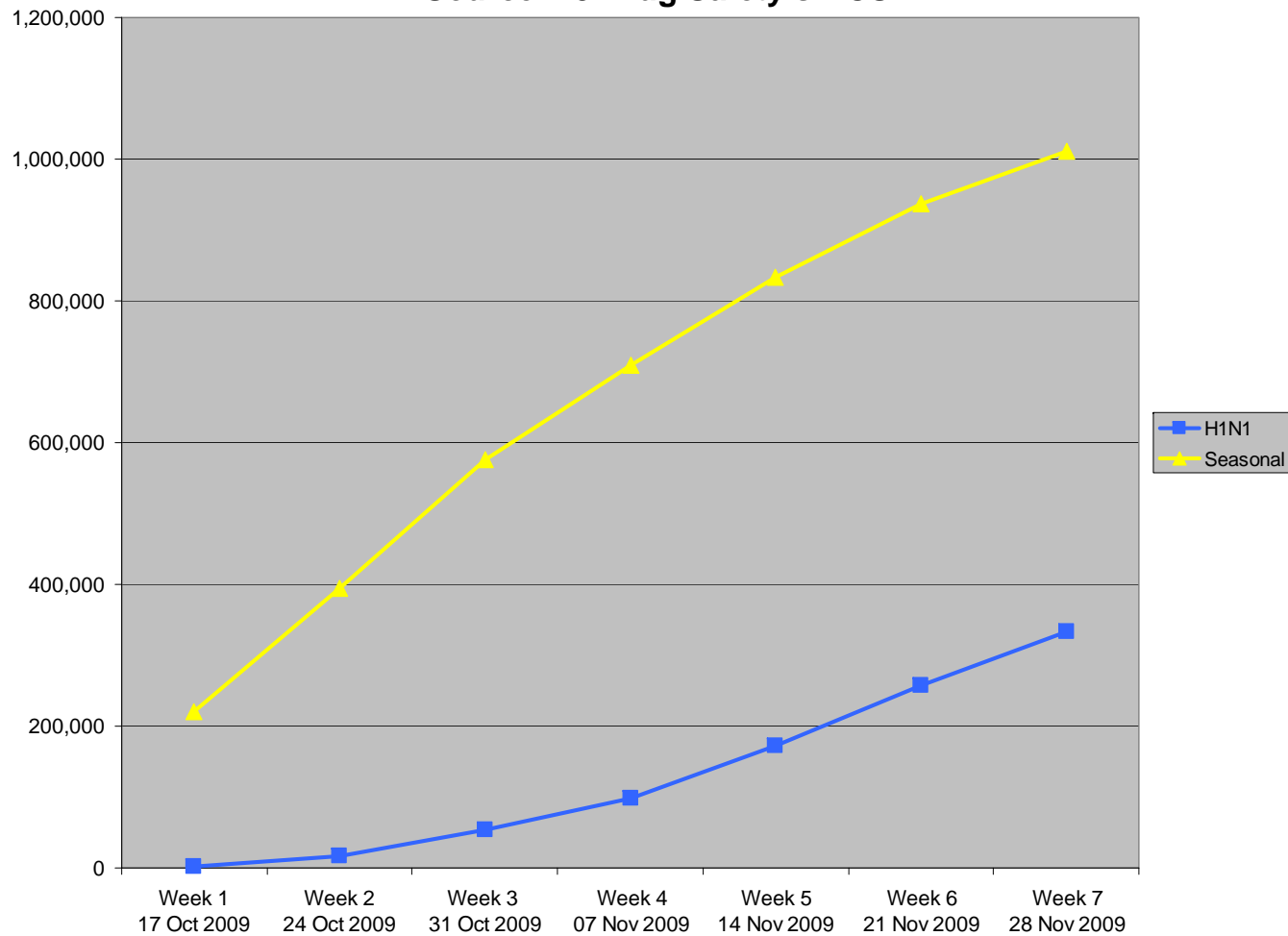
Fall 2009 U.S. Influenza Season
Distribution of Vaccinated Population, by Age and Gender Through 28 Nov 2009

Source: i3 Drug Safety's RCS

| Age Category	H1N1 Vaccine (N=332,433)				Seasonal Flu Vaccine (N=1,010,799)			
	Male (N=150,244)		Female (N=182,189)		Male (N=462,013)		Female (N=548,786)	
	N	%	N	%	N	%	N	%
< 6 months	110	0.1	105	0.1	295	0.1	258	0.0
6 months - 4 years	54,159	36.0	52,063	28.6	114,394	24.8	110,172	20.1
5 to 9 years	35,628	23.7	34,160	18.7	69,363	15.0	67,048	12.2
10 to 17 years	30,659	20.4	29,001	15.9	63,343	13.7	61,773	11.3
18 to 29 years	4,889	3.3	17,593	9.7	16,147	3.5	31,690	5.8
30 to 49 years	12,323	8.2	33,157	18.2	64,408	13.9	103,622	18.9
50 to 64 years	10,635	7.1	14,446	7.9	93,207	20.2	124,843	22.7
65 years and over	1,841	1.2	1,664	0.9	40,856	8.8	49,380	9.0

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Fall 2009 Influenza Season
Cumulative Number of Vaccinations in Pregnant Women

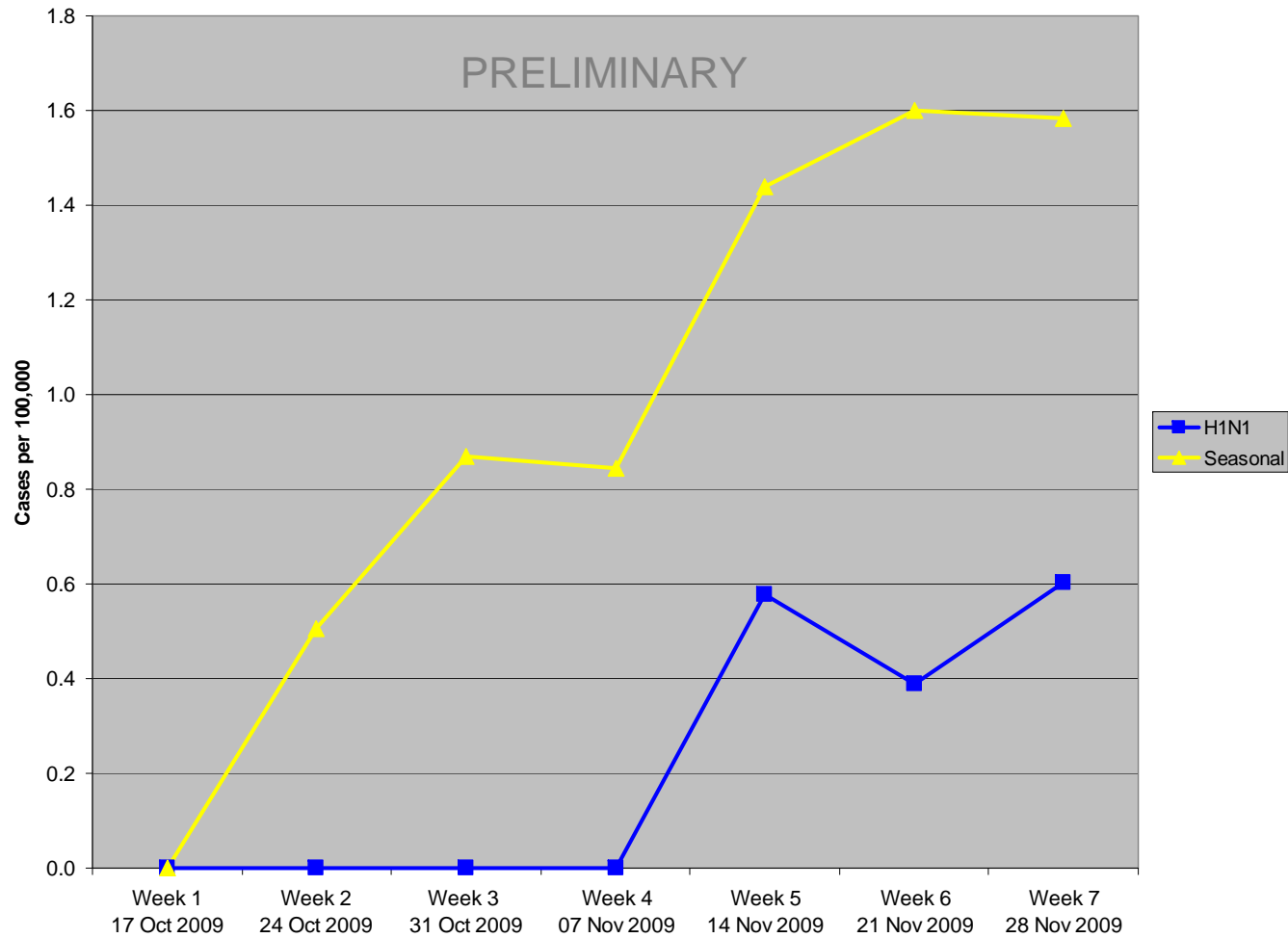**Source: i3 Drug Safety's RCS**
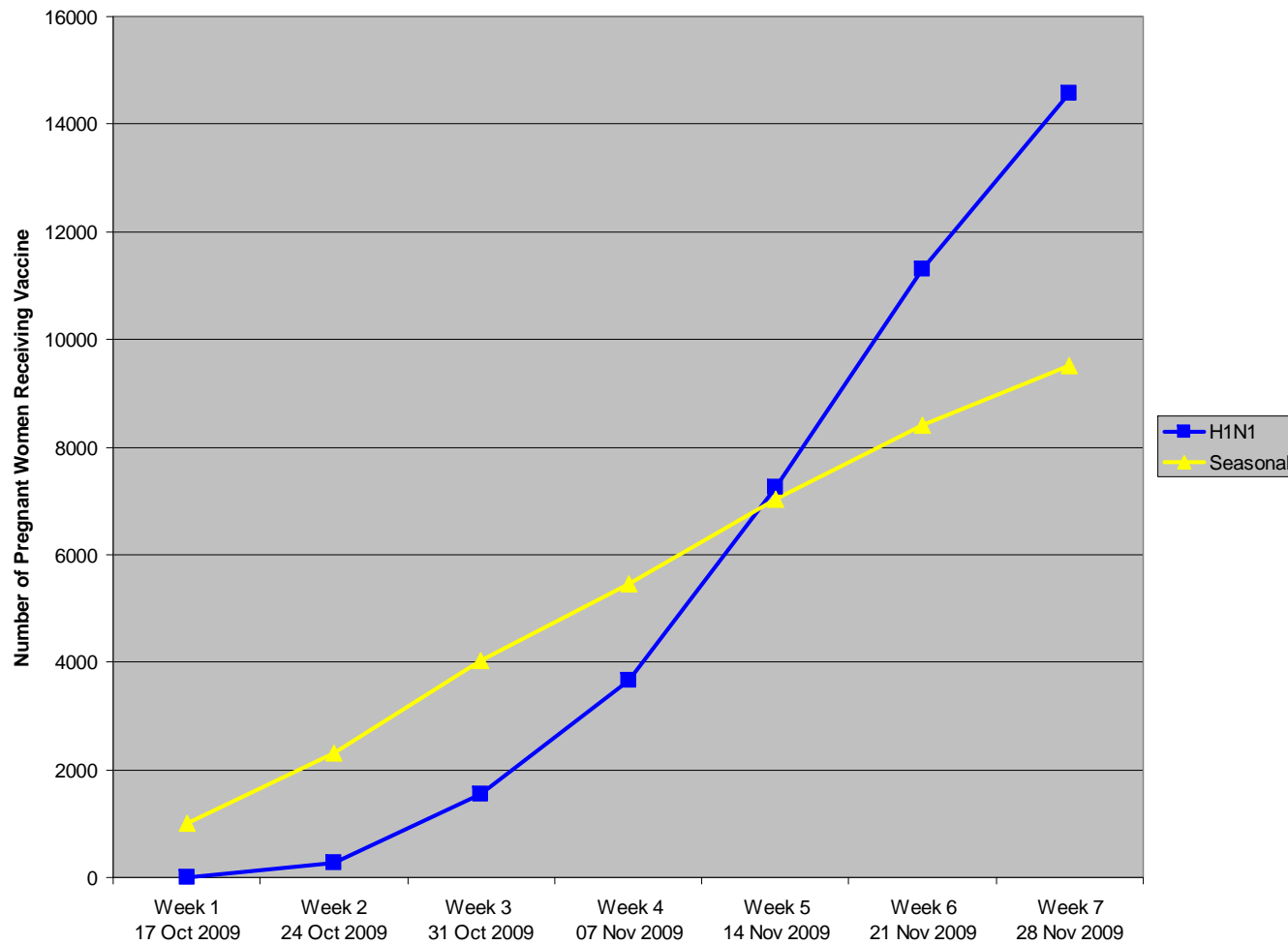
Fall 2009 Influenza Season
Percent of Vaccinations Received by Pregnant Women

Source: i3 Drug Safety's RCS
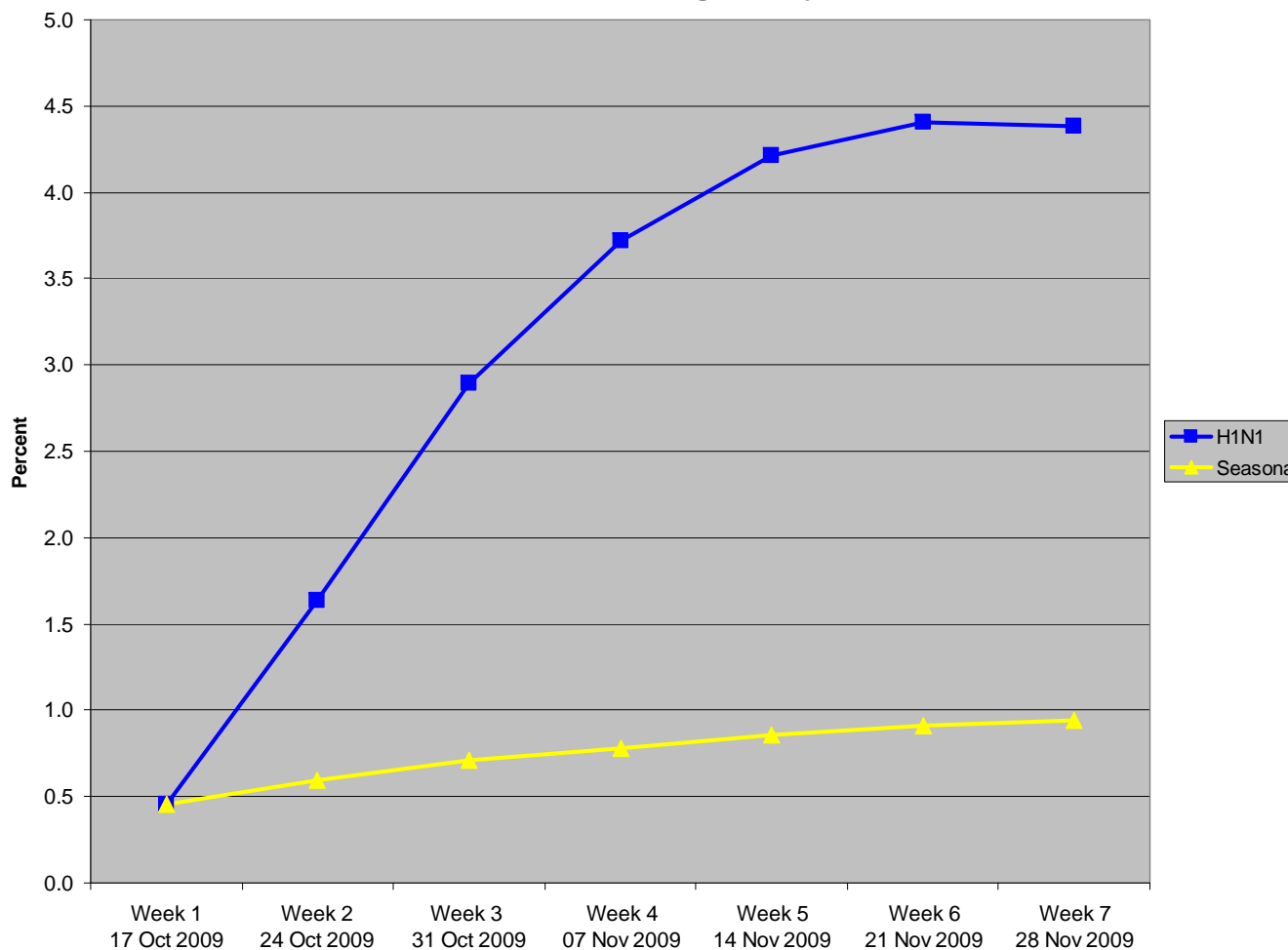
Fall 2009 Influenza Season
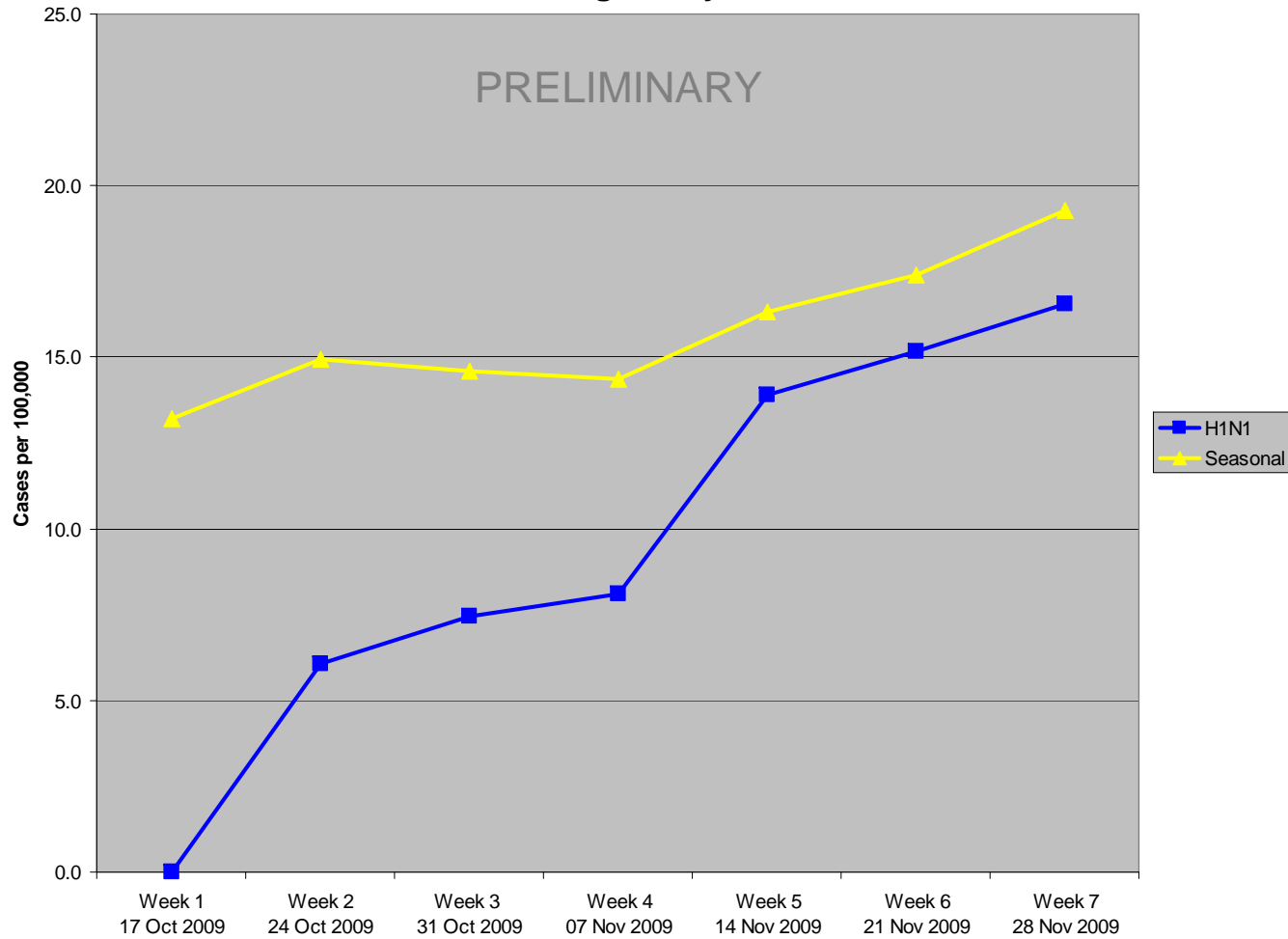# Frequency of Guillain-Barré Syndrome

Source: i3 Drug Safety's RCS

These outcomes are based on preliminary analyses and have not yet been adjudicated.
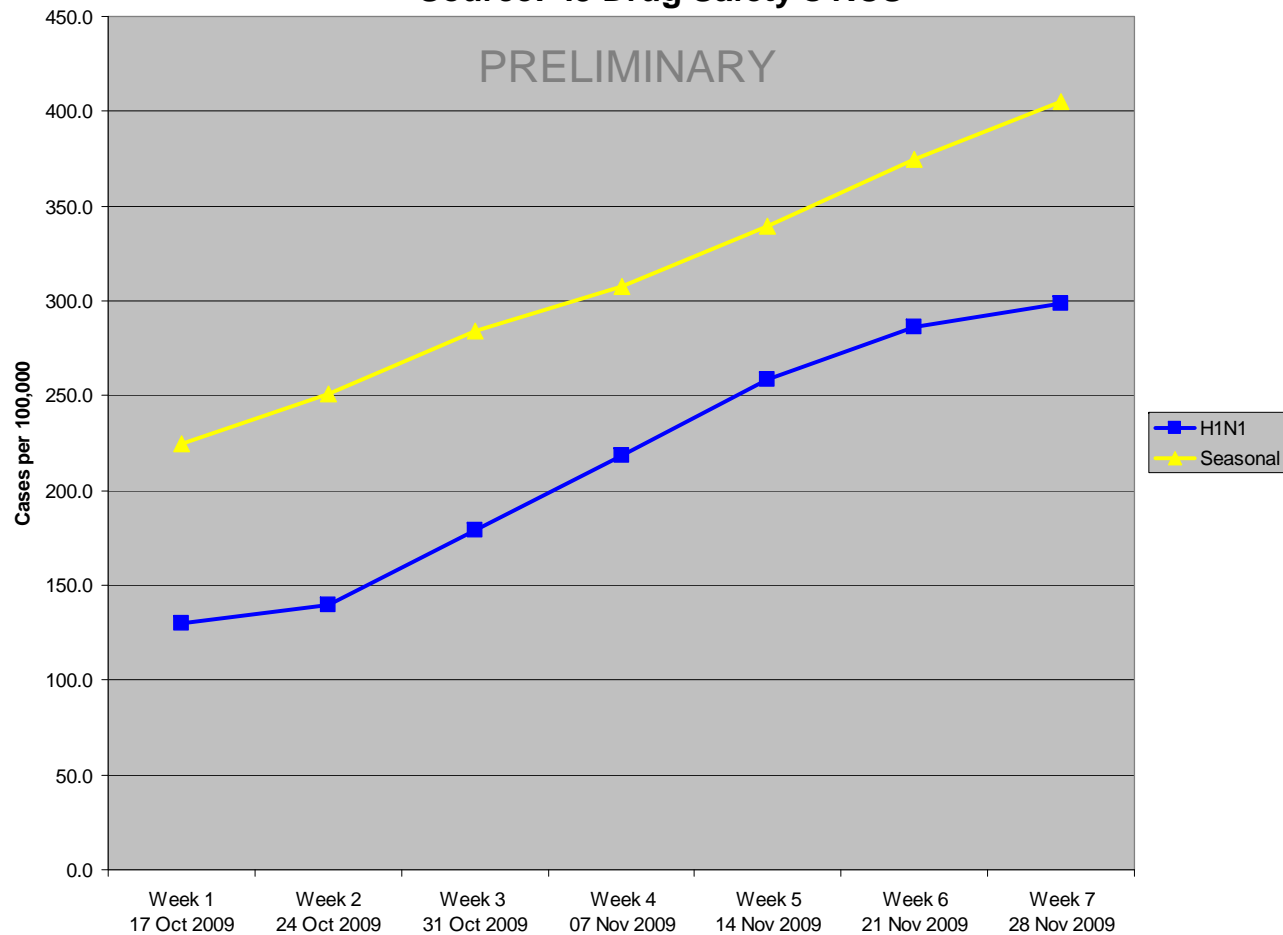
Fall 2009 Influenza Season
Frequency of Anaphylaxis

Source: i3 Drug Safety's RCS

These outcomes are based on preliminary analyses and have not yet been adjudicated.

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Fall 2009 Influenza Season
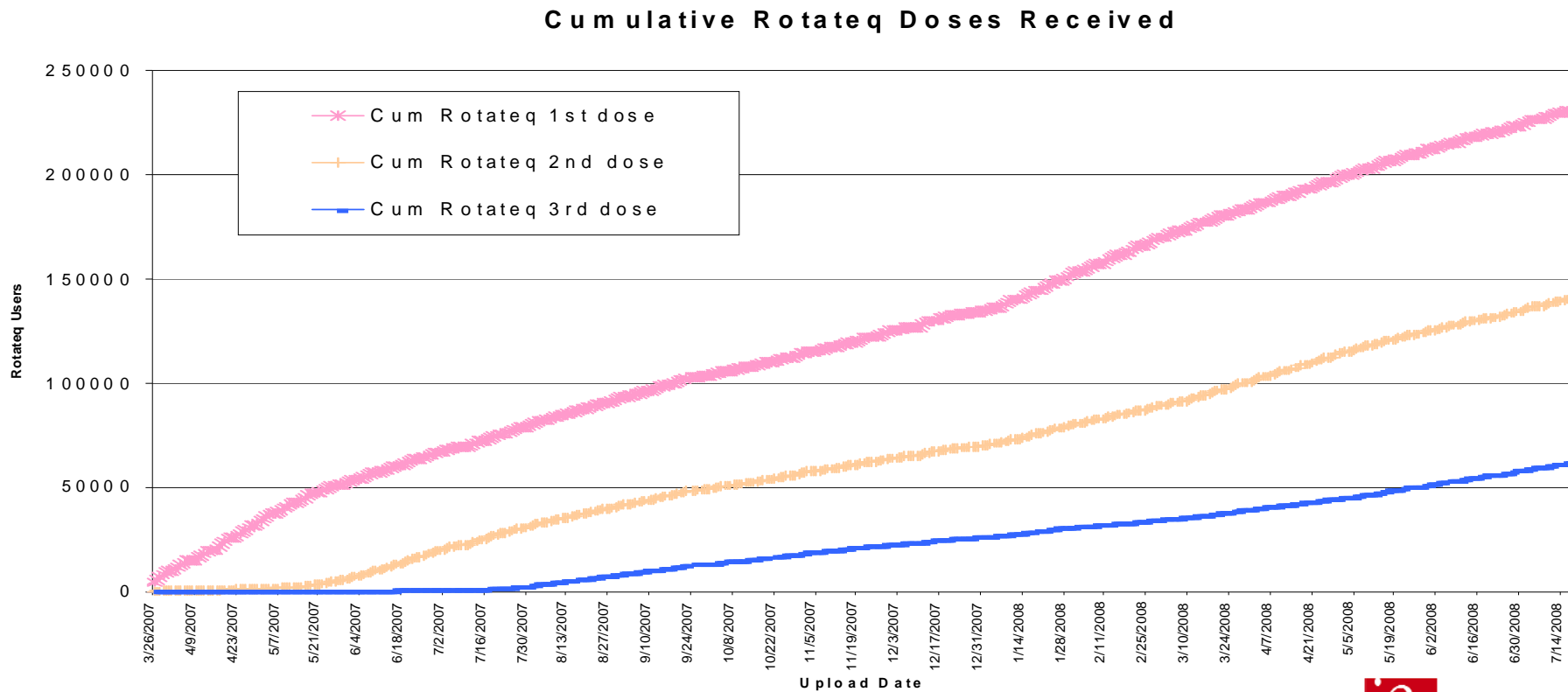**Frequency of Urticaria, Angioneurotic Edema, and Allergic Reactions**

Source: i3 Drug Safety's RCS

These outcomes are based on preliminary analyses and have not yet been adjudicated.

Preliminary Conclusions/Next Steps

- To-date, this pilot has confirmed that RCS enables the rapid accrual of subjects
- We've seen similar results in other studies (e.g. rotavirus vaccine)

Cumulative Rotateq Doses Received

Legend:
- Cum Rotateq 1st dose
- Cum Rotateq 2nd dose
- Cum Rotateq 3rd dose

Y-axis: Rotateq Users (0 – 250000)
X-axis: Upload Date (3/26/2007 – 7/14/2008)

Preliminary Conclusions/Next Steps

- We have not yet evaluated the correlation between the information in RCS and our research database for H1N1 vaccination and outcome tracking
  - Planned, but our research database has not yet 'caught up' with the initial wave of vaccinations from the 2009/10 influenza season
- Previous experience
  - We except a significant number of subjects may not be able to be linked between RCS and our research database based on lack of a common unique identifier between the 2 sources
    - In another study using both RCS and the research database, we linked 112,145/141,552 (79%) infants using SSN alone. When we added an additional identifier of family id to identify infants using a parent SSN, this brought the number down to around 75%.
    - In this same study, we identified 38 outcomes of interests (IS) in the RCS data; we linked 28 of these to our research database
  - For subjects that are able to be linked, we anticipate a strong correlation between outcomes from RCS with outcomes in our research database
    - In the above study, 100% of infants with the outcome of interest in the RCS data had the same outcome of interest in the research database
    - Little to no change in outcomes based on the claims cleaning process has been our observation to-date
- Results from the H1N1 vaccine surveillance project will be very important in further evaluating the correlation between information in RCS and our research database

Preliminary Conclusions/Next Steps

- Additionally, we have not yet evaluated the PPV of outcomes in RCS based on a review of medical records for important outcomes (e.g. Guillain-Barré Syndrome) for H1N1 vaccination and outcome tracking
  - Planned as part of our research protocol

- Previous experience
  - We except this will vary
    - By outcome
    - By algorithm/codes used to identify the outcome

Preliminary Conclusions/Next Steps

- Guillain-Barré Syndrome: our experience from another project
  - 30/105 of possible GBS cases identified by claims diagnosis code alone (ICD-9 357.0) were chart-confirmed, with a PPV of 29%
  - If we used hospitalization plus the GBS diagnosis code, the PPV increased to 41%
  - If we used neurologist visit (any) plus a GBS diagnosis code, the PPV increased to 65%

i3's RCS for Rotavirus Vaccine

Freq of Rotateq doses for kids <=1 yr

The FREQ Procedure

rot_doses_u1	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	85469	37.99	85469	37.99
2	77756	34.56	163225	72.55
3	61761	27.45	224986	100

85,469*1 + 77,756*2 + 61,761*3 = 426,264 infant months = 35,522 infant years

Rotateq unique users with a dx of any intussusception (within 30 days), age <=1year

The FREQ Procedure

rotateq	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	34	100	34	100

Expect 1 case per 2000 infant years (17-18 cases)

i3 Drug Safety experience that ~50% of claims-based cases were confirmed in medical records

Q & A