Duke | MARGOLIS CENTER FOR HEALTH POLICY

Advancing Drug Development for the Prevention and Treatment of Respiratory Syncytial Virus Infections

5/2/2016

Initiation of Pediatric Trials: RSV Bronchiolitis

Prabha Viswanathan, MD
Medical Officer, Division of Antiviral Products
Center for Drug Evaluation and Research, FDA

2

Objectives

- Discuss the types of studies that support initiation of pediatric trials for treatment and prevention products:
  - Which adult populations/disease conditions are preferred?
  - Are adult challenge studies adequate to demonstrate prospect of benefit for infants in bronchiolitis trials?
  - To what extent can non-clinical data be used to support pediatric studies (i.e., animal models of disease)?

Regulatory Framework for Pediatric Clinical Trials

- 21 CFR 50 Subpart D: Additional Safeguards for Children in Clinical Investigations
- Clinical trials in which more than minimal risk to children is presented by an intervention or procedure…may involve children only if..:

  (a) The risk is justified by the anticipated benefit to the subjects;

  (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

  (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

Standard Approach to Pediatric Antiviral Drug Development

- Initial clinical trials to establish safety and efficacy are conducted in adults
- If the infection results in a comparable disease course in adults and children, efficacy in adults can be extrapolated to children
  - Primary objectives of pediatric studies are to evaluate PK and safety

RSV Bronchiolitis

- Conventional paradigm doesn't apply to RSV drug development
- Natural history of bronchiolitis differs from lower respiratory tract infection in older children and adults
  - Anatomy and physiology
  - Host immune response
- Efficacy cannot be extrapolated

Initiation of Pediatric RSV Trials

Data from adult clinical trials and nonclinical studies should:

- Demonstrate prospect for clinical benefit
- Characterize the drug's adverse event profile

TREATMENT OF BRONCHIOLITIS

Treatment of Bronchiolitis

- It is unknown whether reduction of viral load in adults predicts efficacy in treatment of bronchiolitis.
- However, evidence of symptomatic improvement in adults supports the prospect of clinical benefit in infants and young children.
- Therefore, we recommend evaluating both antiviral activity AND clinical signs/symptoms in early phase adults trials.

Populations for Supportive Efficacy Studies

- Patients at risk for severe illness from naturally acquired RSV infection:
  - Elderly adults
  - Immunocompromised adults
- Healthy adults experimentally infected with an acceptable RSV challenge strain

Trial Design for Supportive Efficacy Studies

- Randomized, double-blind, comparative trials are preferred
- Other Possibilities
  - Dose-ranging
  - Duration of treatment
- Subjects should have established infection prior to receiving the investigational product

Endpoints for Supportive Efficacy Studies

- Multiple virologic and clinical endpoints could be explored in Phase 2 studies
- Examples:
  - Change in RSV viral load
  - Change in clinical symptom scores
  - Hospitalization
    - Duration of hospitalization
    - Mechanical ventilation
  - Other indicators of disease progression/resolution

PREVENTION OF BRONCHIOLITIS

Prevention of Bronchiolitis

- Historically, focus has been on passive immunoprophylaxis
  - Scientific basis from observational studies of RSV infection in young infants, which revealed a correlation between circulating maternal anti-RSV antibody levels and decreased severity of disease
- Development of new products for RSV prophylaxis may need supportive evidence of prophylactic activity prior to pediatric trials

Populations for Supportive Efficacy Studies

- Similar to treatment trials
- Patients at risk for symptomatic illness from naturally acquired RSV infection:
  - Elderly adults
  - Immunocompromised adults
- Healthy adults – challenge studies

Trial Design for Supportive Efficacy Studies

- Randomized, double-blind, comparative trials are preferred
  - Naturally acquired infection: conduct studies in areas with documented RSV disease activity
  - Challenge studies: subjects receive the investigational product prior to experimental inoculation
- Data from trials conducted for RSV treatment may also support prophylaxis trials (e.g. oseltamavir for influenza)

Endpoints for Supportive Efficacy Studies

- Multiple clinical endpoints could be explored in Phase 2 studies
- Examples:
  - Prevention of symptomatic illness (laboratory confirmed)
  - Prevention of LRTI
  - Prevention of hospitalization
- Sponsors should discuss proposed endpoints with the Agency during protocol development

Safety Considerations: Treatment and Prophylaxis

- At least 100 adults should be exposed to the drug prior to initiating pediatric trials
  - Exposures should be similar or higher than the proposed pediatric dosage regimen
- Additional data in adults may be needed prior to initiation of pediatric trials depending on:
  - Nonclinical pharmacology/toxicology findings
  - Preliminary safety profile of the drug observed in adults

NON-CLINICAL STUDIES

Role of Nonclinical Studies in Pediatric RSV Drug Development

- Data from nonclinical studies may be used to support both the safety and efficacy of investigational products
- Studies in juvenile and adult animals may serve to fill in the gaps from adult clinical studies

Nonclinical Studies: Safety

- Studies in juvenile animals are recommended, in addition to the standard nonclinical assessments
- Results from juvenile toxicology studies may inform risk for toxicity in young children that otherwise may not be detected

Nonclinical Studies: Efficacy

- Data from adult clinical trials have limited applicability to trials of infants with bronchiolitis
- Animal models may resemble bronchiolitis more closely
- Therefore, data from applicable nonclinical studies may provide important evidence of supportive efficacy to support initiation of pediatric trials for treatment and prophylaxis agents

Summary

- There is a regulatory requirement for the prospect of clinical benefit in pediatric trials
- Supportive efficacy data can be obtained from studies in adults with naturally acquired RSV infection or healthy adults who are experimentally inoculated with RSV challenge strains
- Differences in the natural history of RSV disease in infants versus older children/adults limits the applicability of data between populations
- Safety and efficacy data from adult studies can be augmented with nonclinical studies in juvenile and adult animals

THANK YOU

Duke | MARGOLIS CENTER FOR HEALTH POLICY

Advancing Drug Development for the Prevention and Treatment of Respiratory Syncytial Virus Infections

5/2/2016

Burden, Outcomes and Image of RSV in Elderly & High-risk Persons

Edward Walsh

University of Rochester

Rochester General Hospital

Diagnosis specific Rochester NY (1999-2003)

1471 hospitalizations at one hospital during 4 winters using PCR, serology & culture:

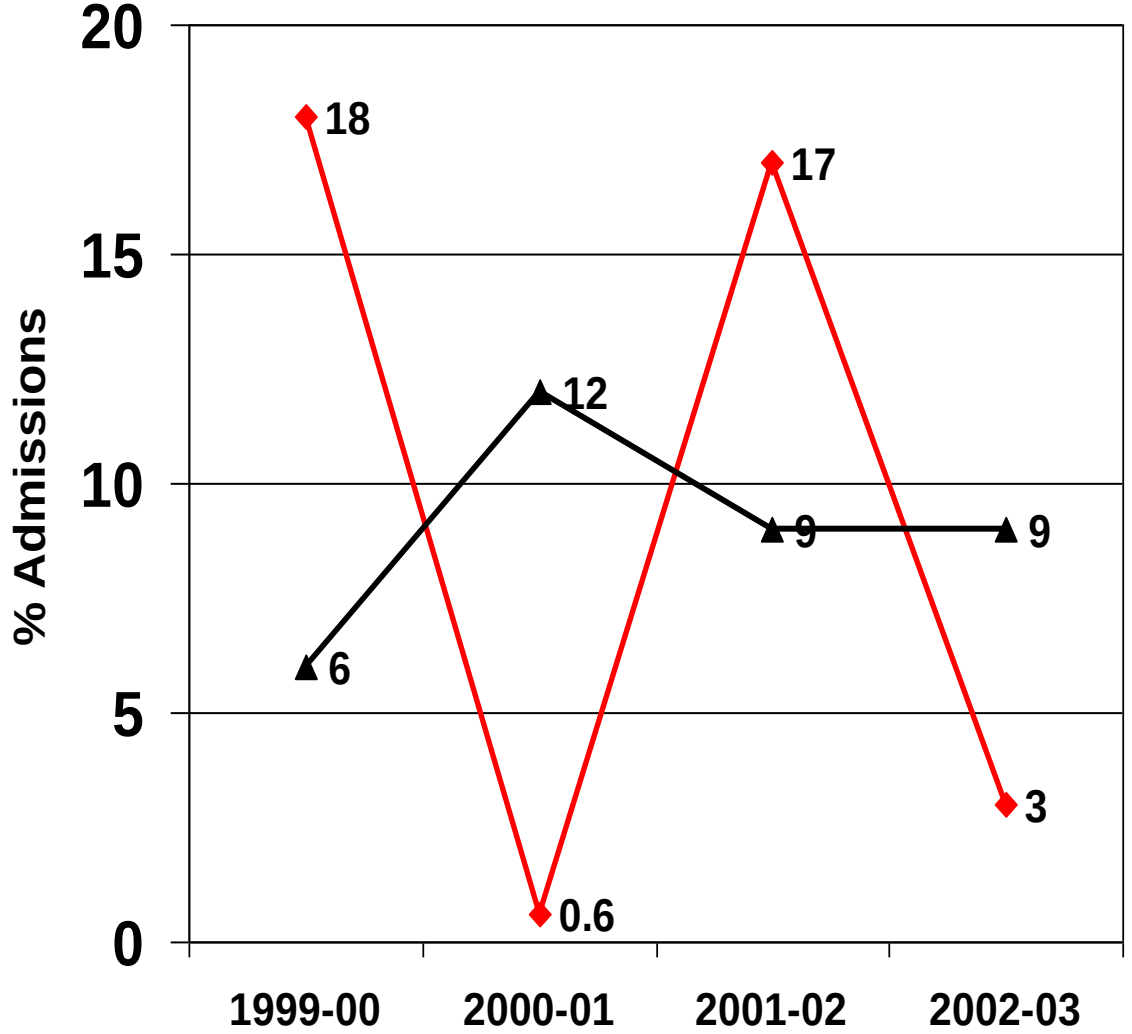
RSV 10.6% vs. Flu 11.6%

Conversion to population base >65 yo

77 hospitalizations/100,000 (86 for Zhou)

Falsey AR, et al. NEJM 205; 352:1749-59

Percent Admissions: RSV and Flu A in 1471 admissions to RGH



Average

RSV - 9.0 %

Flu A - 9.5 %

Falsey et al NEJM 2005;352:1749

Widmer et al., JID 2012;206:56-62

508 hospitalized adults ≥ 65 years

PCR over 3 winters in Nashville,TN

Virus	Incidence (%)	% ICU	mortality
RSV	6.1%	10%	6%
Influenza	6.5%	13%	9%
HMPV	4.5%	6%	0%

Recent data from Hong Kong

Lee N, et al. CID 2013; 57:1572

Retrospective 3 years at 3 hospitals

Diagnosed RSV & Flu by FA on nasal aspirates

Results: 607 RSV 547 Flu

H Zhou, et al. CID 2012;54:1427-36

Negative binomial regression model of Flu and RSV by utilizing respiratory and circulatory hospitalization data from 13 states (HCUP) and national lab diagnostic data

≥ 65 yrs: 86/100,000 person-yrs (309 flu)

50-64 yrs: 12.8/100,000 person-yrs (65 flu)

<1 yr: 2,345/100,000 person-yrs

1-4 yrs: 178/100,000 person-yrs

H Zhou, et al. CID 2012;54:1427-36

Conversion to number of RSV associated US hospitalizations by age group

43,420 adults >50 years of age

122,280 infants & children <5 yrs

Von Asten L, et al. JID 2012;206:628-39

Poisson regression model to estimate mortality from RSV & Flu in elderly adults in The Netherlands.

During 9 years Influenza ~1.6 fold > RSV

Virus	65-74 yr	75-84 yr	≥ 85	≥ 65
Flu A	1,935	6,282	7,201	15,519
RSV	1,305	5,171	7,425	13,902
Flu B		2,209	3,907	6,116

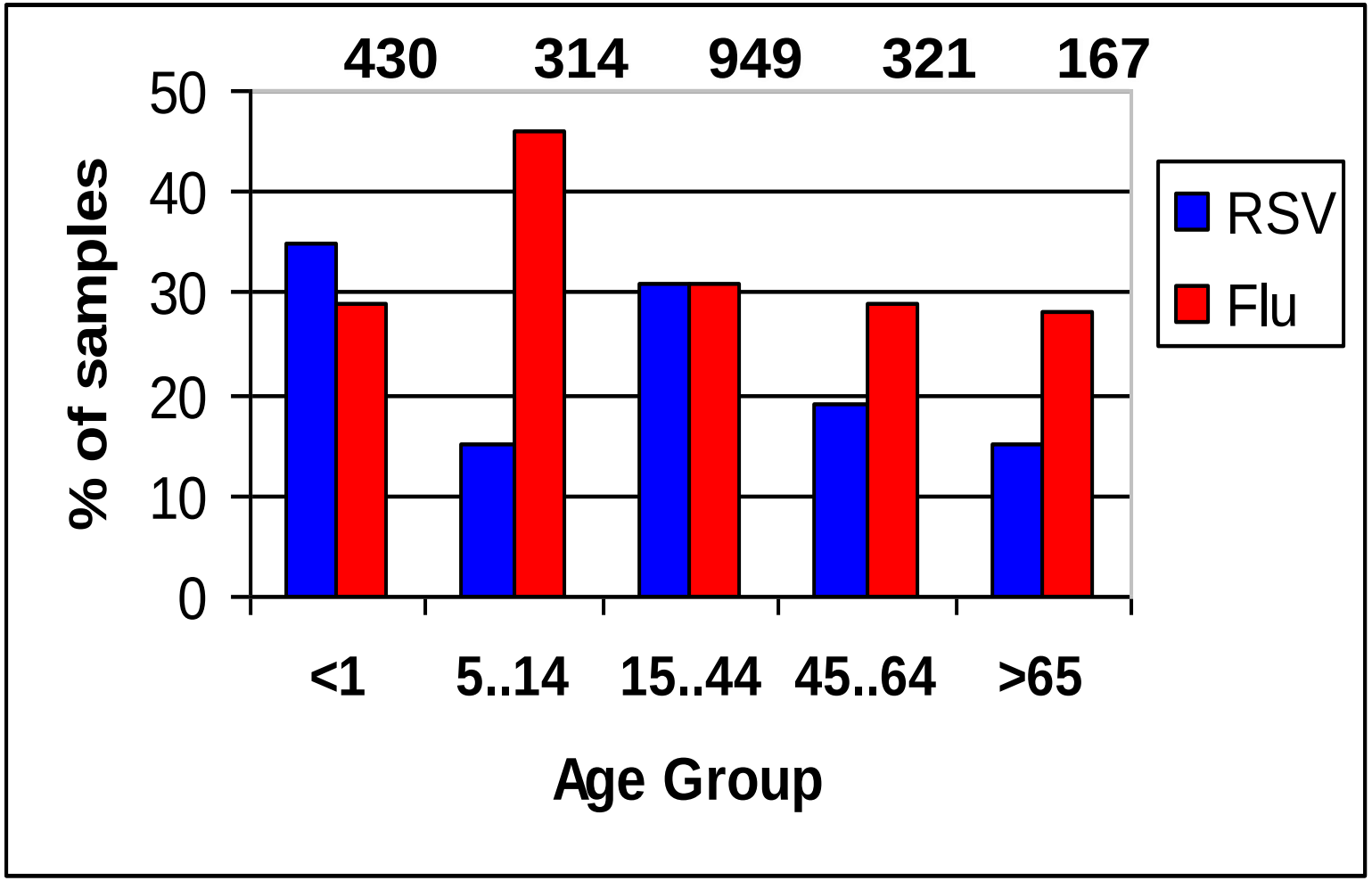
Estimated hospitalization burden associated with influenza & RSV in NYC 2003-2011

Goldstein E. Influenza and other Respiratory Viruses 2015;9:225-233

Rate per 100,000 persons	**50-64 yrs**		**65-74 yrs**		**≥75 yrs**	
	Flu	RSV	Flu	RSV	Flu	RSV
Respiratory Assoc. Hospitalizations	66	27	126	15	288	175
P & I	26	6	55	4	141	57
Chronic Lung Resp Dis	29	7	55	0	87	90
Circulatory Diseases	-20	37	-40	-28	16	199

Office RSV and Influenza 1995-8

Zambon MC. Lancet 358:1410-16, 2001



Recent Marshfield Clinic data

1568 adults>50 yo presenting with MAARI over 6 season

Sundaram ME.
CID 2013; 57:789

Virus	No.	%
Influenza	343	21.9
RSV	170	10.8
Rhinovirus	126	8.0
hMPV	125	8.0
Coronavirus	122	7.8

1326 MAARI cases with 154 RSV (12%) in 4 year period

McClure DL.
PLOS ONE 9:e1025886

Age group (yrs)	Incidence/10,000
50-59	124 (99,156)
60-69	147 (110,196)
≥ 70	199 (153,258)

Modelling of burden of RSV in adults & elderly in UK*

Fleming DM. BMC Infectious Diseases 2015; 15:443

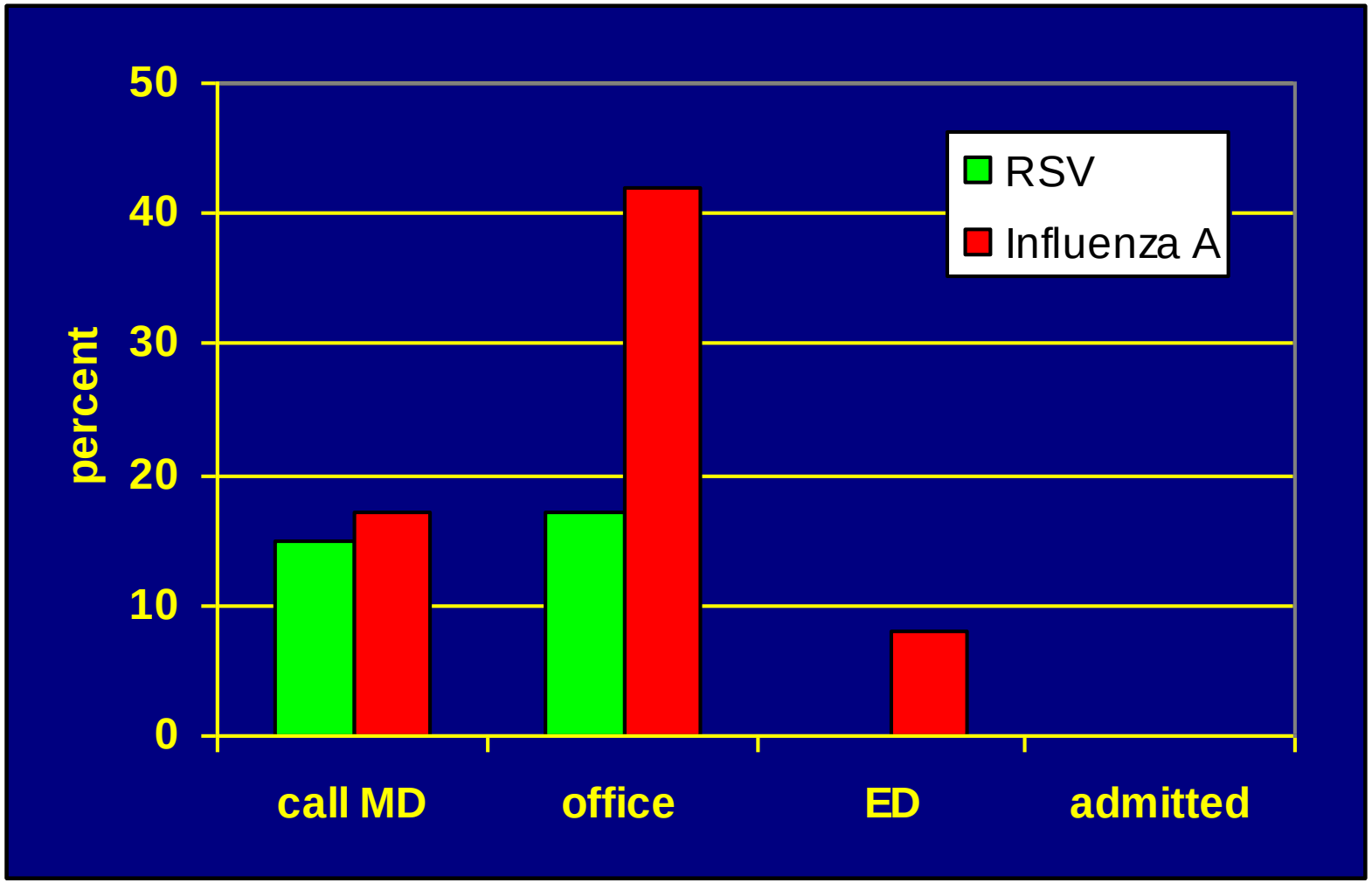
	GP visits	Hospitalizations	Deaths
18+ yrs:	487,247	17,799	8,484
65+ yrs:	175,070	14,039	7,915

High-risk** were 2x more likely to visit a GP and 4x more likely to be hospitalized with a respiratory illness than low-risk persons

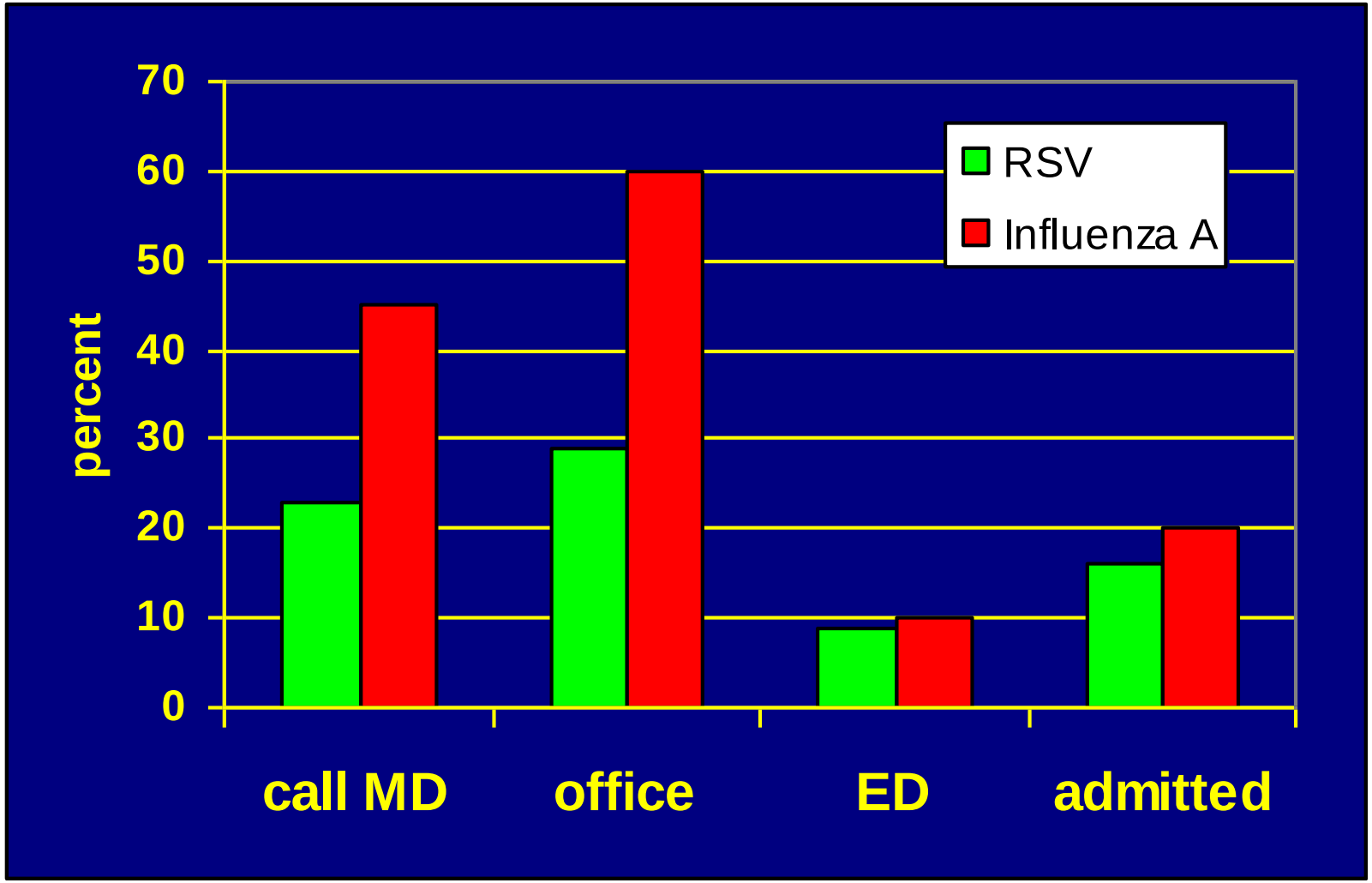
* Population of UK 60 million

**defined as COPD, CHF, DM, liver disease, Cerebrovascular disease, MS

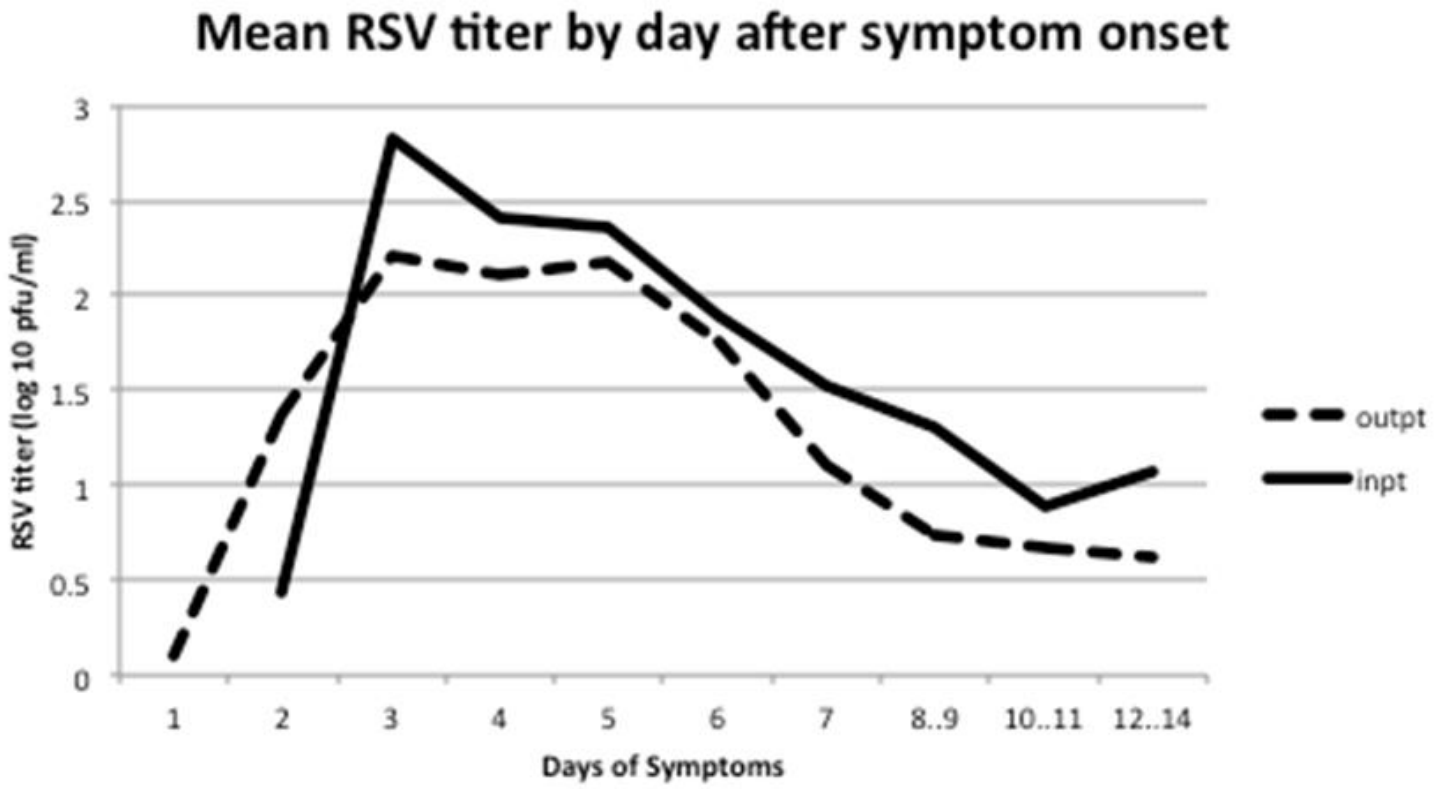
Outcomes in Healthy Elderly



Outcomes in High-Risk Cohort



Viral load according to severity



Walsh E E et al. J Infect Dis. 2013;207:1424-1432

Lee N CID 2013; 57: 1069

	RSV	Influenza
age	75	75
Time to admission	2.6 d	2.0 d
T >37.5 C	75%	94%
wheezing	69%	53%
COPD present	36%	24%
Ventilation	11%	6%
Death	9%	8%

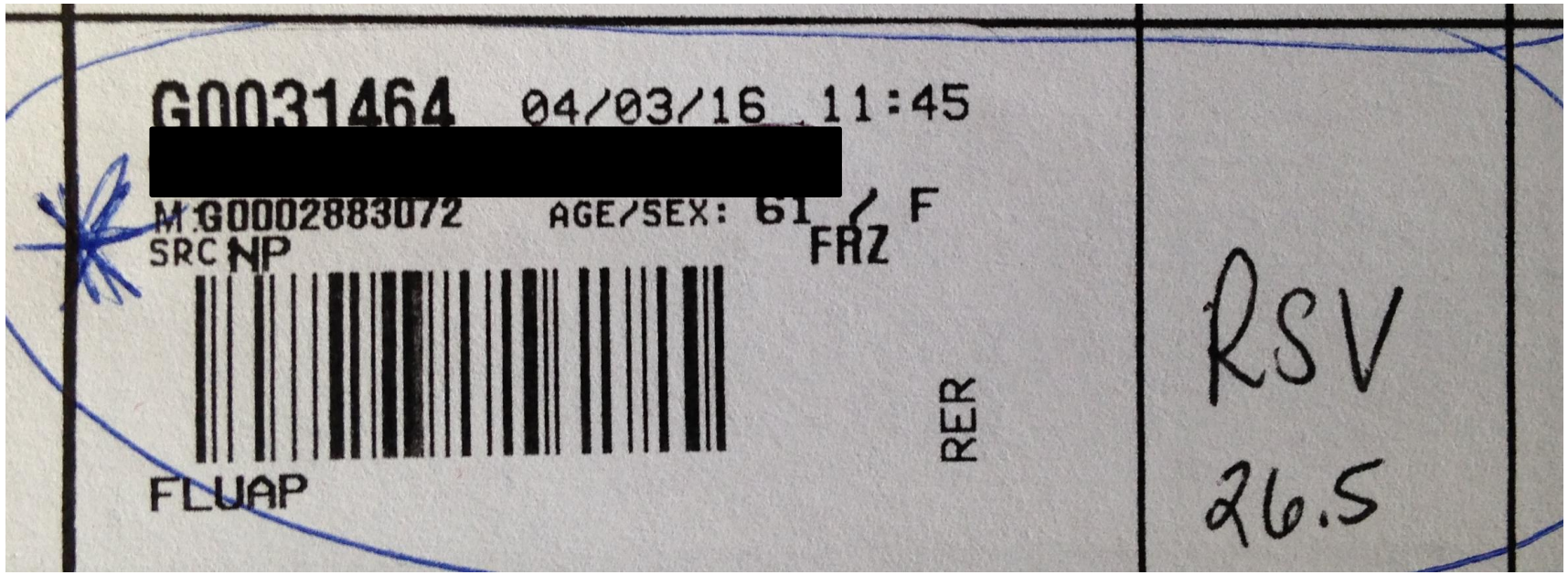
Nasal vs. sputum titers

Peak titer (log_{10}pfu/ml)	Mild disease (n = 61)	Severe disease (n = 50)	P value
Nasal	2.3 ± 1.2	2.8 ± 1.3	.09
Sputum	2.5 ± 1.8	3.3 ± 1.8	.06

100-1000 x lower than in infants

Shedding duration in adults with natural RSV infection

Duration (days)	Mild disease (n = 61)	Severe disease (n = 50)	P value
Nasal	10 ± 5	13 ± 6	.003
Sputum	9 ± 4	10 ± 5	NS


G0031464 04/03/16 11:45
[redacted]
M:G0002883072 AGE/SEX: 61 / F
SRC NP
FRZ
RER
FLUAP
RSV
26.5

[redacted]

Some encounters may be hidden based on the applied filters. Adjust Filters | Reset Filters | Hide Message

Encounter | Episode

Current | +/- 7 Days | All | 6/14/2007 - 4/5/2016

Encounter	Status	Date	Time	Location	Provider	Reason
Orders Only		04/05/2016	0906	RGH PRO MOU CDU OI	Katherine Kristine Copie	Appointment
Admission	Discharged	04/03/2016	1051	RGH OBSERVATION UI	Frank Collins kurpski, I	Influenza [J11.1]
Appointment	Arrived Appt	04/03/2016	1115	RGH RADIOLOGY	Patrick Nolan Martin, MI	Appointment
Ancillary Orders		03/02/2016		RGH MOB RAD MAMM	Berthollet Mpanzu Bavib	Appointment
Ancillary Orders		03/02/2016		RGH MOB RADIOLOGY	Berthollet Mpanzu Bavib	Appointment
Ancillary Orders		03/02/2016		RGH MOB RAD MAMM	Berthollet Mpanzu Bavib	Appointment
Ancillary Orders		12/24/2015		RGH MOB RADIOLOGY	Berthollet Mpanzu Bavib	Appointment
Ultrasound Exam	Completed Appt	12/22/2015	1030	RGH MOB RAD ULTRAS	MOB US 3	RX-Dr.bavibidila, per pt

Loaded 51 of 52. Load All

Encounter

Demographics | Selected Encounter

[redacted]

4/5/2016 Orders Only

MRN: 2883072

Descr [redacted]
Provid
Depar

Progress Notes

No notes of this type exist for this encounter.

Diagnoses

COPD exacerbation - Primary

ICD-10-CM: J44.1
ICD-9-CM: 491.21

Medications Ordered This Encounter

	Disp	Refills	Start	End
albuterol 90 mcg/actuation Inhl inhaler	1 Inhaler	0	4/5/2016	

Inhale 2 puffs into the lungs every 6 (six) hours as needed for Wheezing or Shortness of Breath. - Inhalation

Orders

Created by

Katherine Kristine Copie, FNP on 04/05/2016 09:06 AM

Reprint Req:(In-process or resulted tests will not reprint)

Reprint Requisition

History
Problem List
Demographics
Letters
Place Orders
Call Patient
Send Letter
Write Note
Refill Med
FYI
Patient Station

Rapid Flu/RSV by PCR

Status: **Final result** Visible to patient: **Not Released** Next appt: **None**

4mo ago

INFLUENZA A PCR	Not detected ` Influenza A Sensitivity: >90% Specificity: >90% ` The performance characteristics of the PCR assay are ` dependent on the circulating strain of Influenza virus. ` The PCR assay compares closely to culture.
INFLUENZA B PCR	Not detected ` Influenza B Sensitivity: >80% Specificity: >90% ` The performance characteristics of the PCR assay are ` dependent on the circulating strain of Influenza virus. ` The PCR assay compares closely to culture.
RAPID RSV BY PCR	DETECTED ` Sensitivity: >90% Specificity: >90% ` The performance characteristics of the Simplexa RSV assay ` are dependent on the circulating strain of respiratory syncytial ` virus. The Simplexa RSV assay compares closely to culture. (A)
Resulting Agency	RRHS-RGH

Narrative

Source->Nasopharyngeal

Specimen Collected: 11/14/15 11:29 AM Last Resulted: 11/14/15 1:56 PM

Lab Flowsheet Order Details View Encounter Lab and Collection Details Routing Result History

Results

Rapid Flu/RSV by PCR (Order 149458574)

Result Information

Abnormal

Status: Final result (11/14/2015 1:56 PM)

Provider Status: Ordered

Encounter

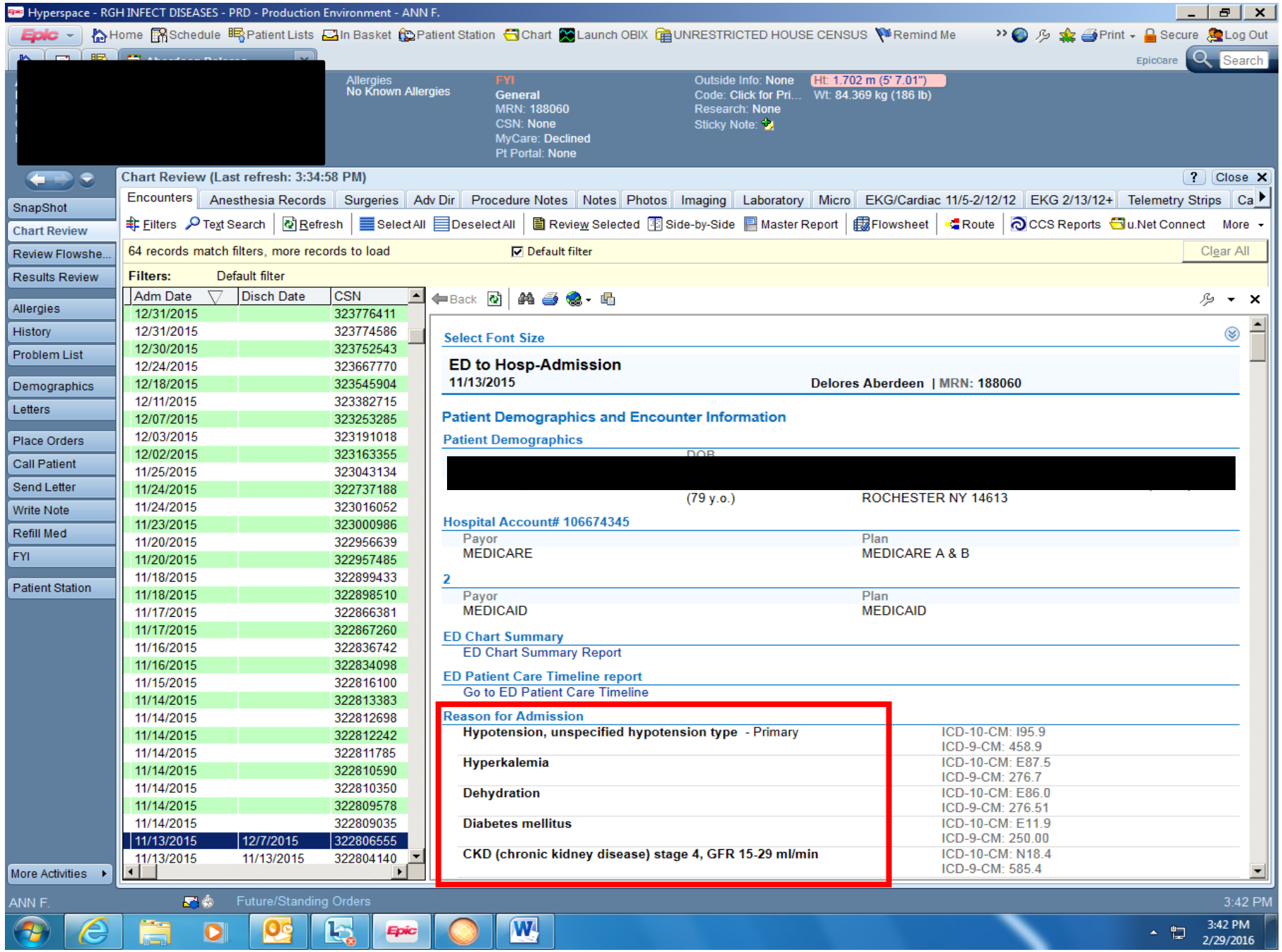
View Encounter

Expand Collapse

More Activities

Extended View: Trend data within the date range (All data within date range shown)

ANN F. Future/Standing Orders


Hyperspace - RGH INFECT DISEASES - PRD - Production Environment - ANN F.
Home
Schedule
Patient Lists
In Basket
Patient Station
Chart
Launch OBIX
UNRESTRICTED HOUSE CENSUS
Remind Me
Print
Secure
Log Out
Search
[redacted]
Allergies
No Known Allergies
FYI
General
MRN: 188060
CSN: None
MyCare: Declined
Pt Portal: None
Outside Info: None
Code: Click for Pri...
Research: None
Sticky Note:
Ht: 1.702 m (5' 7.01")
Wt: 84.369 kg (186 lb)
Chart Review (Last refresh: 3:34:58 PM)
Close
SnapShot
Chart Review
Review Flowshe...
Results Review
Allergies
History
Problem List
Demographics
Letters
Place Orders
Call Patient
Send Letter
Write Note
Refill Med
FYI
Patient Station
More Activities
Encounters
Anesthesia Records
Surgeries
Adv Dir
Procedure Notes
Notes
Photos
Imaging
Laboratory
Micro
EKG/Cardiac 11/5-2/12/12
EKG 2/13/12+
Telemetry Strips
Filters
Text Search
Refresh
Select All
Deselect All
Review Selected
Side-by-Side
Master Report
Flowsheet
Route
CCS Reports
u.Net Connect
More
64 records match filters, more records to load
Default filter
Clear All
Filters:
Default filter
Adm Date
Disch Date
CSN
12/31/2015 323776411
12/31/2015 323774586
12/30/2015 323752543
12/24/2015 323667770
12/18/2015 323545904
12/11/2015 323382715
12/07/2015 323253285
12/03/2015 323191018
12/02/2015 323163355
11/25/2015 323043134
11/24/2015 322737188
11/24/2015 323016052
11/23/2015 323000986
11/20/2015 322956639
11/20/2015 322957485
11/18/2015 322899433
11/18/2015 322898510
11/17/2015 322866381
11/17/2015 322867260
11/16/2015 322836742
11/16/2015 322834098
11/15/2015 322816100
11/14/2015 322813383
11/14/2015 322812698
11/14/2015 322812242
11/14/2015 322811785
11/14/2015 322810590
11/14/2015 322810350
11/14/2015 322809578
11/14/2015 322809035
11/13/2015 12/7/2015 322806555
11/13/2015 11/13/2015 322804140
Back
Select Font Size
ED to Hosp-Admission
11/13/2015
Delores Aberdeen | MRN: 188060
Patient Demographics and Encounter Information
Patient Demographics
DOB
[redacted]
(79 y.o.)
ROCHESTER NY 14613
Hospital Account# 106674345
Payor
MEDICARE
Plan
MEDICARE A & B
2
Payor
MEDICAID
Plan
MEDICAID
ED Chart Summary
ED Chart Summary Report
ED Patient Care Timeline report
Go to ED Patient Care Timeline
Reason for Admission
Hypotension, unspecified hypotension type - Primary
ICD-10-CM: I95.9
ICD-9-CM: 458.9
Hyperkalemia
ICD-10-CM: E87.5
ICD-9-CM: 276.7
Dehydration
ICD-10-CM: E86.0
ICD-9-CM: 276.51
Diabetes mellitus
ICD-10-CM: E11.9
ICD-9-CM: 250.00
CKD (chronic kidney disease) stage 4, GFR 15-29 ml/min
ICD-10-CM: N18.4
ICD-9-CM: 585.4
ANN F.
Future/Standing Orders
3:42 PM
3:42 PM
2/29/2016