Swine Flu

Influenza in Swine in the U.S.: Brief History and Current Status

Bruce H. Janke, DVM, PhD
Veterinary Diagnostic Laboratory
Iowa State University
Ames, IA

History: Original Descriptions

- Earliest written description involved a state fair in Indiana
- In early 1920s, descriptions of the disease in Iowa; similarity to human disease (Spanish flu 1918) recognized; speculations on the cause of the malady
- Isolation and confirmation as a virus in 1930 (Shope) – nasal mucus from pig into a ferret, then into eggs; subsequently from people

?: Who Infected Whom

- ☞ Birds → Pigs → People theory
  - Asia as influenza epicenter attributed to agricultural practices (proximity of ducks, pigs and people)
  - Early 1918 cases in U.S. at Fort Riley, KS – recruits were mostly farm kids

?: Who Infected Whom

- Birds → People → Pigs theory
  - Sequence analysis suggests the 1918 virus was avian virus that passed directly into people <u>or</u>
  - Into an unknown host first (differs from avian viruses from that time)
  - No evidence of prior circulation in swine

Swine as “Mixing Vessels”

- Concept derived from studies that showed:
  - Variation in nucleoprotein in swine greater than in humans or birds
  - Pigs have receptors for both avian and mammalian influenza viruses
  - Pigs could be infected experimentally with avian viruses of 15 HA subtypes
  - Reassortant viruses could be recovered from pigs infected simultaneously with two influenza viruses

Counterpoint Questions: Pandemics of the Past

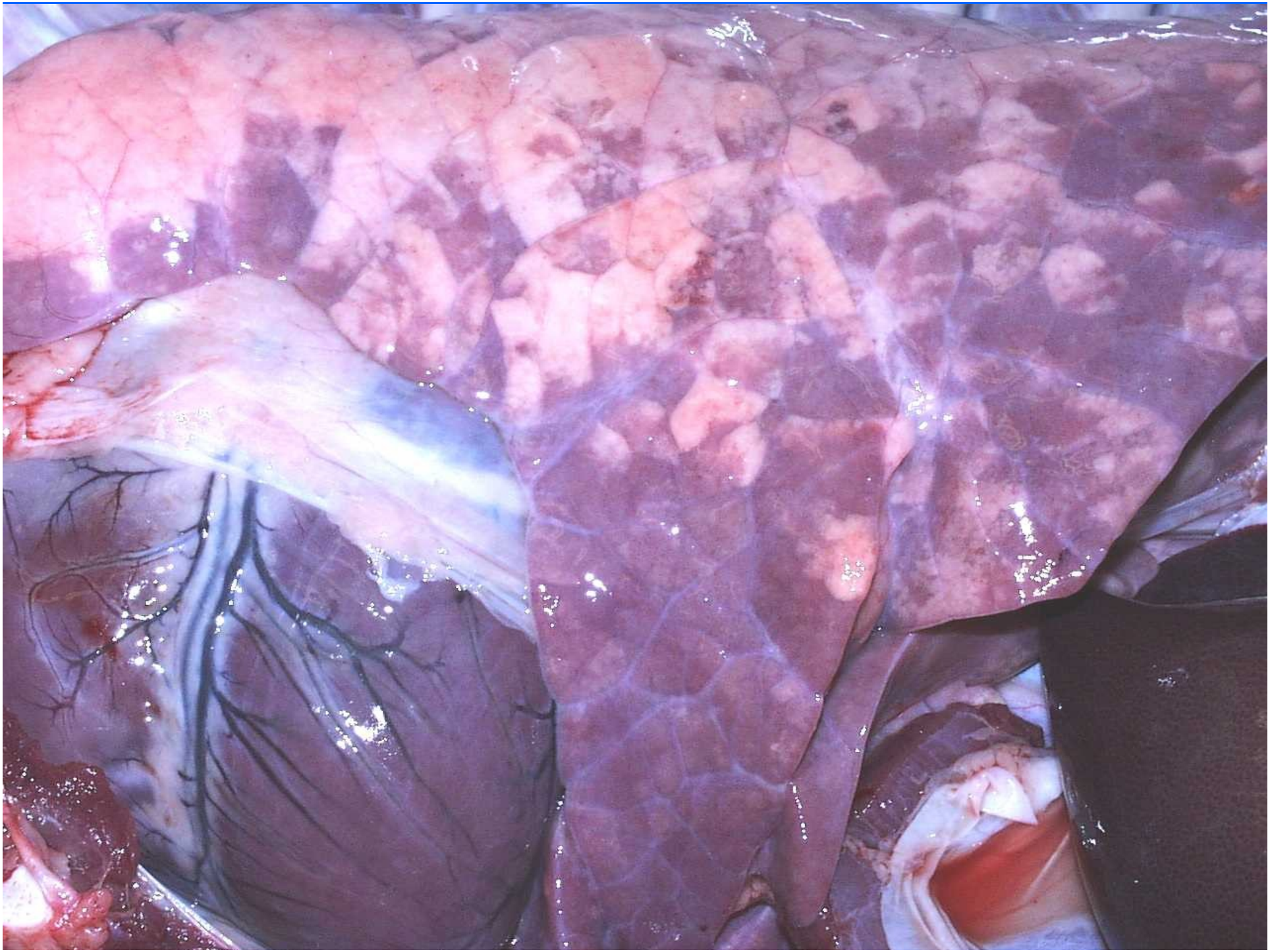
- 1918 (Spanish flu) – original H1N1
  - Totally avian virus
- 1957 (Asian flu) – H2N2
  - Avian H2N2 + pre-existing human H1N1
  - H2N2 had never been found in swine (until 2006)
- 1968 (Hong Kong flu) – H3N2
  - Avian H3 + pre-existing human H2N2
  - Swine were not harboring H2N2
- H5N1 avian viruses in SE Asia
  - Totally avian virus
  - Direct human contact with birds
  - Poorly infectious for swine

Swine as Pariah?

- Cases of infection of humans and poultry with SIV have been and continue to be documented.
- Perception developed of significant risk of infection from swine to other species
- In reality, the evidence (in recent years) indicates that infection of swine with human and avian viruses negatively impacts swine health (reversed risk) →

People → Pigs

- Documented cases
  - In Europe, human H3N2 virus entered swine populations in early 1970s and stayed (minimal disease)
  - In U.S., human H3N2 virus isolated from pigs in Colorado in 1977 (no disease)
  - Human H1N1 virus initially thought to be less likely to infect swine but recently such infections with intact virus and gene introduction as reassortants



SIV in U.S.

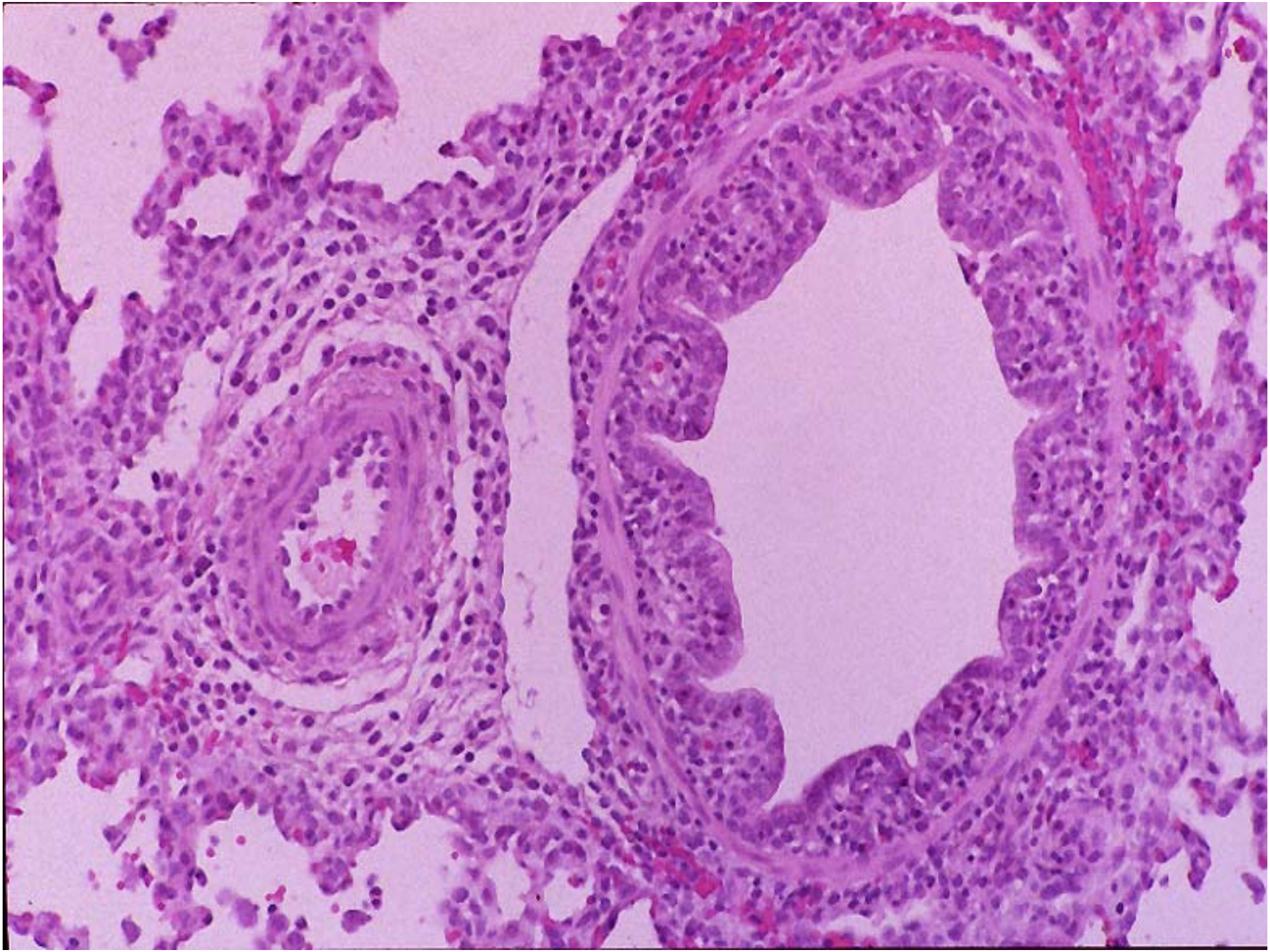
- Entered swine population in 1918
- Not isolated until 1930
- SIV remained unique (a few exceptions) to the U.S. until 1976 when exported to Italy
- H1N1 remained the only subtype of significance in U.S. for 80 yrs

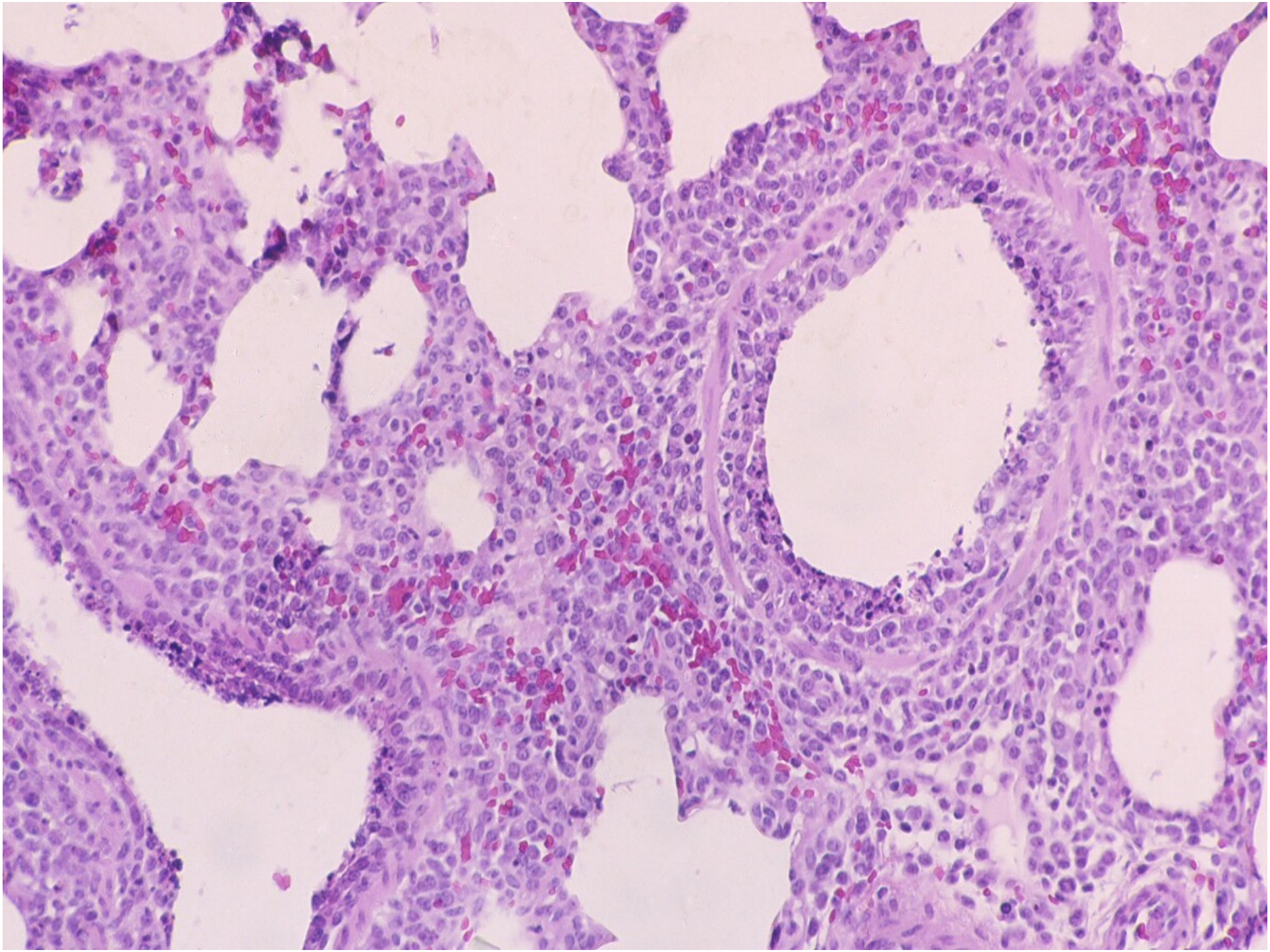
SIV in U.S.

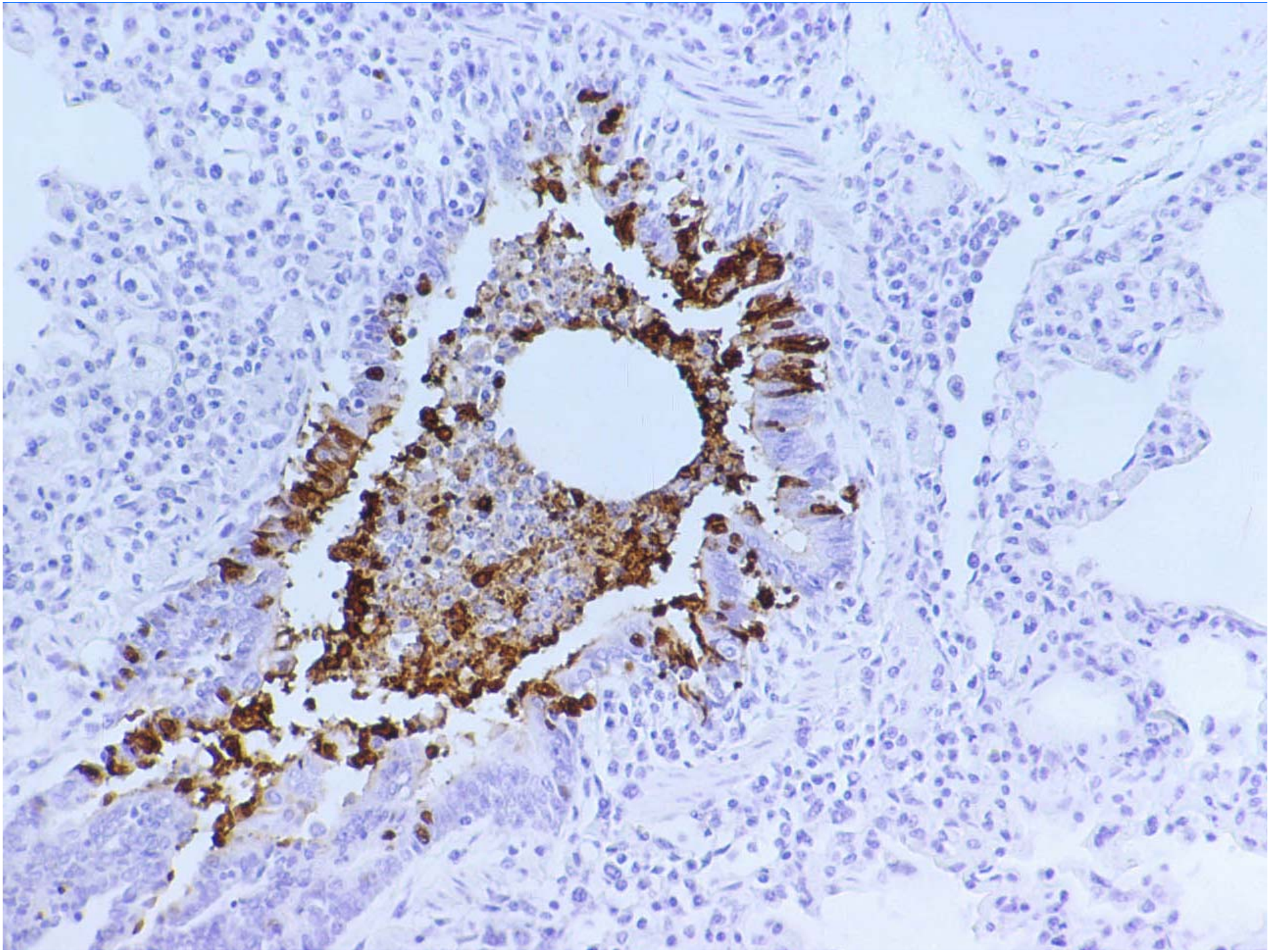
- H1N1 remarkably stable
- Antigenic variants described in late 1980s - early 1990s ("atypical")
  - Canada and U.S.
  - Clinical confusion with PRRSV (PNP – proliferative and necrotizing pneumonia)

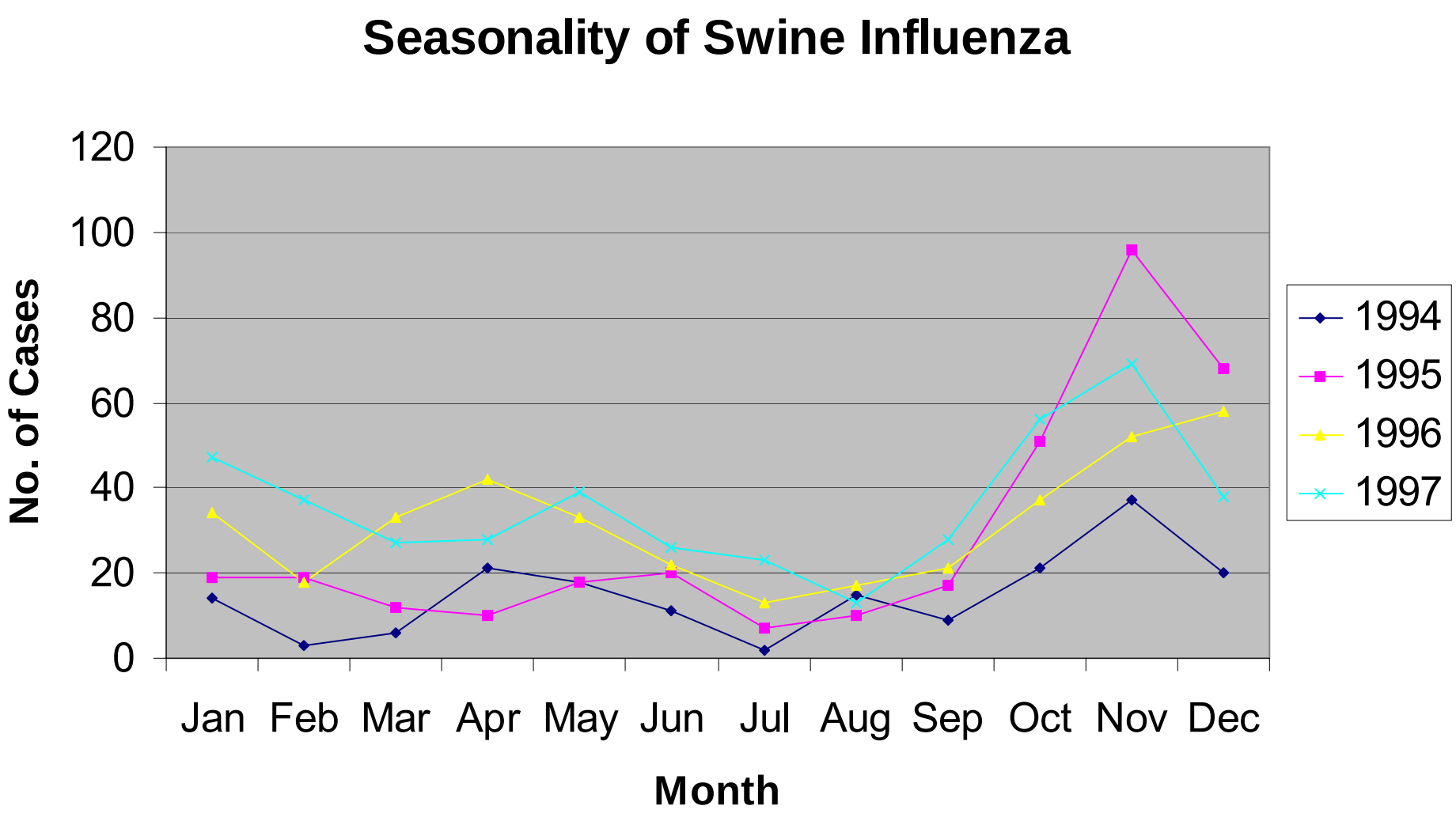
Clinical Disease

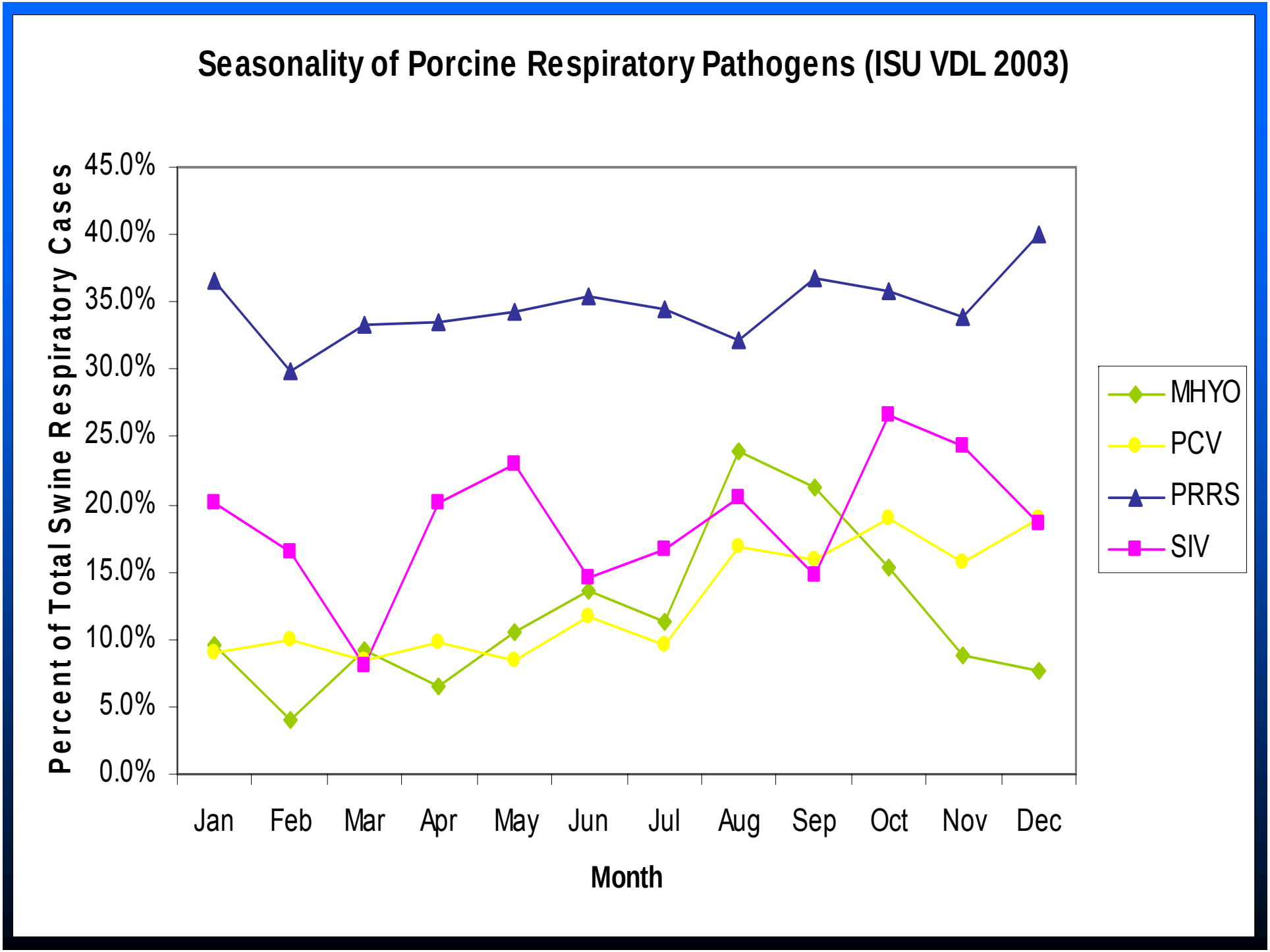
- Hallmark clinical signs –
  - Harsh barking cough
  - High fever, lassitude
  - Rapid course through the herd
- Minimal diagnostic testing conducted
- Minimal treatment measures used
- No vaccine available








Seasonality of Swine Influenza
No. of Cases
120
100
80
60
40
20
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Month
1994
1995
1996
1997


Seasonality of Porcine Respiratory Pathogens (ISU VDL 2003)
Percent of Total Swine Respiratory Cases
45.0%
40.0%
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Month
MHYO
PCV
PRRS
SIV

Swine Pneumonia Cases
ISU VDL 2005 (3435)

- PRRSV 1088 (32%)
- SIV 726 (21%)
- PCV 383 (11%)
- M hyo 320 (9%)

- P multocida 636 (18%)
- S suis 549 (16%)

SIV Age Distribution

- Classically a grow-finish disease
- Early-mid 1990s: More problems in nursery
- 1995-1998: Vaccine (1994) → grow-finish
- 1998-1999: New subtype - Adults, all ages
- 2000-2005: Nursery, grower, finisher
- 2005 - 2008: Nursery, farrowing

H3N2: Antigenic Shift in the U.S.

- H3N2 as a significant pathogen in U.S. swine in 1998
  - Essentially doubled SIV problems - concurrent H1N1 and H3N2
    - 96-98: ~350 cases SIV/yr (ISU)
    - 99: nearly 700 cases SIV (ISU)
  - Similar to the rest of the world in having both H1N1 and H3N2 in swine

H3N2 was not really new to swine in 1998

- Human H3N2 ----------> Swine
  - Wisconsin, 1976 (1.4% seroprev)
  - Colorado, 1977 (isolate, 1975 all hu)
  - Wisconsin, 1988 (1.1% seroprev)
  - Canada, 1990 (isolate, 1975 hu HA)
  - Illinois, 1993 (isolate, unknown HA)
  - Wisconsin, 1997 (8.0% seroprev)
  - Canada 1997 (isolate, 1995 all hu)
  - Nebraska 1998 (isolate, 1995 hu HA)

Other Factors for H3N2 Appearance?

- Avian virus entrance ? (Olsen)
  - 1989 - 0% seroprevalence Dk Alb
  - 1998 - 7.6% seroprevalence Dk Alb
  - Relationship to triple reassortants?

SIV in the U.S. (H3N2)

- Aug 1998: North Carolina H3N2 (Erickson)
  - H3, N2, PB1 from human 1995 H3N2
  - Rest of the genes from classical sw H1N1

- Fall 1998: Midwest (IA, TX, MN) H3N2
  - H3, N2, PB1 from ~ human H3N2
  - NP, M, NS from classical sw H1N1
  - PA, PB2 from an avian virus

Continued Introduction of Human H3N2 into Swine

- H3 & N2 from 1995 human virus (Cluster I – TX 98)
- H3 & N2 from 1997 human virus (Cluster II – CO 99)
- H3 & N2 from 1996 human virus (Cluster III – IL 99, OK 99)

SIV Subtypes: ISU VDL

Year	H1N1	H3N2	Untyp-able	H1& H3	H1N2
1999	46.2 %	38.5	12.8	2.6	0.0
2000	68.4	22.8	7.0	1.8	0.0
2001	67.0	28.6	3.3	1.1	0.0
2002	69.9	20.8	7.2	0.8	1.7
2003	61.7	20.7	4.3	2.7	10.7
2004	56.1	25.4	5.0	2.5	11.1
2005	48.5	35.9	8.7	2.4	4.4

SIV Subtypes: ISU VDL

- 2005
  - H1N1 (431)
  - *H3N2 (407)*
  - H1N2 (33)
- 2007
  - H1N1 (478)
  - H3N2 (113)
  - H1N2 (106)
- 2006 (→ Sept)
  - H1N1 (427)
  - H3N2 (170)
  - H1N1 (23)

2nd Generation Reassortants (H1N2)

- H1N2
  - Reassortment of co-circulating H1N1 and H3N2
    - Classic swine: H1, NP, M, NS
    - Human: N2, PB1
    - Avian: PA, PB2
  - As early as 1998

2nd Generation Reassortants (rH1N1)

- Webby (2001)
  - H1N1 isolates with classic sw H1 and N1 and internal genes of H3N2
    - Classic swine: H1, N1, NP, M, NS
    - Human: PB1
    - Avian: PA, PB2
  - Retrospective study (ISU)
    - rH1N1 displaced cH1N1 almost immediately

Subtype Seroprevalence June 1999

- 1064 sera from 129 herds in 29 counties in IA (10-15 pigs/herd)
- 6-month-old finishers

- H1N1 (39% pigs / 71% herds +)
- H3N2 (64% pigs / 92% herds +)
- Both (30% pigs / 66% herds +)

New Reassortant H1N1 SIV ISU VDL

Year	Swine PA & PB2	Avian PA & PB2	Mixed PA & PB2	Negative PA & PB2	Total Virus Tested
1997	36	0	8	6	50
1998	0	3	0	0	3
1999	4	34	5	7	50
2000	1	38	5	6	50
2001	0	45	5	1	51
2002	0	56	3	1	60
2003	1	36	9	4	50
2004	0	28	0	2	30

PA, PB2 Genes in H1N1 SIV: NC

Year	Swine PA & PB2	Avian PA & PB2	Mixed PA & PB2	Neg (-) PA & PB2	Total Virus Tested
1999	0	11	1	0	12
2000	0	36	2	0	38
2003	0	51	0	0	51

2nd Generation Reassortants (H3N1)

- Not identified until 2004
- Suggests this combination is not as stable and efficient
- Several have been isolated in MN and IA

Introduction of Human H1N1 Viruses into Swine

- Human H1N1 viruses
  - 2003 (Gramer)
    - H1N2 (hu 02/sw) from pigs
  - 2005 (Gramer)
    - H1N1 (hu/hu 04) from pigs
  - 2006 (Olsen)
    - H1N2 (hu/hu 02) from pigs
    - H1N2 (hu 02/sw) from pigs
    - H1N1 (hu PB1/sw) from pigs

Introduction of Human H1N1 Viruses into Swine

- Human H1N1 virus genes
  - Increasing in prevalence
  - Associated with disease (mild?)
  - Serologically undetectable (70% HA homology vs sw H1)
  - Detected by PCR, identified by sequence determination

SIV Case Age Distribution

%	1995	1998	1999	2000	2003	2005
Nursing	5	3	7	6	7	3
Nursery	28	14	21	31	27	43
Grower	39	21	25	29	30	33
Finisher	28	52	36	33	33	19
Adult	0	9	11	1	3	2

One virus core + H + N

- Since emergence of triple reassortant (1998)
- Stable internal gene platform adapted to swine
- Switching external protein genes
  - H3N2
  - H1N2
  - H3N1
  - rH1N1
  - hH1N1

Current U.S. SIVs

- Classic swine H1N1
  - sw H1, N1
  - sw NP, M, NS
  - sw PA, PB1, PB2
- H3N2 (triple reassortant)
  - hu H3, N2
  - sw NP, M, NS
  - av PA, PB2 hu PB1
- H1N2 (2nd generation)
  - sw H1 hu N2
  - sw NP, M, NS
  - av PA, PB2 hu PB1
- H3N1 (2nd generation)
  - hu H3, sw N1
  - sw NP, M, NS
  - av PA, PB2 hu PB1
- Reassortant H1N1
  - sw H1, N1
  - sw NP, M, NS
  - av PA, PB2 hu PB1
- Reassortant hu H1N1, H1N2
  - hu H1,N1-2,sw N1-2
  - sw NP, M, NS
  - av PA, PB2 hu PB1

rH1N1 Antigenic Drift Variants

- Increased tendency to antigenic drift
- H1 (sw) viruses have settled into two clades represented by:
  - A/Sw/MN/01 H1N1
  - A/Sw/IND/99 H1N2 (more ~ to cH1N1)
  - Both H1 variants found in H1N1 and H1N2 viruses
  - Relative abundance initially similar; MN01-like viruses now predominant

Current H1 Viruses in Swine

- rH1N1 like (MN 01)
- H1N2 like (IND 99)
- huH1 (H1 or H1N1 or H1N2)
- cH1N1(classic all swine virus)

H3N2 Antigenic Drift Variants

- Three clades (Webby)
- Clade III (IL/99-like) now predominant (98%)
- Clade III drifting (IL/99 drift variants)
- No new H3N2 reassortment events recently

Regional Differences (Gramer/MN)

- H1 viruses
  - MN & IA – MN 01-like predominant
  - IL, IN, WI, SE U.S. – IND 00-like
  - Western U.S. – Both co-circulate
  - cH1N1 rare in all areas
  - Hu-like H1 viruses more common in SE U.S.
- H3 viruses
  - IL/99-like viruses predominant in all areas

Tip of the Iceberg

- Intact avian viruses into swine
  - H1N1
  - H3N3
  - H4N6
- Intact human viruses into swine
  - H3N2
  - H1N1
  - H1N2

H2N3 SIV

- Isolated from pigs (nursery, grow-finish) with clinical respiratory disease (Gramer MN 2006)
- Triple reassortant virus similar to most current SIVs
  - H2, N3 avian origin
  - PA more recent avian origin
- First report of H2 virus in mammals since H2N2 human pandemic virus in 1957
- No spread; no human illness; HA only 85% homology with 1957 hu H2

Control of SIV Infection

- Measures used
  - Vaccination of sows
  - Vaccination of pigs
- Issues
  - Maternal antibody derived from vaccinated sows can interfere with effective immunization of pigs (timing)
  - Antigenic variation is becoming a major issue

Humoral Response Contributes to Protection

- Circulating aby has been shown to be effective in protection from illness
- May not completely prevent infection, but shedding is reduced & shortened
- Antibody is produced against external and internal proteins
- Degree of protection is related to serum titer (not threshold)
- Inactivated vaccines given IM stimulate a lot of IgG in serum and lung

Effect of Antigenic Variation on Vaccine Protection

- Antigenic variation among H1N1 and H3N2 viruses documented
- Greater than 4-fold differences in cross-reactivity commonly observed among SIVs in nearly all surveys conducted (benchmark for changing viruses in human vaccines)
- Numerous studies with SIVs have shown protection between antigenically diverse viruses
- Field experience more frustrating

Effect of Antigenic Variation on Vaccine Protection

- Problem: Significance of measured sequence homology or serologic cross-reactivity
- Correlation between HA protein amino acid sequence and serologic cross-reactivity not predictable
- Correlation between *in vitro* HI cross-reactivity and cross-protection in the pig not predictable
- Antigenic mass and adjuvant used are important

Antigenic Variation & Cross-Protection: Conclusions

- Unpredictable
- If viruses are antigenically similar, cross-protection is likely
- If viruses are antigenically dissimilar, the degree of cross-protection may be less but not necessarily. Most studies indicate some protection.
- Degree of protection may be partial (just as it varies with titer)

Vaccination and Enhancement of Infection

- First observed in studies on heterologous protection and comparison of killed vs MLV vaccines
- Some pigs vaccinated with killed vaccine and challenged with heterologous virus had more severe disease than non-vaccinated control pigs challenged with same virus

Vaccination and Enhancement of Infection

- Enhancement did not occur in pigs vaccinated with MLV vaccine
- Enhancement did not occur in pigs challenged with homologous virus
- May be related to balance of IgG (higher) and IgA (lower) in lung following vaccination