Supporting Information

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SI Materials and Methods

Immunohistochemistry. The primary antibodies used were: anti-influenza antibody goat polyclonal IgG (Abcam Inc.) or anti-cytokeratin AE1/AE3 mouse monoclonal antibody mixture (Invitrogen Corporation). The primary antibodies were detected using a biotinylated rabbit anti-goat IgG (Invitrogen Corporation), the Vectastain Elite ABC kit (Vector Laboratories), and diaminobenzedine as the chromogen. Negative controls were processed without incubation of the primary antibody. Immunostained sections were lightly counterstained with hematoxylin. All sections were reviewed comprehensively, and were qualitatively compared, by one pathologist (J.K.T.). Representative sections were converted to digital format at 20× magnification using the Aperio XT Scanner (Aperio) and the regions of interest were extracted to prepare micrographs. A subset of micrographs at a higher-power magnification was acquired using the Olympus BX-41 microscope (Olympus America).

Molecular Studies. The four prepandemic peak cases with positive immunohistochemical results for influenza viral antigen were chosen for molecular analysis, as were 17 pandemic peak cases. Fifteen of these 17 were chosen randomly from both influenza viral antigen positive and negative cases; the other two cases had been previously identified as positive for influenza viral RNA (1). PCR products were cloned and sequenced as described (2). Briefly, reverse transcription was performed at 37 °C for 50 min in 20 μL total volume with MMTV-reverse transcriptase and random hexamer primers. One microliter of the cDNA reaction was added to 20 μL PCR mixture including 2 μCi α^{32}P-dATP (3,000 Ci/mmol). Three overlapping primer sets were designed for a portion of the HA1 domain of the 1918 hemagglutinin gene; the PCR mixtures contained 10 mM Tris-HCl, 50 mM KCl, 2.5 mM $MgCl_2$, 200 nM primers, 100 nM dNTPs, and 1 unit Amplitaq Gold (Applied Biosystems Inc.) in a 20-μL total volume. PCR cycling conditions were 10 min at 94 °C; 40 cycles of 94 °C for 30 s, 55 °C for 30 s, 72 °C for 30 s, followed by a 72 °C extension time for 5 min. PCR product (4 μL of the reaction) was separated on a 7% denaturing polyacrylamide gel and visualized by autoradiography. Bands were excised and DNA was purified. After amplification, one-fifth of the reaction was cloned into the pCR2.1 vector, following the manufacturer's instructions (Invitrogen Corporation). Direct PCR using M13F and M13R primers was done on white colonies and the products were sequenced using standard methods.

Molecular Modeling. Theoretical models for all 1918 H1 variants in combination with sialo-pentasaccharides LSTc or LSTa were created with the RosettaDesign functionality (3) of Rosetta3 (4). The 1918 H1 receptor complex (5) was used as the template for in silico substitutions. For the Q189 and R189 receptor-binding analysis, LSTc was computationally docked to the hemagglutinin of A/SC/1/1918 or the model of A/VA/1/1918, respectively, using RosettaLigand (6, 7) with FROG (8) to generate an ensemble of LSTc conformations. For both variants, 1024 ligand docking simulations were carried out and the lowest energy decoys were analyzed as described (6).

1. Reid AH, Fanning TG, Hultin JV, Taubenberger JK (1999) Origin and evolution of the 1918 "Spanish" influenza virus hemagglutinin gene. *Proc Natl Acad Sci USA* 96: 1651–1656.
2. Taubenberger JK, Reid AH, Krafft AE, Bijwaard KE, Fanning TG (1997) Initial genetic characterization of the 1918 "Spanish" influenza virus. *Science* 275:1793–1796.
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4. Leaver-Fay A, et al. (2011) ROSETTA3: An object-oriented software suite for the simulation and design of macromolecules. *Methods Enzymol* 487:545–574.
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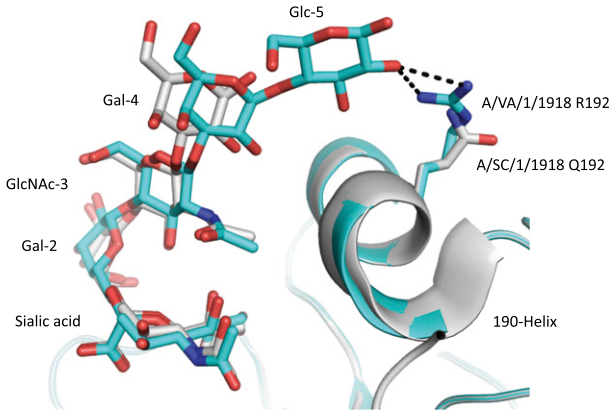

Fig. S1. Theoretical model of A/VA/1/1918 HA receptor-binding domain. This sequence was modeled with the human receptor analog LSTc superposed on a model of the A/South Carolina/1/1918 HA receptor-binding domain (1–5). The models were created by superposition of the LSTc from the H1 subtype A/swine/Iowa/30HA-human receptor complex (1–5) (cyan) sialic acid moiety onto the same group in the 1918-human HA-human receptor complex (gray) and in silico substitution of Q189 (gray) to R189 (cyan). The HA backbone is shown as a ribbon diagram.

1. Gamblin SJ, et al. (2004) The structure and receptor binding properties of the 1918 influenza hemagglutinin. *Science* 303:1838–1842.
2. Stevens J, et al. (2004) Structure of the uncleaved human H1 hemagglutinin from the extinct 1918 influenza virus. *Science* 303:1866–1870.
3. Stevens J, et al. (2006) Glycan microarray analysis of the hemagglutinins from modern and pandemic influenza viruses reveals different receptor specificities. *J Mol Biol* 355:1143–1155.
4. Stevens J, et al. (2006) Structure and receptor specificity of the hemagglutinin from an H5N1 influenza virus. *Science* 312:404–410.
5. Srinivasan A, et al. (2008) Quantitative biochemical rationale for differences in transmissibility of 1918 pandemic influenza A viruses. *Proc Natl Acad Sci USA* 105:2800–2805.

Table S1. Cases examined for the present study

Case*	Location†	Age	1918 Diagnoses‡	Major histopathological findings§	1918 Postmortem lung bacteriological results¶	Gram stain‖	Influenza IHC**	Cytokeratin IHC††	Influenza RT-PCR††
119180511	CD	27	P	AP, Pl, Br	Neg	Gram+ c/w Strep	Pos Br	Neg	Pos
19180602	CD	21	P	AP, Pl, Br, DAD, E	*Streptococcus*, *Staphylococcus*	Gram+ c/w Strep	Pos Br	Pos	Pos
19180603	WR	21	P	AP, Pl, DAD, E	Pneumococcus, *Staphlococcus*	Gram+ c/w Strep	Neg	Pos	N/D
19180621	CJ	22	P	AP, Pl, DAD, E, H, HM	Pneumococcus type III	Gram+ c/w Strep	Neg	Pos	N/D
19180624	WR	18	P	AP, Br, Pl	Pneumococcus, *Streptococcus*	Gram+ c/w Strep	Pos Br	N/D	Pos
19180720	CF	21	P	AP, T	Pneumococcus type II	Gram+ c/w Strep	Neg	Pos	N/D
19180722	CJ	24	P	AP, Pl, Br	Pneumococcus type IV	Gram+ c/w Strep	Pos Br	Pos	Pos
19180730	CD	22	P	AP, DAD, E	Pneumococcus type I	Gram+ c/w Strep	Neg	Pos	N/D
19180808	CD	30	P	AP, Pl, Br, DAD, E	Pneumococcus type I	Gram+ c/w Strep	Neg	Pos	N/D
19180914	CT	N/A	BP	AP	N/A	Gram+ c/w Strep	Pos Br, NM	Pos	N/D
19180921	CU	29	I, P	AP, DAD, E, HM, H	*Staphylococcus aureus*	Gram+ c/w Staph	Pos AM, HM	N/D	Pos
19180922a	CJ	21	I, BP	AP, DAD, H	*Staphylococcus*	Gram+ c/w Staph	Pos Br	N/D	N/D
19180922b	CU	25	I, BP	AP, DAD, E, H	Pneumococcus type IV	Gram+ c/w Strep	Pos AM	Pos	N/D
19180922c	CU	22	I, BP	AOP, DAD, E	Pneumococcus type III	Gram+ c/w Strep	Neg	N/D	N/D
19180923a	CJ	29	I, P	AP, Br, E	Pneumococcus, type II	Gram+ c/w Strep	Pos Br	Pos	N/D
19180923b	CU	28	I, BP	AP, Br, DAD, E, H	"Specimen unsatisfactory"	Gram+ c/w Strep	Pos Br	N/D	N/D
19180923c	CU	N/A	I, BP	AP, Br, DAD, E, H	*Staphylococcus albus*	Gram+ c/w Strep	Pos Br, NM	Pos	N/D
19180924a	CU	31	I, P	AP, Br, DAD(AO), E, H	*Bacillus coli*	Gram - rods	Neg	Pos	N/D
19180924b	CU	31	P	AP, Br, DAD, E,H, HM	Pneumococcus type IV	Gram+ c/w Strep	Neg	Pos	Neg
19180924c	CU	28	I, P	AP, Br, DAD, E, H	Pneumococcus, type IV	Gram+ c/w/ Strep	Neg	N/D	N/D
19180924d	CU	22	I, P	AP, Br, DAD, E, Pl	Pneumococcus, type II	Gram+ c/w Strep and Staph	Pos Br, AM	Pos	Pos
19180924e	CU	31	I, BP	AP, Br, DAD, E, H, HM	*Staphylococcus albus* (heart blood)	Gram+ c/w Strep	Pos Br, AM	Pos	Neg
19180924f	CU	31	I, BP	AOP, Br, DAD(AO), E	Pneumococcus,type III	Gram+ c/w Strep	Pos Br	Pos	N/D
19180925a	CU	29	I, P	AP	Pneumococcus type III	Gram+ c/w Strep	Pos Br, AE, AM	Pos	N/D
19180925b	CU	25	I, BP	AP, Br, DAD, E, H, HM	Pneumococcus, type IV	Gram+ c/w Strep	Neg	Pos	Neg
19180925c	CU	31	I, P	AP, DAD(AO), E, H, T	Neg	Neg	Neg	Pos	Neg
19180925d	CU	27	I, BP	AOP, Br	*Streptococcus*, hemolytic	Gram+ c/w Strep	Neg	N/D	N/D
19180926a	CL	N/A	P	AP, Br, DAD, E	N/A	Gram+ c/w Staph	Neg	Pos	N/D
19180926b	CL	N/A	P	AP, B, Br	N/A	Gram+ c/w Strep	Neg	Pos	N/D
19180926c	CJ	21	I, P	AP, Br	N/A	N/D	N/D	N/D	Pos
19180926d	CU	28	I, P	AP, Br, DAD(AO), E, H, Pl	Pneumococcus type III	Gram+ c/w Strep	Neg	Pos	Pos
19180926e	CU	30	I, P	AP, DAD, E, H	"Specimen unsatisfactory"	Neg	Neg		Pos
19180926f	CU	24	I, P	AP, T	N/A	Gram+ c/w Strep	Neg	Pos	Neg
19180926g	CU	26	I, P	AP	Pneumococcus, type II, and *Streptococcus*, nonhemolytic	Gram+ c/w Strep	Pos AM, NM	N/D	N/D
19180927a	CL	N/A	BP	AP, DAD, E, Br	N/A	Gram+ c/w Strep	Pos Br	Pos	Pos
19180927b	CU	22	I, P	AP	Pneumococcus	Gram+ c/w Strep	Pos Br, AE	Pos	N/D
19180927c	CU	26	I, BP	AP, Br, DAD, E, H, HM	Pneumococcus	Gram+ c/w Strep and Staph	Posi Br, AE, AM	Pos	N/D
19180927d	CU	32	I, P	AP, DAD, E, H	Pneumococcus type III	Gram+ c/w Strep	Neg	N/D	N/D
19180928	CU	25	I, P	AP, Br, DAD, E, H, HM	Pneumococcus, type III	Gram+ c/w Strep	Neg	Neg	N/D
19180929a	WR	28	P	AP, B, Br	Pneumococcus group 2	Gram+ c/w Strep	Pos B, BSG	N/D	N/D
19180929b	CL	N/A	P	AP,B, Br	"Diplococci in sections"	Gram+ c/w Strep	Pos Br	Pos	N/D
19180929c	CU	23	I, P	AOP, Br, DAD(AO), E, Pl	N/A	Gram+ c/w Strep	Not done	N/D	N/D

Table S1. Cont.

Case*	Location†	Age	1918 Diagnoses‡	Major histopathological findings§	1918 Postmortem lung bacteriological results¶	Gram stain‖	Influenza IHC**	Cytokeratin IHC††	Influenza RT-PCR††
19180930a	WR	29	P	AP, DAD, E	Pneumococcus type II	Gram+ c/w Strep, Gram– c/w H flu	Pos B, BSG, AM, NM	Pos	N/D
19180930b	CL	N/A	P	AP,B, Br, DAD, E, HM	N/A	Gram+ c/w Strep	Pos B, BSG, Br, AE, AM, HM	N/D	Pos
19180930c	CL	N/A	P	AP	N/A	Gram+ c/w Strep	Pos Br, AM	Pos	N/D
19180930d	CU	N/A	I, P	AP, Br	*Streptococcus*, nonhemolytic	Gram+ c/w Strep	Neg	Pos	N/D
19181001a	CL	N/A	P	AP, Br, DAD	N/A	Gram+ c/w Strep	Pos Br, AM, NM	N/D	Neg
19181001b	CL	N/A	P	AP	N/A	Gram+ c/w Strep	Neg	Pos	N/D
19181001c	CL	N/A	I, BP	AP, Br	N/A	Gram+ c/w Strep	Pos Br, AE, AM, NM	Pos	N/D
19181001d	CL	N/A	P	AP,DAD, E	N/A	Gram+ c/w Strep	Neg	Pos	Neg
19181001e	CL	N/A	P	AP, DAD, E, H	N/A	Neg	Pos Br	Pos	Pos
19181005	CD	29	I, BP	AP	*Streptococcus*, hemolytic	Gram+ c/w Strep	Neg	Pos	N/D
19181007	WR	N/A	I, P	AP, Br, DAD, E, H	Friedländer's bacillus	Gram+ c/w Strep and Gram– c/w *Klebsiella*	Pos Br, AE, AM, NM	Pos	N/D
19181008a	N/A	N/A	N/A	AP, DAD, E, H	N/A	Gram+ c/w Strep	Neg	N/D	N/D
19181008b	N/A	N/A	N/A	AP, Br, H	N/A	Gram+ c/w Strep	Neg	N/D	N/D
19181008c	N/A	N/A	N/A	AP, Br, DAD, E, H, HM	N/A	Gram+ c/w Strep	Neg	Pos	Pos
19181008d	N/A	N/A	N/A	AP, DAD, E, H	N/A	Gram+ c/w Strep	Pos B, BSG	Pos	N/D
19181008e	N/A	N/A	N/A	AP, Br, H	N/A	Gram+ c/w Strep	Pos Br, AE	Pos	N/D
19181008f	N/A	N/A	N/A	AP, DAD, E, H	N/A	Gram+ c/w Strep	Neg	N/D	N/D
19181008g	N/A	N/A	N/A	AP, Br, DAD, E	N/A	Gram+ c/w Strep	Pos Br	Pos	N/D
19181008h	N/A	N/A	N/A	AP, B, Br, DAD, E	N/A	Gram+ c/w Strep	Neg	Pos	N/D
19181008i	N/A	N/A	N/A	AP, Br, H	N/A	Neg	Neg	N/D	N/D
19181010	CU	31	I, BP	AOP	Pneumococcus, type III	Gram+ c/w Strep and Staph	Neg	Pos	N/D
19181011	CD	22	P	AP, Br, DAD, E	*Streptococcus*, hemolytic	Gram+ c/w Strep	Pos Br	Pos	N/D
19181015	CD	27	I, P	AP, DAD, E, H	*Streptococcus*, hemolytic	Gram+ c/w Strep	Neg	Pos	N/D
19181017	WR	N/A	I, P	AP	Pneumococcus type II, *Staphylococcus*, Friedländer's bacillus	Gram+ c/w Strep and Staph	Pos Br	Pos	Neg
19181018	CG	N/A	I, BP	AP, Br, DAD, E, T	N/A	Gram+ c/w Strep	Pos Br	Pos	N/D
19181024	WR	N/A	I, BP	AP, Br, T	*Streptococcus hemolyticus*, *Staphylococcus*	Gram+ c/w Staph and Strep	Neg	Pos	N/D

*Cases are identified for this study by the date of death (e.g., 19180511 represents May 11, 1918). For dates with more than one case, a small case letter is added to distinguish them (e.g., 19180929a). Medical records for nine of the cases were unavailable, but these cases were accessioned at the Armed Forces Institute of Pathology along with others with a range of death from September 22, 1918 to October 24, 1918. These cases have been arbitrarily assigned a date in the middle of this range, and thus are identified as 19181008a through 19181008i.

†US Army camp locations abbreviated as: CD, Camp Dodge, IA; CF, Camp Funston, KS; CG, Camp Greene, NC; CJ, Camp Jackson, SC; CL, Camp Lee, VA; CT, Camp Travis, TX; CU, Camp Upton, NY; WR, Walter Reed Hospital, Washington, DC.

‡Major diagnoses made in 1918 abbreviated as: BP, Bronchopneumonia; I, Influenza; P, Pneumonia.

§Major histopathological findings on case review abbreviated as: AP, acute pneumonia; AOP, acute and organizing pneumonia; B, bronchitis; Br, bronchiolitis; DAD, diffuse alveolar damage; DAD(AO), acute and organizing DAD; E, pulmonary edema; H, pulmonary hemorrhage; HM, hyaline membrane formation; Pl, pleuritis; T, thrombus formation.

¶Postmortem lung culture results as reported in the 1918 case records.

‖Tissue Gram stain results reported as: "Gram+ c/w Strep," Gram-positive bacteria morphologically consistent with Streptococcal species; "Gram+ c/w Staph," Gram-positive bacteria morphologically consistent with Staphylococcal species; "Gram– rods," Gram-negative rod-shaped bacteria; "Gram– rods c/w *Klebsiella*," Gram-negative bacteria morphologically consistent with *Klebsiella* species; Neg, Negative; N/D, Not done.

**Immunohistochemistry for influenza viral antigen was reported as Pos, positive, with staining in: B, bronchial epithelial cells; BSG, bronchial submucosal glands; Br, bronchiolar epithelial cells; AE, alveolar epithelial cells; AM, alveolar macrophages; HM, hyaline membrane material; NM, intraluminal necrotic epithelial cells and necrotic material; Neg, negative; N/D, not done.

††Pos, positive; Neg; negative; N/D; not done.

Table S2. Clinical features of 1918 pneumonia cases

Characteristic	Value
Symptom onset to hospitalization, median days (range)	3 (0–14)
Hospital length of stay, median days (range)	6 (1–51)
Symptom onset to death, median days (range)	9 (3–16)
Symptom onset to cyanosis, median days (range)	8 (2–14)
Postmortem cardiac findings*, No./Total (%)	6/56 (10.7)
Signs and symptoms on admission [No./Total (%)]	
Temperature > 38 °C	49/55 (89.1)
Headache	34/55 (61.8)
Cough	33/55 (58.2)
Dyspnea or respiratory distress	27/55 (49.1)
URI signs or symptoms	25/55 (45.5)
Chills	25/55 (45.5)
Myalgia/arthralgia	23/55 (41.8)
Malaise	21/55 (38.2)
Pleuritic chest pain	17/55 (30.9)
Gastrointestinal symptoms	13/55 (23.6)
Hemoptysis	6/55 (10.9)
Altered mental status	9/55 (16.4)
Dizziness	5/55 (9.1)
Photophobia or stiff neck	4/55 (7.3)

*Postmortem cardiac findings (no. cases): valvular anomaly (1), patent foramen ovale (1), left ventricular anomaly (1), left ventricular hypertrophy (1), mitral valve thickening (1), chronic endocarditis and mitral stenosis (1).

Table S3. Partial receptor-binding domain sequence of 16 1918 pandemic influenza virus hemagglutinin HA1s

	Case (date of death)	Strain name*	Partial HA protein sequence (residues 172-234 of HA1 domain)†	Source of sequence (case no.)
			EVLVLWGVHHPPTGTDQQSLYQNADAYVSVGSSKYNRRFTPEIAARPKVRDQAGRMNYYWTLL	1918 Consensus Sequence
Pre-pandemic peak	05/11/1918	A/IA/1/1918	. . . . . G	This report (19180511)
	06/02/1918	A/IA/2/1918	. . . . . G	This report (19180602)
	06/24/1918	A/DC/1/1918	. . . . .	This report (19180624)
	07/22/1918	A/SC/2/1918	. . . . . G	This report (19180722)
Pandemic peak	09/21/1918	A/NY/2/1918	. . . . .	This report (19180921)
	09/24/1918	A/NY/3/1918	. . . . . G	This report (19180924d)¶
	09/26/1918	A/NY/1/1918	. . . . . G	Reid, et al. 1999 (1) (19180926e)
	09/26/1918	A/SC/1/1918	. . . . .	Reid, et al. 1999 (1) (19180926c)
	09/26/1918	A/NY/4/1918	. . . . .	This report (19180926d)
	09/27/1918	A/VA/1/1918	. . . . . R	This report (19180927a)
	09/30/1918	A/VA/2/1918	. . . . .	This report (19180930b)
	10/01/1918	A/VA/3/1918	. . . . .	This report (19181001e)
	10/08/1918‡	A/AFIP/1/1918	. . . . .	This report (19181008c)
Post-pandemic peak	11/17/1918§	A/BM/1/1918	. . . . .	Reid, et al. 1999 (1)
	11/13/1918	A/London/1/1918	. . . . . S	Reid, et al. 2003 (2)
	02/13/1919	A/London/1/1919	. . . . . I . G	Reid, et al. 2003 (2)

*Full influenza strain names assigned to these sequences: A/IA/1/1918: A/Iowa/1/1918 (H1); A/IA/2/1918: A/Iowa/2/1918 (H1); A/DC/1/1918: A/District of Columbia/1/1918 (H1); A/SC/2/1918: A/South Carolina/2/1918 (H1); A/NY/2/1918: A/New York/2/1918 (H1); A/NY/3/1918: A/New York/3/1918 (H1); A/NY/1/1918: A/New York/1/1918 (H1N1) (1); A/SC/1/1918: A/South Carolina/1/1918 (H1N1) (1); A/NY/4/1918: A/New York/4/1918 (H1); A/VA/1/1918: A/Virginia/1/1918 (H1); A/VA/2/1918: A/Virginia/2/1918 (H1); A/VA/3/1918: A/Virginia/3/1918 (H1); A/AFIP/1/1918: A/Armed Forces Institute of Pathology/1/1918 (H1) [Location of case not available]; A/BM/1/1918: A/Brevig Mission/1/1918 (H1N1) (1); A/London/1/1918: A/London/1/1918 (H1) (2); A/London/1/1919: A/London/1/1919 (H1) (2).

†Theoretical protein sequences (single letter code) translated from the determined cDNA 1918 sequences as aligned to the HA1 domain sequence of A/SC/1/1918 [GenBank accession no. AAD17229.1], numbering from start of the HA1 domain (sequence aligns to residues 189-254 of open reading frame) (1). Gray highlighted amino acids represent components of the receptor-binding domain (RBD) (3–5). Dots match consensus sequence. Sequences determined for this study were deposited in GenBank (accession nos. JN620390–JN620401).

‡Case was accessioned at the AFIP in conjunction with other cases from September 22, 1918 through October 24, 1918; date of death was arbitrarily set as October 8, 1918.

§The pandemic outbreak in Teller Mission (now Brevig Mission, AK) occurred between November 15–20, 1918; date of death was arbitrarily set as November 17, 1918 (6).

¶Sequence analysis of case 19180924d suggests a polymorphism at HA1 codon 222, with a theoretical translation of both glycine (G) and asparagine (N).

1. Reid AH, Fanning TG, Hultin JV, Taubenberger JK (1999) Origin and evolution of the 1918 "Spanish" influenza virus hemagglutinin gene. *Proc Natl Acad Sci USA* 96:1651–1656.
2. Reid AH, et al. (2003) 1918 influenza pandemic caused by highly conserved viruses with two receptor-binding variants. *Emerg Infect Dis* 9:1249–1253.
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5. Srinivasan A, et al. (2008) Quantitative biochemical rationale for differences in transmissibility of 1918 pandemic influenza A viruses. *Proc Natl Acad Sci USA* 105:2800–2805.
6. Rozell N (2005) Villager's remains lead to 1918 flu breakthrough. *Alaska Science Forum* http://www2.gi.alaska.edu/ScienceForum/ASF17/1772.html (University of Alaska, Fairbanks, Fairbanks, AK).